## Title

# Part I. Oxidative Syntheses of the Illicium Sesquiterpenes Part II. Three-Step Synthesis of the Quassinoid Core Architecture 

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Publication Date
2018
Peer reviewed|Thesis/dissertation

# Part I. Oxidative Syntheses of the Illicium Sesquiterpenes 

 Part II. Three-Step Synthesis of the Quassinoid Core Architecture
## By

Matthew L. Condakes

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy<br>in<br>Chemistry<br>in the<br>Graduate Division<br>of the<br>University of California, Berkeley

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Fall 2018

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# Abstract <br> Part I. Oxidative Syntheses of the Illicium Sesquiterpenes Part II. Three-Step Synthesis of the Quassinoid Core Architecture 

## By

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In this two-part dissertation, strategic and tactical advances are disclosed in service of the total syntheses of complex natural products. The first part (Chapters 1-3) chronicles the development of oxidative strategies toward the synthesis of the Illicium sesquiterpenes - advances that have led to total and formal syntheses of a dozen natural products. Beginning with an introduction (Chapter 1) of prior art in the field, from structural elucidations and biological studies to previous synthetic works, we seek to contextualize the notion of an oxidative synthesis and argue that it not only represents a significant departure from that precedent but also stands as an inherently logical approach to these natural products. In Chapter 2, the path to the first successful iteration of this strategy is traced for the synthesis of the moderately-oxidized pseudoanisatinoids from the terpene feedstock chemical, cedrol. Multiple interesting oxidative transformations discussed in detail along the way. In particular, a novel copper(II) bromide-mediated oxidative lactonization is developed and its mechanism studied. Additionally, an exceptionally challenging directed non-heme mononuclear iron(oxo)-catalyzed oxidation of an unactivated $\mathrm{C}\left(\mathrm{sp}^{3}\right)-\mathrm{H}$ bond is discussed in detail. The chapter concludes with the successful synthesis of multiple pseudoanisatinoids. Chapter 3 addresses the shortcomings of the work described in Chapter 2 and extends the notion of an oxidative synthesis to the more highly oxidized majucinoid Illicium sesquiterpenes. Through multiple directed and non-directed $\mathrm{C}\left(\mathrm{sp}^{3}\right)-\mathrm{H}$ oxidations, the majucinoid core is assembled rapidly, leading to the total and formal syntheses of over a half dozen more natural products. The chapter concludes with a unification of the majucinoid and pseudoanisatinoid routes, providing a persuasive argument for the rational extension of oxidative strategies in complex natural product synthesis.

The second part (Chapter 4) describes burgeoning efforts in the synthesis of quassinoids, degraded triterpene lactone natural products. In this sole chapter, a background on quassinoids is given first, including a history of these compounds' structures, biological activities, and prior syntheses. That discussion then leads into our synthetic work in the area. Drawing on those lessons, we envision a strategy leveraging elements of hidden symmetry in the natural products' structures. In order to execute this strategy, a novel copper-catalyzed double-coupling of epoxy ketones is designed. The strengths and limits of this highly regio- and diastereoselective transformation are explored. Finally, the chapter concludes with an application of this methodology to a three-step synthesis of the full quassinoid ring system, creating a solid foundation for future work in this area.

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## Acknowledgments

So much has happened and changed since beginning graduate school that it almost feels unfair to try and condense all those experiences into one small expression of gratitude. To reflect on more than four years of friendships, adventures, challenges, and - of course - chemistry is a daunting task, and it would be impossible to fully recount everything that shaped my journey. Nevertheless, I hope the following will convey my sincere appreciation to those who have had a large impact on my time here And, in traditional fashion, a disclaimer: if I forget to mention you by name here, know that was not my intent and I hope you'll forgive that oversight.

First, thank you to the multiple professors who have mentored and advocated for me. Even during my undergraduate studies, I was fortunate enough to have had Andy believe in my potential and Ian show me what it takes to conduct top-notch research in synthetic organic chemistry. Thank you for being inspiring teachers; I would not have been set on this path without your guidance. To Richmond, John, Dean, and Kaoru - my qualifying exam committee - I greatly appreciate the time you took to ensure I was on the right track in my second year. I still remember the advice you gave and know it was very helpful in planning my future. In a similar vein, to John and Dean, thank you for writing recommendation letters during my job search. And to Richmond, John, and Kaoru, thank you for serving on my dissertation committee and providing feedback on my work.

And, finally, to Tom: words cannot adequately capture what it has meant to work in your lab. Thank you for this unparalleled opportunity, for your unwavering support, and for your unrivaled ability to push me to succeed. Though the lab has changed so much since I joined, it has been incredibly rewarding to see it excel at all stages and have the chance to influence its course in some small way. I hope your research program continues on its path of success and wish you and your family the best. Thank you.

Next, to the fellow students I have worked most closely with: Teams Illicium and Quassin.

Team Illicium: Kevin, I know you're expecting an effusive essay extolling every element of the efforts we have expended, so I hope not to disappoint. I remember in my first few months how much an of enigma you were. Neither Alec nor I can remember a single conversation with you from that time. Then, something changed (to this day I don't know what), and you decided to open up in a distinctly Kevin-like fashion. Little did I know what lay ahead, since when Tom caught wind of this phenomenon, I quickly found myself working with you on the Illicium project. Truly, I owe so much to all the pioneering work you had done on these molecules. And I echo your sentiments of how the project has shaped and eternally bonded us. It all seems fine now on the other side, but I know how challenging it was at the time, before we had first tasted success. There are few others I would have rather worked with to tackle those problems - I have great respect for your fastidiousness and I know your talents will serve you well at Novartis.

To Taka and Zhi, while you both worked mainly with Kevin, it was still a pleasure having you on the project, and I wish you both the best in your future endeavors. Taka, I still have your goodbye note, which reminds me of your unfailingly considerate nature. To Luiz, it has been a privilege working with you these past few months. The stoic determination with which you carry out your chemistry is inspiring. You are a talented chemist, and I hope you see great success in your career - good luck in Song Lin's group!

Team Quassin: Rachel, I know how trying working on challenging chemistry can be, but to your credit you've persevered. You're ready now to take up the quassin mantle, and I can't wait to read about your future accomplishments. To Alvin, while your tenure on the project may have been short, I am glad that you have found success in the Hartwig group. Thanks again for setting up our group's NMR backup and I hope you get to use those great CS skills to do the machine learning.

Finally, to Stephen - the first undergraduate I mentored - who was uniquely (un)lucky to have worked on both the Illiciums and quassinoids with me: I don't think I can add much here to what I've already told you. You had quite the individual presence in lab. I learned a lot from mentoring you, and it was very rewarding to see you grow into the successful chemist you've become. Good luck in the Baran lab!

Now, to the other graduate students in the lab: To Zach and Chi, I can safely say that the lab would not be what it is today without your pioneering efforts. You both set the bar incredibly high for future students and it was a pleasure to learn from you while you were still around. Zach, I remember working next to you during the (literally) dark days of the coupling and your unsurpassed work ethic that led to success. I imagine I'll be seeing more of you in Boston! Chi, the academic path is not an easy one, but if anyone from the lab is up for it, it's you - I hope you can achieve your goals and I look forward to reading the publications from your independent career. To Xirui, you not only have impeccable fashion sense but also a great eye for chemistry. Can't wait to start at BMS with you! To Karl, it has been a pleasure seeing you mature as a chemist and become a leader of the lab. Best of luck finishing your molecule! To Bingqi, the amount of results you have for any given subgroup speaks to the incredible efforts you put in to any work that you do - I hope you see success soon. To Danny, good luck in ophiobolin land. I'm sure the end is in sight, even if it doesn't always seem that way. You have good chemical insights and I look forward to seeing that in your future work. To Linus, I hope you know all the teasing is in good fun. May you live up to your namesake and impress us all with your chemistry. To Claire, it has been a pleasure working next to you these past few years, and receiving all those texts meant for Christopher. I sincerely hope things will work out for you. To Vasil, it's too bad I'm leaving before your qual - you're working on a tough project and you deserve a bit of celebration. To Andre, while we only overlapped for a few months, I enjoyed discussing your project with you. Good luck getting it off the ground!

To the postdocs of the lab - Yuming, Huck, Silong, Gong, Michael, Drew, Ken, Jun, Martin - you have provided valuable experience that has proved instrumental for finishing multiple projects. Silong, I enjoyed working next to you and it was very fun to have hot pot at your place - I still have your fan, too. And to the other visiting students (don't think I forgot you, Hywel!), masters students, and undergraduates who have come through this lab during my time here: best wishes on your future endeavors.

To those former lab members, thank you for brightening up the lab while you were here. To Fernando, it was nice hearing from about the biological side of some of the lab's natural products. To Nick, it's been great seeing your success in the Francis lab. It's good that you haven't forgotten how to take an NMR or two, either. To Alec, thank you for years of friendship and lunch dates. It was great having you as a roommate, and I'm proud of what you've accomplished in your time
here. I look forward to seeing you and Rebekah in Boston!
Finally, to those outside of lab who have helped keep me sane throughout the years. To Fan and Richard, thank you for keeping me apprised of the happenings in Boston - let's get lunch again when I'm back there for good! To Brandon, I'm glad you finally got to visit, and I hope Berkeley didn't scare you too much. To my blockmates, R.J., Steve, and Rebecca, and to all the other friends that have helped make SF feel like a second home: thank you. Being able to escape to the city was a welcome reprieve from some of the more stressful times in graduate school.

To Jolie, words cannot express what your love and support has meant to me. It's incredible that things have worked out the way they did - I'm very lucky to have you!

To my family, to Mom, Dad, Michael, Novvó, Chris, and Sparky: to you I owe a great deal, both leading up to graduate school and during my time here. I love you all, and hope that you are proud of this chapter of my life.

## List of Abbreviations

| 18-cr-6 | 1,4,7,10,13,16-hexaoxacyclooctadecane |
| :---: | :---: |
| $9-\mathrm{BBN}$ | 9-borabicyclo[3.3.1]nonane |
| [O] | oxidation |
| Ac | acetyl |
| acac | acetylacetonate |
| AIBN | azobisisobutyronitrile |
| $a q$. | aqueous |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| Bn | benzyl |
| BTPP | tert-butyl-imino-tri(pyrrolidino)phosphorane |
| Bz | benzoyl |
| CDI | carbonyldiimidazole |
| CSA | camphorsulfonic acid |
| d.r. | diastereomeric ratio |
| dba | dibenzylideneacetone |
| DBN | 1,5-Diazabicyclo[4.3.0]non-5-ene |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCC | $N, N$ '-dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DFT | density functional theory |
| DHNM | 3,4-dehydroneomajucin |
| DIBAL-H | diisobutylaluminum hydride |
| DIPEA | $\mathrm{N}, \mathrm{N}$-diisopropylethylamine |
| DMAP | 4-dimethylaminopyridine |
| DMDO | dimethyldioxirane |
| DMF | dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMS | dimethyl sulfide |
| DMSO | dimethyl sulfoxide |
| dpm | 2,2,6,6-tetramethyl-3,5-heptanedionato |
| dppe | 1,2-bis(diphenylphosphino)ethane |
| dtbpy | 4,4'-di-tert-butyl-2,2'-dipyridyl |
| EDC | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| ee | enantiomeric excess |
| EI | electron ionization |
| ESI | electrospray ionization |
| esp | $\alpha, \alpha, \alpha^{\prime}, \alpha^{\prime}$-tetramethyl-1,3-benzenedipropionic acid |
| Et | ethyl |
| GABA | $\gamma$-aminobutyric acid |
| Glc | glucose |
| HAT | hydrogen atom transfer |
| HG-II | Hoveyda-Grubbs catalyst, $2^{\text {nd }}$ generation |


| HIV | human immunodeficieny virus |
| :---: | :---: |
| HMDS | hexamethyldisilane |
| HMPA | hexamehtylphosphoric triamide |
| HRMS | high resolution mass spectrometry |
| HWE | Horner-Wadsworth-Emmons |
| Hz | Hertz |
| hv | photoirradiation |
| IBX | 2-iodoxybenzoic acid |
| imid | imidazole |
| $i \mathrm{Pr}$ | iso-propyl |
| IPr | 1,3-bis(2,6-diisopropylphenyl)imidaz-ol-2-ylidene |
| IR | infrared |
| J | coupling constant |
| KHMDS | potassium bis(trimethylsilyl)amide |
| L-selectride | lithium tri-sec-butylborohydride |
| $\mathrm{LD}_{50}$ | median lethal dose |
| LDA | lithiumdiisopropylamide |
| LHMDS | lithium bis(trimethylsilyl)amide |
| $m$ CPBA | meta-chloroperbenzoic acid |
| Me | mehtyl |
| mep | $N, N$ '-dimethyl- $N, N$ '-bis(2-pyridylmethyl)-eth-ane,1,2-diamine |
| MMC | magnesium methyl carbonate |
| MOM | methoxymethyl |
| MoOPH | oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) |
| Ms | mesyl (methanesulfonyl) |
| MS | molecular sieves |
| MVK | methyl vinyl ketone |
| NaHMDS | sodium bis(trimethylsilyl)amide |
| NBS | N -bromosuccinimide |
| $n \mathrm{Bu}$ | butyl |
| NCS | N -chlorosuccinimide |
| Nf | nonaflyl (nonafluorobutanesulfonyl) |
| NGF | nerve growth factor |
| NIS | N -iodosuccinimide |
| NMO | $N$-mehtylmorpholine- N -oxide |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser effect |
| $o$-tol | ortho-tolyl |
| oct | octyl |
| ODB tashironin | 11-O-debenzoyltashironin |
| ODNM | (1R,10S)-2-oxo-3,4-dehydroxyneomajucin |
| PCC | pyridinium chlorochromate |


| PDC | pyridinium dichromate |
| :--- | :--- |
| PDP | $N, N^{\prime}$-bis(2-pyridylmethyl)-2,2'-bipyrrolidine |
| Ph | phenyl |
| Piv | pivaloyl |
| PMP | para-methoxyphenyl |
| ppm | parts per million |
| PPTS | pyridinium para-toluenesulfonate |
| proton-sponge | 1,8 -bis(dimethylamino)naphthalene |
| py | pyridine |
| r.r. | regiomeric ratio |
| Red-Al | sodium bis(2-methoxyethoxy)aluminium hy- |
|  | dride |
| SAR | structure-activity relationship |
| TBAB | tetrabutylammonium bromide |
| TBACl | tetrabutylammonium chloride |
| TBAF | tetrabutylammonium fluoride |
| TBAI | tetrabutylammonium iodide |
| TBDPS | tert-butyldiphenylsilyl |
| TBHP | tert-butylhydroperoxide |
| TBS | tert-butyldimethylsilyl |
| $t$ Bu | tert-butyl |
| TEMPO | $(2,2,6,6-$ Tetramethylpiperidin-1-yl)oxyl |
| TES | triethylsilyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TLC | thin-layer chromatography |
| TMEDA | tetramethylethylenediamine |
| TMS | trimethylsilyl |
| TosMIC | tosylmethyl isocyanide |
| Triton B | benzyltrimethylammonium hydroxide |
| Ts | tosyl (toluenesulfonyl) |
| UV | ultraviolet |
| $\Delta$ | heat |
| $\mu$ m | microwave |
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То Гıaүıó,
$\alpha i \omega v i ́ \alpha ~ \sigma o v \dot{\eta} \mu v \dot{\mu} \mu \nu \eta$

## Part I:

## Oxidative Syntheses <br> of the Illicium Sesquiterpenes

## Chapter 1

## An Introduction to the Illicium Sesquiterpenes

### 1.1 History and Chemical Structures of the Illicium Sesquiterpenes

The Illicium (from the Latin, illicere, to allure, entice) genus of flowering plants is often distinguished by its star-shaped fruit and characteristic aroma (Figure 1.1). ${ }^{1}$ Commonly called "star anise," these plants are located throughout Southeast Asia and the North American tropical zone (Mexico, the Caribbean, and certain areas of the United States of America, like Florida) ${ }^{2}$ and have had broad cultural impact. Edible species, such as the Chinese Illicium verum, have been used to flavor food and beverages for hundreds of years and have seen applications in traditional medicine as well. ${ }^{3}$ Illicium verum has also historically served as the source for shikimic acid, the key precursor for the industrial production of oseltamivir (Tamiflu), an antiviral medicine used to combat influenza. ${ }^{4}$ However, other Illicium species, like the Japanese Illicium anisatum (also called Shikimi), have been noted for their high toxicity and ability to induce convulsions if consumed. ${ }^{5}$ Indeed, in one European incident, trace contamination of the edible $I$. verum with this toxic species was enough to lead to widespread


Figure 1.1. Illicium anisatum, a representative member of the family, as seen in the University of California Botanical Garden at Berkeley. hospitalizations. ${ }^{6}$

Given this background, significant effort has been devoted to deconvoluting the relationship between the secondary metabolites produced by these plants and these observed effects. Over 65 years of effort by various groups have generated countless publications detailing the isolation and characterization of many chemical constituents contained in various segments of Illicium plants. ${ }^{7}$ Some components, like prenylated compounds, flavonoids, and neolignans, are common to a number of other genera and even families of plants. ${ }^{2}$ However, one class of compounds, a collection of highly oxidized sesquiterpene lactones, is unique to the genus. Collectively termed "Illicium sesquiterpenes," these natural products have been linked most definitively to the observed phenotypic effects of the Illicium plants.

As sesquiterpenes, these compounds are composed of a 15 -carbon core and are known to come in three main varieties: seco-prezizaane (1), allo-cedrane (2), and anislactone-type (3) (Figure 1.2A). A fourth, structurally-related class of sesquiterpene skeleton, the cedrane scaffold (4), is included at this point for comparison due to its centrality to the work about to be described. Additionally, for the purposes of this work, the numbering schemes employed have been homogenized based on $\mathbf{1}$, such that each position in $\mathbf{2 , 3}$, and $\mathbf{4}$ corresponds to the respective carbon in $\mathbf{1}$.

Further subdivisions of $\mathbf{1}$ are possible based on the specific lactonization pattern seen on the parent skeleton (Figure 1.2B). "Majucinoids" contain a $\gamma$-lactone fusing the C 12 and C 14 positions, "pseudoanisatinoids" are characterized by an $\varepsilon$-lactone bridging the C 11 and C 14 positions, and "anisatinoids" display a unique spiro- $\beta$-lactone motif between the C13 and C14 positions.
A

|  <br> seco-prezizaane core framework (1) |  |
| :---: | :---: |
|  <br> anislactone-type core framework (3) |  |

B

majucinoids >25 members

anisatinoids ca. 15 members

pseudoanisatinoids $>50$ members

anislactone-type ca. 10 members
C

$(-)$-majucin (5)
(-)-jiadifenoxolane A (6)

(-)-ODNM (7)

(-)-anisatin (12)

(-)-jiadifenin (8)

(-)-anislactone A (13)

(-)-jiadifenolide (9)

(-)-11-O-debenzoy tashironin (10)

(+)-pseudoanisatin (11)
igure 1.2. (A) Sesquiterpene architectures relevant to the current work. Numbering follows a unified system based on 1. (B) Illicium sesquiterpene subtypes as assigned based on lactonization pattern. (C) Representative examples of highly oxidized Illicium natural products. Inset: a low oxidation state natural product for comparison.

Prominent members of each type and subtype are shown in Figure 1.2C to provide relevant examples of complete structures, illustrating the complexity seen in this family of natural products. Majucin (5), the eponymous "majucinoid," has an additional bridging $\delta$-lactone between the C 7 and C11 positions. Jiadifenoxolane A (6), a close congener, has a further bridging ether ring between the C 3 and C 10 positions. More elaborately oxidized members, like ( $1 R, 10 S$ )-2-oxo-3,4-dehydroxyneomajucin, (ODNM, 7), have been isolated, along with the majucinoids jiadifenin (8) and jiadifenolide ( 9 ), which no longer contain the $\delta$-lactone of majucin.

While 11-O-debenzoyltashironin (ODB-tashironin, 10) might prima facie appear to be an allo-cedrane type of natural product, closer scrutiny suggests an intrinsic connection to the pseudoanisatinoid core, as simple retro-aldol of its lactol motif (breaking the C6-C11 single bond) would regenerate the characteristic $\varepsilon$-lactone seen in pseudoanisatin (11). Finally, anisatin (12), with a stunning C13-C14 $\beta$-lactone, rounds out the seco-prezizaane subtypes with its polyhyrdoxylated scaffold and additional C7-C11 majucin-like $\delta$-lactone. Anislactone A (13) is depicted
A

B


pseudoanisatin,
l. anisatum

1a-hydroxypseudoanisatin, l. merrillianum

1,4-epoxy-6-deoxypseudoanisatin, l. dunnianum

(6S)-deoxypseudoanisatin, l. dunnianum

(6R)-deoxypseudoanisatin, l. dunnianum

1-hydroxy-6-deoxypseudoanisatin, l. minwanense

$2 \beta$-hydroxy-6-deoxypseudoanisatin
l. minwanense

$3 \alpha$-hydroxyparviflorolide, l. merrillianum

$3 \alpha$-hydroxymerrillianolide, I. merrillianum


1,8 $\alpha$-dihydroxy-3-deoxycyclopseudoanisatin, I. simonsii

merrillianolide, l. merrillianum


C


parviflorolide, l. parviflorum


3,6-dideoxypseudoanisastin l. merrillianum


3-deoxypseudoanisatin,
l. merrillianum


2a-hydroxyparviflorolide, I. parviflorum


2 $\beta$-hydroxy-3,6-dideoxypseudoanisatin,
I. merrillianum



2,10-epoxy-3-deoxypseudoanisatin, I. merrillianum




3-oxo-ortholactone floridanolide, I. floridanum


1,2-dehydrocycloparvifloralone, I. merrillianum

cycloparvifloralone, l. parviflorum

$2 \alpha$-hydroxy-cycloparvifloralone, I. merrillianum

$3 \alpha$-hydroxycycloparvifloralone, I. merrillianum

majusatone, I. majus

merrillianone, I. merrillianum

neodunnianin, I. dunnianum

Figure 1.3. List of pseudoanisatinoid natural products. (A) An example of the ketone/ketal equilibrium often seen in this subtype. (B) List of compounds containing a C11-C14 ع-lactone and oxidation at C3. (C) List of compounds containing a C11-C14 $\varepsilon$-lactone without oxidation at C3. (D) The dunnianins, natural products containing a unique C3-C11 $\delta$-lactone. (E) List of compounds containing a C4-C11 $\gamma$-lactone. (F) List of compounds containing a bridging $\mathrm{C} 7-\mathrm{C} 11 \delta$-lactone and oxidation at C 3 . ( $\mathbf{G}$ ) List of compounds containing a bridging $\mathrm{C} 7-\mathrm{C} 11 \delta$-lactone and no oxidation at C3. (H) List of remaining pseudoanisatinoids, including C7/C11/C14 ortholactones and C7/C11/C14 ketals.
here to demonstrate the highly compact and contorted structures possible for this family of natural products. Further discussion on the chemistry and biology of this Illicium subtype, though, is regrettably outside the scope of the present work. On the other end of the spectrum, cedrol (14) is included to provide a point of reference to a simple sesquiterpene core that has not been oxidized relative to farnesol, the 15 -carbon precursor to these sesquiterpenes.

In addition to these particularly significant structures, over 100 members of this family have been isolated and characterized (Figures 1.3, $,^{8-33} 1.4,{ }^{34-47} 1.5,{ }^{8,21,29,30,35,48-60}$ and $1.6^{13,21,32,56,58,59,61-}$ ${ }^{70}$ ). For the purposes of this tabulation, seco-prezizaane subtypes have been further divided for ease of compilation based on finer differences in oxidation state and/or lactonization pattern. Additionally, many redundant compounds, including those containing simple variations in appended ester groups, have been omitted so that the focus can be instead on the remarkably diverse variants produced.

Every effort has been made to render the structures faithfully and accurately; however, structural revisions in the field are common. A full 16 years elapsed between the isolation and preliminary characterization of $\mathbf{1 2}$ in 1952 by Lane from I. anisatum and its definitive structural determination by Yamada in $1968 .{ }^{8,48}$ Additionally, the structure of $\mathbf{1 1}$ was debated for quite some time until X-ray analysis confirmed its uncommon $\varepsilon$-lactone. ${ }^{10}$ While crystal structures exist for most if not all of the highest profile members, such data is not available for many other compounds. It can be particularly challenging to ascertain the precise connectivity in the molecule when multiple $\beta$-disposed hydroxyl groups could serve as competent sites for lactonization. Such has been the case for the dunnianins (Figure 1.3D), where it was unclear whether the lactone was between C3 and C11 or C7 and C11 until a crystal structure confirmed the solid state configuration of those compounds. ${ }^{22}$ Further complicating analysis, many compounds exist as inseparable lac-
A


majucin,
I. majus





$2 \alpha$-hydroxy-
neomajucin I. micranthum
2 $\beta$-hydroxy-
neomajucin,
I. micranthum


1,2-dehydroneomajucin,
I. jiadifengpi

1,2-epoxyneomajucin, I. micranthum

jiadifenoxolane B,

jiadifenoxolane A, I. jiadifengpi I. jiadifengpi


jiadifenin, I. jiadifengpi

jiadifenlactone acid,
I. jiadifengpi

jiadifenolide,
I. jiadifengpi

2 $\alpha$-hydroxy-
jiadifenolide, I. jiadifengpi

$2 \beta$-hydroxynorneomajucin,
l. jiadifengpi

jiadifenlactone A, I. jiadifengpi

"jiadifenin," l. jiadifengpi

jiadifenone, I. jiadifengpi

Figure 1.4. List of majucinoid natural products bearing the characteristic C 12 -C14 $\gamma$-lactone. (A) List of compounds containing a bridging C7-C11 $\delta$-lactone. (B) List of compounds containing a bridging C7-C11 $\delta$-lactone and a C3-C4 alkene. (C) List of remaining majucinoids, including nor-derivatives and other rearranged structures.
tone/orthoester mixtures or as ketone/ketal mixtures (e.g., 11 and 15, Figure 1.3A). ${ }^{11}$ These complexities also make structural elucidation based on computed parameters somewhat unreliable. For instance, the absolute configuration of recently isolated illisimonin A (Figure 1.6) was assigned by comparison to a computed electronic circular dichroism spectrum. ${ }^{70}$ However, those calculations suggested an assignment heterochiral to every other Illicium sesquiterpene isolated from that plant and related species. ${ }^{71}$ Given the absence of more compelling data, we have chosen to render it in its homochiral form here (i.e., enantiomeric to the published structure).

Despite these caveats, a few general trends have emerged over the years. The moderately oxidized pseudoanisatinoids (Figure 1.3) have predominated isolation reports, with over 60 members characterized to date. Although structurally diverse, these compounds nevertheless all contain conserved oxidations at $\mathrm{C} 4, \mathrm{C} 7, \mathrm{C} 11$, and C 14 . The majucinoids (Figure 1.4) and anisatinoids (Figure 1.5) also contain those oxidations along with many more; together, they account for another 55 or so natural products. Indeed, it is challenging to imagine more oxidized compounds than 8 (Figure 1.4B) or the veranisatins (Figure 1.5B). Perhaps a consequence of overzealous oxidation, ring-ruptured and nor-derivatives have also been identified (Figure 1.4C). Finally, those compounds with "alternative skeletons" (Figure 1.6) demonstrate how oxidations can make a carbon skeleton fluid and mutable. Many compounds in this section likely arise from deep-seated rearrangements of the parent seco-prezizaane core. Taken together, evidence of oxidation has been documented at every non-quaternary center of $\mathbf{1}$ and a maximum of 13 oxidations (in veranisatins C and E) from farnesol have occurred, making these - per carbon - some of the most highly oxidized secondary metabolites ever isolated.

### 1.2 Biosynthesis of the Illicium Sesquiterpenes

To understand how such highly oxidized structures are formed, it is instructive to consider the proposed biosynthesis of these compounds. While, to the best of our knowledge, no formal genomic and/or feeding studies have been undertaken, Fukuyama has put forth a hypothesis that seeks to tie together the disparate skeletons seen in this family of natural products (Figure 1.7). ${ }^{7}$ Like that of most sesquiterpenes, the biosynthesis of the Illicium sesquiterpenes is thought to begin from farnesyl pyrophosphate. A series of carbocation-based alkene cyclizations and hydride shifts then leads to the acroane skeleton, which is poised to undergo one final cyclization. While this cyclization could occur in an anti-Markovnikov sense to directly forge the allo-cedrane skeleton (2), by analogy to steroid biosynthesis it is more likely that first Markovnikov cyclization occurs to arrive at the cedrane skeleton (4) followed by alkyl migration to give $\mathbf{2} .{ }^{72} \mathbf{2}$ then serves as a key
A


1-hydroxyneoanisatin, I. majus.

2-oxo-6-deoxyneoanisatin, I. majus
B


veranisatin C , I. verum

veranisatin $D$, l. oligandrum

veranisatin $A$, l. verum

veranisatin E, I. oligandrum

veranisatin $B$, l. verum

illihenlactone A, I. henryi


13-hydroxyparviflorolide, l. majus


3,4-dehydroxy-14-hydroxy floridanolide, I. merrillianum

majusanol A, l. majus

Figure 1.5. List of anisatinoid natural products bearing the characteristic C 13 - $\mathrm{C} 14 \beta$-lactone. (A) List of compounds containing a bridging C7-C11 $\delta$-lactone. (B) List of compounds containing a bridging C7-C11 $\delta$-lactone and further oxidation at C12. (C) List of other C13-oxidized compounds, which also share characteristics of pseudoanisatinoids.
Tashironin-type:

tashironin, I. tashiroi
 debenzoyl-7-deoxo$1 \alpha, 7 \alpha$-dihydroxytashironin, I. floridanum

tashironin A ,
l. verum

debenzoyl-7-deoxo-7 $\alpha$ -hydroxy-3-oxo tashironin, I. floridanum


11-O-debenzoyl tashironin, l. tashiroi

debenzoyl-7-deoxo-
7 $\alpha$-hydroxy-
tashironin,
I. floridanum
Oligandrums:

oligandrum $A$, l. oligandrum

oligandrum $B$, l. oligandrum

oligandrum C, I. oligandrum

oligandrum D, I. oligandrum

Anislactone-type:

anislactone A, l. anisatum

anislactone B , l. anisatum

majusanside, I. majus

merrilactone A, l. merrillianum

henrylactone $F$, l. henryi

merrilactone B , I. merrillianum

illisimonin A, l. simonsii

Figure 1.6. List of remaining Illicium sesquiterpenes with non seco-prezizaane skeletons. Included in this selection are the tashironins formally bearing the allo-cedrane skeleton, the illicinolides with a unique C11-C14 carbon-carbon bond, the oligandrums containing a ruptured ring, and the anislactones derived from parent skeleton 3.


Figure 1.7. Fukuyama's proposed biosynthesis of the Illicium sesquiterpenes that accounts for all structural subtypes by invoking rearrangements of the allo-cedrane skeleton.
point for divergence in Fukuyama's biosynthesis. In one pathway, direct carbocation quench and subsequent oxidations deliver ODB-tashironin (11). In another, C6-C11 bond scission generates (presumably) a primary carbocation on the seco-prezizaane skeleton (1), which is quenched and oxidized to the diverse seco-prezizaane family of products. And, finally, in a third pathway, an unexplained $\mathrm{C} 10-\mathrm{C} 11$ bond cleavage, followed by an equally cryptic rearrangement, generates the anislactone-type skeleton (3). While such an explanation does account for the different skeletons observed, it is not wholly consistent with all the modern data accumulated. For instance, it is now known that different subtypes can be isolated from the same species of Illicium plants; do these plants have different cyclase enzymes to produce each subtype? Or is there a more unified interpretation of the data that can provide insights on how these natural products are made?

Towards that end, we wondered if we could reasonably conceive of a single biosynthetic intermeidate that could then be oxidized/oxidatively rearranged to account for every Illicium sesquiterpene subtype (Figure 1.8A). All data for this proposal is necessarily circumstantial and only experimental evidence can ever refute any pathway; nevertheless, our proposal has proved edifying for our own synthetic work. Given the centrality of $\mathbf{2}$ to the Fukuyama proposal, we wondered if the cyclase phase simply stopped there for all members, not just the allo-cedrane ones. Thus we propose a putative hydrocarbon, "illiciol" (16), as the direct biosynthetic precursor to all Illicium sesquiterpenes. ${ }^{73}$ In support of this structure, we note that non-lactone compounds $\mathbf{1 7}$ and 18 bearing the allo-cedrane skeleton have been isolated from I. jiadifengpi. ${ }^{28}$ In contrast, no lower-oxidation members of the seco-prezizaane class or of the anislactone class have ever been reported. Additionally, the stereochemistry of the secondary hydroxyl group at C7 is assigned by inference and comparison to isolated tashironins (Figure 1.6). Illiciol (16) can then undergo the conserved oxidations common to all Illicium sesquiterpenes at C4, C11, and C14, to arrive at intermediate 19. Additionally, the C10 position is often hydroxylated, a variable event that likely occurs
at this point. If hydroxylation takes place on 19, it becomes known natural product 11-O-debenzo-yl-7-deoxo-7 $\alpha$-hydroxytashironin. ${ }^{59}$ Conversion to 10 from 19 can easily be envisioned, thus producing the allo-cedrane subtype of Illicium natural products. 19 is also poised to undergo C6-C11 Grob-type fragmentation to arrive at the pseudoanisatin core. An intermediate trisubstituted C6-C7 alkene (not depicted) would be formed, which could be epoxidized and opened by a carboxylate nucleophile (see section 1.4 .1 for an example of this reactivity in chemical synthesis) to give the pseudoanisatinoid core. Alternatively, the alkene could react directly with the carboxylate in an acidic environment to generate products lacking C6 oxidation. In either case, this transformation then links the seco-prezizaane and allo-cedrane skeletons. From the pseudoanisatin core, oxidations of either the C12 or C13 methyl groups would respectively lead to the majucinoids or anisatinoids.

Finally, to address the anislactone-type subclass, it is interesting to speculate about a latestage skeletal rearrangement involving the pseudoanisatinoid core (Figure 1.8B). Known natural product 20 can be converted to another natural product, oligandrum D (21), by means of an oxidative C-C bond cleavage between C6 and C7. Incidentally, a similar transformation has already been demonstrated abiotically. ${ }^{7} 21$ now has adventitiously placed functional groups for eventual conversion to 13, the flagship anislactone-type member. Specifically, intramolecular aldol reaction between the remaining $\varepsilon$-lactone and pendant methyl ketone could generate tertiary alcohol 22, a structure primed for acid-mediated acyl migration. Were that rearrangement to occur, $\mathbf{1 3}$ and other anislactone-type compounds would be formed, linking finally all subtypes of Illicium sesquiterpenes. Again, it is important to stress the speculative nature of this proposal; however, insights


Figure 1.8. An alternative Illicium biosynthesis with a single precursor, "illiciol" (16). (A) Putative pathway from 16 to Illicium sesquiterpenes bearing the skeletons of 1, or 2. (B) Unified proposal to access the core architecture 3 from 1 involving ring rupture, intramolecular aldol, and acid-mediated rearrangement.
gleamed from it could surely impact how these molecules are made chemically and might inform future work towards the anislactone-type members of the Illicium sesquiterpenes.

### 1.3 A Brief Introduction to the Biological Activities of the Illicium Sesquiterpenes

These structural features and ornate oxidation patterns are not without function either; much initial interest in the Illicium family of natural products stemmed from their putative biological significance. While a comprehensive discussion of the biological activities of these natural products is outside the scope of the present work, it is nevertheless motivating to summarize important overarching themes and discoveries related to these compounds. Initially, as previously stated, much effort was devoted to isolating and identifying the principal component of I. anisatum that leads to its convulsive effects. Empirically, anisatin (12) was observed to produce a convulsive phenotype in mice and was determined to have a median lethal dose $\left(\mathrm{LD}_{50}\right)$ of less than $1.0 \mathrm{mg} / \mathrm{kg}$ - making it, to date, one of the most potent toxins of plant origin. ${ }^{49}$ Other Illicium sesquiterpenes, primarily other anisatinoids containing the spiro- $\beta$-lactone motif, have also been shown to be highly toxic, though none quite reaches the toxicity of anisatin itself. ${ }^{54,55}$

Fortuitously, the relevant biological target of anisatin was quickly determined by analogy to another known neurotoxin, picrotoxin (itself a mixture of picrotin and picrotoxinin). Picrotoxin was known to produce a similar convulsive phenotype and it had also been shown to be a non-competitive antagonist of $\gamma$-aminobutyric acid (GABA) receptors. Anisatin was likewise proven to have the same effect. For both cases, antagonism of this typically inhibitory channel leads to increased frequency of action potential spikes (termed "neuronal hyperexcitation"), which on a phenotypic level causes convulsions and can quickly prove fatal. ${ }^{74}$ Further studies also determined that anisatin likely binds at or near the picrotoxin/barbiturate site; ${ }^{75}$ however, more detailed structural information remains elusive due to the difficulty of studying GABA receptors. As transmembrane proteins, GABA receptors have proven challenging to crystallize; the first crystal structure of a human GABA receptor has only recently been published. ${ }^{76}$ Adding to the complexity, GABA receptors are heteropentameric, containing up to five distinct subunits. While isoform distribution has been mapped, it remains a complicated task to determine whether the observed toxicity derives, for example, from a smaller effect on a more common isoform or a larger effect on one that is more rare. Adding to the puzzle, some anisatinoids are non-toxic, as are a preponderance of the majucinoids, including majucin (5) itself. ${ }^{35}$

The mystery deepened when Fukuyama determined that some Illicium sesquiterpenes are not only non-toxic, but also actually beneficial to neurons (specifically, rat cortical neurons). ${ }^{25}$ These Illicium compounds mimic the effect of small protein growth factors known as neurotrophins and thus have been described as "neurotrophic" as well. Neurotrophins are typically secreted in order to prevent neuronal cell death or induce neuronal progenitor cells to differentiate and grow. After Fukuyama's seminal publication, focus in the field shifted from identifying toxic Illicium components to conducting phenotypic screens in service of characterizing additional neurotrophic compounds. In particular, many majucinoids, including 6, 7, 8, and 9 have since been shown to be neurotrophic (though it should be noted, majucin (5) itself has not been reported to have such activity). Remarkably, 9 has demonstrated neurotrophic effects at concentrations down to $10 \mathrm{nM} .{ }^{43}$

Uncovering the precise source(s) of these effects remains an active area of research; however, two main studies have contributed greatly to current hypotheses. First, Danishefsky demonstrated that the neurotrophic activity of $\mathbf{8}$ was predicated on the additional presence of nerve growth
factors (NGFs), indicating a possible synergistic effect rather than an independent one. ${ }^{77}$ Recently, Shenvi observed that $\mathbf{9}$ and $\mathbf{1 0}$ cause chronic depolarization of neurons by weakly interacting with GABA receptors and proposed that this led to increased neurotrophic factor production, resulting in the observed neurotrophic phenotype. ${ }^{78}$

Even without full mechanistic knowledge, it is challenging to overstate the importance of the phenotypic effects of these neurotrophic Illicium sesquiterpenes. Neurotrophic compounds have been proposed as treatments to therapeutically intractable neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, and Huntington's disease. ${ }^{79}$ Non-peptidyl treatments in particular have attracted interest due to improved pharmacokinetic and pharmacodynamic properties relative to peptides or other biologics. Further advocating for these compounds' promise, Fukuyama recently demonstrated that $\mathbf{9}$ can exert the same neurotrophic effect on human induced pluripotent stem cells. ${ }^{45}$

Despite this excitement, there still remain many unanswered questions about these compounds, even at a basic structural level. For instance, what factors cause some compounds to be highly toxic, and others to be highly beneficial? How large is the chemical space between these phenotypes? It seems clear that oxidation/lactonization patterns play a key role in determining these compounds' activities, and the limited structure-activity relationship (SAR) studies that have been performed to date lend credence to that hypothesis. Most notably, Theodorakis and Danishefsky both showed that C10 hydroxylation of the majucinoid scaffold is indispensable to neurotrophic activity. ${ }^{77,80}$ Still, a total synthesis that could install oxygenation site-selectively and access multiple structural subtypes would be a significant asset to further biological investigations and did not exist when these studies commenced.

### 1.4 Previous Synthetic Studies on Seco-prezizaane Sesquiterpenes

Over the past 35 years, numerous synthetic groups - no doubt enticed by the complex caged architectures and significant biological activities of these molecules - have embarked on total synthesis efforts of Illicium sesquiterpenes. To date, over 25 syntheses have been completed and over a dozen distinct natural products have been synthesized. ${ }^{81}$

Interest in synthetic targets has tracked with the focus of biological studies. That is, initially, many synthetic efforts were directed towards the synthesis of anisatin, with its much-studied neurotoxic activity. One of the first synthetic studies towards the anisatin core was publisehd by the Woodward group in 1982, featuring a creative glyoxalate-ene reaction to forge the key C9-C10 bond and generate a quaternary center. ${ }^{82}$ While thoes efforts were unsuccessful at delivering the natural product, it did not deter others from pursuing their own routes. Kende was next to attempt a synthesis and published one of $( \pm)$-8-deoxyanisatin (hereafter referred to as 10-deoxyanisatin based on modern numbering) in 1985 in only 18 steps. ${ }^{83}$ While technically not an isolated natural product, his work demonstrated the synthesis of the complete anisatin core structure, including the challenging spiro- $\beta$-lactone motif, and strategies employed in his route have been echoed multiple times in the ensuing decades. In 1990, Yamada and Niwa finally addressed the anisatin challenge with a chiral pool synthesis of $\mathbf{1 2}$ in about 40 steps from $(+)$-pulegone. ${ }^{84}$ The next year, they also reported the C 3 deoxygenation of $\mathbf{1 2}$ to generate the natural product (-)-neoanisatin. ${ }^{85}$ Other total and formal syntheses of these compounds have been reported and will also be discussed in the following sections.

As biological interest turned to the neurotrophic Illicium sesquiterpenes, so too did syn-
thetic endeavors. Thus, in the $21^{\text {st }}$ century, synthetic focus shifted massively to favor work towards majucinoids and other neurotrophic compounds. In 2002, Danishefsky reported the first (racemic) synthesis of $\mathbf{7}$ and $\mathbf{8}$; since this report, multiple additional syntheses, including asymmetric variants, have followed. Though only isolated in 2009, 9 has seen the most impressive amount of synthetic work, with the first total synthesis reported by Theodorakis just two years after its structure was disclosed. While outside the scope of the current work, it is important to also recognize the significant efforts spent to prepare anislactone-type compounds, including $\mathbf{1 3}$ as well as merrilactone A (both known neurotrophic factors). ${ }^{86,87}$

The following sections are intended to contextualize our work in the field as well as to highlight truly impressive synthetic transformations that have guided our efforts. As such, emphasis will be placed more on overall strategies and key reactions rather than specific discussions of individual transformations. Syntheses will be grouped chronologically by target to highlight advances both for individual targets as well as the evolution of the field as a whole. Discussion of our own group's preparation of compounds 5 through 11, among others, will follow. 88,89

### 1.4.1 Kende’s 1988 Synthesis of ( $\pm$ )-10-Deoxyanisatin

Thirty years have passed since Kende's synthesis of ( $\pm$ )-10-deoxyanisatin, yet his synthesis remains timeless and rivals efforts put forth in more modern times in terms of efficiency (Scheme 1.1). ${ }^{83}$ This work was the first to recognize the power of assembling the 5,6 -fused seco-prezizaane core by a Robinson annulation. Thus, treating allyl cyclopentenone 23 with a methyl cuprate reagent initiated a sequence wherein the resulting enolate stereoselectively reacted with methyl vinyl ketone derivative 24, leading to eventual Robinson annulation. MMC (25) and diazomethane were then employed in sequence to form dicarbonyl 26. Addition of methyl Grignard to the ketone followed by acid-catalyzed dehydration produced a conjugated diene (not shown), which was deprotonated at the $\gamma$-position to generate an extended enolate that could react at C5 (desired) or C12 (undesired). Although alkylation products at both positions were observed, 27 could nevertheless be isolated and carried forward in serviceable yield. The stereochemistry of the newly formed quaternary center necessitated reduction of the ester to match the C14 alcohol oxidation state of anisatin. Two-step terminal alkene oxidation/lactonization forged key intermediate $\mathbf{2 8}$ containing a pseudoanisatin-like $\varepsilon$-lactone. Indeed, it is easy to imagine a synthesis of the pseudoanisatinoids from this route by switching the benzyl ether for a simple methyl group.
$\mathbf{2 8}$ was isomerized, deprotected, and oxidized to $\mathbf{2 9}$, a substrate with strategically placed functional groups for further oxidation. Chemoselective dihydroxylation of the C3-C4 trisubstituted olefin afforded an intermediate diol selectively from the $\alpha$-face of the molecule. At this point, we gleamed two key inferences for our own work: (1) dihydroxylations of this alkene appear to require a stoichiometric amount of osmium source, as turnover of the intermediate osmylated substrate is slow (potentially due to the alkene being hindered by two adjacent all-carbon quaternary centers) and (2) an $\varepsilon$-lactone seems to block the top face of approach, guiding reagents to approach from the desired $\alpha$-face of the molecule. Epoxidation of the other trisubstituted alkene and aldehyde oxidation then gave carboxylic acid $\mathbf{3 0}$, which contained all the necessary oxidations to complete the synthesis. The $\delta$-lactone of $\mathbf{3 2}$ was created in a putatively biomimetic sense (see section 1.2) by internal opening of the epoxide with a carboxylate nucleophile. Finally, the $\beta$-lactone was cleanly closed by activation of the C13 carboxylic acid to arrive at $\mathbf{3 2}$ in only 18 steps from 23 . In this synthesis, Kende pioneered methods of forming the challenging all-carbon quaternary centers



Scheme 1.1. Kende's synthesis of ( $\pm$ )-10-deoxyanisatin featuring a Robinson annulation to construct the se-co-prezizaane ring system.
found in the seco-prezizaane skeleton and also elegantly installed much of the requisite oxidations in a rapid manner.

### 1.4.2 Loh's 2001 Formal Synthesis of ( $\pm$ )-10-Deoxyanisatin

Loh, in contrast, sought a different approach to core intermediate 28 (Scheme 1.2). ${ }^{90}$ Instead of a Robinson annulation, a dearomatization strategy was envisioned from indanone 33. Judicious directed carboxylation of this substrate followed by Birch reduction led to intermediate diene 34 as an inconsequential mixture of diastereomers. An inspired Eschenmoser-Claisen rearrangement of the allylic alcohol stereoselectively set the C9 quaternary center correctly. Subsequent alkylation of the remaining ester followed by reduction furnished 35, which shares similarities to intermediates seen on the Kende route. Loh finally converged the routes with a two-step lactonization, reproducing intermediate 28, which was known to go on to $\mathbf{3 2}$ in 8 steps. Significantly, this route


Scheme 1.2. Loh's formal synthesis of ( $\pm$ )-10-deoxyanisatin employing a dearomatization strategy followed by an Eschenmoser-Claisen rearrangement.
was the first to recognize how the 6 -membered ring of the seco-prezizaane core might arise from dearomatization of an arene - a strategy that has since been employed in the syntheses of $(-)$-anisatin (13) by T. Fukuyama and (-)-ODB-tashironin (10) by both Danishefsky and Mehta.

### 1.4.3 Yamada's 1990/1991 Synthesis of (-)-Anisatin and (-)-Neoanisatin

Despite the presence of only one additional oxidation in 12 relative to 32, Yamada's synthesis of the former compound required over twice as many steps as Kende's synthesis of the latter, even though both works shared conceptual similarities (Scheme 1.3). ${ }^{84}$ Yamada's synthesis began with 36, the product of a Robinson annulation with a $(+)$-pulegone derivative, similar to Kende's 26. Once again, a double alkylation set the C7 quaternary center, though the electrophile used (see 37) was suboptimal, containing multiple extra carbons that would eventually have to be excised. Early-stage, stoichiometric osmium-mediated dihydroxylation of the C3-C4 trisubstituted alkene proceeded again from the correct $\alpha$-face, properly setting the stereochemistry of the vicinal diol motif seen in 12. Straightforward protection of the diol as its acetonide using $\mathbf{3 8}$ under acidic conditions gave ketone 39. Functional group interconversions transformed this intermediate to alkene 40, which underwent epoxidation (again from the $\alpha$-face) and intramolecular etherification to prepare the substrate for eventual formation of the C7-C11 $\gamma$-lactone. Attention then turned to removing the unwanted carbon atoms attached to C13 and C14. Dienone $\mathbf{4 2}$ was prepared by an elegant double selenium-based oxidation, employing catalytic selenium and stoichiometric iodine(V) oxidant 41. Then, in a three-step sequence, sequential (stoichiometric) osmium-mediated dihydroxylation of one alkene and oxidative cleavage of the resulting intermediate excised one undesired carbon atom. After reduction, repeating those three steps excised the other extra carbons, leading to 43 after acetate protection. Another seven-step sequence installed the final carbon atoms in the


Scheme 1.3. Yamada's total synthesis of (-)-anisatin and (-)-neoanisatin demonstrating the careful and robust synthetic planning required to access highly oxidized compounds.
synthesis through sequential methyl anion additions and also secured the crucial C 10 oxidation seen in 44 . Closure of the $\delta$-lactone and protecting group manipulations converted 44 to 45 , setting the stage for the final act of this synthesis. To reach $\mathbf{1 2}$, the C 13 alcohol was exhaustively oxidized to the carboxylic acid and then tied up as the $\beta$-lactone following Kende's protocol. Cleavage of the acetonide (installed over 30 steps prior!) then finally gave 12, completing the first synthesis of this highly oxidized natural product. A two-step radical deoxygenation sequence of the C 3 position of $\mathbf{1 2}$ then arrived at related natural product (-)-neoanisatin (46) in good yield. ${ }^{85}$ While it is easy to imagine employing modern reagents and techniques to simplify some operations in this synthesis, the overarching strategy remains on solid footing and serves as a good blueprint for future work in the area.

### 1.4.4 T. Fukuyama's 2012 Synthesis of (-)-Anisatin

T. Fukuyama's synthesis of the same natural product, though, took a radical departure from previous precedent and relies on a non-obvious dearomatization sequence (Scheme 1.4). ${ }^{91}$ Starting from compound 47 , which was prepared by a rhodium-catalyzed diastereoselective conjugate addition of the corresponding arylboronic acid into a chiral butenolide, propargylation and functional group manipulations led to arene 48, whose electron-rich structure primed it for oxida-


Scheme 1.4. T. Fukuyama's total synthesis of (-)-anisatin through an elaborate dearomatization strategy exemplifying the diversity of insights possible for natural product synthesis.
tive dearomatization. Thus, treating 48 with a common hypervalent iodine oxidant $\left(\mathrm{PhI}(\mathrm{OAc})_{2}\right)$ in methanol triggered oxidation to a protected ortho-quinone, which then upon heating underwent a key intramolecular Diels-Alder reaction with the pendant alkyne. Horner-Wadsworth-Emmons (HWE) olefination of the resulting ketone followed by reduction produced allylic alcohol 50. An elegant 2,3 -Wittig rearrangement triggered by lithium-tin exchange of an alkylated primary alcohol derivative correctly set the C5 quaternary center. Oxidative cleavage of the bridging olefin then unveiled the desired 6 -membered ring of the seco-prezizaane skeleton, as seen in 51. Unfortunately, however, the 5 -memberd ring was not set correctly and required a further 12 steps, via primary iodide $\mathbf{5 2}$, to finally arrive at lactone $\mathbf{5 4}$. Although the seco-prezizaane skeleton was now in place with the correct C10 oxidation necessary for 12, extraneous oxidations at C12 and C15 were also present and required a further 8 steps to address. First the C 12 oxidation was removed, providing epoxide 55. That epoxide was opened by an amide nucleophile, in a slight departure from the carboxylate seen in Kende's synthesis. The C15 position was then deoxygenated, giving $\delta$-lactone 56. The remainder of the synthesis involved more straightforward manipulations. Thus, the terminal alkene of $\mathbf{5 6}$ was exhaustively oxidized to carboxylic acid $\mathbf{5 7}$, and $\beta$-lactone formation employing an interesting anhydride (58) as activating reagent gave compound 59. Once again, stoichiometric osmium-mediated dihydroxylation proceeded from the desired $\alpha$-face affording $\mathbf{6 0}$, the final protecting group of which was removed under acidic conditions to unveil anisatin (12) after a circuitous 41 steps.

### 1.4.5 Mehta's 2012 Synthesis of (+)-(1S)-Minwanenone

Before diving in to the copious work on the majucinoids, one pseudoanisatinoid synthesis should be mentioned - namely, Mehta's synthesis of the enantiomer of minwanenone (ent-71) (Scheme 1.5). ${ }^{92}$ Comparatively unexplored in the context of total synthesis, the pseudoanisatinoids are marked by an overall lower oxidation state than the anisatinoids or majucinoids. However, that apparent simplicity belies a hidden challenge: by removing certain key carbonyl-based functionalities, transformations commonly employed in seco-prezizaane synthesis (e.g., enolate alkylation and nucleophilic addition) become harder to coordinate. Mehta addressed this problem in the synthesis of ent-71 by pre-installing much of the needed functionality. To begin, chiral silyl ether $\mathbf{6 1}$ was prepared in three steps from commercial materials. Unfortunately, an enzymatic reduction was leveraged on a symmetric precursor to install the chiral center in this compound and thus it was challenging to find conditions leading to the enantiomer of 61 (which would provide natural 71). The peripheries of the enone were modified by various alkylations, first giving vicinal dimethyl compound 62 and then highly substituted ketone 63 . A retro-Diels-Alder reaction to extrude cyclopentadiene unveiled enone 64, a compound reminiscent of ones seen in Danishefsky's earlier synthesis of jiadifenin (8) (see 74, below). Diastereoselective alkylation of this intermediate to forge the C 9 quaternary center proved challenging, as there was only a small influence by the remote stereocenters on this site of reactivity. Nevertheless, $\mathbf{6 6}$ could be isolated as a single isomer by way of $\mathbf{6 5}$, and, from this point, a straightforward sequence of three steps prepared methyl ketone 67. This substrate was well poised to perform an intramolecular aldol reaction (again, likely inspired by Danishefsky's pioneering work, see 76) to yield enone 68 cleanly. At this point, the seco-prezizaane core had been constructed with advantageously positioned functionality for the completion of the synthesis. Enolate alkylation installed the final C15 methyl group seen in 69, and a two-step epimerization sequence inverted the stereochemistry of this compound's C 7 alcohol to



Scheme 1.5. Mehta's total synthesis of the enantiomer of ( - )-minwanenone utilizing certain strategies pioneered by Danishefsky some years prior.
reach 70. Finally, well-known oxidative cleavage of the terminal alkene followed by oxidation and deprotection gave ent-71 in 24 steps from commercial materials, demonstrating how lower oxidation members of the Illicium family can still be accessed using logic developed for other members.

### 1.4.6 Danishefsky's 2004 Synthesis of $( \pm)$-ODNM and ( $\pm$ )-Jiadifenin

When Danishefsky pioneered the first majucinoid synthesis, two challenges likely stood at the forefront of synthetic planning (Scheme 1.6). ${ }^{77,93}$ First, a novel way of constructing the two all-carbon quaternary centers, at C 5 and C 9 , with some degree of diastereoselectivity was required. Second, many oxidations needed to be coordinated seamlessly in the presence of multiple functional groups to arrive at jiadifenin (8). To address the first issue, sequential alkylations of cyclohexanone 72 were explored. While such a sequence could easily have led to intractable mixtures, careful control of conditions allowed for isolation of dialkylated intermediate 73, which set the C5 quaternary center. A further double alkylation sequence set the C9 center in 74 with synthetically useful levels of diastereoselectivity. The seco-prezizaane 5,6 -fused system was completed by transforming the ethyl ester of $\mathbf{7 4}$ into a HWE reagent by reacting it with 75, and then performing an intramolecular olefination. Protecting group manipulation then afforded 76, already containing the enone seen in 8 . Construction of the $\gamma$-lactone proceeded smoothly, forming 77, and




Scheme 1.6. Danishefsky's total synthesis of ( $\pm$ )-ODNM and ( $\pm$ )-jiadifenin representing the first synthetic entry to the majucinoids.
the resulting 1,3-dicarbonyl intermediate was readily oxygenated at C6 and then reduced, giving rise to 78. Manipulations of this sort have proven to be common in majucinoid synthesis. Enolate methylation afforded 79, and oxidative alkene cleavage led to $\mathbf{8 0}$, a compound one hydroxylation away from ( $\pm$ )-ODNM. Unfortunately, selective oxidation of the lactone in presence of the C2 ketone could not be realized and thus the enone had to be reduced under Luche conditions to $\mathbf{8 1}$ before the C10 position could be oxidized using Davis's oxaziridine (82), providing 83 as a single diastereomer. Finally, oxidation of this intermediate using the Jones reagent gave a mixture of 7 and $\mathbf{8}$, which could be all funneled to $\mathbf{8}$ by using the reagent in excess. Notably, to date, every other synthesis of $\mathbf{8}$ has employed this same transformation from 7. With these compounds and intermediates in hand, Danishefsky was able to conduct some preliminary biological and SAR studies (described above, in section 1.3), eventually leading to a full report on results of this synthetic endeavor.

### 1.4.7 Theodorakis's 2011 Synthesis of (-)-ODNM, (-)-Jiadifenin, and (-)-Jiadifenolide

Theodorakis's synthesis of jiadifenolide (9) actually predates his completion of $\mathbf{7}$ and $\mathbf{8}$ by several months; however, as all targets are made through the same common intermediate, it is worthwhile to discuss each route contemporaneously (Scheme 1.7). ${ }^{94,95}$ Like Kende's, Theo-


Scheme 1.7. Theodorakis's enantioselective majucinoid total synthesis which was able to access multiple family members from common intermediate 93.
dorakis's work began with a Robinson annulation to construct the 5,6-fused seco-prezizaane ring system. However, advances in synthetic chemistry since the 1980's are clear. For example, 84 was allylated under palladium catalysis (see, $\mathbf{8 5}, \mathbf{8 6}$ ) and the subsequent Robinson annulation was rendered enantioselective through proline organocatalysis (see 87), providing 88 in $>99 \% e e$, if the reaction were run over a two month period (slightly lower ee was obtained at shorter reaction times). Regardless, $\mathbf{8 8}$ was advanced to $\mathbf{8 9}$, which contained both quaternary centers set stereoselectively, and then to 90 , using a sequence likely inspired by Kende's work. Here, however, the syntheses diverged more dramatically, as palladium catalysis was once again employed to forge a key motif - in this case, the $\gamma$-lactone of the majucinoids through a carboxylation event - and to arrive at 91. Epoxidation of $\mathbf{9 1}$ smoothly gave 92, and installation of the $\delta$-lactone of $\mathbf{9 3}$ echoed Kende's protocol form 25 years prior. Key intermediate $\mathbf{9 3}$ served as a branching point for this synthesis, as it could be carried forward in a series of manipulations to bis $\gamma$-lactone containing intermediate 95. Notably, the power of palladium catalysis was again demonstrated in order to append the final C15 methyl group. Two-step oxidation of the C10 position then completed the first total synthesis of 9 . Returning to key intermediate 93, two-step deoxygenation following a dehydration (Martin sulfurane, 96)/reduction ( $\mathrm{H}_{2}, \mathrm{Pd} / \mathrm{C}$ ) protocol produced 97 . Modifications of this system by oxidations and an enolate methylation provided $\mathbf{7}$ and $\mathbf{8}$ in a route which demonstrated the strengths of
more modern chemistry. Additionally, Theodorakis was able to test intermediates from this route in a biological setting, leading to a preliminary SAR map in a subsequent publication. ${ }^{80}$

### 1.4.8 Zhai's 2012 Synthesis of (-)-ODNM and (-)-Jiadifenin

Zhai's route represents a conceptually distinct approach to 7 and $\mathbf{8}$ (Scheme 1.8). ${ }^{96}$ While previous efforts constructed key carbon-carbon bonds through alkylation and/or annulation events, this work demonstrated the power of direct cyclizations to form challenging bonds. Starting from a simple linear precursor 97 , a series of efficient reactions rapidly built complexity towards protected triol 99 . Notably, by using a Sharpless asymmetric dihydroxylation, $\mathbf{9 9}$ was afforded in enantioenriched form. Five additional carbon atoms were then added to the substrate through an esterification with primary alcohol 100, giving cyclization precursor 101. Although the majority of carbon atoms had been installed, $\mathbf{1 0 1}$ was still a linear substrate, making it unique in the context of seco-prezizaane syntheses. To form key carbon-carbon bonds, a series of cyclization reactions were developed. First, an Ireland-Claisen rearrangement not only formed the majucinoid $\gamma$-lactone but also set the challenging C5 quaternary center of $\mathbf{1 0 2}$ with the correct selectivity. The authors remarked that only the $(Z)$-alkene isomer of $\mathbf{1 0 0}$ gave the desired selectivity for this reaction, likely due to energetic factors in the presumed pericyclic transition state. Next, a Pauson-Khand reaction tied up the 5,6 -fused ring system and created $\mathbf{1 0 3}$. Finally, a third ring-forming reaction


Scheme 1.8. Zhai's total synthesis of (-)-ODNM and (-)-jiadifenin demonstrating the power of concerted cyclizations to rapidly assemble complexity.
was deployed - in this case, a [2+2] photochemical cycloaddition of allene onto the enone of $\mathbf{1 0 3}$. Once again, the desired stereochemistry at a challenging quaternary center was obtained, with $\mathbf{1 0 5}$ as the major product over diastereomeric 104. In the span of a few steps, a highly linear precursor was successfully and extensively cyclized to an impressive polycyclic intermediate. To install the bridging $\delta$-lactone, the 1,1-disubstituted alkene of $\mathbf{1 0 5}$ was oxidatively cleaved and a retro-Claisen reaction ruptured the strained cyclobutanone ring, yielding 106, and enabling endgame manipulations. Saegusa-Ito oxidation of the C 2 ketone followed by deprotection led to 107, a compound one oxidation away from 7. The Davis oxaziridine (82) was once again able to install that oxidation, completing the synthesis of $\mathbf{7}$ and $\mathbf{8}$. Coming in at under 20 steps, this synthesis demonstrated how new synthetic strategies can increase the efficiency of routes to challenging targets.

### 1.4.9 Y. Fukuyama's 2015 Formal Synthesis of ( $\pm$ )-ODNM and ( $\pm$ )-Jiadifenin

Y. Fukuyama's formal synthesis of $\mathbf{7}$ and $\mathbf{8}$ relied heavily on palladium catalysis to forge key bonds, demonstrating the power that chemistry has brought to the field of total synthesis (Scheme 1.9). ${ }^{97}$ Starting from symmetric ketone 108, a series of five steps successfully desymmetrized it to yield vinyl bromide 109. This substrate was advantageously positioned to undergo intramolecular palladium-catalyzed Heck cyclization in order to form the key C9 quaternary stereocenter. Conditions were successfully determined for this transformation and $\mathbf{1 1 0}$ was isolated cleanly. A subsequent 12 -step sequence gave compound $\mathbf{1 1 3}$ by way of $\mathbf{1 1 1}$. $\mathbf{1 1 3}$ was set up for an intramolecular Tsuji-Trost cyclization with the allylic carbonate; however, significant optimization was required before that transformation could be realized. Nevertheless, after optimization, 114 could be produced efficiently. Notably, the second quaternary center of the seco-prezizaane core was set selectively in this reaction, putting into focus the power of palladium catalysis to forge


Scheme 1.9. Y. Fukuyama's formal synthesis of ( $\pm$ )-ODNM and ( $\pm$ )-jiadifenin showcasing the power of palladi-um-catalyzed transformations in organic synthesis.
hindered bonds stereoselectively. Straightforward manipulations of the sidechain recapitulated intermediate 97, via alkene 116. From Theodorakis's work, 97 was known to go on to $\mathbf{7}$ and $\mathbf{8}$ in 5 and 6 steps, respectively. While the key transformations in this route are doubtlessly impressive and speak to the power of palladium catalysis in total synthesis, further advances are needed to be able to access the substrates for those cascades more efficiently.

### 1.4.10 Micalizio's 2016 Synthesis of (-)-Jiadifenin and Related Majucinoids

In 2016, Micalizio disclosed his group's take on majucinoid synthesis (Scheme 1.10). ${ }^{98}$ Previously his lab had developed titanium-based cyclization strategies to arrive at natural product architectures, and this synthesis demonstrates an extension of that work. ${ }^{99}$ Beginning with chiral epoxide 117 (prepared from a Sharpless asymmetric epoxidation), copper catalyzed nucleophilic epoxide opening with functionalized Grignard reagent derived from $\mathbf{1 1 8}$ afforded $\mathbf{1 1 9}$ in short order. A second epoxide formation/opening sequence advanced $\mathbf{1 1 9}$ to $\mathbf{1 2 0}$, which was well poised for the upcoming formal $[2+2+2]$ annulation. Treating $\mathbf{1 2 0}$ with low-valent titanium and alkyne 121 initiated a cyclization reaction that was quenched by addition of benzaldehyde to form seco-prezizaane ring system 122 in good yield and excellent diastereo- and regioselectivity. Functionalization of $\mathbf{1 2 2}$ provided 123, a compound containing an activated methyl ester primed for radical generation. Stoichiometric, osmium-mediated dihydroxylation gave 124, the putative radical cyclization precursor. Despite the differences of this substrate relative to others, dihydroxylation still occurred exclusively from the $\alpha$-face. Homolytic cleavage of the carbon-selenium bond in $\mathbf{1 2 4}$ by tributyltin radical triggered a 5-exo cyclization onto the pendant tetrasubstituted alkene to form the majucinoid $\gamma$-lactone with correct stereochemistry at the C 5 quaternary center. Interestingly, in addition to expected product 126, ethyl ester $\mathbf{1 2 5}$ was isolated. The authors proposed that this product resulted from intramolecular 1,4-hydrogen atom transfer (HAT) from the C11 position to the intermediate C 4 radical, followed by $\beta$-cleavage of the resulting C11 stabilized radical. Mechanistic studies were conducted, including deuterium-labeling experiments, and were found to be in support of that analysis.

Fortuitously, both products 125 and 126 could be brought forward to lactone 128, which was reminiscent of some intermediates seen in the Zhai synthesis of $\mathbf{7}$ and $\mathbf{8}$. A three-step sequence on 128 afforded 129, a protected version of Zhai's $\mathbf{1 0 7}$. At this point, straightforward, precedented transformations took $\mathbf{1 2 9}$ on to 7 and 8. Additionally, a sequence was devised to reach ( $2 S$ )-hy-droxy-3,4-dehydroneomajucin (134), a related natural product. Six steps were required to reach this closely related variant, owing to the need to invert both secondary alcohols at C2 and C10 after they were initially installed. Thus, although $\mathbf{1 3 0}$ - a diastereomer of $\mathbf{1 3 4}$ - was arrived at in only 2 steps, an additional four steps were required to invert both secondary alcohols. The C 2 alcohol was inverted by a Mitsunobu reaction (see 131, 132), and the C10 alcohol was inverted by an oxidation/reduction sequence. Overall, the Micalizio work stands as a successful application of their methodology to the context of complex natural product synthesis. A creative radical cyclization adds to the effort as well. However, lurking under the surface is a cautionary observation: precise control of hydroxylations and their stereochemistry can be challenging on such a rigid scaffold; care must be taken to ensure maximum efficiency in the installation of those oxidations.


Scheme 1.10. Micalizio's enantioselective majucinoid total synthesis based on a key titanium-catalyzed formal $[2+2+2]$ cycloaddition to construct the seco-prezizaane core.

### 1.4.11 Sorensen's 2014 Synthesis of (-)-Jiadifenolide

Although one synthesis of jiadifenolide (9) was already seen in 2011, many more approaches towards this fascinating natural product began to appear in the ensuing years, beginning with Sorensen's work in the area (Scheme 1.11). ${ }^{100}$ Starting from the product of Favorskii-rearrangement of $(+)$-pulegone dibromide, 135, a Robinson annulation with methyl vinyl ketone furnished the 5,6-fused seco-prezizaane ring system in 136, a close match to Yamada's starting material


Scheme 1.11. Sorensen's enantioselective total synthesis of $(-)$-jiadifenolide featuring the first example of an aliphatic $\mathrm{C}\left(\mathrm{sp}^{3}\right)-\mathrm{H}$ bond activation in Illicium synthesis.
36. Once again, though, subsequent steps starkly demonstrated the synthetic advancements that had occurred in the 25 years between the two works. Double methylation of the thermodynamic enolate of 136, followed by functional group manipulations, afforded aldehyde 138. While both quaternary centers were now present in the molecule, the C5 position had yet to be differentiated: selective oxidation of the C14 methyl group would be required to complete the synthesis of any majucinoid. Nevertheless, the aldehyde group in 138 was homologated under the action of TosMIC (139) and acid closed the C4-C11 $\gamma$-lactone of jiadifenolide, cleaving the dioxolane protecting group in the process, and giving rise to $\mathbf{1 4 0}$. Incidentally, while $\mathbf{1 3 9}$ is often a reagent used in heterocycle synthesis, no such products were observed in this case.

With compound $\mathbf{1 4 0}$ in hand, key C-H activation of the C14 methyl group was envisioned using a ketone derivative as the directing group. Thus, an intermediate oxime was generated and then reacted under conditions developed by Sanford to perform palladium-catalyzed C-H acetoxylation. While selectivity for the C14 methyl group was not perfect (C13 oxidation as well as doubly-oxidized products were both observed), $\mathbf{1 4 1}$ could still be isolated in synthetically useful amounts after cleavage of the oxime. Nevertheless, this reaction set an important precedent for the viability of directed $\mathrm{C}-\mathrm{H}$ activation in the synthesis of Illicium natural products. Ketone 141 was then advanced to epoxy lactone $\mathbf{1 4 3}$ by way of $\mathbf{1 4 2}$ in 4 steps by borrowing from strategic transformations disclosed in the Theodorakis synthesis. A further two oxidations at the C10 position (iodination followed by a proposed oxidation-triggered iodoso-Pummerer rearrangement) and hydrolysis of the epoxide then furnished 9 in 21 steps from a chiral pool starting material. Notably, this work introduced the $\mathrm{C}-\mathrm{H}$ activation disconnection into Illicium syntheses, of significant relevance to our own work.

### 1.4.12 Paterson's 2014 Synthesis of ( $\pm$ )-Jiadifenolide

Published shortly after Sorensen's work, Paterson's synthesis of 9 took a conceptually


Scheme 1.12. Paterson's total synthesis of $( \pm)$-jiadifenolide leveraging the power of radical reactions to form hindered bonds.
distinct approach to forming the 5,6 -fused ring system (Scheme 1.12). ${ }^{101}$ Once again, a cyclopentenone building block was chosen as the starting material for the synthesis, but Paterson's selection of $\mathbf{1 4 5}$ was unique, as it was not designed to undergo a Robinson annulation. Rather, Luche reduction and directed epoxidation followed by Meinwald rearrangement and protection quickly led to $\alpha$-hydroxy ketone $\mathbf{1 4 6}$. HWE reaction with $\mathbf{1 4 7}$ on the ketone of $\mathbf{1 4 6}$ with subsequent reduction and protection afforded allylic acetate 148. Ireland-Claisen rearrangement of that substrate and functional group interconversions then produced aldehyde $\mathbf{1 4 9}$, which had the C9 quaternary center set with high levels of diastereocontrol. Fittingly, a boron-bound enolate of butenolide $\mathbf{1 5 0}$ was prepared and reacted with $\mathbf{1 4 9}$ to generate aldol product $\mathbf{1 5 0}$ after protection. In the key step of the synthesis, samarium(II) iodide elicited reduction of the C 4 ketone group with concomitant addition into the pendant butenolide moiety, generating 152 as a single diastereomer after straightforward protecting group manipulations. This impressive transformation set adjacent C4 and C5 stereocenters with high fidelity and completed the seco-prezizaane ring system in a single operation. The authors noted, however, that other similar substrates did not undergo this cyclization efficiently, speaking to the challenges of forming such a hindered, but strategic bond. Seven further steps of oxidations and protecting group removals took 152 on to 9 through intermediate 153. This 23 -step synthesis demonstrated the power of well-designed radical chemistry to construct crucial bonds and stereocenters in the context of natural product total synthesis ${ }^{102}$ - a strategy that has been emulated multiple times even within the context of the synthesis of 9 .

### 1.4.13 Zhang's 2015 Synthesis of (-)-Jiadifenolide and Gademann's 2016 Formal Synthesis of (-)-Jiadifenolide

Two such syntheses inspired by Paterson's radical cyclization were Zhang's total and Gademann's formal synthesis of 9 (Scheme 1.13). ${ }^{103,104}$ These two syntheses are presented together due to significant overlap in their strategy and tactics. In Zhang's work, 154 (the same product of


Scheme 1.13. Zhang's total and Gademann's formal syntheses of ( - -jiadifenolide that are conceptually related to Paterson's pioneering study.
the Favorskii-rearrangement of $(+)$-pulegone seen previously) was taken in two steps to aldehyde intermediate $\mathbf{1 5 5}$ - reminiscent of Paterson's $\mathbf{1 4 9}$, but now with an ester at the C9 quaternary center instead of a terminal alkene. Likewise, a Paterson aldol reaction with identical butenolide $\mathbf{1 5 0}$ gave secondary alcohol $\mathbf{1 5 1}$ as an inconsequential mixture of diastereomers. Reductive removal of the C7 alcohol in a two-step procedure (elimination/hydrogenation) and reduction of the axial ester group gave primary alcohol 157. This compound was then treated under Paterson's conditions for reductive cyclization and the desired product $\mathbf{1 5 8}$ was isolated in moderate yield with good diastereoselectivity.

Key intermediate $\mathbf{1 5 8}$ was also the formal synthesis endpoint for Gademann's route. To reach this compound, Gademann started out with a similar sequence from 135: allylation and ozonolysis gave aldehyde 161, a compound parallel to Zhang's 155. Rather than performing a Paterson aldol, Gademann opted to use a proline-catalyzed (164) organocatalytic reductive condensation between tetronic acid (162) and 161. In this case, the terminal reductant was Hantzsch ester 163 so that $\mathbf{1 6 5}$ could be isolated directly from the reaction mixture. To append the C13 methyl group, a two-step procedure employing triflation and iron-catalyzed cross coupling with methyl Grignard was adopted, yielding 166 very cleanly. Similar to 157 , 166 was treated with samarium(II) iodide;
however, in this case the diastereoselectivity was considerably lower than other iterations of the reaction. While Paterson's $\mathbf{1 4 9}$ had a C7 alcohol to influence transition state conformation and Zhang's $\mathbf{1 5 7}$ contained a potentially chelating primary alcohol at C10, Gademann's $\mathbf{1 6 6}$ had no such biasing factors, potentially leading to the observed erosion of selectivity. Nevertheless, 166 was advanced to $\mathbf{1 5 8}$, completing the formal synthesis.

Returning now to the main synthesis, $\mathbf{1 5 8}$ was primed for the key step: an ambitious formal $[4+1]$ cycloaddition using TMS-diazomethane as the one carbon source. Under the optimized conditions, the anion of TMS-diazomethane was thought to add into the aldehyde, undergo Brook rearrangement and have the resulting anion perform either direct (through a carbene intermediate) or formal (through an anionic path) OH insertion of the pendant tertiary alcohol to give rise to tetracycle 159. The authors also provided a brief substrate table expanding on the scope of this interesting transformation. Further oxidations then took $\mathbf{1 5 9}$ on to $\mathbf{9}$ in 4 steps through the intermediacy of $\mathbf{1 6 0}$. Notably, the Zhang synthesis prepared over 300 mg of natural 9 , highlighting the value of strategic cyclizations in the construction of these polycyclic natural products.


Scheme 1.14. Danishefsky's total synthesis of $( \pm)$-ODB tashironin reliant on a dearomatization-triggered intramolecular Diels-Alder cycloaddition.

### 1.4.14 Danishefsky's 2006 Synthesis of ( $\pm$ )-ODB-Tashironin

Before describing Shenvi's total synthesis of $\mathbf{9}$, a brief foray into syntheses of $\mathbf{1 0}$ is warranted, as Shenvi's work has also been shown to lead to $\mathbf{1 0}$ as well. In 2006, Danishefsky devised an ingenious way of accessing the [2.2.2]-bicyclic allo-cedrane core of $\mathbf{1 0}$ (Scheme 1.14). ${ }^{105}$ Simple aromatic building block 161 was functionalized to aryl bromide 163 via 162 using standard arene chemistry. At this point, palladium-catalyzed cross coupling between 163 and vinyl stannane 164 gave primary alcohol 165 in good yield. Oxidation and addition of alkyne 166 into this substrate then quickly built up racemic secondary alcohol 167. Activation of this alcohol as the mesylate followed by copper-mediated allylic displacement with a methyl anion source led to allene 168. Primed for an oxidative dearomatization reaction, the electron-rich arene of $\mathbf{1 6 8}$ was treated with $\mathrm{PhI}(\mathrm{OAc})_{2}$, a hypervalent iodine oxidant, and underwent intramolecular trapping with the pendant primary alcohol to give a remarkable cyclophane-type structure 169. Perhaps unsurprisingly, this reaction also gave a good amount of Diels-Alder product 170. Intermediate $\mathbf{1 6 9}$ could be fully converted to $\mathbf{1 7 0}$ by brief ( $<5 \mathrm{~min}$ ) heating in a microwave reactor. Overall, this sequence gave a good yield of $\mathbf{1 7 0}$ from arene $\mathbf{1 6 8}$. With the [2.2.2]-bicyclic allo-cedrane skeleton prepared, further operations simply focused on modulating the oxidation state of the molecule to install the appropriate functionalities. Thus, after a further 8 steps, $\mathbf{1 0}$ was prepared for the first time in 22 overall steps from a readily available commercial material.

### 1.4.15 Mehta's 2011 Formal Synthesis of ( $\pm$ )-ODB-Tashironin

Mehta's work on the synthesis of $\mathbf{1 0}$ closely mirrored Danishefsky's; however, Mehta was able to show that elaborate pre-organization of the Diels-Alder substrate was not necessary for a successful transformation (Scheme 1.15). ${ }^{107}$ To demonstrate this point, arene $\mathbf{1 7 5}$ was quickly advanced to alkylated derivative 177, the substrate for intermolecular oxidative dearomatization.


Scheme 1.15. Mehta's formal synthesis of ( $\pm$ )-ODB-tashironin following a similar strategy to Danishefsky's work five years prior.

Treating 177 with $\mathrm{PhI}(\mathrm{OAc})_{2}$ in the presence of alcohol 178 appended the latter nucleophile onto the dearomatized core. This time, no spontaneous Diels-Alder reactivity was observed. Still, thermal conditions were able to convert this substrate to the [2.2.2]-bicycle-containing 179. Ring closing metathesis using the second-generation Hoveyda-Grubbs catalyst completed the allo-cedrane core ring system, and the ensuing synthetic endgame from $\mathbf{1 8 0}$ was largely similar to Danishefsky's. Namely, oxidation state interconversions and protecting group manipulations were necessary to get to $\mathbf{1 8 3}$, a compound reported to go on in one step to 10. ${ }^{108}$ While both these syntheses made clever observations of how the [2.2.2]-bicycle of $\mathbf{1 0}$ could be formed synthetically, it remained to be seen whether interconversion of other Illicium skeletons could also reach this scaffold in order to unify syntheses of these natural products.

### 1.4.16 Shenvi's 2015/2017 Synthesis of (-)-Jiadifenolide, (-)-ODB-Tashironin, and a Related Pseudoanisatinoid

It is fitting to conclude this section with a discussion of Shenvi's synthesis of $\mathbf{9}$ and $\mathbf{1 0}$ as in many ways this work significantly raised expectations for subsequent Illicium syntheses. First, in 2015, a gram-scale synthesis of $\mathbf{9}$ was reported, addressing the material shortages that plagued further biological studies of these interesting compounds. ${ }^{108}$ Then, two years later in a subsequent


Scheme 1.16. Shenvi's exceptionally efficient enantioselective total syntheses of ( - )-jiadifenolide, ( - )-3,6-dide-oxy-10-hydroxypseudoanisatin, and (-)-ODB-tashironin through common intermediate 187.
publication, an intermediate from the original synthesis was carried forward to 10, marking the first reported instance of one synthetic intermediate being used to access multiple Illicium sesquiterpene subtypes (i.e., both the majucinoid and pseudoanisatinoid/allo-cedrane subtypes). ${ }^{78}$ On top of these synthetic efforts, biological studies were also disclosed in the latter publication that significantly shaped current understanding of the mechanism behind these compounds' neurotrophic activity. Nevertheless, these studies were also the beneficiaries of robust precedents, particularly in the disconnections used to arrive at 9 .

A plurality of Illicium seco-prezizaane sesquiterpene syntheses began with formation of the 5,6-fused ring system from a 5-membered ring precursor. Typically, a Robinson annulation or related sequence of transformations forged two key carbon-carbon bonds: the C4-C5 bond and the C8-C9 one. The wide adoption of that reaction is understandable; in particular, the C9 quaternary center could be formed robustly and selectively. However, in each prior synthesis no truly ideal substrate was deployed for that transformation. For instance, starting materials derived from $(+)$-pulegone all lacked the C11 carbon, which often took multiple steps to install. Likewise, Theodorakis's cyclopentadione contained oxygenation at C1 instead of the C15 methyl group, leading to many corrective steps over the course of that synthesis. Perhaps the most enabling insight of Shenvi's route, then, was the judicious selection of a near-ideal set of coupling partners for that transformation.

A butenolide heterodimerization reaction was envisioned for the key formal [4+2] annulation. Specifically, the union of $\mathbf{1 8 5}$ (prepared in three steps from chiral pool source $(+$ )-citronellal) and $\mathbf{1 8 6}$ (prepared in two steps from diketene acetone adduct and hydroxyacetone) to form 187 was targeted as the key step for the synthesis. Many base and Lewis acid combinations were screened to arrive at the optimized conditions, which afforded 187 in high yield and exquisite diastereoselectivity (facial selectivity of the addition of $\mathbf{1 8 5}$ to $\mathbf{1 8 6}$ was controlled solely by the distal C15 methyl group). Notably, 187 could be produced in only 4 steps and contained all the requisite carbon atoms of $\mathbf{9}$, many of which were already at the correct oxidation state. It is challenging to imagine a more efficient or convergent transformation employing this $\mathrm{C} 4 / \mathrm{C} 5$ and $\mathrm{C} 8 / \mathrm{C} 9$ disconnection. The synthesis of 9 was completed in a further 4 steps of straightforward oxidation state adjustments, many of which were at least somewhat precedented in the literature. Importantly, $\mathbf{1 8 8}$ had previously been prepared by Theodorakis; ${ }^{80}$ however, in this route C 10 bromination to reach 189 was employed to maximize efficiency. Thus, the 8 -step route to 9 readily produced over a gram of the natural product, fueling further studies in the area.

Lactone 187 could also be advanced to the pseudoanisatinoid core starting with a two-step sequence of methylation and decarboxylation to provide 190. Elimination of the fused $\gamma$-lactone proved challenging but a successful cascade was identified to afford amide 191. Oxygenation of the C10 position under basic conditions gave alcohol 192, which contained the requisite oxidation state to complete the synthesis of $\mathbf{1 0}$. Cleavage of the ketal followed by lactonization forged $\varepsilon$-lactone 193. Finally, hydrogen atom transfer-initiated hydration of the trisubstituted olefin in 193 led to a mixture of ring-chain tautomers 194 and 10 . Compound 194 itself is a natural product and could be funneled on to $\mathbf{1 0}$ by further treatment under acidic conditions. With this chemistry, multiple Illicium sesquiterpene subtypes were linked and issues of scarcity successfully addressed.

### 1.5 Conclusions and Motivations for Future Illicium Synthesis

In the previous sections, isolation and characterization studies of the Illicium sesquiter-
penes were described. Reference figures containing chemical structures of these natural products were provided along with a detailed examination of leading biosynthetic hypotheses in an attempt to explain the diversity of these sesquiterpene lactones. A brief discussion of these compounds' biological activities was included to help motivate synthetic work in the area. Over fifteen se-co-prezizaane syntheses were then covered to provide a better understanding of the current state of the field, culminating in Shenvi's impressive gram-scale synthesis of 9. What, then, are the frontiers of Illicium sesquiterpene synthesis? What avenues remain open for a synthetic chemist to address?

To answer these questions, consider a subtle disconnect between how Illicium sesquiterpenes differ among themselves and what challenges prior total syntheses focused on. All se-co-prezizaane sesquiterpenes share the same fifteen-carbon skeleton; their specific structures and biological activities are dictated by the precise pattern of hydroxylations and lactonizations decorating that conserved core. However, all prior synthetic efforts focused instead on constructing the carbon-carbon bonds of $\mathbf{2}$, particularly the quaternary centers; comparatively little attention was paid to oxidation state manipulation. Ideally, then, to address this discrepancy, the next generation of syntheses should focus on programmatically installing oxidations on the seco-prezizaane skeleton to access a wide variety of natural and unnatural Illicium sesquiterpenes from a single core.

Our work in this area - that is, to develop a fully oxidative synthesis of Illicium sesquiterpenes - will be described in the ensuing Chapters. We will report the novel discoveries rooted in such an approach as well as the completed syntheses of a dozen natural products from multiple seco-prezizaane subtypes. We are confident this effort represents a conceptually novel way of considering Illicium synthesis and hope that the lessons learned in our studies can be applied more broadly to the field of total synthesis as a whole.

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## Chapter 2

## Oxidative Synthesis <br> of the <br> Pseudoanisatinoids

### 2.1 Introduction to the Oxidative Strategy

The notion of a purely "oxidative synthesis" - that is, the total synthesis of a highly oxidized natural product from a near-hydrocarbon precursor - is far from unprecedented in the literature. ${ }^{1}$ Historically, though, such an approach has been somewhat limited to the synthesis/semi-synthesis of steroid derivatives. ${ }^{2}$ While certain other examples exist, steroids have served as the ideal proving ground for such strategies for two main reasons. First, many low-oxidation state steroids are commercially available at low cost, making it unnecessary to spend effort in attempts to construct hydrocarbon-like skeletons (often a challenging problem in its own right). Second, a wealth of literature on steroidal $\mathrm{C}-\mathrm{H}$ functionalizations has already been amassed, providing much needed heading for expeditions into unknown chemistry. ${ }^{3}$

In the context of an oxidative Illicium synthesis, strictly speaking neither of those advantages was directly present. To the best of our knowledge, there are no commercially available terpenes that contain the seco-prezizaane (1) or allo-cedrane (2) skeletons. Additionally, save for Sorensen's elegant work towards jiadifenolide (9), ${ }^{4}$ studies on Illicium C-H functionalizations were not available at the start of our work. However, moving one step upstream in Illicium biosynthesis (see section 1.2) brought us to the cedrane skeleton (4) and the starting point for our synthesis (Figure 2.1A).
$(+)$-Cedrol (14) was identified as a cheap, commercially available starting material isolated from Texas cedarwood oil. Given its abundance, $\mathbf{1 4}$ could be purchased for about $\$ 0.05 / \mathrm{g}$; additionally, its sourcing made it a naturally renewable feedstock. Fortuitously, the natural enantiomer of $\mathbf{1 4}$ was also homochiral to the Illicium sesquiterpenes, meaning that a successful synthesis using it as a starting material would lead to the correct enantiomer of natural product. Initially, we were interested in targeting pseudoanisatinoid products, eponymous 11 in particular, as a proof-of-concept due to their more accessible oxidation pattern - a net 7 oxidation state increase over $\mathbf{1 4}$. While 11 had not been touted in the literature for interesting biological activity in the same way other family members had been, it had nevertheless been shown to be a selective inhibitor of fly GABA receptors over rat ones, implying utility as an insecticide. ${ }^{5}$ Other Illicium sesquiterpenes, like the majucinoids or anisatinoids, required 10 or more oxidations on $\mathbf{1 4}$, making them more challenging targets.

With starting material and target class selected, our attention turned to planning a synthetic strategy for the oxidative synthesis (Figure 2.1B). Since 14 contained the skeleton of $\mathbf{4}$ and not $\mathbf{1}$, ring shift and ring cleavage reactions had to be incorporated into the synthesis in addition to all the oxidations required. At some point, cleavage of the C6-C11 single bond needed to occur, as did a shift of the $\mathrm{C} 5-\mathrm{C} 7$ single bond. Precedents for each of those transformations existed independently in the literature, but it was unclear how best to combine them in a single synthesis. ${ }^{6,7}$ Additionally, at this point, sites of conserved oxidations (that is, positions oxidized in all potential Illicium sesquiterpene targets) were mapped onto 14: at least $\mathrm{C} 4, \mathrm{C} 7, \mathrm{C} 11$, and C 14 , along with the C6-C11 single bond, would all need to be oxidized over the course of the synthesis. While many of those positions were proximal to the C6 tertiary hydroxyl group and methods for functionalizing them could be imagined, the C 4 position stood out as an unmet challenge. Distal to the one functional group of 14, and flanked by two adjacent all-quaternary centers, the C4 methine was truly buried in a hydrocarbon framework; its functionalization was projected to require a carefully designed substrate.

Nevertheless, with these considerations in mind, a first-generation route was developed


Figure 2.1. (A) Skeletons and chemical structures of starting material 14 and desired target 11. (B) Summary of synthetic strategy to convert $\mathbf{1 4}$ to $\mathbf{1 1}$, or related Illicium sesquiterpenes. (C) Summary of a valiant initial attempt at Illicium sesquiterpene synthesis by Dr. Kevin Hung. Late-stage C14 oxidation stood as an insurmountable challenge. (D) Re-envisioned route in which C14 oxidation would happen early in the synthesis. (E) Sites of known oxidation on 14. Positions marked in green were oxidized in biological systems by enzymes; positions in blue were oxidized abiotically. Oxidations of C1 and C14 have been demonstrated on preparative scale. (F) Substrate-controlled non-directed oxidation of the C1 position by DuBois and Sigman. (G) C6 tertiary alcohol-directed oxidation of the C14 methyl group by Waegell $\left(\mathrm{HgO} / \mathrm{Br}_{2}\right)$ and Suárez $\left(\mathrm{Ph}_{2} \mathrm{Se}(\mathrm{OH})(\mathrm{OAc}), \mathrm{I}_{2}\right)$.
(Figure 2.1C). ${ }^{8}$ In a 14 -step sequence fully detailed in the dissertation of Dr. Kevin Hung (K.H.), 14 was advanced to seco-prezizaane compound 195, which only differed from natural product (-)-debenzoyldunnianin (196) by a lack of oxidation at the C14 methyl group. Many conditions were surveyed to effect a directed oxidation of that position by leveraging the C3 hydroxyl group, including a host of radical-generating protocols and transition metal-catalyzed transformations. Regrettably, no reaction was successful at ever functionalizing that position. ${ }^{9}$ As C14 is one of the sites of conserved oxidation in the Illicium sesquiterpenes, direct repurposing of that route to potentially access other family members was unsuccessful as well. Nevertheless, such setbacks did not uproot the overall concept of an oxidative synthesis; instead, the lessons learned from the first-generation route were used to inform a second-generation synthesis.

Given the importance of C14 oxidation to a successful Illicium sesquiterpene synthesis, we
asked whether that crucial transformation could occur in the early stages of the synthesis (Figure 2.1D). That is, we wondered whether the C 6 tertiary alcohol of $\mathbf{1 4}$ could be used to direct oxidation to C14, potentially creating a compound similar to 197 . That compound could then be carried forward in an analogous sequence to generate 196, or a related natural product, instead of $\mathbf{1 9 5}$. While certainly there were open questions about how the presence of an additional oxidation would impact the viability of previously developed transformations, we nevertheless explored the literature surrounding cedrol oxidations to assess whether such a transformation was even known.

A wealth of information has been reported on oxidations of $\mathbf{1 4}$ (Figure 2.1E). Both biotransformations and chemical oxidations of 14 are well known in the literature. 14 has been exposed to microbes ${ }^{10}$ and fungi ${ }^{11}$ to assess hotspots of oxidative metabolism. Additionally, $\mathbf{1 4}$ has twice been fed to mammals - rabbits ${ }^{12}$ and dogs ${ }^{13}$ - to determine where higher organisms might metabolize the hydrocarbon prior to excretion. Taken together, biotransformations of $\mathrm{C} 1, \mathrm{C} 2, \mathrm{C} 3$, C7, C10, C11, C12, and C15 have all been reported. Notably absent from the list, and relevant for Illicium sesquiterpene synthesis, are C4 and C14.

Chemical transformations, on the other hand, while covering a noticeably smaller portion of sites on 14, have been shown to oxidize key positions for Illicium sesquiterpene synthesis. ${ }^{14}$ Two positions in particular, C 1 and C 14 , can be oxidized selectively and in good yield, making them prime candidates for potential synthetic starting points. DuBois and Sigman, among others, have shown that C 1 can be oxidized in a non-directed sense by a ruthenium catalyst in acidic media to give tertiary alcohol 198 (Figure 2.1F). ${ }^{15}$ While this chemistry would provide an exciting functional handle on a distal site of the starting material, it was shelved in favor for reports on directed functionalization (Figure 2.1G). ${ }^{16}$

Waegell and Suárez each showed that strained tetrahydrofuran 199 could be generated in a single operation from 14. For Waegell, in situ generation of $\mathrm{Br}_{2} \mathrm{O}$ (from HgO and $\mathrm{Br}_{2}$ ) led to an alkyl hypobromite which was photolyzed, generating an alkoxy radical that abstracted a hydrogen atom at the C14 position. Recombination of that alkyl radical with a bromine source followed by intramolecular displacement of the resultant alkyl bromide successfully produced 199. Suárez's protocol was similar, but it employed hypoiodite (in place of hypobromite) photolysis to initiate the radical cascade. Additionally, Suárez included a selenium-based additive to help suppress observed $\beta$-scission of the hydroxy radical (which resulted in diastereomeric secondary iodides at the C7 position). Excited by this direct precedent, we decided to encorporate this reactivity into our own synthesis.

### 2.2 Initial Oxidations and Generation of the Seco-Prezizaane Skeleton

However, to repurpose this transformation for the beginning of a multistep synthesis, we reasoned that it would be very desirable to avoid the use of the highly toxic reagents Waegell and Suárez employed. By simply lowering reaction temperature and employing standard hypoiodite photolysis conditions $\left(\mathrm{PhI}(\mathrm{OAc})_{2}, \mathrm{I}_{2}, h v\right)$, we achieved this goal and could isolate 199 in comparable yield. Notably, 199 could be prepared with no loss of efficiency at well over sixty gram scales (an occasionally non-trivial challenge for batch photoreactions, potentially implicating a radical chain process for this transformation), ensuring a consistent supply of material for further synthetic studies. With 199 in hand, we began the challenging process of adapting previously successful reactions to now a more highly oxidized compound (Scheme 2.1).

The strained either of $\mathbf{1 9 9}$ was smoothly eliminated under the action of methyl Meerwein's


Scheme 2.1. Initial oxidations of the cedrane skeleton and conversion of it to the seco-prezizaane core.
salt $\left(\mathrm{Me}_{3} \mathrm{OBF}_{4}\right)$ and proton sponge ( 1,8 -bis(dimethylamino) naphthalene) to give $\mathbf{2 0 0}$ as a single alkene regioisomer. Other protecting groups, including other alkyl ethers (ethyl), esters (acetyl, benzoyl, and isobutyryl), silyl ethers (trimethylsilyl, tert-butyldimethylsilyl, and triisopropylsilyl), and even a halide (bromide) could be installed under acidic conditions; however, only the alkyl ethers proved sufficiently robust to be carried through the harsh conditions of latter steps.

To access the seco-prezizaane skeleton (1), the C6-C11 carbon-carbon bond needed to be cleaved. Now, with an alkene connecting those atoms, oxidative cleavage represented an obvious way of achieving that transformation. Treating 200 with in situ generated $\mathrm{RuO}_{4}\left(\mathrm{RuCl}_{3}\right.$ and $\left.\mathrm{NaIO}_{4}\right)$ provided keto-acid 201, which was isolated in high purity after a simple acid-base extraction. Importantly, this transformation required careful control of temperature and reaction time, otherwise products from oxidation of the C14 methyl ether began to predominate. With 201 prepared, two conserved methine oxidations remained to be addressed, at C 4 and C 7 . Reasoning that the C7 methine was now adjacent to a ketone and hence an easier oxidation, we explored many conditions for the alpha hydroxylation of the ketone. However, canonical methods, including direct enolate oxygenation, Rubottom-type oxidation, and even metal-mediated transformations (e.g., $\mathrm{Mn}(\mathrm{OAc})_{3}$ ) all were unsuccessful at delivering serviceable amounts of C 7 oxidized products. Copper(II) bromide $\left(\mathrm{CuBr}_{2}\right)$, though, was finally identified as a stoichiometric metal mediator of an intramolecular oxidative lactonization to form keto-lactone 202. Vital to this reaction's success was the inclusion of tert-butanol $(t-\mathrm{BuOH})$ as an additive. In its absence, extensive decomposition of material was observed. We believe $t$ - BuOH might be serving as an acid scavenger for the reaction as two equivalents of hydrobromic acid are theoretically generated for every equivalent of product formed. Attempts to directly quench the acid by addition of bases (both amine-containing and inorganic) suppressed desired reactivity. Furthermore, the high temperature $\left(150{ }^{\circ} \mathrm{C}\right)$ and prolonged reaction time ( 16 h ) precluded use of lower-boiling or less stable acid-scavengers like 2-methyl-2-butene or molecular sieves, leaving $t-\mathrm{BuOH}$ as the most suitable alternative.

With lactone $\mathbf{2 0 2}$ successfully formed, we were well positioned to study the key ring-shift transformation to take the 5,5-fused cedrane skeleton (4) to the 5,6-fused seco-prezizaane one (1). Given the functionality of 202, an $\alpha$-ketol rearrangement was judged to be an expedient way of shifting the C5-C7 bond. ${ }^{17}$ Thus, reacting 202 with KOH and KOt -Bu in DMSO first hydrolyzed
the lactone, generating a presumed dianionic species which then underwent the desired $\alpha$-ketol rearrangement. Seco-prezizaane skeleton 203 was formed in $45 \%$ yield over two steps as a $4: 1$ mixture of diastereomers at the C6 position. The major diastereomer was confirmed to have the desired stereochemistry by X-ray crystallographic analysis. Furthermore, the diastereomeric mixture isolated from the reaction was found to be in thermodynamic equilibrium, as separating the diastereomers and re-subjecting each pure compound back to the reaction conditions reestablished in each case the observed $4: 1$ mixture. Straightforward silylation ( $\mathrm{NaH}, \mathrm{TBSCl}$ ) of the tertiary alcohol in 203 led to 204, a substrate primed to tackle the final - and most challenging - conserved oxidation of the Illicium sesquiterpenes: the C 4 methine position.

### 2.3 Studies on Unusual Transformations: $\mathrm{CuBr}_{2}$ Oxidation, $\alpha$-Ketol Rearrangement, and Fortuitous Formal Synthesis of (-)-11-O-Debenzoyltashironin.

Before discussing that transformation, however, a few exciting observations - including one which led to a formal synthesis of $\mathbf{1 0}$ - deserve mention. First, we were interested in exploring the utility of the $\mathrm{CuBr}_{2}$-mediated oxidative lactonization reaction (Figure 2.2) and better understanding its mechanism (Figure 2.3). While $\mathrm{CuBr}_{2}$ is a well-known reagent in the literature for the alpha bromination of ketones, its utility in forming $\mathrm{C}-\mathrm{O}$ bonds directly is less explored. To the best of our knowledge, prior to our work there were three examples in the literature detailing such


Figure 2.2. (A) Literature report by Numazawa and Nagaoka of a copper(II) bromide-mediated oxidation of a ketone. Stereochemistry of the product is consistent with a carbocation intermediate. (B) Literature report in total synthesis by Toyota, et al. of an oxidative lactonization mediated by copper(II) bromide. (C) Literature report by Miyake on further ketone oxidation products using copper(II) bromide. (D) Substrate scope of our own oxidative lactonization reaction.
a process. ${ }^{18}$
Numazawa and Nagaoka showed that progesterone derivative 205 could be oxidized to $\alpha$-methoxy ketone 206 under the action of $\mathrm{CuBr}_{2}$ (Figure 2.2A). Although they comment in their paper that a bromide intermediate is presumably formed first before being displaced by methanol, they provide no further data to support that claim. The stereochemistry of product, though, suggests either a direct oxidation to the $\alpha$-methoxy ketone or complete dissociation of an initial bromide intermediate to a carbocation prior to trapping by methanol. In 2001, Toyota, Ihara, and coworkers were the first to employ this reactivity of $\mathrm{CuBr}_{2}$ in a total synthesis of ent-kaurene diterpenes (Figure 2.2B). Specifically, they treated methyl ester 207 under Krapcho demethylation conditions ( $\mathrm{LiCl}, \mathrm{DMF}$ ) and included $\mathrm{CuBr}_{2}$ in the reaction to directly afford lactone 208. Once again, an intermediate bromide is postulated. In this case, the stereochemistry of product is consistent with such an intermediate, but is also consistent with a direct lactonization; no further comments or studies on the mechanism were provided. Most recently, in 2007, Miyake reported that exposure of benzoic acid $\mathbf{2 0 9}$ to $\mathrm{CuCl}_{2}$ cleanly formed lactone 210 (Figure 2.2C). However, another substrate provided a curious data point: treating phenol 211 under the same conditions led to a mixture of expected ether 213 and rearranged lactone 212. This observation provided the first data to suggest a cationic pathway might be operative, but it remained unconfirmed whether the same pathway was in operation for the more electron-withdrawing benzoic acid derivatives.

Guided by this precedent, we began exploring the scope of our transformation (Figure 2.2D). Aromatic keto-acids were found to work exceptionally well under these conditions, with 214 being formed in high yield. The reaction conditions were compatible with benzylic $\mathrm{C}-\mathrm{H}$ bonds (see 215) and efficiency was not impacted by the introduction of electron-donating (see 216) or electron-withdrawing (see 217) groups. Increasing the steric bulk proximal to the reaction site as in 218 did not negatively impact the transformation. Additionally, oxidation at tertiary positions (see 219 and our synthetic substrate, 202) proceeded just as readily. Finally, even a simple heteroaromatic structure (see 220) led to the desired product, albeit in a slightly depressed yield. Unfortunately, a simple aliphatic substrate (5-oxohexanoic acid, not shown) did not undergo the desired reaction. Instead, alpha bromination of the ketone was detected; notably, that intermediate did not go on to the desired product under the reaction conditions.

While we had amassed some circumstantial data to suggest a direct oxidative lactonization mechanism was operative (without the intermediacy of a bromide), two unique substrates provided even more evidence for this process (Figure 2.3). Substrate 221 was prepared in a four-step sequence from oleanic acid (not shown) involving: (1) benzyl ester formation, (2) acetate protection, (3) epoxidation with concomitant Meinwald rearrangement, and (4) a $\mathrm{Br}_{2} / \mathrm{HBr}$-mediated ketone bromination/dehydrobromination sequence to produce the enone motif with concomitant debenzylation. ${ }^{19}$ Although there was some precedent in the literature for an oxidative lactonization of this substrate, ${ }^{20}$ when subjected to our conditions, the product from that process (see 223) was only isolated in low (ca. 10\%) yield (Figure 2.3A). The major product ( $72 \%$ yield) of the reaction was characterized as rearranged lactone $\mathbf{2 2 4}$ and its structure was confirmed by X-ray crystallographic analysis (Figure 2.4). Furthermore, $\mathbf{2 2 3}$ was not converted to $\mathbf{2 2 4}$ when resubjected to the reaction conditions. We therefore propose the intermediacy of carbocation 222 to explain the existence of both products. In one path ("path a," in blue), direct attack of the carbocation by the pendant carboxylic acid leads to the formation of the expected product 223. However, in a second path ("path b," in green), Wagner-Meerwein rearrangement of the adjacent methyl group to form a more stable carbocation precedes attack of the carboxylic acid, explaining the preponderance of rearranged
A


C


Figure 2.3. (A) Anomalous reactivity of oleanic acid derivative 221 implicates the intermediacy of a carbocation intermediate $\mathbf{2 2 2}$ en route to $\mathbf{2 2 3}$ and 224. (B) Reactivity of carene derivative $\mathbf{2 2 5}$ also indicates the potential for free carbocations and/or radical pathways. (C) Tentative mechanistic proposal explaining formation of $\mathbf{2 0 2}$ involving enolization of the starting material, oxidation to the cation, and then trapping by the pendant carboxylic acid.

## product 224.

Additionally, cyclopropanated substrate 225 (prepared in one step from (+)-3-carene by oxidative alkene cleavage) was designed to further probe potential carbocation and/or radical intermediates (Figure 2.3B). Remarkably, extensively oxidized products 228 and $\mathbf{2 2 9}$ were isolated as the major products of the reaction. While 228 clearly shows the potential of $\mathrm{CuBr}_{2}$ to perform alpha ketone bromination, the rearranged skeleton of the rest of the product tells a different story. Namely, if carbocation $\mathbf{2 2 6}$ (or potentially a radical equivalent) were formed, facile ring opening


Figure 2.4. Crystal structure of rearranged product $\mathbf{2 2 4} \cdot \mathrm{CDCl}_{3}$ demonstrating its [2.2.2] bicyclic lactone.
of the adjacent cyclopropyl ring followed by trapping by the carboxylic acid would afford enone 227. A further oxidation to the butenolide would then explain the formation of $\mathbf{2 2 8}$ and 229.

Taking these observations together, we believe the following mechanistic proposal to be most consistent with all the data collected (Figure 2.3C). Namely, under the reaction conditions, ketone 201 can enolize to 230 (in support of this, recovered starting material from the reaction is afforded as a mixture of ketone epimers), which then might be transiently oxidized to a radical cation before being fully oxidized to the cation. ${ }^{18 c, 20}$ Closure to the lactone follows, yielding 202. We hope that this analysis might lead to creative use of this reagent, potentially as a way to trigger an oxidative rearrangement during the course of a total synthesis.

Moving on to the $\alpha$-ketol rearrangement step, we were confident that our reaction mixture was the result of a thermodynamic equilibrium; however, basic quantum mechanical calculations performed by K.H. of ground state product energies were never found to be in agreement with the experimental distribution. Reasoning that solvent and counterion might be playing crucial roles in this transformation, we set out with visiting student Luiz F. T. Novaes (L.F.T.N.) to investigate the effects of those parameters on the reaction (Table 2.1). Remarkably, our optimized conditions (Entry 1) were the only ones to significantly favor the formation of $\mathbf{2 0 3}$ over epi-203. Changing the counterion to sodium (Entry 2) eroded selectivity and switching it to lithium (Entry 3) completely shut down the desired reactivity, as did switching to a weaker base (KOH only, Entry 4). Clearly, the thermodynamic equilibrium was not between the ground-state neutral species but rather between anionic ones, with better ratios being obtained the more non-coordinating the cation. Interestingly, adding a crown ether to the reaction (Entry 5) did not further improve selectivity, suggesting a complicated interplay between solvent and cation as well. The importance of solvent was further elucidated by examining product distributions in different solvent systems. Solvents without Lewis basic oxygen atoms (Entries 7 and 8) failed to give desired product, potentially due to their inability to stabilize highly charged species. Both THF (Entry 6) and diglyme (Entry 9) did afford the desired ring shifted compounds, with intriguing selectivities. For reasons not immediately obvious, THF gave completely inverted product selectivity: $>20: 1$ d.r. favoring epi-203. Diglyme proved to have an intermediate effect and gave a mixture of $\mathbf{2 0 3}$ and epi-203, overriding the selectivity seen in THF but not quite reaching as high selectivity as in DMSO. Combined, these results demonstrate the importance of both solvent and counterion choice for the anionic $\alpha$-ketol rearrangement.

Finally, we turned to the deceptively simple silylation step (see step " $f$," Scheme 2.1 ) as yet another source of surprising reactivity. During the work up of the silylation reaction, the crude product was treated with aqueous HCl to funnel over-silylated products to the desired mono silylated compound 204. If the crude mixture was treated with acid for excessively long periods of


| entry | conditions ${ }^{\text {a }}$ | solvent | yield ${ }^{\text {b }}$ | d.r.b |
| :---: | :---: | :---: | :---: | :---: |
| 1 | $\mathrm{KOH}, \mathrm{KOt}$ - Bu | DMSO | 68\% | 3.6.:1 |
| 2 | $\mathrm{NaOH}, \mathrm{NaOt}$ - Bu | DMSO | 65\% | 1.3:1 |
| 3 | LiOH, LiOt-Bu | DMSO | $\begin{gathered} \hline 20 \% 231 \\ (M=H) \\ 45 \% 202 \\ \hline \end{gathered}$ | - |
| 4 | KOH (4 equiv) | DMSO | $\begin{gathered} 70 \% 231 \\ (\mathrm{M}=\mathrm{H}) \\ \hline \end{gathered}$ | - |
| 5 | $\mathrm{KOH}, \mathrm{KOt}$-Bu 18-cr-6 (4.5 equiv) | DMSO | 33\% | 3.8:1 |
| 6 | $\mathrm{KOH}, \mathrm{KOt}$ - Bu | THF | 63\% | 1:>20 |
| 7 | $\mathrm{KOH}, \mathrm{KOt}$ - Bu | MeCN | ${ }^{-c}$ | - |
| 8 | $\mathrm{KOH}, \mathrm{KOt}$ - Bu | DCM | ${ }^{-c}$ | - |
| 9 | $\mathrm{KOH}, \mathrm{KOt}$-Bu | diglyme | 12\% | 1:1.6 |

Table 2.1. Studies on the in situ hydrolysis and $\alpha$-ketol rearrangement of 202. ${ }^{a}$ Reactions performed on 0.06 mmol scale; 1.0 equiv of hydroxide base and 3.0 equiv of tert-butoxide base were used, unless otherwise indicated. ${ }^{b}$ Yield and diastereomeric ratio (d.r.) of the crude reaction mixture following acidic workup were determined by NMR analysis using 5-bromo-1,2,3-trimethoxybenzene as an internal standard. ${ }^{\text {' Intractably complex mixtures. }}$
time, though, a new product lacking any silyl groups began to appear. This product was isolated and characterized as lactone 232, which was afforded as a mixture of diastereomers at the C6 position (Scheme 2.2). ${ }^{21}$ The identity of the major diastereomer was confirmed by X-ray crystallographic analysis and optimized conditions $\left(\mathrm{TsOH} \cdot \mathrm{H}_{2} \mathrm{O}, \Delta\right)$ were developed to take tertiary alcohol 203 directly to 232. In this reaction, an apparent "redox relay" has occurred wherein the oxidation at the C6 position has been transferred to the C8 position. While we have not performed rigorous mechanistic studies on this reaction, it seems reasonable to propose that enolization of the ketone occurs first. In a second step, the hydroxyl (or silyl ether) group is either directly displaced in an $\mathrm{S}_{\mathrm{N}} 2$ ' manner by the pendant carboxylate nucleophile or first departs in an $\mathrm{S}_{\mathrm{N}} 1$-like sense to generate an oxyallyl cation/cyclopropanone intermediate (e.g., 231) which is quenched by attack of the carboxylate.

While initially disquieted by the transfer of crucial C6 oxidation to the rarely-oxidized C8 position, we quickly realized the opportunity in the unexpected result. Specifically, (-)-ODB-tashironin (10) and other allo-cedrane type natural products are known to lack C6 oxidation. Thus, we re-prioritized completing a formal synthesis of $\mathbf{1 0}$ from 232, targeting intermediate $\mathbf{1 9 0}$ from Shenvi's synthesis. ${ }^{22}$ Reductive cleavage of the C8 lactone under the action of lithium naphthalenide smoothly provided acid 233. Although 232 was used as a mixture of diastereomers at C6 for this reaction, $\mathbf{2 3 3}$ was isolated as a single diastereomer (assigned by analysis of a gradient 2D


Scheme 2.2. Formal synthesis of (-)-ODB tashironin (10) featuring a "redox relay" transform and non-heme iron(oxo) catalysis to set key oxidation states.
nOe experiment, see Supporting Information), indicating the reaction conditions were sufficiently basic to facilitate epimerization of that position. The challenging C4 methine position of $\mathbf{2 3 3}$ was oxidized under mononuclear non-heme iron(oxo) catalysis (see section 2.4 for a more complete discussion of this transformation), with the C11 carboxylate directing the catalyst to that hindered site. Desired $\gamma$-lactone 234 was isolated in $56 \%$ yield and an $\varepsilon$-lactone byproduct (235) was also identified in $20 \%$ yield. The latter product likely arose from oxidative demethylation of the labile methyl ether followed by lactonization, and its structure (including C6 stereochemistry) was confirmed by X-ray crystallographic studies. With 234 in hand, a simple demethylation employing in situ generated TMSI (TMSCl, NaI) furnished ketol 190, which Shenvi showed could be advanced to $\mathbf{1 0}$ in 5 steps.

### 2.4 C-H Activation of the Exceptionally Hindered C4 Methine Position

Returning to the main synthesis of the pseudoanisatinoids, we knew that the next stage of the synthesis was predicated on successful oxidation of the C 4 methine position (Figure 2.5). Fortunately, we had developed some guiding precedent for this transformation. It was shown in the first-generation route (Figure 2.5A) that carboxylate-directed non-heme iron(oxo) catalysis, popularized by Christina White in the context of late-stage functionalization, was competent at performing the desired C4 oxidation, generating 238 and 239 from parallel starting material 236 in $52 \%$ combined yield. ${ }^{23,24}$ While White generally favors using ( $S, S$ )-PDP as ligand (see 240, Figure 2.5D), it was shown that an iron architecture built on the mep ligand (see 237, Figure 2.5D) was more efficient for this particular C-H activation. Although an encouraging combined $52 \%$ yield of $\mathrm{C}-\mathrm{H}$ oxidized products was isolated, the product distribution told a more cautionary tale. The major product, 239, had been desilylated. It was known that if desilylated $\mathbf{2 3 6}$ was subjected to the reaction conditions, product yield was dramatically decreased likely due to the lability of the unprotected $\alpha$-ketol motif (primarily due to oxidative degradation). Thus, success of the transformation partially hinged on having a rapid $\mathrm{C}-\mathrm{H}$ activation that could outcompete competitive
A

C



Figure 2.5. Studies on non-heme iron(oxo) catalysis. (A) Remarkable example by K.H. of successful catalysis on a model system. (B) Additional example of catalysis on this architecture. (C) Optimized conditions determined for desired substrate 204. See text for discussion of optimization. (D) Selection of iron catalysts surveyed for this transformation to demonstrate the diversity of ligand architectures studied.
desilylation.
The oxidation of $\mathbf{2 3 3}$ (Figure 2.5B) was not influenced by these concerns, as the $\alpha$-ketol functionality had already been removed. However, $\mathbf{2 3 3}$ contained C14 functionality which was similarly demonstrated to be deleterious to product formation. Under optimized conditions, which exchanged hydrogen peroxide for tert-butylhydroperoxide as terminal oxidant, $\mathbf{2 3 4}$ was formed in good yield, but significant mass was lost to the production of $\mathbf{2 3 5}$, a compound that had not undergone desired C 4 activation. Once again, we had data to suggest the key directed $\mathrm{C}-\mathrm{H}$ activation step needed to outcompete an undirected, undesired process (this time, oxidative demethylation).

Based on this precedent, we were ready to test our main substrate (204) in this transformation (Figure 2.5 C ). Much to our chagrin, very little (ca. 5-10\% yield) of the desired $\mathrm{C}-\mathrm{H}$ activation product $\mathbf{2 4 5}$ was identified when 237 was deployed as catalyst. In retrospect, perhaps such a result should not have been surprising. 204 contained both functional groups previously identified as problematic: a C6 silyl ether, and a C14 methyl ether. Thus, the C-H activation pathway now had to outcompete two degradation processes; additionally, 204 was more highly oxidized than $\mathbf{2 3 6}$
or $\mathbf{2 3 3}$, potentially indicating that the C 4 methine in it was also an intrinsically more deactivated position. Nevertheless, the isolation of some amount of lactonized product 245 impelled us to optimize this reaction, since we (naively, as it turned out) believed this transformation to be the final hurdle before completion of a pseudoanisatinoid synthesis. For this transformation, we surveyed the variation of multiple parameters, representing hundreds of reactions. Thorough study of reaction parameters, including temperature, solvent, concentration, pH , reagent addition rate, and acidic or basic additives, demonstrated that the tolerance window for a successful reaction was extraordinarily narrow. Furthermore, no change to those parameters led to significantly improved yield of the desired product.

Reasoning that we needed to accelerate the $\mathrm{C}-\mathrm{H}$ activation process relative to other non-directed degradation pathways, we turned our attention to iron catalyst design (Figure 2.4D). ${ }^{25}$ While a wealth of literature exists on the ability of different non-heme iron catalysts to activate simple alkane $\mathrm{C}-\mathrm{H}$ bonds, comparatively little information was available on how those complexes might function in a more complex setting, particularly in the presence of a directing group. As such, we attempted to survey as broad an array of parameters as feasible, including counterion identity, ligand architecture, and the presence or absence of metal co-catalysts. In agreement with the literature, non-coordinating anions like $\left[\mathrm{SbF}_{6}\right]^{-},\left[\mathrm{C}(\mathrm{Tf})_{3}\right]^{-},\left[\mathrm{ClO}_{4}\right]^{-}$, and $[\mathrm{OTf}]^{-}$performed the best for this transformation, with $\left[\mathrm{SbF}_{6}\right]^{-}$chosen as slightly more robust than the others. Catalysts with coordinating anions, like chloride, were not competent at performing oxidation chemistry. Ligand architecture was varied modularly by assessing the effects of both different ethylenediamine backbones and pyridine rings on catalyst performance. Rigidifying the backbone, as in 240 and 242, was not successful at improving yield. Likewise, simple modification of pyridine sterics and electronics (see 241, 243) also were not fruitful. However, a marked improvement in reaction profile was observed when catalyst 244, bearing the myrtenal-derived ( $R$ )-mepp ligand, was employed. The bulky ligand, popularized by Costas, is thought to create a shielded environment around the iron nucleus that inhibits catalyst deactivation by dimerization. In our case, we rationalized that having a more active iron center would ensure that the directed pathway was being followed more faithfully before non-directed pathways could begin to abound.

Further screening of metal co-catalysts empirically identified thallium(I) triflate as a beneficial additive. While the precise role of this additive is unknown, its presence routinely led to an increase in $5-10 \%$ isolated yield of desired product. Other acidic and Lewis acidic additives have been shown to facilitate iron oxo formation, leading to more active catalysis, and perhaps a similar effect is seen here. ${ }^{26}$ Thallium(I) salts have also historically been used to sequester halide anions in palladium-catalyzed cross-coupling reactions. ${ }^{27}$ As the final step in iron(II) catalyst synthesis was chloride abstraction by a silver(I) salt, perhaps thallium(I) triflate exerted its effect by sequestering residual chloride ions still bound to the iron center, leading to a higher percentage of active catalyst, while simultaneously not negatively impacting catalysis. More detailed mechanistic studies would be required, though, to tease out the origins of this interesting result. Under these optimized conditions, desired product 245 could be isolated in $20 \%$ yield. Two other C4-oxidized compounds, 246 and 247, were also identified in the crude reaction mixture in $11 \%$ and $6 \%$ yields respectively, along with $18 \%$ yield of recovered starting material, for a combined $37 \%$ yield of C4-oxidized material ( $45 \%$ based on recovered starting material). The identity of the major product was confirmed by X-ray crystallographic studies on a desilylated derivative (see Supporting Information). The presence of minor products lacking the methyl ether and silyl protecting group once again pointed to the harshly oxidizing nature of these conditions and underscored the chal-
A

B



Figure 2.6. Synthetic endgame. (A) Synthesis of (-)-3-deoxypseudoanisatin (251) from $\mathrm{C} 4 \mathrm{C}-\mathrm{H}$ activation products 245 and 246. (B) Literature precedent for dihydroxylation of the C3-C4 olefin. Top: from Kende's synthesis of (-)-10-deoxyanisatin. Bottom: from Yamada's synthesis of (-)-anisatin. (C) Dihydroxylations of 250. Standard conditions gave the undesired $\beta$-diol, while directed ones prepared the $\alpha$-disposed isomer, leading to a synthesis of 11.
lenges still remaining for $\mathrm{C}-\mathrm{H}$ activation reactions in complex molecule synthesis.

### 2.5 Total Synthesis of (-)-3-Deoxypseudoanisatin and (+)-Pseudoanisatin

Although the C 4 oxidation step was still less than ideal (owing to low yields and the use of designer catalyst 244), material throughput was nevertheless sufficient to support late-stage investigations and the synthesis of pseudoanisatinoid natural products (Figure 2.5). Substrates containing a C3-C4 alkene were common intermediates in previous Illicium sesquiterpene syntheses (see section 1.4), and so we chose to target a similar motif on our scaffold (Figure 2.5A). Elimination of the C4-C11 $\gamma$-lactone of $\mathbf{2 4 5}$ proceeded smoothly under the action of ethyl Meerwein's salt $\left(\mathrm{Et}_{3} \mathrm{OPF}_{6}\right)$ and proton sponge. Similar to the opening of the strained tetrahydrofuran ring at the beginning of the synthesis, this reaction likely proceeded by transfer of an ethyl group to the lactone carbonyl followed by elimination to the alkene and ethyl ester seen in 248. Minor product 246 of the $\mathrm{C}-\mathrm{H}$ activation step could also be carried through this reaction, providing parallel product 249 in comparable yield. Parallel two-step deprotections of the (1) alkyl ethers (in situ TMSI) and (2) silyl ethers (TBAF, AcOH) of $\mathbf{2 4 8}$ and $\mathbf{2 4 9}$ converged those products to alkene 250, a substrate primed for the completion of the total synthesis. Notably, while removal of alkyl ethers can often stymie synthetic efforts, both the methyl ether of $\mathbf{2 4 8}$ and even the ethyl ether of $\mathbf{2 4 9}$ were readily cleaved under the reaction conditions. Smooth lactonization to the C11-C14 $\varepsilon$-lactone was also observed under these conditions. Importantly, the order of deprotection did matter, as attempting to deploy TMSI in the presence of an unprotected $\alpha$-ketol motif led to extensive decomposition and no isolation of desired product.

To complete syntheses of pseudoanisatinoid natural products, hydration and dihydroxyl-
ation reactions of the $\mathrm{C} 3-\mathrm{C} 4$ olefin were envisioned. First, cobalt-catalyzed Mukaiyama hydration of the C3-C4 alkene gave (-)-3-deoxypseudoanisatin (251), along with diastereomeric 247 (itself a minor product of the C 4 oxidation as well). Overall, $\mathbf{2 5 1}$ was prepared in 11 steps and net 6 oxidations from 14.

To synthesize (+)-pseudoanisatin (11), an $\alpha$-face selective dihydroxylation of the C3-C4 alkene was needed. When considering literature precedent for this transformation (Figure 2.5B), we were confident that the reagent would approach our substrate from the correct face. Kende's alkene 29, containing a very similar $\varepsilon$-lactone system, exclusively afforded $\alpha$-diol 252. ${ }^{28}$ Similarly, Yamada's olefin 253 lacking an $\varepsilon$-lactone also preferred reagent approach from the $\alpha$-face, leading to $\mathbf{2 5 4} .{ }^{29}$ To our surprise, when $\mathbf{2 5 0}$ was treated under similar conditions, lactone $\mathbf{2 5 5}$ was isolated as the exclusive product and its structure was confirmed by X-ray crystallographic analysis. Clearly some subtle difference in our substrate (perhaps the geometry at C6? Perhaps a lack of substitution at the C13 methyl group?) was enough to completely change the preferred sense of reagent approach. Faced with this final obstacle to our synthesis, we wondered whether - like the commonly known directed epoxidation reaction - a "directed dihydroxylation" reaction existed and would be serviceable in this context. Fortunately, Donohoe had described how pre-complexing osmium tetroxide to TMEDA created a new reagent that appeared to generate "directed" products when the substrate contained an allylic or homoallylic alcohol or trichloroacetamide. ${ }^{30}$ In direct comparison to results with osmium tetroxide/pyridine, the change in selectivity from this reagent was moderate, but noticeable. In our system, a bulky quaternary center spaced the alkene from the tertiary homoallylic alcohol, a less than ideal situation for an intramolecular directed reaction. However, shockingly, when $\mathbf{2 5 0}$ was treated with osmium tetroxide/TMEDA, 257 was isolated as the sole product ( $>15: 1$ d.r.), speaking to the exquisitely compact and caged architectures with which we were working. Inversion of the C3 secondary alcohol by activation as the mesylate followed by presumed intramolecular displacement with a carboxylate (see 258) finally completed the synthesis of $\mathbf{1 1}$, in 12 steps and net 7 oxidations from 14, demonstrating the viability of an oxidative strategy towards Illicium natural products. ${ }^{31}$

### 2.6 Conclusion and Outlook towards Additional Illicium Sesquiterpene Synthesis

In this Chapter, we explored an initial oxidative strategy to the Illicium sesquiterpenes. Renewable chiral pool feedstock (+)-cedrol (14) was selected as the starting material for this route and the moderately-oxidized pseudoanisatinoids were designated as initial targets (Scheme 2.3). The success of this chemistry was predicated on the careful orchestration of site-selective $\mathrm{C}\left(\mathrm{sp}^{3}\right)-\mathrm{H}$ bond functionalizations, with challenging directed C14 and C4 oxidations (see 199 and 245-247, respectively) and a unique C 7 oxidative lactonization (see 202). That latter transformation was further studied and found to be broadly applicable, with the potential for cleanly generating interesting rearranged products (see 224 and $\mathbf{2 2 8} / \mathbf{2 2 9}$ ). Along the way, careful attention to minor product formation unearthed more unique reactivity (see 232) and paved the way for a formal synthesis of 10.

A thorough study of mononuclear non-heme iron(oxo) catalysis for the C 4 oxidation led to the first use of $\mathbf{2 4 4}$ in complex molecule synthesis and hopefully also will inspire others to push the boundaries of C-H activation reactions in total synthesis. Finally, successful synthesis of $\mathbf{1 1}$ relied on a key directed dihydroxylation reaction that truly underscored the influence small structural changes could have on the course of a reaction.





$\begin{gathered}\text { I. } \mathrm{Et}_{3} \mathrm{OPF}_{6}, \\ \text { proton-sponge; } \\ \text { ins } \\ \text { then, aq. TFA } \\ \text { m. TMSCI, } \\ \text { Nal } \mathrm{TBAF},\end{gathered}$
McOH
 $42 \%$
$[3$ steps]

(+)-pseudoanisatin (11)

(-)-3-0xo-
pseudoanisatin (259)

Scheme 2.3. Oxidative synthesis of the pseudoanisatinoids from (+)-cedrol (14).

While this route led to the total synthesis of two natural products and the formal synthesis of three more, including $\mathbf{2 5 9}$ in one step from $\mathbf{1 1},{ }^{32}$ in many ways it was still a preliminary proof of concept. For one, more highly oxidized Illicium sesquiterpenes like the majucinoids and anisatinoids were still out of reach for this chemistry, meaning we could not yet claim our route was a general way to address Illicium natural product synthesis. Furthermore, iron-catalyzed C4 oxidation - though suitable for pseudoanisatinoid synthesis - was deemed impractical for future synthetic development, and fundamentally we held the C 4 oxidation to be an insufficiently addressed challenge. Thus, when continuing on with this work we had two main priorities in the forefront of our mind: (1) to develop an alternative oxidation of the C 4 position and (2) to investigate oxidations leading to the majucinoids and/or anisatinoids. The ensuing Chapter will describe our reali-
zation of these goals, culminating in a unified approach to Illicium sesquiterpene synthesis and the generation of a dozen natural products.

### 2.7 Distribution of Credit and Acknowledgments

The synthesis of $\mathbf{1 9 5}$, upon which much of the work of this chapter was built, was designed by Dr. Kevin Hung (K.H.) and Prof. Thomas J. Maimone (T.J.M.) and executed by K.H. with the assistance of visiting scholar Takahiro Morikawa (T.M.) from Chiba University, Japan. T.J.M. approached M.L.C. with the second-generation route to the pseudoanisatinoids described in this chapter and together T.J.M., M.L.C., and K.H. chose targets and planned the chemistry. M.L.C. and K.H. collaboratively executed, optimized, and characterized the route to the pseudoanisatinoids. Substrate scope and mechanistic studies of the $\mathrm{CuBr}_{2}$ reaction were performed by M.L.C.; K.H. and T.M. are acknowledged for initial development of that transformation. Visiting scholar Luiz F. T. Novaes (L.F.T.N.) from University of Campinas (UNICAMP), Brazil is credited with studies on the $\alpha$-ketol rearrangement. M.L.C., with the assistance of undergraduate Stephen J. Harwood (S.J.H.), completed the formal synthesis of $\mathbf{1 0} \boldsymbol{;}$ K.H. optimized and characterized intermediates in that sequence.

We are grateful to Dr. Hasan Celik (H.C.) and Dr. Jeffrey Pelton (J.P.) for NMR spectroscopic assistance wherein NIH grant GM68933 is acknowledged. Dr. Nicholas S. Settineri (N.S.S.) and Dr. Antonio G. DiPasquale (A.G.D.P.) are acknowledged for X-ray crystallographic analysis wherein support from NIH Shared Instrument Grant (S10-RR027172) is also acknowledged. We are also thankful to Dr. Laura J. McCormick of the Advanced Light Source Synchrotron Facility at Lawrence Berkeley National Laboratory for the crystal structure of compound 255. We are indebted to Professor Yoshiyasu Fukuyama of Tokushima Bruni University, Japan, for kindly providing us with NMR spectra of natural (-)-3-deoxypseudoanisatin (251) and (+)-pseudoanisatin (11).
M.L.C. thanks the University of California, Berkeley and the National Science Foundation (NSF) for a Berkeley Graduate Fellowship and NSF Predoctoral Fellowship (DGE-1106400) respectively.

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# Supporting Information for 

## Chapter 2

Oxidative Synthesis of the Pseudoanisatinoids

## SI2.1 General Procedures:

All reactions were performed in flame- or oven-dried glassware under a positive pressure of nitrogen or argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe. Volatile solvents were removed under reduced pressure rotary evaporation below 35 ${ }^{\circ} \mathrm{C}$. Diglyme was removed under reduced pressure rotary evaporation at $60^{\circ} \mathrm{C}$. Analytical and preparative thin-layer chromatography (TLC) were performed using glass plates pre-coated with silica gel ( $0.25-\mathrm{mm}, 60-\AA ̊$ pore size, Silicycle SiliaPlateTM or MilliporeSigma TLC Silica gel 60 F254) and impregnated with a fluorescent indicator ( 254 nm ). TLC plates were visualized by exposure to ultraviolet light (UV) and then were stained by submersion in an ethanolic anisaldehyde solution, an ethanolic phosphomolybdic/cerium sulfate solution, or a basic aqueous potassium permanganate solution, followed by brief heating on a hot plate. Flash column chromatography was performed employing silica gel purchased from Silicycle (SiliaFlash ${ }^{\circledR}, 60 \AA, 230-400$ mesh, $40-63 \mu \mathrm{~m}$ ). Reaction conditions involving slow addition of reagents were performed with syringe pumps model KDS 100 and KDS 200, obtained from KD Scientific.
$(+)$-Cedrol purchased from Sigma Aldrich was recrystallized from $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}$. The recrystallized material was found to have an optical rotation of $[\alpha]_{\mathrm{D}}=+9.6\left(c 5, \mathrm{CHCl}_{3}\right)$. This value corresponds to $97 \%$ ee when compared to the Merck Index value for enantiopure cedrol $\left([\alpha]_{D}=\right.$ $+9.9, c 5, \mathrm{CHCl}_{3}$ ), and $91 \%$ ee when compared to the value reported by Sigma Aldrich ( $[\alpha]_{\mathrm{D}}=$ $\left.+10.5, c 5, \mathrm{CHCl}_{3}\right) .(+)$-Cedrol purchased from Parchem was used directly as received. The crystalline material was found to have an optical rotation of $[\alpha]_{\mathrm{D}}=+11.9\left(c 5, \mathrm{CHCl}_{3}\right)$.

Anhydrous tetrahydrofuran (THF), dichloromethane (DCM), dimethylformamide (DMF), and acetonitrile ( MeCN ) were obtained by passing these previously degassed solvents through activated alumina columns. Trimethylsilyl chloride (TMSCl) and isopropanol ( $i$-PrOH) were distilled over calcium hydride prior to use. $i$ - PrOH was also degassed prior to use. Lithium naphthalenide, ${ }^{1}\left[\mathrm{Fe}(\mathrm{mep})(\mathrm{MeCN})_{2}\right]\left[\left(\mathrm{SbF}_{6}\right)_{2}\right],{ }^{2}$ and $(R)$-mepp ${ }^{3}$ were prepared from their respective literature procedures. $\left[\mathrm{Fe}((R)\right.$-mepp $\left.)(\mathrm{MeCN})_{2}\right]\left[\left(\mathrm{SbF}_{6}\right)_{2}\right]$ was prepared by an adaption of known literature protocols. ${ }^{2}$ All other solvents and reagents were purchased at the highest commercial grade and were used as received, without further purification.
Proton nuclear magnetic resonance ( 1 H NMR) spectra and carbon nuclear magnetic resonance (13C NMR) spectra were recorded on Bruker AVB 400 ( $400 \mathrm{MHz} / 101 \mathrm{MHz}$ ), Bruker AV 500 ( 500 $\mathrm{MHz} / 126 \mathrm{MHz}$ ), Bruker DRX 500 ( $500 \mathrm{MHz} / 126 \mathrm{MHz}$ ), Bruker AV 600 ( $600 \mathrm{MHz} / 151 \mathrm{MHz}$ ) NMR, Bruker AV 700 ( $700 \mathrm{MHz} / 176 \mathrm{MHz}$ ), and Bruker $900(900 \mathrm{MHz} / 226 \mathrm{MHz}$ ) spectrometers at $23^{\circ} \mathrm{C}$. Fluorine nuclear magnetic resonance (19F NMR) spectra were recorded on a Bruker AVQ $400(376 \mathrm{MHz})$ spectrometer at $23^{\circ} \mathrm{C}$. Proton chemical shifts are expressed as parts per million ( $\mathrm{ppm}, \delta$ scale) and are referenced to residual protium in the NMR solvent $\left(\mathrm{C}_{5} \mathrm{D}_{4} \mathrm{HN}: \delta 8.74, \mathrm{CHCl}_{3}\right.$ : $\delta 7.26, \mathrm{CD}_{2} \mathrm{HOD}: \delta 3.31$ ), except where otherwise indicated. Carbon chemical shifts are expressed as parts per million ( $\mathrm{ppm}, \delta$ scale) and are referenced to the carbon resonance of the NMR solvent $\left(\mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}: \delta 150.35, \mathrm{CDCl}_{3}: \delta 77.16, \mathrm{CD}_{3} \mathrm{OD}: 49.15\right)$, except where otherwise indicated. Fluorine chemical shifts are expressed as part per million (ppm, $\delta$ scale) and are not additionally referenced. Data are represented as follows: chemical shift, multiplicity ( $\mathrm{s}=$ singlet, $\mathrm{d}=$ doublet, $\mathrm{t}=$ triplet, $\mathrm{q}=$ quartet, $\mathrm{p}=$ pentet, $\mathrm{dd}=$ doublet of doublets, $\mathrm{dt}=$ doublet of triplets, $\mathrm{m}=$ multiplet, br $=$ broad), coupling constant (J) in Hertz (Hz), and integration. Infrared (IR) spectra were recorded on a Bruker Alpha FT-IR spectrometer as thin films and are reported in frequency of absorption $\left(\mathrm{cm}^{-1}\right)$. Optical rotations were recorded on a Perkin Elmer polarimeter, model 241. High-resolution mass spectra were obtained at the QB3/Chemistry Mass Spectrometry Facility at University of

California, Berkeley using a Thermo LTQ-FT mass spectrometer, Waters AutoSpec Premier mass spectrometer, and at the Lawrence Berkeley National Laboratory Catalysis Center using a Perkin Elmer AxION 2 TOF mass spectrometer with electrospray ionization (ESI) and electron ionization (EI) techniques. X-ray diffraction data for all compounds except $\mathbf{2 5 5}$ were collected at the Small Molecule X-ray Crystallography Facility (CheXray) at University of California, Berkeley using a Bruker MicroSTAR-H APEX II X-ray source. X-ray diffraction data for compound 255 was collected at the Advanced Light Source Synchrotron Facility at Lawrence Berkeley National Laboratory using a Small-Molecule Crystallography Beamline 11.3.1 (now replaced by Beamline 12.2.1).

## SI2.2 Compound Preparation and Characterization Data

Preparation and characterization data are provided for only a subset of compounds described in Chapter 2. Data for the remaining compounds can be found in the Ph.D. dissertation of K.H. ${ }^{4}$ and/or in our published work. ${ }^{5}$


Ether 199. Cyclohexane ( 1.8 L ) was added to a 3 L flask containing diacetoxyiodobenzene ( $52 \mathrm{~g}, 160 \mathrm{mmol}, 3.0$ equiv) and iodine ( $14 \mathrm{~g}, 54 \mathrm{mmol}, 1.0$ equiv). The suspension was stirred at $23^{\circ} \mathrm{C}$ until the iodine had completely dissolved. At this point, $(+)$-cedrol (14) $(12 \mathrm{~g}, 54 \mathrm{mmol}, 1.0$ equiv) was added in a single portion. The deep purple mixture was irradiated with a 90 W halogen lamp for 1.5 h. The reaction mixture was quenched by addition of saturated $a q$. $\mathrm{NaHCO}_{3} /$ saturated $a q . \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}$ ( $1: 1 \mathrm{v}: v, 800 \mathrm{~mL}$ ) and was stirred vigorously until becoming colorless. The layers were separated and the aqueous layer was extracted with ether ( $3 \times 500 \mathrm{~mL}$ ). The combined organic layers were washed with brine ( $1 \times 1.0 \mathrm{~L}$ ), dried over $\mathrm{MgSO}_{4}$ and concentrated in vacuo. The crude residue was purified by column chromatography $\left(2 \% \rightarrow 5 \% \mathrm{Et}_{2} \mathrm{O}\right.$ in hexanes) to afford ether $199(8.7 \mathrm{~g}$, $40 \mathrm{mmol}, 73 \%$ yield $)$ as a pale yellow oil. $[\alpha]_{\mathrm{D}}=-62.1\left(c 2.9, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ $\delta 3.56(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.45(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.88-1.77(\mathrm{~m}, 2 \mathrm{H}), 1.76-1.70(\mathrm{~m}, 3 \mathrm{H}), 1.69$ - $1.62(\mathrm{~m}, 2 \mathrm{H}), 1.56-1.44(\mathrm{~m}, 2 \mathrm{H}), 1.42-1.35(\mathrm{~m}, 2 \mathrm{H}), 1.34-1.27(\mathrm{~m}, 2 \mathrm{H}) 1.16(\mathrm{~s}, 3 \mathrm{H}), 0.98$ (s, 3H), $0.82(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 84.8,78.2,60.1,59.5,54.0,53.2$, $42.1,35.6,35.0,31.8,30.4,28.2,25.3,18.9,15.9$; IR (thin film) $v_{\max }: 2953,2922,1446,1048 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{15} \mathrm{H}_{24} \mathrm{O}: 220.1827$, found: 220.1832.


Keto-Acid 201. Alkene 200 ( $13 \mathrm{~g}, 55 \mathrm{mmol}, 1.0$ equiv) and sodium periodate ( $59 \mathrm{~g}, 280 \mathrm{mmol}, 5.0$ equiv) were added to a vigorously stirred, biphasic solution of $\mathrm{CCl}_{4}: \mathrm{MeCN}: \mathrm{H}_{2} \mathrm{O}(3: 3: 4 v: v: v, 550 \mathrm{~mL})$. The white suspension was stirred for 15 min before the first portion of $\mathrm{RuCl}_{3} \cdot \mathrm{xH}_{2} \mathrm{O}(0.55 \mathrm{~g}, 2.8 \mathrm{mmol}$, 0.05 equiv) was added. The resulting black solution was stirred at $23^{\circ} \mathrm{C}$ for 30 min , and then a second portion of $\mathrm{RuCl}_{3} \cdot \mathrm{xH}_{2} \mathrm{O}(0.55 \mathrm{~g}, 2.8 \mathrm{mmol}, 0.05$ equiv $)$ was added. After stirring for an additional 30 min , the solution was diluted with $\mathrm{Et}_{2} \mathrm{O}(300 \mathrm{~mL})$ and filtered through celite. $\mathrm{NaOH}(1.0 \mathrm{M}, 250 \mathrm{~mL})$ was added and the layers were separated. The organic layer was extracted with $\mathrm{NaOH}(1.0 \mathrm{M}, 2 \times 250 \mathrm{~mL})$ and the combined aqueous layers were washed with hexanes $(500 \mathrm{~mL})$. The aqueous layers were acidified with $\mathrm{HCl}(12 \mathrm{M}, 100 \mathrm{~mL})$ and were extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 300 \mathrm{~mL})$. The combined organic layers were washed with saturated aq. $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}(500 \mathrm{~mL})$ and brine $(500 \mathrm{~mL})$, dried over $\mathrm{MgSO}_{4}$, filtered, and concentrated in vacuo to afford keto-acid 201 ( $12 \mathrm{~g}, 41 \mathrm{mmol}, 72 \%$ yield) as a pale brown solid which was used in the
next step without further purification. $[\alpha]_{\mathrm{D}}=-28.0\left(c 2.5, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ $11.40(\mathrm{br} \mathrm{s}, 1 \mathrm{H}) 3.17(\mathrm{~s}, 3 \mathrm{H}), 3.10(\mathrm{~d}, J=9.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.06(\mathrm{~d}, J=9.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.65$ (dd, $J=12.8$, $6.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.38(\mathrm{~d}, J=14.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.30(\mathrm{~d}, J=14.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.18(\mathrm{t}, J=8.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.14$ (s, $3 \mathrm{H}), 1.78-1.52(\mathrm{~m}, 4 \mathrm{H}), 1.43(\mathrm{tdd}, J=12.4,8.9,6.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.23(\mathrm{dd}, J=12.0,6.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.19$ $(\mathrm{s}, 3 \mathrm{H}), 0.95(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 209.6,179.2,77.4,58.7,58.7$, $56.0,51.0,49.3,46.2,41.0,37.7,33.4,31.4,27.6,20.9,14.1$; IR (thin film) $v_{\max }: 3182,2936,1699$, $1106 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{O}_{4}[\mathrm{M}-\mathrm{H}]:$ : 281.1753 , found: 281.1808 .

General Procedure for the $\mathbf{C u B r}_{2}$-mediated oxidative lactonization of keto-acids: Diglyme (2 mL ) was added to anhydrous $\mathrm{CuBr}_{2}(135 \mathrm{mg}, 0.6 \mathrm{mmol}, 3.0$ equiv) and substrate ( $0.2 \mathrm{mmol}, 1.0$ equiv). The reaction mixture was heated at $150^{\circ} \mathrm{C}$ for 16 h . The brown suspension was cooled to $23^{\circ} \mathrm{C}$, diluted with acetone ( 2 mL ), and filtered through a pad of celite. The organic residue was concentrated in vacuo at $60^{\circ} \mathrm{C}$ to afford the crude lactone, which was then purified by column chromatography ( $50 \rightarrow 75 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes).


5-benzoyldihydrofuran-2(3H)-one (214). The standard procedure was followed with 5-oxo-5-phenylpentanoic acid ( 38 mg ) to afford 214 as a white solid ( $36 \mathrm{mg}, 0.19 \mathrm{mmol}, 94 \%$ yield). Spectroscopic data were in agreement with previously reported values. ${ }^{6}{ }^{1} \mathrm{H}$ NMR ( $700 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.97$ (d, $J=$ $7.6 \mathrm{~Hz}, 2 \mathrm{H}), 7.63(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.51(\mathrm{t}, J=7.6 \mathrm{~Hz}, 2 \mathrm{H}), 5.82-5.79(\mathrm{~m}, 1 \mathrm{H}), 2.63-2.54(\mathrm{~m}$, 3H), $2.49-2.42(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $176 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 194.5,176.4,134.4,133.7,129.1$ (2C), 128.9 (2C), 78.4, 26.9, 25.1.


5-(4-Methylbenzoyl)dihydrofuran-2(3H)-one (215). The standard procedure was followed with 5-oxo-5-(4-methylphenyl)pentanoic acid ${ }^{7}$ (41 mg ) to afford 215 as a white solid ( $37 \mathrm{mg}, 0.18 \mathrm{mmol}, 91 \%$ yield). Spectroscopic data were in agreement with previously reported values. ${ }^{6}{ }^{1} \mathrm{H}$ NMR (700 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 7.86(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 7.30(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 5.78(\mathrm{dd}, J=8.3$, $4.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.61-2.53(\mathrm{~m}, 3 \mathrm{H}), 2.45-2.40(\mathrm{~m}, 1 \mathrm{H}), 2.42(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $176 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 194.0,176.5,145.5,131.2,129.8$ (2C), 129.0 (2C), 78.3, 27.0, 25.2, 21.9.


5-(4-Methoxybenzoyl)dihydrofuran-2(3H)-one (216). The standard procedure was followed with 5-oxo-5-(4-methoxyphenyl)pentanoic acid $^{7}(45 \mathrm{mg})$ to afford 216 as a white solid ( $41 \mathrm{mg}, 0.19 \mathrm{mmol}, 93 \%$ yield). Spectroscopic data were in agreement with previously reported values. ${ }^{6}{ }^{1} \mathrm{H}$ NMR ( $700 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.96(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 6.97(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 5.75$ (dd, $J=7.8,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.89(\mathrm{~s}, 3 \mathrm{H}), 2.65-2.52(\mathrm{~m}, 3 \mathrm{H}), 2.50-2.41(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 176 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 192.8,176.5,164.5,131.4(2 \mathrm{C}), 126.8,114.4$ (2C), 78.3, 55.7, 27.1, 25.2.


5-(4-fluorobenzoyl)dihydrofuran-2(3H)-one (217). The standard procedure was followed with 5-oxo-5-(4-methoxyphenyl)pentanoic acid ${ }^{7}$ (42 mg ) to afford 217 as a white solid ( $37 \mathrm{mg}, 0.18 \mathrm{mmol}, 89 \%$ yield). Spectroscopic data were in agreement with previously reported values. ${ }^{6}{ }^{1} \mathrm{H}$ NMR ( $700 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 8.03(\mathrm{dd}, J=8.5,5.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.19(\mathrm{t}, J=8.5 \mathrm{~Hz}, 2 \mathrm{H}), 5.73(\mathrm{dd}, J=8.1,4.7$ $\mathrm{Hz}, 1 \mathrm{H}), 2.63-2.55(\mathrm{~m}, 3 \mathrm{H}), 2.54-2.47(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (176 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 192.9,176.2$,
$166.5(\mathrm{~d}, J=257.2 \mathrm{~Hz}), 131.8(\mathrm{~d}, J=9.5 \mathrm{~Hz}, 2 \mathrm{C}), 130.3(\mathrm{~d}, J=3.1 \mathrm{~Hz}), 116.1(\mathrm{~d}, J=22.0 \mathrm{~Hz}, 2 \mathrm{C})$, 78.4, 27.0, 24.8; ${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-101.64(\mathrm{tt}, J=8.5,5.3 \mathrm{~Hz}$ ).


5-benzoyl-4,4-dimethyldihydrofuran-2(3H)-one (218). The standard procedure was followed with 3,3-dimethyl-5-oxo-5-phenylpentanoic acid ${ }^{8}$ ( 44 mg ) to afford 218 as a white solid ( $41 \mathrm{mg}, 0.19 \mathrm{mmol}, 94 \%$ yield). Spectroscopic data were in agreement with previously reported values. ${ }^{9}{ }^{1} \mathrm{H}$ NMR ( 700 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 7.94(\mathrm{dd}, J=8.3,1.2 \mathrm{~Hz}, 2 \mathrm{H}), 7.65(\mathrm{tt}, J=7.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.53$ (dd, $J=8.3,7.5 \mathrm{~Hz}, 2 \mathrm{H}), 5.51(\mathrm{~s}, 1 \mathrm{H}), 2.58(\mathrm{~d}, J=17.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.33(\mathrm{~d}, J=17.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.38$ (s, 3H), 0.98 (s, 3H); ${ }^{13} \mathrm{C}$ NMR ( $176 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 195.8,175.8,136.0,134.4,129.2$ (2C), 128.7 (2C), 85.6, 42.0, 40.8, 28.5, 23.7.


3',4'-dihydro-1'H,3H-spiro[furan-2,2'-naphthalene]-1',5(4H)-dione (219). The standard procedure was followed with 3-(1-oxo-1,2,3,4-tetrahydronaphtha-len-2-yl)propanoic acid ${ }^{10}(44 \mathrm{mg})$ to afford 219 as a white solid $(41 \mathrm{mg}, 0.19$ $\mathrm{mmol}, 94 \%$ yield). Spectroscopic data were in agreement with previously reported values. ${ }^{6}{ }^{1} \mathrm{H}$ NMR $\left(700 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.06(\mathrm{dd}, J=7.6,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.54$ (td, $J=7.6,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.36(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.28(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.19(\mathrm{dt}, J=17.1,5.2 \mathrm{~Hz}$, 1H), 3.09 (ddd, $J=17.1,10.1,4.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.78 (ddd, $J=17.8,10.8,9.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.61$ (ddd, J = $13.3,10.1,5.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.60 (ddd, $\mathrm{J}=17.8,9.6,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.55(\mathrm{ddd}, J=12.8,9.8,2.5 \mathrm{~Hz}, 1 \mathrm{H})$, $2.30(\mathrm{ddd}, J=13.3,5.2,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.15(\mathrm{dt}, J=12.8,10.8,9.6 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 176 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 193.7,176.3,143.1,134.6,130.1,128.9,128.6,127.4,85.2,34.6,29.7,28.0,25.8$.


5-(thiophene-2-carbonyl)dihydrofuran-2(3H)-one (220). The standard procedure was followed with 5-oxo-5-(thiophen-2-yl)pentanoic acid ${ }^{11}(40 \mathrm{mg})$ to afford 220 as a white solid ( $32 \mathrm{mg}, 0.17 \mathrm{mmol}, 82 \%$ yield). Spectroscopic data were in agreement with previously reported values. ${ }^{7}{ }^{1} \mathrm{H}$ NMR $(700 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right) \delta 7.92(\mathrm{dd}, J=3.9,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.77(\mathrm{dd}, J=5.0,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.20(\mathrm{dd}, J=5.0,3.9 \mathrm{~Hz}$, $1 \mathrm{H}), 5.53$ (dd, $J=8.2,4.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.66-2.55(\mathrm{~m}, 3 \mathrm{H}), 2.55-2.50(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (176 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta 188.1,176.2,140.4,135.8,134.2,128.8,79.5,27.1,25.5$.

Oleanic acid derivatives 223 and 224. The standard procedure was followed with acid $221{ }^{12}$ (105 mg ) to afford $\mathbf{2 2 3}$ as a white solid ( $9 \mathrm{mg}, 0.02 \mathrm{mmol} 9 \%$ yield) and rearranged product $\mathbf{2 2 4}$ as a white solid ( $74 \mathrm{mg}, 0.14 \mathrm{mmol}, 72 \%$ yield).

223. $[\alpha]_{\mathrm{D}}=+57.6\left(c 0.5, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR $\left(700 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.98$ $(\mathrm{s}, 1 \mathrm{H}), 4.49(\mathrm{dd}, J=11.9,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.00-2.93(\mathrm{~m}, 1 \mathrm{H}), 2.12-$ $2.08(\mathrm{~m}, 1 \mathrm{H}), 2.07(\mathrm{~s}, 3 \mathrm{H}), 2.00(\mathrm{dt}, J=13.2,3.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.87$ (td, $J=$ $13.5,6.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.80(\mathrm{dq}, J=12.5,3.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.77-1.65(\mathrm{~m}, 5 \mathrm{H})$, $1.64-1.51(\mathrm{~m}, 4 \mathrm{H}), 1.46(\mathrm{~s}, 3 \mathrm{H}), 1.45-1.41(\mathrm{~m}, 1 \mathrm{H}), 1.41-1.34$ $(\mathrm{m}, 3 \mathrm{H}), 1.34-1.29(\mathrm{~m}, 1 \mathrm{H}), 1.28(\mathrm{~s}, 3 \mathrm{H}), 1.28-1.24(\mathrm{~m}, 1 \mathrm{H}), 0.99$ (s, 3H), 0.97 (s, 6H), 0.93 (s, 3H), 0.92 (s, 3H); ${ }^{13} \mathrm{C}$ NMR ( 176 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 192.3,183.4,178.6,170.9,121.7,87.8,79.5,50.3,45.9$, $43.9,43.5,41.6,40.3,38.2,36.6,36.0,34.0,33.9,33.1,31.6,30.0,28.0,27.2,25.8,24.4,23.79$, $23.78,23.0,21.2,20.2,17.1,16.6$; IR (thin film) $v_{\max }: 2950,1778,1736,1667,1245,755 \mathrm{~cm}^{-1}$;

HRMS (EI) calcd for $\mathrm{C}_{32} \mathrm{H}_{45} \mathrm{O}_{5}: 510.3345$, found: 510.3351 .
 $44.9,41.7,39.7,39.0,37.8,36.5,35.1,33.51,33.46,33.3,31.3,28.0,26.6,24.5,24.1,23.6,21.7$, 21.4, 20.9, 20.6, 20.4, 18.8, 16.4; IR (thin film) $v_{\max }$ : 2944, 1731, 1676, $1245,751 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{32} \mathrm{H}_{45} \mathrm{O}_{5}: 510.3345$, found: 510.3350 .

Carene derivatives 228 and 229. The standard procedure was followed with $2-((1 R, 3 S)-2,2-\mathrm{di}-$ methyl-3-(2-oxopropyl)cyclopropyl)acetic acid ${ }^{13}$ ( $\mathbf{2 2 5}$, derived from ( + )-3 carene, 36 mg ) to afford 228 as an off-white solid ( $15 \mathrm{mg}, 0.06 \mathrm{mmol}, 29 \%$ yield) and 229 as a pale yellow oil ( 7 mg , $0.04 \mathrm{mmol}, 18 \%$ yield).

228. ${ }^{1} \mathrm{H}$ NMR $\left(700 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.31(\mathrm{~d}, J=16.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.89(\mathrm{~d}, J=16.1$ $\mathrm{Hz}, 1 \mathrm{H}), 6.27(\mathrm{~s}, 1 \mathrm{H}), 4.03(\mathrm{~s}, 2 \mathrm{H}), 1.59(\mathrm{~s}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $176 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 190.0,170.5,166.4,131.9,130.1,120.6,86.6,33.0,25.7$; IR (thin film) $v_{\max }$ : 1746, 1693, 1618, $1582 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{10} \mathrm{H}_{11} \mathrm{O}_{3}{ }^{79} \mathrm{Br}$ : 257.9892, found: 257.9891 .

229. ${ }^{1} \mathrm{H} \operatorname{NMR}\left(700 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.13(\mathrm{~d}, J=16.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.60(\mathrm{~d}, J=$ $16.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.21(\mathrm{~s}, 1 \mathrm{H}), 2.39(\mathrm{~s}, 3 \mathrm{H}), 1.57(\mathrm{~s}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 176 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 196.9,170.6,167.0,134.5,130.1,119.9,86.6,28.5,25.7$; IR (thin film) $v_{\max }: 1750,1699,1677 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{O}_{3}: 180.0786$, found: 180.0787 .


Tertiary alcohol 203. $\mathrm{KOt} t-\mathrm{Bu}(9.7 \mathrm{~g}, 87 \mathrm{mmol}, 3.0$ equiv) and finely ground $\mathrm{KOH}(1.6 \mathrm{~g}, 29 \mathrm{mmol}, 1.0$ equiv) were dissolved in DMSO ( 260 mL ). Crude lactone 202 (ca. $8.0 \mathrm{~g}, 29 \mathrm{mmol}, 1.0$ equiv) was added and the resulting dark brown solution was stirred at $23^{\circ} \mathrm{C}$ for 14 h . The reaction was diluted with DCM ( 300 mL ) and $\mathrm{HCl}(1.0 \mathrm{M}, 100 \mathrm{~mL})$. The layers were separated and the organic layer was further washed with $\mathrm{HCl}(0.10 \mathrm{M}, 5 \times 100 \mathrm{~mL})$ and brine $(100 \mathrm{~mL})$. The organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (dry loading, $10 \rightarrow 50 \%$ EtOAc in hexanes) to afford desired tertiary alcohol $\mathbf{2 0 3}(5.5 \mathrm{~g}, 18 \mathrm{mmol}, 45 \%$ yield over two steps, $4: 1$ d.r.). The diastereomers can be separated by an additional purification ( $50 \rightarrow 80 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes) and both pure diastereomers can be resubjected to the reaction conditions to give again a $4: 1$ mixture of diastereomers. Major diastereomer (203): $=-10.0^{\circ}\left(c 0.2, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 10.20(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.96$ (br s, 1H), $3.38(\mathrm{~d}, J=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.33(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.29(\mathrm{~s}, 3 \mathrm{H}), 3.17(\mathrm{~d}, J=9.8 \mathrm{~Hz}, 1 \mathrm{H})$, $2.74(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.46(\mathrm{~d}, J=15.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.27(\mathrm{~d}, J=14.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.14(\mathrm{~d}, J=14.5 \mathrm{~Hz}$,
$1 \mathrm{H}), 1.99-1.82(\mathrm{~m}, 3 \mathrm{H}), 1.70(\mathrm{tt}, J=8.3,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.43(\mathrm{~s}, 3 \mathrm{H}), 1.38-1.22(\mathrm{~m}, 1 \mathrm{H}), 0.84(\mathrm{~d}$, $J=5.8 \mathrm{~Hz}, 3 \mathrm{H}), 0.69(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(151 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 214.2,178.1,80.2,77.3,59.1,50.3$, $47.7,44.8,42.6,40.9,38.7,30.8,23.9,22.1,15.9,13.7$; IR (thin film) $v_{\text {max }}: 3467,2955,2874,1702$, $1101 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{O}_{5}[\mathrm{M}-\mathrm{H}]:$ 297.1702, found: 297.1654.


Silylated alcohol 204. Tertiary alcohol 203 ( $2.8 \mathrm{~g}, 9.4 \mathrm{mmol}, 1.0$ equiv) was dissolved in THF ( 50 mL ). Sodium hydride ( $60 \mathrm{wt} \%, 1.9 \mathrm{~g}, 47 \mathrm{mmol}, 5.0$ equiv) was added and the reaction was stirred at $23{ }^{\circ} \mathrm{C}$ for $30 \mathrm{~min} . \mathrm{TBSCl}$ ( $5.6 \mathrm{~g}, 38 \mathrm{mmol}, 4.0$ equiv) was then added and the reaction was stirred at 65 ${ }^{\circ} \mathrm{C}$ for $8 \mathrm{~h} . \mathrm{HCl}(3.0 \mathrm{M}, 50 \mathrm{~mL})$ was added carefully and the biphasic mixture was stirred vigorously at $65^{\circ} \mathrm{C}$ for an additional 16 h . The reaction was cooled to $23^{\circ} \mathrm{C}$ and diluted with DCM ( 50 mL ). The layers were separated and the aqueous layer was further extracted with DCM ( $2 \times 100 \mathrm{~mL}$ ). The combined organic layers were washed with brine ( 100 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography ( $5 \rightarrow 25 \%$ EtOAc in hexanes) to afford silylated alcohol 203 ( $3.4 \mathrm{~g}, 8.3 \mathrm{mmol}, 88 \%$ yield) as a viscous oil which often solidified upon standing. $[\alpha]_{\mathrm{D}}=-2.9\left(c 1.6, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR ( 500 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 9.37(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.45(\mathrm{~d}, J=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.26(\mathrm{~s}, 3 \mathrm{H}), 3.18(\mathrm{~d}, J=15.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.00(\mathrm{~d}$, $J=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.90-2.86(\mathrm{~m}, 1 \mathrm{H}), 2.43(\mathrm{~d}, J=15.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.26(\mathrm{~d}, J=14.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.14(\mathrm{~d}$, $J=14.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.99-1.82(\mathrm{~m}, 3 \mathrm{H}), 1.77(\mathrm{dt}, J=15.1,5.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.40(\mathrm{~s}, 3 \mathrm{H}), 1.36-1.29(\mathrm{~m}$, $1 \mathrm{H}), 0.87(\mathrm{~s}, 9 \mathrm{H}), 0.83(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.64(\mathrm{~s}, 3 \mathrm{H}), 0.16(\mathrm{~s}, 3 \mathrm{H}), 0.03(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 126 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 212.7,178.7,84.1,76.6,59.0,49.7,48.4,44.0,42.8,42.3,38.8,30.8,26.3,23.9$, $22.6,19.1,17.2,14.0,-2.5,-2.6$; IR (thin film) $v_{\max }: 3160,2952,2882,1721,1702,1471,1140$, $835 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{22} \mathrm{H}_{39} \mathrm{O}_{5} \mathrm{Si}[\mathrm{M}-\mathrm{H}]:: 411.2567$, found: 411.2522 .


Acid 233. The mixture of lactones 232 and epi-232 (1.4:1 d.r., 98 mg ) was dissolved in anhydrous THF ( 3.4 mL ) and cooled to $-78^{\circ} \mathrm{C}$. A solution of $[\mathrm{Li}]^{+}\left[\mathrm{C}_{10} \mathrm{H}_{8}\right]^{--}(1.35 \mathrm{M}, 0.75 \mathrm{~mL}, 1.0 \mathrm{mmol}$, ca. 3.0 equiv $)$ was added dropwise to the solution. After 10 minutes, $\mathrm{HCl}(0.1 \mathrm{M}, 10 \mathrm{~mL})$ and $\mathrm{Et}_{2} \mathrm{O}(10$ mL ) were added and the reaction mixture was warmed to room temperature. The layers were separated, and the aqueous layer was further extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 10 \mathrm{~mL})$. The combined organic layers were extracted with $\mathrm{NaOH}(2 \mathrm{M}, 2 \times 20 \mathrm{~mL})$. The aqueous layer was then acidified with $\mathrm{HCl}(c a .11 .5 \mathrm{M}, 10 \mathrm{~mL})$ and extracted with EtOAc ( $3 \times 20 \mathrm{~mL}$ ). The combined organic layers were washed with brine ( $1 \times 30 \mathrm{~mL}$ ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated in vacuo. The crude residue was purified by column chromatography ( $30 \rightarrow 80 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes) to afford acid 233 ( $74 \mathrm{mg}, 0.27 \mathrm{mmol}, 74 \%$ yield over two steps) as a white solid. $[\alpha]_{\mathrm{D}}=-73.0(c 2.0$, $\mathrm{CHCl}_{3}$ ); ${ }^{1} \mathrm{H}$ NMR ( $700 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 10.8(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.30(\mathrm{~s}, 3 \mathrm{H}), 3.04(\mathrm{~d}, J=9.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.96$ (d, $J=9.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.92(\mathrm{~d}, J=16.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.75(\mathrm{q}, J=6.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.69(\mathrm{dd}, J=9.0,3.8 \mathrm{~Hz}$, $1 \mathrm{H}), 2.32(\mathrm{~d}, J=16.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.27(\mathrm{~d}, J=14.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.18(\mathrm{~d}, J=14.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.90$ (dddd, $J$ $=14.2,10.4,9.0,3.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.84-1.76(\mathrm{~m}, 2 \mathrm{H}), 1.61-1.54(\mathrm{~m}, 1 \mathrm{H}), 1.40-1.29(\mathrm{~m}, 1 \mathrm{H}), 0.93$ (d, $J=6.7 \mathrm{~Hz}, 3 \mathrm{H}), 0.88(\mathrm{~d}, J=6.2 \mathrm{~Hz}, 3 \mathrm{H}), 0.58(\mathrm{~s}, 3 \mathrm{H})$; IR (thin film) $v_{\max }: 3204,2955,2875$, 1726, 1705, $1105 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{O}_{4}[\mathrm{M}-\mathrm{H}]^{-}: 281.1758$, found: 281.1753.


Hemiketal 190. Lactone 234 ( $10 \mathrm{mg}, 0.036 \mathrm{mmol}, 1.0$ equiv) and sodium iodide ( $27 \mathrm{mg}, 0.18 \mathrm{mmol}, 5.0$ equiv) were dissolved in $\mathrm{MeCN}(0.4 \mathrm{~m})$. TM$\mathrm{SCl}(45 \mu \mathrm{~L}, 0.36 \mathrm{mmol}, 10.0$ equiv) was added dropwise and the solution was heated at $80^{\circ} \mathrm{C}$ for 45 min . Upon cooling to room temperature, the reaction mixture was quenched with saturated $a q . \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}(5.0 \mathrm{~mL})$. The layers were separated, and the aqueous layer was extracted with EtOAc ( $3 \times 5.0 \mathrm{~mL}$ ). The combined organic layers were washed with brine ( $1 \times 10 \mathrm{~mL}$ ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated in vacuo. The crude residue was purified by preparative TLC $\left(100 \% \mathrm{Et}_{2} \mathrm{O}\right)$ to give hemiketal $190(4.4 \mathrm{mg}, 0.016,46 \%)$ as a colorless oil. Characterization data were in agreement with previously reported values. ${ }^{14}[\alpha]_{\mathrm{D}}=-18.7\left(c 0.31, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 3.85(\mathrm{~d}, J=$ $9.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.68(\mathrm{~d}, J=9.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.90(\mathrm{~d}, J=18.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.73(\mathrm{~d}, J=18.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.50$ $(\mathrm{s}, 1 \mathrm{H}), 2.23(\mathrm{~d}, J=13.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.06-2.02(\mathrm{~m}, 1 \mathrm{H}), 1.96-1.90(\mathrm{~m}, 1 \mathrm{H}), 1.89-1.82(\mathrm{~m}, 3 \mathrm{H})$, $1.76(\mathrm{~d}, J=13.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.36-1.29(\mathrm{~m}, 1 \mathrm{H}), 1.06(\mathrm{~s}, 3 \mathrm{H}), 1.05(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H}), 1.00(\mathrm{~d}, J=$ $7.0 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 176.9,106.7,100.9,71.3,50.8,50.6,49.9,49.0,43.7$, 38.4, 34.9, 32.1, 15.1, 14.4, 7.9; IR (thin film) $v_{\text {max }}: 3402,2937,2880,1746,1644,1265,1196$, 1015, $966 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{O}_{4}[\mathrm{M}-\mathrm{H}]: 265.1445$, found: 265.1442.

## Iron-catalyzed C-H activation reaction:

This procedure is adapted from the slow addition protocol developed by White and coworkers. ${ }^{15}$ Silylated alcohol 204 ( $50 \mathrm{mg}, 0.12 \mathrm{mmol}, 1.0$ equiv) was dissolved in $\mathrm{MeCN}(0.40 \mathrm{~mL}$ ) and $\mathrm{Tl}(\mathrm{OTf})(21 \mathrm{mg}, 0.060 \mathrm{mmol}, 0.50$ equiv) was added. TBHP ( $70 \%$ aqueous solution, $77 \mathrm{mg}, 0.60$ mmol, 5.0 equiv) and $\left[\mathrm{Fe}((R)-\mathrm{mepp})(\mathrm{MeCN})_{2}\right]\left[\left(\mathrm{SbF}_{6}\right)_{2}\right](64 \mathrm{mg}, 0.060 \mathrm{mmol}, 0.50$ equiv) were dissolved separately in $\mathrm{MeCN}(0.40 \mathrm{~mL}$ each) and taken up in syringes. The two solutions were added over the course of 1 h by syringe pumps to the solution of substrate. At the conclusion of reagent addition, the reaction was directly concentrated and then purified by column chromatography ( $10 \rightarrow 50 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes) to afford lactone 245 ( $10 \mathrm{mg}, 0.024 \mathrm{mmol}, 20 \%$ ), lactone 246 ( 5 $\mathrm{mg}, 0.013 \mathrm{mmol}, 11 \%)$, and lactone $247(2 \mathrm{mg}, 0.007 \mathrm{mmol}, 6 \%)$. Also isolated from the reaction was recovered 204 ( $9 \mathrm{mg}, 0.022 \mathrm{mmol}, 18 \%$ ).


Lactone 246. $[\alpha]_{\mathrm{D}}=-44.4\left(c 0.3, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \mathrm{NMR}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 3.87$ (d, $J=9.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.54(\mathrm{~d}, J=9.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.90(\mathrm{~d}, J=18.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.75$ $(\mathrm{d}, J=18.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.49(\mathrm{td}, J=13.1,6.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.36(\mathrm{~s}, 1 \mathrm{H}), 2.13(\mathrm{dp}, J$ $=13.5,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.06(\mathrm{~d}, J=13.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.96(\mathrm{~d}, J=13.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.87$ (dd, $J=13.1,5.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.73(\mathrm{dt}, J=12.5,6.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.40(\mathrm{~s}, 3 \mathrm{H}), 1.26-$ $1.16(\mathrm{~m}, 1 \mathrm{H}), 1.07(\mathrm{~s}, 3 \mathrm{H}), 0.99(\mathrm{~d}, J=7.0 \mathrm{~Hz}, 3 \mathrm{H}), 0.94(\mathrm{~s}, 9 \mathrm{H}), 0.23(\mathrm{~s}, 3 \mathrm{H})$, $0.18(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 177.1,105.3,101.9,82.0,71.4,50.8,48.2,48.1,46.6$, $38.7,35.8,32.0,26.7,19.1,18.0,15.2,12.7,-1.1,-1.2$; IR (thin film) $v_{\text {max }}: 3399,2956,2858,1769$, 1746, 1208, $834 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{21} \mathrm{H}_{36} \mathrm{O}_{5} \mathrm{SiNa}[\mathrm{M}+\mathrm{Na}]^{+}: 419.2229$, found: 419.2235.


Ethyl ester 248. Triethyloxonium hexafluorophosphate ( $370 \mathrm{mg}, 1.5 \mathrm{mmol}, 3.0$ equiv) and 1,8-bis(dimethylamino)naphthalene (Proton-Sponge ${ }^{\oplus}, 0.32 \mathrm{~g}, 1.5$ mmol, 3.0 equiv) were charged into a 100 mL round bottom flask containing lactone 245 ( $210 \mathrm{mg}, 0.50 \mathrm{mmol}, 1.0$ equiv). The reactants were then dissolved in 1,2-dichloroethane ( 21 mL ) at $23^{\circ} \mathrm{C}$. The orange solution was heated at 85 ${ }^{\circ} \mathrm{C}$ for 12 h . The reaction mixture was cooled to room temperature and $a q$. TFA
( $1: 1 \mathrm{v}: \mathrm{v}, 20 \mathrm{~mL}$ ) was added. The biphasic mixture was stirred vigorously for 45 min . Saturated aq . $\mathrm{NaHCO}_{3}(100 \mathrm{~mL})$ was carefully added, followed by DCM $(50 \mathrm{~mL})$. The layers were separated and the aqueous layer was extracted with DCM ( $2 \times 50 \mathrm{~mL}$ ). The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo. The crude residue was purified by column chromatography ( $10 \% \rightarrow 25 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes) to afford ethyl ester $248(140 \mathrm{mg}, 0.33 \mathrm{mmol}, 66 \%$ yield $)$ as a colorless oil. Recovered starting material ( $\mathbf{2 4 5}, 46 \mathrm{mg}, 0.11 \mathrm{mmol}, 22 \%$ ) could also be isolated from the reaction mixture. $[\alpha]_{\mathrm{D}}=-51.3\left(c 0.2, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \mathrm{NMR}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.76(\mathrm{~d}, J=$ $2.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.09-4.00(\mathrm{~m}, 2 \mathrm{H}), 3.16(\mathrm{~d}, J=9.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.15(\mathrm{~s}, 3 \mathrm{H}), 3.13(\mathrm{~d}, J=9.2 \mathrm{~Hz}, 1 \mathrm{H})$, $2.93(\mathrm{~d}, J=13.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.64(\mathrm{~d}, J=15.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.54(\mathrm{~d}, J=13.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.34-2.24(\mathrm{~m}, 2 \mathrm{H})$, $2.29(\mathrm{~d}, J=15.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.18-2.10(\mathrm{~m}, 1 \mathrm{H}), 1.28(\mathrm{~s}, 3 \mathrm{H}), 1.24(\mathrm{~s}, 3 \mathrm{H}), 1.23(\mathrm{t}, J=7.2 \mathrm{~Hz}, 3 \mathrm{H})$, $1.10(\mathrm{~d}, J=6.6 \mathrm{~Hz}, 3 \mathrm{H}), 0.85(\mathrm{~s}, 9 \mathrm{H}), 0.08(\mathrm{~s}, 3 \mathrm{H}),-0.05(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C} \mathrm{NMR}\left(151 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ $\delta 211.3,171.9,148.0,129.3,81.5,77.1,60.0,58.6,53.3,50.1,49.8,49.1,38.5,38.0,26.1,18.6$, $18.5,17.7,14.3,14.2,-1.6,-3.4$; IR (thin film) $v_{\max }$ : 2653, 2855, 1717, 1104, $833 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{24} \mathrm{H}_{42} \mathrm{O}_{5} \mathrm{SiNa}[\mathrm{M}+\mathrm{Na}]^{+}: 461.2699$, found: 461.2700 .

$\boldsymbol{\varepsilon}$-lactone SI-1. Ethyl ester 248 ( $34 \mathrm{mg}, 0.080 \mathrm{mmol}, 1.0$ equiv) and sodium iodide ( $56 \mathrm{mg}, 0.38 \mathrm{mmol}, 5.0$ equiv) were dissolved in $\mathrm{MeCN}(3.4 \mathrm{~mL})$. TMSCl $(0.10 \mathrm{~mL}, 0.77 \mathrm{mmol}, 10$ equiv) was added dropwise and the solution was heated at $80^{\circ} \mathrm{C}$ for 12 h . The orange solution was cooled to $23^{\circ} \mathrm{C}$ and diluted with EtO$\mathrm{Ac}(5.0 \mathrm{~mL})$ and saturated $a q . \mathrm{NaHCO}_{3} /$ saturated $a q . \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}(1: 1 \mathrm{v}: v, 5.0 \mathrm{~mL})$. The layers were separated and the aqueous layer was extracted with EtOAc (5.0 $\mathrm{mL})$. The combined organic layers were washed with brine ( 5.0 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The product, an off-white solid, was generally of sufficient purity to be used directly in the next step. An analytical sample of $\varepsilon$-lactone SI-1 could be isolated by preparative TLC (30\% EtOAc in hexanes), affording a white. Subjecting the doubly ethylated ester (249) to the same conditions also afforded SI-1 in comparable yield (70\%). $[\alpha]_{\mathrm{D}}=-27.4\left(c 0.5, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 5.66(\mathrm{t}, J=2.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.95(\mathrm{~d}, J=12.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.85(\mathrm{~d}, J=12.8$ $\mathrm{Hz}, 1 \mathrm{H}), 2.79(\mathrm{~d}, J=14.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.64-2.52(\mathrm{~m}, 4 \mathrm{H}), 2.33-2.24(\mathrm{~m}, 1 \mathrm{H}), 2.00(\mathrm{ddd}, J=16.2$, $9.8,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.36(\mathrm{~s}, 3 \mathrm{H}), 1.27(\mathrm{~s}, 3 \mathrm{H}), 1.09(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}), 0.83(\mathrm{~s}, 9 \mathrm{H}), 0.10(\mathrm{~s}, 3 \mathrm{H})$, $-0.06(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 207.4,173.1,148.9,125.1,80.2,74.2,49.4,49.3$, $49.2,47.4,39.8,38.8,25.8,18.5,17.1,16.6,15.4,-0.8,-3.8$. IR (thin film) $v_{\max }: 2953,2855,1741$, $1720,1128,833 \mathrm{~cm}^{-1} ;$ HRMS (ESI) calcd for $\mathrm{C}_{21} \mathrm{H}_{34} \mathrm{O}_{4} \mathrm{SiNa}[\mathrm{M}+\mathrm{Na}]^{+}: 401.2124$, found: 401.2079 .


Diol 255. $\varepsilon$-lactone $250\left(2.5 \mathrm{mg}, 0.0095 \mathrm{mmol}, 1.0\right.$ equiv) and $\mathrm{OsO}_{4}(3.6 \mathrm{mg}$, $0.014 \mathrm{mmol}, 1.5$ equiv) were dissolved in pyridine ( $300 \mu \mathrm{~L}$ ) and stirred at room temperature for 12 h . The dark brown solution was concentrated in vac$u o$ and the crude residue was resuspended in $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(3: 1 v: v, 300 \mu \mathrm{~L})$. Sodium bisulfite ( 20 mg ) was added and the solution was heated at $60^{\circ} \mathrm{C}$ for 4 h . The pink solution was cooled to $23{ }^{\circ} \mathrm{C}$ and $\mathrm{EtOAc}(5.0 \mathrm{~mL})$ and $\mathrm{H}_{2} \mathrm{O}$ $(5.0 \mathrm{~mL})$ were added. The layers were separated and the aqueous layer was further extracted with EtOAc ( $2 \times 5.0 \mathrm{~mL}$ ). The combined organic layers were washed with brine ( 10 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo to afford diol 255 ( $1.8 \mathrm{mg}, 0.0054 \mathrm{mmol}, 63 \%$ ), a white foam, as a single diastereomer (> 15:1 d.r.). $[\alpha]_{\mathrm{D}}=-49.2\left(c 0.1 . \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \mathrm{NMR}(900 \mathrm{MHz}$, $\left.\mathrm{CD}_{3} \mathrm{OD}\right) \delta 4.81(\mathrm{dd}, J=11.3,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.80(\mathrm{~d}, J=9.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.51(\mathrm{~d}, J=9.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.84$ (d, $J=19.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.77(\mathrm{~d}, J=19.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.10(\mathrm{dt}, J=13.4,6.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.07(\mathrm{~d}, J=13.4$
$\mathrm{Hz}, 1 \mathrm{H}), 1.97-1.95(\mathrm{~m}, 1 \mathrm{H}), 1.94(\mathrm{~d}, J=13.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.28(\mathrm{~s}, 3 \mathrm{H}), 1.20-1.16(\mathrm{~m}, 1 \mathrm{H}), 1.17$ $(\mathrm{s}, 3 \mathrm{H}), 0.96(\mathrm{~d}, J=7.0 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $\left.226 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 179.3,106.8,99.4,79.2,76.6$, $72.4,51.5,49.4,49.3,42.1,41.1,39.8,17.9,14.1,13.2$; IR (thin film) $v_{\max }: 3415,3368,2955,1754$, 1633, $1557 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{O}_{6} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 321.1314$, found: 321.1319.

## SI2.3 Preparation and Characterization Data for Natural Products, with Tabulated Comparisons to Reported Isolation Data

## SI2.3.1 (-)-3-Deoxypseudoanisatin (251)

## SI2.3.1.1 Preparation and Characterization Data for 215



A stock solution of $\mathrm{Co}(\mathrm{acac})_{2}(0.1 \mathrm{mg}, 0.0005 \mathrm{mmol}, 0.1$ equiv) in THF ( 0.3 $\mathrm{mL})$ was added to neat alkene $250\left(1.3 \mathrm{mg}, 0.005 \mathrm{mmol}, 1.0\right.$ equiv) at $0{ }^{\circ} \mathrm{C}$. $\mathrm{PhSiH}_{3}\left(2.4 \mu \mathrm{~L}, 0.02 \mathrm{mmol}, 4.0\right.$ equiv) was added and dry $\mathrm{O}_{2}$ gas was sparged through the mixture for 1 min . The solution was kept under a positive pressure of oxygen and was stirred vigorously for 24 h at $0^{\circ} \mathrm{C}$. Saturated aq. $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}$ $(1.0 \mathrm{~mL})$ and EtOAc $(1 \mathrm{~mL})$ were added, the layers were separated, and the aqueous layer was further extracted with $\operatorname{EtOAc}(3 \times 1.0 \mathrm{~mL})$. The combined organic layers were washed with brine ( $1 \times 5.0 \mathrm{~mL}$ ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated in vacuo. The crude residue was purified by preparative TLC ( $100 \% \mathrm{EtOAc}$ ) to afford lactone $247(0.7 \mathrm{mg}, 0.0025 \mathrm{mmol}, 50 \%$ yield) and (-)-3-deoxypseudoanisatin ( $\mathbf{2 5 1}, 0.4 \mathrm{mg}, 0.0015 \mathrm{mmol}, 29 \%$ yield), both of which were colorless oils. Characterization data were in agreement with previously reported values. ${ }^{16}[\alpha]_{\mathrm{D}}=$ -23.1 ( c 0.13, MeOH); ${ }^{1} \mathrm{H}$ NMR ( $\left.900 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 4.45(\mathrm{~d}, J=13.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.94(\mathrm{~d}, J=13.9$ $\mathrm{Hz}, 1 \mathrm{H}), 3.00(\mathrm{dd}, J=15.9,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.66(\mathrm{dd}, J=15.2,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.57(\mathrm{ddq}, J=9.8,9.5$, 7.1 Hz, 1H), 2.42 (d, $J=15.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.32(\mathrm{~d}, J=15.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.26$ (ddd, $J=14.2,11.7,5.5$ $\mathrm{Hz}, 1 \mathrm{H}), 2.08(\mathrm{dtd}, J=13.8,9.5,5.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.71(\mathrm{ddd}, J=14.2,9.5,3.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.34$ (dddd, $J$ $=13.8,11.7,9.8,3.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.31(\mathrm{~s}, 3 \mathrm{H}), 1.15(\mathrm{~s}, 3 \mathrm{H}), 0.93(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 900 $\left.\mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 208.4,176.5,88.4,79.3,71.1,50.5,47.9,43.4,41.7,36.6,30.5,28.9,17.9,14.3$, 14.0; IR (thin film) $v_{\max }: 3383,2955,1732,1466,1432,1379,1309,1160,1102,1063,918 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{O}_{5} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 305.1359$, found: 305.1355.

## SI2.3.1.2 (-)-3-Deoxypseudoanisatin ${ }^{1} H$ Spectra Comparison:


(-)-3-deoxypseudoanisatin
$\left.\begin{array}{|c|c|c|}\hline \text { Position } & \begin{array}{c}{ }^{1} \mathrm{H} \text { NMR ( } \delta \text { ) } \\ \text { Natural Sample } \\ \left(400 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right)^{16}\end{array} & \begin{array}{c}\left.{ }^{1} \mathrm{H} \text { NMR ( } \delta\right) \\ \text { Synthetic Sample } \\ (900 \mathrm{MHz}, \mathrm{CD}, \mathrm{OD})\end{array} \\ \hline \mathbf{1} & 2.55(\mathrm{qdd}, J=7.0,3.5,1.0 \mathrm{~Hz}, 1 \mathrm{H}) & 2.57(\mathrm{ddq}, J=9.8,9.5,7.1 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \mathbf{2 \beta} & \begin{array}{c}1.35(\mathrm{dddd}, J=12.0,9.5, \\ 5.5,1.0 \mathrm{~Hz}, 1 \mathrm{H})\end{array} & \begin{array}{c}1.34(\mathrm{dddd}, J=13.8,11.7, \\ 9.8,3.8 \mathrm{~Hz}, 1 \mathrm{H})\end{array} \\ \hline \mathbf{2 \alpha} & 2.07(\mathrm{dddd}, J=12.0,11.8, & 2.08(\mathrm{dtd}, J=13.8,9.5, \\ 5.5 \mathrm{~Hz}, 1 \mathrm{H})\end{array}\right]$
*The chemical shift of proton $3 \alpha$ appears to have been tabulated incorrectly in the original publication. Direct spectral comparison with a spectrum of natural (-)-3-deoxypseudoanisatin kindly provided by Prof. Y. Fukuyama indicates the chemical shift is very close to $\delta=2.26 \mathrm{ppm}$, in agreement with the synthetic sample's value.

## SI2.3.1.3 (-)-3-Deoxypseudoanisatin ${ }^{13} \mathrm{C}$ Spectra Comparison:


(-)-3-deoxypseudoanisatin

| Position | ${ }^{13} \mathrm{C} \mathrm{NMR} \mathrm{( } \mathrm{\delta)}$ <br> Natural Sample <br> $\left(101 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right)^{16}$ | ${ }^{13} \mathrm{C} \mathrm{NMR}(\delta)$ <br> Synthetic Sample <br> $\left(226 \mathrm{MHz}, \mathrm{CD}{ }_{3} \mathrm{OD}\right)$ |
| :---: | :---: | :---: |
| $\mathbf{1}$ | 41.6 | 41.7 |
| $\mathbf{2}$ | 28.7 | 28.9 |
| $\mathbf{3}$ | 30.3 | 30.5 |
| $\mathbf{4}$ | 88.2 | 88.4 |
| $\mathbf{5}^{*}$ | 48.5 | 47.9 |
| $\mathbf{6}$ | 79.2 | 79.3 |
| $\mathbf{7}$ | 208.2 | 208.4 |
| $\mathbf{8}$ | 36.4 | 36.6 |
| $\mathbf{9}$ | 50.1 | 50.5 |
| $\mathbf{1 0}$ | 43.2 | 43.4 |
| $\mathbf{1 1}$ | 176.4 | 176.5 |
| $\mathbf{1 2}$ | 17.7 | 17.9 |
| $\mathbf{1 3}$ | 14.2 | 14.3 |
| $\mathbf{1 4}$ | 70.9 | 71.1 |
| $\mathbf{1 5}$ | 13.9 | 14.0 |

*The somewhat large discrepancy of these values can most likely be attributed to interference by the $\mathrm{CD}_{3} \mathrm{OD}$ solvent peak; see the direct spectral comparison in Section SI2.6 for further detail.

## SI2.3.2 (+)-Pseudoanisatin (11) \& Cyclopseudoanisatin (15)

## SI2.3.2.1 Preparation and Characterization Data for 11 \& 15



To a solution of crude triol $257(7.7 \mathrm{mg}, 0.026 \mathrm{mmol}, 1.0$ equiv) in DCM $(0.30 \mathrm{~mL})$ at $23{ }^{\circ} \mathrm{C}$ was added pyridine ( $21 \mu \mathrm{~L}, 0.26 \mathrm{mmol}, 10$ equiv) and $\mathrm{MsCl}(20 \mu \mathrm{~L}, 0.26 \mathrm{mmol}, 10$ equiv). The solution was stirred for 12 h , then $\mathrm{NaOH}(2.0 \mathrm{M}, 300 \mu \mathrm{~L})$ was added and the solution subsequently stirred for $2 \mathrm{~h} . \mathrm{HCl}(2.0 \mathrm{M}, 5.0 \mathrm{~mL})$ and $\mathrm{EtOAc}(5.0 \mathrm{~mL})$ were added and the layers were separated. The aqueous layer was further extracted with $\mathrm{EtOAc}(2 \times 5.0$ $\mathrm{mL})$. The combined organic layers were washed with brine ( 10 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude residue was purified by preparative TLC $(10 \% \mathrm{MeOH}$ in DCM) to afford pseudoanisatin ( $5.5 \mathrm{mg}, 0.018 \mathrm{mmol}, 80 \%$ over two steps) as a white solid (mp $=200^{\circ} \mathrm{C}$, decomp.). NMR samples for this compound were referenced to an internal standard of tetramethylsilane ( $\delta=0.00$ ). Pseudoanisatin is afforded as $\sim 5: 1$ isomeric mixture of the depicted structure and its hemiketal (15). NMR resonances corresponding to the hemiketal are marked with an asterisk. Data for both $\mathbf{1 1}$ and $\mathbf{1 5}$ were in agreement with the reported values. ${ }^{17,18,19}[\alpha]_{\mathrm{D}}=+5.5$ (c 0.5, MeOH); ${ }^{1} \mathrm{H}$ NMR ( $900 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}$ ) $\delta 8.81(\mathrm{~s}, 1 \mathrm{H}), 7.55(\mathrm{~d}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.50(\mathrm{~s}, 1 \mathrm{H})$, $6.99^{*}(\mathrm{~d}, J=4.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.06(\mathrm{~d}, J=13.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.19^{*}(\mathrm{~d}, J=13.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.80(\mathrm{ddd}, J=7.7$, $4.7,2.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.74^{*}(\mathrm{ddd}, J=7.1,4.2,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.22^{*}(\mathrm{~d}, J=13.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.99(\mathrm{~d}, J=13.4$ $\mathrm{Hz}, 1 \mathrm{H}), 3.90(\mathrm{dd}, J=14.8,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.56^{*}(\mathrm{~d}, J=14.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.26(\mathrm{dd}, \mathrm{J}=16.1,2.0 \mathrm{~Hz}, 1 \mathrm{H})$, $2.89^{*}(\mathrm{~d}, J=14.4 \mathrm{~Hz}, 1 \mathrm{H}) 2.83(\mathrm{~d}, \mathrm{~J}=16.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.77(\mathrm{~d}, \mathrm{~J}=14.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.75-2.70(\mathrm{~m}, 2 \mathrm{H}$, overlaps with 1 H from ketal), $2.67-2.60^{*}(\mathrm{~m}, 1 \mathrm{H}), 2.30^{*}(\mathrm{~d}, J=13.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.17^{*}(\mathrm{~d}, J=13.5$ $\mathrm{Hz}, 1 \mathrm{H}), 1.79^{*}(\mathrm{~s}, 3 \mathrm{H}), 1.77(\mathrm{~s}, 3 \mathrm{H}), 1.66^{*}(\mathrm{~s}, 3 \mathrm{H}), 1.65(\mathrm{~s}, 3 \mathrm{H}), 1.61^{*}$ (ddd, $J=13.7,10.7,3.1 \mathrm{~Hz}$, 1H) $1.50(\mathrm{ddd}, \mathrm{J}=12.6,9.6,2.8 \mathrm{~Hz}, 1 \mathrm{H}), 0.89(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}, 3 \mathrm{H}), 0.88^{*}(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (226 MHz, C $5_{5} \mathrm{D}$ ) $\delta$ 206.8, 174.6*, 174.4, 110.7*, 92.1*, 84.7, 80.2*, 79.4, 78.3, 73.1*, 71.6*, 69.6, 52.3*, 52.0*, 48.9, 47.8, 44.4*, 44.3*, 43.9, 43.2, 40.3, 39.8*, 35.3, 33.8*, 19.0*, $18.5,16.9^{*}, 14.2^{*}, 14.0,13.9$; IR (thin film) $v_{\max }: 3366,2953,2851,1716,1651,1634,1020 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{O}_{6} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 321.1314$, found: 321.1283.

## SI2.3.2.2 (+)-Pseudoanisatin ${ }^{1} H$ Spectra Comparison:


(+)-pseudoanisatin

| Position | $\begin{gathered} { }^{1} \mathrm{H} \text { NMR }(\delta) \\ \text { Natural Sample } \\ \left(360 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)^{17} \\ \hline \end{gathered}$ | $\begin{gathered} { }^{1} \mathrm{H} \text { NMR }(\delta) \\ \text { Natural Sample } \\ \left(500 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)^{18} \\ \hline \end{gathered}$ | $\begin{gathered} { }^{1} \mathrm{H} \text { NMR }(\delta) \\ \text { Synthetic Sample } \\ \left(900 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right) \\ \hline \end{gathered}$ |
| :---: | :---: | :---: | :---: |
| 1 | 2.80-2.55 (m, 2H) | 2.65 (m, 1H) | 2.75-2.70 (m, 2H) |
| 2 | $\begin{aligned} & 2.80-2.55(\mathrm{~m}, 2 \mathrm{H}) \\ & 1.55-1.43(\mathrm{~m}, 1 \mathrm{H}) \end{aligned}$ | $\begin{gathered} \hline 2.75(\mathrm{~m}, 1 \mathrm{H}) \\ 1.51(\mathrm{ddd}, J=13.7, \\ 10.1,2.8 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ | $\begin{gathered} \hline 2.75-2.70(\mathrm{~m}, 2 \mathrm{H}) \\ 1.50(\mathrm{ddd}, J=12.6, \\ 9.6,2.8 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ |
| 3 | 4.80-4.75 (m, 1H) | $\begin{gathered} \hline 4.81(\mathrm{dd}, J=7.7, \\ 2.8 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ | $\begin{gathered} 4.80(\mathrm{ddd}, J=7.7, \\ 4.7,2.8 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ |
| 4 | - | - | - |
| 5 | - | - | - |
| 6 | - | - | - |
| 7 | - | - | - |
| 8 | $\begin{gathered} \hline 3.24(\mathrm{dd}, J=16, \\ 2.5 \mathrm{~Hz}, 1 \mathrm{H}) \\ 2.74(\mathrm{~d}, J=15 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ | $\begin{gathered} \hline 3.20(\mathrm{dd}, J=16.1, \\ 1.6 \mathrm{~Hz}, 1 \mathrm{H}) \\ 2.76(\mathrm{~d}, J=16.1 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ | $\begin{gathered} \hline 3.26(\mathrm{dd}, J=16.1, \\ 2.0 \mathrm{~Hz}, 1 \mathrm{H}) \\ 2.83(\mathrm{~d}, J=16.1 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ |
| 9 | - | - | - |
| 10 | $\begin{gathered} \hline 3.88(\mathrm{dd}, J=15, \\ 2.5 \mathrm{~Hz}, 1 \mathrm{H}) \\ 2.74(\mathrm{~d}, J=15 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ | $\begin{gathered} \hline 3.84(\mathrm{dd}, J=14.8, \\ 1.6 \mathrm{~Hz}, 1 \mathrm{H}) \\ 2.72(\mathrm{~d}, J=14.8 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ | $\begin{gathered} \hline 3.90(\mathrm{dd}, J=14.8, \\ 2.0 \mathrm{~Hz}, 1 \mathrm{H}) \\ 2.77(\mathrm{~d}, J=14.8 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ |
| 11 | - | - | - |
| 12 | 1.74 (s, 3H) | 1.73 (s, 3H) | 1.77 (s, 3H) |
| 13 | 1.63 (s, 3H) | 1.63 (s, 3H) | 1.65 (s, 3H) |
| 14 | $\begin{aligned} & 6.03(\mathrm{~d}, J=14 \mathrm{~Hz}, 1 \mathrm{H}) \\ & 3.96(\mathrm{~d}, J=14 \mathrm{~Hz}, 1 \mathrm{H}) \\ & \hline \end{aligned}$ | $\begin{aligned} & 5.99(\mathrm{~d}, J=13.2 \mathrm{~Hz}, 1 \mathrm{H}) \\ & 3.96(\mathrm{~d}, J=13.2 \mathrm{~Hz}, 1 \mathrm{H}) \\ & \hline \end{aligned}$ | $\begin{aligned} & \hline 6.06(\mathrm{~d}, J=13.4 \mathrm{~Hz}, 1 \mathrm{H}) \\ & 3.99(\mathrm{~d}, J=13.4 \mathrm{~Hz}, 1 \mathrm{H}) \\ & \hline \end{aligned}$ |
| 15 | 0.88 (d, $J=7 \mathrm{~Hz}, 3 \mathrm{H})$ | 0.88 (d, $J=7.6 \mathrm{~Hz}, 3 \mathrm{H})$ | 0.89 (d, $J=6.8 \mathrm{~Hz}, 3 \mathrm{H})$ |
| 4-OH/ | - | - | 8.81 (s, 1H) |
| 6-OH | - | - | 7.50 (s, 1H) |
| 3-OH | - | - | 7.55 (d, $J=4.7 \mathrm{~Hz}, 1 \mathrm{H})$ |

## SI2.3.2.3 (+)-Pseudoanisatin ${ }^{13}$ C Spectra Comparison:


(+)-pseudoanisatin

| Position | ${ }^{13} \mathrm{C} \mathrm{NMR} \mathrm{( } \mathrm{\delta)}$ <br> Natural Sample <br> $\left(90 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)^{17}$ | ${ }^{13} \mathrm{C}$ NMR ( $\left.\delta\right)$ <br> Synthetic Sample <br> $\left(226 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)$ |
| :---: | :---: | :---: |
| $\mathbf{1}$ | 40.2 | 40.3 |
| $\mathbf{2}$ | 43.8 | 43.9 |
| $\mathbf{3}$ | 78.2 | 78.3 |
| $\mathbf{4}$ | 84.7 | 84.7 |
| $\mathbf{5}$ | 48.8 | 48.9 |
| $\mathbf{6}$ | 79.3 | 79.4 |
| $\mathbf{7}$ | 206.5 | 206.8 |
| $\mathbf{8}$ | 43.1 | 43.2 |
| $\mathbf{9}$ | 47.7 | 47.8 |
| $\mathbf{1 0}$ | 35.2 | 35.3 |
| $\mathbf{1 1}$ | 174.3 | 174.4 |
| $\mathbf{1 2}$ | 18.4 | 18.5 |
| $\mathbf{1 3}$ | 13.8 | 13.9 |
| $\mathbf{1 4}$ | 69.6 | 69.6 |
| $\mathbf{1 5}$ | 13.9 | 13.9 |

## SI2.3.2.3 Cyclopseudoanisatin ${ }^{1} \mathbf{H}$ Spectra Comparison:


cyclopseudoanisatin

| Position | $\begin{gathered} \hline{ }^{1} \mathrm{H} \text { NMR }(\delta) \\ \text { Natural Sample } \\ \left(400 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}+\right. \\ \left.5 \% \mathrm{D}_{2} \mathrm{O}\right)^{19} \\ \hline \end{gathered}$ | ${ }^{1} \mathrm{H}$ NMR ( $\delta$ ) Synthetic Sample ( $900 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}$ ) |
| :---: | :---: | :---: |
| 1 | $2.65(\mathrm{~m}, 1 \mathrm{H})^{a}$ | 2.75-2.70 (m, 2H) ${ }^{\text {a }}$ |
| 2 | $\begin{aligned} & 2.75(\mathrm{~m}, 1 \mathrm{H})^{a} \\ & 1.62(\mathrm{~m}, 1 \mathrm{H})^{a} \end{aligned}$ | $\begin{gathered} \hline 2.75-2.70(\mathrm{~m}, 2 \mathrm{H})^{a} \\ 1.61(\mathrm{ddd}, 13.7,10.7,3.1 \\ \mathrm{Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ |
| 3 | $\begin{gathered} 4.71(\mathrm{dd}, J=7.0, \\ 3.0 \mathrm{~Hz}, 1 \mathrm{H}) \end{gathered}$ | $\begin{gathered} \hline 4.74(\mathrm{ddd}, J=7.1, \\ 4.2,3.1 \mathrm{~Hz}, 1 \mathrm{H}) \end{gathered}$ |
| 4 | - | - |
| 5 | - | - |
| 6 | - | - |
| 7 | - | - |
| 8 | $\begin{gathered} 2.22(\mathrm{dd}, J=14.0 \mathrm{~Hz}, 1 \mathrm{H}) \\ 2.12(\mathrm{~d}, J=14.0 \mathrm{~Hz}, 1 \mathrm{H}) \end{gathered}$ | $\begin{aligned} & 2.30(\mathrm{~d}, J=13.5 \mathrm{~Hz}, 1 \mathrm{H}) \\ & 2.17(\mathrm{~d}, J=13.5 \mathrm{~Hz}, 1 \mathrm{H}) \end{aligned}$ |
| 9 | - | - |
| 10 | $\begin{aligned} & 3.51(\mathrm{~d}, J=15.0 \mathrm{~Hz}, 1 \mathrm{H}) \\ & 2.85(\mathrm{~d}, J=15.0 \mathrm{~Hz}, 1 \mathrm{H}) \end{aligned}$ | $\begin{aligned} & 3.56(\mathrm{~d}, J=14.4 \mathrm{~Hz}, 1 \mathrm{H}) \\ & 2.89(\mathrm{~d}, J=14.4 \mathrm{~Hz}, 1 \mathrm{H}) \end{aligned}$ |
| 11 | - | - |
| 12 | 1.74 (s, 3H) | 1.79 (s, 3H) |
| 13 | 1.61 (s, 3H) | 1.66 (s, 3H) |
| 14 | $\begin{aligned} & 5.12(\mathrm{~d}, J=13.0 \mathrm{~Hz}, 1 \mathrm{H}) \\ & 4.17(\mathrm{~d}, J=13.0 \mathrm{~Hz}, 1 \mathrm{H}) \end{aligned}$ | $\begin{aligned} & 5.19(\mathrm{~d}, J=13.7 \mathrm{~Hz}, 1 \mathrm{H}) \\ & 4.22(\mathrm{~d}, J=13.7 \mathrm{~Hz}, 1 \mathrm{H}) \\ & \hline \end{aligned}$ |
| 15 | $0.88(\mathrm{~m}, 3 \mathrm{H})^{a}$ | 0.89 (d, $J=6.8 \mathrm{~Hz}, 3 \mathrm{H})$ |

## SI2.3.2.4 Cyclopseudoanisatin ${ }^{13}$ C Spectra Comparison:


cyclopseudoanisatin

| Position | ${ }^{13} \mathrm{C}$ NMR $(\delta)$ <br> Natural Sample <br> $\left(100 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)^{17}$ | ${ }^{13} \mathrm{C}$ NMR ( $\delta$ ) <br> Synthetic Sample <br> $\left(226 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)$ |
| :---: | :---: | :---: |
| $\mathbf{1}$ | 44.2 | 44.3 |
| $\mathbf{2}$ | 44.4 | 44.4 |
| $\mathbf{3}$ | 73.0 | 73.1 |
| $\mathbf{4}$ | 91.9 | 92.1 |
| $\mathbf{5}$ | 51.7 | 52.0 |
| $\mathbf{6}$ | 79.8 | 80.2 |
| $\mathbf{7}$ | 109.5 | 110.7 |
| $\mathbf{8}$ | 39.7 | 39.8 |
| $\mathbf{9}$ | 52.6 | 52.3 |
| $\mathbf{1 0}$ | 33.7 | 33.8 |
| $\mathbf{1 1}$ | $c a .175^{*}$ | 174.6 |
| $\mathbf{1 2}$ | 18.9 | 19.0 |
| $\mathbf{1 3}$ | 16.8 | 16.9 |
| $\mathbf{1 4}$ | 71.5 | 71.6 |
| $\mathbf{1 5}$ | 14.1 | 14.2 |

*Tentative assignment due to poor signal-to-noise ratio

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## SI2.5 X-Ray Crystallographic Data

## SI2.5.1 X-Ray Crystallographic Data for Tertiary Alcohol 203



A colorless prism $0.050 \times 0.040 \times 0.040 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using $\varphi$ and $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $100.0 \%$ complete to $67.000^{\circ}$ in q. A total of 60372 reflections were collected covering the indices, $-7<=h<=7,-16<=k<=16,-22<=k<=22.2783$ reflections were found to be symmetry independent, with an $\mathrm{R}_{\text {int }}$ of 0.0319 . Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $\mathrm{P} 2_{2} 2_{1} 2_{1}$ (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Absolute stereochemistry was unambiguously determined to be $R$ at all chiral centers.

Table SI2.5.1.1. Crystal data and structure refinement for compound 203.

| Identification code | 203 |
| :---: | :---: |
| Empirical formula | $\mathrm{C}_{16} \mathrm{H}_{26} \mathrm{O}_{5}$ |
| Formula weight | 298.37 |
| Temperature/K | 100(2) |
| Crystal system | orthorhombic |
| Space group | P2, 2, 21 |
| a ( $\AA$ ) | 6.1706(5) |
| b ( $\AA$ ) | 13.4053(10) |
| $\mathrm{c}(\AA)$ | 18.2977(13) |
| $\alpha{ }^{\circ}{ }^{\circ}$ | 90 |
| $\beta\left({ }^{\circ}\right)$ | 90 |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume ( $\AA^{3}$ ) | 1513.6(2) |
| Z | 4 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.309 |
| $\mu\left(\mathrm{mm}^{1}\right)$ | 0.786 |
| F (000) | 648.0 |
| Crystal size ( $\mathrm{mm}^{3}$ ) | $0.050 \times 0.040 \times 0.040$ |
| Radiation | $\mathrm{CuK} \alpha(\lambda=1.54178)$ |
| $2 \Theta$ range for data collection ( ${ }^{\circ}$ ) | 8.176 to 136.828 |
| Index ranges | $-7 \leq \mathrm{h} \leq 7,-16 \leq \mathrm{k} \leq 16,-22 \leq 1 \leq 22$ |
| Reflections collected | 60372 |
| Independent reflections | $2783\left[\mathrm{R}_{\mathrm{int}}=0.0319, \mathrm{R}_{\text {sigm }}=0.0099\right]$ |
| Data/restraints/parameters | 2783/0/196 |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.063 |
| Final R indexes [ $\mathrm{I}>=2 \sigma$ ( I ] | $\mathrm{R}_{1}=0.0255, \mathrm{wR}_{2}=0.0671$ |
| Final R indexes [all data] | $\mathrm{R}_{1}=0.0256, \mathrm{wR}_{2}=0.0672$ |
| Largest diff. peak/hole (e $\AA^{-3}$ ) | 0.18/-0.17 |
| Flack parameter | 0.00(2) |

Table SI2.5.1.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 203. Ueq is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| C1 | $2181(2)$ | $5995.1(11)$ | $3305.7(8)$ | $13.3(3)$ |
| C2 | $3538(3)$ | $6822.9(11)$ | $3682.1(8)$ | $16.2(3)$ |
| C3 | $2216(3)$ | $7782.4(12)$ | $3541.6(8)$ | $18.6(3)$ |
| C4 | $805(3)$ | $7580.3(11)$ | $2855.5(8)$ | $16.0(3)$ |
| C5 | $1390(2)$ | $6518.1(11)$ | $2588.5(8)$ | $13.1(3)$ |
| C6 | $2996(2)$ | $6529.6(11)$ | $1929.7(7)$ | $13.1(3)$ |
| C7 | $3907(2)$ | $5453.7(11)$ | $1794.9(8)$ | $13.5(3)$ |
| C8 | $4938(3)$ | $5102.6(10)$ | $2507.3(8)$ | $14.3(3)$ |
| C9 | $3488(3)$ | $5030.7(11)$ | $3161.9(8)$ | $16.3(3)$ |
| C10 | $129(2)$ | $5751.0(12)$ | $3757.8(8)$ | $15.6(3)$ |
| C11 | $423(3)$ | $5183.0(11)$ | $4467.2(8)$ | $16.6(3)$ |
| C12 | $4123(3)$ | $6675.5(13)$ | $4486.2(8)$ | $20.5(3)$ |
| C13 | $4954(3)$ | $7241.3(11)$ | $2016.5(8)$ | $16.1(3)$ |
| C14 | $1854(3)$ | $6915.9(11)$ | $1237.5(8)$ | $15.5(3)$ |
| C15 | $-1022(3)$ | $6817.0(13)$ | $421.8(8)$ | $20.6(4)$ |
| C16 | $2226(3)$ | $4690.3(11)$ | $1537.0(8)$ | $16.2(3)$ |
| O1 | $1520(2)$ | $4446.2(9)$ | $4544.2(6)$ | $27.8(3)$ |
| O2 | $-771.6(19)$ | $5568.6(9)$ | $5003.2(6)$ | $21.2(3)$ |
| O3 | $-234.7(18)$ | $6495.6(8)$ | $1118.4(6)$ | $17.3(2)$ |
| O4 | $5542.7(17)$ | $5481.1(8)$ | $1243.1(5)$ | $15.5(2)$ |
| O5 | $6857.0(18)$ | $4891.5(8)$ | $2522.6(6)$ | $17.9(2)$ |

Table SI2.5.1.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 203. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h 2 a^{*} 2 \mathrm{U}_{11}+2 \mathrm{hka} * \mathrm{~b}^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | $13.4(7)$ | $14.8(7)$ | $11.8(6)$ | $0.2(5)$ | $0.2(6)$ | $0.8(6)$ |
| C2 | $14.4(7)$ | $19.4(7)$ | $14.8(7)$ | $-0.4(6)$ | $-0.1(6)$ | $-1.8(6)$ |
| C3 | $22.0(8)$ | $15.9(7)$ | $17.9(7)$ | $-2.4(6)$ | $-0.2(6)$ | $-0.4(6)$ |
| C4 | $16.7(7)$ | $15.1(7)$ | $16.1(7)$ | $0.1(6)$ | $1.3(6)$ | $3.5(6)$ |
| C5 | $12.7(7)$ | $14.4(7)$ | $12.2(7)$ | $1.0(6)$ | $0.2(5)$ | $-0.3(6)$ |
| C6 | $12.8(7)$ | $13.6(7)$ | $13.0(7)$ | $0.6(5)$ | $0.6(6)$ | $-0.4(6)$ |
| C7 | $12.6(7)$ | $15.7(7)$ | $12.3(6)$ | $-2.1(6)$ | $1.5(6)$ | $-0.4(6)$ |
| C8 | $16.2(7)$ | $10.3(6)$ | $16.5(7)$ | $-2.8(5)$ | $-0.5(6)$ | $-0.2(5)$ |
| C9 | $19.3(7)$ | $16.3(7)$ | $13.4(7)$ | $1.3(6)$ | $-0.1(6)$ | $2.9(6)$ |
| C10 | $13.9(7)$ | $19.9(8)$ | $13.0(7)$ | $1.2(6)$ | $0.0(6)$ | $-0.3(6)$ |
| C11 | $15.7(7)$ | $18.3(7)$ | $15.7(7)$ | $0.5(6)$ | $1.4(6)$ | $-2.7(6)$ |
| C12 | $20.0(8)$ | $26.4(8)$ | $15.2(7)$ | $-2.2(6)$ | $-4.1(6)$ | $-1.8(6)$ |
| C13 | $15.7(7)$ | $15.7(7)$ | $16.7(7)$ | $0.0(6)$ | $2.2(6)$ | $-2.6(6)$ |
| C14 | $15.6(7)$ | $16.6(7)$ | $14.4(7)$ | $2.8(6)$ | $1.8(6)$ | $-1.2(6)$ |
| C15 | $19.4(8)$ | $26.9(8)$ | $15.5(7)$ | $6.4(6)$ | $-3.8(6)$ | $-1.1(7)$ |
| C16 | $16.1(7)$ | $14.9(7)$ | $17.6(7)$ | $-1.1(6)$ | $-0.2(6)$ | $-1.3(6)$ |
| O1 | $37.0(7)$ | $24.8(6)$ | $21.5(6)$ | $7.3(5)$ | $7.4(5)$ | $10.5(6)$ |
| O2 | $24.2(6)$ | $26.0(6)$ | $13.3(5)$ | $5.1(4)$ | $3.0(5)$ | $5.6(5)$ |
| O3 | $14.2(5)$ | $23.5(6)$ | $14.1(5)$ | $5.6(4)$ | $-1.4(4)$ | $-0.9(5)$ |
| O4 | $12.1(5)$ | $21.3(5)$ | $13.2(5)$ | $-2.2(4)$ | $1.2(4)$ | $-0.4(4)$ |
| O5 | $15.2(6)$ | $19.5(5)$ | $19.0(5)$ | $-2.3(4)$ | $-1.5(5)$ | $1.4(4)$ |

Table SI2.5.1.4. Bond Lengths for 203.

| Atom | Atom | Length $(\mathbf{\AA})$ | Atom | Atom | Length $(\mathbf{\AA})$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | C 9 | $1.546(2)$ | C 6 | C 7 | $1.5675(19)$ |
| C 1 | C 10 | $1.547(2)$ | C 7 | O 4 | $1.4281(18)$ |
| C 1 | C 2 | $1.552(2)$ | C 7 | C 8 | $1.525(2)$ |
| C 1 | C 5 | $1.5658(19)$ | C 7 | C 16 | $1.532(2)$ |
| C 2 | C 12 | $1.528(2)$ | C 8 | O 5 | $1.218(2)$ |
| C 2 | C 3 | $1.545(2)$ | C 8 | C 9 | $1.498(2)$ |
| C 3 | C 4 | $1.551(2)$ | C 10 | C 11 | $1.516(2)$ |
| C 4 | C 5 | $1.5480(19)$ | C 11 | O 1 | $1.206(2)$ |
| C 5 | C 6 | $1.5607(19)$ | C 11 | O 2 | $1.3313(19)$ |
| C 6 | C 14 | $1.5390(19)$ | C 14 | O 3 | $1.4236(19)$ |
| C 6 | C 13 | $1.548(2)$ | C 15 | O 3 | $1.4303(18)$ |

Table SI2.5.1.5. Bond Angles for 203.

| Atom | Atom | Atom | Angle ( ${ }^{\mathbf{}} \mathbf{)}$ | Atom | Atom | Atom | Angle ( ${ }^{\mathbf{}} \mathbf{)}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C 9 | C 1 | C 10 | $109.93(12)$ | C 13 | C 6 | C 7 | $107.66(12)$ |
| C 9 | C 1 | C 2 | $113.07(13)$ | C 5 | C 6 | C 7 | $109.89(11)$ |
| C 10 | C 1 | C 2 | $110.84(12)$ | O 4 | C 7 | C 8 | $108.52(12)$ |
| C 9 | C 1 | C 5 | $113.22(12)$ | O 4 | C 7 | C 16 | $106.14(11)$ |
| C 10 | C 1 | C 5 | $106.72(12)$ | C 8 | C 7 | C 16 | $109.86(12)$ |
| C 2 | C 1 | C 5 | $102.70(12)$ | O 4 | C 7 | C 6 | $109.94(11)$ |
| C 12 | C 2 | C 3 | $113.12(13)$ | C 8 | C 7 | C 6 | $107.40(11)$ |
| C 12 | C 2 | C 1 | $117.55(13)$ | C 16 | C 7 | C 6 | $114.85(12)$ |
| C 3 | C 2 | C 1 | $103.68(12)$ | O 5 | C 8 | C 9 | $123.19(14)$ |
| C 2 | C 3 | C 4 | $106.60(12)$ | O 5 | C 8 | C 7 | $119.79(14)$ |
| C 5 | C 4 | C 3 | $106.57(12)$ | C 9 | C 8 | C 7 | $117.02(13)$ |
| C 4 | C 5 | C 6 | $112.51(11)$ | C 8 | C 9 | C 1 | $113.19(12)$ |
| C 4 | C 5 | C 1 | $102.71(11)$ | C 11 | C 10 | C 1 | $117.78(13)$ |
| C 6 | C 5 | C 1 | $117.00(12)$ | O 1 | C 11 | O 2 | $122.87(14)$ |
| C 14 | C 6 | C 13 | $103.56(12)$ | O 1 | C 11 | C 10 | $125.37(14)$ |
| C 14 | C 6 | C 5 | $110.39(12)$ | O 2 | C 11 | C 10 | $111.69(13)$ |
| C 13 | C 6 | C 5 | $114.99(11)$ | O 3 | C 14 | C 6 | $114.03(12)$ |
| C 14 | C 6 | C 7 | $110.14(11)$ | C 14 | O 3 | C 15 | $108.94(11)$ |

Table SI2.5.1.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 203.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H2 | 4927 | 6886 | 3404 | 19 |
| H3A | 3197 | 8355 | 3455 | 22 |
| H3B | 1286 | 7936 | 3968 | 22 |
| H4A | -754 | 7620 | 2980 | 19 |
| H4B | 1120 | 8078 | 2470 | 19 |
| H5 | 24 | 6183 | 2426 | 16 |
| H9A | 4381 | 4879 | 3598 | 20 |
| H9B | 2465 | 4470 | 3091 | 20 |
| H10A | -608 | 6388 | 3873 | 19 |
| H10B | -863 | 5361 | 3443 | 19 |
| H12A | 2796 | 6662 | 4780 | 31 |
| H12B | 5048 | 7227 | 4649 | 31 |
| H12C | 4902 | 6043 | 4545 | 31 |
| H13A | 5578 | 7382 | 1535 | 24 |
| H13B | 6052 | 6926 | 2327 | 24 |
| H13C | 4473 | 7866 | 2242 | 24 |
| H14A | 1709 | 7650 | 1273 | 19 |
| H14B | 2779 | 6769 | 809 | 19 |
| H15A | -1063 | 7548 | 408 | 31 |
| H15B | -2484 | 6553 | 344 | 31 |
| H15C | -57 | 6571 | 37 | 31 |
| H16A | 1755 | 4858 | 1040 | 24 |
| H16B | 974 | 4702 | 1867 | 24 |
| H16C | 2872 | 4023 | 1539 | 24 |
| H2A | -641 | 5216 | 5380 | 32 |
| H4 | 6765 | 5540 | 1440 | 23 |
|  |  |  |  |  |

## SI2.5.2. X-Ray Crystallographic Data for Rearranged Oleanic Acid Derivative $224 \cdot \mathbf{C D C l}_{3}$



A colorless block $0.28 \times 0.17 \times 0.13 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at $100(2) \mathrm{K}$ using $\omega$ scans. Crystal-to-detector distance was 30.23 mm and exposure time was 0.50 seconds per frame using a scan width of $0.5^{\circ}$. Data collection was $100 \%$ complete to $74.000^{\circ}$ in $\theta$. A total of 48462 reflections were collected covering the indices $-8<=\mathrm{h}<=8,-17<=\mathrm{k}<=18,-38<=1<=38$. 6546 reflections were founded to be symmetry independent, with an $\mathrm{R}_{\text {int }}$ of 0.0434 . Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $\mathrm{P} 2_{1} 2_{1} 2_{1}$ (No. 19). The data were integrated and scaled using the CrysAlis ${ }^{\text {Pro }}$ 1.171.39.46e software program. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table SI2.5.2.1. Crystal data and structure refinement for 224.

| Identification code | 224 |
| :---: | :---: |
| Empirical formula | $\mathrm{C}_{33} \mathrm{H}_{47} \mathrm{Cl}_{3} \mathrm{O}_{5}$ |
| Formula weight | 630.05 |
| Temperature (K) | 100(2) |
| Crystal system | orthorhombic |
| Space group | P2, 2, $2_{1}$ |
| a ( $\AA$ ) | 6.83561(4) |
| b ( $\AA$ ) | 15.11333(9) |
| c ( $\AA$ ) | 30.94568(18) |
| $\alpha{ }^{\circ}{ }^{\circ}$ | 90 |
| $\beta\left({ }^{\circ}\right)$ | 90 |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume ( $\AA^{3}$ ) | 3196.96(3) |
| Z | 4 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.309 |
| $\mu\left(\mathrm{mm}^{-1}\right)$ | 2.907 |
| $\mathrm{F}(000)$ | 1344.0 |
| Crystal size ( $\mathrm{mm}^{3}$ ) | $0.280 \times 0.170 \times 0.130$ |
| Radiation | $\mathrm{CuK} \alpha(\lambda=1.54184)$ |
| $2 \Theta$ range for data collection ${ }^{\circ}$ ) | 5.712 to 149 |
| Index ranges | $-8 \leq \mathrm{h} \leq 8,-17 \leq \mathrm{k} \leq 18,-38 \leq 1 \leq 38$ |
| Reflections collected | 48462 |
| Independent reflections | $6546\left[\mathrm{R}_{\mathrm{itt}}=0.0434, \mathrm{R}_{\text {sigma }}=0.0177\right]$ |
| Data/restraints/parameters | 6546/0/378 |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.056 |
| Final R indexes [ $\mathrm{I}>=2 \sigma$ (I)] | $\mathrm{R}_{1}=0.0483, \mathrm{wR}_{2}=0.1394$ |
| Final R indexes [all data] | $\mathrm{R}_{1}=0.0488, \mathrm{wR}_{2}=0.1398$ |
| Largest diff. peak/hole (e $\AA^{-3}$ ) | 1.56/-0.70 |
| Flack parameter | 0.013(4) |

Table SI2.5.2.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 224. $U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $y$ | $z$ | U(eq) |
| :---: | :---: | :---: | :---: | :---: |
| C1 | 5487(6) | 1669(3) | 5218.6(13) | 30.3(8) |
| C2 | 5623(5) | 2659(2) | 5286.6(12) | 23.7(7) |
| C3 | 6013(5) | 3779(2) | 5828.0(11) | 17.8(6) |
| C4 | 4022(5) | 4211(2) | 5830.8(11) | 19.4(6) |
| C5 | 4184(5) | 5190(2) | 5963.7(10) | 17.9(6) |
| C6 | 5145(4) | 5315(2) | 6410.5(10) | 15.1(6) |
| C7 | 3669(5) | 4986(2) | 6754.0(11) | 17.8(6) |
| C8 | 7136(4) | 4802(2) | 6409.5(10) | 15.3(6) |
| C9 | 7070(5) | 3810(2) | 6266.1(11) | 16.9(6) |
| C10 | 6130(5) | 3186(2) | 6600.1(12) | 22.9(7) |
| C11 | 9180(5) | 3502(2) | 6185.0(13) | 24.1(7) |
| C12 | 8235(5) | 4952(2) | 6831.1(10) | 15.7(6) |
| C13 | 8740(5) | 5927(2) | 6898.1(10) | 15.2(6) |
| C14 | 6926(4) | 6536(2) | 6884.1(9) | 14.2(6) |
| C15 | 5757(5) | 6379(2) | 7305.2(10) | 17.9(6) |
| C16 | 5690(4) | 6291(2) | 6486.0(10) | 14.2(6) |
| C17 | 5168(5) | 6917(2) | 6199.6(10) | 15.8(6) |
| C18 | 5960(5) | 7820(2) | 6189.9(10) | 16.2(6) |
| C19 | 7894(4) | 7967(2) | 6433.1(9) | 13.2(6) |
| C20 | 9495(5) | 7514(2) | 6158.4(10) | 17.7(6) |
| C21 | 7539(4) | 7535(2) | 6880.5(10) | 13.8(6) |
| C22 | 9244(5) | 7743(2) | 7185.0(10) | 16.7(6) |
| C23 | 9295(5) | 8741(2) | 7282.4(10) | 17.5(6) |
| C24 | 7891(5) | 9237(2) | 6974.5(10) | 15.2(6) |
| C25 | 5894(5) | 8884(2) | 7084.8(10) | 15.6(6) |
| C26 | 8285(5) | 8978(2) | 6497.1(10) | 14.4(6) |
| C27 | 10309(5) | 9330(2) | 6358.1(10) | 16.9(6) |
| C28 | 10451(5) | 10348(2) | 6403.5(11) | 19.7(7) |
| C29 | 9064(6) | 10812(2) | 6084.7(12) | 26.8(8) |
| C30 | 12566(6) | 10625(2) | 6305.8(12) | 26.1(8) |
| C31 | 9958(5) | 10615(2) | 6871.7(11) | 21.5(7) |
| C32 | 8011(5) | 10242(2) | 7030.1(11) | 19.3(6) |
| C33 | 3324(7) | 8924(3) | 5108.5(13) | 37.0(9) |
| C11 | 2177.7(19) | 7949.6(8) | 4927.7(4) | 48.1(3) |
| C12 | 1671(2) | 9805.0(8) | 5128.4(3) | 45.9(3) |
| Cl3 | 5264(2) | 9218.1(9) | 4760.6(4) | 51.0(3) |


| O1 | $5583(5)$ | $3203.0(18)$ | $5006.1(9)$ | $32.1(6)$ |
| :--- | :--- | :--- | :--- | :--- |
| O2 | $5812(4)$ | $2846.9(15)$ | $5710.3(8)$ | $21.3(5)$ |
| O3 | $5200(4)$ | $8399.0(16)$ | $5967.6(8)$ | $25.9(6)$ |
| O4 | $5769(3)$ | $7995.4(15)$ | $7044.6(7)$ | $14.4(4)$ |
| O5 | $4481(3)$ | $9293.5(16)$ | $7203.9(8)$ | $21.1(5)$ |

Table SI2.5.2.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 224. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} \mathrm{a}^{* 2} \mathrm{U}_{11}+2 \mathrm{hka} \mathrm{hb}^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | $33(2)$ | $23.5(18)$ | $35(2)$ | $-10.3(15)$ | $-2.4(17)$ | $-1.3(16)$ |
| C2 | $18.6(16)$ | $24.7(17)$ | $27.7(17)$ | $-8.7(14)$ | $-1.1(14)$ | $0.7(13)$ |
| C3 | $16.8(15)$ | $15.0(14)$ | $21.7(15)$ | $-1.9(12)$ | $0.3(12)$ | $-3.0(12)$ |
| C4 | $16.2(15)$ | $21.2(15)$ | $20.9(15)$ | $-3.3(13)$ | $-2.3(12)$ | $-0.6(13)$ |
| C5 | $14.2(14)$ | $20.2(15)$ | $19.2(14)$ | $-0.7(12)$ | $-2.0(12)$ | $1.6(13)$ |
| C6 | $10.7(13)$ | $18.2(15)$ | $16.3(14)$ | $-0.4(11)$ | $0.3(11)$ | $1.5(11)$ |
| C7 | $13.6(14)$ | $20.8(15)$ | $19.0(14)$ | $0.0(12)$ | $2.0(12)$ | $-1.3(12)$ |
| C8 | $11.1(13)$ | $17.9(14)$ | $16.9(14)$ | $3.4(12)$ | $1.3(11)$ | $-1.0(12)$ |
| C9 | $13.6(14)$ | $16.3(15)$ | $20.7(15)$ | $-0.2(12)$ | $-0.1(12)$ | $0.8(12)$ |
| C10 | $24.8(17)$ | $17.3(15)$ | $26.6(17)$ | $2.8(13)$ | $-0.8(14)$ | $-3.0(13)$ |
| C11 | $17.4(16)$ | $19.7(16)$ | $35.1(19)$ | $-3.6(14)$ | $-0.1(14)$ | $2.7(13)$ |
| C12 | $14.1(14)$ | $16.4(15)$ | $16.6(14)$ | $3.4(11)$ | $-0.8(12)$ | $1.6(12)$ |
| C13 | $12.4(14)$ | $17.1(15)$ | $16.0(14)$ | $0.7(12)$ | $-2.3(11)$ | $0.6(11)$ |
| C14 | $12.8(13)$ | $17.3(14)$ | $12.5(13)$ | $0.4(11)$ | $-0.3(11)$ | $0.7(12)$ |
| C15 | $18.1(15)$ | $20.9(15)$ | $14.7(14)$ | $0.7(12)$ | $2.4(12)$ | $-0.9(12)$ |
| C16 | $10.0(13)$ | $19.6(15)$ | $13.1(13)$ | $-2.1(11)$ | $0.6(11)$ | $0.3(12)$ |
| C17 | $14.1(14)$ | $18.6(15)$ | $14.6(14)$ | $-1.1(11)$ | $-2.9(11)$ | $1.2(12)$ |
| C18 | $18.6(15)$ | $17.8(15)$ | $12.2(13)$ | $-1.7(11)$ | $-1.4(12)$ | $2.9(12)$ |
| C19 | $13.7(13)$ | $15.0(14)$ | $11.1(13)$ | $-0.3(11)$ | $1.0(11)$ | $0.2(12)$ |
| C20 | $20.1(15)$ | $18.4(15)$ | $14.7(14)$ | $-0.6(11)$ | $3.9(12)$ | $0.7(13)$ |
| C21 | $11.5(14)$ | $18.8(15)$ | $11.0(13)$ | $-0.5(11)$ | $2.8(11)$ | $3.7(12)$ |
| C22 | $15.2(14)$ | $21.3(15)$ | $13.5(13)$ | $1.7(11)$ | $-1.2(12)$ | $0.6(12)$ |
| C23 | $15.7(14)$ | $23.8(16)$ | $13.1(13)$ | $-2.1(12)$ | $-1.0(12)$ | $-1.9(13)$ |
| C24 | $14.9(14)$ | $17.3(14)$ | $13.5(14)$ | $-2.0(11)$ | $0.5(11)$ | $-0.5(12)$ |
| C25 | $15.9(15)$ | $18.9(15)$ | $12.1(13)$ | $-3.8(11)$ | $-0.8(12)$ | $0.6(13)$ |
| C26 | $16.2(14)$ | $15.5(14)$ | $11.3(13)$ | $-1.0(11)$ | $0.4(11)$ | $-0.1(12)$ |
| C27 | $17.0(15)$ | $17.1(15)$ | $16.6(14)$ | $-0.6(11)$ | $3.0(12)$ | $-1.6(12)$ |
| C28 | $24.2(17)$ | $16.2(15)$ | $18.8(15)$ | $-0.4(12)$ | $1.8(13)$ | $-3.1(13)$ |
| C29 | $33.2(19)$ | $20.0(16)$ | $27.1(17)$ | $2.2(14)$ | $-3.7(15)$ | $-0.6(15)$ |
| C30 | $29.0(19)$ | $22.4(17)$ | $26.9(18)$ | $-1.0(13)$ | $5.5(15)$ | $-10.1(15)$ |
| C31 | $23.3(17)$ | $20.8(15)$ | $20.4(16)$ | $-5.2(12)$ | $2.5(13)$ | $-4.9(13)$ |
| C32 | $19.7(16)$ | $18.3(15)$ | $19.9(15)$ | $-6.3(12)$ | $1.3(13)$ | $-3.3(13)$ |
| C33 | $36(2)$ | $51(3)$ | $23.8(18)$ | $6.6(17)$ | $-2.4(18)$ | $1(2)$ |
| C11 | $49.2(6)$ | $42.1(6)$ | $52.9(6)$ | $-3.0(5)$ | $3.9(5)$ | $-8.2(5)$ |
| C12 | $60.1(7)$ | $47.4(6)$ | $30.3(5)$ | $-4.5(4)$ | $-4.2(5)$ | $19.0(6)$ |
| C13 | $49.9(7)$ | $51.0(7)$ | $52.0(7)$ | $-3.2(5)$ | $17.2(5)$ | $-13.8(6)$ |
|  |  |  |  |  |  |  |


| O1 | $40.9(16)$ | $29.7(13)$ | $25.7(13)$ | $-5.9(11)$ | $-2.5(12)$ | $-0.9(12)$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O2 | $22.2(12)$ | $17.2(11)$ | $24.5(11)$ | $-4.9(9)$ | $-0.2(10)$ | $-0.5(10)$ |
| O3 | $33.8(14)$ | $17.8(11)$ | $26.0(12)$ | $4.8(9)$ | $-14.3(11)$ | $0.5(11)$ |
| O4 | $12.6(10)$ | $17.1(10)$ | $13.4(9)$ | $-1.9(8)$ | $1.8(8)$ | $1.0(8)$ |
| O5 | $15.5(11)$ | $23.1(12)$ | $24.7(11)$ | $-6.1(9)$ | $2.7(9)$ | $2.3(10)$ |

Table SI2.5.2.4. Bond Lengths for 224.

| Atom | Atom | Length ( $\AA$ ) | Atom | Atom | Length ( $\AA$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | C2 | 1.513(5) | C18 | C19 | 1.537(4) |
| C2 | O1 | 1.196(5) | C19 | C20 | 1.546(4) |
| C2 | O2 | 1.348(4) | C19 | C21 | $1.550(4)$ |
| C3 | O2 | $1.462(4)$ | C19 | C26 | 1.563(4) |
| C3 | C4 | 1.510(5) | C21 | O4 | 1.485(4) |
| C3 | C9 | 1.537(5) | C21 | C22 | 1.532(4) |
| C4 | C5 | 1.539(4) | C22 | C23 | 1.538(4) |
| C5 | C6 | 1.542(4) | C23 | C24 | 1.547(4) |
| C6 | C16 | 1.540(4) | C24 | C25 | 1.505(4) |
| C6 | C7 | 1.547(4) | C24 | C32 | 1.531(4) |
| C6 | C8 | 1.566(4) | C24 | C26 | 1.552(4) |
| C8 | C12 | 1.522(4) | C25 | O5 | 1.205(4) |
| C8 | C9 | 1.564(4) | C25 | O4 | 1.351(4) |
| C9 | C11 | 1.537(4) | C26 | C27 | 1.543(4) |
| C9 | C10 | 1.540(5) | C27 | C28 | 1.549(4) |
| C12 | C13 | 1.528(4) | C28 | C30 | $1.535(5)$ |
| C13 | C14 | 1.545(4) | C28 | C29 | 1.537(5) |
| C14 | C16 | 1.539(4) | C28 | C31 | 1.541(4) |
| C14 | C15 | 1.547(4) | C31 | C32 | $1.526(5)$ |
| C14 | C21 | 1.567(4) | C33 | C12 | 1.747(5) |
| C16 | C17 | $1.345(5)$ | C33 | Cl1 | 1.760(5) |
| C17 | C18 | 1.468(4) | C33 | Cl 3 | 1.765(5) |
| C18 | O3 | 1.228(4) |  |  |  |

Table SI2.5.2.5. Bond Angles for 224.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | C2 | O2 | 124.3(3) | C18 | C19 | C21 | 104.0(2) |
| O1 | C2 | C1 | 125.3(3) | C20 | C19 | C21 | 114.5(2) |
| O2 | C2 | C1 | 110.5(3) | C18 | C19 | C26 | 110.5(2) |
| O2 | C3 | C4 | 109.5(3) | C20 | C19 | C26 | 112.4(3) |
| O2 | C3 | C9 | 107.1(3) | C21 | C19 | C26 | 109.0(2) |
| C4 | C3 | C9 | 113.9(3) | O4 | C21 | C22 | 108.3(2) |
| C3 | C4 | C5 | 110.6(3) | O4 | C21 | C19 | 103.6(2) |
| C4 | C5 | C6 | 112.8(3) | C22 | C21 | C19 | 110.1(3) |
| C16 | C6 | C5 | 110.9(3) | O4 | C21 | C14 | 103.4(2) |
| C16 | C6 | C7 | 111.2(3) | C22 | C21 | C14 | 113.4(2) |
| C5 | C6 | C7 | 107.4(3) | C19 | C21 | C14 | 117.0(2) |
| C16 | C6 | C8 | 105.3(2) | C21 | C22 | C23 | 109.8(3) |
| C5 | C6 | C8 | 107.9(2) | C22 | C23 | C24 | 109.9(3) |
| C7 | C6 | C8 | 114.1(3) | C25 | C24 | C32 | 112.0(3) |
| C12 | C8 | C9 | 113.5(3) | C25 | C24 | C23 | 104.5(2) |
| C12 | C8 | C6 | 110.7(3) | C32 | C24 | C23 | 112.3(3) |
| C9 | C8 | C6 | 116.7(3) | C25 | C24 | C26 | 106.5(3) |
| C11 | C9 | C3 | 106.7(3) | C32 | C24 | C26 | 110.4(3) |
| C11 | C9 | C10 | 108.4(3) | C23 | C24 | C26 | 110.8(3) |
| C3 | C9 | C10 | 112.2(3) | O5 | C25 | O4 | 119.2(3) |
| C11 | C9 | C8 | 108.0(3) | O5 | C25 | C24 | 127.9(3) |
| C3 | C9 | C8 | 107.1(3) | O4 | C25 | C24 | 112.9(3) |
| C10 | C9 | C8 | 114.1(3) | C27 | C26 | C24 | 109.5(3) |
| C8 | C12 | C13 | 111.7(3) | C27 | C26 | C19 | 117.1(3) |
| C12 | C13 | C14 | 113.0(3) | C24 | C26 | C19 | 109.7(2) |
| C16 | C14 | C13 | 108.6(2) | C26 | C27 | C28 | 111.9(3) |
| C16 | C14 | C15 | 110.7(3) | C30 | C28 | C29 | 109.3(3) |
| C13 | C14 | C15 | 107.4(2) | C30 | C28 | C31 | 108.7(3) |
| C16 | C14 | C21 | 111.9(2) | C29 | C28 | C31 | 110.4(3) |
| C13 | C14 | C21 | 111.1(2) | C30 | C28 | C27 | 108.2(3) |
| C15 | C14 | C21 | 107.0(2) | C29 | C28 | C27 | 110.8(3) |
| C17 | C16 | C14 | 120.3(3) | C31 | C28 | C27 | 109.3(3) |
| C17 | C16 | C6 | 120.6(3) | C32 | C31 | C28 | 113.3(3) |
| C14 | C16 | C6 | 119.0(3) | C31 | C32 | C24 | 112.1(3) |
| C16 | C17 | C18 | 124.7(3) | C12 | C33 | Cl 1 | 111.2(3) |
| O3 | C18 | C17 | 121.2(3) | C12 | C33 | Cl 3 | 108.4(3) |
| O3 | C18 | C19 | 122.3(3) | Cl1 | C33 | C13 | 110.6(3) |


| C17 | C18 | C19 | $116.2(3)$ | C2 | O2 | C3 | $117.0(3)$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C18 | C19 | C20 | $106.0(2)$ | C25 | O4 | C21 | $116.5(2)$ |

Table SI2.5.2.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters ( $\AA^{2} \times 10^{3}$ ) for 224.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H1A | 6705 | 1389 | 5314 | 46 |
| H1B | 5277 | 1545 | 4911 | 46 |
| H1C | 4390 | 1433 | 5387 | 46 |
| H3 | 6848 | 4080 | 5607 | 21 |
| H4A | 3156 | 3896 | 6036 | 23 |
| H4B | 3432 | 4170 | 5539 | 23 |
| H5A | 2858 | 5455 | 5969 | 21 |
| H5B | 4963 | 5511 | 5744 | 21 |
| H7A | 2763 | 5465 | 6827 | 27 |
| H7B | 4378 | 4801 | 7014 | 27 |
| H7C | 2932 | 4483 | 6638 | 27 |
| H8 | 7946 | 5105 | 6184 | 18 |
| H10A | 4705 | 3258 | 6594 | 34 |
| H10B | 6622 | 3330 | 6889 | 34 |
| H10C | 6464 | 2572 | 6530 | 34 |
| H11A | 9164 | 2928 | 6038 | 36 |
| H11B | 9866 | 3444 | 6462 | 36 |
| H11C | 9857 | 3937 | 6004 | 36 |
| H12A | 9456 | 4599 | 6829 | 19 |
| H12B | 7422 | 4743 | 7075 | 19 |
| H13A | 9671 | 6115 | 6671 | 18 |
| H13B | 9397 | 5997 | 7181 | 18 |
| H15A | 5772 | 5748 | 7376 | 27 |
| H15B | 4403 | 6576 | 7265 | 27 |
| H15C | 6356 | 6716 | 7541 | 27 |
| H17 | 4218 | 6764 | 5988 | 19 |
| H20A | 9141 | 6894 | 6110 | 27 |
| H20B | 10749 | 7543 | 6311 | 27 |
| H20C | 9611 | 7818 | 5880 | 27 |
| H22A | 10492 | 7560 | 7049 | 20 |
| H22B | 9088 | 7408 | 7458 | 20 |
| H23A | 10643 | 8967 | 7244 | 21 |
| H23B | 8899 | 8846 | 7586 | 21 |
| H26 | 7294 | 9298 | 6318 | 17 |
| H27A | 10555 | 9163 | 6054 | 20 |
| H27B | 11333 | 9050 | 6538 | 20 |
|  |  |  |  |  |


| H29A | 9288 | 10581 | 5793 | 40 |
| :---: | :---: | :---: | :---: | :---: |
| H29B | 9314 | 11450 | 6088 | 40 |
| H29C | 7706 | 10699 | 6170 | 40 |
| H30A | 13454 | 10329 | 6508 | 39 |
| H30B | 12693 | 11267 | 6338 | 39 |
| H30C | 12902 | 10455 | 6009 | 39 |
| H31A | 11015 | 10404 | 7065 | 26 |
| H31B | 9917 | 11268 | 6891 | 26 |
| H32A | 6931 | 10523 | 6867 | 23 |
| H32B | 7841 | 10391 | 7339 | 23 |
| H33 | 3860 | 8821 | 5405 | 44 |

## SI2.5.3. X-Ray Crystallographic Data for Redox Relay Product 232



A colorless prism $0.11 \times 0.08 \times 0.06 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at $100(2) \mathrm{K}$ using $\omega$ scans. Exposure time was 0.50 seconds per frame using a scan width of $0.5^{\circ}$. Data collection was $42 \%$ complete to $25.55^{\circ}$ in $\theta$. A total of 19608 reflections were collected covering the indices $-9<=\mathrm{h}<=9,-11<=\mathrm{k}<=11,-11<=1<=11.2637$ reflections were founded to be symmetry independent, with an $R_{\text {int }}$ of 0.0226 . Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P2 (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table SI2.5.3.1. Crystal data and structure refinement for 232.

| Identification code | $\mathbf{2 3 2}$ |
| :--- | :--- |
| Empirical formula | $\mathrm{C}_{16} \mathrm{H}_{24} \mathrm{O}_{4}$ |
| Formula weight | 280.37 |
| Temperature $(\mathrm{K})$ | 100.0 |
| Crystal system | monoclinic |
| Space group | $\mathrm{P}_{1}$ |
| a $(\AA)$ | $8.0619(8)$ |
| $\mathrm{b}(\AA)$ | $9.8882(10)$ |
| c $(\AA)$ | $9.804(1)$ |
| $\alpha\left(^{\circ}\right)$ | 90 |
| $\beta\left(^{\circ}\right)$ | $113.579(4)$ |
| $\gamma\left(^{\circ}\right)$ | 90 |
| Volume $\left(\AA^{3}\right)$ | $716.30(13)$ |
| Z | 2 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}{ }^{3}\right)$ | 1.2998 |
| $\mu\left(\mathrm{~mm}{ }^{-1}\right)$ | 0.092 |
| $\mathrm{~F}(000)$ | 304.2 |
| Crystal size $\left(\mathrm{mm}{ }^{3}\right)$ | $0.11 \times 0.08 \times 0.06$ |
| Radiation | $\mathrm{Mo} \mathrm{K} \alpha(\lambda=0.71073)$ |
| $2 \Theta$ range for data collection $\left({ }^{\circ}\right)$ | 4.54 to 50.9 |
| Index ranges | $-9 \leq \mathrm{h} \leq 9,-11 \leq \mathrm{k} \leq 11,-11 \leq 1 \leq 11$ |
| Reflections collected | 19608 |
| Independent reflections | $2637\left[\mathrm{R}_{\text {int }}=0.0226, \mathrm{R}_{\text {sigma }}=0.0114\right]$ |
| Data/restraints/parameters | $2637 / 1 / 277$ |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.115 |
| Final R indexes $[\mathrm{I}>=2 \sigma(\mathrm{I})]$ | $\mathrm{R}_{1}=0.0237, \mathrm{wR}{ }_{2}=0.0630$ |
| Final R indexes $[$ all data $]$ | $\mathrm{R}_{1}=0.0240, \mathrm{wR}{ }_{2}=0.0633$ |
| Largest diff. peak/hole $\left(\mathrm{e} \AA \AA^{-3}\right)$ | $0.15 /-0.14$ |
| Flack parameter | $-0.1(5)$ |
|  |  |

Table SI2.5.3.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for $232 . U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| O1 | $-4527.9(11)$ | $-4957.4(9)$ | $-9528.5(9)$ | $17.51(19)$ |
| O2 | $-4845.8(12)$ | $-3496.1(9)$ | $-11346.2(10)$ | $22.7(2)$ |
| O3 | $-8030.8(11)$ | $-2909.2(8)$ | $-5484.6(9)$ | $17.68(19)$ |
| O4 | $-2876.4(12)$ | $-3961.7(10)$ | $-6788.1(10)$ | $27.1(2)$ |
| C5 | $-4325.7(15)$ | $-4471.7(12)$ | $-7035.5(13)$ | $16.0(2)$ |
| C6 | $-5376.3(16)$ | $-5198.8(12)$ | $-8499.2(13)$ | $15.3(2)$ |
| C7 | $-5362.9(16)$ | $-3910.2(11)$ | $-10430.4(13)$ | $17.4(3)$ |
| C8 | $-7203.4(15)$ | $-4862.8(11)$ | $-6559.3(12)$ | $13.7(2)$ |
| C9 | $-8179.0(15)$ | $-4238.2(12)$ | $-8137.8(13)$ | $13.8(2)$ |
| C10 | $-3967.5(17)$ | $-4916.2(14)$ | $-4420.7(13)$ | $20.2(3)$ |
| C11 | $-5228.1(15)$ | $-4349.6(12)$ | $-5938.6(13)$ | $15.4(2)$ |
| C12 | $-7309.5(15)$ | $-4637.1(11)$ | $-9245.6(12)$ | $13.6(2)$ |
| C13 | $-6921.5(16)$ | $-3428.9(12)$ | $-10069.7(13)$ | $15.7(2)$ |
| C14 | $-10213.6(16)$ | $-4588.9(12)$ | $-8940.8(13)$ | $17.8(3)$ |
| C15 | $-8125.9(16)$ | $-4340.2(12)$ | $-5561.3(13)$ | $16.0(2)$ |
| C16 | $-8505.7(19)$ | $-5953.6(13)$ | $-11786.1(15)$ | $23.4(3)$ |
| C17 | $-10491.9(16)$ | $-4997.5(14)$ | $-10519.5(14)$ | $20.1(3)$ |
| C18 | $-8835.6(18)$ | $-2398.4(14)$ | $-4545.4(14)$ | $20.3(3)$ |
| C19 | $-8685.7(16)$ | $-5637.5(12)$ | $-10330.9(13)$ | $17.1(2)$ |
| C20 | $-7318.9(17)$ | $-6413.4(12)$ | $-6524.2(14)$ | $17.6(3)$ |

Table SI2.5.3.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times \mathbf{1 0}^{3}\right)$ for 232. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} \mathrm{a}^{* 2} \mathrm{U}_{11}+2 \mathrm{hka} \mathrm{hb}^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{12}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{23}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | $18.1(4)$ | $18.3(4)$ | $19.4(4)$ | $1.5(3)$ | $11.0(3)$ | $0.8(3)$ |
| O2 | $28.7(4)$ | $20.6(4)$ | $26.1(4)$ | $-2.4(4)$ | $18.5(4)$ | $1.1(4)$ |
| O3 | $23.0(4)$ | $13.6(4)$ | $20.8(4)$ | $1.0(3)$ | $13.4(4)$ | $-1.6(3)$ |
| O4 | $16.8(4)$ | $39.0(6)$ | $24.9(5)$ | $-8.7(4)$ | $7.5(4)$ | $-2.8(4)$ |
| C5 | $14.1(6)$ | $15.6(6)$ | $17.2(6)$ | $2.0(4)$ | $4.9(5)$ | $3.1(4)$ |
| C6 | $16.1(5)$ | $14.4(6)$ | $17.8(6)$ | $0.6(4)$ | $9.1(4)$ | $0.3(4)$ |
| C7 | $18.9(6)$ | $15.0(6)$ | $19.1(6)$ | $-2.9(4)$ | $8.4(5)$ | $-2.7(4)$ |
| C8 | $14.3(5)$ | $12.4(5)$ | $14.9(5)$ | $0.6(4)$ | $6.2(4)$ | $0.8(4)$ |
| C9 | $13.7(5)$ | $11.3(6)$ | $16.6(5)$ | $-0.0(4)$ | $6.4(4)$ | $0.5(4)$ |
| C10 | $17.5(6)$ | $25.2(7)$ | $15.2(6)$ | $3.5(5)$ | $3.7(5)$ | $0.5(5)$ |
| C11 | $14.2(5)$ | $13.2(6)$ | $17.9(6)$ | $0.7(4)$ | $5.5(5)$ | $-0.8(4)$ |
| C12 | $14.3(5)$ | $12.6(6)$ | $13.6(5)$ | $-0.7(4)$ | $5.4(4)$ | $0.5(4)$ |
| C13 | $17.3(5)$ | $13.3(5)$ | $17.5(6)$ | $-0.5(4)$ | $8.1(5)$ | $1.6(5)$ |
| C14 | $13.9(6)$ | $20.6(6)$ | $18.9(6)$ | $-0.3(4)$ | $6.5(5)$ | $0.7(5)$ |
| C15 | $18.5(6)$ | $13.7(5)$ | $17.7(6)$ | $-0.3(5)$ | $9.2(5)$ | $1.3(4)$ |
| C16 | $27.0(7)$ | $23.9(7)$ | $20.6(6)$ | $-6.2(6)$ | $10.7(5)$ | $-6.1(5)$ |
| C17 | $15.0(6)$ | $23.0(6)$ | $20.2(6)$ | $-2.7(5)$ | $4.8(4)$ | $0.7(5)$ |
| C18 | $23.1(7)$ | $21.1(7)$ | $19.9(6)$ | $1.4(5)$ | $12.1(5)$ | $-3.4(5)$ |
| C19 | $17.6(6)$ | $15.6(6)$ | $17.4(6)$ | $-4.0(5)$ | $6.1(5)$ | $-1.2(5)$ |
| C20 | $19.9(6)$ | $13.6(6)$ | $20.7(6)$ | $0.1(5)$ | $9.6(5)$ | $1.0(4)$ |

Table SI2.5.3.4. Bond Lengths for 232.

| Atom | Atom | Length $(\mathbf{\AA})$ | Atom | Atom | Length $(\mathbf{\AA})$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | C6 | $1.4475(13)$ | C8 | C11 | $1.5455(16)$ |
| O1 | C7 | $1.3532(15)$ | C 8 | C 15 | $1.5362(15)$ |
| O2 | C7 | $1.2029(15)$ | C 8 | C 20 | $1.5373(16)$ |
| O3 | C15 | $1.4174(14)$ | C 9 | C 12 | $1.5606(15)$ |
| O3 | C18 | $1.4149(15)$ | C 9 | C 14 | $1.5484(16)$ |
| O4 | C5 | $1.2048(15)$ | C 10 | C 11 | $1.5335(16)$ |
| C5 | C6 | $1.5236(16)$ | C 12 | C 13 | $1.5427(15)$ |
| C5 | C11 | $1.5251(16)$ | C 12 | C 19 | $1.5483(16)$ |
| C6 | C 12 | $1.5365(16)$ | C 14 | C 17 | $1.5269(17)$ |
| C7 | C 13 | $1.5120(16)$ | C 16 | C 19 | $1.5230(17)$ |
| C8 | C 9 | $1.5560(16)$ | C 17 | C 19 | $1.5297(17)$ |

Table SI2.5.3.5. Bond Angles for 232.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C7 | O1 | C6 | 109.36(8) | C14 | C9 | C8 | 115.34(9) |
| C18 | O3 | C15 | 111.21(10) | C14 | C9 | C12 | 105.60(9) |
| C6 | C5 | O4 | 121.07(10) | C8 | C11 | C5 | 113.79(9) |
| C11 | C5 | O4 | 121.51(11) | C10 | C11 | C5 | 109.72(10) |
| C11 | C5 | C6 | 117.33(10) | C10 | C11 | C8 | 116.14(10) |
| C5 | C6 | O1 | 109.82(9) | C9 | C12 | C6 | 114.35(9) |
| C12 | C6 | O1 | 106.29(9) | C13 | C12 | C6 | 98.61(9) |
| C12 | C6 | C5 | 110.72(9) | C13 | C12 | C9 | 114.23(9) |
| O2 | C7 | O1 | 121.19(10) | C19 | C12 | C6 | 114.07(9) |
| C13 | C7 | O1 | 109.31(9) | C19 | C12 | C9 | 104.00(9) |
| C13 | C7 | O2 | 129.50(11) | C19 | C12 | C13 | 111.99(9) |
| C11 | C8 | C9 | 107.01(9) | C12 | C13 | C7 | 103.91(9) |
| C15 | C8 | C9 | 108.61(9) | C17 | C14 | C9 | 105.72(10) |
| C15 | C8 | C11 | 108.90(9) | C8 | C15 | O3 | 109.87(9) |
| C20 | C8 | C9 | 114.02(10) | C19 | C17 | C14 | 103.90(10) |
| C20 | C8 | C11 | 112.38(10) | C16 | C19 | C12 | 117.67(10) |
| C20 | C8 | C15 | 105.79(9) | C17 | C19 | C12 | 101.80(9) |
| C12 | C9 | C8 | 113.75(9) | C17 | C19 | C16 | 114.49(11) |

Table SI2.5.3.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters ( $\AA^{2} \times 10^{3}$ ) for 232.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\boldsymbol{z}(\mathrm{eq})$ |
| :---: | :--- | :--- | :--- | :---: |
| H14a | $-10551(18)$ | $-5326(15)$ | $-8480(15)$ | $11(3)$ |
| H11 | $-5307(18)$ | $-3375(17)$ | $-5842(15)$ | $17(3)$ |
| H9 | $-8007(18)$ | $-3302(16)$ | $-7968(15)$ | $11(3)$ |
| H16a | $-9430(20)$ | $-6560(17)$ | $-12389(18)$ | $26(4)$ |
| H19 | $-8580(20)$ | $-6497(17)$ | $-9794(17)$ | $22(4)$ |
| H6 | $-5334(18)$ | $-6160(15)$ | $-8307(14)$ | $9(3)$ |
| H13a | $-7930(20)$ | $-3166(16)$ | $-10942(17)$ | $17(3)$ |
| H15a | $-7509(18)$ | $-4730(14)$ | $-4558(15)$ | $10(3)$ |
| H20a | $-6900(20)$ | $-6687(18)$ | $-5480(19)$ | $29(4)$ |
| H10a | $-3830(20)$ | $-5908(19)$ | $-4508(18)$ | $29(4)$ |
| H18a | $-8790(20)$ | $-1459(18)$ | $-4609(17)$ | $22(4)$ |
| H17a | $-11570(20)$ | $-5640(19)$ | $-10987(18)$ | $26(4)$ |
| H10b | $-2780(20)$ | $-4519(17)$ | $-4136(17)$ | $22(4)$ |
| H17b | $-10730(20)$ | $-4183(19)$ | $-11199(19)$ | $30(4)$ |
| H13b | $-6550(20)$ | $-2627(18)$ | $-9418(19)$ | $31(4)$ |
| H20b | $-6550(20)$ | $-6850(20)$ | $-6926(18)$ | $33(4)$ |
| H18b | $-8180(20)$ | $-2634(17)$ | $-3504(19)$ | $30(4)$ |
| H16b | $-8650(20)$ | $-5129(18)$ | $-12418(18)$ | $27(4)$ |
| H16c | $-7280(20)$ | $-6405(18)$ | $-11607(18)$ | $31(4)$ |
| H10c | $-4420(20)$ | $-4694(16)$ | $-3639(17)$ | $22(4)$ |
| H20c | $-8540(20)$ | $-6730(16)$ | $-7040(16)$ | $19(3)$ |
| H15b | $-9440(19)$ | $-4633(14)$ | $-5957(15)$ | $13(3)$ |
| H18c | $-10080(20)$ | $-2688(17)$ | $-4842(19)$ | $26(4)$ |
| H14b | $-10990(20)$ | $-3862(18)$ | $-8884(19)$ | $32(4)$ |

## SI2.5.4. X-Ray Crystallographic Data for $\varepsilon$-Lactone 235



A colorless prism $0.28 \times 0.2 \times 0.2 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at $100(2) \mathrm{K}$ using $\omega$ scans. Exposure time was 0.50 seconds per frame using a scan width of $2^{\circ}$. Data collection was $44 \%$ complete to $78.95^{\circ}$ in $\theta$. A total of 28219 reflections were collected covering the indices $-10<=\mathrm{h}<=10,-14<=\mathrm{k}<=14$, $-17<=1<=17.5484$ reflections were founded to be symmetry independent, with an $R_{\text {int }}$ of 0.0295 . Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P2 (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table SI2.5.4.1. Crystal data and structure refinement for 235.

| Identification code | $\mathbf{2 3 5}$ |
| :--- | :--- |
| Empirical formula | $\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{O}_{3}$ |
| Formula weight | 250.32 |
| Temperature $(\mathrm{K})$ | $100(2)$ |
| Crystal system | monoclinic |
| Space group | $\mathrm{P}_{1}$ |
| $\mathrm{a}(\AA)$ | $8.38830(10)$ |
| $\mathrm{b}(\AA)$ | $11.55480(10)$ |
| $\mathrm{c}(\AA)$ | $13.55300(10)$ |
| $\alpha\left(^{\circ}\right)$ | 90 |
| $\beta\left({ }^{\circ}\right)$ | $96.3190(10)$ |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume $\left(\AA^{3}\right)$ | $1305.65(2)$ |
| Z | 4 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.273 |
| $\mu\left(\right.$ mm $\left.{ }^{-1}\right)$ | 0.697 |
| $\mathrm{~F}(000)$ | 544.0 |
| Crystal size $\left(\mathrm{mm}{ }^{3}\right)$ | $0.28 \times 0.2 \times 0.2$ |
| Radiation | $\mathrm{CuK} \alpha(\lambda=1.54184)$ |
| $2 \Theta$ range for data collection $\left({ }^{\circ}\right)$ | 6.562 to 157.894 |
| Index ranges | $-10 \leq \mathrm{h} \leq 10,-14 \leq \mathrm{k} \leq 14,-17 \leq 1 \leq 17$ |
| Reflections collected | 28219 |
| Independent reflections | $5484\left[\mathrm{R}_{\text {int }}=0.0295, \mathrm{R}_{\text {sigma }}=0.0144\right]$ |
| Data/restraints $/$ parameters | $5484 / 1 / 331$ |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.055 |
| Final R indexes $[\mathrm{I}>=2 \sigma(\mathrm{I})]$ | $\mathrm{R}_{1}=0.0285, \mathrm{wR}{ }_{2}=0.0745$ |
| Final R indexes $[$ all data $]$ | $\mathrm{R}_{1}=0.0286, \mathrm{wR} \mathrm{R}_{2}=0.0745$ |
| Largest diff. peak/hole $\left(\mathrm{e} \AA \AA^{-3}\right)$ | $0.18 /-0.15$ |
| Flack parameter | $-0.08(5)$ |
|  |  |

Table SI2.5.4.2. Fractional Atomic Coordinates ( $\times 10^{4}$ ) and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for $\mathbf{2 3 5} . \mathrm{U}_{\text {eq }}$ is defined as $1 / 3$ of the trace of the orthogonalized $\mathrm{U}_{\mathrm{ij}}$ tensor.

| Atom | $\boldsymbol{x}$ | $y$ | $z$ | U(eq) |
| :---: | :---: | :---: | :---: | :---: |
| O1 | 8739.2(15) | 1907.1(10) | 8802.8(9) | 21.7(3) |
| O3 | 9789.0(15) | 3882.0(11) | 10473.9(9) | 22.3(3) |
| O4 | 4220.3(16) | 8087.4(11) | 3564.9(10) | 27.5(3) |
| O6 | 6114.3(15) | 5929.0(12) | 4826.5(10) | 26.5(3) |
| O2 | 12175.2(16) | 3207.7(12) | 10305.4(10) | 30.8(3) |
| O5 | 5024.3(19) | 6931.3(13) | 5946.8(10) | 33.7(3) |
| C7 | 11181(2) | 3935.1(15) | 10063.2(12) | 20.2(3) |
| C26 | 3289.9(19) | 4565.6(14) | 3510.0(12) | 17.1(3) |
| C4 | 9694.8(19) | 3598.9(15) | 8067.1(12) | 17.9(3) |
| C3 | 8566.4(19) | 2942.3(14) | 8663.2(12) | 16.4(3) |
| C6 | 11392.9(19) | 4858.5(14) | 9300.4(12) | 18.0(3) |
| C27 | 1930(2) | 4421.2(15) | 2656.9(13) | 21.0(3) |
| C1 | 6256(2) | 2891.4(15) | 9698.7(13) | 22.2(3) |
| C19 | 2416(2) | 6582.3(14) | 3879.5(13) | 19.3(3) |
| C14 | 10638(2) | 5521.6(15) | 7504.7(12) | 20.6(3) |
| C5 | 10101.0(19) | 4854.8(14) | 8403.4(11) | 15.8(3) |
| C15 | 11602(2) | 6620.3(16) | 7778.3(14) | 24.6(4) |
| C24 | 4919(2) | 5002.4(15) | 3240.7(13) | 19.6(3) |
| C11 | 8560(2) | 5484.8(14) | 8601.2(12) | 18.1(3) |
| C2 | 7143.7(19) | 3604.6(15) | 8983.7(12) | 17.9(3) |
| C18 | 3883(2) | 7065.9(15) | 3459.9(12) | 19.9(3) |
| C8 | 8609(2) | 4807.9(16) | 10362.4(12) | 22.0(4) |
| C20 | 2556.0(19) | 5325.8(14) | 4267.9(12) | 17.3(3) |
| C22 | 4925(2) | 6098.4(16) | 5403.4(12) | 23.9(4) |
| C23 | 6148(2) | 4939.2(17) | 4169.9(14) | 24.3(4) |
| C9 | 7603.4(19) | 4850.2(15) | 9345.0(12) | 18.7(3) |
| C28 | 351(2) | 4576.6(17) | 3141.1(14) | 24.8(4) |
| C17 | 4790(2) | 6262.2(16) | 2830.5(12) | 20.5(3) |
| C29 | 842(2) | 4819.8(16) | 4256.0(13) | 22.0(3) |
| C16 | 6379(2) | 6803.1(19) | 2607.9(15) | 30.1(4) |
| C30 | 770(2) | 3714.8(17) | 4879.3(14) | 28.8(4) |
| C21 | 3502(2) | 5295.3(16) | 5307.2(12) | 21.8(3) |
| C10 | 6096(2) | 5552.4(17) | 9485.9(17) | 28.9(4) |
| C12 | 7693(2) | 5721.6(17) | 7561.9(14) | 26.0(4) |
| C25 | 5502(2) | 4170.4(17) | 2471.9(14) | 27.4(4) |
| C13 | 9038(2) | 5801.1(19) | 6870.6(14) | 31.0(4) |

Table SI2.5.4.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times \mathbf{1 0}^{3}\right)$ for 235. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[\mathrm{~h}^{2} \mathrm{a}^{* 2} \mathrm{U}_{11}+2 \mathrm{hka}^{*} \mathrm{~b}^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | 24.5(6) | 15.3(6) | 25.4(6) | 0.2(5) | 2.3 (5) | 0.1(5) |
| O3 | 21.1(6) | 27.3(7) | 18.5(5) | 2.9(5) | 1.8(4) | -4.7(5) |
| O4 | 32.9(7) | 17.4(6) | 31.1(7) | 3.1(5) | -1.3(5) | -4.2(5) |
| O6 | 22.0(6) | 29.1(7) | 26.6(6) | 3.0(5) | -4.7(5) | -5.0(5) |
| O2 | 27.8(7) | 31.4(7) | 32.7(7) | 8.5(6) | 0.5(6) | 5.1(6) |
| O5 | 45.9(8) | 26.0(7) | 27.0(6) | -3.9(6) | -6.5(6) | -6.4(6) |
| C7 | 19.1(8) | 23.9(9) | 17.2(7) | -0.9(6) | -0.6(6) | -2.8(6) |
| C26 | 18.4(7) | 14.6(7) | 18.5(7) | 0.7(6) | 3.4(6) | 1.5(6) |
| C4 | 19.4(7) | 16.0(7) | 18.9(7) | -2.7(6) | 4.9(6) | -0.7(6) |
| C3 | 16.9(7) | 15.4(8) | 16.2(7) | -2.4(6) | -1.5(6) | -2.5(6) |
| C6 | 14.4(7) | 19.4(8) | 20.5(7) | -0.3(6) | 2.6(6) | -1.3(6) |
| C27 | 21.9(8) | 19.9(8) | 20.9(8) | -1.1(6) | 0.4(6) | -1.5(6) |
| C1 | 20.4(8) | 21.6(9) | 25.3(8) | -1.4(7) | 6.3(6) | -4.0(7) |
| C19 | 21.1(8) | 15.4(8) | 21.7(8) | -0.2(6) | 3.2(6) | 2.9(6) |
| C14 | 24.9(8) | 19.7(8) | 17.9(7) | 1.9(6) | 5.1(6) | -3.0(7) |
| C5 | 16.4(7) | 14.8(7) | 16.5(7) | 0.2(6) | 3.1(6) | -1.8(6) |
| C15 | 28.3(9) | 19.9(8) | 26.3(8) | 3.4(6) | 6.1(7) | -5.2(7) |
| C24 | 17.6(7) | 20.4(8) | 21.3(8) | $2.6(6)$ | 3.5(6) | 3.6(6) |
| C11 | 16.2(7) | 13.5(8) | 24.5(8) | 0.5(6) | 2.4(6) | -0.3(6) |
| C2 | 15.9(7) | 17.8(8) | 19.8(7) | -1.0(6) | 1.7(6) | -1.5(6) |
| C18 | 21.1(8) | 17.4(8) | 19.8(7) | 3.4(6) | -3.5(6) | -0.4(7) |
| C8 | 20.5(8) | 25.4(9) | 21.1(8) | -6.7(7) | 7.6(6) | -3.9(7) |
| C20 | 16.9(7) | 16.0(7) | 19.1(7) | -0.3(6) | 2.9(6) | 0.6(6) |
| C22 | 29.7(9) | 21.5(9) | 18.4(7) | 3.3(7) | -6.6(7) | -1.2(7) |
| C23 | 18.5(8) | 26.4(9) | 27.6(9) | 4.6(7) | 0.8(7) | 3.0(7) |
| C9 | 16.6(7) | 16.7(8) | 23.1(8) | -3.1(6) | 4.0(6) | -1.3(6) |
| C28 | 19.1(8) | 25.0(9) | 29.6(9) | -1.5(7) | 0.2(7) | -3.6(7) |
| C17 | 18.6(7) | 22.9(8) | 20.4(7) | 4.8(7) | 3.1(6) | -0.4(7) |
| C29 | 19.3(8) | 21.0(8) | 26.7(8) | -0.6(7) | 6.7(6) | -0.6(6) |
| C16 | 22.7(9) | 33.0(10) | 35.3(10) | 9.1(8) | 5.9(7) | -2.6(8) |
| C30 | 32.1(9) | 25.0(9) | 31.0(9) | 1.3(8) | 10.4(7) | -8.3(8) |
| C21 | 27.3(9) | 20.6(8) | 17.9(8) | 0.3(7) | 3.8(6) | -0.3(7) |
| C10 | 20.6(8) | 20.7(9) | 47.1(11) | -3.6(8) | 11.5(8) | 1.5(7) |
| C12 | 23.6(8) | 21.9(8) | 30.7(9) | 7.7(7) | -4.3(7) | -1.0(7) |
| C25 | 27.7(9) | 28.4(9) | 28.0(9) | 1.4(7) | 11.7(7) | 6.2(8) |
| C13 | 33.3(10) | 35.4(11) | 23.0(8) | 9.9(8) | -2.2(7) | -6.2(8) |

Table SI2.5.4.4. Bond Lengths for 235.

| Atom | Atom | Length $(\mathbf{\AA})$ | Atom | Atom | Length $(\AA)$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | C3 | $1.217(2)$ | C14 | C5 | $1.550(2)$ |
| O3 | C7 | $1.349(2)$ | C14 | C15 | $1.529(2)$ |
| O3 | C8 | $1.454(2)$ | C14 | C13 | $1.546(3)$ |
| O4 | C18 | $1.218(2)$ | C5 | C11 | $1.533(2)$ |
| O6 | C22 | $1.348(2)$ | C24 | C23 | $1.539(2)$ |
| O6 | C23 | $1.451(2)$ | C24 | C17 | $1.558(2)$ |
| O2 | C7 | $1.204(2)$ | C24 | C25 | $1.537(2)$ |
| O5 | C22 | $1.209(2)$ | C11 | C9 | $1.541(2)$ |
| C7 | C6 | $1.510(2)$ | C11 | C12 | $1.537(2)$ |
| C26 | C27 | $1.542(2)$ | C2 | C9 | $1.555(2)$ |
| C26 | C24 | $1.538(2)$ | C18 | C17 | $1.520(2)$ |
| C26 | C20 | $1.531(2)$ | C8 | C9 | $1.536(2)$ |
| C4 | C3 | $1.514(2)$ | C20 | C29 | $1.550(2)$ |
| C4 | C5 | $1.548(2)$ | C20 | C21 | $1.539(2)$ |
| C3 | C2 | $1.521(2)$ | C22 | C21 | $1.506(3)$ |
| C6 | C5 | $1.537(2)$ | C9 | C10 | $1.532(2)$ |
| C27 | C28 | $1.551(2)$ | C28 | C29 | $1.548(2)$ |
| C1 | C2 | $1.527(2)$ | C17 | C16 | $1.532(2)$ |
| C19 | C18 | $1.518(2)$ | C29 | C30 | $1.536(2)$ |
| C19 | C20 | $1.544(2)$ | C12 | C13 | $1.547(3)$ |

Table SI2.5.4.5. Bond Angles for 235.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C7 | O3 | C8 | 122.27(13) | C3 | C2 | C1 | 111.26(14) |
| C22 | O6 | C23 | 122.39(14) | C3 | C2 | C9 | 112.36(13) |
| O3 | C7 | C6 | 119.16(14) | C1 | C2 | C9 | 114.90(13) |
| O2 | C7 | O3 | 117.44(16) | O4 | C18 | C19 | 120.02(16) |
| O2 | C7 | C6 | 123.35(16) | O4 | C18 | C17 | 122.21(16) |
| C24 | C26 | C27 | 117.47(13) | C19 | C18 | C17 | 117.49(15) |
| C20 | C26 | C27 | 104.25(13) | O3 | C8 | C9 | 114.64(13) |
| C20 | C26 | C24 | 113.85(14) | C26 | C20 | C19 | 109.37(13) |
| C3 | C4 | C5 | 116.29(13) | C26 | C20 | C29 | 102.56(13) |
| O1 | C3 | C4 | 120.31(15) | C26 | C20 | C21 | 113.32(13) |
| O1 | C3 | C2 | 122.27(15) | C19 | C20 | C29 | 108.39(13) |
| C4 | C3 | C2 | 117.17(14) | C21 | C20 | C19 | 110.21(14) |
| C7 | C6 | C5 | 114.44(13) | C21 | C20 | C29 | 112.65(13) |
| C26 | C27 | C28 | 105.43(13) | O6 | C22 | C21 | 119.37(15) |
| C18 | C19 | C20 | 116.08(14) | O5 | C22 | O6 | 117.61(17) |
| C15 | C14 | C5 | 114.46(14) | O5 | C22 | C21 | 122.94(17) |
| C15 | C14 | C13 | 111.41(15) | O6 | C23 | C24 | 114.09(14) |
| C13 | C14 | C5 | 103.35(14) | C11 | C9 | C2 | 111.30(13) |
| C4 | C5 | C14 | 107.96(13) | C8 | C9 | C11 | 109.17(13) |
| C6 | C5 | C4 | 110.41(13) | C8 | C9 | C2 | 110.24(14) |
| C6 | C5 | C14 | 112.31(13) | C10 | C9 | C11 | 109.01(14) |
| C11 | C5 | C4 | 109.52(13) | C10 | C9 | C2 | 110.49(14) |
| C11 | C5 | C6 | 113.28(13) | C10 | C9 | C8 | 106.50(14) |
| C11 | C5 | C14 | 103.02(13) | C29 | C28 | C27 | 106.63(13) |
| C26 | C24 | C23 | 108.83(14) | C18 | C17 | C24 | 112.95(14) |
| C26 | C24 | C17 | 111.26(13) | C18 | C17 | C16 | 111.17(16) |
| C23 | C24 | C17 | 110.52(14) | C16 | C17 | C24 | 115.06(15) |
| C25 | C24 | C26 | 108.25(15) | C28 | C29 | C20 | 103.03(13) |
| C25 | C24 | C23 | 106.90(14) | C30 | C29 | C20 | 113.62(15) |
| C25 | C24 | C17 | 110.94(14) | C30 | C29 | C28 | 111.33(15) |
| C5 | C11 | C9 | 113.47(13) | C22 | C21 | C20 | 112.90(14) |
| C5 | C11 | C12 | 104.32(14) | C11 | C12 | C13 | 105.22(14) |
| C12 | C11 | C9 | 117.14(14) | C14 | C13 | C12 | 107.32(14) |

Table SI2.5.4.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 235.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H26 | 3481.03 | 3786.47 | 3821.84 | 20 |
| H4A | 9215.74 | 3619.83 | 7366.27 | 21 |
| H4B | 10710.21 | 3158.26 | 8088.96 | 21 |
| H6A | 12455.31 | 4755.34 | 9058.59 | 22 |
| H6B | 11390.06 | 5624.85 | 9626.91 | 22 |
| H27A | 1972.23 | 3644.37 | 2352.73 | 25 |
| H27B | 2015.12 | 5013.4 | 2137.52 | 25 |
| H1A | 6025.79 | 2120.03 | 9417.84 | 33 |
| H1B | 5247.24 | 3277.79 | 9801.39 | 33 |
| H1C | 6924.65 | 2818.78 | 10335.6 | 33 |
| H19A | 1496.86 | 6623.59 | 3356.02 | 23 |
| H19B | 2165.41 | 7089.18 | 4430.79 | 23 |
| H14 | 11287.99 | 4994.6 | 7121.36 | 25 |
| H15A | 10965.04 | 7144.57 | 8146.48 | 37 |
| H15B | 11864.6 | 7003.51 | 7171.62 | 37 |
| H15C | 12594.96 | 6417.11 | 8192.18 | 37 |
| H11 | 8884.62 | 6251.78 | 8900.63 | 22 |
| H2 | 6375.67 | 3701.27 | 8370.64 | 21 |
| H8A | 9172 | 5556.8 | 10477.48 | 26 |
| H8B | 7875.34 | 4719.05 | 10881.94 | 26 |
| H23A | 5941.96 | 4229.71 | 4545.34 | 29 |
| H23B | 7235.55 | 4871.85 | 3957.05 | 29 |
| H28A | -278.16 | 5231.76 | 2830.4 | 30 |
| H28B | -309.94 | 3866.36 | 3056.9 | 30 |
| H17 | 4117.54 | 6207.87 | 2175.33 | 25 |
| H29 | 113.79 | 5418.53 | 4494.47 | 26 |
| H16A | 7076.62 | 6911.82 | 3229.8 | 45 |
| H16B | 6169.79 | 7554 | 2282.97 | 45 |
| H16C | 6905.99 | 6289.59 | 2168.5 | 45 |
| H30A | 1508.05 | 3136.96 | 4657.82 | 43 |
| H30B | -325.08 | 3406.37 | 4797.26 | 43 |
| H30C | 1080.08 | 3896.14 | 5580.53 | 43 |
| H21A | 2777.55 | 5511.77 | 5806.21 | 26 |
| H21B | 3878.93 | 4495.16 | 5453.54 | 26 |
| H10A | 6403.53 | 6342.67 | 9688.92 | 43 |
| H10B | 5529.02 | 5188.78 | 9999.59 | 43 |
|  |  |  |  |  |


| H10C | 5391.7 | 5574.98 | 8859.42 | 43 |
| :---: | :---: | :---: | :---: | :---: |
| H12A | 7083.12 | 6455.78 | 7554.55 | 31 |
| H12B | 6941.5 | 5084.83 | 7351.58 | 31 |
| H25A | 5534.75 | 3380.21 | 2736 | 41 |
| H25B | 6578.83 | 4398.88 | 2330.16 | 41 |
| H25C | 4764.84 | 4201.5 | 1859.13 | 41 |
| H13A | 8840.45 | 5240.08 | 6318.63 | 37 |
| H13B | 9074.54 | 6588.7 | 6586.37 | 37 |

## SI2.5.5. X-Ray Crystallographic Data for Desilylated 245 (245desTBS)



A colorless plate $0.060 \times 0.050 \times 0.030 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at $100(2) \mathrm{K}$ using $\varphi$ and $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 20 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $100.0 \%$ complete to $67.000^{\circ}$ in $\theta$. A total of 108342 reflections were collected covering the indices, $-9<=h<=10,-25<=k<=20,-31<=l<=31.8537$ reflections were found to be symmetry independent, with an $\mathrm{R}_{\mathrm{int}}$ of 0.0440 . Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $\mathrm{P} 2_{2} 2_{1} 2_{1}$ (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined from the diffraction data.

Table SI2.5.5.1. Crystal data and structure refinement for 245desTBS.

| Identification code | 245desTBS |
| :--- | :--- |
| Empirical formula | $\mathrm{C}_{16} \mathrm{H}_{24} \mathrm{O}_{5}$ |
| Formula weight | 296.35 |
| Temperature $(\mathrm{K})$ | $100(2)$ |
| Crystal system | orthorhombic |
| Space group | $\mathrm{P} 212^{2} 2_{1}$ |
| $\mathrm{a}(\AA)$ | $8.3035(2)$ |
| $\mathrm{b}(\AA)$ | $21.4423(6)$ |
| $\mathrm{c}(\AA)$ | $26.1632(7)$ |
| $\alpha\left(^{\circ}\right)$ | 90 |
| $\beta\left({ }^{\circ}\right)$ | 90 |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume $\left(\AA^{\circ}\right)$ | $4658.3(2)$ |
| Z | 12 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.268 |
| $\mu\left(\mathrm{~mm}^{-1}\right)$ | 0.766 |
| $\mathrm{~F}(000)$ | 1920.0 |
| Crystal size $\left(\mathrm{mm}{ }^{3}\right)$ | $0.060 \times 0.050 \times 0.030$ |
| Radiation | $\mathrm{CuK} \alpha(\lambda=1.54178)$ |
| $2 \Theta$ range for data collection $\left({ }^{\circ}\right)$ | 5.328 to 136.978 |
| Index ranges | $-9 \leq \mathrm{h} \leq 10,-25 \leq \mathrm{k} \leq 20,-31 \leq 1 \leq 31$ |
| Reflections collected | 108342 |
| Independent reflections | $8537\left[\mathrm{R}_{\text {int }}=0.0440, \mathrm{R}_{\text {sigma }}=0.0231\right]$ |
| Data/restraints $/$ parameters | $8537 / 0 / 583$ |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.060 |
| Final R indexes $[\mathrm{I}>=2 \sigma(\mathrm{I})]$ | $\mathrm{R}_{1}=0.0407, \mathrm{wR}{ }_{2}=0.0873$ |
| Final R indexes $[$ all data $]$ | $\mathrm{R}_{1}=0.0450, \mathrm{wR}{ }_{2}=0.0892$ |
| Largest diff. peak/hole $\left(\mathrm{e} \AA \AA^{-3}\right)$ | $0.22 /-0.19$ |
| Flack parameter | $0.04(4)$ |
|  |  |

Table SI2.5.5.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 245desTBS. $U_{\text {eq }}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $y$ | $z$ | U(eq) |
| :---: | :---: | :---: | :---: | :---: |
| C1 | -6921(4) | -1949.4(14) | 777.6(12) | 28.6(7) |
| C2 | -7559(4) | -1607.5(14) | 293.7(12) | 26.8(6) |
| C3 | -7152(4) | -1902.8(14) | -224.2(12) | 30.1(7) |
| C4 | -7274(5) | -1371.0(16) | -599.1(12) | 38.1(8) |
| C5 | -6455(4) | -838.0(15) | -309.7(12) | 31.4(7) |
| C6 | -7172(4) | -886.9(14) | 240.6(11) | 26.1(6) |
| C7 | -5972(4) | -603.8(14) | 628.4(12) | 28.8(7) |
| C8 | -5265(4) | -1021.0(15) | 1026.2(11) | 30.6(7) |
| C9 | -5179(4) | -1717.3(15) | 895.8(12) | 30.5(7) |
| C10 | -10038(4) | -1093.0(14) | 346.6(11) | 29.5(7) |
| C11 | -8841(4) | -580.1(14) | 284.1(12) | 28.9(7) |
| C12 | -6540(4) | -192.3(15) | -555.5(13) | 38.2(8) |
| C13 | -6951(4) | -2662.9(14) | 693.4(13) | 35.4(8) |
| C14 | -8036(4) | -1817.0(15) | 1234.1(12) | 33.5(7) |
| C15 | -9367(4) | -991.3(17) | 1666.4(13) | 42.2(8) |
| C16 | -4318(5) | -2082.9(17) | 1308.9(13) | 42.6(8) |
| C17 | -3605(4) | 227.7(14) | 3428.4(12) | 30.3(7) |
| C18 | -4358(4) | -441.3(14) | 3405.2(12) | 27.7(6) |
| C19 | -4025(4) | -866.8(15) | 3865.7(11) | 30.3(7) |
| C20 | -4439(4) | -1513.9(15) | 3673.7(12) | 33.1(7) |
| C21 | -3693(4) | -1513.3(14) | 3142.2(12) | 29.6(7) |
| C22 | -4066(4) | -859.8(15) | 2912.9(11) | 28.3(7) |
| C23 | -2691(4) | -653.7(15) | 2551.3(12) | 32.1(7) |
| C24 | -2025(4) | -12.1(15) | 2626.7(12) | 32.1(7) |
| C25 | -1901(4) | 209.2(14) | 3181.9(13) | $31.9(7)$ |
| C26 | -6841(4) | -529.8(15) | 2989.1(12) | 30.9(7) |
| C27 | -5699(4) | -835.5(16) | 2636.0(12) | 33.8(7) |
| C28 | -4112(4) | -2072.9(16) | 2810.4(13) | 39.7(8) |
| C29 | -3494(4) | 451.4(16) | 3986.9(13) | 39.3(8) |
| C30 | -4677(4) | 695.9(16) | 3150.2(14) | 40.4(8) |
| C31 | -6087(5) | 859(2) | 2374.4(17) | 65.6(13) |
| C32 | -992(4) | 824.0(16) | 3210.6 (15) | 44.3(9) |
| C33 | -297(4) | 1788.8(15) | 569.4(11) | 30.5(7) |
| C34 | -1002(4) | 2166.2(14) | 1027.1(12) | 27.9(6) |
| C35 | -637(4) | 2870.2(14) | 1041.9(13) | 35.0(7) |


| C36 | $-867(4)$ | $3050.4(14)$ | $1595.0(14)$ | $37.9(8)$ |
| :---: | :---: | :---: | :---: | :---: |
| C37 | $-53(4)$ | $2515.9(14)$ | $1871.7(12)$ | $34.1(7)$ |
| C38 | $-654(4)$ | $1920.7(14)$ | $1588.7(11)$ | $27.1(6)$ |
| C39 | $604(4)$ | $1391.6(13)$ | $1647.9(11)$ | $27.7(6)$ |
| C40 | $1324(4)$ | $1121.1(14)$ | $1173.8(12)$ | $28.2(7)$ |
| C41 | $1421(4)$ | $1558.6(14)$ | $708.0(12)$ | $29.4(7)$ |
| C42 | $-3484(4)$ | $1841.2(14)$ | $1353.2(12)$ | $30.8(7)$ |
| C43 | $-2328(4)$ | $1708.1(15)$ | $1773.4(12)$ | $31.5(7)$ |
| C44 | $-214(5)$ | $2509.9(18)$ | $2453.4(14)$ | $47.6(9)$ |
| C45 | $-265(5)$ | $2192.1(18)$ | $83.3(13)$ | $42.4(9)$ |
| C46 | $-1379(4)$ | $1227.3(16)$ | $456.4(13)$ | $38.1(8)$ |
| C47 | $-2747(5)$ | $396.6(17)$ | $864.2(18)$ | $55.0(11)$ |
| C48 | $2318(4)$ | $1242.2(16)$ | $272.4(13)$ | $37.2(8)$ |
| O1 | $-8292(3)$ | $-1167.9(10)$ | $1272.3(8)$ | $34.6(5)$ |
| O2 | $-9333(2)$ | $-1650.9(9)$ | $322.8(8)$ | $28.7(5)$ |
| O3 | $-11486(3)$ | $-1045.6(11)$ | $400.8(10)$ | $40.7(6)$ |
| O4 | $-4656(3)$ | $-815.3(11)$ | $1415.5(8)$ | $40.9(6)$ |
| O5 | $-4300(3)$ | $-1757.1(10)$ | $426.3(8)$ | $31.7(5)$ |
| O6 | $-4950(3)$ | $486.0(12)$ | $2647.3(9)$ | $45.8(6)$ |
| O7 | $-6126(2)$ | $-351.5(10)$ | $3422.5(8)$ | $31.0(5)$ |
| O8 | $-8282(3)$ | $-447.7(11)$ | $2922.7(9)$ | $38.8(6)$ |
| O9 | $-1475(3)$ | $281.2(12)$ | $2271.4(9)$ | $44.6(6)$ |
| O10 | $-1052(3)$ | $-267.2(10)$ | $3451.2(8)$ | $32.4(5)$ |
| O11 | $-1641(3)$ | $898.7(10)$ | $915.8(9)$ | $38.9(5)$ |
| O12 | $-2765(3)$ | $2141.9(10)$ | $968.3(8)$ | $32.6(5)$ |
| O13 | $-4913(3)$ | $1729.8(11)$ | $1343.1(9)$ | $39.8(6)$ |
| O14 | $1920(3)$ | $606.7(10)$ | $1171.7(9)$ | $38.7(6)$ |
| O15 | $2291(3)$ | $2098.4(10)$ | $873.3(9)$ | $31.5(5)$ |

Table SI2.5.5.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 245desTBS. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[\mathrm{~h}^{2} \mathrm{a}^{* 2} \mathrm{U}_{11}+2 \mathrm{hka} \mathrm{h}^{*} \mathrm{~b}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | $31.0(18)$ | $25.3(15)$ | $29.4(16)$ | $1.4(12)$ | $3.3(13)$ | $-2.8(13)$ |
| C2 | $18.6(15)$ | $28.6(16)$ | $33.3(16)$ | $-5.3(13)$ | $0.2(12)$ | $-1.7(12)$ |
| C3 | $23.2(16)$ | $31.8(16)$ | $35.3(17)$ | $-7.3(13)$ | $-2.1(13)$ | $-2.1(13)$ |
| C4 | $46(2)$ | $38.9(19)$ | $29.0(16)$ | $-5.1(14)$ | $1.7(15)$ | $2.4(16)$ |
| C5 | $28.6(16)$ | $32.7(16)$ | $33.0(16)$ | $0.4(13)$ | $4.7(14)$ | $-0.6(14)$ |
| C6 | $23.8(15)$ | $24.4(15)$ | $30.1(15)$ | $0.8(12)$ | $0.4(13)$ | $-1.0(12)$ |
| C7 | $26.7(16)$ | $24.3(15)$ | $35.6(16)$ | $-5.2(12)$ | $2.0(13)$ | $-5.1(13)$ |
| C8 | $26.6(16)$ | $38.0(17)$ | $27.1(16)$ | $-4.0(13)$ | $4.0(13)$ | $-5.6(14)$ |
| C9 | $27.9(16)$ | $34.1(17)$ | $29.4(15)$ | $1.0(13)$ | $1.2(13)$ | $-0.4(14)$ |
| C10 | $27.3(17)$ | $29.5(16)$ | $31.6(16)$ | $-3.3(12)$ | $1.3(13)$ | $-2.0(13)$ |
| C11 | $27.6(16)$ | $27.3(15)$ | $31.8(16)$ | $-1.1(13)$ | $-0.1(13)$ | $-0.6(13)$ |
| C12 | $38(2)$ | $36.2(18)$ | $40.7(19)$ | $6.7(14)$ | $8.6(16)$ | $-1.0(15)$ |
| C13 | $34.7(19)$ | $26.2(16)$ | $45.3(19)$ | $2.9(14)$ | $0.7(15)$ | $-2.0(14)$ |
| C14 | $34.4(18)$ | $33.8(17)$ | $32.4(17)$ | $3.7(13)$ | $3.8(14)$ | $-3.6(14)$ |
| C15 | $39(2)$ | $53(2)$ | $35.2(18)$ | $-9.1(16)$ | $8.4(15)$ | $-1.9(17)$ |
| C16 | $41(2)$ | $48(2)$ | $39.1(19)$ | $5.7(16)$ | $-6.9(16)$ | $-0.2(18)$ |
| C17 | $27.2(16)$ | $28.4(16)$ | $35.4(17)$ | $1.3(13)$ | $3.0(14)$ | $4.2(13)$ |
| C18 | $21.3(15)$ | $33.1(17)$ | $28.8(15)$ | $1.1(13)$ | $1.8(12)$ | $1.7(13)$ |
| C19 | $27.5(17)$ | $35.7(17)$ | $27.6(15)$ | $2.3(13)$ | $1.1(13)$ | $-1.4(14)$ |
| C20 | $31.1(17)$ | $31.7(17)$ | $36.6(17)$ | $4.6(13)$ | $0.6(14)$ | $-3.6(14)$ |
| C21 | $24.0(16)$ | $30.8(16)$ | $34.1(16)$ | $0.0(13)$ | $-2.6(13)$ | $-0.4(13)$ |
| C22 | $21.7(16)$ | $36.5(17)$ | $26.8(15)$ | $0.0(13)$ | $1.2(12)$ | $0.3(13)$ |
| C23 | $29.5(17)$ | $40.4(18)$ | $26.4(16)$ | $1.9(13)$ | $2.7(13)$ | $1.3(14)$ |
| C24 | $20.9(15)$ | $38.2(17)$ | $37.2(17)$ | $11.9(14)$ | $4.0(13)$ | $6.4(13)$ |
| C25 | $24.5(17)$ | $27.0(16)$ | $44.2(18)$ | $4.4(13)$ | $0.4(14)$ | $-0.9(13)$ |
| C26 | $28.2(18)$ | $32.3(17)$ | $32.1(16)$ | $5.4(13)$ | $-0.2(13)$ | $1.6(14)$ |
| C27 | $26.7(17)$ | $43.6(19)$ | $31.1(16)$ | $-1.5(14)$ | $-1.2(13)$ | $6.4(15)$ |
| C28 | $34.8(19)$ | $37.8(19)$ | $47(2)$ | $-8.3(15)$ | $0.5(16)$ | $-2.8(15)$ |
| C29 | $37.6(19)$ | $34.4(18)$ | $46(2)$ | $-6.9(15)$ | $4.4(16)$ | $0.3(15)$ |
| C30 | $31.3(19)$ | $33.7(18)$ | $56(2)$ | $6.9(16)$ | $7.1(16)$ | $5.4(15)$ |
| C31 | $40(2)$ | $87(3)$ | $70(3)$ | $42(3)$ | $5(2)$ | $18(2)$ |
| C32 | $33(2)$ | $36.5(19)$ | $63(2)$ | $2.9(17)$ | $6.2(17)$ | $-3.1(16)$ |
| C33 | $30.3(18)$ | $33.1(17)$ | $27.9(16)$ | $1.5(13)$ | $-4.2(13)$ | $-5.0(14)$ |
| C34 | $20.1(15)$ | $28.1(15)$ | $35.4(16)$ | $3.6(13)$ | $-1.8(12)$ | $0.5(12)$ |
| C35 | $29.0(17)$ | $28.0(16)$ | $48.0(19)$ | $8.0(14)$ | $-2.2(15)$ | $3.5(14)$ |
| C36 | $29.1(18)$ | $25.3(16)$ | $59(2)$ | $-6.4(15)$ | $-3.0(16)$ | $0.1(14)$ |
|  |  |  |  |  |  |  |


| C37 | $29.7(18)$ | $30.5(17)$ | $42.0(18)$ | $-8.7(14)$ | $-4.7(14)$ | $1.8(14)$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C38 | $25.8(16)$ | $26.7(15)$ | $29.0(15)$ | $-3.3(12)$ | $-0.8(13)$ | $-0.3(13)$ |
| C39 | $27.9(16)$ | $25.4(15)$ | $29.7(15)$ | $4.2(12)$ | $-2.0(13)$ | $-0.2(13)$ |
| C40 | $24.1(16)$ | $24.7(16)$ | $35.8(16)$ | $-1.9(12)$ | $-2.3(13)$ | $-0.6(13)$ |
| C41 | $28.2(16)$ | $28.3(16)$ | $31.6(16)$ | $-3.1(13)$ | $0.3(13)$ | $-2.6(13)$ |
| C42 | $27.8(17)$ | $25.0(15)$ | $39.6(18)$ | $-1.8(13)$ | $-1.0(14)$ | $0.4(13)$ |
| C43 | $26.6(17)$ | $31.6(17)$ | $36.5(17)$ | $-0.9(13)$ | $0.9(13)$ | $-0.4(14)$ |
| C44 | $47(2)$ | $53(2)$ | $43(2)$ | $-16.1(17)$ | $-2.7(17)$ | $0.7(19)$ |
| C45 | $36(2)$ | $57(2)$ | $33.4(18)$ | $9.9(16)$ | $-2.5(15)$ | $4.4(18)$ |
| C46 | $30.0(18)$ | $46(2)$ | $38.7(18)$ | $-7.4(15)$ | $-6.8(15)$ | $-2.6(15)$ |
| C47 | $37(2)$ | $33(2)$ | $95(3)$ | $-13(2)$ | $1(2)$ | $-10.8(17)$ |
| C48 | $34.2(19)$ | $40.1(19)$ | $37.2(18)$ | $-2.8(15)$ | $6.5(15)$ | $0.4(15)$ |
| O1 | $37.4(13)$ | $34.0(12)$ | $32.3(11)$ | $-3.8(9)$ | $11.4(10)$ | $-1.4(10)$ |
| O2 | $22.3(11)$ | $25.9(11)$ | $37.8(12)$ | $-3.8(9)$ | $1.6(9)$ | $-2.8(9)$ |
| O3 | $23.4(12)$ | $38.5(13)$ | $60.2(15)$ | $-8.3(11)$ | $3.9(11)$ | $-1.4(10)$ |
| O4 | $44.4(15)$ | $47.8(14)$ | $30.5(12)$ | $-7.1(10)$ | $-3.8(11)$ | $-8.2(12)$ |
| O5 | $25.8(11)$ | $34.0(12)$ | $35.3(12)$ | $-5.2(9)$ | $2.8(9)$ | $-2.4(10)$ |
| O6 | $36.5(14)$ | $56.2(16)$ | $44.8(14)$ | $18.6(12)$ | $0.2(11)$ | $13.3(12)$ |
| O7 | $21.8(11)$ | $39.0(12)$ | $32.3(11)$ | $-0.3(9)$ | $4.1(9)$ | $2.4(9)$ |
| O8 | $24.1(12)$ | $49.5(14)$ | $43.0(13)$ | $3.9(11)$ | $1.2(10)$ | $4.0(11)$ |
| O9 | $40.0(14)$ | $47.8(14)$ | $46.0(14)$ | $18.6(12)$ | $9.6(12)$ | $2.9(12)$ |
| O10 | $25.2(12)$ | $36.1(12)$ | $36.1(12)$ | $3.6(10)$ | $0.2(10)$ | $3.3(10)$ |
| O11 | $33.8(13)$ | $30.2(12)$ | $52.7(14)$ | $-1.7(10)$ | $-3.5(11)$ | $-9.4(10)$ |
| O12 | $24.2(11)$ | $33.0(12)$ | $40.4(13)$ | $4.0(10)$ | $-7.2(9)$ | $1.4(9)$ |
| O13 | $22.6(12)$ | $42.5(14)$ | $54.2(15)$ | $2.8(11)$ | $-4.1(11)$ | $-1.4(11)$ |
| O14 | $43.2(14)$ | $27.0(12)$ | $46.0(14)$ | $-0.6(10)$ | $1.6(11)$ | $6.4(11)$ |
| O15 | $25.0(12)$ | $27.7(11)$ | $41.9(13)$ | $1.2(9)$ | $-2.2(10)$ | $-1.7(9)$ |

Table SI2.5.5.4. Bond Lengths for 245desTBS.

| Atom | Atom | Length (A) | Atom | Atom | Length $(\AA)$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | C14 | $1.538(4)$ | C22 | C23 | $1.547(4)$ |
| C1 | C13 | $1.546(4)$ | C23 | C24 | $1.496(5)$ |
| C1 | C2 | $1.556(4)$ | C24 | O9 | $1.212(4)$ |
| C1 | C9 | $1.560(4)$ | C24 | C25 | $1.532(5)$ |
| C2 | O2 | $1.477(3)$ | C25 | O10 | $1.427(4)$ |
| C2 | C3 | $1.534(4)$ | C25 | C32 | $1.521(4)$ |
| C2 | C6 | $1.584(4)$ | C26 | O8 | $1.221(4)$ |
| C3 | C4 | $1.508(5)$ | C26 | O7 | $1.336(4)$ |
| C4 | C5 | $1.531(4)$ | C26 | C27 | $1.477(4)$ |
| C5 | C12 | $1.528(4)$ | C30 | O6 | $1.409(4)$ |
| C5 | C6 | $1.562(4)$ | C31 | O6 | $1.428(4)$ |
| C6 | C11 | $1.538(4)$ | C33 | C46 | $1.531(4)$ |
| C6 | C7 | $1.546(4)$ | C33 | C45 | $1.538(4)$ |
| C7 | C8 | $1.493(4)$ | C33 | C41 | $1.553(5)$ |
| C8 | O4 | $1.220(4)$ | C33 | C34 | $1.559(4)$ |
| C8 | C9 | $1.533(4)$ | C34 | O12 | $1.473(4)$ |
| C9 | O5 | $1.431(4)$ | C34 | C35 | $1.540(4)$ |
| C9 | C16 | $1.515(4)$ | C34 | C38 | $1.587(4)$ |
| C10 | O3 | $1.215(4)$ | C35 | C36 | $1.510(5)$ |
| C10 | O2 | $1.334(4)$ | C36 | C37 | $1.515(4)$ |
| C10 | C11 | $1.491(4)$ | C37 | C44 | $1.528(5)$ |
| C14 | O1 | $1.412(4)$ | C37 | C38 | $1.558(4)$ |
| C15 | O1 | $1.416(4)$ | C38 | C43 | $1.541(4)$ |
| C17 | C30 | $1.526(4)$ | C38 | C39 | $1.550(4)$ |
| C17 | C29 | $1.541(4)$ | C39 | C40 | $1.494(4)$ |
| C17 | C25 | $1.555(4)$ | C40 | O14 | $1.209(4)$ |
| C17 | C18 | $1.566(4)$ | C40 | C41 | $1.540(4)$ |
| C18 | O7 | $1.481(4)$ | C41 | O15 | $1.431(4)$ |
| C18 | C19 | $1.536(4)$ | C41 | C48 | $1.521(4)$ |
| C18 | C22 | $1.588(4)$ | C42 | O13 | $1.211(4)$ |
| C19 | C20 | $1.515(4)$ | C42 | O12 | $1.337(4)$ |
| C20 | C21 | $1.523(4)$ | C42 | C43 | $1.487(4)$ |
| C21 | C28 | $1.521(4)$ | C46 | O11 | $1.410(4)$ |
| C21 | C22 | $1.555(4)$ | C47 | O11 | $1.421(4)$ |
| C22 | C27 | $1.539(4)$ |  |  |  |
|  |  |  |  |  |  |

Table SI2.5.5.5. Bond Angles for 245desTBS.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C14 | C1 | C13 | 106.5(3) | C21 | C22 | C18 | 103.1(2) |
| C14 | C1 | C2 | 109.8(3) | C24 | C23 | C22 | 117.1(3) |
| C13 | C1 | C2 | 110.2(3) | O9 | C24 | C23 | 121.0(3) |
| C14 | C1 | C9 | 110.2(3) | O9 | C24 | C25 | 122.8(3) |
| C13 | C1 | C9 | 111.0(3) | C23 | C24 | C25 | 115.8(3) |
| C2 | C1 | C9 | 109.1(2) | O10 | C25 | C32 | 110.5(3) |
| O2 | C2 | C3 | 103.8(2) | O10 | C25 | C24 | 106.2(2) |
| O2 | C2 | C1 | 105.5(2) | C32 | C25 | C24 | 110.4(3) |
| C3 | C2 | C1 | 116.7(3) | O10 | C25 | C17 | 105.2(2) |
| O2 | C2 | C6 | 105.5(2) | C32 | C25 | C17 | 114.1(3) |
| C3 | C2 | C6 | 106.3(2) | C24 | C25 | C17 | 109.9(3) |
| C1 | C2 | C6 | 117.5(2) | O8 | C26 | O7 | 121.0(3) |
| C4 | C3 | C2 | 104.3(2) | O8 | C26 | C27 | 127.1(3) |
| C3 | C4 | C5 | 102.3(3) | O7 | C26 | C27 | 111.9(3) |
| C12 | C5 | C4 | 116.6(3) | C26 | C27 | C22 | 106.6(3) |
| C12 | C5 | C6 | 115.5(3) | O6 | C30 | C17 | 109.2(3) |
| C4 | C5 | C6 | 103.7(2) | C46 | C33 | C45 | 107.0(3) |
| C11 | C6 | C7 | 111.3(2) | C46 | C33 | C41 | 109.5(3) |
| C11 | C6 | C5 | 112.5(2) | C45 | C33 | C41 | 110.9(3) |
| C7 | C6 | C5 | 109.4(2) | C46 | C33 | C34 | 109.6(3) |
| C11 | C6 | C2 | 103.2(2) | C45 | C33 | C34 | 110.5(3) |
| C7 | C6 | C2 | 117.1(2) | C41 | C33 | C34 | 109.3(2) |
| C5 | C6 | C2 | 102.9(2) | O12 | C34 | C35 | 103.5(2) |
| C8 | C7 | C6 | 118.4(3) | O12 | C34 | C33 | 105.9(2) |
| O4 | C8 | C7 | 121.9(3) | C35 | C34 | C33 | 117.0(3) |
| O4 | C8 | C9 | 121.3(3) | O12 | C34 | C38 | 105.5(2) |
| C7 | C8 | C9 | 116.5(3) | C35 | C34 | C38 | 105.4(2) |
| O5 | C9 | C16 | 109.9(3) | C33 | C34 | C38 | 118.0(2) |
| O5 | C9 | C8 | 105.8(2) | C36 | C35 | C34 | 104.5(3) |
| C16 | C9 | C8 | 111.5(3) | C35 | C36 | C37 | 102.0(3) |
| O5 | C9 | C1 | 106.5(2) | C36 | C37 | C44 | 116.3(3) |
| C16 | C9 | C1 | 114.4(3) | C36 | C37 | C38 | 104.5(3) |
| C8 | C9 | C1 | 108.2(3) | C44 | C37 | C38 | 116.0(3) |
| O3 | C10 | O2 | 121.0(3) | C43 | C38 | C39 | 111.1(2) |
| O3 | C10 | C11 | 127.6(3) | C43 | C38 | C37 | 112.5(3) |
| O2 | C10 | C11 | 111.3(3) | C39 | C38 | C37 | 109.7(3) |
| C10 | C11 | C6 | 107.1(2) | C43 | C38 | C34 | 102.9(2) |


| O1 | C 14 | C 1 | $109.1(2)$ | C 39 | C 38 | C 34 | $117.3(2)$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C 30 | C 17 | C 29 | $106.4(3)$ | C 37 | C 38 | C 34 | $103.1(2)$ |
| C 30 | C 17 | C 25 | $110.4(3)$ | C 40 | C 39 | C 38 | $118.1(3)$ |
| C 29 | C 17 | C 25 | $110.3(3)$ | O 14 | C 40 | C 39 | $121.4(3)$ |
| C 30 | C 17 | C 18 | $110.5(3)$ | O 14 | C 40 | C 41 | $122.1(3)$ |
| C 29 | C 17 | C 18 | $110.2(3)$ | C 39 | C 40 | C 41 | $116.2(2)$ |
| C 25 | C 17 | C 18 | $108.9(2)$ | O 15 | C 41 | C 48 | $109.9(3)$ |
| O 7 | C 18 | C 19 | $103.4(2)$ | O 15 | C 41 | C 40 | $106.2(2)$ |
| O 7 | C 18 | C 17 | $106.0(2)$ | C 48 | C 41 | C 40 | $110.3(3)$ |
| C 19 | C 18 | C 17 | $116.2(3)$ | O 15 | C 41 | C 33 | $106.1(2)$ |
| O 7 | C 18 | C 22 | $104.5(2)$ | C 48 | C 41 | C 33 | $114.6(3)$ |
| C 19 | C 18 | C 22 | $105.8(2)$ | C 40 | C 41 | C 33 | $109.3(3)$ |
| C 17 | C 18 | C 22 | $119.2(2)$ | O 13 | C 42 | O 12 | $121.1(3)$ |
| C 20 | C 19 | C 18 | $104.1(2)$ | O 13 | C 42 | C 43 | $127.7(3)$ |
| C 19 | C 20 | C 21 | $102.1(2)$ | O 12 | C 42 | C 43 | $111.2(3)$ |
| C 28 | C 21 | C 20 | $115.3(3)$ | C 42 | C 43 | C 38 | $107.1(3)$ |
| C 28 | C 21 | C 22 | $116.4(3)$ | O 11 | C 46 | C 33 | $108.6(3)$ |
| C 20 | C 21 | C 22 | $105.8(2)$ | C 14 | O 1 | C 15 | $114.2(2)$ |
| C 27 | C 22 | C 23 | $110.6(2)$ | C 10 | O 2 | C 2 | $112.6(2)$ |
| C 27 | C 22 | C 21 | $112.8(3)$ | C 30 | O 6 | C 31 | $113.2(3)$ |
| C 23 | C 22 | C 21 | $110.3(3)$ | C 26 | O 7 | C 18 | $112.2(2)$ |
| C 27 | C 22 | C 18 | $103.2(2)$ | C 46 | O 11 | C 47 | $113.4(3)$ |
| C 23 | C 22 | C 18 | $116.6(3)$ | C 42 | O 12 | C 34 | $112.5(2)$ |

Table SI2.5.5.6. Torsion Angles for 245desTBS

| A | B | C | D | Angle ( ${ }^{\circ}$ ) | A | B | C | D | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C14 | C1 | C2 | O2 | -37.4(3) | C23 | C24 | C25 | C32 | 171.9(3) |
| C13 | C1 | C2 | O2 | 79.6(3) | O9 | C24 | C25 | C17 | 125.9(3) |
| C9 | C1 | C2 | O2 | -158.3(2) | C23 | C24 | C25 | C17 | -61.3(3) |
| C14 | C1 | C2 | C3 | -152.1(3) | C30 | C17 | C25 | O10 | -176.5(3) |
| C13 | C1 | C2 | C3 | -35.1(4) | C29 | C17 | C25 | O10 | 66.1(3) |
| C9 | C1 | C2 | C3 | 87.0(3) | C18 | C17 | C25 | O10 | -55.0(3) |
| C14 | C1 | C2 | C6 | 79.9(3) | C30 | C17 | C25 | C32 | 62.1(4) |
| C13 | C1 | C2 | C6 | -163.1(3) | C29 | C17 | C25 | C32 | -55.2(4) |
| C9 | C1 | C2 | C6 | -41.0(3) | C18 | C17 | C25 | C32 | -176.3(3) |
| O2 | C2 | C3 | C4 | 87.2(3) | C30 | C17 | C25 | C24 | -62.5(3) |
| C1 | C2 | C3 | C4 | -157.1(3) | C29 | C17 | C25 | C24 | -179.9(3) |
| C6 | C2 | C3 | C4 | -23.8(3) | C18 | C17 | C25 | C24 | 59.0(3) |
| C2 | C3 | C4 | C5 | 42.3(3) | O8 | C26 | C27 | C22 | -176.3(3) |
| C3 | C4 | C5 | C12 | -172.8(3) | O7 | C26 | C27 | C22 | 2.1(4) |
| C3 | C4 | C5 | C6 | -44.7(3) | C23 | C22 | C27 | C26 | -134.5(3) |
| C12 | C5 | C6 | C11 | 47.5(4) | C21 | C22 | C27 | C26 | 101.4(3) |
| C4 | C5 | C6 | C11 | -81.4(3) | C18 | C22 | C27 | C26 | -9.1(3) |
| C12 | C5 | C6 | C7 | -76.9(3) | C29 | C17 | C30 | O6 | -174.6(3) |
| C4 | C5 | C6 | C7 | 154.3(3) | C25 | C17 | C30 | O6 | 65.7(3) |
| C12 | C5 | C6 | C2 | 157.9(3) | C18 | C17 | C30 | O6 | -54.9(3) |
| C4 | C5 | C6 | C2 | 29.1(3) | C46 | C33 | C34 | O12 | -37.0(3) |
| O2 | C2 | C6 | C11 | 3.9(3) | C45 | C33 | C34 | O 12 | 80.7(3) |
| C3 | C2 | C6 | C11 | 113.8(3) | C41 | C33 | C34 | O12 | -157.1(2) |
| C1 | C2 | C6 | C11 | -113.4(3) | C46 | C33 | C34 | C35 | -151.7(3) |
| O2 | C2 | C6 | C7 | 126.6(3) | C45 | C33 | C34 | C35 | -34.0(4) |
| C3 | C2 | C6 | C7 | -123.5(3) | C41 | C33 | C34 | C35 | 88.3(3) |
| C1 | C2 | C6 | C7 | 9.3(4) | C46 | C33 | C34 | C38 | 80.8(3) |
| O2 | C2 | C6 | C5 | -113.3(3) | C45 | C33 | C34 | C38 | -161.5(3) |
| C3 | C2 | C6 | C5 | -3.5(3) | C41 | C33 | C34 | C38 | -39.3(3) |
| C1 | C2 | C6 | C5 | 129.4(3) | O12 | C34 | C35 | C36 | 85.5(3) |
| C11 | C6 | C7 | C8 | 118.1(3) | C33 | C34 | C35 | C36 | -158.5(3) |
| C5 | C6 | C7 | C8 | -116.8(3) | C38 | C34 | C35 | C36 | -25.0(3) |
| C2 | C6 | C7 | C8 | -0.3(4) | C34 | C35 | C36 | C37 | 42.9(3) |
| C6 | C7 | C8 | O4 | -160.9(3) | C35 | C36 | C37 | C44 | -173.7(3) |
| C6 | C7 | C8 | C9 | 25.4(4) | C35 | C36 | C37 | C38 | -44.4(3) |
| O4 | C8 | C9 | O5 | -118.0(3) | C36 | C37 | C38 | C43 | -82.0(3) |
| C7 | C8 | C9 | O5 | 55.8(3) | C44 | C37 | C38 | C43 | 47.5(4) |


| O4 | C8 | C9 | C16 | 1.6(4) | C36 | C37 | C38 | C39 | 153.8(3) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C7 | C8 | C9 | C16 | 175.4(3) | C44 | C37 | C38 | C39 | -76.7(4) |
| O4 | C8 | C9 | C1 | 128.3(3) | C36 | C37 | C38 | C34 | 28.2(3) |
| C7 | C8 | C9 | C1 | -58.0(3) | C44 | C37 | C38 | C34 | 157.6(3) |
| C14 | C1 | C9 | O5 | -170.1(2) | O12 | C34 | C38 | C43 | 6.1(3) |
| C13 | C1 | C9 | O5 | 72.1(3) | C35 | C34 | C38 | C43 | 115.2(3) |
| C2 | C1 | C9 | O5 | -49.5(3) | C33 | C34 | C38 | C43 | -111.9(3) |
| C14 | C1 | C9 | C16 | 68.2(3) | O12 | C34 | C38 | C39 | 128.4(3) |
| C13 | C1 | C9 | C16 | -49.6(4) | C35 | C34 | C38 | C39 | -122.5(3) |
| C2 | C1 | C9 | C16 | -171.1(3) | C33 | C34 | C38 | C39 | 10.4(4) |
| C14 | C1 | C9 | C8 | -56.8(3) | O12 | C34 | C38 | C37 | -111.0(3) |
| C13 | C1 | C9 | C8 | -174.5(2) | C35 | C34 | C38 | C37 | -1.9(3) |
| C2 | C1 | C9 | C8 | 63.9(3) | C33 | C34 | C38 | C37 | 131.0(3) |
| O3 | C10 | C11 | C6 | 178.9(3) | C43 | C38 | C39 | C40 | 114.2(3) |
| O2 | C10 | C11 | C6 | -2.8(3) | C37 | C38 | C39 | C40 | -120.8(3) |
| C7 | C6 | C11 | C10 | -127.4(3) | C34 | C38 | C39 | C40 | -3.8(4) |
| C5 | C6 | C11 | C10 | 109.4(3) | C38 | C39 | C40 | O14 | -157.9(3) |
| C2 | C6 | C11 | C10 | -0.9(3) | C38 | C39 | C40 | C41 | 28.2(4) |
| C13 | C1 | C14 | O1 | -169.4(3) | O14 | C40 | C41 | O15 | -118.2(3) |
| C2 | C1 | C14 | O1 | -50.1(3) | C39 | C40 | C41 | O15 | 55.7(3) |
| C9 | C1 | C14 | O1 | 70.1(3) | O14 | C40 | C41 | C48 | 0.8(4) |
| C30 | C17 | C18 | O7 | -34.1(3) | C39 | C40 | C41 | C48 | 174.7(3) |
| C29 | C17 | C18 | O7 | 83.3(3) | O14 | C40 | C41 | C33 | 127.7(3) |
| C25 | C17 | C18 | O7 | -155.6(2) | C39 | C40 | C41 | C33 | -58.4(3) |
| C30 | C17 | C18 | C19 | -148.3(3) | C46 | C33 | C41 | O15 | -172.5(2) |
| C29 | C17 | C18 | C19 | -30.9(4) | C45 | C33 | C41 | O15 | 69.6(3) |
| C25 | C17 | C18 | C19 | 90.2(3) | C34 | C33 | C41 | O15 | -52.4(3) |
| C30 | C17 | C18 | C22 | 83.2(3) | C46 | C33 | C41 | C48 | 66.1(3) |
| C29 | C17 | C18 | C22 | -159.5(3) | C45 | C33 | C41 | C48 | -51.8(4) |
| C25 | C17 | C18 | C22 | -38.3(4) | C34 | C33 | C41 | C48 | -173.8(3) |
| O7 | C18 | C19 | C20 | 80.8(3) | C46 | C33 | C41 | C40 | -58.3(3) |
| C17 | C18 | C19 | C20 | -163.6(3) | C45 | C33 | C41 | C40 | -176.2(3) |
| C22 | C18 | C19 | C20 | -28.8(3) | C34 | C33 | C41 | C40 | 61.8(3) |
| C18 | C19 | C20 | C21 | 42.9(3) | O13 | C42 | C43 | C38 | 178.2(3) |
| C19 | C20 | C21 | C28 | -171.3(3) | O12 | C42 | C43 | C38 | -4.8(3) |
| C19 | C20 | C21 | C22 | -41.1(3) | C39 | C38 | C43 | C42 | -127.6(3) |
| C28 | C21 | C22 | C27 | 41.7(4) | C37 | C38 | C43 | C42 | 109.1(3) |
| C20 | C21 | C22 | C27 | -87.8(3) | C34 | C38 | C43 | C42 | -1.2(3) |
| C28 | C21 | C22 | C23 | -82.6(3) | C45 | C33 | C46 | O11 | -170.9(3) |


| C 20 | C 21 | C 22 | C 23 | $147.9(3)$ | C 41 | C 33 | C 46 | O 11 | $68.8(3)$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C 28 | C 21 | C 22 | C 18 | $152.3(3)$ | C 34 | C 33 | C 46 | O 11 | $-51.1(3)$ |
| C 20 | C 21 | C 22 | C 18 | $22.8(3)$ | C 1 | C 14 | O 1 | C 15 | $177.2(3)$ |
| O 7 | C 18 | C 22 | C 27 | $12.5(3)$ | O 3 | C 10 | O 2 | C 2 | $-175.9(3)$ |
| C 19 | C 18 | C 22 | C 27 | $121.3(3)$ | C 11 | C 10 | O 2 | C 2 | $5.7(3)$ |
| C 17 | C 18 | C 22 | C 27 | $-105.6(3)$ | C 3 | C 2 | O 2 | C 10 | $-117.7(3)$ |
| O 7 | C 18 | C 22 | C 23 | $133.9(3)$ | C 1 | C 2 | O 2 | C 10 | $119.0(3)$ |
| C 19 | C 18 | C 22 | C 23 | $-117.3(3)$ | C 6 | C 2 | O 2 | C 10 | $-6.1(3)$ |
| C 17 | C 18 | C 22 | C 23 | $15.9(4)$ | C 17 | C 30 | O 6 | C 31 | $173.5(3)$ |
| O 7 | C 18 | C 22 | C 21 | $-105.1(3)$ | O 8 | C 26 | O 7 | C 18 | $-174.8(3)$ |
| C 19 | C 18 | C 22 | C 21 | $3.7(3)$ | C 27 | C 26 | O 7 | C 18 | $6.7(4)$ |
| C 17 | C 18 | C 22 | C 21 | $136.8(3)$ | C 19 | C 18 | O 7 | C 26 | $-122.8(3)$ |
| C 27 | C 22 | C 23 | C 24 | $103.6(3)$ | C 17 | C 18 | O 7 | C 26 | $114.5(3)$ |
| C 21 | C 22 | C 23 | C 24 | $-130.9(3)$ | C 22 | C 18 | O 7 | C 26 | $-12.3(3)$ |
| C 18 | C 22 | C 23 | C 24 | $-13.8(4)$ | C 33 | C 46 | O 11 | C 47 | $174.9(3)$ |
| C 22 | C 23 | C 24 | O 9 | $-150.0(3)$ | O 13 | C 42 | O 12 | C 34 | $-173.4(3)$ |
| C 22 | C 23 | C 24 | C 25 | $37.1(4)$ | C 43 | C 42 | O 12 | C 34 | $9.4(4)$ |
| O9 | C 24 | C 25 | O 10 | $-120.7(3)$ | C 35 | C 34 | O 12 | C 42 | $-120.3(3)$ |
| C 23 | C 24 | C 25 | O 10 | $52.0(3)$ | C 33 | C 34 | O 12 | C 42 | $116.1(3)$ |
| O9 | C 24 | C 25 | C 32 | $-0.8(4)$ | C 38 | C 34 | O 12 | C 42 | $-9.8(3)$ |

Table SI2.5.5.7. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters ( $\AA^{2} \times 10^{3}$ ) for 245desTBS.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H3A | -6050.53 | -2079.89 | -221.73 | 36 |
| H3B | -7927.16 | -2237.44 | -310.13 | 36 |
| H4A | -8411.26 | -1270.43 | -677.19 | 46 |
| H4B | -6700.27 | -1467.57 | -921.23 | 46 |
| H5 | -5287.55 | -948.35 | -282.7 | 38 |
| H7A | -5071.77 | -418.71 | 432.31 | 35 |
| H7B | -6526.1 | -257.45 | 806.53 | 35 |
| H11A | -8875.36 | -296.61 | 582.59 | 35 |
| H11B | -9080.87 | -335.35 | -27.52 | 35 |
| H12A | -5904.16 | -190.48 | -871.12 | 57 |
| H12B | -6105.81 | 118.93 | -318.18 | 57 |
| H12C | -7663.12 | -91.22 | -634.73 | 57 |
| H13A | -6762.71 | -2875.4 | 1019.65 | 53 |
| H13B | -6105.58 | -2779.47 | 450.03 | 53 |
| H13C | -8002.99 | -2786.28 | 557.2 | 53 |
| H14A | -9078.11 | -2033.34 | 1185.22 | 40 |
| H14B | -7538.47 | -1974.56 | 1552.77 | 40 |
| H15A | -10425.28 | -1178.72 | 1603.37 | 63 |
| H15B | -9469.8 | -536.08 | 1672.6 | 63 |
| H15C | -8951.25 | -1136.94 | 1995.95 | 63 |
| H16A | -4248.26 | -2522.2 | 1208.11 | 64 |
| H16B | -4918.31 | -2048.48 | 1630.23 | 64 |
| H16C | -3230.94 | -1914.47 | 1355.84 | 64 |
| H19A | -2881.04 | -842.35 | 3969.99 | 36 |
| H19B | -4711.85 | -750.88 | 4160.14 | 36 |
| H20A | -5618.82 | -1577.22 | 3657.66 | 40 |
| H20B | -3954.97 | -1840.49 | 3892.71 | 40 |
| H21 | -2500.25 | -1528.42 | 3194.13 | 36 |
| H23A | -1795.12 | -954.96 | 2587.59 | 39 |
| H23B | -3089.14 | -684.9 | 2195.56 | 39 |
| H27A | -5605.92 | -593.77 | 2314.89 | 41 |
| H27B | -6071.03 | -1261.92 | 2551.79 | 41 |
| H28A | -3711.19 | -2454.4 | 2972.76 | 60 |
| H28B | -3611.8 | -2024.95 | 2473.49 | 60 |
| H28C | -5283.96 | -2099.86 | 2771.37 | 60 |
| H29A | -3267.2 | 899.87 | 3993.36 | 59 |
|  |  |  |  |  |


| H29B | -2627.07 | 226.55 | 4161.77 | 59 |
| :---: | :---: | :---: | :---: | :---: |
| H29C | -4518.33 | 370.22 | 4160.84 | 59 |
| H30A | -5715.74 | 738.72 | 3332.56 | 49 |
| H30B | -4147.21 | 1109.41 | 3142.79 | 49 |
| H31A | -7120.28 | 855.64 | 2555.46 | 98 |
| H31B | -6233.55 | 688.46 | 2029.94 | 98 |
| H31C | -5687.53 | 1287.78 | 2350.66 | 98 |
| H32A | -917.58 | 958.37 | 3567.8 | 67 |
| H32B | -1566.53 | 1140.95 | 3011.62 | 67 |
| H32C | 93.53 | 768.73 | 3070.8 | 67 |
| H35A | 480.39 | 2954.48 | 929.63 | 42 |
| H35B | -1388.93 | 3103.4 | 818.89 | 42 |
| H36A | -2023.06 | 3077.79 | 1684.56 | 45 |
| H36B | -338.39 | 3453.29 | 1672.82 | 45 |
| H37 | 1123.79 | 2552.16 | 1796.28 | 41 |
| H39A | 1494.97 | 1552.23 | 1861.99 | 33 |
| H39B | 88.88 | 1047.5 | 1840.14 | 33 |
| H43A | -2317.61 | 1256.45 | 1852.06 | 38 |
| H43B | -2638.53 | 1938.31 | 2086.19 | 38 |
| H44A | 382.2 | 2862.68 | 2597.84 | 71 |
| H44B | 225.3 | 2118.91 | 2588.28 | 71 |
| H44C | -1353.37 | 2544.1 | 2547.21 | 71 |
| H45A | -12.78 | 1929.34 | -212.45 | 64 |
| H45B | 558.51 | 2516.61 | 118.63 | 64 |
| H45C | -1320.95 | 2387.43 | 34.16 | 64 |
| H46A | -2419.82 | 1370.16 | 313.64 | 46 |
| H46B | -855.61 | 951.56 | 202.43 | 46 |
| H47A | -3808.56 | 560.33 | 770.61 | 83 |
| H47B | -2825.61 | 171.7 | 1189.39 | 83 |
| H47C | -2368.97 | 111.48 | 597.18 | 83 |
| H48A | 2415.17 | 1532.11 | -15.52 | 56 |
| H48B | 1722.54 | 870.74 | 163.43 | 56 |
| H48C | 3394.73 | 1120 | 388.73 | 56 |
| H5A | -3397.95 | -1585.23 | 461.93 | 48 |
| H10 | -80.25 | -264.95 | 3362.12 | 49 |
| H15 | 3208.06 | 1991.06 | 976.75 | 47 |
|  |  |  |  |  |

## SI2.5.6. X-Ray Crystallographic Data for 255



Table SI2.5.6.1. Crystal data and structure refinement for 255.

| Identification code | 255 |
| :---: | :---: |
| Empirical formula | $\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{O}_{6}$ |
| Formula weight | 298.34 |
| Temperature (K) | 100.15 |
| Crystal system | monoclinic |
| Space group | C2 |
| $\mathrm{a}(\AA)$ | 11.0943(8) |
| $\mathrm{b}(\AA)$ | 15.9054(12) |
| $\mathrm{c}(\AA)$ | 8.2791(7) |
| $\alpha\left({ }^{\circ}\right)$ | 90 |
| $\beta\left({ }^{\circ}\right.$ ) | 93.753(4) |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume ( $\AA^{3}$ ) | 1457.8(2) |
| Z | 4 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.3592 |
| $\mu\left(\mathrm{mm}^{-1}\right)$ | 0.854 |
| $\mathrm{F}(000)$ | 642.2 |
| Crystal size ( $\mathrm{mm}^{3}$ ) | $0.14 \times 0.11 \times 0.01$ |
| Radiation | synchrotron ( $\lambda=1.5498$ ) |
| $2 \Theta$ range for data collection ( ${ }^{\circ}$ ) | 9.78 to 134.78 |
| Index ranges | $-13 \leq \mathrm{h} \leq 13,-18 \leq \mathrm{k} \leq 18,-9 \leq 1 \leq 9$ |
| Reflections collected | 19523 |
| Independent reflections | $2497\left[\mathrm{R}_{\text {int }}=0.0742, \mathrm{R}_{\text {digma }}=0.0401\right]$ |
| Data/restraints/parameters | 2497/3/201 |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.055 |
| Final R indexes [ $\mathrm{I}>=2 \sigma$ ( I$)$ ] | $\mathrm{R}_{1}=0.0435, \mathrm{wR}_{2}=0.1036$ |
| Final R indexes [all data] | $\mathrm{R}_{1}=0.0581, \mathrm{wR}_{2}=0.1138$ |
| Largest diff. peak/hole (e $\AA^{-3}$ ) | 0.31/-0.32 |
| Flack parameter | -0.0(2) |

Table SI2.5.6.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 255. $U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| C1 | $7217(2)$ | $5030.1(14)$ | $3283(3)$ | $27.4(5)$ |
| C2 | $7206(2)$ | $5968.8(15)$ | $2766(3)$ | $33.2(5)$ |
| C3 | $7108(3)$ | $6553.2(18)$ | $4227(4)$ | $48.8(8)$ |
| C4 | $8287(2)$ | $6141.5(15)$ | $1735(3)$ | $37.5(6)$ |
| C5 | $8498(3)$ | $7068.5(18)$ | $1381(4)$ | $51.9(8)$ |
| C6 | $7875(2)$ | $5638.8(15)$ | $201(3)$ | $34.8(6)$ |
| C7 | $6171(3)$ | $6131.2(17)$ | $1473(3)$ | $40.1(6)$ |
| C8 | $8106(2)$ | $4712.1(15)$ | $433(3)$ | $33.8(6)$ |
| C9 | $7588(2)$ | $4357.4(15)$ | $1981(3)$ | $29.2(5)$ |
| C10 | $6394(2)$ | $3876.4(16)$ | $1599(3)$ | $35.9(6)$ |
| C11 | $5494(2)$ | $4213.6(15)$ | $2674(3)$ | $33.1(6)$ |
| C12 | $8558(2)$ | $3808.3(16)$ | $2945(3)$ | $36.4(6)$ |
| C13 | $8755(3)$ | $2922.9(18)$ | $2312(4)$ | $47.9(8)$ |
| C14 | $8218(2)$ | $3866.3(17)$ | $4697(3)$ | $39.6(6)$ |
| C15 | $7979(2)$ | $4800.7(17)$ | $4859(3)$ | $34.6(6)$ |
| O1 | $9360.9(15)$ | $5785.3(12)$ | $2520(2)$ | $39.5(5)$ |
| O2 | $8389.4(16)$ | $5950.9(12)$ | $-1193(2)$ | $40.4(5)$ |
| O3 | $6581.0(15)$ | $5766.5(12)$ | $3(2)$ | $40.1(5)$ |
| O4 | $4441.5(15)$ | $4003.7(12)$ | $2760(2)$ | $42.4(5)$ |
| O5 | $5967.9(14)$ | $4826.1(11)$ | $3639.3(19)$ | $32.5(4)$ |
| O6 | $7408.9(16)$ | $5022.2(12)$ | $6304(2)$ | $43.7(5)$ |

Table SI2.5.6.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 255. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} \mathrm{U}_{11}+2 h k a^{*} b^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{12}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{23}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | $24.6(11)$ | $34.9(12)$ | $23.3(12)$ | $-3.0(9)$ | $5.7(9)$ | $-2.8(10)$ |
| C2 | $35.6(12)$ | $30.8(12)$ | $33.7(14)$ | $1.6(10)$ | $7.4(10)$ | $-5.0(10)$ |
| C3 | $65(2)$ | $37.8(14)$ | $45.3(18)$ | $-4.4(14)$ | $14.0(15)$ | $-11.8(13)$ |
| C4 | $38.2(14)$ | $39.0(14)$ | $35.0(15)$ | $-5.3(11)$ | $0.4(11)$ | $1.5(12)$ |
| C5 | $64(2)$ | $42.2(16)$ | $49.6(19)$ | $-13.2(14)$ | $5.3(15)$ | $1.7(14)$ |
| C6 | $33.3(13)$ | $40.0(15)$ | $31.1(15)$ | $-1.7(11)$ | $2.4(11)$ | $0.6(11)$ |
| C7 | $39.0(15)$ | $40.8(14)$ | $41.1(16)$ | $6.9(12)$ | $6.9(12)$ | $-1.2(12)$ |
| C8 | $33.5(13)$ | $40.0(13)$ | $28.8(14)$ | $-0.1(11)$ | $8.8(10)$ | $-3.7(11)$ |
| C9 | $27.9(13)$ | $33.4(12)$ | $26.2(13)$ | $0.4(10)$ | $2.1(10)$ | $-4.4(10)$ |
| C10 | $27.5(13)$ | $43.6(14)$ | $36.8(15)$ | $-2.1(11)$ | $2.6(11)$ | $-9.1(12)$ |
| C11 | $30.6(14)$ | $35.3(14)$ | $33.2(14)$ | $-2.3(10)$ | $1.5(10)$ | $-2.6(11)$ |
| C12 | $30.8(13)$ | $37.6(14)$ | $40.6(15)$ | $3.8(11)$ | $0.5(11)$ | $2.1(11)$ |
| C13 | $48.5(18)$ | $42.8(15)$ | $53(2)$ | $7.7(13)$ | $3.9(14)$ | $-0.6(14)$ |
| C14 | $38.6(14)$ | $44.7(14)$ | $34.4(15)$ | $0.3(12)$ | $-5.3(11)$ | $3.8(12)$ |
| C15 | $35.7(13)$ | $46.6(14)$ | $21.5(13)$ | $-7.1(11)$ | $2.5(10)$ | $-2.6(11)$ |
| O1 | $31.0(9)$ | $53.7(11)$ | $33.8(10)$ | $-7.6(8)$ | $2.3(8)$ | $4.1(8)$ |
| O2 | $41.3(10)$ | $54.3(11)$ | $25.9(10)$ | $-9.3(9)$ | $4.4(7)$ | $3.4(8)$ |
| O3 | $32.2(9)$ | $51.2(11)$ | $36.8(11)$ | $5.6(8)$ | $1.9(8)$ | $-0.3(9)$ |
| O4 | $30.5(10)$ | $47.8(11)$ | $49.1(12)$ | $-5.5(8)$ | $3.8(8)$ | $-7.2(9)$ |
| O5 | $26.6(8)$ | $41.3(9)$ | $30.2(9)$ | $-5.3(7)$ | $5.9(6)$ | $-6.3(8)$ |
| O6 | $45.1(11)$ | $61.1(12)$ | $25.6(9)$ | $-15.0(9)$ | $8.0(8)$ | $-6.5(9)$ |

Table SI2.5.6.4. Bond Lengths for 255.

| Atom | Atom | Length ( $\AA \mathbf{A})$ | Atom | Atom | Length ( $\AA \mathbf{(})$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | C 2 | $1.553(3)$ | C6 | O3 | $1.449(3)$ |
| C1 | C9 | $1.592(3)$ | C7 | O3 | $1.448(3)$ |
| C1 | C15 | $1.551(3)$ | C8 | C9 | $1.545(3)$ |
| C1 | O5 | $1.472(3)$ | C9 | C10 | $1.544(3)$ |
| C2 | C3 | $1.536(3)$ | C9 | C12 | $1.564(3)$ |
| C2 | C4 | $1.542(4)$ | C10 | C11 | $1.481(3)$ |
| C2 | C7 | $1.539(4)$ | C11 | O4 | $1.221(3)$ |
| C4 | C5 | $1.524(4)$ | C11 | O5 | $1.345(3)$ |
| C4 | C6 | $1.545(4)$ | C12 | C13 | $1.523(4)$ |
| C4 | O1 | $1.435(3)$ | C12 | C14 | $1.525(4)$ |
| C6 | C8 | $1.506(4)$ | C14 | C15 | $1.517(4)$ |
| C6 | O2 | $1.411(3)$ | C15 | O6 | $1.434(3)$ |

Table SI2.5.6.5. Bond Angles for 255.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C9 | C1 | C2 | $117.2(2)$ | O3 | C6 | O2 | $108.01(19)$ |
| C15 | C1 | C2 | $116.9(2)$ | O3 | C7 | C2 | $104.8(2)$ |
| C15 | C1 | C9 | $105.12(18)$ | C9 | C8 | C6 | $113.2(2)$ |
| O5 | C1 | C2 | $106.03(18)$ | C8 | C9 | C1 | $116.3(2)$ |
| O5 | C1 | C9 | $106.02(17)$ | C10 | C9 | C1 | $102.45(17)$ |
| O5 | C1 | C15 | $104.36(18)$ | C10 | C9 | C8 | $111.79(19)$ |
| C3 | C2 | C1 | $111.4(2)$ | C12 | C9 | C1 | $103.26(18)$ |
| C4 | C2 | C1 | $109.34(19)$ | C12 | C9 | C8 | $110.3(2)$ |
| C4 | C2 | C3 | $115.2(2)$ | C12 | C9 | C10 | $112.3(2)$ |
| C7 | C2 | C1 | $110.2(2)$ | C11 | C10 | C9 | $107.49(19)$ |
| C7 | C2 | C3 | $111.0(2)$ | O4 | C11 | C10 | $128.4(2)$ |
| C7 | C2 | C4 | $99.1(2)$ | O5 | C11 | C10 | $111.5(2)$ |
| C5 | C4 | C2 | $114.4(2)$ | O5 | C11 | O4 | $120.1(2)$ |
| C6 | C4 | C2 | $99.42(19)$ | C13 | C12 | C9 | $116.8(2)$ |
| C6 | C4 | C5 | $112.5(2)$ | C14 | C12 | C9 | $104.3(2)$ |
| O1 | C4 | C2 | $109.4(2)$ | C14 | C12 | C13 | $115.7(2)$ |
| O1 | C4 | C5 | $109.6(2)$ | C15 | C14 | C12 | $101.5(2)$ |
| O1 | C4 | C6 | $111.1(2)$ | C14 | C15 | C1 | $104.2(2)$ |
| C8 | C6 | C4 | $111.3(2)$ | O6 | C15 | C1 | $113.5(2)$ |
| O2 | C6 | C4 | $112.1(2)$ | O6 | C15 | C14 | $113.8(2)$ |
| O2 | C6 | C8 | $112.0(2)$ | C7 | O3 | C6 | $108.96(19)$ |
| O3 | C6 | C4 | $105.0(2)$ | C11 | O5 | C1 | $112.16(18)$ |
| O3 | C6 | C8 | $108.08(19)$ |  |  |  |  |

Table SI2.5.6.6. Hydrogen Bonds for 255.

| $\mathbf{D}$ | $\mathbf{H}$ | $\mathbf{A}$ | $\mathbf{d}(\mathbf{D}-\mathbf{H}) / \AA$ | $\mathbf{d}(\mathbf{H}-\mathbf{A}) / \AA$ | $\mathbf{d}(\mathbf{D}-\mathbf{A}) / \AA$ | $\mathbf{D}-\mathbf{H}-\mathbf{A} /{ }^{\circ}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O 1 | H 1 | $\mathrm{O}^{1}$ | $0.902(5)$ | $1.907(7)$ | $2.804(2)$ | $172(3)$ |
| O 2 | H 2 | $\mathrm{O}^{2}$ | $0.901(5)$ | $1.830(10)$ | $2.713(3)$ | $166(3)$ |
| O6 | H 6 | $\mathrm{O}^{3}$ | $0.901(5)$ | $1.896(13)$ | $2.765(2)$ | $161(3)$ |

Table SI2.5.6.7. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters ( $\AA^{2} \times 10^{3}$ ) for 255.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H3a | $7010(20)$ | $7135(2)$ | $3851(4)$ | $73.2(11)$ |
| H3b | $6409(12)$ | $6389(9)$ | $4821(16)$ | $73.2(11)$ |
| H3c | $7844(9)$ | $6509(11)$ | $4943(14)$ | $73.2(11)$ |
| H5a | $8700(20)$ | $7368(3)$ | $2399(5)$ | $77.8(12)$ |
| H5b | $9169(13)$ | $7123(2)$ | $670(20)$ | $77.8(12)$ |
| H5c | $7765(7)$ | $7310(4)$ | $840(30)$ | $77.8(12)$ |
| H7a | $5416(3)$ | $5858.3(17)$ | $1776(3)$ | $48.1(8)$ |
| H7b | $6023(3)$ | $6741.7(17)$ | $1335(3)$ | $48.1(8)$ |
| H8a | $7741(2)$ | $4404.8(15)$ | $-518(3)$ | $40.6(7)$ |
| H8b | $8988(2)$ | $4610.4(15)$ | $484(3)$ | $40.6(7)$ |
| H10a | $6111(2)$ | $3958.1(16)$ | $451(3)$ | $43.1(7)$ |
| H10b | $6516(2)$ | $3267.4(16)$ | $1795(3)$ | $43.1(7)$ |
| H12 | $9345(2)$ | $4110.1(16)$ | $2893(3)$ | $43.7(7)$ |
| H13a | $9439(12)$ | $2663(5)$ | $2933(17)$ | $71.9(11)$ |
| H13b | $8026(7)$ | $2586(4)$ | $2430(20)$ | $71.9(11)$ |
| H13c | $8927(19)$ | $2950(2)$ | $1167(7)$ | $71.9(11)$ |
| H14a | $7488(2)$ | $3530.1(17)$ | $4877(3)$ | $47.5(7)$ |
| H14b | $8890(2)$ | $3679.6(17)$ | $5460(3)$ | $47.5(7)$ |
| H15 | $8768(2)$ | $5104.5(17)$ | $4859(3)$ | $41.5(7)$ |
| H1 | $10051(16)$ | $5830(20)$ | $2010(40)$ | $59.3(7)$ |
| H2 | $7960(30)$ | $5690(20)$ | $-2010(30)$ | $60.6(7)$ |
| H6 | $6760(20)$ | $4685(18)$ | $6370(40)$ | $65.5(7)$ |

SI2.6 ${ }^{1} \mathrm{H},{ }^{13} \mathrm{C}$, and ${ }^{19} \mathrm{~F}$ NMR Spectra





















$8^{\circ} \angle 8$































## Chapter 3

## Oxidative Synthesis <br> of the <br> Majucinoids

### 3.1 Introduction to Highly Oxidized Illicium Sesquiterpene Synthesis

With pseudoanisatinoid syntheses successfully completed, our focus shifted to the more highly oxidized (and biologically active) majucinoids and related anisatinoids and the challenges such compounds present to a synthetic chemist (Figure 3.1). Previously, efforts towards $\mathbf{1 1}$ had demonstrated the viability of an oxidative strategy from 14 (Figure 3.1A). ${ }^{1}$ However, the execution of that strategy was not perfect; challenging C 4 methine oxidation by non-heme iron(oxo) catalysis depressed the efficiency of the route (and the chemists working on it) and a means to access oxidation at the C12 or C13 positions was non-obvious. Therefore, when designing a new sequence, those considerations weighed at the forefront of our planning. Furthermore, in addition to exhaustive oxidation of either the C12 or C13 methyl group, a successful synthesis would require selective oxidation of the C10 position as well. First, though, we sought a way to address the C 4 methine oxidation. Due to the hindered nature of the C 4 site, as well as the existence of more readily oxidized methine positions (particularly at C 1 ), ${ }^{2}$ we believed a directed oxidation would likely be required. While we had employed a carboxylic acid as a directing group in our pseudoanisatinoid synthesis, ${ }^{3}$ we sought a different, more rigid substrate in this iteration to better insure against non-directed pathways. With such requirements, our attention naturally turned to using a secondary alcohol as a directing group and once again calling upon an oxygen-centered radical to perform a challenging oxidation. This Chapter will describe the successful implementation of that strategy to access a significant portion of all majucinoid natural products (Figure 3.1B); additionally, preliminary studies towards $\mathbf{1 3}$ will be recounted along the way, along with a final unification of our synthetic routes.


Figure 3.1. (A) Synthetic roadmap to Illicium sesquiterpenes from (+)-cedrol. Key oxidations required to synthesize anisatinoids and majucinoids are highlighted. (B) Subset of majucinoids successfully targeted by this route. Inset: anisatin, a compound potentially accessible through this route as well.

### 3.2 The C4 Methine Oxidation Revisited

Having decided to pursue an alcohol-directed C 4 oxidation, we were encouraged to find a report by Waegell in the literature detailing a similar transformation on a simpler substrate. ${ }^{4}$ Thus, we set out to recapture that reaction on our own system (Figure 3.2A). From alkene 200, the starting point of our pseudoanisatinoid synthesis, a three-step procedure of (1) alkene hydroboration/ oxidation, (2) alcohol oxidation, and (3) diastereoselective ketone reduction quickly and cleanly afforded secondary alcohol $\mathbf{2 6 2} .262$ was then treated under hypoiodite photolysis conditions popularized by Suárez in an attempt to selectively activate the C4 position, as Waegell saw with his $\mathrm{Pb}(\mathrm{OAc})_{4}$ system. However, once again, we found that the presence of additional oxidation at the C14 position had dramatically impacted the course of a reaction. Although our system was able to oxidize the C 4 position, giving $\mathbf{2 6 5}$, the oxidation was not selective. In fact, the major pathway for the reaction was unexpected oxidation of the C14 position, giving acetal 264 as a mixture of diastereomers at that position. It is known that 1,5 -hydrogen atom transfers (HAT) are generally more facile than other $1, n$-HATs, primarily due to a lack of entropic penalty in the transition state. At the same time, $1,5-\mathrm{HATs}$ are thought to be at an enthalpic disadvantage when compared with $1,6-\mathrm{HATs} .{ }^{5}$ Therefore, for our system, we rationalized that the rigid geometry minimized entropic differences while having exceptionally weak $\mathrm{C} 14 \mathrm{C}-\mathrm{H}$ bonds (likely around $92 \mathrm{kcal} / \mathrm{mol}$ ) magnified the enthalpic differences as well, leading to the observed preference in radical intermediate 263 for 1,6-HAT.

Since the geometry of this system was largely constrained, it was deemed prudent to vary instead the energetics of $\mathrm{C}-\mathrm{H}$ bond cleavage by changing the substituents at the C 14 position. While deuterating that position led to an increase of C 4 oxidation relative to C 14 (in fact, deuterated 265 then became the major product), such a sequence was deemed impractical for larger scale synthesis. We therefore turned to exchange of protecting group as a way to modulate the bond strengths of the $\mathrm{C} 14 \mathrm{C}-\mathrm{H}$ bonds. While $\mathrm{C}-\mathrm{H}$ bonds adjacent to an ether center are significantly weaker (by ca. $5 \mathrm{kcal} / \mathrm{mol}$ ) than a methine $\mathrm{C}-\mathrm{H}$ bond, ${ }^{6}$ bonds next to an ester are slightly stronger (by $c a .1 \mathrm{kcal} / \mathrm{mol}$ ), leading us to select an acetate protecting group for the C 14 position (Figure 3.2B). ${ }^{7}$ Synthesis of acetate-protected $\mathbf{2 6 7}$ followed in a straightforward way from chemistry already developed. Namely, the strained tetrahydrofuran ring (199, not shown) could be opened in the same pot under acylium ion generating conditions $\left(\mathrm{Ac}_{2} \mathrm{O}, \mathrm{H}_{3} \mathrm{PO}_{4}\right)$ to generate alkene 266. In an optimized two-step procedure, 266 was converted to C 4 oxidation substrate 267. Remarkably, when 267 was subjected to the reaction conditions, no trace of C14 oxidation was observed and the desired C4 oxidation product $\mathbf{2 6 8}$ was isolated in near-quantitative yield. The incredible efficiency of this transformation permitted the reaction to be run routinely on over decagram scale with commercially available reagents - a vast improvement over the previous iron-catalyzed process.

Interested in further studying the subtle effects governing the selectivity in this reaction, we turned to calculations to tease out the geometric relationships between reacting centers. ${ }^{8}$ As a first approximation of entropic effects, a series of ground state energy minimizations were performed primarily to assess the distances of the oxygen center to each reactive site (Figure 3.2C). Here, we interrogated the structures of 14, 262, and 267 to obtain a range of data on successful HAT processes. Additionally, a crystal structure of $\mathbf{1 4}$ was procured to qualitatively validate calculated distances in the energy-minimized structures.

In the literature, it has variably been proposed that the most efficient $1,5-\mathrm{HAT}$ processes


14




1,6-HAT
path b

265, 43\%, 15.1 dr
266, 34\%

B


[X-ray] of 14


14 (calculated)


262 (calculated)


267 (calculated)

Figure 3.2. (A) Initial exploration of an alcohol-directed $C 4$ oxidation where the substrate also contained a C14 methoxy group. An unexpected 1,6-HAT process was found to predominate. (B) Redesign of the C4 oxidation substrate to now contain a C14 acetate group. The desired 1,5-HAT process became the exclusive reaction pathway. (C) Calculated structures of various $\mathrm{C}-\mathrm{H}$ oxidation substrates and the measured $\mathrm{O} \cdot \cdots \mathrm{C}$ distances between reactive centers.
occur when the oxygen radical is either $<3 \AA$ away from the reacting carbon center or when it is in the range of 2.5-2.7 $\AA .{ }^{5,9}$ For 14, in the crystal structure, that distance was $2.89 \AA$, slightly high but still in an acceptable range. A calculated distance of $2.90 \AA$ was in close agreement with that value, giving us reasonable confidence in the calculations of subsequent structures for which X-ray crystallographic data was not available. For $\mathbf{2 6 2}$ and 267, the distances to the C 4 sites were $3.098 \AA$ and $3.074 \AA$, respectively, at the long end of those commonly seen in highly efficient transformations. Interestingly, the distances to the C14 sites were $3.232 \AA$ and $3.185 \AA$, respectively - both within $0.15 \AA$ of the C 4 value despite the interpolation of an additional atom. Calculations, then, appeared to corroborate what was observed experimentally; namely, the C4 1,5-HAT might be slightly more
challenging than a typical one, and the C14 1,6-HAT slightly more favorable. Including further enthalpic factors likely pushed the substrate to favor the $1,6-\mathrm{HAT}$ pathway. By rationally modulating the $\mathrm{C}-\mathrm{H}$ bond strength, we were able to favor the desired pathway exclusively, providing us with ample material for mid-stage investigations of challenging oxidations.

### 3.3 Towards Highly Oxidized Illicium Sesquiterpenes

### 3.3.1 Oxidations of the C13 Position

Emboldened by the successful C4 oxidation, we next turned our attention to the oxidation of the unactivated methyl groups at C12 and C13. Oxidation of the former would be an entry to the majucinoids; reactivity at the latter was unprecedented in the literature of cedrane functionalization and would lead to anisatinoids. Towards this latter transformation, we again opted for alcohol-based directing groups (Scheme 3.1).

Literature surrounding 1,3-diol synthesis (conceptually a 1,4-functionalization) by $\mathrm{C}-\mathrm{H}$ activation, though, is far scanter than the extensive body of work devoted to 1,5 -functionalizations, particularly when the site of desired functionalization is a strong methyl $\mathrm{C}-\mathrm{H}$ bond ( BDE ca. 101 $\mathrm{kcal} / \mathrm{mol} v s$. tertiary C-H BDE ca. $97 \mathrm{kcal} / \mathrm{mol}) .{ }^{6 \mathrm{~b}, 10,11}$ Equally sparsely precedented is the use of a primary alcohol as a directing group, owing to the lack of transition state preorganization imparted by such a freely-rotating motif. Furthermore, the C7 methine was equivalently spaced as the C13 methyl from C14, adding questions of regiochemistry on to an already daunting list of challenges. Nevertheless, two directing groups were prepared in parallel: primary sulfamate $\mathbf{2 7 0}$ and silyl ether 272.


Scheme 3.1. Oxidations of the C 13 position. Top path: sulfamate-directed C13 nitrenoid insertion. Bottom path: Directed C13 silylation followed by Fleming-Tamao oxidation.

Reports of rhodium-catalyzed nitrenoid insertion into primary $\mathrm{C}-\mathrm{H}$ bonds are rare and rarer still when there is an accessible tertiary $\mathrm{C}-\mathrm{H}$ position, yet when 270 was subjected to standard conditions popularized by DuBois, highly crystalline cyclic sulfamate 271 was isolated as the sole product of $\mathrm{C}-\mathrm{H}$ functionalization. ${ }^{12,13} \mathrm{X}$-ray studies unambiguously confirmed that the oxidation had occurred at the desired C13 site. While a confluence of effects surely led to the observed selectivity, we postulated that the directing group perhaps was not as freely-rotating as initially considered. In particular, the C12 methyl group, jutting out over C 7 , might have biased the directing group away from that site and towards the only other accessible center: the C13 methyl. A similar result was seen for the silyl ether using chemistry developed by Hartwig. ${ }^{10 b, 14}$ In this pathway, an isolable intermediate five-membered cyclic silane was formed first under rhodium catalysis, which was then oxidized under Fleming-Tamao conditions to provide diol 273 (again confirmed by X-ray analysis). A significant portion of the mass balance, though, was lost to hydrosilylation of the directing group onto norbornene, emphasizing the challenging nature of this transformation.

While both pathways had provided the requisite oxidation, each still left something to be desired. The sulfamate chemistry, while robust, nevertheless had installed a $\mathrm{C}-\mathrm{N}$ bond, not the optimal C-O bond. Although literature reports indicate the possible oxidation of sulfamates to ketones, initial attempts for our substrate were met with mixed results. ${ }^{15}$ Conversely, while the silylation chemistry had forged a $\mathrm{C}-\mathrm{O}$ bond, the overall yield for that transformation was deemed somewhat low for synthetic development. In light of this, we focused instead on the more promising route underway towards the majucinoids.

### 3.3.2 Oxidation of the $\mathbf{C 1 2}$ Position

Before addressing C12 oxidation, it was necessary to once again cleave the C6-C11 bond. However, whereas previously facile olefin oxidative cleavage was employed for 200, for $\mathbf{2 6 8}$ only a single bond connected those two sites. Remarkably, though, the same conditions developed for the former transformation (in situ $\mathrm{RuO}_{4}$ ) were transferable to the latter (Scheme 3.2). For mechanistic insights into this surprising transformation, we turned to work by Waegell which suggested that such a process could be occurring by a series of $\mathrm{C}-\mathrm{H}$ oxidations followed by a $\mathrm{C}-\mathrm{C}$ oxidation. ${ }^{2, \mathrm{~b}}$ Indeed, at low reaction conversions, tertiary alcohol 274 could be identified - the presumed product of a ruthenium-catalyzed substrate-controlled $\mathrm{C}-\mathrm{H}$ hydroxylation. That tertiary alcohol then likely directed a second $\mathrm{C}-\mathrm{H}$ hydroxylation event to the adjacent C 11 site to generate an intermediate diol (which was not isolated or identified) that underwent rapid $\mathrm{C}-\mathrm{C}$ oxidation, giving keto-lactone 275 as the major product. An additional minor product, 276, could also be isolated from the reaction conditions bearing further oxidation at the C 1 methine, throwing into stark relief the power of ruthenium catalysis to oxidize unactivated aliphatic $\mathrm{C}-\mathrm{H}$ bonds.

The methyl ketone of $\mathbf{2 7 5}$ provided an obvious avenue to C12 oxidation. Many methods exist for the selective hydroxylation of such a position; however, we required the carboxylic acid oxidation state and desired to access that functionality in a single operation. While such ambitious transformations are known, substrates are usually limited to aromatic methyl ketones; the corresponding transformation on an aliphatic methyl ketones has been less studied. Impressively, treating 275 with stoichiometric amounts of selenium dioxide effected this transformation with concomitant oxidation of the C7 position, giving highly oxidized $\alpha$-keto ester 277 after methylation. Even more surprisingly, a small amount of globally-oxidized 278 could also be isolated from the reaction mixture. ${ }^{16}$ The structure of this bis( $\alpha$-keto ester) was confirmed through X-ray crys-


Scheme 3.2. Mid-stage oxidations and access to the majucinoid C12-C14 lactone
tallographic studies. Despite containing all the requisite oxidations seen in the majucinoids (and jiadifenolide in particular), $\mathbf{2 7 8}$ proved challenging to handle and its yield could not be optimized. Thus, while we could identify certain transformations to carry this intermediate on to jiadifenolide, a preparative scale solution still eluded us. On the other hand, 277 could be optimized for by the inclusion of molecular sieves. Mechanistically, pathways leading to the formation or suppression of 278 remained unclear. Control experiments indicated 277 (or its seco acid) did not go on to form 278 under the reaction conditions, indicating that the C10 oxidation in 278 occurred before completion of the oxidations of the methyl ketone. Further mechanistic studies were hindered by the observation that C7 and C12 oxidations were rate-competitive and led to intractably complex mixtures of products prior to completion of the oxidation. Nevertheless, 277 was then advanced to enol lactone 279 by a cascade process involving (1) 1,2-reduction of the C6 ketone, (2) acetate cleavage, (3) lactonization, and (4) alkene isomerization. The sequence from 268 to 279 was only three steps, yet in those three steps, net 6 oxidations were installed onto the cedrane skeleton, delivering highly oxidized compounds with unparalleled efficiency.

### 3.4 Completion of the Majucinoid Synthesis \& Unification of the Routes

With the majority of majucinoid oxidations now installed, $\mathbf{2 7 9}$ was set to undergo the pivotal ring shift from the 5,5 -cedrane system to the 5,6 -seco-prezizaane one. Once again, an $\alpha$-ketol rearrangement was envisioned. ${ }^{17}$ Previously, installation of the C 7 oxidation was challenging (see 202), partially due to the difficulty in accessing a reactive enol or enolate species. For 279, though, the C6 ketone already existed exclusively as the enol tautomer, hinting that hydroxylation might be more facile. Although the oxidation was projected to be easier, the actual rearrangement posed challenges on two fronts. First, the C5-C7 bond would now have to be migrated transannularly, imposing restrictions on accessible geometries. Additionally, the intermediate $\beta$-hydroxy- $\alpha$-ketolactone was sure to be more labile than the simpler $\alpha$-ketol studied previously. Nevertheless, com-


281

Scheme 3.3. Stereochemical considerations for the oxidation and $\alpha$-ketol rearrangement of 279.
plementary methods of oxidizing the C7 position were investigated (Scheme 3.3). Empirically, we determined that DMDO could oxidize 279 to $\alpha$-hydroxy ketone $\mathbf{2 8 0}$ as a single diastereomer. $\mathbf{2 8 0}$ was quite labile under acidic or basic conditions; therefore, we turned to thermal conditions to effect the skeletal reorganization. Gratifyingly, simply heating $\mathbf{2 8 0}$ to $170^{\circ} \mathrm{C}$ coaxed the C5-C6 bond to migrate, and a subsequent directed reduction $\left(\mathrm{Me}_{4} \mathrm{NBH}(\mathrm{OAc})_{3}\right)$ cleanly afforded diol $\mathbf{1 8 8}$ as a single diastereomer (structure confirmed by X-ray crystallographic studies).

Alternatively, 279 could be treated with selenium dioxide to prepare epimeric $\alpha$-ketol 281. While it remains unclear why these two oxidants give such pronounced differences in diastereoselectivity, it is possible that DMDO engages 279 in an intermolecular transition state, while selenium dioxide performs an intramolecular oxidation (via 2,3 rearrangement) after binding to the enol oxygen, leading to the observed divergence in product formation. Unfortunately, $\mathbf{2 8 1}$ resisted subsequent $\alpha$-ketol rearrangement under a variety of acidic, basic, and thermal conditions. The stereochemistry of the initial oxidation was confirmed by X-ray crystallographic studies of a reduced analog (282). While both $\mathbf{2 8 0}$ and $\mathbf{2 8 1}$ appear able to access stereoelectronically allowed conformations for bond migration, it is possible that an additional intramolecular hydrogen bond in 280 facilitates the transformation - an effect occasionally seen in thermal $\alpha$-ketol rearrangements.

The preparation of $\mathbf{1 8 8}$ also marked the completion of a formal synthesis of $(-)$-jiadifenolide (9) (Scheme 3.4). ${ }^{18,19} 188$ was shown by Theodorakis and Shenvi to go on to $\mathbf{9}$ after two sequential C10 oxidations. Not satisfied with simply recapitulating prior work, we also desired to solve unaddressed issues in majucinoid synthesis by streamlining access to other known natural products and also completing a synthesis of (-)-majucin (5) itself - a compound previously inaccessible due to its specific oxidation pattern.

Alkene 283 was also a known intermediate that Theodorakis had prepared in the same


Scheme 3.4. Completion of the total and formal syntheses of multiple majucinoid natural products.
route as $\mathbf{1 8 8}$. However, conversion from $\mathbf{1 8 8}$ to $\mathbf{2 8 3}$ was unknown before our work. While a seemingly straightforward translactonization/dehydration process, it was challenging to find the precise conditions (solvent and acid catalyst in particular) most suitable for the reaction. Eventually, TsOH in refluxing $n$-butanol was found to cleanly transfer the lactone to the secondary alcohol with concomitant C4 dehydration. Crucial to the success of the reaction, water had to be continuously removed as treating $\mathbf{2 8 3}$ with aqueous acid quickly regenerated $\mathbf{1 8 8}$. The preparation of $\mathbf{2 8 3}$ completed formal synthesis of (-)-ODNM (7) in two steps and (-)-jiadifenin (8) in three steps.

To achieve the first chemical synthesis of other natural products, C10 oxidation still needed to be addressed. Due to the concavity of 283, though, C10 hydroxylation occurred exclusively from the undesired face, necessitating a second epimerization step. While a standard oxidation/ reduction sequence was suitable for the transformation, we found success leveraging ruthenium transfer hydrogenation catalyst, $\left[\mathrm{Ru}_{2}\left(\mathrm{PEt}_{3}\right)_{6}(\mathrm{OTf})_{3}\right][\mathrm{OTf}]$, recently reported by Hartwig to execute the analogous sequence to $\mathbf{2 8 4}$ but in a single step. ${ }^{20}$ Fortuitously, $\mathbf{2 8 4}$ also turned out to be a natural product in its own right, known as 3,4-dehydroneomajucin (DHNM). Manganese-catalyzed hydration of $\mathbf{2 8 4}$ prepared neurotoxic natural product ( - )-neomajucin (285) for the first time as a single diastereomer. ${ }^{21}$ Dihydroxylation of $\mathbf{2 8 4}$ using conditions (OsO ${ }_{4} \cdot$ TMEDA) pioneered in our previous work to $(+)$-pseudoanisatin (11) then cleanly gave (-)-majucin (5) as a single diastereomer. ${ }^{22}$ While theoretically this reagent could be directed by either the C 10 or C 6 homoallylic alcohol to give diastereomeric products, we believe the lactone architecture in this case intrinsically biases the reagent to the desired face. Neurotrophic natural product (-)-jiadifenoxolane A (6) was also synthesized in a straightforward way from $\mathbf{5}$ by intramolecular displacement of an activated C3 alcohol, reminiscent of chemistry used in early studies on (-)-anisatin (13). ${ }^{23}$

With the completion of multiple majucinoid syntheses and the previous completion of a route to the pseudoanisatinoids, we had demonstrated diverse routes from (+)-cedrol (14) to various Illicium sesquiterpene natural products. ${ }^{1,24}$ However, it was deemed tedious to have two independent routes from 14 to arrive at each natural product family. Ideally, a single route would be diversified late-stage to maximize material throughput. Again, due to a desire to avoid the


250
[2 steps to pseudoanisatin] $\xrightarrow[75 \%]{\text { a. } \mathrm{Me}_{4} \mathrm{NBH}(\mathrm{OAc})_{3}}$

287

| d. $\mathrm{NaBH}_{4}$ |
| :---: | :---: |
| $\mathrm{NiCl}_{2}$ |\(| \begin{gathered}14 \% <br>

[2 steps]\end{gathered}\)
286


[3 steps to majucin]



Scheme 3.5. Late stage unification of routes to majucinoids and pseudoanisatinoids by convergence to intermediate 288. Studies are ongoing to advance $\mathbf{2 8 8}$ on to other pseudoanisatinoid natural products, like 290.
iron-catalyzed C4 oxidation, we opted to convert a majucinoid intermediate to a pseudoanisatinoid one (Scheme 3.5) - a strategy used by Shenvi in the synthesis of $\mathbf{1 0} .{ }^{25}$ Key intermediate $\mathbf{2 8 8}$ was selected as the point of convergence due to it containing both a majucin-like lactone and a pseu-doanisatin-like C12 methyl group. Preparation of $\mathbf{2 8 8}$ from known pseudoanisatinoid intermediate 250 was easily realized by directed reduction $\left(\mathrm{Me}_{4} \mathrm{NBH}(\mathrm{OAc})_{3}\right)$ of the ketone group.

In a departure from a focus on oxidative chemistry, selective reduction of the C12-C14 lactone of $\mathbf{2 8 3}$ now had to be executed. To avoid undesired reactivity with the C7-C11 lactone, an un-optimized, three-step protocol was created involving (1) selective reduction of an $\alpha$-hydroxy lactone, (2) dithiolane formation, and (3) selective dithiolane reduction that took 283 to common intermediate 288. In order to demonstrate the utility of this intermediate, synthesis of the natural product (-)-debenzoyldunnianin (290) was attempted, as we believed an endgame sequence similar to what we had developed for pseudoanisatin (11) would also serve well in this context. However, osmium-mediated dihydroxylation of $\mathbf{2 8 8}$ led to an unexpected aldehyde-containing product, 289. Efforts are still ongoing to advance 289, or a derivative thereof, to the natural product.

### 3.5 Conclusion

In this Chapter, we conquered two challenges limiting our first oxidative synthesis. First, we developed a robust, scalable, and high-yielding direct C 4 oxidation from simple secondary alcohol 267. Then, we rapidly accessed the higher oxidation states required for majucinoid synthesis. Enol lactone 279 was synthesized from 268 in only 3 steps, representing a net 6 oxidation state increase. Along the way, we gained an appreciation for the subtle nuances that guide the success of directed reactions. Initially, a reaction that "should" have worked - namely $\mathbf{2 6 2}$ to $\mathbf{2 6 5}$ - gave an unexpected product (see 264) and required reevaluation of our substrate. Conversely, directed oxidation of the C13 methyl group by all literature accounts "shouldn't" have worked and yet two independent methods were identified to execute that transformation (see 271, 273). Taken together, these lessons argue for the importance of synthesis in pushing the limits of understanding chemical reactivity.



Scheme 3.6. Oxidative synthesis of the majucinoids from (+)-cedrol.
We then proceeded to complete our oxidative synthesis of the majucinoids (Scheme 3.6). Targeting 188 and $\mathbf{2 8 3}$, we reached total and formal syntheses of over a half dozen majucinoids in rapid succession, including the eponymous majucin (5) - a previously inaccessible natural product. Not content with reaching only majucinoids with this robust route, we also converted 283 to pseudoanisatinoid 288, an entry point to members of that subtype as well. All in all, over the course of the studies described in the past two Chapters, a dozen Illicium sesquiterpenes have been synthesized (Figure 3.3A). Of equal importance, every key oxidation on the seco-prezizaane skeleton had also now been realized abiotically (Figure 3.3B), speaking to the power of $\mathrm{C}-\mathrm{H}$ functionalizations in total synthesis. At the same time, execution of those oxidations was far from perfect and concessionary reductions were often necessary, indicating the space still available for the development of more highly selective oxidation chemistry.

(+)-pseudoanisatin (11)
$[12$ steps] [net 7 O]

(-)-jiadifenolide (9) [12 steps] [net 10 O]


(-)-3-0xo-
pseudoanisatin (259)
[13 steps]
[net 8 O]

(-)-ODNM (7) [13 steps]
[net 11 O]

(-)-jiadifenoxolane A (6) [15 steps]
[net 10 O]

(-)-3-deoxypseudoanisatin (251) [11 steps] [net 6 O]

(-)-jiadifenin (8) [14 steps] [net 12 O]

(-)-3,6-dideoxy-10-hydroxypseudoanisatin (194) [14 steps] [net 6 O]

(-)-DHNM (284) [13 steps] [net 9 O]


Figure 3.3. (A) List of natural products synthesized over the course of these studies, with associated step counts and net oxidation increases relative to $(+)$-cedrol (14). (B) Oxidation heat maps of the seco-prezizaane core (1). Left: distribution of oxidations seen in natural products. Right: sites successfully oxidized abiotically during this work. (C) Summary of seco-prezizaane natural products synthesized by this oxidative strategy.

Nevertheless, we had achieved what we had initially intended by developing a unified, oxidative synthesis of the Illicium sesquiterpenes. While there are obvious extensions to this work, including the synthesis of anisatinoids and even the putative biomimetic synthesis of anislac-tone-type compounds, we hope the impact of the chemistry here will be even more far-reaching. We hope that this work - both the successes and the pitfalls - will serve as a guide for others interested in exploring oxidative syntheses. It is up to synthetic chemists now to push these chemistries to their limits and create inspiring works that transcend previously insurmountable barriers.

### 3.6 Distribution of Credit and Acknowledgments

Much of the work shown in this Chapter would not have been possible without all of the foundational knowledge gained in Chapter 2. Based on that information, M.L.C. proposed the strategy to the majucinoids, with input from T.J.M. and K.H. M.L.C. and K.H. collaboratively executed, optimized, and characterized the route to the majucinoids, with M.L.C. pioneering studies up to the formal synthesis endpoints and K.H. advancing those compounds onto the natural products. M.L.C. was responsible for the sulfamate-directed C13 oxidation, while K.H. studied the
silyl-directed variant. Ground state calculations for 14 and 267 were performed by K.H. with assistance from the Molecular Graphics and Computation Facility. Ground state calculations for 262 were performed by M.L.C. in an analogous way. S.J.H. contributed to early-stage investigations, including optimization of the synthesis of 267. L.F.T.N. was instrumental in unifying the routes to pseudoanisatinoids from majucinoids.

We thank Prof. John F. Hartwig, Dr. Christopher K. Hill, Dr. Ala Bunescu, and Caleb Karmel for samples of the various rhodium and iridium catalysts surveyed over the course of these studied and for helpful discussions on alcohol epimerization and $\mathrm{C}-\mathrm{H}$ silylation chemistries. We are grateful to H.C. and J.P. for NMR spectroscopic assistance wherein NIH grant GM68933 is acknowledged. N.S.S. and A.G.D.P. are acknowledged for X-ray crystallographic analysis wherein support from NIH Shared Instrument Grant (S10-RR027172) is also acknowledged.
M.L.C. thanks the University of California, Berkeley and the NSF for a Berkeley Graduate Fellowship and NSF Predoctoral Fellowship (DGE-1106400) respectively.

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# Supporting Information for 

## Chapter 3

Oxidative Synthesis of the Majucinoids

## SI3.1 General Procedures:

All reactions were performed in flame- or oven-dried glassware under a positive pressure of nitrogen or argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe. Volatile solvents were removed under reduced pressure rotary evaporation below 35 ${ }^{\circ} \mathrm{C}$. Diglyme was removed under reduced pressure rotary evaporation at $60^{\circ} \mathrm{C}$. Analytical and preparative thin-layer chromatography (TLC) were performed using glass plates pre-coated with silica gel ( $0.25-\mathrm{mm}, 60-\AA ̊$ pore size, Silicycle SiliaPlateTM or MilliporeSigma TLC Silica gel 60 F254) and impregnated with a fluorescent indicator ( 254 nm ). TLC plates were visualized by exposure to ultraviolet light (UV) and then were stained by submersion in an ethanolic anisaldehyde solution, an ethanolic phosphomolybdic/cerium sulfate solution, or a basic aqueous potassium permanganate solution, followed by brief heating on a hot plate. Flash column chromatography was performed employing silica gel purchased from Silicycle (SiliaFlash ${ }^{\circledR}, 60 \AA, 230-400$ mesh, $40-63 \mu \mathrm{~m}$ ). Reaction conditions involving slow addition of reagents were performed with syringe pumps model KDS 100 and KDS 200, obtained from KD Scientific.
$(+)$-Cedrol purchased from Sigma Aldrich was recrystallized from $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}$. The recrystallized material was found to have an optical rotation of $[\alpha]_{\mathrm{D}}=+9.6\left(c 5, \mathrm{CHCl}_{3}\right)$. This value corresponds to $97 \%$ ee when compared to the Merck Index value for enantiopure cedrol ( $[\alpha]_{D}=$ +9.9 , c $5, \mathrm{CHCl}_{3}$ ), and $91 \%$ ee when compared to the value reported by Sigma Aldrich ( $[\alpha]_{\mathrm{D}}=$ +10.5, c $\left.5, \mathrm{CHCl}_{3}\right)$. (+)-Cedrol purchased from Parchem was used directly as received. The crystalline material was found to have an optical rotation of $[\alpha]_{\mathrm{D}}=+11.9\left(c 5, \mathrm{CHCl}_{3}\right)$.

Anhydrous THF, DCM, DMF, and MeCN were obtained by passing these previously degassed solvents through activated alumina columns. TMEDA and $i$-PrOH were distilled over calcium hydride prior to use. $i$-PrOH was also degassed prior to use. Dess-Martin Periodinane (DMP) was prepared from 2-iodobenzoic acid according to the literature protocols. ${ }^{1}$ Dimethyldioxirane (DMDO) and oxodiperoxymolybdenum-(pyridine)(hexamethylphosphoric triamide) (MoOPH) were prepared according to the corresponding Organic Synthesis procedures. ${ }^{2,3}$ All other solvents and reagents were purchased at the highest commercial grade and were used as received, without further purification.

Proton nuclear magnetic resonance (1H NMR) spectra and carbon nuclear magnetic resonance (13C NMR) spectra were recorded on Bruker AV 500 ( $500 \mathrm{MHz} / 126 \mathrm{MHz}$ ), Bruker DRX $500(500 \mathrm{MHz} / 126 \mathrm{MHz})$, Bruker AV $600(600 \mathrm{MHz} / 151 \mathrm{MHz})$ NMR, Bruker AV 700 (700 $\mathrm{MHz} / 176 \mathrm{MHz}$ ), and Bruker $900(900 \mathrm{MHz} / 226 \mathrm{MHz})$ spectrometers at $23^{\circ} \mathrm{C}$. Proton chemical shifts are expressed as parts per million ( $\mathrm{ppm}, \delta$ scale) and are referenced to residual protium in the NMR solvent $\left(\mathrm{C}_{5} \mathrm{D}_{4} \mathrm{HN}: \delta 8.74, \mathrm{CHCl}_{3}: \delta 7.26, \mathrm{CD}_{2} \mathrm{HOD}: \delta 3.31\right)$, except where otherwise indicated. Carbon chemical shifts are expressed as parts per million (ppm, $\delta$ scale) and are referenced to the carbon resonance of the NMR solvent $\left(\mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}: \delta 150.35, \mathrm{CDCl}_{3}: \delta 77.16, \mathrm{CD}_{3} \mathrm{OD}: 49.15\right)$, except where otherwise indicated. Data are represented as follows: chemical shift, multiplicity (s $=$ singlet, $\mathrm{d}=$ doublet, $\mathrm{t}=$ triplet, $\mathrm{q}=$ quartet, $\mathrm{p}=$ pentet, $\mathrm{dd}=$ doublet of doublets, $\mathrm{dt}=$ doublet of triplets, $\mathrm{m}=$ multiplet, $\mathrm{br}=$ broad), coupling constant $(\mathrm{J})$ in Hertz (Hz), and integration. Infrared (IR) spectra were recorded on a Bruker Alpha FT-IR spectrometer as thin films and are reported in frequency of absorption $\left(\mathrm{cm}^{-1}\right)$. Optical rotations were recorded on a Perkin Elmer polarimeter, model 241. High-resolution mass spectra were obtained at the QB3/Chemistry Mass Spectrometry Facility at University of California, Berkeley using a Thermo LTQ-FT mass spectrometer, Waters AutoSpec Premier mass spectrometer, and at the Lawrence Berkeley National Laboratory Catalysis Center using a Perkin Elmer AxION 2 TOF mass spectrometer with electrospray ionization
(ESI) and electron ionization (EI) techniques. X-ray diffraction data for all compounds were collected at the Small Molecule X-ray Crystallography Facility (CheXray) at University of California, Berkeley using a Bruker MicroSTAR-H APEX II Xray source.

## SI3.2 Compound Preparation and Characterization Data

Preparation and characterization data are provided for only a subset of compounds described in Chapter 3. Data for the remaining compounds can be found in the Ph.D. dissertation of K.H. ${ }^{4}$ and/or in our published work. ${ }^{5}$


Alcohol 260. Alkene 200 ( $586 \mathrm{mg}, 2.5 \mathrm{mmol}, 1.0$ equiv) was dissolved in THF $(7.5 \mathrm{~mL})$ and cooled to $0{ }^{\circ} \mathrm{C} . \mathrm{BH}_{3} \cdot \mathrm{THF}(1 \mathrm{M}$ in THF, $3.0 \mathrm{~mL}, 3.0 \mathrm{mmol}, 1.2$ equiv) was added dropwise and the resulting solution was warmed to $23^{\circ} \mathrm{C}$ and stirred for 1.5 h . The reaction mixture was re-cooled to $0^{\circ} \mathrm{C}$ and $\mathrm{H}_{2} \mathrm{O}(1.0 \mathrm{~mL})$ was added dropwise [Caution: vigorous gas evolution], followed by NaOH $(3 \mathrm{M}, 3.0 \mathrm{~mL})$ and $\mathrm{H}_{2} \mathrm{O}_{2}\left(50 \mathrm{wt} \%\right.$ in $\mathrm{H}_{2} \mathrm{O}, 0.7 \mathrm{~mL}, 12.5 \mathrm{mmol}, 5.0$ equiv). The mixture was warmed to $23^{\circ} \mathrm{C}$ and stirred for 10 min . $\mathrm{Et}_{2} \mathrm{O}(10 \mathrm{~mL})$, hexanes ( 10 mL ), and $\mathrm{H}_{2} \mathrm{O}(5$ mL ) were added and the layers were separated. The organic phase was further washed with $\mathrm{H}_{2} \mathrm{O}$ ( $2 \times 5 \mathrm{~mL}$ ) and brine ( 5 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography ( $20 \rightarrow 50 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes) to afford alcohol $260\left(535 \mathrm{mg}, 2.1 \mathrm{mmol}, 85 \%\right.$ yield) as a white solid. $[\alpha]_{\mathrm{D}}=+7.2\left(c \quad 1.3, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR ( 700 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 3.78(\mathrm{ddd}, J=10.4,9.8,6.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.35(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.30(\mathrm{~s}, 3 \mathrm{H}), 3.26(\mathrm{~d}$, $J=8.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.99(\mathrm{ddd}, J=12.0,6.5,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.84(\mathrm{dq}, J=12.8,6.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.80(\mathrm{dd}, J=$ $4.8,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.76(\mathrm{ddd}, J=11.3,4.8,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.73(\mathrm{dq}, J=7.3,6.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.69$ (ddd, $J$ $=8.8,7.3,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.58(\mathrm{dqd}, J=10.4,7.2,2.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.51(\mathrm{ddt}, J=12.4,8.8,6.3 \mathrm{~Hz}, 1 \mathrm{H})$, 1.46 (br s, 1H), 1.42 (ddq, $J=12.8,7.2,6.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.30$ (ddt, $J=12.4,7.3,6.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.23$ (dd, $J=11.3,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.22(\mathrm{dd}, J=12.0,9.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.10(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 3 \mathrm{H}), 1.03(\mathrm{~s}, 3 \mathrm{H}), 0.86$ (d, $J=7.2 \mathrm{~Hz}, 3 \mathrm{H}$ ); ${ }^{13} \mathrm{C}$ NMR ( $176 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 80.1,73.1,59.0,54.7,54.5,53.4,48.9,46.7$, 46.2, 44.0, 41.7, 36.7, 26.4, 23.8, 17.5, 15.7; IR (thin film) $v_{\max }$ : 3228, 2933, 2871, 1475, 1446, $1109, \mathrm{~cm}^{-1} ;$ HRMS (EI) calcd for $\mathrm{C}_{16} \mathrm{H}_{28} \mathrm{O}_{2}: 252.2089$, found: 252.2089 .


Ketone 261. Alcohol 260 ( $515 \mathrm{mg}, 2.0 \mathrm{mmol}, 1.0$ equiv) was dissolved in DCM ( 20 mL ). $t$ - $\mathrm{BuOH}(0.6 \mathrm{~mL}, 6.1 \mathrm{mmol}, 3.0$ equiv) was added followed by DMP ( $1.3 \mathrm{~g}, 3.1 \mathrm{mmol}, 1.5$ equiv). The milky white suspension was stirred at $23^{\circ} \mathrm{C}$ for 30 min . $\mathrm{Et}_{2} \mathrm{O}(20 \mathrm{~mL})$ and hexanes $(20 \mathrm{~mL})$ were added followed by saturated aqueous solutions of $\mathrm{NaHCO}_{3}(20 \mathrm{~mL})$ and $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}(5 \mathrm{~mL})$. The biphasic mixture was stirred vigorously until clear. The layers were separated and the organic phase was further washed sequentially with a saturated $\mathrm{NaHCO}_{3}$ solution ( 20 mL ), $\mathrm{H}_{2} \mathrm{O}(20 \mathrm{~mL}), \mathrm{NaOH}(0.1 \mathrm{M}, 20 \mathrm{~mL})$, and brine $(20 \mathrm{~mL})$. The organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude material was typically of sufficient purity to be used crude in the next step. An analytically pure sample of $\mathbf{2 6 1}$ could be prepared by preparative TLC $\left(30 \% \mathrm{Et}_{2} \mathrm{O}\right.$ in hexanes). $=-7.3\left(c 1.0, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(700 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 3.25(\mathrm{~s}, 3 \mathrm{H}), 3.15(\mathrm{~d}$, $J=8.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.01(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.51(\mathrm{qd}, J=7.0,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.34(\mathrm{~d}, J=14.5 \mathrm{~Hz}, 1 \mathrm{H})$, $2.32(\mathrm{~d}, J=14.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.15(\mathrm{t}, J=4.5,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.04(\mathrm{dd}, J=12.0,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.92-1.84$ $(\mathrm{m}, 2 \mathrm{H}), 1.77(\mathrm{~d}, J=12.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.64(\mathrm{t}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.58-1.52(\mathrm{~m}, 1 \mathrm{H}), 1.47-1.41(\mathrm{~m}$,
$1 \mathrm{H}), 1.36-1.30(\mathrm{~m}, 1 \mathrm{H}), 1.13(\mathrm{~d}, J=7.0 \mathrm{~Hz}, 3 \mathrm{H}), 0.86(\mathrm{~d}, J=6.7 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 176 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 213.2,79.8,58.7,55.9,55.7,54.5,51.8$ (2C, overlapping), 49.1, 46.2, 41.6, 37.1, 26.3, 23.2, 15.7, 13.9; IR (thin film) $v_{\max }$ : 2952, 2873, 1706, 1106, $\mathrm{cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{16} \mathrm{H}_{26} \mathrm{O}_{2}$ : 250.1933, found: 250.1936 .


Alcohol 262. Ketone 261 ( $c a .500 \mathrm{mg}, 2.0 \mathrm{mmol}, 1.0$ equiv) was dissolved in $\mathrm{MeOH}(20 \mathrm{~mL}) . \mathrm{NaBH}_{4}(150 \mathrm{mg}, 4.0 \mathrm{mmol}, 2.0$ equiv) was added and the resulting solution was stirred at $23^{\circ} \mathrm{C}$ for $30 \mathrm{~min} . \mathrm{HCl}(3.0 \mathrm{M}, 2.0 \mathrm{~mL})$ was carefully added followed by $\mathrm{Et}_{2} \mathrm{O}(20 \mathrm{~mL})$ and hexanes $(20 \mathrm{~mL})$. The layers were separated and the organic phase was further washed with $\mathrm{H}_{2} \mathrm{O}(10 \mathrm{~mL})$ and brine ( 10 mL ), filtered, and concentrated. The crude residue was purified by column chromatography ( $10 \rightarrow 30 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes) to afford alcohol 262 ( $407 \mathrm{mg}, 1.6$ $\mathrm{mmol}, 79 \%$ yield over two steps) as a thick oil which solidified upon standing. $[\alpha]_{\mathrm{D}}=-27.8$ (c 1.1, $\mathrm{CHCl}_{3}$ ); ${ }^{1} \mathrm{H}$ NMR $\left(700 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 4.01-3.97(\mathrm{~m}, 1 \mathrm{H}), 3.60(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.46(\mathrm{~d}, J=$ $9.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.35(\mathrm{~s}, 3 \mathrm{H}), 2.77(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 2.53(\mathrm{dd}, J=9.3,5.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.02(\mathrm{qd}, J=7.3,3.0 \mathrm{~Hz}$, $1 \mathrm{H}), 1.89(\mathrm{dd}, J=11.3,4.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.92-1.79(\mathrm{~m}, 2 \mathrm{H}), 1.82$ (dddd, $J=11.7,8.5,6.4,5.9 \mathrm{~Hz}$, $1 \mathrm{H}), 1.74(\mathrm{dd}, J=4.8,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.72(\mathrm{qt}, J=7.2,5.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.56(\mathrm{dddd}, J=12.6,9.3,8.5$, $5.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.45(\mathrm{dq}, J=12.6,5.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.35(\mathrm{dq}, J=11.7,5.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.13(\mathrm{~d}, J=11.3 \mathrm{~Hz}$, $1 \mathrm{H}), 1.13(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 3 \mathrm{H}), 1.03(\mathrm{~s}, 3 \mathrm{H}), 0.87(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $176 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ $79.9,69.6,58.6,53.2,52.9,48.9,48.2,47.4,43.7,43.2,41.9,35.8,25.7,24.0,16.6,15.7$; IR (thin film) $v_{\max }: 3473,2931,2820,1448,1104 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{16} \mathrm{H}_{28} \mathrm{O}_{2}: 252.2089$, found: 252.2089.

Ethers 264 and 265. Alcohol $262(50 \mathrm{mg}, 0.2 \mathrm{mmol}, 1.0$ equiv) was dissolved in DCM ( 6.7 mL ) and cooled to $0^{\circ} \mathrm{C} \cdot \mathrm{PhI}(\mathrm{OAc})_{2}\left(192 \mathrm{mg}, 0.6 \mathrm{mmol}, 3.0\right.$ equiv) and $\mathrm{I}_{2}(50 \mathrm{mg}, 0.2 \mathrm{mmol}, 1.0$ equiv) were added. The purple solution was brought into a cold room ( $c a 5^{\circ} \mathrm{C}$ ) where it was vigorously stirred and irradiated by a 90 W halogen lamp for $1 \mathrm{~h} . \mathrm{Et}_{2} \mathrm{O}(5 \mathrm{~mL})$ and hexanes $(5 \mathrm{~mL})$ were added followed by saturated aqueous solutions of $\mathrm{NaHCO}_{3}(5 \mathrm{~mL})$ and $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}(1 \mathrm{~mL})$. The biphasic mixture was stirred vigorously while being warmed to room temperature. When the solution had turned colorless, the layers were separated and the organic phase was further washed with saturated $\mathrm{NaHCO}_{3}$ solution ( 5 mL ), $\mathrm{H}_{2} \mathrm{O}(5 \mathrm{~mL}), \mathrm{NaOH}(0.1 \mathrm{M}, 5 \mathrm{~mL})$, and brine $(5 \mathrm{~mL})$. The organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo to afford a crude mixture of ethers epi-264, 264, and 265. NMR yield of the crude reaction mixture with 1,3,5-trimethoxybenzene as an internal standard indicated epi-264 was formed in $17 \%$ yield, 264 was formed in $26 \%$ yield, and 265 was formed in $34 \%$ yield, for a combined $77 \%$ yield in a 1:1.5:2 ratio of products. The crude mixture was purified by column chromatography ( $4 \rightarrow 19 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes $+1 \% \mathrm{Et}_{3} \mathrm{~N}$ ) to afford $264(10 \mathrm{mg}, 0.04 \mathrm{mmol}, 20 \%$ yield) , and $265(16 \mathrm{mg}, 0.06 \mathrm{mmol}, 32 \%)$ as clear, colorless oils. Epi-264 was unstable to the purification conditions, and 264 was observed to contain a small amount (ca. 10\%) of hydrolysis products.

264. $[\alpha]_{\mathrm{D}}=-66.0\left(c 1.0, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \mathrm{NMR}\left(700 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 4.70(\mathrm{~s}, 1 \mathrm{H})$, $4.12(\mathrm{p}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.51(\mathrm{~s}, 3 \mathrm{H}), 2.55(\mathrm{ddd}, J=10.6,8.3,2.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.09$ (dtd, $J=13.6,8.7,7.7,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.93(\mathrm{ddd}, J=11.3,6.1,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.86$ $(\mathrm{p}, J=7.4,6.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.82(\mathrm{dt}, J=13.6,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.67(\mathrm{qd}, J=7.5,2.5 \mathrm{~Hz}$, $1 \mathrm{H}), 1.60-1.45(\mathrm{~m}, 5 \mathrm{H}), 1.26-1.19(\mathrm{~m}, 2 \mathrm{H}), 1.14(\mathrm{~d}, J=7.4 \mathrm{~Hz}, 3 \mathrm{H}), 1.14$ (dd,
$J=11.3,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.01(\mathrm{~s}, 3 \mathrm{H}), 0.84(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(176 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 104.1$, $76.3,57.5,53.9,51.1,49.8,49.0,46.6,41.5,40.1,39.0,35.4,26.5,22.4,20.7,18.8$; IR (thin film) $v_{\max }: 2954,2868,1009 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{16} \mathrm{H}_{26} \mathrm{O}_{2}: 250.1933$, found: 250.1936.

265. $[\alpha]_{\mathrm{D}}=+8.0\left(c 1.6, \mathrm{CHCl}_{3}\right){ }^{1} \mathrm{H} \operatorname{NMR}\left(700 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 4.12(\mathrm{~d}, J=4.7$ $\mathrm{Hz}, 1 \mathrm{H}), 3.88(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.55(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.33(\mathrm{~s}, 3 \mathrm{H}), 2.14(\mathrm{t}$, $J=2.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.87(\mathrm{dt}, J=11.8,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.85-1.79(\mathrm{~m}, 2 \mathrm{H}), 1.73(\mathrm{qd}$, $J=7.5,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.71-1.67(\mathrm{~m}, 1 \mathrm{H}), 1.67-1.63(\mathrm{~m}, 1 \mathrm{H}), 1.63-1.60(\mathrm{~m}$, $1 \mathrm{H}), 1.59(\mathrm{~d}, J=10.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.49(\mathrm{~d}, J=11.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.35(\mathrm{dd}, J=13.3$, $6.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.17(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.98(\mathrm{~s}, 3 \mathrm{H}), 0.91(\mathrm{~d}, J=6.3 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 176 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 102.0,83.0,78.6,62.8,59.0,54.1,49.2,43.6,42.8,42.0,40.7,36.2,28.4,23.7,19.5$, 14.9; IR (thin film) $v_{\max }$ : 2951, 2869, $1106 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{16} \mathrm{H}_{26} \mathrm{O}_{2}: 250.1933$, found: 250.1936.


Alkene 266. Cyclohexane ( 1.8 L ) was added to a 3 L flask containing diacetoxyiodobenzene ( $42.5 \mathrm{~g}, 132 \mathrm{mmol}, 1.1$ equiv) and iodine ( $12.2 \mathrm{~g}, 48 \mathrm{mmol}$, 0.4 equiv). The suspension was stirred at room temperature until the iodine had completely dissolved. At this point, (+)-cedrol ( $26.7 \mathrm{~g}, 120 \mathrm{mmol}, 1.0$ equiv) was added in a single portion. The deep purple mixture was irradiated with a 90 W halogen lamp for 1.5 h . Upon consumption of the starting material, the lamp was turned off and acetic anhydride ( $113 \mathrm{~mL}, 1.2 \mathrm{~mol}, 10.0$ equiv) and phosphoric acid $(85 \%, 14.7 \mathrm{~mL}, 240 \mathrm{mmol}$, 2.0 equiv) were added sequentially. The resulting solution was stirred for 30 min before being carefully quenched with saturated $a q . \mathrm{NaHCO}_{3}(750 \mathrm{~mL})$ and saturated $a q$. $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}(250 \mathrm{~mL})$. The layers were separated and the aqueous layer was extracted with $\mathrm{Et}_{2} \mathrm{O}(2 \times 750 \mathrm{~mL})$. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography $\left(1 \% \rightarrow 5 \% \mathrm{Et}_{2} \mathrm{O}\right.$ in hexanes) to afford alkene $7(21.1 \mathrm{~g}, 80$ mmol, $67 \%$ yield) as a pale yellow oil. $[\alpha]_{\mathrm{D}}=-99.7\left(c 2.3, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \mathrm{NMR}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ $\delta 5.26(\mathrm{dt}, J=4.1,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.00(\mathrm{~d}, J=10.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.90(\mathrm{~d}, J=10.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.18(\mathrm{dt}, J$ $=17.0,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.04(\mathrm{~s}, 3 \mathrm{H}), 1.96(\mathrm{~d}, J=3.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.90-1.83(\mathrm{~m}, 1 \mathrm{H}), 1.82-1.73(\mathrm{~m}$, $2 \mathrm{H}), 1.73-1.65(\mathrm{~m}, 2 \mathrm{H}), 1.64(\mathrm{~d}, J=2.0 \mathrm{~Hz}, 3 \mathrm{H}), 1.62-1.55(\mathrm{~m}, 1 \mathrm{H}), 1.45(\mathrm{~d}, J=11.1 \mathrm{~Hz}, 1 \mathrm{H})$, $1.43-1.35(\mathrm{~m}, 2 \mathrm{H}), 1.01(\mathrm{~s}, 3 \mathrm{H}), 0.85(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(151 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 171.5$, 139.1, 120.71, 72.4, 55.9, 53.4, 52.4, 51.6, 41.3, 40.3, 38.8, 36.3, 25.4, 24.1, 21.2, 20.6, 15.5; IR (thin film) $v_{\text {max }}: 2939,2873,1740,1470,1372,1235,1031 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{17} \mathrm{H}_{26} \mathrm{O}_{2}$ : 262.1933, found: 262.1935 .


Ketone 291. Alkene 266 ( $2.0 \mathrm{~g}, 7.6 \mathrm{mmol}, 1.0$ equiv) was dissolved in degassed THF ( 30 mL ) and cooled to $0^{\circ} \mathrm{C} . \mathrm{BH}_{3} \cdot \mathrm{THF}(1 \mathrm{M}$ in THF, $9.9 \mathrm{~mL}, 9.9 \mathrm{mmol}$, 1.3 equiv) was added dropwise over 15 min . At the conclusion of the addition, the resulting solution was allowed to warm to room temperature and stirred for 1.5h. In a separate flask, pyridine ( $30.7 \mathrm{~mL}, 382 \mathrm{mmol}, 50$ equiv) was dissolved in DCM $(160 \mathrm{~mL})$ and was cooled to $0^{\circ} \mathrm{C} . \mathrm{CrO}_{3}$ was added portion-wise over $20 \mathrm{~min}(4 \times 4.8 \mathrm{~g}$ portions, $19.1 \mathrm{~g}, 191 \mathrm{mmol}, 25$ equiv) and the suspension was warmed to room temperature and stirred for 30 min . Upon completion of the hydroboration reaction (as judged by TLC), the so-prepared $\mathrm{CrO}_{3} \cdot 2$ py solution was added to the reaction mixture in two portions over 30 min , with the first portion being added carefully to quench unreacted borane. The suspension
was further diluted with $\mathrm{DCM}(150 \mathrm{~mL})$, filtered through celite, washed with $1 \mathrm{M} \mathrm{HCl}(100 \mathrm{~mL})$ and concentrated in vacuo. The crude ketone was afforded as a red oil (ca. 1.85 g ) and was used directly in the next step without further purification. An analytical sample was isolated by preparative TLC ( $20 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes). $[\alpha]_{\mathrm{D}}=-26.1\left(c 1.4, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 3.85$ (d, $J=11.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.83(\mathrm{~d}, J=11.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.54(\mathrm{qd}, J=7.1,3.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.33(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 2.16$ (br t, $J=4.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.05 (br dd, $J=12.3,4.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.93-1.84(\mathrm{~m}, 2 \mathrm{H}), 1.80(\mathrm{br} \mathrm{d}, J=12.1$ $\mathrm{Hz}, 1 \mathrm{H}), 1.74(\mathrm{br} \mathrm{t}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.60-1.52(\mathrm{~m}, 1 \mathrm{H}), 1.46-1.38(\mathrm{~m}, 1 \mathrm{H}), 1.38-1.29(\mathrm{~m}, 1 \mathrm{H})$, $1.10(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}), 0.99(\mathrm{~s}, 3 \mathrm{H}), 0.85(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(151 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ $212.2,171.0,71.0,56.0,55.8,54.8,51.7,51.5,48.0,46.1,41.6,37.1,26.4,23.0,21.0,15.6,14.2 ;$ IR (thin film) $v_{\text {max }}$ : 2951, 2875, 1735, 1700, 1362, 1234, $1035 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{17} \mathrm{H}_{26} \mathrm{O}_{3}$ : 278.1882, found: 278.1880 .


Alcohol 267. Ketone 291 ( ca. $1.85 \mathrm{~g}, 6.6 \mathrm{mmol}, 1.0$ equiv) was dissolved in $\mathrm{MeOH}(66 \mathrm{~mL})$ and cooled to $0^{\circ} \mathrm{C} . \mathrm{NaBH}_{4}(375 \mathrm{mg}, 9.9 \mathrm{mmol}, 1.5$ equiv) was added in 3 portions over 30 min . At the end of the addition, the reaction mixture was quenched with $a q . \mathrm{HCl}(1 \mathrm{M}, 50 \mathrm{~mL})$ and diluted with $\mathrm{Et}_{2} \mathrm{O} /$ hexanes $(1: 1,100 \mathrm{~mL})$. The layers were separated and the aqueous phase was further extracted with $\mathrm{Et}_{2} \mathrm{O} /$ hexanes ( $1: 1,2 \times 50 \mathrm{~mL}$ ). The combined organic layers were washed with brine ( 50 mL ), dried over $\mathrm{MgSO}_{4}$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography $(10 \% \rightarrow 15 \%$ EtOAc in hexanes) to afford alcohol $267\left(1.56 \mathrm{~g}, 5.6 \mathrm{mmol}, 72 \%\right.$ yield over two steps) as a white solid. $[\alpha]_{\mathrm{D}}=-29.3$ (c 1.5, $\mathrm{CHCl}_{3}$ ); ${ }^{1} \mathrm{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 4.41(\mathrm{~d}, J=10.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.39(\mathrm{~d}, J=10.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.01$ (q, $J=3.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.54(\mathrm{dd}, J=9.3,6.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.03(\mathrm{~s}, 3 \mathrm{H}), 1.92(\mathrm{ddq}, J=11.4,7.6,3.9,3.2$ $\mathrm{Hz}, 1 \mathrm{H}), 1.86(\mathrm{dd}, J=11.5,4.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.83-1.76(\mathrm{~m}, 4 \mathrm{H}), 1.69(\mathrm{~h}, J=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.63(\mathrm{br} \mathrm{s}$, $1 \mathrm{H}), 1.59-1.49(\mathrm{~m}, 1 \mathrm{H}), 1.41(\mathrm{dq}, J=12.7,6.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.32(\mathrm{dq}, J=12.2,6.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.15(\mathrm{~d}$, $J=11.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.08(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 3 \mathrm{H}), 1.01(\mathrm{~s}, 3 \mathrm{H}), 0.84(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 151 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 171.6,72.8,69.8,53.1,52.9,50.7,47.4,47.0,43.1,43.0,41.8,36.0,26.0,23.3$, $21.2,17.3,15.7$; IR (thin film) $v_{\max }: 3502,2932,2872,1715,1324,1244,1028 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{17} \mathrm{H}_{28} \mathrm{O}_{3} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 303.1936$, found: 303.1937.


Ether 268. Alcohol 267 ( $6.0 \mathrm{~g}, 21.4 \mathrm{mmol}, 1.0$ equiv) was dissolved in degassed $\mathrm{DCM}(710 \mathrm{~mL})$ and cooled to $0^{\circ} \mathrm{C} . \operatorname{PhI}(\mathrm{OAc})_{2}(20.7 \mathrm{~g}, 64.2 \mathrm{mmol}, 3.0$ equiv) was added followed by iodine ( $5.4 \mathrm{~g}, 21.4 \mathrm{mmol} 1.0$ equiv). The deep purple mixture was brought into a cold room $\left(c a .5^{\circ} \mathrm{C}\right)$ and irradiated with a 90 W halogen lamp for 1.5 h . Upon consumption of the starting material, the reaction mixture was removed from the cold room and quickly quenched with saturated $a q$. $\mathrm{NaHCO}_{3}(250 \mathrm{~mL})$ and saturated $a q$. $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}(50 \mathrm{~mL})$. The layers were separated and the aqueous layer was extracted with DCM ( 300 mL ). The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude residue was purified by column chromatography $(5 \% \rightarrow 10 \%$ EtOAc in hexanes) to afford ether $268(5.5 \mathrm{~g}, 19.7 \mathrm{mmol}, 93 \%$ yield $)$ as a clear, colorless oil. $[\alpha]_{\mathrm{D}}=-1.0\left(c 4.3, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 4.53(\mathrm{~d}, J=10.8 \mathrm{~Hz}, 1 \mathrm{H})$, 4.38 (d, $J=10.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.14$ (d, $J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.12$ (s, 1H), 2.04 (d, $J=1.2 \mathrm{~Hz}, 3 \mathrm{H}), 1.95-$ $1.79(\mathrm{~m}, 3 \mathrm{H}), 1.76(\mathrm{qd}, J=7.7,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.73-1.58(\mathrm{~m}, 4 \mathrm{H}), 1.54(\mathrm{~d}, J=11.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.41$ (h, $J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.13(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H}), 0.96(\mathrm{~s}, 3 \mathrm{H}), 0.92(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 151 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 171.4,101.7,82.9,70.1,62.9,54.7,48.3,43.5,42.8,42.0,40.6,36.2,28.7,22.8$,
21.2, 19.8, 14.9; IR (thin film) $v_{\text {max }}$ : 2951, 2872, 1736, 1372, 1241, $1031 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{17} \mathrm{H}_{26} \mathrm{O}_{3} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 301.1780$, found: 303.1782 .


Sulfamate 270. First, a solution of sulfamoyl chloride was prepared by the following procedure: chlorosulfonyl isocyanate ( $130 \mu \mathrm{~L}, 1.5 \mathrm{mmol}, 1.5$ equiv) was dissolved in $\mathrm{MeCN}(0.75 \mathrm{~mL})$ and cooled to $0^{\circ} \mathrm{C}$. Formic acid ( $57 \mu \mathrm{~L}, 1.5 \mathrm{mmol}, 1.5$ equiv) was added and the resulting solution was stirred at $0^{\circ} \mathrm{C}$ for 1 h and then was allowed to warm to $23^{\circ} \mathrm{C}$ and stirred at that temperature for 12 h . In a separate flask, sodium hydride ( $60 \mathrm{wt} \%$ in mineral oil, 43 mg , 1.1 equiv) was washed with hexanes ( $3 \times 1 \mathrm{~mL}$ ) and dried under high vacuum for 10 min . DMF ( 1 mL ) was added and the suspension was cooled to $0^{\circ} \mathrm{C}$. Alcohol 269 (236 $\mathrm{mg}, 1.0 \mathrm{mmol}, 1.0$ equiv) was dissolved in DMF ( 0.5 mL ) and added dropwise to the suspension of sodium hydride. The reaction mixture was allowed to warm to $23^{\circ} \mathrm{C}$ and was stirred at that temperature for 1 h before being re-cooled to $0^{\circ} \mathrm{C}$. The sulfamoyl chloride solution $(1.5 \mathrm{mmol}$ assumed) was added dropwise and the resulting solution was allowed to warm to $23^{\circ} \mathrm{C}$ and stirred at that temperature for $4 \mathrm{~h} . \mathrm{H}_{2} \mathrm{O}(5 \mathrm{~mL})$ was carefully added followed by $\mathrm{Et}_{2} \mathrm{O}(5 \mathrm{~mL})$. The layers were separated and the aqueous layer was further extracted with $\mathrm{Et}_{2} \mathrm{O}(2 \times 5 \mathrm{~mL})$. The combined organic layers were washed with brine ( 5 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography ( $50 \rightarrow 80 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes) to afford sulfamate 270 as a white solid. $[\alpha]_{\mathrm{D}}=+0.8\left(c 2.0, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \mathrm{NMR}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ $5.01(\mathrm{~s}, 2 \mathrm{H}), 4.70(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.49(\mathrm{~d}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.18(\mathrm{~d}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.14(\mathrm{t}, J$ $=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.93(\mathrm{dt}, J=12.1,3.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.88-1.83(\mathrm{~m}, 2 \mathrm{H}), 1.80(\mathrm{qd}, J=7.6,1.9 \mathrm{~Hz}, 1 \mathrm{H})$, $1.74-1.61(\mathrm{~m}, 4 \mathrm{H}), 1.57(\mathrm{~d}, J=12.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.45-1.37(\mathrm{~m}, 1 \mathrm{H}), 1.18(\mathrm{dd}, J=7.6,1.0 \mathrm{~Hz}, 3 \mathrm{H})$, $1.05(\mathrm{~s}, 3 \mathrm{H}), 0.92(\mathrm{~d}, J=6.2 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $\left.151 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 101.9,83.1,77.0,63.1,54.6$, $48.6,43.2,42.6,41.9,40.5,36.2,28.7,22.4,19.9,14.8$; IR (thin film) $v_{\max }: 3357,3279,2955,2871$, 1373, $1178 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{25} \mathrm{O}_{4} \mathrm{NNaS}[\mathrm{M}+\mathrm{Na}]^{+}: 338.1397$, found: 338.1394.


Cyclic sulfamate 271. $\mathrm{Rh}_{2}(\mathrm{esp})_{2}(3 \mathrm{mg}, 0.002 \mathrm{mmol}, 3 \mathrm{~mol} \%)$ and $\mathrm{PhI}(\mathrm{OPiv})_{2}$ ( $78 \mathrm{mg}, 0.095 \mathrm{mmol}, 1.5$ equiv) were combined as solids. Sulfamate 270 (40 $\mathrm{mg}, 0.063 \mathrm{mmol}, 1.0$ equiv) was dissolved in benzene $(1 \mathrm{~mL})$ and added to the mixture. The resulting suspension was stirred at $23^{\circ} \mathrm{C}$ for 16 h . The reaction mixture was directly concentrated in vacuo and purified by column chromatography to afford cyclic sulfamate $271(25 \mathrm{mg}, 0.04 \mathrm{mmol}, 63 \%$ yield $)$ as a white solid. $[\alpha]_{\mathrm{D}}=+2.0\left(c 0.5, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.06(\mathrm{dd}, J=$ $12.3,2.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.97(\mathrm{~d}, J=12.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.42(\mathrm{t}, J=9.5,5.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.21(\mathrm{~d}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H})$, $3.50(\mathrm{dd}, J=14.8,9.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.31(\mathrm{dt}, J=14.8,5.3,2.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.49(\mathrm{t}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.94$ $-1.83(\mathrm{~m}, 3 \mathrm{H}), 1.81(\mathrm{dt}, J=12.7,3.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.74-1.59(\mathrm{~m}, 4 \mathrm{H}), 1.59-1.51(\mathrm{~m}, 2 \mathrm{H}), 1.23(\mathrm{~d}$, $J=7.4 \mathrm{~Hz}, 3 \mathrm{H}), 0.95(\mathrm{~d}, J=6.4 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 100.1,83.1,77.5,63.3$, $50.7,49.9,46.6,42.6,42.4,42.0,40.0,35.7,28.2,19.5,14.6$; IR (thin film) $v_{\max }: 3300,2951,2874$, $1361,1185 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{O}_{4} \mathrm{NNaS}[\mathrm{M}+\mathrm{Na}]^{+}: 336.1246$, found: 336.1243.

Keto lactone 275 and alcohol 276. Ether 269 ( $8.9 \mathrm{~g}, 32.0 \mathrm{mmol}, 1.0$ equiv) was dissolved in $\mathrm{MeCN}: \mathrm{CCl}_{4}: \mathrm{H}_{2} \mathrm{O}(2: 2: 3,320 \mathrm{~mL})$ and $\mathrm{KBrO}_{3}(26.7 \mathrm{~g}, 160 \mathrm{mmol}, 5.0$ equiv $)$ was added. The biphasic mixture was stirred vigorously at room temperature for 10 min before $\mathrm{RuCl}_{3} \cdot \mathrm{xH}_{2} \mathrm{O}$ (199 $\mathrm{mg}, 0.96 \mathrm{mmol}, 0.03$ equiv) was added. The orange/brown solution was heated at $75^{\circ} \mathrm{C}$ for 24
h. At that point, the suspension was cooled to room temperature and another portion of $\mathrm{KBrO}_{3}$ ( $26.7 \mathrm{~g}, 160 \mathrm{mmol}, 5.0$ equiv) and $\mathrm{RuCl}_{3} \cdot \mathrm{xH}_{2} \mathrm{O}(199 \mathrm{mg}, 0.96 \mathrm{mmol}, 0.03$ equiv) was added. The suspension was re-heated at $75^{\circ} \mathrm{C}$ for another 24 h . The suspension was then cooled to room temperature again and a final portion of $\mathrm{RuCl}_{3} \cdot \mathrm{XH}_{2} \mathrm{O}(199 \mathrm{mg}, 0.96 \mathrm{mmol}, 0.03$ equiv) was added (no additional $\mathrm{KBrO}_{3}$ was added with it). The suspension was once again heated at $75^{\circ} \mathrm{C}$ for another 24 h . At the conclusion of the 72 h reaction, the resulting mixture was cooled to room temperature and diluted with $\operatorname{EtOAc}(500 \mathrm{~mL})$ and water $(500 \mathrm{~mL})$. The layers were separated and the aqueous layer was extracted with EtOAc $(250 \mathrm{~mL})$. The combined organic layers were washed with saturated aq. $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}(250 \mathrm{~mL})$, water ( 500 mL ), and brine ( 500 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude residue was purified by column chromatography ( $30 \% \rightarrow 50 \% \mathrm{EtOAc}$ in hexanes) to afford keto lactone 275 as a white solid ( $7.1 \mathrm{~g}, 23 \mathrm{mmol}, 72 \%$ yield). A C1 hydroxylated derivative, alcohol 276, ( $750 \mathrm{mg}, 2.3 \mathrm{mmol}, 7 \%$ yield) could also be isolated from this mixture (eluting the column with $100 \% \mathrm{EtOAc}$ ) as a white solid.


Keto lactone 275: $[\alpha]_{\mathrm{D}}=-16.0\left(c\right.$ 1.7, $\left.\mathrm{CHCl}_{3}\right)$; ${ }^{1} \mathrm{H} \operatorname{NMR}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ $4.04(\mathrm{~d}, J=11.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.96(\mathrm{~d}, J=11.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.75$ (dd, $J=12.7,6.8 \mathrm{~Hz}$, $1 \mathrm{H}), 2.71(\mathrm{~d}, J=19.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.40(\mathrm{~d}, J=19.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.21(\mathrm{dd}, J=13.2$, $12.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.18(\mathrm{~s}, 3 \mathrm{H}), 1.99(\mathrm{~s}, 3 \mathrm{H}), 1.95(\mathrm{dd}, J=13.2,5.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.89$ (dd, $J=13.2,6.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.80-1.72(\mathrm{~m}, 2 \mathrm{H}), 1.69-1.61(\mathrm{~m}, 1 \mathrm{H}), 1.31(\mathrm{~s}$, $3 \mathrm{H}), 1.23-1.13(\mathrm{~m}, 1 \mathrm{H}), 1.03(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(151 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ $\delta 206.9,177.4,169.8,106.0,65.6,58.8,55.2,49.5,46.4,39.8,37.3,35.3,31.4,31.2,20.7,20.1$, 14.2; IR (thin film) $v_{\max }$ : 2954, 2876, 1768, 1740, 1703, 1362, 1235, $1038 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{17} \mathrm{H}_{24} \mathrm{O}_{5} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 331.1521$, found: 331.1520 .


Alcohol 276: $[\alpha]_{\mathrm{D}}=-118.0\left(c 0.5, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 4.06$ (d, $J=11.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.97(\mathrm{~d}, J=11.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.04(\mathrm{dd}, J=12.3,7.0 \mathrm{~Hz}, 1 \mathrm{H})$, 2.68 (d, $J=19.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.64(\mathrm{~d}, J=19.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.32$ (dd, $J=13.2,7.0 \mathrm{~Hz}$, $1 \mathrm{H}), 2.23(\mathrm{td}, J=13.6,6.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.18(\mathrm{~s}, 3 \mathrm{H}), 2.03(\mathrm{dd}, J=13.2,12.3 \mathrm{~Hz}$, $1 \mathrm{H}), 2.00(\mathrm{~s}, 3 \mathrm{H}), 1.88(\mathrm{dd}, J=13.6,5.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.75(\mathrm{dd}, J=13.6,6.1 \mathrm{~Hz}$, $1 \mathrm{H}), 1.67(\mathrm{td}, J=13.6,5.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.37(\mathrm{~s}, 3 \mathrm{H}), 1.35(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 126 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 207.9,177.0,169.9,107.2,82.1,66.1,61.3,59.4,49.1,42.0,38.67,35.4,33.0$, $31.3,24.5,20.8,20.4$; IR (thin film) $v_{\max }$ : 3742, 2957, 1742, 1701, 1234, 1198, $1092 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{14} \mathrm{H}_{24} \mathrm{O}_{6} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 319.1158$, found: 319.1151 .

Methyl esters 277 and 278. Keto-lactone 275 ( 616 mg , $2.0 \mathrm{mmol}, 1.0$ equiv) and $\mathrm{SeO}_{2}$ ( 777 mg , 7.0 mmol , 3.5 equiv) were dissolved in diglyme ( 6 mL ) and heated at $120^{\circ} \mathrm{C}$ for 3 h . The reaction mixture was cooled to $23^{\circ} \mathrm{C}$ and acetone ( 6 mL ), $\mathrm{K}_{2} \mathrm{CO}_{3}(970 \mathrm{mg}, 7.0 \mathrm{mmol}, 3.5$ equiv), and Me${ }_{2} \mathrm{SO}_{4}(200 \mu \mathrm{~L}, 2.0 \mathrm{mmol}, 1.0$ equiv) were added sequentially. The suspension was stirred for 30 min before being filtered through a pad of celite and directly concentrated. The crude residue was purified by column chromatography ( $60 \rightarrow 100 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes) to afford $278(108 \mathrm{mg}, 0.30$ $\mathrm{mmol}, 15 \%$ yield) and $277(444 \mathrm{mg}, 1.27 \mathrm{mmol}, 63 \%$ yield).


278: $[\alpha]_{\mathrm{D}}=-106.9\left(c \quad 1.0, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(700 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.22(\mathrm{~s}$, $1 \mathrm{H}), 4.54(\mathrm{~d}, J=11.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.99(\mathrm{~d}, J=11.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.93(\mathrm{~s}, 3 \mathrm{H}), 2.36$ (dqd, $J=12.9,7.1,6.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.29 (dd, $J=14.2,5.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.13$ (dt, $J=12.9,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.02(\mathrm{ddd}, J=14.2,13.2,6.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.82(\mathrm{~s}, 3 \mathrm{H})$, $1.48(\mathrm{dtd}, J=13.2,12.9,5.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.46(\mathrm{~s}, 3 \mathrm{H}), 1.16(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( $176 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 192.4,181.9,165.5,161.8,160.3,146.4$, $141.1,101.7,69.0,65.1,53.3,52.5,46.4,34.3,33.6,20.4,16.3,15.8$; IR (thin film) $v_{\max }: 2957$, $2875,1792,1771,1746,1680,1185 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{18} \mathrm{H}_{20} \mathrm{O}_{8} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 387.1050$, found: 387.1048.


277: $[\alpha]_{\mathrm{D}}=-96.7\left(c \quad 0.6 \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.16(\mathrm{~s}, 1 \mathrm{H})$, $4.42(\mathrm{~d}, J=11.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.14(\mathrm{~d}, J=11.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.89(\mathrm{~s}, 3 \mathrm{H}), 2.79(\mathrm{~d}, J=$ $18.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.48(\mathrm{~d}, J=18.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.07-1.99(\mathrm{~m}, 1 \mathrm{H}), 1.97-1.93(\mathrm{~m}$, $1 \mathrm{H}), 1.94(\mathrm{~s}, 3 \mathrm{H}), 1.92-1.84(\mathrm{~m}, 2 \mathrm{H}), 1.40(\mathrm{ddd}, J=13.1,12.2,4.6 \mathrm{~Hz}, 1 \mathrm{H})$, $1.36(\mathrm{~s}, 3 \mathrm{H}), 1.12(\mathrm{~d}, J=6.7 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $176 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 183.2$, 176.4, 169.9, 162.6, 153.3, 139.9, 104.6, 66.2, 63.8, 53.1, 53.1, 43.3, 34.1, $33.7,32.5,20.7,18.6,15.1$; IR (thin film) $v_{\text {max }}: 2958,2873,1774,1740,1673,1605,1285 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{18} \mathrm{H}_{22} \mathrm{O}_{7} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 373.1263$, found: 373.1256.


Enol lactone 279. Crude methyl ester 277 (ca. 560 mg , $1.6 \mathrm{mmol}, 1.0$ equiv) was dissolved in THF ( 16 mL ) and cooled to $-78^{\circ} \mathrm{C}$. L-Selectride ( 1 M in THF, $1.9 \mathrm{~mL}, 1.9 \mathrm{mmol}, 1.2$ equiv) was added and the solution was stirred for 30 min . $\mathrm{KOH}(1 \mathrm{M}$ in $\mathrm{MeOH}, 16 \mathrm{~mL}, 16 \mathrm{mmol}, 10.0$ equiv) was added, the reaction mixture was allowed to warm to room temperature and stirred for 30 min . DCM ( 25 mL ) and $\mathrm{HCl}(1 \mathrm{M}, 25 \mathrm{~mL})$ were added and the layers were separated. The aqueous layer was extracted with DCM ( $2 \times 25 \mathrm{~mL}$ ). The combined organic layers were washed with half-saturated brine ( 25 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude residue was purified by column chromatography ( $35 \% \rightarrow$ $45 \%$ EtOAc in hexanes) to afford enol lactone 279 ( $228 \mathrm{mg}, 0.82 \mathrm{mmol}, 50 \%$ over two steps) as a white solid. $[\alpha]_{\mathrm{D}}=-167.1\left(c 1.4 \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.58(\mathrm{~s}, 1 \mathrm{H}), 4.60$ (d, $J=11.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.16(\mathrm{~d}, J=11.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.81(\mathrm{~d}, J=17.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.81(\mathrm{~d}, J=18.9 \mathrm{~Hz}$, $1 \mathrm{H}), 2.51(\mathrm{~d}, J=17.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.35(\mathrm{~d}, J=18.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.12(\mathrm{ddd}, J=12.7,11.4,6.7 \mathrm{~Hz}, 1 \mathrm{H})$, $2.05-1.99(\mathrm{~m}, 2 \mathrm{H}), 1.82(\mathrm{dd}, J=14.5,7.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.59(\mathrm{dq}, J=12.0,6.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.38(\mathrm{~s}, 3 \mathrm{H})$, $1.05(\mathrm{~d}, J=6.4 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 175.8,163.2,135.7,132.8,106.9,74.8$, $62.7,46.7,45.6,38.6,36.7,35.1,31.7,22.5,14.8$; IR (thin film) $v_{\max }: 3315,2975,2891,1763$, $1708 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{18} \mathrm{O}_{5} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 301.1052$, found: 301.1042.


Lactol 286. $\mathrm{LiBH}_{4}(16 \mathrm{mg}, 0.72 \mathrm{mmol}, 20$ equiv) was suspended in THF ( 1 mL ) and cooled to $0^{\circ} \mathrm{C}$ and acetic acid ( $51 \mu \mathrm{~L}, 0.90 \mathrm{mmol}, 25$ equiv) was added dropwise to it. After 5 min , a solution of lactone $\mathbf{2 8 3}$ ( $10 \mathrm{mg}, 0.04 \mathrm{mmol}$, 1.0 equiv) in THF ( 1 mL ) was added dropwise, and the reaction was stirred at $0{ }^{\circ} \mathrm{C}$ for 2 h . The reaction mixture was quenched by dropwise addition of sat. aq. $\mathrm{NH}_{4} \mathrm{Cl}(2 \mathrm{~mL})$ and stirred vigorously for 1 h . The mixture was diluted with a solution of $\mathrm{KHF}_{2}(500 \mathrm{mg})$ in $\mathrm{H}_{2} \mathrm{O}(8 \mathrm{~mL})$ and EtOAc $(10 \mathrm{~mL})$ was added. The layers were separated and the aqueous phase was further extracted with EtOAc ( $2 \times 10 \mathrm{~mL}$ ). The combined organic layers
were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude residue was purified by preparative TLC ( $80 \%$ EtOAc in hexanes) to afford lactol 286 ( $5 \mathrm{mg}, 0.02 \mathrm{mmol}, 51 \%$ yield), a white foam, as a single diastereomer. $[\alpha]_{\mathrm{D}}=-29.5\left(c 0.2, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ $5.77(\mathrm{dd}, J=3.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.54(\mathrm{~s}, 1 \mathrm{H}), 4.66(\mathrm{dd}, J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.07(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.83(\mathrm{~d}$, $J=9.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.46(\mathrm{br} \mathrm{d}, J=9.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.39(\mathrm{~s}, 1 \mathrm{H}), 2.54(\mathrm{~d}, J=18.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.38$ (ddd, $J=$ $15.8,7.6,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.33(\mathrm{dd}, J=18.4,2.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.09(\mathrm{ddq}, J=10.8,7.6,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.04$ (dd, $J=13.8,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.95(\mathrm{ddd}, J=15.8,10.8,1.5 \mathrm{~Hz}, 2 \mathrm{H}), 1.92(\mathrm{ddd}, J=13.8,2.7,1.6 \mathrm{~Hz}$, 1H), 1.41 (br s, 3H), $1.02(\mathrm{~d}, J=7.0 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(151 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 171.2,148.5,128.0$, $98.6,80.3,79.4,78.7,45.0,44.7,43.8,37.9,37.5,31.5,23.1,13.9$; IR (thin film) $v_{\max }: 3409,2956$, 2904, 1716, 1377, 1223, 1017, $932 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{20} \mathrm{O}_{5} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 303.1203$, found: 303.1198 .


Lactone 288. Procedure A: Lactone 250 ( $6 \mathrm{mg}, 0.02 \mathrm{mmol}, 1.0$ equiv) and acetic acid ( $19 \mu \mathrm{~L}, 0.33 \mathrm{mmol}$, 15 equiv) were dissolved in $\mathrm{MeCN}(2.5 \mathrm{~mL})$ and cooled to $0^{\circ} \mathrm{C} . \mathrm{Me}_{4} \mathrm{NBH}(\mathrm{OAc})_{3}(29 \mathrm{mg}, 0.110 \mathrm{mmol}, 5$ equiv) was added and the solution was stirred at $0^{\circ} \mathrm{C}$ for 16 h . The reaction mixture was quenched by the addition of sat. aq. $\mathrm{NaHCO}_{3}(10 \mathrm{~mL})$ and $\mathrm{EtOAc}(10 \mathrm{~mL})$ was added. The layers were separated and the aqueous phase was further extracted with EtOAc ( $2 \times 10 \mathrm{~mL}$ ). The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude residue was purified by preparative TLC ( $80 \%$ EtOAc in hexanes) to afford lactone $\mathbf{2 8 8}(4 \mathrm{mg}, 0.016 \mathrm{mmol}$, $75 \%$ yield), a white foam, as a single diastereomer.

Procedure B: Lactol 286 ( $3.0 \mathrm{mg}, 0.011 \mathrm{mmol}, 1.0$ equiv) and 1,2-ethanedithiol ( 3.0 mg , $0.032 \mathrm{mmol}, 3.0$ equiv) were dissolved in $\mathrm{DCM}(1.0 \mathrm{~mL})$ and cooled to $0{ }^{\circ} \mathrm{C} . \mathrm{BF}_{3} \cdot \mathrm{Et}_{2} \mathrm{O}(4.0 \mu \mathrm{~L}$, $0.032 \mathrm{mmol}, 3.0$ equiv) was added and the solution was stirred at $0^{\circ} \mathrm{C}$ for 3 h . The reaction mixture was quenched by the addition of sat. aq. $\mathrm{NaHCO}_{3}(2 \mathrm{~mL})$ and extracted with $\mathrm{DCM}(3 \times 5 \mathrm{~mL})$. The organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. Next, dithiolane 287 (ca. 3 mg ) was dissolved in methanol/THF ( $3: 1,0.8 \mathrm{~mL}$ ), $\mathrm{NiCl}_{2}\left(10.8 \mathrm{mg}, 0.084 \mathrm{mmol}, 8.0\right.$ equiv) and $\mathrm{NaBH}_{4}$ ( $10 \mathrm{mg}, 0.25 \mathrm{mmol}, 24.0$ equiv) were sequentially added to the solution at room temperature. The reaction mixture was stirred for 15 min before being filtered through a pad of celite. The product was purified by preparative TLC ( $80 \% \mathrm{EtOAc}$ in hexanes) to afford lactone 288 ( $0.4 \mathrm{mg}, 0.0015$ $\mathrm{mmol}, 14 \%$ over two steps $) .[\alpha]_{\mathrm{D}}=+27.0(c 0.2, \mathrm{MeOH}) ;{ }^{1} \mathrm{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.78$ (dd, $J=3.4,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.37(\mathrm{dd}, J=4.2,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.32(\mathrm{~d}, J=11.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.26(\mathrm{~d}, J=11.1$ $\mathrm{Hz}, 1 \mathrm{H}$ ), 2.61 (d, $J=18.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.47$ (ddd, $J=16.0,7.9,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.27$ (dd, $J=18.8,2.7$ $\mathrm{Hz}, 1 \mathrm{H}), 2.14$ (ddq, $J=10.5,7.9,7.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.13$ (ddd, $J=13.6,2.7,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.00$ (ddd, $J$ $=16.0,10.5,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.92(\mathrm{dd}, J=13.6,4.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.36(\mathrm{~s}, 3 \mathrm{H}), 1.25(\mathrm{~s}, 3 \mathrm{H}), 1.02(\mathrm{~d}, J=$ $7.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 171.3,148.9,130.1,83.2,74.0,64.9,46.7,45.2,44.5$, $38.2,38.1,32.2,21.9,19.0,14.4$; IR (thin film) $v_{\text {max }}: 2937,2896,1718,1634,1457,980,845 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{O}_{4} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 289.1410$, found: 289.1405 .


Aldehyde 289 A solution of $\mathrm{OsO}_{4}(7.2 \mathrm{mg}, 0.028 \mathrm{mmol}, 1.5$ equiv) in pyridine $(1.0 \mathrm{~mL})$ was added to neat lactone $\mathbf{2 8 8}(5.0 \mathrm{mg}, 0.019 \mathrm{mmol}, 1.0$ equiv). The resulting solution was stirred at $23{ }^{\circ} \mathrm{C}$ for 12 h . The volatiles were removed in vacuo and the residue was diluted with $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(3: 1,2.0 \mathrm{~mL})$. Sodium bisulfite ( $29 \mathrm{mg}, 0.28 \mathrm{mmol}, 15$ equiv) was added as a solid, the resulting mixture was heated at $60^{\circ} \mathrm{C}$ for 4 h . The dark purple reaction mixture was cooled
to $23^{\circ} \mathrm{C}$, diluted with brine $(6 \mathrm{~mL})$ and extracted with EtOAc ( $3 \times 10 \mathrm{~mL}$ ). The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude residue was purified by preparative TLC (EtOAc) to afford aldehyde $\mathbf{2 8 9}(3.6 \mathrm{mg}, 0.012 \mathrm{mmol}, 64 \%$ yield) as a single diastereomer. $[\alpha]_{\mathrm{D}}=-56.0\left(c 0.1, \mathrm{CHCl}_{3}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 9.66(\mathrm{~s}, 1 \mathrm{H}), 5.29(\mathrm{dd}, J$ $=9.5,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.23(\mathrm{~s}, 1 \mathrm{H}), 4.50(\mathrm{~s}, 1 \mathrm{H}), 4.40(\mathrm{dd}, J=3.9,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.60(\mathrm{ddq}, J=10.0$, $9.5,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.45(\mathrm{~d}, J=19.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.44$ (ddd, $J=14.5,2.8,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.28$ (dd, $J=19.5$, $2.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.19(\mathrm{~s}, 1 \mathrm{H}), 1.78(\mathrm{dt}, J=14.3,100,9.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.74(\mathrm{dd}, J=14.5,3.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.68$ (ddd, $J=14.3,9.3,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.51(\mathrm{~s}, 3 \mathrm{H}), 1.37(\mathrm{~s}, 3 \mathrm{H}), 0.84(\mathrm{~d}, J=7.0 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 151 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 201.8,169.8,84.9,82.9,76.2,70.8,56.0,46.8,39.6,36.6,33.9,26.2,20.7,13.7$, 13.6; IR (thin film) $v_{\max }: 3390,2956,2929,2874,1718,1371,1077,994,962,754 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{O}_{6} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 321.1309$, found: 321.1309 .

## SI3.3 Preparation and Characterization Data for Natural Products, with Tabulated Comparisons to Reported Isolation Data

## SI3.3.1 (-)-Neomajucin (285)

## SI3.3.1.1 Preparation and Characterization Data for 285

(-)-3,4-dehydroneomajucin (284, $4.5 \mathrm{mg}, 0.015 \mathrm{mmol}, 1.0$ equiv) and $\mathrm{Mn}(\mathrm{dpm})_{3}(1.9 \mathrm{mg}, 0.0031$ mmol, 0.2 equiv) were dissolved in $\mathrm{DCM} / i-\mathrm{PrOH}\left(4: 1,0.3 \mathrm{~mL}\right.$ ) and cooled to $0^{\circ} \mathrm{C}$. TBHP ( $c a .5$ M in decane, $4.6 \mu \mathrm{~L}, 0.023 \mathrm{mmol}, 1.5$ equiv) and $\mathrm{PhSiH}_{3}(3.8 \mu \mathrm{~L}, 0.031 \mathrm{mmol}, 2.0$ equiv) were added sequentially. Dry $\mathrm{O}_{2}$ gas was sparged through the mixture for 1 min . The reaction mixture was kept under a positive pressure of $\mathrm{O}_{2}$ and vigorous stirring was continued for 20 h at $0{ }^{\circ} \mathrm{C}$. Saturated aq. $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}(1.0 \mathrm{~mL})$ and $\operatorname{EtOAc}(1 \mathrm{~mL})$ were added, the layers were separated, and the aqueous layer was further extracted with $\operatorname{EtOAc}(3 \times 1.0 \mathrm{~mL})$. The combined organic layers were washed with brine ( $1 \times 5.0 \mathrm{~mL}$ ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated in vacuo. The crude residue was purified by preparative TLC (50\% EtOAc in hexanes) to afford (-)-neomajucin (285, 2.4 mg , $0.0075 \mathrm{mmol}, 50 \%$ yield) as a white foam. NMR samples for this compound were referenced to an internal standard of tetramethylsilane $(\delta=0.00)$. Characterization data were in agreement with the previously reported values. ${ }^{6}[\alpha]_{\mathrm{D}}=-45.2\left(c 0.25, p\right.$-dioxane); ${ }^{1} \mathrm{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right) \delta 8.76$ (d, $J=5.0 \mathrm{~Hz}, 1 \mathrm{H}), 8.49(\mathrm{~s}, 1 \mathrm{H}), 5.73(\mathrm{~s}, 1 \mathrm{H}), 5.12(\mathrm{dd}, J=3.4,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.02(\mathrm{~d}, J=11.0 \mathrm{~Hz}$, $1 \mathrm{H}), 4.67(\mathrm{~d}, J=5.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.19(\mathrm{~d}, J=11.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.01(\mathrm{dd}, J=14.3,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.90$ (ddq, $J=9.5,8.6,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.40(\mathrm{ddd}, J=11.8,11.6,6.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.29$ (dtd, $J=12.2,9.4,6.4 \mathrm{~Hz}$, $1 \mathrm{H}), 2.00(\mathrm{dd}, J=14.3,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.98(\mathrm{ddd}, J=11.8,9.4,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.91$ (dddd, $J=12.2$, $11.6,8.6,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.70(\mathrm{~s}, 3 \mathrm{H}), 1.18(\mathrm{~d}, J=7.0 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}$ ) $\delta 177.8$, $175.1,83.9,80.7,79.7,72.6,70.7,50.9,47.5,39.4,31.7,31.6,27.4,21.5,14.4$; IR (thin film) $v_{\max }$ : $3384,2932,1767,1718,1371,1223,1120,1085,998,752 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{19} \mathrm{O}_{7}$ [M-H]: 311.1136, found: 311.1134.

## SI3.3.1.2 (-)-Neomajucin ${ }^{1} \mathrm{H}$ Spectra Comparison:


(-)-neomajucin

| Position | ${ }^{1} \mathrm{H}$ NMR $(\delta)$ Natural Sample $\left(400 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)^{6}$ | ${ }^{1} \mathrm{H}$ NMR ( $\delta$ ) Synthetic Sample $\left(600 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)$ |
| :---: | :---: | :---: |
| 1 | 2.90 (m, 1H) | 2.90 (ddq, $J=9.5,8.6,7.0 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 2* | $\begin{aligned} & 2.39(\mathrm{~m}, 1 \mathrm{H})^{*} \\ & 2.29(\mathrm{~m}, 1 \mathrm{H}) \end{aligned}$ | $\begin{gathered} 2.29(\mathrm{dtd}, J=12.2,9.4,6.4 \mathrm{~Hz}, 1 \mathrm{H}) \\ 1.91(\text { dddd, } J=12.2,11.6,8.6,2.5 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ |
| 3* | 1.85-2.05 (m, 2H)* | $\begin{gathered} 2.40(\mathrm{ddd}, J=11.8,11.6,6.4 \mathrm{~Hz}, 1 \mathrm{H}) \\ 1.98(\mathrm{ddd}, J=11.8,9.4,2.5 \mathrm{~Hz}, 1 \mathrm{H}) \end{gathered}$ |
| 4-OH | - | 5.73 (s, 1H) ${ }^{\text { }}$ |
| 6-OH | - | 8.49 (s, 1H) ${ }^{\text { }}$ |
| 7 | 5.12 (dd, $J=2.6,2.5 \mathrm{~Hz}, 1 \mathrm{H})$ | 5.12 (dd, $J=3.4,2.5 \mathrm{~Hz}, 1 \mathrm{H})$ |
| $8 \beta$ | 2.00 (dd, $J=14.2,2.6 \mathrm{~Hz}, 1 \mathrm{H})$ | 2.00 (dd, $J=14.3,3.4 \mathrm{~Hz}, 1 \mathrm{H})$ |
| $8 \alpha$ | 3.01 (dd, $J=14.2,2.5 \mathrm{~Hz}, 1 \mathrm{H})$ | 3.01 (dd, $J=14.3,2.5 \mathrm{~Hz}, 1 \mathrm{H})$ |
| $10 \beta$ | 4.66 (br d, $J=4.8 \mathrm{~Hz}, 1 \mathrm{H})$ | 4.67 (d, $J=5.0 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 10-OH | 8.78 (br d, $J=4.8 \mathrm{~Hz}, 1 \mathrm{H})$ | 8.76 (d, $J=5.0 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 13 | 1.70 (br s, 3H) | 1.70 (s, 3H) |
| $14 \beta$ | 4.19 (d, $J=11.0 \mathrm{~Hz}, 1 \mathrm{H})$ | 4.19 (d, $J=11.0 \mathrm{~Hz}, 1 \mathrm{H})$ |
| $14 \alpha$ | 5.02 (d, $J=11.0 \mathrm{~Hz}, 1 \mathrm{H})$ | 5.02 (d, $J=11.0 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 15 | 1.18 (d, $J=7.0 \mathrm{~Hz}, 3 \mathrm{H})$ | 1.18 (d, $J=7.0 \mathrm{~Hz}, 3 \mathrm{H})$ |

*Protons on positions 2 and 3 are likely misassigned in the original publications. Without higher field instrumentation, it was presumably challenging to accurately characterize the multiplicities and/or 2D HSQC correlations (carbons 2 and 3 are separated in chemical shift by only 0.1-0.2 ppm ) of these protons, leading to the observed assignments.
${ }^{*}$ Indicates tentative assignment.

SI3.3.1.3 (-)-Neomajucin ${ }^{13}$ C Spectra Comparison:

(-)-neomajucin

| Position | ${ }^{13} \mathrm{C} \mathrm{NMR} \mathrm{( } \mathrm{\delta)}$ <br> Natural Sample <br> $\left(101 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)^{6}$ | ${ }^{13} \mathrm{C} \mathrm{NMR} \mathrm{( } \mathrm{\delta)}$ <br> Synthetic Sample <br> $\left(151 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)$ |
| :---: | :---: | :---: |
| $\mathbf{1}$ | 39.4 | 39.4 |
| $\mathbf{2}$ | 31.4 | 31.6 |
| $\mathbf{3}$ | 31.6 | 31.7 |
| $\mathbf{4}$ | 84.1 | 83.9 |
| $\mathbf{5}$ | 47.5 | 47.5 |
| $\mathbf{6}$ | 79.6 | 79.7 |
| $\mathbf{7}$ | 80.5 | 80.7 |
| $\mathbf{8}$ | 27.5 | 27.4 |
| $\mathbf{9}$ | 51.0 | 50.9 |
| $\mathbf{1 0}$ | 70.7 | 70.7 |
| $\mathbf{1 1}$ | 174.8 | 175.1 |
| $\mathbf{1 2}$ | 177.2 | 177.8 |
| $\mathbf{1 3}$ | 21.4 | 21.5 |
| $\mathbf{1 4}$ | 72.6 | 72.6 |
| $\mathbf{1 5}$ | 14.3 | 14.4 |

## SI3.3.2 (-)-Majucin (5)

## SI3.3.2.1 Preparation and Characterization Data for 5

TMEDA ( $5.6 \mu \mathrm{~L}, 0.037 \mathrm{mmol}, 1.0$ equiv) and $\mathrm{OsO}_{4}(9.5 \mathrm{mg}, 0.037 \mathrm{mmol}, 1.0$ equiv) were combined in $\mathrm{DCM}(3.7 \mathrm{~mL})$ at $-78^{\circ} \mathrm{C}$, creating a bright orange-red solution. The so-prepared $\mathrm{OsO}_{4}{ }^{\bullet} \mathrm{T}$ MEDA solution was quickly added via syringe into neat 284 ( $11 \mathrm{mg}, 0.037 \mathrm{mmol}, 1.0$ equiv) at $-78^{\circ} \mathrm{C}$ and the reaction mixture was slowly warmed up to $0^{\circ} \mathrm{C}$ over 2 h , upon which the solution had turned completely golden-brown. Water ( 3.7 mL ) was added directly to the reaction mixture, followed by sodium bisulfite ( $40 \mathrm{mg}, 0.37 \mathrm{mmol}, 10.0$ equiv). The resulting biphasic mixture was vigorously stirred at room temperature for 16 h . During this time, the organic layer gradually turned colorless, while the aqueous phase turned a deep purple. $\mathrm{HCl}(2 \mathrm{M}, 5 \mathrm{~mL}$ ) and EtOAc (5 mL ) were added and the layers were separated. The aqueous layer was further extracted with EtO$\mathrm{Ac}(5 \times 5 \mathrm{~mL})$. The combined organic layers were washed with brine ( 10 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude residue was purified by preparative TLC $(100 \% \mathrm{EtOAc})$ to afford (-)-majucin ( $7.5 \mathrm{mg}, 0.023 \mathrm{mmol}, 61 \%$ ), a white solid, as a single diastereomer. Characterization data were in agreement with the literature. ${ }^{6}[\alpha]_{\mathrm{D}}=-60.7$ (c 0.15, dioxane); ${ }^{1} \mathrm{H}$ NMR (700 $\mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}$, referenced to $\mathrm{Me}_{4} \mathrm{Si}$ at $\left.\delta=0.00 \mathrm{ppm}\right) \delta 8.96(\mathrm{br} \mathrm{d}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 8.41(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, 6.94 (br s, 1H), 5.25 (br s, 1H), 5.21 (br dd, $J=9.1,4.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.15$ (dd, $J=3.4,2.4 \mathrm{~Hz}, 1 \mathrm{H})$, 5.12 (br d, $J=10.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.66(\mathrm{~d}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.31(\mathrm{~d}, J=10.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.12(\mathrm{dd}, J=14.2$, $2.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.03(\mathrm{ddq}, J=10.3,9.1,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.48(\mathrm{dt}, J=12.8,9.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.22(\mathrm{ddd}, J=$ $12.8,10.3,4.3 \mathrm{~Hz}, 1 \mathrm{H}), 2.05(\mathrm{dd}, J=14.2,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.95(\mathrm{br} \mathrm{s}, 3 \mathrm{H}), 1.11$ (d, $J=7.0 \mathrm{~Hz}, 3 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}$, referenced to $\mathrm{Me}_{4} \mathrm{Si}$ at $\delta=0.00 \mathrm{ppm}$ ) $\delta 177.9,174.9,82.9,80.7,80.0$, $72.7,72.5,70.4,51.6,47.6,43.0,38.2,27.1,20.9,14.2$. IR (thin film) $v_{\max }: 3390,2936,1719,1077$ $\mathrm{cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{19} \mathrm{O}_{8}[\mathrm{M}-\mathrm{H}]: 327.1085$, found: 327.1082.

## SI3.3.2.3 (-)-Majucin ${ }^{1} H$ NMR spectra comparison:


(-)-majucin

| Position | ${ }^{1} \mathrm{H}$ NMR $(\delta)$ Natural Sample $\left(400 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)^{6}$ | $\begin{gathered} { }^{1} \mathrm{H} \text { NMR }(\delta) \\ \text { Synthetic Sample } \\ \left(700 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right) \end{gathered}$ |
| :---: | :---: | :---: |
| 1 | 3.02 (ddq, $J=10.2,9.5,7.0 \mathrm{~Hz}, 1 \mathrm{H})$ | 3.03 (ddq, $J=10.3,9.1,7.0 \mathrm{~Hz}, 1 \mathrm{H})$ |
| $2 \beta$ | 2.48 (dt, $J=12.6,9.5 \mathrm{~Hz}, 1 \mathrm{H})$ | 2.48 (dt, $J=12.8,9.1 \mathrm{~Hz}, 1 \mathrm{H})$ |
| $2 \alpha$ | 2.21 (ddd, $J=12.6,10.2,4.4 \mathrm{~Hz}, 1 \mathrm{H})$ | 2.22 (ddd, $J=12.8,10.3,4.3 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 3 | 5.21 (dd, $J=9.5,4.4 \mathrm{~Hz}, 1 \mathrm{H})$ | 5.22 (dd, $J=9.1,4.3 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 3-OH | - | 5.25 (br s, 1H) |
| 4-OH | - | 6.94 (br s, 1H)* |
| 5 | - | - |
| 6-OH | - | 8.41 (br s, 1H)* |
| 7 | 5.14 (dd, $J=3.3,2.2 \mathrm{~Hz}, 1 \mathrm{H})$ | 5.15 (dd, $J=3.4,2.4 \mathrm{~Hz}, 1 \mathrm{H})$ |
| $8 \beta$ | 2.05 (dd, $J=14.3,3.3 \mathrm{~Hz}, 1 \mathrm{H})$ | 2.05 (dd, $J=14.2,3.4 \mathrm{~Hz}, 1 \mathrm{H})$ |
| $8 \alpha$ | 3.11 (dd, $J=14.3,2.2 \mathrm{~Hz}, 1 \mathrm{H})$ | 3.12 (dd, $J=14.2,2.4 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 9 | - | - |
| 10 | 4.65 (br d, $J=4.5 \mathrm{~Hz}, 1 \mathrm{H})$ | 4.66 (d, $J=4.7 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 10-OH | 8.95 (br d, $J=4.5 \mathrm{~Hz}, 1 \mathrm{H})$ | 8.96 (br d, $J=4.7 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 11 | - | - |
| 12 | - | - |
| 13 | 1.95 (br s, 3H) | 1.95 (br s, 3H) |
| 14 | $\begin{gathered} \hline 4.30(\mathrm{~d}, J=10.8 \mathrm{~Hz}, 1 \mathrm{H}) \\ 5.11(\mathrm{br} \mathrm{~d}, J=10.8 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ | $\begin{gathered} \hline 4.31(\mathrm{~d}, J=10.9 \mathrm{~Hz}, 1 \mathrm{H}) \\ 5.12(\mathrm{br} \mathrm{~d}, J=10.9 \mathrm{~Hz}, 1 \mathrm{H}) \\ \hline \end{gathered}$ |
| 15 | 1.10 (d, $J=7.0 \mathrm{~Hz}, 3 \mathrm{H})$ | 1.11 (d, $J=7.0 \mathrm{~Hz}, 3 \mathrm{H})$ |

*Indicates tentative assignment.

SI3.3.2.4 (-)-Majucin ${ }^{13} \mathrm{C}$ NMR spectra comparison:

(-)-majucin

| Position | ${ }^{13} \mathrm{C} \mathrm{NMR} \mathrm{( } \mathrm{\delta)}$ <br> Natural Sample <br> $\left(101 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)^{6}$ | ${ }^{13} \mathrm{C} \mathrm{NMR} \mathrm{( } \mathrm{\delta)}$ <br> Synthetic Sample <br> $\left(151 \mathrm{MHz}, \mathrm{C}_{5} \mathrm{D}_{5} \mathrm{~N}\right)$ |
| :---: | :---: | :---: |
| $\mathbf{1}$ | 38.0 | 38.2 |
| $\mathbf{2}$ | 42.9 | 43.0 |
| $\mathbf{3}$ | 72.7 | 72.7 |
| $\mathbf{4}$ | 82.8 | 82.9 |
| $\mathbf{5}$ | 47.5 | 47.6 |
| $\mathbf{6}$ | 79.9 | 80.0 |
| $\mathbf{7}$ | 80.6 | 80.7 |
| $\mathbf{8}$ | 27.1 | 27.1 |
| $\mathbf{9}$ | 51.5 | 51.6 |
| $\mathbf{1 0}$ | 70.3 | 70.4 |
| $\mathbf{1 1}$ | 174.7 | 174.9 |
| $\mathbf{1 2}$ | 177.6 | 177.9 |
| $\mathbf{1 3}$ | 20.9 | 20.9 |
| $\mathbf{1 4}$ | 72.4 | 72.5 |
| $\mathbf{1 5}$ | 14.1 | 14.2 |

## SI3.3.3 (-)-Jiadifenoxolane A (6)

## SI3.3.3.1 Preparation and Characterization Data for 6

(-)-Majucin (5, $3.0 \mathrm{mg}, 0.009 \mathrm{mmol}, 1.0$ equiv) and pyridine ( $7.4 \mu \mathrm{~L}, 0.09 \mathrm{mmol}, 10.0$ equiv) were dissolved in 1,2-dichloroethane ( 0.3 mL ) . $\mathrm{MsCl}(3.6 \mu \mathrm{~L}, 0.045 \mathrm{mmol}, 5.0$ equiv) was added and the solution was stirred for 2 h at room temperature. At this point, the reaction mixture was heated to $80^{\circ} \mathrm{C}$ and stirred at that temperature for 15 h . The solution was cooled to room temperature and $\mathrm{HCl}(1 \mathrm{M}, 1 \mathrm{~mL})$ and $\mathrm{EtOAc}(2 \mathrm{~mL})$ were added. The aqueous layer was further extracted with EtOAc ( $5 \times 2 \mathrm{~mL}$ ). The combined organic layers were washed with brine ( 10 mL ), dried over Na${ }_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude residue was purified by preparative TLC $(100 \% \mathrm{EtO}-$ $\mathrm{Ac})$ to afford (-)-jiadifenoxolane A (6, $2.6 \mathrm{mg}, 0.008 \mathrm{mmol}, 92 \%$ ) as an amorphous white solid. Characterization data were in agreement with the literature. ${ }^{7}[\alpha]_{\mathrm{D}}=-62.0(c 0.1, \mathrm{MeOH}) ;{ }^{1} \mathrm{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 4.71(\mathrm{br} \mathrm{d}, J=11.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.67(\mathrm{brd}, J=3.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.37(\mathrm{~s}, 1 \mathrm{H}), 4.09(\mathrm{br}$ $\mathrm{s}, 1 \mathrm{H}), 4.01(\mathrm{~d}, J=11.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.60(\mathrm{dqd}, J=10.3,7.1,5.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.30(\mathrm{br} \mathrm{dd}, J=13.2,10.3$ $\mathrm{Hz}, 1 \mathrm{H}), 2.23$ (br d, $J=14.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.15$ (dd, $J=14.5,3.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.34 (br s, 3 H ), 1.23 (dd, $J$ $=13.2,5.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.07(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(151 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta 178.8,171.2,82.0$, $81.4,81.1,77.5,74.9,73.5,51.5,46.2,39.9,34.5,22.6,20.1,13.4$; IR (thin film) $v_{\max }: 3434,2959$, 1766, 1738, $1012 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{15} \mathrm{H}_{17} \mathrm{O}_{7}[\mathrm{M}-\mathrm{H}]: 309.0980$, found: 309.0979.
(-)-Jiadifenoxolane A ${ }^{\mathbf{1}} \mathbf{H}$ NMR Spectra Comparison:


## (-)-jiadifenoxolane A

| Position | $\begin{gathered} { }^{1} \mathrm{H} \text { NMR }(\delta) \\ \text { Natural Sample } \\ \left(600 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right)^{7} \\ \hline \end{gathered}$ | $\begin{gathered} { }^{1} \mathrm{H} \text { NMR }(\delta) \\ \text { Synthetic Sample } \\ \left(600 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \\ \hline \end{gathered}$ |
| :---: | :---: | :---: |
| 1 | 2.59 (dqd, $J=10.3,7.1,5.4 \mathrm{~Hz}, 1 \mathrm{H})$ | 2.60 (dqd, $J=10.3,7.1,5.5 \mathrm{~Hz}, 1 \mathrm{H})$ |
| $2 \beta$ | 2.30 (ddd, $J=13.0,10.3,2.6 \mathrm{~Hz}, 1 \mathrm{H})$ | 2.30 (br dd, $J=13.2,10.3 \mathrm{~Hz}, 1 \mathrm{H})$ |
| $2 \alpha$ | 1.22 (dd, $J=13.0,5.4 \mathrm{~Hz}, 1 \mathrm{H})$ | 1.23 (dd, $J=13.2,5.5 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 3 | 4.08 (d, $J=2.6 \mathrm{~Hz}, 1 \mathrm{H})$ | 4.09 (br s, 1H) |
| 4 | - | - |
| 5 | - | - |
| 6 | - | - |
| 7 | 4.66 (dd, $J=4.0,1.9 \mathrm{~Hz}, 1 \mathrm{H})$ | 4.67 (br d, $J=3.8 \mathrm{~Hz}, 1 \mathrm{H})$ |
| $8 \beta$ | 2.15 (dd, $J=14.7,4.0 \mathrm{~Hz}, 1 \mathrm{H})$ | 2.15 (dd, $J=14.6,3.5 \mathrm{~Hz}, 1 \mathrm{H})$ |
| $8 \alpha$ | 2.23 (dd, $J=14.7,1.9 \mathrm{~Hz}, 1 \mathrm{H})$ | 2.23 (br d, $J=14.6 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 9 | - | - |
| 10 | 4.36 (s,1H) | 4.37 (s, 1H) |
| 11 | - | - |
| 12 | - | - |
| 13 | 1.33 (d, $J=1.1 \mathrm{~Hz}, 3 \mathrm{H})$ | 1.34 (br s, 3H) |
| $14 \beta$ | 4.70 (dd, $J=11.1,1.1 \mathrm{~Hz}, 1 \mathrm{H})$ | 4.71 (br d, $J=11.2 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 14 $\alpha$ | 4.00 (d, $J=11.1 \mathrm{~Hz}, 1 \mathrm{H})$ | 4.01 (d, $J=11.2 \mathrm{~Hz}, 1 \mathrm{H})$ |
| 15 | 1.06 (d, $J=7.1 \mathrm{~Hz}, 3 \mathrm{H})$ | 1.07 (d, $J=7.1 \mathrm{~Hz}, 3 \mathrm{H})$ |

## (-)-Jiadifenoxolane $\mathbf{A}^{13} \mathbf{C}$ NMR Spectra Comparison:



## (-)-jiadifenoxolane A

| Position | ${ }^{13} \mathrm{C}$ NMR ( $\delta$ ) <br> Natural Sample <br> $\left(150 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right)^{7}$ | ${ }^{13} \mathrm{C}$ NMR ( $\delta$ ) <br> Synthetic Sample <br> $\left(151 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right)$ |
| :---: | :---: | :---: |
| $\mathbf{1}$ | 34.5 | 34.5 |
| $\mathbf{2}$ | 39.9 | 39.9 |
| $\mathbf{3}$ | 82.0 | 82.0 |
| $\mathbf{4}$ | 81.4 | 81.4 |
| $\mathbf{5}$ | 46.1 | 46.2 |
| $\mathbf{6}$ | 77.5 | 77.5 |
| $\mathbf{7}$ | 81.1 | 81.1 |
| $\mathbf{8}$ | 20.1 | 20.1 |
| $\mathbf{9}$ | 51.5 | 51.5 |
| $\mathbf{1 0}$ | 73.5 | 73.5 |
| $\mathbf{1 1}$ | 171.2 | 171.2 |
| $\mathbf{1 2}$ | 178.9 | 178.8 |
| $\mathbf{1 3}$ | 22.6 | 22.6 |
| $\mathbf{1 4}$ | 74.9 | 74.9 |
| $\mathbf{1 5}$ | 13.4 | 13.4 |

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## SI3.5 X-Ray Crystallographic Data

## SI3.5.1 X-Ray Crystallographic Data for (+)-Cedrol (14)



A colorless prism $0.40 \times 0.25 \times 0.20 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at $100(2) \mathrm{K}$ using $\varphi$ and $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $99.5 \%$ complete to $74.5^{\circ}$ in $\theta$. A total of 28928 reflections were collected covering the indices, $-19<=h<=10,-19<=k<=19,-13<=l<=13.5517$ reflections were found to be symmetry independent, with an $\mathrm{R}_{\mathrm{int}}$ of 0.0313 . Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $\mathrm{P} 2_{1} 2_{1} 2$ (No. 18). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined from the diffraction data.

Table SI3.5.1.1. Crystal data and structure refinement for $\mathbf{1 4}$.

| Identification code | 14 |
| :---: | :---: |
| Empirical formula | $\mathrm{C}_{15} \mathrm{H}_{26} \mathrm{O}$ |
| Formula weight | 222.37 |
| Temperature (K) | 100(2) |
| Crystal system | orthorhombic |
| Space group | P2,2,2 |
| a (A) | 15.67480(12) |
| $\mathrm{b}(\AA)$ | 15.62810(14) |
| c ( $\AA$ ) | 11.08919(9) |
| $\alpha{ }^{\circ}$ ) | 90 |
| $\beta\left({ }^{\circ}\right)$ | 90 |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume ( $\AA^{3}$ ) | 2716.49(4) |
| Z | 8 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.0874 |
| $\mu\left(\mathrm{mm}^{-1}\right)$ | 0.492 |
| $\mathrm{F}(000)$ | 994.6 |
| Crystal size ( $\mathrm{mm}^{3}$ ) | $0.4 \times 0.25 \times 0.2$ |
| Radiation | $\mathrm{Cu} \mathrm{K} \mathrm{\alpha}(\lambda=1.54184)$ |
| $2 \Theta$ range for data collection ${ }^{\circ}$ ) | 7.98 to 149 |
| Index ranges | $\begin{aligned} & -19 \leq \mathrm{h} \leq 10,-19 \leq \mathrm{k} \leq 19,-13 \leq 1 \leq \\ & 13 \end{aligned}$ |
| Reflections collected | 28928 |
| Independent reflections | 5517 [ $\left.\mathrm{R}_{\mathrm{int}}=0.0313, \mathrm{R}_{\text {sigma }}=0.0155\right]$ |
| Data/restraints/parameters | 5517/0/313 |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.041 |
| Final R indexes [I>=2 ${ }^{\text {(I) }}$ ] | $\mathrm{R}_{1}=0.0294, \mathrm{wR}_{2}=0.0778$ |
| Final R indexes [all data] | $\mathrm{R}_{1}=0.0296, \mathrm{wR}_{2}=0.0780$ |
| Largest diff. peak/hole (e $\AA^{-3}$ ) | 0.19/-0.11 |
| Flack parameter | 0.02(14) |

Table SI3.5.1.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for $\mathbf{1 4} . U_{\text {eq }}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| O2 | $4578.2(6)$ | $5768.5(6)$ | $8561.2(9)$ | $30.51(19)$ |
| O1 | $4274.7(6)$ | $5499.9(6)$ | $6142.0(9)$ | $29.72(18)$ |
| C22 | $3393.6(6)$ | $7623.1(7)$ | $9963.1(10)$ | $22.4(2)$ |
| C25 | $4089.0(7)$ | $6172.9(6)$ | $9494.5(9)$ | $20.0(2)$ |
| C26 | $4678.3(6)$ | $6362.6(6)$ | $10580.4(9)$ | $17.35(19)$ |
| C13 | $2667.6(6)$ | $6498.3(6)$ | $5282.5(9)$ | $18.8(2)$ |
| C28 | $5419.0(6)$ | $7021.8(6)$ | $10390.4(9)$ | $18.23(19)$ |
| C27 | $4151.5(6)$ | $6820.6(6)$ | $11547.8(9)$ | $20.2(2)$ |
| C23 | $3710.8(7)$ | $7002.2(7)$ | $8981.7(9)$ | $22.6(2)$ |
| C12 | $1965.3(7)$ | $5137.0(7)$ | $5347.2(9)$ | $22.9(2)$ |
| C11 | $2735.1(6)$ | $5599.3(6)$ | $5908.0(9)$ | $19.5(2)$ |
| C29 | $5913.4(7)$ | $6955.5(8)$ | $9202.3(10)$ | $25.4(2)$ |
| C8 | $3687.2(7)$ | $4957.7(8)$ | $4293.8(10)$ | $26.3(2)$ |
| C14 | $3482.2(7)$ | $7045.6(7)$ | $5252.6(10)$ | $25.4(2)$ |
| C7 | $2870.5(7)$ | $4744.4(7)$ | $3589.0(10)$ | $27.0(2)$ |
| C6 | $2113.6(7)$ | $5299.1(6)$ | $3995.2(9)$ | $21.1(2)$ |
| C24 | $3373.8(8)$ | $5554.8(7)$ | $9845.0(12)$ | $30.8(3)$ |
| C9 | $3543.4(7)$ | $5060.3(7)$ | $5658.3(9)$ | $22.7(2)$ |
| C21 | $4042.3(6)$ | $7714.3(6)$ | $10987.8(9)$ | $18.4(2)$ |
| C5 | $2363.2(7)$ | $6265.2(6)$ | $3979.7(9)$ | $19.8(2)$ |
| C15 | $2006.9(7)$ | $7029.3(7)$ | $5987.3(10)$ | $25.6(2)$ |
| C17 | $3845.4(7)$ | $8409.0(7)$ | $11940.8(10)$ | $25.1(2)$ |
| C30 | $6078.1(7)$ | $6874.6(7)$ | $11403.4(11)$ | $27.0(2)$ |
| C20 | $4955.2(6)$ | $7911.4(6)$ | $10494.2(9)$ | $18.8(2)$ |
| C18 | $4732.4(8)$ | $8604.8(8)$ | $12459.6(11)$ | $32.1(3)$ |
| C4 | $1595.0(8)$ | $6724.7(7)$ | $3415.4(10)$ | $28.5(2)$ |
| C2 | $1304.2(8)$ | $5223.4(8)$ | $3189.8(11)$ | $29.5(2)$ |
| C19 | $5320.5(7)$ | $8601.8(7)$ | $11356.2(12)$ | $29.7(2)$ |
| C10 | $3488.7(9)$ | $4186.3(7)$ | $6273.3(11)$ | $32.2(3)$ |
| C3 | $1287.0(9)$ | $6070.8(8)$ | $2488.7(12)$ | $33.4(3)$ |
| C16 | $3431.6(8)$ | $9214.3(7)$ | $11409.9(12)$ | $30.8(2)$ |
| C1 | $1248.6(10)$ | $4440.9(9)$ | $2369.6(14)$ | $44.5(3)$ |

Table SI3.5.1.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 14. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} \mathrm{U}_{11}+2 h k a^{*} b^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{12}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{23}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O2 | $42.9(5)$ | $25.0(4)$ | $23.6(4)$ | $-0.2(4)$ | $3.5(4)$ | $-8.7(4)$ |
| O1 | $30.0(4)$ | $30.2(4)$ | $29.0(5)$ | $7.4(3)$ | $-10.0(3)$ | $-4.5(4)$ |
| C22 | $18.5(5)$ | $21.1(5)$ | $27.5(5)$ | $2.5(4)$ | $-2.7(4)$ | $-0.3(4)$ |
| C25 | $21.4(5)$ | $17.9(4)$ | $20.6(5)$ | $-0.8(4)$ | $-1.6(4)$ | $-2.2(4)$ |
| C26 | $19.6(4)$ | $15.6(4)$ | $16.8(4)$ | $1.4(4)$ | $-0.4(4)$ | $2.1(3)$ |
| C13 | $21.9(5)$ | $18.9(4)$ | $15.8(4)$ | $2.1(4)$ | $0.8(4)$ | $0.6(4)$ |
| C28 | $16.1(4)$ | $18.7(4)$ | $20.0(4)$ | $1.0(4)$ | $-1.1(4)$ | $-0.8(4)$ |
| C27 | $21.5(5)$ | $21.6(5)$ | $17.6(4)$ | $-0.3(4)$ | $3.8(4)$ | $1.7(4)$ |
| C23 | $23.7(5)$ | $22.2(5)$ | $22.1(5)$ | $0.9(4)$ | $-7.9(4)$ | $-0.7(4)$ |
| C12 | $26.1(5)$ | $19.6(5)$ | $22.9(5)$ | $-1.4(4)$ | $0.9(4)$ | $3.8(4)$ |
| C11 | $23.7(5)$ | $20.2(5)$ | $14.7(4)$ | $2.1(4)$ | $1.7(4)$ | $1.3(4)$ |
| C29 | $20.3(5)$ | $29.0(5)$ | $26.9(5)$ | $0.6(4)$ | $6.1(4)$ | $-0.7(5)$ |
| C8 | $27.9(5)$ | $29.7(5)$ | $21.3(5)$ | $11.3(4)$ | $-0.3(4)$ | $-4.7(4)$ |
| C14 | $29.0(5)$ | $22.7(5)$ | $24.5(5)$ | $-2.2(4)$ | $-1.6(4)$ | $1.7(4)$ |
| C7 | $35.7(6)$ | $24.2(5)$ | $21.0(5)$ | $8.6(4)$ | $-3.4(5)$ | $-4.6(4)$ |
| C6 | $25.2(5)$ | $18.6(5)$ | $19.5(5)$ | $1.2(4)$ | $-2.7(4)$ | $-0.6(4)$ |
| C24 | $28.4(6)$ | $23.6(5)$ | $40.5(6)$ | $-8.1(5)$ | $-3.1(5)$ | $-1.5(5)$ |
| C9 | $26.7(5)$ | $21.9(5)$ | $19.4(5)$ | $5.9(4)$ | $-3.1(4)$ | $-0.8(4)$ |
| C21 | $17.7(4)$ | $18.0(5)$ | $19.5(5)$ | $1.4(4)$ | $1.5(4)$ | $-0.0(4)$ |
| C5 | $24.3(5)$ | $19.3(5)$ | $15.8(5)$ | $2.8(4)$ | $0.0(4)$ | $1.0(4)$ |
| C15 | $30.9(5)$ | $23.8(5)$ | $22.3(5)$ | $8.0(4)$ | $0.9(4)$ | $-2.8(4)$ |
| C17 | $27.4(5)$ | $24.2(5)$ | $23.7(5)$ | $5.2(4)$ | $3.3(4)$ | $-4.5(4)$ |
| C30 | $22.1(5)$ | $28.2(5)$ | $30.6(6)$ | $5.0(4)$ | $-7.9(4)$ | $-4.5(5)$ |
| C20 | $17.6(4)$ | $17.1(5)$ | $21.6(5)$ | $-0.7(4)$ | $-0.1(4)$ | $0.2(4)$ |
| C18 | $37.0(6)$ | $27.9(6)$ | $31.2(6)$ | $7.2(5)$ | $-8.3(5)$ | $-12.1(5)$ |
| C4 | $35.3(6)$ | $24.1(5)$ | $26.2(5)$ | $5.8(4)$ | $-8.8(5)$ | $0.6(4)$ |
| C2 | $30.8(6)$ | $27.9(6)$ | $29.7(6)$ | $-0.2(5)$ | $-8.5(5)$ | $-1.3(4)$ |
| C19 | $25.0(5)$ | $21.9(5)$ | $42.1(6)$ | $-1.1(4)$ | $-5.5(5)$ | $-7.8(5)$ |
| C10 | $44.2(7)$ | $23.8(5)$ | $28.6(6)$ | $9.3(5)$ | $-6.2(5)$ | $2.8(5)$ |
| C3 | $38.4(6)$ | $30.9(6)$ | $30.8(6)$ | $4.0(5)$ | $-13.6(5)$ | $-0.4(5)$ |
| C16 | $32.3(6)$ | $24.3(5)$ | $35.8(6)$ | $8.6(4)$ | $1.0(5)$ | $-6.2(5)$ |
| C1 | $53.0(8)$ | $31.8(7)$ | $48.8(8)$ | $-1.6(6)$ | $-23.2(7)$ | $-8.3(6)$ |

Table SI3.5.1.4. Bond Lengths for 14.

| Atom | Atom | Length (Å) | Atom | Atom | Length ( $\AA$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| O2 | C25 | 1.4348(13) | C12 | C6 | 1.5381(14) |
| O1 | C9 | 1.4401(13) | C11 | C9 | 1.5464(14) |
| C22 | C23 | 1.5405(15) | C8 | C7 | 1.5365(15) |
| C22 | C21 | 1.5315(14) | C8 | C9 | 1.5382(14) |
| C25 | C26 | 1.5463(14) | C7 | C6 | 1.5369(14) |
| C25 | C23 | $1.5345(14)$ | C6 | C5 | 1.5598(14) |
| C25 | C24 | $1.5300(15)$ | C6 | C2 | 1.5561(14) |
| C26 | C28 | 1.5664(13) | C9 | C10 | 1.5292(15) |
| C26 | C27 | 1.5313(13) | C21 | C17 | 1.5462(14) |
| C13 | C11 | 1.5705(13) | C21 | C20 | 1.5626(13) |
| C13 | C14 | 1.5372(14) | C5 | C4 | 1.5354(14) |
| C13 | C5 | 1.5645(13) | C17 | C18 | 1.5354(16) |
| C13 | C15 | 1.5401(14) | C17 | C16 | 1.5334(16) |
| C28 | C29 | 1.5321(14) | C20 | C19 | 1.5511(14) |
| C28 | C30 | 1.5435(14) | C18 | C19 | 1.5321(18) |
| C28 | C20 | 1.5731(14) | C4 | C3 | 1.5275(16) |
| C27 | C21 | 1.5382(13) | C2 | C3 | 1.5358(17) |
| C12 | C11 | 1.5377(14) | C2 | C1 | 1.5266(17) |

Table SI3.5.1.5. Bond Angles for 14.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C21 | C22 | C23 | 111.62(8) | C5 | C6 | C7 | 110.43(9) |
| C26 | C25 | O2 | 109.09(8) | C2 | C6 | C12 | 115.07(9) |
| C23 | C25 | O2 | 108.13(9) | C2 | C6 | C7 | 114.72(9) |
| C23 | C25 | C26 | 110.94(8) | C2 | C6 | C5 | 105.77(8) |
| C24 | C25 | O2 | 107.26(9) | C11 | C9 | O1 | 109.01(8) |
| C24 | C25 | C26 | 111.16(9) | C8 | C9 | O1 | 107.42(9) |
| C24 | C25 | C23 | 110.14(9) | C8 | C9 | C11 | 110.67(8) |
| C28 | C26 | C25 | 117.66(8) | C10 | C9 | O1 | 107.74(9) |
| C27 | C26 | C25 | 108.24(8) | C10 | C9 | C11 | 111.14(9) |
| C27 | C26 | C28 | 100.75(8) | C10 | C9 | C8 | 110.72(9) |
| C14 | C13 | C11 | 116.83(8) | C27 | C21 | C22 | 106.79(8) |
| C5 | C13 | C11 | 102.71(8) | C17 | C21 | C22 | 116.10(8) |
| C5 | C13 | C14 | 111.28(8) | C17 | C21 | C27 | 112.57(8) |
| C15 | C13 | C11 | 107.65(8) | C20 | C21 | C22 | 111.50(8) |
| C15 | C13 | C14 | 105.65(9) | C20 | C21 | C27 | 102.62(8) |
| C15 | C13 | C5 | 112.89(8) | C20 | C21 | C17 | 106.48(8) |
| C29 | C28 | C26 | 116.50(8) | C6 | C5 | C13 | 106.96(8) |
| C30 | C28 | C26 | 107.47(8) | C4 | C5 | C13 | 120.44(9) |
| C30 | C28 | C29 | 106.09(8) | C4 | C5 | C6 | 105.10(8) |
| C20 | C28 | C26 | 103.23(7) | C18 | C17 | C21 | 102.43(8) |
| C20 | C28 | C29 | 110.88(8) | C16 | C17 | C21 | 113.47(9) |
| C20 | C28 | C30 | 112.82(8) | C16 | C17 | C18 | 111.31(10) |
| C21 | C27 | C26 | 101.63(8) | C21 | C20 | C28 | 105.94(8) |
| C25 | C23 | C22 | 113.26(9) | C19 | C20 | C28 | 119.29(8) |
| C6 | C12 | C11 | 101.43(8) | C19 | C20 | C21 | 105.03(8) |
| C12 | C11 | C13 | 100.89(8) | C19 | C18 | C17 | 104.18(9) |
| C9 | C11 | C13 | 117.61(8) | C3 | C4 | C5 | 102.07(9) |
| C9 | C11 | C12 | 108.34(8) | C3 | C2 | C6 | 103.84(9) |
| C9 | C8 | C7 | 113.63(9) | C1 | C2 | C6 | 116.71(10) |
| C6 | C7 | C8 | 111.82(8) | C1 | C2 | C3 | 112.84(10) |
| C7 | C6 | C12 | 108.03(8) | C18 | C19 | C20 | 105.79(9) |
| C5 | C6 | C12 | 102.01(8) | C2 | C3 | C4 | 103.35(9) |

Table SI3.5.1.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters ( $\AA^{2} \times 10^{3}$ ) for 14 .

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H22a | $3288.1(6)$ | $8191.5(7)$ | $9598.3(10)$ | $26.8(3)$ |
| H22b | $2846.8(6)$ | $7410.6(7)$ | $10294.7(10)$ | $26.8(3)$ |
| H26 | $4911.9(6)$ | $5815.4(6)$ | $10911.0(9)$ | $20.8(2)$ |
| H27a | $3593.9(6)$ | $6536.8(6)$ | $11673.8(9)$ | $24.3(2)$ |
| H27b | $4461.5(6)$ | $6848.7(6)$ | $12324.6(9)$ | $24.3(2)$ |
| H23a | $3228.4(7)$ | $6856.5(7)$ | $8443.4(9)$ | $27.2(2)$ |
| H23b | $4150.2(7)$ | $7293.8(7)$ | $8489.4(9)$ | $27.2(2)$ |
| H12a | $1971.0(7)$ | $4518.0(7)$ | $5536.5(9)$ | $27.5(3)$ |
| H12b | $1419.6(7)$ | $5388.9(7)$ | $5623.0(9)$ | $27.5(3)$ |
| H11 | $2649.6(6)$ | $5661.6(6)$ | $6797.3(9)$ | $23.4(2)$ |
| H29a | $6177(5)$ | $6389(2)$ | $9142(4)$ | $38.1(3)$ |
| H29b | $5521.2(13)$ | $7040(6)$ | $8524.3(10)$ | $38.1(3)$ |
| H29c | $6358(4)$ | $7396(4)$ | $9181(4)$ | $38.1(3)$ |
| H8a | $4110.0(7)$ | $4497.0(8)$ | $4158.6(10)$ | $31.5(3)$ |
| H8b | $3931.4(7)$ | $5495.5(8)$ | $3971.9(10)$ | $31.5(3)$ |
| H14a | $3690(3)$ | $7133(5)$ | $6077.0(11)$ | $38.0(3)$ |
| H14b | $3921(2)$ | $6752(3)$ | $4778(7)$ | $38.0(3)$ |
| H14c | $3355.3(15)$ | $7601(2)$ | $4884(7)$ | $38.0(3)$ |
| H7a | $2973.1(7)$ | $4836.1(7)$ | $2717.7(10)$ | $32.4(3)$ |
| H7b | $2727.4(7)$ | $4133.3(7)$ | $3709.2(10)$ | $32.4(3)$ |
| H24a | $3090(4)$ | $5345(5)$ | $9114.8(12)$ | $46.2(4)$ |
| H24b | $3614.9(11)$ | $5070(3)$ | $10291(7)$ | $46.2(4)$ |
| H24c | $2958(3)$ | $5853.0(17)$ | $10354(7)$ | $46.2(4)$ |
| H5 | $2860.0(7)$ | $6335.1(6)$ | $3422.4(9)$ | $23.8(2)$ |
| H15a | $1478(2)$ | $6700(2)$ | $6070(7)$ | $38.5(3)$ |
| H15b | $2233(2)$ | $7164(5)$ | $6789(3)$ | $38.5(3)$ |
| H15c | $1889(4)$ | $7562(3)$ | $5551(4)$ | $38.5(3)$ |
| H17 | $3471.3(7)$ | $8165.6(7)$ | $12585.8(10)$ | $30.1(3)$ |
| H30a | $5807.3(17)$ | $6971(6)$ | $12188.2(11)$ | $40.5(3)$ |
| H30b | $6290(4)$ | $6285.5(19)$ | $11362(5)$ | $40.5(3)$ |
| H30c | $6555(3)$ | $7274(4)$ | $11303(5)$ | $40.5(3)$ |
| H20 | $4901.2(6)$ | $8163.8(6)$ | $9669.1(9)$ | $22.5(2)$ |
| H18a | $4739.3(8)$ | $9169.8(8)$ | $12863.1(11)$ | $38.5(3)$ |
| H18b | $4906.8(8)$ | $8160.9(8)$ | $13047.0(11)$ | $38.5(3)$ |
| H4a | $1149.5(8)$ | $6845.6(7)$ | $4024.9(10)$ | $34.2(3)$ |
| H4b | $1768.0(8)$ | $7266.9(7)$ | $3023.8(10)$ | $34.2(3)$ |
|  |  |  |  |  |


| H2 | $796.0(8)$ | $5214.7(8)$ | $3734.7(11)$ | $35.4(3)$ |
| :---: | :---: | :---: | :---: | :---: |
| H19a | $5912.0(7)$ | $8457.5(7)$ | $11594.1(12)$ | $35.6(3)$ |
| H19b | $5321.3(7)$ | $9169.8(7)$ | $10961.1(12)$ | $35.6(3)$ |
| H10a | $4044.1(19)$ | $3900(3)$ | $6226(8)$ | $48.3(4)$ |
| H10b | $3330(6)$ | $4262.6(8)$ | $7121(3)$ | $48.3(4)$ |
| H10c | $3057(5)$ | $3836(2)$ | $5867(6)$ | $48.3(4)$ |
| H3a | $702.8(9)$ | $6206.6(8)$ | $2208.7(12)$ | $40.1(3)$ |
| H3b | $1674.1(9)$ | $6049.5(8)$ | $1783.9(12)$ | $40.1(3)$ |
| H16a | $3784(3)$ | $9431(4)$ | $10747(6)$ | $46.2(4)$ |
| H16b | $2862(3)$ | $9073.2(16)$ | $11105(8)$ | $46.2(4)$ |
| H16c | $3384(6)$ | $9653(2)$ | $12038(3)$ | $46.2(4)$ |
| H1c | $1738(4)$ | $4435(4)$ | $1820(8)$ | $66.8(5)$ |
| H1d | $1252(8)$ | $3920.0(9)$ | $2861.6(15)$ | $66.8(5)$ |
| H1e | $719(4)$ | $4465(4)$ | $1900(8)$ | $66.8(5)$ |
| H1a | $4212(17)$ | $5646(17)$ | $6810(30)$ | $18(6)$ |
| H2a | $4727(18)$ | $5290(20)$ | $8780(30)$ | $32(8)$ |
| H1b | $4686(19)$ | $5170(20)$ | $6120(30)$ | $43(9)$ |
| H2b | $4400(20)$ | $5680(20)$ | $7950(30)$ | $35(9)$ |

Table SI3.5.1.7. Atomic Occupancy for 14.

| Atom | Occupancy | Atom | Occupancy |
| :---: | :---: | :---: | :---: |
| H1a | 0.500000 | H1b | 0.500000 |
| H2a | 0.500000 | H2b | 0.500000 |

## SI3.5.2 X-Ray Crystallographic Data for Cyclic Sulfamate 271



A colorless plate $0.20 \times 0.18 \times 0.08 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at $100(2) \mathrm{K}$ using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $99.5 \%$ complete to $74.5^{\circ}$ in $\theta$. A total of 16205 reflections were collected covering the indices, $-9<=h<=9,-15<=k<=15,-20<=k=18.3008$ reflections were found to be symmetry independent, with an $\mathrm{R}_{\text {int }}$ of 0.0300 . Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $\mathrm{P} 2_{1} 2_{1} 2_{1}(\mathrm{No} .19)$. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined from the diffraction data.

Table SI3.5.2.1. Crystal data and structure refinement for 271.

| Identification code | 271 |
| :---: | :---: |
| Empirical formula | $\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{NO}_{4} \mathrm{~S}$ |
| Formula weight | 313.40 |
| Temperature (K) | 100(2) |
| Crystal system | orthorhombic |
| Space group | P2, 2, 2, |
| a (A) | 7.42853(7) |
| b ( $\AA$ ) | 12.26292(11) |
| c ( $\AA$ ) | 16.19471(13) |
| $\alpha\left({ }^{\circ}\right)$ | 90 |
| $\beta\left({ }^{\circ}\right)$ | 90 |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume ( $\AA^{3}$ ) | 1475.27(2) |
| Z | 4 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.411 |
| $\mu\left(\mathrm{mm}^{-1}\right)$ | 2.094 |
| F(000) | 672.0 |
| Crystal size ( $\mathrm{mm}^{3}$, | $0.2 \times 0.18 \times 0.08$ |
| Radiation | $\mathrm{CuK} \alpha(\lambda=1.54184)$ |
| $2 \Theta$ range for data collection ( ${ }^{\circ}$ ) | 10.926 to 148.944 |
| Index ranges | $-9 \leq \mathrm{h} \leq 9,-15 \leq \mathrm{k} \leq 15,-20 \leq 1 \leq 18$ |
| Reflections collected | 16205 |
| Independent reflections | $3008\left[\mathrm{R}_{\mathrm{int}}=0.0300, \mathrm{R}_{\text {sigma }}=0.0151\right]$ |
| Data/restraints/parameters | 3008/0/196 |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.020 |
| Final R indexes [I>=2 $\sigma$ (I)] | $\mathrm{R}_{1}=0.0263, \mathrm{wR}_{2}=0.0700$ |
| Final R indexes [all data] | $\mathrm{R}_{1}=0.0264, \mathrm{wR}_{2}=0.0700$ |
| Largest diff. peak/hole (e $\AA^{-3}$ ) | 0.22/-0.35 |
| Flack parameter | -0.003(6) |

Table SI3.5.2.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 271. $U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\boldsymbol{U}(\mathbf{e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| S1 | $5753.0(7)$ | $3596.0(4)$ | $4793.1(3)$ | $19.15(13)$ |
| O2 | $4727.2(19)$ | $4611.4(11)$ | $5160.9(9)$ | $21.0(3)$ |
| O4 | $7620(2)$ | $3877.3(12)$ | $4762.3(10)$ | $24.7(3)$ |
| O1 | $4170(2)$ | $5377.8(11)$ | $7569.5(8)$ | $20.2(3)$ |
| O3 | $4841(2)$ | $3309.0(13)$ | $4053.0(9)$ | $27.0(4)$ |
| N1 | $5520(3)$ | $2643.8(14)$ | $5463.5(10)$ | $18.5(4)$ |
| C8 | $5253(3)$ | $4869.9(16)$ | $6016.9(12)$ | $18.6(4)$ |
| C7 | $5869(3)$ | $2958.7(15)$ | $6336.9(11)$ | $17.5(4)$ |
| C9 | $2661(3)$ | $3667.4(17)$ | $6620.3(12)$ | $18.6(4)$ |
| C13 | $2255(3)$ | $5177.1(17)$ | $7665.8(13)$ | $21.9(4)$ |
| C12 | $2282(3)$ | $4366.7(17)$ | $8376.8(13)$ | $21.9(4)$ |
| C5 | $4934(3)$ | $4289.4(16)$ | $7510.8(12)$ | $17.2(4)$ |
| C10 | $2606(3)$ | $2865.8(16)$ | $7354.5(12)$ | $19.6(4)$ |
| C2 | $4824(3)$ | $2942.4(17)$ | $8640.3(12)$ | $20.9(4)$ |
| C6 | $4706(3)$ | $3945.7(16)$ | $6596.0(12)$ | $16.2(4)$ |
| C11 | $3619(3)$ | $3530.6(17)$ | $8016.4(12)$ | $18.8(4)$ |
| C4 | $6759(3)$ | $4241.5(17)$ | $7942.5(12)$ | $21.5(4)$ |
| C3 | $6334(3)$ | $3776.2(18)$ | $8803.4(13)$ | $24.3(5)$ |
| C14 | $1479(3)$ | $4663.9(18)$ | $6874.8(13)$ | $21.6(4)$ |
| C1 | $3865(3)$ | $2543.1(19)$ | $9414.7(13)$ | $26.0(5)$ |
| C15 | $1061(3)$ | $5496.1(19)$ | $6197.7(14)$ | $28.8(5)$ |

Table SI3.5.2.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 271. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} U_{11}+2 h k a^{*} b^{*} U_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| S1 | $23.4(2)$ | $19.0(2)$ | $15.1(2)$ | $0.91(18)$ | $2.87(19)$ | $3.88(19)$ |
| O2 | $28.2(7)$ | $18.5(7)$ | $16.2(6)$ | $1.3(6)$ | $2.1(6)$ | $5.0(6)$ |
| O4 | $25.5(7)$ | $22.5(7)$ | $26.0(7)$ | $3.6(6)$ | $7.6(6)$ | $1.7(6)$ |
| O1 | $24.0(7)$ | $15.6(6)$ | $20.8(7)$ | $-1.7(5)$ | $2.4(6)$ | $0.0(6)$ |
| O3 | $36.6(9)$ | $29.6(8)$ | $14.9(7)$ | $-2.0(6)$ | $-1.0(6)$ | $8.7(7)$ |
| N1 | $21.8(9)$ | $17.0(8)$ | $16.7(8)$ | $-0.7(6)$ | $0.3(7)$ | $0.2(7)$ |
| C8 | $23.4(10)$ | $16.2(9)$ | $16.2(9)$ | $1.0(7)$ | $1.8(8)$ | $0.2(7)$ |
| C7 | $20.5(9)$ | $16.4(9)$ | $15.7(8)$ | $0.0(7)$ | $0.9(8)$ | $-0.5(8)$ |
| C9 | $20.2(9)$ | $18.9(9)$ | $16.7(9)$ | $-1.4(8)$ | $1.1(7)$ | $-0.5(8)$ |
| C13 | $23.9(10)$ | $19.7(10)$ | $22.3(10)$ | $-1.4(8)$ | $4.2(8)$ | $5.2(8)$ |
| C12 | $24.4(10)$ | $22.5(10)$ | $18.9(9)$ | $-1.3(8)$ | $5.0(8)$ | $0.5(9)$ |
| C5 | $21.0(9)$ | $14.2(8)$ | $16.6(9)$ | $-1.3(7)$ | $1.8(7)$ | $-0.7(7)$ |
| C10 | $21.0(9)$ | $19.5(9)$ | $18.4(9)$ | $-0.7(8)$ | $2.6(8)$ | $-2.5(8)$ |
| C2 | $27.6(11)$ | $19.6(9)$ | $15.6(9)$ | $-0.5(8)$ | $1.6(8)$ | $-1.1(8)$ |
| C6 | $19.8(10)$ | $14.4(8)$ | $14.4(8)$ | $0.8(7)$ | $1.2(7)$ | $-0.4(7)$ |
| C11 | $22.7(9)$ | $17.4(9)$ | $16.3(8)$ | $-0.6(8)$ | $3.4(7)$ | $-1.8(8)$ |
| C4 | $23.8(10)$ | $21.3(10)$ | $19.5(9)$ | $-0.1(8)$ | $-1.2(8)$ | $-2.9(8)$ |
| C3 | $29.5(11)$ | $24.7(11)$ | $18.6(9)$ | $1.2(8)$ | $-3.7(8)$ | $-2.4(9)$ |
| C14 | $17.7(9)$ | $24.5(10)$ | $22.6(10)$ | $1.1(8)$ | $1.8(8)$ | $1.8(8)$ |
| C1 | $36.7(13)$ | $24.0(10)$ | $17.3(9)$ | $0.7(8)$ | $2.1(9)$ | $-1.7(9)$ |
| C15 | $29.8(12)$ | $30.6(11)$ | $25.9(10)$ | $0.8(9)$ | $-2.2(9)$ | $8.8(10)$ |

Table SI3.5.2.4. Bond Lengths for 271.

| Atom | Atom | Length $(\AA)$ | Atom | Atom | Length $(\AA)$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| S1 | O2 | $1.5768(14)$ | C13 | C12 | $1.521(3)$ |
| S1 | O4 | $1.4300(16)$ | C13 | C14 | $1.539(3)$ |
| S1 | O3 | $1.4210(16)$ | C12 | C11 | $1.543(3)$ |
| S1 | N1 | $1.6037(17)$ | C5 | C6 | $1.549(3)$ |
| O2 | C8 | $1.475(2)$ | C5 | C11 | $1.578(3)$ |
| O1 | C13 | $1.452(3)$ | C5 | C4 | $1.527(3)$ |
| O1 | C5 | $1.453(2)$ | C10 | C11 | $1.543(3)$ |
| N1 | C7 | $1.489(2)$ | C2 | C11 | $1.530(3)$ |
| C8 | C6 | $1.526(3)$ | C2 | C3 | $1.541(3)$ |
| C7 | C6 | $1.545(3)$ | C2 | C1 | $1.523(3)$ |
| C9 | C10 | $1.543(3)$ | C4 | C3 | $1.539(3)$ |
| C9 | C6 | $1.558(3)$ | C14 | C15 | $1.530(3)$ |
| C9 | C14 | $1.560(3)$ |  |  |  |

Table SI3.5.2.5. Bond Angles for 271.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O2 | S1 | N1 | $105.49(8)$ | C4 | C5 | C11 | $106.81(16)$ |
| O4 | S1 | O2 | $106.94(8)$ | C11 | C10 | C9 | $100.71(16)$ |
| O4 | S1 | N1 | $107.69(10)$ | C11 | C2 | C3 | $103.08(17)$ |
| O3 | S1 | O2 | $106.49(9)$ | C1 | C2 | C11 | $114.93(18)$ |
| O3 | S1 | O4 | $119.52(10)$ | C1 | C2 | C3 | $114.37(17)$ |
| O3 | S1 | N1 | $109.83(10)$ | C8 | C6 | C7 | $105.43(15)$ |
| C8 | O2 | S1 | $113.38(12)$ | C8 | C6 | C9 | $115.96(17)$ |
| C13 | O1 | C5 | $103.53(15)$ | C8 | C6 | C5 | $110.88(16)$ |
| C7 | N1 | S1 | $115.82(13)$ | C7 | C6 | C9 | $112.38(16)$ |
| O2 | C8 | C6 | $110.33(16)$ | C7 | C6 | C5 | $114.31(16)$ |
| N1 | C7 | C6 | $111.33(16)$ | C5 | C6 | C9 | $98.16(15)$ |
| C10 | C9 | C6 | $100.64(15)$ | C12 | C11 | C5 | $101.72(16)$ |
| C10 | C9 | C14 | $106.29(15)$ | C10 | C11 | C12 | $107.44(17)$ |
| C6 | C9 | C14 | $112.58(16)$ | C10 | C11 | C5 | $104.66(15)$ |
| O1 | C13 | C12 | $100.34(16)$ | C2 | C11 | C12 | $116.12(17)$ |
| O1 | C13 | C14 | $110.30(16)$ | C2 | C11 | C5 | $104.99(16)$ |
| C12 | C13 | C14 | $111.57(17)$ | C2 | C11 | C10 | $119.67(18)$ |
| C13 | C12 | C11 | $98.98(15)$ | C5 | C4 | C3 | $104.30(17)$ |
| O1 | C5 | C6 | $105.65(15)$ | C4 | C3 | C2 | $103.89(16)$ |
| O1 | C5 | C11 | $105.42(16)$ | C13 | C14 | C9 | $109.22(16)$ |
| O1 | C5 | C4 | $110.62(16)$ | C15 | C14 | C9 | $116.58(17)$ |
| C6 | C5 | C11 | $105.55(15)$ | C15 | C14 | C13 | $113.57(18)$ |
| C4 | C5 | C6 | $121.62(17)$ |  |  |  |  |

Table SI3.5.2.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters ( $\AA^{2} \times 10^{3}$ ) for 271.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H8A | 4661.72 | 5555.03 | 6192.8 | 22 |
| H8B | 6572.26 | 4979.14 | 6045.45 | 22 |
| H7A | 7158.49 | 3143.87 | 6403.57 | 21 |
| H7B | 5599.09 | 2332.68 | 6702.43 | 21 |
| H9 | 2236.92 | 3323.33 | 6095.27 | 22 |
| H13 | 1596.09 | 5858.73 | 7818.93 | 26 |
| H12A | 1080.86 | 4041.67 | 8475.87 | 26 |
| H12B | 2735.87 | 4699.81 | 8893.13 | 26 |
| H10A | 1354.98 | 2704.27 | 7526.24 | 24 |
| H10B | 3236.11 | 2175.42 | 7224.7 | 24 |
| H2 | 5369.29 | 2295.87 | 8358.94 | 25 |
| H4A | 7298.26 | 4977.61 | 7985.96 | 26 |
| H4B | 7600.32 | 3759.48 | 7639.8 | 26 |
| H3A | 5919.64 | 4357.85 | 9182.27 | 29 |
| H3B | 7405.43 | 3417.32 | 9045.12 | 29 |
| H14 | 288.45 | 4350.79 | 7038.91 | 26 |
| H1A | 3349.17 | 3166.93 | 9709.6 | 39 |
| H1B | 4728.1 | 2167.84 | 9773.55 | 39 |
| H1C | 2901.46 | 2037.58 | 9259.03 | 39 |
| H15A | 2099.83 | 5977.7 | 6120.61 | 43 |
| H15B | 10.53 | 5930.48 | 6358.86 | 43 |
| H15C | 803.5 | 5113.1 | 5679.81 | 43 |
| H1 | $4620(40)$ | $2320(20)$ | $5385(15)$ | $22(7)$ |

## SI3.5.3 X-Ray Crystallographic Data for diol 273



A colorless prism $0.10 \times 0.08 \times 0.05 \mathrm{~mm}$ in size was mounted on Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $100 \%$ complete to $79.0^{\circ}$ in $\theta$. A total of 14264 reflections were collected covering the indices, $-11<=h<=10,-8<=k<=7,-15<=k<=12.2801$ reflections were found to be symmetry independent, with an $\mathrm{R}_{\mathrm{int}}$ of 0.0320 . Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $\mathrm{P} 2_{1}$ (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined from the diffraction data.

Table SI3.5.3.1. Crystal data and structure refinement for 273.

| Identification code | $\mathbf{2 7 3}$ |
| :--- | :--- |
| Empirical formula | $\mathrm{C}_{15} \mathrm{H}_{24} \mathrm{O}_{3}$ |
| Formula weight | 252.34 |
| Temperature $(\mathrm{K})$ | $100(2)$ |
| Crystal system | monoclinic |
| Space group | $\mathrm{P}_{1}{ }_{1}$ |
| $\mathrm{a}(\AA)$ | $8.7529(2)$ |
| $\mathrm{b}(\AA)$ | $6.37230(10)$ |
| $\mathrm{c}(\AA)$ | $11.9743(2)$ |
| $\alpha\left(^{\circ}\right)$ | 90 |
| $\beta\left(^{\circ}\right)$ | $90.872(2)$ |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume $\left(\AA^{3}\right)$ | $667.80(2)$ |
| Z | 2 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.255 |
| $\mu\left(\mathrm{~mm}{ }^{-1}\right)$ | 0.682 |
| $\mathrm{~F}(000)$ | 276.0 |
| Crystal size $/ \mathrm{mm}^{3}$ | $0.1 \times 0.08 \times 0.05$ |
| Radiation | $\mathrm{CuKa}(\lambda=1.54184)$ |
| $2 \Theta$ range for data collection $\left({ }^{\circ}\right)$ | 7.384 to 158.008 |
| Index ranges | $-11 \leq \mathrm{h} \leq 10,-8 \leq \mathrm{k} \leq 7,-15 \leq 1 \leq 12$ |
| Reflections collected | 14264 |
| Independent reflections | $2801\left[\mathrm{R}_{\text {int }}=0.0426, \mathrm{R}_{\text {sigma }}=0.0255\right]$ |
| Data/restraints $/$ parameters | $2801 / 1 / 173$ |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.091 |
| Final R indexes $[\mathrm{I}>=2 \sigma(\mathrm{I})]$ | $\mathrm{R}_{1}=0.0320, \mathrm{wR}{ }_{2}=0.0816$ |
| Final R indexes $[$ all data $]$ | $\mathrm{R}_{1}=0.0335, \mathrm{wR}{ }_{2}=0.0826$ |
| Largest diff. peak/hole $\left(\mathrm{e} \AA \AA^{-3}\right)$ | $0.17 /-0.23$ |
| Flack parameter | $0.02(9)$ |
|  |  |

Table SI3.5.3.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 273. $U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| O1 | $3418.5(15)$ | $2122(2)$ | $2234.9(11)$ | $18.6(3)$ |
| O2 | $1279.0(16)$ | $2058(2)$ | $4464.3(11)$ | $20.6(3)$ |
| O3 | $781.4(17)$ | $7957(2)$ | $3975.7(12)$ | $21.6(3)$ |
| C5 | $3600(2)$ | $3964(3)$ | $2929.0(15)$ | $15.3(4)$ |
| C14 | $822(2)$ | $3134(3)$ | $3454.3(16)$ | $19.6(4)$ |
| C8 | $3279(2)$ | $2965(3)$ | $1122.6(15)$ | $19.1(4)$ |
| C4 | $4732(2)$ | $3506(3)$ | $3889.0(17)$ | $20.9(4)$ |
| C15 | $2011(2)$ | $6480(3)$ | $4078.9(16)$ | $19.3(4)$ |
| C11 | $1685(2)$ | $5832(3)$ | $1976.3(15)$ | $16.7(4)$ |
| C13 | $1978(2)$ | $4816(3)$ | $3143.6(15)$ | $16.3(4)$ |
| C10 | $402(2)$ | $2792(4)$ | $789.5(17)$ | $24.2(4)$ |
| C9 | $1781(2)$ | $4219(3)$ | $998.2(15)$ | $18.2(4)$ |
| C6 | $4376(2)$ | $5670(3)$ | $2164.1(15)$ | $17.8(4)$ |
| C7 | $4674(2)$ | $4389(3)$ | $1092.1(16)$ | $20.4(4)$ |
| C12 | $3098(2)$ | $7245(3)$ | $1883.0(16)$ | $19.1(4)$ |
| C2 | $5797(2)$ | $6394(4)$ | $2830.9(17)$ | $22.7(4)$ |
| C3 | $6253(2)$ | $4424(4)$ | $3493.9(18)$ | $25.7(5)$ |
| C1 | $7065(3)$ | $7372(4)$ | $2141.6(19)$ | $32.4(5)$ |

Table SI3.5.3.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 273. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} \mathrm{U}_{11}+2 h k a * b^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | $23.3(7)$ | $13.6(6)$ | $18.8(6)$ | $-1.6(6)$ | $-1.5(5)$ | $1.6(5)$ |
| O2 | $24.5(7)$ | $18.4(7)$ | $19.0(7)$ | $4.2(6)$ | $1.5(5)$ | $-0.7(6)$ |
| O3 | $24.7(7)$ | $18.5(7)$ | $21.9(7)$ | $-0.3(6)$ | $5.0(6)$ | $3.7(6)$ |
| C5 | $17.9(8)$ | $12.7(8)$ | $15.3(8)$ | $-0.8(7)$ | $0.1(7)$ | $0.3(7)$ |
| C14 | $18.6(9)$ | $20.8(10)$ | $19.2(9)$ | $2.3(8)$ | $-0.7(7)$ | $-1.1(8)$ |
| C8 | $24.3(10)$ | $17.4(9)$ | $15.6(9)$ | $-2.9(8)$ | $1.4(7)$ | $-0.5(8)$ |
| C4 | $21.7(9)$ | $20.9(11)$ | $20.1(9)$ | $2.1(8)$ | $-2.9(7)$ | $1.6(8)$ |
| C15 | $20.8(9)$ | $19.4(9)$ | $17.8(9)$ | $-1.4(8)$ | $-0.2(7)$ | $2.3(8)$ |
| C11 | $18.7(9)$ | $15.8(9)$ | $15.7(9)$ | $0.9(7)$ | $-0.8(7)$ | $2.2(7)$ |
| C13 | $18.5(9)$ | $15.4(9)$ | $15.1(9)$ | $0.0(7)$ | $-0.9(6)$ | $0.0(7)$ |
| C10 | $25.0(10)$ | $27.0(11)$ | $20.4(10)$ | $-3.4(8)$ | $-4.8(8)$ | $-3.0(8)$ |
| C9 | $21.5(9)$ | $19.0(10)$ | $14.1(8)$ | $0.9(8)$ | $-1.5(7)$ | $0.7(7)$ |
| C6 | $19.2(9)$ | $17.7(9)$ | $16.5(9)$ | $-0.5(7)$ | $0.1(7)$ | $-2.1(7)$ |
| C7 | $19.2(9)$ | $24.0(11)$ | $18.3(9)$ | $-0.1(8)$ | $3.1(7)$ | $0.9(8)$ |
| C12 | $24.3(9)$ | $15.7(9)$ | $17.2(9)$ | $1.7(7)$ | $0.0(7)$ | $-0.8(8)$ |
| C2 | $19.9(9)$ | $26.3(11)$ | $22.0(10)$ | $-1.5(8)$ | $-1.4(7)$ | $-4.9(8)$ |
| C3 | $18.8(10)$ | $34.2(13)$ | $24.0(10)$ | $1.2(9)$ | $-3.1(7)$ | $-0.2(9)$ |
| C1 | $25.4(10)$ | $40.6(14)$ | $31.1(11)$ | $2.9(10)$ | $-0.4(9)$ | $-11.7(10)$ |

Table SI3.5.3.4. Bond Lengths for 273.

| Atom | Atom | Length $(\mathbf{\AA})$ | Atom | Atom | Length $(\AA \mathbf{)}$ |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | C5 | $1.445(2)$ | C15 | C13 | $1.542(3)$ |  |
| O1 | C8 | $1.440(2)$ | C11 | C13 | $1.558(2)$ |  |
| O2 | C14 | $1.442(2)$ | C11 | C9 | $1.562(3)$ |  |
| O3 | C15 | $1.433(2)$ | C11 | C12 | $1.535(3)$ |  |
| C5 | C4 | $1.534(3)$ | C10 | C 9 | $1.528(3)$ |  |
| C5 | C13 | $1.546(3)$ | C6 | C7 | $1.547(3)$ |  |
| C5 | C6 | $1.582(3)$ | C6 | C12 | $1.536(3)$ |  |
| C14 | C13 | $1.524(3)$ | C6 | C2 | $1.539(3)$ |  |
| C8 | C9 | $1.541(3)$ | C2 | C3 | $1.534(3)$ |  |
| C8 | C7 | $1.522(3)$ | C2 | C1 | $1.526(3)$ |  |
| C4 | C3 | $1.536(3)$ |  |  |  |  |

Table SI3.5.3.5. Bond Angles for 273.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C8 | O1 | C5 | $103.66(14)$ | C14 | C13 | C11 | $114.23(15)$ |
| O1 | C5 | C4 | $109.93(15)$ | C15 | C13 | C5 | $110.80(15)$ |
| O1 | C5 | C13 | $106.71(14)$ | C15 | C13 | C11 | $111.52(16)$ |
| O1 | C5 | C6 | $105.65(14)$ | C8 | C9 | C11 | $108.93(15)$ |
| C4 | C5 | C13 | $121.77(15)$ | C10 | C9 | C8 | $112.08(17)$ |
| C4 | C5 | C6 | $106.66(15)$ | C10 | C9 | C11 | $117.57(16)$ |
| C13 | C5 | C6 | $104.98(15)$ | C7 | C6 | C5 | $101.36(15)$ |
| O2 | C14 | C13 | $111.25(15)$ | C12 | C6 | C5 | $104.97(15)$ |
| O1 | C8 | C9 | $110.06(15)$ | C12 | C6 | C7 | $107.12(15)$ |
| O1 | C8 | C7 | $100.83(15)$ | C12 | C6 | C2 | $119.89(18)$ |
| C7 | C8 | C9 | $111.74(17)$ | C2 | C6 | C5 | $104.86(15)$ |
| C5 | C4 | C3 | $104.45(16)$ | C2 | C6 | C7 | $116.33(17)$ |
| O3 | C15 | C13 | $112.52(15)$ | C8 | C7 | C6 | $98.58(15)$ |
| C13 | C11 | C9 | $112.91(15)$ | C11 | C12 | C6 | $100.71(16)$ |
| C12 | C11 | C13 | $100.79(14)$ | C3 | C2 | C6 | $103.01(17)$ |
| C12 | C11 | C9 | $106.18(15)$ | C1 | C2 | C6 | $115.49(17)$ |
| C5 | C13 | C11 | $97.81(14)$ | C1 | C2 | C3 | $115.40(18)$ |
| C14 | C13 | C5 | $114.13(16)$ | C2 | C3 | C4 | $104.56(16)$ |
| C14 | C13 | C15 | $108.14(15)$ |  |  |  |  |

Table SI3.5.3.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 273.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H14A | -190.28 | 3792.91 | 3560.1 | 23 |
| H14B | 724.77 | 2107.93 | 2836.6 | 23 |
| H8 | 3340.33 | 1831.23 | 547.67 | 23 |
| H4A | 4822.49 | 1977.38 | 4020.99 | 25 |
| H4B | 4402.8 | 4193.08 | 4586.98 | 25 |
| H15A | 1949.6 | 5766.6 | 4811.37 | 23 |
| H15B | 2994.77 | 7243.99 | 4058.66 | 23 |
| H11 | 712.35 | 6655.68 | 1948.6 | 20 |
| H10A | 334.27 | 2434.77 | -5.76 | 36 |
| H10B | -531.36 | 3521.63 | 1009.96 | 36 |
| H10C | 520.38 | 1505.01 | 1230.34 | 36 |
| H9 | 1888.57 | 5073.85 | 303.47 | 22 |
| H7A | 4676.75 | 5285.74 | 416.97 | 25 |
| H7B | 5640.79 | 3585.66 | 1144.03 | 25 |
| H12A | 3075.36 | 8413 | 2427.59 | 23 |
| H12B | 3200.23 | 7820.61 | 1119.85 | 23 |
| H2A | 5456.93 | 7473.41 | 3379.62 | 27 |
| H3A | 6922.11 | 4792.32 | 4138.38 | 31 |
| H3B | 6794.49 | 3411.64 | 3013.95 | 31 |
| H1A | 7433.76 | 6342.61 | 1600.95 | 49 |
| H1B | 7909.16 | 7799.58 | 2637.87 | 49 |
| H1C | 6664.69 | 8603.38 | 1743.19 | 49 |
| H3 | $-20(40)$ | $7600(60)$ | $4430(30)$ | $53(9)$ |
| H2 | $1230(40)$ | $760(60)$ | $4310(30)$ | $50(9)$ |

## SI3.5.4 X-Ray Crystallographic Data for Bis( $\alpha$-keto)ester 278



A colorless prism $0.21 \times 0.14 \times 0.08 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $75 \%$ complete to $74.5^{\circ}$ in $\theta$. A total of 32705 reflections were collected covering the indices, $-14<=h<=14,-14<=k<=14,-11<=l<=15.3557$ reflections were found to be symmetry independent, with an $R_{\text {int }}$ of 0.0463 . Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $\mathrm{P} 2_{1} 2_{1} 2_{1}$ (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined from the diffraction data.

Table SI3.5.4.1. Crystal data and structure refinement for 278.

| Identification code | 278 |
| :--- | :--- |
| Empirical formula | $\mathrm{C}_{18} \mathrm{H}_{20} \mathrm{O}_{8}$ |
| Formula weight | 364.34 |
| Temperature $(\mathrm{K})$ | $100(2)$ |
| Crystal system | orthorhombic |
| Space group | $\mathrm{P}_{2},_{1} 2_{1}$ |
| $\mathrm{a}(\AA \AA)$ | $11.91510(10)$ |
| $\mathrm{b}(\AA \AA)$ | $11.95600(10)$ |
| $\mathrm{c}\left(\AA^{\AA}\right)$ | $12.22890(10)$ |
| $\alpha\left(^{\circ}\right)$ | 90 |
| $\beta\left(^{\circ}\right)$ | 90 |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume $\left(\AA^{3}\right)$ | $1742.09(3)$ |
| Z | 4 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.389 |
| $\mu\left(\mathrm{~mm}{ }^{-1}\right)$ | 0.933 |
| $\mathrm{~F}(000)$ | 768.0 |
| Crystal size $\left(\mathrm{mm}{ }^{3}\right)$ | $0.210 \times 0.140 \times 0.080$ |
| Radiation | $\mathrm{CuK} \mathrm{\alpha}(\lambda=1.54184)$ |
| $2 \Theta$ range for data collection $\left(^{\circ}\right)$ | 10.366 to 149.006 |
| Index ranges | $-14 \leq \mathrm{h} \leq 14,-14 \leq \mathrm{k} \leq 14,-11 \leq 1 \leq 15$ |
| Reflections collected | 32705 |
| Independent reflections | $3557\left[\mathrm{R}_{\text {int }}=0.0463, \mathrm{R}_{\text {sigma }}=0.0149\right]$ |
| Data/restraints $/$ parameters | $3557 / 0 / 239$ |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.048 |
| Final R indexes [I>=2 $\sigma(\mathrm{I})]$ | $\mathrm{R}_{1}=0.0290, \mathrm{wR} \mathrm{R}_{2}=0.0766$ |
| Final R indexes [all data $]$ | $\mathrm{R}_{1}=0.0291, \mathrm{wR} \mathrm{R}_{2}=0.0767$ |
| Largest diff. peak/hole $\left(\mathrm{e} \AA^{-3}\right)$ | $0.17 /-0.22$ |
| Flack parameter | $-0.05(4)$ |

Table SI3.5.4.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 278. $U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| C1 | $9477.4(16)$ | $3818.0(17)$ | $5337.3(16)$ | $28.9(4)$ |
| C2 | $9219.5(14)$ | $4969.1(15)$ | $5807.5(14)$ | $19.6(4)$ |
| C3 | $9566.0(15)$ | $5132.1(15)$ | $7007.6(14)$ | $21.4(3)$ |
| C4 | $8924.7(14)$ | $6179.7(15)$ | $7359.5(14)$ | $19.1(3)$ |
| C5 | $7760.8(13)$ | $6012.1(13)$ | $6866.9(12)$ | $14.7(3)$ |
| C6 | $6672.6(13)$ | $4403.4(14)$ | $7086.6(13)$ | $15.5(3)$ |
| C7 | $7147.5(14)$ | $4364.0(14)$ | $5916.4(13)$ | $15.8(3)$ |
| C8 | $7948.4(13)$ | $5331.4(13)$ | $5802.8(13)$ | $14.9(3)$ |
| C9 | $7663.4(13)$ | $6151.4(14)$ | $4922.3(12)$ | $15.7(3)$ |
| C10 | $7272.7(13)$ | $7116.3(14)$ | $5320.4(13)$ | $15.1(3)$ |
| C11 | $7014.3(13)$ | $8103.3(14)$ | $4650.4(13)$ | $15.9(3)$ |
| C12 | $7188.8(14)$ | $8014.4(14)$ | $3408.7(13)$ | $16.6(3)$ |
| C13 | $8168.0(17)$ | $8797.9(16)$ | $1913.2(14)$ | $25.7(4)$ |
| C14 | $7072.8(14)$ | $7076.3(14)$ | $6557.2(12)$ | $15.4(3)$ |
| C15 | $7431.9(16)$ | $8118.7(14)$ | $7209.9(14)$ | $22.2(4)$ |
| C16 | $5808.8(14)$ | $6934.8(15)$ | $6746.3(14)$ | $18.8(3)$ |
| C17 | $4792.2(14)$ | $5996.6(16)$ | $5308.4(15)$ | $21.6(4)$ |
| C18 | $4347.9(16)$ | $4875.9(17)$ | $4974.9(17)$ | $28.3(4)$ |
| O1 | $7116.0(10)$ | $5289.5(9)$ | $7612.7(9)$ | $15.3(2)$ |
| O2 | $6027.2(10)$ | $3759.4(10)$ | $7499.4(10)$ | $20.5(3)$ |
| O3 | $6875.9(11)$ | $3664.3(10)$ | $5256.5(10)$ | $21.5(3)$ |
| O4 | $6660.2(10)$ | $8983.5(10)$ | $5012.1(10)$ | $21.4(3)$ |
| O5 | $6670.9(11)$ | $7387.0(11)$ | $2828.7(10)$ | $24.1(3)$ |
| O6 | $7942.7(11)$ | $8761.9(10)$ | $3080.3(9)$ | $20.4(3)$ |
| O7 | $5394.0(10)$ | $5915.5(10)$ | $6248.7(10)$ | $18.2(3)$ |
| O8 | $4639.4(11)$ | $6868.9(12)$ | $4832.6(11)$ | $28.4(3)$ |

Table SI3.5.4.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 278. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} U_{11}+2 h k a^{*} b^{*} U_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | $27.5(9)$ | $32.2(10)$ | $27.0(9)$ | $-0.8(8)$ | $5.3(8)$ | $12.3(8)$ |
| C2 | $16.4(8)$ | $23.2(9)$ | $19.3(8)$ | $4.9(7)$ | $3.2(6)$ | $4.1(6)$ |
| C3 | $16.8(8)$ | $25.0(8)$ | $22.4(8)$ | $5.4(7)$ | $-1.0(7)$ | $-0.2(7)$ |
| C4 | $18.6(8)$ | $21.8(8)$ | $16.9(7)$ | $3.8(7)$ | $-3.1(6)$ | $-4.2(6)$ |
| C5 | $16.6(7)$ | $16.4(7)$ | $11.0(7)$ | $2.1(6)$ | $1.4(6)$ | $-2.2(6)$ |
| C6 | $15.8(7)$ | $15.8(7)$ | $14.8(7)$ | $1.9(6)$ | $-1.5(6)$ | $0.7(6)$ |
| C7 | $18.1(7)$ | $14.8(7)$ | $14.3(7)$ | $2.3(6)$ | $0.0(6)$ | $2.8(6)$ |
| C8 | $16.5(8)$ | $15.4(7)$ | $12.7(7)$ | $0.8(6)$ | $1.8(6)$ | $0.9(6)$ |
| C9 | $17.0(7)$ | $18.1(7)$ | $12.1(7)$ | $2.2(6)$ | $0.0(6)$ | $-1.3(6)$ |
| C10 | $15.1(7)$ | $17.3(7)$ | $12.9(7)$ | $1.5(6)$ | $-0.5(6)$ | $-1.8(6)$ |
| C11 | $14.3(7)$ | $17.3(7)$ | $16.0(7)$ | $1.0(6)$ | $-0.9(6)$ | $-1.1(6)$ |
| C12 | $17.7(8)$ | $15.5(7)$ | $16.7(7)$ | $4.2(6)$ | $-2.8(6)$ | $1.9(6)$ |
| C13 | $34.8(10)$ | $24.3(9)$ | $18.0(8)$ | $7.8(7)$ | $4.9(7)$ | $3.7(8)$ |
| C14 | $19.1(8)$ | $15.2(7)$ | $11.9(7)$ | $0.3(6)$ | $1.0(6)$ | $0.6(6)$ |
| C15 | $31.5(9)$ | $16.8(7)$ | $18.4(7)$ | $-3.0(7)$ | $-1.2(7)$ | $-1.1(7)$ |
| C16 | $20.4(8)$ | $18.8(8)$ | $17.2(7)$ | $-2.0(6)$ | $3.1(6)$ | $2.3(6)$ |
| C17 | $13.8(7)$ | $31.2(9)$ | $19.6(8)$ | $0.8(7)$ | $0.3(6)$ | $4.1(7)$ |
| C18 | $21.8(8)$ | $35.0(10)$ | $28.0(9)$ | $-7.7(8)$ | $-4.8(7)$ | $2.7(7)$ |
| O1 | $18.2(5)$ | $16.6(5)$ | $11.3(5)$ | $1.8(4)$ | $1.2(4)$ | $-3.0(4)$ |
| O2 | $20.1(6)$ | $20.9(6)$ | $20.4(6)$ | $4.3(5)$ | $1.6(5)$ | $-3.2(5)$ |
| O3 | $27.9(6)$ | $17.6(6)$ | $19.0(6)$ | $-2.3(5)$ | $-2.2(5)$ | $0.2(5)$ |
| O4 | $25.5(6)$ | $17.4(6)$ | $21.1(6)$ | $-0.2(5)$ | $0.4(5)$ | $3.2(5)$ |
| O5 | $25.7(6)$ | $27.3(6)$ | $19.4(6)$ | $-1.6(5)$ | $-4.4(5)$ | $-3.6(5)$ |
| O6 | $26.9(6)$ | $18.9(6)$ | $15.4(6)$ | $3.4(5)$ | $2.2(5)$ | $-3.2(5)$ |
| O7 | $15.6(5)$ | $20.6(6)$ | $18.6(6)$ | $1.0(5)$ | $-0.9(5)$ | $0.2(5)$ |
| O8 | $24.2(6)$ | $34.8(7)$ | $26.1(6)$ | $7.8(6)$ | $-2.2(6)$ | $6.5(6)$ |

Table SI3.5.4.4. Bond Lengths for 278.

| Atom | Atom | Length $(\AA \mathbf{\AA})$ | Atom | Atom | Length $(\AA \mathbf{\AA})$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | C2 | $1.523(3)$ | C 9 | C10 | $1.336(2)$ |
| C2 | C3 | $1.537(2)$ | C10 | C11 | $1.469(2)$ |
| C2 | C8 | $1.575(2)$ | C10 | C14 | $1.532(2)$ |
| C3 | C4 | $1.529(2)$ | C11 | O4 | $1.217(2)$ |
| C4 | C5 | $1.525(2)$ | C11 | C12 | $1.536(2)$ |
| C5 | O1 | $1.4725(18)$ | C12 | O5 | $1.203(2)$ |
| C5 | C8 | $1.551(2)$ | C12 | O6 | $1.329(2)$ |
| C5 | C14 | $1.560(2)$ | C13 | O6 | $1.453(2)$ |
| C6 | O2 | $1.200(2)$ | C14 | C16 | $1.533(2)$ |
| C6 | O1 | $1.347(2)$ | C14 | C15 | $1.541(2)$ |
| C6 | C7 | $1.540(2)$ | C16 | O7 | $1.449(2)$ |
| C7 | O3 | $1.207(2)$ | C17 | O8 | $1.208(2)$ |
| C7 | C8 | $1.506(2)$ | C17 | O7 | $1.359(2)$ |
| C8 | C9 | $1.495(2)$ | C17 | C18 | $1.497(3)$ |

Table SI3.5.4.5. Bond Angles for 278.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | C2 | C3 | 114.89(15) | C10 | C9 | C8 | 112.51(14) |
| C1 | C2 | C8 | 116.17(15) | C9 | C10 | C11 | 124.29(14) |
| C3 | C2 | C8 | 103.11(13) | C9 | C10 | C14 | 112.77(14) |
| C4 | C3 | C2 | 103.79(13) | C11 | C10 | C14 | 122.90(14) |
| C5 | C4 | C3 | 103.63(13) | O4 | C11 | C10 | 124.37(15) |
| O1 | C5 | C4 | 107.87(12) | O4 | C11 | C12 | 117.77(15) |
| O1 | C5 | C8 | 106.68(12) | C10 | C11 | C12 | 117.86(14) |
| C4 | C5 | C8 | 105.62(13) | O5 | C12 | O6 | 126.00(15) |
| O1 | C5 | C14 | 110.77(12) | O5 | C12 | C11 | 123.82(15) |
| C4 | C5 | C14 | 117.81(13) | O6 | C12 | C11 | 110.09(13) |
| C8 | C5 | C14 | 107.45(12) | C10 | C14 | C16 | 107.77(13) |
| O2 | C6 | O1 | 123.72(15) | C10 | C14 | C15 | 116.30(14) |
| O2 | C6 | C7 | 127.38(15) | C16 | C14 | C15 | 106.50(14) |
| O1 | C6 | C7 | 108.89(13) | C10 | C14 | C5 | 100.57(12) |
| O3 | C7 | C8 | 129.85(15) | C16 | C14 | C5 | 112.93(13) |
| O3 | C7 | C6 | 122.98(15) | C15 | C14 | C5 | 112.83(13) |
| C8 | C7 | C6 | 107.16(13) | O7 | C16 | C14 | 111.38(13) |
| C9 | C8 | C7 | 115.22(13) | O8 | C17 | O7 | 123.28(17) |
| C9 | C8 | C5 | 103.15(12) | O8 | C17 | C18 | 126.03(17) |
| C7 | C8 | C5 | 103.55(13) | O7 | C17 | C18 | 110.69(16) |
| C9 | C8 | C2 | 113.65(13) | C6 | O1 | C5 | 111.73(11) |
| C7 | C8 | C2 | 113.44(13) | C12 | O6 | C13 | 116.20(14) |
| C5 | C8 | C2 | 106.24(13) | C17 | O7 | C16 | 118.39(14) |

Table SI3.5.4.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 278.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H1A | 9132 | 3242 | 5797 | 43 |
| H1B | 10292 | 3705 | 5318 | 43 |
| H1C | 9175 | 3766 | 4594 | 43 |
| H2 | 9643 | 5530 | 5363 | 24 |
| H3A | 9346 | 4479 | 7456 | 26 |
| H3B | 10386 | 5246 | 7072 | 26 |
| H4A | 8885 | 6235 | 8166 | 23 |
| H4B | 9284 | 6864 | 7067 | 23 |
| H9 | 7751 | 6003 | 4164 | 19 |
| H13A | 7475 | 8981 | 1520 | 39 |
| H13B | 8444 | 8067 | 1670 | 39 |
| H13C | 8736 | 9370 | 1762 | 39 |
| H15A | 8174 | 8364 | 6963 | 33 |
| H15B | 7463 | 7935 | 7990 | 33 |
| H15C | 6886 | 8720 | 7092 | 33 |
| H16A | 5656 | 6916 | 7542 | 23 |
| H16B | 5406 | 7584 | 6433 | 23 |
| H18A | 4769 | 4287 | 5353 | 42 |
| H18B | 4432 | 4784 | 4183 | 42 |
| H18C | 3552 | 4823 | 5171 | 42 |

## SI3.5.5 X-Ray Crystallographic Data for Enol Lactone 279



A colorless block $0.06 \times 0.05 \times 0.03 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at $100(2) \mathrm{K}$ using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $100 \%$ complete to $68.4^{\circ}$ in $\theta$. A total of 16873 reflections were collected covering the indices, $-8<=h<=8,-12<=k<=15,-17<=l<=16.2420$ reflections were found to be symmetry independent, with an $\mathrm{R}_{\text {int }}$ of 0.0351 . Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $\mathrm{P} 2_{1} 2_{1} 2_{1}$ (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined from the diffraction data.

Table SI3.5.5.1. Crystal data and structure refinement for 279.

| Identification code | $\mathbf{2 7 9}$ |
| :--- | :--- |
| Empirical formula | $\mathrm{C}_{15} \mathrm{H}_{18} \mathrm{O}_{5}$ |
| Formula weight | 278.29 |
| Temperature $(\mathrm{K})$ | $100(2)$ |
| Crystal system | orthorhombic |
| Space group | $\mathrm{P}_{1} 2_{1} 2_{1}$ |
| $\mathrm{a}(\AA)$ | $7.1443(3)$ |
| $\mathrm{b}(\AA)$ | $12.9075(5)$ |
| $\mathrm{c}(\AA)$ | $14.2650(6)$ |
| $\alpha\left({ }^{\circ}\right)$ | 90 |
| $\beta\left(^{\circ}\right)$ | 90 |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume $\left(\AA^{3}\right)$ | $1315.45(9)$ |
| Z | 4 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.405 |
| $\mu\left(\mathrm{~mm}{ }^{-1}\right)$ | 0.876 |
| $\mathrm{~F}(000)$ | 592.0 |
| Crystal size $\left(\mathrm{mm}{ }^{3}\right)$ | $0.060 \times 0.050 \times 0.030$ |
| Radiation | $\mathrm{CuK} \alpha(\lambda=1.54178)$ |
| $2 \Theta$ range for data collection $\left({ }^{\circ}\right)$ | 9.24 to 136.742 |
| Index ranges | $-8 \leq \mathrm{h} \leq 8,-12 \leq \mathrm{k} \leq 15,-17 \leq 1 \leq 16$ |
| Reflections collected | 16873 |
| Independent reflections | $2420\left[\mathrm{R}_{\text {int }}=0.0351, \mathrm{R}_{\text {sigma }}=0.0261\right]$ |
| Data/restraints $/$ parameters | $2420 / 0 / 184$ |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.064 |
| Final R indexes $[\mathrm{I}>=2 \sigma(\mathrm{I})]$ | $\mathrm{R}_{1}=0.0295, \mathrm{wR} \mathrm{R}_{2}=0.0762$ |
| Final R indexes [all data $]$ | $\mathrm{R}_{1}=0.0300, \mathrm{wR}{ }_{2}=0.0767$ |
| Largest diff. peak/hole $\left(\mathrm{e} \AA \AA^{-3}\right)$ | $0.20 /-0.15$ |
| Flack parameter | $-0.10(10)$ |
|  |  |

Table SI3.5.5.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 279. $U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| C1 | $297(3)$ | $4449.0(16)$ | $5687.0(14)$ | $25.5(4)$ |
| C2 | $-587(3)$ | $5391.3(17)$ | $5215.2(14)$ | $29.0(5)$ |
| C3 | $256(3)$ | $6289.2(16)$ | $5767.7(15)$ | $27.0(4)$ |
| C4 | $2321(3)$ | $5989.9(14)$ | $5856.6(13)$ | $21.6(4)$ |
| C5 | $3478(3)$ | $6318.3(15)$ | $6740.2(12)$ | $21.5(4)$ |
| C6 | $5015(3)$ | $7105.3(16)$ | $6543.0(14)$ | $26.0(4)$ |
| C7 | $6899(3)$ | $6331.8(16)$ | $7763.4(13)$ | $24.9(4)$ |
| C8 | $6060(3)$ | $5330.2(15)$ | $7476.2(12)$ | $23.0(4)$ |
| C9 | $4430(3)$ | $5316.0(16)$ | $7025.5(13)$ | $22.4(4)$ |
| C10 | $3322(3)$ | $4399.3(16)$ | $6707.0(14)$ | $26.4(4)$ |
| C11 | $2383(3)$ | $4770.2(14)$ | $5792.8(13)$ | $20.8(4)$ |
| C12 | $3603(3)$ | $4577.7(16)$ | $4928.6(15)$ | $28.2(4)$ |
| C13 | $3968(3)$ | $5614.6(16)$ | $4483.0(13)$ | $23.2(4)$ |
| C14 | $-64(3)$ | $3403.3(18)$ | $5224.2(17)$ | $35.5(5)$ |
| C15 | $2215(3)$ | $6722.1(18)$ | $7534.2(14)$ | $29.8(5)$ |
| O1 | $6247(2)$ | $7196.4(11)$ | $7355.7(10)$ | $29.5(3)$ |
| O2 | $3249(2)$ | $6374.8(10)$ | $5013.2(9)$ | $25.5(3)$ |
| O3 | $8099(2)$ | $6385.2(12)$ | $8357.1(10)$ | $32.7(4)$ |
| O4 | $6972(2)$ | $4459.8(11)$ | $7751.7(10)$ | $27.8(3)$ |
| O5 | $4787(2)$ | $5809.6(12)$ | $3766.3(10)$ | $31.7(4)$ |

Table SI3.5.5.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 279. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} U_{11}+2 h k a^{*} b^{*} U_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{\mathbf{1}}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | $20.9(9)$ | $30.6(11)$ | $25.0(9)$ | $5.5(8)$ | $-2.5(8)$ | $-2.8(8)$ |
| C2 | $22.8(9)$ | $36.5(12)$ | $27.6(10)$ | $5.3(9)$ | $-2.9(8)$ | $2.6(9)$ |
| C3 | $25.8(11)$ | $29.7(10)$ | $25.6(9)$ | $3.2(8)$ | $-0.2(8)$ | $8.1(9)$ |
| C4 | $25.9(10)$ | $20.5(9)$ | $18.3(9)$ | $3.4(7)$ | $4.3(7)$ | $1.9(8)$ |
| C5 | $23.2(10)$ | $21.1(9)$ | $20.4(9)$ | $0.5(7)$ | $3.0(8)$ | $-0.1(8)$ |
| C6 | $30.1(11)$ | $20.4(9)$ | $27.6(10)$ | $-0.2(8)$ | $2.6(9)$ | $-2.8(9)$ |
| C7 | $21.1(9)$ | $30.7(10)$ | $22.9(9)$ | $-6.3(8)$ | $7.3(8)$ | $-4.4(8)$ |
| C8 | $24.4(9)$ | $25.1(10)$ | $19.5(8)$ | $0.1(8)$ | $2.0(7)$ | $-1.6(8)$ |
| C9 | $25.1(9)$ | $22.1(9)$ | $19.8(8)$ | $2.7(7)$ | $1.5(7)$ | $-2.7(8)$ |
| C10 | $27.4(10)$ | $21.8(9)$ | $30.0(10)$ | $5.8(8)$ | $-7.7(8)$ | $-2.8(8)$ |
| C11 | $20.4(9)$ | $18.7(9)$ | $23.2(9)$ | $1.5(7)$ | $-1.9(7)$ | $0.0(8)$ |
| C12 | $28.6(10)$ | $22.9(10)$ | $33.2(10)$ | $-2.8(8)$ | $5.7(9)$ | $0.2(8)$ |
| C13 | $21.1(9)$ | $27.2(10)$ | $21.5(9)$ | $-1.9(8)$ | $-0.5(8)$ | $1.8(8)$ |
| C14 | $29.1(11)$ | $32.4(11)$ | $44.9(13)$ | $5.5(10)$ | $-13.0(10)$ | $-8.5(10)$ |
| C15 | $28.0(10)$ | $38.9(11)$ | $22.6(9)$ | $-4.4(9)$ | $3.6(8)$ | $2.2(9)$ |
| O1 | $30.6(8)$ | $23.7(7)$ | $34.2(8)$ | $-7.2(6)$ | $1.0(7)$ | $-4.8(6)$ |
| O2 | $34.4(8)$ | $21.6(7)$ | $20.4(6)$ | $3.8(5)$ | $5.6(6)$ | $1.5(6)$ |
| O3 | $26.4(7)$ | $41.3(9)$ | $30.5(7)$ | $-11.5(6)$ | $-0.4(7)$ | $-5.7(7)$ |
| O4 | $25.3(7)$ | $27.5(7)$ | $30.5(7)$ | $0.9(6)$ | $-8.7(6)$ | $-1.4(6)$ |
| O5 | $31.3(8)$ | $40.2(9)$ | $23.5(7)$ | $2.2(6)$ | $8.1(6)$ | $3.2(7)$ |

Table SI3.5.5.4. Bond Lengths for 279.

| Atom | Atom | Length ( $\mathbf{\AA})$ | Atom | Atom | Length $(\mathbf{\AA})$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | C14 | $1.525(3)$ | C7 | O3 | $1.207(3)$ |
| C1 | C2 | $1.527(3)$ | C7 | O1 | $1.342(3)$ |
| C1 | C11 | $1.555(3)$ | C7 | C8 | $1.483(3)$ |
| C2 | C3 | $1.525(3)$ | C8 | C9 | $1.330(3)$ |
| C3 | C4 | $1.530(3)$ | C8 | O4 | $1.357(2)$ |
| C4 | O2 | $1.461(2)$ | C9 | C10 | $1.494(3)$ |
| C4 | C5 | $1.566(3)$ | C10 | C11 | $1.543(3)$ |
| C4 | C11 | $1.578(3)$ | C11 | C12 | $1.530(3)$ |
| C5 | C9 | $1.517(3)$ | C12 | C13 | $1.504(3)$ |
| C5 | C6 | $1.522(3)$ | C13 | O5 | $1.205(2)$ |
| C5 | C15 | $1.539(3)$ | C13 | O2 | $1.341(2)$ |
| C6 | O1 | $1.460(2)$ |  |  |  |

Table SI3.5.5.5. Bond Angles for 279.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C14 | C1 | C2 | $116.39(17)$ | O1 | C7 | C8 | $117.72(17)$ |
| C14 | C1 | C11 | $116.13(17)$ | C9 | C8 | O4 | $123.29(18)$ |
| C2 | C1 | C11 | $103.11(16)$ | C9 | C8 | C7 | $119.96(18)$ |
| C3 | C2 | C1 | $102.37(16)$ | O4 | C8 | C7 | $116.61(17)$ |
| C2 | C3 | C4 | $103.39(16)$ | C8 | C9 | C10 | $128.43(18)$ |
| O2 | C4 | C3 | $106.47(16)$ | C8 | C9 | C5 | $120.70(18)$ |
| O2 | C4 | C5 | $109.36(15)$ | C10 | C9 | C5 | $110.85(16)$ |
| C3 | C4 | C5 | $120.47(17)$ | C9 | C10 | C11 | $103.99(15)$ |
| O2 | C4 | C11 | $106.21(15)$ | C12 | C11 | C10 | $112.52(16)$ |
| C3 | C4 | C11 | $105.92(16)$ | C12 | C11 | C1 | $115.12(16)$ |
| C5 | C4 | C11 | $107.56(16)$ | C10 | C11 | C1 | $114.61(16)$ |
| C9 | C5 | C6 | $107.15(16)$ | C12 | C11 | C4 | $102.98(15)$ |
| C9 | C5 | C15 | $110.75(15)$ | C10 | C11 | C4 | $105.85(16)$ |
| C6 | C5 | C15 | $109.45(16)$ | C1 | C11 | C4 | $104.17(16)$ |
| C9 | C5 | C4 | $102.82(15)$ | C13 | C12 | C11 | $107.14(16)$ |
| C6 | C5 | C4 | $114.37(15)$ | O5 | C13 | O2 | $120.78(19)$ |
| C15 | C5 | C4 | $112.01(16)$ | O5 | C13 | C12 | $128.95(19)$ |
| O1 | C6 | C5 | $109.99(15)$ | O2 | C13 | C12 | $110.26(16)$ |
| O3 | C7 | O1 | $120.21(19)$ | C7 | O1 | C6 | $119.10(15)$ |
| O3 | C7 | C8 | $122.1(2)$ | C13 | O2 | C4 | $112.92(15)$ |

Table SI3.5.5.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters ( $\AA^{2} \times 10^{3}$ ) for 279.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H1 | -237.24 | 4409.37 | 6333.97 | 31 |
| H2A | -241.49 | 5429.75 | 4544.03 | 35 |
| H2B | -1967.82 | 5379 | 5272.22 | 35 |
| H3A | -337.61 | 6353.84 | 6392.08 | 32 |
| H3B | 110.95 | 6951.45 | 5425.22 | 32 |
| H6A | 5749.54 | 6883.13 | 5989.89 | 31 |
| H6B | 4448.78 | 7787.64 | 6401.48 | 31 |
| H10A | 2372.63 | 4203.56 | 7180.33 | 32 |
| H10B | 4147.98 | 3797.55 | 6587.99 | 32 |
| H12A | 4797.36 | 4246.86 | 5113.09 | 34 |
| H12B | 2948.02 | 4115.22 | 4482.52 | 34 |
| H14A | -1407.12 | 3249.88 | 5241.9 | 53 |
| H14B | 622.38 | 2862.27 | 5561.97 | 53 |
| H14C | 360.26 | 3425.52 | 4571.21 | 53 |
| H15A | 1360.68 | 6170.7 | 7734.22 | 45 |
| H15B | 1487.57 | 7315.48 | 7308.11 | 45 |
| H15C | 2991.85 | 6937.42 | 8065.72 | 45 |
| H4 | 7929.01 | 4624.11 | 8059.71 | 42 |

## SI3.5.6 X-Ray Crystallographic Data for Diol 188



A colorless block $0.30 \times 0.24 \times 0.10 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $100 \%$ complete to $28.4^{\circ}$ in $\theta$. A total of 44058 reflections were collected covering the indices, $-11<=h<=11,-12<=k<=11,-23<=l<=23.3442$ reflections were found to be symmetry independent, with an $R_{\text {int }}$ of 0.0421 . Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $\mathrm{P} 2_{1} 2_{1} 2_{1}$ (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined from the diffraction data.

Table SI3.5.6.1. Crystal data and structure refinement for $\mathbf{1 8 8}$.

| Identification code | $\mathbf{1 8 8}$ |
| :--- | :--- |
| Empirical formula | $\mathrm{C}_{15} \mathrm{H}_{20} \mathrm{O}_{6}$ |
| Formula weight | 296.31 |
| Temperature $/ \mathrm{K}$ | $100(2)$ |
| Crystal system | orthorhombic |
| Space group | $\mathrm{P}_{1} 2_{1} 2_{1}$ |
| a $(\AA)$ | $8.8553(9)$ |
| $\mathrm{b}(\AA)$ | $8.9979(9)$ |
| $\mathrm{c}(\AA \AA)$ | $17.3614(18)$ |
| $\alpha\left(^{\circ}\right)$ | 90 |
| $\beta\left(^{\circ}\right)$ | 90 |
| $\gamma\left(^{\circ}\right)$ | 90 |
| Volume $\left(\AA^{3}\right)$ | $1383.3(2)$ |
| Z | 4 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.423 |
| $\mu\left(\mathrm{~mm}^{-1}\right)$ | 0.110 |
| $\mathrm{~F}(000)$ | 632.0 |
| Crystal size $\left(\mathrm{mm}{ }^{3}\right)$ | $0.300 \times 0.240 \times 0.100$ |
| Radiation | $\mathrm{MoK} \alpha(\lambda=0.71073)$ |
| $2 \Theta$ range for data collection $\left(^{\circ}\right)$ | 4.692 to 56.71 |
| Index ranges | $-11 \leq \mathrm{h} \leq 11,-12 \leq \mathrm{k} \leq 11,-23 \leq 1 \leq 23$ |
| Reflections collected | 44058 |
| Independent reflections | $3442\left[\mathrm{R}_{\text {int }}=0.0421, \mathrm{R}_{\text {sigma }}=0.0181\right]$ |
| Data/restraints $/$ parameters | $3442 / 0 / 270$ |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.046 |
| Final R indexes $[\mathrm{I}>=2 \sigma(\mathrm{I})]$ | $\mathrm{R}_{1}=0.0306, \mathrm{wR} \mathrm{R}_{2}=0.0812$ |
| Final R indexes [all data $]$ | $\mathrm{R}_{1}=0.0319, \mathrm{wR}{ }_{2}=0.0822$ |
| Largest diff. peak $/$ hole $\left(\mathrm{e} \AA^{-3}\right)$ | $0.30 /-0.18$ |
| Flack parameter | $-0.2(2)$ |
|  |  |

Table SI3.5.6.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 188. $U_{\text {eq }}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| C1 | $3257.4(19)$ | $8060.3(18)$ | $3784.8(9)$ | $16.3(3)$ |
| C2 | $2906(2)$ | $7196.9(18)$ | $3072.8(10)$ | $15.0(3)$ |
| C3 | $2467.1(18)$ | $5630.6(17)$ | $3343.9(9)$ | $12.7(3)$ |
| C4 | $2974.5(18)$ | $5614.5(17)$ | $4217.0(9)$ | $12.0(3)$ |
| C5 | $1573(2)$ | $5213.2(18)$ | $4679.4(9)$ | $15.7(3)$ |
| C6 | $263(2)$ | $5803(2)$ | $4197.2(10)$ | $18.4(3)$ |
| C7 | $713.6(18)$ | $5379.2(19)$ | $3375.7(10)$ | $15.9(3)$ |
| C8 | $-202(2)$ | $6114(2)$ | $2740.4(12)$ | $25.6(4)$ |
| C9 | $4403.3(18)$ | $4720.2(17)$ | $4402.6(9)$ | $12.8(3)$ |
| C10 | $4702(2)$ | $4654.5(19)$ | $5273.9(9)$ | $16.9(3)$ |
| C11 | $5812.2(19)$ | $5396.3(19)$ | $4002.0(10)$ | $16.0(3)$ |
| C12 | $6016.0(18)$ | $2861.9(18)$ | $3834.0(9)$ | $14.6(3)$ |
| C13 | $4357.5(18)$ | $3123.1(17)$ | $4061.8(9)$ | $12.8(3)$ |
| C14 | $3324.1(18)$ | $2975.9(17)$ | $3339.9(9)$ | $12.9(3)$ |
| C15 | $3235.8(19)$ | $4402.4(17)$ | $2872.8(9)$ | $13.6(3)$ |
| O1 | $3489.4(16)$ | $9385.4(13)$ | $3835.5(8)$ | $23.4(3)$ |
| O2 | $3330.7(15)$ | $7183.5(12)$ | $4404.3(7)$ | $15.6(2)$ |
| O3 | $6753.1(14)$ | $4164.0(13)$ | $3755.2(7)$ | $19.0(3)$ |
| O4 | $6616.9(15)$ | $1689.9(14)$ | $3730.3(7)$ | $18.9(3)$ |
| O5 | $3914.0(15)$ | $2087.0(13)$ | $4629.9(7)$ | $16.2(2)$ |
| O6 | $3815.8(14)$ | $1823.6(13)$ | $2836.5(7)$ | $15.9(2)$ |

Table SI3.5.6.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 188. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} U_{11}+2 h k a^{*} b^{*} U_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{\mathbf{1 3}}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | $16.3(7)$ | $13.1(7)$ | $19.5(7)$ | $0.8(6)$ | $1.3(6)$ | $0.7(6)$ |
| C2 | $19.7(8)$ | $10.4(7)$ | $15.0(7)$ | $1.0(6)$ | $0.2(6)$ | $1.2(6)$ |
| C3 | $15.2(7)$ | $9.8(6)$ | $13.1(7)$ | $0.6(5)$ | $-0.8(6)$ | $0.3(6)$ |
| C4 | $15.6(7)$ | $7.7(6)$ | $12.8(7)$ | $-0.6(5)$ | $0.2(5)$ | $-1.6(5)$ |
| C5 | $16.0(7)$ | $14.8(7)$ | $16.3(7)$ | $1.0(6)$ | $2.8(6)$ | $0.0(6)$ |
| C6 | $15.2(7)$ | $17.2(8)$ | $22.7(9)$ | $0.5(7)$ | $2.2(6)$ | $2.4(6)$ |
| C7 | $12.2(7)$ | $15.9(7)$ | $19.6(7)$ | $0.7(6)$ | $-1.1(6)$ | $1.4(6)$ |
| C8 | $18.5(9)$ | $34.2(11)$ | $24.0(9)$ | $4.7(8)$ | $-4.4(7)$ | $5.3(8)$ |
| C9 | $12.9(7)$ | $11.1(6)$ | $14.3(7)$ | $0.7(6)$ | $-1.5(6)$ | $-0.8(6)$ |
| C10 | $20.9(8)$ | $16.1(7)$ | $13.6(7)$ | $0.6(6)$ | $-3.8(6)$ | $-2.1(6)$ |
| C11 | $14.1(7)$ | $13.1(7)$ | $20.9(8)$ | $1.0(6)$ | $-0.3(6)$ | $-1.1(6)$ |
| C12 | $15.1(7)$ | $17.2(7)$ | $11.3(6)$ | $1.8(6)$ | $-2.3(6)$ | $0.8(6)$ |
| C13 | $13.0(7)$ | $10.9(6)$ | $14.5(7)$ | $-0.3(6)$ | $0.6(6)$ | $-0.4(6)$ |
| C14 | $13.2(7)$ | $10.6(6)$ | $15.0(7)$ | $-1.2(6)$ | $0.9(6)$ | $-0.1(6)$ |
| C15 | $15.9(7)$ | $11.9(7)$ | $13.0(7)$ | $0.6(5)$ | $0.1(6)$ | $1.1(6)$ |
| O1 | $33.7(7)$ | $9.8(5)$ | $26.8(6)$ | $-0.6(5)$ | $1.0(6)$ | $-3.0(5)$ |
| O2 | $20.9(6)$ | $9.8(5)$ | $16.2(5)$ | $-1.1(4)$ | $-0.8(5)$ | $-1.1(5)$ |
| O3 | $13.1(5)$ | $18.0(6)$ | $25.8(6)$ | $2.2(5)$ | $2.0(5)$ | $-0.2(5)$ |
| O4 | $19.0(6)$ | $20.2(6)$ | $17.3(5)$ | $0.4(5)$ | $-1.4(5)$ | $6.2(5)$ |
| O5 | $21.9(6)$ | $10.6(5)$ | $16.1(5)$ | $2.3(4)$ | $1.2(5)$ | $-0.1(5)$ |
| O6 | $19.3(6)$ | $11.0(5)$ | $17.4(5)$ | $-3.1(5)$ | $-0.3(5)$ | $2.1(4)$ |

Table SI3.5.6.4. Bond Lengths for $\mathbf{1 8 8}$.

| Atom | Atom | Length $(\mathbf{\AA})$ | Atom | Atom | Length $(\AA)$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | O1 | $1.213(2)$ | C7 | C8 | $1.521(2)$ |
| C1 | O2 | $1.335(2)$ | C9 | C10 | $1.537(2)$ |
| C1 | C2 | $1.493(2)$ | C9 | C11 | $1.553(2)$ |
| C2 | C3 | $1.536(2)$ | C9 | C13 | $1.555(2)$ |
| C3 | C15 | $1.534(2)$ | C11 | O3 | $1.452(2)$ |
| C3 | C7 | $1.570(2)$ | C12 | O4 | $1.195(2)$ |
| C3 | C4 | $1.581(2)$ | C12 | O3 | $1.348(2)$ |
| C4 | O2 | $1.4827(18)$ | C12 | C13 | $1.539(2)$ |
| C4 | C5 | $1.521(2)$ | C13 | O5 | $1.4128(19)$ |
| C4 | C9 | $1.534(2)$ | C13 | C14 | $1.558(2)$ |
| C5 | C6 | $1.526(2)$ | C14 | O6 | $1.4242(19)$ |
| C6 | C7 | $1.529(2)$ | C14 | C15 | $1.520(2)$ |

Table SI3.5.6.5. Bond Angles for 188.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | C1 | O2 | 120.93(16) | C4 | C9 | C11 | 111.30(13) |
| O1 | C1 | C2 | 127.37(16) | C10 | C9 | C11 | 108.51(14) |
| O2 | C1 | C2 | 111.69(14) | C4 | C9 | C13 | 112.55(13) |
| C1 | C2 | C3 | 106.06(13) | C10 | C9 | C13 | 110.09(13) |
| C15 | C3 | C2 | 112.66(13) | C11 | C9 | C13 | 102.28(13) |
| C15 | C3 | C7 | 110.72(14) | O3 | C11 | C9 | 107.10(13) |
| C2 | C3 | C7 | 113.17(13) | O4 | C12 | O3 | 122.42(15) |
| C15 | C3 | C4 | 112.23(13) | O4 | C12 | C13 | 126.76(15) |
| C2 | C3 | C4 | 103.31(12) | O3 | C12 | C13 | 110.82(13) |
| C7 | C3 | C4 | 104.24(13) | O5 | C13 | C12 | 110.11(13) |
| O2 | C4 | C5 | 106.49(13) | O5 | C13 | C9 | 110.58(12) |
| O2 | C4 | C9 | 106.14(12) | C12 | C13 | C9 | 102.36(12) |
| C5 | C4 | C9 | 115.95(13) | O5 | C13 | C14 | 110.02(13) |
| O2 | C4 | C3 | 105.19(12) | C12 | C13 | C14 | 109.93(12) |
| C5 | C4 | C3 | 106.04(13) | C9 | C13 | C14 | 113.59(12) |
| C9 | C4 | C3 | 116.15(13) | O6 | C14 | C15 | 107.64(12) |
| C4 | C5 | C6 | 104.36(13) | O6 | C14 | C13 | 112.09(13) |
| C5 | C6 | C7 | 103.08(14) | C15 | C14 | C13 | 112.81(13) |
| C8 | C7 | C6 | 115.38(15) | C14 | C15 | C3 | 110.29(12) |
| C8 | C7 | C3 | 116.05(15) | C1 | O2 | C4 | 112.06(12) |
| C6 | C7 | C3 | 104.77(14) | C12 | O3 | C11 | 110.86(13) |
| C4 | C9 | C10 | 111.66(14) |  |  |  |  |

Table SI3.5.6.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 188.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H2A | $3820(30)$ | $7200(30)$ | $2793(14)$ | $27(6)$ |
| H2B | $2140(30)$ | $7760(30)$ | $2768(13)$ | $25(6)$ |
| H5 | $3970(30)$ | $1220(30)$ | $4435(13)$ | $17(5)$ |
| H5A | $1500(30)$ | $4160(30)$ | $4706(13)$ | $25(6)$ |
| H5B | $1590(30)$ | $5650(30)$ | $5220(14)$ | $26(6)$ |
| H6 | $3730(40)$ | $1000(30)$ | $3088(17)$ | $41(8)$ |
| H6A | $-720(30)$ | $5400(30)$ | $4347(14)$ | $25(6)$ |
| H6B | $230(30)$ | $6900(30)$ | $4234(13)$ | $27(6)$ |
| H7 | $620(30)$ | $4290(30)$ | $3328(12)$ | $17(5)$ |
| H8A | $230(30)$ | $5910(30)$ | $2215(16)$ | $37(7)$ |
| H8B | $-230(30)$ | $7240(30)$ | $2796(14)$ | $28(6)$ |
| H8C | $-1270(30)$ | $5800(30)$ | $2771(15)$ | $31(6)$ |
| H10A | $3940(30)$ | $4170(30)$ | $5534(14)$ | $20(6)$ |
| H10B | $5700(30)$ | $4160(30)$ | $5404(15)$ | $33(7)$ |
| H10C | $4820(30)$ | $5680(30)$ | $5456(13)$ | $20(5)$ |
| H11A | $5600(30)$ | $6000(20)$ | $3545(12)$ | $15(5)$ |
| H11B | $6440(30)$ | $5960(30)$ | $4346(13)$ | $21(6)$ |
| H14 | $2350(30)$ | $2710(20)$ | $3546(11)$ | $13(5)$ |
| H15A | $2630(20)$ | $4210(20)$ | $2411(12)$ | $13(5)$ |
| H15B | $4220(30)$ | $4710(30)$ | $2720(12)$ | $18(5)$ |

## SI3.5.7 X-Ray Crystallographic Data for Diol 282



A colorless prism $0.24 \times 0.10 \times 0.05 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $100 \%$ complete to $28.4^{\circ}$ in $\theta$. A total of 36087 reflections were collected covering the indices, $-12<=h<=12,-9<=k<=9,-15<=l<=15.3542$ reflections were found to be symmetry independent, with an $\mathrm{R}_{\text {int }}$ of 0.0363 . Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $\mathrm{P} 2_{1}$ (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined from the diffraction data.

Table SI3.5.7.1. Crystal data and structure refinement for 282.

| Identification code | 282 |
| :---: | :---: |
| Empirical formula | $\mathrm{C}_{15} \mathrm{H}_{20} \mathrm{O}_{6}$ |
| Formula weight | 296.31 |
| Temperature (K) | 100(2) |
| Crystal system | monoclinic |
| Space group | P2, |
| a ( $\AA$ ) | 9.1952(3) |
| b ( $\AA$ ) | 7.0323(2) |
| $\mathrm{c}(\AA)$ | 11.6867(4) |
| $\alpha\left({ }^{\circ}\right.$ ) | 90 |
| $\beta\left({ }^{\circ}\right)$ | 110.960(2) |
| $\gamma\left({ }^{\circ}\right.$ ) | 90 |
| Volume ( $\AA^{3}$ ) | 705.70(4) |
| Z | 2 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.394 |
| $\mu\left(\mathrm{mm}^{-1}\right)$ | 0.108 |
| $\mathrm{F}(000)$ | 316.0 |
| Crystal size ( $\mathrm{mm}^{3}$ ) | $0.240 \times 0.100 \times 0.050$ |
| Radiation | $\operatorname{MoK} \alpha(\lambda=0.71073)$ |
| $2 \Theta$ range for data collection $\left({ }^{\circ}\right.$ ) | 3.732 to 56.748 |
| Index ranges | $-12 \leq \mathrm{h} \leq 12,-9 \leq \mathrm{k} \leq 9,-15 \leq 1 \leq 15$ |
| Reflections collected | 36087 |
| Independent reflections | $3542\left[\mathrm{R}_{\mathrm{int}}=0.0363, \mathrm{R}_{\text {cigma }}=0.0215\right]$ |
| Data/restraints/parameters | 3542/1/270 |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.060 |
| Final R indexes [I>=2 $\sigma(\mathrm{I})$ ] | $\mathrm{R}_{1}=0.0335, \mathrm{wR}_{2}=0.0889$ |
| Final R indexes [all data] | $\mathrm{R}_{1}=0.0355, \mathrm{wR}_{2}=0.0899$ |
| Largest diff. peak/hole (e $\AA^{-3}$ ) | 0.30/-0.20 |
| Flack parameter | 0.4(2) |

Table SI3.5.7.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 282. $U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| C1 | $8980(2)$ | $6688(3)$ | $1298.4(18)$ | $18.8(4)$ |
| C2 | $9992(2)$ | $5062(3)$ | $1094.8(18)$ | $20.2(4)$ |
| C3 | $8966(2)$ | $2676(3)$ | $2177(2)$ | $20.4(4)$ |
| C4 | $7602(2)$ | $4009(3)$ | $1973.8(17)$ | $16.3(4)$ |
| C5 | $6443(2)$ | $3757(3)$ | $652.1(18)$ | $21.2(4)$ |
| C6 | $8261(2)$ | $6058(3)$ | $2226.2(17)$ | $16.4(4)$ |
| C7 | $6926(2)$ | $7231(3)$ | $2339.8(17)$ | $16.4(4)$ |
| C8 | $6267(2)$ | $5939(3)$ | $3102.9(17)$ | $16.4(4)$ |
| C9 | $4472(2)$ | $5832(3)$ | $2686.9(18)$ | $18.8(4)$ |
| C10 | $3684(3)$ | $7398(4)$ | $3157(2)$ | $26.4(4)$ |
| C11 | $4189(2)$ | $3802(3)$ | $3048(2)$ | $22.6(4)$ |
| C12 | $5297(2)$ | $2599(3)$ | $2627.5(19)$ | $20.0(4)$ |
| C13 | $6755(2)$ | $3841(3)$ | $2909.8(16)$ | $15.9(4)$ |
| C14 | $8173(2)$ | $4596(3)$ | $4943.9(17)$ | $18.2(4)$ |
| C15 | $7083(2)$ | $6250(3)$ | $4489.0(18)$ | $18.9(4)$ |
| O1 | $7848.7(17)$ | $7252(3)$ | $169.5(13)$ | $23.2(3)$ |
| O2 | $10855.7(18)$ | $5362(2)$ | $537.8(14)$ | $26.0(3)$ |
| O3 | $9951.5(17)$ | $3307(2)$ | $1504.2(14)$ | $23.6(3)$ |
| O4 | $9521.0(16)$ | $5939(2)$ | $3384.0(13)$ | $18.5(3)$ |
| O5 | $7858.0(16)$ | $3213(2)$ | $4098.1(12)$ | $17.7(3)$ |
| O6 | $9156.8(16)$ | $4409(2)$ | $5951.6(13)$ | $22.3(3)$ |

Table SI3.5.7.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 282. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} \mathrm{U}_{11}+2 h k a^{*} b^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | $15.4(8)$ | $21.6(10)$ | $19.2(9)$ | $3.6(7)$ | $5.9(7)$ | $1.5(7)$ |
| C2 | $17.6(8)$ | $24.0(10)$ | $16.6(8)$ | $-1.7(8)$ | $3.3(7)$ | $1.9(7)$ |
| C3 | $21.5(10)$ | $17.5(10)$ | $23.2(10)$ | $1.2(7)$ | $9.2(8)$ | $1.9(8)$ |
| C4 | $16.2(8)$ | $15.4(9)$ | $16.5(8)$ | $-0.1(7)$ | $4.6(7)$ | $0.3(7)$ |
| C5 | $22.1(10)$ | $21.3(10)$ | $16.7(9)$ | $-2.1(8)$ | $2.7(7)$ | $-3.0(8)$ |
| C6 | $14.6(8)$ | $17.6(9)$ | $15.7(8)$ | $0.0(7)$ | $3.6(7)$ | $0.2(7)$ |
| C7 | $14.7(8)$ | $14.3(9)$ | $19.0(9)$ | $1.2(7)$ | $4.6(7)$ | $0.6(7)$ |
| C8 | $14.5(8)$ | $17.0(9)$ | $16.2(8)$ | $-0.5(7)$ | $3.6(7)$ | $0.2(7)$ |
| C9 | $15.0(8)$ | $20.6(10)$ | $19.8(9)$ | $0.9(8)$ | $4.9(7)$ | $0.5(7)$ |
| C10 | $19.0(10)$ | $27.4(11)$ | $33.1(11)$ | $-3.4(9)$ | $9.8(9)$ | $2.3(9)$ |
| C11 | $18.2(9)$ | $24.9(10)$ | $23.4(9)$ | $1.5(8)$ | $5.9(8)$ | $-3.8(8)$ |
| C12 | $17.8(9)$ | $17.1(10)$ | $22.9(9)$ | $0.8(8)$ | $4.3(7)$ | $-3.0(7)$ |
| C13 | $15.2(8)$ | $15.4(8)$ | $14.3(8)$ | $0.6(7)$ | $1.9(7)$ | $-0.5(7)$ |
| C14 | $16.3(8)$ | $21.5(10)$ | $16.6(9)$ | $0.2(7)$ | $5.7(7)$ | $-1.2(8)$ |
| C15 | $19.5(9)$ | $18.8(10)$ | $16.5(9)$ | $-1.3(7)$ | $4.2(7)$ | $0.2(8)$ |
| O1 | $17.2(7)$ | $30.1(8)$ | $20.6(7)$ | $9.1(6)$ | $4.5(5)$ | $1.6(6)$ |
| O2 | $24.0(7)$ | $31.6(9)$ | $25.1(7)$ | $0.0(6)$ | $12.1(6)$ | $4.2(6)$ |
| O3 | $23.6(7)$ | $22.1(8)$ | $27.4(8)$ | $0.9(6)$ | $11.9(6)$ | $5.4(6)$ |
| O4 | $16.9(6)$ | $16.7(7)$ | $18.0(7)$ | $-0.1(6)$ | $1.5(5)$ | $-1.2(6)$ |
| O5 | $18.8(6)$ | $16.0(7)$ | $15.5(6)$ | $1.7(5)$ | $2.4(5)$ | $1.3(5)$ |
| O6 | $22.9(7)$ | $22.2(7)$ | $16.6(7)$ | $1.4(6)$ | $0.6(5)$ | $0.1(6)$ |

Table SI3.5.7.4. Bond Lengths for 282.

| Atom | Atom | Length ( $\mathbf{\AA})$ | Atom | Atom | Length ( $\AA \mathbf{\AA})$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | O1 | $1.414(2)$ | C7 | C8 | $1.541(3)$ |
| C1 | C6 | $1.524(3)$ | C8 | C15 | $1.538(3)$ |
| C1 | C2 | $1.545(3)$ | C8 | C9 | $1.546(3)$ |
| C2 | O2 | $1.212(3)$ | C8 | C13 | $1.582(3)$ |
| C2 | O3 | $1.329(3)$ | C9 | C10 | $1.524(3)$ |
| C3 | O3 | $1.465(2)$ | C9 | C11 | $1.537(3)$ |
| C3 | C4 | $1.515(3)$ | C11 | C12 | $1.534(3)$ |
| C4 | C5 | $1.541(3)$ | C12 | C13 | $1.534(3)$ |
| C4 | C6 | $1.550(3)$ | C13 | O5 | $1.465(2)$ |
| C4 | C13 | $1.557(3)$ | C14 | O6 | $1.208(2)$ |
| C6 | O4 | $1.435(2)$ | C14 | O5 | $1.343(2)$ |
| C6 | C7 | $1.523(3)$ | C14 | C15 | $1.503(3)$ |

Table SI3.5.7.5. Bond Angles for 282.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | C1 | C6 | $112.55(16)$ | C7 | C8 | C9 | $116.32(16)$ |
| O1 | C1 | C2 | $110.27(16)$ | C15 | C8 | C13 | $103.08(15)$ |
| C6 | C1 | C2 | $109.47(17)$ | C7 | C8 | C13 | $106.06(14)$ |
| O2 | C2 | O3 | $117.58(19)$ | C9 | C8 | C13 | $103.61(15)$ |
| O2 | C2 | C1 | $120.04(19)$ | C10 | C9 | C11 | $115.03(17)$ |
| O3 | C2 | C1 | $122.38(18)$ | C10 | C9 | C8 | $116.28(17)$ |
| O3 | C3 | C4 | $111.38(16)$ | C11 | C9 | C8 | $103.03(16)$ |
| C3 | C4 | C5 | $108.84(17)$ | C12 | C11 | C9 | $103.14(16)$ |
| C3 | C4 | C6 | $107.44(16)$ | C11 | C12 | C13 | $104.28(17)$ |
| C5 | C4 | C6 | $112.36(16)$ | O5 | C13 | C12 | $106.72(15)$ |
| C3 | C4 | C13 | $115.90(16)$ | O5 | C13 | C4 | $109.77(14)$ |
| C5 | C4 | C13 | $110.82(16)$ | C12 | C13 | C4 | $120.66(16)$ |
| C6 | C4 | C13 | $101.32(15)$ | O5 | C13 | C8 | $106.37(14)$ |
| O4 | C6 | C7 | $110.70(15)$ | C12 | C13 | C8 | $106.91(15)$ |
| O4 | C6 | C1 | $106.14(15)$ | C4 | C13 | C8 | $105.57(15)$ |
| C7 | C6 | C1 | $118.23(17)$ | O6 | C14 | O5 | $121.84(19)$ |
| O4 | C6 | C4 | $104.72(15)$ | O6 | C14 | C15 | $126.95(19)$ |
| C7 | C6 | C4 | $104.35(15)$ | O5 | C14 | C15 | $111.06(16)$ |
| C1 | C6 | C4 | $111.99(16)$ | C14 | C15 | C8 | $105.97(16)$ |
| C6 | C7 | C8 | $103.13(15)$ | C2 | O3 | C3 | $125.25(16)$ |
| C15 | C8 | C7 | $112.38(16)$ | C14 | O5 | C13 | $111.91(15)$ |
| C15 | C8 | C9 | $113.71(16)$ |  |  |  |  |

Table SI3.5.7.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters ( $\AA^{2} \times 10^{3}$ ) for 282.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H1 | $8240(30)$ | $8140(50)$ | $-170(30)$ | $30(7)$ |
| H1A | $9750(30)$ | $7820(40)$ | $1700(30)$ | $26(7)$ |
| H3A | $8580(30)$ | $1430(40)$ | $1880(20)$ | $21(6)$ |
| H3B | $9660(30)$ | $2580(40)$ | $3030(30)$ | $24(7)$ |
| H4 | $9820(40)$ | $6900(60)$ | $3610(30)$ | $40(9)$ |
| H5A | $6930(30)$ | $4010(40)$ | $10(30)$ | $28(7)$ |
| H5B | $6090(30)$ | $2480(40)$ | $560(20)$ | $16(6)$ |
| H5C | $5570(30)$ | $4680(40)$ | $470(20)$ | $20(6)$ |
| H7A | $6190(30)$ | $7470(40)$ | $1560(30)$ | $25(6)$ |
| H7B | $7330(30)$ | $8350(40)$ | $2720(20)$ | $16(6)$ |
| H9 | $4070(30)$ | $5840(40)$ | $1790(20)$ | $13(5)$ |
| H10A | $3970(40)$ | $8550(60)$ | $2910(30)$ | $41(9)$ |
| H10B | $2540(30)$ | $7200(40)$ | $2770(20)$ | $20(6)$ |
| H10C | $4050(30)$ | $7150(40)$ | $4050(20)$ | $22(6)$ |
| H11A | $3070(30)$ | $3560(40)$ | $2660(20)$ | $28(7)$ |
| H11B | $4520(30)$ | $3760(40)$ | $3970(30)$ | $27(7)$ |
| H12A | $4830(30)$ | $2310(40)$ | $1730(30)$ | $26(6)$ |
| H12B | $5540(30)$ | $1390(50)$ | $2990(30)$ | $32(8)$ |
| H15A | $7660(30)$ | $7350(40)$ | $4730(20)$ | $16(6)$ |
| H15B | $6350(30)$ | $6170(40)$ | $4900(20)$ | $21(6)$ |

## SI3.5.8 X-Ray Crystallographic Data for (-)-Majucin (5)



A colorless prism $0.26 \times 0.17 \times 0.10 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at $100(2) \mathrm{K}$ using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $100 \%$ complete to $28.4^{\circ}$ in $\theta$. A total of 24403 reflections were collected covering the indices, $-9<=h<=9,-16<=k<=15,-21<=l<=21.3431$ reflections were found to be symmetry independent, with an $\mathrm{R}_{\text {int }}$ of 0.0367 . Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $\mathrm{P} 2_{1} 2_{1} 2_{1}$ (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined from the diffraction data.

Table SI3.5.8.1. Crystal data and structure refinement for 5.

| Identification code | 5 |
| :---: | :---: |
| Empirical formula | $\mathrm{C}_{15} \mathrm{H}_{20} \mathrm{O}_{8}$ |
| Formula weight | 328.31 |
| Temperature (K) | 100(2) |
| Crystal system | orthorhombic |
| Space group | P2, 2, 2 , |
| a (A) | 6.9941(3) |
| b ( $\AA$ ) | 12.1369(6) |
| $\mathrm{c}(\AA)$ | 16.1722(8) |
| $\alpha{ }^{\circ}{ }^{\circ}$ | 90 |
| $\beta{ }^{\circ}{ }^{\circ}$ | 90 |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume ( $\AA^{3}$ ) | 1372.80(11) |
| Z | 4 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.588 |
| $\mu\left(\mathrm{mm}^{-1}\right)$ | 0.130 |
| $\mathrm{F}(000)$ | 696.0 |
| Crystal size ( $\mathrm{mm}^{3}$ ) | $0.260 \times 0.170 \times 0.100$ |
| Radiation | $\operatorname{MoK} \alpha(\lambda=0.71073)$ |
| $2 \Theta$ range for data collection ${ }^{\circ}$ ) | 4.196 to 56.704 |
| Index ranges | $\begin{aligned} & -9 \leq \mathrm{h} \leq 9,-16 \leq \mathrm{k} \leq 15,-21 \leq 1 \leq \\ & 21 \end{aligned}$ |
| Reflections collected | 24403 |
| Independent reflections | $\begin{aligned} & 3431\left[\mathrm{R}_{\text {int }}=0.0367, \mathrm{R}_{\text {sigma }}=\right. \\ & 0.0214] \end{aligned}$ |
| Data/restraints/parameters | 3431/0/226 |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.053 |
| Final R indexes [I>=2 ${ }^{\text {(I) }}$ ] | $\mathrm{R}_{1}=0.0300, \mathrm{wR}_{2}=0.0755$ |
| Final R indexes [all data] | $\mathrm{R}_{1}=0.0310, \mathrm{wR}_{2}=0.0761$ |
| Largest diff. peak/hole (e $\AA^{-3}$ ) | 0.31/-0.22 |
| Flack parameter | 0.1(3) |

Table SI3.5.8.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 5 . $U_{\text {eq }}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| C1 | $6376(3)$ | $6696.6(14)$ | $6026.9(11)$ | $11.7(3)$ |
| C2 | $6079(2)$ | $5694.8(14)$ | $6590.6(10)$ | $9.9(3)$ |
| C3 | $7658(2)$ | $5383.4(13)$ | $7211.5(10)$ | $10.2(3)$ |
| C4 | $7814(3)$ | $6218.8(14)$ | $7933.2(11)$ | $13.0(3)$ |
| C5 | $7238(2)$ | $4216.2(14)$ | $7567.2(10)$ | $10.7(3)$ |
| C6 | $9254(3)$ | $3835.7(15)$ | $7808.7(11)$ | $12.8(3)$ |
| C7 | $9688(3)$ | $5249.1(15)$ | $6865.2(11)$ | $12.8(3)$ |
| C8 | $6425(3)$ | $3353.1(14)$ | $6953.1(11)$ | $11.7(3)$ |
| C9 | $8349(3)$ | $3416.0(15)$ | $5694.9(12)$ | $13.9(3)$ |
| C10 | $6986(3)$ | $4300.7(14)$ | $5352.7(11)$ | $12.2(3)$ |
| C11 | $5474(2)$ | $4778.7(14)$ | $5954.1(10)$ | $10.3(3)$ |
| C12 | $4776(2)$ | $3772.0(14)$ | $6434.1(11)$ | $11.8(3)$ |
| C13 | $3923(3)$ | $5424.2(14)$ | $5460.8(11)$ | $12.6(3)$ |
| C14 | $3312(3)$ | $4945.1(16)$ | $4631.7(12)$ | $16.5(4)$ |
| C15 | $4691(3)$ | $6624.5(15)$ | $5417.3(11)$ | $14.3(3)$ |
| O1 | $6388(2)$ | $7728.1(10)$ | $6456.0(9)$ | $14.2(3)$ |
| O2 | $4390.5(18)$ | $5953.2(11)$ | $7067.9(8)$ | $12.2(3)$ |
| O3 | $5998.6(19)$ | $4317.7(11)$ | $8249.4(8)$ | $13.1(3)$ |
| O4 | $9676.4(19)$ | $3118.0(11)$ | $8292.9(8)$ | $15.9(3)$ |
| O5 | $10580.1(19)$ | $4417.5(11)$ | $7400.3(8)$ | $15.1(3)$ |
| O6 | $7991.3(19)$ | $2946.3(10)$ | $6434.0(8)$ | $14.0(3)$ |
| O7 | $9706(2)$ | $3106.2(12)$ | $5302.9(9)$ | $19.5(3)$ |
| O8 | $8061(2)$ | $5132.2(11)$ | $4952.0(9)$ | $16.7(3)$ |

Table SI3.5.8.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 4. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} U_{11}+2 h k a^{*} b^{*} U_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | $13.2(7)$ | $8.4(7)$ | $13.6(8)$ | $0.7(6)$ | $-0.4(6)$ | $0.3(6)$ |
| C2 | $9.4(7)$ | $9.8(7)$ | $10.6(7)$ | $0.2(6)$ | $1.4(6)$ | $1.3(6)$ |
| C3 | $10.8(7)$ | $9.0(7)$ | $10.8(7)$ | $1.3(6)$ | $0.6(6)$ | $0.8(6)$ |
| C4 | $15.2(8)$ | $11.0(8)$ | $12.7(8)$ | $-1.1(6)$ | $-1.0(6)$ | $-0.6(7)$ |
| C5 | $12.2(7)$ | $9.9(7)$ | $9.9(7)$ | $0.6(6)$ | $-0.2(6)$ | $0.3(6)$ |
| C6 | $14.3(8)$ | $12.1(8)$ | $11.8(8)$ | $-2.9(6)$ | $-1.2(6)$ | $1.4(6)$ |
| C7 | $10.6(7)$ | $13.7(8)$ | $14.2(8)$ | $2.6(7)$ | $-0.2(6)$ | $1.1(6)$ |
| C8 | $14.0(8)$ | $10.7(7)$ | $10.4(8)$ | $-0.7(6)$ | $2.7(6)$ | $0.6(6)$ |
| C9 | $15.7(8)$ | $11.7(8)$ | $14.2(8)$ | $-2.7(6)$ | $0.0(6)$ | $-1.0(6)$ |
| C10 | $14.0(8)$ | $11.8(8)$ | $10.9(8)$ | $-0.3(6)$ | $1.3(6)$ | $-0.9(6)$ |
| C11 | $11.4(7)$ | $9.4(7)$ | $10.0(7)$ | $0.0(6)$ | $0.5(6)$ | $0.0(6)$ |
| C12 | $12.8(7)$ | $10.8(7)$ | $11.9(7)$ | $0.1(6)$ | $0.1(6)$ | $-1.5(6)$ |
| C13 | $11.4(8)$ | $13.2(8)$ | $13.1(8)$ | $1.3(7)$ | $-1.3(6)$ | $0.6(6)$ |
| C14 | $18.3(9)$ | $16.8(9)$ | $14.4(8)$ | $-0.6(7)$ | $-3.7(7)$ | $-1.4(7)$ |
| C15 | $16.8(8)$ | $12.8(8)$ | $13.3(8)$ | $1.7(6)$ | $-3.0(7)$ | $0.9(7)$ |
| O1 | $14.2(6)$ | $9.1(6)$ | $19.4(6)$ | $-1.3(5)$ | $0.2(5)$ | $-0.2(5)$ |
| O2 | $11.3(6)$ | $13.2(6)$ | $12.0(6)$ | $0.5(5)$ | $2.9(5)$ | $1.5(5)$ |
| O3 | $15.3(6)$ | $11.4(6)$ | $12.4(6)$ | $0.0(5)$ | $4.0(5)$ | $-1.1(5)$ |
| O4 | $17.7(6)$ | $13.1(6)$ | $17.1(6)$ | $0.3(5)$ | $-2.6(5)$ | $3.8(5)$ |
| O5 | $11.3(6)$ | $16.0(6)$ | $18.0(6)$ | $2.7(5)$ | $0.1(5)$ | $2.4(5)$ |
| O6 | $16.6(6)$ | $11.6(6)$ | $13.7(6)$ | $-0.4(5)$ | $1.8(5)$ | $3.1(5)$ |
| O7 | $19.1(6)$ | $18.5(7)$ | $20.8(7)$ | $-1.2(5)$ | $5.2(6)$ | $4.4(5)$ |
| O8 | $21.7(7)$ | $15.0(7)$ | $13.5(6)$ | $0.7(5)$ | $6.6(5)$ | $-2.3(5)$ |

Table SI3.5.8.4. Bond Lengths for 5.

| Atom | Atom | Length $(\AA)$ | Atom | Atom | Length $(\AA)$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | O1 | $1.431(2)$ | C6 | O5 | $1.340(2)$ |
| C1 | C2 | $1.534(2)$ | C7 | O5 | $1.469(2)$ |
| C1 | C15 | $1.539(2)$ | C8 | O6 | $1.466(2)$ |
| C2 | O2 | $1.446(2)$ | C8 | C12 | $1.514(2)$ |
| C2 | C3 | $1.539(2)$ | C9 | O7 | $1.202(2)$ |
| C2 | C11 | $1.573(2)$ | C 9 | O6 | $1.348(2)$ |
| C3 | C7 | $1.535(2)$ | C9 | C10 | $1.539(2)$ |
| C3 | C4 | $1.550(2)$ | C10 | O8 | $1.415(2)$ |
| C3 | C5 | $1.557(2)$ | C10 | C11 | $1.549(2)$ |
| C5 | O3 | $1.408(2)$ | C11 | C12 | $1.528(2)$ |
| C5 | C6 | $1.534(2)$ | C11 | C13 | $1.558(2)$ |
| C5 | C8 | $1.551(2)$ | C13 | C14 | $1.523(3)$ |
| C6 | O4 | $1.208(2)$ | C13 | C15 | $1.554(2)$ |

Table SI3.5.8.5. Bond Angles for 5.

| Atom | Atom | Atom | Angle ( $\mathbf{c}^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | C1 | C2 | $113.96(14)$ | O5 | C7 | C3 | $104.53(13)$ |
| O1 | C1 | C15 | $111.41(14)$ | O6 | C8 | C12 | $111.40(13)$ |
| C2 | C1 | C15 | $103.43(14)$ | O6 | C8 | C5 | $108.67(14)$ |
| O2 | C2 | C1 | $104.82(13)$ | C12 | C8 | C5 | $114.03(14)$ |
| O2 | C2 | C3 | $106.91(13)$ | O7 | C9 | O6 | $118.83(17)$ |
| C1 | C2 | C3 | $119.04(14)$ | O7 | C9 | C10 | $121.19(17)$ |
| O2 | C2 | C11 | $106.42(13)$ | O6 | C9 | C10 | $119.93(15)$ |
| C1 | C2 | C11 | $101.99(13)$ | O8 | C10 | C9 | $109.45(15)$ |
| C3 | C2 | C11 | $116.51(14)$ | O8 | C10 | C11 | $112.52(14)$ |
| C7 | C3 | C2 | $116.83(14)$ | C9 | C10 | C11 | $117.28(15)$ |
| C7 | C3 | C4 | $106.22(14)$ | C12 | C11 | C10 | $103.74(14)$ |
| C2 | C3 | C4 | $112.40(14)$ | C12 | C11 | C13 | $116.10(14)$ |
| C7 | C3 | C5 | $102.28(13)$ | C10 | C11 | C13 | $110.00(14)$ |
| C2 | C3 | C5 | $109.21(14)$ | C12 | C11 | C2 | $108.59(13)$ |
| C4 | C3 | C5 | $109.29(14)$ | C10 | C11 | C2 | $119.44(14)$ |
| O3 | C5 | C6 | $113.10(14)$ | C13 | C11 | C2 | $99.62(13)$ |
| O3 | C5 | C8 | $109.57(14)$ | C8 | C12 | C11 | $107.88(14)$ |
| C6 | C5 | C8 | $107.25(14)$ | C14 | C13 | C15 | $114.52(15)$ |
| O3 | C5 | C3 | $109.02(13)$ | C14 | C13 | C11 | $117.03(15)$ |
| C6 | C5 | C3 | $101.22(14)$ | C15 | C13 | C11 | $104.70(14)$ |
| C8 | C5 | C3 | $116.56(14)$ | C1 | C15 | C13 | $106.80(14)$ |
| O4 | C6 | O5 | $122.01(16)$ | C6 | O5 | C7 | $111.01(13)$ |
| O4 | C6 | C5 | $127.38(16)$ | C9 | O6 | C8 | $120.28(14)$ |
| O5 | C6 | C5 | $110.61(14)$ |  |  |  |  |

Table SI3.5.8.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 5 .

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H1A | 7604 | 6610 | 5717 | 14 |
| H4A | 8146 | 6947 | 7714 | 19 |
| H4B | 8808 | 5976 | 8319 | 19 |
| H4C | 6585 | 6262 | 8223 | 19 |
| H7A | 9651 | 4994 | 6284 | 15 |
| H7B | 10397 | 5954 | 6891 | 15 |
| H8A | 5942 | 2717 | 7286 | 14 |
| H10 | 6241 | 3928 | 4905 | 15 |
| H12A | 3687 | 3976 | 6794 | 14 |
| H12B | 4345 | 3192 | 6046 | 14 |
| H13 | 2754 | 5444 | 5817 | 15 |
| H14A | 4382 | 4985 | 4242 | 25 |
| H14B | 2229 | 5368 | 4414 | 25 |
| H14C | 2931 | 4174 | 4706 | 25 |
| H15A | 5124 | 6799 | 4849 | 17 |
| H15B | 3676 | 7153 | 5574 | 17 |
| H1 | $7520(50)$ | $7920(30)$ | $6539(18)$ | $38(8)$ |
| H2 | $4300(40)$ | $5510(20)$ | $7438(18)$ | $26(7)$ |
| H3 | $5410(40)$ | $3700(20)$ | $8342(17)$ | $28(7)$ |
| H8 | $8280(50)$ | $4970(30)$ | $4500(20)$ | $56(11)$ |

## SI3.6 ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR Spectra








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## Part II:

## Three-Step Synthesis of the Quassinoid Core Architecture

## Chapter 4

# An Introduction <br> to the <br> Quassinoids 

## \&

Development
of a
Three-Step Core Synthesis

### 4.1 History and Chemical Structures of the Quassinoids

In the 1700 's, a Surinamese freedman, Graman Quassi, gained fame as a healer. In particular, he was known for a bitter tea he brewed to treat intestinal parasites. The plant from which he derived this medicinal tea was named Quassia amara by renowned botanist Carl Linneaus in his honor. A century passed until the principal bitter component of this plant was isolated in 1835 by Winckler and named, "quassin." ${ }^{1}$ Even before the chemical structure of quassin was elucidated, many of its physical properties were catalogued, including its exceptionally bitter taste - allegedly 50 times more bitter than quinine - and presumed therapeutic value. An additional century passed, though, before Valenta and Carman independently solved the structure of quassin (292) with the assistance of newly available NMR techniques. ${ }^{2}$ Structural determinations of other quassinoids, the bitter principles of the Simaroubaceae family of plants, followed in short order and some trends became apparent (Figure 4.1). ${ }^{3}$

The prototypical quassinoid contains a 20 -carbon skeleton with three fused carbocyclic six-membered rings and a fourth $\delta$-lactone ring (Figure 4.1A). Naively, it might then be thought that quassinoids are diterpene lactones. However, attempts to trace out isoprene units on the skeleton lead to frustration, as quassinoids are better characterized as extensively degraded triterpenes (see Section 4.2, below, on the biosynthesis of these compounds). ${ }^{4}$ In further support of this notion, all quassinoids are highly oxidized and no parent "quassinane" terpene has been isolated (Figure 4.1B). The flagship member, quassin (292), displays a characteristic 1,2-oxygenation pattern on the A - and C-rings and a dense array of seven contiguous stereocenters. Bruceolide (293)


$\mathrm{R}=\mathrm{H}$, bruceolide (293)
$R=R_{1}$, bruceantin (294)
$R=R_{2}$, brucein A (295)
$R=R_{3}$, brucein $C(296)$

longilactone (297)


quassin (292)


eurycomalactone (298)


C20, tetracyclic
|||



Figure 4.1. (A) Quassinoid skeleton with rings and carbon positions labeled. (B) Chemical structures of select quassinoids. (C-F) Summary of different skeletal subtypes, including variants with different carbon counts.
and its esters (see 294-296) are even more oxidized and have an additional oxomethylene bridge over the C-ring. The final two natural products depicted, longilactone (297) and eurycomalactone (298), demonstrate how these rampant oxidations can lead to the further excision of carbon atoms. Overall, quassinoids are divided into subtypes based on precisely how many carbon atoms they have lost relative to their presumed parent triterpene (Figures 4.1C-F). C20 quassinoids (Figure 4.1 C ) abound and can be further subdivided based on the presence or absence of an oxomethylene bridge. The second major class, C19 quassinoids (Figure 4.1D), have most commonly lost a carbon from the D-ring lactone, though other oxidative rearrangements are possible. C18 (Figure 4.1E) and C25 (Figure 4.1F) quassinoids are less common and also less studied; they are included here for completeness but will not be discussed extensively.

### 4.2 Proposed Quassinoid Biosynthesis

After describing these ornate structures, it is natural to wonder about their biosynthetic origin. Unfortunately, studies of quassinoid biosynthesis have remained empirical owing to challenges associated with directly probing plant metabolism. Still, these empirical observations nevertheless
A


B Isolated from same plant:




Figure 4.2. (A) Proposed quassinoid biosynthesis from a triterpene precursor (B) Evidence for co-production of quassinoids and limonoids by the same plant (C) Reasonable interconversion between quassinoid and limonoid skeletons.
have led to a reasonable, but high-level, proposal (Figure 4.2A). ${ }^{5}$ Namely, 2,3-oxidosqualene (299) - the precursor for plant-derived triterpenes - is thought to undergo enzyme-mediated cyclization to apotirucallol (300). Extensive oxidations then begin the process of excising the ten or more carbons necessary to get to the majority of quassinoids. First, five carbons are excised, including one of the methyl groups attached to C 4 , leading 301, or a related structure. Further oxidations arrive at $\mathbf{3 0 2}$, containing the characteristic quassinoid D-ring lactone. $\mathbf{3 0 2}$ is then thought to go on to the uncommon C25 quassinoids by sidechain elaboration. If, instead, the sidechain is removed oxidatively, the C20 quassinoid skeleton is unveiled, which serves as the obvious precursor to many of the isolated natural products.

Two additional observations have been levied in support of this biosynthetic hypothesis. First, Kamiuchi isolated both perforaquassin A (303) and perforin A (304) from the same Simaroubaceae plant source (Figure 4.2B). ${ }^{6}$ Perforin A is a limonoid, a tetranortriterpene containing a substituted furan ring, and can be thought of as a putative upstream link in quassinoid biosynthesis. A second study by Okogun inadvertently deepened the link between limonoid and quassinoid biosynthesis (Figure 4.2C). ${ }^{7}$ While studying transformations of gedunin (305), a limonoid, Okogun noted that treating it under basic conditions led to the expulsion of furfural and presumed formation of merogedunin (306), containing the quassinoid D-ring lactone. Regrettably, 306 was not actually isolated from that reaction and its presence was only inferred based on analogy to similar transformations and the presence of the extruded byproduct furfural. Nevertheless, these circumstantial observations at least provided some grounding for quassinoid biosynthetic origins. Important for our synthetic purposes, we noted that these biotransformations tended to occur on the periphery of the skeleton; throughout quassinoid biosynthesis, the B-ring remained relatively untouched.

### 4.3 A Brief Discussion of Quassinoid Biological Activities

Before elaborating on the synthetic interest in quassinoids, though, a discussion of their medicinal properties is warranted. Often, impressive and/or diverse biological activities of a natural product family impel total synthesis efforts and the quassinoids are no different. From their first reported use by Quassi in the 1700 's, quassinoids have been thought to possess significant medicinal value. Since that initial report, quassinoids have been shown in more modern times to variably possess anti-cancer, ${ }^{8}$ anti-malaria, ${ }^{9}$ anti-HIV, ${ }^{10}$ anti-ulcer, ${ }^{11}$ and insect antifeedant ${ }^{12}$ effects. In fact, bruceantin (294) has even been taken through Phase II clinical trials in humans as a treatment for various types of solid tumors. ${ }^{13}$ Although those studies were eventually halted due to a lack of efficacy, ${ }^{14}$ a recent proposal suggests that bruceantin should be retried in hematological (i.e., non-solid) tumors, given reports of its efficacy in that area. ${ }^{15}$

Despite the breadth of literature demonstrating the empirical medicinal effects of quassinoids, comparably little is known about their precise mechanism of action (Figure 4.3). It has been proposed that certain quassinoids, like bruceantin (294) and glaucarubolone (307) exert their biological influence through an electrophilic C4 site on the A-ring (Figure 4.3A). ${ }^{16}$ A biological nucleophile could perform a Michael addition into the diosphenol (for 294) or enone (for 307), leading to a covalent adduct and the observed effects. Importantly, intramolecular hydrogen bonding is also thought to contribute to this reactivity, activating what would otherwise be potentially challenging sites for addition. In support of this proposal, limited SAR studies have shown the importance of an A-ring enone for anti-cancer effects. ${ }^{17}$ Comparing 307 to a reduced natural product, glaucarubol


Fgure 4.3. (A) Proposed origin of quassinoid bioactivity involving covalent modification of biological nucleophiles. (B) Comparisons of the anti-cancer activity of compounds containing an A-ring Michael acceptor (in red) against similar compounds lacking that motif (in blue).
(308), shows an over three order of magnitude difference in efficacy against a cancer cell extract. A similar trend is seen between $\Delta^{13,(18)}$-dehydroglaucarubinone (309) and shinjulactone A (310), where loss of the A-ring enone sharply cuts compound potency. It should be cautioned, however, that reduction of the ketone creates a different steric (tetrahedral vs. trigonal) and electronic (hydrogen bond acceptor vs. donor) environment at what is presumably a crucial binding motif and it is not improbable a portion of the observed effect could be due to those differences alone.

Additionally, to the best of our knowledge, no covalently modified proteins have been pulled down experimentally. One study did observe that bruceantin can inhibit protein synthesis and that a partially unsaturated A-ring is necessary for such inhibition. ${ }^{18}$ Still, the precise function of the A-ring unsaturation was not explored. Another, more recent, study observed that bruceantin strongly downregulates c-Myc (a transcription factor upregulated in certain cancers), leading to apoptosis through a mitochondrial pathway - a mechanism distinct from the inhibition of protein synthesis. ${ }^{19}$ Furthermore, neither study can satisfactorily explain the origin of the host of different biological activities other quassinoids display, suggesting that studying these natural products might allow for many new and exciting biological discoveries. ${ }^{20}$

### 4.4 Previous Synthetic Studies on Quassinoids

These biological activities did not go unnoticed by the synthetic community, and many groups initiated programs towards quassinoid synthesis. A number of approaches to the quassinoid core ring system have been reported, with strategies ranging from elaborate Diels-Alder cycloadditions (both inter- and intramolecular variants) to other pericyclic rearrangements and even semisynthesis attempts from steroidal starting materials. ${ }^{21}$ However, there remain only four completed syntheses of quassin (292): Grieco's in 1984, ${ }^{22}$ Watt's in 1990, ${ }^{23}$ Valenta's in 1991, ${ }^{24}$ and Shing's in 2000. ${ }^{25}$ A number of other quassinoids, including the therapeutically relevant bruceantin (294), ${ }^{26}$ have also been synthesized, primarily by Grieco over the course of his career. ${ }^{27}$ In the following subsections, each of these works will be described in an effort to highlight key transformations in quassinoid synthesis that have informed our own emergent work in the field.

### 4.4.1 Grieco's 1993 Synthesis of ( $\pm$ )-Bruceantin (294)

With its 10 contiguous stereocenters and elaborate oxidation pattern, bruceantin (294) rep-


Scheme 4.1. Grieco's synthesis of ( $\pm$ )-bruceantin which drew on collaborative studies with Heathcock. The synthesis is notable for its efficient access to the core skeleton.
resents perhaps the most complex member of the quassinoid family. Nevertheless, undeterred, Grieco embarked on its synthesis as part of his larger research program studying the quassinoids (Scheme 4.1). His work was aided by some initial studies done in collaboration with Heathcock six years prior. In 1987, Heathcock and Grieco had disclosed an impressive 8 -step route from simple cyclohexanone building block 311 to polycyclic intermediate 315. In this chemistry, $\mathbf{3 1 1}$ was converted in a single step to tricycle $\mathbf{3 1 2}$ through two consecutive Robinson-type annulations. Protecting group interconversions and oxidation state manipulations then brought $\mathbf{3 1 2}$ on to 315 by way of $\mathbf{3 1 3}$ and 314. Notably, the majority of carbon-carbon bonds required for a synthesis of 294 had already been formed at this point. Thus, the task ahead of Grieco seemed straightforward: append on the final carbons of $\mathbf{2 9 4}$ and adjust oxidation states to reach the natural product. However, the execution of that strategy was anything but - it required a further 35 or so steps to complete the synthesis. First, in a 6 -step sequence, the final carbon atoms (excluding the ester sidechain) of 294 were added using straightforward carbonyl chemistry, giving first $\mathbf{3 1 6}$ with a methyl ester and then 317 with all the requisite functionality. Installation of the oxomethylene bridge was then elegantly executed: enol ether $\mathbf{3 1 7}$ was treated with a brominating reagent to produce an intermediate tertiary bromide (not shown). An advantageously positioned primary alcohol was then poised to
displace that hindered functionality, giving cyclic ether 318. In many ways, the most challenging aspects of bruceantin synthesis were already addressed at this point; however, 27 more steps were required to actually complete the synthesis of 294. Many oxidation state manipulations and subtle adjustments of protecting groups were necessary; for instance, a full 10 steps were used to simply create the trans-diol motif of the C-ring from essentially a ketone precursor, speaking to the challenges of working with such a densely functionalized substrate. While certainly modern chemistry might be able to cut down on extraneous steps, Grieco's chemistry nevertheless was able to prepare an extraordinarily complex molecule - a feat that, to this day, remains uncontested.

### 4.4.2 Grieco's 1984 Synthesis of ( $\pm$ )-Quassin

In contrast to work on bruceantin, many groups have tackled the synthesis of quassin; however, a compelling argument can be made for Grieco's 1984 work (the first completed synthesis and still the shortest) to still be considered the current gold standard (Scheme 4.2). Showcasing many classic synthetic transformations, this route began with derivatization of the Wieland-Miescher ketone (324) to access cyclopropanated intermediate 325. Functionalizations and E1cB-type rupturing of the cyclopropane ring gave ketone $\mathbf{3 2 6}$ that was then oxidized in two steps to enone $\mathbf{3 2 7}$. Although the A-ring was not yet at the proper oxidation state, attention was first directed towards completing the carbocyclic quassinoid framework. In the key step of the synthesis, intermolecular Diels-Alder reaction between $\mathbf{3 2 7}$ and the depicted diene forged tricyclic compound $\mathbf{3 2 8}$ in good yield and high regio- and diastereoselectivities. It was noted, however, that the diene tended to polymerize under the reaction conditions, somewhat curtailing the efficiency of the process. Another six steps converted $\mathbf{3 2 8}$ to diketone $\mathbf{3 2 9}$, which contained the full quassinoid ring system. At this point, two-step simultaneous installation of both diosphenols followed by lactol oxidation


Scheme 4.2. Grieco's synthesis of ( $\pm$ )-quassin featuring an ambitious and challenging intermolecular Diels-Alder cycloaddition to construct the carbon skeleton. The success of that reaction inspired further work by the Grieco group on factors governing Diels-Alder cycloadditions.
prepared racemic quassin ${ }^{28}$ in 21 steps from 324. Grieco's synthesis contains a number of subtle, but important, lessons. First, the endgame installation of oxidation hints at the hidden symmetry present in quassinoids with the A- and C-ring 1,2-dioxygenation patterns. Second, rapid access to the carbon skeleton of quassinoids can still be undermined by non-ideal functional group placements. It is not unreasonable to wonder whether more optimal coupling partners in the Diels-Alder reaction could have led to an even more rapid route. Regardless, at least in terms of step count Grieco's route remains the most efficient synthesis of quassin to date.

### 4.4.3 Watt's 1990 Synthesis of (+)-Quassin

Watt's synthesis of $\mathbf{2 9 2}$ clearly drew inspiration from Grieco's seminal work (Scheme 4.3). Beginning from the same starting material, $\mathbf{3 2 4}$ (but this time prepared in enantiopure form), this route prepared dienophile $\mathbf{3 3 2}$ in 10 steps, nicely paralleling Grieco's 9 -step synthesis of dienophile 327. Watt's 332, though, contained extraneous oxidation in the form of an aldehyde. While that additional electron-withdrawing group certainly facilitated the ensuing intramolecular Diels-Alder reaction with a Danishefsky diene derivative, it also would have to be reduced off prior to successful completion of a synthesis of 292. Nevertheless, Diels-Alder adduct 333 was carried through a 7 -step sequence consisting largely of protecting group manipulations to get at key D-ring precursor 334 containing a primary bromide. Under radical generating conditions, that bromide was abstracted by tributyltin radical, triggering a 6 -exo reductive radical cyclization on the pendant enone motif, producing 335 in good yield. Although $\mathbf{3 3 5}$ contained the full quassinoid ring system, 13 steps were still required to advance it on to 292, representing a total of 35 steps from $\mathbf{3 2 4}$. Once again, efficient formation of the carbocyclic core was stymied by non-advantageous positioning of resulting functionality, calling into question the use of $\mathbf{3 2 4}$ as a desirable starting material.


Scheme 4.3. Watt's synthesis of (+)-quassin which took significant inspiration from Grieco's work in both starting material selection and in key carbon-carbon bond forming steps. An elegant 6 -exo radical cyclization to complete the quassinoid ring system, though, sets the synthesis apart from other works.

### 4.4.4 Valenta's 1995 Synthesis of ( $\pm$ )-Quassin

Valenta was an early player in the quassinoid field, having conducted some of the seminal NMR elucidation studies. Publications from that group chronicle a sixteen year long synthetic saga towards the synthesis of $\mathbf{2 9 2}$ by an inventive sequence of bond-making and bond-breaking steps (Scheme 4.4). Full discussion of the strengths and weaknesses of this route, though, is somewhat hampered by the lack of consistently reported yields and experimental conditions. Nevertheless, the overarching strategy is creative and represents a departure from the previous work of Grieco and Watt. Quinone 336 and diene 337 were brought together in an intermolecular Diels-Alder reaction, creating [2.2.2]-bicycle $\mathbf{3 8 8}$ as a mixture of diastereomers. 10 steps advanced that compound on to overbred intermediate 339, primed for $\mathrm{C}-\mathrm{C}$ bond scission. Indeed, treatment of cis-diol with periodic acid cleaved the polycyclic structure to yield $\mathbf{3 4 0}$ after reduction, a structure which could more easily be mapped onto the quassinoid skeleton. Six more steps completed construction of the full quassinoid ring system (see 342) and a further seven furnished quassin (292). Despite the somewhat circuitous route, this 32 -step synthesis was of comparable efficiency to Watt's and truly demonstrated some unique chemistry along the way.


Scheme 4.4. Valenta's imaginative synthesis of $( \pm)$-quassin that demonstrates a non-obvious sequence towards the full ring system. An inventive $\mathrm{C}-\mathrm{C}$ bond fragmentation event on an overbred intermediate finally unveils carbon architectures more easily relatable to the natural product.

### 4.4.5 Shing's 2000 Synthesis of (+)-Quassin

The most recent synthesis of 292 was completed in 2000 by Shing (Scheme 4.5). In this route, $(+)$-carvone was mapped on to the quassinoid C-ring. Once again, the carbocyclic skeleton was constructed in a rapid manner, but many steps had to be spent sculpting that starting point into the natural product itself. Beginning from ( + )-carvone derivative 343, direct aldol reaction with 344 formed a crucial carbon-carbon bond adjacent to the ketone with high levels of diastereose-


Scheme 4.5. Shing's synthesis of (+)-quassin from the chiral pool. Like prior works, this route was quick to arrive at the core ring system through elegant pericyclic reactions but less efficient at ensuring all oxidations were correctly installed.
lectivity and acetate protection of the resulting secondary alcohol prevented retro-aldol decomposition from occurring. The so-formed intermediate then underwent a pericyclic cascade in which chelotropic extrusion of sulfur dioxide unveiled a diene that then participated in an intramolecular Diels-Alder reaction with the pendant isopropenyl group, rapidly assembling tricycle 345. Notably, this intermediate contained all but one of the requisite carbon-carbon bonds of 292. However, it took a further 13 steps to arrive at $\mathbf{3 4 7}$, a compound poised to complete the D-ring. Treating 347 with strong base initiated intramolecular aldol reaction, closing that last ring as seen in 348. 10 steps were then required to complete the synthesis of $\mathbf{2 9 2}$ in 28 overall steps, due to multiple oxidation state adjustments and functional group interconversions.

### 4.4.6 Other Quassinoid Syntheses

As mentioned before, in addition to quassin (292) and bruceantin (294), Grieco has synthesized a number of related quassinoids during his career. While explicit discussion of those syntheses is outside of the scope of this work, a selection of quassinoids synthesized by Grieco is provided below for reference (Figure 4.4). Notably, each successive synthesis built upon the observations of prior works and demonstrated the challenges associated with making even seemingly inconsequential changes to oxidation patterns.

### 4.5 Retrosynthetic Analysis

Taking these precedents together, a few key patterns begin to emerge. Given the array of fused six-membered rings, the Diels-Alder reaction can be a quite powerful transformation. Indeed, every quassin synthesis employed that reaction in some capacity. Additionally, significant efficiency was lost in each prior work due to the need for extensive functional group modifications

quassin (292)

bruceantin (294)

$14 \beta, 15 \beta$-dihydroxyklaineanone (350)

castelanolide (351)

shinjulactone $C$ (351)

glaucarubinone (352)

glaucarubolone (307)

chaparrinone (353)

Figure 4.4. A short selection of quassinoids synthesized by Grieco demonstrating the diversity of structures accessible by his chemistry.
after the carbon skeleton was constructed. With these considerations in mind, we were inspired by Mandell's approach to quassinoid synthesis (Scheme 4.6) when developing our own retrosynthetic analysis. ${ }^{29}$ Key to Mandell's work was the heterodimerization of aldehyde 354 and acid chloride 355 through the enolate to provide bis(orthoquinone) 356. Although unsuccessful, an ambitious intramolecular Diels-Alder reaction of that substrate would have constructed 357, a compound with not only the full quassinoid ring system but also advantageously placed oxidation for rapid completion of the synthesis (a projected $c a .15$ steps total form commercial materials). Failure of this substrate to undergo productive reaction was likely due to difficulty in accessing the reactive diene conformation, among other factors. Nevertheless, their insight on the hidden symmetry of these molecules helped crystallize our own retrosynthetic analysis (Figure 4.5).

Since bringing together nearly complete A- and C-rings in order to make the Band D-rings had been attempted unsuccessfully, we reasoned that building the A - and C -rings from a pre-constructed B-ring not only would represent a conceptual departure from previous successful syntheses (which built the ring system linearly) but would also address the shortcomings of previous routes (Figure 4.5A). Namely, we observed that the B-ring was largely conserved throughout the quassinoid family, but variations existed in the precise 1,2-oxida-


Scheme 4.6. Mandell's unsuccessful dimerization approach to quassinoid synthesis centered around a provocative bis(orthoquinone) intramolecular Diels-Alder cycloaddition.



Figure 4.5. (A) Structural insights which inspired our retrosynthetic analysis. (B) Proposed double vinylation transform followed by formation of the full ring system. (C) Identification of the vinyl triflate of an epoxy ketone as a suitable "double electrophile" for the desired reaction.
tion pattern of the A - and C - rings. We therefore envisioned a flexible transformation that would functionalize a terpene B-ring core with two C2 units amenable to facile oxidation state manipulations (Figure 4.5B). Appending a side chain and then having the system undergo two successive ring-forming reactions would then provide access to a highly functionalized quassinoid ring system.
To realize this double vinylation (Figure 4.5 C ), we were inspired by two separate reports of ketone functionalizations. In one, Wender showed that various organometallic reagents (including Gringards, cuprates, and organolithium reagents) could engage the enolates, enol ethers, and enol phosphates of epoxy ketones in $\mathrm{S}_{\mathrm{N}} 2^{\prime}$ reactions, forcing a presumed nucleophile into an electrophilic role. ${ }^{30}$ In the other, McMurry had showed that cuprates could undergo successful cross-coupling with vinyl triflates in the absence of other transition-metal mediatiors. ${ }^{31}$ Taking these reports together, we envisioned a copper-catalyzed process to convert carvone epoxide (358, derived in one step from ( - )-carvone or available to purchase) into functionalized cyclohexenol $\mathbf{3 6 0}$ through the intermediacy of enol triflate 359. In principle, this sequence could lead to the desired double vinylation, notwithstanding many potential pitfalls associated with such an ambitious transformation. ${ }^{32}$ For example, it was unclear whether it would be possible to differentiate the cross-coupling and $\mathrm{S}_{\mathrm{N}} 2$ ' pathways in order to achieve selective coupling of two distinct nucleophiles. Additionally, despite precedents for copper-catalyzed allylic substitution reactions to favor anti- $\mathrm{S}_{\mathrm{N}} 2$ ' addition, those regio- and stereochemical outcomes were unknown in our specific system where the bulky isopropenyl group of 358 might depress intrinsic selectivities. ${ }^{33}$

### 4.6 Development of a Novel Double Coupling Reaction

Undeterred by these challenges, we set out to explore this chemistry on model epoxy ketone 361 with methyl Grignard as nucleophile to form cyclohexenol 362 (Table 4.1). However, as we tried to prepare large amounts of intermediate vinyl triflate, we were dismayed to note its lack of stability as a neat liquid. While small amounts could be routinely prepared and used directly, we sought a more tenable solution that would allow for more rapid screening of reaction conditions. Reasoning that both the triflation and subsequent couplings were anionic reactions run in THF as solvent, we wondered whether it was, in fact, actually necessary to isolate the vinyl triflate intermediate. Gratifyingly, when we attempted the combined sequence in a "one-pot" sense, no erosion of yield was observed, giving us an avenue for rapid optimization of reaction conditions. Initially, we assessed the effects of different copper(I) salts on the reaction and were pleased to note that many proved competent at performing both couplings, all in comparable yields (entries 1-5); how-
361
${ }^{a}$ Table 4.1. ${ }^{a}$ Standard reaction conditions: epoxide ( 0.1 mmol , 1.0 equiv), LHMDS ( $0.1 \mathrm{mmol}, 1.0$ equiv), $\operatorname{PhNTf}_{2}$ ( 0.1 mmol, 1.0 equiv), $-78 \rightarrow 0{ }^{\circ} \mathrm{C}, 5 \mathrm{~min}$; then add a solution of $\mathrm{MeMgBr}(0.3 \mathrm{mmol}, 3.0$ equiv), $[\mathrm{Cu}]$ ( $\mathrm{x} \mathrm{mol} \%$ ), and additive, $0{ }^{\circ} \mathrm{C}, 1 \mathrm{~h} .{ }^{b} \mathrm{~mol} \%$ with respect to epoxide starting material. ${ }^{c}$ Additives included at 5.0 equiv. ${ }^{d}$ Isolated yield of 362 after column chromatography. ${ }^{e}$ Determined by ${ }^{1} \mathrm{H}$ NMR of the crude reaction mixture. ${ }^{f}$ Reaction performed using 1.0 mmol of epoxide.
ever, they differed in the syn/anti ratio (d.r.) of allylic substitution. While most enforced the expected anti-addition, one copper center which was ligated with a bulky N-heterocyclic carbene (NHC) ligand (entry 5) slightly favored the syn-diastereomer, potentially indicating a different mechanistic regime. Of all the sources examined, cationic copper(I) species, tetrakis(acetonitrile)copper(I) hexafluorophosphate $\left[\mathrm{Cu}(\mathrm{MeCN})_{4}\right]\left[\mathrm{PF}_{6}\right]$ (entry 4), gave the highest diastereomeric ratio and was thus selected for further development.

Often, polar additives can significantly affect the selectivity of metal-catalyzed processes and a similar effect was noted here (entries 6-8). Hexamethylphosphoric triamide (HMPA, entry 6) in particular was observed to influence the allylic substitution towards near exclusive formation of the an$t i$-diastereomer. Furthermore, varying the catalyst loading did not have an additional effect on the reaction's diastereoselectivity, but did impact isolated yield of product. Specifically, if the amount of catalyst used was lowered below $15 \mathrm{~mol} \%(5 \mathrm{~mol} \%$ with respect to the organometallic reagent), a precipitous drop in isolated yield was observed.

With these optimized conditions in hand, we then proceeded to examine the scope of this novel transformation (Figure 4.6). ${ }^{34}$ While it can be more challenging to cross-couple aryl and vinyl nucleophiles with copper catalysis owing to their reduced reactivity relative to alkyl nucleophiles, we were pleasantly surprised to note that many such nucleophiles were tolerated in our chemistry (Figure 4.6A). Notably, both electron-rich and electron-poor nucleophiles were equally competent partners for the transformation (see 363-368), as were polycyclic aromatic ones (see 369), providing products as one major isomer in moderate to good yields. ${ }^{35}$ Important for further quassinoid studies, products arising from vinyl nucleophile couplings (see 370, 371) were isolated as single diastereomers. X-ray crystallographic data of $\mathbf{3 6 8}$ and $\mathbf{3 7 1}$ confirmed the continued an$t i$-stereochemistry of allylic substitution.

Not all nucleophiles gave these selectivities, however (Figure 4.6B), and two such outliers deserve special mention. First, $\mathbf{3 7 2}$ - the product formed when using the di-Grignard reagent derived from $2,2^{\prime}$-dibromobiphenyl - exclusively underwent cross-coupling and $\mathrm{S}_{\mathrm{N}} 2$ (not $\mathrm{S}_{\mathrm{N}} 2^{\prime}$ ) opening of the epoxide to form an all-carbon quaternary center. This surprising course of events likely occurred due to the intramolecular, and perhaps non-catalyzed, nature of the second step. Second, $\mathbf{3 7 3}$ - the product of coupling allyl Grignard - was formed as a $1: 1$ mixture of syn and anti diastereomers (though exclusively as the $\mathrm{S}_{\mathrm{N}} 2$ ' regioisomer). Allyl Grignard is known to be an exceptionally reactive species, and perhaps this erosion of selectivity is due to that intrinsically high reagent nucleophilicity.

Moving forward to different epoxide substrates, we were pleased to find that this meth-





Figure 4.6. ${ }^{a}$ Copper-catalyzed double coupling of epoxy ketones and Grignard reagents: (A) Scope with two of the same Grignard reagents. (B) Anomalous products, see main text for further discussion. (C) Use of different epoxides. (D) Coupling of two different nucleophiles. ${ }^{a}$ Reactions were run with 1.0 mmol of epoxide under the optimized conditions. Reported yields are of products isolated as single isomers, except where otherwise indicated. ${ }^{b} 10: 1$ d.r. ${ }^{c} \mathrm{CuI}$ used in place of $\left[\mathrm{Cu}(\mathrm{MeCN})_{4}\right]\left[\mathrm{PF}_{6}\right]$ and no HMPA added. ${ }^{d} 2.0$ equiv of 2,2 '-biphenyldimagnesium bromide used as nucleophile. ${ }^{e}$ NMR yield using 1,3,5-trimethoxybenzene as an internal standard. $30 \mathrm{~mol} \%$ loading of $\left[\mathrm{Cu}(\mathrm{MeCN})_{4}\right]$ [ $\mathrm{PF}_{6}$ ] used.
odology tolerated a number of different steric environments around the six-membered epoxy ketones (Figure 4.6C). Exchanging the simple methyl group of $\mathbf{3 6 1}$ for a bulkier phenyl one did not suppress product formation (see 374). Likewise, appending an additional methyl group onto the epoxide substrate at the 3-position did not subvert the reaction to prepare 375. It should be noted, however, that the tertiary allylic alcohol motif of that entry was extremely sensitive to acid, but could be isolated if precautions were taken. Finally, and most importantly for future quassinoid synthesis, both diastereomers of carvone epoxide were tested under the reaction conditions and were found to readily form product (see 376, 377). Remarkably, both were produced as single diastereomers, even 377 where the nucleophile presumably had to approach from the same face as the bulky isopropenyl group - an auspicious sign for our future endeavors.

Finally, we were able to expand this methodology into a true three-component coupling;
that is, a reaction where we could execute the selective coupling of two different nucleophiles in the same pot (Figure 4.6D). At low reaction temperatures $\left(-78{ }^{\circ} \mathrm{C}\right)$, we observed that products from only cross-coupling were present in the reaction mixture. Although it might be the case that these products were being formed selectively, we cannot conclusively rule out the possibility that the allylic substitution only product was also being generated but decomposed under the reaction conditions prior to a successful cross-coupling event. It was then possible to add in the second nucleophile that would perform the allylic substitution upon warming the reaction mixture to 0 ${ }^{\circ} \mathrm{C}$. Using this procedure, differentially substituted products $\mathbf{3 7 8 - 3 8 2}$ were formed selectively and in a modular manner. Since only the order of nucleophile addition and reaction temperature - and not nucleophile identity - controlled the reaction's selectivity, it was possible to easily prepare isomeric compounds $\mathbf{3 8 1}$ and $\mathbf{3 8 2}$ by simply switching which Grignard was added to the reaction first. Single crystal X-ray diffraction studies of $\mathbf{3 8 2}$ confirmed the continued sense of anti allylic substitution and verified the proposed connectivity of this tandem process. Taken together, these substrates encouraged us to pursue this chemistry further in the context of quassinoid synthesis.

### 4.7 Three-Step Synthesis of the Quassinoid Core Architecture

To access the quassinoid ring system, we desired a double vinylation of carvone epoxide (Scheme 4.6). Selecting a dioxene-based Grignard as the coupling partner due to its strategically positioned oxidation, we carried out the novel coupling and were please to observe $\mathbf{3 8 3}$ as the major product of the reaction, as a single diastereomer in good yield. Once again, the anti sense of allylic substitution was validated by X-ray crystallographic analysis. Notably, this reaction was also scalable, with multiple grams of the functionalized product prepared in a single pass.

The diene and allylic alcohol of $\mathbf{3 8 3}$ then indicated to us that an intramolecular Diels-Alder reaction might be able to forge the C - and D-rings of the quassinoid skeleton. ${ }^{36}$ A number of side chains were examined for competency in this transformation; unfortunately, few proved stable to standard cycloaddition conditions (both thermal and acid-catalyzed) owing to the tendency of the derivatized allylic alcohol to be expelled by the very electron rich adjacent dienyl system. Of the few that were stable, an even smaller selection was actually capable of undergoing the cycloaddition itself. One such dienophile was substituted chloromethyl methyl ether 384. Under optimized conditions, alkylation of the free allylic alcohol occurred first, leading to diastereomeric acetals (ca. $1: 1$ d.r.). These acetals then each underwent intramolecular Diels-Alder cyclization after further heating. Interestingly, while the first alkylation was not stereoselective, the ensuing Diels-Alder transformations each proceeded with high levels of endo/exo selectivity indicating that the acetal position exerted a strong influence on that transformation. Specifically, one acetal isomer coaxed the Diels-Alder reaction into giving exclusively endo isomer 385. The diastereomeric acetal led to the formation of exo product $\mathbf{3 8 6}$ selectively over endo product $\mathbf{3 8 7}$ (ca. 3:1 exo:endo). Overall, we isolated two major isomers: endo isomer $\mathbf{3 8 5}$ and exo isomer $\mathbf{3 8 6}$ in near equal amounts (ca. 1.3:1 d.r.), which were carried through in subsequent chemistry as an inconsequential mixture. ${ }^{37}$ Stereochemistry for all compounds was assigned by thorough nOe experiments, and X-ray crystallographic data of $\mathbf{3 8 6}$ unambiguously confirmed the assignment of that compound's stereochemistry.

To complete the quassinoid ring system, we targeted an A-ring synthesis by means of a dioxene oxidation/rearrangement/cyclization cascade. Inspired by prior work in the literature that suggested epoxidation of substituted dioxenes initiated rapid rearrangement to an aldehyde product, ${ }^{38}$ we wondered whether we could identify acidic conditions that not only triggered this rear-





385, 35\%

387, 9\%
not included in
DMDO/ene reaction DMDO/ene reaction
390






Scheme 4.6. 3-step synthesis of the full quassinoid ring system.
rangement but then also encouraged the aldehyde to undergo an intramolecular ene reaction with the pendant isopropenyl group. In practice, treating a mixture of $\mathbf{3 8 5}$ and $\mathbf{3 8 6}$ with DMDO led to a mixture of intermediate epoxides (388) that could then be subjected to various Lewis acids in the same pot to instigate the desired cascade transformation. Trimethylaluminum was found to not only rearrange $\mathbf{3 8 8}$ to aldehydes $\mathbf{3 8 9}$ but also promote the subsequent ene reaction, cleanly providing secondary alcohols 390 (from 385) and 391 (from 386) as single isomers at the newly formed secondary alcohol center. The stereochemistry of $\mathbf{3 9 1}$ was further confirmed by X-ray diffraction studies. In this way, the full quassinoid ring system was completed in only three steps from commercially available carvone epoxide (358). Along the way, 5 carbon-carbon bonds and 7 stereocenters were formed, speaking to the complementary powers of tandem catalysis and synthetic strategy at crafting highly functionalized architectures with exceptional efficiency. ${ }^{39}$

### 4.8 Conclusion

In the previous sections, we described the historical perspectives on the quassinoids - from their isolation and characterization to studies on their biological activities and chemical syntheses - that led us to our own inchoate work in the area. Impelled by a desire to access this bioac-
tive scaffold more efficiently, we were determined to leverage hidden symmetry elements in the quassinoid system towards a rapid synthesis of these fascinating natural products. In order to do so, we developed a novel double coupling reaction that transforms simple and readily available epoxy ketones to highly functionalized cyclohexenols in one pot. The significant substrate scope of this reaction, along with its high stereochemical fidelity, speaks to its potential for use not only in quassinoid synthesis but in other complex scenarios as well. Taking this methodology on to our planned synthetic substrate enabled a rapid synthesis of the quassinoid core architecture. In only 3 steps, 5 carbon-carbon bonds and 7 stereocenters were formed. Indispensable to the construction of such complexity, each step made use of tandem and/or cascade processes. Inspired by this logic, efforts remain ongoing to complete the synthesis of quassin and related quassinoids. We hope this logic will transcend quassinoid synthesis, though, and inspire others to pursue creative strategies that assemble complex architectures, ushering in a reimagining of synthetic organic chemistry.

### 4.9 Distribution of Credit and Acknowledgments

The route to the full quassinoid architecture was conceptualized by M.L.C. and T.J.M. M.L.C. solely executed, optimized, and characterized that synthetic route. M.L.C. initially developed the copper-catalyzed double coupling reaction. Under the guidance of M.L.C., S.J.H. explored a preliminary substrate scope of this transformation. Rachel Z. Rosen (R.Z.R.) completed the optimization of this reaction and determined conditions for the coupling of two different nucleophiles. M.L.C. and R.Z.R. collaboratively executed and characterized the final substrate scope.

We are grateful to H.C. for NMR spectroscopic assistance wherein NIH grant GM68933 is acknowledged. N.S.S., Dr. Simon Teat (S.T.), and Peter Waller (P.W.) are acknowledged for X-ray crystallographic analysis wherein support from NIH Shared Instrument Grant (S10-RR027172) is also acknowledged.
M.L.C. thanks the University of California, Berkeley and the NSF for a Berkeley Graduate Fellowship and NSF Predoctoral Fellowship (DGE-1106400) respectively.

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# Supporting Information for 

## Chapter 4

Introduction<br>to the<br>Quassinoids

## \&

Development
of a
Three-Step Core Synthesis

## SI4.1 General Procedures:

All reactions were performed in flame- or oven-dried glassware under a positive pressure of nitrogen or argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe. Volatile solvents were removed under reduced pressure rotary evaporation below $35^{\circ} \mathrm{C}$. Analytical and preparative thin-layer chromatography (TLC) were performed using glass plates pre-coated with silica gel ( $250 \mu \mathrm{~m}$ thickness, $10 \mu \mathrm{~m}$ particle size, MilliporeSigma) impregnated with a fluorescent indicator ( 254 nm ). TLC plates were visualized by exposure to ultraviolet light (UV) and then were stained by submersion in an ethanolic anisaldehyde solution, followed by brief heating on a hot plate. Flash column chromatography was performed employing silica gel purchased from Fisher ( $60 \AA$, 230-400 mesh, 40-63 $\mu \mathrm{m}$ ).

Anhydrous tetrahydrofuran (THF), diethyl ether ( $\mathrm{Et}_{2} \mathrm{O}$ ), toluene ( PhMe ), and dichloromethane (DCM) were obtained by passing these previously degassed solvents through activated alumina columns. Hexamethylphosphoric triamide (HMPA) was distilled over calcium hydride and stored under inert atmosphere. Though commercially available, cis-carvone epoxide could also be prepared according to the literature procedure. ${ }^{1}$ Additional epoxide substrates were prepared following established literature protocols, ${ }^{2}$ with the exception of 2,3-epoxy-2-methyl-cyclohexanone, which is uncharacterized in the literature. Dimethyldioxirane (DMDO) was prepared according to the Organic Synthesis procedure. ${ }^{3}$ Lithium bis(trimethylsilyl)amide was purchased as a 1.0 M solution in THF from MilliporeSigma and used as received. N-Phenyl-bis(trifluoromethanesulfonamide) was purchased from Oakwood Chemicals and used as received. Grignard reagents were purchased from MilliporeSigma and used as received, except where otherwise indicated. $\left[\mathrm{Cu}(\mathrm{MeCN})_{4}\right]\left[\mathrm{PF}_{6}\right]$ was purchased from MilliporeSigma and used as received. All other solvents and reagents, including additional copper sources, were purchased at the highest commercial grade and used as received, without additional purification.

Proton nuclear magnetic resonance ( ${ }^{1} \mathrm{H} N \mathrm{NMR}$ ) spectra and carbon nuclear magnetic resonance ( ${ }^{13} \mathrm{C}$ NMR) spectra were recorded on Bruker DRX $500(500 \mathrm{MHz} / 126 \mathrm{MHz})$, Bruker AV $500(500 \mathrm{MHz} / 126 \mathrm{MHz}$ ), Bruker AV $600(600 \mathrm{MHz} / 151 \mathrm{MHz}$ ), or Bruker AV 700 ( $700 \mathrm{MHz} / 176$ MHz ) spectrometers at $23^{\circ} \mathrm{C}$. Fluorine nuclear magnetic resonance ( ${ }^{1} \mathrm{~F} N \mathrm{NR}$ ) spectra were recorded on a Bruker AVQ $400(376 \mathrm{MHz})$ spectrometer at $23{ }^{\circ} \mathrm{C}$. Proton chemical shifts are expressed as parts per million (ppm, $\delta$ scale) and are referenced to residual protium in the NMR solvent $\left(\mathrm{CHCl}_{3}: \delta 7.26, \mathrm{C}_{6} \mathrm{D}_{5} \mathrm{H}: \delta 7.16, \mathrm{CD}_{2} \mathrm{HOD}: \delta 3.31\right)$. Carbon chemical shifts are expressed as parts per million ( $\mathrm{ppm}, \delta$ scale) and are referenced to the carbon resonance of the NMR solvent $\left(\mathrm{CDCl}_{3}: \delta 77.16, \mathrm{C}_{6} \mathrm{D}_{6}: 128.06, \mathrm{CD}_{3} \mathrm{OD}: \delta 49.00\right)$. Fluorine chemical shifts are expressed as parts per million (ppm, $\delta$ scale) and are not additionally referenced. Data are represented as follows: chemical shift, multiplicity ( $\mathrm{s}=$ singlet, $\mathrm{d}=$ doublet, $\mathrm{t}=$ triplet, $\mathrm{q}=$ quartet, $\mathrm{m}=$ multiplet, $\mathrm{br}=$ broad), coupling constant $(J)$ in Hertz $(\mathrm{Hz})$, and integration. Infrared (IR) spectra were recorded on a Bruker Alpha FT-IR spectrometer as thin films and are reported in frequency of absorption $\left(\mathrm{cm}^{-1}\right)$. Optical rotations were recorded on a Perkin Elmer polarimeter, model 241. High-resolution mass spectra were obtained at the QB3/Chemistry Mass Spectrometry Facility at University of California, Berkeley using a Thermo LTQ-FT mass spectrometer, and at the Lawrence Berkeley National Laboratory Catalysis Center using a Perkin Elmer AxION 2 TOF mass spectrometer. X-ray diffraction data for all compounds were collected at the Small Molecule X-ray Crystallography Facility (CheXray) at University of California, Berkeley using a Bruker MicroSTAR-H APEX II QUAZAR X-ray source.

SI4.2 Standard Procedure for the Cu-Catalyzed Double Coupling Reaction Between Epoxy Ketones and Grignard Reagents Employing Two of the Same Nucleophiles


A solution of epoxy ketone ( $1.0 \mathrm{mmol}, 1.0$ equiv) in THF ( 2 mL ) was cooled to $-78^{\circ} \mathrm{C}$. LHMDS ( 1.0 M in THF, $1.0 \mathrm{~mL}, 1.0 \mathrm{mmol}, 1.0$ equiv) was added dropwise and the resulting solution was stirred for 10 min . N-Phenyl-bis(trifluoromethanesulfonamide) ( $357 \mathrm{mg}, 1.0 \mathrm{mmol}, 1.0$ equiv) was then added as a solid and the solution was warmed to $0^{\circ} \mathrm{C}$ and stirred for 10 min . In a separate flask, at $23^{\circ} \mathrm{C},\left[\mathrm{Cu}(\mathrm{MeCN})_{4}\right]\left[\mathrm{PF}_{6}\right](55 \mathrm{mg}, 0.15 \mathrm{mmol}, 0.15$ equiv) was suspended in THF ( 1 mL ). The desired Grignard reagent (typically 1.0 M in THF, $3.0 \mathrm{~mL}, 3.0 \mathrm{mmol}, 3.0$ equiv) was added dropwise to the suspension, followed by HMPA ( $0.87 \mathrm{~mL}, 5.0 \mathrm{mmol}, 5.0$ equiv). The mixture was stirred until homogeneous and cooled to $0^{\circ} \mathrm{C}$. The so-prepared cuprate solution was then directly added to the vinyl triflate solution and the reaction mixture was stirred at $0{ }^{\circ} \mathrm{C}$ until product formation was complete (typically $1-2 \mathrm{~h}$ ). The reaction mixture was diluted with $\mathrm{Et}_{2} \mathrm{O}$ :hexanes ( $1: 1,20 \mathrm{~mL}$ ) and quenched with a $9: 1$ saturated aqueous ammonium chloride:saturated aqueous ammonium hydroxide solution ( 5 mL ). The biphasic suspension was stirred vigorously until the aqueous layer had turned a deep blue. The layers were separated and the organic layer was further washed with water ( $2 \times 10 \mathrm{~mL}$ ) and brine $(10 \mathrm{~mL})$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude residue was purified by silica gel chromatography, and due to the instability of products to acid, chromatographic eluents were buffered with triethylamine (typically $27 \rightarrow 47 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes $+3 \% \mathrm{Et}_{3} \mathrm{~N}$ ). Residence time of the compounds on the column was likewise minimized. Products were afforded as solid, single isomers, except where otherwise indicated.

SI4.3 Standard Procedure for the Cu-Catalyzed Double Coupling Reaction Between Epoxy Ketones and Grignard Reagents Employing Two Different Same Nucleophiles


A solution of epoxy ketone ( $1.0 \mathrm{mmol}, 1.0$ equiv) in THF ( 2 mL ) was cooled to $-78^{\circ} \mathrm{C}$. LHMDS ( 1.0 M in THF, $1.0 \mathrm{~mL}, 1.0 \mathrm{mmol}, 1.0$ equiv) was added dropwise and the resulting solution was stirred for 10 min . N -Phenyl-bis(trifluoromethanesulfonamide) ( $1.0 \mathrm{mmol}, 1.0$ equiv) was then added as a solid and the solution was warmed to $0^{\circ} \mathrm{C}$ and stirred for 10 min before being re-cooled to $-78{ }^{\circ} \mathrm{C}$. In a separate flask, at $23^{\circ} \mathrm{C},\left[\mathrm{Cu}(\mathrm{MeCN})_{4}\right]\left[\mathrm{PF}_{6}\right](55 \mathrm{mg}, 0.15 \mathrm{mmol}, 0.15$ equiv) was suspended in THF ( 1 mL ). The desired Grignard reagent for cross-coupling (typically 1.0 M in THF, $2.0 \mathrm{~mL}, 2.0 \mathrm{mmol}, 2.0$ equiv) was added dropwise to the suspension, followed by HMPA ( $0.87 \mathrm{~mL}, 5.0 \mathrm{mmol}, 5.0$ equiv). The mixture was stirred until homogeneous, cooled briefly to 0 ${ }^{\circ} \mathrm{C}$, and then added dropwise to the vinyl triflate solution. Conversion to the cross-coupled product was carefully monitored and addition was stopped when full conversion was observed (typically when only $80-90 \%$ of the solution - or $c a .1 .6-1.8$ equiv of Grignard reagent - had been added). At the end of addition, the reaction was stirred for 1 h at $-78^{\circ} \mathrm{C}$. The desired Grignard reagent for allylic substitution (typically 1.0 M in THF, $2.0 \mathrm{~mL}, 2.0 \mathrm{mmol}, 2.0$ equiv) was then added dropwise. The solution was allowed to warm to $0^{\circ} \mathrm{C}$ and was stirred at that temperature for a further hour, or until complete conversion to product. The reaction mixture was diluted with $\mathrm{Et}_{2} \mathrm{O}$ :hexanes ( $1: 1,20 \mathrm{~mL}$ ) and quenched with a $9: 1$ saturated aqueous ammonium chloride:saturated aqueous ammonium hydroxide solution ( 5 mL ). The biphasic suspension was stirred vigorously until the aqueous layer had turned a deep blue. The layers were separated and the organic layer was further washed with water ( $2 \times 10 \mathrm{~mL}$ ) and brine ( 10 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude residue was purified by silica gel chromatography (typically $27 \rightarrow 47 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes $+3 \% \mathrm{Et}_{3} \mathrm{~N}$ ). Products were afforded as solid, single isomers, except where otherwise indicated.

## SI4.4 Preparation and Characterization Data

Preparation and characterization data are provided for only a subset of compounds described in Chapter 4. Data for the remaining compounds can be found in the upcoming Ph.D. dissertation of R.Z.R and/or in our published work. ${ }^{4}$

## SI4.4.1 Preparation and Characterization Data for Products from Coupling Two of the Same Nucleophiles:



Substrate 364: The standard procedure was followed with 2,3-ep-oxy-2-methyl-cyclohexanone ( $126 \mathrm{mg}, 1.0 \mathrm{mmol}, 1.0$ equiv) and $4-\mathrm{me}-$ thoxyphenylmagnesium bromide ( 0.5 M in THF, $6.0 \mathrm{~mL}, 3.0 \mathrm{mmol}, 3.0$ equiv) to afford $364(168 \mathrm{mg}, 0.52 \mathrm{mmol}, 52 \%)$ as a white solid ( $>20: 1$ d.r.). ${ }^{1} \mathrm{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.03(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.98(\mathrm{~d}, J$ $=8.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.75(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 2 \mathrm{H}), 6.72(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 2 \mathrm{H}), 4.20$ $\mathrm{OH}(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.74$ (s, 3H), 3.72 (s, 3H), $3.72-3.69$ (m, 1H), 2.28 (td, $J$ $=13.4,5.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.88(\mathrm{tdd}, J=13.4,3.4,2.9 \mathrm{~Hz}, 1 \mathrm{H}), 1.81(\mathrm{~s}, 3 \mathrm{H})$, $1.72-1.62(\mathrm{~m}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 158.0,157.9,137.5,135.4,134.7,133.0,129.9$ (2C), 129.8 (2C), 113.5 (2C), 113.3 (2C), 68.7, 55.3, 55.2, 46.1, 27.3, 27.1, 18.2; IR (thin film) $v_{\max }: 3352,2930,1607,1508,1240 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{21} \mathrm{H}_{24} \mathrm{O}_{3} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 347.1623$, found: 347.1628.


Substrate 368: The standard procedure was followed with 2,3 -ep-oxy-2-methyl-cyclohexanone ( $126 \mathrm{mg}, 1.0 \mathrm{mmol}, 1.0$ equiv) and 4-fluorophenylmagnesium bromide ( 1.0 M in THF, $3.0 \mathrm{~mL}, 3.0 \mathrm{mmol}, 3.0$ equiv) to afford 368 ( $128 \mathrm{mg}, 0.43 \mathrm{mmol}, 43 \%$ ) as a white solid ( $>20: 1$ d.r.). ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.06(\mathrm{dd}, J=8.5,5.6 \mathrm{~Hz}, 2 \mathrm{H}), 7.00(\mathrm{dd}, J=8.5$, $5.6 \mathrm{~Hz}, 2 \mathrm{H}), 6.88(\mathrm{t}, J=8.5 \mathrm{~Hz}, 2 \mathrm{H}), 6.87(\mathrm{t}, J=8.5 \mathrm{~Hz}, 2 \mathrm{H}), 4.23(\mathrm{dt}, J=$ $4.7,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.72(\mathrm{tq}, J=3.0,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.31(\mathrm{tdd}, J=13.2,5.7,3.0$ $\mathrm{Hz}, 1 \mathrm{H}), 1.88$ (dddd, $J=14.0,13.2,5.0,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.79(\mathrm{~d}, J=1.6 \mathrm{~Hz}$, $3 \mathrm{H}), 1.76(\mathrm{~d}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.71(\mathrm{ddt}, J=14.0,5.7,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.66(\mathrm{ddt}, J=13.2,5.0,3.0 \mathrm{~Hz}$, 1H); ${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 161.42(\mathrm{~d}, \mathrm{~J}=245 \mathrm{~Hz}$ ), 161.39 (d, J = 242 Hz ), 138.7 (d, $J=$ $3.2 \mathrm{~Hz}), 137.8(\mathrm{~d}, J=3.5 \mathrm{~Hz}), 136.6,134.1,130.4(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 2 \mathrm{C}), 130.1(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{C})$, $115.0(\mathrm{~d}, \mathrm{~J}=21 \mathrm{~Hz}, 2 \mathrm{C}), 114.9(\mathrm{~d}, \mathrm{~J}=21 \mathrm{~Hz}, 2 \mathrm{C}), 68.4,46.2,27.22,27.16,18.1 ;{ }^{19} \mathrm{~F}$ NMR (376 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta-115.30(\mathrm{tt}, J=8.5,5.6 \mathrm{~Hz}),-116.38(\mathrm{tt}, J=8.5,5.6 \mathrm{~Hz})$; IR (thin film) $v_{\max }: 3333$, 2934, 1602, $1505 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{19} \mathrm{H}_{18} \mathrm{OF}_{2}: 300.1326$, found: 300.1326.


Substrate 369: Magnesium turnings ( $80 \mathrm{mg}, 3.3 \mathrm{mmol}, 1.1$ equiv) were suspended in THF ( 3.0 mL ) and a crystal of iodine $(<10 \mathrm{mg})$ was added. The magnesium suspension was heated at $65^{\circ} \mathrm{C}$. Separately, 2-bromonaphthalene ( $620 \mathrm{mg}, 3.0 \mathrm{mmol} 1.0$ equiv) was dissolved in THF ( 3.0 mL ) and then added dropwise to the heated magnesium suspension. Upon completion of addition, the resulting brown-gray solution was heated at $65^{\circ} \mathrm{C}$ for a further hour. The so-prepared 2-naphthylmagnesium bromide solution was used in the coupling step without further purification ( 0.5 M assumed). The
standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone ( $126 \mathrm{mg}, 1.0 \mathrm{mmol}$, 1.0 equiv) and 2-naphthylmagnesium bromide ( 0.5 M in THF, $6.0 \mathrm{~mL}, 3.0 \mathrm{mmol}, 3.0$ equiv) to afford 369 ( $147 \mathrm{mg}, 0.40 \mathrm{mmol}, 40 \%$ ) as a white solid ( $>20: 1$ d.r.). ${ }^{1} \mathrm{H}$ NMR ( $700 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.77(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.75(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.73-7.70(\mathrm{~m}, 3 \mathrm{H}), 7.66(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H})$, $7.63(\mathrm{~s}, 2 \mathrm{H}), 7.43(\mathrm{t}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.41-7.34(\mathrm{~m}, 4 \mathrm{H}), 7.31(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.36(\mathrm{dd} J=$ $3.7,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.11(\mathrm{~d}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.48$ (dddd, $J=13.9,13.3,5.7,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.03$ (tdd, $J$ $=13.9,3.7,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.94(\mathrm{~d}, J=1.8 \mathrm{~Hz}, 3 \mathrm{H}), 1.86(\mathrm{dq}, J=13.3,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.86(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, 1.79 (ddt, $J=13.9,5.7,3.0 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $176 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 140.7,139.8,137.5,134.2$, 133.3, 133.2, 132.2, 132.1, 127.9, 127.8, 127.7, 127.61, 127.59, 127.56 (2C, overlapping), 127.5, $127.4,127.2,125.89,125.87,125.6,125.3,68.7,47.0,27.22,27.20,18.3$; IR (thin film) $v_{\max }: 3357$, 2933, 1629, 1598, $745 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{27} \mathrm{H}_{24} \mathrm{O}: 364.1827$, found: 364.1829.


Substrate 371: The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone ( $126 \mathrm{mg}, 1.0 \mathrm{mmol}, 1.0$ equiv) and vinylmagnesium bromide $(1.0 \mathrm{M}$ in THF, $3.0 \mathrm{~mL}, 3.0 \mathrm{mmol}, 3.0$ equiv) to afford $371(56 \mathrm{mg}, 0.35 \mathrm{mmol}, 35 \%)$ as a white solid (> 20:1 d.r.). ${ }^{1} \mathrm{H}$ NMR ( $700 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 6.67(\mathrm{dd}, J=17.5,11.2 \mathrm{~Hz}$, $1 \mathrm{H}), 5.78$ (ddd, $J=17.3,10.3,6.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.22(\mathrm{dd}, J=17.5,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.13$ (dd, $J=11.2,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.04(\mathrm{dt}, J=10.3,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.89(\mathrm{dt}, J=17.3,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.98(\mathrm{t}, J=$ $2.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.16$ (dtt, $J=6.1,2.4,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 1.95$ (br s, 3 H ), 1.90 (dddd, $J=14.6,12.1,4.8,2.3$ $\mathrm{Hz}, 1 \mathrm{H}$ ), 1.84 (dddd, $J=14.3,13.7,4.3,2.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.69 (ddt, $J=13.7,4.8,2.3 \mathrm{~Hz}, 1 \mathrm{H}$ ), 1.59 (br $\mathrm{s}, 1 \mathrm{H}), 1.58$ (ddt, $J=12.1,4.3,2.3 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 140.5,134.3,133.9$, $133.1,115.5,115.3,69.5,37.7,27.0,23.3,17.3$; IR (thin film) $v_{\max }: 3161,2924,1636,1418 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{11} \mathrm{H}_{16} \mathrm{O}_{:}$164.1201, found: 164.1200.

SI4.4.2 Preparation and Characterization Data for Products with an Alternative Epoxide Starting Material:


Substrate 376: The standard procedure was followed with trans-carvone epoxide ( $166 \mathrm{mg}, 1.0 \mathrm{mmol}, 1.0$ equiv) and 4 -methoxyphenylmagnesium bromide ( 0.5 M in THF, $6.0 \mathrm{~mL}, 3.0 \mathrm{mmol}, 3.0$ equiv) to afford $376(189 \mathrm{mg}, 0.52 \mathrm{mmol}, 52 \%)$ as a white solid ( $>20: 1$ d.r.). $[\alpha]_{\mathrm{D}}=$ $+143\left(c 0.8, \mathrm{C}_{6} \mathrm{H}_{6}\right) ;{ }^{1} \mathrm{H}$ NMR $\left(700 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 6.96(\mathrm{~d}, J=8.3 \mathrm{~Hz}$, $2 \mathrm{H}), 6.90(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 2 \mathrm{H}), 6.71(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 2 \mathrm{H}), 6.70(\mathrm{~d}, J=8.3$ $\mathrm{Hz}, 2 \mathrm{H}), 4.90(\mathrm{~s}, 1 \mathrm{H}), 4.84(\mathrm{~s}, 1 \mathrm{H}), 4.23$ (ddd, $J=9.4,6.0,4.8 \mathrm{~Hz}, 1 \mathrm{H})$, $3.74(\mathrm{~d}, J=4.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.73(\mathrm{~s}, 3 \mathrm{H}), 3.72(\mathrm{~s}, 3 \mathrm{H}), 2.42(\mathrm{dt}, J=6.0,4.8$ $\mathrm{Hz}, 1 \mathrm{H}), 2.10(\mathrm{dt}, J=13.7,4.8 \mathrm{~Hz}, 1 \mathrm{H}), 2.03(\mathrm{dt}, J=13.7,6.0 \mathrm{~Hz}, 1 \mathrm{H})$, $1.98(\mathrm{~d}, J=9.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.81(\mathrm{~s}, 3 \mathrm{H}), 1.77(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C} \mathrm{NMR}\left(151 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 157.92,157.89$, $150.1,135.73,135.71,134.6,133.5,123.0$ (2C), 129.9 (2C), 113.5 (2C), 113.3 (2C), 111.3, 70.4, $55.3,55.2,50.8,47.4,33.2,21.9,17.2$; IR (thin film) $v_{\max }: 3371,2931,1643,1509,1241 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{24} \mathrm{H}_{28} \mathrm{O}_{3} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 387.1931$, found: 387.1928.


Substrate 377: This compound was prepared in a departure from the standard procedure in the following way: $\left[\mathrm{Cu}(\mathrm{MeCN})_{4}\right]\left[\mathrm{PF}_{6}\right]$ was used at $30 \mathrm{~mol} \%$ loading. This modified standard procedure was followed with cis-carvone epoxide ( $166 \mathrm{mg}, 1.0 \mathrm{mmol}, 1.0$ equiv) and 4 -methoxyphe-nyl-magnesium bromide ( 0.5 M in THF, $6.0 \mathrm{~mL}, 3.0 \mathrm{mmol}, 3.0$ equiv) to afford 377 ( $186 \mathrm{mg}, 0.51 \mathrm{mmol}, 51 \%$ ) as a white solid ( $>20: 1$ d.r.). $[\alpha]_{D}$ $=-96.3\left(c 0.3, \mathrm{C}_{6} \mathrm{D}_{6}\right) ;{ }^{1} \mathrm{H}$ NMR $\left(700 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 6.93(\mathrm{~d}, J=8.7 \mathrm{~Hz}$, $2 \mathrm{H}), 6.80(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 6.65(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 4 \mathrm{H}), 4.72(\mathrm{q}, J=1.6$ $\mathrm{Hz}, 1 \mathrm{H}), 4.68(\mathrm{~d}, J=1.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.19(\mathrm{t}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.71(\mathrm{~s}, 6 \mathrm{H})$, 3.54 (d, $J=7.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), 2.68 (ddd, $J=10.4,7.8,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.00$ (ddd, $J=13.7,10.4,4.7 \mathrm{~Hz}$, $1 \mathrm{H}), 1.91(\mathrm{dt}, J=13.7,4.7,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.71(\mathrm{~d}, J=1.8 \mathrm{~Hz}, 3 \mathrm{H}), 1.70(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 1.66(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (151 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 157.70,157.67,147.4,138.1,135.6,134.2,131.9,130.0$ (2C), 129.9 (2C), 113.3 (2C), 113.1 (2C), 111.3, 69.8, 55.19, 55.16, 51.3, 45.7, 34.9, 21.2, 18.7; IR $v_{\text {max }}: 3361$, 2932, 1646, $1508 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{24} \mathrm{H}_{28} \mathrm{O}_{3} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 387.1931$, found: 387.1928.

## SI4.4.2 Preparation and Characterization Data for Products from Coupling Two Different Nucleophiles:



Substrate 378: The standard procedure was followed with 2,3-ep-oxy-2-methyl-cyclohexanone ( $126 \mathrm{mg}, 1.0 \mathrm{mmol}, 1.0$ equiv) and 4-fluorophenylmagnesium bromide ( 1.0 M in THF, $2.0 \mathrm{~mL}, 2.0 \mathrm{mmol}, 2.0$ equiv) followed by 4-methoxyphenylmagnesium bromide $(0.5 \mathrm{M}$ in THF, $4.0 \mathrm{~mL}, 2.0 \mathrm{mmol}, 2.0$ equiv) to afford $378(163 \mathrm{mg}, 0.52 \mathrm{mmol}$, $52 \%$ ) as a white foam (this product was isolated as a $\sim 15: 1$ inseparable 'он mixture with 368). ${ }^{1} \mathrm{H}$ NMR ( $700 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.03$ (d, $J=8.7 \mathrm{~Hz}$, $2 \mathrm{H}), 7.02(\mathrm{dd}, J=8.4,5.6 \mathrm{~Hz}, 2 \mathrm{H}), 6.87(\mathrm{dd}, J=9.4,8.4 \mathrm{~Hz}, 2 \mathrm{H}), 6.77$ $(\mathrm{d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 4.23(\mathrm{t}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.74(\mathrm{~s}, 3 \mathrm{H}), 3.69(\mathrm{tq}, J=3.0,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.31(\mathrm{tdd}, J$ $=13.4,5.8,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.06(\mathrm{~s}, 1 \mathrm{H}), 1.93(\mathrm{tdd}, J=13.4,5.0,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.80(\mathrm{~d}, J=2.0 \mathrm{~Hz}, 3 \mathrm{H})$, 1.71 (ddt, $J=13.4,5.8,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.68(\mathrm{ddt}, J=13.4,5.0,3.0 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 176 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta 161.3(\mathrm{~d}, J=244.9 \mathrm{~Hz}), 157.9,138.1(\mathrm{~d}, J=3.2 \mathrm{~Hz}), 137.0,135.0,133.6,130.3(\mathrm{~d}, J=$ $7.7 \mathrm{~Hz}, 2 \mathrm{C}), 129.6$ (2C), 114.7 (d, $J=21.1 \mathrm{~Hz}, 2 \mathrm{C}), 113.5$ (2C), 68.5, 55.2, 46.1, 27.3, 27.2, 18.1; ${ }^{19}$ F NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta-115.63\left(\mathrm{tt}, J=9.4,5.5 \mathrm{~Hz}\right.$ ); IR (thin film) $v_{\text {max }}: 3355,2934,1602$, 1582, $1442 \mathrm{~cm}^{-1}$; HRMS (EI) calcd for $\mathrm{C}_{20} \mathrm{H}_{21} \mathrm{OF}: 312.1526$, found: 312.1529 .

## SI4.4.3 Preparation and Characterization Data for Synthetic Studies on the Quassinoid Core Architecture:

ODioxene (SI-2): Although commercially available, dioxene can also be prepared in a rapid, economical fashion from readily accessible starting materials. Described here is a modification of known literature protocols ${ }^{5}$ to produce dioxene on large scale. Dioxane ( $85 \mathrm{~mL}, 1.0 \mathrm{~mol}, 1.0$ equiv) was placed in a 500 mL flask and a reflux condenser was attached. In addition to the inlet tubing at the top of the condenser providing a positive pressure of nitrogen, outlet tubing to a beaker containing $4 \mathrm{M} \mathrm{NaOH}(1000 \mathrm{~mL})$ was connected. Sulfuryl chloride (162 $\mathrm{mL}, 2.0 \mathrm{~mol}, 2.0$ equiv) was added dropwise over 30 min . After this addition was completed, the cooling bath was removed and the resulting pale yellow solution was heated at $40^{\circ} \mathrm{C}$ for 16 h . The solution was then heated at $65^{\circ} \mathrm{C}$ for 4 h at which point it gradually turned colorless. The solution was cooled to room temperature and argon was sparged through to displace any trace acidic gas. The crude product was concentrated under reduced pressure and the resulting trans-2,3-dichloro-1,4-dioxane was used immediately in the next step without further purification. This highly sensitive intermediate gradually decomposes over time and is best used fresh for subsequent chemistry.

Magnesium metal ( $36 \mathrm{~g}, 1.5 \mathrm{~mol}, 1.5$ equiv) was suspended in THF ( 250 mL ). The so-prepared crude trans-2,3-dichloro-1,4-dioxane ( 1.0 mol assumed, 1.0 equiv) was added neat to that suspension dropwise. After Grignard initiation, addition was continued to maintain a steady reflux. The resulting suspension was heated at $65^{\circ} \mathrm{C}$ for 4 h . The gray suspension was cooled to room temperature and filtered through Celite. Additional THF (ca. 200 mL ) was used to wash the filter cake and quantitate transfer. The crude solution was directly distilled ( $100^{\circ} \mathrm{C}$, house vacuum) into a flask cooled to $-78^{\circ} \mathrm{C}$. Dioxene was found to readily azeotrope with THF and so purified dioxene was afforded as a solution in THF ( $0.65 \mathrm{M}, 28 \mathrm{~g}, 330 \mathrm{mmol}, 33 \%$ over two steps, as judged by ${ }^{1} \mathrm{H}$ NMR analysis).


Diene 383: The procedure for the preparation of this compound represents a significant departure from the standard conditions and thus will be described in full. Carvone epoxide ( $332 \mathrm{mg}, 2.0 \mathrm{mmol} 1.0$ equiv) was dissolved in THF $(4.0 \mathrm{~mL})$ and cooled to $-78^{\circ} \mathrm{C}$. LHMDS ( 1.0 M in THF, $2.0 \mathrm{~mL}, 2.0 \mathrm{mmol}$, 1.0 equiv) was added dropwise and the resulting solution was briefly warmed to $0^{\circ} \mathrm{C}(<5 \mathrm{~min})$ before being cooled back to $-78^{\circ} \mathrm{C}$. N-Phenyl-bis(trifluoromethanesulfonamide) ( $750 \mathrm{mg}, 2.1 \mathrm{mmol}, 1.05$ equiv) was added as a solid and the reaction mixture was warmed to $0^{\circ} \mathrm{C}$. In a separate flask, dioxene ( 0.65 M in THF, $12.3 \mathrm{~mL}, 8.0 \mathrm{mmol}, 4.0$ equiv) was cooled to $0^{\circ} \mathrm{C} . n-\mathrm{BuLi}(2.5 \mathrm{M}$ in hexanes, 3.0 $\mathrm{mL}, 7.4 \mathrm{mmol}, 3.7$ equiv) was added and the pale yellow solution was stirred for 1 h . In another separate flask, $\mathrm{CuI}\left(133 \mathrm{mg}, 0.7 \mathrm{mmol}, 0.35\right.$ equiv) was combined with anhydrous $\mathrm{MgBr}_{2}(1.3 \mathrm{~g}$, $7.0 \mathrm{mmol}, 3.5$ equiv). To this mixture of solids was rapidly added the dioxene-lithium solution. The cloudy suspension was stirred at room temperature for 30 min before being added dropwise to the vinyl triflate at $0^{\circ} \mathrm{C}$. A wide-bore needle was used and care was taken during this operation to ensure all solids were transferred along with the solution. The reaction mixture was allowed to warm to room temperature slowly and was stirred for 16 h . The reaction mixture was diluted with EtOAc ( 50 mL ) and quenched with a 9:1 saturated aqueous ammonium chloride:saturated aqueous ammonium hydroxide solution ( 10 mL ). The biphasic suspension was stirred vigorously until the aqueous layer had turned a deep blue. The layers were separated and the organic layer was further washed with water ( $2 \times 10 \mathrm{~mL}$ ) and brine $(10 \mathrm{~mL})$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated.

The crude residue was purified by silica gel chromatography ( $27 \rightarrow 37 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes $+3 \%$ $\mathrm{Et}_{3} \mathrm{~N}$ ) to afford diene $\mathbf{3 8 3}(370 \mathrm{mg}, 1.1 \mathrm{mmol}, 58 \%)$ as a white solid. $[\alpha]_{\mathrm{D}}=+176\left(c 1.0, \mathrm{C}_{6} \mathrm{D}_{6}\right)$; ${ }^{1} \mathrm{H}$ NMR ( $700 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 5.94(\mathrm{~s}, 1 \mathrm{H}), 5.73(\mathrm{~s}, 1 \mathrm{H}), 4.82(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.66(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.16-$ $4.11(\mathrm{~m}, 2 \mathrm{H}), 4.08-4.00(\mathrm{~m}, 3 \mathrm{H}), 3.92-3.85(\mathrm{~m}, 4 \mathrm{H}), 2.94(\mathrm{dq}, J=5.8,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.46$ (ddd, $J=13.7,5.8,2.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.18(\mathrm{td}, J=13.7,4.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.98(\mathrm{~d}, J=1.6 \mathrm{~Hz}, 3 \mathrm{H}), 1.78(\mathrm{br} \mathrm{s}$, $3 \mathrm{H}), 1.73$ (dt, $J=13.7,2.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.58(\mathrm{br} \mathrm{s}, 1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( $176 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 147.5,136.3$, $135.7,134.5,129.6,126.9,124.4,109.9,69.2,64.6,64.5,64.4,64.0,42.0,38.3,32.5,22.9,19.1$; IR (thin film) $v_{\text {max }}$ : $3419,3034,1673,1478,1143 \mathrm{~cm}^{-1}$; HRMS (ESI): calcd for $\mathrm{C}_{18} \mathrm{H}_{25} \mathrm{O}_{5}[\mathrm{M}+\mathrm{H}]^{+}$: 321.1657, found: 321.1654 .
 $3.0 \mathrm{mmol}, 1.0$ equiv) $)^{6}$ and acetyl chloride ( $430 \mu \mathrm{~L}, 6.0 \mathrm{mmol}, 2.0$ equiv) were combined with a crystal of iodine ( $8 \mathrm{mg}, 0.03 \mathrm{mmol}, 0.01$ equiv). The mixture was stirred at rt for 6 h . The crude residue was directly concentrated and then azeotroped from benzene ( $3 \times 5 \mathrm{~mL}$ ). The dienophile was used immediately in the next step without further purification (ca. 480 mg , near quantitative mass recovery). This crude product typically contained $c a$. $5 \%$ recovered starting material and $c a .5 \%$ (2E)-4-oxo-2-butenoic acid, along with some decomposition products; a purity of $80 \%$ was conservatively assumed by ${ }^{1} \mathrm{H}$ NMR analysis for the subsequent step. Tabulated ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR data of this unpurified material were obtained: ${ }^{1} \mathrm{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{C}_{6} \mathrm{D}_{6}\right) \delta 7.00(\mathrm{dd}, J=15.6,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.11(\mathrm{dd}, J=15.6,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 5.34(\mathrm{ddq}, J=$ $4.7,1.3,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.30(\mathrm{~s}, 3 \mathrm{H}), 2.97(\mathrm{~d}, J=1.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{C}_{6} \mathrm{D}_{6}$ ) $\delta 165.6$, 142.6, 122.4, 95.3, 57.2, 51.4.

Diels-Alder Reaction: Diene 383 ( $320 \mathrm{mg}, 1.0 \mathrm{mmol}, 1.0$ equiv) was dissolved in $\mathrm{PhMe}(10 \mathrm{~mL}$ ) and $\mathrm{N}, \mathrm{N}$-diisopropylethylamine ( $0.67 \mathrm{~mL}, 4.0 \mathrm{mmol}, 4.0$ equiv) was added at room temperature. Dienophile 384 (crude from previous operation, $328 \mathrm{mg}, 2.0 \mathrm{mmol}, 2.0$ equiv) was dissolved in $\mathrm{PhMe}(5 \mathrm{~mL})$ and added dropwise to the solution. The reaction mixture was stirred at room temperature for 12 h and then diluted with further $\mathrm{PhMe}(10 \mathrm{~mL})$ and HMDS $(2.5 \mathrm{~mL})$. A reflux condenser was attached and the solution was heated at $110{ }^{\circ} \mathrm{C}$ for 3 d . The reaction mixture was cooled to room temperature and concentrated. The crude residue was directly purified by silica gel chromatography ( $7 \rightarrow 47 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes $+3 \% \mathrm{Et}_{3} \mathrm{~N}$; products are very sensitive to acid) to afford the desired product as a mixture of diastereomers ( $\sim 1.3: 1$ d.r. as judged by ${ }^{1} \mathrm{H}$ NMR analysis, $279 \mathrm{mg}, 0.62 \mathrm{mmol}, 62 \%)$. A small amount of additional diastereomers was isolated as well ( $\sim 11: 1$ d.r., $40 \mathrm{mg}, 0.09 \mathrm{mmol}, 9 \%$ ). The two major diastereomers were used in subsequent chemistry as a mixture but could be separated by very careful preparatory TLC ( $2 \%$ THF in DCM). The two additional diastereomers could not be separated from each other; in this case, only the primary component of that mixture is reported.


Diels-Alder Adduct 385: $[\alpha]_{\mathrm{D}}=+6.7\left(c 0.7, \mathrm{C}_{6} \mathrm{D}_{6}\right) ;{ }^{1} \mathrm{H}$ NMR (600 $\left.\mathrm{MHz}, \mathrm{C}_{6} \mathrm{D}_{6}\right) \delta 6.03(\mathrm{~s}, 1 \mathrm{H}), 5.53(\mathrm{~d}, J=4.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.93(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, 4.89 (br s, 1H), 4.46 (dd, $J=8.0,5.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.38(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H})$, $3.79(\mathrm{dd}, J=13.2,7.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.71(\mathrm{~d}, J=5.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.50(\mathrm{~s}, 3 \mathrm{H})$, $3.48-3.30(\mathrm{~m}, 8 \mathrm{H}), 3.28(\mathrm{~s}, 3 \mathrm{H}), 2.83(\mathrm{dd}, J=13.2,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.48$ (ddd, $J=14.6,9.7,8.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.35$ (ddd, $J=9.7,7.7,5.4 \mathrm{~Hz}, 1 \mathrm{H})$, 1.85 (ddd, $J=14.6,7.7,5.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.71$ (br s, 3 H ), $1.52(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$

NMR (176 MHz, $\mathrm{C}_{6} \mathrm{D}_{6}$ ) $\delta 171.1,146.8,143.6,136.4,131.0,124.6,111.1,104.3,82.2,71.2,68.2$, $66.8,64.0,63.6,55.0,51.4,51.1,43.2,42.7,42.1,36.9,31.4,26.4,23.1$; IR (thin film) vmax: 2978, 1745, 1671, $1096 \mathrm{~cm}^{-1}$; HRMS (ESI): calcd for $\mathrm{C}_{24} \mathrm{H}_{33} \mathrm{O}_{8}[\mathrm{M}+\mathrm{H}]^{+}: 449.2175$, found: 449.2180 .


Diels-Alder Adduct 386: $[\alpha]_{\mathrm{D}}=-66.4\left(c \quad 1.2, \mathrm{C}_{6} \mathrm{D}_{6}\right) ;{ }^{1} \mathrm{H}$ NMR (600 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 5.88(\mathrm{~s}, 1 \mathrm{H}), 4.84(\mathrm{~d}, J=6.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.84(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, $4.74(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 4.66(\mathrm{dd}, J=7.3,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.98-3.84(\mathrm{~m}, 8 \mathrm{H}), 3.80$ $(\mathrm{dt}, J=11.7,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.76(\mathrm{~s}, 3 \mathrm{H}), 3.48(\mathrm{~d}, J=5.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.34$ (s, 3H), $3.16(\mathrm{dd}, J=7.3,3.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.42-2.36(\mathrm{~m}, 3 \mathrm{H}), 1.87-1.81$ $(\mathrm{m}, 1 \mathrm{H}), 1.80(\mathrm{br} \mathrm{s}, 3 \mathrm{H}), 1.15(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ 175.7, 147.6, 143.2, 138.4, 123.8, 115.7, 109.9, 104.8, 83.6, 68.7, 66.0, $64.4,64.1,63.8,56.0,52.5,51.9,45.2,40.8,38.0,35.2,27.8,24.1,23.0$; IR (thin film) $v_{\max }: 2956$, 1736, 1671, 1646, $1091 \mathrm{~cm}^{-1}$; HRMS (ESI): calcd for $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{8} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 471.1995$, found: 471.1999.


Diels-Alder Adduct 387: Afforded as a $\sim 11: 1$ mixture of diastereomers; major reported. $[\alpha]_{\mathrm{D}}=-17.7\left(c \quad 1.1, \mathrm{C}_{6} \mathrm{D}_{6}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}(700 \mathrm{MHz}$, $\left.\mathrm{C}_{6} \mathrm{D}_{6}\right) \delta 6.02(\mathrm{~s}, 1 \mathrm{H}), 4.94(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.90-4.85(\mathrm{~m}, 1 \mathrm{H})$, $4.83-4.79(\mathrm{~m}, 1 \mathrm{H}), 4.37(\mathrm{~d}, J=9.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.37(\mathrm{t}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H})$, $3.75(\mathrm{~d}, J=6.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.59(\mathrm{~s}, 3 \mathrm{H}), 3.53-3.50(\mathrm{~m}, 1 \mathrm{H}), 3.48(\mathrm{dd}, J$ $=12.8,9.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.45(\mathrm{~s}, 3 \mathrm{H}), 3.43-3.40(\mathrm{~m}, 2 \mathrm{H}), 3.39-3.36(\mathrm{~m}$, $2 \mathrm{H}), 3.33-3.28(\mathrm{~m}, 3 \mathrm{H}), 3.00(\mathrm{dd}, J=12.8,8.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.49(\mathrm{q}, J=$ $9.7,6.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.41(\mathrm{dt}, J=14.4,8.0,6.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.02(\mathrm{ddd}, J=14.4,9.7,8.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.67-$ $1.64(\mathrm{~m}, 3 \mathrm{H}), 1.08(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $176 \mathrm{MHz}, \mathrm{C}_{6} \mathrm{D}_{6}$ ) $\delta 170.1,147.2,142.3,136.5,125.7,124.5$, $111.0,106.7,80.9,68.9,66.5,65.8,64.0,63.6,55.4,51.3,49.8,44.2,43.2,42.9,36.3,31.7,23.3$, 22.3; IR (thin film) $v_{\max }: 2965,1740,1565,1435,1137 \mathrm{~cm}^{-1}$; HRMS (ESI): calcd for $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{8} \mathrm{Na}$ [M+Na] ${ }^{+}$: 471.1995, found: 471.2000.

Oxidation/Ene Reaction: The purified mixture of Diels-Alder products 385 and 386 ( $\sim 1.3: 1$ d.r., $200 \mathrm{mg}, 0.45 \mathrm{mmol}, 1.0$ equiv) was dissolved in DCM ( 7.5 mL ) and cooled to $-40^{\circ} \mathrm{C}$. Freshly prepared and titrated DMDO ( 0.06 M in acetone, $7.5 \mathrm{~mL}, 0.45 \mathrm{mmol}, 1.0$ equiv) was then added dropwise. At the conclusion of the addition ( $<5 \mathrm{~min}$ ), the reaction mixture was further diluted with $\mathrm{DCM}(7.5 \mathrm{~mL})$ and $\mathrm{AlMe}_{3}(2.0 \mathrm{M}$ in hexanes, $330 \mu \mathrm{~L}, 0.67 \mathrm{mmol}, 1.5$ equiv) was added dropwise. The resulting solution was allowed to warm to $0{ }^{\circ} \mathrm{C}$ over 5 min before $\mathrm{H}_{2} \mathrm{O}(20 \mu \mathrm{~L})$ was added. An aqueous solution of $\mathrm{NaOH}(3 \mathrm{M}, 20 \mu \mathrm{~L})$ was added followed by additional $\mathrm{H}_{2} \mathrm{O}(50 \mu \mathrm{~L})$. When no further bubbling was observed, $\mathrm{MgSO}_{4}$ was added and the suspension was warmed to room temperature and stirred for 15 min . The mixture was filtered through celite, the residue was concentrated, and the crude product was purified by column chromatography ( $47 \rightarrow 97 \% \mathrm{EtOAc}$ in hexanes + $3 \% \mathrm{Et}_{3} \mathrm{~N}$ ) to afford quassin architectures 390 and 391 ( $\sim 1.3: 1$ d.r. as judged by ${ }^{1} \mathrm{H}$ NMR analysis, $116 \mathrm{mg}, 0.25 \mathrm{mmol}, 57 \%)$. These diastereomers could be separated by careful preparatory TLC ( $7 \%$ THF in DCM) and were subsequently characterized as single compounds:


Quassin Architecture 390: $[\alpha]_{\mathrm{D}}=+79.4\left(c \quad 0.8, \mathrm{CD}_{3} \mathrm{OD}\right) ;{ }^{1} \mathrm{H}$ NMR ( $700 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) $\delta 5.00(\mathrm{~d}, J=4.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.85(\mathrm{t}, J=2.0 \mathrm{~Hz}$, $1 \mathrm{H}), 4.76(\mathrm{t}, J=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.41(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.07(\mathrm{dd}, J=$ $8.6,2.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.03(\mathrm{td}, J=7.1,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.97(\mathrm{td}, J=7.1,3.4$ $\mathrm{Hz}, 1 \mathrm{H}), 3.92(\mathrm{dt}, J=8.2,7.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.88-3.81(\mathrm{~m}, 2 \mathrm{H}), 3.79-$ 3.75 (m, 1H), 3.73 (dt, $J=8.2,7.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.70-3.68(\mathrm{~m}, 1 \mathrm{H}), 3.68$ $(\mathrm{s}, 3 \mathrm{H}), 3.67(\mathrm{~d}, J=5.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.67(\mathrm{dd}, J=3.8,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.49$ (dd, $J=13.4,7.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), $3.26(\mathrm{~s}, 3 \mathrm{H}), 2.77$ (ddt, $J=14.6,3.8,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 2.51$ (dt, $J=12.0$, $7.5,5.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.38$ (ddd, $J=15.0,12.0,8.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.31$ (dd, $J=13.3,4.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.26$ (dd, $J=14.6,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.55(\mathrm{ddd}, J=15.0,7.5,2.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.22(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 176 MHz , $\left.\mathrm{CD}_{3} \mathrm{OD}\right) \delta 173.3,147.2,147.1,129.1,112.3,110.6,105.1,82.9,71.7,70.0,69.4,67.7,66.3,65.1$, $55.4,53.0,52.1,43.3,42.2,41.7,37.0,36.0,32.7,27.8$; IR (thin film) $v_{\max }: 3488,2954,1742,1653$, $1437 \mathrm{~cm}^{-1} ;$ HRMS (ESI) calcd for $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{9} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 487.1944$, found: 487.1947 .


Quassin Architecture 391: $[\alpha]_{\mathrm{D}}=-41.8$ (c 1.0, $\left.\mathrm{CD}_{3} \mathrm{OD}\right)$; ${ }^{1} \mathrm{H}$ NMR ( $700 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) $\delta 4.82$ (t, $J=2.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 4.81 (d, $J=5.6 \mathrm{~Hz}$, $1 \mathrm{H}), 4.73(\mathrm{t}, J=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.67(\mathrm{dd}, J=7.5,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.98-$ $3.91(\mathrm{~m}, 3 \mathrm{H}), 3.88-3.82(\mathrm{~m}, 3 \mathrm{H}), 3.79-3.75(\mathrm{~m}, 2 \mathrm{H}), 3.75(\mathrm{~s}, 3 \mathrm{H})$, $3.71-3.67$ (m, 2H), 3.61 (t, $J=3.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.35 (s, 3H), 3.09 (dd, $J$ $=7.5,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.71$ (ddt, $J=14.3,3.1,2.2 \mathrm{~Hz}, 1 \mathrm{H}), 2.66$ (ddd, $J$ $=13.8,6.1,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.50(\mathrm{td}, J=13.8,2.9 \mathrm{~Hz}, 1 \mathrm{H}), 2.39(\mathrm{dd}, J=$ $5.6,3.4 \mathrm{~Hz}, 1 \mathrm{H}), 2.27(\mathrm{dt}, J=14.3,3.1,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 1.49(\mathrm{dtd}, J=13.8,3.1,1.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.16(\mathrm{~s}$, $3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $176 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}$ ) $\delta 176.9,148.3,146.4,112.8,112.0,111.9,106.3,85.3,71.2$, $69.9,66.6,66.0,65.3,64.8,55.9,54.0,52.8,46.4,41.6,39.0,36.6,36.4,30.9,25.5$; IR (thin film) $v_{\max }: 3451,2919,1735,1652,1436 \mathrm{~cm}^{-1}$; HRMS (ESI) calcd for $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{9} \mathrm{Na}[\mathrm{M}+\mathrm{Na}]^{+}: 487.1944$, found: 487.1951.

## SI4.5 References:

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## SI4.6 X-Ray Crystallogrpahic Data

## SI4.6.1 X-Ray Crystallographic Data for Substrate 368



A colorless prism $0.20 \times 0.18 \times 0.07 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $100 \%$ complete to $79.1^{\circ}$ in $\theta$. A total of 41015 reflections were collected covering the indices, $-33<=h<=33,-34<=k<=31,-13<=l<=14.3304$ reflections were found to be symmetry independent, with an $\mathrm{R}_{\text {int }}$ of 0.0417 . Indexing and unit cell refinement indicated a rhombohedral, trigonal lattice. The space group was found to be R-3 (No. 148). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016.

Table SI4.6.1.1. Crystal data and structure refinement for $\mathbf{3 6 8}$.

| Identification code | $\mathbf{3 6 8}$ |
| :--- | :--- |
| Empirical formula | $\mathrm{C}_{10} \mathrm{H}_{18} \mathrm{~F}_{2} \mathrm{O}$ |
| Formula weight | 300.33 |
| Temperature $(\mathrm{K})$ | $100(2)$ |
| Crystal system | trigonal |
| Space group | $\mathrm{R}-3$ |
| $\mathrm{a}(\AA)$ | $26.8452(2)$ |
| $\mathrm{b}(\AA)$ | $26.8452(2)$ |
| $\mathrm{c}\left(\AA^{\AA}\right)$ | $11.23090(10)$ |
| $\alpha\left(^{\circ}\right)$ | 90 |
| $\beta\left(^{\circ}\right)$ | 90 |
| $\gamma\left(^{\circ}\right)$ | 120 |
| Volume $\left(\AA^{3}\right)$ | $7009.36(12)$ |
| Z | 18 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.281 |
| $\mu\left(\mathrm{~mm}{ }^{-1}\right)$ | 0.776 |
| $\mathrm{~F}(000)$ | 2844.0 |
| Crystal size $\left(\mathrm{mm}{ }^{3}\right)$ | $0.2 \times 0.18 \times 0.07$ |
| Radiation | $\mathrm{CuKa}(\lambda=1.54184)$ |
| $2 \Theta$ range for data collection $\left({ }^{\circ}\right)$ | 6.586 to 158.188 |
| Index ranges | $-33 \leq \mathrm{h} \leq 33,-34 \leq \mathrm{k} \leq 31,-13 \leq 1 \leq 14$ |
| Reflections collected | 41015 |
| Independent reflections | $3304\left[\mathrm{R}_{\text {int }}=0.0417, \mathrm{R}_{\text {sigma }}=0.0142\right]$ |
| Data/restraints $/$ parameters | $3304 / 0 / 204$ |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.059 |
| Final R indexes $[\mathrm{I}=2 \sigma(\mathrm{I})]$ | $\mathrm{R}_{1}=0.0447, \mathrm{wR} \mathrm{R}_{2}=0.1205$ |
| Final R indexes [all data $]$ | $\mathrm{R}_{1}=0.0463, \mathrm{wR} \mathrm{R}_{2}=0.1217$ |
| Largest diff. peak $/$ hole $\left(\mathrm{e} \AA^{\AA-3}\right)$ | $1.07 /-0.23$ |
|  |  |

Table SI4.6.1.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for $\mathbf{3 6 8} . U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| F2 | $4706.2(4)$ | $5311.7(4)$ | $-416.8(7)$ | $34.2(2)$ |
| O1 | $3904.0(4)$ | $6112.5(5)$ | $6525.9(9)$ | $28.7(2)$ |
| F1 | $3457.0(5)$ | $2749.2(4)$ | $5482.4(11)$ | $49.8(3)$ |
| C14 | $3826.5(6)$ | $5108.6(5)$ | $2722.8(12)$ | $21.7(3)$ |
| C8 | $3681.7(6)$ | $4376.3(6)$ | $5088.5(12)$ | $24.3(3)$ |
| C7 | $3768.2(6)$ | $4969.4(6)$ | $4958.9(12)$ | $22.9(3)$ |
| C15 | $4398.1(6)$ | $5237.3(6)$ | $2729.5(12)$ | $24.5(3)$ |
| C19 | $3559.1(6)$ | $5043.9(6)$ | $1621.0(12)$ | $26.0(3)$ |
| C2 | $4073.9(6)$ | $5388.1(6)$ | $5752.5(12)$ | $25.5(3)$ |
| C6 | $3497.8(6)$ | $5067.9(6)$ | $3860.3(12)$ | $22.6(3)$ |
| C17 | $4415.8(6)$ | $5238.9(6)$ | $620.1(12)$ | $26.5(3)$ |
| C16 | $4698.1(6)$ | $5302.0(6)$ | $1677.7(13)$ | $26.9(3)$ |
| C18 | $3853.3(6)$ | $5110.5(6)$ | $562.4(13)$ | $28.5(3)$ |
| C9 | $3131.9(6)$ | $3891.6(6)$ | $5062.5(13)$ | $28.1(3)$ |
| C5 | $3437.9(6)$ | $5604.9(6)$ | $4001.9(12)$ | $27.8(3)$ |
| C3 | $4194.7(6)$ | $5997.7(6)$ | $5581.0(12)$ | $26.7(3)$ |
| C4 | $4013.7(7)$ | $6109.8(6)$ | $4373.3(13)$ | $30.1(3)$ |
| C10 | $3051.9(7)$ | $3343.2(6)$ | $5200.1(15)$ | $34.0(3)$ |
| C11 | $3528.2(7)$ | $3283.7(6)$ | $5343.0(15)$ | $35.0(3)$ |
| C13 | $4147.7(7)$ | $4289.9(7)$ | $5224.7(15)$ | $34.6(3)$ |
| C1 | $4317.6(7)$ | $5303.0(7)$ | $6893.1(14)$ | $36.0(4)$ |
| C12 | $4079.2(7)$ | $3746.1(7)$ | $5350.1(17)$ | $39.8(4)$ |

Table SI4.6.1.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 368. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} \mathrm{U}_{11}+2 h k a * b^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| F2 | $41.7(5)$ | $38.7(5)$ | $25.3(4)$ | $3.5(3)$ | $10.4(4)$ | $22.4(4)$ |
| O1 | $29.8(5)$ | $27.8(5)$ | $25.3(5)$ | $-4.4(4)$ | $3.9(4)$ | $12.0(4)$ |
| F1 | $61.3(7)$ | $25.7(5)$ | $66.1(7)$ | $3.3(4)$ | $2.0(5)$ | $24.4(5)$ |
| C14 | $23.3(6)$ | $17.7(6)$ | $23.1(6)$ | $0.3(5)$ | $1.8(5)$ | $9.6(5)$ |
| C8 | $26.6(7)$ | $23.8(6)$ | $21.6(6)$ | $1.7(5)$ | $0.6(5)$ | $11.9(5)$ |
| C7 | $21.9(6)$ | $23.5(6)$ | $22.3(6)$ | $2.5(5)$ | $2.1(5)$ | $10.7(5)$ |
| C15 | $24.0(6)$ | $24.7(6)$ | $23.7(7)$ | $-1.3(5)$ | $-1.9(5)$ | $11.4(5)$ |
| C19 | $24.2(7)$ | $29.2(7)$ | $25.9(7)$ | $-1.3(5)$ | $-2.0(5)$ | $14.3(6)$ |
| C2 | $24.9(6)$ | $26.5(7)$ | $23.5(6)$ | $0.7(5)$ | $0.1(5)$ | $11.5(5)$ |
| C6 | $21.1(6)$ | $24.2(6)$ | $22.4(6)$ | $1.0(5)$ | $0.8(5)$ | $11.3(5)$ |
| C17 | $33.3(7)$ | $23.3(6)$ | $23.6(7)$ | $2.2(5)$ | $7.6(5)$ | $14.7(6)$ |
| C16 | $23.0(6)$ | $27.4(7)$ | $30.1(7)$ | $-1.0(5)$ | $2.9(5)$ | $12.5(5)$ |
| C18 | $34.1(7)$ | $31.4(7)$ | $22.5(7)$ | $-1.3(5)$ | $-2.9(5)$ | $18.2(6)$ |
| C9 | $25.9(7)$ | $28.8(7)$ | $29.0(7)$ | $1.2(5)$ | $2.6(5)$ | $13.3(6)$ |
| C5 | $35.7(7)$ | $34.6(7)$ | $22.1(6)$ | $2.2(5)$ | $3.0(5)$ | $24.3(6)$ |
| C3 | $25.6(7)$ | $24.5(7)$ | $26.9(7)$ | $-1.6(5)$ | $4.8(5)$ | $10.3(5)$ |
| C4 | $42.2(8)$ | $24.1(7)$ | $26.4(7)$ | $2.6(5)$ | $8.2(6)$ | $18.4(6)$ |
| C10 | $29.6(7)$ | $24.9(7)$ | $38.2(8)$ | $-0.9(6)$ | $2.2(6)$ | $6.8(6)$ |
| C11 | $45.2(9)$ | $23.1(7)$ | $38.8(8)$ | $2.7(6)$ | $2.2(7)$ | $18.6(7)$ |
| C13 | $25.8(7)$ | $27.1(7)$ | $48.1(9)$ | $5.7(6)$ | $-1.5(6)$ | $11.2(6)$ |
| C1 | $41.6(9)$ | $34.6(8)$ | $30.0(8)$ | $-3.7(6)$ | $-9.9(6)$ | $17.7(7)$ |
| C12 | $34.6(8)$ | $34.4(8)$ | $57.0(11)$ | $5.3(7)$ | $-2.0(7)$ | $22.1(7)$ |

Table SI4.6.1.4. Bond Lengths for 368.

| Atom | Atom | Length (A) | Atom | Atom | Length (A)) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| F2 | C17 | $1.3601(15)$ | C19 | C18 | $1.389(2)$ |
| O1 | C3 | $1.4389(16)$ | C2 | C3 | $1.5132(19)$ |
| F1 | C11 | $1.3586(17)$ | C2 | C1 | $1.507(2)$ |
| C14 | C15 | $1.3941(18)$ | C6 | C5 | $1.5366(18)$ |
| C14 | C19 | $1.3972(19)$ | C17 | C16 | $1.373(2)$ |
| C14 | C6 | $1.5253(18)$ | C17 | C18 | $1.372(2)$ |
| C8 | C7 | $1.4968(18)$ | C9 | C10 | $1.386(2)$ |
| C8 | C9 | $1.3972(19)$ | C5 | C4 | $1.518(2)$ |
| C8 | C13 | $1.390(2)$ | C3 | C4 | $1.521(2)$ |
| C7 | C2 | $1.3449(19)$ | C10 | C11 | $1.375(2)$ |
| C7 | C6 | $1.5203(18)$ | C11 | C12 | $1.376(2)$ |
| C15 | C16 | $1.3908(19)$ | C13 | C12 | $1.384(2)$ |

Table SI4.6.1.5. Bond Angles for 368.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C15 | C14 | C19 | $117.97(12)$ | F2 | C17 | C16 | $118.79(13)$ |
| C15 | C14 | C6 | $122.61(12)$ | F2 | C17 | C18 | $118.38(13)$ |
| C19 | C14 | C6 | $119.33(12)$ | C18 | C17 | C16 | $122.82(13)$ |
| C9 | C8 | C7 | $121.23(12)$ | C17 | C16 | C15 | $118.04(13)$ |
| C13 | C8 | C7 | $120.95(12)$ | C17 | C18 | C19 | $118.39(13)$ |
| C13 | C8 | C9 | $117.82(13)$ | C10 | C9 | C8 | $121.15(14)$ |
| C8 | C7 | C6 | $115.49(11)$ | C4 | C5 | C6 | $109.19(11)$ |
| C2 | C7 | C8 | $121.99(12)$ | O1 | C3 | C2 | $106.97(11)$ |
| C2 | C7 | C6 | $122.50(12)$ | O1 | C3 | C4 | $110.74(12)$ |
| C16 | C15 | C14 | $121.54(13)$ | C2 | C3 | C4 | $114.25(11)$ |
| C18 | C19 | C14 | $121.23(13)$ | C5 | C4 | C3 | $110.59(11)$ |
| C7 | C2 | C3 | $122.05(12)$ | C11 | C10 | C9 | $118.51(14)$ |
| C7 | C2 | C1 | $124.50(13)$ | F1 | C11 | C10 | $119.23(14)$ |
| C1 | C2 | C3 | $113.43(12)$ | F1 | C11 | C12 | $118.18(14)$ |
| C14 | C6 | C5 | $110.35(11)$ | C10 | C11 | C12 | $122.59(14)$ |
| C7 | C6 | C14 | $112.49(11)$ | C12 | C13 | C8 | $122.07(14)$ |
| C7 | C6 | C5 | $111.24(11)$ | C11 | C12 | C13 | $117.84(14)$ |

Table SI4.6.1.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 368 .

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H15 | 4587.1 | 5281.93 | 3469.94 | 29 |
| H19 | 3168.72 | 4952.72 | 1595.58 | 31 |
| H6 | 3101.59 | 4728.98 | 3776.96 | 27 |
| H16 | 5086.77 | 5387.4 | 1690.59 | 32 |
| H18 | 3669.6 | 5068.14 | -183.87 | 34 |
| H9 | 2807.13 | 3938.64 | 4948.4 | 34 |
| H5A | 3313.52 | 5692.61 | 3238.7 | 33 |
| H5B | 3143.66 | 5534.2 | 4612.33 | 33 |
| H3 | 4617.69 | 6264.16 | 5674.47 | 32 |
| H4A | 3984.32 | 6462.67 | 4414.11 | 36 |
| H4B | 4308.74 | 6171.85 | 3771.47 | 36 |
| H10 | 2676.49 | 3015.83 | 5195.9 | 41 |
| H13 | 4525.12 | 4614.27 | 5231.85 | 41 |
| H1A | 4129.25 | 4891.6 | 7078.94 | 54 |
| H1B | 4250.16 | 5505.96 | 7542.48 | 54 |
| H1C | 4732.06 | 5456.03 | 6799.58 | 54 |
| H12 | 4402.08 | 3693.85 | 5438.22 | 48 |
| H1 | $4071(9)$ | $6511(10)$ | $6653(19)$ | $54(6)$ |

## SI4.6.2 X-Ray Crystallographic Data for Substrate 371



A colorless needle $0.24 \times 0.06 \times 0.05 \mathrm{~mm}$ in size was mounted on Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at $100(2) \mathrm{K}$ using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $100 \%$ complete to $79.1^{\circ}$ in $\theta$. A total of 10823 reflections were collected covering the indices, $-28<=h<=14,-28<=k<=27,-9<=l<=9.2055$ reflections were found to be symmetry independent, with an $\mathrm{R}_{\text {int }}$ of 0.0386 . Indexing and unit cell refinement indicated a body centered, tetragonal lattice. The space group was found to be I4 $/ \mathrm{a}$ (No. 88). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016.

Table SI4.6.2.1. Crystal data and structure refinement for $\mathbf{3 7 1}$.

| Identification code | $\mathbf{3 7 1}$ |
| :--- | :--- |
| Empirical formula | $\mathrm{C}_{11} \mathrm{H}_{16} \mathrm{O}$ |
| Formula weight | 164.24 |
| Temperature $(\mathrm{K})$ | $100(2)$ |
| Crystal system | tetragonal |
| Space group | $\mathrm{I}_{4} / \mathrm{a}$ |
| $\mathrm{a}(\AA)$ | $22.7253(4)$ |
| $\mathrm{b}(\AA)$ | $22.7253(4)$ |
| $\mathrm{c}(\AA)$ | $7.5782(2)$ |
| $\alpha\left(^{\circ}\right)$ | 90 |
| $\beta\left({ }^{\circ}\right)$ | 90 |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume $\left(\AA^{3}\right)$ | $3913.68(17)$ |
| Z | 16 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.115 |
| $\mu\left(\mathrm{~mm}^{-1}\right)$ | 0.533 |
| $\mathrm{~F}(000)$ | 1440.0 |
| Crystal size $\left(\mathrm{mm}{ }^{3}\right)$ | $0.24 \times 0.06 \times 0.05$ |
| Radiation | $\mathrm{CuK} \alpha(\lambda=1.54184)$ |
| $2 \Theta$ range for data collection $\left({ }^{\circ}\right)$ | 7.78 to 158.146 |
| Index ranges | $-28 \leq \mathrm{h} \leq 14,-28 \leq \mathrm{k} \leq 27,-9 \leq 1 \leq 9$ |
| Reflections collected | 10823 |
| Independent reflections | $2055\left[\mathrm{R}_{\mathrm{int}}=0.0386, \mathrm{R}_{\text {sigma }}=0.0215\right]$ |
| Data/restraints $/$ parameters | $2055 / 0 / 173$ |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.081 |
| Final R indexes $[\mathrm{I}>=2 \sigma(\mathrm{I})]$ | $\mathrm{R}_{1}=0.0529, \mathrm{wR}{ }_{2}=0.1395$ |
| Final R indexes $[$ all data $]$ | $\mathrm{R}_{1}=0.0579, \mathrm{wR} \mathrm{R}_{2}=0.1431$ |
| Largest diff. peak/hole $\left(\mathrm{e} \AA \AA^{-3}\right)$ | $0.22 /-0.18$ |
|  |  |

Table SI4.6.2.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for $\mathbf{3 7 1} . U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| O1 | $2139.1(5)$ | $4573.3(5)$ | $3787.1(16)$ | $33.7(3)$ |
| C9 | $1648.5(7)$ | $3358.2(7)$ | $5843(2)$ | $29.2(4)$ |
| C2 | $1563.1(7)$ | $3938.6(7)$ | $5556(2)$ | $29.1(4)$ |
| C3 | $1622.6(7)$ | $4208.7(7)$ | $3739(2)$ | $30.0(4)$ |
| C6 | $1835.0(7)$ | $2941.2(7)$ | $4375(2)$ | $32.2(4)$ |
| C10 | $1579.2(7)$ | $3107.6(7)$ | $7620(2)$ | $33.9(4)$ |
| C1 | $1424.5(8)$ | $4379.6(8)$ | $6981(2)$ | $34.2(4)$ |
| C4 | $1671.8(8)$ | $3764.3(8)$ | $2259(2)$ | $33.8(4)$ |
| C7 | $1352.6(8)$ | $2535.0(8)$ | $3743(2)$ | $38.2(4)$ |
| C5 | $2092.6(8)$ | $3275.9(8)$ | $2794(2)$ | $35.9(4)$ |
| C11 | $1659.0(9)$ | $2550.2(8)$ | $8087(3)$ | $42.7(5)$ |
| C8 | $791.7(9)$ | $2564.4(9)$ | $4127(3)$ | $46.6(5)$ |

Table SI4.6.2.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 371. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} \mathrm{U}_{11}+2 h k a^{*} b^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | $32.6(6)$ | $33.7(6)$ | $34.7(7)$ | $7.0(5)$ | $-4.5(5)$ | $-6.4(4)$ |
| C9 | $26.1(7)$ | $30.7(8)$ | $31.0(8)$ | $-2.8(6)$ | $-0.2(6)$ | $-0.1(6)$ |
| C2 | $25.0(7)$ | $31.4(8)$ | $30.9(8)$ | $-0.7(6)$ | $0.4(6)$ | $-0.5(6)$ |
| C3 | $26.3(7)$ | $30.4(8)$ | $33.4(8)$ | $0.9(6)$ | $-2.4(6)$ | $-1.4(6)$ |
| C6 | $34.3(8)$ | $28.6(8)$ | $33.7(9)$ | $-2.2(7)$ | $-1.4(7)$ | $3.8(6)$ |
| C10 | $35.7(8)$ | $33.8(8)$ | $32.2(9)$ | $-0.3(7)$ | $0.9(7)$ | $-1.0(6)$ |
| C1 | $36.9(9)$ | $30.7(8)$ | $35.1(9)$ | $-3.3(7)$ | $2.2(7)$ | $1.4(7)$ |
| C4 | $37.2(9)$ | $36.2(9)$ | $28.0(8)$ | $2.3(7)$ | $-0.3(7)$ | $-4.1(7)$ |
| C7 | $47.6(10)$ | $29.0(8)$ | $38.0(10)$ | $-2.3(7)$ | $-3.9(8)$ | $-0.8(7)$ |
| C5 | $36.8(9)$ | $37.4(9)$ | $33.4(9)$ | $-6.7(7)$ | $4.6(7)$ | $1.8(7)$ |
| C11 | $54.6(11)$ | $35.5(9)$ | $37.9(10)$ | $4.8(8)$ | $-1.3(8)$ | $-2.4(8)$ |
| C8 | $44.6(10)$ | $39.4(10)$ | $55.7(12)$ | $-3.6(9)$ | $-5.1(9)$ | $-7.5(8)$ |

Table SI4.6.2.4. Bond Lengths for $\mathbf{3 7 1}$.

| Atom | Atom | Length $(\AA)$ | Atom | Atom | Length $(\AA)$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | C 3 | $1.4373(18)$ | C 3 | C 4 | $1.513(2)$ |
| C 9 | C 2 | $1.351(2)$ | C 6 | C 7 | $1.511(2)$ |
| C9 | C 6 | $1.522(2)$ | C 6 | C 5 | $1.535(2)$ |
| C9 | C 10 | $1.470(2)$ | C 10 | C 11 | $1.328(2)$ |
| C2 | C 3 | $1.513(2)$ | C 4 | C 5 | $1.520(2)$ |
| C2 | C 1 | $1.506(2)$ | C 7 | C 8 | $1.309(3)$ |

Table SI4.6.2.5. Bond Angles for $\mathbf{3 7 1}$.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C2 | C 9 | C6 | $122.01(15)$ | C2 | C3 | C4 | $114.22(14)$ |
| C2 | C9 | C10 | $120.68(15)$ | C9 | C6 | C5 | $111.63(14)$ |
| C10 | C9 | C6 | $117.29(14)$ | C7 | C6 | C9 | $114.20(14)$ |
| C9 | C2 | C3 | $121.99(15)$ | C7 | C6 | C5 | $109.40(14)$ |
| C9 | C2 | C1 | $124.35(15)$ | C11 | C10 | C $9 ~$ | $126.80(17)$ |
| C1 | C2 | C3 | $113.63(14)$ | C3 | C4 | C5 | $109.65(14)$ |
| O1 | C3 | C2 | $106.50(13)$ | C8 | C7 | C6 | $127.22(17)$ |
| O1 | C3 | C4 | $110.05(13)$ | C4 | C5 | C6 | $109.26(14)$ |

Table SI4.6.2.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 371 .

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H1 | $2115(10)$ | $4837(11)$ | $2950(40)$ | $55(7)$ |
| H11A | $1590(10)$ | $2414(10)$ | $9360(30)$ | $53(6)$ |
| H11B | $1777(10)$ | $2240(11)$ | $7220(40)$ | $57(7)$ |
| H8A | $622(10)$ | $2883(11)$ | $4920(30)$ | $58(7)$ |
| H8B | $488(12)$ | $2276(11)$ | $3650(30)$ | $62(7)$ |
| H3 | $1266(9)$ | $4473(9)$ | $3520(30)$ | $36(5)$ |
| H4A | $1267(9)$ | $3597(8)$ | $2020(30)$ | $34(5)$ |
| H6 | $2164(8)$ | $2695(8)$ | $4900(30)$ | $35(5)$ |
| H4B | $1801(9)$ | $3966(9)$ | $1190(30)$ | $39(5)$ |
| H5A | $2496(10)$ | $3446(9)$ | $3160(30)$ | $46(6)$ |
| H1A | $1766(12)$ | $4470(12)$ | $7700(40)$ | $72(8)$ |
| H5B | $2168(8)$ | $3000(9)$ | $1800(30)$ | $33(5)$ |
| H10 | $1467(9)$ | $3374(9)$ | $8570(30)$ | $37(5)$ |
| H1B | $1081(11)$ | $4270(11)$ | $7730(40)$ | $62(7)$ |
| H7 | $1502(10)$ | $2212(10)$ | $2910(30)$ | $49(6)$ |
| H1C | $1334(13)$ | $4757(13)$ | $6500(40)$ | $81(9)$ |

## SI4.6.3 X-Ray Crystallographic Data for Substrate 382



A colorless prism $0.22 \times 0.22 \times 0.05 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at $100(2) \mathrm{K}$ using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $97 \%$ complete to $74.5^{\circ}$ in $\theta$. A total of 8543 reflections were collected covering the indices, $-6<=h<=6,-9<=k<=7,-39<=l<=39.2588$ reflections were found to be symmetry independent, with an $\mathrm{R}_{\text {int }}$ of 0.0288 . Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $\mathrm{P}_{1} 2_{1} 2_{1}$ (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016.

Although racemic starting material was used to prepare this crystal, spontaneous resolution appears to have occurred. Due to this unexpected outcome, identifying anomalous dispersion was not prioritized during data collection and thus insufficient data exists to definitively assign the absolute stereochemistry of the crystal. It has been rendered here in the enantiomer that corresponds to how the structure was depicted in the main text.

Table SI4.6.3.1. Crystal data and structure refinement for $\mathbf{3 8 2}$.

| Identification code | $\mathbf{3 8 2}$ |
| :--- | :--- |
| Empirical formula | $\mathrm{C}_{16} \mathrm{H}_{20} \mathrm{O}_{2}$ |
| Formula weight | 244.32 |
| Temperature $(\mathrm{K})$ | $100(2)$ |
| Crystal system | orthorhombic |
| Space group | $\mathrm{P} 2_{1} 2_{1} 2_{1}$ |
| $\mathrm{a}(\AA)$ | $5.52630(10)$ |
| $\mathrm{b}(\AA)$ | $7.5880(2)$ |
| $\mathrm{c}(\AA)$ | $31.5641(6)$ |
| $\alpha\left({ }^{\circ}\right)$ | 90 |
| $\beta\left(^{\circ}\right)$ | 90 |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume $\left(\AA^{3}\right)$ | $1323.60(5)$ |
| Z | 4 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.226 |
| $\mu\left(\right.$ mm $\left.{ }^{-1}\right)$ | 0.622 |
| $\mathrm{~F}(000)$ | 528.0 |
| Crystal size $\left(\mathrm{mm}{ }^{3}\right)$ | $0.22 \times 0.22 \times 0.05$ |
| Radiation | $\mathrm{CuK} \alpha(\lambda=1.54184)$ |
| $2 \Theta$ range for data collection $\left({ }^{\circ}\right)$ | 11.214 to 148.98 |
| Index ranges | $-6 \leq \mathrm{h} \leq 6,-9 \leq \mathrm{k} \leq 7,-39 \leq 1 \leq 39$ |
| Reflections collected | 8543 |
| Independent reflections | $2588\left[\mathrm{R}_{\text {int }}=0.0288, \mathrm{R}_{\text {sigma }}=0.0177\right]$ |
| Data/restraints $/$ parameters | $2588 / 0 / 177$ |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.069 |
| Final R indexes $[\mathrm{I}>=2 \sigma(\mathrm{I})]$ | $\mathrm{R}_{1}=0.0330, \mathrm{wR}{ }_{2}=0.0866$ |
| Final R indexes [all data $]$ | $\mathrm{R}_{1}=0.0334, \mathrm{wR}{ }_{2}=0.0869$ |
| Largest diff. peak/hole $\left(\mathrm{e} \AA \AA^{-3}\right)$ | $0.20 /-0.20$ |
| Flack parameter | $0.32(9)$ |
|  |  |

Table SI4.6.3.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for $\mathbf{3 8 2} . U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| O2 | $1794(2)$ | $6540.2(16)$ | $7924.5(4)$ | $20.9(3)$ |
| O1 | $448(3)$ | $7688(2)$ | $5139.8(4)$ | $27.6(3)$ |
| C13 | $2178(3)$ | $6437(2)$ | $7495.1(5)$ | $17.2(3)$ |
| C11 | $1301(3)$ | $5520(2)$ | $6782.1(5)$ | $18.0(3)$ |
| C12 | $717(3)$ | $5526(2)$ | $7214.4(5)$ | $18.2(3)$ |
| C15 | $4756(3)$ | $7314(2)$ | $6919.8(5)$ | $19.0(3)$ |
| C14 | $4213(3)$ | $7336(2)$ | $7347.1(5)$ | $18.9(3)$ |
| C10 | $3309(3)$ | $6411(2)$ | $6628.0(5)$ | $17.1(3)$ |
| C16 | $-354(3)$ | $5741(2)$ | $8082.8(5)$ | $22.9(4)$ |
| C3 | $2928(3)$ | $5013(2)$ | $5888.4(5)$ | $18.9(4)$ |
| C4 | $1121(3)$ | $5253(2)$ | $5608.2(5)$ | $21.1(4)$ |
| C9 | $3936(3)$ | $6516(2)$ | $6157.5(5)$ | $18.7(4)$ |
| C8 | $3202(3)$ | $8323(2)$ | $5977.1(5)$ | $21.4(4)$ |
| C7 | $495(3)$ | $8354(2)$ | $5891.8(5)$ | $22.4(4)$ |
| C6 | $-160(3)$ | $7003(2)$ | $5555.3(5)$ | $21.6(4)$ |
| C1 | $5779(4)$ | $2875(3)$ | $6222.9(6)$ | $28.0(4)$ |
| C5 | $181(4)$ | $3849(3)$ | $5313.1(6)$ | $28.2(4)$ |
| C2 | $4100(3)$ | $3290(2)$ | $5938.6(6)$ | $24.8(4)$ |

Table SI4.6.3.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 382. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} \mathrm{U}_{11}+2 h k a^{*} b^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O2 | $25.0(6)$ | $22.7(6)$ | $15.1(5)$ | $0.5(5)$ | $-0.4(5)$ | $-3.1(5)$ |
| O1 | $26.0(7)$ | $41.5(8)$ | $15.2(6)$ | $5.9(5)$ | $0.7(5)$ | $3.2(6)$ |
| C13 | $19.3(8)$ | $16.8(7)$ | $15.5(7)$ | $1.9(6)$ | $-1.6(6)$ | $2.4(7)$ |
| C11 | $17.3(8)$ | $18.2(7)$ | $18.6(7)$ | $-1.7(6)$ | $-1.5(6)$ | $-1.6(7)$ |
| C12 | $17.8(8)$ | $18.2(7)$ | $18.5(7)$ | $1.3(6)$ | $1.1(6)$ | $-2.4(7)$ |
| C15 | $15.6(8)$ | $19.1(7)$ | $22.4(8)$ | $1.1(6)$ | $0.3(7)$ | $-2.0(7)$ |
| C14 | $17.3(8)$ | $19.0(7)$ | $20.3(8)$ | $-1.1(6)$ | $-4.8(7)$ | $-1.1(7)$ |
| C10 | $16.3(8)$ | $17.1(7)$ | $17.9(7)$ | $0.0(6)$ | $0.0(6)$ | $0.8(7)$ |
| C16 | $24.6(9)$ | $25.8(8)$ | $18.2(7)$ | $2.4(7)$ | $3.5(7)$ | $-0.2(8)$ |
| C3 | $18.9(8)$ | $22.2(8)$ | $15.5(7)$ | $-0.8(6)$ | $3.7(7)$ | $-1.2(7)$ |
| C4 | $20.4(8)$ | $27.4(9)$ | $15.5(7)$ | $-2.0(7)$ | $2.2(7)$ | $-1.8(7)$ |
| C9 | $15.8(7)$ | $22.3(8)$ | $17.9(7)$ | $-0.4(7)$ | $1.0(6)$ | $-1.6(7)$ |
| C8 | $25.0(9)$ | $20.8(8)$ | $18.5(8)$ | $1.0(7)$ | $1.9(7)$ | $-3.3(7)$ |
| C7 | $25.2(9)$ | $23.9(8)$ | $18.1(7)$ | $2.1(7)$ | $1.2(7)$ | $3.2(8)$ |
| C6 | $17.9(8)$ | $31.9(9)$ | $14.9(7)$ | $2.1(7)$ | $2.3(6)$ | $1.5(7)$ |
| C1 | $27.3(10)$ | $24.4(9)$ | $32.5(9)$ | $-1.0(8)$ | $-1.0(8)$ | $1.9(8)$ |
| C5 | $29.2(10)$ | $33.2(10)$ | $22.2(8)$ | $-5.1(8)$ | $-3.7(8)$ | $-0.2(8)$ |
| C2 | $27.1(9)$ | $22.9(8)$ | $24.3(8)$ | $-4.3(7)$ | $0.7(7)$ | $0.3(8)$ |

Table SI4.6.3.4. Bond Lengths for $\mathbf{3 8 2}$.

| Atom | Atom | Length $(\mathbf{\AA})$ | Atom | Atom | Length $(\mathbf{\AA})$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| O2 | C13 | $1.3743(19)$ | C3 | C4 | $1.346(2)$ |
| O2 | C16 | $1.423(2)$ | C3 | C9 | $1.527(2)$ |
| O1 | C6 | $1.450(2)$ | C3 | C2 | $1.468(2)$ |
| C13 | C12 | $1.384(2)$ | C4 | C6 | $1.514(2)$ |
| C13 | C14 | $1.396(2)$ | C4 | C5 | $1.508(2)$ |
| C11 | C12 | $1.402(2)$ | C9 | C8 | $1.539(2)$ |
| C11 | C10 | $1.388(2)$ | C8 | C7 | $1.520(3)$ |
| C15 | C14 | $1.382(2)$ | C7 | C6 | $1.519(2)$ |
| C15 | C10 | $1.399(2)$ | C1 | C2 | $1.329(3)$ |
| C10 | C9 | $1.527(2)$ |  |  |  |

Table SI4.6.3.5. Bond Angles for $\mathbf{3 8 2}$.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C13 | O2 | C16 | $116.79(13)$ | C2 | C3 | C9 | $116.36(15)$ |
| O2 | C13 | C12 | $124.74(15)$ | C3 | C4 | C6 | $122.55(16)$ |
| O2 | C13 | C14 | $115.26(14)$ | C3 | C4 | C5 | $124.46(17)$ |
| C12 | C13 | C14 | $120.00(15)$ | C5 | C4 | C6 | $112.98(15)$ |
| C10 | C11 | C12 | $121.58(16)$ | C10 | C9 | C3 | $114.77(14)$ |
| C13 | C12 | C11 | $119.36(16)$ | C10 | C9 | C8 | $110.27(13)$ |
| C14 | C15 | C10 | $121.65(16)$ | C3 | C9 | C8 | $111.30(13)$ |
| C15 | C14 | C13 | $119.70(16)$ | C7 | C8 | C9 | $109.81(15)$ |
| C11 | C10 | C15 | $117.70(15)$ | C6 | C7 | C8 | $110.35(15)$ |
| C11 | C10 | C9 | $123.23(15)$ | O1 | C6 | C4 | $107.81(14)$ |
| C15 | C10 | C9 | $119.01(14)$ | O1 | C6 | C7 | $109.61(15)$ |
| C4 | C3 | C9 | $122.33(16)$ | C4 | C6 | C7 | $113.76(14)$ |
| C4 | C3 | C2 | $121.26(17)$ | C1 | C2 | C3 | $126.33(18)$ |

Table SI4.6.3.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for $\mathbf{3 8 2}$.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H11 | 319.64 | 4903.17 | 6594.18 | 22 |
| H12 | -639.44 | 4922.97 | 7311.5 | 22 |
| H15 | 6117.03 | 7913.55 | 6823.83 | 23 |
| H14 | 5199.06 | 7947.68 | 7535.2 | 23 |
| H16A | -1731.63 | 6213.76 | 7936.72 | 34 |
| H16B | -499.1 | 5978.24 | 8380.45 | 34 |
| H16C | -278.03 | 4490.41 | 8038.04 | 34 |
| H9 | 5703.24 | 6446.56 | 6137.26 | 22 |
| H8A | 3616.43 | 9242.85 | 6177.8 | 26 |
| H8B | 4076.54 | 8544.44 | 5716.09 | 26 |
| H7A | -375.73 | 8093.92 | 6151.22 | 27 |
| H7B | 19.15 | 9519.46 | 5797.1 | 27 |
| H6 | -1909.02 | 6797.36 | 5566.26 | 26 |
| H5A | 1489.57 | 3397.83 | 5145.11 | 42 |
| H5B | -1029.6 | 4345.74 | 5130.56 | 42 |
| H5C | -517.15 | 2908.42 | 5475.86 | 42 |
| H2 | 3621.13 | 2402.75 | 5753.48 | 30 |
| H1 | $-810(70)$ | $7790(50)$ | $4995(11)$ | $72(10)$ |
| H1A | $6390(50)$ | $1700(30)$ | $6232(7)$ | $32(6)$ |
| H1B | $6420(50)$ | $3700(30)$ | $6438(8)$ | $37(6)$ |

## SI4.6.4 X-Ray Crystallographic Data for Substrate 383



A colorless prism $0.16 \times 0.13 \times 0.05 \mathrm{~mm}$ in size was mounted on Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $99 \%$ complete to $68.3^{\circ}$ in $\theta$. A total of 20223 reflections were collected covering the indices, $-9<=h<=9,-7<=k<=7,-18<=l<=19.2984$ reflections were found to be symmetry independent, with an $\mathrm{R}_{\text {int }}$ of 0.0352 . Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $\mathrm{P}_{1}$ (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Absolute stereochemistry was unambiguously determined from the diffraction data.

Table SI4.6.4.1. Crystal data and structure refinement for $\mathbf{3 8 3}$.

| Identification code | 383 |
| :---: | :---: |
| Empirical formula | $\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{O}_{5}$ |
| Formula weight | 320.39 |
| Temperature (K) | 99.97 |
| Crystal system | monoclinic |
| Space group | P2, |
| a ( $\AA$ ) | 8.0320(3) |
| b ( $\AA$ ) | 6.3518(2) |
| c ( $\AA$ ) | 16.1371(6) |
| $\alpha\left({ }^{\circ}\right.$ ) | 90 |
| $\beta\left({ }^{\circ}\right)$ | 93.7797(15) |
| $\gamma\left(^{\circ}\right.$ ) | 90 |
| Volume ( $\AA^{3}$ ) | 821.49(5) |
| Z | 2 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.2951 |
| $\mu\left(\mathrm{mm}^{-1}\right)$ | 0.768 |
| $\mathrm{F}(000)$ | 345.2 |
| Crystal size ( $\mathrm{mm}^{3}$ ) | $0.16 \times 0.13 \times 0.05$ |
| Radiation | $\mathrm{Cu} \mathrm{K} \alpha(\lambda=1.54178)$ |
| $2 \Theta$ range for data collection ( ${ }^{\circ}$ ) | 5.48 to 136.56 |
| Index ranges | $-9 \leq \mathrm{h} \leq 9,-7 \leq \mathrm{k} \leq 7,-18 \leq 1 \leq 19$ |
| Reflections collected | 20223 |
| Independent reflections | $2984\left[\mathrm{R}_{\mathrm{int}}=0.0352, \mathrm{R}_{\text {sigma }}=0.0192\right]$ |
| Data/restraints/parameters | 2984/1/297 |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.096 |
| Final R indexes [I $>=2 \sigma$ (I)] | $\mathrm{R}_{1}=0.0243, \mathrm{wR}_{2}=0.0616$ |
| Final R indexes [all data] | $\mathrm{R}_{1}=0.0249, \mathrm{wR}_{2}=0.0620$ |
| Largest diff. peak/hole (e $\AA^{-3}$ ) | 0.13/-0.12 |
| Flack parameter | 0.02(11) |

Table SI4.6.4.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for $\mathbf{3 8 3} . U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| O1 | $-2348.9(11)$ | $-217.9(14)$ | $3233.7(6)$ | $26.7(2)$ |
| O2 | $-7451.1(11)$ | $-860.9(14)$ | $1044.1(6)$ | $28.1(2)$ |
| O3 | $-2480.9(11)$ | $4804.0(14)$ | $1581.5(6)$ | $25.1(2)$ |
| O4 | $-941.7(11)$ | $3337.3(15)$ | $4135.2(6)$ | $30.9(2)$ |
| O5 | $456.6(12)$ | $2965.6(14)$ | $974.2(6)$ | $30.1(2)$ |
| C6 | $-3794.2(14)$ | $1429.3(18)$ | $1641.2(7)$ | $19.5(2)$ |
| C7 | $-6284.3(16)$ | $1141(2)$ | $3629.5(8)$ | $27.4(3)$ |
| C8 | $-4374.1(15)$ | $2035.6(19)$ | $2492.8(8)$ | $20.3(2)$ |
| C9 | $-2942.5(15)$ | $1816(2)$ | $3133.5(7)$ | $21.4(3)$ |
| C10 | $-2331.4(16)$ | $2669.7(18)$ | $1418.6(7)$ | $20.1(3)$ |
| C11 | $-939.0(15)$ | $1845(2)$ | $1157.6(8)$ | $24.0(3)$ |
| C12 | $-4030.0(16)$ | $-641(2)$ | $301.7(8)$ | $24.6(3)$ |
| C13 | $-4487.6(14)$ | $-107(2)$ | $1165.2(7)$ | $20.6(2)$ |
| C14 | $-2258.7(15)$ | $3459(2)$ | $3539.3(8)$ | $24.9(3)$ |
| C15 | $-6165.3(18)$ | $-429(2)$ | $4171.2(9)$ | $32.8(3)$ |
| C16 | $-5878.5(15)$ | $-1445(2)$ | $1470.2(8)$ | $22.9(3)$ |
| C17 | $-712.3(17)$ | $-239(2)$ | $3650.4(9)$ | $32.4(3)$ |
| C18 | $-650.5(19)$ | $1210(3)$ | $4392.5(9)$ | $34.3(3)$ |
| C19 | $-5992.5(15)$ | $875(2)$ | $2712.5(8)$ | $22.8(3)$ |
| C20 | $-5966.9(16)$ | $-1388(2)$ | $2408.8(8)$ | $23.6(3)$ |
| C21 | $-875.6(19)$ | $5781(2)$ | $1680.6(9)$ | $31.3(3)$ |
| C22 | $137(2)$ | $5199(2)$ | $960.6(10)$ | $34.5(3)$ |
| C23 | $-6715.1(19)$ | $3323(2)$ | $3884.7(10)$ | $33.8(3)$ |

Table SI4.6.4.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 383. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} \mathrm{U}_{11}+2 h k a^{*} b^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{12}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{23}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | $21.9(4)$ | $26.4(5)$ | $30.8(5)$ | $-0.9(4)$ | $-4.4(4)$ | $3.3(4)$ |
| O2 | $21.4(4)$ | $29.7(5)$ | $32.4(5)$ | $-4.2(4)$ | $-4.9(4)$ | $-1.8(4)$ |
| O3 | $28.3(4)$ | $18.5(4)$ | $28.9(5)$ | $-3.0(4)$ | $3.8(4)$ | $0.4(4)$ |
| O4 | $27.2(5)$ | $40.7(6)$ | $24.3(4)$ | $-7.2(4)$ | $-3.7(4)$ | $-3.6(4)$ |
| O5 | $23.8(4)$ | $29.3(5)$ | $38.2(5)$ | $-6.6(4)$ | $9.9(4)$ | $-1.3(4)$ |
| C6 | $18.0(5)$ | $19.9(6)$ | $20.5(6)$ | $1.6(5)$ | $1.0(4)$ | $2.3(5)$ |
| C7 | $19.1(6)$ | $36.9(8)$ | $26.8(7)$ | $-5.0(5)$ | $5.2(5)$ | $-5.1(6)$ |
| C8 | $20.0(6)$ | $18.7(6)$ | $22.1(6)$ | $-0.7(5)$ | $1.8(5)$ | $-0.6(5)$ |
| C9 | $20.8(6)$ | $23.4(6)$ | $20.2(6)$ | $-2.6(5)$ | $3.4(5)$ | $0.9(5)$ |
| C10 | $24.4(6)$ | $17.5(6)$ | $18.1(5)$ | $-1.4(5)$ | $-0.8(5)$ | $0.5(5)$ |
| C11 | $23.2(6)$ | $22.8(6)$ | $26.2(6)$ | $-4.2(5)$ | $3.2(5)$ | $0.4(5)$ |
| C12 | $25.6(6)$ | $25.6(7)$ | $22.5(6)$ | $-0.7(5)$ | $0.3(5)$ | $-1.6(5)$ |
| C13 | $19.2(6)$ | $20.2(6)$ | $22.2(6)$ | $1.1(5)$ | $-0.4(5)$ | $0.8(5)$ |
| C14 | $22.4(6)$ | $31.8(7)$ | $20.6(6)$ | $-2.9(5)$ | $1.5(5)$ | $-0.8(5)$ |
| C15 | $33.7(7)$ | $42.1(9)$ | $23.2(7)$ | $-1.4(7)$ | $6.1(6)$ | $-1.0(6)$ |
| C16 | $20.3(6)$ | $22.4(6)$ | $25.8(6)$ | $-3.1(5)$ | $-0.6(5)$ | $-2.7(5)$ |
| C17 | $23.6(6)$ | $36.7(8)$ | $35.6(7)$ | $0.9(6)$ | $-7.1(6)$ | $6.6(7)$ |
| C18 | $28.5(7)$ | $47.8(9)$ | $26.1(7)$ | $-4.6(6)$ | $-2.8(6)$ | $7.2(6)$ |
| C19 | $18.6(6)$ | $26.9(6)$ | $22.9(6)$ | $-1.9(5)$ | $2.7(5)$ | $-1.1(5)$ |
| C20 | $21.7(6)$ | $24.2(6)$ | $25.1(6)$ | $-4.8(5)$ | $3.5(5)$ | $0.9(5)$ |
| C21 | $34.1(7)$ | $24.7(6)$ | $35.6(8)$ | $-10.5(6)$ | $5.8(6)$ | $-0.8(6)$ |
| C22 | $38.0(8)$ | $31.0(8)$ | $35.5(8)$ | $-11.6(6)$ | $9.4(6)$ | $1.3(6)$ |
| C23 | $32.5(7)$ | $37.0(8)$ | $33.1(8)$ | $-3.4(7)$ | $10.8(6)$ | $-6.3(6)$ |

Table SI4.6.4.4. Bond Lengths for 383.

| Atom | Atom | Length ( $\AA$ ) | Atom | Atom | Length ( $\AA$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| O1 | C9 | 1.3830(15) | C7 | C19 | 1.5227(17) |
| O1 | C17 | $1.4366(16)$ | C7 | C23 | 1.493(2) |
| O2 | C16 | 1.4460(15) | C8 | C9 | 1.5013(16) |
| O3 | C10 | $1.3876(15)$ | C8 | C19 | 1.5555(16) |
| O3 | C21 | 1.4304(17) | C9 | C14 | 1.3312(19) |
| O4 | C14 | 1.3840(15) | C10 | C11 | 1.3283(18) |
| O4 | C18 | $1.4286(19)$ | C12 | C13 | 1.5031(16) |
| O5 | C11 | $1.3763(15)$ | C13 | C16 | 1.5114(16) |
| O5 | C22 | $1.4415(18)$ | C16 | C20 | 1.5214(17) |
| C6 | C8 | 1.5291(16) | C17 | C18 | 1.508(2) |
| C6 | C10 | $1.4785(17)$ | C19 | C20 | 1.5193(18) |
| C6 | C13 | 1.3403(17) | C21 | C22 | 1.508(2) |
| C7 | C15 | 1.325(2) |  |  |  |

Table SI4.6.4.5. Bond Angles for 383.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C17 | O1 | C9 | 111.16(10) | C11 | C10 | C6 | 124.48(11) |
| C21 | O3 | C10 | 110.88(11) | C10 | C11 | O5 | 125.39(11) |
| C18 | O4 | C14 | 110.97(10) | C12 | C13 | C6 | 125.29(11) |
| C22 | O5 | C11 | 111.44(10) | C16 | C13 | C6 | 120.72(11) |
| C10 | C6 | C8 | 112.22(10) | C16 | C13 | C12 | 113.97(10) |
| C13 | C6 | C8 | 123.97(10) | C9 | C14 | O4 | 124.72(13) |
| C13 | C6 | C10 | 123.76(11) | C13 | C16 | O2 | 110.02(10) |
| C19 | C7 | C15 | 123.26(13) | C20 | C16 | O2 | 111.75(10) |
| C23 | C7 | C15 | 121.64(13) | C20 | C16 | C13 | 113.26(10) |
| C23 | C7 | C19 | 115.10(12) | C18 | C17 | O1 | 110.32(12) |
| C9 | C8 | C6 | 109.31(9) | C17 | C18 | O4 | 110.49(11) |
| C19 | C8 | C6 | 113.21(10) | C8 | C19 | C7 | 110.70(10) |
| C19 | C8 | C9 | 114.37(10) | C20 | C19 | C7 | 115.12(11) |
| C8 | C9 | O1 | 114.18(10) | C20 | C19 | C8 | 110.21(10) |
| C14 | C9 | O1 | 123.16(11) | C19 | C20 | C16 | 110.25(10) |
| C14 | C9 | C8 | 122.58(12) | C22 | C21 | O3 | 109.61(12) |
| C6 | C10 | O3 | 113.23(10) | C21 | C22 | O5 | 109.51(12) |
| C11 | C10 | O3 | 122.03(11) |  |  |  |  |

Table SI4.6.4.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters ( $\AA^{2} \times 10^{3}$ ) for 383 .

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H2 | $-7569(11)$ | $452(3)$ | $1064(10)$ | $42.2(3)$ |
| H11 | $-903.6(15)$ | $360(2)$ | $1092.2(8)$ | $28.8(3)$ |
| H17a | $-500(20)$ | $-1710(30)$ | $3813(11)$ | $38(4)$ |
| H8 | $-4623(18)$ | $3490(30)$ | $2476(9)$ | $23(3)$ |
| H12a | $-5030(20)$ | $-860(30)$ | $-56(10)$ | $26(3)$ |
| H21a | $-1037(19)$ | $7290(30)$ | $1691(10)$ | $27(4)$ |
| H14 | $-2630(18)$ | $4970(30)$ | $3433(9)$ | $22(3)$ |
| H19 | $-6900(17)$ | $1620(20)$ | $2405(8)$ | $16(3)$ |
| H12b | $-3380(20)$ | $-1970(30)$ | $322(11)$ | $37(4)$ |
| H15a | $-5890(20)$ | $-1940(30)$ | $4017(12)$ | $44(5)$ |
| H22a | $1240(20)$ | $5900(30)$ | $1007(10)$ | $33(4)$ |
| H15b | $-6330(20)$ | $-140(30)$ | $4738(11)$ | $33(4)$ |
| H23a | $-7750(20)$ | $3740(30)$ | $3583(10)$ | $32(4)$ |
| H18a | $-1520(20)$ | $830(30)$ | $4754(11)$ | $36(4)$ |
| H16 | $-5673(16)$ | $-2910(20)$ | $1324(8)$ | $15(3)$ |
| H20a | $-7024(19)$ | $-2160(20)$ | $2552(9)$ | $22(4)$ |
| H23b | $-5920(20)$ | $4380(30)$ | $3738(11)$ | $43(5)$ |
| H23c | $-6810(20)$ | $3480(30)$ | $4474(12)$ | $45(5)$ |
| H18b | $430(20)$ | $1160(30)$ | $4703(10)$ | $33(4)$ |
| H20b | $-5042(19)$ | $-2140(20)$ | $2648(9)$ | $20(4)$ |
| H17b | $110(20)$ | $250(20)$ | $3216(10)$ | $30(4)$ |
| H22b | $-440(20)$ | $5550(30)$ | $432(11)$ | $39(5)$ |
| H21b | $-260(20)$ | $5280(20)$ | $2220(10)$ | $30(4)$ |
| H12c | $-3390(20)$ | $540(30)$ | $77(10)$ | $29(4)$ |

## SI4.6.5 X-Ray Crystallographic Data for Diels Alder Adduct 386



A colorless prism $0.22 \times 0.11 \times 0.04 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at $100(2) \mathrm{K}$ using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $100 \%$ complete to $74.5^{\circ}$ in $\theta$. A total of 22974 reflections were collected covering the indices, $-9<=h<=9,-25<=k<=25,-10<=k<=10.4646$ reflections were found to be symmetry independent, with an $R_{\text {int }}$ of 0.0521 . Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $\mathrm{P} 2_{1}$ (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined from the diffraction data.

Table SI4.6.5.1. Crystal data and structure refinement for $\mathbf{3 8 6}$.

| Identification code | 386 |
| :---: | :---: |
| Empirical formula | $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{8}$ |
| Formula weight | 448.49 |
| Temperature (K) | 100(2) |
| Crystal system | monoclinic |
| Space group | P2, |
| a (A) | 7.47360(10) |
| b ( $\AA$ ) | 20.0163(2) |
| c ( $\AA$ ) | 8.26160(10) |
| $\alpha\left({ }^{\circ}\right)$ | 90 |
| $\beta\left({ }^{\circ}\right)$ | 113.345(2) |
| $\gamma\left({ }^{\circ}\right)$ | 90 |
| Volume ( $\AA^{3}$ ) | 1134.71(3) |
| Z | 2 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.313 |
| $\mu\left(\mathrm{mm}^{-1}\right)$ | 0.813 |
| $\mathrm{F}(000)$ | 480.0 |
| Crystal size ( $\mathrm{mm}^{3}$ ) | $0.220 \times 0.100 \times 0.040$ |
| Radiation | $\mathrm{CuK} \alpha(\lambda=1.54184)$ |
| $2 \Theta$ range for data collection ( ${ }^{\circ}$ ) | 8.836 to 148.972 |
| Index ranges | $-9 \leq \mathrm{h} \leq 9,-25 \leq \mathrm{k} \leq 25,-10 \leq 1 \leq 10$ |
| Reflections collected | 22974 |
| Independent reflections | $4646\left[\mathrm{R}_{\text {int }}=0.0521, \mathrm{R}_{\text {sigma }}=0.0291\right]$ |
| Data/restraints/parameters | 4646/1/312 |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.102 |
| Final R indexes [I>=2 $\sigma$ ( I )] | $\mathrm{R}_{1}=0.0396, \mathrm{wR}_{2}=0.1091$ |
| Final R indexes [all data] | $\mathrm{R}_{1}=0.0408, \mathrm{wR}_{2}=0.1098$ |
| Largest diff. peak/hole (e $\AA^{-3}$ ) | 0.20/-0.17 |
| Flack parameter | -0.04(10) |

Table SI4.6.5.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for $\mathbf{3 8 6} . U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $y$ | $z$ | U(eq) |
| :---: | :---: | :---: | :---: | :---: |
| C1 | 11350(5) | 2772.2(18) | 10359(5) | 50.5(8) |
| C2 | 8252(4) | 3241.2(12) | 8809(4) | 34.3(5) |
| C3 | 6577(3) | 3617.7(12) | 8978(3) | 30.6(5) |
| C4 | 4803(4) | 3618.2(12) | 7207(3) | 30.2(5) |
| C5 | 1816(4) | 3055.0(13) | 5816(4) | 38.8(6) |
| C6 | 745(4) | 3707.2(13) | 5543(4) | 41.7(6) |
| C7 | 3756(3) | 4279.4(12) | 6698(3) | 28.2(4) |
| C8 | 4544(3) | 4873.3(11) | 7300(3) | 26.8(4) |
| C9 | 6680(3) | 4908.8(12) | 8551(3) | 28.6(5) |
| C10 | 7974(4) | 4949.1(13) | 7506(4) | 35.0(5) |
| C11 | 7231(3) | 4309.3(12) | 9820(3) | 31.0(5) |
| C12 | 6487(4) | 4508.9(13) | 11226(3) | 34.6(5) |
| C13 | 3910(6) | 4385.6(17) | 12158(5) | 51.8(8) |
| C14 | 7079(3) | 5478.6(12) | 9892(3) | 31.7(5) |
| C15 | 5967(4) | 6120.4(12) | 9216(3) | 30.7(5) |
| C16 | 3780(3) | 5996.7(11) | 8292(3) | 28.4(5) |
| C17 | 2557(4) | 6626.6(12) | 7742(3) | 30.6(5) |
| C18 | 3275(4) | 7221.4(14) | 7649(4) | 40.2(6) |
| C19 | 425(4) | 6535.3(13) | 7312(4) | 37.8(6) |
| C20 | 3313(3) | 5505.4(11) | 6715(3) | 27.5(5) |
| C21 | 3356(3) | 5844.7(11) | 5098(3) | 29.3(5) |
| C22 | 1802(4) | 5871.4(13) | 3584(3) | 35.4(5) |
| C23A | 3342(18) | 6660(5) | 2461(15) | 44(2) |
| C24A | 5232(9) | 6329(3) | 3638(7) | 36.6(18) |
| C23B | 3603(15) | 6427(5) | 2345(13) | 35.5(17) |
| C24B | 4733(8) | 6699(3) | 4109(7) | 33.1(16) |
| O1 | 9679(3) | 3128.8(11) | 10390(3) | 41.4(5) |
| O2 | 8349(3) | 3065.8(12) | 7447(3) | 47.8(5) |
| O3 | 3561(3) | 3094.1(9) | 7353(2) | 34.6(4) |
| O4 | 1924(3) | 4243.9(9) | 5354(2) | 34.3(4) |
| O5 | 4584(3) | 4280.0(10) | 10793(2) | 38.3(4) |
| O6 | 6584(3) | 5217.8(9) | 11299(2) | 36.0(4) |
| O7 | 1739(3) | 6200.1(11) | 2090(2) | 42.6(5) |
| O8 | 5095(3) | 6150.7(9) | 5334(2) | 34.9(4) |

Table SI4.6.5.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 386. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} U_{11}+2 h k a^{*} b^{*} U_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{\mathbf{1 3}}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | $39.9(14)$ | $49.2(17)$ | $68(2)$ | $20.3(15)$ | $27.2(14)$ | $20.7(13)$ |
| C2 | $35.8(12)$ | $25.3(12)$ | $45.8(14)$ | $7.2(10)$ | $20.6(11)$ | $5.2(9)$ |
| C3 | $31.3(11)$ | $24.8(11)$ | $38.6(12)$ | $7.1(10)$ | $16.9(10)$ | $6.6(9)$ |
| C4 | $34.6(11)$ | $22.6(11)$ | $34.1(11)$ | $0.4(9)$ | $14.4(10)$ | $2.0(9)$ |
| C5 | $43.0(13)$ | $23.4(12)$ | $43.0(13)$ | $-3.1(10)$ | $9.6(11)$ | $-3.7(10)$ |
| C6 | $35.6(13)$ | $23.1(12)$ | $54.5(16)$ | $1.7(11)$ | $5.1(12)$ | $-2.8(10)$ |
| C7 | $32.0(10)$ | $24.5(10)$ | $26.9(10)$ | $2.4(9)$ | $10.2(9)$ | $2.5(9)$ |
| C8 | $30.4(11)$ | $23.3(10)$ | $25.9(9)$ | $1.5(8)$ | $10.5(8)$ | $2.2(9)$ |
| C9 | $29.4(11)$ | $23.6(11)$ | $30.2(10)$ | $1.6(9)$ | $8.8(9)$ | $3.1(8)$ |
| C10 | $34.8(11)$ | $31.0(12)$ | $41.0(12)$ | $1.3(10)$ | $17.1(10)$ | $-0.3(10)$ |
| C11 | $28.9(10)$ | $28.5(11)$ | $32.7(11)$ | $4.9(9)$ | $9.0(9)$ | $4.6(9)$ |
| C12 | $38.6(12)$ | $32.0(12)$ | $28.7(12)$ | $5.7(9)$ | $8.4(10)$ | $5.9(10)$ |
| C13 | $68(2)$ | $47.2(18)$ | $53.9(17)$ | $-3.7(14)$ | $39.3(16)$ | $-2.1(14)$ |
| C14 | $29.9(11)$ | $32.0(12)$ | $27.8(11)$ | $-1.1(9)$ | $5.9(9)$ | $0.9(9)$ |
| C15 | $33.3(11)$ | $24.5(11)$ | $30.1(11)$ | $-3.0(8)$ | $8.0(9)$ | $-2.5(9)$ |
| C16 | $32.0(11)$ | $21.9(11)$ | $28.9(10)$ | $1.0(8)$ | $9.6(8)$ | $0.5(9)$ |
| C17 | $33.6(12)$ | $24.2(10)$ | $31.6(11)$ | $-1.1(9)$ | $10.2(10)$ | $2.0(9)$ |
| C18 | $37.8(13)$ | $25.7(12)$ | $49.6(15)$ | $0.1(11)$ | $9.2(11)$ | $0.3(10)$ |
| C19 | $36.3(13)$ | $28.3(13)$ | $47.0(14)$ | $2.9(10)$ | $14.7(11)$ | $4.9(9)$ |
| C20 | $28.8(11)$ | $20.8(10)$ | $29.1(11)$ | $1.1(8)$ | $7.3(9)$ | $-1.2(8)$ |
| C21 | $33.3(11)$ | $21.2(10)$ | $31.3(11)$ | $0.7(9)$ | $10.5(9)$ | $-1.8(9)$ |
| C22 | $39.8(13)$ | $29.9(12)$ | $30.7(11)$ | $3.4(10)$ | $7.9(10)$ | $-2.1(10)$ |
| C23A | $61(5)$ | $23(5)$ | $41(4)$ | $15(4)$ | $12(3)$ | $7(4)$ |
| C24A | $52(3)$ | $28(3)$ | $34(3)$ | $1(2)$ | $21(2)$ | $-4(2)$ |
| C23B | $48(4)$ | $22(4)$ | $36(3)$ | $11(4)$ | $16(3)$ | $1(3)$ |
| C24B | $44(3)$ | $21(3)$ | $37(3)$ | $8(2)$ | $20(2)$ | $3.3(19)$ |
| O1 | $34.9(9)$ | $41.0(10)$ | $51.1(11)$ | $14.5(9)$ | $19.9(8)$ | $15.1(8)$ |
| O2 | $47.9(11)$ | $47.9(12)$ | $53.2(12)$ | $-0.5(10)$ | $26.1(10)$ | $12.2(10)$ |
| O3 | $37.1(9)$ | $21.6(8)$ | $42.3(10)$ | $2.7(7)$ | $12.8(8)$ | $0.8(7)$ |
| O4 | $35.4(8)$ | $22.5(8)$ | $34.6(8)$ | $0.7(7)$ | $2.6(7)$ | $-1.3(7)$ |
| O5 | $44.6(10)$ | $38.1(10)$ | $36.9(9)$ | $2.0(8)$ | $21.2(8)$ | $2.1(8)$ |
| O6 | $44.7(10)$ | $32.2(9)$ | $28.4(8)$ | $1.5(7)$ | $11.5(7)$ | $4.8(7)$ |
| O7 | $46.4(11)$ | $45.3(11)$ | $27.6(8)$ | $7.8(8)$ | $5.5(7)$ | $-3.7(8)$ |
| O8 | $36.5(9)$ | $30.7(9)$ | $32.5(9)$ | $7.2(7)$ | $8.5(7)$ | $-6.1(7)$ |

Table SI4.6.5.4. Bond Lengths for 386.

| Atom | Atom | Length ( $\AA \mathbf{)}$ | Atom | Atom | Length $(\AA)$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | O1 | $1.447(3)$ | C12 | O6 | $1.421(3)$ |
| C2 | O2 | $1.208(3)$ | C13 | O5 | $1.422(3)$ |
| C2 | O1 | $1.338(3)$ | C14 | O6 | $1.450(3)$ |
| C2 | C3 | $1.514(3)$ | C14 | C15 | $1.512(3)$ |
| C3 | C4 | $1.536(3)$ | C15 | C16 | $1.526(3)$ |
| C3 | C11 | $1.540(4)$ | C16 | C17 | $1.517(3)$ |
| C4 | O3 | $1.437(3)$ | C16 | C20 | $1.558(3)$ |
| C4 | C7 | $1.510(3)$ | C17 | C18 | $1.321(4)$ |
| C5 | O3 | $1.417(3)$ | C17 | C19 | $1.500(4)$ |
| C5 | C6 | $1.501(4)$ | C20 | C21 | $1.510(3)$ |
| C6 | O4 | $1.437(3)$ | C21 | C22 | $1.328(3)$ |
| C7 | C8 | $1.332(3)$ | C21 | O8 | $1.379(3)$ |
| C7 | O4 | $1.381(3)$ | C22 | O7 | $1.383(3)$ |
| C8 | C9 | $1.521(3)$ | C23A | O7 | $1.444(13)$ |
| C8 | C20 | $1.526(3)$ | C23A | C24A | $1.514(13)$ |
| C9 | C10 | $1.533(3)$ | C24A | O8 | $1.488(5)$ |
| C9 | C14 | $1.534(3)$ | C23B | O7 | $1.400(10)$ |
| C9 | C11 | $1.538(3)$ | C23B | C24B | $1.469(12)$ |
| C11 | C12 | $1.526(3)$ | C24B | O8 | $1.444(5)$ |
| C12 | O5 | $1.399(3)$ |  |  |  |

Table SI4.6.5.5. Bond Angles for 386.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O2 | C2 | O1 | 122.8(2) | O6 | C14 | C9 | 105.83(19) |
| O2 | C2 | C3 | 126.0(2) | C15 | C14 | C9 | 116.36(19) |
| O1 | C2 | C3 | 111.2(2) | C14 | C15 | C16 | 111.7(2) |
| C2 | C3 | C4 | 110.2(2) | C17 | C16 | C15 | 114.5(2) |
| C2 | C3 | C11 | 111.3(2) | C17 | C16 | C20 | 111.44(18) |
| C4 | C3 | C11 | 115.44(19) | C15 | C16 | C20 | 111.18(19) |
| O3 | C4 | C7 | 112.5(2) | C18 | C17 | C19 | 120.9(2) |
| O3 | C4 | C3 | 105.17(19) | C18 | C17 | C16 | 123.8(2) |
| C7 | C4 | C3 | 114.96(19) | C19 | C17 | C16 | 115.3(2) |
| O3 | C5 | C6 | 109.5(2) | C21 | C20 | C8 | 115.6(2) |
| O4 | C6 | C5 | 110.7(2) | C21 | C20 | C16 | 112.32(18) |
| C8 | C7 | O4 | 119.8(2) | C8 | C20 | C16 | 110.57(18) |
| C8 | C7 | C4 | 125.1(2) | C22 | C21 | O8 | 122.6(2) |
| O4 | C7 | C4 | 114.7(2) | C22 | C21 | C20 | 122.3(2) |
| C7 | C8 | C9 | 119.0(2) | O8 | C21 | C20 | 115.07(19) |
| C7 | C8 | C20 | 120.0(2) | C21 | C22 | O7 | 124.6(2) |
| C9 | C8 | C20 | 121.0(2) | O7 | C23A | C24A | 110.0(7) |
| C8 | C9 | C10 | 110.23(19) | O8 | C24A | C23A | 108.3(6) |
| C8 | C9 | C14 | 112.14(19) | O7 | C23B | C24B | 114.6(7) |
| C10 | C9 | C14 | 112.4(2) | O8 | C24B | C23B | 106.8(5) |
| C8 | C9 | C11 | 110.6(2) | C2 | O1 | C1 | 115.2(2) |
| C10 | C9 | C11 | 111.5(2) | C5 | O3 | C4 | 111.15(19) |
| C14 | C9 | C11 | 99.50(18) | C7 | O4 | C6 | 113.97(19) |
| C12 | C11 | C9 | 103.56(19) | C12 | O5 | C13 | 113.1(2) |
| C12 | C11 | C3 | 115.7(2) | C12 | O6 | C14 | 110.48(19) |
| C9 | C11 | C3 | 116.23(19) | C22 | O7 | C23B | 109.9(4) |
| O5 | C12 | O6 | 111.5(2) | C22 | O7 | C23A | 112.4(5) |
| O5 | C12 | C11 | 111.1(2) | C21 | O8 | C24B | 109.5(3) |
| O6 | C12 | C11 | 105.4(2) | C21 | O8 | C24A | 112.7(3) |
| O6 | C14 | C15 | 108.9(2) |  |  |  |  |

Table SI4.6.5.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters ( $\AA^{2} \times 10^{3}$ ) for 386 .

| Atom | $\boldsymbol{x}$ | $y$ | $z$ | U(eq) |
| :---: | :---: | :---: | :---: | :---: |
| H1A | 10926 | 2343 | 9758 | 76 |
| H1B | 12287 | 2694 | 11570 | 76 |
| H1C | 11968 | 3038 | 9727 | 76 |
| H3 | 6187 | 3357 | 9818 | 37 |
| H4 | 5261 | 3490 | 6265 | 36 |
| H5A | 987 | 2690 | 5942 | 47 |
| H5B | 2124 | 2956 | 4781 | 47 |
| H6A | -479 | 3679 | 4473 | 50 |
| H6B | 400 | 3797 | 6563 | 50 |
| H10A | 7776 | 4550 | 6769 | 52 |
| H10B | 9344 | 4976 | 8325 | 52 |
| H10C | 7629 | 5347 | 6755 | 52 |
| H11 | 8686 | 4300 | 10406 | 37 |
| H12 | 7366 | 4319 | 12391 | 42 |
| H13A | 4862 | 4206 | 13269 | 78 |
| H13B | 2657 | 4158 | 11858 | 78 |
| H13C | 3744 | 4866 | 12290 | 78 |
| H14 | 8505 | 5581 | 10384 | 38 |
| H15A | 6441 | 6335 | 8380 | 37 |
| H15B | 6218 | 6430 | 10216 | 37 |
| H16 | 3378 | 5766 | 9169 | 34 |
| H18A | 2438 | 7599 | 7305 | 48 |
| H18B | 4628 | 7272 | 7926 | 48 |
| H19A | -221 | 6972 | 7088 | 57 |
| H19B | 255 | 6320 | 8306 | 57 |
| H19C | -153 | 6255 | 6259 | 57 |
| H20 | 1933 | 5361 | 6389 | 33 |
| H22 | 654 | 5649 | 3523 | 42 |
| H23A | 3119 | 7063 | 3051 | 53 |
| H23B | 3424 | 6801 | 1344 | 53 |
| H24A | 5454 | 5922 | 3062 | 44 |
| H24B | 6338 | 6638 | 3856 | 44 |
| H23C | 3474 | 6778 | 1460 | 43 |
| H23D | 4341 | 6052 | 2126 | 43 |
| H24C | 5979 | 6888 | 4164 | 40 |
| H24D | 3990 | 7056 | 4395 | 40 |

Table SI4.6.5.7. Atomic Occupancy for 386.

| Atom | Occupancy | Atom | Occupancy | Atom | Occupancy |
| :---: | :---: | :---: | :---: | :---: | :---: |
| C23A | $0.488(11)$ | H23A | $0.488(11)$ | H23B | $0.488(11)$ |
| C23B | $0.512(11)$ | H23C | $0.512(11)$ | H23D | $0.512(11)$ |
| C24A | $0.488(11)$ | H24A | $0.488(11)$ | H24B | $0.488(11)$ |
| C24B | $0.512(11)$ | H24C | $0.512(11)$ | H24D | $0.512(11)$ |

## SI4.6.6 X-Ray Crystallographic Data for Quassin Architecture 391



A colorless block $0.38 \times 0.24 \times 0.15 \mathrm{~mm}$ in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using $\omega$ scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of $2.0^{\circ}$. Data collection was $100 \%$ complete to $28.3^{\circ}$ in $\theta$. A total of 82913 reflections were collected covering the indices, $-14<=h<=14,-10<=k<=10,-17<=l<=17$. 5843 reflections were found to be symmetry independent, with an $\mathrm{R}_{\mathrm{int}}$ of 0.0378 . Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $\mathrm{P}_{1}$ (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2016). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2016. Absolute stereochemistry was unambiguously determined from the diffraction data.

Table SI4.6.6.1. Crystal data and structure refinement for 391.

| Identification code | $\mathbf{3 9 1}$ |
| :--- | :--- |
| Empirical formula | $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{9}$ |
| Formula weight | 464.49 |
| Temperature $(\mathrm{K})$ | $100(2)$ |
| Crystal system | monoclinic |
| Space group | $\mathrm{P}_{2}{ }_{1}$ |
| $\mathrm{a}(\AA)$ | $11.1125(4)$ |
| $\mathrm{b}(\AA)$ | $8.0779(3)$ |
| $\mathrm{c}\left(\AA^{\AA}\right)$ | $13.1558(5)$ |
| $\alpha\left(^{\circ}\right)$ | 90 |
| $\beta\left(^{\circ}\right)$ | $98.011(2)$ |
| $\gamma\left(^{\circ}\right)$ | 90 |
| Volume $\left(\AA^{3}\right)$ | $1169.41(8)$ |
| Z | 2 |
| $\rho_{\text {calc }}\left(\mathrm{g} / \mathrm{cm}^{3}\right)$ | 1.319 |
| $\mu\left(\mathrm{~mm}{ }^{-1}\right)$ | 0.101 |
| $\mathrm{~F}(000)$ | 496.0 |
| Crystal size $\left(\mathrm{mm}{ }^{3}\right)$ | $0.380 \times 0.240 \times 0.150$ |
| Radiation | $\mathrm{MoK} \alpha(\lambda=0.71073)$ |
| $2 \Theta$ range for data collection $\left(^{\circ}\right)$ | 3.126 to 56.662 |
| Index ranges | $-14 \leq \mathrm{h} \leq 14,-10 \leq \mathrm{k} \leq 10,-17 \leq 1 \leq 17$ |
| Reflections collected | 82913 |
| Independent reflections | $5843\left[\mathrm{R}_{\text {int }}=0.0378, \mathrm{R}_{\text {sigma }}=0.0181\right]$ |
| Data/restraints $/$ parameters | $5843 / 1 / 313$ |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.064 |
| Final R indexes [I>=2 $\sigma(\mathrm{I})]$ | $\mathrm{R}_{1}=0.0305, \mathrm{wR} \mathrm{R}_{2}=0.0805$ |
| Final R indexes [all data $]$ | $\mathrm{R}_{1}=0.0321, \mathrm{wR} \mathrm{R}_{2}=0.0821$ |
| Largest diff. peak/hole $\left(\mathrm{e} \AA^{\AA-3}\right)$ | $0.30 /-0.20$ |
| Flack parameter | $-0.08(16)$ |

Table SI4.6.6.2. Fractional Atomic Coordinates $\left(\times 10^{4}\right)$ and Equivalent Isotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for $391 . U_{e q}$ is defined as $1 / 3$ of the trace of the orthogonalized $U_{i j}$ tensor.

| Atom | $\boldsymbol{x}$ | $y$ | $z$ | U(eq) |
| :---: | :---: | :---: | :---: | :---: |
| C1 | 11777.7(18) | 674(3) | 1990.8(19) | 32.2(5) |
| C2 | 10174.1(15) | 2443(2) | 2275.4(14) | 20.3(4) |
| C3 | 8965.5(15) | 3201(2) | 1829.1(13) | 15.7(3) |
| C4 | 9077.8(15) | 5095(2) | 1888.4(13) | 16.0(3) |
| C5 | 9635.1(17) | 7292(2) | 879.9(15) | 23.3(4) |
| C6 | 8338.3(17) | 7840(3) | 642.6(14) | 22.7(4) |
| C7 | 7874.2(14) | 5950(2) | 1941.1(12) | 13.9(3) |
| C8 | $7073.0(14)$ | 5365(2) | 2524.4(12) | 12.1(3) |
| C9 | 7353.4(14) | 3712(2) | 3069.2(12) | 13.4(3) |
| C10 | 8133.0(16) | 3908(2) | 4128.2(13) | 16.9(3) |
| C11 | 7944.3(14) | 2493(2) | 2381.3(12) | 14.7(3) |
| C12 | 6866.1(15) | 1798(2) | 1650.0(13) | 17.3(3) |
| C13 | 5724.1(19) | 2086(3) | 6.6(15) | 33.2(5) |
| C14 | 6193.7(15) | 2739(2) | 3179.2(12) | 14.7(3) |
| C15 | 5116.1(15) | 3733(2) | 3412.7(13) | 15.3(3) |
| C16 | 4810.1(14) | 5111(2) | 2615.9(13) | 13.5(3) |
| C17 | 5903.7(14) | 6302(2) | 2605.9(12) | 12.1(3) |
| C18 | 5993.5(14) | 7583(2) | 3481.1(12) | 12.8(3) |
| C19 | 7287.1(16) | 7827(2) | 5013.4(13) | 20.1(4) |
| C20 | 7906.3(15) | 8523(2) | 4153.7(14) | 18.8(3) |
| C21 | 4777.4(15) | 8501(2) | 3486.9(12) | 14.8(3) |
| C22 | 3789.1(15) | 7253(2) | 3640.9(13) | 17.5(3) |
| C23 | 3656.1(15) | 6002(2) | 2784.4(13) | 16.4(3) |
| C24 | 2596.7(16) | 5675(3) | 2219.9(16) | 24.2(4) |
| O1 | 10618.3(12) | 1437.4(18) | 1612.2(11) | 24.8(3) |
| O2 | 10669.1(14) | 2698(3) | 3129.8(12) | 40.4(4) |
| O3 | 9647.8(11) | 5543.9(17) | 1019.6(10) | 20.7(3) |
| O4 | 7692.3(11) | 7487.5(16) | 1491.8(10) | 18.8(3) |
| O5 | 6673.9(11) | 2722.3(18) | 742.9(9) | 21.7(3) |
| O6 | 5847.1(11) | 1933.1(16) | 2195.5(9) | 16.3(2) |
| O7 | 6332.1(11) | 6844.7(16) | 4465.1(9) | 15.7(2) |
| O8 | 6903.2(10) | 8797.7(15) | 3361.7(9) | 15.8(2) |
| O9 | 4398.4(11) | 9318.3(16) | 2543.9(10) | 17.2(3) |

Table SI4.6.6.3. Anisotropic Displacement Parameters $\left(\AA^{2} \times 10^{3}\right)$ for 386. The anisotropic displacement factor exponent takes the form: $-2 \pi^{2}\left[h^{2} a^{* 2} \mathrm{U}_{11}+2 h k a^{*} b^{*} \mathrm{U}_{12}+\ldots\right]$.

| Atom | $\mathbf{U}_{11}$ | $\mathbf{U}_{22}$ | $\mathbf{U}_{33}$ | $\mathbf{U}_{23}$ | $\mathbf{U}_{13}$ | $\mathbf{U}_{12}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | 17.8(9) | 27.5(10) | 50.8(13) | 6.1(10) | 2.8(8) | 11.3(8) |
| C2 | 14.1(7) | 22.7(9) | 23.7(9) | 2.4(7) | 1.3(6) | 1.9(7) |
| C3 | 12.7(7) | 19.0(8) | 15.2(7) | -0.3(6) | 1.1(6) | 3.9(6) |
| C4 | 13.7(7) | 19.0(8) | 15.6(7) | 1.0(6) | 3.0(6) | 0.5(6) |
| C5 | 21.9(8) | 22.8(10) | 27.7(9) | 4.8(8) | 12.2(7) | -1.9(7) |
| C6 | 26.1(9) | 23.4(10) | 20.7(8) | 7.1(7) | 10.3(7) | 2.2(7) |
| C7 | 14.6(7) | 13.7(8) | 13.2(7) | $0.2(6)$ | 0.7(6) | 0.7(6) |
| C8 | 11.7(7) | 12.4(8) | 11.6(7) | -1.9(6) | -0.7(5) | 0.6(6) |
| C9 | 14.4(7) | 12.4(7) | 13.3(7) | -0.2(6) | 1.7(5) | $1.2(6)$ |
| C10 | 18.9(8) | 18.2(9) | 12.7(7) | 0.9(6) | -0.9(6) | 1.6(6) |
| C11 | 15.3(7) | 14.7(8) | 13.9(7) | 0.0(6) | 1.3(6) | 2.4(6) |
| C12 | 16.2(8) | 17.0(8) | 19.1(8) | -4.1(7) | 3.1(6) | 0.1(6) |
| C13 | 26.9(10) | 50.9(14) | 19.6(9) | -7.9(9) | -4.9(7) | -10.0(9) |
| C14 | 17.8(7) | 13.0(8) | 13.3(7) | 0.2(6) | 2.5(6) | -0.9(6) |
| C15 | 16.2(7) | 13.3(8) | 17.1(7) | 1.1(6) | 4.7(6) | -1.4(6) |
| C16 | 11.7(7) | 13.5(8) | 15.4(7) | 0.2(6) | 1.7(6) | -1.5(6) |
| C17 | 11.2(7) | 12.9(7) | 12.1(7) | -0.1(6) | 0.9(5) | -0.3(6) |
| C18 | 13.4(7) | 11.9(7) | 13.0(7) | 0.5(6) | 1.8(5) | -0.7(6) |
| C19 | 19.7(8) | $22.7(9)$ | 16.3(8) | -3.2(7) | -2.5(6) | -1.2(7) |
| C20 | 13.9(7) | 20.0(9) | 21.1(8) | -2.0(7) | -2.6(6) | -0.8(7) |
| C21 | 14.9(7) | 13.3(8) | 16.2(7) | -0.8(6) | 2.1(6) | 1.8(6) |
| C22 | 15.1(7) | 18.1(9) | 20.3(8) | 0.7(7) | 6.0(6) | 2.0(6) |
| C23 | 13.6(7) | 14.9(8) | 21.3(8) | 3.6(7) | 5.0(6) | -0.7(6) |
| C24 | 15.5(8) | $22.0(9)$ | 34.3(10) | -1.9(8) | 1.1(7) | -1.4(7) |
| O1 | 17.4(6) | 24.6(7) | 31.9(7) | 0.1(6) | 2.3(5) | 9.5(5) |
| O2 | 27.5(7) | 61.4(12) | 28.4(8) | -6.0(8) | -9.8(6) | 19.2(8) |
| O3 | 19.7(6) | 22.0(7) | 22.6(6) | 1.8(5) | 10.1(5) | 1.1(5) |
| O4 | 20.2(6) | 16.6(6) | 21.7(6) | 5.6(5) | 9.8(5) | 2.2(5) |
| O5 | 18.9(6) | 31.0(7) | 13.9(6) | -1.5(5) | -2.1(4) | -5.4(6) |
| O6 | 16.0(6) | 15.7(6) | 17.3(6) | -3.5(5) | 2.5(4) | -1.5(5) |
| O7 | 18.0(6) | 17.0(6) | 11.5(5) | -0.1(5) | -0.6(4) | -1.2(5) |
| O8 | 13.3(5) | 15.2(6) | 17.9(6) | 0.1(5) | -0.8(4) | -2.6(5) |
| O9 | 13.5(5) | 15.3(6) | 22.1(6) | 3.6(5) | -0.3(5) | -0.3(5) |

Table SI4.6.6.4. Bond Lengths for 391.

| Atom | Atom | Length (A) | Atom | Atom | Length $(\AA \mathbf{\AA})$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| C1 | O1 | $1.452(2)$ | C12 | O5 | $1.399(2)$ |
| C2 | O2 | $1.198(2)$ | C12 | O6 | $1.427(2)$ |
| C2 | O1 | $1.336(2)$ | C13 | O5 | $1.425(2)$ |
| C2 | C3 | $1.517(2)$ | C14 | O6 | $1.452(2)$ |
| C3 | C4 | $1.536(3)$ | C14 | C15 | $1.508(2)$ |
| C3 | C11 | $1.540(2)$ | C15 | C16 | $1.534(2)$ |
| C4 | O3 | $1.429(2)$ | C16 | C23 | $1.514(2)$ |
| C4 | C7 | $1.515(2)$ | C16 | C17 | $1.552(2)$ |
| C5 | O3 | $1.424(2)$ | C17 | C18 | $1.541(2)$ |
| C5 | C6 | $1.498(3)$ | C18 | O7 | $1.4275(19)$ |
| C6 | O4 | $1.438(2)$ | C18 | O8 | $1.4328(19)$ |
| C7 | C8 | $1.340(2)$ | C18 | C21 | $1.542(2)$ |
| C7 | O4 | $1.378(2)$ | C19 | O7 | $1.436(2)$ |
| C8 | C17 | $1.520(2)$ | C19 | C20 | $1.512(3)$ |
| C8 | C9 | $1.527(2)$ | C20 | O8 | $1.433(2)$ |
| C9 | C14 | $1.533(2)$ | C21 | O9 | $1.416(2)$ |
| C9 | C10 | $1.543(2)$ | C21 | C22 | $1.525(2)$ |
| C9 | C11 | $1.544(2)$ | C22 | C23 | $1.505(2)$ |
| C11 | C12 | $1.535(2)$ | C23 | C24 | $1.328(3)$ |

Table SI4.6.6.5. Bond Angles for 391.

| Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) | Atom | Atom | Atom | Angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| O2 | C2 | O1 | 123.62(17) | C15 | C14 | C9 | 116.62(14) |
| O2 | C2 | C3 | 124.03(18) | C14 | C15 | C16 | 110.71(13) |
| O1 | C2 | C3 | 112.34(15) | C23 | C16 | C15 | 110.89(13) |
| C2 | C3 | C4 | 108.70(15) | C23 | C16 | C17 | 112.75(14) |
| C2 | C3 | C11 | 109.79(14) | C15 | C16 | C17 | 110.89(13) |
| C4 | C3 | C11 | 113.93(14) | C8 | C17 | C18 | 114.84(13) |
| O3 | C4 | C7 | 114.42(14) | C8 | C17 | C16 | 111.70(13) |
| O3 | C4 | C3 | 104.72(14) | C18 | C17 | C16 | 112.30(12) |
| C7 | C4 | C3 | 112.97(14) | O7 | C18 | O8 | 106.55(12) |
| O3 | C5 | C6 | 108.18(16) | O7 | C18 | C17 | 112.23(13) |
| O4 | C6 | C5 | 110.45(14) | O8 | C18 | C17 | 110.55(12) |
| C8 | C7 | O4 | 119.59(14) | O7 | C18 | C21 | 108.47(12) |
| C8 | C7 | C4 | 121.79(15) | O8 | C18 | C21 | 107.67(13) |
| O4 | C7 | C4 | 117.95(14) | C17 | C18 | C21 | 111.16(12) |
| C7 | C8 | C17 | 120.50(15) | O7 | C19 | C20 | 102.20(13) |
| C7 | C8 | C9 | 117.94(14) | O8 | C20 | C19 | 102.26(13) |
| C17 | C8 | C9 | 121.52(13) | O9 | C21 | C22 | 107.02(13) |
| C8 | C9 | C14 | 111.91(13) | O9 | C21 | C18 | 111.93(13) |
| C8 | C9 | C10 | 112.72(14) | C22 | C21 | C18 | 109.29(14) |
| C14 | C9 | C10 | 109.93(13) | C23 | C22 | C21 | 109.98(13) |
| C8 | C9 | C11 | 110.99(13) | C24 | C23 | C22 | 122.63(16) |
| C14 | C9 | C11 | 99.22(13) | C24 | C23 | C16 | 121.77(17) |
| C10 | C9 | C11 | 111.32(13) | C22 | C23 | C16 | 115.59(14) |
| C12 | C11 | C3 | 113.72(13) | C2 | O1 | C1 | 115.16(16) |
| C12 | C11 | C9 | 104.01(13) | C5 | O3 | C4 | 110.95(14) |
| C3 | C11 | C9 | 116.18(14) | C7 | O4 | C6 | 116.89(14) |
| O5 | C12 | O6 | 110.55(14) | C12 | O5 | C13 | 113.46(15) |
| O5 | C12 | C11 | 110.66(14) | C12 | O6 | C14 | 110.62(12) |
| O6 | C12 | C11 | 105.17(13) | C18 | O7 | C19 | 107.91(13) |
| O6 | C14 | C15 | 107.50(13) | C18 | O8 | C20 | 107.68(13) |
| O6 | C14 | C9 | 105.53(12) |  |  |  |  |

Table SI4.6.6.6. Hydrogen Atom Coordinates $\left(\AA \times 10^{4}\right)$ and Isotropic Displacement Parameters ( $\AA^{2} \times 10^{3}$ ) for 391 .

| Atom | $\boldsymbol{x}$ | $\boldsymbol{y}$ | $\boldsymbol{z}$ | $\mathbf{U ( e q )}$ |
| :---: | :---: | :---: | :---: | :---: |
| H1A | 12027 | -48 | 1459 | 48 |
| H1B | 11697 | 18 | 2604 | 48 |
| H1C | 12392 | 1537 | 2165 | 48 |
| H3 | 8794 | 2880 | 1089 | 19 |
| H4 | 9643 | 5383 | 2523 | 19 |
| H5A | 10086 | 7591 | 308 | 28 |
| H5B | 10030 | 7844 | 1511 | 28 |
| H6A | 8309 | 9044 | 500 | 27 |
| H6B | 7943 | 7259 | 22 | 27 |
| H10A | 8880 | 4511 | 4050 | 25 |
| H10B | 8341 | 2812 | 4420 | 25 |
| H10C | 7673 | 4526 | 4587 | 25 |
| H11 | 8298 | 1561 | 2827 | 18 |
| H12 | 7015 | 611 | 1492 | 21 |
| H13A | 5728 | 2662 | -649 | 50 |
| H13B | 4940 | 2261 | 251 | 50 |
| H13C | 5851 | 899 | -89 | 50 |
| H14 | 6387 | 1874 | 3721 | 18 |
| H15A | 5301 | 4228 | 4105 | 18 |
| H15B | 4405 | 2994 | 3409 | 18 |
| H16 | 4655 | 4572 | 1926 | 16 |
| H17 | 5725 | 6953 | 1956 | 15 |
| H19A | 7852 | 7138 | 5485 | 24 |
| H19B | 6956 | 8720 | 5409 | 24 |
| H20A | 8335 | 9571 | 4361 | 23 |
| H20B | 8492 | 7723 | 3932 | 23 |
| H21 | 4861 | 9326 | 4059 | 18 |
| H22A | 4004 | 6681 | 4307 | 21 |
| H22B | 3008 | 7836 | 3653 | 21 |
| H9 | $4900(30)$ | $10030(40)$ | $2440(20)$ | $34(7)$ |
| H24A | $1830(20)$ | $6300(40)$ | $2337(19)$ | $31(7)$ |
| H24B | $2510(20)$ | $4890(40)$ | $1640(20)$ | $33(7)$ |
|  |  |  |  |  |

SI4.7 ${ }^{1} \mathrm{H},{ }^{13} \mathrm{C}$, and ${ }^{19} \mathrm{~F}$ NMR Spectra


























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