Title
I.) Total Synthesis of Aryltetralin Lignans by a C-H Arylation Strategy II.) Total Synthesis of Complex Meroterpenes

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I.) Total Synthesis of Aryltetralin Lignans by a C-H Arylation Strategy
II.) Total Synthesis of Complex Meroterpenes

By

Chi Pan Ting

A dissertation submitted in partial satisfaction of the

requirements for the degree of

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in

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of the

Universtity of California, Berkeley

Committee in Charge:

Professor Thomas Maimone, Chair
Professor Richmond Sarpong
Professor John Hartwig
Professor Gary Firestone

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Abstract

1.) Total Synthesis of Aryltetralin Lignans by a C-H Arylation strategy
2.) Total synthesis of Complex Meroterpenex

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Chi Pan Ting

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Thomas J. Maimone, Chair

Podophyllotoxin-based glycosidic derivatives have seen numerous uses in cancer chemotherapy. However, these analogs are derived solely from semisynthetic modifications of the natural product, and the inherent restriction of semisynthesis has prevented further development of new analogs with fewer side effects. In the first chapter of this dissertation, a concise and modular synthesis of the prototypical aryltetralin lignan, podophyllotoxin, is disclosed. Central to the overall strategy is a palladium-catalyzed C-H arylation reaction as the point of diversification. From an advanced intermediate, a two-step sequence furnishes not only the natural product but also fully synthetic podophyllotoxin analogs. Moreover, this work uncovered subtle previously overlooked conformational effects governing reductive elimination from high-valent palladium centers.

In the second chapter, a general strategy for the synthesis of complex meroterpene natural products is reported. First, a modular 10-step synthesis of the flagship PPAP, hyperforin, is disclosed. The synthetic approach includes two key transformations 1.) a novel annulation reaction between lithium enolates and diketene, and 2.) an oxidative ring expansion reaction mediated by hypervalent iodine. Second, the substrate scope of the diketene annulation reaction is reported. Finally, a synthesis of berkeleyone A, a complex meroterpene derived from 3,5-dimethylorsellinic acid, is reported in thirteen steps.

TABLE OF CONTENTS

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List of abbreviations

AIBN = azobisisobutyronitrile

Ar = aryl

b = broad

B_2pin_2 = bis(pinacolato)diboron

cat. = catalyst

$CDCl_3$ = deuterated chloroform

Me = methyl

d = doublet

DG = directing group

equiv. = equivalents

μv = microwave

H_2O = water

HMPA = hexamethylphosphoric triamide

HRMS = high resolution mass spectrometry

IR = infrared

Imid. = imidazole

KHMDS = potassium bis(trimethylsilyl)amide

LAH = lithium aluminum hydride

LDA = lithium diisopropylamide

LTMP = lithium 2,2,6,6-tetramethylpiperidide

m = multiplet

m-CPBA = *meta*-chloroperoxybenzoic acid

mp = melting point

n-BuLi = *n*-butyllithium

[O] = oxidation

PG = protecting group

PhH = benzene

Piv = pivalate

prenyl = 3,3-dimethylallyl

q = quartet

s = singlet

t = triplet

t-AmylOH = *tert*-amyl alcohol

t-BuOH = *tert*-butanol

TBAF = tetrabutyl ammonium fluoride

TBS = *tert*-butyldimethylsilyl

TFA = trifluoroacetate

THF = tetrahydrofuran

TIPS = triisopropylsilyl

TMEDA = tetramethylethylenediamine

TMS = trimethylsilyl

TLC = thin layer chromatography

Ts = tosyl

Chapter 1
Total Synthesis of Aryltetralin Lignans by a C-H Arylation Strategy

Chi P. Ting

1.1. Introduction: Isolation, Bioactivity, and Past Syntheses

Podophyllotoxin (**1**) is an aryltetralin lignan natural product produced by the plant families *Podophyllum peltatum* and *Podophyllum emodi* endemic to China and India.[1] Stucturally, podophyllotoxin (**1**) contains four contiguous stereocenters, two electron rich aromatic rings, and a strained and reactive *trans*-lactone (Figure 1). Since its isolation in 1753 by Linnaeus,[2] podophyllotoxin has been found to possess numerous important biological activities, such as the ability to combat tuberculosis, gonorrhea, syphilis, venereal warts, and cancer.[3] The cytotoxicity of podophyllotoxin is attributed to its binding of tubulin, preventing the formation of the mitotic spindle during metaphase, and ultimately resulting in cell division failure.[4]

Semisynthetic modifications of the natural product have resulted in two clinically-approved, glycoside-containing analogues, etoposide (**2**) and teniposide (**3**), that are used in the treatment of lung, skin, and testicular cancer (Figure 1).[5] The cytotoxicity of etoposide and teniposide are comparable to that of the natural product, except these glycosidic analogs exhibit no inhibition of tubulin. Instead their biological activity stems from their association with a complex formed from topoisomerase II and double-stranded DNA (dsDNA).[6] In 2011, a X-ray crystal structure of etoposide bound to the DNA/topoisomerase IIβ complex was reported.[7] Topoisomerase II is an enzyme that normally unwinds supercoiled DNA by a double strand cleavage and re-assembly process.[8] In the presence of this enzyme-DNA complex, etoposide and teniposide were observed to induce permanent double strand cleavage of DNA ultimately leading to cell death.[5] The structural features key to this switch in mechanism of action are epimerization and glycosylation of the C4 hydroxyl group and demethylation of the C4' methoxy group.[6] The dimethoxyphenol E ring in etoposide is instrumental to the cytotoxicity of these analogues as minor modifications to the oxygen substituents by Kadow *et al.* resulted in lower cytotoxicity.[9]

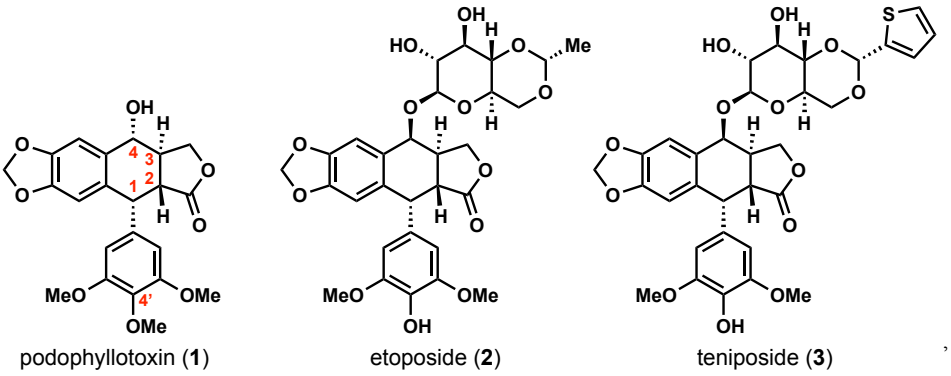


Figure 1. Podophyllotoxin and Analogs

Amongst the patients that use etoposide, 2-3% of them develop acute myeloid leukemia caused by chromosal translocation, and this undesired side effect is believed to be caused by metabolites of etoposide.[10] It is known that the dimethoxy E-ring of etoposide can be metabolized via cytochrome p450-mediated oxidative demethylation (Figure 2).[11] The resulting catechol can be oxidized by myeloperoxidases or other oxidases to produce etoposide quinone (Figure 2).[12] The Osheroff group has reported that etoposide quinone causes higher levels of enzyme-mediated DNA cleavage than the parent drug and functions via covalent modification of topoisomerase IIβ.[13] All these results suggest that etoposide quinone contributes to etoposide-related leukemogenesis through an interaction with topoisomerase IIβ.[13]

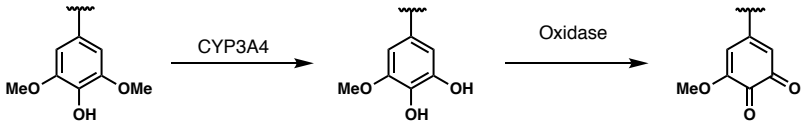


Figure 2. Metabolism of Etoposide via cytochrome p450 oxidation

Besides the E ring, the *trans*-lactone is also a vital structural feature for maintaining the bioactivity of these molecules as the *cis*-lactone diastereomer is essentially inactive. Gensler proposed that the structural rigidity of the *trans*-lactone restricts the rotation of the E ring maintaining its function.[14] Podophyllotoxin is known to epimerize under basic conditions to its more thermodynamically favored *cis*-epimer, picropodophyllotoxin (**4**). The thermodynamics of the system is heavily in favor of the *cis*-lactone with an equilibrium constant of 37 (Figure 3a).[14]

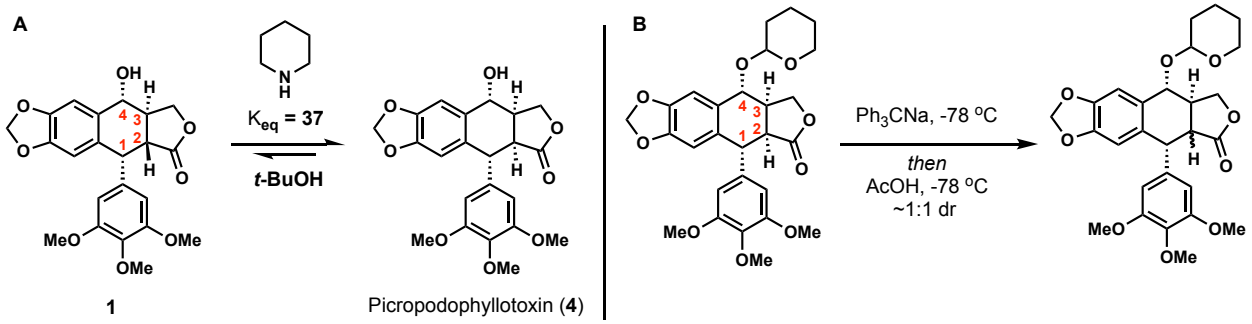


Figure 3. (a) Thermodynamics of **1** and **4** (b) Epimerization of C4-protected picropodophyllotoxin

Due to its biological properties and structural complexity, numerous total syntheses of podophyllotoxin have been published.[15] Containing four contiguous stereocenters and a base sensitive *trans*-lactone, podophyllotoxin presents a formidable synthetic challenge. In the landmark synthesis by Gensler, a kinetic deprotonation-reprotonation of C2 successfully transformed picropodophyllotoxin (**4**) into podophyllotoxin (Figure 3b).[16] Many total syntheses of podophyllotoxin still utilize this late stage epimerization despite the low diastereoselectivity (~1:1 d.r.) *vide infra*.

In 1988, Meyers and co-workers reported the first asymmetric synthesis of (-)-podophyllotoxin in 24 steps.[17] The key step involved a diastereoselective addition (92:8 dr) of an aryl lithium directed by a chiral oxazoline (Figure 4). In the same year, Macdonald and Durst published a synthesis of podophyllotoxin using an intramolecular Diels-Alder with a tethered dienophile.[18] Remarkably, all four stereocenters of podophyllotoxin were set in a single step in the Durst synthesis. In 1991, Peterson *et al.*, utilized a $SnCl_4$-mediated Friedel-Crafts and decarboxylation sequence to assemble the cyclohexane core.[19] A pyrone Diels-Alder reaction strategy was employed by Jones (1987) which was elaborated into an asymmetric synthesis in 1993 with dienophile containing a chiral (-)-menthol auxiliary.[20,21] In 2000, Berkowitz and co-workers employed an isobenzofuran Diels-Alder with dimethyl acetylenedicarboxylate to synthesize the C-ring of podophyllotoxin.[22] An enzymatic desymmetrization with porcine pancreatic lipase led to an enantioselective synthesis of podophyllotoxin.[22]

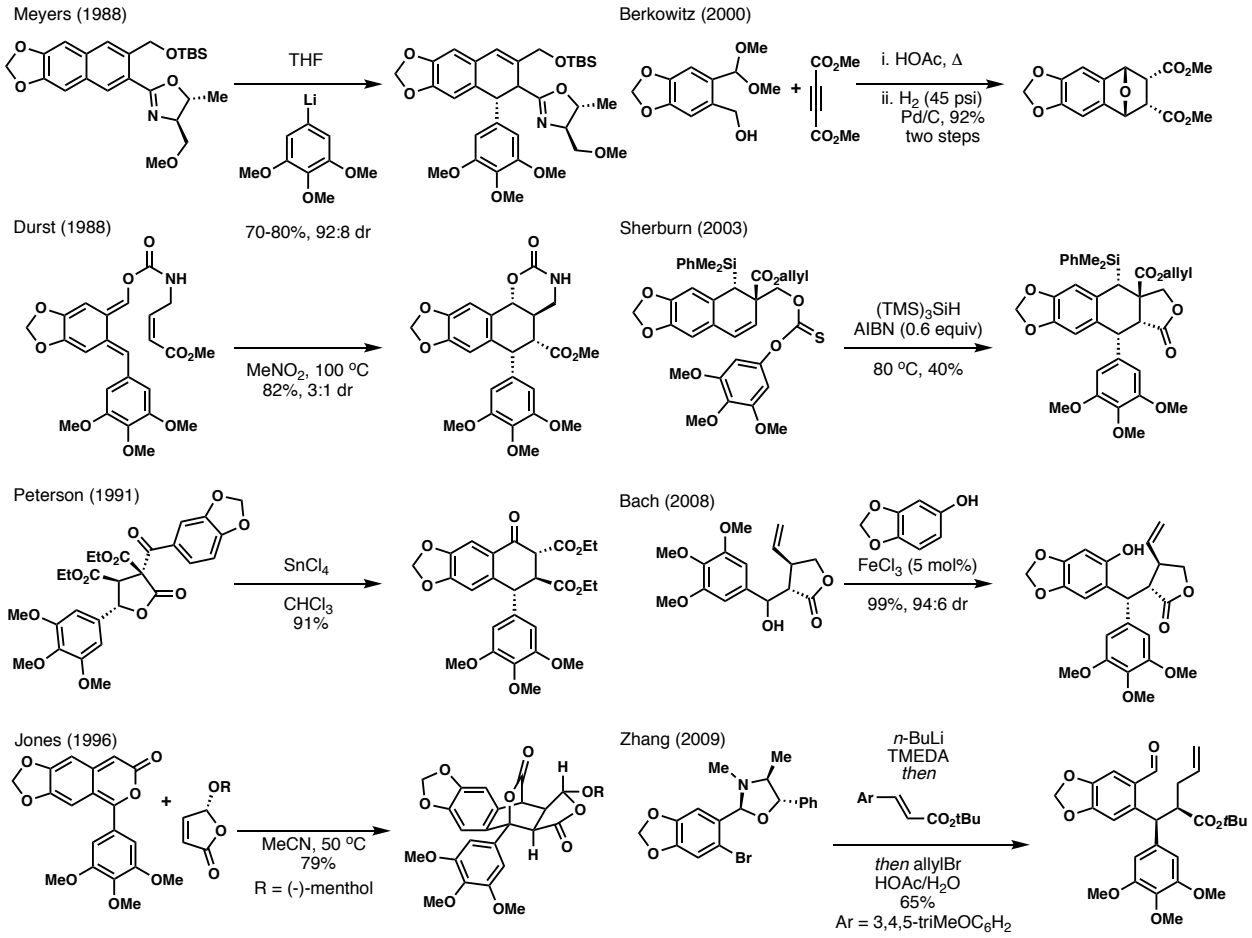


Figure 4. Key transformations in previous podophyllotoxin syntheses

In 2003, Sherburn implemented a novel radical carboxyarylation to assemble the *cis*-lactone and deliver the trimethoxybenzene group of podophyllotoxin.[23] In 2008, Bach and co-workers reported an iron trichloride catalyzed Friedal-Crafts reaction to install the B-ring of podophyllotoxin.[24] Finally in 2009, Zhang co-workers elaborated their 2006 synthesis of podophyllotoxin into an asymmetric synthesis with a diastereoselective Michael-addition of an aryl lithiate containing a chiral oxazoline auxiliary.[25,26] The Berkowitz and Meyers syntheses necessitated the use of Gensler's late stage epimerization to access the natural product.[17,22] These examples represent a large portion of the reported total syntheses of podophyllotoxin.

Two hundred years after its isolation, a highly efficient synthetic route to **1**, and derivatives thereof, which is both concise and flexible does not exist. Although semisynthetic modifications of the natural product were critical in developing podophyllotoxin as a template for new anti-cancer pharmaceuticals, the inherent restrictions of semisynthesis has prevented further development of new analogs. The syntheses shown, although novel, do not provide an easy solution for the modification of the B and E ring. Moreover, E-ring analogs may prevent metabolism of etoposide and eliminate the undesired side effects of the current therapeutic. Difficulty associated with modifying the aromatic residues of the podophyllotoxin has prompted us to pursue a fully synthetic route as a gateway into a wide array of new anti-cancer therapeutics based on this important natural product platform.

1.2. Retrosynthetic Analysis: A C-H Arylation Disconnection

An important step in our retrosynthetic analysis was recognizing that a diastereoselective C-H arylation could install the E ring aromatics of podophyllotoxin. Such an approach would allow for the preparation of numerous analogs from a common synthetic intermediate (Figure 5). *β*-Arylation by directed C-H activation has been developed by Yu and Daugulis using an assortment of amide directing groups.[27] We felt that a diastereoselective arylation could be achieved via the *cis*-palladacycle **6** where the benzylic C-H bond is activated. Intermediate **7** in turn could be assembled through a regioselective Diels-Alder reaction between benzocyclobutenol **8** and a dienophile with a directing group. The *trans*-dienophile will establish the stereochemistry of the *trans*-lactone removing the need for Gensler's late stage kinetic epimerization. Based on literature precedent, the Diels-Alder reaction should result in a *cis* relationship between C3 and C4 leading to *epi*-**1**.[28] *Epi*-**1** and **1** can be easily interconverted and both compounds under glycosylation conditions result in the *β*-glucoside.[6a] Protected cyclobutenol **8** can be formed via a three-step sequence from commercially available, inexpensive 6-bromopiperonal.[29] The remaining steps after the C-H activation involve reduction, lactonization and a deprotection sequence to yield *epi*-**1**. If successful, this would represent the most concise and modular synthesis of a key precursor to etoposide analogs.

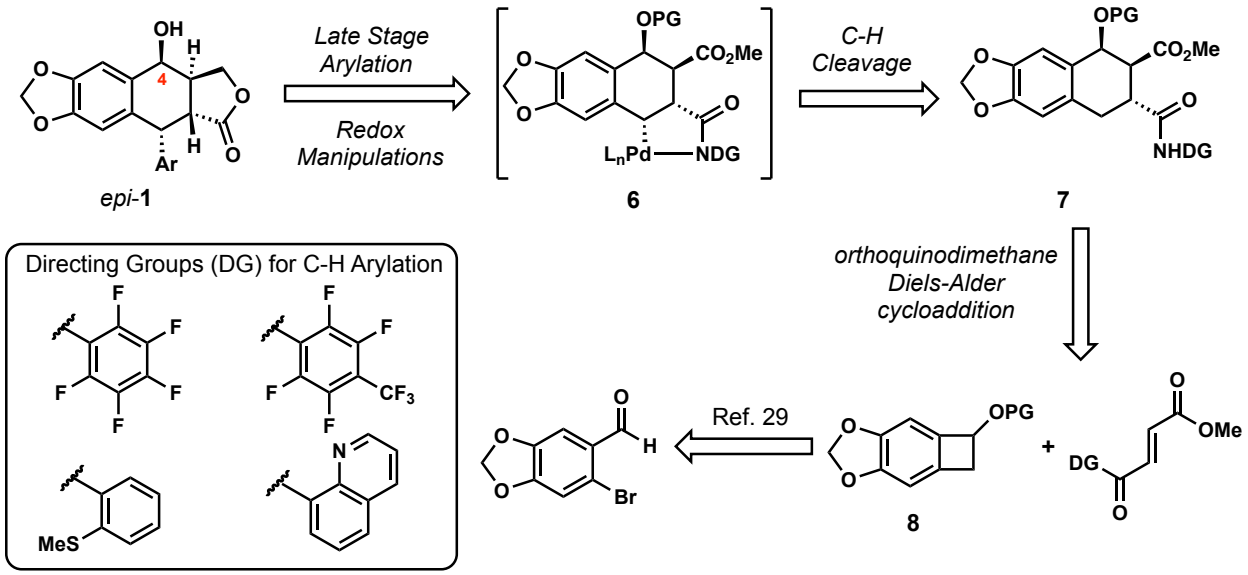
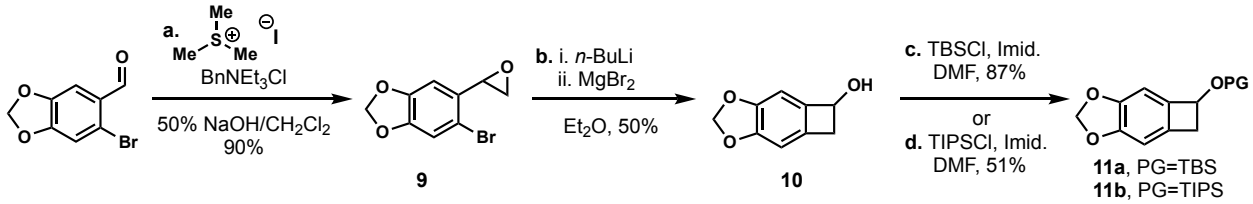


Figure 5. Retrosynthetic analysis of 4-*epi*-podophyllotoxin

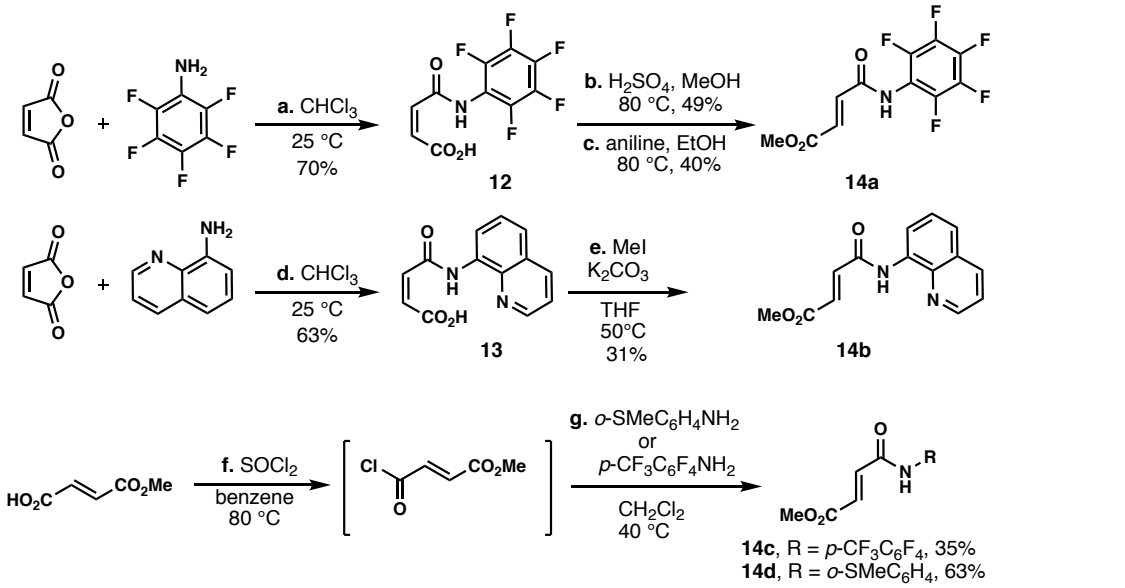
1.3. Initial Synthetic Efforts

Using the phase-transfer catalyst benzyl triethylammonium chloride and excess trimethylsulfonium iodide, 6-bromopiperonal was cleanly converted to epoxide **9** via a modified Corey-Chaykovsky reaction.[29] Epoxide **9** was then subjected to lithium halogen exchange, followed by transmetallation and Lewis acid-promoted intramolecular epoxide opening with two equivalents of $MgBr_2$ to form cyclobutenol **10** in 50% yield.[29] Silyl protection of the hydroxyl group of cyclobutenol **10** afforded either the *tert*-butyldimethylsilyl (TBS)-protected cyclobutenol **11a** or the triisopropylsilyl (TIPS)-protected cyclobutenol **11b** in short order and on multi-gram (>10 g) scale (Scheme 1).



Scheme 1. Synthesis of Silyl-Protected Benzocyclobutenols

Next we sought to devise a route to prepare different dienophiles containing amide directing groups for use in the Diels-Alder reaction. We found that aniline addition to maleic anhydride followed by esterification and alkene isomerization is an effective way to produce a variety of different dienophiles (Scheme 2).[30] Addition of pentafluoroaniline and 8-aminoquinoline to maleic anhydride proceeded to form **12** and **13** in 70% and 63% yield respectively. Esterification of **12** using catalytic sulfuric acid and methanol as solvent afforded the methyl ester in 49% yield, and isomerization was accomplished using aniline to afford dienophile **14a** in 40% yield. Presumably, isomerization occurred through a Michael addition/elimination sequence to yield the thermodynamic isomer.



Scheme 2. Synthesis of dienophiles

Under acidic conditions, esterification of **13** was unsuccessful. Fortunately, under basic conditions, **13** was esterified and isomerized in a single step using potassium carbonate and methyl iodide, thereby affording dienophile **14b** in 31% yield (unoptimized). Due to the significant electron-withdrawing nature of the *p*-CF_3 group, tetrafluoro-*p*-trifluoromethyl-aniline did not react with maleic anhydride even at 110 °C in toluene. Instead, the acid chloride of mono-methyl fumarate (prepared by reacting the free acid with thionyl chloride) had to be employed and led to a 35% yield of amide **14c** (Scheme 2).[27a] A similar procedure allowed for the synthesis of the *ortho*-thiomethylaniline dienophile **14d** in 63% yield.

Under thermal conditions, benzocyclobutenols are known to undergo electrocyclic ring opening to form *ortho*-quinodimethanes (*o*-QM) which can serve as dienes in the Diels-Alder reaction. Using symmetric dienophiles that do not possess acidic protons, intermolecular Diels-Alder reactions of this system have been reported to give cycloadducts with C4 configuration resembling etoposide.[28] We anticipated that an unsymmetrical dienophile containing an ester and an amide would result in the correct regioselectivity based on the greater electron donation of the lone pair from the amide nitrogen into the π* orbital of the C-O double bond, relative to the oxygen of the ester (Figure 6).

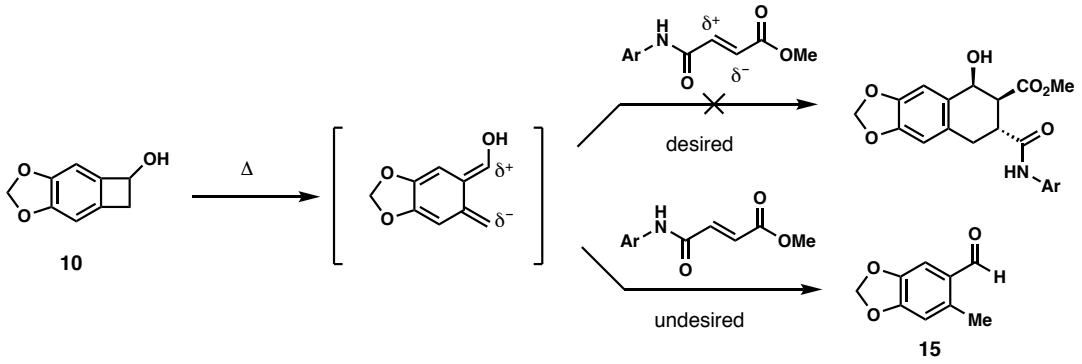
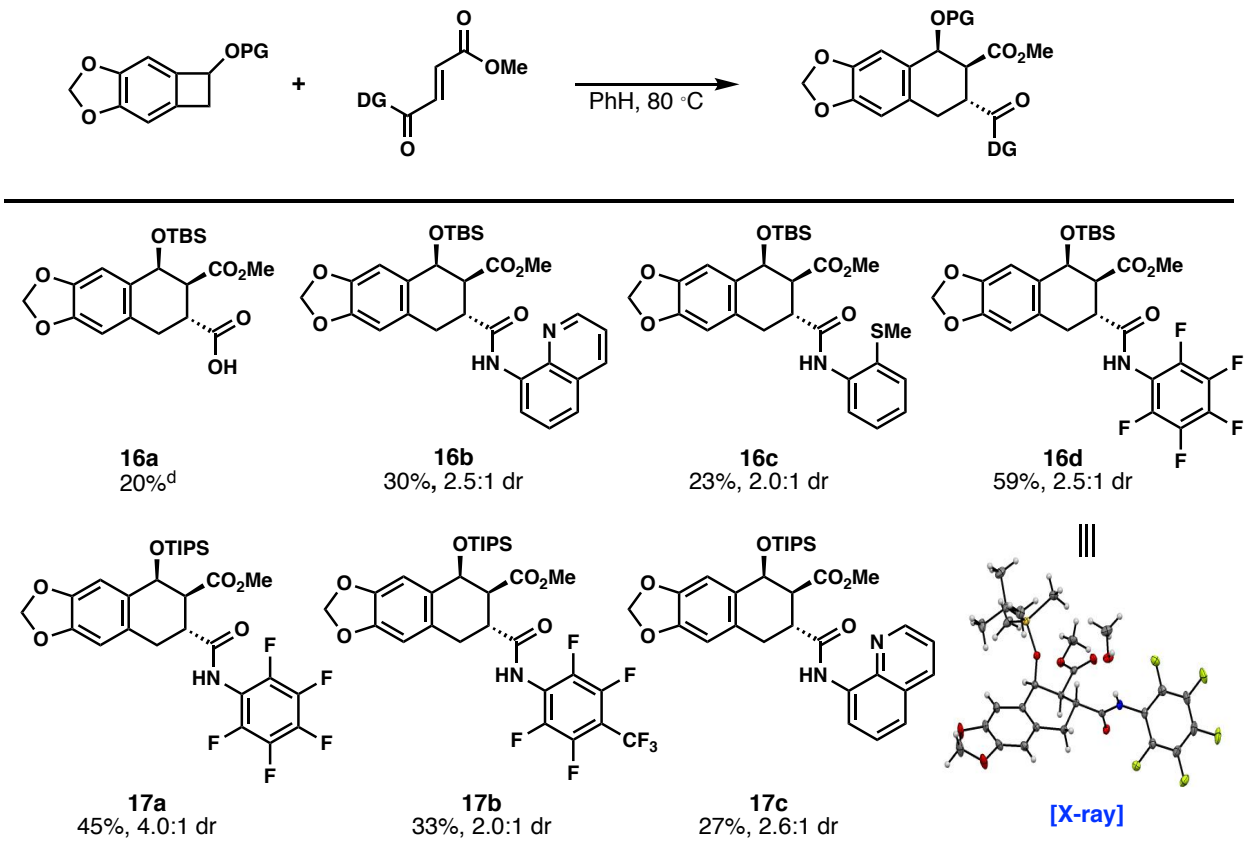


Figure 6: Expected Regioselectivity of the Diels-Alder Reaction

Heating cyclobutenol **10** with various dienophiles containing acidic protons quantitatively afforded the undesired *o*-tolualdehyde (**15**) (Figure 6). The formation of the *o*-tolualdehyde was presumed to proceed through the o-QM acting as a vinylogous enol that tautomerizes to **15**.[31] With this assumption, a TBS-protected benzocyclobutenol was examined. The Diels-Alder reaction proceeded to form the cycloadducts with acceptable yields and greater than 2.0:1 d.r. with various dienophiles (Figure 7). The major diastereomer of cycloadduct **16d** was determined by X-ray crystallography and displayed the stereochemistry resembling that of etoposide. Major diastereomers of other cycloadducts were assigned by analogy to **16d**. Under basic conditions (K_2CO_3 and ZnO), the Diels-Alder reaction using mono-methyl fumarate as a dienophile resulted in the carboxylic acid cycloadduct **16a** in 20% yield.

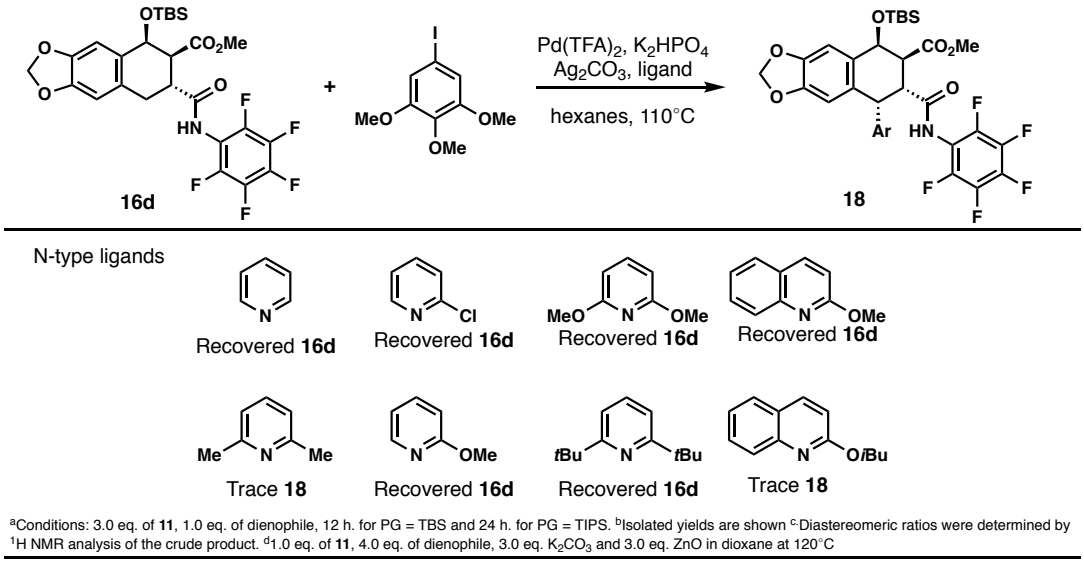


[a]Conditions: 3.0 eq. of **11**, 1.0 eq. of dienophile, 12 h. for PG = TBS and 24 h. for PG = TIPS. [b]Isolated yields are shown [c]Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude product. [d]1.0 eq. of **11**, 4.0 eq. of dienophile, 3.0 eq. K_2CO_3 and 3.0 eq. ZnO in dioxane at 120°C

Figure 7. Diels-Alder Reaction Substrate Scope

TIPS-protected cyclobutenols resulted in lower yields and required longer reaction times but occurred with higher diastereoselectivity than their TBS counterparts. For example, the TBS-protected cyclobutenol (**11a**) reacted with **14a** to afford **16d** in 59% yield and 2.5:1 d.r. after a reaction time of 12 hours. The TIPS-protected cyclobutenol (**11b)** reacted with **14a** to afford **17a** in 45% yield and 4.0:1 d.r. over a reaction time of 24 hours. In all Diels-Alder reactions using amide dienophiles, cyclobutenol was used in 3:1 excess relative to the dienophile. However, the unreacted cyclobutenol could easily be recovered and re-subjected to subsequent Diels-Alder reactions.

Inspired by conditions reported by Yu *et al.* for the *β*-arylation of methylene C-H bonds, our initial investigations began with aryl iodide substrates, $Pd(TFA)_2$ as catalyst, K_2HPO_4 as base, hexane as solvent, Ag_2CO_3 as an additive, and a nitrogen-based ligand.[27a] Our preliminary ligand screen included various pyridine and quinoline-type ligands that were optimized for *β*-arylation. Trace amounts (<5%) of the key arylated product (**18)** were observed when using 2,6-lutidine and 2-isobutoxyquinoline as ligand, while the other nitrogen-based ligands resulted in recovered starting material (Figure 8). Frequently, products were obtained that were derived from elimination of the OTBS group, aromatization, or cyclization of the amide to make a naphthyl phthalamide.

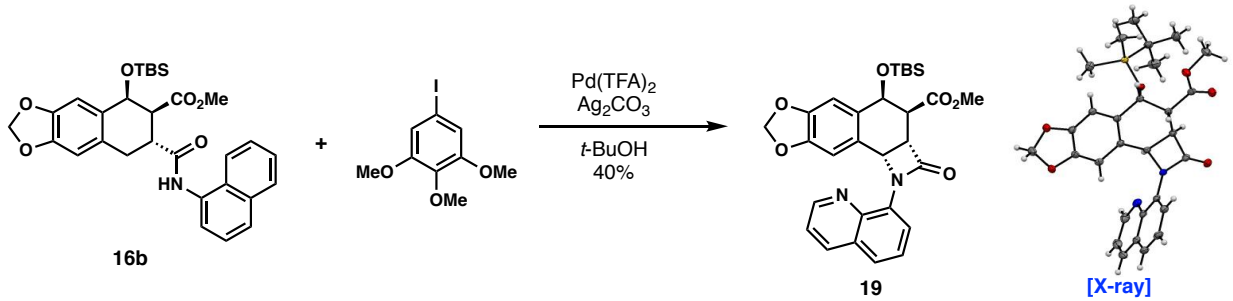


[a]Conditions: 3.0 eq. of **11**, 1.0 eq. of dienophile, 12 h. for PG = TBS and 24 h. for PG = TIPS. [b]Isolated yields are shown [c]Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude product. [d]1.0 eq. of **11**, 4.0 eq. of dienophile, 3.0 eq. K_2CO_3 and 3.0 eq. ZnO in dioxane at 120°C

Figure 8. Preliminary Ligand Screen

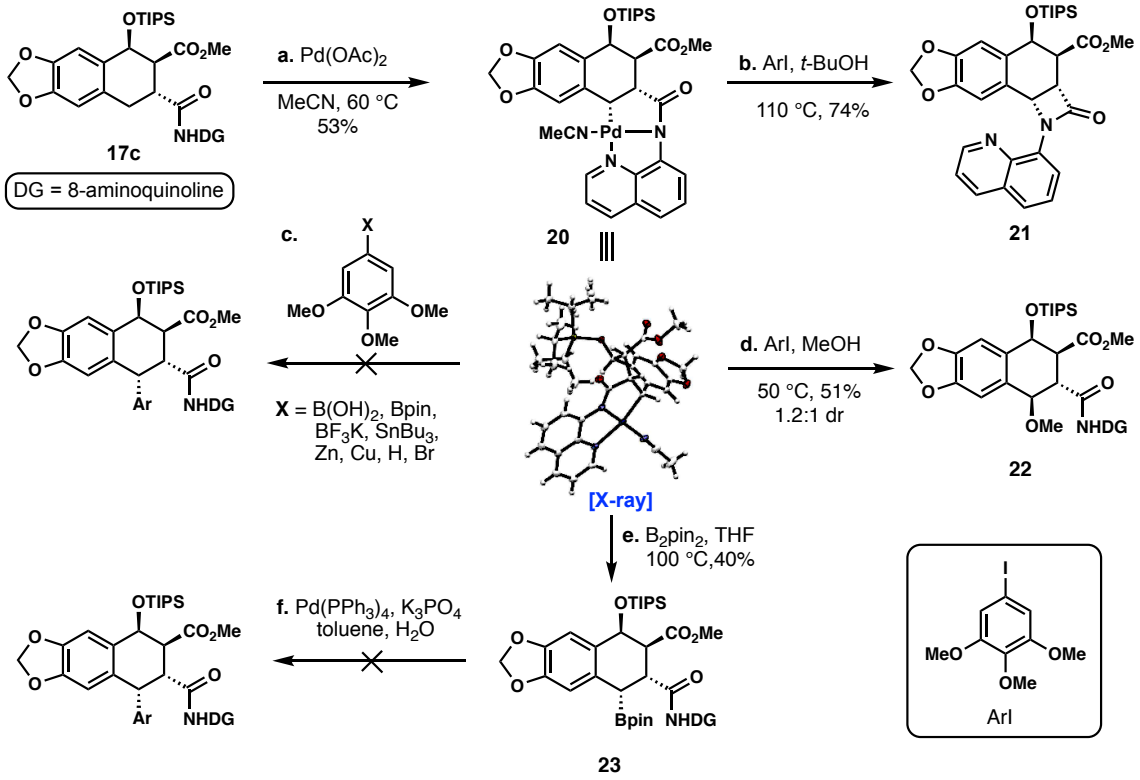
Switching from a TBS to TIPS protecting group for the benzylic hydroxyl moiety did not improve the yield of **18** and failed to prevent elimination and aromatization of the substrate. A solvent screen using common solvents for C-H activation such as 1,2-dichloroethane, toluene, *tert*-butanol and hexafluoroisopropanol, also failed to improve the yield of **18**. A variety of directing groups including the carboxylic acid, tetrafluoro-*p*-trifluoromethylaniline, *o*-thiomethyl aniline, and 8-aminoquinoline directing groups also failed to improve the yield of **18**.

Interestingly, reactions of cycloadduct **16b** under conditions implemented by Daugulis afforded *β*-lactam **19** in 40% yield by direct C-N bond formation at the benzylic position (Scheme 3).[27b] The resonances in the ^{1}H NMR spectrum of **19** were broad. Fortunately, the structure of this unexpected side product was unambiguously confirmed by X- ray analysis (Scheme 3). While somewhat surprising to us at first, Chen has shown that azetidines can be formed by Pd(II)/(IV) C-H activation of methyl groups using a hypervalent iodine reagent as a stoichiometric oxidant.[32] A major difference in our case was the lack of strong oxidants and the activation of a sterically congested secondary, benzylic C-H bond. Although this did not provide the desired product, this result was motivating in that it showed that the benzylic C-H bond can be functionalized. Concurrent with our investigations, Shi and co-workers reported the synthesis of *α*-amino-*β*-lactams by C-H amination of benzylic C-H bonds with sodium iodate ($NaIO_3$) and acetic anhydride as additive.[33]



Scheme 3. Unexpected *β*-Lactam Formation

To further probe the mechanism of β-lactam formation, cycloadduct **17c** was allowed to react with stoichiometric $Pd(OAc)_2$ in acetonitrile to afford palladacycle **20** in 53% yield (Scheme 4). X-ray crystallographic analysis showed a square planar Pd(II) complex bound to the substrate at the benzylic position and the 8-aminoquinoline directing group in a bidentate mode. MeCN was incorporated from the solvent as the final ligand on palladium. When palladacycle **20** is heated in the presence of aryl iodide, reductive elimination to form β-lactam **21** occurred within minutes at 110 °C. In the original communication from Daugulis and co-workers, (using the same 8-aminoquinoline directing group) treatment of a palladacycle (made from pivalic amide) with aryl iodide resulted in the C-H arylated product, with no C-N bond formation observed.[27b] A solvent screen showed that the reaction with methanol as solvent incorporated a methoxy group at the benzylic position to afford ether **22** (1.2:1.d.r).

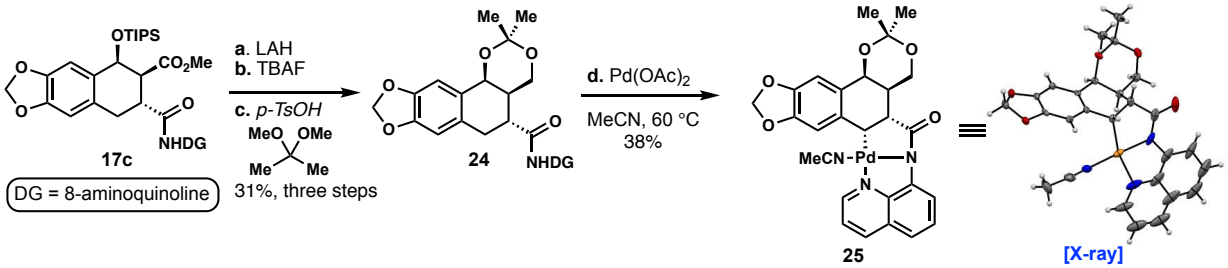


Scheme 4. Synthesis of compound **20** and its reactivity

Reaction of palladacycle **20** with various aryl sources derived from bromides, boronic acids, esters, trifluoroborates, stannanes, organozinc reagents, and organocuprate all failed to give the arylated product. Attempted oxidative coupling using just 3,4,5-trimethoxybenzene also did not yield the arylated product. Fortunately, reaction of palladacycle **20** with bis(pinacolato) diboron resulted in the C-H borylated product **23**. However, Suzuki-Miyaura cross coupling conditions did not produce any of the desired arylated product.

1.4. Total synthesis of Podophyllotoxin

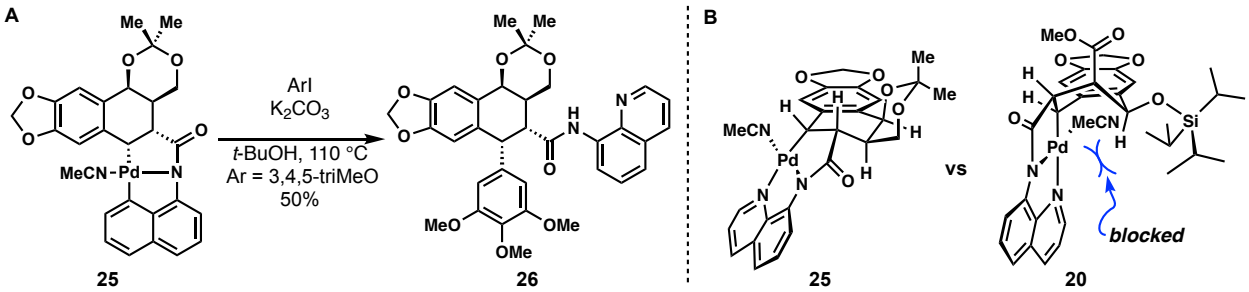
Having extensively studied the C-H arylation of cycloadducts **16** and **17** with minimal success, we wondered if a conformationally-distinct substrate would result in the desired C-C bond formation over undesired C-N bond formation. Cycloadduct **17c** was subjected to lithium aluminum hydride reduction of the ester group, desilylation with TBAF, and protection of the resulting 1,3-diol group with 2,2-dimethoxypropane to afford acetonide **24** in 31% yield over three steps (Scheme 5). Acetonide **24** was treated with stoichiometric $Pd(OAc)_2$ in acetonitrile to afford palladium complex **25** in 38% yield. The structure of palladium (II) complex was secured by X-ray diffraction studies clearly showing the desired C-H bond activation had occured (Scheme **5**). The complex was square planar with respect to the palladium center bound to the tridentate substrate and acetonitrile.



Scheme 5. Synthesis of palladium complex **25**

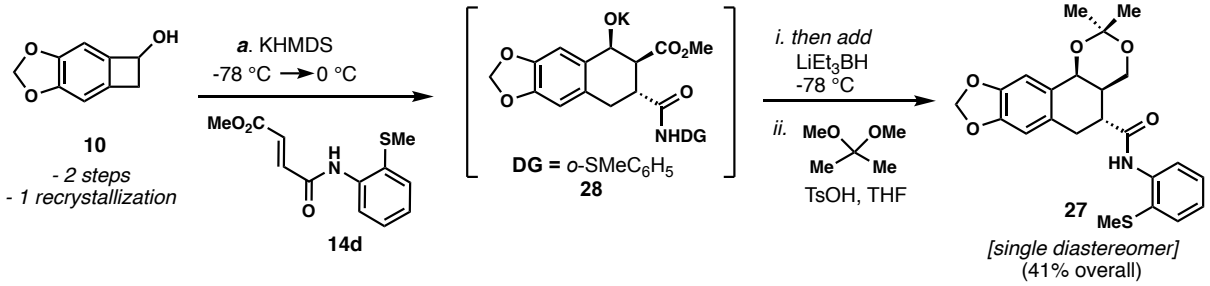
Complex **25** was allowed to react with trimethoxyiodobenzene and K_2CO_3 in refluxing *tert*-butanol, identical conditions that previously resulted in *β*-lactam formation, yet gratifyingly the desired arylated product (**26**) was obtained in 50% yield under these conditions (Scheme 6).

Upon investigation of the solid-state structures of both palladium (II) complexes, we noticed a clear conformational difference between the two compounds (Scheme 6b). In complex **25**, a normal half-chair conformation of the C-ring was observed with the palladium atom in a pseudo-equatorial position. While in complex **20**, the C-ring is in a twist-boat confirmation with the palladium atom in the axial position accommodating the bulky OTIPS group to position it in the equatorial position, the close proximity of the palladium atom to the axial hydrogen atom in **20** might prevent desired C-C bond reductive elimination due to build up of strain as the axial C-C_{aryl} bond begins to form and the resulting Pd-ligated amide is forced to rotate under this crowded ring system.



Scheme 6. a.) Stoichoimetric reductive elimination experiment with **25**. b.) Conformation difference between **20** and **25**.

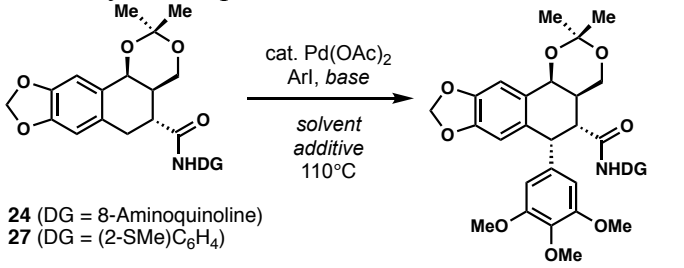
After our stoichiometric studies, we optimized the synthesis of acetonide **27**. By deprotonating benzocyclobutenol **10** with KHMDS, a low temperature, anionic electrocyclic ring opening occurred followed by a Diel-Alder reaction with dienophile **14d** affording intermediate **28**.[34] *In-situ* reduction by lithium triethylborohydride followed by ketalization with 2,2-dimethoxypropane in *p*-toluenesulfonic acid acid afforded acetonide **27** in 41% yield as a single diastereomer from benzocyclobutenol **10**.



Scheme 7. Optimized synthesis of acetonide **27**

With acetonide **24** and **27** in hand, many conditions were attempted to furnish a catalytic C-H arylation reaction. Acetonide **24** with the 8-aminoquinoline group was first examined with $Pd(OAc)_2$, CsOAc and AgOAc in toluene only resulting in 5% yield of the desired product (Entry 1, Table 1). Changing the base to Ag_2CO_3 and the solvent to *t*-amyl alcohol resulted in 10% yield of **26** (Entry 2). Inspired by the Baran synthesis of piperarborenine and the pioneering work of Daugulis,[27b] we decided to investigate the *o*-thiomethyl aniline directing group.[35] Remarkably, when acetonide **27** was used with $Pd(OAc)_2$, K_2CO_3, aryl iodide and *t*-amyl alcohol, the arylated product was obtained in 35% yield (Table 1, Entry 3). The addition of pivalic acid did not improve the yield (Entry 4). Inspired by work of Chen[36] and Shi,[37] the

Table 1: Pd-catalyzed C-H arylation optimization[a]



24 (DG = 8-Aminoquinoline)
27 (DG = (2-SMe)C_6H_4)

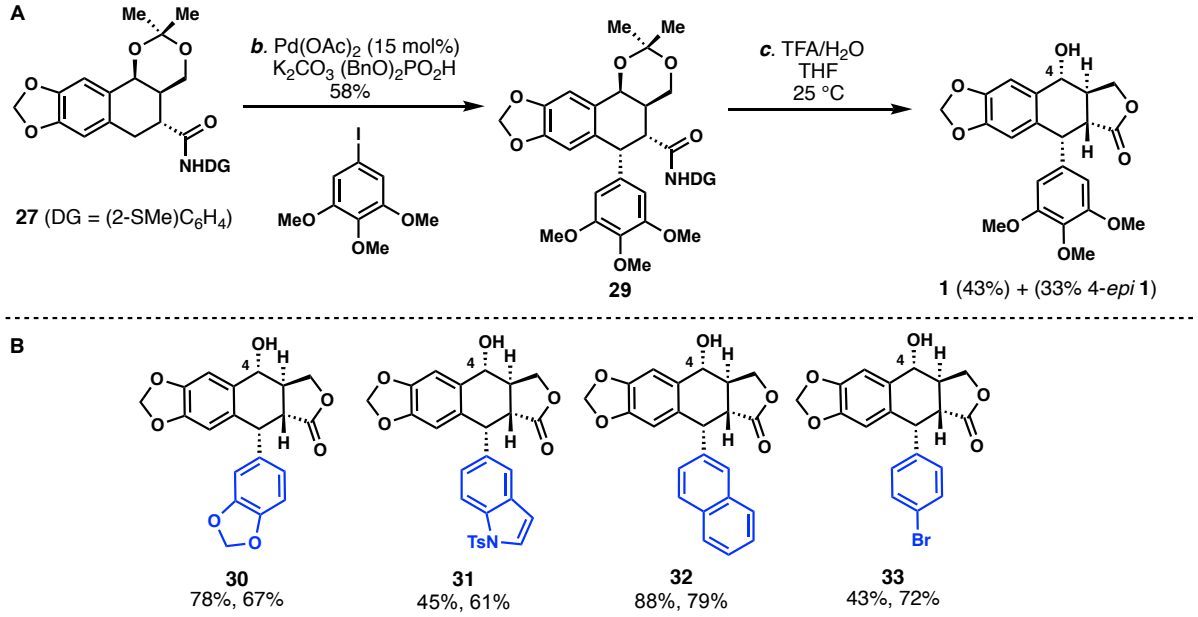
26 (DG = 8-Aminoquinoline)
29 (DG = (2-SMe)C_6H_4)

Entry	Substrate	Base	Solvent	Additive	Yield[b]
1	24	CsOAc	toluene	AgOAc	5%
2	24	Ag_2CO_3	*t*-AmylOH	None	10%
3	27	K_2CO_3	*t*-AmylOH	none	35%
4	27	K_2CO_3	*t*-AmylOH	40% PivOH	35%
5	27	K_2CO_3	*t*-AmylOH	40% $(BnO)_2PO_2H$	45%
6	27	K_2CO_3	*t*-AmylOH	40% $(BnO)_2PO_2H$	58%[c,d]

[a] Conditions: **24** or **27** (0.02 mmol), $Pd(OAc)_2$ (20 mol%), base (3.0 equiv), ArI (4.0 equiv), solvent (1 mL), 110°C [b] Yield determined by ^1H NMR spectroscopy using 2-chloroquinoline as an internal standard. [c] Yield of isolated product. [d] $Pd(OAc)_2$ loading=15 mol%, ArI (2 equiv), K_2CO_3 (1.5 equiv), [**27**] = 0.1 M, t=50 h, 15% recovered **27** also isolated. ArI=3,4,5-trimethoxyiodobenzene.

addition of dibenzyl phosphoric acid was essential in increasing the yield to 45% (Entry 5). Upon optimization of concentration and reaction time, we obtained compound **29** in 58% yield with decreased equivalencies of aryl iodide and lower palladium loadings (Entry 6, Table 1).

After improving the C-H arylation reaction, numerous conditions were tested to advance compound **29** to podophyllotoxin (**1**) or 4-*epi*-podophyllotoxin (*epi*-1) (not shown). Subjecting compound **29** to trifluoroacetic acid and water produced podophyllotoxin directly in 76% yield as a 1.5:1 mixture of C4 diastereomers (Scheme 8a). Remarkably, in a single reaction the acetonide group was deprotected, the directing group was hydrolyzed by intramolecular lactonization, and the benzylic alcohol was serendipitously epimerized to afford the natural product. Significantly, the C-H arylation reaction was positioned as the penultimate step in the synthesis, and this two-step procedure was quickly applied to various aryl iodides for the synthesis of unnatural podophyllotoxin analogs (**30-33**, Scheme 8b).[38]



Scheme 8. a.) Total synthesis of **1** and 4-*epi* **1**. b.) Fully synthetic podophyllotoxins (first yield is for C-H arylation, second yield is for lactone formation) 1.5:1 dr at C4

1.5. Conclusion and distribution of credit

In conclusion, we have developed a concise synthesis of podophyllotoxin (five operations from commercial materials) showcasing the power of state-of-the-art C-H functionalization methodology in a complex molecular setting.[39-43] In addition, we showed that this synthesis allows for the expedient syntheses of unnatural podophyllotoxin base analogs inaccessible by semi-synthetic means.

This project could not have been more educational for a young graduate student as it taught the values of persistence in the field of total synthesis. It oftentimes is the case that the best conditions are never the ones we try first, but we never know whether it's the next reaction or next thousand will we be thrilled with the joys of discovery. Moreover, this work uncovered subtle previously overlooked conformational effects governing reductive elimination from high-valent palladium centers. The podophyllotoxin synthesis was designed by Thomas Maimone and myself and executed solely by me.

1.6. References

1. Liu, Y.Q.; Yang, L.; Tian X. *Current Bioactive Compounds* **2007**, *3*, 37. and references therein.
2. Macrae Donald, W.; Neil Towers, G. H. *Phytochemistry* **1984**, *23,* 1207.
3. Slevin, M. L. *Cancer* **1991**, *67*, 319.
4. Bedows, E.; Hatfield, G. M. *J. Nat. Prod* **1982**, *45*, 725-729.
5. Hande, K. R. *Eur. J. Cancer* **1998**, *34*, 1514-1521.
6. (a) Stahelin, H.F.; von Wartburg, A. *Cancer Research* **1991**, *51,* 5. (b) Linnaeus C.V., *Species Plantrum*, Stockholm: salvius. **1753**; p 505.
7. Wu, C. C.; Li, T. L.; Farh, L.; Lin, F. Y.; Lin T. S.; Yu, Y. J.; Yen, T. J.; Chiang, C. W.; Chan, N. L. *Science*, **2011**, *333*, 459.
8. McKinnon, P. J. *Nature Reviews Neuroscience* **2016**, *17*, 673.
9. Vyas, D. M.; Saulnier, M. G.; Kadow, J. F. *Eur. Pat. Appl. EP.* **1989**, *297,* 594.
10. Pui, C. H.; Ribeiro, R. C.; Hancock, M. L.; Rivera, G. K.; Evans, W. E.; Raimondi, S. C.; Head, D. R.; Behm, F. G.; Mahmoud, M. H.; Sandlund, J. T. *N. Engl. J. Med.* **1991**, *325*, 1682.
11. Relling, M. V.; Evans, R.; Dass, C.; Desiderio, D. M.; Nemec, J. *J. Pharmacol. Exp. Ther.* **1992**, *261*, 491.
12. Haim, N.; Roman, J.; Nemec, J.; Sinha, B. K. *Biochem. Biophys. Res. Commun*. **1986**, *135*, 215.
13. Smith, N. A.; Byl, J. W.; Mercer, S. L.; Deweese, J. E.; Osheroff, N. *Biochemistry* **2014**, *53,* 3229-3236.
14. Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.* **1966**, *31,* 3224.
15. Ward, R. S. *Synthesis* **1992,** 719−730 and references therein.
16. Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.* **1966**, *31,* 4004.
17. Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7854.
18. Macdonald, D. I.; Durst, T. *J. Org. Chem*. **1988**, *53*, 3663.
19. Peterson, J. R.; Hoang, D. D.; Rogers, R. D. *Synthesis* **1991**, 275.
20. Jones, D. W.; Thompson, A. M. *J. Chem. Soc., Chem. Commun.* **1987**, 1797.
21. Bush, E. J.; Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1993**, 1200.
22. Berkowitz D.B.; Choi S.; Maeng J.H. *J. Org. Chem*. **2000**, *65,* 847.
23. Reynolds, A. J.; Scott, A. J.; Turner, C. I.; Sherburn, M. S. *J. Am. Chem. Soc.* **2003**, *125,* 12108−12109.
24. Stadler, D.; Bach, T. *Angew. Chem. Int. Ed.* **2008***, 47,* 7557.
25. Wu, Y.; Zhang, H.; Zhao, Y.; Zhao, J.; Chen, J.; Li, L. *Org. Lett.* **2007**, *9*, 1199
26. Wu, Y.; Zhao, J.; Chen, J.; Pan, C.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 597.
27. (a) Wasa. M.; Chan K. L.; Zhang X. G.; He J.; Miura M.; Yu J.Q. *J. Am. Chem. Soc.* **2012,** *134,* 18570. (b) Shabashov D.; Daugulis O. *J. Am. Chem. Soc.* **2010**, *1342,* 3965.
28. Takinami M.; Ukaji Y.; Inomata K. *Tetrahedron: Asymmetry* **2006**, *17,* 1554.
29. Dhawan K.L.; Gowland B.D.; Durst T. *J. Org. Chem.* **1980**, *45,* 922.
30. Sánchez A.; Pedroso E.; Grandas A. *Eur. J. Org. Chem.*, **2010**, 2600.
31. Hickman, D. N.; Hodgetts, K. J.; Mackman, P. S.; Wallace, T. W.; Wardleworth, J. M. *Tetrahedron* **1996**, *52*, 2235.
32. He G.; Zhao Y.; Zhang S.; Lu C.; Chen G. *J. Am. Chem. Soc.* **2012**, *134,* 3.
33. Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem.* **2013**, *125*, 13833.

34. Choy, W.; Yang, H. *J. Org. Chem*. **1988**, *53*, 5796.
35. a) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc*. **2011**, *133*, 19076. b) Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem*. **2012**, *124*, 7625; *Angew. Chem. Int. Ed.* **2012**, *51*, 7507.
36. a) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. b) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G.; *J. Am. Chem. Soc.* **2013**, *135*, 2124.
37. Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci*. **2013**, *4*, 3906.
38. Ting, C. P.; Maimone, T. J. *Angew. Chem. Int. Ed.* **2014***, 53,* 3115.
39. Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
40. Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976.
41. Chen, D.Y.-K.; Youn, S. W. *Chem. – Eur. J.* **2012**, *18,* 9452.
42. Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826.
43. Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 2.
44. Aslam, S. N.; Stevenson, P.C.; Phythian, S.J.; Veitch, N.C.; Hall, D.R. *Tetrahedron* **2006**, *62***,** 4214.

Supplementary Information for:

Chapter 1:
Total synthesis of Podophyllotoxin by a C-H Arylation Strategy

General Procedures

Unless stated otherwise, all reactions were performed in oven-dried or flame-dried glassware sealed with rubber septa under a nitrogen atmosphere. Dry tetrahydrofuran (THF), dichloromethane, toluene, hexane, acetonitrile, and diethyl ether were obtained by passing these previously degassed solvents through activated alumina columns. Anhydrous methanol and benzene were used directly from SureSeal® bottles from Aldrich. Volatile amines, and ethanol were distilled over calcium hydride before use. Reactions were monitored by thin layer chromatography (TLC) on SilicycleSiliaplate^{TM} glass backed TLC plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized by UV irradiation and potassium permanganate stain. Volatile solvents were removed under reduced pressure with a rotary evaporator. Flash column chromatography was performed using Silicycle F60 Å, 230x400 mesh silica gel (40-63 μm). ^{1}H NMR and ^{13}C NMR spectra were obtained on a with Bruker spectrometers operating at 400, 500, 600 MHz for ^{1}H, 150 MHz for ^{13}C in $CDCl_3$, or 365 MHz for ^{19}F. Chemical shifts are reported relative to the residual solvent signal (^{1}H NMR: $\delta = 7.26$; ^{13}C NMR: $\delta = 77.16$). NMR data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Splitting is reported with the following symbols: s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, m = multiplet. IR spectra were taken on a Nicolet 380 spectrometer as thin films on NaCl plates and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained by the mass spectral facility at the University of California, Berkeley using a Finnigan LTQFT mass spectrometer (Thermo electron corporation). X-ray crystal structures were obtained by the X-ray crystallography facility at the University of California, Berkeley.

Compound 9. Epoxide **9** was prepared according to the procedure reported by Durst and coworkers.[29] A flame-dried 1 L flask was charged with 6-bromopiperonal (15.0 g, 66.0 mmol, 1.0 equiv), trimethylsulfonium iodide (35.9 g, 176 mmol, 2.7 equiv), and benzyltriethylammonium chloride (600 mg, 2.60 mmol, 0.040 equiv). Dichloromethane (90 mL) was added and the reaction mixture cooled to 0 °C. To the rapidly stirring solution was added NaOH (50 wt %, 90 mL, 1.1 mol, 16 equiv) dropwise via addition funnel. The reaction mixture was warmed to room temperature and stirred vigorously overnight. The reaction mixture was quenched with H_2O (200 mL) and extracted with dichloromethane (3 x 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford **9** (10.8 g, 90%) as a white solid: mp 54-55 ^oC Spectral data matched that previously reported by Durst and coworkers[29]: ^1H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.60 (s, 1H), 5.90 (s, 2H), 4.05 (dd, J = 3.9, 2.4 Hz, 1H), 3.05 (dd, J = 5.7, 4.2 Hz, 1H), 2.52 (dd, J = 5.7, 4.2 Hz, 1 H).

Compound 10. Benzocyclobutenol **10** was prepared according to the procedure reported by Durst and coworkers.[29] A flame-dried flask was charged with epoxide **9** (5.01 g, 20.6 mmol, 1.0 equiv). The reaction flask was evacuated and backfilled with nitrogen gas three times followed by the addition of ether (120 mL). Under an argon atmosphere, *n*-BuLi (2.5 M in hexanes, 9.1 mL, 23 mmol, 1.1 equiv) was added dropwise at -78 °C. After stirring for 15 minutes at -78 °C, solid $MgBr_2$ (7.58 g, 41.2 mmmol, 2.0 equiv) was added rapidly in one portion. The reaction mixture was stirred for 30 minutes at -78 °C, warmed to room temperature, and stirred for one additional hour. The reaction was quenched with sat. NH_4Cl (100 mL) and extracted with ether (3 x 200 mL). The combined organic layers were washed with brine, and concentrated *in vacuo*. The crude product was purified by column chromatography (gradient 10% → 25% ether in hexanes) to afford **10** (1.7 g, 50%) as a white solid: mp 118-120 °C; Spectral data matched that previously reported by Durst and coworkers[29]: ^1H NMR (600 MHz, $CDCl_3$) δ 6.71 (s, 1 H), 6.61 (s, 1 H), 5.87 (s, 2 H), 5.10 (dd, J = 4.5, 1.0 Hz, 1 H), 3.41 (dd, J =14.0, 4.5 Hz, 1 H), 2.83 (dd, J = 14.0, 1.0 Hz, 1 H), 2.23 (bs, 1 H).

Compound 11a. A 250 mL flame-dried round-bottom flask was charged with *tert*butyldimethylsilyl chloride (4.13 g, 27.4 mmol, 3.0 equiv), imidazole (1.87 g, 27.4 mmol, 3.0 equiv) and **10** (1.49 g, 9.10 mmol, 1.0 equiv). The reaction flask was evacuated and backfilled with nitrogen three times. DMF (55 mL) was added and the reaction mixture was stirred for 12 hour at room temperature. The reaction was quenched with H_2O (100 mL) and extracted with ether (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 5% → 20% CH_2Cl_2 in hexanes) to afford **11a** (2.5 g, 97%) as a white solid: mp 34-37 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 6.68 (s, 1 H), 6.62 (s, 1 H), 5.87 (s, 2 H), 5.15 (d, J = 4.2 Hz, 1 H), 3.36 (dd, J =13.2, 4.2, 1 H), 2.88 (d, J = 13.2 Hz, 1 H), 0.94 (s, 9 H), -0.146 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 147.1, 140.6, 134.8, 105.4, 104.3, 100.3, 69.4, 41.0, 26.1, 18.4, -4.35, -4.41.

Compound 11b. A flame-dried reaction tube was charged with triisopropylsilyl chloride (560 mg, 3.00 mmol, 3.0 equiv), imidazole (204 mg, 3.00 mmol, 3.0 equiv) and **10** (130 mg, 0.98 mmol, 1.0 equiv). The reaction flask was evacuated and backfilled with nitrogen three times. DMF (55 mL) was added and the reaction mixture was stirred for 12 hours at room temperature. The reaction was quenched with H_2O (20 mL) and extracted with ether (30 mL x 3). The organic

layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 5% → 25% CH_2Cl_2 in hexanes) to afford **11b** (160 mg, 50%) as a clear oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.70 (s, 1 H), 6.63 (s, 1 H), 5.87 (s, 2 H), 5.20 (d, *J* = 1.8 Hz, 1 H), 3.38 (dd, *J* = 13.2, 1.8, 1 H), 2.90 (d, *J* = 13.2 Hz, 1 H), 1.17 (sep, 3 H), 1.11 (d, *J* = 7.2 Hz, 18 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.5, 147.1, 140.9, 134.8, 105.4, 104.3, 100.3, 69.4, 41.4, 18.1, 12.3.

Compound 12.[30] A flame-dried round-bottom flask was charged with maleic anhydride (2.10 g, 21.4 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled three times with nitrogen followed by the addition of anhydrous $CHCl_3$ (100mL). Anhydrous THF (10 mL) was added until the maleic anhydride was fully dissolved. A solution containing pentafluoroaniline (4.01 g, 21.9 mmol, 1.02 equiv) in anhydrous $CHCl_3$ (20 mL) was added dropwise to the maleic anhydride solution with stirring at room temperature. Solid precipitate was observed after 10 minutes. After 12 hours, the reaction mixture was filtered affording **12** (2.3 g, 49%) as a white solid which was used without further purification: mp 104-106 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.91 (bs, 1 H), 10.50 (bs, 1 H), 6.52 (d, *J* = 12.0 Hz, 1 H), 6.39 (d, *J* = 12.0 Hz, 1 H); ^{13}C NMR (150 MHz, d_6-DMSO) δ 166.8, 163.3 131.2, 129.7; ^{19}F NMR (376 MHz, d_6-DMSO) δ -143.9 (d, *J* = 18.8 Hz), -157.2 (t, *J* = 22.6 Hz), -162.7 (t, *J* = 22.6 Hz); Carbons that are heavily coupled to fluorine were not observed in ^{13}C NMR.

Compound 14a. *i*. A flame-dried round-bottom flask was charged with **12** (24.8 g, 88.3 mmol). The reaction vessel was evacuated and backfilled three times with nitrogen followed by the addition of anhydrous methanol (500 mL). Concentrated H_2SO_4 (2 drops) was added into the reaction flask. The reaction mixture was heated at 80 ^{o}C for 12 hours. Solvent was evaporated *in vacuo*, and the crude product was recrystallized from ether to yield the *cis* methyl ester (12.8 g, 49%) as a white solid: mp 134-136 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.84 (bs, 1 H), 6.48 (d, *J* = 13.8 Hz, 1 H), 6.36 (d, *J* = 13.8 Hz, 1 H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 161.9, 138.3, 126.9, 53.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -143.2 (d, *J* = 15.0 Hz), -156.1 (t, *J* = 22.6 Hz), -161.6 (t, *J* = 22.6 Hz); Carbons that are heavily split by fluorine were not observed in ^{13}C NMR.
ii. A flame-dried reaction tube was charged with *cis*-methyl ester (100 mg, 0.34 mmol, 1 equiv) and aniline (32 mg, 0.34 mmol, 1 equiv). The reaction vessel was evacuated and backfilled three times with nitrogen. Ethanol (3 mL) was added, and the reaction mixture was stirred at 80 °C for 12 hours. The reaction mixture was cooled to room temperature and quenched with 1 M HCl (20 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by column chromatography (gradient 10% → 20% EtOAc in hexanes) to afford **14a** (40 mg, 40%) as a white solid: mp 131-133 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (bs, 1 H), 7.25 (d, *J* = 15.6 Hz, 1 H), 7.00 (d, *J* = 15.6 Hz, 1 H), 3.82 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 161.8, 143.8, 142.1, 138.8, 137.1, 134.4, 132.6, 111.1, 52.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -143.2 (d, *J* = 15.0 Hz), -154.5 (t, *J* = 22.6 Hz), -160.8 (t, *J* = 22.6 Hz); Carbons that are heavily split by fluorine were not observed in ^{13}C NMR.

Compound 13.[30] A 100 mL flame-dried round-bottom flask was charged with maleic anhydride (680. mg, 6.94 mmol, 1.0 equiv). Anhydrous $CHCl_3$ (10 mL) was added under a nitrogen atmosphere followed by THF (1 mL) to fully dissolve the maleic anhydride. In a separate flask, 8-aminoquinoline (1.00 g, 6.94 mmol, 1.0 equiv) was dissolved in a minimal amount of $CHCl_3$ and added dropwise to the stirred solution of maleic anhydride. Within 10 minutes, a brown solid started to precipitate. The reaction mixture was stirred for an additional 5 hours followed by filtration of the brown solid. The solid was washed with ether (3 x 20 mL) and afforded **13** (1.1 g, 63%) as a brown solid: mp 214-216 °C; ^{1}H NMR (600 MHz, d_6-DMSO) δ 8.96 (d, J = 3.6 Hz, 1 H), 8.70 (d, J = 7.8 Hz, 1 H), 8.43 (d, J = 7.8 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 1 H), 7.63 (m, 3 H), 6.72 (d, J = 15.0 Hz, 1 H; ^{13}C NMR (150 MHz, d_6-DMSO) δ 166.4, 162.4, 149.1, 138.7, 137.6, 136.6, 134.2, 131.1, 127.9, 126.8, 123.1, 122.2, 118.3.

Compound 14b. A flame-dried round-bottom flask equipped with a reflux condenser was charged with **13** (1.0 g, 4.1 mmol, 1 equiv), K_2CO_3 (1.1 g, 8.2 mmol, 2 equiv) and THF (50 mL). Under an atmosphere of nitrogen, methyl iodide (0.75 mL, 12 mmol, 3 equiv) was added dropwise to the stirred reaction mixture. The reaction vessel was heated at 50°C for 20 hours. After cooling to room temperature, the reaction mixture was quenched with H_2O (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with 100 mL of brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (gradient 20% → 30% EtOAc in hexanes) to afford **14b** (330 mg, 31%) as a yellow solid: mp 122-124 °C; ^{1}H NMR (600 MHz, d_6-DMSO) δ 10.2 (bs, 1 H), 8.84 (m, 2 H), 8.18 (dd, J = 7.8, 0.6 Hz, 1 H), 7.56 (m, 2 H), 7.48 (dd, J = 4.2, 4.2 Hz, 1 H), 7.29 (d, J = 15.0 Hz, 1 H), 7.02 (d, J = 15.0 Hz, 1 H), 3.85 (s, J = 15.0 Hz, 3 H); ^{13}C NMR (150 MHz, d_6-DMSO) δ 166.2, 161.8, 148.6, 138.6, 137.4, 136.6, 134.1, 130.9, 128.1, 127.5, 122.7, 122.0, 117.4, 52.5.

Compound 14c. *i*.) Compound **14c** was synthesized using a procedure reported by Yu *et al.*[27] A flame-dried round bottom flask was charged with mono-methyl fumarate (1.00 g, 7.69 mmol, 1.0 equiv). Under an atmosphere of nitrogen, anhydrous benzene (20 mL) and thionyl chloride (2.40 mL, 33.1 mmol, 4.3 equiv) were added. The reaction mixture was heated to 65 °C with stirring for 12 h. After cooling to room temperature, the volatiles were removed *in vacuo*, and the acid chloride formed was used without further purification.

ii.) The vessel containing the acid chloride was charged with 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline (3.31 g, 14.2 mmol, 1.8 equiv) and toluene (10 mL). The reaction vessel was heated to 110°C and held at this temperature for 12 h. The reaction mixture was cooled to room temperature and quenched with sat. $NaHCO_3$ solution followed by extraction with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (gradient 20% → 30% EtOAc in hexanes) to afford **14c** (926 mg, 35%) as a white solid: mp 171-173 °C; ^{1}H NMR (600 MHz, d_6-DMSO) δ 11.18 (bs, 1 H), 7.27 (d, J = 15.6 Hz, 1 H), 6.82 (d, J = 15.6 Hz, 1 H), 3.77 (s, 3 H); ^{13}C NMR (150 MHz, d_6-DMSO) δ 165.0, 161.4, 134.7, 131.5, 52.2; ^{19}F NMR (376 MHz, d_6-DMSO) δ -54.5 (t, J = 18.8 Hz), -141.4 (d, J = 14.3 Hz), -141.7 to -141.8 (m). Carbons that are heavily split by fluorine were not observed in ^{13}C NMR.

Compound 14d. *i.* Compound **14d** was synthesized using a procedure reported by Yu *et al.*[27] A flame-dried round bottom flask was charged with mono-methyl fumarate (2.10 g, 16.2 mmol, 1.0 equiv). Under an atmosphere of nitrogen, anhydrous benzene (20 mL) and thionyl chloride (3.40 mL, 19.4 mmol, 1.2 equiv) were added. The reaction mixture was heated to 80 °C for 12 h. After cooling to room temperature, the volatiles were removed *in vacuo*, and the crude acid chloride used without further purification.
ii. The flask containing the crude acid chloride was charged with dichloromethane (120 mL), cooled to 0 °C under nitrogen, and 2-thiomethyl aniline (5.58 g, 19.4 mmol, 1.2 equiv) was added. The reaction mixture was warmed to 40 °C and stirred at this temperature for 1 h. After cooling to room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane (3 x 300 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (gradient 10% → 20% EtOAc in hexanes) to afford **14d** (2.56 g, 63%) as a white solid: mp 84-87 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (bs, 1 H), 8.45 (d, J = 8.4 Hz, 1 H), 7.53 (d, J = 8.4 Hz, 1 H), 7.33 (m, 1 H), 7.12 (m, 1 H), 7.12, (d, J = 15.6 Hz, 1 H), 6.97 (d, J = 15.6 Hz, 1 H), 3.84 (s, 3 H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.0, 161.6,138.1, 137.1, 133.7, 131.3, 129.4, 125.7, 125.4, 120.8, 52.5, 19.5; IR (thin film) 3313, 3060, 2951, 1727, 1649, 1580 cm^{-1}; HRMS (ESI) calcd for $[C_{12}H_{14}O_3NS]^+$ $(M+H)^+$: *m/z* 252.0689, found 252.0688.

Compound 15. A flame-dried reaction tube was charged with **10** (20 mg, 0.12 mmol, 1.0 equiv) and **14a** (70 mg, 0.24 mmol, 2.0 equiv). The reaction vessel was evacuated and backfilled three times with nitrogen followed by the addition of toluene (1 mL). The reaction vessel was heated to 110 ^{o}C for 12 hr. The reaction mixture was cooled to room temperature prior to the evaporation of solvent *in vacuo*. The crude mixture was purified by column chromatography (gradient 40% → 80% DCM in hexanes) to afford **15** (18 mg, 90%) as a white solid. Compound **15** was previous prepared by Aslam and coworkers and all spectra data matched[44]: mp 84-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.24 (s, 1H), 6.65 (s, 1H), 5.99 (s, 2H), 2.57 (s, 3H).

Compound 16a. A flame-dried 500 mL round-bottom flask was charged with **11a** (1.22 g, 4.39 mmol, 1.0 equiv), mono-methyl fumarate (2.92 g, 17.6 mmol, 4.0 equiv), zinc oxide (1.79 g, 22.0 mmol, 5.0 equiv), and anhydrous K_2CO_3 (3.04 g, 22.0 mmol, 5.0 equiv). Under a nitrogen atmosphere, dioxane (100 mL) was added and the reaction mixture heated to 120 °C and held at this temperature for 6 h. Upon cooling to room temperature, the suspension was filtered through Celite, and the filtrate concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 20% → 30% EtOAc in hexanes) to afford **16a** (330 mg, 20%) as a white solid: mp 127-129 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.65 (bs, 1 H), 6.66 (s, 1 H), 6.59 (s, 1 H), 5.93 (d, J = 10.2 Hz, 1 H), 5.08 (s, 1 H), 3.75 (s, 3 H), 3.54 (dd, J = 17.4, 9.6 Hz, 1 H), 3.24 (dd, J = 16.2 Hz, 6.6 Hz, 1 H), 2.99 (d, J = 10.8 Hz, 1 H), 2.82 (dd, J = 18.0, 10.2 Hz, 1 H), 0.77 (s, 9 H), 0.07 (s, 3 H), -0.14 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.7, 172.2, 147.7, 145.7, 129.9, 127.9, 108.8, 108.5, 101.0, 70.1, 51.9, 48.8, 36.7, 31.2, 25.6, 17.8, -4.04, -4.90.

Compound 16b. A flame-dried 250 mL round-bottom flask was charged with **11a** (1.27 g, 4.57 mmol, 3.0 equiv), **14b** (390 mg, 1.52 mmol, 1.0 equiv) and benzene (40 mL). The reaction mixture was heated at 80 °C and held at this temperature for 12 h. Upon cooling to room

temperature, the reaction mixture was concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 10% → 25% EtOAc in hexanes) to afford a 2.5:1 mixture of diastereomers. The mixture was recrystallized using 10% EtOAc in hexanes to afford **16b** (240 mg, 30% yield) as a white solid: mp 158-160 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.10 (bs, 1 H), 8.83 (d, *J* = 3.6 Hz, 1 H), 8.76 (d, *J* = 7.2 Hz, 1 H), 8.15 (d, *J* = 8.4 Hz, 1 H), 7.53-7.44 (m, 3 H), 6.71 (s, 1 H), 6.61 (s, 1 H), 5.95 (d, *J* = 18.0 Hz, 2H) 5.18 (d, *J* = 2.4 Hz, 1H), 3.70-3.67 (m, 4 H), 3.32 (dd, *J* = 16.8, 7.2 Hz, 1 H), 3.21 (dd, *J* = 10.2, 2.4 Hz, 1H), 3.00 (dd, *J* = 16.8, 3.6 Hz, 1H), 0.83 (s, 9 H), 0.11 (s, 3 H), -0.080 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 172.6, 148.4, 147.8, 145.9, 138.6, 136.4, 134.9, 130.2, 128.7, 128.1, 127.5, 121.7, 121.6, 116.7, 108.9, 108.7, 101.2, 70.8, 52.1, 49.6, 39.9, 32.6, 25.9, 18.3, -3.77, -4.59; IR (thin film) 3353, 3050, 2953, 2929, 2895, 2856, 1742, 1687 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{25}O_6N_2Si]^+$ $(M+H)^+$: *m/z* 535.2259, found 535.2256.

Compound 16c. A flame-dried 250 mL round-bottom flask was charged with **11a** (2.52 g, 9.08 mmol, 3.0 equiv), **14d** (760 mg, 3.03 mmol, 1.0 equiv), and benzene (50 mL). The reaction mixture was heated at 80 °C and held at this temperature for 12 h. Upon cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 10% → 20% EtOAc in hexanes) to afford a 2.0:1 mixture of diastereomers. The mixture was recrystallized from pure EtOAc to afford **16c** (370 mg, 23% yield) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (bs, 1 H), 8.29 (d, *J* = 7.8 Hz, 1 H), 7.50 (d, *J* = 7.8, 1 H), 7.28 (m, 1 H), 7.05 (m, 1 H), 6.68 (s, 1 H), 6.62 (s, 1 H), 5.94 (d, *J* = 17.4 Hz, 2 H), 5.14 (d, *J* = 2.4 Hz, 1 H), 3.71 (s, 3 H), 3.48 (td, *J* = 10.8, 9.6, 7.2 Hz, 1 H), 3.18 (dd, *J* = 16.8, 7.2 Hz, 1 H), 3.10 (dd, *J* = 10.8, 2.4 Hz, 1 H), 2.99 (dd, *J* = 16.8, 9.6 Hz, 1 H), 0.81 (s, 9 H), 0.10 (s, 3 H), -0.13 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 172.6, 147.9, 145.9, 138.9, 133.5, 130.0, 129.2, 128.6, 125.5, 124.4, 120.9, 109.0, 108.7, 101.2, 70.8, 52.2, 49.7, 39.3, 32.4, 25.9, 19.1, 18.3, -3.69, -4.71.

Compound 16d. A flame-dried 500 mL round-bottom flask was charged with **11a** (3.07 g, 10.8 mmol, 3.0 equiv), **14a** (1.06 g, 3.59 mmol, 1.0 equiv) and benzene (100 mL). The reaction mixture was heated at 80 °C and held at this temperature for 12 h. Upon cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 5% → 10% EtOAc in hexanes) to afford a 2.5:1 mixture of diastereomers. The mixture was recrystallized from ether and hexanes to afford **16d** (1.2 g, 59%) as a white solid: mp 174-175 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (bs, 1 H), 6.66 (s, 1 H), 6.63 (s, 1 H), 5.94 (d, *J* = 15.6 Hz, 2 H), 5.13 (s, 1 H), 3.77 (s, 3 H), 3.58 (td, *J* = 15.0, 13.8, 13.8 Hz, 1 H), 3.19 (dd, *J* = 16.2, 7.2 Hz, 1 H), 3.01 (m, 2 H), 0.79 (s, 9 H), 0.09 (s, 3 H), -0.13 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.6, 173.0, 148.1, 146.0, 129.8, 128.3, 108.8, 101.2, 70.9, 52.4, 50.0, 38.1, 31.6, 25.9, 18.2, -3.84, -4.65; ^{19}F NMR (376 MHz, $CDCl_3$) δ -144.0 (d, *J* = 18.8 Hz), -156.0 (t, *J* = 22.6 Hz), -161.7 (t, *J* = 22.6 Hz); IR (thin film) 3263, 2954, 2931, 2896, 2858, 1743, 1682, 1654 cm^{-1}; HRMS (ESI) calcd for $[C_{26}H_{28}O_6N_1F_5NaSi]^+$ $(M+Na)^+$: *m/z* 596.1498, found 596.1498; Carbons that are heavily split by fluorine were not observed in ^{13}C NMR. X-ray crystal structure was obtained via slow vapor diffusion of heptane into diisopropyl ether containing **16d**.

Compound 17a. A flame-dried 100 mL round-bottom flask was charged with **11b** (3.33 g, 10.3 mmol, 2.0 equiv), **14a** (1.5 g, 5.1 mmol, 1.0 equiv) and benzene (30 mL). The reaction was heated at 80 °C and held at this temperature for 24 h. Upon cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 5% → 20% EtOAc in hexanes) to afford a 4.0:1 mixture of diastereomers. The mixture was recrystallized using 30% ether in hexanes to afford **17a** (1.4 g, 45% yield) as a white solid: mp 183-184 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (bs, 1 H), 6.74 (s, 1 H), 6.66 (s, 1 H), 5.93 (d, *J* = 13.8 Hz, 2H), 5.31 (s, 1H), 3.77 (s, 3 H), 3.69 (td, *J* = 10.8, 7.8, 7.8 Hz, 1 H), 3.26 (dd, *J* = 16.2, 7.8 Hz, 1 H), 3.03 (dd, *J* = 16.2, 7.8 Hz, 1H), 2.98 (d, *J* = 10.8, 1H), 1.01-0.98 (m, 12 H), 0.86 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.6, 173.2, 148.2, 146.9, 130.6, 128.7, 109.1, 108.5, 101.2, 71.5, 52.3, 50.5, 37.9, 30.9, 18.3, 18.0, 13.1; ^{19}F NMR (376.5 MHz , $CDCl_3$) δ -144.1 (d, *J* = 26.4 Hz), -156.0 (t, *J* = 22.6 Hz), -161.7 (t, *J* = 22.6 Hz); IR (thin film) 3261, 2946, 2867, 1742, 1681 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{34}O_6N_1F_5NaSi]^+$ $(M+H)^+$: *m/z* 638.1968, found 638.1976. Carbons that are heavily split by fluorine were not observed in ^{13}C NMR.

Compound 17b. A flame-dried 500 mL round-bottom flask was charged with **11b** (7.5 g, 23 mmol, 4.0 equiv), **14c** (2.0 g, 5.8 mmol, 1.0 equiv) and anhydrous benzene (150 mL). The reaction mixture was heated at 80 °C and held at this temperature for 24 h. Upon cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 20% → 30% EtOAc in hexanes) to afford a 2.0:1 mixture of diastereomers. The mixture was recrystallized using 20% ether in hexanes to afford **17b** (1.2 g, 27% yield) as a white solid: mp 167-168 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (bs, 1 H), 6.74 (s, 1 H), 6.65 (s, 1 H), 5.94 (d, *J* = 7.2 Hz, 2 H), 5.31 (d, *J* = 2.0 Hz, 1 H), 3.77 (s, 3 H), 3.72 (td, *J* = 10.8, 8.0, 8.0 Hz, 1 H), 3.26 (dd, *J* = 16.4, 8.0 Hz, 1 H), 3.03 (dd, *J* = 16.4, 8.0 Hz, 1 H), 2.96 (d, *J* = 2.0 Hz, 1 H), 1.01 - 0.97 (m, 12 H), 0.85 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1, 173.3, 148.1, 145.9, 130.4, 128.5, 108.9, 108.6, 101.2, 71.3, 52.4, 50.5, 38.0, 30.8, 18.3, 18.0, 13.1; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -55.2 (t, *J* = 22.6 Hz, CF_3), -140.1, -142.4 (d, *J* = 15.1 Hz); IR (thin film) 3256, 2947, 2868, 1743, 1687, 1655, 1508 cm^{-1}; HRMS (ESI) calcd for $[C_{30}H_{34}O_6N_1F_7NaSi]^+$ $(M+H)^+$: *m/z* 688.1936, found 688.1947. Carbons that are heavily split by fluorine were not observed in ^{13}C NMR.

Compound 17c. A flame-dried 500 mL round-bottom flask was charged with **11b** (7.51 g, 23.4 mmol, 3.0 equiv), **14b** (2.00 g, 7.81 mmol, 1.0 equiv) and benzene (150 mL). The reaction mixture was heated at 80 °C and held at this temperature 24 h. Upon cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 5% → 20% EtOAc in hexanes) to afford a 2.6:1 mixture of diastereomers. The mixture was recrystallized using 10% EtOAc in hexanes to afford **17c** (1.2 g, 27% yield) as a white solid: mp 200-201 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.1 (bs, 1 H), 8.85 (s, 1 H), 8.75 (d, *J* = 6.6 Hz, 1 H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.51 - 7.49 (m, 2H), 7.47 – 7.45 (m, 1H), 6.79 (s, 1H), 6.64 (s, 1H), 5.93 (d, *J* = 13.2 Hz, 2H), 5.36 (s, 1H), 3.81 - 3.77 (m, 1H), 3.70 (s, 3H), 3.37 (dd, *J* = 16.4, 7.8 Hz, 1H), 3.19 (d, *J* = 10.5 Hz, 1H), 3.01 (dd, *J* = 16.4, 7.8 Hz, 1H), 1.05 - 1.01 (m, 12 H), 0.90 (d, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.4, 172.5, 148.2, 147.7, 145.6, 138.9, 136.4, 134.7, 130.8, 128.9, 127.9, 127.3, 121.5, 121.4, 116.5, 108.7, 108.4,

100.9, 71.3, 51.8, 49.8, 39.5, 31.9, 18.2, 17.9, 13.0; IR (thin film) 3365, 2951, 2858, 1736, 1686, 1526, 1486 cm^{-1}; HRMS (ESI) calcd for $[C_{32}H_{41}O_6N_2Si]^+$ $(M+H)^+$: *m/z* 577.2728, found 577.2732.

General Procedure for Ligand Screen

Compound OTIPS-**18**. Ten flame-dried 10 mL reaction tubes were charged with **17a** (20 mg, 0.033 mmol, 1.0 equiv), aryl iodide (40 mg, 0.14 mmol, 4.0 equiv), Ag_2CO_3 (27 mg, 0.10 mmol, 3.0 equiv), K_2HPO_4 (7.0 mg, 0.040 mmol, 1.2 equiv) and $Pd(TFA)_2$ (4.0 mg, 0.0012 mmol, 0.35 equiv) each.[4] Under a nitrogen atmosphere, 2,6-lutidene (2.0 mg, 0.023 mmol, 0.70 equiv) was added to each tube followed by the addition hexanes (0.5 ml). The reaction vessels were heated at 110 °C for 24 hours. After cooling to room temperature, the reaction mixture from each tube was combined, washed with 1 M HCl (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography using 20% EtOAc in hexanes as an elution gradient. The eluting fractions were concentrated *in vacuo*, and purified by preparatory TLC using 5% acetone in toluene as solvent to afford OTIPS-**18** (2.1 mg, 0.8%) of white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.82 (s, 1 H), 6.76 (bs, 1 H), 6.47 (s, 1 H), 6.21 (s, 2 H), 5.94 (s, 2 H), 5.42 (s, 1 H), 4.62 (d, *J* = 7.5 Hz, 1 H), 4.00 (dd, *J* = 11.0, 7.5 Hz, 1 H), 3.80 (s, 3 H), 3.72 (s, 3 H), 3.71 (s, 6 H), 3.39 (d, *J* = 11.0 Hz, 1 H), 1.05 - 1.02 (m, 12 H), 0.89 (d, *J* = 6.6 Hz, 9 H); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -143.5 (d, *J* = 18.8 Hz), -156.2 (t, *J* = 26.4 Hz), -161.7 (t, *J* = 33.9 Hz).

Compound 19. A flame-dried reaction tube was charged with **16b** (50 mg, 0.094 mmol, 1.0 equiv), aryl iodide (110 mg, 0.375 mmol, 4.0 equiv), $Pd(OAc)_2$ (4.0 mg, 0.019 mmol, 0.2 equiv), and Ag_2CO_3 (78 mg, 0.282 mmol, 3.0 equiv). Under a nitrogen atmosphere, *t*-BuOH (2 mL) was added into the reaction vessel. The reaction mixture was stirred for 24 hours at 110 °C. After cooling to room temperature, the reaction was quenched with 1 M HCl and the mixture extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography using (gradient 10% → 25% EtOAc in hexanes) to afford **19** (20 mg, 40% yield) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.00 (d, *J* = 3.0 Hz, 1 H), 8.13 (d, *J* = 7.8 Hz, 1 H), 7.89 (d, *J* = 7.2 Hz, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.47 - 7.42 (m, 2 H), 6.96 (bs, 1 H), 6.88 (bs, 1 H), 6.36 (d, *J* = 4.8 Hz, 1 H), 5.80 (d, *J* = 39.6 Hz, 2 H), 5.22 (bs, 1 H), 4.14 (bs, 1 H), 3.77 (bs, 1 H), 3.60 (bs, 3 H), 0.90 (bs, 9 H), 0.260 (bs, 3 H), 0.158 (bs, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 149.3, 141.8, 136.1, 132.6, 129.1, 126.4, 125.4, 121.6, 100.8, 60.9, 56.2, 51.7, 46.7, 29.6, 25.7, 18.2, -4.82, -5.02. X-ray crystal structure was obtained by slow diffusion of pentane into ether containing **19**.

Compound 20. A flame-dried 10 mL reaction tube was charged with **17c** (100 mg, 0.17 mmol, 1.0 equiv), $Pd(OAc)_2$ (39 mg, 0.17 mmol, 1.0 equiv) and acetonitrile (5 mL). The reaction mixture was heated to 60 °C and held at this temperature for 2 h. A yellow solid precipitated over the course of the reaction and was collected by filtration. The solid was washed with ether (3 x 10 mL) to afford **20** (65 mg, 53% yield) as yellow crystals: mp 242-250 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.99 (d, *J* = 7.2 Hz, 1 H), 8.20 (s, 1 H), 8.11 (d, *J* = 1.8 Hz, 1 H), 7.47-7.45 (m, 1 H), 7.26-7.23 (m, 2 H), 7.01 (s, 1 H), 6.57 (s, 1 H), 5.84 (d, *J* = 27.4, 2 H), 4.04 (d, *J* = 7.2 Hz, 1 H), 3.58 (s, 1 H), 3.50 (s, 3 H), 3.19 (d, *J* = 7.2 Hz, 1 H), 2.19 (s, 3 H), 1.16-1.14 (m, 3 H), 1.02

(d, J = 6.6 Hz, 18 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.9, 173.8, 146.6, 146.4, 145.7, 145.3, 143.7, 138.8, 138.1, 131.4, 129..8, 129.1, 121.3, 120.8, 118.9, 118.1, 70.4, 54.3, 52.5, 51.4, 25.0, 18.3, 18.2, 12.7, 3.4; IR (thin film) 2944, 2865, 1729, 1609, 1569, 1500 cm^{-1}; HRMS (ESI) calcd for $[C_{34}H_{41}O_6N_3PdNaSi]^+$ $(M+H)^+$: *m/z* 744.1700, found 744.1699. X-ray crystal structure was obtained by layering pentane over dichloromethane containing **20**.

Compound 21. A flame-dried reaction tube was charged with **20** (30 mg, 0.040 mol, 1.0 equiv), aryl iodide (24 mg, (0.080 mmol, 2.0 equiv), and *t*BuOH (1 mL). The reaction vessel was heated to 110 °C for 2 h. After cooling to room temperature, the reaction mixture was quenched with sat. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by preparative TLC using a 30% EtOAc in hexanes eluting solvent to afford **21** (12 mg, 52% NMR yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (d, J = 3.0 Hz, 1 H), 8.13 (d, J = 7.0 Hz, 1 H), 7.86 (d, J = 7.0 Hz, 1 H), 7.47 - 7.45 (m, 3 H), 7.07 (bs, 1 H), 6.88 (bs, 1 H), 6.36 (bs, 1 H), 5.81 (d, J = 31.5 Hz, 2 H), 5.38 (bs, 1 H), 4.13 (bs, 1 H), 3.74 (bs, 1 H), 3.56 (bs, 3 H), 1.26 (bs, 3 H), 0.88 (bs, 18 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 149.3, 141.8, 136.1, 132.8, 129.1, 126.5, 125.3, 121.6, 100.8, 68.4, 58.1, 51.6, 47.0, 29.6, 18.1, 12.6 (extreme peak broadening was observed for several resonances); HRMS (ESI) calcd for $[C_{32}H_{39}O_6N_2Si]^+$ $(M+H)^+$: *m/z* 575.2572, found 575.2574.

Compound 22 and *epi*-**22**. A flame-dried reaction tube was charged with **20** (30 mg, 0.042 mmol, 1.0 equiv) and aryl iodide (48 mg, 0.16 mmol, 3.9 equiv). The reaction vessel was evacuated and backfilled with nitrogen three times followed by the addition of anhydrous methanol (1 mL). The reaction vessel was heated to 70 °C and held at this temperature for 24 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The crude mixture was purified by column chromatography using 20% EtOAc in hexanes as the eluting solvent to afford **22** and *epi*-**22** (13 mg, 51% yield) as a 1.2:1 mixture of diastereomers: Major diastereomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (bs, 1 H), 8.86 (d, J = 1.6 Hz, 1 H), 8.78 (d, J = 1.6 Hz, 1 H), 8.16 (d, J = 1.6 Hz, 1 H), 7.53 – 7.45 (m, 3 H), 6.96 (s, 1 H), 6.82 (s, 1 H), 5.99 (d, J = 3.6 Hz, 2 H), 5.22 (d, J = 2.8 Hz, 1 H), 4.83 (d, J = 9.6 Hz, 1 H), 3.94 – 3.85 (m, 1 H), 3.67 (s, 3 H), 3.49 (s, 3 H), 3.33 (dd, J = 10.9, 2.0 Hz, 1 H), 1.08 - 0.96 (m, 12 H), 0.97 – 0.93 (m, 9 H); Minor diastereomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (bs, 1 H), 8.86 (d, J = 1.6 Hz, 1 H), 8.77 (d, J = 1.6 Hz, 1 H), 8.15 (d, J = 1.6 Hz, 1 H), 7.53 – 7.45 (m, 3 H), 6.96 (s, 1 H), 6.92 (s, 1 H), 5.96 (d, J = 4.0 Hz, 2 H), 5.52 (d, J = 4.8 Hz, 1 H), 5.05 (d, J = 5.6 Hz, 1 H), 3.81 – 3.78 (m, 2 H), 3.72 (s, 3 H), 3.54 (s, 3 H), 1.08 - 0.96 (m, 12 H), 0.97 – 0.93 (m, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 172.6, 172.0, 170.5, 148.5, 148.3, 148.3, 147.3, 147.1, 147.0, 138.8, 138.8, 136.3, 136.3, 134.9, 134.9, 132.0, 131.9, 130.0, 129.3, 128.1, 128.1, 127.5, 127.4, 121.7, 121.6, 121.6, 121.5, 116.9, 116.7, 108.2, 107.5, 107.4, 107.1, 101.3, 101.2, 79.0, 77.8, 70.6, 70.2, 58.1, 55.2, 52.0, 51.9, 49.2, 48.5, 47.3, 44.6, 29.8, 18.4, 18.2, 18.2, 18.1, 13.2, 12.8.

Compound 23. A flame-dried reaction tube was charged with **20** (10 mg, 0.014 mmol, 1.0 equiv) and bis(pinacolato) diboron (8.0 mg, 0.028 mmol, 2.0 equiv). Under a nitrogen atmosphere, THF (2 mL) was added to the reaction flask. The reaction vessel was heated at 100 °C and held at this temperature for 4 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* which was then purified by column chromatography using 20% ether in hexanes to afford **23** (4.0 mg, 40% yield) as a colorless oil: ^{1}H NMR (600 MHz,

$CDCl_3$) δ 10.39 (bs, 1 H), 8.83 (d, *J* = 2.9 Hz, 1 H), 8.76 – 8.74 (m, 1 H), 8.14 (d, *J* = 8.2 Hz, 1 H), 7.51 - 7.49 (m, 2 H), 7.46 – 7.43 (m, 1 H), 6.82 (s, 1 H), 6.80 (s, 1 H), 5.91 (d, *J* = 8.8 Hz, 2 H), 5.39 (d, *J* = 3.4 Hz, 1 H), 3.83 (dd, *J* = 10.4, 6.6 Hz, 1 H), 3.70 (s, 3 H), 3.63 (dd, *J* = 10.4, 3.4 Hz, 1 H), 2.97 (d, *J* = 6.5 Hz, 1 H), 1.22 (s, 6 H), 1.15 (s, 6 H), 1.08 – 1.06 (m, 12 H), 0.90 (m, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 173.0, 148.2, 147.1, 144.9, 138.6, 136.1, 134.5, 131.2, 129.9, 127.9, 127.2, 121.6, 121.5, 116.8, 108.5, 108.2, 100.6, 82.8, 71.2, 51.7, 49.2, 43.3, 29.7, 24.8, 24.6, 18.2, 18.0, 13.2.

Compound 24. *i.* A flame-dried round-bottom flask was charged with ester **17c** (1.30 g, 2.25 mmol, 1.0 equiv) and anhydrous THF (60 mL). The reaction vessel was evacuated and backfilled with nitrogen, cooled to -78 °C, and $LiAlH_4$ solution (1.0 M in THF, 4.5 mL, 4.5 mmol, 2.0 equiv) added dropwise. After 15 minutes at -78 °C, the reaction mixture was warmed to 0 °C, stirred for 10 minutes at this temperature, and slowly quenched by the addition of EtOAc (1 mL) followed by saturated aqueous ammonium chloride (1 ml). The reaction mixture was diluted with 10% Rochelle's salt solution (100 ml) and thoroughly extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 10% → 20% EtOAc in hexanes) to afford **SI-1** (470 mg, 38% yield) as a white solid: mp = 151 - 153 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.14 (bs, 1H), 8.94 – 8.62 (m, 2H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.92 (s, 1H), 6.71 (s, 1H), 5.94 (d, *J* = 6.8 Hz, 2H), 5.11 (d, *J* = 4.1 Hz, 1H), 3.86 (dd, *J* = 10.9, 6.5 Hz, 1H), 3.65 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.15 – 3.06 (m, 2H), 3.05 – 2.97 (m, 1H), 2.71 (bs, 1H), 2.58 (dt, *J* = 6.3, 3.2 Hz, 1H), 1.19 – 1.12 (m, 3H), 1.10 (d, *J* = 7.1 Hz, 9H), 1.01 (d, *J* = 7.1 Hz, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 148.4, 147.0, 146.0, 138.7, 136.5, 134.7, 132.6, 128.9, 128.1, 127.5, 121.8, 121.7, 116.9, 108.6, 106.9, 100.9, 72.0, 64.3, 45.8, 42.9, 31.0, 18.4, 18.2, 12.9; IR (thin film) 3435, 3345, 2942, 2866, 1683, 1529 cm^{-1}; HRMS (ESI) calcd for $[C_{31}H_{41}O_5N_2Si]^+$ $(M+H)^+$: *m/z* 549.2779, found 549.2774.
ii. A flame-dried round-bottom flask was charged with **S1** (547 mg, 1.00 mmol, 1.0 equiv) and anhydrous THF (10 mL). The reaction vessel was evacuated and backfilled with nitrogen, cooled to -78 °C, and a TBAF solution (1 M in THF, 2.0 mL, 2.0 mmol, 2.0 eq) added dropwise. After 15 minutes of stirring at -78 °C, the reaction mixture was warmed to room temperature and stirred for an additional 4 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (20 mL) and thoroughly extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude diol (528 mg) as a white solid that was used without further purification.
iii. The vessel containing the crude product was charged with *p*-toluenesulfonic acid monohydrate (16.0 mg, 0.08 mmol, 0.1 equiv), 2,2-dimethoxypropane (12.0 mL), and anhydrous THF (20 mL). The reaction mixture was stirred for 12 h. before it was quenched with 50 mL sat. $NaHCO_3$ solution and extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 20% → 50% EtOAc in hexanes) to afford **24** (432 mg, 81% yield from **S1**) as a white solid: mp 236-239 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (bs, 1H), 8.81 (d, *J* = 3.2 Hz, 2H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 7.0 Hz, 2H), 7.45 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.73 (s, 1H), 6.61 (s, 1H), 5.92 (d, *J* = 11.3 Hz, 2H), 4.92 (d, *J* = 3.0 Hz, 1H), 4.22 (dd, *J* = 12.5, 3.3 Hz, 1H), 3.96 (d, *J* = 11.9 Hz, 1H), 3.57 (dt, *J* = 11.4, 5.7 Hz, 1H), 3.35 – 3.01 (m, 2H), 2.11 (d, *J* = 13.1 Hz, 1H), 1.62 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 148.6, 148.1, 146.5, 138.6, 136.4, 134.5, 129.7, 128.1, 127.8, 127.5,

121.9, 121.8, 116.6, 109.8, 108.5, 101.2, 99.5, 68.5, 62.0, 41.0, 36.9, 33.5, 29.8, 19.6; IR (thin film) 3324, 2985, 1674, 1525, 1483, 1275 cm^{-1}; HRMS (ESI) calcd for $[C_{25}H_{25}O_5N_2]^+$ $(M+H)^+$: *m/z* 433.1758, found 433.1751.

Compound 25. A flame-dried reaction tube was charged with acetonide **24** (80 mg, 0.18 mmol, 1.0 equiv), $Pd(OAc)_2$ (41 mg, 0.18 mmol, 1.0 equiv) and acetonitrile (8 mL). The reaction mixture was heated to 60 °C and held at this temperature for 90 minutes. After cooling to room temperature, the yellow solid precipitate was collected by filtration, washed with ether (3 x 10 mL), and dried under high vacuum to afford **25** (40 mg, 38% yield) as yellow crystals: mp = 231-232 °C (decomposition); ^1H NMR (600 MHz, $CDCl_3$) δ 9.02 (d, *J* = 7.9 Hz, 1H), 8.26 (d, *J* = 4.6 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.31 (dd, *J* = 8.4, 4.6 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.03 (s, 1H), 6.63 (s, 1H), 5.90 (d, *J* = 4.7 Hz, 1H), 5.88 (s, 1H), 5.82 (s, 1H), 4.10 (d, *J* = 7.9 Hz, 1H), 3.59 (d, *J* = 4.0 Hz, 1H), 3.51 (s, 3H), 3.21 (d, *J* = 7.8 Hz, 1H), 2.19 (s, 3H), 1.16 (m, *J* = 7.1 Hz, 3H), 1.02 (dd, *J* = 7.4 Hz, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.9, 173.8, 146.6, 146.4, 145.7, 145.3, 143.7, 138.8, 138.1, 131.4, 129..8, 129.1, 121.3, 120.8, 118.9, 118.1, 70.4, 54.3, 52.5, 51.4, 25.0, 18.3, 18.2, 12.7, 3.4; IR (thin film) 3005, 2989, 1603, 1275, 1261, 764, 750 cm^{-1}; HRMS (ESI) calcd for $[C_{27}H_{26}O_5N_3Pd]^+$ $(M+H)^+$: *m/z* 578.0908, found 578.0902. X-ray quality crystals were obtained by slow diffusion of a dichloromethane/ether solution of **25** with hexane.

Stoichiometric Reaction of palladacycle 25.

Compound 26. A flame-dried reaction tube was charged with **25** (9.0 mg, 0.017 mol, 1.0 equiv), 3,4,5-trimethoxyiodobenzene (15 mg, 0.052 mmol, 3.0 equiv), K_2CO_3 (2.3 mg, 0.017 mmol, 1.0 equiv) and *t*-BuOH (1 mL). The reaction vessel was evacuated and backfilled with nitrogen three times. The reaction vessel placed into a pre-heated 110 °C oil bath and stirred for 5 h. After cooling to room temperature, the reaction mixture was quenched with a saturated aqueous NaI solution and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by preparative TLC (10% ether in dichloromethane) to afford the C-C coupled product **26** (5.0 mg, 49% yield) as a white solid as well as the *β*-lactam (1.0 mg, 10% yield). **Compound 26**: white solid: mp 222-225 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 9.92 (bs, 1H), 8.87 – 8.74 (m, 1H), 8.61 – 8.55 (m, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 7.48 (dd, *J* = 11.3, 4.4 Hz, 3H), 6.81 (s, 1H), 6.47 (s, 1H), 6.01 (s, 2H), 5.93 (d, *J* = 21.4 Hz, 2H), 5.05 (d, *J* = 3.7 Hz, 1H), 4.60 (d, *J* = 5.8 Hz, 1H), 4.26 (dd, *J* = 12.5, 4.8 Hz, 1H), 3.98 (dd, *J* = 12.7, 3.6 Hz, 1H), 3.84 (dd, *J* = 12.1, 5.9 Hz, 1H), 3.59 (s, 3H), 3.35 (s, 6H), 2.51 (d, *J* = 12.0 Hz, 1H), 1.64 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 152.6, 148.3, 148.2, 147.0, 138.3, 137.0, 136.6, 136.3, 134.2, 131.9, 128.2, 127.8, 127.3, 121.7, 121.4, 116.4, 109.4, 109.0, 106.8, 101.1, 99.7, 67.5, 61.9, 60.5, 55.7, 48.7, 46.2, 31.3, 27.9, 20.7; IR (thin film) 2924, 1693, 1588.5, 1484, 1325 cm^{-1}; HRMS (ESI) calcd for $[C_{34}H_{35}O_8N_2]^+$ $(M+H)^+$: *m/z* 599.2388, found 599.2374.

Screening conditions for Table 1.

A flame-dried reaction tube was charged with acetonide **24** or **27** (10 mg, 1.0 equiv), 3,4,5-trimethoxyiodobenzene (4.0 equiv), $Pd(OAc)_2$ (20 mol%), base (3.0 equiv), and additive (where appropriate). The reaction vessel was evacuated and backfilled with argon. This cycle was repeated two times followed by the addition of solvent (1.0 mL). The reaction vessel was placed into a pre-heated 110 °C oil bath a stirring for 24 h. After cooling to room temperature, the

reaction mixture was diluted with dichloromethane and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo*, 2-chloroquinoline standard added, and the yield determined by ^{1}H NMR analysis.

Compound 27. *i*.) A flame-dried round-bottom flask was charged with **10** (250 mg, 1.52 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen and this cycle repeated twice. Anhydrous THF (30 mL) was added, the reaction cooled to -78 °C, and KHMDS (0.5 M solution in toluene, 3.3 mL, 1.65 mmol, 1.1 eq) was added dropwise. After stirring for 15 minutes, a solution of dienophile **14d** (190 mg, 0.757 mmol, 0.5 equiv) in anhydrous THF (2 mL) was added dropwise to the dark purple reaction mixture. The reaction mixture was stirred for 5 min at -78 °C, warmed to 0 °C, stirred 30 minutes at this temperature, and cooled back to -78 °C. Super Hydride solution (1 M in THF, 3.0 mL, 3.0 mmol, 4.0 equiv) was added dropwise at -78 °C and the reaction mixture stirred for 30 minutes at this temperature. The reaction mixture was warmed to 0 °C, stirred for an additional 30 minutes, and carefully quenched was saturated aqueous NH_4Cl solution (30 mL), and thoroughly extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a short pad of silica gel and concentrated *in vacuo* to afford a yellow oil which was taken on crude.
ii.) The crude diol was dissolved in 2,2-dimethoxypropane/THF(2:1 *v:v,* 15 mL) and *p*-toluenesulfonic acid monohydrate (15.0 mg, 0.08 mmol, 0.1 equiv) was added. The reaction mixture was stirred for 12 hours at room temperature, quenched with 20 mL sat. $NaHCO_3$ solution and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (10% → 15% EtOAc in hexanes) to afford **27** (134 mg, 41% yield) as a single diastereomer; white solid: mp 209-211 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.77 (bs, 1H), 8.42 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.3 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.70 (s, 1H), 6.61 (s, 1H), 5.91 (d, J = 18.6 Hz, 2H), 4.99 – 4.81 (m, 1H), 4.19 (dd, J = 13.0, 3.2 Hz, 1H), 3.91 (d, J = 12.6 Hz, 1H), 3.41 (dt, J = 11.8, 5.9 Hz, 1H), 3.16 (dd, J = 16.4, 12.3 Hz, 1H), 3.00 (dd, J = 16.5, 4.7 Hz, 1H), 2.37 (s, 3H), 1.99 (d, J = 11.2 Hz, 1H), 1.62 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 148.1, 146.5, 138.6, 133.7, 129.6, 129.3, 127.7, 125.5, 124.6, 120.5, 109.7, 108.5, 101.2, 99.5, 68.6, 61.8, 40.8, 37.1, 33.1, 30.0, 19.4, 19.2; IR (thin film) 3241, 2869, 1688, 1579, 1513, 1484 cm^{-1}; HRMS (ESI) calcd for $[C_{23}H_{25}O_5NNaS]^+$ $(M+Na)^+$: *m/z* 450.1346, found 450.1341.

Compound 29. A flame-dried reaction tube was charged with **27** (26 mg, 0.061 mol, 1.0 equiv), 3,4,5-trimethoxyiodobenzene (34 mg, 0.121 mmol, 2.0 equiv), $Pd(OAc)_2$ (2.0 mg, 0.009 mmol, 0.15 equiv), K_2CO_3 (16 mg, 0.116 mmol, 1.0 equiv.) and dibenzyl phosphate (7.0 mg, 0.024 mmol, 0.4 equiv). The reaction vessel was evacuated and backfilled with argon and this cycle repeated twice. *t*-AmylOH (0.6 mL). The reaction vessel was heated to 110 °C for 50 h. After cooling to room temperature, the reaction mixture was quenched with sat. NaI solution and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (gradient 20% → 40% EtOAc in hexanes) to afford the arylated product **29** (21.0 mg, 58% yield) as well as recovered starting material (4 mg, 15%); white solid: mp 221-225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (bs, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.32 – 7.20 (m, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.79 (s, 1H), 6.46 (s, 1H), 6.03 (s, 2H), 5.95 (d, J = 1.4 Hz, 1H), 5.91 (d, J = 1.4 Hz, 1H), 5.03 (d, J = 3.6 Hz, 1H), 4.50 (d, J = 5.8 Hz,

1H), 4.22 (dd, *J* = 12.4, 4.7 Hz, 1H), 3.92 (dd, *J* = 12.4, 3.6 Hz, 1H), 3.73 (s, 3H), 3.70 (dd, *J* = 12.1, 5.7 Hz, 1H), 3.50 (s, 6H), 2.45 – 2.38 (m, 1H), 2.36 (s, 3H), 1.63 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 152.9, 148.5, 147.3, 138.4, 137.3, 136.7, 133.2, 132.0, 129.2, 128.2, 124.8, 124.5, 120.2, 109.6, 109.2, 107.0, 101.4, 99.9, 67.7, 62.0, 60.9, 56.0, 48.8, 46.3, 31.4, 29.9, 28.2, 20.7, 19.3; IR (thin film) 3002, 2933, 2836, 1702, 1587, 1504 cm^{-1}; HRMS (ESI) calcd for $[C_{32}H_{35}O_8NNaS]^+$ $(M+Na)^+$: *m/z* 616.1976, found 616.1972.

Podophyllotoxin (1). A reaction tube was charged with arylated product **29** (43 mg, 0.072 mol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen and this cycle repeated twice prior to the addition of THF (2 mL) and deionized water (1 mL). At 0 °C, trifluoroacetic acid (0.2 mL) was added dropwise to the reaction mixture. The reaction was warmed to room temperature and monitored by TLC for the consumption of starting material. After three hours, the reaction vessel was cooled to 0 °C and added additional water (1 mL) and trifluoroacetic acid (1.8 mL). The reaction mixture was warmed to room temperature and stirred for 24 hrs. The crude mixture was cooled to 0 °C, diluted with EtOAc, quenched with sat. $NaHCO_3$ solution and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (gradient 10% → 30% ether in dichloromethane) to afford podophyllotoxin **1** (13 mg, 44% yield) and 4-*epi*-podophyllotoxin 4-*epi*-**1** (10 mg, 34% yield)
Podophyllotoxin (**1**): white solid: mp 182-185 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.51 (s, 1H), 6.37 (s, 2H), 5.98 (d, *J* = 12.2 Hz, 2H), 4.77 (d, *J* = 9.5 Hz, 1H), 4.70 – 4.54 (m, 2H), 4.09 (t, *J* = 9.5 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 6H), 2.84 (dd, *J* = 14.4, 4.7 Hz, 1H), 2.82 – 2.71 (m, 1H), 2.03 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5, 152.8, 148.0, 147.9, 137.5, 135.6, 133.3, 131.4, 110.0, 108.6, 106.5, 101.7, 73.1, 71.5, 61.0, 56.5, 45.5, 44.3, 41.0; IR (thin film) 3465, 2893, 2837, 1773, 1587, 1482 cm^{-1}; HRMS (ESI) calcd for $[C_{22}H_{22}O_8Na]^+$ $(M+Na)^+$: *m/z* 437.1207, found 437.1206.
4-*epi*-**1**: white solid: mp 214-217 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.56 (s, 1H), 6.28 (s, 2H), 5.99 (d, *J* = 15.8 Hz, 2H), 4.87 (d, *J* = 3.3 Hz, 1H), 4.62 (d, *J* = 5.1 Hz, 1H), 4.44 – 4.27 (m, 2H), 3.80 (s, 3H), 3.74 (s, 6H), 3.28 (dd, *J* = 14.1, 5.1 Hz, 1H), 2.84 (tdt, *J* = 11.0, 7.8, 3.3 Hz, 1H), 1.74 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 152.8, 148.8, 147.7, 137.5, 135.2, 132.2, 132.1, 110.8, 109.1, 108.5, 101.8, 67.7, 67.0, 60.9, 56.5, 44.1, 40.7, 38.5; IR (thin film) 3450, 3005, 2989, 1774, 1729, 1589 cm^{-1}; HRMS (ESI) calcd for $[C_{22}H_{22}O_8Na]^+$ $(M+Na)^+$: *m/z* 437.1207, found 437.1207.

Compound 30. i. A flame-dried reaction tube was charged with acetonide **29** (50 mg, 0.117 mmol, 1.0 equiv), 5-iodobenzo[d][1,3]dioxole (58 mg, 0.234 mmol, 2.0 equiv), $Pd(OAc)_2$ (4.0 mg, 0.018 mmol, 0.15 equiv), K_2CO_3 (25 mg, 0.181 mmol, 1.5 equiv.) and dibenzyl phosphate (13.0 mg, 0.047 mmol, 0.4 equiv). The reaction vessel was evacuated and backfilled with argon and this cycle repeated twice. t-AmylOH (1.2 mL) was added and the sealed reaction vessel was heated to 110 °C for 50 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc (10 mL) and quenched with saturated aqueous NaI solution (10 mL). The mixture was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by column chromatography (20% EtOAc in hexanes) to afford the arylated product (**SI-2**) (50.0 mg, 78% yield) as a white foam: mp 140 – 142 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.16 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H),

6.78 (s, 1H), 6.59 (d, J = 7.9 Hz, 1H), 6.43 (s, 1H), 6.40 (d, J = 7.6 Hz, 1H), 6.28 (s, 1H), 5.91 (d, J = 10.7 Hz, 2H), 5.86 (d, J = 4.2 Hz, 2H), 5.01 (d, J = 3.5 Hz, 1H), 4.46 (d, J = 5.7 Hz, 1H), 4.18 (dd, J = 12.5, 4.4 Hz, 1H), 3.88 (dd, J = 12.7, 3.1 Hz, 1H), 3.69 (dd, J = 12.1, 5.7 Hz, 1H), 2.45 – 2.34 (m, 4H), 1.62 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 148.5, 147.6, 147.3, 146.7, 138.4, 135.0, 133.3, 132.3, 129.3, 128.3, 125.0, 124.4, 122.9, 120.6, 109.9, 109.5, 109.3, 108.0, 101.3, 101.1, 99.7, 67.9, 61.8, 48.4, 46.0, 31.0, 28.6, 20.5, 19.2; IR (thin film) 2959, 2925, 2854, 2360, 1699, 1505, 1486, 1436, 1275, 1260, 1231, 1039, 749 cm^{-1}; HRMS (ESI) calcd for $[C_{30}H_{29}O_7NNaS]^+$ $(M+Na)^+$: m/z 570.1557, found 570.1576.

ii. A reaction tube was charged with the arylated product **SI-2** (40 mg, 0.073 mmol, 1.0 equiv). THF (2 mL) and H_2O (2 mL) were added and the mixture cooled to 0 °C whereupon trifluoroacetic acid (0.2 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 3 hours under an atmosphere of nitrogen. After three hours, the reaction vessel was cooled back to 0 °C and additional trifluoroacetic acid (1.8 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The reaction mixture was diluted with EtOAc (10 mL), and quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with EtOAc (3 x 25 mL), and the combined organic layers washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (gradient 30% → 40% EtOAc in hexanes) to afford the title compound (18 mg, 67% yield) as 1.4:1 mixture of C-4 epimers. An analytically pure sample of **30** could be obtained by preparative thin layer chromatography. **30** (major diastereomer): white solid: mp 180 - 182 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 (s, 1H), 6.69 (d, J = 8.0, 1H), 6.64 – 6.59 (m, 2H), 6.46 (s, 1H), 5.96 (s, 2H), 5.90 (dd, J = 7.5, 1.4, 2H), 4.75 (d, J = 9.4, 1H), 4.60 (dd, J = 8.8, 7.0, 1H), 4.56 (d, J = 4.7, 1H), 4.09 (d, J = 9.0, 1H), 2.82 (dd, J = 14.2, 4.8, 1H), 2.80 – 2.72 (m, 1H), 1.96 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3, 148.1, 147.9, 147.6, 146.9, 133.8, 133.2, 131.8, 124.4, 111.3, 109.9, 107.9, 106.3, 101.6, 101.2, 73.1, 71.5, 45.3, 43.8, 40.9; IR (thin film) 3411, 3005, 2359, 2340, 1767, 1502, 1482, 1257, 1260, 1037, 764 cm^{-1}; HRMS (ESI) calcd for $[C_{20}H_{16}O_7Na]^+$ $(M+Na)^+$: m/z 391.0788, found 391.0799.

Compound 31. i. A flame-dried reaction tube was charged with acetonide **29** (50 mg, 0.117 mmol, 1.0 equiv), 5-iodo-1-tosyl-1H-indole (93 mg, 0.234 mmol, 2.0 equiv), $Pd(OAc)_2$ (4.0 mg, 0.018 mmol, 0.15 equiv), K_2CO_3 (25 mg, 0.181 mmol, 1.5 equiv.) and dibenzyl phosphate (13.0 mg, 0.047 mmol, 0.4 equiv). The reaction vessel was evacuated and backfilled with argon and this cycle repeated twice. t-AmylOH (1.2 mL) was added and the sealed reaction vessel was heated to 110 °C for 50 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc (10 mL) and quenched with saturated aqueous NaI solution (10 mL). The mixture was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by column chromatography (gradient 20% → 30% EtOAc in hexanes) to afford the arylated product (**SI-3**) (37.0 mg, 45% yield) as a white solid: mp 103 - 105 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.06 (d, J = 8.2, 1H), 7.76 (d, J = 8.7, 1H), 7.72 (d, J = 8.4, 2H), 7.48 (d, J = 7.8, 1H), 7.45 (d, J = 3.7, 1H), 7.24 (t, J = 7.6, 1H), 7.21 (d, J = 8.0, 2H), 7.07 (t, J = 7.6, 1H), 6.95 (s, 1H), 6.87 (d, J = 8.6, 1H), 6.81 (s, 1H), 6.43 (d, J = 3.7, 1H), 6.37 (s, 1H), 5.89 (d, J = 12.9, 2H), 5.04 (d, J = 3.6, 1H), 4.62 (d, J = 5.6, 1H), 4.15 (dd, J = 12.7, 4.6, 1H), 3.84 (dd, J = 12.6, 3.3, 1H), 3.73 (dd, J = 12.1, 5.7, 1H), 2.45 – 2.36 (m, 1H), 2.35 (s, 3H), 2.27 (s, 3H), 1.62 (s, 3H),

1.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 148.4, 147.2, 145.0, 138.4, 136.3, 135.7, 134.0, 133.4, 132.5, 130.8, 130.1, 130.0, 129.2, 128.4, 127.0, 127.0, 126.6, 126.4, 125.0, 124.4, 122.3, 120.4,113.0, 109.6, 109.2, 109.0, 101.3, 100.2, 99.8, 67.8, 61.8, 48.5, 46.1, 31.1, 28.4, 21.8, 20.6, 19.0; IR (thin film) 3337, 3054, 2988, 2885, 1733, 1649, 1578, 1371, 1091, 754 cm^{-1}; HRMS (ESI) calcd. for $[C_{38}H_{36}O_7N_2NaS_2]^+$ $(M+Na)^+$: m/z 719.1856, found 719.1884.

ii. A reaction tube was charged with the arylated product **SI-3** (20 mg, 0.029 mmol, 1.0 equiv). THF (1 mL) and H_2O (1 mL) were added and the mixture cooled to 0 °C whereupon trifluoroacetic acid (0.1 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 3 hours under an atmosphere of nitrogen. After three hours, the reaction vessel was cooled back to 0 °C and additional trifluoroacetic acid (1 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The reaction mixture was diluted with EtOAc (10 mL), and quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with EtOAc (3 x 25 mL), and the combined organic layers washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (gradient 30% → 40% EtOAc in hexanes) to afford the title compound (9 mg, 61% yield) as an inseparable 1.3:1 mixture of C-4 epimers (preparative thin layer chromatography was unsuccessful). ^{1}H NMR resonances corresponding to the major and minor isomers could be deduced from this mixture. **31** (major): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, J = 8.7, 1H), 7.76 (d, J = 8.4, 2H), 7.52 (d, J = 3.6, 1H), 7.26 (s, 1H), 7.24 (d, J = 8.3, 2H), 7.16 – 7.10 (m, 2H), 6.56 (d, J = 3.6, 1H), 6.41 (s, 1H), 5.95 (d, J = 1.7, 1H), 4.78 (d, J = 9.4, 1H), 4.71 (d, J = 4.9, 1H), 4.54 (dd, J = 8.8, 7.2, 1H), 4.08 (dd, J = 10.3, 8.8, 1H), 2.87 (dd, J = 14.2, 5.1, 1H), 2.82 – 2.72 (m, 1H), 2.36 (s, 3H), 2.02 (bs, 1H). (minor): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 8.6, 1H), 7.76 (d, J = 8.0, 2H), 7.51 (d, J = 3.8, 1H), 7.24 (d, J = 8.1, 2H), 7.17 (s, 1H), 7.03 (d, J = 8.7, 1H), 6.89 (s, 1H), 6.54 (d, J = 3.7, 1H), 6.46 (s, 1H), 5.96 (d, J = 7.2, 2H), 4.89 (d, J = 3.5, 1H), 4.72 (d, J = 5.3, 1H), 4.36 (dd, J = 10.8, 8.2, 1H), 4.29 (t, J = 8.1, 1H), 3.32 (dd, J = 14.2, 5.2, 1H), 2.91 – 2.80 (m, 1H), 2.36 (s, 3H), 1.82 (d, J = 4.2 1H). ^{13}C NMR (150 MHz, $CDCl_3$) (combined minor and major) δ = 175.0, 174.3, 148.9, 148.1, 147.9, 147.7, 145.2, 145.1, 135.6, 135.6, 135.1, 134.7, 134.0, 134.0, 133.3, 132.8, 132.0, 131.9, 130.7, 130.6, 130.2, 130.2, 127.5, 127.4, 127.1, 126.7, 126.7, 123.8, 123.6, 112.9, 112.9, 110.7, 110.0, 109.1, 109.0, 108.9, 106.4, 101.7, 101.6, 73.1, 71.5, 67.8, 67.0, 45.4, 44.0, 43.8, 40.7, 40.6, 38.2, 21.8; IR (thin film) 3458, 3056, 2913, 17773, 1596, 1483 cm^{-1}; HRMS (ESI) calcd for $[C_{28}H_{23}O_7NNaS]^+$ $(M+Na)^+$: m/z 540.1087, found 540.1095.

Compound 32. i. A flame-dried reaction tube was charged with acetonide **29** (50 mg, 0.117 mmol, 1.0 equiv), 2-iodonaphthalene (59 mg, 0.234 mmol, 2.0 equiv), $Pd(OAc)_2$ (4.0 mg, 0.018 mmol, 0.15 equiv), K_2CO_3 (25 mg, 0.181 mmol, 1.5 equiv.) and dibenzyl phosphate (13.0 mg, 0.047 mmol, 0.4 equiv). The reaction vessel was evacuated and backfilled with argon and this cycle repeated twice. t-AmylOH (1.2 mL) was added and the sealed reaction vessel was heated to 110 °C for 50 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc (10 mL) and quenched with saturated aqueous NaI solution (10 mL). The mixture was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by column chromatography (gradient 20% → 30% EtOAc in hexanes) to afford the arylated product **(SI-4**) (57.0 mg, 88% yield) as a white solid: mp 218 - 220 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.07 (d, J = 8.2, 1H), 7.75 – 7.70 (m, 1H), 7.64 (d, J = 8.5, 1H), 7.59 – 7.54 (m, 1H), 7.49

(dd, J = 7.9, 1.6, 1H), 7.41 – 7.34 (m, 2H), 7.28 (d, J = 1.7, 1H), 7.22 (t, J = 8.4, 7.9, 1H), 7.05 (t, J = 7.7, 1H), 7.02 (d, J = 8.5, 1H), 6.85 (s, 1H), 6.44 (s, 1H), 5.92 (s, 1H), 5.90 (s, 1H), 5.10 (d, J = 3.5, 1H), 4.72 (d, J = 5.8, 1H), 4.18 (dd, J = 12.6, 4.5, 1H), 3.87 (dd, J = 12.7, 3.2, 1H), 3.81 (dd, J = 12.1, 5.8, 1H), 2.50 – 2.44 (m, 1H), 2.30 (s, 3H), 1.64 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 148.6, 147.3, 138.8, 138.5, 133.3, 133.3, 132.7, 132.2, 129.2, 128.6, 128.5, 127.9, 127.8, 127.8, 127.7, 126.1, 125.9, 125.0, 124.4, 120.5, 109.7, 109.3, 101.3, 99.7, 68.0, 61.8, 48.8, 46.1, 31.2, 28.6, 20.5, 19.1; IR (thin film) 3334, 2988, 1539, 1577, 1435, 1230, 1163, 1038, 749 cm^{-1}; HRMS (ESI) calcd for $[C_{33}H_{31}O_5NNaS]^+$ $(M+Na)^+$: m/z 576.1815, found 576.1833.

ii. A reaction tube was charged with the arylated product **SI-4** (34 mg, 0.061 mmol, 1.0 equiv). THF (2 mL) and H_2O (2 mL) were added and the mixture cooled to 0 °C whereupon trifluoroacetic acid (0.2 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 3 hours under an atmosphere of nitrogen. After three hours, the reaction vessel was cooled back to 0 °C and additional trifluoroacetic acid (1.8 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The reaction mixture was diluted with EtOAc (10 mL), and quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with EtOAc (3 x 25 mL), and the combined organic layers washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (gradient 30% → 40% EtOAc in hexanes) to afford the title compound (18 mg, 79% yield) as 1.4:1 mixture of C-4 epimers. An analytically pure sample of **32** could be obtained by preparative thin layer chromatography. **32** (major diastereomer): white solid: mp 122 - 124 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 1H), 7.76 – 7.71 (m, 2H), 7.48 – 7.40 (m, 4H), 7.19 (s, 1H), 6.48 (s, 1H), 6.03 – 5.90 (m, 2H), 4.85 – 4.79 (m, 2H), 4.56 (dd, J = 8.9, 7.2, 1H), 4.10 (dd, J = 10.3, 8.9, 1H), 2.94 (dd, J = 14.3, 5.0, 1H), 2.85 (dtd, J = 14.2, 10.0, 7.2, 1H), 2.05 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 148.2, 148.0, 137.7, 133.4, 133.1, 132.7, 131.7, 130.0, 129.0, 128.2, 127.7, 127.7, 126.2, 110.1, 106.4, 101.7, 73.2, 71.5, 45.4, 44.3, 41.0; IR (thin film) 3411, 3005, 2359, 2340, 1767, 1502, 1482, 1257, 1260, 1037, 764 cm^{-1}; HRMS (ESI) calcd for $[C_{23}H_{18}O_5Na]^+$ $(M+Na)^+$: m/z 397.1046, found 397.1058.

Compound 33. i. A flame-dried reaction tube was charged with acetonide **29** (50 mg, 0.117 mmol, 1.0 equiv), 1-bromo-4-iodobenzene (66 mg, 0.233 mmol, 2.0 equiv), $Pd(OAc)_2$ (4.0 mg, 0.018 mmol, 0.15 equiv), K_2CO_3 (25 mg, 0.181 mmol, 1.5 equiv.) and dibenzyl phosphate (13.0 mg, 0.047 mmol, 0.4 equiv). The reaction vessel was evacuated and backfilled with argon and this cycle repeated twice. t-AmylOH (1.2 mL) was added and the sealed reaction vessel was heated to 110 °C for 50 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc (10 mL) and quenched with saturated aqueous NaI solution (10 mL). The mixture was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by column chromatography (gradient 20% → 30% EtOAc in hexanes) to afford the arylated product (**SI-5**) as a white solid contaminated with a small amount of an inseparable byproduct (43% yield based on ^{1}H NMR analysis): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.14 (d, J = 8.1, 1H), 7.51 (d, J = 7.8, 1H), 7.31 – 7.26 (m, 3H), 7.08 (t, J = 7.8, 1H), 6.79 (s, 1H), 6.73 (d, J = 8.5, 2H), 6.38 (s, 1H), 5.92 (d, J = 11.9, 2H), 5.02 (d, J = 3.4, 1H), 4.49 (d, J = 5.7, 1H), 4.17 (dd, J = 12.6, 4.3, 1H), 3.86 (dd, J = 12.6, 3.0, 1H), 3.74 (dd, J = 12.1, 5.8, 1H), 2.39 (s, 3H), 2.33 – 2.28 (m,

1H), 1.62 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 148.6, 147.4, 140.3, 138.3, 133.4, 131.7, 131.4, 131.3, 129.3, 128.5, 125.1, 124.6, 121.4, 120.5, 109.4, 109.4, 101.4, 99.7, 67.9, 61.8, 48.2, 45.7, 31.0, 28.7, 20.4, 19.2; IR (thin film) 3304, 2925, 1506, 1275, 1260, 1232, 1077, 764, 749 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{28}O_5NBrNaS]^+$ $(M+Na)^+$: m/z 604.0764, found 604.0786.

ii. A reaction tube was charged with the arylated product **SI-5** (22 mg, 0.038 mmol, 1.0 equiv). THF (1 mL) and H_2O (1 mL) were added and the mixture cooled to 0 °C whereupon trifluoroacetic acid (0.1 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 3 hours under an atmosphere of nitrogen. After three hours, the reaction vessel was cooled back to 0 °C and additional trifluoroacetic acid (0.9 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The reaction mixture was diluted with EtOAc (10 mL), and quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with EtOAc (3 x 25 mL), and the combined organic layers washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (gradient 30% → 40% EtOAc in hexanes) to afford the title compound (11 mg, 72% yield) as 1.6:1 mixture of C-4 epimers. An analytically pure sample of **33** could be obtained by preparative thin layer chromatography. **33** (major diastereomer): white solid: mp 216 - 218 °C; ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ 7.41 (d, J = 8.5, 2H), 7.20 (s, 1H), 7.10 (d, J = 8.4, 2H), 6.47 (s, 1H), 5.98 (d, J = 4.4, 2H), 4.96 (bs, 1H), 4.82 (d, J = 9.7, 1H), 4.62 (d, J = 5.2, 1H), 4.51 (dd, J = 8.7, 7.1, 1H), 4.16 (dd, J = 10.5, 8.6, 1H), 3.13 (dd, J = 14.4, 5.3, 1H), 2.77 – 2.65 (m, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2CO$) δ 175.1, 148.6, 148.6, 141.5, 136.2, 134.1, 132.0, 131.7, 121.6, 110.2, 107.7, 102.5, 72.7, 72.2, 45.4, 44.5, 41.7; IR (thin film) 3456, 3004, 2970, 1738, 1365, 1229, 1217, 757 $cm.^{-1}$

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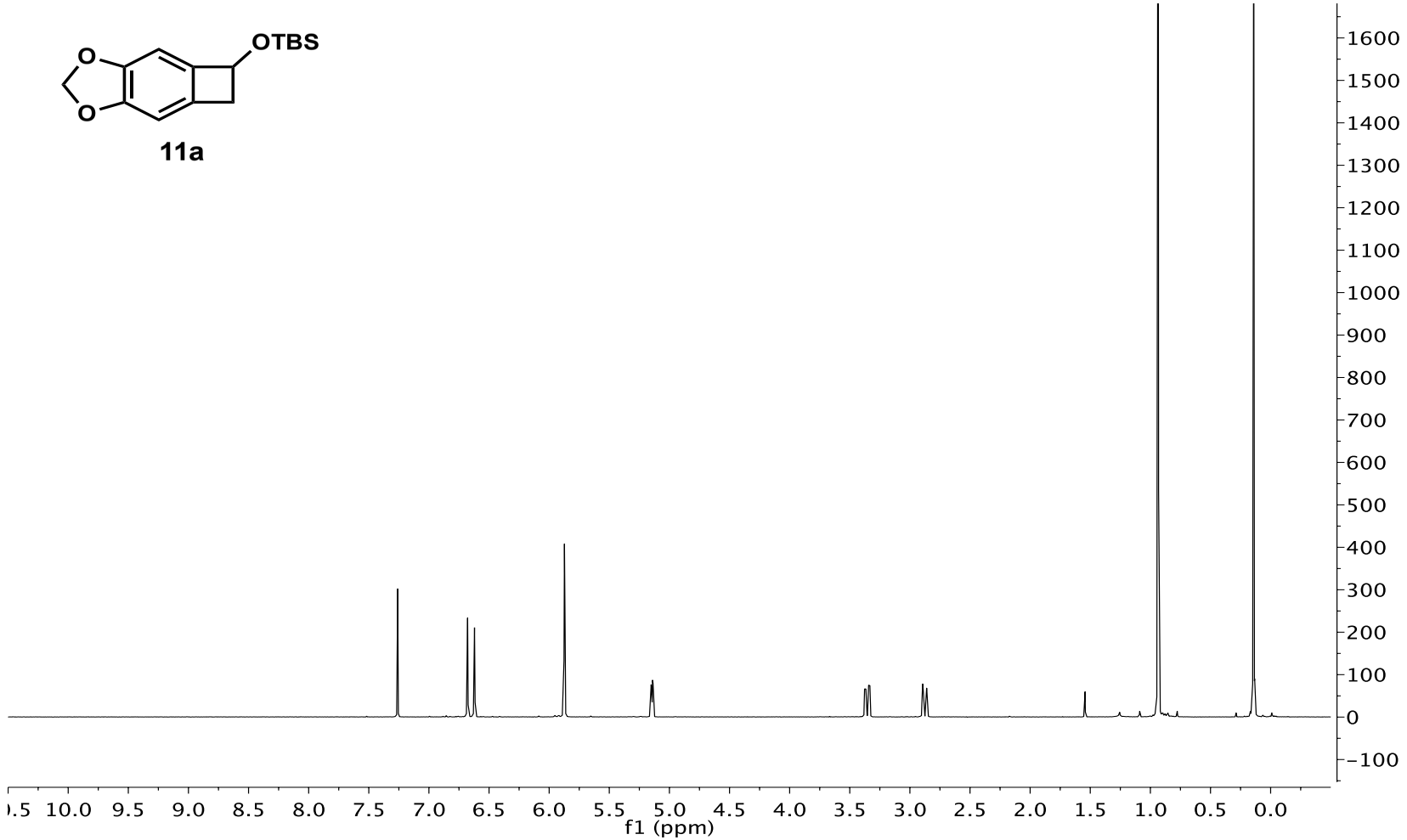
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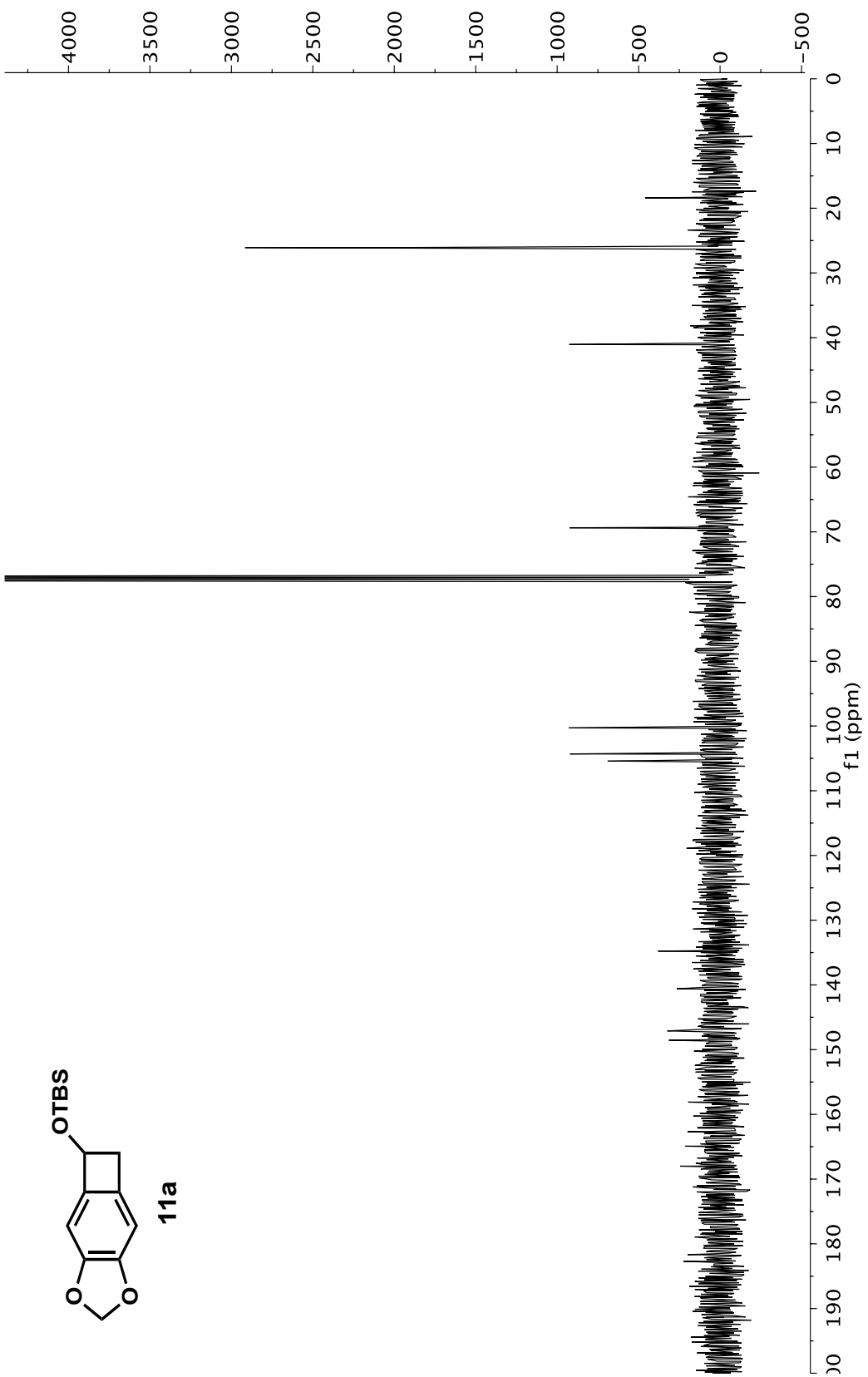
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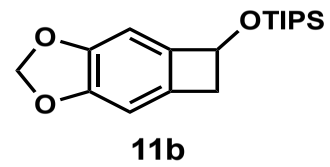
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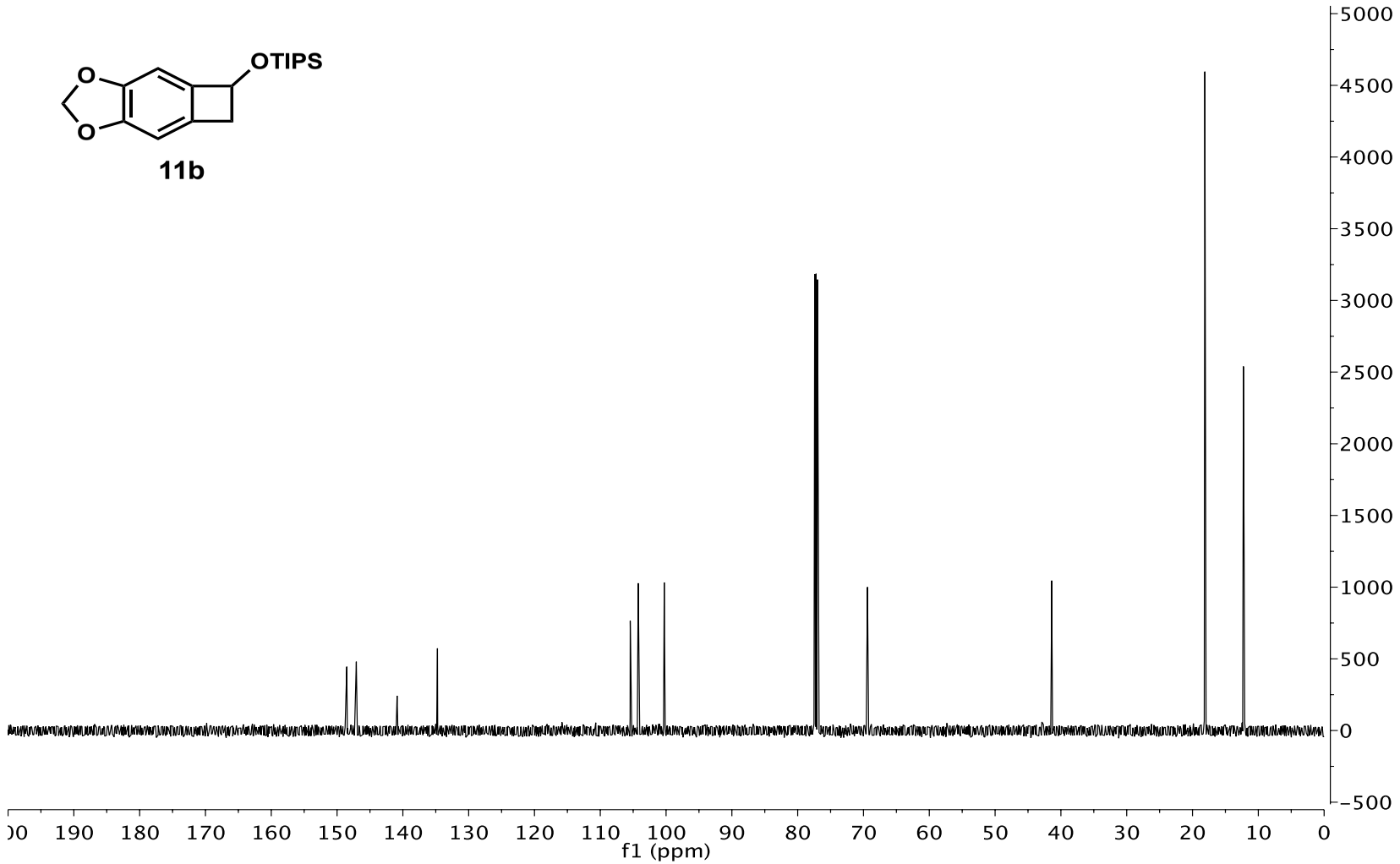
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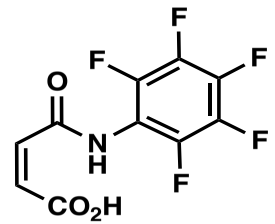
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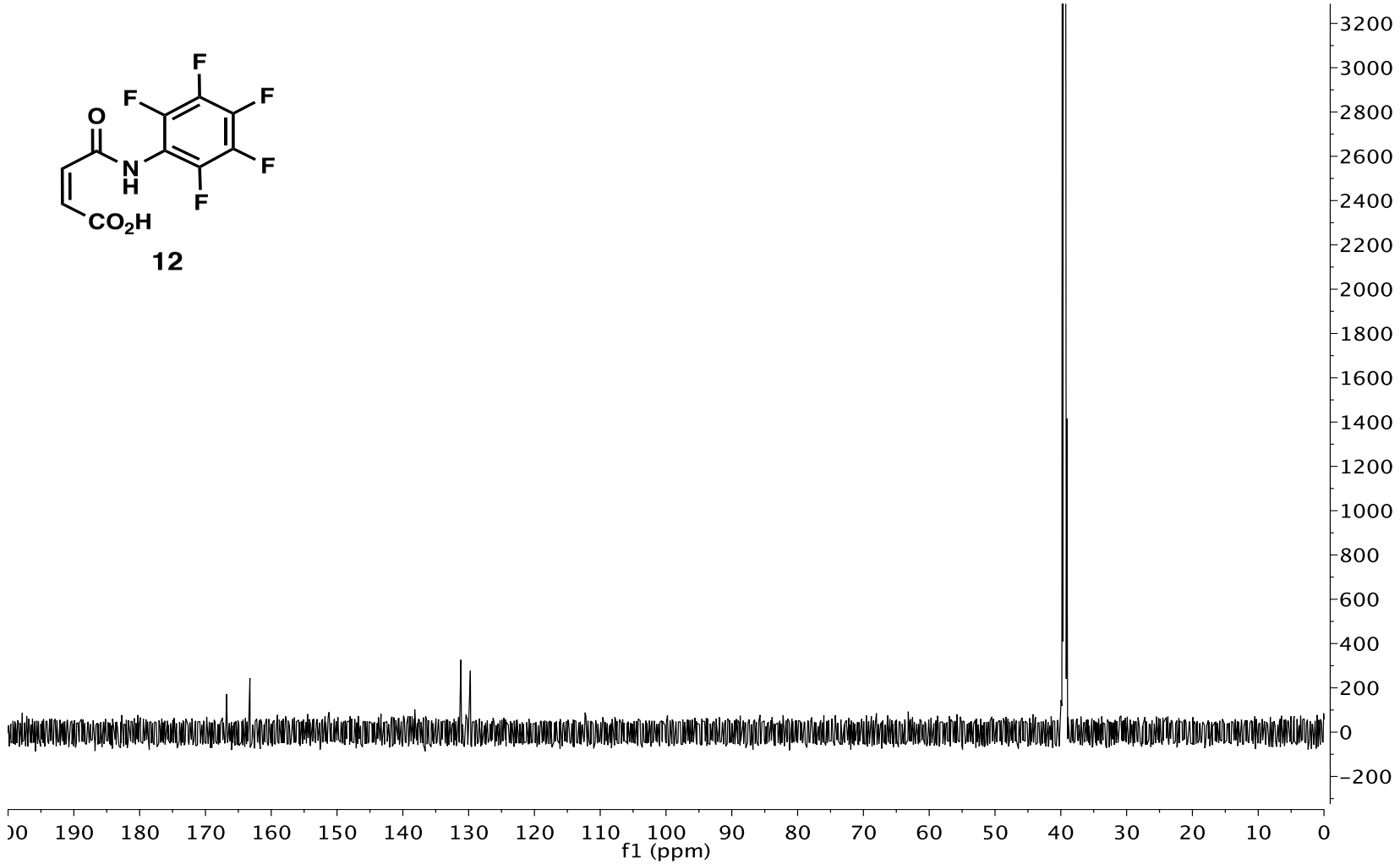
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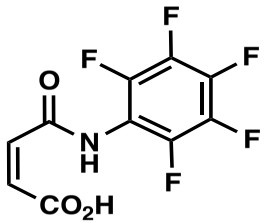
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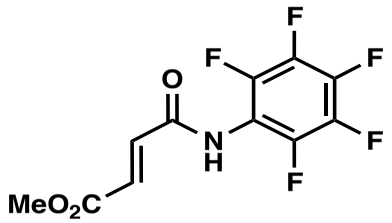
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F
N
H
F
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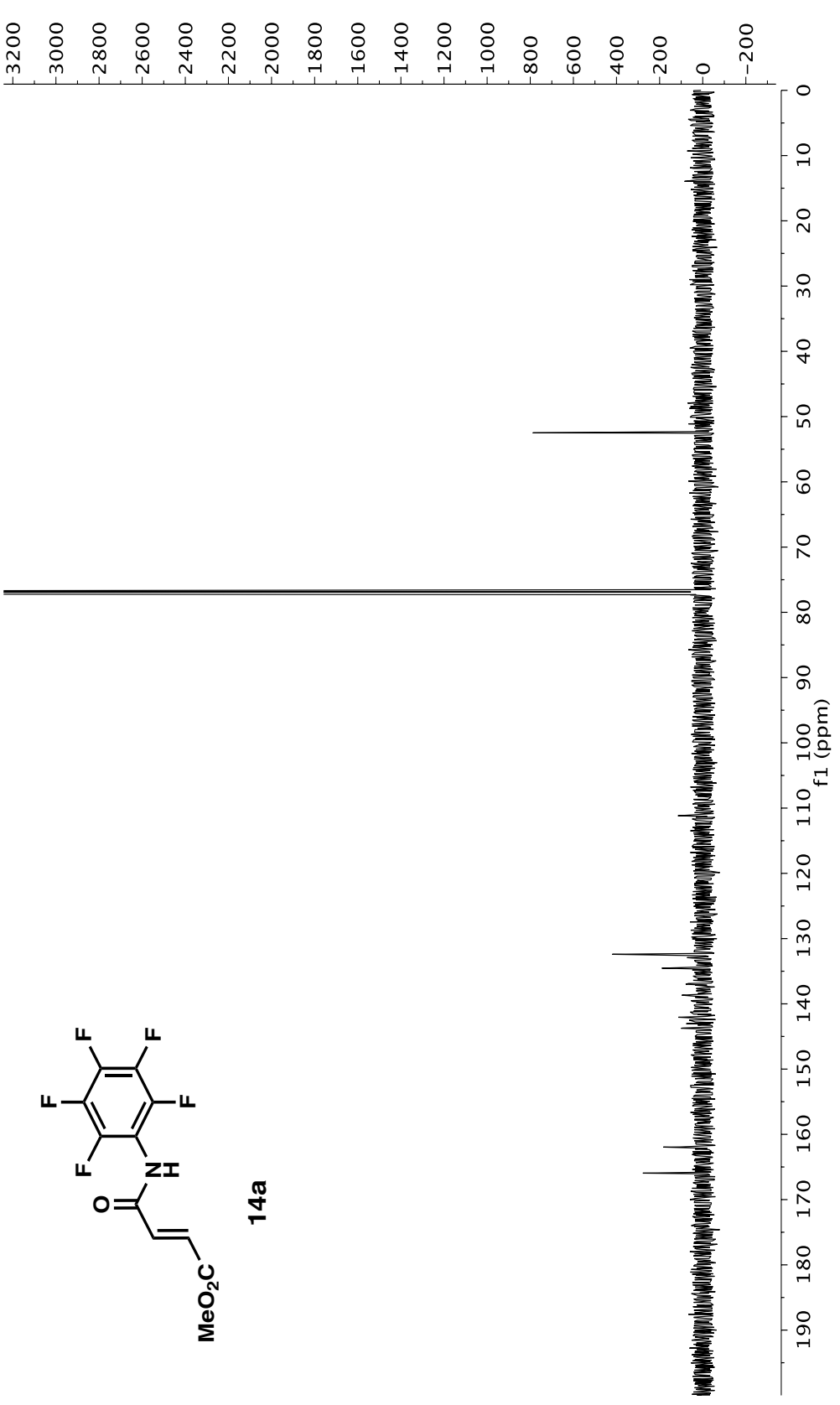
f1 (ppm)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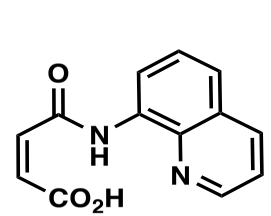
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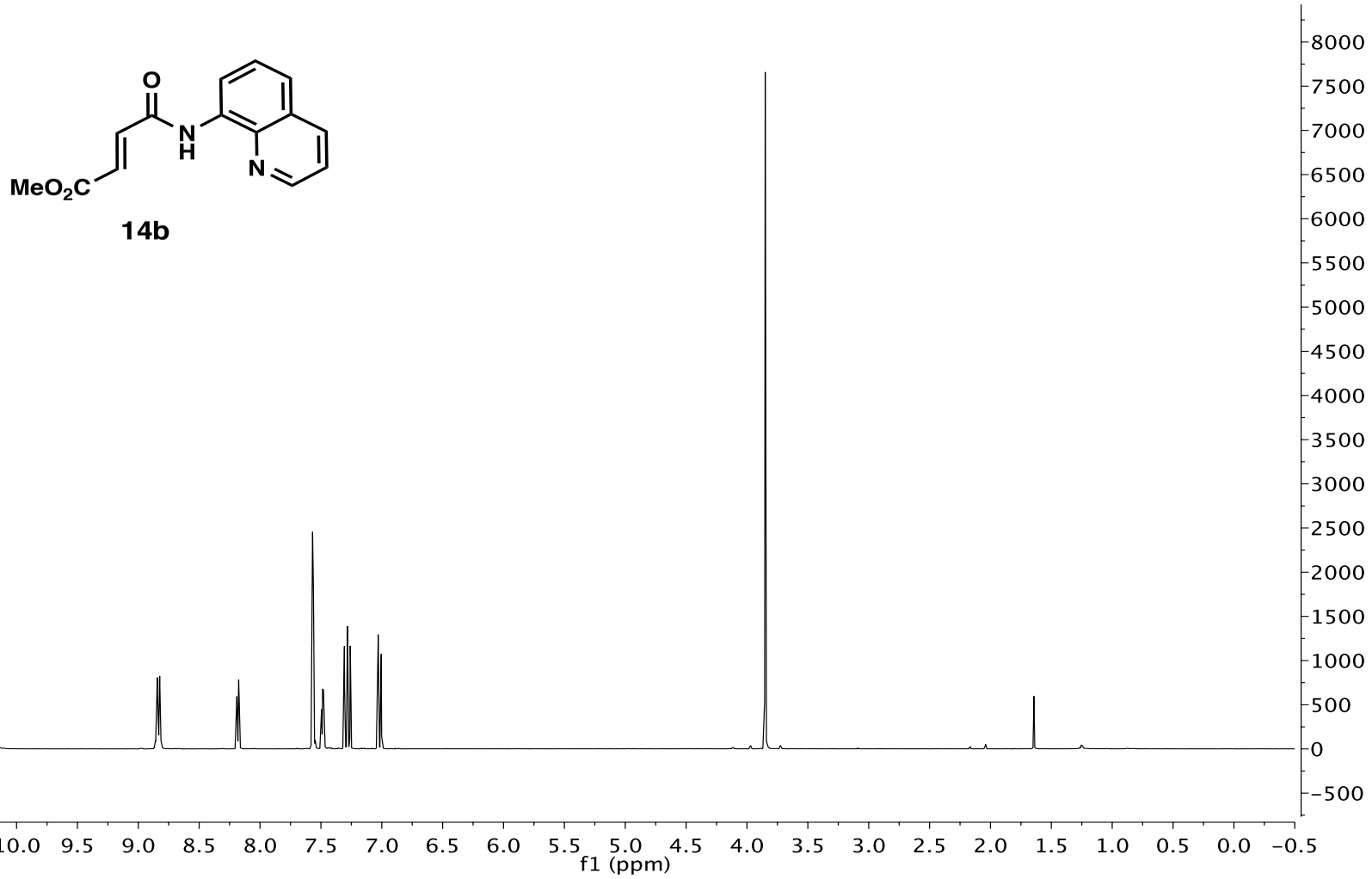
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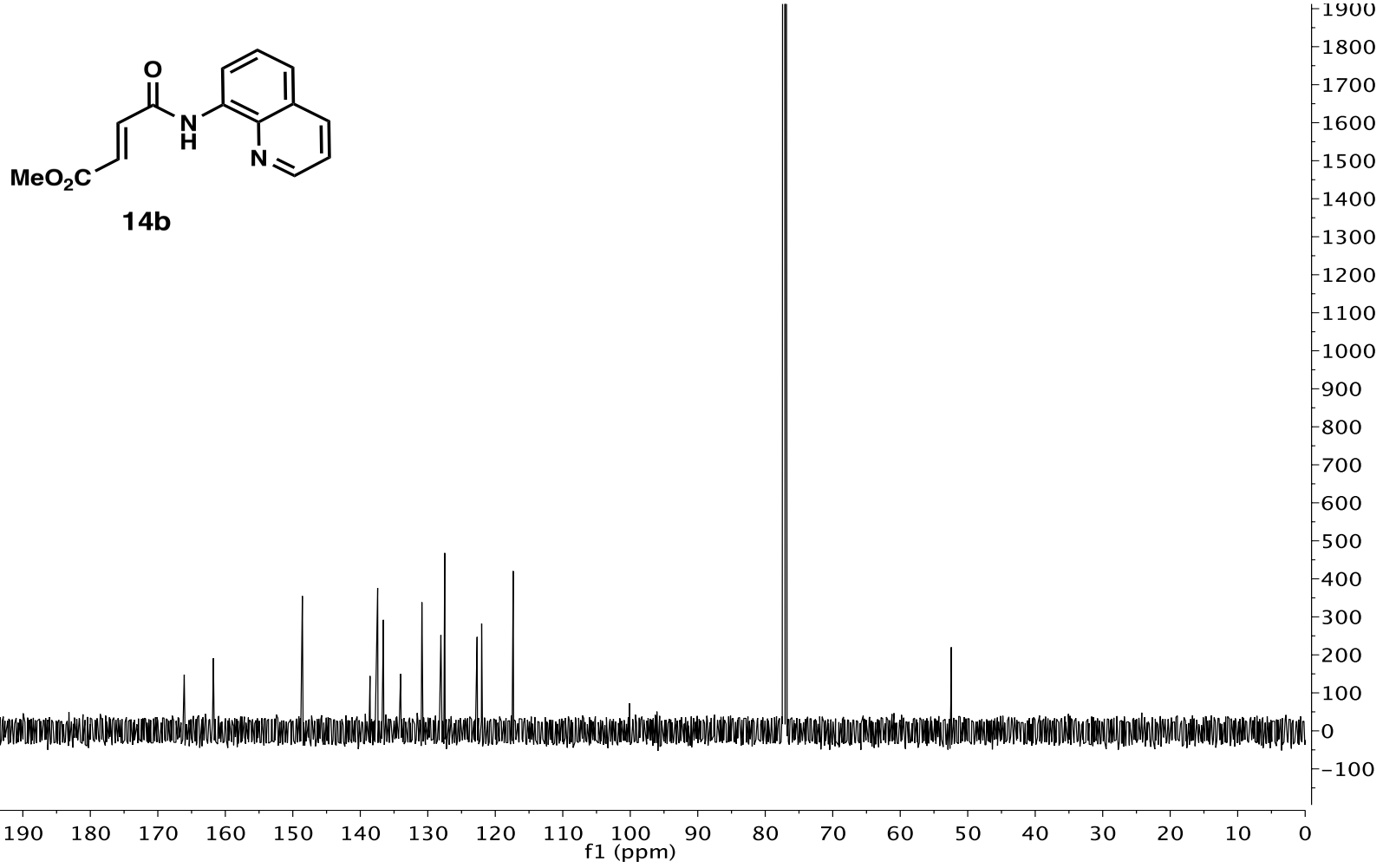
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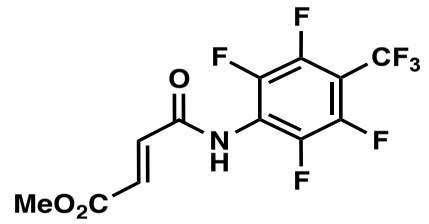
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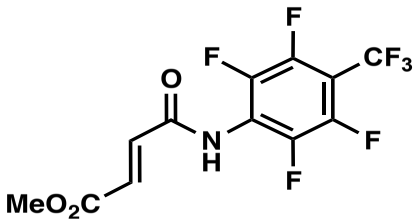
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H
F
F
MeO2C

14c

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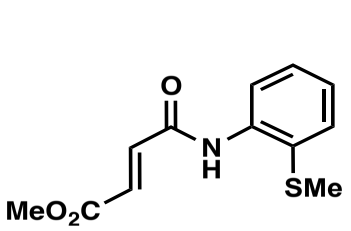
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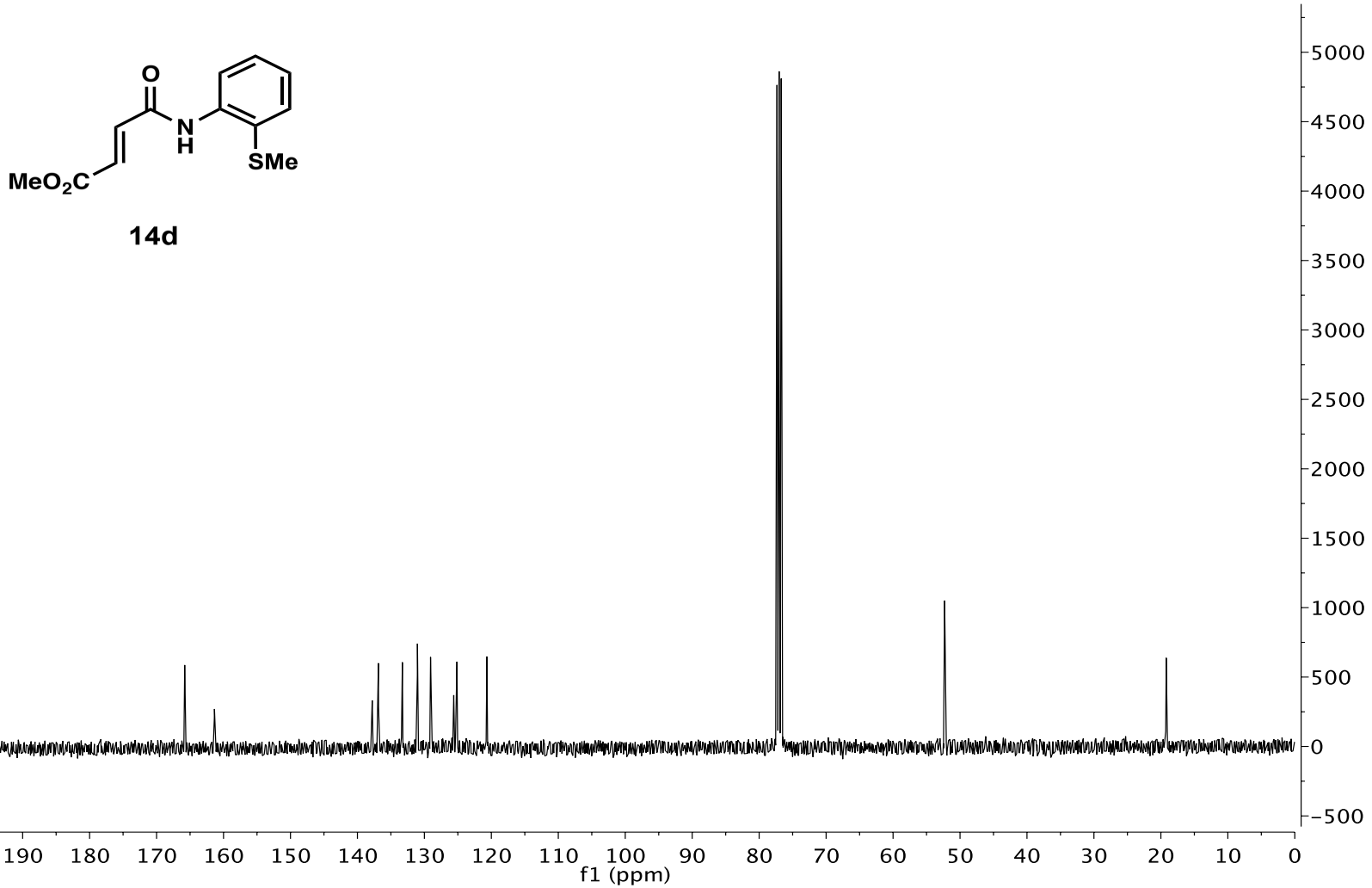
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H
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MeO2C
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4000
3500
3000
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1000
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−500
190
180
170
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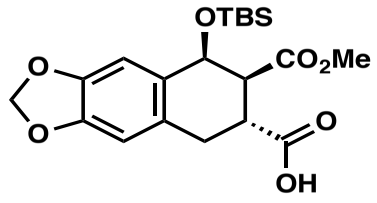
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OH

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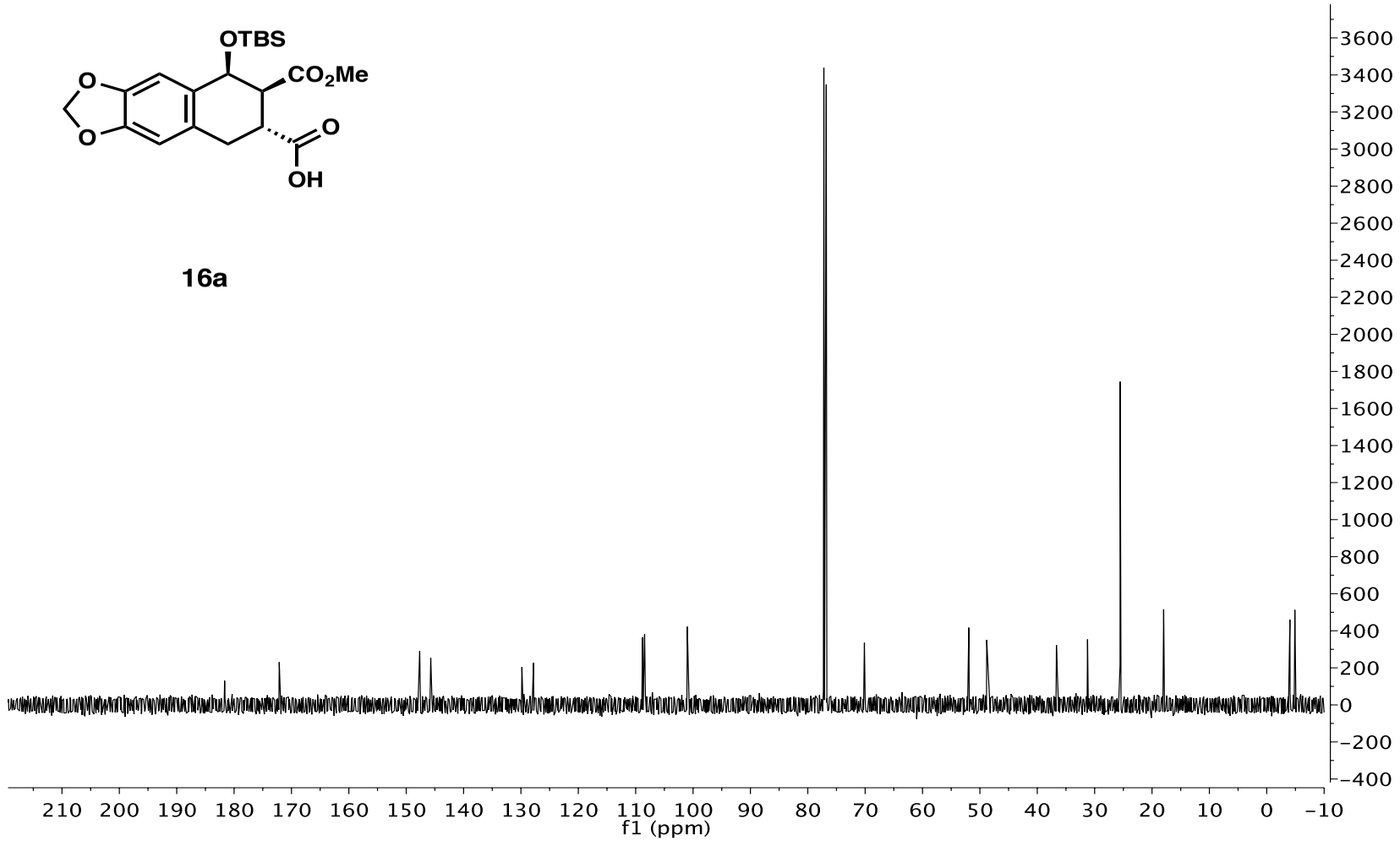
f1 (ppm)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1400
1200
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800
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200
0
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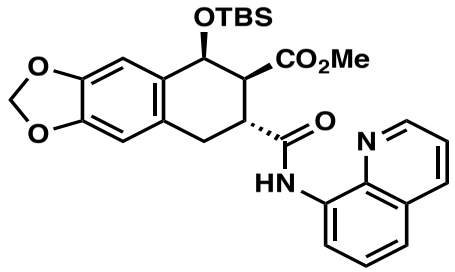
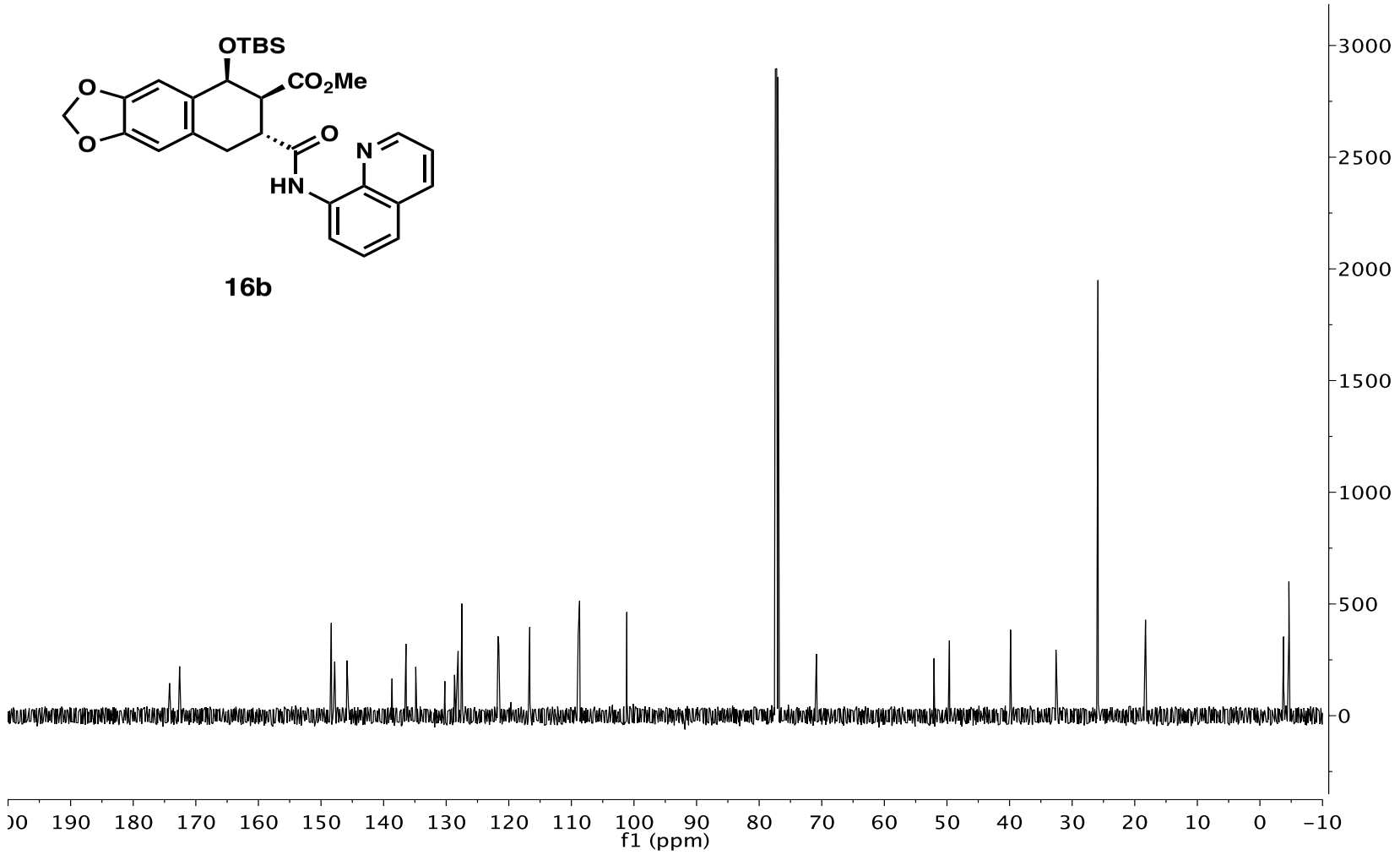
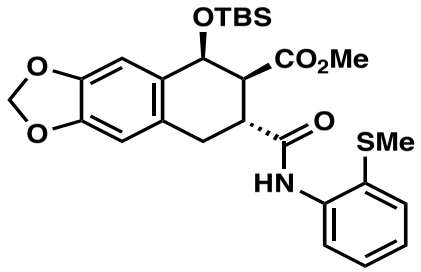
−400
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


OTBS
CO2Me
O
O
O
N
HN

16b

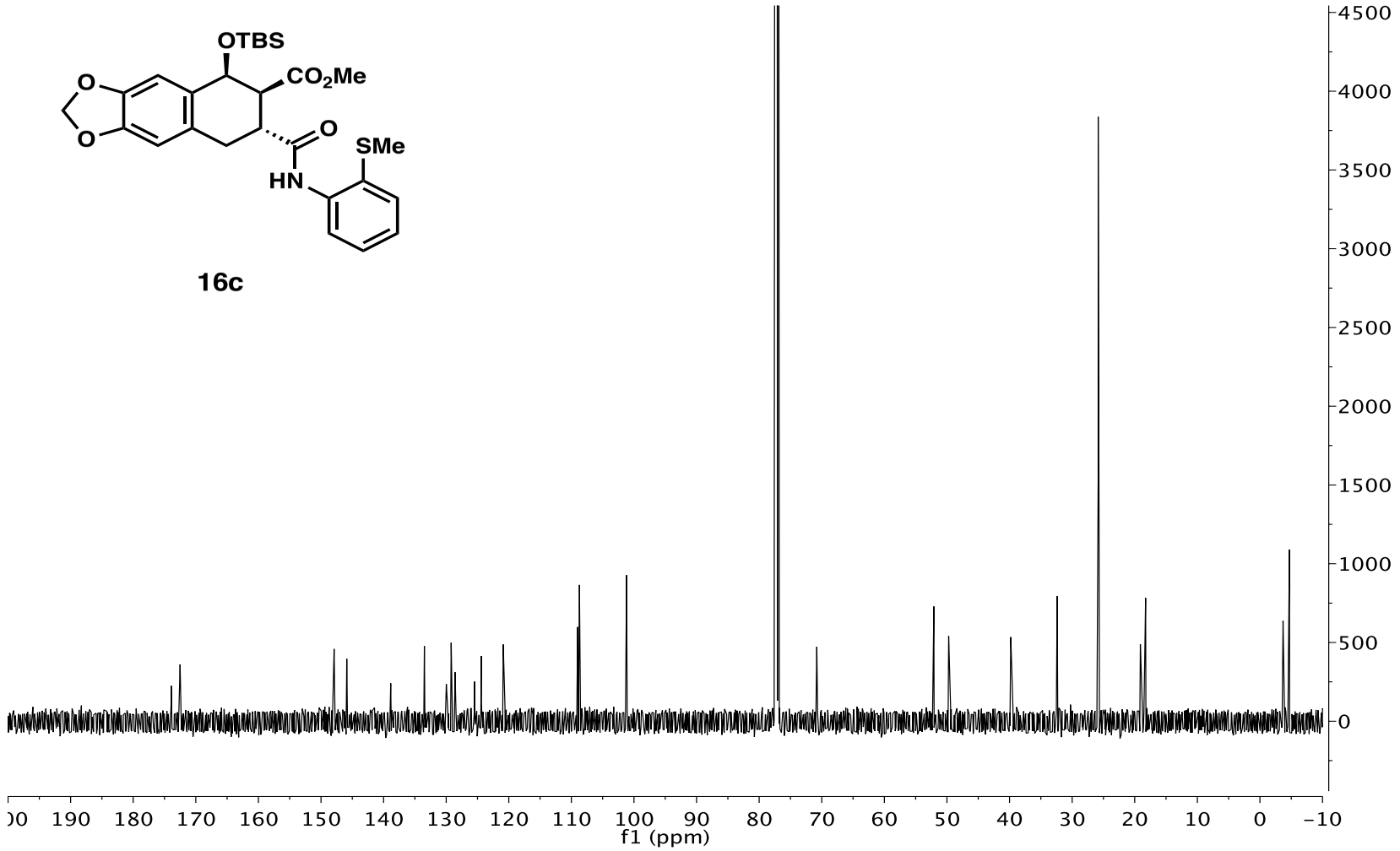
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

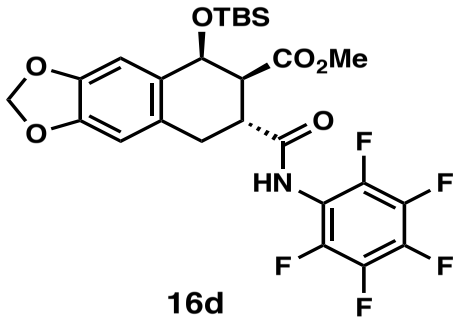

OTBS
CO2Me
O
O
O
HN
N
16b
3000
2500
2000
1500
1000
500
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)


OTBS
CO2Me
O
O
O
HN
SMe

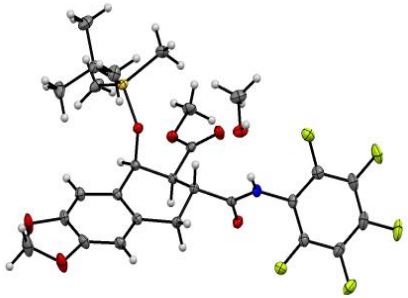
16c

6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


OTBS
CO2Me
O
O
O
HN
SMe
16c
4500
4000
3500
3000
2500
2000
1500
1000
500
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

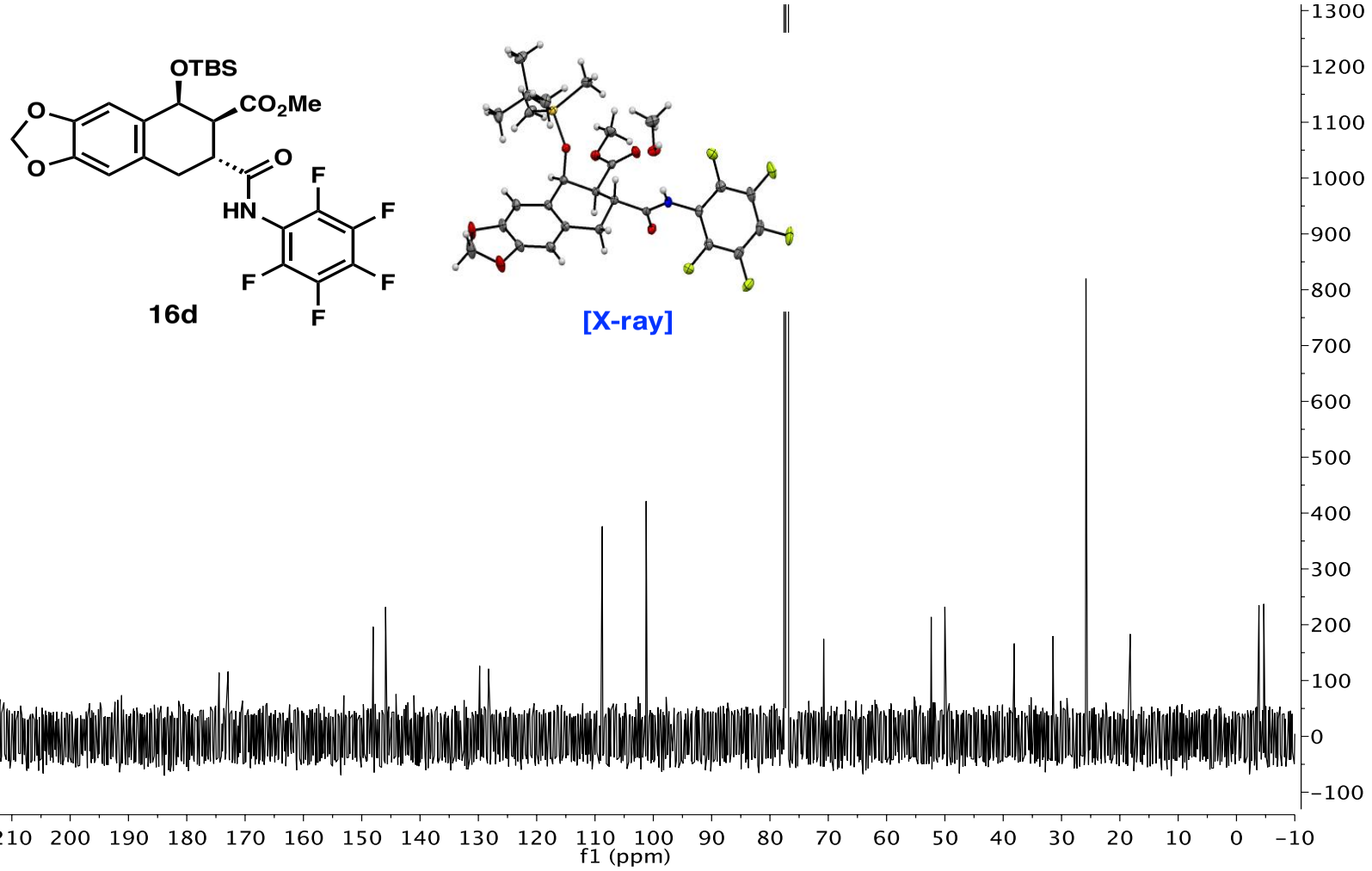

OTBS
CO2Me
O
O
O
HN
F
F
F
F
F

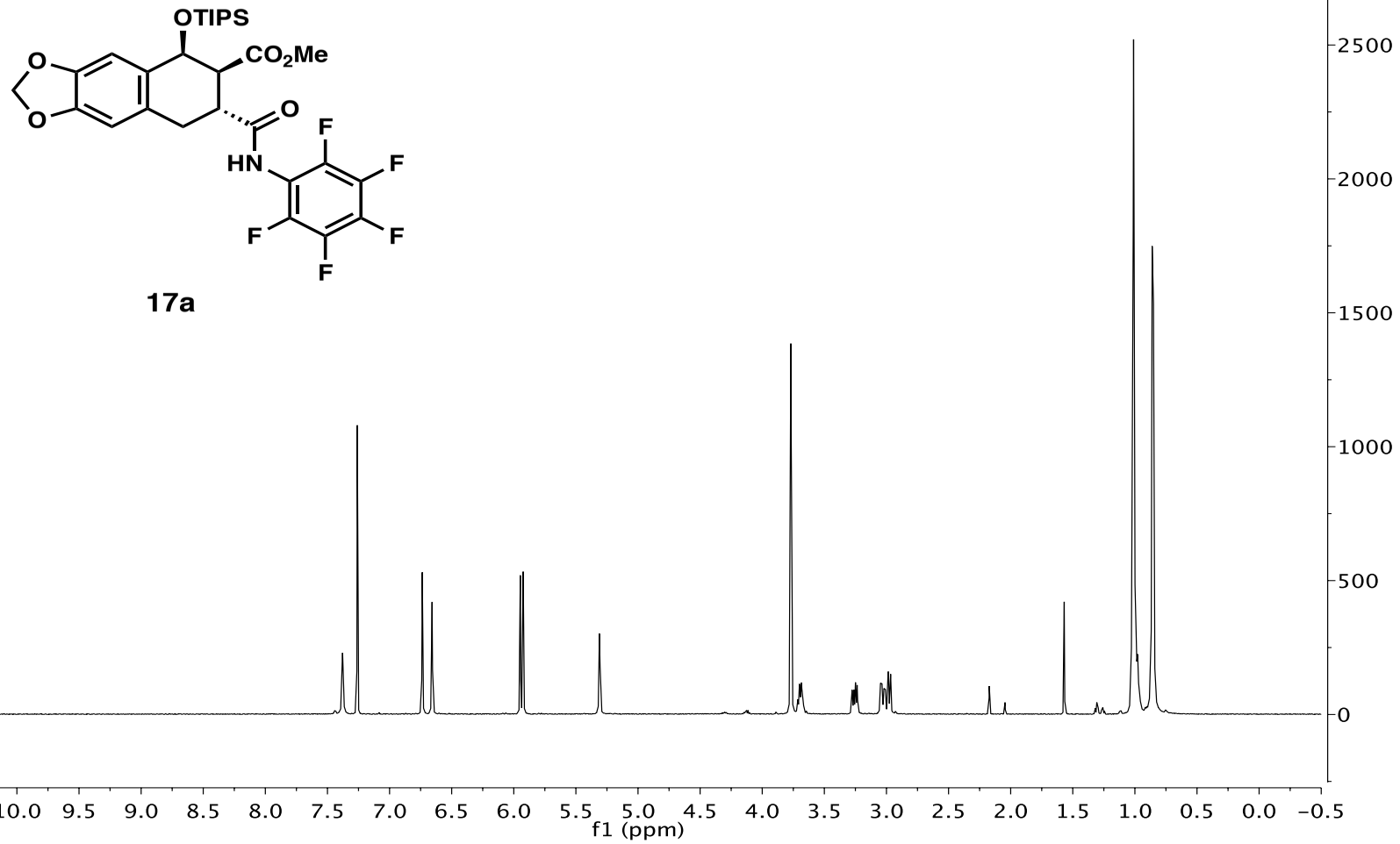
16d

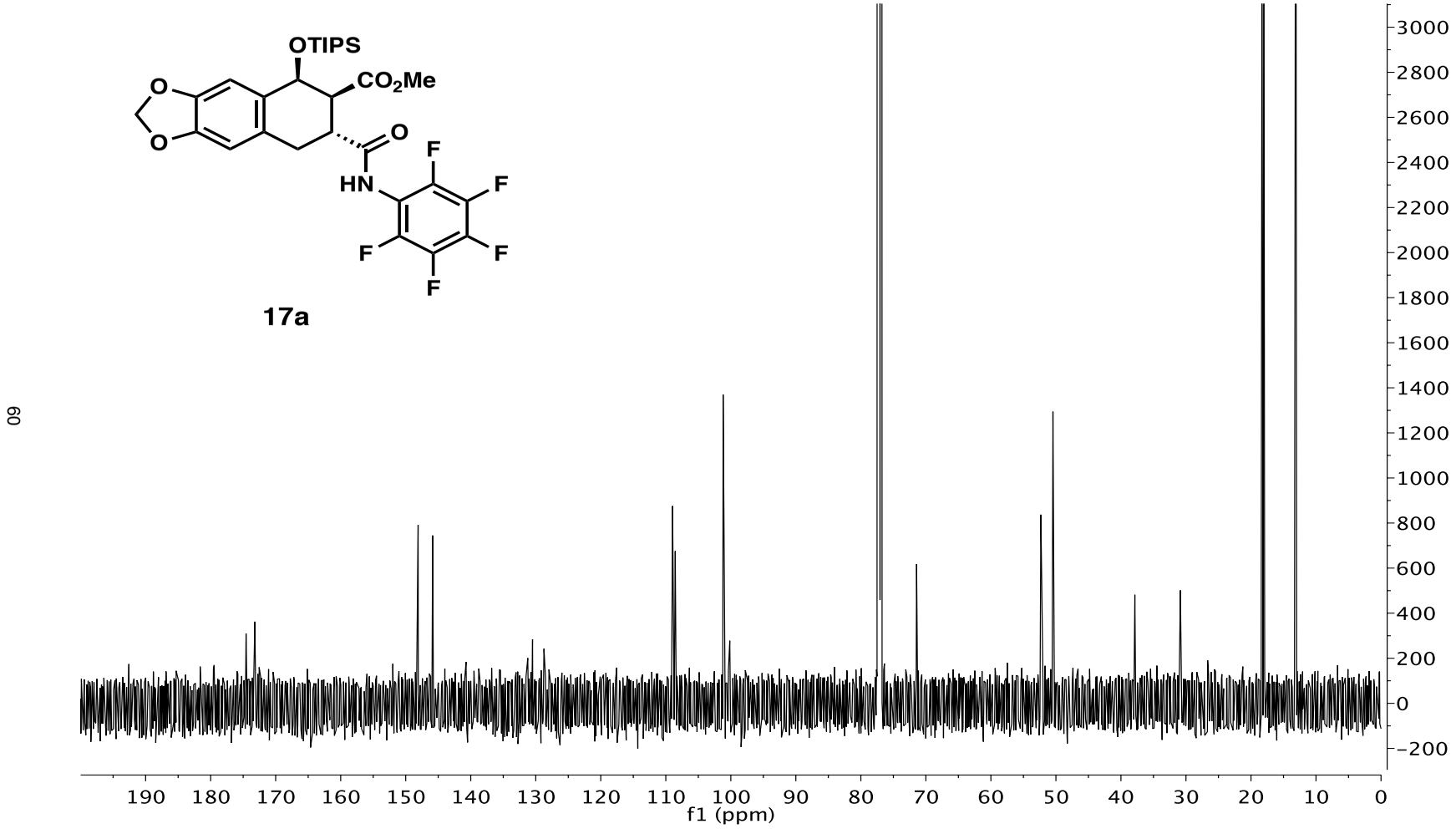


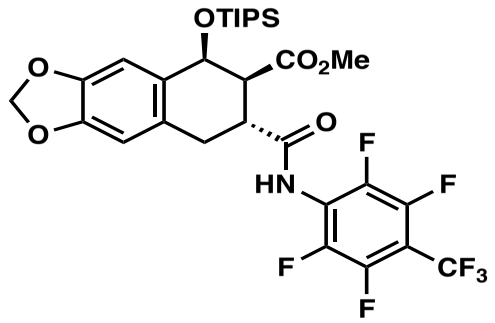
[X-ray]

3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OTBS
CO2Me
O
O
O
HN
F
F
F
F
F
16d
[X-ray]
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

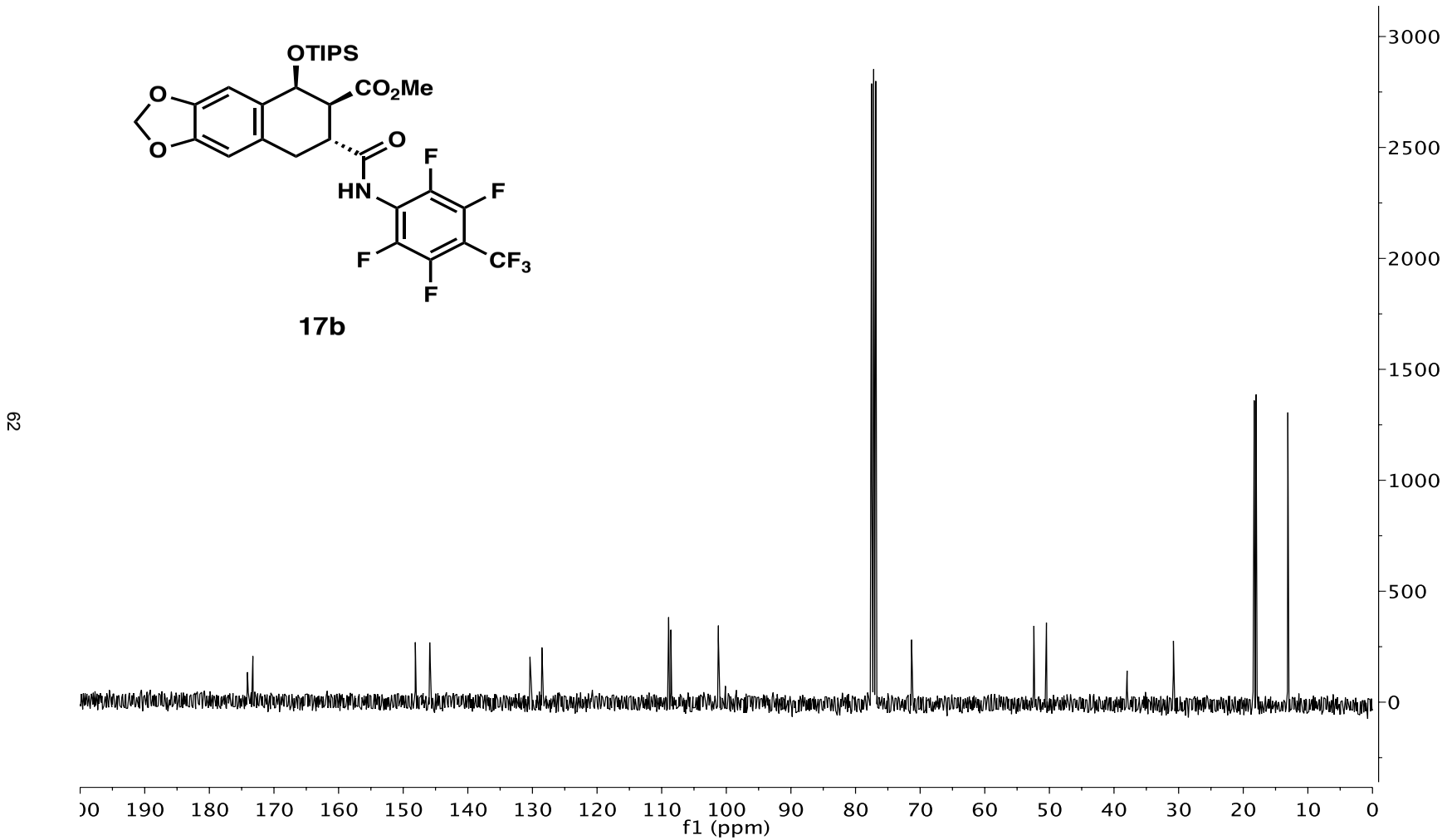

OTIPS
CO2Me
O
O
O
HN
F
F
F
F
F
17a
2500
2000
1500
1000
500
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

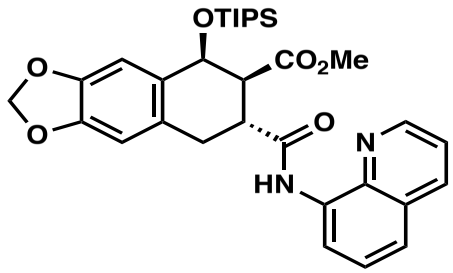

OTIPS
CO2Me
O
O
O
HN
F
F
F
F
F
17a
60
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OTIPS
CO2Me
O
O
O
HN
F
F
F
F
CF3

17b

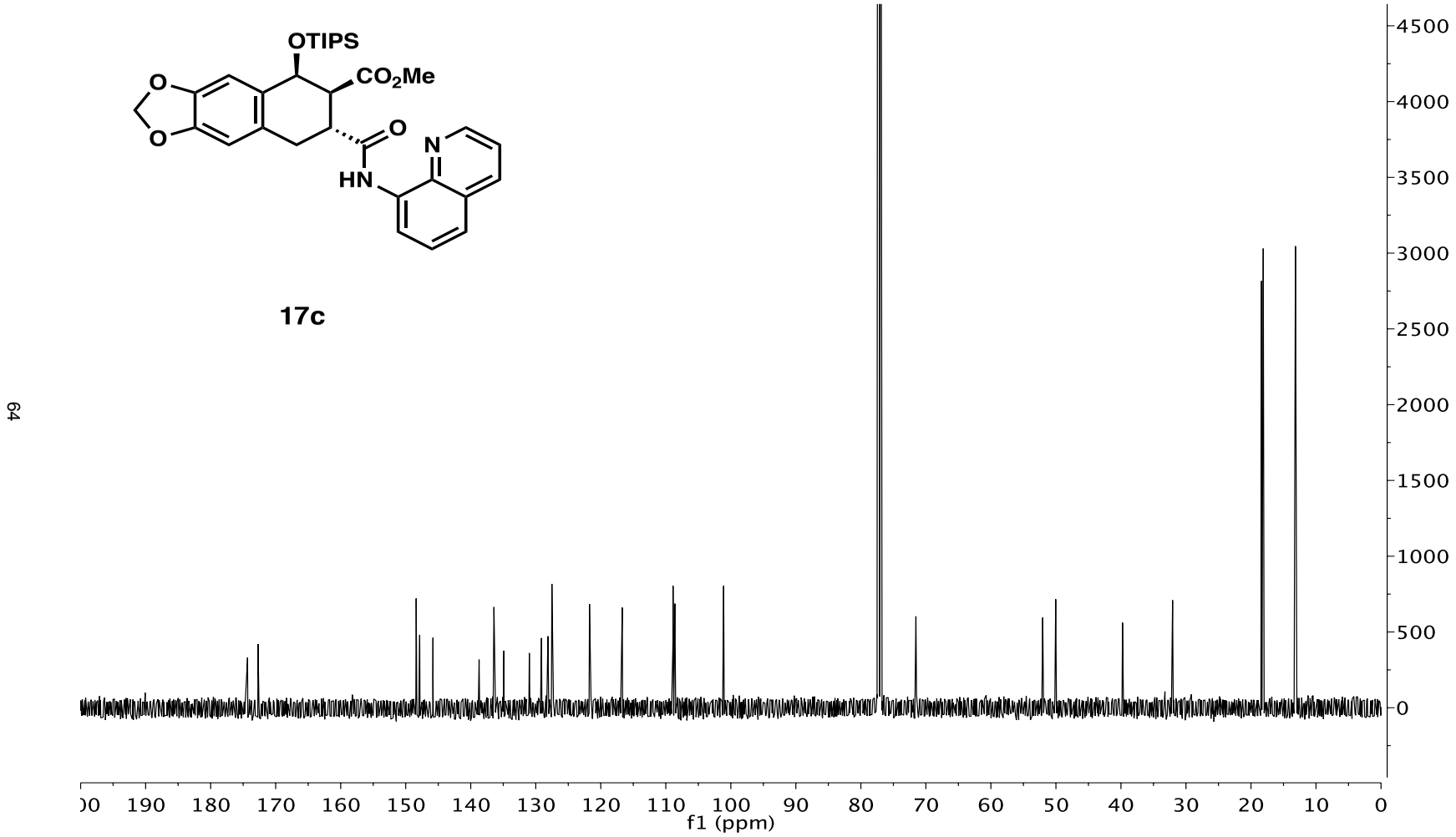
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

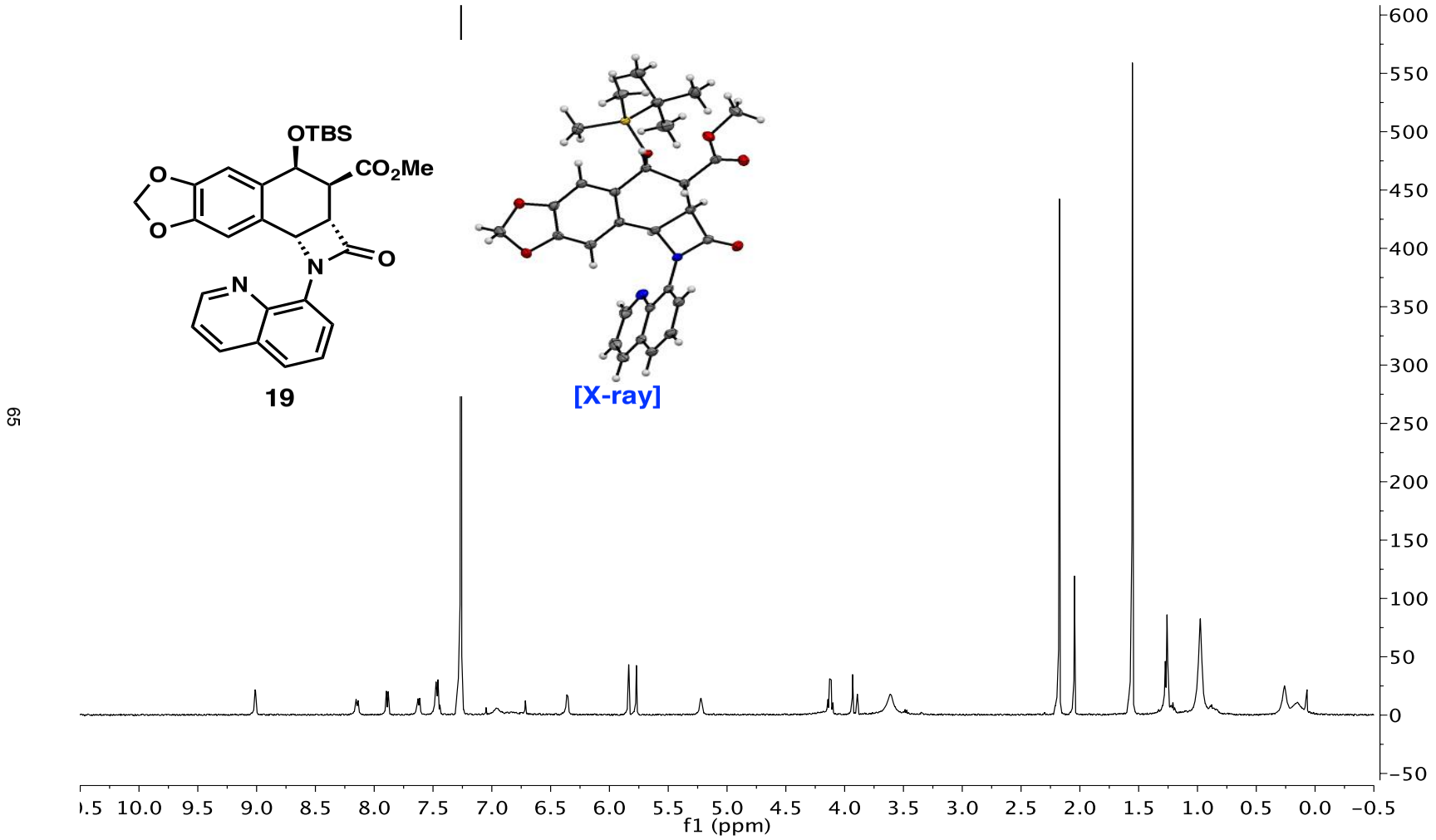

OTIPS
CO2Me
O
O
O
HN
F
F
F
F
CF3
17b
62
3000
2500
2000
1500
1000
500
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

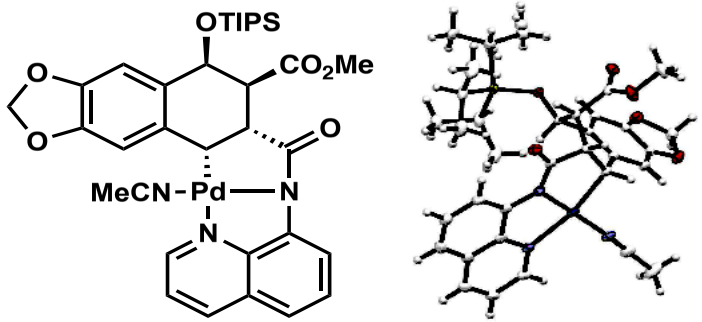

OTIPS
CO2Me
O
O
O
N
HN

17c

7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


OTIPS
CO2Me
O
O
O
HN
N
17c
64
4500
4000
3500
3000
2500
2000
1500
1000
500
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

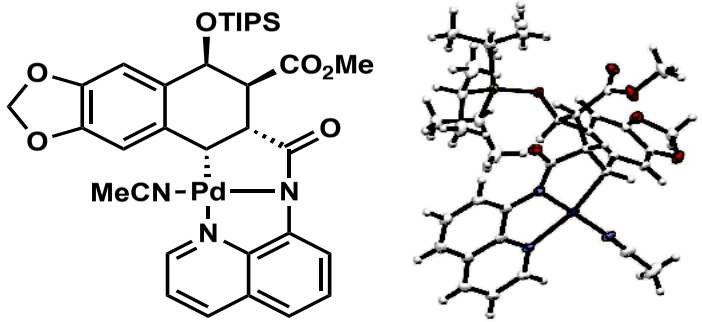

OTBS
CO2Me
O
O
N
O
N
19
[X-ray]
65
600
550
500
450
400
350
300
250
200
150
100
50
0
−50
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


OTIPS
CO2Me
O
O
O
MeCN–Pd–N
N

20

[X-ray]

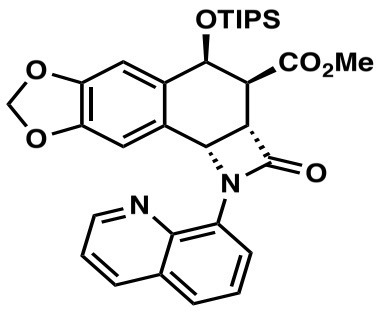
3500
3000
2500
2000
1500
1000
500
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


OTIPS
CO2Me
O
O
O
MeCN–Pd–N
N

20

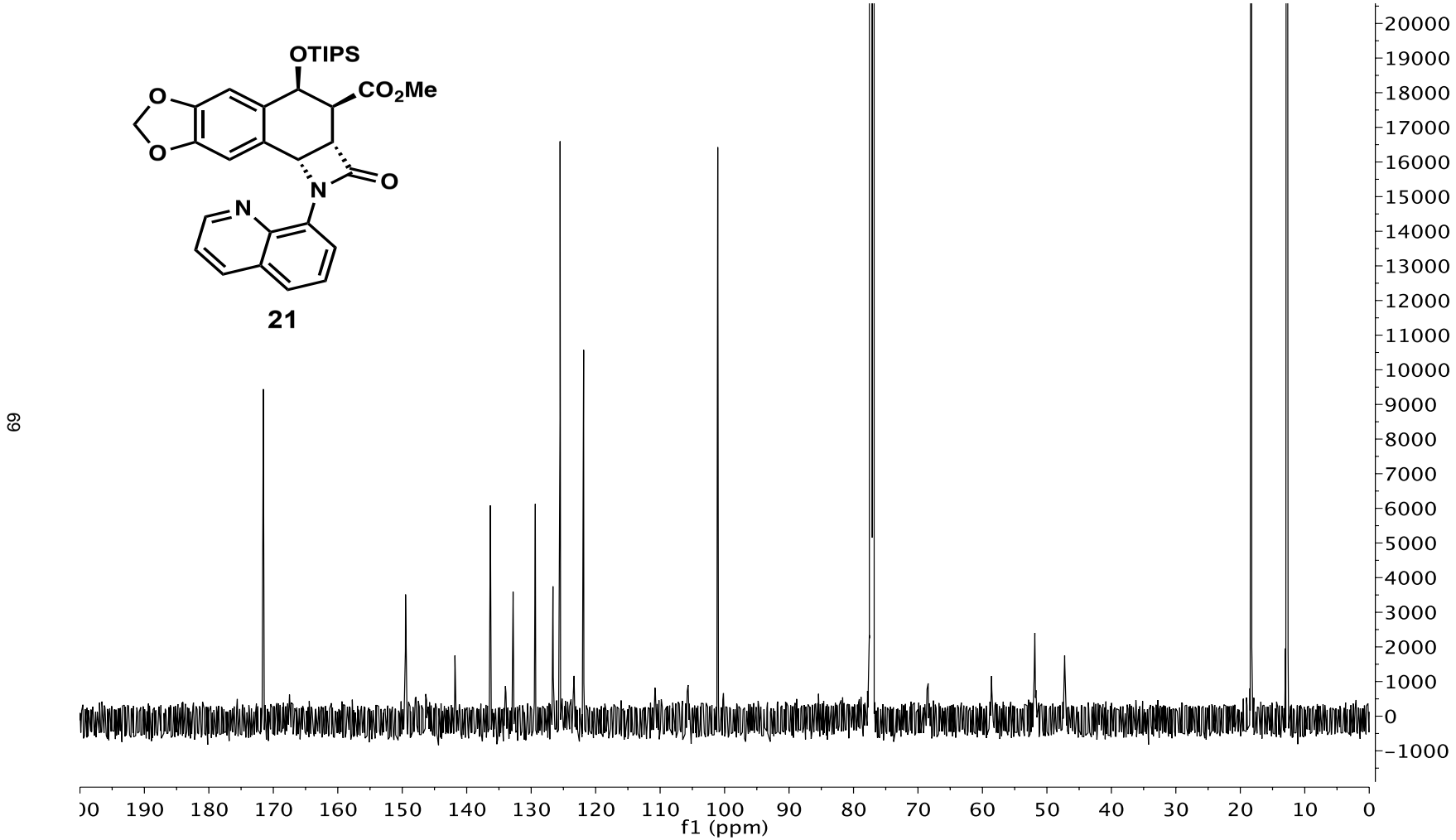
[X-ray]

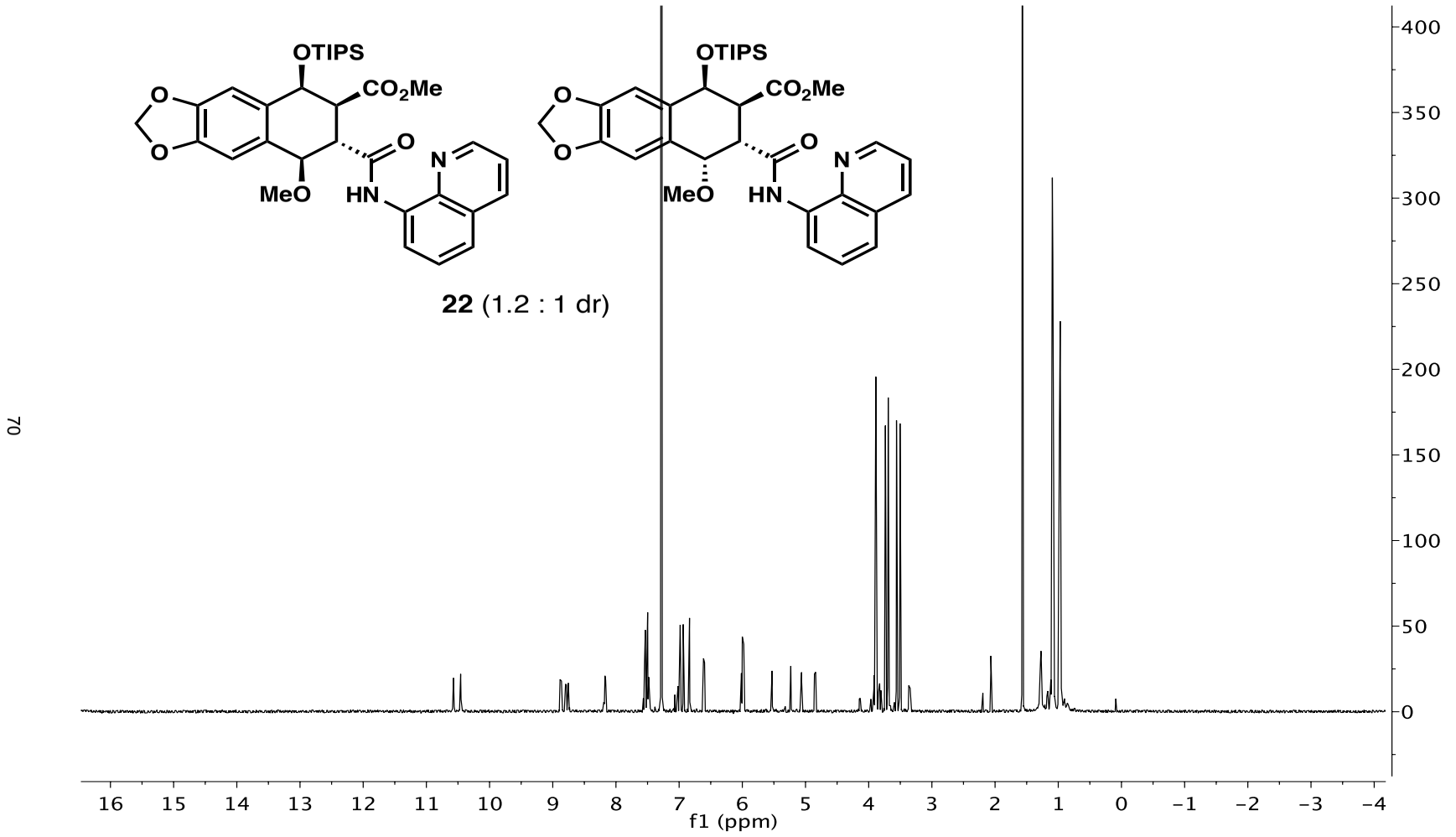
67
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

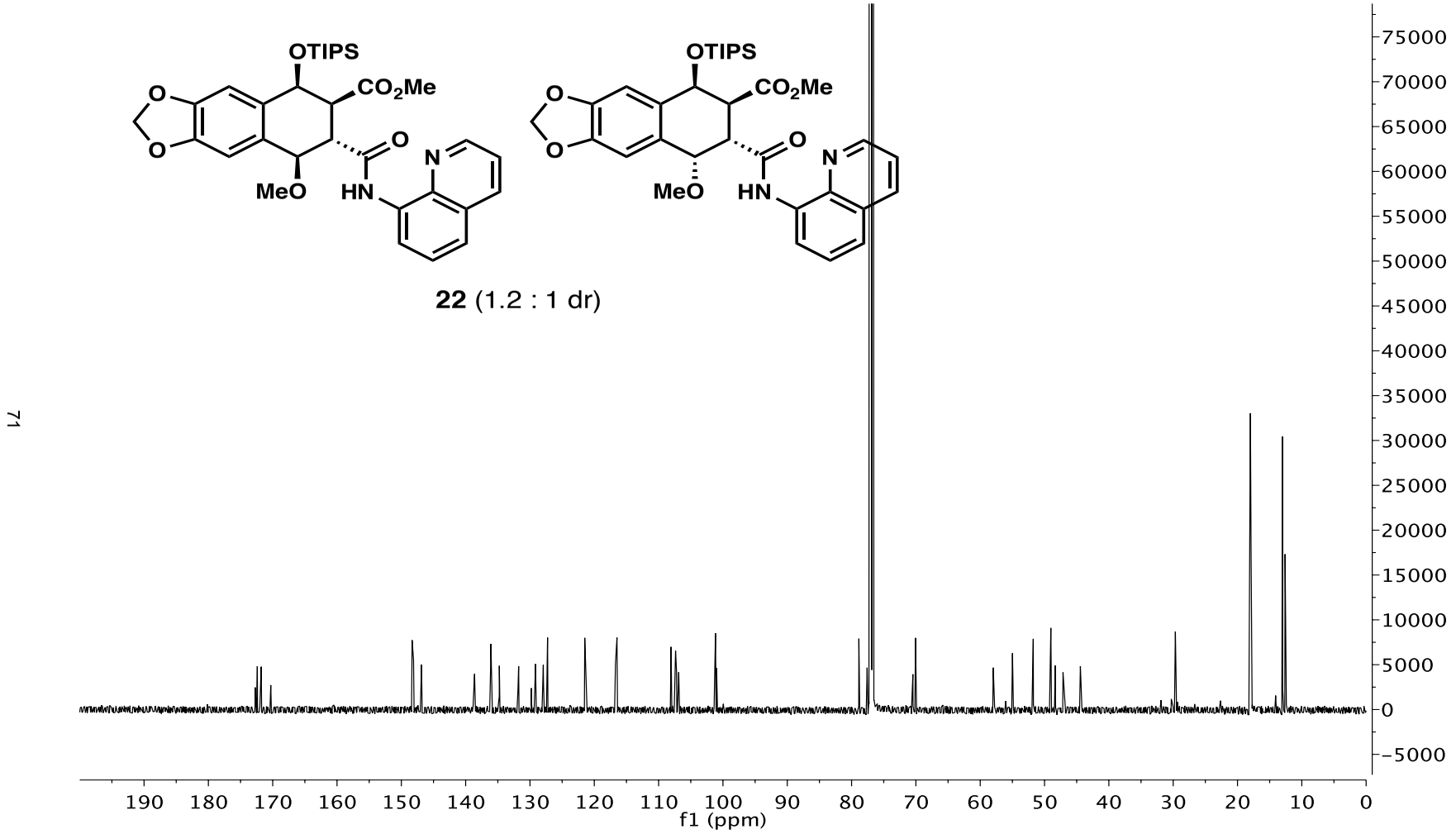

OTIPS
CO2Me
O
O
O
N
N

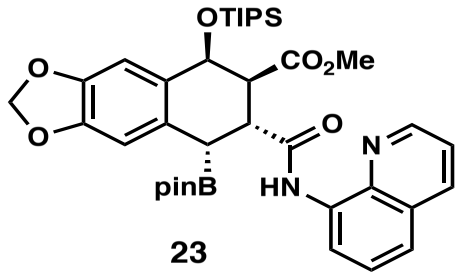
21

2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
−200
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


OTIPS
CO2Me
O
O
O
N
N
21
69
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

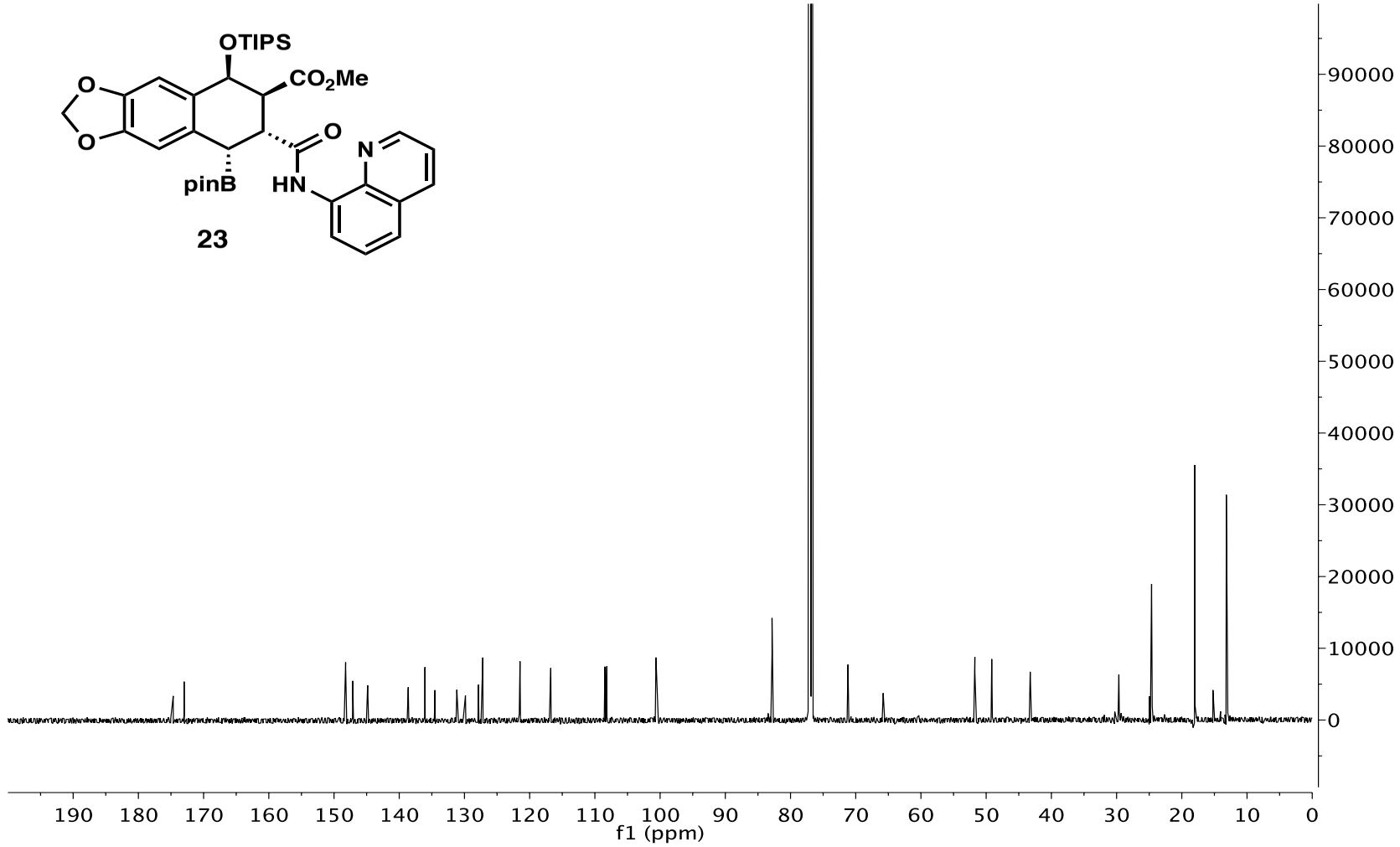

OTIPS
CO2Me
O
O
O
MeO
HN
N
OTIPS
CO2Me
O
O
O
MeO
HN
N
22 (1.2 : 1 dr)
400
350
300
250
200
150
100
50
0
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
−3
−4
f1 (ppm)

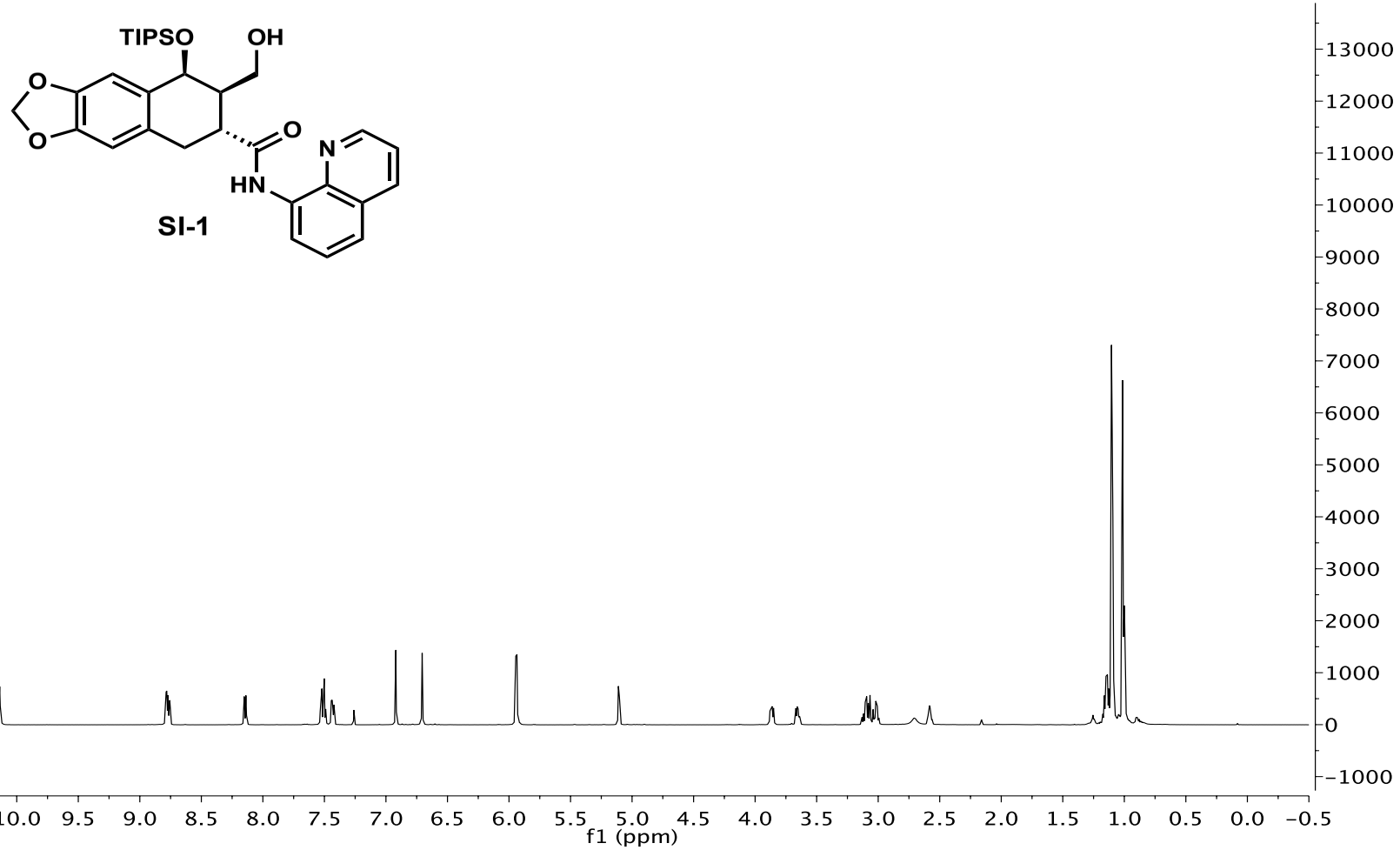

OTIPS
CO2Me
O
O
O
MeO
HN
N
OTIPS
CO2Me
O
O
O
MeO
HN
N
22 (1.2 : 1 dr)
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
−5000
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

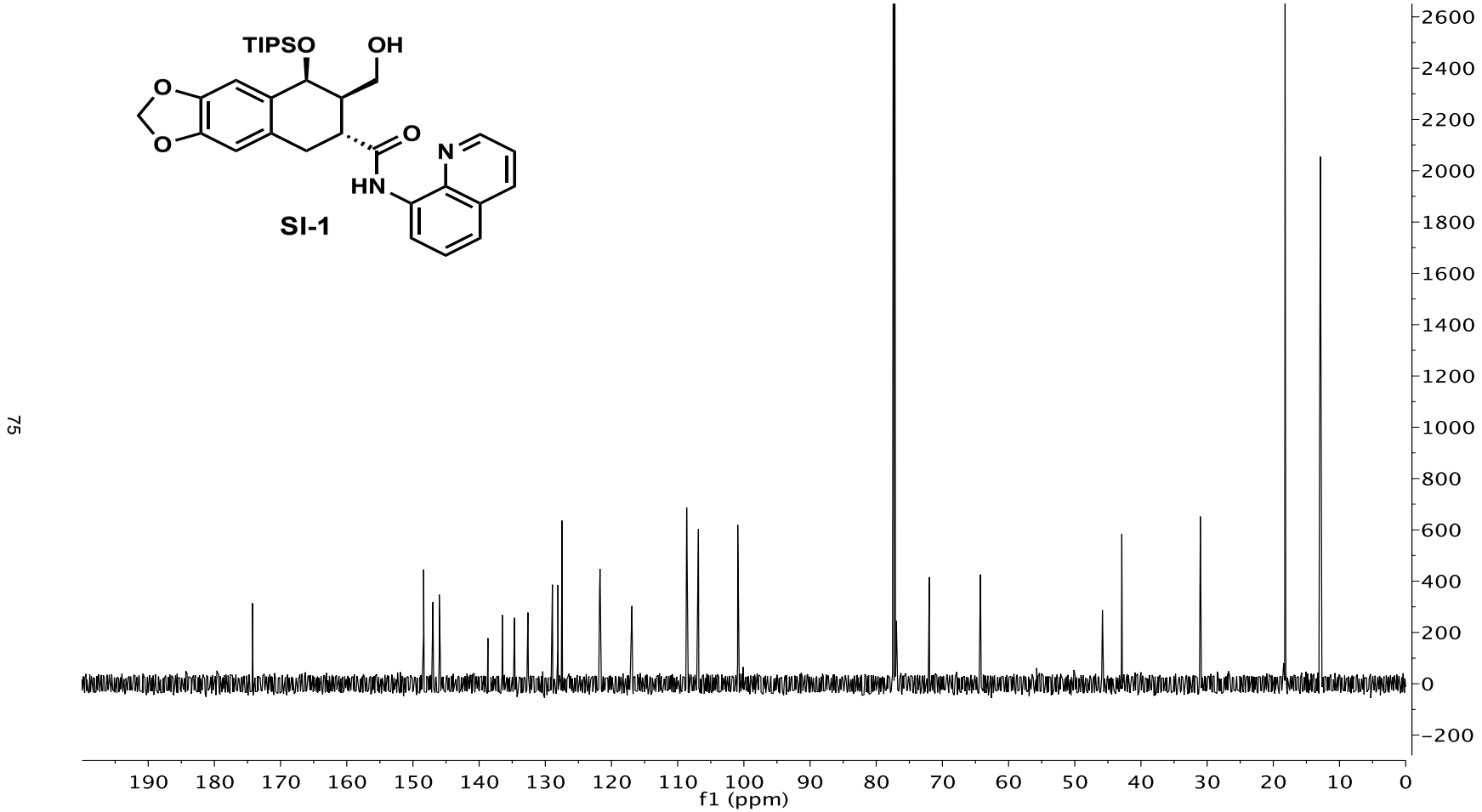

OTIPS
CO2Me
O
O
O
N
pinB
HN

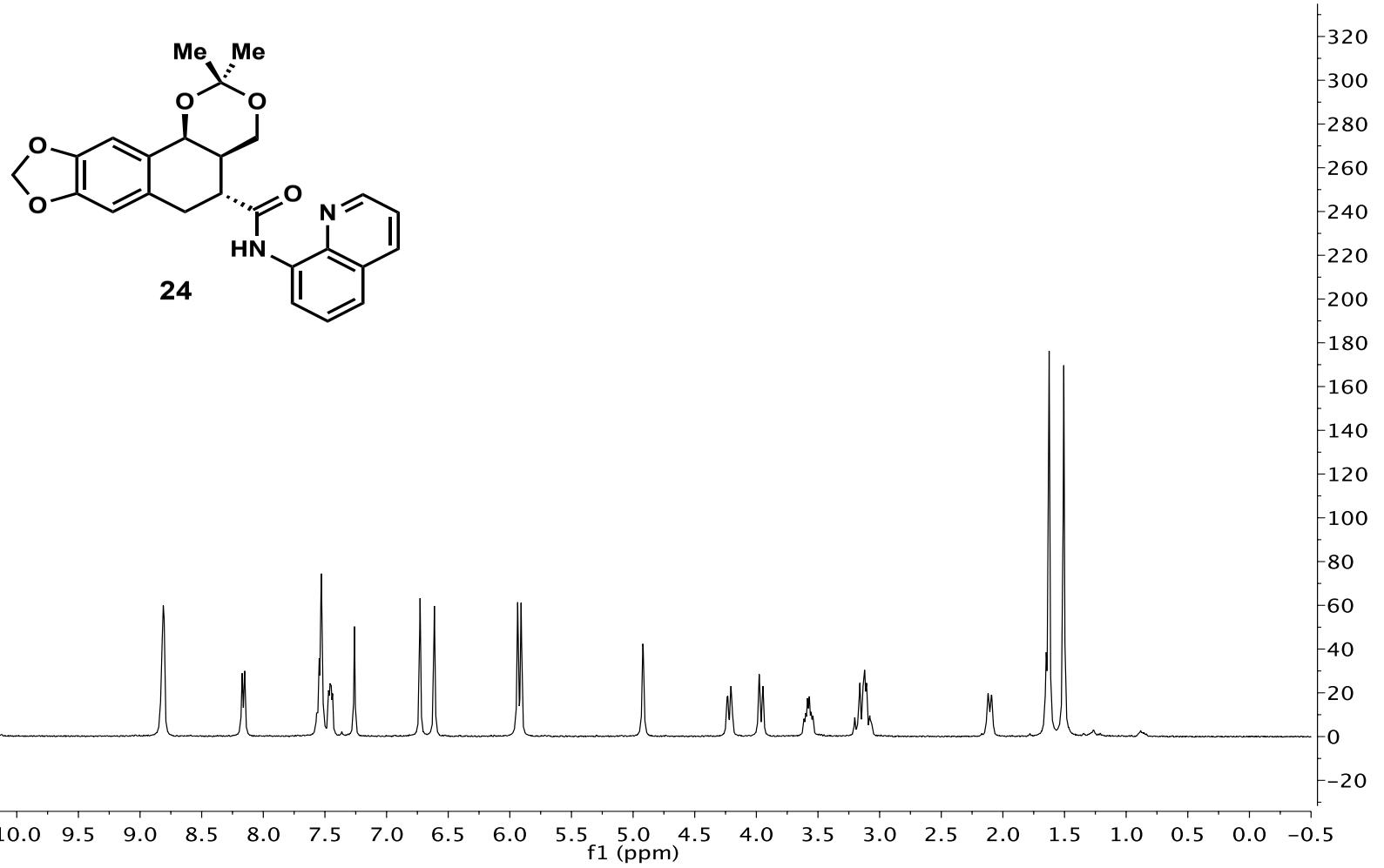
23

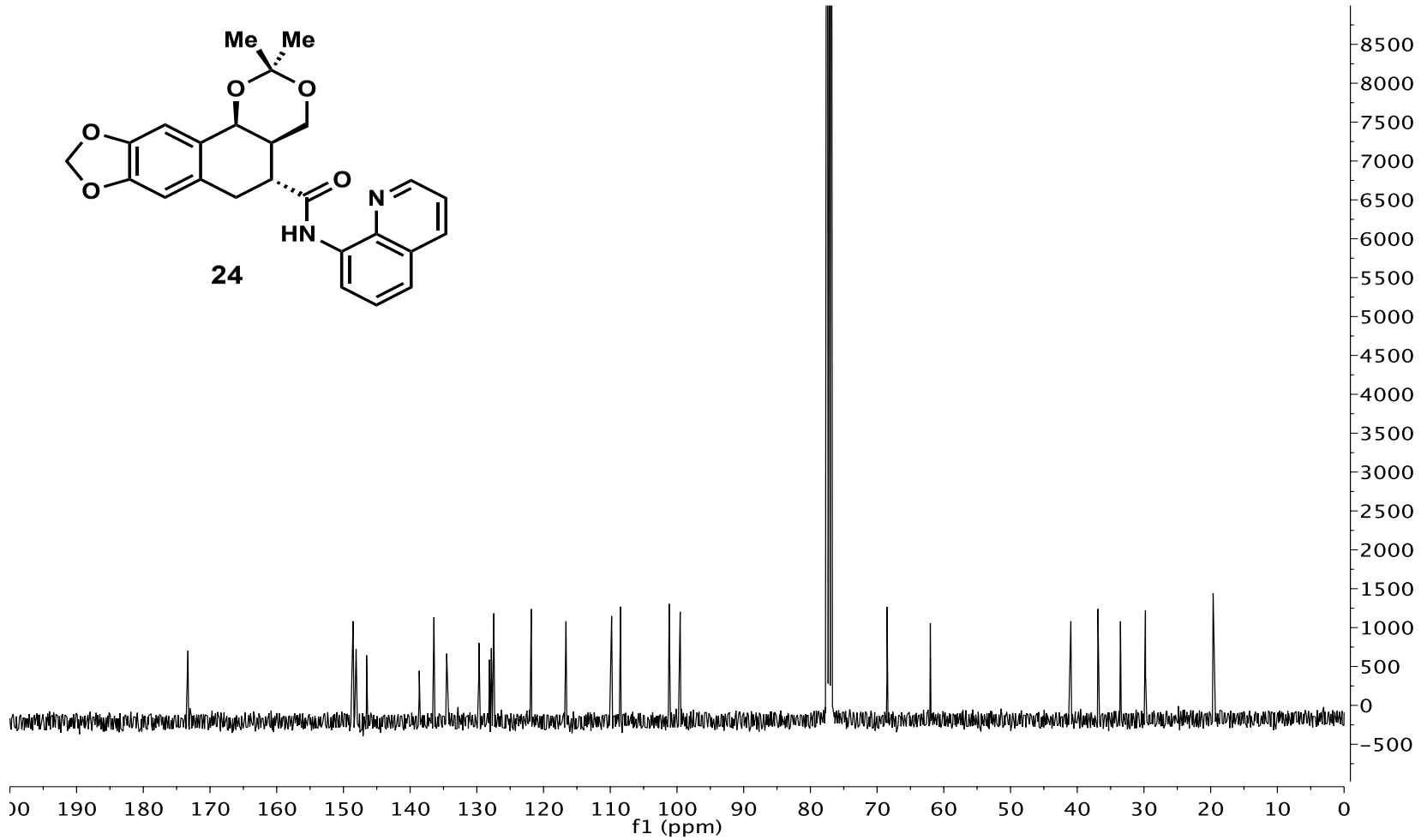
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
..0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


OTIPS
CO2Me
O
O
O
pinB
HN
N
23
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

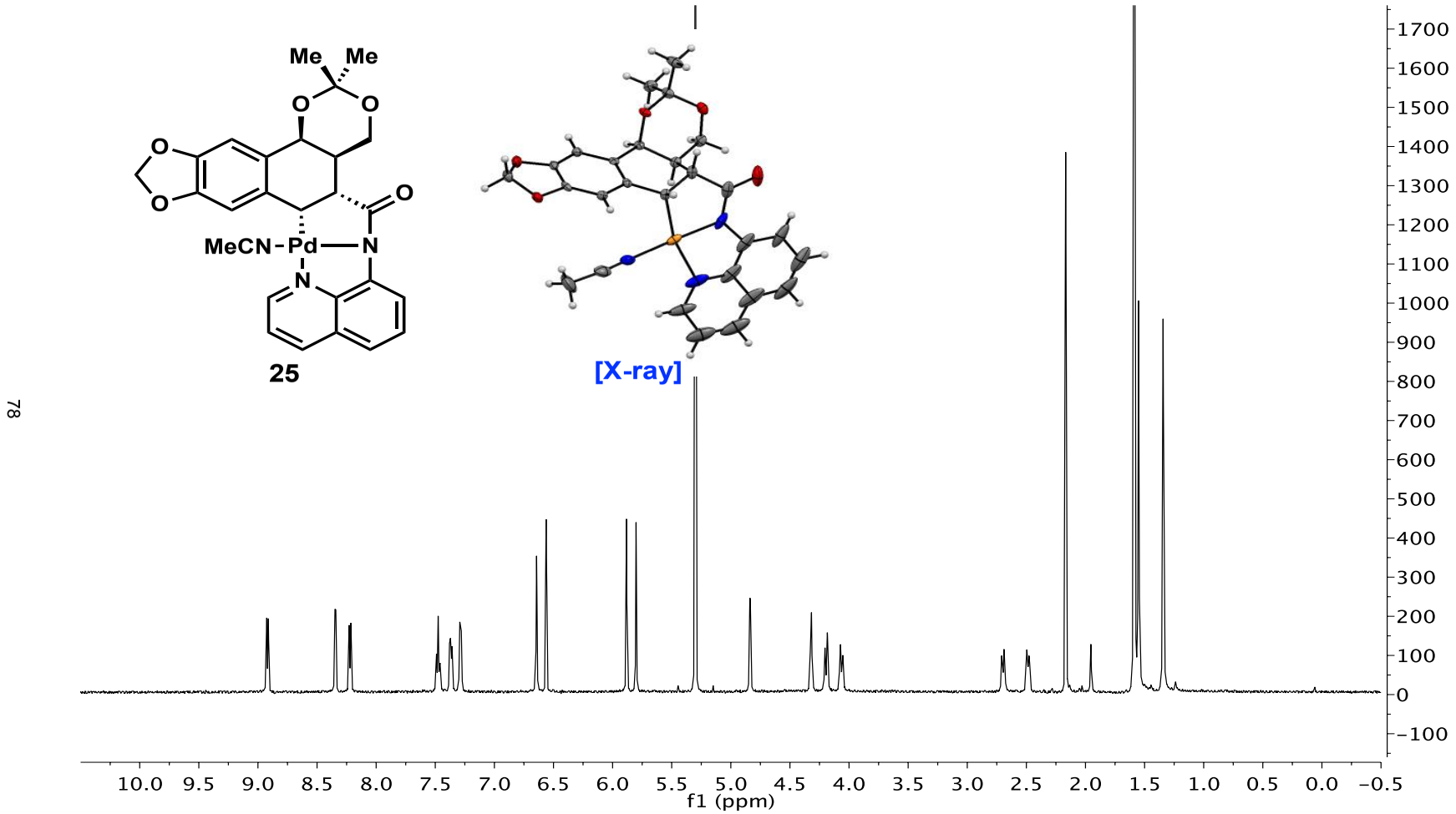

TIPSO
OH
O
O
O
N
HN
SI-1
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

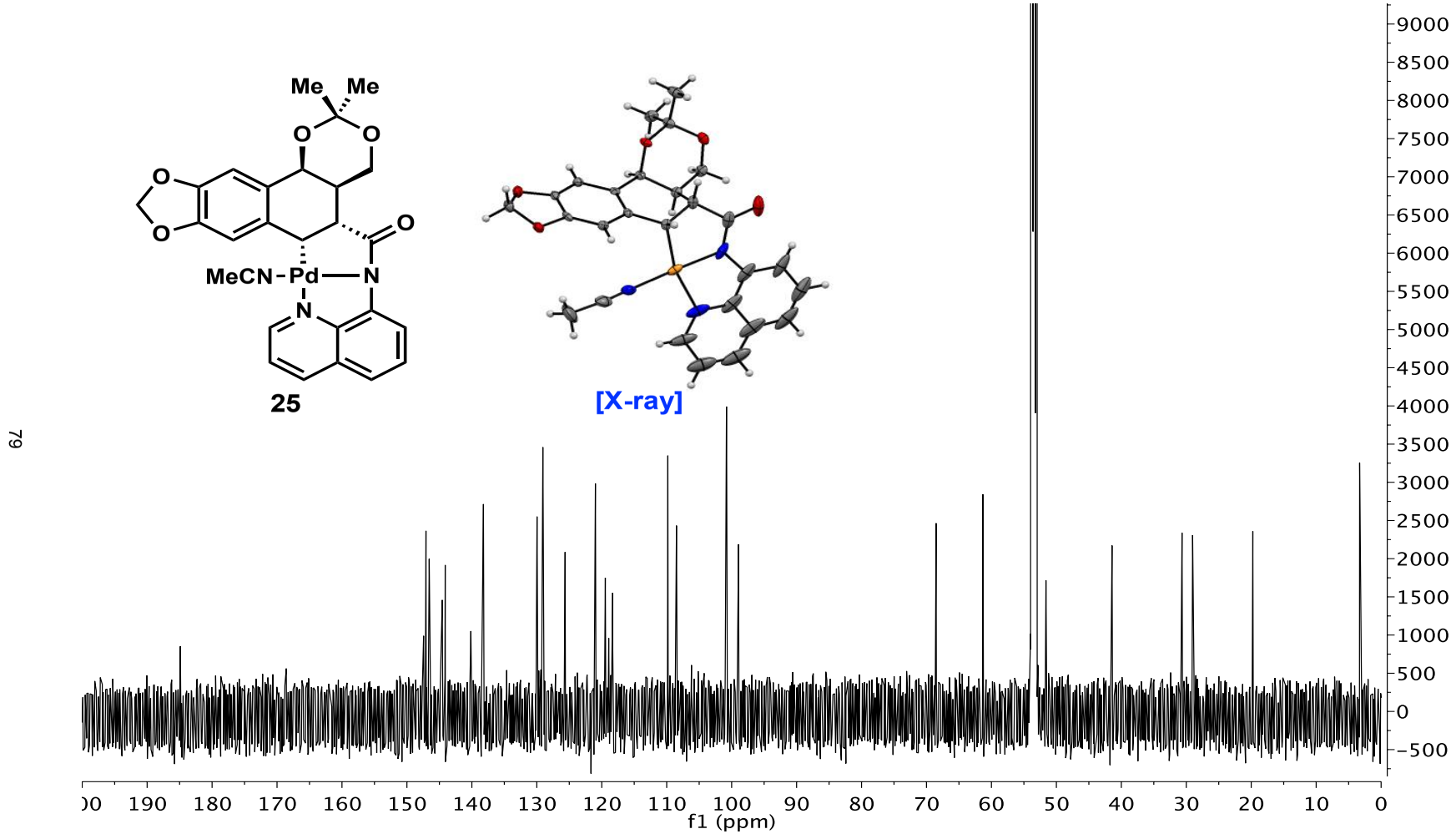

TIPSO
OH
O
O
O
N
HN
SI-1
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

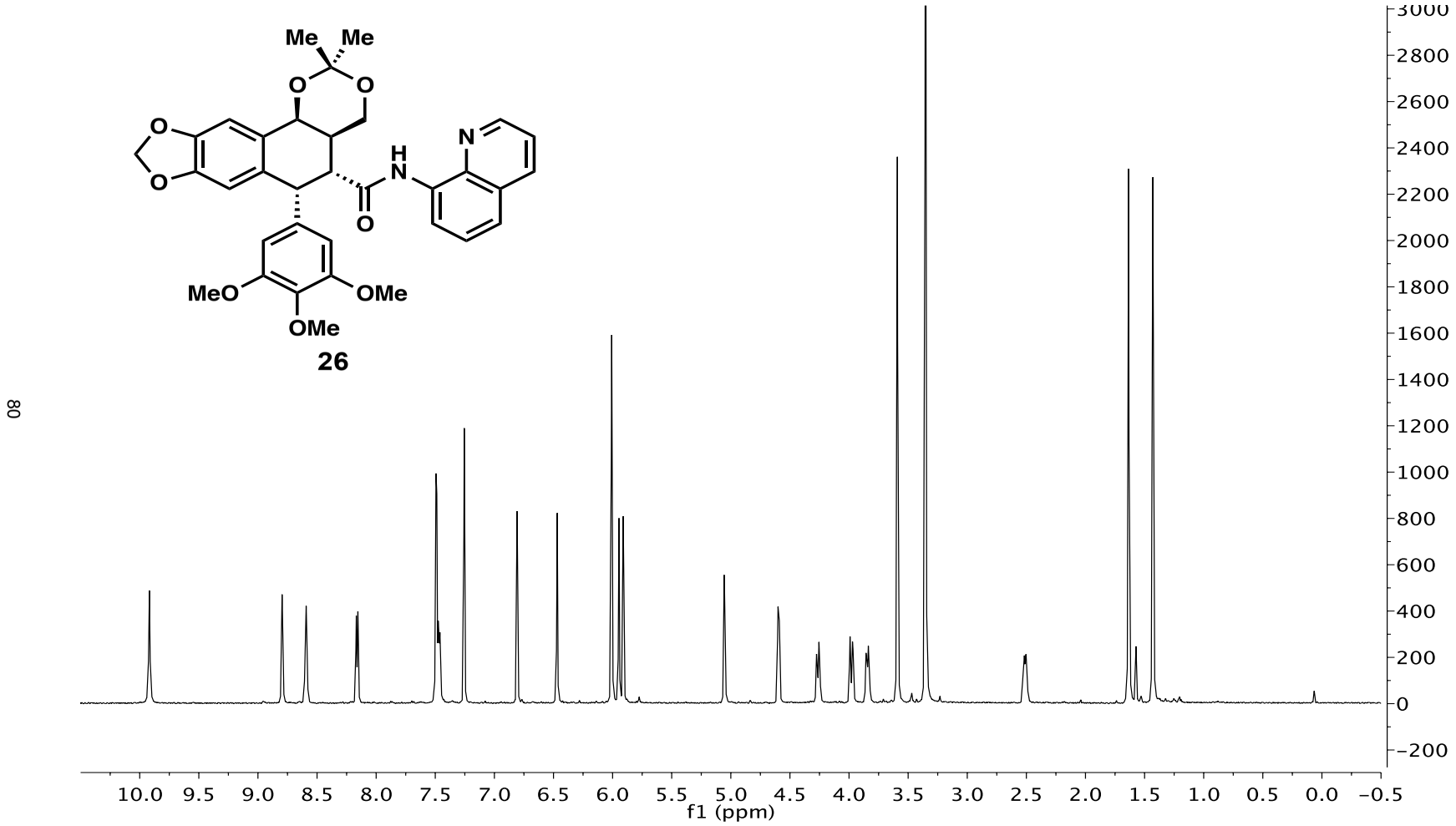

Me
Me
O
O
O
O
O
HN
N
24
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
−20
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
f1 (ppm)

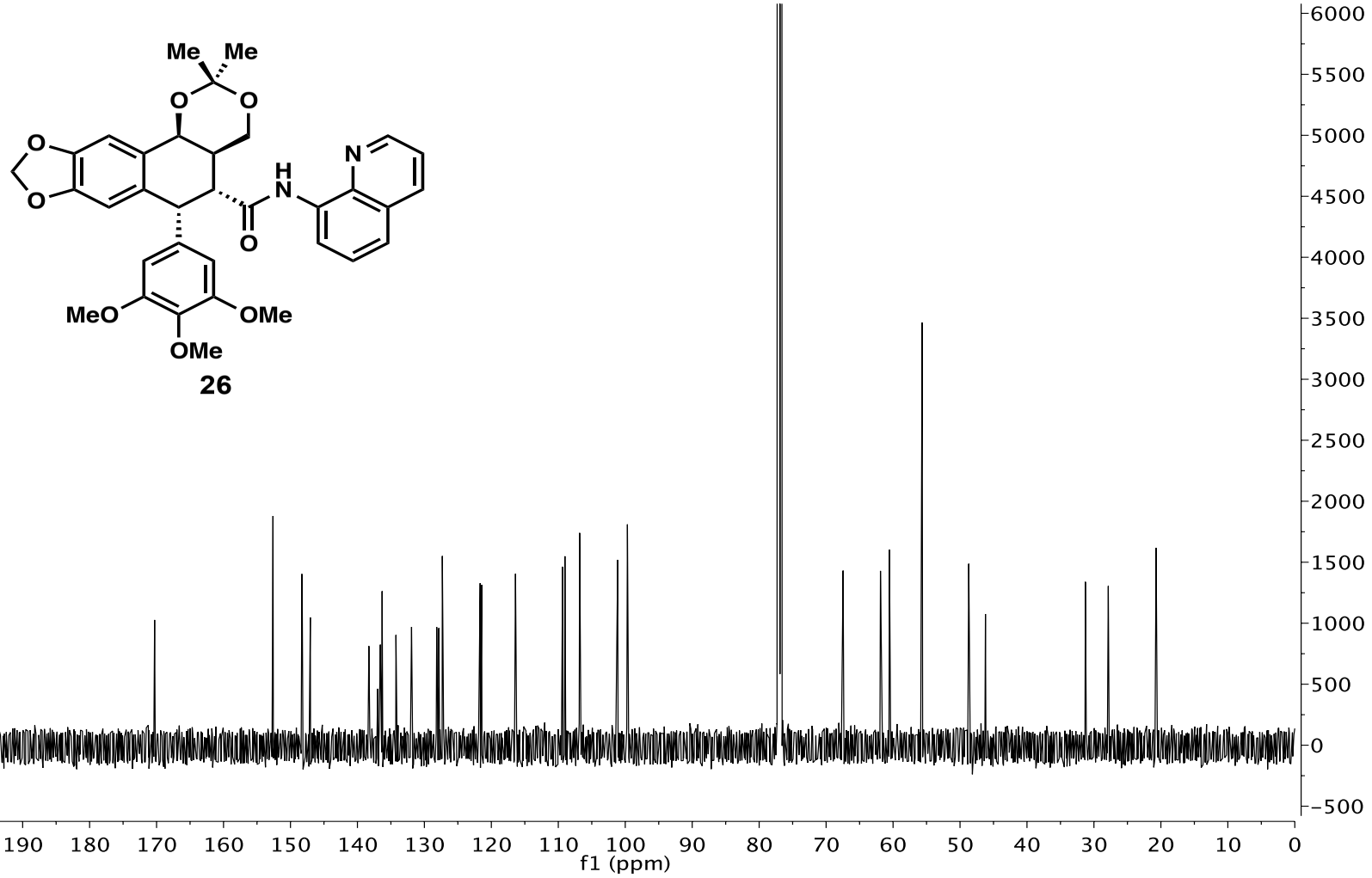

Me
Me
O
O
O
O
O
HN
N
24
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

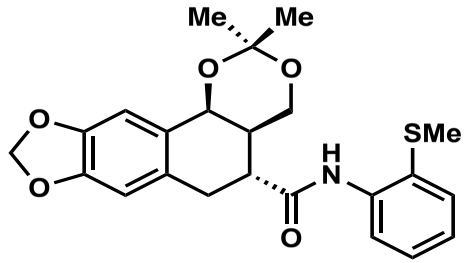
77


Me
Me
O
O
O
O
O
MeCN–Pd–N
N
25
[X-ray]
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


Me
Me
O
O
O
O
O
MeCN–Pd–N
N
25
[X-ray]
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
Me
O
O
O
O
H
N
N
O
MeO
OMe
OMe
26
80
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

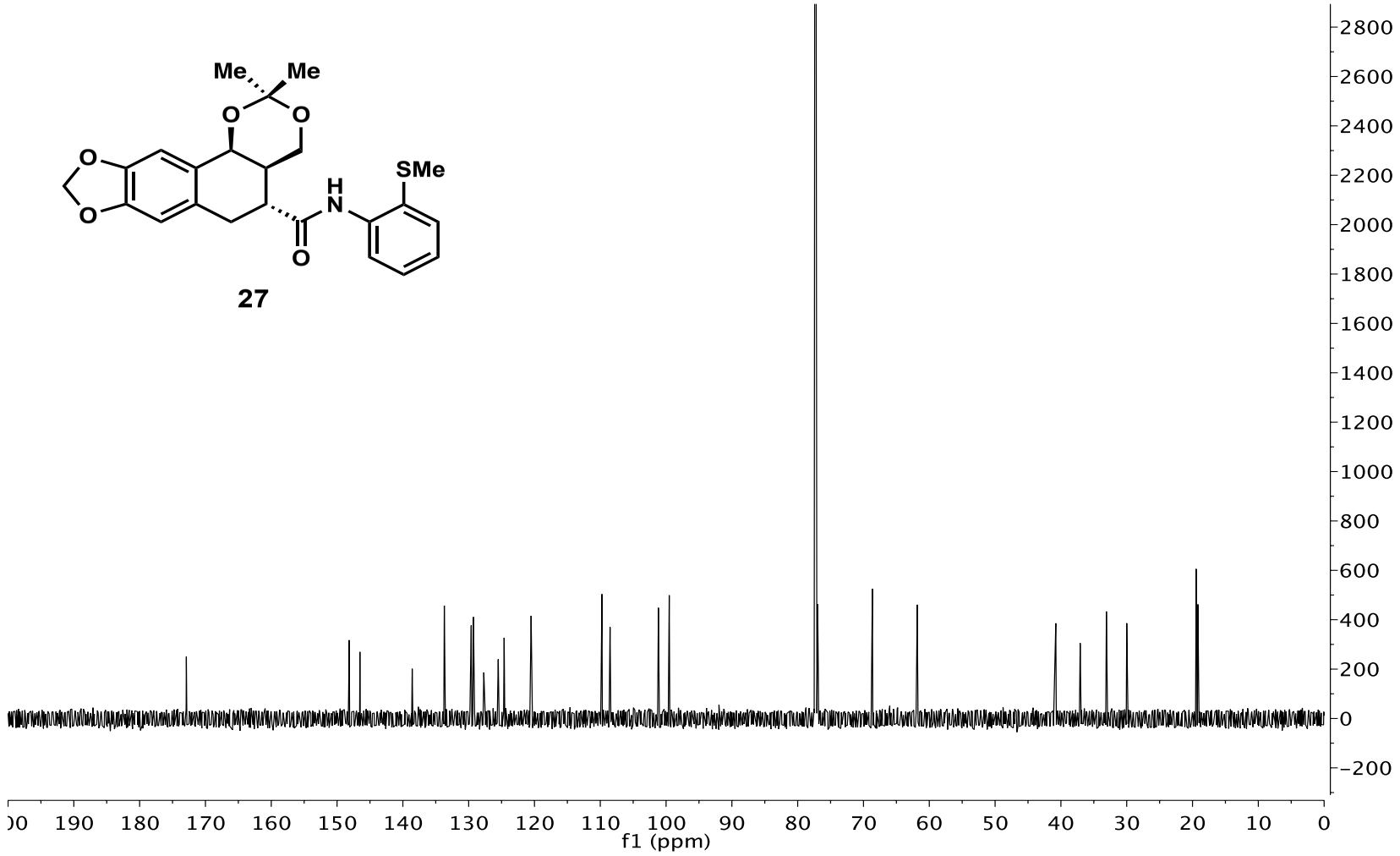

Me
Me
O
O
O
O
H
N
N
O
MeO
OMe
OMe
26
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

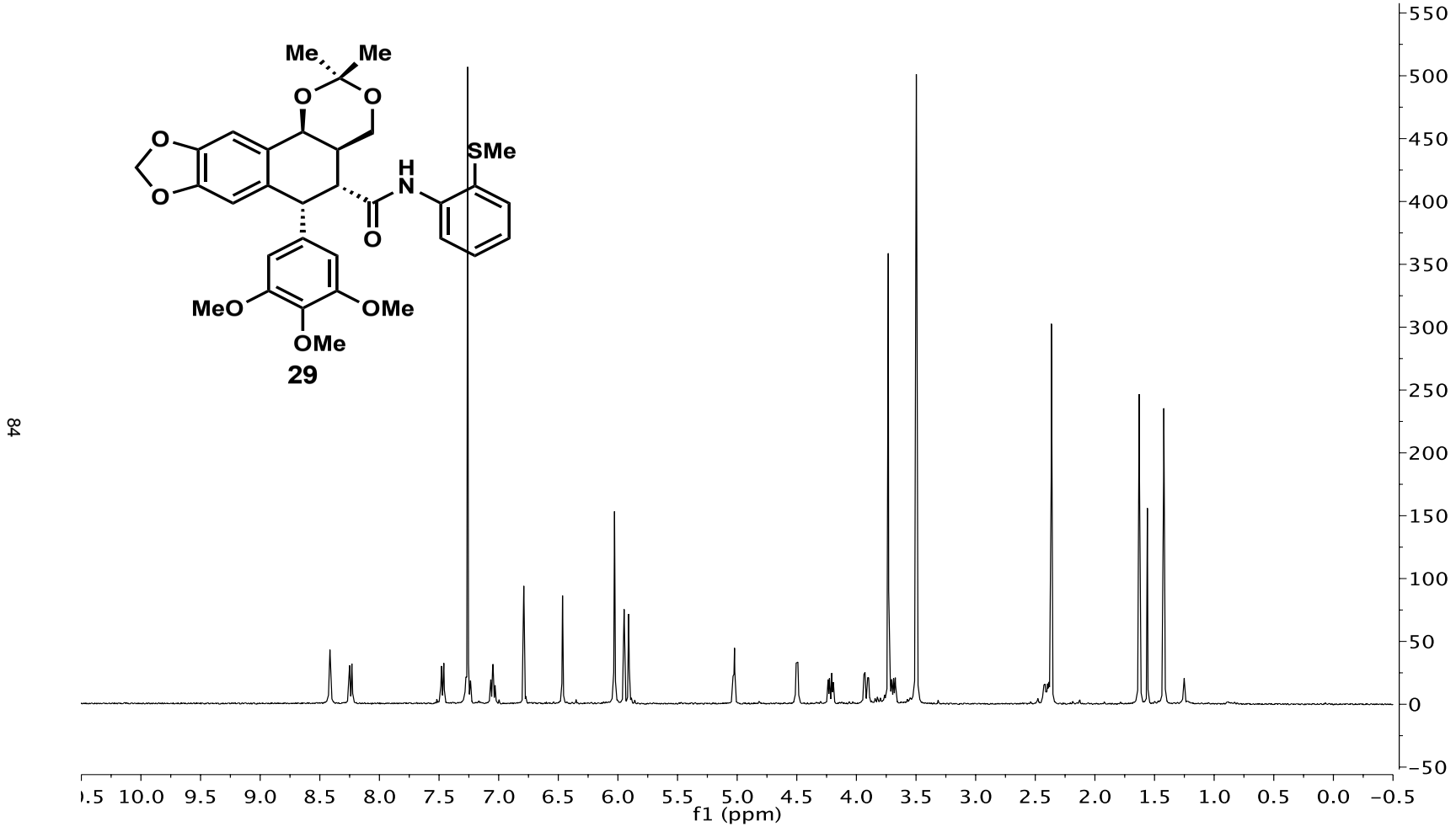

Me
Me
O
O
O
O
H
N
SMe
O

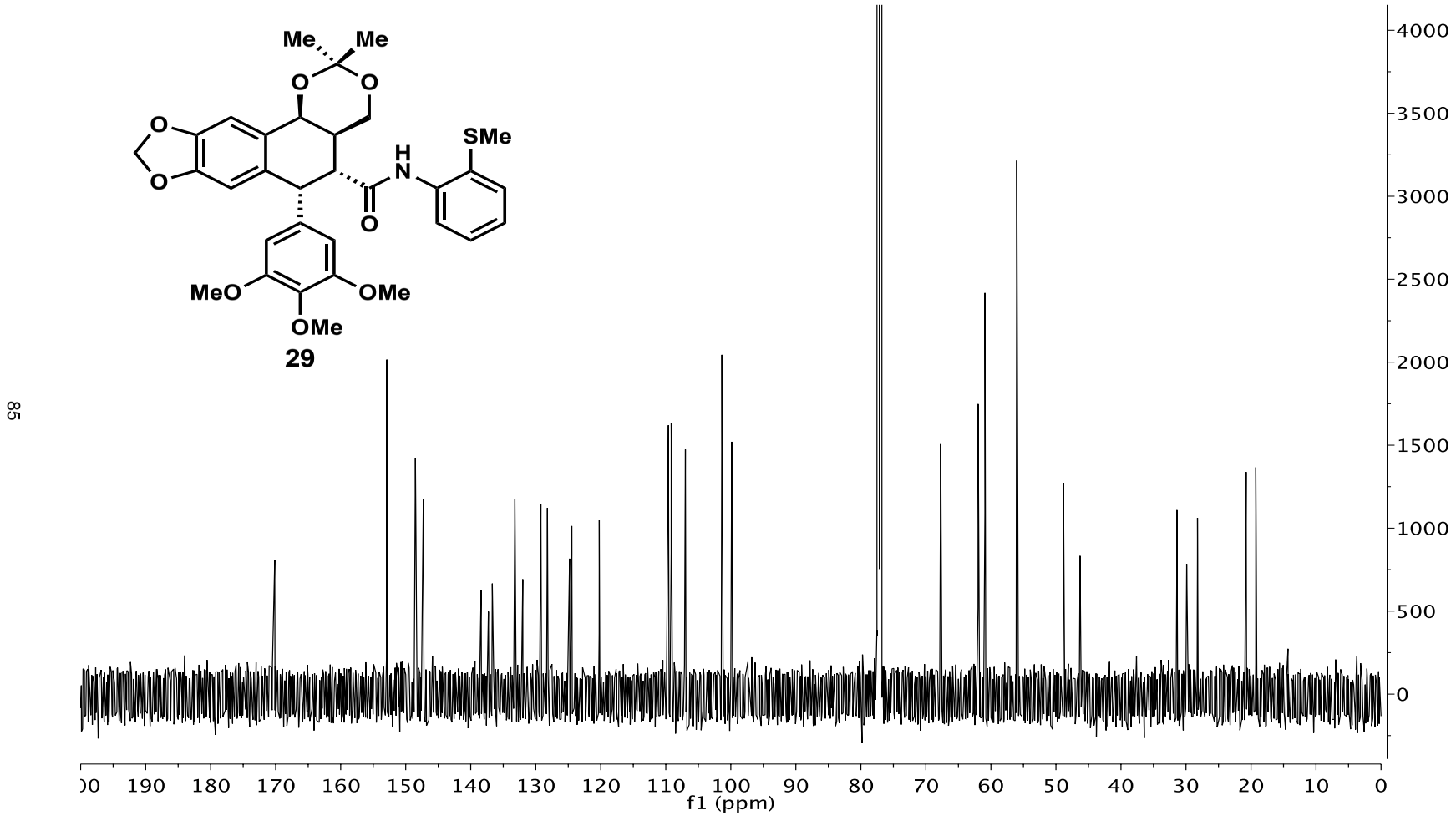
27

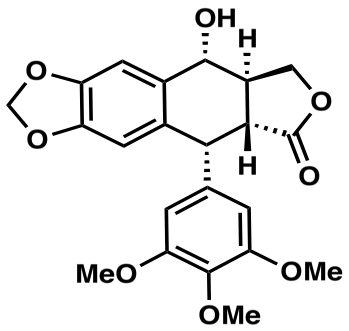
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

82


Me
Me
O
O
O
O
H
N
SMe
O
27
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

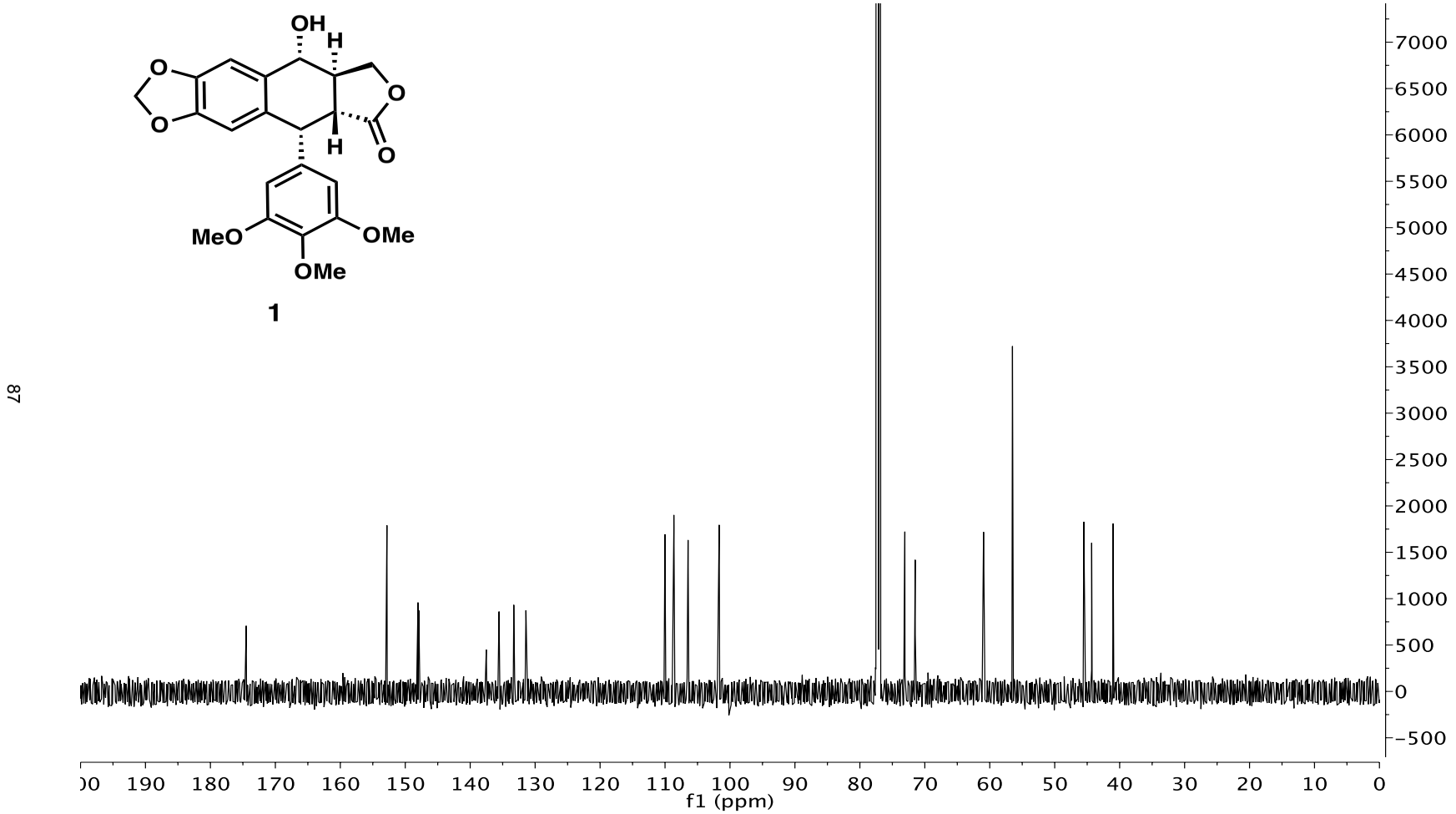

Me
Me
O
O
O
O
H
N
SMe
O
MeO
OMe
OMe
29
550
500
450
400
350
300
250
200
150
100
50
0
−50
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
f1 (ppm)

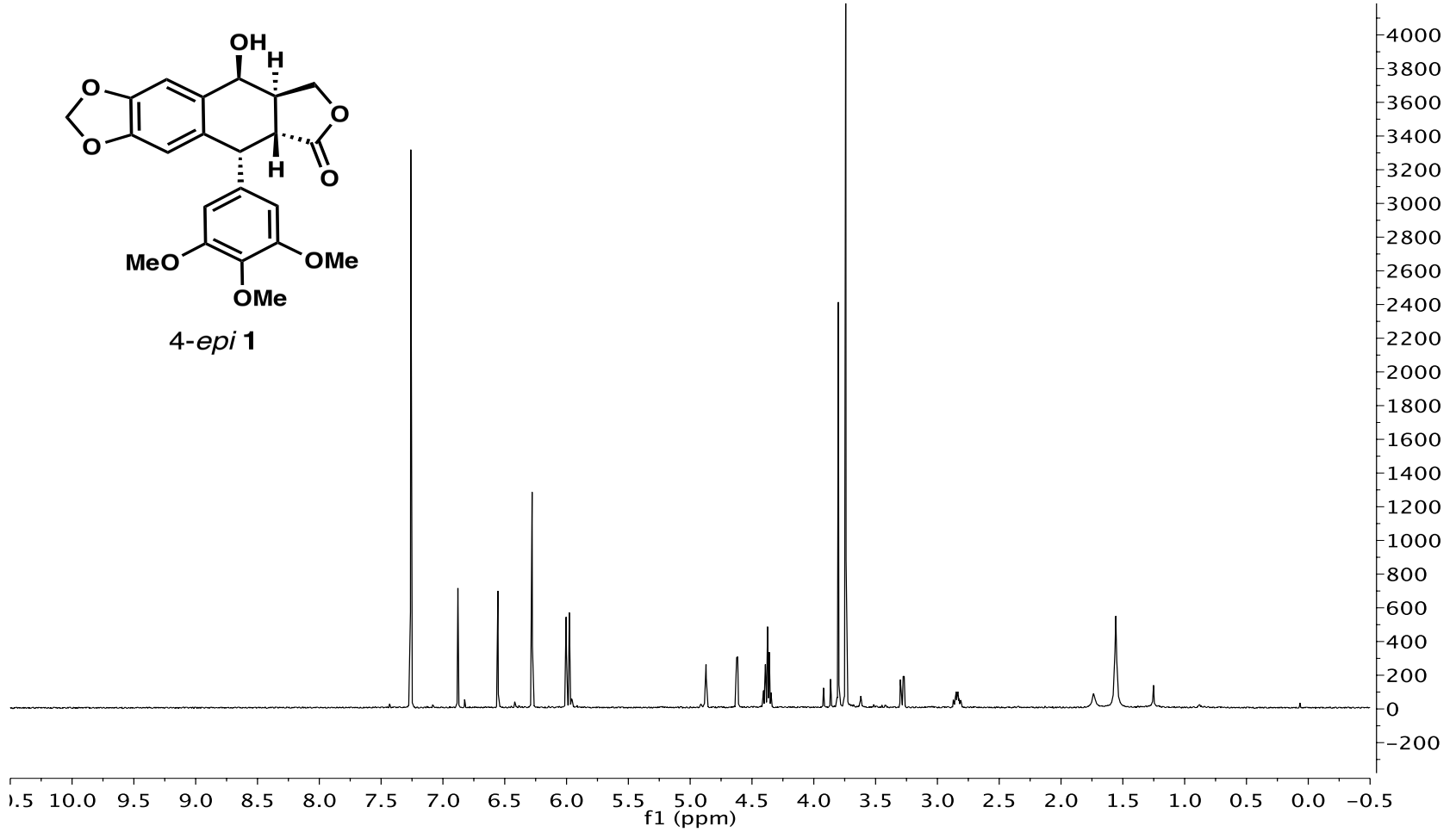

Me
Me
O
O
O
O
H
N
SMe
O
MeO
OMe
OMe
29
4000
3500
3000
2500
2000
1500
1000
500
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

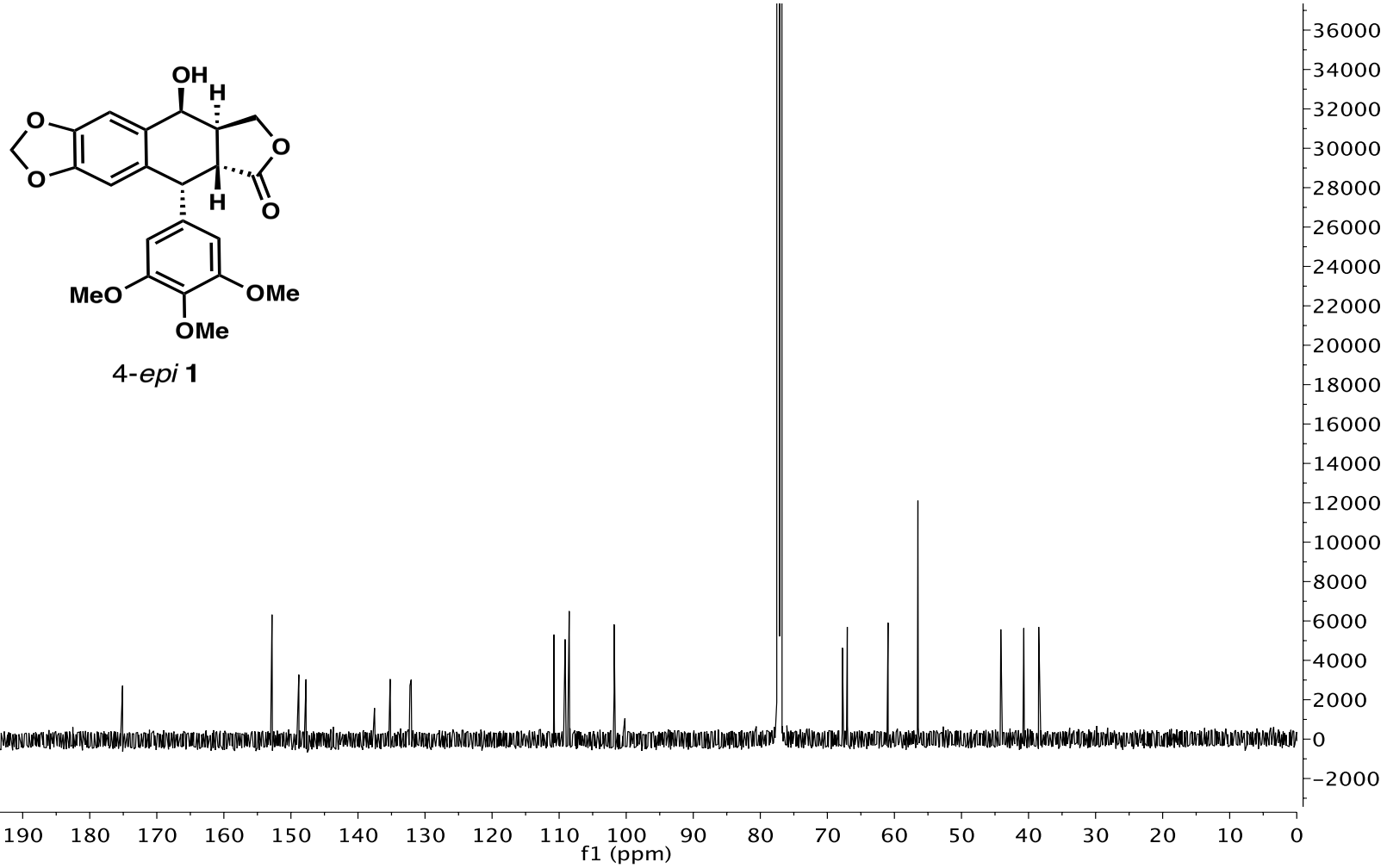

OH
H
O
O
O
H
O
MeO
OMe
OMe

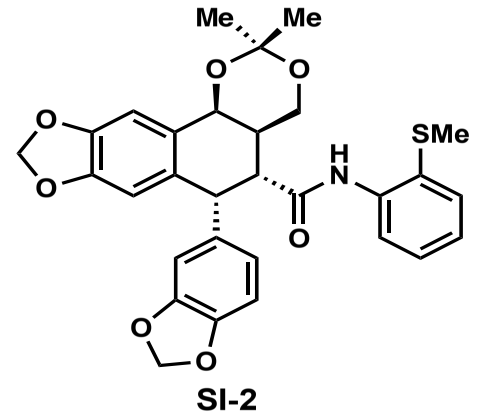
1

9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
f1 (ppm)


OH
H
O
O
O
H
O
MeO
OMe
OMe
1
87
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

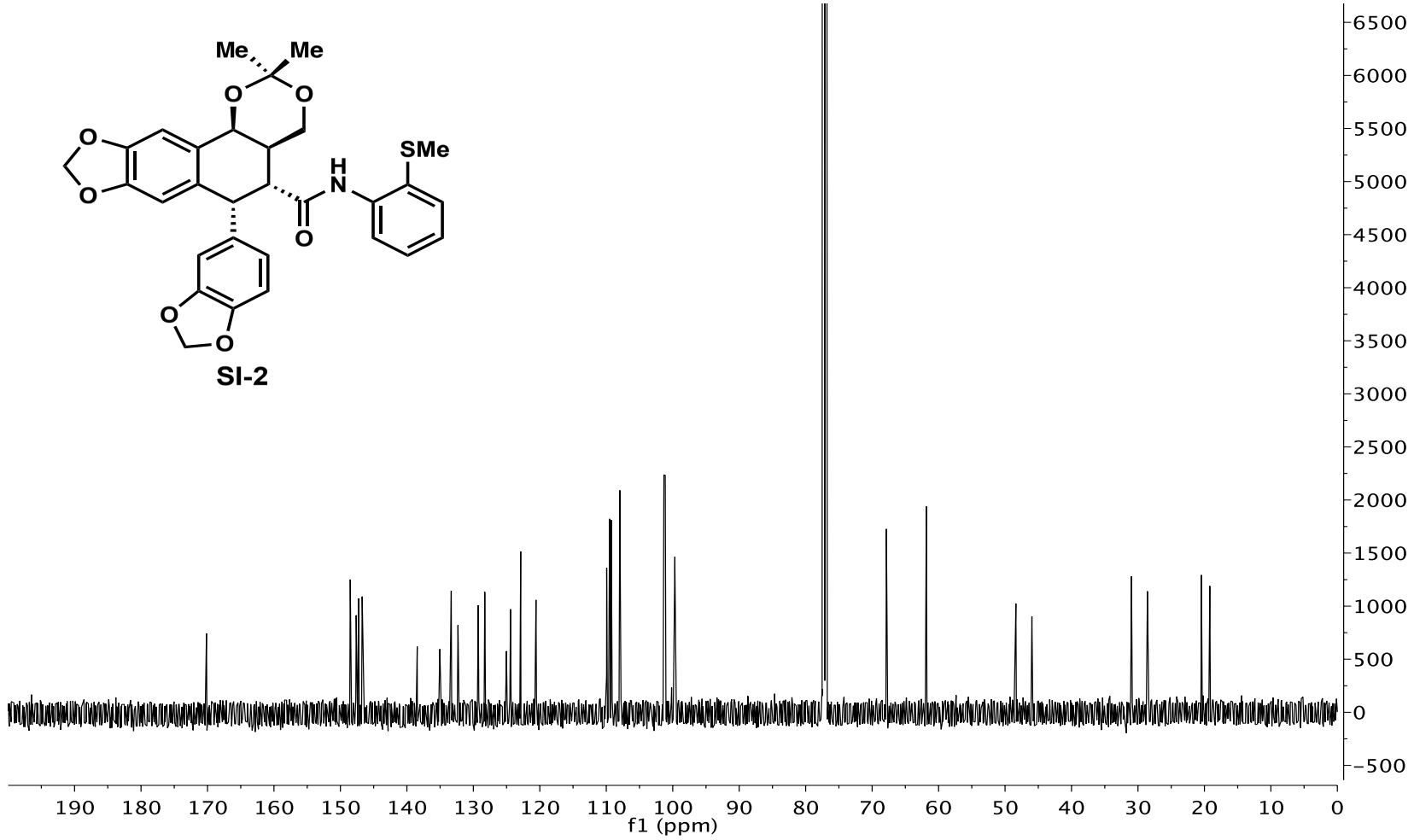

OH
H
O
O
O
O
H
MeO
OMe
OMe
4-epi 1
88
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

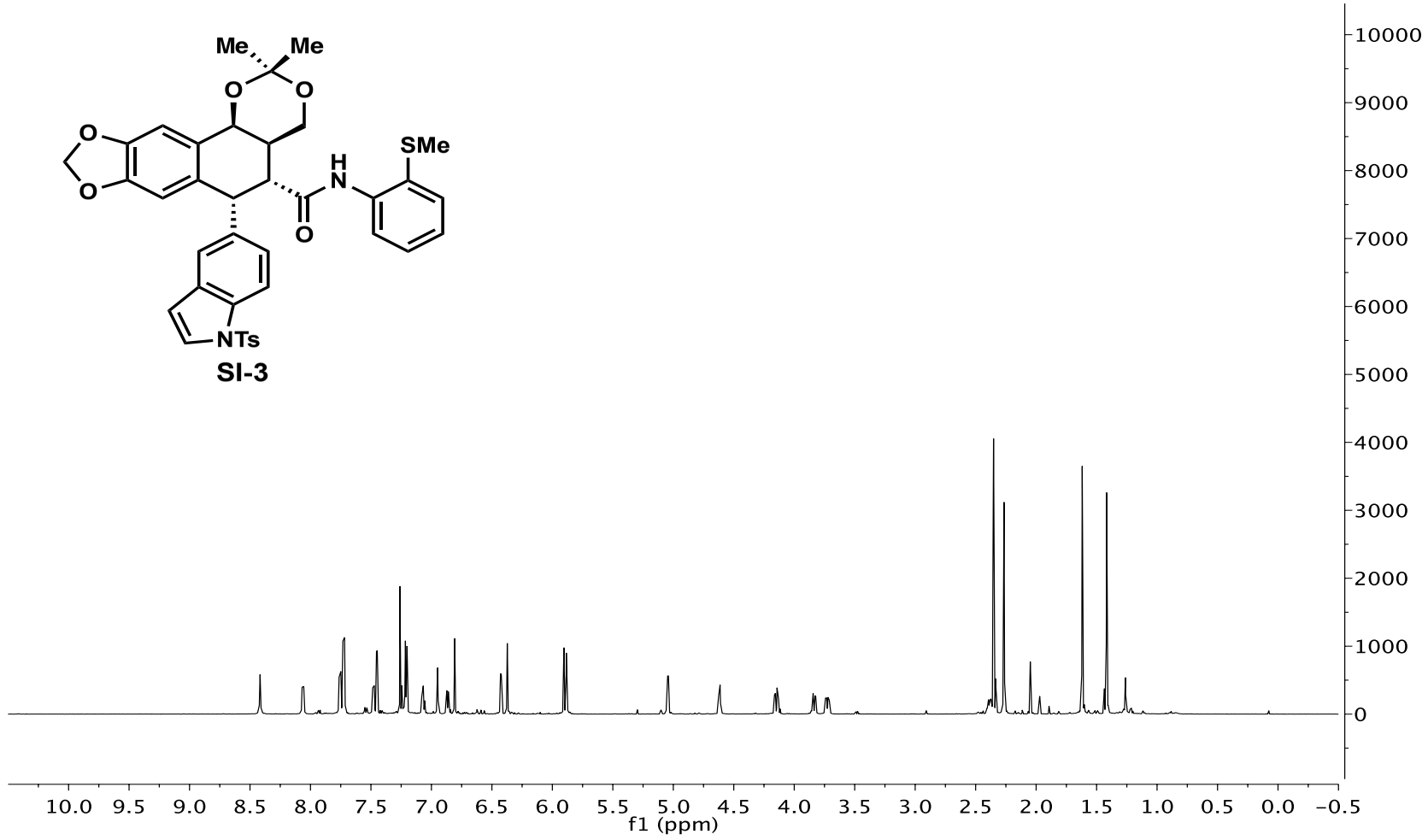

OH
H
O
O
O
O
H
O
MeO
OMe
OMe
4-epi 1
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
−2000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

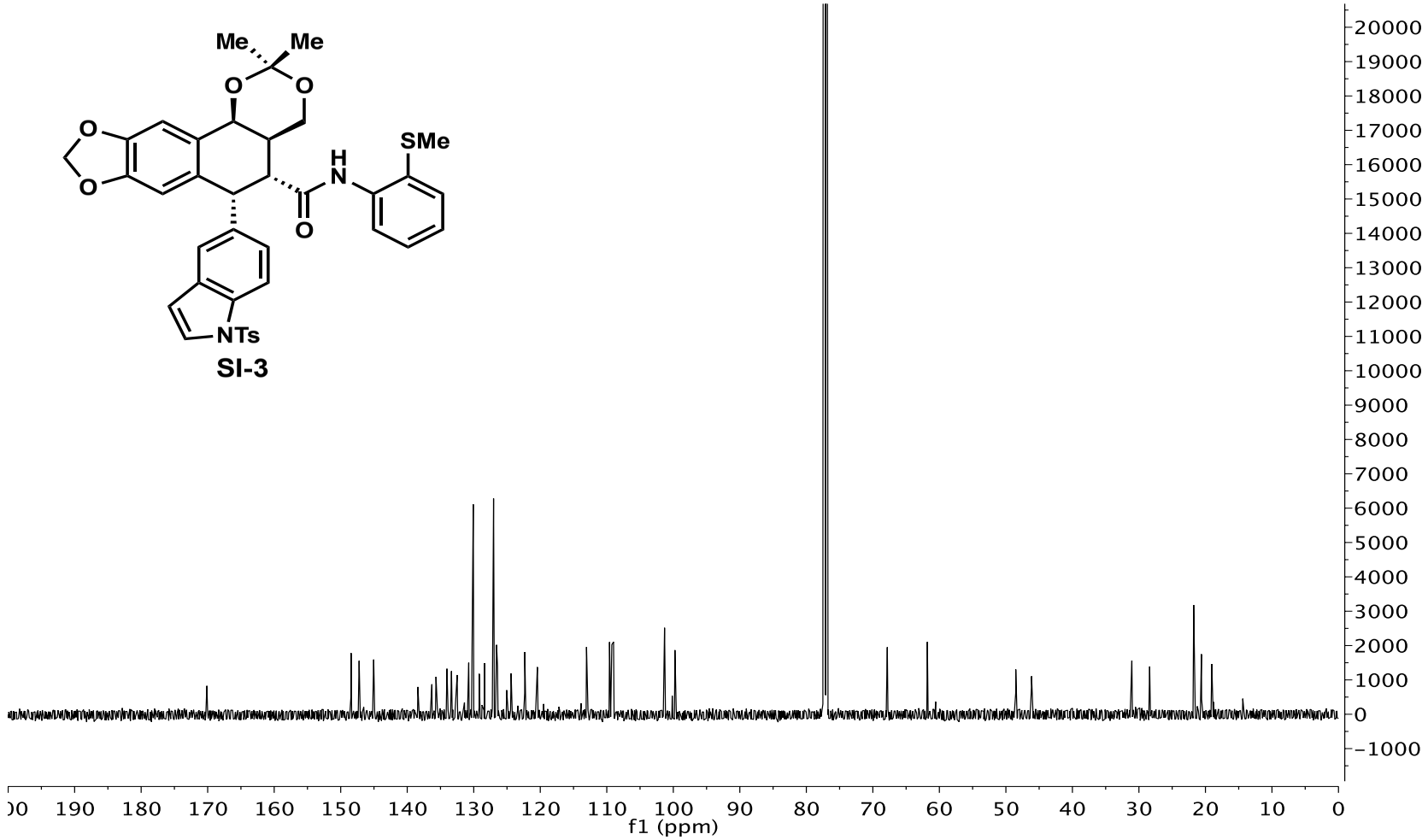

Me
Me
O
O
O
O
O
O
H
N
SMe
O

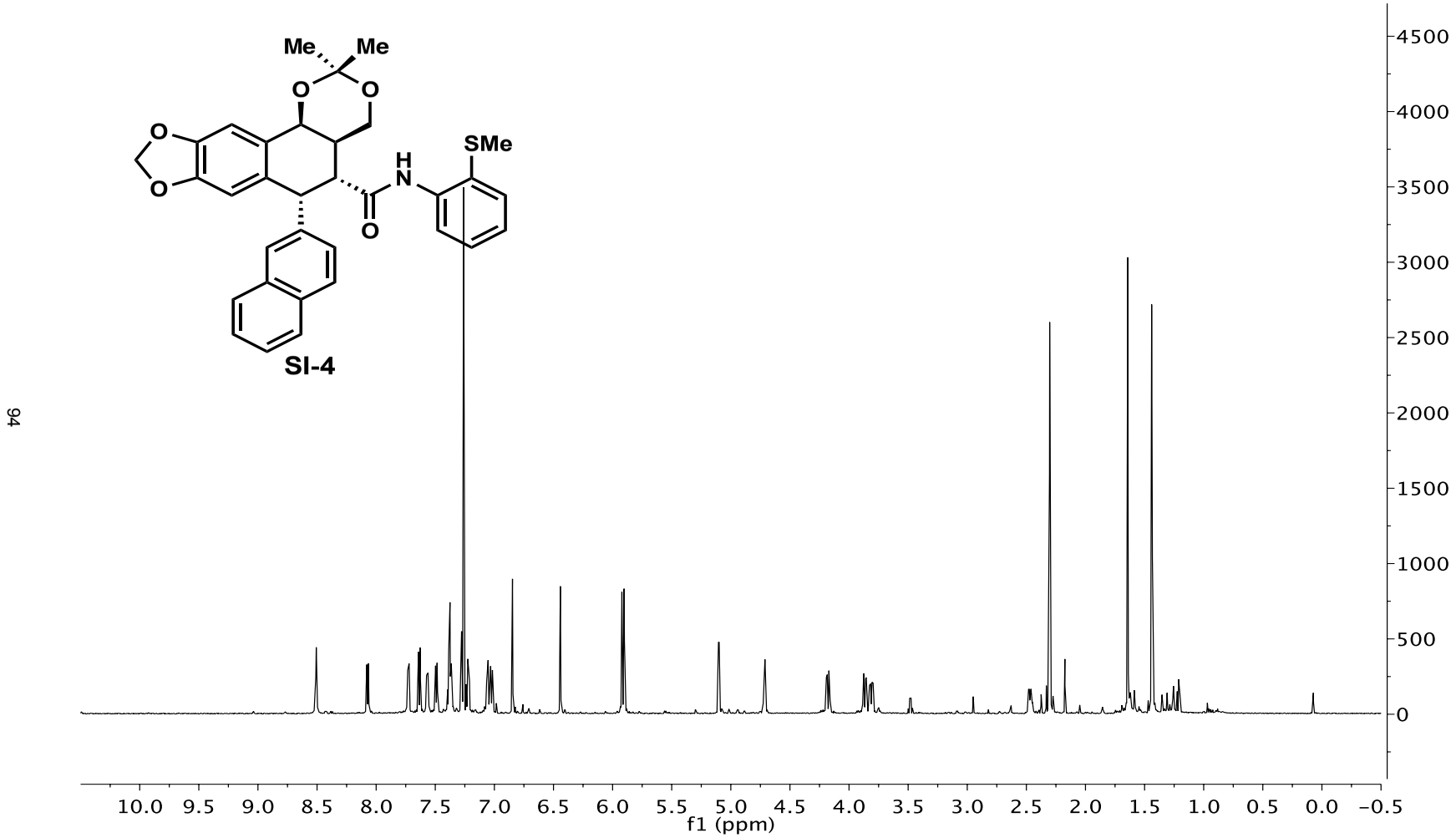
SI-2

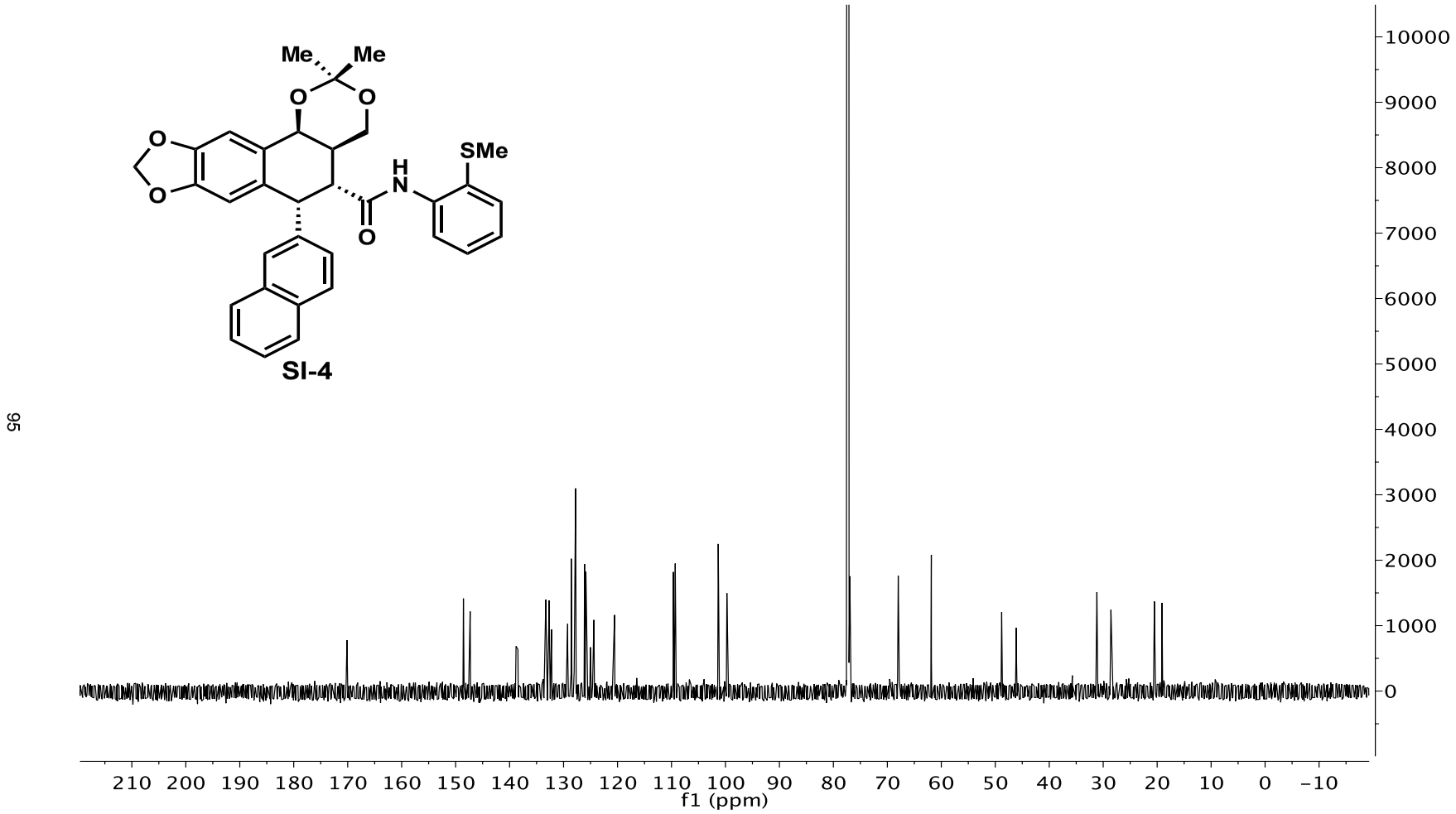
90
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

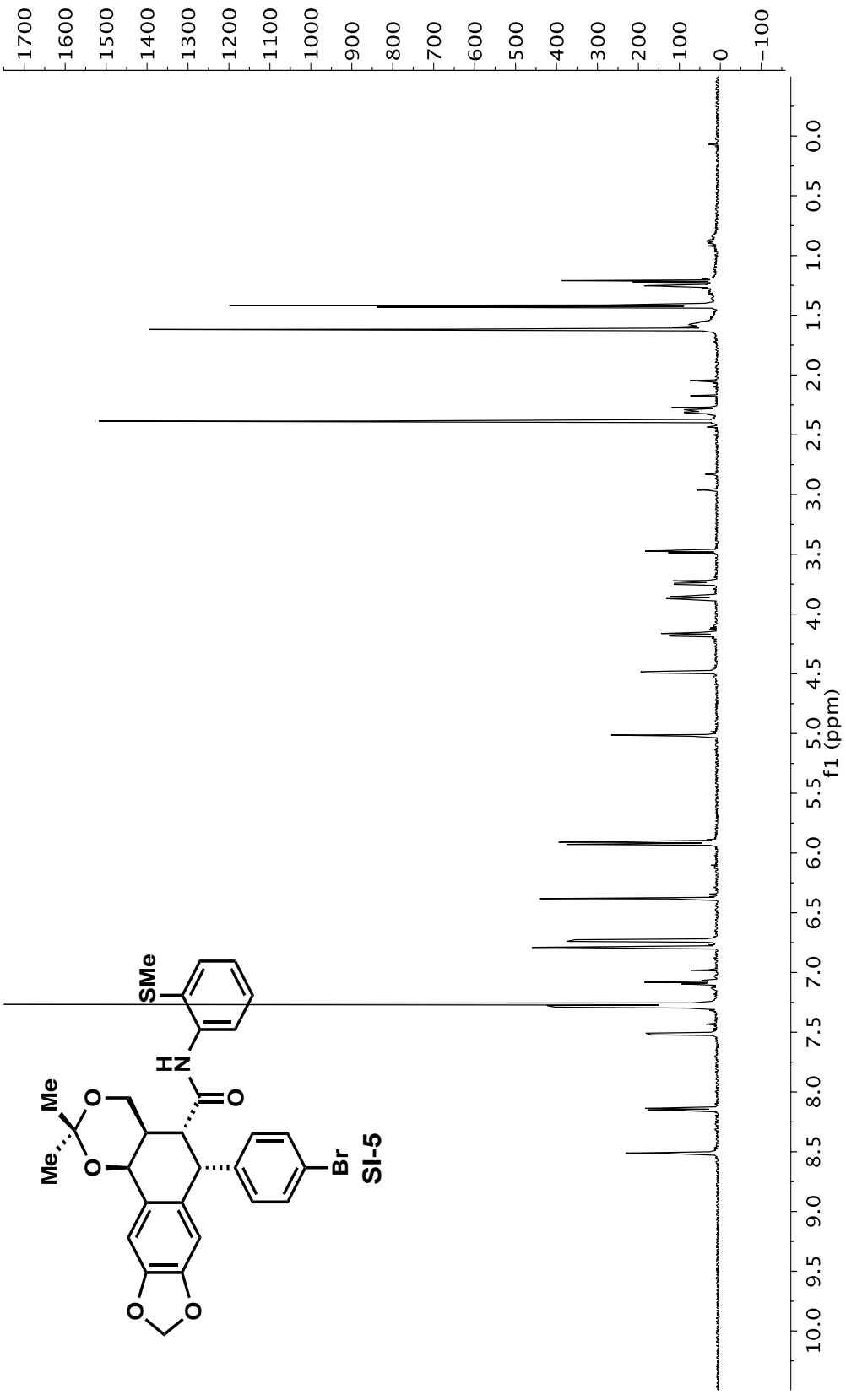

Me
Me
O
O
O
O
H
N
SMe
O
O
O
SI-2
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

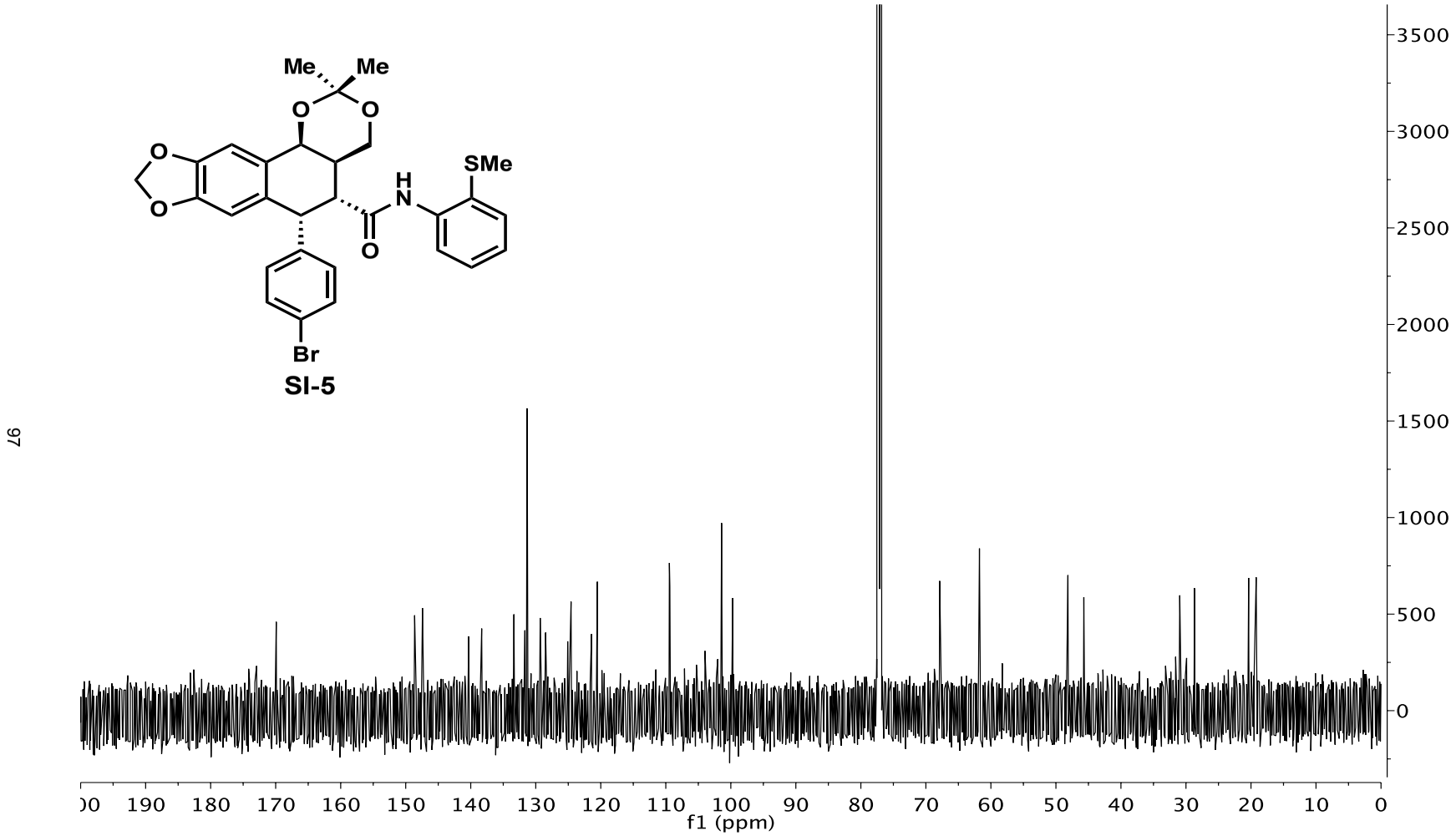

Me
Me
O
O
O
O
H
N
SMe
O
NTs
SI-3
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

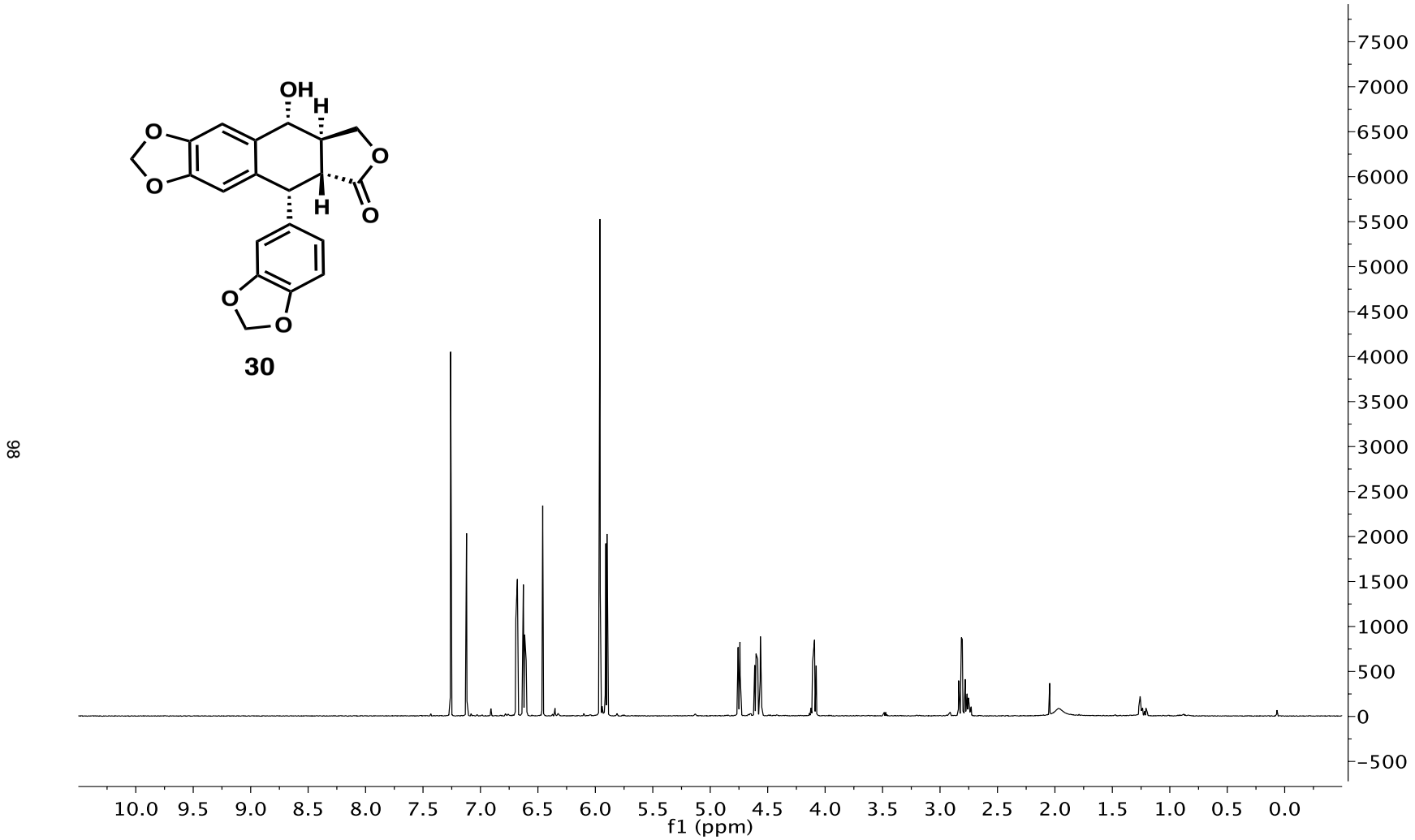

Me
Me
O
O
O
O
H
N
SMe
O
NTs
SI-3
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

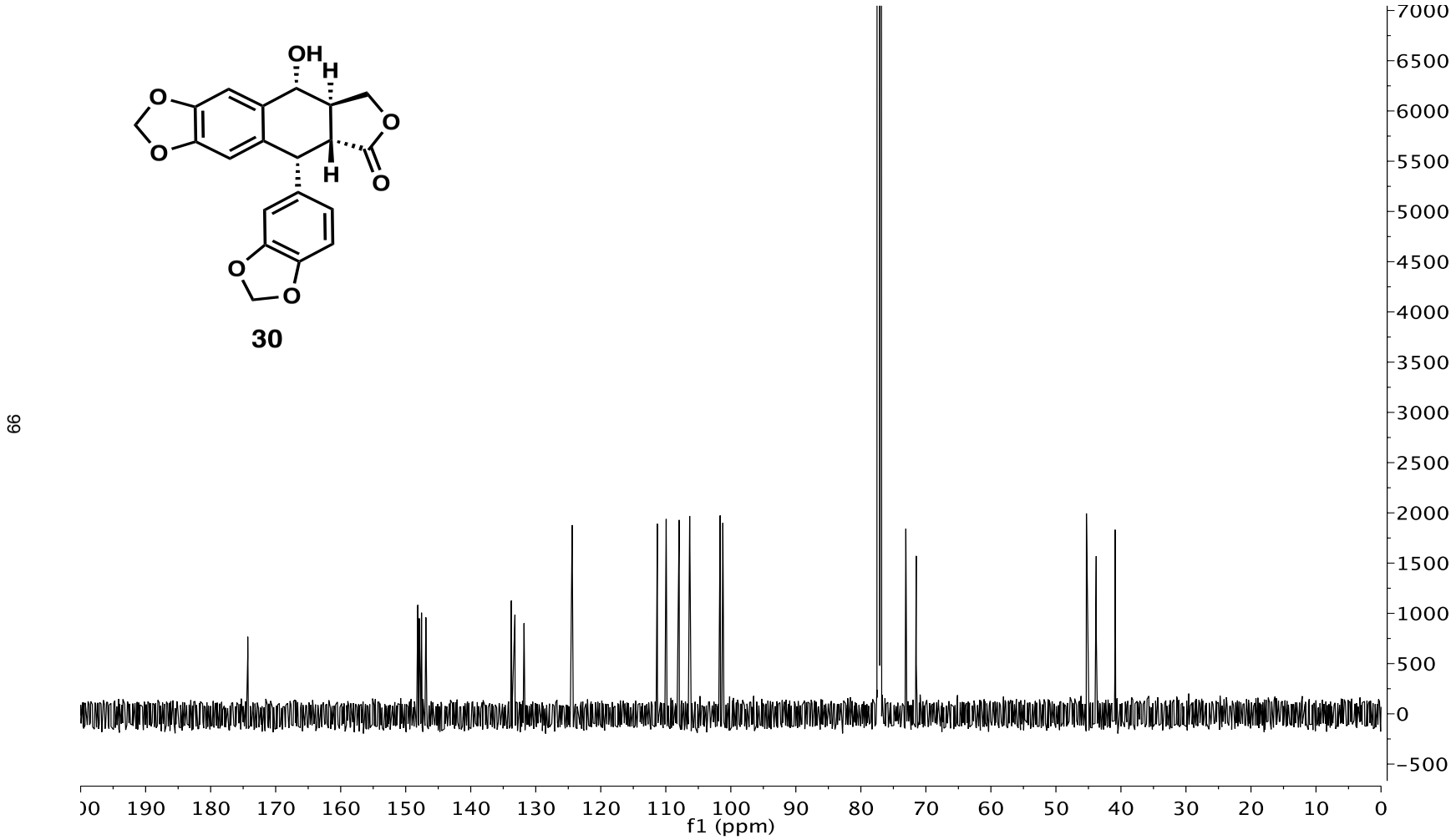

Me
Me
O
O
O
O
H
N
SMe
O
SI-4
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

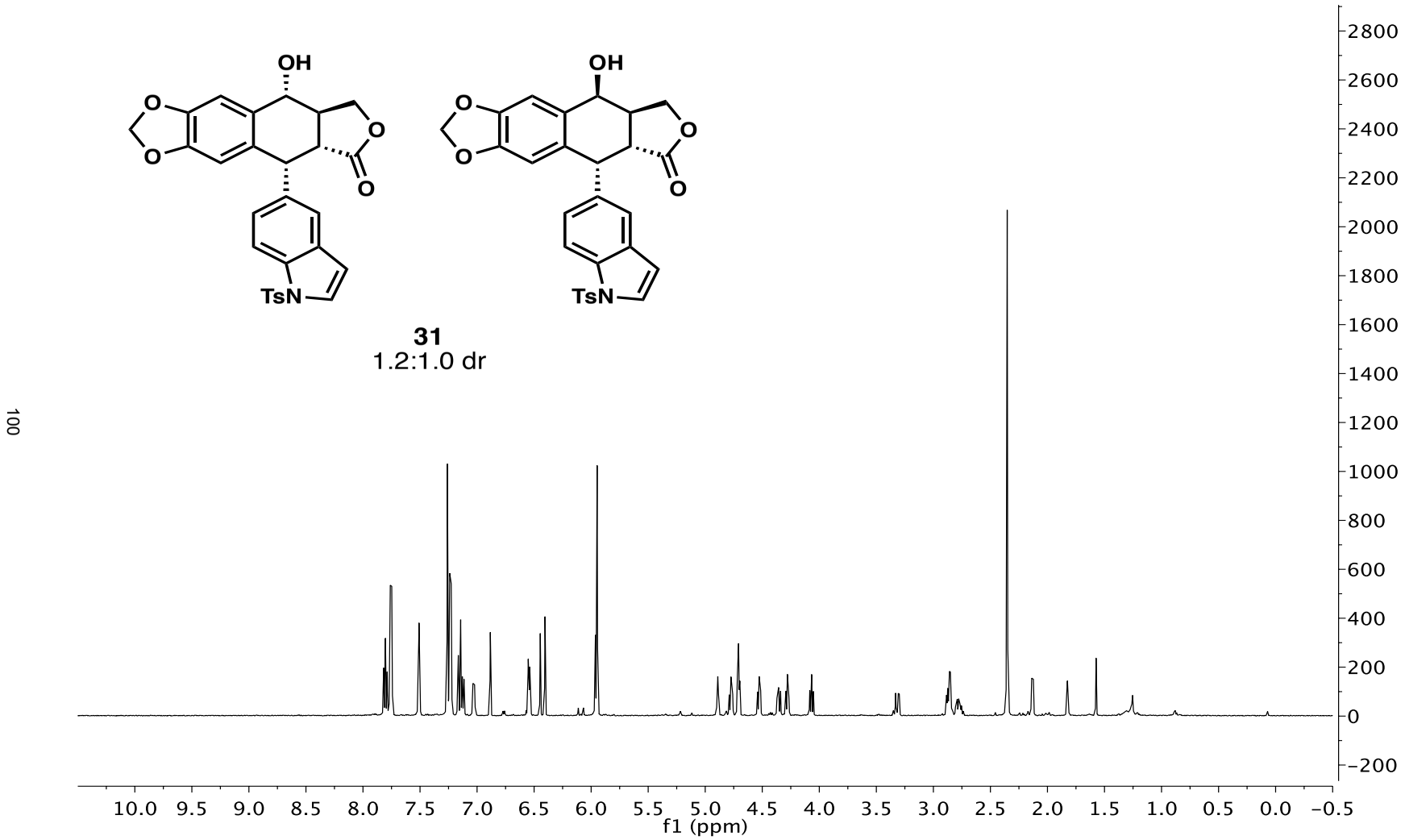

Me
Me
O
O
O
O
H
N
SMe
O
SI-4
96
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

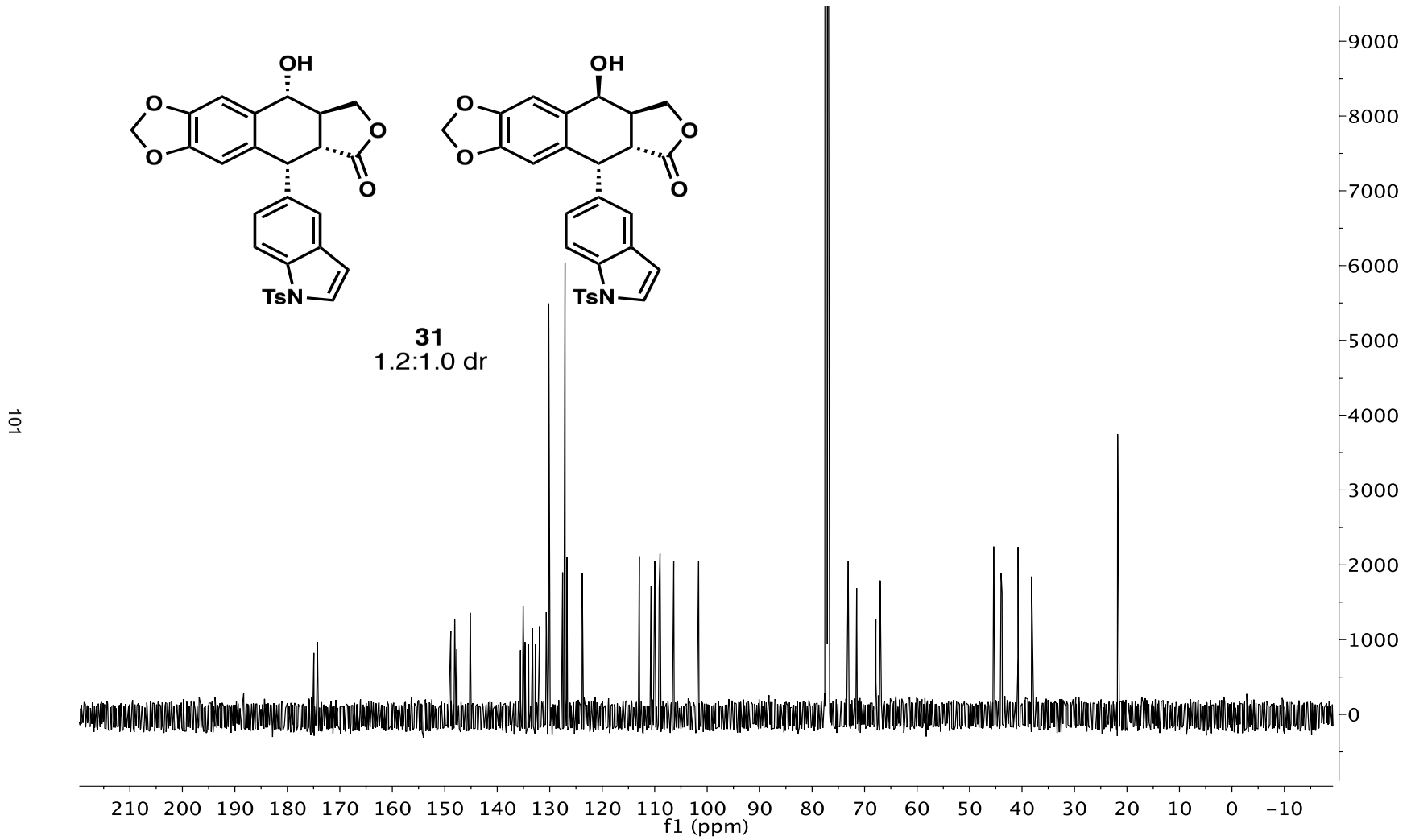

SMe
H
N
O
Me
Me
O
O
Br
SI-5
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

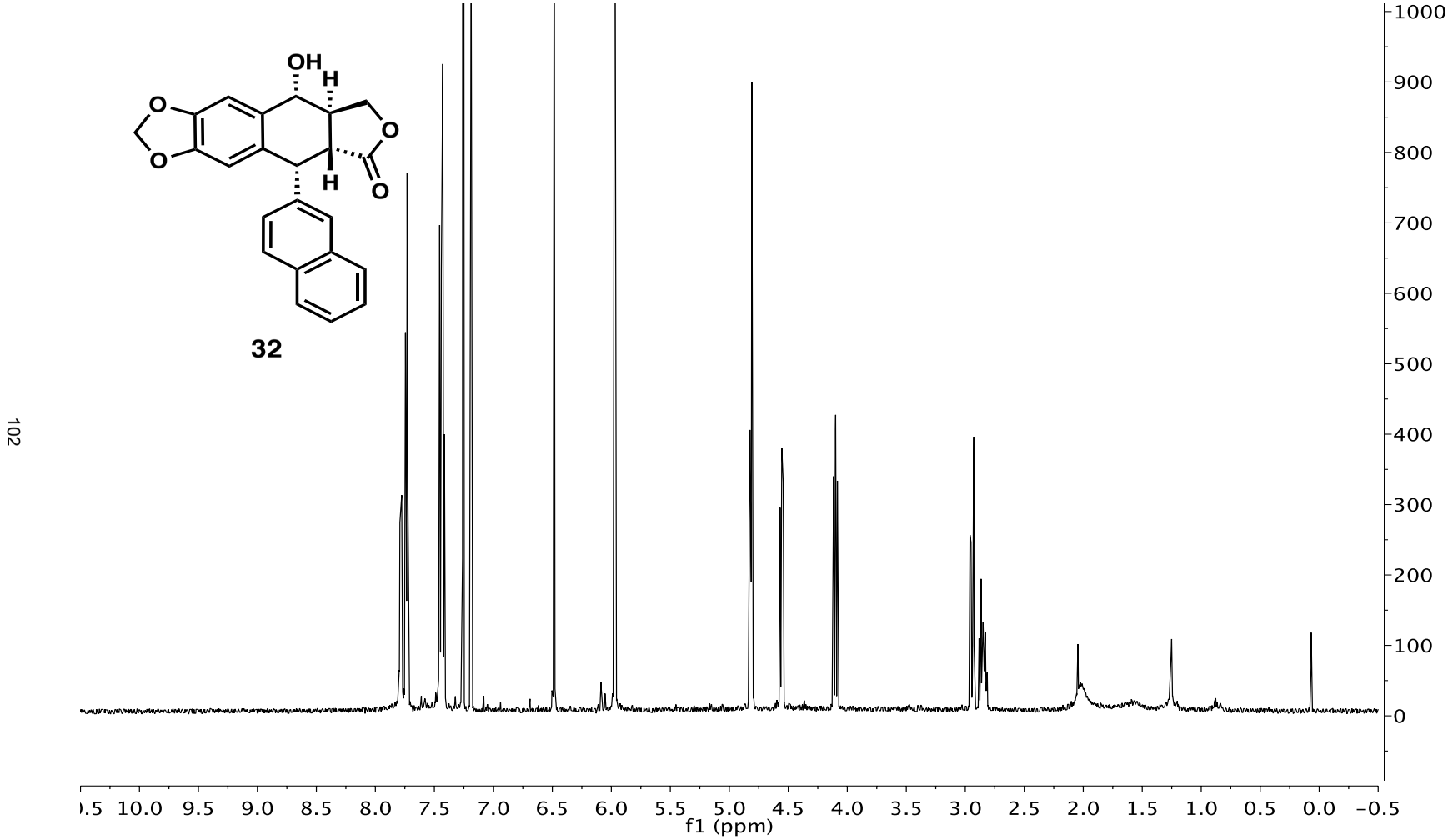

Me
Me
O
O
O
O
H
N
SMe
O
Br
SI-5
97
3500
3000
2500
2000
1500
1000
500
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

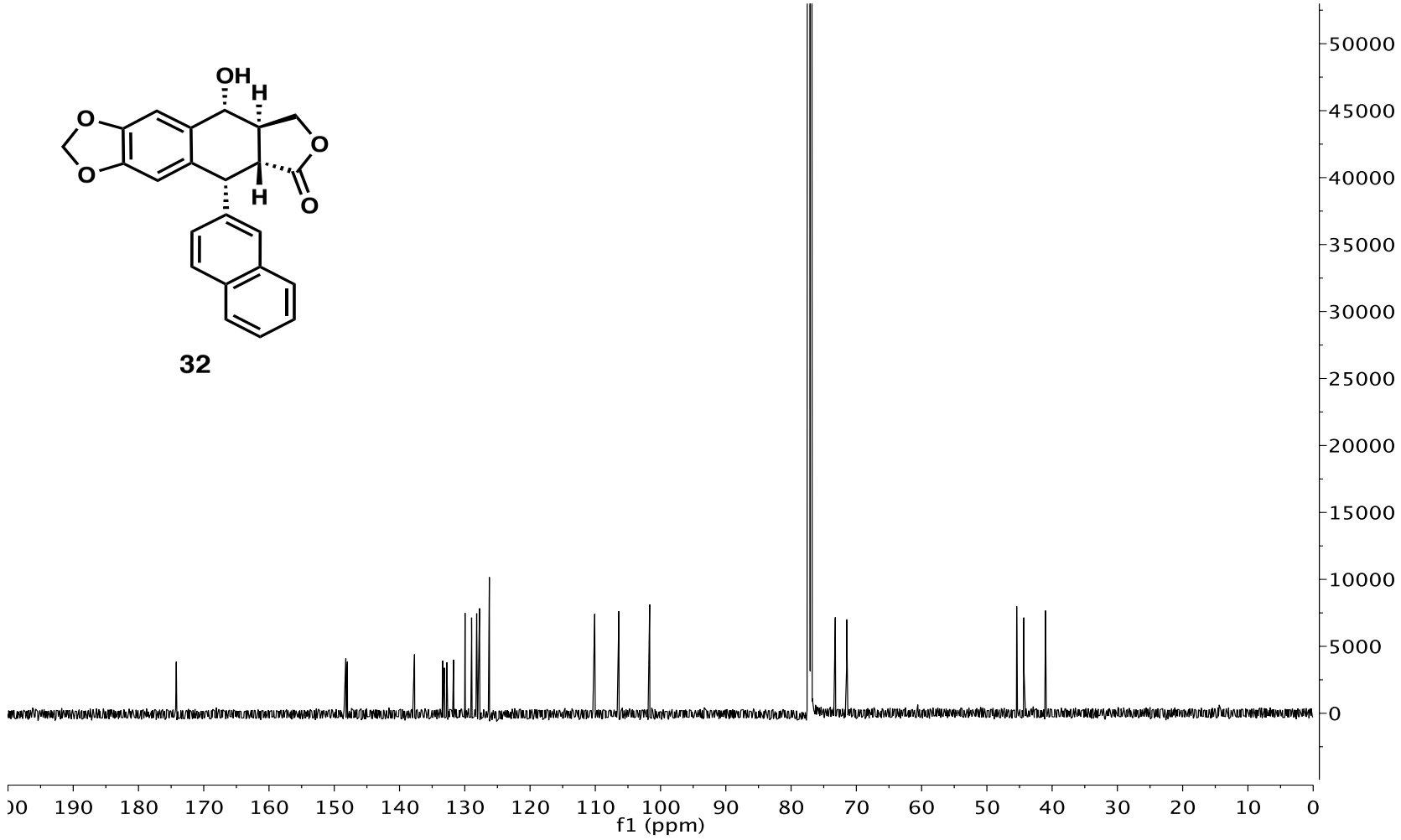

OH
H
O
O
O
O
H
O
O
30
98
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

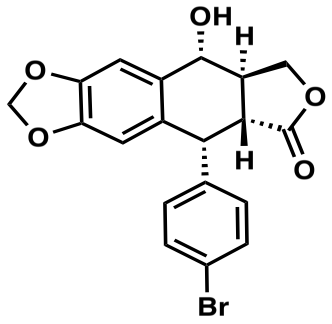

OH
H
O
O
O
O
H
O
O
30
99
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
O
O
O
O
TsN
OH
O
O
O
O
TsN
31
1.2:1.0 dr
100
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


OH
O
O
O
O
TsN
OH
O
O
O
O
TsN
31
1.2:1.0 dr
101
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


OH
H
O
O
O
O
H
32
1000
900
800
700
600
500
400
300
200
100
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


OH
H
O
O
O
O
H
32
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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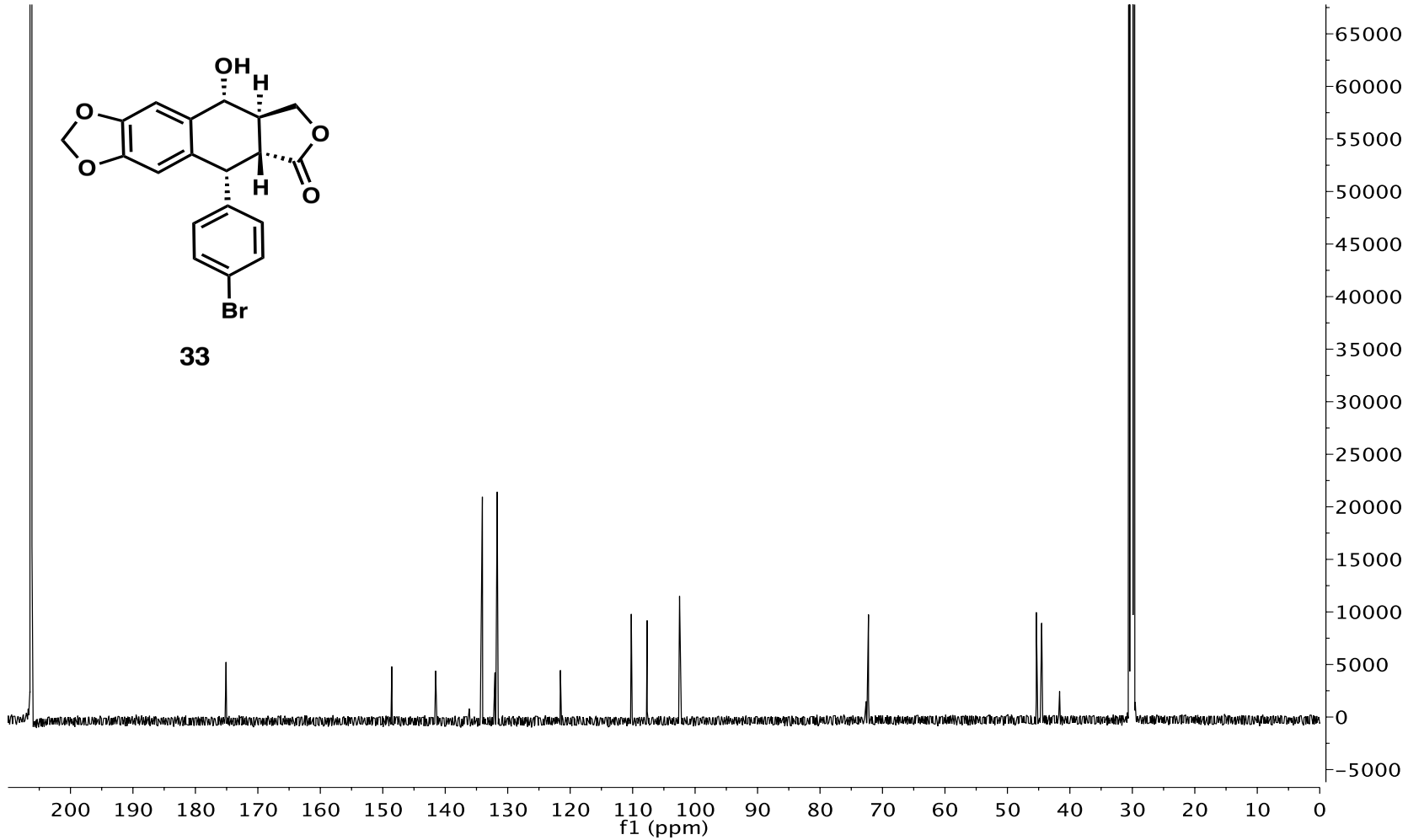
H
O
O
O
H
O
Br

33

2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)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H
O
O
O
H
O
Br
33
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
−5000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Crystal Structure Determination of Compound 16d

A colorless blade 0.060 x 0.040 x 0.030 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 1.0°. Data collection was 98.5% complete to 67.000° in θ. A total of 52236 reflections were collected covering the indices, -14<=*h*<=14, -8<=*k*<=8, -37<=*l*<=37. 5135 reflections were found to be symmetry independent, with an R_{int} of 0.0238. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/n (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2011) 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-2012). 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-2012.

Table 1. Crystal data and structure refinement for compound **16d**.

X-ray ID	Compound **16d**	
Sample/notebook ID	CT-01300	
Empirical formula	C27 H32 F5 N O7 Si	
Formula weight	605.62	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 12.4021(10) Å	α= 90°.
	b = 7.3403(6) Å	β= 91.142(2)°.
	c = 31.441(3) Å	γ = 90°.
Volume	2861.6(4) $Å^3$	
Z	4	
Density (calculated)	1.406 Mg/m^3	
Absorption coefficient	1.427 mm^{-1}	
F(000)	1264	
Crystal size	0.060 x 0.040 x 0.030 mm^3	
Crystal color/habit	colorless blade	
Theta range for data collection	2.811 to 68.227°.	
Index ranges	-14<=h<=14, -8<=k<=8, -37<=l<=37	
Reflections collected	52236	
Independent reflections	5135 [R(int) = 0.0238]	
Completeness to theta = 67.000°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.869	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5135 / 0 / 378	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma(I)]	R1 = 0.0312, wR2 = 0.0816	
R indices (all data)	R1 = 0.0316, wR2 = 0.0819	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.314 and -0.259 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **16d**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8073(1)	-157(2)	1832(1)	14(1)
C(2)	8083(1)	-1492(2)	1459(1)	14(1)
C(3)	7203(1)	-993(2)	1128(1)	14(1)
C(4)	6111(1)	-798(2)	1330(1)	15(1)
C(5)	5190(1)	-1002(2)	1064(1)	19(1)
C(6)	4212(1)	-651(2)	1239(1)	21(1)
C(7)	2498(1)	64(3)	1355(1)	36(1)
C(8)	4126(1)	-127(2)	1661(1)	21(1)
C(9)	4999(1)	35(2)	1929(1)	20(1)
C(10)	6019(1)	-320(2)	1757(1)	16(1)
C(11)	6985(1)	-253(2)	2057(1)	17(1)
C(12)	8945(1)	-617(2)	2162(1)	15(1)
C(13)	10205(1)	615(2)	2680(1)	17(1)
C(14)	9986(1)	-161(2)	3072(1)	20(1)
C(15)	10781(1)	-352(2)	3382(1)	26(1)
C(16)	11813(1)	238(2)	3303(1)	29(1)
C(17)	12052(1)	1034(2)	2919(1)	27(1)
C(18)	11247(1)	1224(2)	2612(1)	21(1)
C(19)	9181(1)	-1495(2)	1256(1)	16(1)
C(20)	10251(1)	-2805(2)	726(1)	23(1)
C(21)	7660(1)	-799(2)	81(1)	25(1)
C(22)	9193(1)	2114(2)	451(1)	25(1)
C(23)	6820(1)	3076(2)	260(1)	20(1)
C(24)	6788(1)	4563(2)	603(1)	25(1)
C(25)	7196(1)	3915(2)	-162(1)	29(1)
C(26)	5680(1)	2308(2)	194(1)	30(1)
C(27)	9745(1)	4151(2)	1608(1)	29(1)
N(1)	9395(1)	836(2)	2362(1)	16(1)
O(1)	3194(1)	-777(2)	1054(1)	31(1)
O(2)	3058(1)	119(2)	1757(1)	31(1)
O(3)	9178(1)	-2196(1)	2257(1)	18(1)

O(4)	9946(1)	-624(1)	1378(1)	22(1)
O(5)	9206(1)	-2614(1)	916(1)	18(1)
O(6)	7494(1)	701(1)	936(1)	16(1)
O(7)	9117(1)	4220(1)	1981(1)	24(1)
F(1)	8983(1)	-697(1)	3157(1)	26(1)
F(2)	10560(1)	-1082(1)	3761(1)	37(1)
F(3)	12589(1)	61(2)	3605(1)	42(1)
F(4)	13054(1)	1628(2)	2845(1)	38(1)
F(5)	11472(1)	2049(1)	2244(1)	28(1)
Si(1)	7779(1)	1221(1)	439(1)	16(1)

Table 3. Bond lengths [Å] and angles [°] for compound **16d.**

C(1)-C(12)	1.5211(17)	C(15)-F(2)	1.3396(17)
C(1)-C(2)	1.5286(17)	C(15)-C(16)	1.378(2)
C(1)-C(11)	1.5361(17)	C(16)-F(3)	1.3438(17)
C(1)-H(1)	1.0000	C(16)-C(17)	1.380(2)
C(2)-C(19)	1.5161(17)	C(17)-F(4)	1.3404(17)
C(2)-C(3)	1.5368(17)	C(17)-C(18)	1.382(2)
C(2)-H(2)	1.0000	C(18)-F(5)	1.3401(16)
C(3)-O(6)	1.4322(15)	C(19)-O(4)	1.2010(17)
C(3)-C(4)	1.5138(17)	C(19)-O(5)	1.3474(16)
C(3)-H(3)	1.0000	C(20)-O(5)	1.4457(15)
C(4)-C(10)	1.3951(18)	C(20)-H(20A)	0.9800
C(4)-C(5)	1.4091(19)	C(20)-H(20B)	0.9800
C(5)-C(6)	1.366(2)	C(20)-H(20C)	0.9800
C(5)-H(5)	0.9500	C(21)-Si(1)	1.8665(14)
C(6)-O(1)	1.3826(17)	C(21)-H(21A)	0.9800
C(6)-C(8)	1.388(2)	C(21)-H(21B)	0.9800
C(7)-O(2)	1.430(2)	C(21)-H(21C)	0.9800
C(7)-O(1)	1.4336(19)	C(22)-Si(1)	1.8722(15)
C(7)-H(7A)	0.9900	C(22)-H(22A)	0.9800
C(7)-H(7B)	0.9900	C(22)-H(22B)	0.9800
C(8)-C(9)	1.363(2)	C(22)-H(22C)	0.9800
C(8)-O(2)	1.3761(16)	C(23)-C(26)	1.532(2)
C(9)-C(10)	1.4104(18)	C(23)-C(24)	1.5355(19)
C(9)-H(9)	0.9500	C(23)-C(25)	1.5421(19)
C(10)-C(11)	1.5103(18)	C(23)-Si(1)	1.8865(14)
C(11)-H(11A)	0.9900	C(24)-H(24A)	0.9800
C(11)-H(11B)	0.9900	C(24)-H(24B)	0.9800
C(12)-O(3)	1.2301(16)	C(24)-H(24C)	0.9800
C(12)-N(1)	1.3537(17)	C(25)-H(25A)	0.9800
C(13)-C(14)	1.3879(19)	C(25)-H(25B)	0.9800
C(13)-C(18)	1.3878(19)	C(25)-H(25C)	0.9800
C(13)-N(1)	1.4125(17)	C(26)-H(26A)	0.9800
C(14)-F(1)	1.3370(16)	C(26)-H(26B)	0.9800
C(14)-C(15)	1.381(2)	C(26)-H(26C)	0.9800

C(27)-O(7)	1.4221(18)	N(1)-H(1A)	0.8800
C(27)-H(27A)	0.9800	O(6)-Si(1)	1.6534(9)
C(27)-H(27B)	0.9800	O(7)-H(7)	0.8400
C(27)-H(27C)	0.9800		

C(12)-C(1)-C(2)	111.33(10)	O(1)-C(7)-H(7B)	110.1
C(12)-C(1)-C(11)	107.17(10)	H(7A)-C(7)-H(7B)	108.4
C(2)-C(1)-C(11)	110.10(10)	C(9)-C(8)-O(2)	127.61(13)
C(12)-C(1)-H(1)	109.4	C(9)-C(8)-C(6)	122.57(13)
C(2)-C(1)-H(1)	109.4	O(2)-C(8)-C(6)	109.78(12)
C(11)-C(1)-H(1)	109.4	C(8)-C(9)-C(10)	117.13(12)
C(19)-C(2)-C(1)	110.21(10)	C(8)-C(9)-H(9)	121.4
C(19)-C(2)-C(3)	110.23(10)	C(10)-C(9)-H(9)	121.4
C(1)-C(2)-C(3)	110.50(10)	C(4)-C(10)-C(9)	120.41(12)
C(19)-C(2)-H(2)	108.6	C(4)-C(10)-C(11)	122.02(11)
C(1)-C(2)-H(2)	108.6	C(9)-C(10)-C(11)	117.50(11)
C(3)-C(2)-H(2)	108.6	C(10)-C(11)-C(1)	114.04(10)
O(6)-C(3)-C(4)	109.25(10)	C(10)-C(11)-H(11A)	108.7
O(6)-C(3)-C(2)	108.14(10)	C(1)-C(11)-H(11A)	108.7
C(4)-C(3)-C(2)	111.59(10)	C(10)-C(11)-H(11B)	108.7
O(6)-C(3)-H(3)	109.3	C(1)-C(11)-H(11B)	108.7
C(4)-C(3)-H(3)	109.3	H(11A)-C(11)-H(11B)	107.6
C(2)-C(3)-H(3)	109.3	O(3)-C(12)-N(1)	122.45(12)
C(10)-C(4)-C(5)	121.07(12)	O(3)-C(12)-C(1)	122.39(11)
C(10)-C(4)-C(3)	121.18(11)	N(1)-C(12)-C(1)	115.02(11)
C(5)-C(4)-C(3)	117.64(11)	C(14)-C(13)-C(18)	117.94(12)
C(6)-C(5)-C(4)	117.23(12)	C(14)-C(13)-N(1)	121.72(12)
C(6)-C(5)-H(5)	121.4	C(18)-C(13)-N(1)	120.32(12)
C(4)-C(5)-H(5)	121.4	F(1)-C(14)-C(15)	118.89(12)
C(5)-C(6)-O(1)	128.94(13)	F(1)-C(14)-C(13)	119.88(12)
C(5)-C(6)-C(8)	121.54(13)	C(15)-C(14)-C(13)	121.21(13)
O(1)-C(6)-C(8)	109.50(12)	F(2)-C(15)-C(16)	119.57(13)
O(2)-C(7)-O(1)	107.90(12)	F(2)-C(15)-C(14)	120.80(14)
O(2)-C(7)-H(7A)	110.1	C(16)-C(15)-C(14)	119.62(14)
O(1)-C(7)-H(7A)	110.1	F(3)-C(16)-C(15)	119.80(14)
O(2)-C(7)-H(7B)	110.1	F(3)-C(16)-C(17)	119.73(14)

C(15)-C(16)-C(17)	120.46(13)	H(24A)-C(24)-H(24B)	109.5
F(4)-C(17)-C(16)	120.29(13)	C(23)-C(24)-H(24C)	109.5
F(4)-C(17)-C(18)	120.43(14)	H(24A)-C(24)-H(24C)	109.5
C(16)-C(17)-C(18)	119.27(14)	H(24B)-C(24)-H(24C)	109.5
F(5)-C(18)-C(17)	119.18(13)	C(23)-C(25)-H(25A)	109.5
F(5)-C(18)-C(13)	119.32(12)	C(23)-C(25)-H(25B)	109.5
C(17)-C(18)-C(13)	121.48(13)	H(25A)-C(25)-H(25B)	109.5
O(4)-C(19)-O(5)	123.18(11)	C(23)-C(25)-H(25C)	109.5
O(4)-C(19)-C(2)	125.10(12)	H(25A)-C(25)-H(25C)	109.5
O(5)-C(19)-C(2)	111.72(11)	H(25B)-C(25)-H(25C)	109.5
O(5)-C(20)-H(20A)	109.5	C(23)-C(26)-H(26A)	109.5
O(5)-C(20)-H(20B)	109.5	C(23)-C(26)-H(26B)	109.5
H(20A)-C(20)-H(20B)	109.5	H(26A)-C(26)-H(26B)	109.5
O(5)-C(20)-H(20C)	109.5	C(23)-C(26)-H(26C)	109.5
H(20A)-C(20)-H(20C)	109.5	H(26A)-C(26)-H(26C)	109.5
H(20B)-C(20)-H(20C)	109.5	H(26B)-C(26)-H(26C)	109.5
Si(1)-C(21)-H(21A)	109.5	O(7)-C(27)-H(27A)	109.5
Si(1)-C(21)-H(21B)	109.5	O(7)-C(27)-H(27B)	109.5
H(21A)-C(21)-H(21B)	109.5	H(27A)-C(27)-H(27B)	109.5
Si(1)-C(21)-H(21C)	109.5	O(7)-C(27)-H(27C)	109.5
H(21A)-C(21)-H(21C)	109.5	H(27A)-C(27)-H(27C)	109.5
H(21B)-C(21)-H(21C)	109.5	H(27B)-C(27)-H(27C)	109.5
Si(1)-C(22)-H(22A)	109.5	C(12)-N(1)-C(13)	121.31(11)
Si(1)-C(22)-H(22B)	109.5	C(12)-N(1)-H(1A)	119.3
H(22A)-C(22)-H(22B)	109.5	C(13)-N(1)-H(1A)	119.3
Si(1)-C(22)-H(22C)	109.5	C(6)-O(1)-C(7)	104.49(11)
H(22A)-C(22)-H(22C)	109.5	C(8)-O(2)-C(7)	104.80(11)
H(22B)-C(22)-H(22C)	109.5	C(19)-O(5)-C(20)	115.00(10)
C(26)-C(23)-C(24)	108.74(12)	C(3)-O(6)-Si(1)	131.28(8)
C(26)-C(23)-C(25)	108.93(12)	C(27)-O(7)-H(7)	109.5
C(24)-C(23)-C(25)	109.39(12)	O(6)-Si(1)-C(21)	111.79(6)
C(26)-C(23)-Si(1)	110.47(9)	O(6)-Si(1)-C(22)	106.17(6)
C(24)-C(23)-Si(1)	109.16(9)	C(21)-Si(1)-C(22)	110.69(7)
C(25)-C(23)-Si(1)	110.13(10)	O(6)-Si(1)-C(23)	107.65(5)
C(23)-C(24)-H(24A)	109.5	C(21)-Si(1)-C(23)	110.60(6)
C(23)-C(24)-H(24B)	109.5	C(22)-Si(1)-C(23)	109.81(7)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for compound **16d**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	14(1)	15(1)	14(1)	0(1)	0(1)	0(1)
C(2)	12(1)	15(1)	14(1)	0(1)	0(1)	0(1)
C(3)	15(1)	14(1)	14(1)	0(1)	0(1)	-1(1)
C(4)	14(1)	14(1)	18(1)	0(1)	0(1)	0(1)
C(5)	18(1)	20(1)	20(1)	-4(1)	-2(1)	-1(1)
C(6)	14(1)	23(1)	27(1)	-4(1)	-6(1)	-1(1)
C(7)	15(1)	49(1)	45(1)	-18(1)	-5(1)	6(1)
C(8)	12(1)	22(1)	29(1)	-4(1)	3(1)	0(1)
C(9)	18(1)	21(1)	20(1)	-3(1)	3(1)	-1(1)
C(10)	15(1)	15(1)	18(1)	0(1)	0(1)	0(1)
C(11)	14(1)	23(1)	14(1)	-2(1)	1(1)	1(1)
C(12)	13(1)	18(1)	13(1)	0(1)	2(1)	0(1)
C(13)	17(1)	16(1)	19(1)	-4(1)	-3(1)	2(1)
C(14)	20(1)	20(1)	22(1)	-2(1)	-2(1)	-2(1)
C(15)	32(1)	26(1)	20(1)	1(1)	-7(1)	2(1)
C(16)	26(1)	30(1)	30(1)	-3(1)	-14(1)	4(1)
C(17)	15(1)	30(1)	36(1)	-6(1)	-5(1)	1(1)
C(18)	20(1)	21(1)	22(1)	-2(1)	1(1)	2(1)
C(19)	16(1)	17(1)	14(1)	2(1)	-1(1)	3(1)
C(20)	20(1)	28(1)	22(1)	-1(1)	9(1)	3(1)
C(21)	37(1)	21(1)	17(1)	-2(1)	0(1)	3(1)
C(22)	23(1)	31(1)	22(1)	5(1)	3(1)	-3(1)
C(23)	23(1)	17(1)	19(1)	0(1)	-4(1)	0(1)
C(24)	28(1)	20(1)	27(1)	-4(1)	-2(1)	4(1)
C(25)	42(1)	24(1)	22(1)	5(1)	-1(1)	3(1)
C(26)	27(1)	23(1)	40(1)	4(1)	-14(1)	0(1)
C(27)	39(1)	25(1)	24(1)	3(1)	6(1)	2(1)
N(1)	15(1)	15(1)	17(1)	0(1)	-4(1)	1(1)
O(1)	12(1)	45(1)	37(1)	-16(1)	-6(1)	2(1)
O(2)	11(1)	45(1)	38(1)	-14(1)	2(1)	2(1)
O(3)	20(1)	15(1)	18(1)	1(1)	-3(1)	1(1)

O(4)	14(1)	27(1)	24(1)	-4(1)	1(1)	-2(1)
O(5)	16(1)	23(1)	16(1)	-2(1)	3(1)	1(1)
O(6)	18(1)	16(1)	14(1)	1(1)	0(1)	-1(1)
O(7)	34(1)	16(1)	22(1)	0(1)	5(1)	1(1)
F(1)	23(1)	33(1)	23(1)	5(1)	-1(1)	-7(1)
F(2)	45(1)	44(1)	22(1)	10(1)	-10(1)	-3(1)
F(3)	32(1)	54(1)	40(1)	0(1)	-24(1)	3(1)
F(4)	13(1)	51(1)	51(1)	-2(1)	-5(1)	-3(1)
F(5)	20(1)	36(1)	27(1)	3(1)	4(1)	-2(1)
Si(1)	18(1)	16(1)	13(1)	0(1)	0(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **16d**.

	x	y	z	U(eq)
H(1)	8189	1108	1724	17
H(2)	7933	-2743	1569	17
H(3)	7164	-1962	905	17
H(5)	5246	-1369	776	23
H(7A)	2309	1313	1262	44
H(7B)	1823	-647	1379	44
H(9)	4923	372	2218	23
H(11A)	6980	-1350	2240	21
H(11B)	6918	824	2244	21
H(20A)	10499	-1612	628	35
H(20B)	10196	-3643	483	35
H(20C)	10767	-3291	937	35
H(21A)	8210	-1701	162	37
H(21B)	7767	-418	-214	37
H(21C)	6942	-1340	106	37
H(22A)	9200	3354	567	38
H(22B)	9474	2127	162	38
H(22C)	9647	1327	632	38
H(24A)	6289	5528	512	38
H(24B)	7512	5077	645	38
H(24C)	6545	4034	870	38
H(25A)	7231	2962	-379	44
H(25B)	7913	4456	-119	44
H(25C)	6685	4859	-254	44
H(26A)	5429	1791	461	45
H(26B)	5690	1354	-24	45
H(26C)	5192	3287	101	45
H(27A)	10328	5050	1630	43
H(27B)	9286	4427	1359	43
H(27C)	10054	2930	1578	43

H(1A)	9179	1941	2293	19
H(7)	9063	5305	2063	36

Crystal Structure Determination of Compound 19

A colorless prism 0.060 x 0.050 x 0.030 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 1.0°. Data collection was 97.4% complete to 67.000° in θ. A total of 21250 reflections were collected covering the indices, -13<=*h*<=13, -13<=*k*<=13, -15<=*l*<=14. 4740 reflections were found to be symmetry independent, with an R_{int} of 0.0214. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P -1 (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) 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-2013). 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-2013.

Table 1. Crystal data and structure refinement for compound **19**.

X-ray ID	Compound **19**	
Sample/notebook ID	PdCycle	
Empirical formula	C29 H32 N2 O6 Si	
Formula weight	532.65	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 10.9235(11) Å	α= 76.245(3)°.
	b = 11.3482(12) Å	β= 71.783(3)°.
	c = 12.5125(13) Å	γ = 65.804(3)°.
Volume	1333.1(2) $Å^3$	
Z	2	
Density (calculated)	1.327 Mg/m^3	
Absorption coefficient	1.165 mm^{-1}	
F(000)	564	
Crystal size	0.060 x 0.050 x 0.030 mm^3	
Crystal color/habit	colorless prism	
Theta range for data collection	3.749 to 68.276°.	
Index ranges	-13<=h<=13, -13<=k<=13, -15<=l<=14	
Reflections collected	21250	
Independent reflections	4740 [R(int) = 0.0214]	
Completeness to theta = 67.000°	97.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.884	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4740 / 0 / 349	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2sigma(I)]	R1 = 0.0317, wR2 = 0.0811	
R indices (all data)	R1 = 0.0329, wR2 = 0.0820	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.374 and -0.314 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **19**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7241(1)	-65(1)	2262(1)	16(1)
C(2)	6668(1)	-1141(1)	2711(1)	16(1)
C(3)	7561(1)	-2451(1)	2661(1)	18(1)
C(4)	6971(1)	-3380(1)	3053(1)	18(1)
C(5)	6517(2)	-5212(1)	3477(2)	30(1)
C(6)	5559(1)	-3059(1)	3489(1)	19(1)
C(7)	4665(1)	-1795(1)	3552(1)	18(1)
C(8)	5242(1)	-820(1)	3141(1)	16(1)
C(9)	4283(1)	586(1)	3191(1)	16(1)
C(10)	4945(1)	1340(1)	3553(1)	16(1)
C(11)	6321(1)	1270(1)	2716(1)	17(1)
C(12)	7487(1)	1048(1)	3257(1)	18(1)
C(13)	3125(2)	29(1)	834(1)	26(1)
C(14)	1176(1)	1373(1)	2879(1)	26(1)
C(15)	2251(1)	3005(1)	732(1)	21(1)
C(16)	3542(2)	3070(2)	-194(1)	33(1)
C(17)	1713(2)	4115(1)	1457(1)	30(1)
C(18)	1116(2)	3163(1)	169(1)	27(1)
C(19)	3965(1)	2735(1)	3676(1)	18(1)
C(20)	1700(2)	4006(1)	4589(1)	28(1)
C(21)	9558(1)	-1057(1)	3002(1)	17(1)
C(22)	9826(1)	-1326(1)	4051(1)	21(1)
C(23)	11099(1)	-2257(1)	4246(1)	24(1)
C(24)	12080(1)	-2925(1)	3389(1)	24(1)
C(25)	11846(1)	-2657(1)	2291(1)	21(1)
C(26)	12840(1)	-3278(1)	1362(1)	26(1)
C(27)	12565(2)	-2921(1)	318(1)	28(1)
C(28)	11282(2)	-1942(1)	192(1)	25(1)
C(29)	10580(1)	-1698(1)	2080(1)	18(1)
N(1)	8285(1)	-104(1)	2826(1)	16(1)
N(2)	10305(1)	-1351(1)	1033(1)	21(1)

O(1)	7616(1)	-4714(1)	3110(1)	25(1)
O(2)	5255(1)	-4174(1)	3846(1)	26(1)
O(3)	4006(1)	1229(1)	2116(1)	17(1)
O(4)	4215(1)	3700(1)	3220(1)	26(1)
O(5)	2755(1)	2744(1)	4386(1)	24(1)
O(6)	7664(1)	1619(1)	3866(1)	25(1)
Si(1)	2670(1)	1384(1)	1652(1)	16(1)

Table 3. Bond lengths [Å] and angles [°] for compound **19**.

C(1)-N(1)	1.4995(15)	C(14)-H(14A)	0.9800
C(1)-C(2)	1.5086(17)	C(14)-H(14B)	0.9800
C(1)-C(11)	1.5601(17)	C(14)-H(14C)	0.9800
C(1)-H(1)	1.0000	C(15)-C(16)	1.536(2)
C(2)-C(8)	1.3981(18)	C(15)-C(17)	1.5364(19)
C(2)-C(3)	1.4080(17)	C(15)-C(18)	1.5387(17)
C(3)-C(4)	1.3718(18)	C(15)-Si(1)	1.8843(13)
C(3)-H(3)	0.9500	C(16)-H(16A)	0.9800
C(4)-O(1)	1.3783(15)	C(16)-H(16B)	0.9800
C(4)-C(6)	1.3850(19)	C(16)-H(16C)	0.9800
C(5)-O(2)	1.4252(17)	C(17)-H(17A)	0.9800
C(5)-O(1)	1.4349(17)	C(17)-H(17B)	0.9800
C(5)-H(5A)	0.9900	C(17)-H(17C)	0.9800
C(5)-H(5B)	0.9900	C(18)-H(18A)	0.9800
C(6)-C(7)	1.3698(18)	C(18)-H(18B)	0.9800
C(6)-O(2)	1.3760(15)	C(18)-H(18C)	0.9800
C(7)-C(8)	1.4076(18)	C(19)-O(4)	1.2045(16)
C(7)-H(7)	0.9500	C(19)-O(5)	1.3401(16)
C(8)-C(9)	1.5117(16)	C(20)-O(5)	1.4426(15)
C(9)-O(3)	1.4285(15)	C(20)-H(20A)	0.9800
C(9)-C(10)	1.5350(16)	C(20)-H(20B)	0.9800
C(9)-H(9)	1.0000	C(20)-H(20C)	0.9800
C(10)-C(19)	1.5161(17)	C(21)-C(22)	1.3698(19)
C(10)-C(11)	1.5233(18)	C(21)-N(1)	1.4131(16)
C(10)-H(10)	1.0000	C(21)-C(29)	1.4261(18)
C(11)-C(12)	1.5296(16)	C(22)-C(23)	1.4126(18)
C(11)-H(11)	1.0000	C(22)-H(22)	0.9500
C(12)-O(6)	1.2117(16)	C(23)-C(24)	1.369(2)
C(12)-N(1)	1.3665(16)	C(23)-H(23)	0.9500
C(13)-Si(1)	1.8605(14)	C(24)-C(25)	1.416(2)
C(13)-H(13A)	0.9800	C(24)-H(24)	0.9500
C(13)-H(13B)	0.9800	C(25)-C(26)	1.414(2)
C(13)-H(13C)	0.9800	C(25)-C(29)	1.4234(18)
C(14)-Si(1)	1.8598(14)	C(26)-C(27)	1.362(2)

C(26)-H(26)	0.9500	C(28)-H(28)	0.9500
C(27)-C(28)	1.415(2)	C(29)-N(2)	1.3657(17)
C(27)-H(27)	0.9500	O(3)-Si(1)	1.6646(9)
C(28)-N(2)	1.3190(18)		

N(1)-C(1)-C(2)	115.40(10)	O(3)-C(9)-C(10)	106.86(10)
N(1)-C(1)-C(11)	86.48(9)	C(8)-C(9)-C(10)	109.97(10)
C(2)-C(1)-C(11)	116.18(10)	O(3)-C(9)-H(9)	109.2
N(1)-C(1)-H(1)	112.2	C(8)-C(9)-H(9)	109.2
C(2)-C(1)-H(1)	112.2	C(10)-C(9)-H(9)	109.2
C(11)-C(1)-H(1)	112.2	C(19)-C(10)-C(11)	111.88(10)
C(8)-C(2)-C(3)	120.54(11)	C(19)-C(10)-C(9)	110.86(10)
C(8)-C(2)-C(1)	119.33(11)	C(11)-C(10)-C(9)	110.09(10)
C(3)-C(2)-C(1)	120.10(11)	C(19)-C(10)-H(10)	108.0
C(4)-C(3)-C(2)	117.22(11)	C(11)-C(10)-H(10)	108.0
C(4)-C(3)-H(3)	121.4	C(9)-C(10)-H(10)	108.0
C(2)-C(3)-H(3)	121.4	C(10)-C(11)-C(12)	114.86(11)
C(3)-C(4)-O(1)	128.32(12)	C(10)-C(11)-C(1)	116.24(10)
C(3)-C(4)-C(6)	122.07(12)	C(12)-C(11)-C(1)	86.17(9)
O(1)-C(4)-C(6)	109.59(11)	C(10)-C(11)-H(11)	112.4
O(2)-C(5)-O(1)	108.13(10)	C(12)-C(11)-H(11)	112.4
O(2)-C(5)-H(5A)	110.1	C(1)-C(11)-H(11)	112.4
O(1)-C(5)-H(5A)	110.1	O(6)-C(12)-N(1)	131.98(12)
O(2)-C(5)-H(5B)	110.1	O(6)-C(12)-C(11)	135.41(12)
O(1)-C(5)-H(5B)	110.1	N(1)-C(12)-C(11)	92.58(10)
H(5A)-C(5)-H(5B)	108.4	Si(1)-C(13)-H(13A)	109.5
C(7)-C(6)-O(2)	128.05(12)	Si(1)-C(13)-H(13B)	109.5
C(7)-C(6)-C(4)	122.03(12)	H(13A)-C(13)-H(13B)	109.5
O(2)-C(6)-C(4)	109.91(11)	Si(1)-C(13)-H(13C)	109.5
C(6)-C(7)-C(8)	117.07(12)	H(13A)-C(13)-H(13C)	109.5
C(6)-C(7)-H(7)	121.5	H(13B)-C(13)-H(13C)	109.5
C(8)-C(7)-H(7)	121.5	Si(1)-C(14)-H(14A)	109.5
C(2)-C(8)-C(7)	121.05(11)	Si(1)-C(14)-H(14B)	109.5
C(2)-C(8)-C(9)	120.53(11)	H(14A)-C(14)-H(14B)	109.5
C(7)-C(8)-C(9)	118.42(11)	Si(1)-C(14)-H(14C)	109.5
O(3)-C(9)-C(8)	112.35(10)	H(14A)-C(14)-H(14C)	109.5

H(14B)-C(14)-H(14C)	109.5	N(1)-C(21)-C(29)	120.03(11)
C(16)-C(15)-C(17)	109.68(12)	C(21)-C(22)-C(23)	120.95(13)
C(16)-C(15)-C(18)	109.16(12)	C(21)-C(22)-H(22)	119.5
C(17)-C(15)-C(18)	108.81(11)	C(23)-C(22)-H(22)	119.5
C(16)-C(15)-Si(1)	110.33(9)	C(24)-C(23)-C(22)	120.21(13)
C(17)-C(15)-Si(1)	110.16(9)	C(24)-C(23)-H(23)	119.9
C(18)-C(15)-Si(1)	108.67(9)	C(22)-C(23)-H(23)	119.9
C(15)-C(16)-H(16A)	109.5	C(23)-C(24)-C(25)	120.30(12)
C(15)-C(16)-H(16B)	109.5	C(23)-C(24)-H(24)	119.8
H(16A)-C(16)-H(16B)	109.5	C(25)-C(24)-H(24)	119.8
C(15)-C(16)-H(16C)	109.5	C(26)-C(25)-C(24)	122.90(12)
H(16A)-C(16)-H(16C)	109.5	C(26)-C(25)-C(29)	117.25(13)
H(16B)-C(16)-H(16C)	109.5	C(24)-C(25)-C(29)	119.82(13)
C(15)-C(17)-H(17A)	109.5	C(27)-C(26)-C(25)	119.42(13)
C(15)-C(17)-H(17B)	109.5	C(27)-C(26)-H(26)	120.3
H(17A)-C(17)-H(17B)	109.5	C(25)-C(26)-H(26)	120.3
C(15)-C(17)-H(17C)	109.5	C(26)-C(27)-C(28)	118.99(13)
H(17A)-C(17)-H(17C)	109.5	C(26)-C(27)-H(27)	120.5
H(17B)-C(17)-H(17C)	109.5	C(28)-C(27)-H(27)	120.5
C(15)-C(18)-H(18A)	109.5	N(2)-C(28)-C(27)	124.18(14)
C(15)-C(18)-H(18B)	109.5	N(2)-C(28)-H(28)	117.9
H(18A)-C(18)-H(18B)	109.5	C(27)-C(28)-H(28)	117.9
C(15)-C(18)-H(18C)	109.5	N(2)-C(29)-C(25)	123.04(12)
H(18A)-C(18)-H(18C)	109.5	N(2)-C(29)-C(21)	118.55(11)
H(18B)-C(18)-H(18C)	109.5	C(25)-C(29)-C(21)	118.41(12)
O(4)-C(19)-O(5)	124.19(12)	C(12)-N(1)-C(21)	131.17(11)
O(4)-C(19)-C(10)	126.24(12)	C(12)-N(1)-C(1)	94.74(9)
O(5)-C(19)-C(10)	109.57(11)	C(21)-N(1)-C(1)	133.57(10)
O(5)-C(20)-H(20A)	109.5	C(28)-N(2)-C(29)	117.09(12)
O(5)-C(20)-H(20B)	109.5	C(4)-O(1)-C(5)	105.38(10)
H(20A)-C(20)-H(20B)	109.5	C(6)-O(2)-C(5)	105.55(10)
O(5)-C(20)-H(20C)	109.5	C(9)-O(3)-Si(1)	126.19(8)
H(20A)-C(20)-H(20C)	109.5	C(19)-O(5)-C(20)	116.44(10)
H(20B)-C(20)-H(20C)	109.5	O(3)-Si(1)-C(14)	109.62(6)
C(22)-C(21)-N(1)	119.68(12)	O(3)-Si(1)-C(13)	110.80(6)
C(22)-C(21)-C(29)	120.25(12)	C(14)-Si(1)-C(13)	109.15(7)

O(3)-Si(1)-C(15)	105.36(5)
C(14)-Si(1)-C(15)	110.53(6)
C(13)-Si(1)-C(15)	111.32(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for compound **19**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	13(1)	18(1)	19(1)	0(1)	-7(1)	-6(1)
C(2)	17(1)	17(1)	16(1)	-1(1)	-7(1)	-7(1)
C(3)	15(1)	20(1)	21(1)	-3(1)	-6(1)	-6(1)
C(4)	19(1)	14(1)	23(1)	-1(1)	-9(1)	-4(1)
C(5)	23(1)	16(1)	50(1)	-3(1)	-6(1)	-7(1)
C(6)	20(1)	17(1)	22(1)	2(1)	-9(1)	-10(1)
C(7)	16(1)	18(1)	21(1)	0(1)	-7(1)	-7(1)
C(8)	17(1)	16(1)	16(1)	0(1)	-7(1)	-6(1)
C(9)	14(1)	16(1)	18(1)	1(1)	-6(1)	-6(1)
C(10)	15(1)	15(1)	20(1)	0(1)	-7(1)	-6(1)
C(11)	16(1)	15(1)	21(1)	1(1)	-7(1)	-7(1)
C(12)	15(1)	17(1)	23(1)	1(1)	-5(1)	-9(1)
C(13)	26(1)	24(1)	32(1)	-6(1)	-9(1)	-11(1)
C(14)	18(1)	33(1)	26(1)	1(1)	-6(1)	-13(1)
C(15)	19(1)	20(1)	24(1)	2(1)	-11(1)	-7(1)
C(16)	28(1)	34(1)	33(1)	12(1)	-11(1)	-15(1)
C(17)	37(1)	18(1)	38(1)	1(1)	-22(1)	-8(1)
C(18)	25(1)	27(1)	30(1)	-1(1)	-15(1)	-5(1)
C(19)	18(1)	19(1)	22(1)	-2(1)	-9(1)	-7(1)
C(20)	22(1)	20(1)	35(1)	-8(1)	-4(1)	-1(1)
C(21)	14(1)	16(1)	24(1)	1(1)	-6(1)	-8(1)
C(22)	19(1)	22(1)	24(1)	-1(1)	-7(1)	-10(1)
C(23)	23(1)	25(1)	28(1)	4(1)	-14(1)	-11(1)
C(24)	17(1)	20(1)	36(1)	3(1)	-12(1)	-8(1)
C(25)	16(1)	16(1)	32(1)	0(1)	-5(1)	-9(1)
C(26)	17(1)	18(1)	39(1)	-2(1)	-2(1)	-7(1)
C(27)	24(1)	24(1)	32(1)	-6(1)	4(1)	-12(1)
C(28)	26(1)	27(1)	23(1)	-2(1)	-1(1)	-15(1)
C(29)	16(1)	16(1)	25(1)	1(1)	-5(1)	-10(1)
N(1)	14(1)	17(1)	20(1)	-1(1)	-7(1)	-7(1)
N(2)	20(1)	23(1)	22(1)	0(1)	-4(1)	-12(1)

O(1)	19(1)	13(1)	43(1)	-3(1)	-10(1)	-5(1)
O(2)	20(1)	13(1)	43(1)	1(1)	-9(1)	-8(1)
O(3)	16(1)	17(1)	20(1)	3(1)	-8(1)	-7(1)
O(4)	23(1)	16(1)	39(1)	-1(1)	-8(1)	-8(1)
O(5)	18(1)	17(1)	32(1)	-6(1)	-2(1)	-4(1)
O(6)	20(1)	25(1)	37(1)	-11(1)	-9(1)	-8(1)
Si(1)	14(1)	16(1)	20(1)	0(1)	-7(1)	-7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **19**.

	x	y	z	U(eq)
H(1)	7570	31	1416	19
H(3)	8532	-2681	2368	22
H(5A)	6463	-5557	2844	36
H(5B)	6690	-5929	4107	36
H(7)	3699	-1584	3859	21
H(9)	3391	625	3756	19
H(10)	5134	910	4311	19
H(11)	6218	2017	2093	20
H(13A)	3786	128	113	39
H(13B)	2287	49	685	39
H(13C)	3541	-805	1274	39
H(14A)	1375	498	3304	38
H(14B)	347	1617	2603	38
H(14C)	1021	1997	3375	38
H(16A)	3316	3925	-652	49
H(16B)	3852	2390	-680	49
H(16C)	4280	2935	160	49
H(17A)	2431	4027	1815	44
H(17B)	887	4074	2044	44
H(17C)	1478	4954	973	44
H(18A)	257	3223	752	40
H(18B)	1409	2408	-228	40
H(18C)	960	3958	-375	40
H(20A)	2033	4481	4923	42
H(20B)	862	3897	5112	42
H(20C)	1487	4498	3870	42
H(22)	9145	-881	4655	25
H(23)	11275	-2420	4975	28
H(24)	12921	-3571	3532	29
H(26)	13692	-3939	1465	31

H(27)	13224	-3324	-316	33
H(28)	11113	-1693	-544	30

Crystal Structure Determination of Compound 20

A yellow prism 0.080 x 0.030 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 30 seconds per frame using a scan width of 0.5°. Data collection was 99.6% complete to 25.000° in θ. A total of 26736 reflections were collected covering the indices, -10<=*h*<=10, -23<=*k*<=29, -17<=*l*<=17. 5801 reflections were found to be symmetry independent, with an R_{int} of 0.0351. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/n (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) 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-2013). 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-2013.

Table 1. Crystal data and structure refinement for compound **20**.

X-ray ID	Compound **20**	
Sample/notebook ID	CT-02140	
Empirical formula	C34 H41 N3 O6 Pd Si	
Formula weight	722.19	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 9.0304(3) Å	α= 90°.
	b = 24.4173(9) Å	β= 91.9960(10)°.
	c = 14.4594(5) Å	γ = 90°.
Volume	3186.33(19) $Å^3$	
Z	4	
Density (calculated)	1.505 Mg/m^3	
Absorption coefficient	0.670 mm^{-1}	
F(000)	1496	
Crystal size	0.080 x 0.030 x 0.020 mm^3	
Crystal color/habit	yellow prism	
Theta range for data collection	1.637 to 25.344°.	
Index ranges	-10<=h<=10, -23<=k<=29, -17<=l<=17	
Reflections collected	26736	
Independent reflections	5801 [R(int) = 0.0351]	
Completeness to theta = 25.000°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.867	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5801 / 0 / 414	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2sigma(I)]	R1 = 0.0299, wR2 = 0.0653	
R indices (all data)	R1 = 0.0405, wR2 = 0.0706	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.467 and -0.443 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **20**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	438(3)	9046(1)	672(2)	17(1)
C(2)	1433(3)	8560(1)	684(2)	15(1)
C(3)	1656(3)	8264(1)	-140(2)	18(1)
C(4)	2612(3)	7831(1)	-94(2)	17(1)
C(5)	3960(3)	7086(1)	-396(2)	23(1)
C(6)	3341(3)	7675(1)	717(2)	16(1)
C(7)	3133(3)	7941(1)	1538(2)	15(1)
C(8)	2174(3)	8390(1)	1510(2)	14(1)
C(9)	1773(3)	8701(1)	2370(2)	14(1)
C(10)	74(3)	8741(1)	2358(2)	15(1)
C(11)	-394(3)	9150(1)	1583(2)	16(1)
C(12)	-169(3)	9724(1)	1984(2)	16(1)
C(13)	1377(3)	10539(1)	1820(2)	18(1)
C(14)	952(3)	10838(1)	2582(2)	23(1)
C(15)	1594(3)	11353(1)	2778(2)	26(1)
C(16)	2630(3)	11581(1)	2232(2)	24(1)
C(17)	3075(3)	11296(1)	1440(2)	20(1)
C(18)	4136(3)	11497(1)	827(2)	24(1)
C(19)	4521(3)	11199(1)	79(2)	24(1)
C(20)	3855(3)	10687(1)	-76(2)	21(1)
C(21)	2449(3)	10776(1)	1236(2)	17(1)
C(22)	2806(3)	9349(1)	-1536(2)	26(1)
C(23)	3317(4)	9193(2)	-2449(2)	40(1)
C(24)	5335(3)	8942(1)	3445(2)	29(1)
C(25)	5208(4)	9219(2)	2509(2)	43(1)
C(26)	6313(3)	9292(1)	4110(2)	31(1)
C(27)	3673(6)	8165(2)	4860(3)	21(1)
C(28)	3799(7)	7609(2)	4386(4)	27(1)
C(27A)	4314(13)	8085(3)	4642(6)	20(3)
C(28A)	3164(12)	7642(4)	4667(7)	22(3)
C(29)	4928(3)	8241(1)	5595(2)	27(1)

C(30)	2697(3)	9317(1)	4617(2)	28(1)
C(31)	1231(4)	9173(2)	5076(2)	52(1)
C(32)	2471(4)	9835(1)	4040(2)	35(1)
C(33)	-648(3)	8182(1)	2274(2)	17(1)
C(34)	-2872(3)	7713(1)	1889(2)	33(1)
N(1)	895(2)	10012(1)	1561(1)	16(1)
N(2)	2850(2)	10480(1)	474(1)	17(1)
N(3)	2416(2)	9461(1)	-822(2)	20(1)
O(1)	3024(2)	7494(1)	-813(1)	23(1)
O(2)	4277(2)	7238(1)	545(1)	21(1)
O(3)	2370(2)	8459(1)	3195(1)	16(1)
O(4)	-83(2)	7754(1)	2501(1)	22(1)
O(5)	-2053(2)	8221(1)	1950(1)	30(1)
O(6)	-895(2)	9880(1)	2643(1)	21(1)
Si(1)	3536(1)	8730(1)	3977(1)	20(1)
Pd(1)	1688(1)	9726(1)	408(1)	16(1)

Table 3. Bond lengths [Å] and angles [°] for compound **20**.

C(1)-C(2)	1.489(4)	C(15)-C(16)	1.363(4)
C(1)-C(11)	1.560(3)	C(15)-H(15)	0.9500
C(1)-Pd(1)	2.052(3)	C(16)-C(17)	1.411(4)
C(1)-H(1)	1.0000	C(16)-H(16)	0.9500
C(2)-C(8)	1.410(3)	C(17)-C(18)	1.416(4)
C(2)-C(3)	1.414(3)	C(17)-C(21)	1.416(4)
C(3)-C(4)	1.364(4)	C(18)-C(19)	1.358(4)
C(3)-H(3)	0.9500	C(18)-H(18)	0.9500
C(4)-C(6)	1.379(4)	C(19)-C(20)	1.402(4)
C(4)-O(1)	1.386(3)	C(19)-H(19)	0.9500
C(5)-O(1)	1.427(3)	C(20)-N(2)	1.327(3)
C(5)-O(2)	1.429(3)	C(20)-H(20)	0.9500
C(5)-H(5A)	0.9900	C(21)-N(2)	1.377(3)
C(5)-H(5B)	0.9900	C(22)-N(3)	1.136(3)
C(6)-C(7)	1.370(3)	C(22)-C(23)	1.464(4)
C(6)-O(2)	1.390(3)	C(23)-H(23A)	0.9800
C(7)-C(8)	1.398(4)	C(23)-H(23B)	0.9800
C(7)-H(7)	0.9500	C(23)-H(23C)	0.9800
C(8)-C(9)	1.511(3)	C(24)-C(25)	1.515(4)
C(9)-O(3)	1.422(3)	C(24)-C(26)	1.541(4)
C(9)-C(10)	1.537(3)	C(24)-Si(1)	1.894(3)
C(9)-H(9)	1.0000	C(24)-H(24)	1.0000
C(10)-C(33)	1.517(4)	C(25)-H(25A)	0.9800
C(10)-C(11)	1.549(3)	C(25)-H(25B)	0.9800
C(10)-H(10)	1.0000	C(25)-H(25C)	0.9800
C(11)-C(12)	1.528(3)	C(26)-H(26A)	0.9800
C(11)-H(11)	1.0000	C(26)-H(26B)	0.9800
C(12)-O(6)	1.236(3)	C(26)-H(26C)	0.9800
C(12)-N(1)	1.354(3)	C(27)-C(28)	1.526(7)
C(13)-C(14)	1.386(4)	C(27)-C(29)	1.538(5)
C(13)-N(1)	1.406(3)	C(27)-Si(1)	1.881(4)
C(13)-C(21)	1.429(4)	C(27)-H(27)	1.0000
C(14)-C(15)	1.410(4)	C(28)-H(28A)	0.9800
C(14)-H(14)	0.9500	C(28)-H(28B)	0.9800

C(28)-H(28C)	0.9800	C(31)-H(31B)	0.9800
C(27A)-C(28A)	1.501(14)	C(31)-H(31C)	0.9800
C(27A)-C(29)	1.517(9)	C(32)-H(32A)	0.9800
C(27A)-Si(1)	1.963(9)	C(32)-H(32B)	0.9800
C(27A)-H(27A)	1.0000	C(32)-H(32C)	0.9800
C(28A)-H(28D)	0.9800	C(33)-O(4)	1.204(3)
C(28A)-H(28E)	0.9800	C(33)-O(5)	1.341(3)
C(28A)-H(28F)	0.9800	C(34)-O(5)	1.446(3)
C(29)-H(29A)	0.9800	C(34)-H(34A)	0.9800
C(29)-H(29B)	0.9800	C(34)-H(34B)	0.9800
C(29)-H(29C)	0.9800	C(34)-H(34C)	0.9800
C(30)-C(32)	1.527(4)	N(1)-Pd(1)	1.965(2)
C(30)-C(31)	1.542(4)	N(2)-Pd(1)	2.119(2)
C(30)-Si(1)	1.879(3)	N(3)-Pd(1)	2.023(2)
C(30)-H(30)	1.0000	O(3)-Si(1)	1.6556(18)
C(31)-H(31A)	0.9800		

C(2)-C(1)-C(11)	115.3(2)	O(2)-C(5)-H(5B)	110.0
C(2)-C(1)-Pd(1)	108.16(17)	H(5A)-C(5)-H(5B)	108.4
C(11)-C(1)-Pd(1)	108.06(16)	C(7)-C(6)-C(4)	122.0(2)
C(2)-C(1)-H(1)	108.4	C(7)-C(6)-O(2)	128.4(2)
C(11)-C(1)-H(1)	108.4	C(4)-C(6)-O(2)	109.6(2)
Pd(1)-C(1)-H(1)	108.4	C(6)-C(7)-C(8)	116.8(2)
C(8)-C(2)-C(3)	119.1(2)	C(6)-C(7)-H(7)	121.6
C(8)-C(2)-C(1)	120.8(2)	C(8)-C(7)-H(7)	121.6
C(3)-C(2)-C(1)	120.1(2)	C(7)-C(8)-C(2)	121.9(2)
C(4)-C(3)-C(2)	117.6(2)	C(7)-C(8)-C(9)	122.5(2)
C(4)-C(3)-H(3)	121.2	C(2)-C(8)-C(9)	115.4(2)
C(2)-C(3)-H(3)	121.2	O(3)-C(9)-C(8)	112.8(2)
C(3)-C(4)-C(6)	122.5(2)	O(3)-C(9)-C(10)	112.63(19)
C(3)-C(4)-O(1)	127.5(2)	C(8)-C(9)-C(10)	106.9(2)
C(6)-C(4)-O(1)	110.0(2)	O(3)-C(9)-H(9)	108.1
O(1)-C(5)-O(2)	108.6(2)	C(8)-C(9)-H(9)	108.1
O(1)-C(5)-H(5A)	110.0	C(10)-C(9)-H(9)	108.1
O(2)-C(5)-H(5A)	110.0	C(33)-C(10)-C(9)	111.7(2)
O(1)-C(5)-H(5B)	110.0	C(33)-C(10)-C(11)	114.6(2)

C(9)-C(10)-C(11)	107.2(2)	C(19)-C(20)-H(20)	118.5
C(33)-C(10)-H(10)	107.7	N(2)-C(21)-C(17)	121.6(2)
C(9)-C(10)-H(10)	107.7	N(2)-C(21)-C(13)	117.6(2)
C(11)-C(10)-H(10)	107.7	C(17)-C(21)-C(13)	120.9(2)
C(12)-C(11)-C(10)	106.7(2)	N(3)-C(22)-C(23)	178.8(3)
C(12)-C(11)-C(1)	114.1(2)	C(22)-C(23)-H(23A)	109.5
C(10)-C(11)-C(1)	112.3(2)	C(22)-C(23)-H(23B)	109.5
C(12)-C(11)-H(11)	107.8	H(23A)-C(23)-H(23B)	109.5
C(10)-C(11)-H(11)	107.8	C(22)-C(23)-H(23C)	109.5
C(1)-C(11)-H(11)	107.8	H(23A)-C(23)-H(23C)	109.5
O(6)-C(12)-N(1)	126.3(2)	H(23B)-C(23)-H(23C)	109.5
O(6)-C(12)-C(11)	120.6(2)	C(25)-C(24)-C(26)	109.5(3)
N(1)-C(12)-C(11)	113.1(2)	C(25)-C(24)-Si(1)	116.5(2)
C(14)-C(13)-N(1)	127.0(2)	C(26)-C(24)-Si(1)	112.3(2)
C(14)-C(13)-C(21)	118.0(2)	C(25)-C(24)-H(24)	105.9
N(1)-C(13)-C(21)	115.0(2)	C(26)-C(24)-H(24)	105.9
C(13)-C(14)-C(15)	120.3(3)	Si(1)-C(24)-H(24)	105.9
C(13)-C(14)-H(14)	119.8	C(24)-C(25)-H(25A)	109.5
C(15)-C(14)-H(14)	119.8	C(24)-C(25)-H(25B)	109.5
C(16)-C(15)-C(14)	122.3(3)	H(25A)-C(25)-H(25B)	109.5
C(16)-C(15)-H(15)	118.9	C(24)-C(25)-H(25C)	109.5
C(14)-C(15)-H(15)	118.9	H(25A)-C(25)-H(25C)	109.5
C(15)-C(16)-C(17)	119.3(3)	H(25B)-C(25)-H(25C)	109.5
C(15)-C(16)-H(16)	120.4	C(24)-C(26)-H(26A)	109.5
C(17)-C(16)-H(16)	120.4	C(24)-C(26)-H(26B)	109.5
C(16)-C(17)-C(18)	123.7(3)	H(26A)-C(26)-H(26B)	109.5
C(16)-C(17)-C(21)	119.2(2)	C(24)-C(26)-H(26C)	109.5
C(18)-C(17)-C(21)	117.1(2)	H(26A)-C(26)-H(26C)	109.5
C(19)-C(18)-C(17)	120.6(3)	H(26B)-C(26)-H(26C)	109.5
C(19)-C(18)-H(18)	119.7	C(28)-C(27)-C(29)	110.7(4)
C(17)-C(18)-H(18)	119.7	C(28)-C(27)-Si(1)	110.6(3)
C(18)-C(19)-C(20)	119.0(3)	C(29)-C(27)-Si(1)	114.2(3)
C(18)-C(19)-H(19)	120.5	C(28)-C(27)-H(27)	107.0
C(20)-C(19)-H(19)	120.5	C(29)-C(27)-H(27)	107.0
N(2)-C(20)-C(19)	122.9(3)	Si(1)-C(27)-H(27)	107.0
N(2)-C(20)-H(20)	118.5	C(27)-C(28)-H(28A)	109.5

C(27)-C(28)-H(28B)	109.5	C(30)-C(32)-H(32B)	109.5
H(28A)-C(28)-H(28B)	109.5	H(32A)-C(32)-H(32B)	109.5
C(27)-C(28)-H(28C)	109.5	C(30)-C(32)-H(32C)	109.5
H(28A)-C(28)-H(28C)	109.5	H(32A)-C(32)-H(32C)	109.5
H(28B)-C(28)-H(28C)	109.5	H(32B)-C(32)-H(32C)	109.5
C(28A)-C(27A)-C(29)	113.0(8)	O(4)-C(33)-O(5)	123.0(2)
C(28A)-C(27A)-Si(1)	110.7(7)	O(4)-C(33)-C(10)	125.7(2)
C(29)-C(27A)-Si(1)	110.9(5)	O(5)-C(33)-C(10)	111.2(2)
C(28A)-C(27A)-H(27A)	107.3	O(5)-C(34)-H(34A)	109.5
C(29)-C(27A)-H(27A)	107.3	O(5)-C(34)-H(34B)	109.5
Si(1)-C(27A)-H(27A)	107.3	H(34A)-C(34)-H(34B)	109.5
C(27A)-C(28A)-H(28D)	109.5	O(5)-C(34)-H(34C)	109.5
C(27A)-C(28A)-H(28E)	109.5	H(34A)-C(34)-H(34C)	109.5
H(28D)-C(28A)-H(28E)	109.5	H(34B)-C(34)-H(34C)	109.5
C(27A)-C(28A)-H(28F)	109.5	C(12)-N(1)-C(13)	125.0(2)
H(28D)-C(28A)-H(28F)	109.5	C(12)-N(1)-Pd(1)	118.98(17)
H(28E)-C(28A)-H(28F)	109.5	C(13)-N(1)-Pd(1)	115.63(16)
C(27)-C(29)-H(29A)	109.5	C(20)-N(2)-C(21)	118.9(2)
C(27)-C(29)-H(29B)	109.5	C(20)-N(2)-Pd(1)	130.71(19)
H(29A)-C(29)-H(29B)	109.5	C(21)-N(2)-Pd(1)	110.43(16)
C(27)-C(29)-H(29C)	109.5	C(22)-N(3)-Pd(1)	175.1(2)
H(29A)-C(29)-H(29C)	109.5	C(4)-O(1)-C(5)	105.52(19)
H(29B)-C(29)-H(29C)	109.5	C(6)-O(2)-C(5)	105.45(19)
C(32)-C(30)-C(31)	108.9(3)	C(9)-O(3)-Si(1)	128.37(15)
C(32)-C(30)-Si(1)	114.3(2)	C(33)-O(5)-C(34)	115.8(2)
C(31)-C(30)-Si(1)	113.9(2)	O(3)-Si(1)-C(30)	112.54(12)
C(32)-C(30)-H(30)	106.4	O(3)-Si(1)-C(27)	101.27(14)
C(31)-C(30)-H(30)	106.4	C(30)-Si(1)-C(27)	104.1(2)
Si(1)-C(30)-H(30)	106.4	O(3)-Si(1)-C(24)	111.44(11)
C(30)-C(31)-H(31A)	109.5	C(30)-Si(1)-C(24)	110.97(13)
C(30)-C(31)-H(31B)	109.5	C(27)-Si(1)-C(24)	116.0(2)
H(31A)-C(31)-H(31B)	109.5	O(3)-Si(1)-C(27A)	102.8(3)
C(30)-C(31)-H(31C)	109.5	C(30)-Si(1)-C(27A)	121.0(3)
H(31A)-C(31)-H(31C)	109.5	C(24)-Si(1)-C(27A)	96.9(4)
H(31B)-C(31)-H(31C)	109.5	N(1)-Pd(1)-N(3)	176.55(9)
C(30)-C(32)-H(32A)	109.5	N(1)-Pd(1)-C(1)	84.85(9)

N(3)-Pd(1)-C(1)	95.86(9)
N(1)-Pd(1)-N(2)	81.26(8)
N(3)-Pd(1)-N(2)	98.17(9)
C(1)-Pd(1)-N(2)	165.83(

9)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for compound **20**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	18(1)	21(1)	11(1)	0(1)	-1(1)	2(1)
C(2)	14(1)	19(1)	13(1)	1(1)	0(1)	-1(1)
C(3)	19(1)	22(1)	12(1)	1(1)	-3(1)	0(1)
C(4)	20(1)	18(1)	14(1)	-4(1)	3(1)	-3(1)
C(5)	27(2)	21(1)	20(2)	-4(1)	2(1)	3(1)
C(6)	14(1)	14(1)	19(1)	1(1)	2(1)	-2(1)
C(7)	14(1)	18(1)	14(1)	3(1)	-1(1)	-3(1)
C(8)	12(1)	16(1)	12(1)	1(1)	1(1)	-5(1)
C(9)	14(1)	16(1)	12(1)	1(1)	-2(1)	-1(1)
C(10)	16(1)	18(1)	12(1)	-2(1)	0(1)	1(1)
C(11)	15(1)	21(1)	14(1)	1(1)	-1(1)	2(1)
C(12)	18(1)	18(1)	12(1)	3(1)	-1(1)	4(1)
C(13)	21(1)	18(1)	16(1)	2(1)	-2(1)	4(1)
C(14)	27(2)	24(2)	18(1)	2(1)	5(1)	2(1)
C(15)	36(2)	24(2)	19(2)	-5(1)	2(1)	4(1)
C(16)	31(2)	16(1)	25(2)	-2(1)	-5(1)	1(1)
C(17)	19(1)	19(1)	20(1)	5(1)	-4(1)	3(1)
C(18)	21(2)	21(1)	29(2)	5(1)	-3(1)	-1(1)
C(19)	20(2)	27(2)	25(2)	9(1)	2(1)	-1(1)
C(20)	18(1)	27(2)	18(1)	6(1)	4(1)	5(1)
C(21)	18(1)	19(1)	14(1)	3(1)	-2(1)	8(1)
C(22)	29(2)	27(2)	21(2)	3(1)	0(1)	9(1)
C(23)	48(2)	54(2)	18(2)	-4(1)	4(2)	23(2)
C(24)	19(2)	36(2)	31(2)	-11(1)	-3(1)	-3(1)
C(25)	28(2)	76(3)	24(2)	-12(2)	6(1)	-20(2)
C(26)	24(2)	36(2)	33(2)	-6(1)	-2(1)	-7(1)
C(29)	26(2)	35(2)	18(1)	4(1)	-7(1)	1(1)
C(30)	27(2)	39(2)	17(2)	-9(1)	3(1)	-10(1)
C(31)	42(2)	83(3)	31(2)	-18(2)	14(2)	-20(2)
C(32)	36(2)	35(2)	34(2)	-13(1)	-5(2)	10(2)
C(33)	16(1)	23(2)	11(1)	-4(1)	3(1)	0(1)

C(34)	23(2)	28(2)	47(2)	-9(1)	-6(1)	-9(1)
N(1)	19(1)	18(1)	12(1)	0(1)	3(1)	2(1)
N(2)	18(1)	19(1)	15(1)	2(1)	0(1)	4(1)
N(3)	24(1)	22(1)	15(1)	3(1)	1(1)	8(1)
O(1)	28(1)	24(1)	16(1)	-5(1)	0(1)	7(1)
O(2)	26(1)	20(1)	19(1)	-2(1)	0(1)	8(1)
O(3)	20(1)	18(1)	11(1)	1(1)	-4(1)	-3(1)
O(4)	19(1)	21(1)	26(1)	1(1)	2(1)	-3(1)
O(5)	18(1)	25(1)	45(1)	-3(1)	-10(1)	-4(1)
O(6)	23(1)	22(1)	18(1)	0(1)	7(1)	4(1)
Si(1)	25(1)	20(1)	13(1)	1(1)	-5(1)	-7(1)
Pd(1)	19(1)	18(1)	10(1)	1(1)	2(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **20**.

	x	y	z	U(eq)
H(1)	-316	9001	154	20
H(3)	1159	8363	-705	21
H(5A)	4893	7058	-733	27
H(5B)	3459	6726	-421	27
H(7)	3616	7825	2098	18
H(9)	2182	9081	2324	17
H(10)	-213	8903	2962	18
H(11)	-1478	9099	1444	20
H(14)	224	10694	2974	28
H(15)	1294	11548	3308	32
H(16)	3048	11928	2384	29
H(18)	4582	11845	939	28
H(19)	5231	11336	-332	29
H(20)	4134	10480	-597	25
H(23A)	4403	9202	-2443	60
H(23B)	2921	9451	-2914	60
H(23C)	2970	8823	-2601	60
H(24)	5899	8595	3347	35
H(25A)	4641	9559	2561	64
H(25B)	4700	8975	2064	64
H(25C)	6201	9303	2295	64
H(26A)	7269	9361	3831	47
H(26B)	6474	9096	4696	47
H(26C)	5818	9641	4224	47
H(27)	2721	8163	5193	25
H(28A)	4693	7602	4021	41
H(28B)	2925	7549	3977	41
H(28C)	3859	7320	4855	41
H(27A)	5158	7940	4285	23
H(28D)	3585	7319	4982	34

H(28E)	2848	7543	4034	34
H(28F)	2310	7774	5002	34
H(29A)	4978	7920	6001	40
H(29B)	4734	8569	5964	40
H(29C)	5873	8284	5289	40
H(30)	3420	9413	5131	33
H(31A)	941	9476	5476	77
H(31B)	1365	8840	5448	77
H(31C)	455	9112	4596	77
H(32A)	1761	9762	3527	53
H(32B)	3420	9949	3792	53
H(32C)	2088	10128	4429	53
H(34A)	-2258	7430	1610	49
H(34B)	-3776	7766	1505	49
H(34C)	-3136	7596	2511	49

Crystal Structure Determination of Compound 25

A yellow plate 0.050 x 0.040 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame using a scan width of 0.5°. Data collection was 100.0% complete to 25.000° in θ. A total of 30179 reflections were collected covering the indices, -11<=*h*<=11, -28<=*k*<=28, -11<=*l*<=12. 4332 reflections were found to be symmetry independent, with an R_{int} of 0.0465. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/c (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) 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-2013). 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-2013.

Table 1. Crystal data and structure refinement for compound **25**.

X-ray ID	Compound **25**	
Sample/notebook ID	CT-03137	
Empirical formula	C27 H25 N3 O5 Pd	
Formula weight	577.90	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 9.8890(4) Å	α= 90°.
	b = 23.6908(8) Å	β= 95.860(2)°.
	c = 10.1530(4) Å	γ = 90°.
Volume	2366.20(16) $Å^3$	
Z	4	
Density (calculated)	1.622 Mg/m^3	
Absorption coefficient	0.830 mm^{-1}	
F(000)	1176	
Crystal size	0.050 x 0.040 x 0.020 mm^3	
Crystal color/habit	yellow plate	
Theta range for data collection	1.719 to 25.359°.	
Index ranges	-11<=h<=11, -28<=k<=28, -11<=l<=12	
Reflections collected	30179	
Independent reflections	4332 [R(int) = 0.0465]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.823	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4332 / 0 / 328	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0396, wR2 = 0.0977	
R indices (all data)	R1 = 0.0520, wR2 = 0.1056	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.539 and -0.862 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **25**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2472(7)	-126(2)	2124(5)	55(2)
C(2)	2107(8)	-522(2)	1075(6)	68(2)
C(3)	3172(9)	-751(2)	492(6)	70(2)
C(4)	4500(8)	-621(2)	833(5)	60(2)
C(5)	5618(9)	-829(2)	253(6)	65(2)
C(6)	6903(9)	-693(2)	684(6)	65(2)
C(7)	7201(7)	-298(2)	1749(5)	56(2)
C(8)	6134(6)	-51(2)	2318(4)	42(1)
C(9)	4789(6)	-217(2)	1893(4)	44(1)
C(10)	7398(5)	636(2)	3780(4)	30(1)
C(11)	7077(4)	1187(2)	4450(4)	19(1)
C(12)	5774(4)	1130(1)	5145(3)	16(1)
C(13)	5171(3)	1677(1)	5508(3)	14(1)
C(14)	4230(3)	1685(2)	6466(3)	16(1)
C(15)	3614(3)	2182(2)	6719(3)	15(1)
C(16)	2507(4)	2886(2)	7613(4)	22(1)
C(17)	3893(3)	2680(1)	6082(4)	16(1)
C(18)	4823(3)	2694(1)	5174(4)	15(1)
C(19)	5465(3)	2185(1)	4888(3)	12(1)
C(20)	6523(3)	2214(1)	3924(3)	14(1)
C(21)	8840(4)	2539(2)	3883(4)	19(1)
C(22)	8116(4)	1729(2)	2585(4)	21(1)
C(23)	6886(4)	1648(2)	3358(3)	16(1)
C(24)	8530(4)	2975(2)	2789(4)	24(1)
C(25)	10025(4)	2721(2)	4843(4)	30(1)
C(26)	1831(5)	899(2)	5145(5)	37(1)
C(27)	653(5)	1050(3)	5846(6)	62(2)
N(1)	3745(5)	15(2)	2494(4)	43(1)
N(2)	6245(4)	386(1)	3257(3)	31(1)
N(3)	2775(4)	810(1)	4656(4)	28(1)
O(1)	2606(2)	2280(1)	7541(3)	20(1)

O(2)	3091(2)	3112(1)	6482(3)	21(1)
O(3)	7721(2)	2464(1)	4648(2)	16(1)
O(4)	9211(2)	2006(1)	3371(3)	22(1)
O(5)	8573(4)	470(1)	3683(3)	47(1)
Pd(1)	4523(1)	614(1)	3931(1)	24(1)

Table 3. Bond lengths [Å] and angles [°] for compound **25**.

C(1)-N(1)	1.320(7)	C(16)-O(1)	1.441(4)
C(1)-C(2)	1.438(8)	C(16)-H(16A)	0.9900
C(1)-H(1)	0.9500	C(16)-H(16B)	0.9900
C(2)-C(3)	1.371(10)	C(17)-C(18)	1.368(5)
C(2)-H(2)	0.9500	C(17)-O(2)	1.381(4)
C(3)-C(4)	1.359(10)	C(18)-C(19)	1.406(5)
C(3)-H(3)	0.9500	C(18)-H(18)	0.9500
C(4)-C(5)	1.395(9)	C(19)-C(20)	1.504(5)
C(4)-C(9)	1.446(7)	C(20)-O(3)	1.455(4)
C(5)-C(6)	1.340(10)	C(20)-C(23)	1.518(5)
C(5)-H(5)	0.9500	C(20)-H(20)	1.0000
C(6)-C(7)	1.438(8)	C(21)-O(3)	1.426(4)
C(6)-H(6)	0.9500	C(21)-O(4)	1.428(4)
C(7)-C(8)	1.384(7)	C(21)-C(25)	1.509(5)
C(7)-H(7)	0.9500	C(21)-C(24)	1.525(5)
C(8)-N(2)	1.405(5)	C(22)-O(4)	1.436(5)
C(8)-C(9)	1.412(8)	C(22)-C(23)	1.526(5)
C(9)-N(1)	1.367(7)	C(22)-H(22A)	0.9900
C(10)-O(5)	1.240(5)	C(22)-H(22B)	0.9900
C(10)-N(2)	1.345(6)	C(23)-H(23)	1.0000
C(10)-C(11)	1.521(5)	C(24)-H(24A)	0.9800
C(11)-C(12)	1.537(5)	C(24)-H(24B)	0.9800
C(11)-C(23)	1.553(5)	C(24)-H(24C)	0.9800
C(11)-H(11)	1.0000	C(25)-H(25A)	0.9800
C(12)-C(13)	1.489(5)	C(25)-H(25B)	0.9800
C(12)-Pd(1)	2.058(4)	C(25)-H(25C)	0.9800
C(12)-H(12)	1.0000	C(26)-N(3)	1.122(6)
C(13)-C(19)	1.403(5)	C(26)-C(27)	1.470(7)
C(13)-C(14)	1.414(5)	C(27)-H(27A)	0.9800
C(14)-C(15)	1.363(5)	C(27)-H(27B)	0.9800
C(14)-H(14)	0.9500	C(27)-H(27C)	0.9800
C(15)-O(1)	1.383(4)	N(1)-Pd(1)	2.122(4)
C(15)-C(17)	1.385(5)	N(2)-Pd(1)	1.974(4)
C(16)-O(2)	1.440(4)	N(3)-Pd(1)	2.001(4)

N(1)-C(1)-C(2)	122.4(6)	C(23)-C(11)-H(11)	109.6
N(1)-C(1)-H(1)	118.8	C(13)-C(12)-C(11)	114.3(3)
C(2)-C(1)-H(1)	118.8	C(13)-C(12)-Pd(1)	115.7(2)
C(3)-C(2)-C(1)	115.6(6)	C(11)-C(12)-Pd(1)	105.0(2)
C(3)-C(2)-H(2)	122.2	C(13)-C(12)-H(12)	107.1
C(1)-C(2)-H(2)	122.2	C(11)-C(12)-H(12)	107.1
C(4)-C(3)-C(2)	124.4(6)	Pd(1)-C(12)-H(12)	107.1
C(4)-C(3)-H(3)	117.8	C(19)-C(13)-C(14)	118.6(3)
C(2)-C(3)-H(3)	117.8	C(19)-C(13)-C(12)	122.0(3)
C(3)-C(4)-C(5)	126.8(6)	C(14)-C(13)-C(12)	119.3(3)
C(3)-C(4)-C(9)	116.9(6)	C(15)-C(14)-C(13)	118.6(3)
C(5)-C(4)-C(9)	116.3(6)	C(15)-C(14)-H(14)	120.7
C(6)-C(5)-C(4)	122.9(6)	C(13)-C(14)-H(14)	120.7
C(6)-C(5)-H(5)	118.5	C(14)-C(15)-O(1)	128.4(3)
C(4)-C(5)-H(5)	118.5	C(14)-C(15)-C(17)	122.2(3)
C(5)-C(6)-C(7)	121.1(6)	O(1)-C(15)-C(17)	109.3(3)
C(5)-C(6)-H(6)	119.5	O(2)-C(16)-O(1)	107.2(3)
C(7)-C(6)-H(6)	119.5	O(2)-C(16)-H(16A)	110.3
C(8)-C(7)-C(6)	118.8(6)	O(1)-C(16)-H(16A)	110.3
C(8)-C(7)-H(7)	120.6	O(2)-C(16)-H(16B)	110.3
C(6)-C(7)-H(7)	120.6	O(1)-C(16)-H(16B)	110.3
C(7)-C(8)-N(2)	125.8(5)	H(16A)-C(16)-H(16B)	108.5
C(7)-C(8)-C(9)	119.3(5)	C(18)-C(17)-O(2)	128.8(3)
N(2)-C(8)-C(9)	114.8(4)	C(18)-C(17)-C(15)	121.0(3)
N(1)-C(9)-C(8)	118.8(4)	O(2)-C(17)-C(15)	110.2(3)
N(1)-C(9)-C(4)	119.8(6)	C(17)-C(18)-C(19)	117.9(3)
C(8)-C(9)-C(4)	121.3(5)	C(17)-C(18)-H(18)	121.0
O(5)-C(10)-N(2)	126.3(4)	C(19)-C(18)-H(18)	121.0
O(5)-C(10)-C(11)	123.3(4)	C(13)-C(19)-C(18)	121.6(3)
N(2)-C(10)-C(11)	110.3(3)	C(13)-C(19)-C(20)	121.4(3)
C(10)-C(11)-C(12)	110.6(3)	C(18)-C(19)-C(20)	117.0(3)
C(10)-C(11)-C(23)	107.4(3)	O(3)-C(20)-C(19)	105.9(3)
C(12)-C(11)-C(23)	110.1(3)	O(3)-C(20)-C(23)	109.8(3)
C(10)-C(11)-H(11)	109.6	C(19)-C(20)-C(23)	114.4(3)
C(12)-C(11)-H(11)	109.6	O(3)-C(20)-H(20)	108.8

C(19)-C(20)-H(20)	108.8
C(23)-C(20)-H(20)	108.8
O(3)-C(21)-O(4)	109.3(3)
O(3)-C(21)-C(25)	106.2(3)
O(4)-C(21)-C(25)	106.0(3)
O(3)-C(21)-C(24)	111.8(3)
O(4)-C(21)-C(24)	112.0(3)
C(25)-C(21)-C(24)	111.3(3)
O(4)-C(22)-C(23)	111.5(3)
O(4)-C(22)-H(22A)	109.3
C(23)-C(22)-H(22A)	109.3
O(4)-C(22)-H(22B)	109.3
C(23)-C(22)-H(22B)	109.3
H(22A)-C(22)-H(22B)	108.0
C(20)-C(23)-C(22)	108.4(3)
C(20)-C(23)-C(11)	111.5(3)
C(22)-C(23)-C(11)	114.3(3)
C(20)-C(23)-H(23)	107.5
C(22)-C(23)-H(23)	107.5
C(11)-C(23)-H(23)	107.5
C(21)-C(24)-H(24A)	109.5
C(21)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(21)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(21)-C(25)-H(25A)	109.5
C(21)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(21)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
N(3)-C(26)-C(27)	175.5(5)
C(26)-C(27)-H(27A)	109.5
C(26)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5
C(26)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5
H(27B)-C(27)-H(27C)	109.5
C(1)-N(1)-C(9)	120.8(5)
C(1)-N(1)-Pd(1)	129.3(4)
C(9)-N(1)-Pd(1)	109.8(3)
C(10)-N(2)-C(8)	126.7(4)
C(10)-N(2)-Pd(1)	118.0(3)
C(8)-N(2)-Pd(1)	115.2(3)
C(26)-N(3)-Pd(1)	174.9(4)
C(15)-O(1)-C(16)	104.7(3)
C(17)-O(2)-C(16)	104.3(3)
C(21)-O(3)-C(20)	114.4(2)
C(21)-O(4)-C(22)	113.6(3)
N(2)-Pd(1)-N(3)	177.33(13)
N(2)-Pd(1)-C(12)	83.27(14)
N(3)-Pd(1)-C(12)	97.51(14)
N(2)-Pd(1)-N(1)	81.04(17)
N(3)-Pd(1)-N(1)	98.16(16)
C(12)-Pd(1)-N(1)	164.30(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for compound **25**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	92(4)	35(3)	32(3)	14(2)	-18(3)	-35(3)
C(2)	111(6)	41(3)	46(4)	15(3)	-15(4)	-37(3)
C(3)	139(7)	32(3)	36(3)	11(2)	-11(4)	-34(4)
C(4)	132(6)	22(2)	24(3)	9(2)	8(3)	-18(3)
C(5)	150(7)	16(2)	32(3)	5(2)	27(4)	-5(3)
C(6)	142(7)	23(3)	39(3)	7(2)	50(4)	14(3)
C(7)	121(5)	17(2)	34(3)	8(2)	36(3)	17(3)
C(8)	93(4)	15(2)	22(2)	6(2)	23(3)	2(2)
C(9)	100(4)	16(2)	18(2)	7(2)	13(3)	-5(2)
C(10)	44(3)	23(2)	25(2)	9(2)	17(2)	11(2)
C(11)	25(2)	20(2)	13(2)	4(2)	5(2)	8(2)
C(12)	20(2)	16(2)	11(2)	4(1)	3(1)	3(1)
C(13)	13(2)	16(2)	12(2)	0(1)	-1(1)	2(1)
C(14)	16(2)	16(2)	15(2)	2(1)	0(1)	0(1)
C(15)	8(2)	27(2)	11(2)	-2(2)	1(1)	0(1)
C(16)	19(2)	29(2)	17(2)	-3(2)	6(2)	4(2)
C(17)	12(2)	18(2)	18(2)	-5(1)	-1(1)	3(1)
C(18)	16(2)	15(2)	16(2)	1(1)	0(1)	0(1)
C(19)	11(2)	18(2)	7(2)	-3(1)	-3(1)	-1(1)
C(20)	15(2)	17(2)	9(2)	1(1)	-1(1)	0(1)
C(21)	17(2)	30(2)	11(2)	-3(2)	7(2)	-3(2)
C(22)	29(2)	22(2)	12(2)	-2(2)	8(2)	0(2)
C(23)	20(2)	19(2)	9(2)	0(1)	2(1)	1(1)
C(24)	30(2)	26(2)	17(2)	-3(2)	9(2)	-6(2)
C(25)	19(2)	53(3)	20(2)	-3(2)	4(2)	-6(2)
C(26)	29(3)	33(2)	46(3)	5(2)	-13(2)	-5(2)
C(27)	22(3)	73(4)	90(5)	6(3)	7(3)	15(2)
N(1)	80(3)	23(2)	24(2)	10(2)	-6(2)	-22(2)
N(2)	61(3)	15(2)	20(2)	0(1)	17(2)	8(2)
N(3)	25(2)	22(2)	34(2)	4(2)	-4(2)	-6(2)
O(1)	15(1)	26(1)	20(1)	-3(1)	7(1)	-1(1)

O(2)	20(1)	21(1)	24(2)	-2(1)	8(1)	4(1)
O(3)	12(1)	28(1)	8(1)	-3(1)	3(1)	-4(1)
O(4)	19(1)	31(2)	17(1)	-1(1)	6(1)	3(1)
O(5)	54(2)	41(2)	52(2)	9(2)	30(2)	25(2)
Pd(1)	41(1)	15(1)	16(1)	2(1)	0(1)	-6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **25**.

	x	y	z	U(eq)
H(1)	1770	40	2567	66
H(2)	1189	-619	803	81
H(3)	2968	-1019	-196	85
H(5)	5461	-1077	-482	78
H(6)	7629	-861	279	78
H(7)	8115	-208	2057	67
H(11)	7853	1293	5114	23
H(12)	6021	918	5988	19
H(14)	4031	1350	6925	19
H(16A)	1544	3002	7597	26
H(16B)	3009	3026	8442	26
H(18)	5028	3036	4750	18
H(20)	6189	2471	3179	16
H(22A)	8431	1357	2296	25
H(22B)	7848	1957	1784	25
H(23)	6107	1529	2712	19
H(24A)	7791	2837	2154	36
H(24B)	9344	3038	2333	36
H(24C)	8255	3331	3176	36
H(25A)	9808	3079	5255	45
H(25B)	10832	2769	4368	45
H(25C)	10205	2432	5529	45
H(27A)	969	1196	6728	93
H(27B)	88	715	5934	93
H(27C)	116	1341	5344	93

Chapter 2
Total Synthesis of Complex Meroterpenes

2.1 Introduction and background

The polycyclic polyprenylated acylphloroglucinols (PPAPs) are a family of plant-derived meroterpene natural products.[1] Structurally, PPAPs possess a conserved bicyclo[3.3.1] nonane-2,4,9-trione carbon skeleton that is decorated with various prenyl or geranyl side chains (Figure 1).[2] Common oxidation patterns include a C9 bridging ketone in addition to carbonyl groups in the C2 and C4 positions. This 1,3-diketone group exists in solution as its enol tautomer and is known to be air sensitive.[3] Many PPAPs are assembled in nature by cyclization of the 1,3-diketone moiety onto one of the many pendant olefins.[4] Moreover, PPAPs bear a conserved quaternary carbon center at C8. While many PPAPs possess *gem*-dimethyl groups at this position, PPAPs such as hyperforin (**1**, Figure 2) contain an all-carbon stereocenter at this position, a notoriously difficult structural motif for chemical synthesis within this class of natural products.[5]

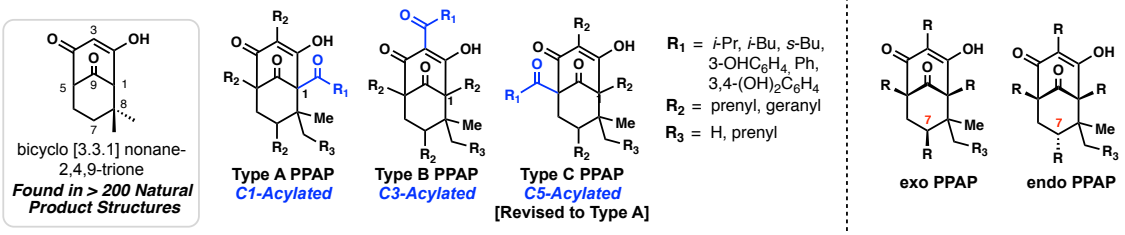


Figure 1. Polycyclic Polyprenylated Acylphloroglucinols

The family of PPAP natural products is further subdivided into three groups based on the position of the acyl group (Figure 1, shown in blue).[1] In type A PPAPs, the acyl group resides in the C1 bridgehead position directly adjacent the C8 quaternary carbon center. Type A PPAPs are the most common subtype with over 80 compounds of this subtype isolated to date. For type B PPAPs, the acyl group is located at the C3 position between the β-hydroxyenone. Finally, type C PPAPs possess an acyl group on the C5 bridgehead position on the opposite side of the quaternary carbon center. Recently, Xu and co-workers have reported the structural revision of all of the type C PPAPs into the type A framework based on NMR analysis and DFT calculations.[6] In 2001, Cuesta-Rubio and co-workers reported the structure revision of nemorosone then considered to be a type C PPAP to a type A PPAP.[7] In addition to the three subtypes, PPAPs are also classified based on the stereochemistry of the C7 alkyl group. When the C7 group is in the equatorial position, it is referred to as an *exo*-PPAP. If it is in the axial position, it is an *endo*-PPAP, which, can undergo further cyclization to furnish an adamantyl skeleton.

The following pages contain a majority of the PPAP natural products isolated to date (Figures 2-5).[1a,8,9] Type A PPAPs can undergo various cyclizations between the β-hydroxyenone with any of the pendant olefins. Cyclizations that occur between the C4 carbonyl and the C5 prenyl group results in products derived from 5-*exo* or 6-*endo* cyclizations (Figure 2).[10,11] Either carbonyl (C2 or C4) may react with the C3 prenyl group to afford corresponding ethers (Figure 3).[12,13] For type A *endo*-PPAPs, cyclization at the C3 position of β-hydroxyenone with the C7 prenyl group results in formation of adamantyl or homoadamantyl (tricyclo-[4.3.1.1]-undecane) skeletons (Figure 4).[8] Type B

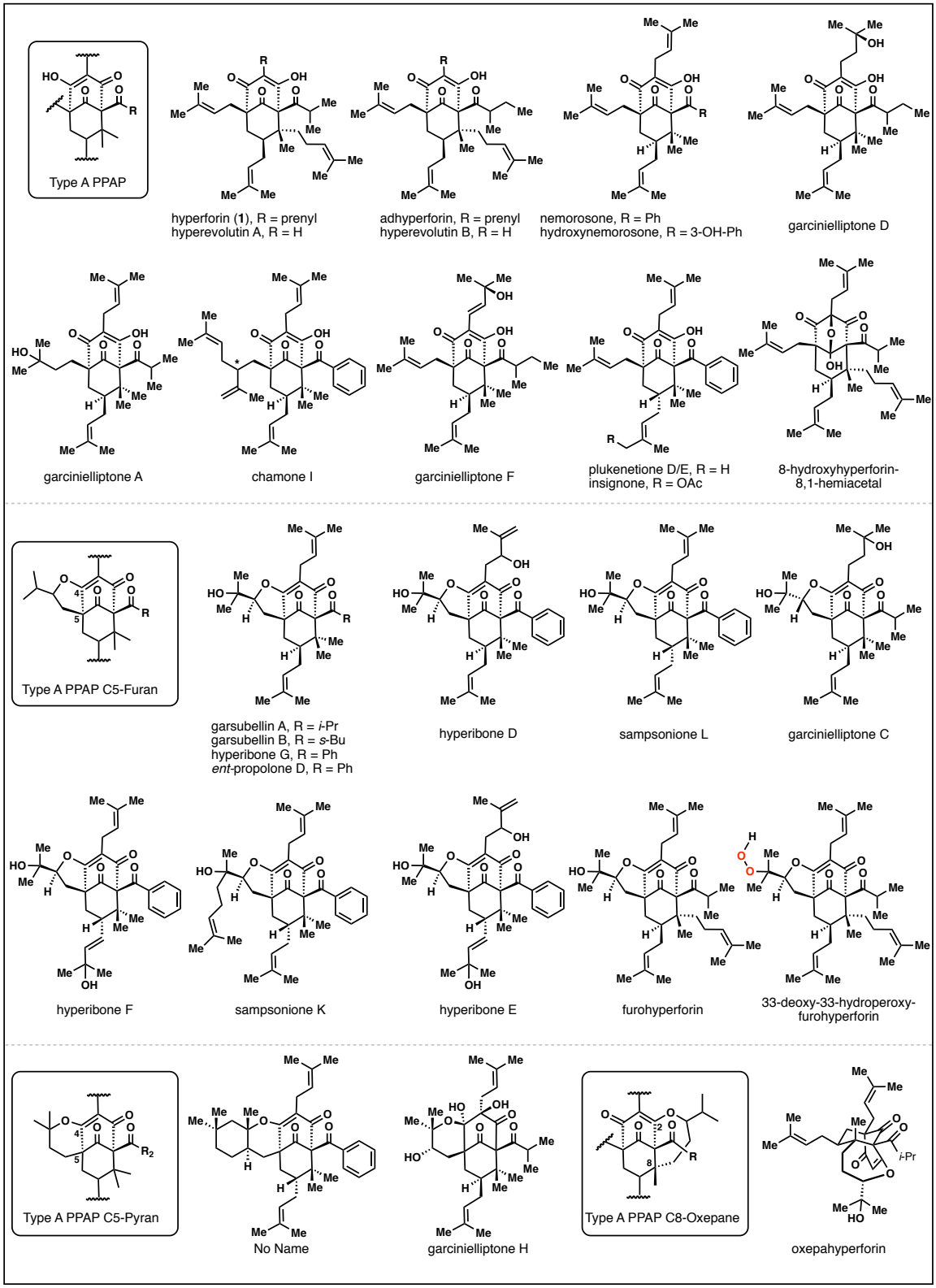


Figure 2. Type A PPAPs, *stereoconfiguration unassigned

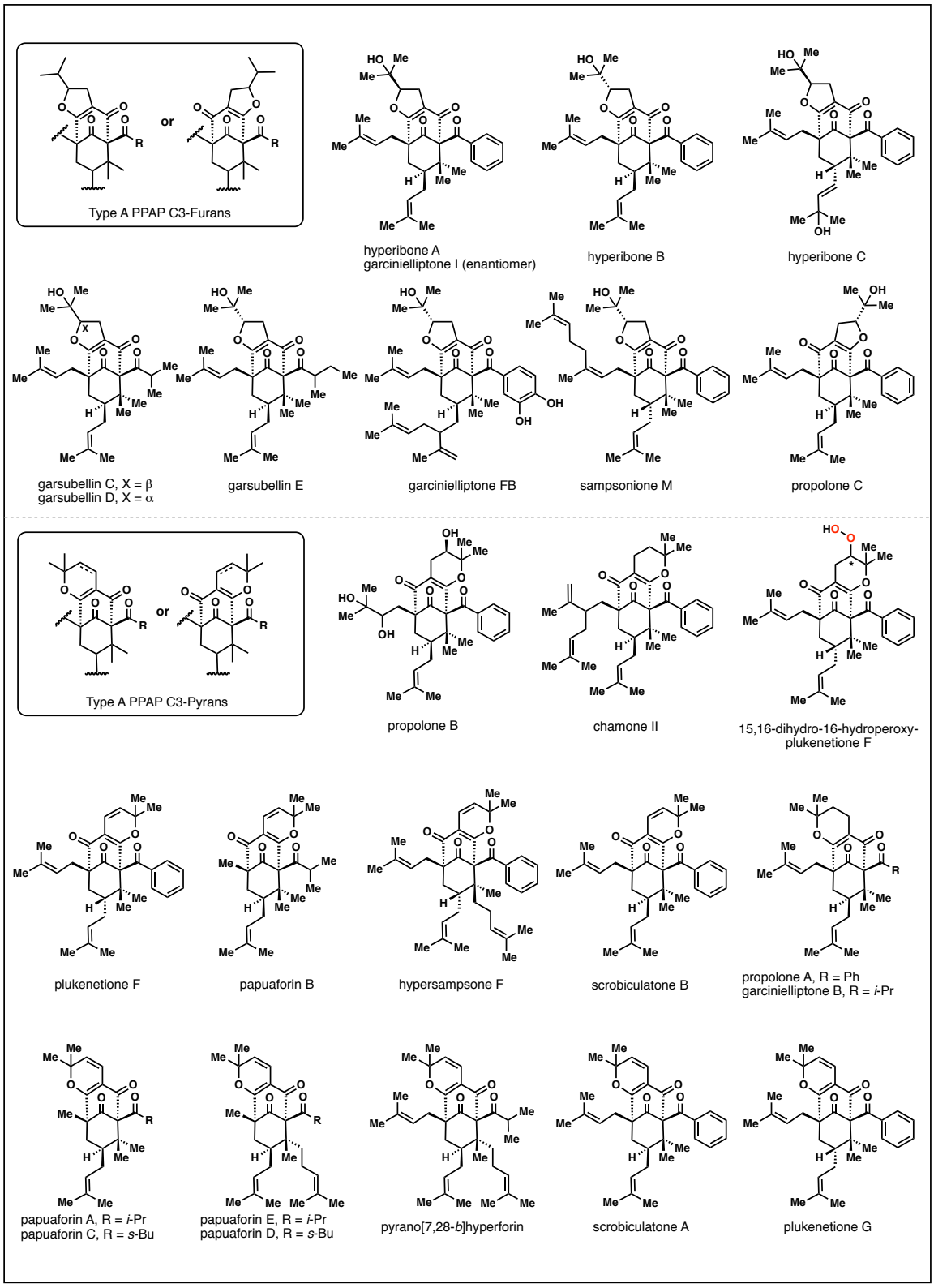


Figure 3. Type A PPAPs (continued), *stereoconfiguration unassigned

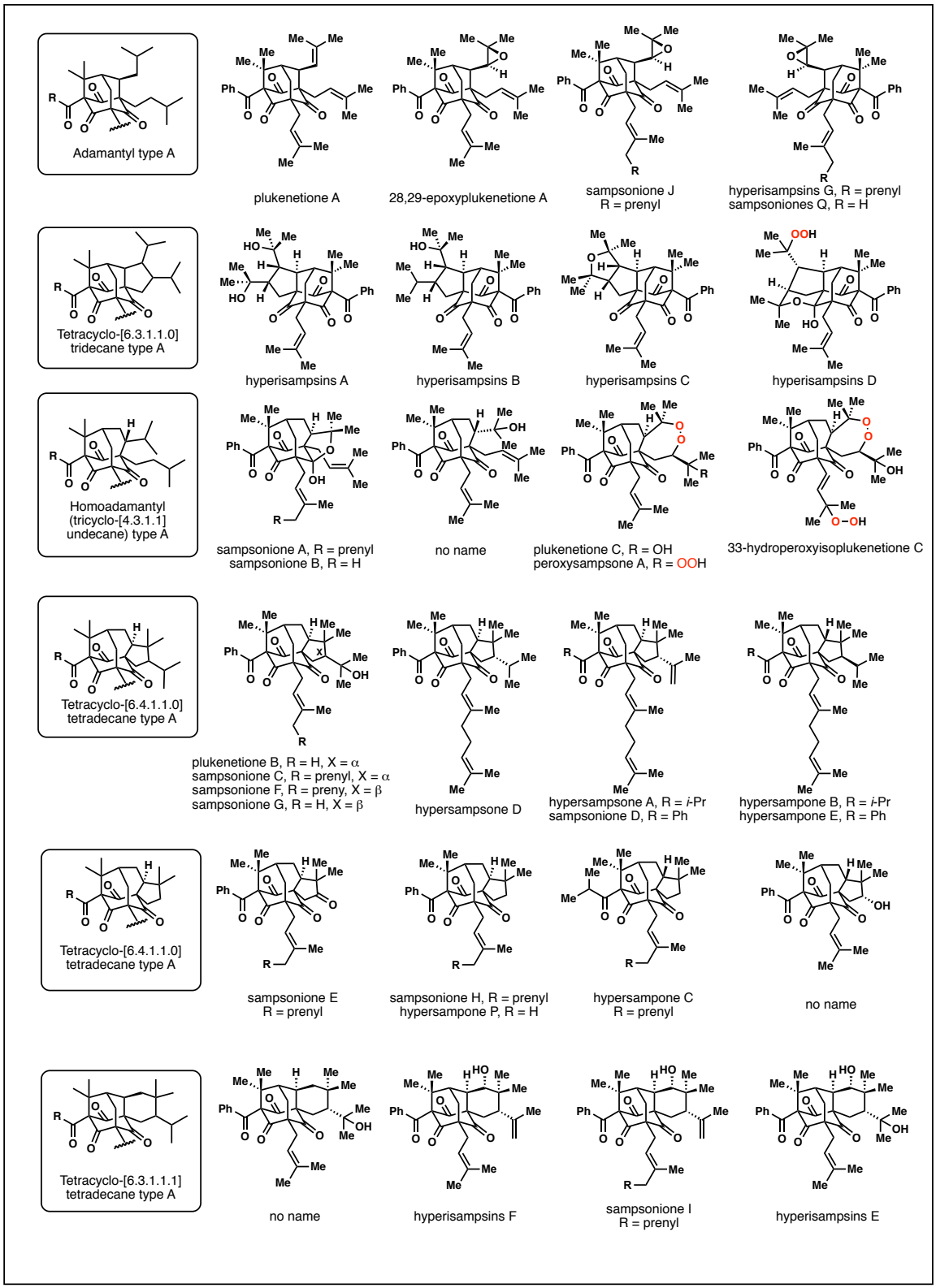


Figure 4. Type A PPAPs (continued)

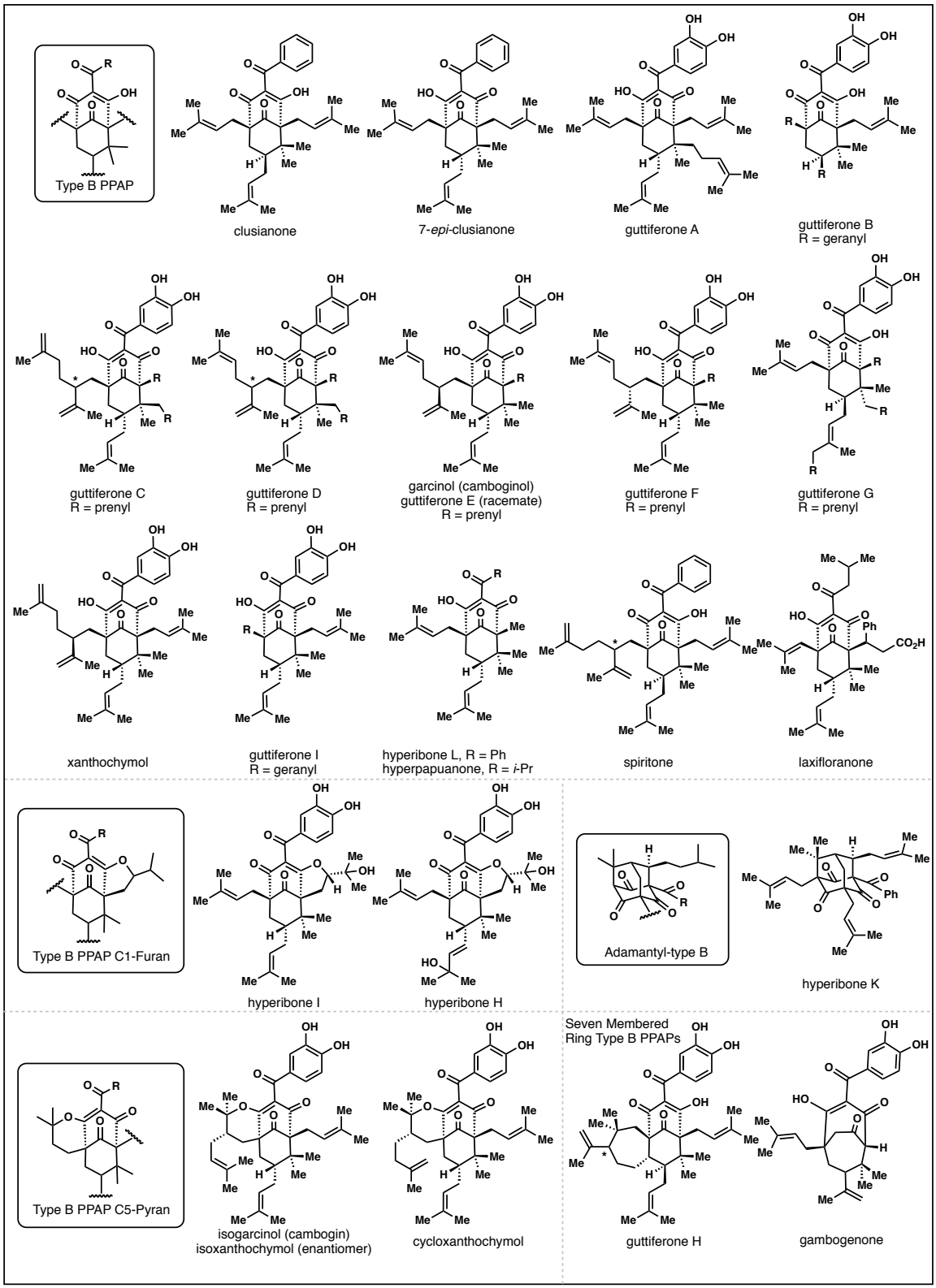


Figure 5. Type B PPAPs, *stereoconfiguration unassigned

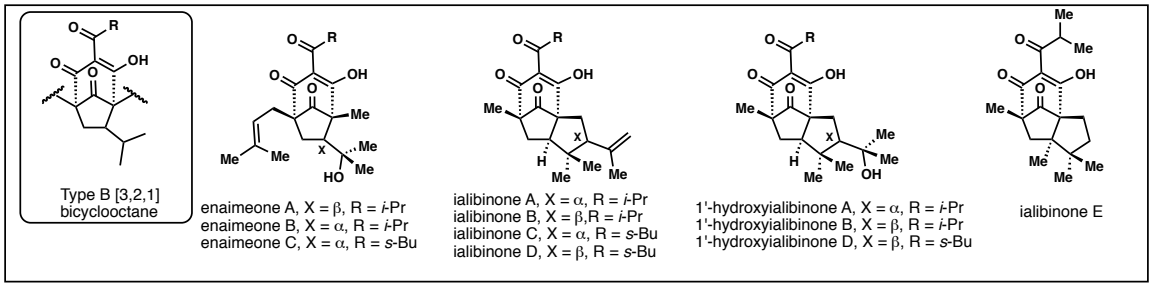
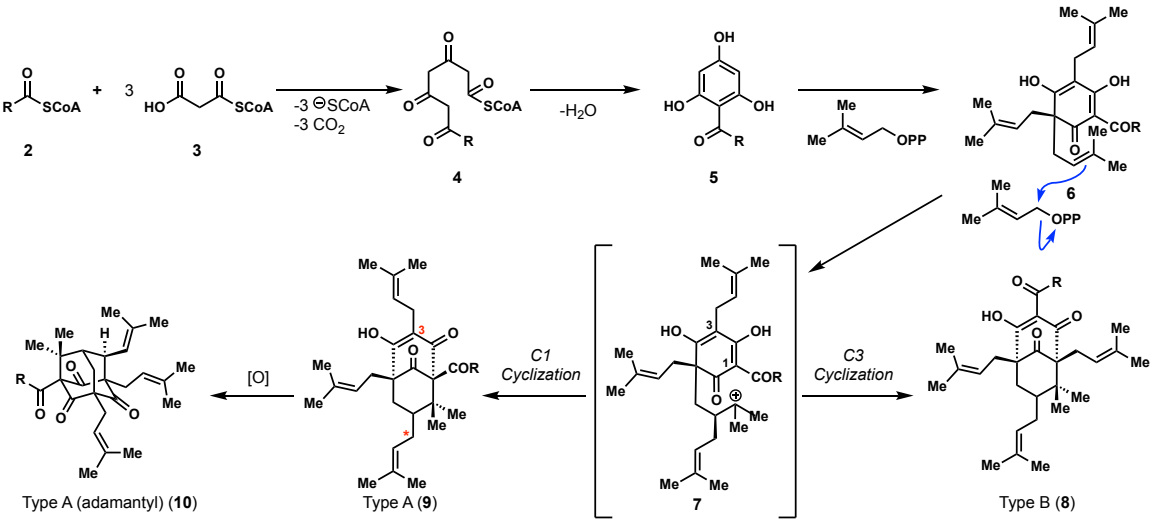


Figure 6. Type B PPAPs containing a bicyclo[3.2.1] octane skeleton

PPAPs also undergo cyclizations at the C1 and C5 prenyl groups to afford various ether based natural products (Figure 5).[4] Several type B PPAPs contain a unique bicyclo [3.2.1]-octane carbon skeleton (See Figure 6).[14]

Biosynthesis

The biosynthesis of PPAP natural products was proposed by Cuesta-Rubio in 2001 and remains commonly accepted to-date.[7] PPAPs are meroterpenes derived from both polyketide and terpene biosynthesis.[15] The acylphloroglucinol core is assembled by decarboxylative Claisen condensations of one acyl CoA (**2**) and three malonyl CoA (**3**) subunits. Dieckmann condensation of tetramer **4** produces the aromatic triphenol, acylphloroglucinol **5**. A benzophenone synthase from *Hypericum androsaemum* was found to catalyze this condensation reaction (R = Ph, Scheme 1).[16] Alkylation with two prenyl diphosphate units affords the fully substituted triphenol. The prenyltransferase associated with incorporating the first prenyl group has been identified from *Humulus lupulus* and *Hypericum calycinum* (R = *i*-Pr, Scheme 1).[17] However no enzymes have been identified for the second prenylation. Finally, a dearomative alkylation results in the formation of compound **6** which attacks another unit of prenyl diphosphate generating tertiary carbocation **7**. Cyclization from C3 position produces the type B (**8**) carbon skeleton while cyclization from C1 position affords the type A (**9**) carbon skeleton. Enzymes responsible for the dearomative prenylation or cationic cyclization have not



Scheme 1. Proposed Biosynthesis of PPAPs. Proposed Biosynthesis of PPAPs

been identified. *Endo*-PPAPs can further cyclize to afford the adamantyl type PPAPs **10**. While the type A and type B PPAPs can be derived from a common precursor (**6**), type C PPAPs require a different isomer *via* regioselective dearomative alkylation. This biosynthetic conundrum has caused skepticism regarding the type C structures long before the recent structural revisions.[7]

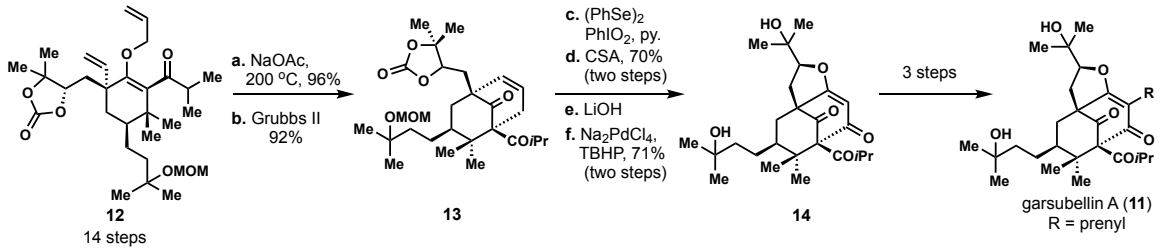
Hyperforin (**1**) remains one of the few PPAPs whose biosynthesis has been studied. Feeding studies on *Hypericum perforatum* with ^{13}C labeled [1-^{13}C]glucose and [U-$^{13}C6$] glucose resulted in labeled hyperforin (**1**) supporting the general proposed mechanism of PPAP biosynthesis.[18] These experiments also showed that the isoprene units were synthesized through the deoxyxylulose pathway as opposed to the mevalonate pathway.[18-19]

Isolation and Biological Activity of hyperforin

In 1975, Bristol and co-workers deduced the molecular structure of hyperforin (**1**) by extensive chemical degradation.[20] Hyperforin was isolated from St. John's wort (*hypericum perforatum*, SJW) which has been used as an herbal remedy for depression in ancient Greece and modern times.[21] In Germany, SJW is approved for the treatment mild or moderate depression.[22] Currently, hyperforin is considered to be responsible for the antidepressant properties of SJW.[23] At concentrations of 0.1-1.0 μM hyperforin and adhyperforin inhibit the synaptosomal uptake of many neurotransmitters such as serotonin, dopamine, norepinephrine, γ-aminobutyric acid (GABA), and L-glutamate *in vitro*.[24] Hyperforin has shown antibacterial activity toward penicillin resistant and methicillin-resistant *Staphylococcus aureus*.[25] Studies have also documented the effects of **1** as an antimalarial against *plasmodium falciparum* (IC_{50} = 1.5 μM).[26] Additionally, hyperforin has also been shown to increase xenobiotic metabolism by binding the pregnane X receptor and the steroid X receptor increasing expression of cytochrome P450.[27,28]

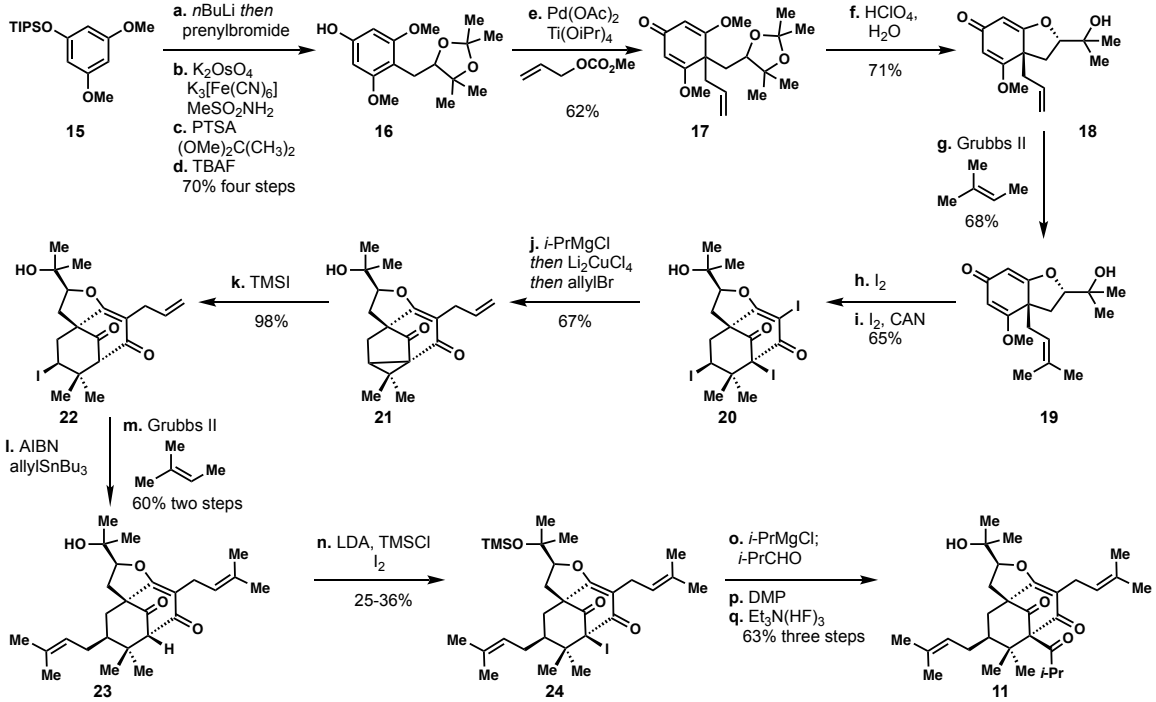
Syntheses of PPAP Natural Products

In 2005, Shibasaki and co-workers reported the total synthesis of garsubellin A (**11**) in 23 steps from *β*-ethoxycyclohexenone (Scheme 2).[29] A Claisen rearrangement of the advanced intermediate **12** followed by olefin metathesis furnished the bicyclo [3.3.1] nonane skeleton of **13**. Allylic oxidation *via* Barton's conditions,[30] followed by deprotection of the alcohol and the diol groups set the stage for a key Wacker oxidation to assemble the tricyclic core of garsubellin A (See **13** to **14**, Scheme 2). Installation of the remaining prenyl group and elimination of the tertiary alcohol produced garsubellin A (**11**). The strategy was shown to be amenable to asymmetric synthesis via enantioselective alkylation of *β*-ethoxycyclohexenone with Koga's amine.[31]



Scheme 2. Shibasaki's total synthesis of garsubellin A (**11**)

Danishefsky and co-workers' total synthesis of garsubellin A (**11**) commenced with differentially-protected triphenol **15**.[32] Compound **15** was subjected to a four-step sequence providing acetonide **16** *via* directed *ortho*-lithiation followed by prenylation, an osmium catalyzed dihydroxylation, acetonide formation with 2,2-dimethoxypropane and desilylation of the triisopropylsilyl group. At this point in the synthesis, palladium catalyzed dearomative allylation provided dienone **17** in 62% yield. Diastereoselective etherification of **17** with perchloric acid produced ether **18** as the thermodynamic product which was subjected to cross metathesis with 2-methyl-2-butene. A double iodination event effectively produced the bicyclo [3,3,1] nonane carbocyclic skeleton from compound **19**. Another iodination (I_2, CAN) reaction installed the vinyl iodide resulting in triiodide **20**. Upon treating triiodide **20** with isopropylmagnesium chloride, a transannular Wharton cyclopropanation occurred followed by a magnesium-iodide exchange of the vinyl iodide which was quenched with allyl bromide. The cyclopropane group of **21** was ruptured with TMSI in excellent yield to produce **22**. Compound **22** was subjected to Keck allylation conditions to install a second allyl group and double cross metathesis provided compound **23** in 60% yield over two steps.

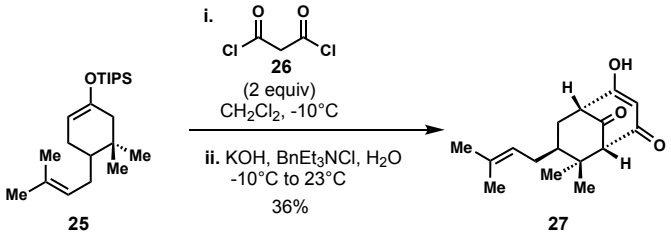


Scheme 3. Danishefsky's total synthesis of garsubellin (**11**).

The Danishefsky group discovered that LDA with TMSCl and I_2 allowed for iodination of the C1 bridgehead position to afford iodide **24** in yields ranging from 25-36%. Remarkably, this process likely proceeds through a bridgehead anion that is not resonance stabilized by the neighboring carbonyls. Compound **24** was subjected to magnesium-halogen exchange followed by an aldol-like reaction with isobutyraldehyde

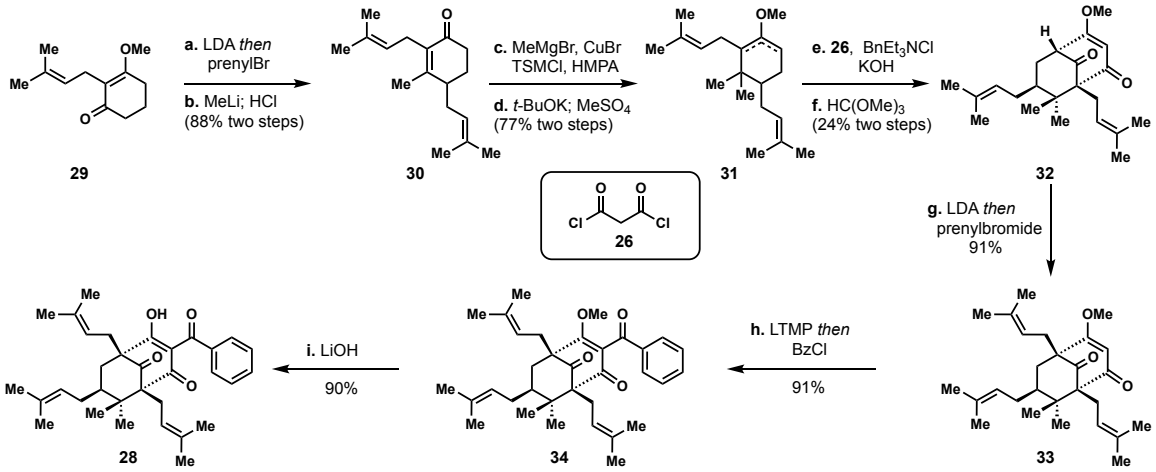
and then oxidation to afford the isopropyl ketone.[33] A final desilylation reaction unveiled garsubellin A (**11**). In 2007, Danishefsky also reported a total synthesis of clusianone in 2007 utilizing a similar strategy.[33]

Several annulation approaches have been reported to access PPAP natural products. Stoltz and co-workers were first to recognize the utility of the Effenberger annulation reaction for the synthesis of the bicyclo[3.3.1] nonane motif in their progress towards garsubellin A (Scheme 4).[34] Upon subjecting silyl enol ether **25** to malonyl dichloride (**26**), followed by KOH mediated annulation, bicycle **27** was obtained in 36% yield.



Scheme 4. Stoltz's modified Effenberger cyclization approach towards the PPAPs

This essential finding influenced numerous synthetic groups in their total syntheses of PPAPs.[1d] In 2006, Simpkins and co-workers reported the total synthesis of clusianone (**28**) (Scheme 5).[35] Starting with vinylogous methyl ester **29**, α-prenylation with LDA and prenyl bromide followed by 1,2-addition of MeLi and Stork-Danheiser rearrangement produced enone **30** in 88% yield over two steps. The conjugate addition of methyl cuprate followed by *O*-methylation of the ketone group afforded a mixture of isomeric methyl enol ethers (**31**). Both constitutional isomers were subjected to the Effenberger cyclization conditions reported by Stoltz.[34] The resulting β-hydroxyenone was regioselectively methylated to afford compound **32** in 24% isolated yield over two steps.

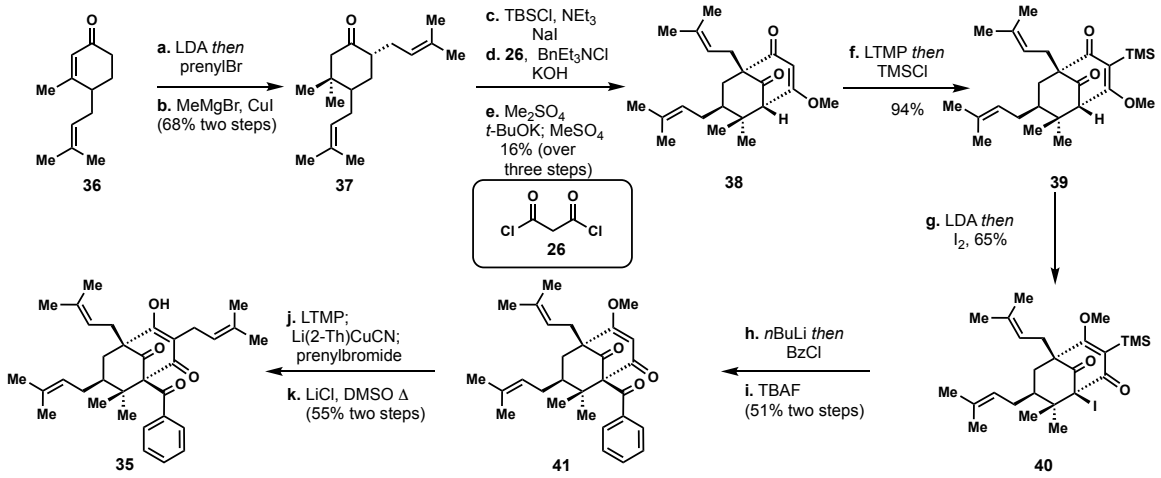


Scheme 5. Simpkins' total synthesis of clusianone (**28**)

Recognizing the acidity of the bridgehead proton, the Simpkins group generated the bridgehead anion with LDA and quenched the carbanion with prenylbromide. Directed

ortho-lithiation of **33** with LTMP followed by acylation with benzoyl chloride occurred in 91% yield to afford methyl clusianone **34**. Demethylation (LiOH) afforded clusianone (**28**) in excellent yield. The Simpkins group has also reported a formal synthesis of garsubellin A intercepting a key intermediate in Danishefsky's route.[36]

In 2010, Simpkins and co-workers reported a synthesis of nemorosone **35** using a similar approach (Scheme 6).[37] Starting with enone **36**, α-prenylation followed by conjugate addition of methyl cuprate produced ketone **37** in good yield. Ketone **37** was activated by silylation with TBSCl, NaI, triethylamine and subjected to Effenberger cyclization conditions. After methylation of the resulting *β*-hydroxyenone with dimethyl sulfate, compound **38** was obtained in 16% over three steps. Direct ortho-lithiation and silylation of **38** resulted in vinylsilane **39**. The bridgehead position was iodinated (LDA, I_2) in good yield to afford iodide **40**. The benzoyl group in nemorosone was installed by lithium halogen exchange and acylation with benzoyl chloride. Desilylation with TBAF produced compound **41** in 51% over two steps. The final prenyl group was installed by direct *ortho*-lithiation, transmetallation onto copper and quenching with prenyl bromide. The 2-thienyl ligand on copper is known to be a non-transferable ligand increasing the theoretical yield associated with dimeric Gilman cuprates.[38] Krapcho demethylation unveiled nemorosone **35** in 55% yield over two steps.

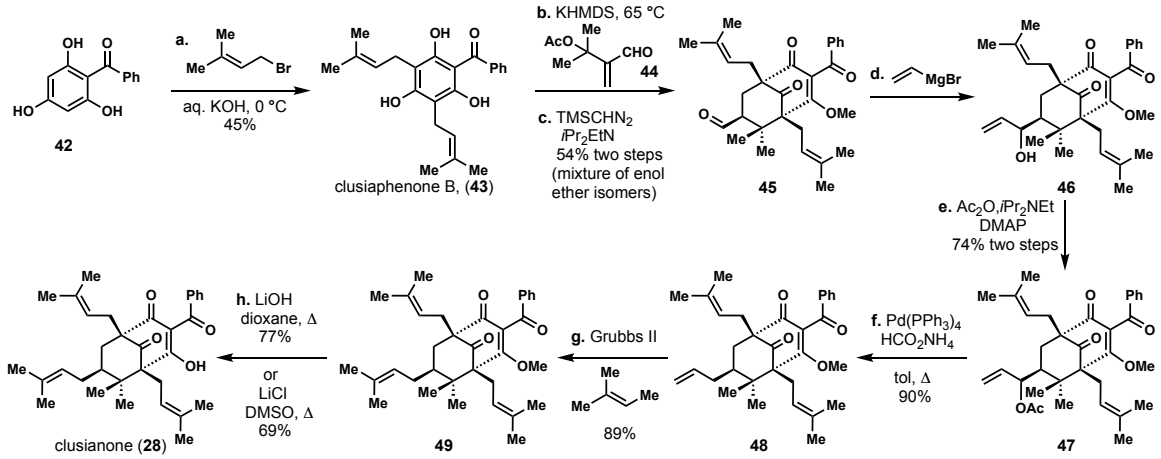


Scheme 6. Simpkins' total synthesis of nemorosone (**35**)

Other research groups including the Marazano (2007)[39] and Coltart (2010)[40] have also utilized the Effenberger cyclization in their respective syntheses of clusianone (**28**) as well.

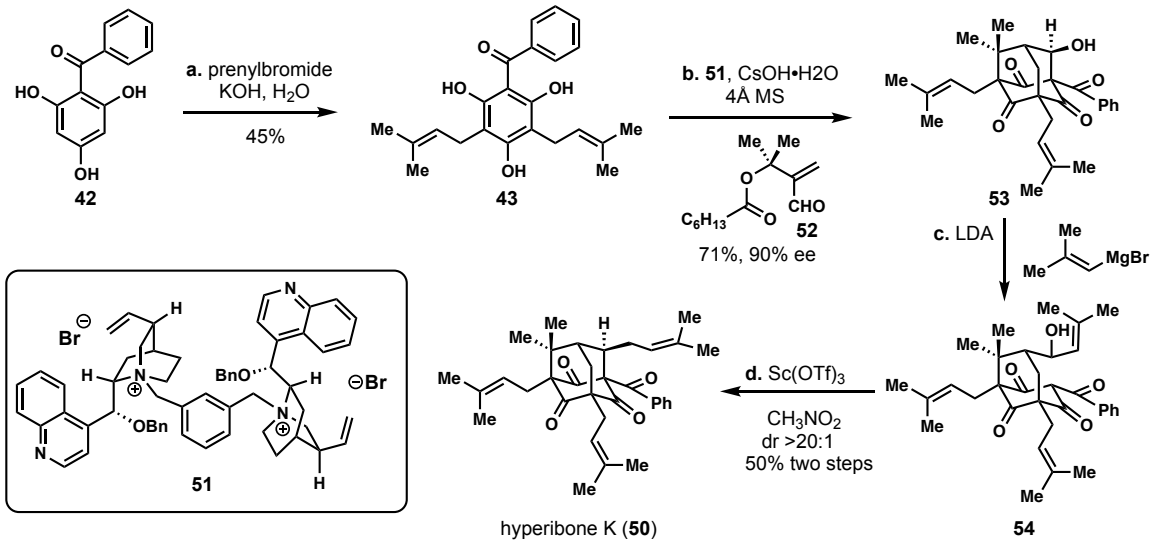
Biomimetic total syntheses of PPAPs has been extensively studied by Porco and co-workers.[41-45] The advantages associated with this strategy cannot be understated as 1) the precursors are easily synthesized triphenol compounds, and 2) the annulation of these compounds generates two adjacent quarternary carbon centers allowing for rapid assembly of molecular complexity. Porco and co-workers first reported a biomimetic synthesis of clusianone (**28**) in 2007 (Scheme 7).[41] Acylphloroglucinol **42** was prenylated with aqueous KOH and prenyl bromide to afford clusiaphenone B (**43**) in 45% yield.[46] Remarkably, dearomative annulation of **43** with enal **44** afforded the PPAP nucleus in a single step. After methylation with trimethylsilyldiazomethane ($TMSCHN_2$), a mixture of regioisomeric enol ethers **45** were obtained in 54% yield over two steps (only one of

which is shown for clarity, Scheme 7). Upon addition of vinyl magnesiumbromide to the aldehyde group, allyl alcohol **46** was obtained which was subsequently acetylated with acetic anhydride and Hünig's base in 74% yield over two steps (See **46** to **47**, Scheme 7). A reductive transposition reaction with $Pd(PPh_3)_4$ and ammonium formate produced the allyl group in 90% yield. An olefin metathesis reaction installed the final prenyl group of clusianone (See **48** to **49**, Scheme 7). Demethylation via LiOH in dioxane (77% yield) or LiCl in DMSO (69% yield) produced clusianone **28**.



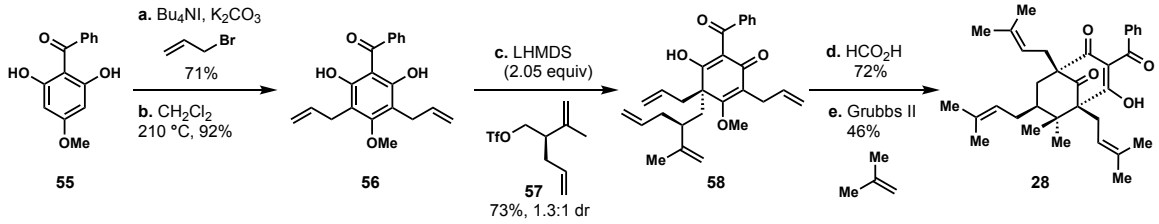
Scheme 7. Porco's total synthesis of clusianone (**28**)

The Porco group also reported an enantioselective total synthesis of (–)-hyperibone K (**50**) (Scheme 8), the only known adamantyl type B PPAP.[42,47] A similar double prenylation of **42** resulted in compound **43**. A dearomative double Michael addition, aldol cascade with cinchonine-derived catalyst **51**, and heptanoate aldehyde **52** afforded adamantyl compound **53** in 71% yield and 90% enantiomeric excess.[48] Compound **53** coaxed into a retroaldol process and following addition of 2-methyl-1-propenylmagnesium bromide allylic alcohol **54** was produced. Ionization of the alcohol moiety with $Sc(OTf)_3$ followed by cyclization of the 1,3-diketone group furnished (–)-hyperibone K (**50**) in 50% yield as the major diastereomer (20:1 dr). In addition, Porco and co-workers reported a total synthesis of plukenetione A in 2010 *via* a similar dearomative annulation strategy.[43]



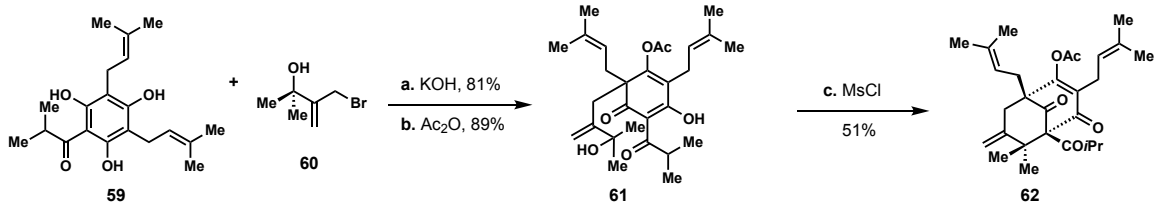
Scheme 8. Porco's total synthesis of hyperibone K (**50**)

In 2014, Boyce and Porco reported a biomimetic cationic cyclization to afford (–)-clusianone (**28**) in only six steps.[45] Starting their synthesis with **55**, double *O*-allylation of the diphenol proceeded in 71% yield. A double thermal Claisen rearrangement (210 ^{o}C) produced **56** in 92% yield. Dearomative alkylation with the enantiopure (*R*)-triflate **57** afforded a 1.3:1 mixture of diastereomers. The (*S,S*)-isomer (**58**, shown) was utilized in completing the total synthesis of (-)-clusianone. Upon investigation of numerous acids, formic acid proved essential. The authors propose a unique mechanism of hemiketal formation by 1,2-addition of formic acid, which would enhance the nucleophilicity of the enol ether.[45] Upon UPLC-mass spectroscopy analysis, starting material adducts with one or three formates were observed. Olefin metathesis with isobutylene and Grubbs second generation catalyst afforded (–)-clusianone (**28**) in six steps from commercial starting material.



Scheme 9. Porco's enantioselective total synthesis of (-)-clusianone (**28**)

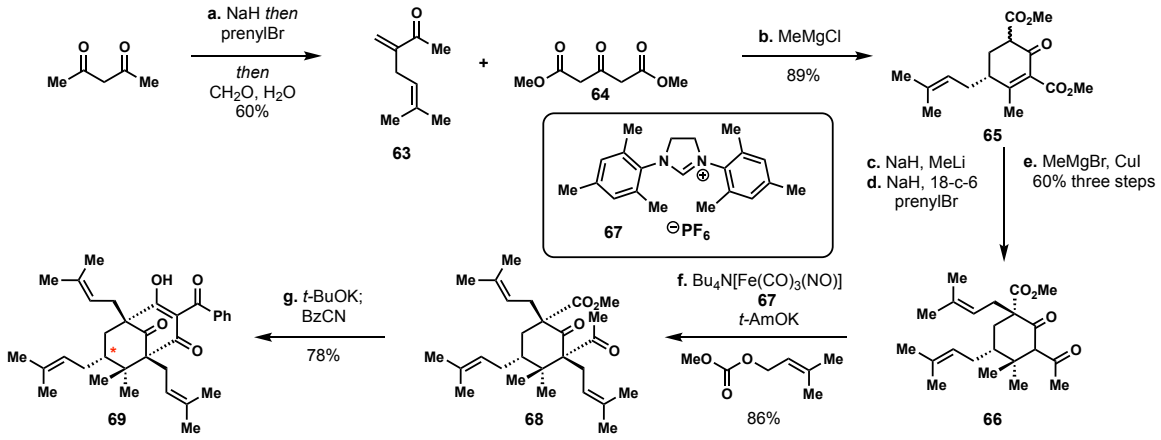
The Couladouros group has applied a similar biomimetic cyclization strategy for the synthesis of type A PPAPs.[49] Dearomative alkylation of triphenol **59** with allyl bromide **60** occurred in 81% yield. Regioselective *O*-acylation with acetic anhydride afforded compound **61** in 89% yield. The differentiated enol ethers allowed for selective annulation after activation of the allylic alcohol to afford the type A framework (**62**) in 51% yield. However, the Couladouros group was unable to stereoselectively install the C7 prenyl group present in PPAP natural products.[49]



Scheme 10. Couladouros' progress towards the total synthesis of type A PPAPs

Other biomimetic syntheses were reported by George and co-workers involving an impressive radical cascade in their synthesis of ialibinone A and B (not shown).[50]

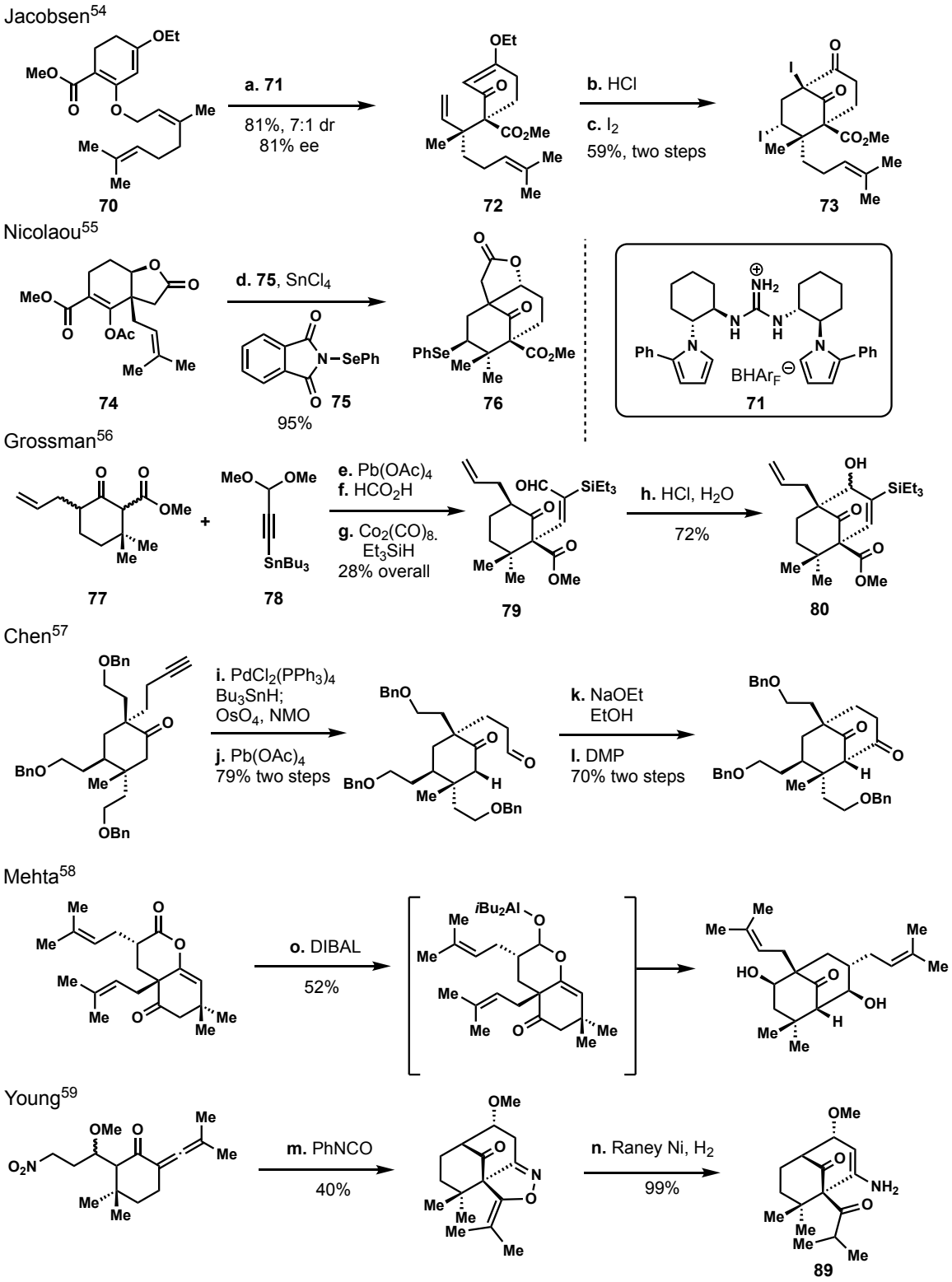
Plietker and co-workers reported an efficient and modular synthesis of *endo*-PPAPs *via* a Dieckmann cyclization strategy (Scheme 11).[51] In their total synthesis of 7-*epi*-clusianone, acetylacetone was prenylated (NaH, prenyl bromide), followed by formylative deacylation affording enone **63** in 60% yield. A Robinson annulation of enone **63** and dimethyl 1,3-acetonedicarboxylate (**64**) afforded cyclohexenone **65**. The *β*-ketoester was protected by deprotonation with NaH and 1,2-addition of MeLi afforded the methyl ketone. The *β*-ketoester was then prenylated with prenylbromide followed by 1,4-addition of methyl cuprate to yield diketone **66** in 60% yield over three steps. Diketone **66** was then subjected to an iron catalyzed prenylation reaction developed by Plietker.[52] When employing the 1,3-dimesitylimidazolin-2-ylidene hexafluorophosphate ligand **67** and $Bu_4N[Fe(CO)_3(NO)]$ as catalyst, the prenylation was selective for the carbon atom of the 1,3-diketone group. Acylation of **68** with benzoyl cyanide and intramolecular Dieckmann condensation produced 7-*epi*-clusianone (**69**). In the same communication, Plietker and co-workers also synthesized hyperpapuanone, hyperibone L, and oblongifolin A showcasing the generality of this approach towards *endo* PPAPs.[51] In a separate account, Plietker utilized a similar strategy for the synthesis of guttiferone A and its C6 epimer.[53]



Scheme 11. Plietker total synthesis of 7-*epi*-clusianone

Many other research groups have reported progress towards PPAP natural products (Scheme 12). The Jacobsen group have reported a enantioselective Claisen rearrangement of allyl enol ether **70** with thiourea catalyst **71** to afford compound **72** (81% yield, 81% ee) which possesses the all carbon stereocenter in hyperforin.[54]

Iodination followed by iodocyclization of the vinylogous enol ether afforded iodide **73** in 59% yield over two

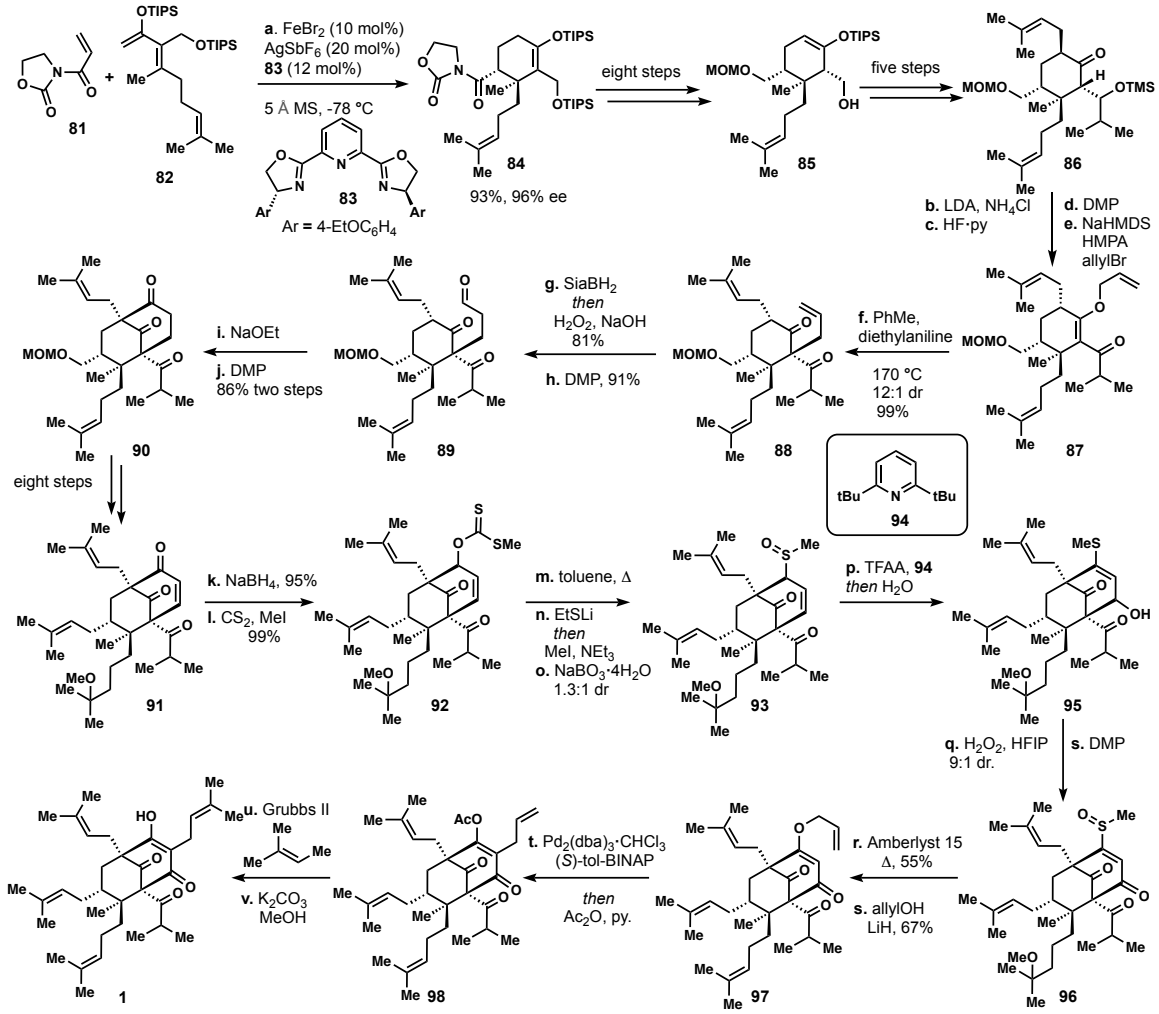


Scheme 12. Progress towards various PPAP natural products

steps.[54] Nicolaou and co-workers developed a selenocyclization of enol ether **74** with *N*-(phenylseleno)phthalimide (**75**) and tin tetrachloride to furnish bicycle **76**.[55] Grossman utilized a $Pb(OAc)_4$ mediated alkynylation of *β*-ketoester **77** with stannane **78** in their progress towards the synthesis of garsubellin A.[56] Formic acid mediated deacetalation, followed by hydrosilylation ($CO_2(CO)_8$, Et_3SiH) afforded vinylsilane **79**. Intramolecular aldol reaction mediated by hydrochloric acid afforded compound **80** in 72% yield. Chen[57] and Mehta,[58] in their progress towards the total synthesis of PPAPs, utilized an intramolecular aldol reaction to furnish the bicyclo [3.3.1] nonane skeleton. The Young group executed an interesting allene/nitrile oxide [3+2] cycloaddition strategy in their progress towards hyperevolutin A.[59]

Total Syntheses of Hyperforin

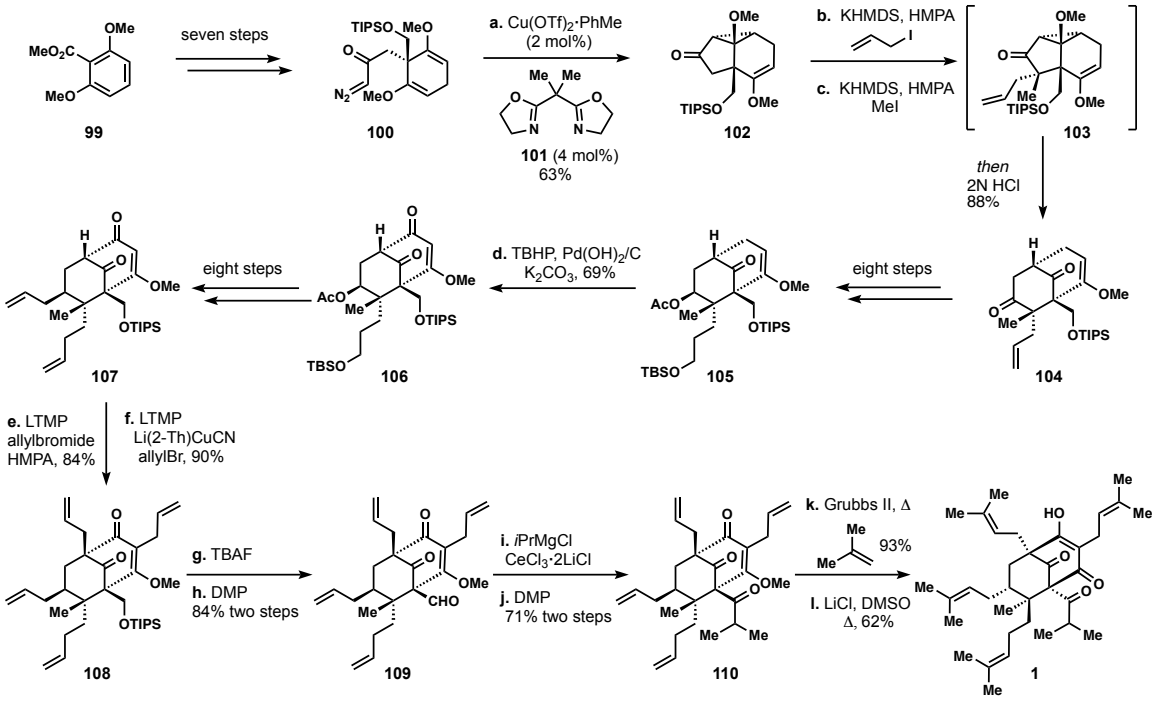
In 2010, Shibasaki reported the first total synthesis of hyperforin.[60] This landmark synthesis occurred in 51 steps from commercially available starting materials, highlighting the unique challenges hyperforin presents over other PPAP natural products (Scheme 13). An iron catalyzed enantioselective Diels-Alder reaction between



Scheme 13. Shibasaki's Total Synthesis of *ent*-hyperforin

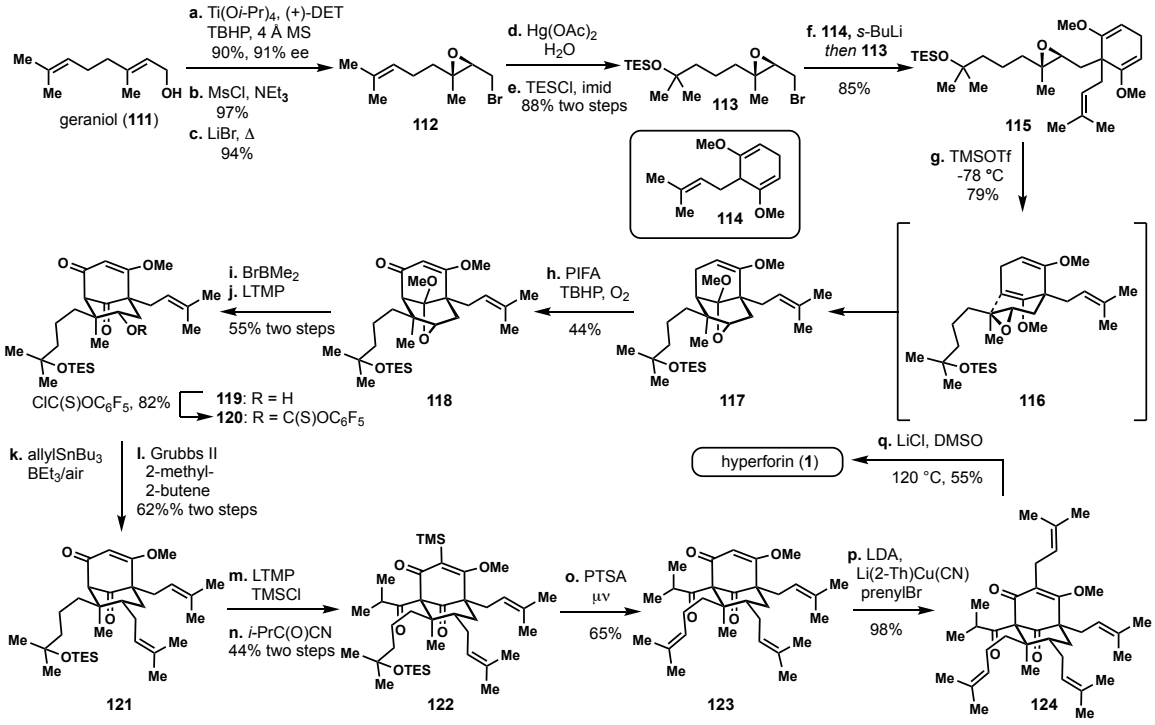
reaction between α,β-unsaturated amide **81** and diene **82** begins the synthesis**.** Using pyBOX ligand **83**, enol ether **84** was obtained in 93% yield and 96 % ee.[61] Eight steps were used to convert the oxazolidinone into a MOM-protected alcohol, deprotect the TIPS-protected alcohol and isomerize the silyl enol ether this producing compound **85**. Another five steps were implemented to incorporate a prenyl group, oxidize the primary alcohol, add an isopropyl Grignard into the newly formed aldehyde group and protect the resulting secondary alcohol. With compound **86** in hand, the prenyl group was epimerized with LDA and the TMS-protected secondary alcohol was deprotected and then oxidized with Dess-Martin periodinane. Using NaHMDS and HMPA as a polar additive, the enolate was selectively *O*-allylated with allyl bromide. Compound **87** was subjected to a thermal Claisen rearrangement at 170 ^{o}C to produce diketone **88** in excellent yield and diastereoselectivity. The monosubstituted olefin was then subjected to hydroboration/oxidation followed by DMP oxidation to furnish aldehyde **89**. Intramolecular aldol reaction followed by DMP oxidation furnished ketone **90** in 86% yield. Another eight steps were required to install the C7 prenyl group and the enone of the β-hydroxyenone in hyperforin. Compound **91** was subjected to $NaBH_4$ reduction of the enone followed by xanthate formation with carbon disulfide and MeI. Xanthate **92** was subjected to thermal a [1,3] isomerization followed, by thioester cleavage and methylation.[62] The methyl sulfide was oxidized with $NaBO_3$ to sulfoxide **93**. A vinylogous Pummerer rearrangement with TFAA and di-*tert*-butylpyridine (**94**) installed the alcohol group in compound **95**.[63] Reoxidation of the sulfide to the sulfoxide followed by DMP oxidation produced compound **96**. The tertiary alcohol group was then eliminated by treatment with PTSA and nucleophilic substitution of methylthiol with allyl alcohol ensued in good yield (See **96** to **97**). A palladium catalyzed Claisen rearrangement with Pd_2dba_3 and (*S*)-BINAP followed by acylation of the 1,3-diketone produced compound **98**. Olefin metathesis and deacylation finally afforded *ent*-hyperforin.

Nakada and co-workers reported the total synthesis of hyperforin via an intramolecular cyclopropanation approach (Scheme 14).[64] Diazo compound **100** was obtained from arene **99** *via* a Birch reduction followed by six steps. Copper (II) triflate in the presence of bisoxazoline ligand **101** catalyzed an intramolecular cyclopronanation to afford cyclopropane **102**.[65] Double alkylation with allyl iodide and then methyl iodide produced intermediate **103** which was subjected to acid mediated C-C bond fragmentation to afford ketone **104**. Eight steps converted the pendent allyl group to a TBS protected alcohol and the ketone moiety into an acetate (See **104** to **105**). A palladium hydroxide catalyzed allylic oxidation afforded vinylogous ester **106**. Eight steps incorporated the allyl group and one-carbon homologation of the existing allyl chain into the homoprenyl group of hyperforin. With bicycle **107** in hand, bridgehead allylation (LTMP, allylbromide) followed by allylation of the vinyl position resulted in compound **108**. Desilylation followed by DMP oxidation afforded aldehyde **109**. Isopropyl magnesium chloride reacted with aldehyde **109** and the product was subsequently oxidized to ketone **110**. Global olefin metathesis with isobutylene and Grubbs II catalyst occurred in high yield. Demethylation with LiCl unveiled hyperforin in 35 steps.[64]



Scheme 14. Nakada's total synthesis of hyperforin (**1**)

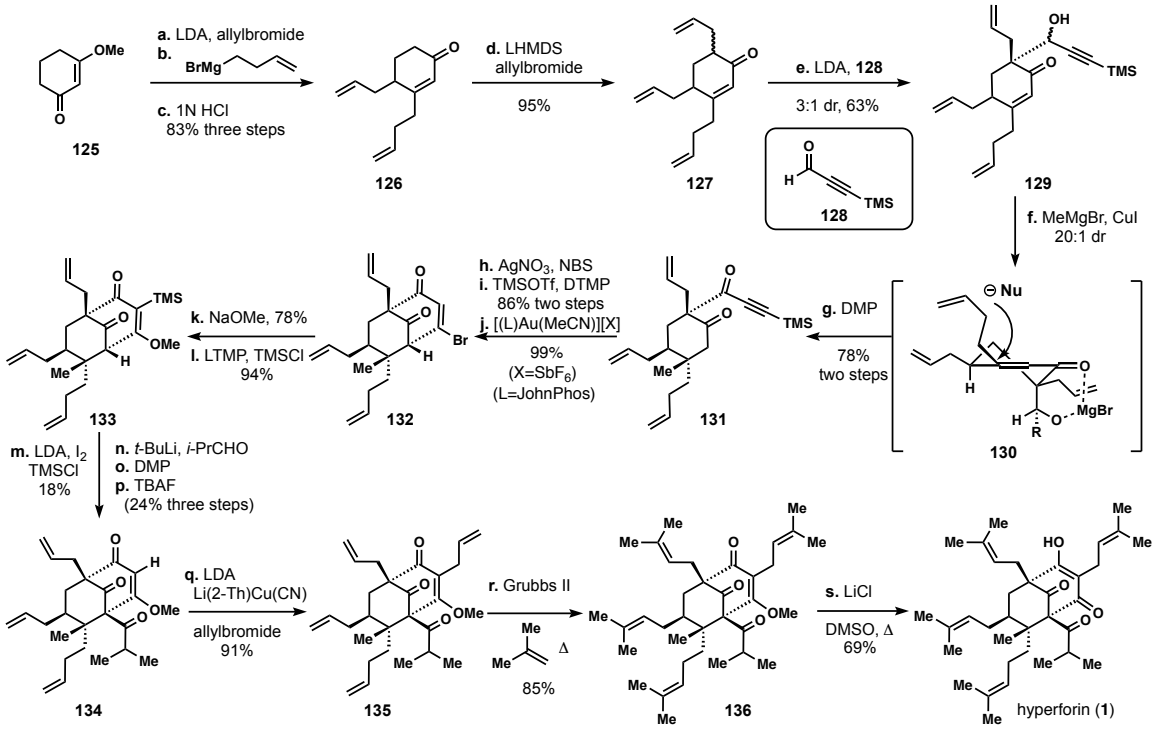
In 2012, Shair and co-worker reported the first asymmetric synthesis of (+)-hyperforin (Scheme 15).[66] Starting from commercially available geraniol (**111**), a Sharpless asymmetric epoxidation furnished the corresponding epoxide in 90% yield and 91% ee. Two step mesylation and bromide displacement produced epoxybromide **112**. The pendant olefin was protected *via* oxymecuration and silylation of the newly formed tertiary alcohol to afford compound **113**. Enol ether **114** was synthesized in two steps via Birch reduction and regioselective prenylation. The union of **113** and **114** occurred by deprotonation with *s*-BuLi and alkylation with **113** to afford compound **115**. Trimethylsilyl triflate mediated a diastereoselective epoxide opening *via* chair-like transition state **116**, and subsequent ketalization to afford ketal **117** in 79% yield. The methyl enol ether was subjected to allylic oxidation conditions (PIFA, TBHP and O_2) resulting in enone **118** in 44% yield.[67] The ketal was demethylated with $BrBMe_2$ followed by base mediated deketalization (LTMP) affording alcohol **119** in 55% yield over two steps. Alcohol **119** was converted to a Barton ester (**120**), and upon radical allylation conditions (BEt_3, $allylSnBu_3$, air) followed by olefin metathesis compound **121** was obtained. The C3 vinyl position was protected with TMSCl thus allowing for bridgehead acylation (LTMP then isobutyryl cyanide) producing **122** in 44% yield over two steps. This direct acylation protocol was an improvement from the stepwise iodination, aldol and oxidation sequence disclosed by Danishefsky in 2006.[31] The OTES group was eliminated with *p*-toluenesulfonic acid and microwave irradiation to reform the homoprenyl group of hyperforin. Desilylation of the vinylsilane occurred in the same reaction to afford **123** in 65% yield. Directed *ortho*-lithiation followed by addition of Li(2-Th)Cu(CN) and prenylbromide installed the last prenyl group to afford methylhyperforin (**124**).[38] Demethylation with LiCl provided hyperforin (**1**) in 55% yield. Shair's synthesis of hyperforin showed



Scheme 15. Shair's total synthesis of hyperforin (**1**)

monumental improvement in synthetic efficiency toward this challenging PPAP target. The direct bridgehead acylation reaction was significant to avoid known multistep sequences in installing the isopropylketone group of hyperforin. In 2015, Shair and co-workers reported the total synthesis of (-)-nemorosone and (+)-secohyperforin via a similar strategy.[68]

In 2014, Barriault and co-workers reported a gold-catalyzed 6-*endo* cyclization to furnish the PPAP skeleton in their synthesis of hyperforin (Scheme 16).[69] *β*-Methoxycyclohexenone (**125**) was subjected to enolate allylation (LDA, allyl bromide) followed by 1,2-addition of homoallylmagnesium bromide and Stork-Danheiser rearrangement to obtain enone **126** in 83% yield over three steps. Another enolate allylation afforded compound **127** which was subjected to an aldol reaction with ynal **128** (63% yield, 3:1 dr). Propargyl alcohol **129** was treated with methylmagnesium bromide and CuI to elicit a highly diastereoselective conjugate addition reaction. A chelate model was proposed to explain the high diastereoselectivity observed (See **130**). After DMP oxidation, diketone **131** was obtained in 78% yield over two steps. Next, the TMS group was replaced with a bromide via $AgNO_3$ and NBS. Silyl enol ether formation (TBSOTf, DTMP) followed by a gold-catalyzed cyclization afforded bicycle **132** in good yield.[70] The vinylbromide group of **132** was substituted with methoxide and the C3 vinyl position silylated by directed *ortho*-lithiation. With compound **133** in hand, a three step sequence reported by Danishefsky installed the isopropylketone and desilylation afforded compound **134**.[31] The authors noted that Shair's one-pot procedure for acylation resulted in no reaction with



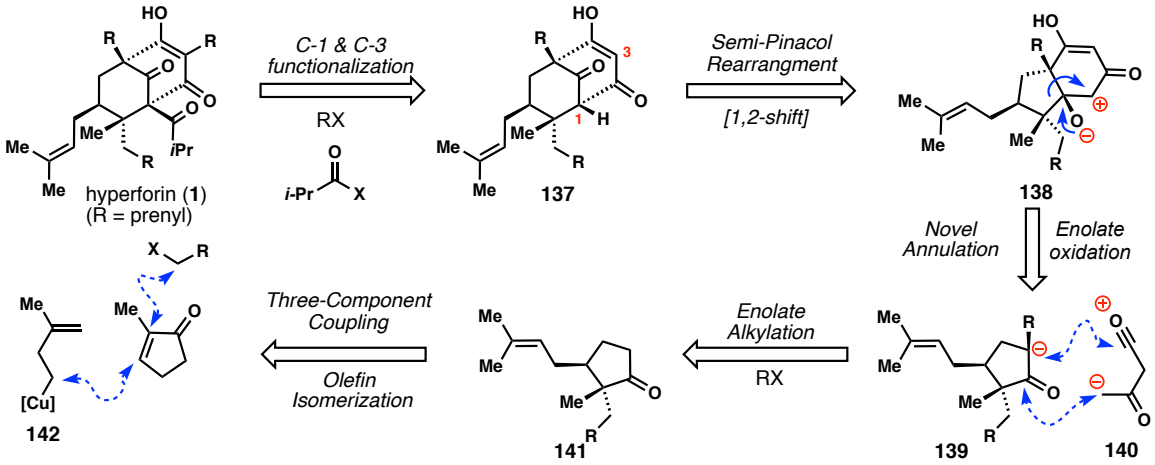
Scheme 16. Barriault's total synthesis of hyperforin (**1**)

this specific vinylogous ester regioisomer.[66,69] Compound **134** was subjected to directed *ortho*-lithiation, transmetallated onto copper(I), and quenched with allyl bromide. Compound **135** was then subjected to global olefin metathesis with Grubbs II catalyst and isobutylene to afford methylhyperforin **136** in 85% yield. Demethylation (LiCl, DMSO) unveiled racemic hyperforin in 17 steps.

Despite extensive research efforts dedicated to the total synthesis of PPAPs, structure-activity relationship studies of this class of natural products have been lacking primarily due to difficulties associated with systemically modifying the different appendages on the bicyclo [3.3.1] nonane core of these natural products.[71]

2.2 Retrosynthesis of Hyperforin

In our retrosynthesis, hyperforin (**1**) was proposed to be synthesized from simplified bicyclo[3.3.1] nonane **137** by stepwise incorporation of the C-3 prenyl group and the C-1 isopropyl ketone in analogy to previous syntheses (Scheme 17). We envisioned assembly of the bicyclo [3,3,1] nonane carbocyclic skeleton by ring expansion of a fused 5,6-bicycle, a unique disconnection from all prior syntheses. A semi-pinacol rearrangement was designed and proposed to occur through intermediate **138**, itself generated by the oxidation of an enolate. Next, a hypothetical annulation reaction between enolate **139** and acylium ion **140** was envisioned to incorporate the *β*-hydroxy-1,3-cyclohexanone group in a single step. The conjugate acid of **139** can be synthesized from enolate alkylation of **141** which is prepared by a three-component coupling reaction and olefin isomerization (Scheme 17).



Scheme 17. Retrosynthetic analysis of hyperforin

The ability to access multiple PPAPs and their analogs influenced our retrosynthetic design. The appendages on hyperforin are proposed to be installed by reliable enolate alkylation chemistry and use commericial or easily-accessible chemicals. The described synthetic plan allows for the preparation of a highly substituted bicyclo [3.3.1] nonane 1,3,5-trione motif and serves as a platform for the construction of highly diverse PPAPs modifiable at every position (Figure 7).

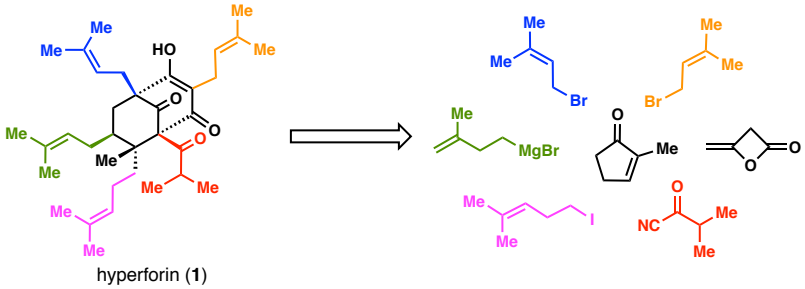
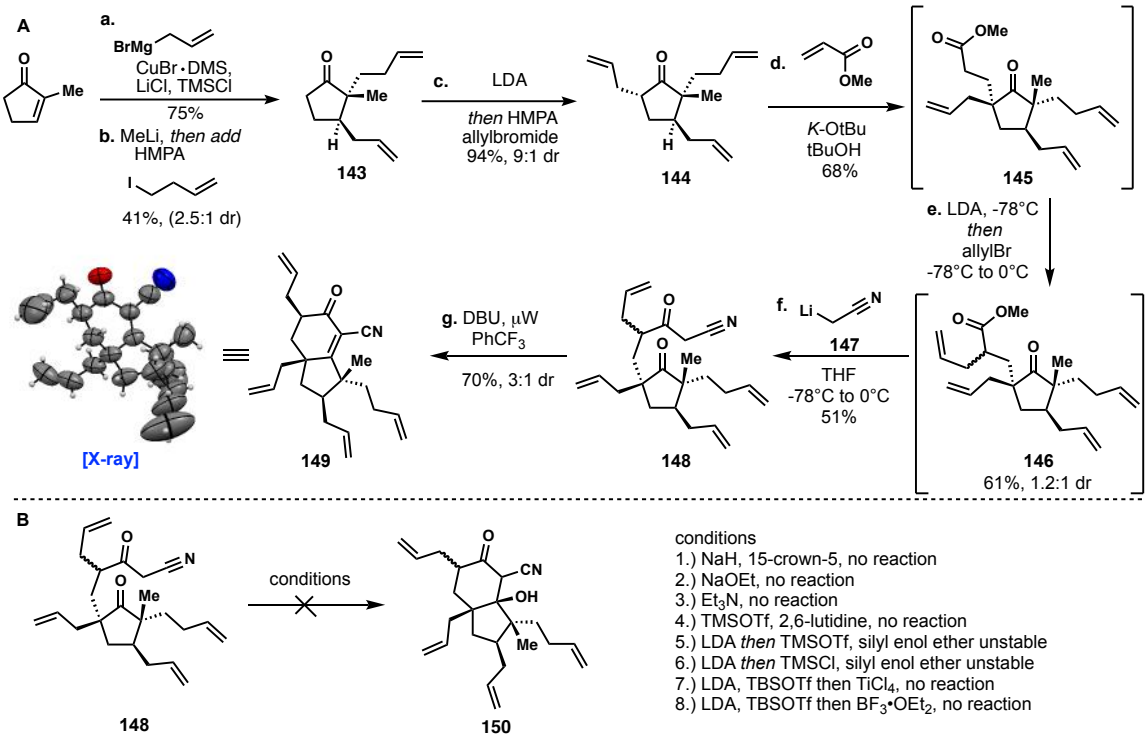


Figure 7. Modularity of the proposed retrosynthesis.

2.3. Initial Foray into the Total Synthesis of Hyperforin.

The early stages of our investigations involved the use of a model substrate containing allyl groups instead of prenyl groups due to ease of synthesis. Our study commenced with 2-methylcyclopentenone, copper-mediated conjugate addition of allylmagnesium bromide to 2-methylcyclopentenone and silylation.[72] Desilylation with methyllithium and enolate alkylation with homoallyl iodide produced a 2.5:1 mixture of diastereomers (See **143**).[73] Subsequent enolate alkylation with LDA and allylbromide afforded cyclopentanone **144** in excellent yield as an inconsequential mixture of diastereomers. The addition of HMPA and exactly one equivalent of base and



Scheme 18. A. Synthesis of enone **149**. B. Attempled aldol reaction of **148**

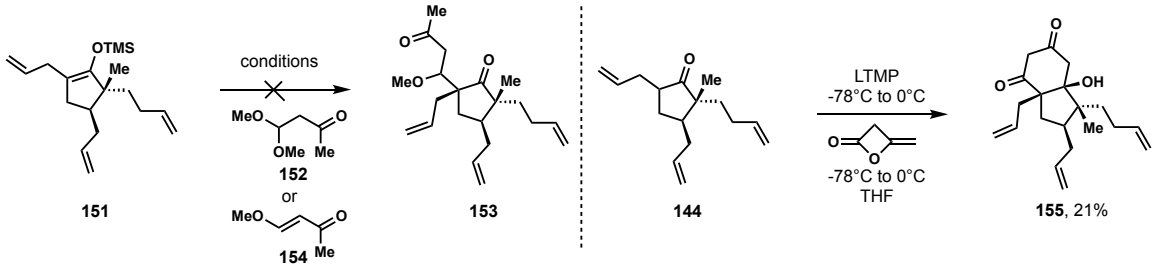
electrophile were essential in preventing double allylation. Cyclopentanone **144** was subjected to potassium *tert*-butoxide and methyl acrylate inducing a Michael addition affording compound **145** in 68% yield. Another allylation (LDA, allylbromide) afforded cyclopentanone **146** as a 1.2:1 mixture of diastereomers. Deprotonation of **145** at low temperature was key to preventing an undesired retro-Michael reaction. Enolates derived from ethyl acetate or methylisopropylketone failed to undergo Claisen condensation with **146**. Fortunately, the lithiate of acetonitrile (**147**) was identified as a competent nucleophile for a Claisen-like reaction affording β-ketonitrile **148** in 51% yield. The selective addition of isopropylmagnesium bromide to the nitrile group was envisioned to introduce the isopropyl ketone removing the need for late-stage bridgehead acylation, a reaction which is notoriously and highly substrate dependent.[31,66,69]

At this stage in the synthesis, an intramolecular aldol would allow access to compound **150**, the substrate for the proposed oxidative rearrangement (Scheme 18B). However, under numerous conditions, no carbon-carbon bond formation was detected.

Basic conditions including inorganic bases (NaH, NaOEt) and organic bases (NEt_3, LDA) resulted in the recovery of starting material. A possible explanation for this could be that the aldolate undergoes reversion to the starting material.[29] Alternatively, the electrophilic ketone group may be too sterically hindered to react as it is flanked by two adjacent all-carbon stereocenters. We then decided to investigate Mukaiyama-aldol reactions as a means for trapping the aldolate as the silanol. Silyl enol ether formation with TMSOTf or TMSCl resulted in recovered starting material. The TBS enol ether, however, was obtained by LDA and TBSOTf. The crude mixture was then directly subjected to Lewis acid ($TiCl_4$ or BF_3•OEt_2) resulting in the recovery of the starting β-ketonitrile **148**. When β-ketonitrile **148** was treated with DBU under microwave irradiation (150 °C) aldol condensation proceed smoothly to provide enone **149** in 70% yield (Scheme 18a). The mixture of diastereomers was enriched to a 3:1 ratio. The X-ray structure of the β diastereomer of **149** was obtained to confirm the structure. The 1,4-addition of hydroxide or alkoxides were unsuccessful for reinstallation of the tertiary alcohol needed for rearrangement.

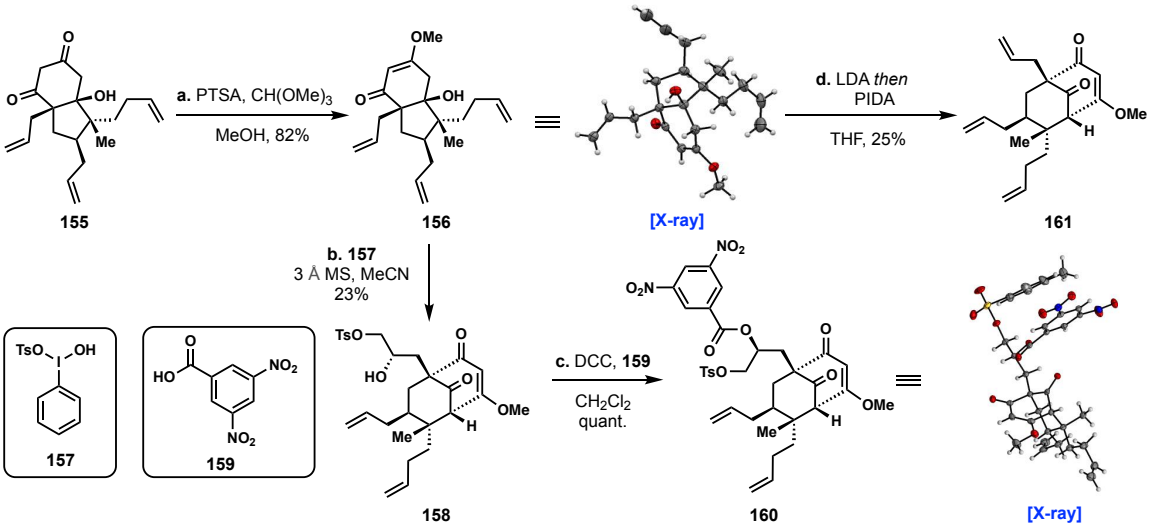
Our efforts then turned toward investigating different electrophiles that would allow access to the 1,3-diketone in hyperforin. Initially, a Mukaiyama-aldol was envisioned between silyl enol ether **151** and acetal **152**. β-Methoxy ketone **153** would be converted to the diketone of hyperforin by oxidation. Unfortunately, various Lewis acids ($TiCl_4$, BF_3 and TMSOTf) failed to provide the desired product. Next, vinylogous ester **154** was envisioned to afford the same product by a Mukaiyama-Michael reaction. The same Lewis acids only resulted in recovery of the parent ketone of the starting material (**144**).

We recognized that compound **154** would still require an additional oxidation to access the 1,3-diketone of hyperforin. However, we were unaware of any annulation reaction that would directly provide the desired oxidation state in the product. The discovery of diketene as an annulation partner was not our initial intention, but a solution that developed with cognizance of step and redox economy.[74] Ketone **144** was subjected to LHMDS and the resulting lithium enolate reacted with diketene to afford diketone **155** in 21% yield respectively (Scheme 19).[75] Although the yield of the annulation reaction was modest the reaction proved insensitive to scale and diketone **155** was prepared on gram scale. Significant amounts of recovered starting material (30% yield) were obtained which could be the result of intermolecular proton transfer from product to the enolate of the starting material. Utilizing different bases with larger counterions (Na^+, K^+) resulted in higher yields of an undesired *O*-acylated product.[76]



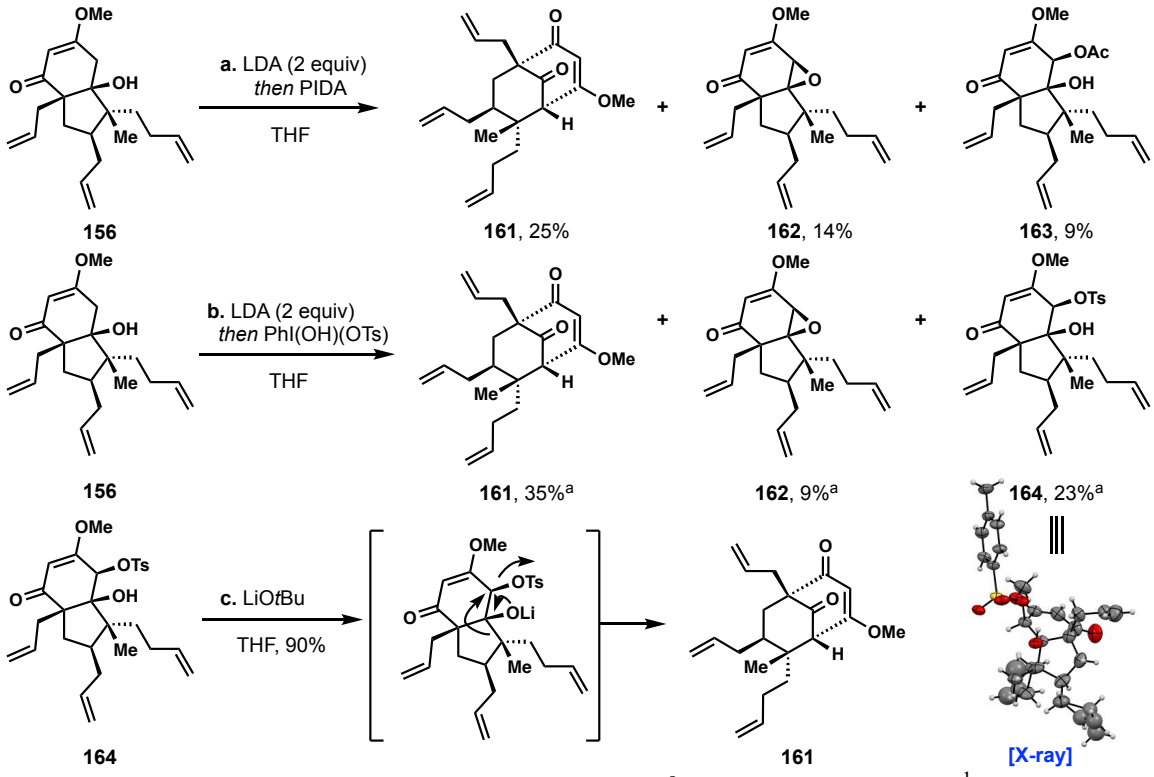
Scheme 19. Discovery of a novel diketene annulation reaction

Concurrent with our attempted optimization, diketone **155** was advanced to vinylogous methyl ester **156** by acidic methylation (PTSA, $CH(OMe)_3$) (Scheme 20).[36] The regioselectivity of the methylation reaction was unambiguously determined by X-ray diffraction studies. Compound **156** was subjected to Koser's reagent (PhI(OH)(OTs), **157**) under anhydrous conditions.[77] The oxidative rearrangement proceeded along with undesired olefin functionalization, a known transformation for cationic hypervalent iodine reagents, resulting in compound **158** in 23% yield.[78] Upon derivatization of the secondary alcohol group with 3,5-dinitrobenzoic acid (**159**), compound **160**, containing the bicyclo [3.3.1] nonane, was confirmed by X-ray diffraction. Although the yield of the rearrangement product remained modest, olefin functionalization appeared to be diastereoselective. Finally, the addition of a strong lithium amide base (LDA, 2 equiv) followed by addition of diacetoxyiodobenzene allowed for oxidative rearrangement of **156** to afford bicycle **161** in 25% yield without undesired olefin functionalization. The oxidative rearrangement reaction also produced epoxide **162** and acetoxylated compound **163** in 14% and 9% yields respectively (Scheme 21). In our attempts to optimize this reaction, different hypervalent iodine reagents were utilized as oxidants after lithium amide deprotonation (Scheme 21).



Scheme 20. Initial investigations into the oxidative ring expansion

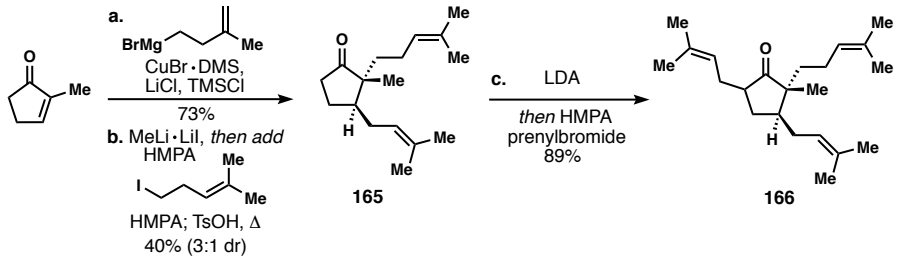
Koser's reagent resulted in a higher yield of the desired compound **161** (35% yield). Side products were identified as epoxide **162** (9%) alongside tosylate **164** (23% yield). The diastereoselectivity of tosylate addition was determined by X-ray diffraction studies and found to occur on the convex face of the bicycle. The addition of lithium *tert*-butoxide promoted the semipinacol rearrangement of tosylate **164** to bicycle **161** in excellent yield. It is worth noting that acetate **163** derived from PIDA was not a competent rearrangement substrate. We propose that the rearrangement occurs through a hypervalent iodine intermediate, but when Koser's reagent is used the bicycle **161** is obtained in higher yield due to the additional rearrangement pathway of the tosylate (Scheme 21).



Scheme 21. Oxidative rearrangement optimization. [a.] Yield determined by ^{1}H NMR.

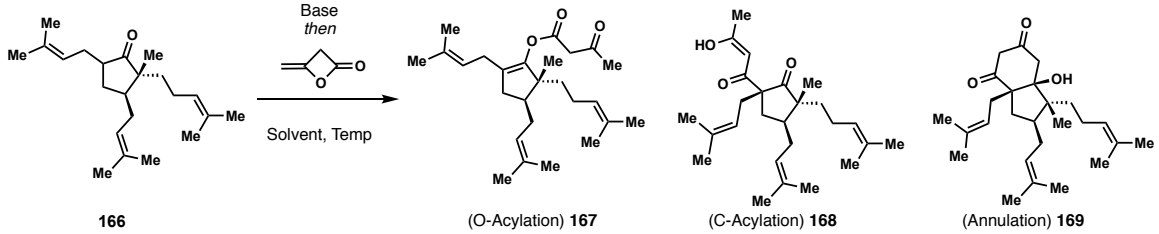
2.4. Total synthesis of Hyperforin.

Having achieved the desired oxidative semipinacol rearrangement for our model substrate, we turned to the actual substrate containing the prenyl groups present in hyperforin. Our synthesis commenced with a copper-mediated conjugate addition of 3-methyl-3-butenylmagnesium bromide to 2-methylcyclopentenone followed by silylation to afford the silyl enol ether in 73% yield (Scheme 22).[72] The silyl enol ether was treated with methyllithium, and the resulting lithium enolate was alkylated with homoprenyliodide. Finally, tosic acid catalyzed olefin isomerization furnished cyclopentanone **165** in 40% yield as a 3:1 mixture of diastereomers. Enolate prenylation (LDA, prenyl bromide) produced cyclopentanone **166** in 89% yield. Through this simple sequence, multi-gramg quantities of **166** have been procured.



Scheme 22. Synthesis of cyclopentanone building block **166**

Significant efforts was devoted to improving the diketene annulation reaction (Table 1). Byproducts derived from O-acylation (**167**) and C-acylation (**168**) were also isolated. For all reactions, recovered starting material was also reisolated. Interestingly, prior to the reaction, the starting material was predominantly the α-diastereomer, but after the reaction the recovered, starting material was epimerized to the β-diastereomer. This observation was crucial to confirm the complete enolization of the starting material.

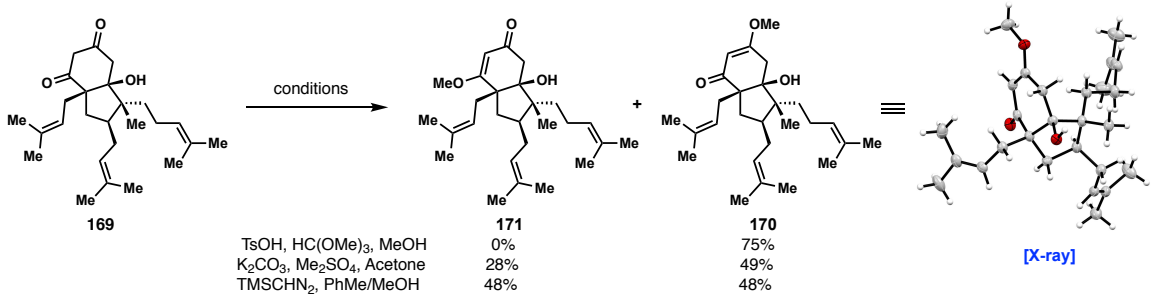


Entry	Base/Solvent	Temp (°C)	Yield of **167** (%)[a]	Yield of **168** (%)[a]	Yield of **169** (%)[a]	Recovered **166**[a]
1	LDA/THF	-78 to -0	17	3	11	30
2	LHMDS/THF	-78 to -0	5	2	9	23
3	*t*-BuLi/THF	-78 to -0	24	11	17	42
4	LTMP/THF	-78 to -0	8	6	21	24
5	LTMP/Et_2O	-78 to -0	0	9	9	25
6	LTMP/THF:CPME	-78 to -0	14	10	15	19
7	LTMP/THF:iPr_2O	-78 to -0	11	17	19	20
8	LTMP/THF:Et_2O	-40	14	6	35[b]	22[b]

Table 1. Optimization of the diketene annulation reaction for total synthesis of hyperforin. [a.]Yield determined by ^{1}H NMR. [b.]Isolated Yield

Various lithium bases were tested, and LTMP resulted in the highest yield of the desired annulation product (21%, See Entries 1-4, Table 1). When the reaction solvent was switched from THF to ether, the yield for the desired annulation product decreased to 9%, but no *O*-acylation was observed (Entry 5, Table 1). Mixed ethereal solvent systems were examined and it was found that a 1:1 mixture of THF/Et_2O resulted in the highest yield (35%, Entry 8, Table 1). Mukaiyama-type acylations with silyl enol ethers were briefly attempted but only resulted in polymerization of diketene.

With adequate amounts of diketone **169** in hand, the 1,3-diketone group was converted to its corresponding vinylogous methyl ester (Scheme 23). *p*-Toluenesulfonic acid and trimethylorthoformate resulted in the regioselective methylation of the distal ketone in 75% yield. The structure of the constitutional isomer was confirmed by X-ray diffraction analysis. Notably, Barriault and co-workers reported that Shair's one pot bridgehead acylation procedure failed on this constitutional isomer series.[66,69] Dimethylsulfate and potassium carbonate afforded a 1.8:1 mixture favoring the undesired regioisomer **170**, but trimethylsilyldiazomethane afforded a 1:1 mixture of separable regioisomers in 96% yield. The undesired regioisomer (**170**) was recycled by basic hydrolysis (KOH, dioxane) to afford diketone **169** in 60% yield.

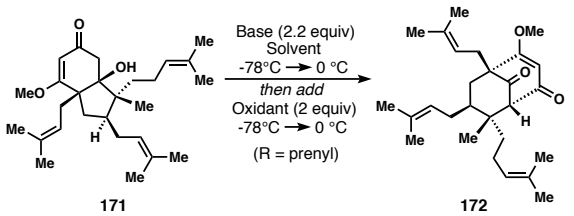


Scheme 23. Studies on the regioselective methylation of diketone **169**

With access to the desired isomer **171**, similar oxidative rearrangement conditions that worked on the model substrate were examined (Scheme 24). Surprisingly, LDA followed by the addition of $PhI(OAc)_2$ resulted in only 11% yield of bicycle **172**.[77] The addition of a series of oxidants (Cu^{II}, Fe^{III}, NBS, I_2) did not result in higher yields of the desired product (Entry 2-5, Scheme 24a). More reactive hypervalent iodine oxidants improved the yield of bicycle **172**. PIFA resulted in 23% yield, and the highly reactive dicyanoiodobenzene improved the yield to 40%.[79] Inspired by known conditions for the Favorskii ring-contraction of steroidal framework, potassium hydroxide and basic methanol resulted in 92% yield of **172**.[80] The use of a weaker base presumably generated the highly reactive anionic species in low concentrations and allowed for a high yielding rearrangement reaction to cocur. The dianionic intermediate is proposed to engage iodosobenzene, known to be generated under these conditions, to form intermediate **173** which rearrange by a semi-pinacol reaction to afford **172**.

Bicycle **172** was subjected to directed *ortho*-lithiation and chlorination by tosyl chloride to afford vinyl chloride **174** in excellent yield. Chloride **174** was then subjected to Shair's one pot acylation procedure (LTMP then *i*-PrCOCN) affording compound **175**

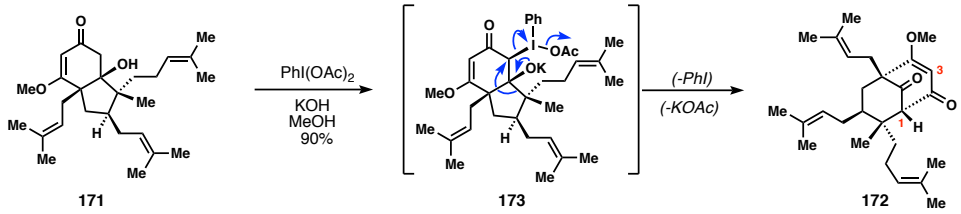
A



Entry	Base/solvent	Oxidant	Yield (%)[a]
1	LDA/THF	$PhI(OAc)_2$	11
2	LDA/THF	I_2	15
3	LDA/THF	NBS	9
4	LDA/THF	$Fe(acac)_3$	6
5	LDA/THF	$Cu(2\text{-ethylhexanoate})_2$	0
6	LDA/THF	$PhI(OTFA)_2$	23
7	LDA/THF	$PhI(CN)_2$	40[b]
8	KOH/MeOH	$PhI(OAc)_2$	92[b,c,d]

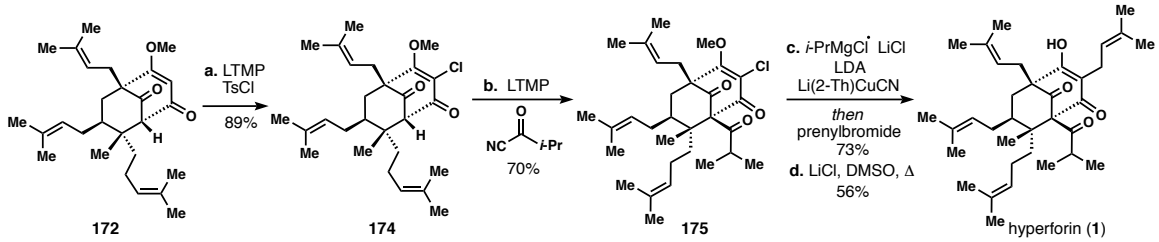
[a] yield determined by ^1H NMR. [b] isolated yield. [c] T = 25 °C. [d] [KOH] = 1.8 M.

B



Scheme 24. A.) Optimization of oxidative rearrangement reaction, B.) Possible mechanism of oxidative rearrangement

in 70% yield.[66] The increased yield for this transformation could be rationalized by inductive stabilization by the chlorine atom facilitating the challenging deprotonation. Compound **175** was subjected to magnesium-chloride exchange with Turbo Grignard, transmetallation onto Li(2-Th)Cu(CN), and quenched with prenylbromide.[38] Large amounts of dehalogenated side product was obtained perhaps due to the generated isopropylchloride as a proton source *via* E2 elimination. The addition of LDA improved the yield to 73%. Finally, demethylation (LiCl, DMSO) unveiled hyperforin (**1**) in 56% yield. As previously reported, hyperforin **1** is light and oxygen sensitive.[1a] During purification, it was necessary to remove light and act quickly to limit exposure to oxygen. Hyperforin was prepared in ten steps from commercially available 2-methylcyclopentenone, thus completing the most concise synthesis of this natural product reported to date.[81,82]



Scheme 25. Total synthesis of hyperforin

2.5. Development of a Novel Diketene Reaction

We investigated other ketone substrates that could undergo the diketene annulation reaction (Figure 8). Sterically hindered ketone substrates required polar solvents such as THF for annulation. This was the case for diisopropylketone which was deprotonated with LTMP and annulated with diketene in 1:1 THF/ether mixture to afford **176** in 59% yield. Under identical conditions, arylketones such as isopropylphenyl ketone resulted in primarily O-acylation. When the reaction solvent was switched to pure Et_2O, annulation occurred to afford **177** in 44% yield. For arylketones, this general procedure was adopted to afford other cyclic 1,3-diketones (**178-182**) in modest yield. For the propiophenone-diketene adduct (**178**), the diastereoselectivity of annulation was confirmed unambiguously by X-ray diffraction showing a clear trans-relationship between the methyl and aryl group. A model for the diastereoselectivity of this reaction is proposed to occur through a six-membered chair-like transition state with the methyl and aryl groups in the equatorial position (Figure 9).

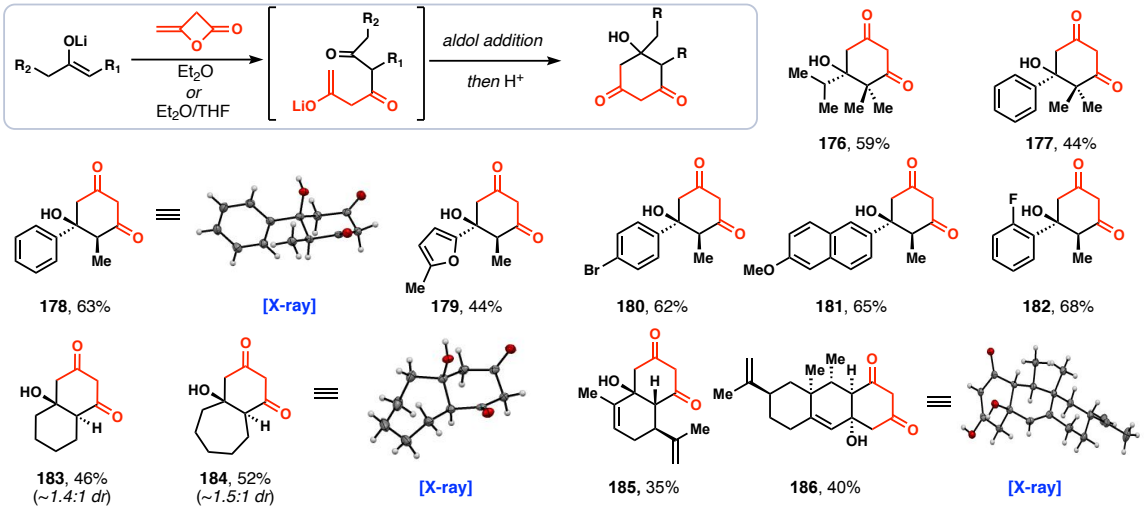


Figure 8. Diketene Annulation Substrate Scope

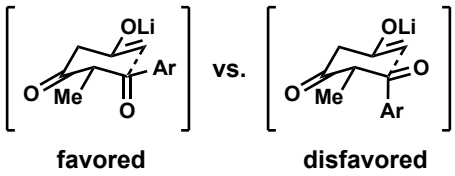


Figure 9. Diastereoselectivity model for annulation

While the cyclopentanone **166** in the hyperforin synthesis exhibited complete *cis* diastereoselectivity of annulation, cyclohexanone and cycloheptanone resulted in more of the *trans* diastereomer (**183** and **184**). The diastereoselectivity was once again confirmed by X-ray crystal analysis. Higher yields for annulation of the six-membered ring ketones were obtained by methyllithium desilylation of the silyl enol ether followed by annulation with diketene. Similar observations were made on enone substrates (–)-carvone and (+)-nootkatone (See products **185** and **186**). For enone substrates, the *cis* diastereomer was obtained predominantly due to conformational restrictions of the starting material. In conclusion, the diketene annulation shows modest generality with regards to ketone substrate scope, but can prepare previously unknown chemical entities.

2.6. Meroterpenes Derived from 3,5-dimethylorsellinic Acid.

Berkeleyone A (**187**) was isolated by Stierle and co-workers from the fungus *Penicillium rubrum* found in the Berkeley Pit, a lake with a high concentrations of toxic metals and an extremely low pH (Figure 10).[83] Structurally related compounds such as berkeleytrione (**188**) and berkeleydione (**189**) were also isolated from the same species.[84] The berkeleyone family of natural products belong a larger group of natural products (>100 compounds) derived from 3,5-dimethylorsellinic acid (DMOA, **198**). These natural products include, but are not limited to, andibenin (**190**), simplicissin (**191**), tropolactones (See **192**), terretonins (See **193**), andrastins (See **194**-**195**) and austins (See **196**-**197**) (Figure 10).[85]

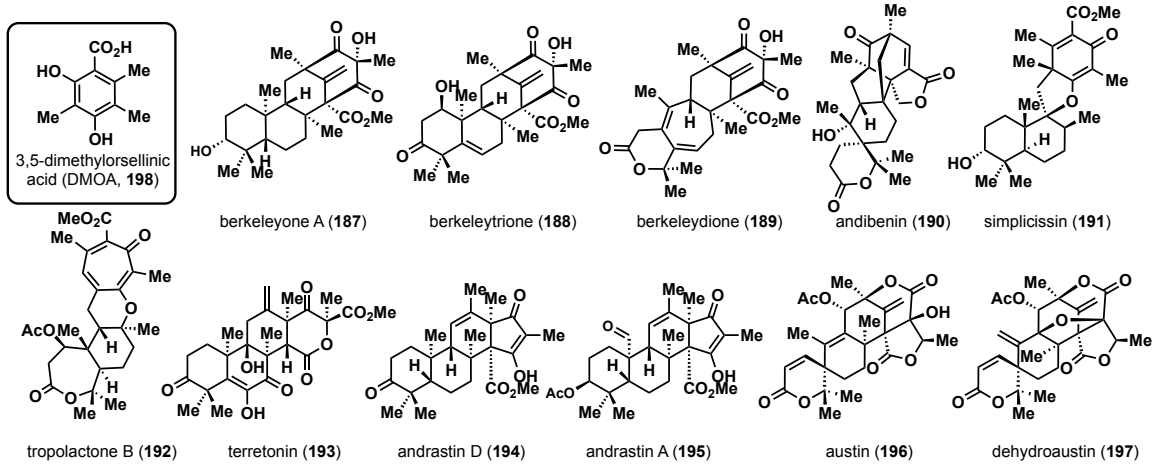
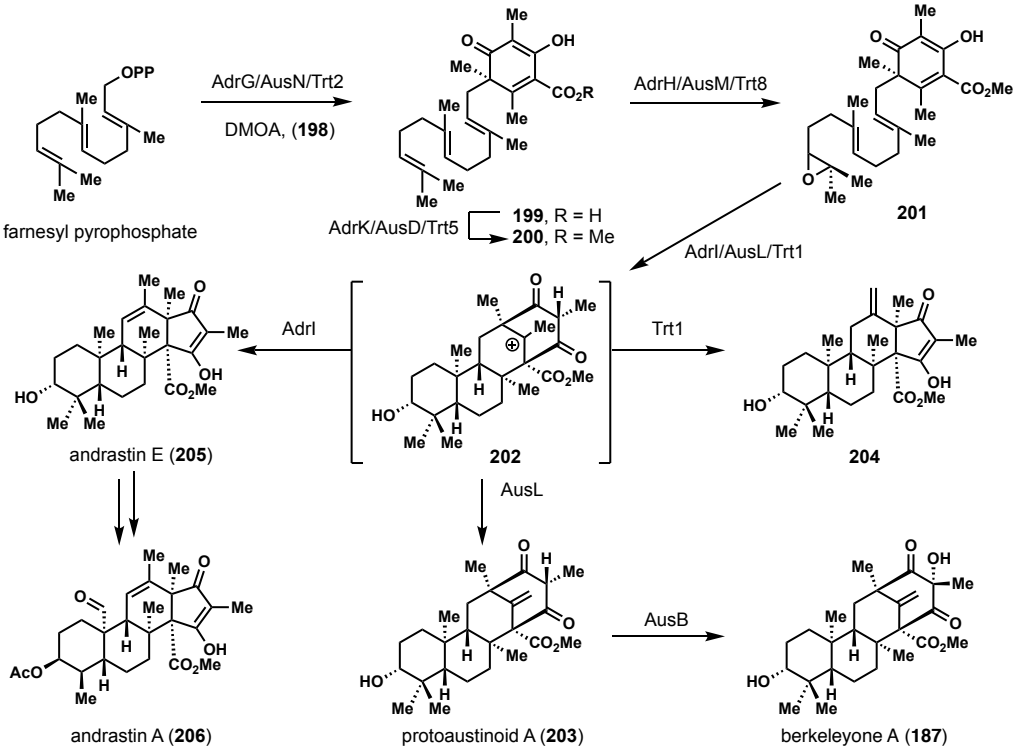


Figure 10. Fungal meroterpenes derived from 3,5-dimethylorsellinic acid (DMOA)

Unlike PPAPs, DMOA-derived natural product biosynthesis has been extensively studied.[86] Similarities in the biosynthesis of these molecules involve the union of farnesyl pyrophosphate and DMOA (**198**), followed by methylation of the benzoic acid (See **199** to **200**) and the epoxidation of the terminal alkene group of the product to produce compound **201**. Enzymes for the biosynthesis of austin (Aus), andrastin A (Adr) and terretonin (Trt) have been identified (Scheme 26).[87,88,89] The point of divergence in the biosynthesis of these compounds is after cationic polyene cyclization to afford carbocation **202**. While in austin (**196**) biosynthesis, AusL terminates by elimination to produce protoaustinoid A (**203**),[87] enzymes for terretonin and andrastin A biosynthesis, Trt1 and AdrI catalyze a [1,2] acyl shift rearrangement to furnish a fused [6,6,6,5] tetracycle.[87,88] Trt1 produces the exocyclic olefin in preterretonin A **204**, and AdrI produces andrastin E (**205**), which is further functionalized to furnish andrastin A (**206**). Protoaustinoid A (**203**) is known to be oxidized by AusB to synthesize berkeleyone A.[87] The isolation group reported that **203** can also undergo aerobic oxidation to produce berkeleyone A.[83]

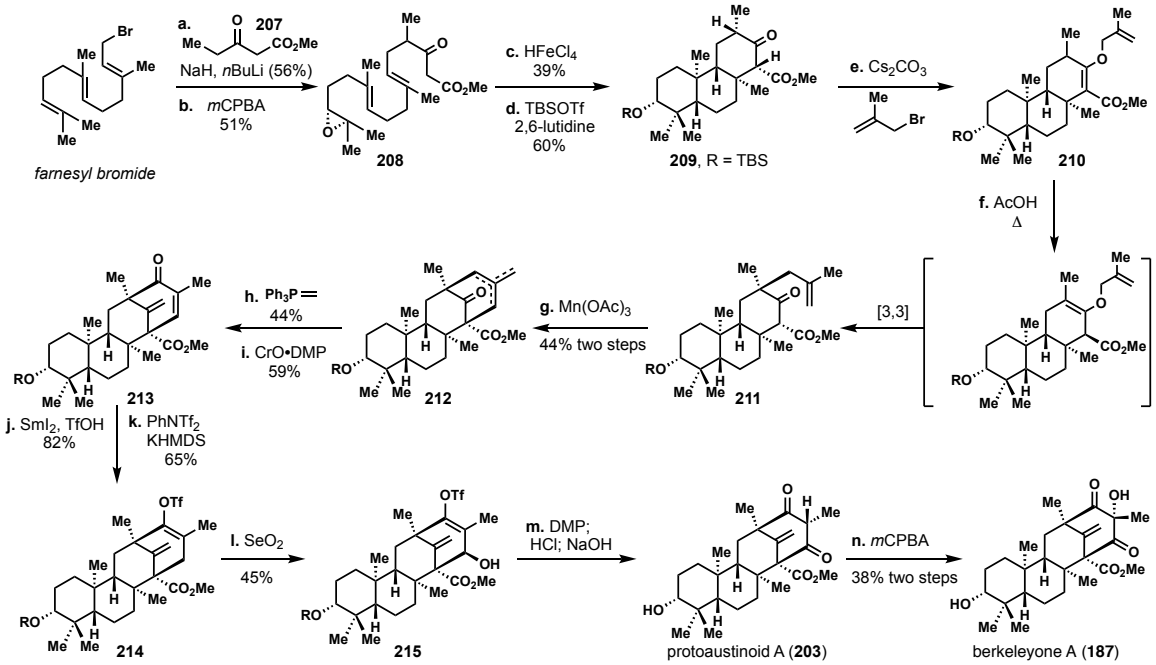
Berkeleyone A is an inhibitor of caspase-1 and interleukin-1β (IL-1β) production.[83] After inflammasome generation in the monocytic leukemia cell line THP-1, berkeleyone A (**187**) alleviated the production of IL-1β. In addition, **7** was the most potent of the berkeleyone natural products tested.[90]



Scheme 26. Point of divergence in the biosynthesis of DMOA-derived meroterpenes

Total Syntheses of Berkeleyone A

There are two reported total syntheses of berkeleyone A, one by our group in 2016[93] and one by the Newhouse group in 2017.[91] The Newhouse synthesis commenced with the alkylation of the dienolate of of methyl 3-oxopentanoate **207** by farnesyl bromide in 56% yield (Scheme 27). The terminal alkene group of the resulting product was epoxidized by *m*CPBA in 51% yield. Epoxide **208** was subjected to a polyene cyclization mediated by $HFeCl_4$. Remarkably, this is the first example of a polyene cyclization that is terminated by carbon-cyclization of a β-ketoester. The secondary alcohol group in was protected with TBSOTf to afford compound **209** which was then subjected to enolate *O*-alkylation by 3-bromo-2-methylpropene with cesium carbonate as base (See **209** to **210**). At this stage in the synthesis, olefin isomerization mediated by acetic acid followed by Claisen rearrangement successfully furnished β-ketoester **211**. With conditions reported by Snider and co-workers,[92] oxidative cyclization mediated by $Mn(OAc)_3$ produced the bicyclo [3.3.1] nonane **212** in 41% yield over two steps. In six steps, the Newhouse group accessed the tetracyclic core of berkeleyone A. Compound

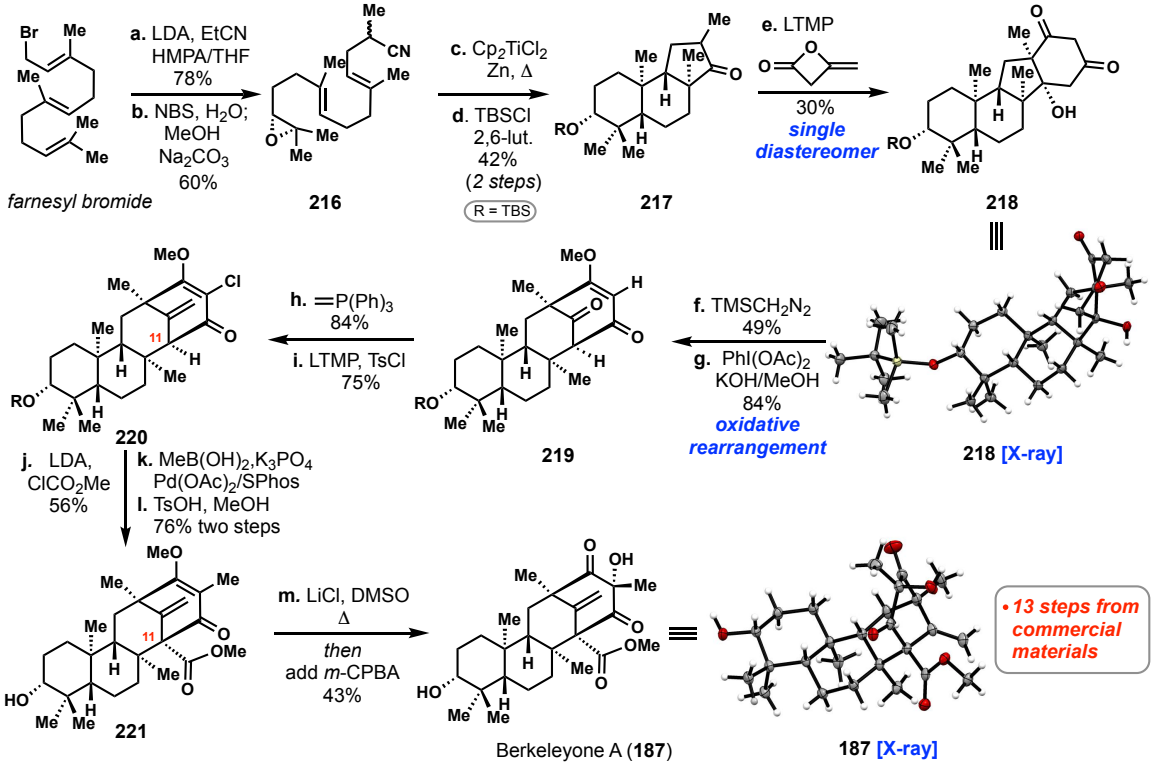


Scheme 27. Newhouse's 2017 total synthesis of Berkeleyone A

212 was subjected to Wittig olefination followed by allylic oxidation by CrO_3-3,5-dimethylpyrazole complex to furnish compound **213** in good yield. In order to install the β-hydroxyenone in the natural product, the authors identified that the vinyl triflate **214**, accessed by SmI_2 reduction and triflation, was a suitable substrate for SeO_2 mediated allylic oxidation to afford alcohol **215**. Protoaustinoid A (**203**) was produced after DMP oxidation and subsequent deprotection steps. Finally, *m*CPBA oxidation produced berkeleyone A (**187**) in 13 steps from commercial materials.

2.7. Total Synthesis of Berkeleyone A

In 2016, we reported the total synthesis of berkeleyone A (**187**) also from farnesyl bromide, yet utilizing a disparate approach (Scheme 28).[93] Our synthesis commenced with the alkylation of proprionitrile with farnesyl bromide. A one-pot hydroxybromination followed by epoxide formation furnished epoxide **216**. Epoxide **216** was subjected to reductive radical cyclization developed by Fernandez and co-workers.[94] An *in-situ* generated Ti(III) intermediate reduced the epoxide to a tertiary radical which cyclized across the olefins and nitrile. The secondary alcohol of the product was protected by TBSOTf to produce tricycle **217** in 42% yield over two steps. At this stage, our berkeleyone A synthesis proceeded through steps similar to those employed in our hyperforin work. Tricycle **217** was subjected to diketene annulation reaction to afford tetracycle **218** in 30% yield with 35% recovered starting material. The structure of tetracycle **218** was unambiguously determined by X-ray diffraction studies. An unselective methylation of **218** with trimethylsilyldiazomethane followed by oxidative rearrangement with PIDA afforded the bicyclo [3.3.1] nonane in berkeleyone A. Compound **219** was subjected to an elevated temperature (65 °C) Wittig olefination to install the exocyclic olefin of the natural product in 84% yield. At room temperature, little to no product was obtained attesting to the steric hindrance of the bridging ketone group. Moreover, it was essential that the olefin be installed prior to chlorination or bridgehead acylation as the β-methoxyenone became more reactive to olefination. Chlorination of the vinyl position (LTMP, TsCl) afforded vinyl chloride **220**. Despite having removed one of the carbonyls that stabilized the bridgehead anion, the C11 methyl ester was successful installed *via* deprotonation with LTMP and acylation with methylchloroformate. Suzuki cross coupling of the vinyl chloride with methyl boronic



Scheme 28. Maimone's 2016 total synthesis of Berkeleyone A

acid followed by *p*-toluenesulfonic acid mediated desilylation of the TBS ether furnished compound **221**. Demethylation with LiCl provided protoaustinoid A which was oxidized with *m*CPBA in the same reaction vessel to produce berkeleyone A in thirteen steps.

Despite both syntheses of berkeleyone A being equally concise (13 steps each), the synthesis by the Newhouse group revealed the difficulties associated with assembling the β-hydroxyenone motif via late stage redox manipulations.[91] In our synthesis the functionality embedded in diketene is converted smoothly into the β-hydroxyenone in the natural product in a single step highlighting the utility of this transformation in the synthesis of complex meroterpene natural products.[93]

2.8. Conclusion and Acknowledgements

In conclusion, we have developed an annulation reaction between diketene and lithium enolates allowing for the synthesis of previously inaccessible 1,3-cyclohexadiones in a single step from ketone starting materials. Moreover, we highlighted the utility of this method to the field of complex meroterpene total synthesis by synthesizing hyperforin and berkeleyone A. Similar to how the venerable Robinson annulation has seen myriad use in the synthesis of steroidal natural products, one can envision the continued use of the diketene annulation reaction in the field of meroterpene total synthesis.

The hyperforin synthesis was designed by Thomas Maimone and myself and solely executed by me. The diketene annulation reaction was conceptualized and realized in the laboratory by myself with guidance from Thomas Maimone. The berkeleyone A synthesis was designed by Thomas Maimone and executed by Dr. Gong Xu and myself. Undergraduate student Mr. Xianhuang Zeng is acknowledged for his contributions to broadening the substrate scope of the diketene annulation reaction and prouding assistance with scale-up efforts.

2.9. References

1. For reviews of PPAP natural products see: (a.) Ciochina, R.; Grossman, R. B. *Chem Rev*. **2006**, *106*, 3963. (b.) Singh, I. P.; Sidana, J.; Bharate, S. B.; Foley, W. *J. Nat. Prod. Rep.* **2010**, *27*, 393. (c.) Njardarson, J. T. *Tetrahedron* **2011**, *67*, 7631. (d.) Richard, J.-A.; Pouwer, R. H.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.* **2012**, *51*, 4536
2. Moss, G. P. *Pure Appl. Chem*. **1999**, *71*, 513.
3. Orth, H. C. J.; Rentel, C.; Schmidt, P. C. J. *Pharm. Pharmacol*. **1999**, *51*, 193.
4. (a.) Sang, S. M.; Liao, C. H.; Pan, M. H.; Rosen, R. T.; Lin-Shiau, S. Y.; Lin, J. K.; Ho, C. T. *Tetrahedron* **2002**, *58*, 10095. (b.) Sang, S. M.; Pan, M. H.; Cheng, X. F.; Bai, N. S.; Stark, R. E.; Rosen, R. T.; Lin-Shiau, S. Y.; Lin, J. K.; Ho, C. T. *Tetrahedron* **2001**, *57*, 9931.
5. Büschleb, M.; Dorich, S.; Hanessian, S.; Tao, D.; Schenthal, K. B.; Overman, L. E. *Angew. Chem. Int. Ed.* **2016**, *55*, 4156.
6. Yang, X-W.; Yang, W.; Xu, G. *J. Nat. Prod.* **2017**, *80*, 103.
7. Cuesta-Rubio, O.; Velez-Castro, H.; Frontana-Uribe, B. A.; Cardenas, J. *Phytochemistry* **2001**, *57*, 279.
8. Cruz, F. G.; Teixeira, J. S. *J. Braz. Chem. Soc*. **2004**, *15*, 504.
9. Wu, S.-B.; Long, C.; Kennelly, E. J. *Nat. Prod. Rep.* **2014**, *31*, 1158.
10. Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull*. **1997**, *45*, 947.
11. Hernandez, I. M.; Fernandez, M. C.; Cuesta-Rubio, O.; Piccinelli, A. L.; Rastrelli, L. *J. Nat. Prod.* **2005**, *68*, 931.
12. Krishnamurthy, N.; Lewis, Y. S.; Ravindranath, B. *Tetrahedron Lett*. **1981**, *22*, 793.
13. Cuesta-Rubio, O.; A., C. C.; Rojas, N.; Velez Castro, H.; Rastreli, L.; Aquino, R. *J. Nat. Prod*. **1999**, *62*, 1013.
14. Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2000**, *63*, 104.
15. (a.) Flores-Sanchez, I. J.; Verpoorte, R. *Plant Physiol. Biochem*. **2009**, *47*, 167. (b.) Klundt, T.; Bocola, M.; Beuerle, T.; Liu, B.; Beerhues, L. *J. Biol. Chem*. **2009**, *284*, 30957.
16. Liu, B.; Falkenstein-Paul, H.; Schmidt, W.; Beerhues, L. *Plant J.* **2003**, *34*, 847.
17. (a.) Tsurumaru, Y.; Sasaki, K.; Miyawaki, T.; Uto, Y.; Momma, T.; Umemoto, N.; Momose, M.; Yazaki, K. *Biochem. Biophys. Res. Commun*. **2012**, *417*, 393. (b.) Boubakir, Z.; Beuerle, T.; Liu, B.; Beerhues, L. *Phytochemistry* **2005**, *66*, 51.
18. Adam, P.; Arigoni, D.; Bacher, A.; Elsenreich, W. *J. Med. Chem*. **2002**, *45*, 4786.
19. Rohmer, M.; Knani, M.; Simonin, P.; Sutter, B.; Sahm, H. *Biochem. J.* **1993**, *295*, 517.
20. Bystrov, N. S.; Chernov, B. K.; Dobrynin, V. N.; Kolosov, M. N. *Tetrahedron Lett*. **1975**, *16*, 2791.
21. For a recent review on the chemistry and biology of hyperforin, see: Richard, J.-A. *Eur. J. Org. Chem*. **2014**, 273.
22. Shelton, R. C.; Keller, M. B.; Gelenberg, A.; Dunner, D. L.; Hirschfeld, R.; Thase, M. E.; Russell, J.; Lydiard, R.D.; Crits-Christoph, P.; Gallop, R.; Todd, L.; Hellerstein, D.; Goodnick, P.; Keitner, G.; Stahl, S. M.; Halbreich, U. *JAMA*, **2001**, *285*, 1978.

23. Mennini, T.; Gobbi, M. *Life Sci*. **2004**, *75*, 1021.
24. Muller, W. E.; Singer, A.; Wonnemann, M.; Hafner, U.; Rolli, M.; Schafer, C. *Pharmacopsychiatry* **1998**, *31*, 16.
25. Schempp, C. M.; Pelz, K.; Wittmer, A.; Schopf, E.; Simon, J. C. *Lancet* **1999**, *353*, 2129.
26. Verotta, L.; Appendino, G.; Bombardelli, E.; Brun, R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1544.
27. Vogel, G. *Science* **2001**, *291*, 35.
28. Wentworth, J. M.; Agostini, M.; Love, J.; Schwabe, J. W.; Chatterjee, V. K. *Journal of Endocrinology* **2000**, *166*, R11–R16.
29. Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2005**, *127*, 14200.
30. Barton, D. H. R.; Crich, D. *Tetrahedron* **1985**, *41*, 4359
31. Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829.
31. Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2006**, *128*, 1048.
32. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.
33. Tsukano, C.; Siegel, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed*. **2007**, *46*, 8840.
34. Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943.
35. Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. *Org. Lett*. **2006**, *8*, 5283.
36. Ahmad, N. M.; Rodeschini, V.; Simpkins, N. S.; Ward, S. E.; Blake, A. J. *J. Org. Chem*. **2007**, *72*, 4803.
37. Simpkins, N. S.; Taylor, J. D.; Weller, M. D.; Hayes, C. J. *Synlett* **2010**, 639.
38. Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.
39. Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C. *Org. Lett*. **2007**, *9*, 287.
40. Garnsey, M. R.; Lim, D.; Yost, J. M.; Coltart, D. M. *Org. Lett.* **2010**, *12*, 5234.
41. Qi, J.; Porco, J. A. *J. Am. Chem. Soc*. **2007**, *129*, 12682.
42. Zhang, Q.; Mitasev, B.; Qi, J.; Porco, J. A. *J. Am. Chem. Soc*. **2010**, *132*, 14212.
43. Qi, J.; Beeler, A. B.; Zhang, Q.; Porco, J. A. *J. Am. Chem. Soc*. **2010**, *132*, 13642.
44. Zhang, Q.; Porco, J. A. *Org. Lett*. **2012**, *14*, 1796.
45. Boyce, J. H.; Porco, J. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 7832.
46. Delle Monache, F.; Monache, G. D.; Gacs-Baitz, E. *Phytochemistry* **1991**, *30*, 2003.
47. (a) O' Donnell, M. J. *Acc. Chem. Res*. **2004**, *37*, 506. (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res*. **2004**, *37*, 518.
48. Tanaka, N.; Takaishi, Y.; Shikishima, Y.; Nakanishi, Y.; Bastow, K.; Lee, K. H.; Honda, G.; Ito, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O. *J. Nat. Prod.* **2004**, *67*, 1870.
49. Couladouros, E. A.; Dakanali, M.; Demadis, K. D.; Vidali, V. P. *Org. Lett.* **2009**, *11*, 4430.
50. George, J. H.; Hesse, M. D.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 3532.
51. Biber, N.; Moews, K.; Plietker, B. *Nat. Chem*. **2011**, *3*, 938.

52. a. Plietker, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 1469. b. Plietker, B.; Dieskau, A.; Mows, K.; Jatsch, A. *Angew. Chem. Int. Ed*. **2008**, *47*, 198.
53. Horeischi, F.; Biber, N.; Plietker, B. *J. Am. Chem. Soc*. **2014**, *136*, 4026.
54. Uyeda, C.; Rçtheli, A. R.; Jacobsen, E. N. *Angew. Chem. Int. Ed*. **2010**, *49*, 9753.
55. Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc*. **1999**, *121*, 4724.
56. Ciochina, R.; Grossman, R. B. *Org. Lett*. **2003**, *5*, 4619.
57. Mehta, G.; Bera, M. K. *Tetrahedron Lett*. **2006**, *47*, 689.
58. Richard, J.-A.; Chen, D. Y.-K. *Eur. J. Org. Chem*. **2012**, 484.
59. Young, D. G. J.; Zeng, D. *J. Org. Chem*. **2002**, *67*, 3134.
60. (a) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed*. **2010**, *49*, 1103. (b) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2010**, *66*, 6569.
61. Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett*. **2004**, *6*, 4387.
62. Taguchi, T.; Kawazoe, Y.; Nakao, M. *Tetrahedron Lett.* **1963**, *4*, 131.
63. Feldman, K.; Fodor, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14964.
64. Uwamori, M.; Nakada, M. *Tetrahedron Lett*. **2013**, *54*, 2022.
65. Abe, M.; Nakada, M. *Tetrahedron Lett*. **2006**, *47*, 6347.
66. Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc*. **2012**, *135*, 644.
67. Zhao, Y.; Yeung, Y.-Y. *Org. Lett.* **2010**, *12*, 2128.
68. Sparling, B. A.; Tucker, J. K.; Moebius, D. C.; Shair, M. D. *Org. Lett.* **2015**, *17*, 3398.
69. Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed*. **2014**, *53*, 6701.
70. Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev*. **2012**, *41*, 2448.
71. Grenning, A.J.; Boyce, J.H.; Porco, J.A. Jr. *J. Am. Chem. Soc*. **2014**, *136*, 11799.
72. Lipshutz, B .H.; Hackmann, C. *J. Org. Chem*. **1994**, *59*, 7437.
73. Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253.
74. Burns, N.Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem. Int. Ed*. **2009**, *48*, 2854.
75. Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241.
76. House, H. O.; A'uerbach, R. A.; Gall, M.; Peet, N. P. *J. Org. Chem.* **1973**, *38*, 514.
77. Moriarty, R. M.; Prakash, I.; Musallam, H. A. *Tetrahedron Lett.* **1984**, *25*, 5867.
78. Chen, J.-M.; Huang, X. *Synthesis*, **2004**, 1557.
79. Dohi, T.; Morimoto, K.; Takenaga, N.; Goto, A.; Maruyama, A.; Kiyono, Y.; Tohma, H.; Kita, Y. *J. Org. Chem*. **2007**, *72*, 109.
80. Daum, S. J. *Tetrahedron Lett.* **1984**, *25*, 4725.
81. Ting, C. P.; Maimone, T. J., *J. Am. Chem. Soc.* **2015**, *137,* 10516.
82. Ting, C. P.; Maimone, T. J., *Synlett* **2016***, 27,* 1443.
83. Stierle, D. B.; Stierle, A. A.; Patacini, B.; McIntyre, K.; Girtsman, T.; Bolstad, E. *J. Nat. Prod.* **2011**, *74*, 2273.
84. Stierle, D.; Stierle, A.; Hobbs, J. D.; Stokken, J.; Clardy, J. *Org. Lett*. **2004**, *6*, 1049.
85. Geris, R.; Simpson, T. J. *Nat. Prod. Rep*. **2009**, *26*, 1063.
86. Matsuda, Y.; Abe, I. *Nat. Prod. Rep*. **2016**, *33*, 26.
87. Lo, H.-C.; Entwistle, R.; Guo, C.-J.; Ahuja, M.; Szewczyk, E.; Hung, J.-H.; Chiang, Y.- M.; Oakley, B.; Wang, C. C. *J. Am. Chem. Soc.* **2012**, *134*, 4709.
88. Matsuda, Y.; Awakawa, T.; Itoh, T.; Wakimoto, T.; Kushiro, T.; Fujii, I.; Ebizuka, Y.; Abe, I. *ChemBioChem* **2012**, *13*, 1738.

89. Matsuda, Y.; Awakawa, T.; Abe, I. *Tetrahedron* **2013**, *69*, 8199.
90. Sollberger, G.; Strittmatter, G. E.; Garstkiewicz, M.; Sand, J.; Beer, H.-D. *Innate Immun*. **2014**, *20*, 115.
91. Elkin, M.; Szewczyk, S. M.; Scruse, A. C.; Newhouse, T. R. *J. Am. Chem. Soc.* **2017**, *139*, 1790.
92. Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.
93. Ting, C. P.; Xu, G.; Zeng, X.; Maimone, T. J. *J. Am. Chem. Soc.* **2016**, *138*, 14868.
94. Fernández-Mateos, A.; Teijó n, P. H.; Clemente, R. R.; González, R. R.; González, F. S. *Synlett* **2007**, *2007*, 2718.

Supplementary Information for:

Chapter 2:
Total synthesis of Complex Meroterpenes

General Procedures

Unless otherwise stated, all reactions were performed in oven-dried or flame-dried glassware under an atmosphere of dry nitrogen or argon. Dry tetrahydrofuran (THF), dichloromethane, toluene, hexane, acetonitrile, dimethylformamide (DMF) and diethyl ether were obtained by passing these previously degassed solvents through activated alumina columns. Anhydrous DMSO was purchased from Aldrich stored over molecular sieves and used as received. Amines and HMPA were distilled from calcium hydride prior to use. Diketene was freshly distilled immediately before use and was colorless. Copper(I) bromide dimethylsulfide complex was stored in a glovebox and small portions removed and manipulated on the benchtop. Lithium chloride was stored in a 160 °C oven and flame-dried under high vacuum before use. If indicated, solvents were further degassed by bubbling a stream of argon through the solvent for 10 minutes in an ultrasound bath. Reactions were monitored by thin layer chromatography (TLC) on Silicycle Siliaplate^{TM} G TLC plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized by UV irradiation and staining with *p*-anisaldehyde, phosphomolybdic acid, or potassium permanganate developing agents. Volatile solvents were removed under reduced pressure using a rotary evaporator. Flash column chromatography was performed using Silicycle F60 silica gel (60Å, 230-400 mesh, 40-63 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker AV, AVQ, and DRX spectrometers operating at 300, 400, 500, or 600 MHz for ^{1}H (75, 100, 125, and 150 MHz for ^{13}C) in $CDCl_3$, benzene-d_6, or acetone-d_6. Chemical shifts are reported relative to the residual solvent signal (^{1}H NMR: δ = 7.26 ($CDCl_3$); ^{13}C NMR: δ = 77.16 ($CDCl_3$). NMR data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Splitting is reported with the following symbols: s = singlet, bs = broad singlet, d = doublet, t = triplet, app t = apparent triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, hept = heptet, m = multiplet. IR spectra were taken on a Nicolet 380 spectrometer as thin films on NaCl plates and are reported in frequency of absorption (cm^{-1}). Only selected resonances are reported. High-resolution mass spectra (HRMS) were obtained by the mass spectral facility at the University of California, Berkeley using a Finnigan LTQFT mass spectrometer (Thermo electron corporation). X-ray crystallographic analyses were performed at the UC-Berkeley College of Chemistry X-ray crystallography facility.

Compound 143. *i.* A 1 L flame-dried reaction flask was charged with anhydrous lithium chloride (7.0 g, 165 mmol, 2.2 equiv) and copper bromide dimethylsulfide complex (33.5 g, 165 mmol, 2.2 equiv). The reaction vessel was evacuated and backfilled with nitrogen and this process repeated for a total of three times. THF (500 mL) was added and the mixture was stirred for 5 minutes at 25 °C and then cooled to -78 °C whereupon allylmagnesium bromide (1 M in Et_2O, 150 mL, 150 mmol, 2.0 equiv) was added dropwise. The resulting dark brown solution was stirred for 30 minutes at -78 °C before adding TMSCl (20.1 mL, 165 mmol, 2.2 equiv) and 2-methylcyclopentenone (7.2 g, 75 mmol, 1.0 equiv) quickly in succession. The reaction mixture was stirred for 60 minutes at -78 °C and then triethylamine (20 mL) was added. The reaction vessel was slowly warmed to 25 °C over the course of 1 hour and then saturated *aq*. NH_4OH/saturated *aq*. NH_4Cl (9:1 *v:v*, 200 mL) added, resulting in a dark blue colored solution. The reaction mixture was filtered through Celite, and then extracted with ether (3 x 300 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (1% → 2% Et_2O in hexanes) to afford the silyl enol ether product (11.9 g, 75% yield) as a colorless oil.

ii. A 250 mL flame-dried reaction flask was charged with silyl enol ether (11.9 g, 57 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen and this process repeated for a total of three times followed by the addition of THF (350 mL). After cooling the reaction flask to 0 °C, methyllithium (1.0 M in ether, 39.0 mL, 62 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 1 hr. HMPA (75 mL) was added at 0 ° C followed by cooling to -78 °C and the addition of 4-iodo-1-butene (11 mL, 102 mmol, 1.6 equiv). The colorless solution was warmed to 5 °C and stirred for 30 h at which point it was quenched with deionized H_2O (50 mL) and diluted with ether (100 mL). After organic layer was washed with deionized H_2O (2 x 50 mL). The combined aqueous layers were extracted with ether (2 x 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford a yellow oil. The crude residue was purified by silica gel column chromatography (1% → 2% Et_2O in hexanes) to afford the ketone **143** (4.5 g, 40% yield, 2.5:1 dr) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 – 5.62 (m, 3H), 5.17 – 4.85 (m, 6H), 2.45 – 2.20 (m, 2H), 2.15 – 2.01 (m, 4H), 2.01 – 1.91 (m, 1H), 1.91 – 1.76 (m, 1H), 1.75 – 1.64 (m, 1H), 1.52 – 1.39 (m, 2H), 1.05 (minor isomer, s, 3H), 0.86 (major isomer, s, 3H); ^{13}C NMR major isomer (100 MHz, $CDCl_3$) δ 223.4, 138.7, 136.9, 116.3, 114.8, 51.3, 42.5, 37.5, 35.1, 34.8, 29.1, 25.0, 18.0; ^{13}C NMR minor isomer (100 MHz, $CDCl_3$) δ 222.3, 138.7, 137.1, 116.3, 114.8, 50.9, 48.0, 36.1, 34.3, 30.4, 28.3, 24.3, 20.4.

Ketone 144. A 500 mL flame-dried reaction flask was charged with ketone **143** (4.5 g, 23 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (200 mL). After cooling the reaction vessel to -78 °C, a freshly prepared solution of lithium diisopropylamide (0.52 M in THF, 48 mL, 25 mmol, 1.0 equiv) was added dropwise via syringe resulting in a light yellow solution. The reaction mixture was stirred for 30 minutes at -78 °C and then 30 minutes at 0 °C. Dry hexamethylphosphoramide was then added to the reaction mixture at 0 °C and

the mixture re-cooled to -78 °C. Freshly distilled allylbromide (2.2 mL, 26 mmol, 1.1 equiv) was added dropwise at -78 °C and the resulting pale yellow solution stirred for 15 minutes at this temperature and then warmed to 0 °C, stirred 15 minutes at this temperature, and then quenched with deionized water (20 mL). The reaction mixture was diluted with ether (100 mL), and the organic layer was washed with deionized water (2 x 20 mL). The combined aqueous layers were extracted with ether (2 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (1% → 2% Et_2O in hexanes) to afford ketone **144** (5.4 g, 94% yield, mixture of diastereomers) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 5.89 – 5.67 (m, 3H), 5.14 – 4.89 (m, 6H), 2.42 – 2.33 (m, 1H), 2.26 (m, 1H), 2.13 – 1.98 (m, 2H), 1.93 (m, 1H), 1.89 – 1.79 (m, 2H), 1.76 – 1.61 (m, 2H), 1.58 – 1.54 (m, 1H), 1.47 – 1.40 (m, 1H), 1.03 (minor isomer, s, 3H), 0.91 (major isomer, s, 3H).

Ketone 148. A 100 mL flame-dried flask was charged with ketone **144** (1.1 g, 4.7 mmol, 1.0 equiv). Potassium *tert*-butoxide (120 mg, 1.0 mmol, 0.2 equiv) was then added. The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of *t*-BuOH (20 mL) and methyl acrylate (0.47 mL, 5.2 mmol, 1.1 equiv). The resulting pale yellow solution stirred for 60 minutes at room temperature and then quenched with deionized water (20 mL). The reaction mixture was diluted with ethyl acetate (100 mL), and the organic layer was washed with deionized water (2 x 20 mL). The combined aqueous layers were extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (5% → 10% Et_2O in hexanes) to afford methyl ester (1.02 g, 68% yield) as a colorless oil.

ii. A 100 mL flame-dried flask was charged with the methyl ester from the previous reaction. The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (45 mL). After cooling the reaction vessel to -78 °C, a freshly prepared solution of lithium diisopropylamide (0.52 M in THF, 6.8 mL, 3.4 mmol, 1.1 equiv) was added dropwise via syringe resulting in a light yellow solution. The reaction mixture was stirred for 30 minutes at -78 °C and then 30 minutes at 0 °C. Freshly distilled allylbromide (0.3 mL, 3.5 mmol, 1.1 equiv) was added dropwise at -78 °C and the resulting pale yellow solution stirred for 15 minutes at this temperature and then warmed to 0 °C, stirred 15 minutes at this temperature, and then quenched with saturated NH_4Cl in deionized water (20 mL). The reaction mixture was diluted with ether (100 mL), and the organic layer was washed with deionized water (2 x 20 mL). The combined aqueous layers were extracted with ether (2 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (3% → 5% Et_2O in hexanes) to afford the allylated product (700 mg, 61% yield, 1.2:1 mixture of diastereomers) as a colorless oil.

iii. A 100 mL flame-dried flask was charged with diisopropylamine (0.9 mL, 6.5 mmol, 3.3 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in

total) followed by the addition of THF (45 mL). The reaction vessel was cooled to -78 °C and added *n*-BuLi (2.5 mL, 6.1 mmol, 3.2 equiv) dropwise. After 15 minutes, the reaction vessel was warmed to 0 °C and maintained at this temperature for 30 minutes. The reaction vessel was recooled to -78 °C and added acetonitrile (0.3 mL, 5.9 mmol, 3.0 equiv). After 60 minutes, the reaction vessel was warmed to 0 °C and maintained at this temperature for 10 minutes. The reaction vessel was recooled to -78 °C. In a separate reaction vessel, the product from the previous reaction was dissolved in THF (10 mL) and was transferred to the other flask dropwise via syringe. The reaction mixture was stirred for 30 minutes at -78 °C and then 30 minutes at 0 °C before the addition of saturated NH_4Cl in deionized water (20 mL). The reaction mixture was diluted with ether (100 mL), and the organic layer was washed with deionized water (2 x 20 mL). The combined aqueous layers were extracted with ether (2 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% → 20% Et_2O in hexanes) to afford compound **148** (370 mg, 51% yield, 1.2:1 mixture of diastereomers) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87 – 5.46 (m, 4H), 5.16 – 4.90 (m, 8H), 3.79 (major isomer, d, J = 19.8 Hz, 1H), 3.72 (minor isomer, d, J = 19.6 Hz, 1H), 3.67 – 3.52 (m, 1H), 3.10 (minor isomer, dt, J = 9.9, 6.9 Hz, 1H), 2.82 (major isomer, dddd, J = 17.0, 12.2, 8.4, 4.5 Hz, 1H), 2.33 – 2.19 (m, 2H), 2.19 – 2.02 (m, 3H), 2.02 – 1.93 (m, 1H), 1.88 (ddd, J = 16.4, 14.0, 7.2 Hz, 1H), 1.82 – 1.71 (m, 1H), 1.71 – 1.36 (m, 5H), 0.81 (major isomer, s, 3H), 0.79 (minor isomer, s, 3H). ^{13}C NMR both isomers (150 MHz, $CDCl_3$-*d*) δ 227.3, 225.2, 200.8, 200.5, 138.9, 138.4, 138.4, 136.9, 136.8, 136.7, 133.9, 133.7, 133.6, 133.4, 133.3, 133.2, 119.4, 119.3, 119.2, 119.2, 116.5, 116.3, 115.0, 114.9, 114.7, 113.6, 52.2, 52.0, 51.7, 51.5, 51.3, 50.3, 47.1, 46.4, 45.4, 45.0, 41.1, 40.4, 40.4, 40.3, 38.9, 38.8, 38.8, 38.4, 38.2, 37.3, 37.1, 37.0, 36.9, 36.1, 35.9, 35.9, 34.7, 34.6, 34.0, 33.4, 33.1, 32.2, 30.4, 29.9, 29.3, 28.6, 27.9, 21.2, 18.4, 17.4.

A flame-dried 20 mL microwave vessel was charged with compound **148** (200 mg, 0.54 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) prior to being sealed with an aluminium cap with a septum. The reaction vessel was added trifluorotoluene (15 mL) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.1 mL, 0.66 mmol, 1.2 equiv). The reaction vessel was heated at 150 °C in a microwave reactor for 30 minutes. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (10% → 20% Et_2O in hexanes) to afford compound **149** (140 mg, 70% yield, 3.0:1 mixture of diastereomers) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ 5.92 – 5.57 (m, 4H), 5.30 – 4.91 (m, 8H), 2.64 (m, 2H), 2.44 – 2.28 (m, 3H), 2.28 – 2.12 (m, 4H), 2.04 (m, 2H), 1.91 (m, 1H), 1.81 (m, 1H), 1.77 – 1.58 (m, 3H), 1.54 (minor isomer, s, 3H), 1.47 – 1.35 (m, 1H), 1.30 (major isomer, s, 3H). ^{13}C NMR both isomers (150 MHz, $CDCl_3$-*d*) δ 195.7, 194.8, 137.4, 136.7, 136.3, 134.5, 134.4, 132.4, 132.4, 119.4, 119.1, 117.9, 117.8, 116.5, 116.4, 115.3, 115.2, 113.1, 108.6, 51.7, 47.1, 44.1, 43.4, 41.3, 38.8, 36.7, 36.2, 35.5, 34.8, 28.7, 21.3. A single crystal of **149** for X-ray diffraction studies was obtained by slow evaporation from cyclohexane.

Diketone 155. A 20 mL flame-dried reaction tube was charged with compound **144** (2.9 g, 12.5 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of degassed THF (120 mL). The reaction

vessel was cooled to -78 °C and freshly prepared lithium bis(trimethylsilyl)amide (0.45 M in THF, 29 mL, 13.1 mmol, 1.1 equiv) was added dropwise resulting in a light yellow colored solution. The reaction mixture was stirred for 60 minutes at -78 °C and then 60 minutes at 0 °C. After this period, the reaction mixture was cooled to -78 °C and freshly distilled diketene (1.1 mL, 13.8 mmol, 1.1 equiv) was rapidly in one portion resulting in a bright yellow solution. The reaction vessel was maintained at this temperature for 60 minutes and then 60 minutes at 0 °C and then quenched with saturated *aq*. NH_4Cl (100 mL) at this temperature. The reaction mixture was extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc in hexanes → 30% EtOAc in hexanes) to afford the annulated product **155** (800 mg, 21% yield) as a red/orange colored oil: ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ δ 5.75 (dddt, J = 17.0, 13.7, 10.0, 6.8 Hz, 2H), 5.58 (ddt, J = 15.3, 10.3, 7.3 Hz, 1H), 5.13 – 4.87 (m, 6H), 3.64 (d, J = 18.2 Hz, 1H), 3.16 (d, J = 18.2 Hz, 1H), 2.83 – 2.64 (m, 2H), 2.55 (dd, J = 14.3, 7.5 Hz, 1H), 2.44 (dd, J = 20.1, 14.4 Hz, 2H), 2.27 (s, 1H), 2.19 (dd, J = 14.2, 7.3 Hz, 2H), 2.14 – 1.93 (m, 1H), 1.84 (td, J = 13.1, 12.1, 7.8 Hz, 1H), 1.51 – 1.32 (m, 2H), 1.32 – 1.16 (m, 2H), 1.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.7, 203.3, 138.5, 137.0, 132.9, 118.7, 116.2, 115.1, 84.2, 61.1, 52.1, 50.4, 50.4, 44.1, 41.2, 36.6, 35.3, 34.5, 28.4, 27.1, 14.9.

Compound 156. A 100 mL flame-dried reaction flask was charged with compound **155** (300 mg, 0.95 mmol, 1.0 equiv) and *para*-toluenesulfonic acid monohydrate (18 mg, 0.10 mmol, 0.1 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of MeOH (30 mL). The reaction mixture was added trimethylorthoformate (0.17 mL, 1.1 mmol 1.1 equiv) and heated to 60 °C and maintained at this temperature for 3 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc in hexanes) to afford compound **156** (258 mg, 82% yield) as a red/orange colored oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 – 5.58 (m, 3H), 5.38 (d, J = 1.6 Hz, 1H), 5.12 – 4.79 (m, 7H), 3.68 (s, 3H), 2.70 – 2.58 (m, 2H), 2.54 (ddt, J = 14.0, 6.7, 1.5 Hz, 1H), 2.47 (dd, J = 18.2, 1.7 Hz, 1H), 2.35 (dd, J = 13.9, 8.1 Hz, 1H), 2.17 (dddd, J = 13.2, 5.5, 3.7, 1.7 Hz, 1H), 2.07 – 1.84 (m, 2H), 1.81 (s, 1H), 1.62 (dtd, J = 12.0, 8.6, 3.8 Hz, 1H), 1.29 (dd, J = 13.4, 9.1 Hz, 1H), 1.25 – 1.16 (m, 1H), 1.10 (ddd, J = 13.2, 11.5, 5.3 Hz, 1H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 174.1, 139.1, 138.1, 134.8, 117.4, 115.5, 114.4, 102.6, 84.8, 59.0, 56.1, 51.9, 43.0, 40.7, 39.0, 38.3, 37.4, 37.1, 29.3, 14.7. After standing in air, compound **156** crystallized into orange single crystals for X-ray diffraction studies.

Compound 158. A 100 mL flame-dried reaction flask was charged with compound **156** (70 mg, 0.21 mmol, 1.0 equiv) and 3 Å mol. sieves (70 mg). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of acetonitrile (7 mL). The reaction mixture cooled to 0 °C and added Koser's reagent (166 mg, 0.42 mmol 2.0 equiv) After 60 minutes, the reaction mixture was warmed to room temperature for 2 h. At that time, the reaction mixture was quenched with water (5 mL) at this temperature. The reaction mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in*

vacuo. The crude residue was purified by column chromatography (2% Et_2O in hexanes → 10% Et_2O in hexanes) to afford compound **158** (25 mg, 23% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.81 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 5.83 – 5.65 (m, 2H), 5.67 – 5.52 (m, 1H), 5.08 – 4.92 (m, 4H), 4.03 – 3.88 (m, 2H), 3.77 (s, 3H), 3.68 (d, J = 8.7 Hz, 1H), 3.18 (s, 1H), 2.44 (s, 3H), 2.31 (m, 1H), 2.20 (m, 1H), 2.08 – 1.99 (m, 2H), 1.95 (n, 7.1 Hz, 1H), 1.84 (dd, J = 14.9, 9.6 Hz, 1H), 1.79 – 1.65 (m, 2H), 1.59 (m, 3H), 1.37 (t, J = 13.2 Hz, 1H), 1.29 – 1.22 (m, 1H), 1.22 – 1.12 (m, 1H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 197.2, 174.9, 144.9, 138.4, 136.2, 133.1, 130.2, 130.0, 128.2, 128.1, 117.5, 114.9, 106.1, 77.4, 73.9, 66.2, 62.9, 61.5, 57.0, 44.7, 40.5, 38.6, 37.9, 34.2, 34.0, 27.6, 21.8, 17.6.

Compound 159.
A 10 mL flame-dried reaction tube was charged with compound **158** (10 mg, 0.02 mmol, 1.0 equiv), 3,5-dinitrobenzoic acid (15 mg, 0.06 mmol, 3.3 equiv), DCC (15 mg, 0.07 mmol, 7.0 equiv), DMAP (4 mg, 0.03, 1.5 equiv) and CH_2Cl_2 (2 mL). After 2 hours, the reaction mixture was added ether (3 mL) and filtered through Celite. The reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (40% EtOAc in hexanes) producing compound **159** as a white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ 9.21 (t, J = 2.2 Hz, 1H), 9.06 (d, J = 2.1 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 5.80 – 5.64 (m, 2H), 5.64 – 5.46 (m, 1H), 5.30 – 5.20 (m, 1H), 5.04 – 4.87 (m, 4H), 4.30 – 4.22 (m, 2H), 3.74 (s, 3H), 3.06 (s, 1H), 2.39 (s, 3H), 2.28 (dd, J = 15.1, 6.9 Hz, 2H), 2.05 (s, 1H), 2.02 – 1.88 (m, 2H), 1.75-1.50 (m, 4H), 1.44 – 1.30 (m, 1H), 1.10 (d, J = 12.1 Hz, 2H), 1.02 – 0.95 (m, 1H), 0.80 (s, 3H). Compound **159** was dissolved in ether and upon vapor diffusion of pentane single crystals were obtained for X-ray diffraction studies.

Bicycle 161. A 20 mL flame-dried reaction tube was charged with compound **156** (50 mg, 0.15 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (a total of three times) followed by the addition of THF (5 mL). The reaction was cooled to -78 °C and a freshly prepared solution of lithium diisopropylamide (0.52 M in THF, 0.60 mL, 0.30 mmol, 2.0 equiv) was added dropwise. The resulting orange colored solution was stirred for 30 minutes at -78 °C and then 15 minutes at 0 °C. During this time, the reaction mixture was cooled to -78 °C and added solid diacetoxyiodobenzene (50 mg, 0.16 mmol, 1.1 equiv). The resulting yellow solution was stirred for 30 minutes at -78 °C and then 30 minutes at 0 °C. At this time, the reaction mixture was quenched with saturated *aq*. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% Et_2O in hexanes → 20% Et_2O in hexanes) to afford bicycle **161** (13 mg, 25% yield) as a yellow oil, epoxide **162** (7 mg, 14% yield) as a yellow oil and acetate **163** (5 mg, 9% yield) as a yellow oil. Compound **161**: ^{1}H NMR (400 MHz, $CDCl_3$)
δ 5.83 – 5.67 (m, 3H), 5.67 – 5.50 (m, 1H), 5.14 – 4.89 (m, 6H), 3.74 (s, 3H), 3.11 (s, 1H), 2.55 – 2.37 (m, 2H), 2.33 – 2.13 (m, 2H), 2.04 – 1.87 (m, 2H), 1.79 – 1.49 (m, 3H), 1.48 – 1.33 (m, 2H), 1.32 – 1.07 (m, 2H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 197.0, 174.4, 138.6, 136.6, 134.1, 118.3, 117.1, 114.8, 106.2, 63.3, 61.8, 56.7, 44.6, 40.5, 38.6, 38.0, 34.8, 34.3, 27.6, 17.6.

Compound 162. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 – 5.56 (m, 3H), 5.27 (d, J = 1.9 Hz, 1H), 5.09 – 4.86 (m, 6H), 3.73 (s, 3H), 3.33 (d, J = 2.0 Hz, 1H), 2.63 (dd, J = 13.5, 6.7 Hz, 1H), 2.27 (d, J = 7.3 Hz, 2H), 2.23 – 2.10 (m, 1H), 2.00 – 1.78 (m, 3H), 1.68 – 1.52 (m, 1H), 1.48 – 1.36 (m, 1H), 1.36 – 1.17 (m, 4H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 168.4, 138.2, 136.7, 133.7, 117.8, 115.9, 114.6, 102.2, 75.6, 56.1, 54.1, 53.4, 44.7, 43.1, 42.8, 35.0, 34.1, 33.9, 28.3, 16.5.

Compound 163. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 – 5.56 (m, 3H), 5.50 (s, 1H), 5.09 – 4.84 (m, 6H), 3.80 – 3.73 (m, 1H), 3.71 (s, 3H), 2.62 – 2.46 (m, 2H), 2.40 (dd, J = 14.1, 7.3 Hz, 1H), 2.27 (d, J = 8.4 Hz, 1H), 2.17 (s, 3H), 2.09 – 1.82 (m, 4H), 1.63 (dtt, J = 15.3, 10.9, 5.3 Hz, 2H), 1.34 (dd, J = 13.1, 8.8 Hz, 1H), 1.24 (m, 3H), 1.06 (ddd, J = 9.1, 6.1, 2.2 Hz, 2H), 0.99 (s, 3H), 0.93 – 0.79 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 171.2, 169.7, 138.7, 138.1, 135.1, 117.1, 115.5, 114.7, 105.2, 83.5, 68.3, 58.8, 56.6, 51.7, 42.9, 39.6, 39.2, 38.6, 36.2, 29.9, 29.4, 21.2, 14.7.

Compound 164. A 10 mL flame-dried reaction tube was charged with compound **156** (20 mg, 0.06 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (a total of three times) followed by the addition of THF (2 mL). The reaction was cooled to -78 °C and a freshly prepared solution of lithium diisopropylamide (0.52 M in THF, 0.24 mL, 0.12 mmol, 2.0 equiv) was added dropwise. The resulting orange colored solution was stirred for 30 minutes at -78 °C and then 15 minutes at 0 °C. During this time, the reaction mixture was cooled to -78 °C and added Koser's reagent (24 mg, 0.06 mmol, 1.0 equiv) in THF (1 mL). The resulting yellow solution was stirred for 30 minutes at -78 °C and then 30 minutes at 0 °C. At this time, the reaction mixture was quenched with saturated *aq*. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. 1,3,5-Trimethoxybenzene (10 mg) was added as an NMR standard. The crude residue was purified by column chromatography (10% Et_2O in hexanes → 20% Et_2O in hexanes) to afford tosylate **164** (7 mg, 23% yield) as a white crystalline solid. Compound **164**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 5.85 – 5.55 (m, 3H), 5.41 (s, 1H), 5.06 (s, 1H), 5.06 – 4.81 (m, 6H), 3.49 (s, 3H), 2.79 (bs, 1H), 2.59 – 2.47 (m, 2H), 2.47 (s, 3H), 2.33 – 2.22 (m, 1H), 2.17 (ddd, J = 13.7, 5.9, 4.2 Hz, 1H), 2.03 – 1.88 (m, 3H), 1.61 (ddt, J = 12.1, 8.5, 4.4 Hz, 1H), 1.42 – 1.32 (m, 1H), 1.03 (s, 3H), 0.99 – 0.84 (m, 2H). Compound **164** was dissolved in ether and upon vapor diffusion of pentane single crystals were obtained for X-ray diffraction studies.

Procedure for semi-pinacol rearrangement of Compound **164** to Compound **161**.

A 100 mL flame-dried reaction flask was charged with compound **164** (102 mg, 0.20 mmol, 1.0 equiv) and lithium *tert*-butoxide (90 mg, 1.1 mmol, 5.5 equiv). The reaction vessel was evacuated and backfilled with nitrogen (a total of three times), cooled to -78 °C followed by the dropwise addition of THF (17 mL). The resulting orange colored

solution was stirred for 30 minutes at -78 °C and then 30 minutes at 0 °C. At this time, the reaction mixture was quenched with saturated *aq*. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% Et_2O in hexanes → 20% Et_2O in hexanes) to afford bicycle **161** (61 mg, 90% yield) as a colorless oil.

Ketone 165. *i.* A 1 L flame-dried flask was charged with anhydrous lithium chloride (6.6 g, 156 mmol, 1.2 equiv) and copper bromide dimethylsulfide complex (32.0 g, 156 mmol, 1.2 equiv). The reaction vessel was evacuated and backfilled with nitrogen and this process repeated for a total of three times. THF (600 mL) was added and the mixture was stirred for 5 minutes at 25°C and then cooled to -78 °C whereupon (3-methylbut-3-en-1-yl)magnesium bromide (1 M in Et_2O), 130 mL, 130 mmol, 1 equiv) was added dropwise. The resulting dark brown solution was stirred for 30 minutes at -78 °C before adding TMSCl (20.0 mL, 156 mmol, 1.2 equiv) and 2-methylcyclopentenone (10.0 g, 104.1 mmol, 0.8 equiv) quickly in succession. The reaction mixture was stirred for 60 minutes at -78 °C and then triethylamine (20 mL) was added. The reaction vessel was slowly warmed to 25 °C over the course of 1 hour and then saturated *aq*. NH_4OH/saturated *aq*. NH_4Cl (9:1 *v:v*, 200 mL) added, resulting in a dark blue colored solution. The reaction mixture was filtered through Celite, and then extracted with ether (3 x 300 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (1% → 2% Et_2O in hexanes) to afford the silyl enol ether product (18.1 g, 73% yield) as a colorless oil.

ii. A 250 mL flame-dried flask was charged with silyl enol ether (442 mg, 1.85 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen and this process repeated for a total of three times followed by the addition of THF (60 mL). After cooling the reaction flask to 0 °C, methyllithium lithium-iodide complex (1.0 M in ether, 2.2 mL, 2.20 mmol, 1.2 equiv) was added and the reaction mixture was stirred for 1 hr. HMPA (10 mL) was added at 0 ° C followed by cooling to -78 °C and the addition of 5-iodo-2-methylpent-2-ene (1.3 mL, 9.25 mmol, 5.0 equiv). The colorless solution was warmed to 5 °C and stirred for 30 h at which point it was quenched with deionized H_2O (50 mL) and diluted with ether (100 mL). After organic layer was washed with deionized H_2O (2 x 50 mL). The combined aqueous layers were extracted with ether (2 x 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford a yellow oil. The crude material was dissolved in benzene (50 mL) under an atmosphere of nitrogen and *p*-toluenesulfonic acid monohydrate (35 mg, 0.185 mmol, 0.1 equiv) was added. The reaction mixture heated to 70 °C for 24 h, cooled to room temperature, and the brown solution concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (1% → 2% Et_2O in hexanes) followed by chromatography on $AgNO_3$ impregnated silica gel (2% Et_2O in hexanes) to afford the ketone **165** (184 mg, 40% yield, 3:1 dr) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$-*d*) δ 5.17 (t, *J* = 7.2 Hz, 1H), 5.04 (t, *J* = 7.1 Hz, 1H), 2.33 (dd, *J* = 17.2, 8.4 Hz, 1H), 2.18 – 2.10 (m, 1H), 2.05 (m, 3H), 1.94 (m, 2H), 1.78 – 1.72 (m, 1H), 1.71 (s, 3H), 1.65 (s, 3H), 1.63 (s, 3H), 1.62 – 1.59 (m, 1H), 1.57 (s, 3H), 1.49 – 1.39 (m, 1H), 1.37 (ddd, *J* = 13.9,

11.7, 5.0 Hz, 1H), 0.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$-*d*)) δ 223.76, 132.60, 131.76, 124.42, 122.70, 51.46, 43.28, 37.58, 36.11, 28.70, 25.93, 25.77, 25.10, 23.44, 17.99, 17.95, 17.71; IR (thin film) 2966, 2924, 2857, 1739, 1451, 1407 cm^{-1}; HRMS (EI) calcd for [$C_{17}H_{28}O_1$]: m/z 248.2140, found 248.2142.

Ketone 166. A 50 mL flame-dried flask was charged with ketone **165** (440 mg, 1.77 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (20 mL). After cooling the reaction vessel to -78 °C, a freshly prepared solution of lithium diisopropylamide (0.52 M in THF, 3.60 mL, 1.86 mmol, 1.1 equiv) was added dropwise via syringe resulting in a light yellow solution. The reaction mixture was stirred for 30 minutes at -78 °C and then 30 minutes at 0 °C. Dry hexamethylphosphoramide was then added to the reaction mixture at 0 °C and the mixture re-cooled to -78 °C. Freshly distilled prenylbromide (0.22 mL, 1.95 mmol, 1.1 equiv) was added dropwise at -78 °C and the resulting pale yellow solution stirred for 15 minutes at this temperature and then warmed to 0 °C, stirred 15 minutes at this temperature, and then quenched with deionized water (20 mL). The reaction mixture was diluted with ether (100 mL), and the organic layer was washed with deionized water (2 x 20 mL). The combined aqueous layers were extracted with ether (2 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (1% → 2% Et_2O in hexanes) to afford ketone **166** (498 mg, 89% yield, 13:1 mixture of diastereomers) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$-*d*) δ 5.14 (t, *J* = 6.7 Hz, 1H), 5.12 – 5.01 (m, 2H), 2.28 (tt, *J* = 9.0, 4.1 Hz, 1H), 2.22 (dt, *J* = 12.4, 5.9 Hz, 1H), 2.12 (dt, *J* = 12.9, 5.9 Hz, 1H), 2.09 – 1.99 (m, 2H), 1.94 (tt, *J* = 12.5, 5.8 Hz, 1H), 1.90 – 1.82 (m, 1H), 1.81 – 1.76 (m, 1H), 1.76 – 1.72 (m, 1H), 1.71 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.65 – 1.63 (m, 1H), 1.62 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.55 (dd, *J* = 12.7, 4.8 Hz, 1H), 1.33 (td, *J* = 13.0, 4.9 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$-*d*) δ 224.85, 133.57, 132.55, 131.73, 124.46, 122.90, 121.89, 52.35, 46.43, 41.08, 36.03, 29.98, 29.31, 28.71, 25.94, 25.93, 25.80, 23.41, 18.24, 17.99, 17.72; IR (thin film) 2966, 2916, 2858, 1734, 1451, 1376 cm; HRMS (EI) calcd for [$C_{22}H_{36}O_1$]: m/z 316.2766, found 316.2763.

Diketone 169. A 20 mL flame-dried reaction tube was charged with compound **166** (100 mg, 0.32 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of degassed THF (5 mL) and Et_2O (5 mL). The reaction vessel was cooled to -78 °C and freshly prepared lithium 2,2,6,6-tetramethylpiperidide (0.45 M in THF, 0.80 mL, 0.36 mmol, 1.2 equiv) was added dropwise resulting in a light yellow colored solution. The reaction mixture was stirred for 30 minutes at -78 °C and then 60 minutes at 0 °C. After this period, the reaction mixture was cooled to -40 °C and freshly distilled diketene (30 μL, 0.38 mmol, 1.2 equiv) was rapidly in one portion resulting in a bright yellow solution. The reaction vessel was maintained at this temperature for 90 minutes and then quenched with saturated *aq*. NH_4Cl (20 mL) at this temperature. The reaction mixture was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (5% Et_2O in hexanes → 15% EtOAc in hexanes) to afford the annulated product **169** (44 mg, 35% yield) as a red/orange colored oil and recovered starting material **166** (22 mg, 22%

yield) as a white solid (mp = 99-101 °C) precipitates: ^{1}H NMR (600 MHz, $CDCl_3$-*d*) δ 5.11 – 5.00 (m, 2H), 4.95 – 4.89 (m, 1H), 3.66 (d, *J* = 18.0 Hz, 1H), 3.11 (d, *J* = 18.0 Hz, 1H), 2.79 – 2.68 (m, 2H), 2.49 (dd, *J* = 15.2, 7.0 Hz, 1H), 2.46 – 2.36 (m, 2H), 2.17 – 2.06 (m, 2H), 2.06 – 1.97 (m, 1H), 1.94 (s, 1H), 1.80 – 1.72 (m, 1H), 1.68 (s, 9H), 1.62 (s, 3H), 1.59 (s, 6H), 1.41 – 1.30 (m, 2H), 1.26 (t, *J* = 12.9 Hz, 1H), 1.17 (td, *J* = 13.2, 4.6 Hz, 1H), 1.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.4, 203.8, 135.2, 132.5, 132.3, 124.5, 122.8, 118.4, 84.3, 61.2, 52.0, 50.5, 50.4, 45.0, 37.5, 35.2, 34.7, 29.2, 26.2, 26.0, 25.8, 22.9, 18.3, 18.0, 18.0, 14.9; IR (thin film) 3520, 3375, 2968, 2923, 2878, 1733 cm^{-1}; HRMS (ESI) calcd for $[C_{26}H_{39}O_3]$+ (M+H)+: m/z 399.2905, found 399.2904. Additional purification of mixed fractions by column chromatography (2% Et_2O in hexanes → 10% Et_2O in hexanes) afforded O-acylated product **167** (17 mg, 14% yield) and C-acylated product **168** (8.0 mg, 6% yield).

O-acylated product (mixture of enol and keto tautomers) **167** as a colorless oil ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 12.00 (enol tautomer, s, 1H), 5.24 – 4.96 (m, 3H), 3.55 (keto tautomer, s, 2H), 2.69 – 2.52 (m, 2H), 2.30 (s, 10H), 2.15 – 1.81 (m, 20H), 1.69 (dd, J = 3.2, 1.5 Hz, 18H), 1.68 – 1.66 (m, 15H), 1.61 (d, J = 1.4 Hz, 10H), 1.59 (d, J = 1.3 Hz, 6H), 1.59 – 1.56 (m, 15H), 1.40 – 1.25 (m, 6H), 0.97 (td, J = 7.5, 5.8 Hz, 3H), 0.90 (d, J = 1.8 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 176.5, 170.7, 164.7, 147.1, 147.0, 133.0, 132.8, 132.0, 131.9, 131.2, 131.1, 125.4, 125.0, 124.9, 124.9, 123.3, 123.2, 120.4, 120.3, 89.2, 49.9, 48.7, 48.6, 42.8, 42.4, 38.6, 38.5, 35.7, 35.7, 30.2, 29.2, 26.5, 26.4, 25.8, 25.7, 23.3, 21.3, 19.0, 17.9, 17.7, 17.7, 17.6, 17.5.

C-acylated product **168** (enol tautomer) as a colorless oil ^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ 15.17 (s, 1H), 5.84 (s, 1H), 5.27 – 5.17 (m, 1H), 5.03 – 4.96 (m, 1H), 4.94 – 4.85 (m, 1H), 2.75 (dd, J = 12.8, 5.9 Hz, 1H), 2.55 (dd, J = 14.5, 8.0 Hz, 1H), 2.34 (dd, J = 14.6, 7.0 Hz, 1H), 2.16 – 2.07 (m, 1H), 2.02 (s, 3H), 2.00 – 1.96 (m, 2H), 1.96 – 1.79 (m, 3H), 1.77 – 1.71 (s, 3H), 1.69 – 1.65 (s, 3H), 1.65 – 1.62 (m, 6H), 1.59 – 1.57 (m, 3H), 1.53 – 1.49 (m, 3H), 1.37 – 1.24 (m, 3H), 0.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 220.9, 194.5, 185.5, 135.3, 132.3, 131.6, 124.1, 122.4, 118.6, 97.8, 65.5, 52.5, 40.1, 36.8, 36.0, 32.4, 28.7, 25.8, 25.8, 25.5, 23.2, 18.7, 17.9, 17.8, 17.4.

Vinylogous Esters 170 and **171**. A flame-dried 50 mL flask was charged with compound **169** (200 mg, 0.50 mmol, 1 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of toluene (16 mL) and methanol (4 mL). A solution of trimethylsilyldiazomethane (2.0 M in hexanes, 0.40 mL, 0.75 mmol, 1.5 equiv) was added dropwise to the reaction mixture and the resulting yellow solution was stirred for 30 minutes. The reaction mixture was quenched with *aq*. acetic acid (1M solution, 10 mL) and extracted with ether (3 x 50 mL). The combined organic layers were washed with saturated sodium carbonate, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% → 20% EtOAc in hexanes) to afford compound **170** (100 mg, 48%) and compound **171** (100 mg, 48%) both as red/orange oils. Both compounds could be crystallized by cooling hexane solutions to – 20 °C, (compound **171**, white solid, mp = 83-84 °C; compound **170**, white solid, mp = 85-86 °C). **Regioisomer 170:** ^{1}H NMR (600 MHz, $CDCl_3$-*d*) δ

5.38 (s, 1H), 5.16 – 5.04 (m, 2H), 4.93 (t, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 2.64 (d, *J* = 17.9 Hz, 1H), 2.60 (dd, *J* = 13.2, 7.8 Hz, 1H), 2.48 (dd, *J* = 14.7, 6.5 Hz, 1H), 2.43 (d, *J* = 18.0 Hz, 1H), 2.36 (dd, *J* = 14.6, 8.4 Hz, 1H), 2.10 – 2.03 (m, 1H), 2.00 – 1.91 (m, 1H), 1.90 (s, 1H), 1.89 – 1.82 (m, 2H), 1.67 (s, 3H), 1.66 (s, 3H), 1.63 (s, 3H), 1.59 (s, 6H), 1.55 (s, 3H), 1.27 (dd, *J* = 13.6, 9.2 Hz, 1H), 1.13 (td, *J* = 12.5, 12.0, 4.4 Hz, 1H), 1.09 – 1.01 (m, 1H), 0.97 (s, 3H), 0.95 – 0.92 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.7, 174.5, 134.3, 132.1, 131.6, 125.2, 124.2, 120.5, 102.9, 85.2, 59.2, 56.2, 52.1, 44.4, 40.0, 38.3, 37.5, 35.6, 32.1, 26.4, 26.2, 26.1, 23.9, 18.4, 18.3, 18.1, 15.0; IR (thin film) 3474, 2967, 2923, 2856, 1617, 1451 cm^{-1}; HRMS (EI) calcd for [$C_{27}H_{42}O_3$]: m/z 414.3134, found 414.3138. **Regioisomer 171:** ^{1}H NMR (600 MHz, $CDCl_3$-*d*) δ 5.44 (s, 1H), 5.04 (m, 2H), 4.94 (t, *J* = 7.1 Hz, 1H), 3.66 (s, 3H), 2.69 (d, *J* = 17.0 Hz, 1H), 2.59 (dd, *J* = 14.6, 9.1 Hz, 1H), 2.42 (dd, *J* = 15.0, 5.7 Hz, 1H), 2.39 (d, *J* = 17.1 Hz, 1H), 2.35 (dd, *J* = 13.4, 7.3 Hz, 1H), 2.10 – 2.04 (m, 1H), 2.03 – 1.98 (m, 1H), 1.97 (s, 1H), 1.93 – 1.84 (m, 2H), 1.67 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.59 (s, 3H), 1.53 (s, 3H), 1.52 – 1.46 (m, 1H), 1.42 (dd, *J* = 13.2, 10.0 Hz, 1H), 1.23 (td, *J* = 12.8, 12.3, 4.9 Hz, 1H), 1.17 (td, *J* = 13.0, 12.6, 4.9 Hz, 1H), 0.96 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.5, 180.3, 134.4, 131.9, 131.3, 124.9, 123.9, 120.6, 103.6, 84.8, 56.3, 53.8, 51.8, 46.6, 45.5, 40.3, 39.9, 35.9, 30.6, 26.1, 26.0, 25.8, 23.6, 18.1, 18.0, 17.8, 15.3; IR (thin film) 3349, 2967, 2926, 2856, 1719, 1637 cm^{-1}; HRMS (ESI) calcd for [$C_{27}H_{41}O_3Na$]$^+$ $(M+Na)^+$: m/z 437.3026, found 437.3028.

Procedure for the Basic Hydrolysis of 170. A 100 mL flame-dried reaction flask was charged with vinylogous ester **170** (450 mg, 1.09 mmol, 1 equiv) and sodium hydroxide (900 mg, 22.5 mmol, 21 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of dioxane (23 mL) and deionized water (23 mL). The reaction mixture was heated to 80°C and kept at this temperature for 18 h. The reaction mixture was then cooled to room temperature, acidified with 1 M HCl (pH 1-2), and extracted with EtOAc (3 x 40 mL). The combined organic washed with brine (5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc in hexanes) to afford diketone **169** (248 mg, 57% yield) as an orange oil.

Bicycle 172. A 25 mL flame-dried flask was charged with compound **171** (50 mg, 0.121 mmol, 1.0 equiv), (Diacetoxyiodo)benzene (100 mg, 0.311 mmol, 2.6 equiv), and potassium hydroxide (500 mg, 8.93 mmol, 74 equiv). The reaction vessel was evacuated and backfilled with nitrogen (a total of three times) followed by the addition of MeOH (5 mL). The reaction was stirred at room temperature for 2 h. The resulting orange solution was concentrated in vacuo, diluted with EtOAc, washed with saturated aq. NH_4Cl (10 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The crude residue was purified by column chromatography (15% Et_2O in hexanes) to afford bicycle **172** (46 mg, 92% yield) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.71 (s, 1H), 5.07 (t, J = 7.2 Hz, 1H), 5.01 – 4.89 (m, 2H), 3.74 (s, 3H), 3.13 (s, 1H), 2.51 – 2.30 (m, 3H), 2.13 (m, 1H), 1.93 (dd, J = 13.9, 3.8 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.69z (s, 3H), 1.67 (s, 6H), 1.65 (s, 3H), 1.64 (s, 3H), 1.61 – 1.58 (m, 1H), 1.56 (s, 3H), 1.51 (td, J = 13.0, 4.3 Hz, 1H), 1.45 – 1.37 (m, 1H), 1.26 (m, 2H), 0.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.2, 194.0,

177.6, 133.8, 133.3, 131.8, 124.5, 122.7, 119.6, 106.5, 70.7, 57.1, 56.9, 46.1, 41.0, 39.4, 38.7, 29.9, 27.8, 26.1, 26.0, 25.9, 22.0, 18.2, 18.1, 17.9, 17.8; IR (thin film) 2967, 2925, 2880, 1734, 1655, 1599 cm^{-1}; HRMS (EI) calcd for [$C_{27}H_{40}O_3$]: m/z 412.2977, found 412.2978.

Procedure for Oxidative Ring Expansion using LDA as base (Table 1).
A 10 mL flame-dried flask was charged with compound **171** (50 mg, 0.121 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (a total of three times) followed by the addition of THF (5 mL). The reaction was cooled to -78 °C and a freshly prepared solution of lithium diisopropylamide (0.52 M in THF, 0.80 mL, 0.42 mmol, 3.5 equiv) was added dropwise. The resulting orange colored solution was stirred for 15 minutes at -78 °C and then 30 minutes at 0 °C. During this time, a separate flame-dried 25 mL flask was charged with [bis(trifluoroacetoxy)iodo]benzene (94 mg, 0.218 mmol, 1.8 equiv) and the flask evacuated and backfilled with nitrogen (three times in total) followed by the addition of dichloromethane (5 mL). To the vessel containing PIFA was addition trimethylsilylcyanide (0.55 uL, 0.435 mmol, 3.6 equiv) at 0 °C and the mixture stirred at that temperature for 30 minutes. Both flasks were then cooled to -78 °C, and the dianion of compound **171** was cannula transferred into the flask containing the hypervalent iodine oxidant. The resulting yellow solution was stirred for 15 minutes at -78 °C and then 15 minutes at 0 °C. At this time, the reaction mixture was quenched with saturated *aq*. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% Et_2O in hexanes → 20% EtOAc in hexanes) to afford bicycle **172** (20 mg, 40% yield) as a yellow oil.

Chloride 174. A 25 mL flame-dried reaction flask was charged with compound **172** (110 mg, 0.267 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (10 mL). After cooling the reaction vessel to -78 °C, a solution of freshly prepared lithium 2,2,6,6-tetramethylpiperidide (0.50 M in THF, 1.25 mL, 0.625 mmol, 2.3 equiv) was added dropwise resulting in a light yellow colored solution.The reaction mixture was stirred for 60 minutes at -78 °C and then *p*-toluenesulfonyl chloride (120 mg, 0.628 mmol, 2.3 equiv) added as a solution in THF. The reaction mixture was maintained at -78 °C for 15 minutes, warmed to 0 °C for 15 minutes, and then quenched with saturated *aq*. $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% CH_2Cl_2 in hexanes → 5% ether in hexanes) affording **174** (106 mg, 89% yield) as a yellow oil: ^1H NMR (600 MHz, $CDCl_3$-*d*) δ 5.06 (t, *J* = 7.4 Hz, 1H), 4.97 (t, *J* = 5.9 Hz, 1H), 4.93 (t, *J* = 6.9 Hz, 1H), 4.20 (s, 3H), 3.34 (s, 1H), 2.48 (dd, *J* = 14.9, 5.6 Hz, 1H), 2.41 – 2.31 (m, 2H), 2.14 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.02 (dd, *J* = 14.0, 4.1 Hz, 1H), 1.85 (tt, *J* = 12.8, 5.3 Hz, 1H), 1.70 (s, 3H), 1.68 – 1.64 (m, 12H), 1.64 – 1.59 (m, 1H), 1.56 (s, 3H), 1.51 (dd, *J* = 12.8, 4.5 Hz, 1H), 1.42 (ddd, *J* = 13.8, 11.7, 3.4 Hz, 1H), 1.22 (tt, *J* = 13.1, 5.9 Hz, 1H), 1.01 – 0.91 (m, 1H), 0.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.2, 187.9, 172.3, 134.2, 133.7, 132.0, 124.2, 122.4, 119.4, 115.7, 70.6, 62.8, 60.2, 46.9, 41.1, 39.5, 38.6, 30.7, 27.7, 26.0, 26.0, 25.9, 21.9, 18.2, 18.2, 17.9, 17.8; IR (thin film) 2967, 2925,

2878, 1735, 1673, 1579 cm^{-1}; HRMS (EI) calcd for [$C_{27}H_{39}ClO_3$]: m/z 446.2588, found 446.2587.

Chloride 175. Two 20 mL flame-dried reaction tubes were charged with compound **174** (2 x 46 mg, 0.206 mmol, 1.0 equiv). The reaction vessels were evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (1 mL). The reaction mixtures were cooled to -78 °C and a freshly prepared solution of lithium 2,2,6,6-tetramethylpiperidide (0.50 M in THF, 0.62 mL, 0.31 mmol, 3.2 equiv) was added dropwise to each vessel resulting in a light brown colored solution. The reaction mixtures were stirred for 10 minutes at -78°C, warmed to 0 °C and stirred 5 minutes, and then re-cooled to -78 °C. Isobutyryl cyanide (50 μL, 0.49 mmol, 5 equiv) was added dropwise to both vessels at -78 °C. The reaction mixtures were slowly warmed to -35 °C over the course of 30 minutes at which point they were quenched with saturated *aq*. $NaHCO_3$ solution (5 mL). The two reaction mixtures were combined and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (2% ether in hexanes) to afford the chloride product **175** (75 mg, 70% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 5.02 (t, *J* = 7.1 Hz, 1H), 4.99 – 4.89 (m, 2H), 4.25 (s, 3H), 2.52 (dd, *J* = 14.6, 5.4 Hz, 1H), 2.42 (dd, *J* = 14.6, 7.9 Hz, 1H), 2.16 – 2.03 (m, 3H), 2.03 – 1.96 (m, 1H), 1.94 (dd, *J* = 13.6, 4.0 Hz, 1H), 1.88 – 1.81 (m, 2H), 1.81 – 1.73 (m, 1H), 1.70 (s, 3H), 1.68 (m, 6H), 1.64 (s, 3H), 1.59 (s, 3H), 1.56 (s, 3H), 1.47 (t, *J* = 5.4 Hz, 1H), 1.45 – 1.39 (m, 1H), 1.13 (d, *J* = 6.5 Hz, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 2.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 205.2, 187.3, 172.0, 134.7, 133.9, 131.5, 124.6, 122.3, 119.1, 116.1, 84.5, 77.4, 63.0, 60.7, 50.3, 43.0, 39.6, 36.6, 30.6, 27.4, 26.1, 26.0, 25.9, 25.0, 21.6, 20.6, 18.3, 18.2, 17.9, 13.9; IR (thin film) 2924, 2869, 2852, 1734, 1663, 1582 cm-1; HRMS (EI) calcd for [$C_{31}H_{45}ClO_4$]: m/z 516.3006, found 516.2999.

***O*-methylhyperforin.** A 10 mL flame-dried flask was charged with compound **SI-1** (50 mg, 0.10 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (5 mL). The solution was cooled to 0 °C and *i*-PrMgCl•LiCl solution (1.3 M in Et_2O, 0.26 mL, 0.34 mmol, 3.4 equiv) was added dropwise. After 15 minutes at 0 °C, the reaction mixture was warmed to room temperature and stirred for 75 minutes. The reaction vessel was then cooled to -78 °C, and freshly prepared lithium diisopropylamide (0.52 M in THF, 0.73 mL, 0.38 mmol, 3.8 equiv) was added dropwise. After stirring for 20 minutes at this temperature, 2-thienyl(cyano)copperlithium (0.25 M in THF, 2.7 mL, 0.68 mmol, 7 equiv) was added dropwise. The reaction mixture was stirred for 5 minutes at -78 °C and then warmed to -40 °C and stirred an additional 30 minutes. The mixture was then re-cooled to -78 °C and freshly distilled prenyl bromide (190 μL, 1.7 mmol, 17 equiv) was added. The reaction mixture was warmed to -30 °C over the course of 90 minutes and then quenched with saturated *aq*. NH_4Cl and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (2% Et_2O in hexanes) affording *O*-methylhyperforin **SI-1** (39 mg, 73% yield) as a colorless oil.: ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 5.09 – 5.02 (m, 2H), 5.02 – 4.97 (m, 1H), 4.97 – 4.92 (m, 1H), 3.92 (s, 3H),

3.18 (d, J = 6.5 Hz, 2H), 2.50 (dd, J = 14.8, 6.1 Hz, 1H), 2.40 (dd, J = 14.7, 7.4 Hz, 1H), 2.09 (t, J = 14.1 Hz, 2H), 1.98 (septet, J = 6.4 Hz, 1H), 1.93 – 1.84 (m, 3H), 1.79 – 1.71 (m, 1H), 1.69 – 1.65 (m, 15H), 1.64 (s, 3H), 1.63 – 1.60 (m, 1H), 1.59 (s, 3H), 1.56 (s, 3H), 1.46 – 1.40 (m, 1H), 1.40 – 1.35 (m, 1H), 1.11 (d, J = 6.5 Hz, 3H), 1.02 (d, J = 6.5 Hz, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 207.3, 194.1, 174.1, 134.0, 133.5, 133.2, 131.2, 127.7, 125.0, 122.7, 121.9, 119.9, 84.3, 62.6, 58.9, 49.4, 43.4, 42.8, 39.1, 36.7, 30.3, 27.3, 26.1, 26.0, 25.9, 25.8, 25.1, 23.7, 21.5, 20.6, 18.3, 18.14, 18.13, 17.9, 13.8; IR (thin film) 2967, 2926, 2873, 1730, 1720, 1646 cm^{-1}; HRMS (ESI) calcd for$[C_{36}H_{53}O_4Na]$+ $(M+Na)^+$: m/z 573.3914 found 573.3913.

Hyperforin (1). [Note: The following procedure was conducted in the dark. Solvents used were degassed with argon for 10 minutes prior to use]. A 10 mL flame-dried reaction tube was charged with compound *O*-methylhyperforin (53 mg, 0.096 mmol, 1 equiv) and dry lithium chloride (40 mg, 0.95 mmol, 10 equiv). The reaction vessel was evacuated and backfilled with nitrogen three times followed by the addition of DMSO (2 mL). The reaction mixture was heated to 120 °C and kept at this temperature for 30 minutes. The reaction mixture was then cooled to room temperature, diluted with H_2O, and extracted with 1:1 hexane:EtOAc (3 x 20 mL). The combined organic layers extracts were washed with H_2O (3 x 5 mL), washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford a yellow oil. The crude residue was purified by column chromatography (2% → 5% EtOAc in hexanes) to afford hyperforin (29 mg, 56% yield) as an oil: ^{1}H NMR (600 MHz, MeOD-d_4) δ 5.12 (t, J = 6.4 Hz, 1H), 5.04 – 4.96 (m, 3H), 3.16 (dd, J = 14.8, 7.2 Hz, 1H), 3.10 (dd, J = 14.8, 6.9 Hz, 1H), 2.52 (dd, J = 14.9, 6.8 Hz, 1H), 2.43 (dd, J = 14.6, 7.1 Hz, 1H), 2.14 – 2.12 (m, 1H), 2.11 – 2.04 (m, 1H), 2.04 – 1.97 (m, 1H), 1.97 – 1.89 (m, 2H), 1.80 – 1.74 (m, 3H), 1.73 (s, 3H), 1.72 – 1.69 (m, 6H), 1.68 (s, 3H), 1.67 – 1.66 (s, 3H), 1.65 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.41 (t, J = 12.7 Hz, 1H), 1.11 (d, J = 6.5 Hz, 3H), 1.06 (d, J = 6.5 Hz, 3H), 1.00 (s, J = 2.7 Hz, 3H); ^{13}C NMR (150 MHz, MeOD-d_4) δ 212.2, 209.3, 134.9, 134.5, 133.8, 132.1, 126.4, 124.1, 123.0, 122.3, 121.3, 49.9, 43.4, 41.1, 38.3, 31.0, 29.0, 26.4, 26.3, 26.3, 26.2, 25.8, 22.9, 22.3, 21.4, 18.5, 18.4, 18.4, 18.1, 15.6; IR (thin film) 3314, 2968, 2927, 2874, 1723, 1602 cm^{-1}; HRMS (ESI) calcd for$[C_{35}H_{51}O_4]^+$ $(M+H)^+$: m/z 535.3793 found 535.3783.

Procedure for the Annulation of Lithium Enolates with Diketene

General Procedure A: Enolate generation by desilylation of a trimethylsilyl enol ether with MeLi

A flame-dried reaction tube was charged with the trimethylsilyl enol ether (0.89 mmol, 1.1 equiv). The reaction vessel was evacuated and backfilled with nitrogen (process performed three times in total) and then added Et2O (4 mL). After cooling the reaction to 0 °C, methyllithium (1.6 M in Et2O, 0.80 mmol, 1.0 equiv) was added and the reaction mixture stirred for 1 hour. The reaction mixture was warmed to room temperature and monitored by TLC for consumption of the starting silyl enol ether. The reaction vessel was then cooled to -40 °C and freshly distilled diketene (0.89 mmol, 1.0 equiv) was rapidly added resulting in the formation of white precipitate. The suspension was stirred for 1 hour and then quenched with 1 M HCl (5 mL) and slowly warmed to room temperature. The reaction mixture was diluted in EtOAc (15 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with brine, dried over MgSO4, and concentrated *in vacuo* to afford a yellow oil. The crude residue was purified by silica gel column chromatography to afford the annulated product.

General Procedure B: Enolate generation by ketone deprotonation with LTMP

A 20 mL flame-dried reaction tube was charged with 2,2,6,6-tetramethylpiperidine (0.19 mL, 1.1 mmol, 1.1 equiv). The reaction vessel was evacuated and backfilled with nitrogen three times followed by the addition of Et2O (2.5 mL) or THF (2.5 mL). After cooling the reaction vessel to -78°C, n-BuLi (2.5 M in hexanes, 0.42 mL, 1.05 mmol was added dropwise resulting in a light yellow solution. The reaction mixture was stirred for 30 minutes at -78°C and then 15 minutes at 0°C. After re-cooling the reaction vessel to -78°C, the ketone (1.0 mmol, 1.1 equiv) was added dropwise as a solution in Et2O (2.5 mL). The reaction mixture was stirred for 30 minutes at -78°C and then 30 minutes at 0°C. The reaction mixture was cooled to -40°C and freshly distilled diketene (84 μL, 1.1 mmol, 1.1 equiv) was added rapidly in one portion resulting in the formation of white precipitate. The reaction vessel was maintained at this temperature for 60 minutes then quenched with 1 M HCl (20 mL). The reaction mixture was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine, dried over MgSO4, and concentrated *in vacuo*. The crude residue was purified by column chromatography to afford the annulated product.

Compound 176. Following general procedure B (0.42 mmol scale) using THF/Et_2O (1:1) as solvent, the title compound was isolated by silica gel column chromatography (50%→ 60% EtOAc in hexanes) as a white solid (49 mg, 59% yield).

mp: 108-113 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.43 (d, *J* = 20.0 Hz, 1H), 3.38 (d, *J* = 20.0 Hz, 1H), 2.87 (d, *J* = 17.0 Hz, 1H), 2.64 (d, *J* = 17.0 Hz, 1H), 2.10 (sept, *J* = 6.9 Hz, 1H), 2.02 (bs, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$): δ 207.1, 204.3, 77.7, 53.6, 53.1, 43.4, 34.8, 21.9, 19.1, 18.3, 18.0 ppm

IR (neat): 3595, 3473, 2988, 2970, 2571, 1611 cm^{-1}
HRMS (ESI): calcd. for $[C_{11}H_{17}O_3]^-$ $(M-H)^-$: m/z 197.1183, found 197.1175.

Compound 177. Following general procedure B (0.40 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (40%→ 50% EtOAc in hexanes) as a white solid (41 mg, 44% yield).
mp: 135-137 °C
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 – 7.38 (m, 4H), 7.38 – 7.33 (m, 1H), 3.74 (d, *J* = 16.1 Hz, 1H), 3.65 (d, *J* = 18.4 Hz, 1H), 3.46 (dd, *J* = 18.4, 2.2 Hz, 1H), 2.72 (dd, *J* = 16.2, 2.2 Hz, 1H), 2.23 (bs, 1H), 1.22 (s, 3H), 1.02 (s, 3H) ppm
^{13}C NMR (100 MHz, $CDCl_3$): δ 206.7, 202.8, 141.3, 128.4, 128.2, 126.3, 78.3, 54.0, 52.7, 50.8, 22.7, 17.9 ppm
IR (neat): 3379, 2985, 2925, 2892, 1734, 1700 cm^{-1}
HRMS (ESI): calcd. for $[C_{14}H_{15}O_3]^-$ $(M-H)^-$: m/z 231.1027, found 231.1037

Compound 178. Following general procedure B (1.0 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (20%→50% EtOAc in hexanes) as a white crystalline solid (138 mg, 63% yield).
mp: 171-173 °C
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.37 (m, 4H), 7.36 – 7.30 (m, 1H), 3.60 (d, *J* = 20.0 Hz, 1H), 3.55 (d, *J* = 20.0 Hz, 1H), 3.26 (d, *J* = 15.8 Hz, 1H), 3.18 (q, *J* = 6.8 Hz, 1H), 2.88 (dd, *J* = 15.7, 1.6 Hz, 1H), 2.14 (bs, 1H), 0.94 (d, *J* = 6.8 Hz, 3H) ppm
^{13}C NMR (150 MHz, $CDCl_3$): δ 203.0, 201.6, 143.3, 129.1, 127.9, 124.5, 76.2, 57.3, 55.8, 53.4, 8.5 ppm
IR (neat): 3379, 3029, 2996, 2899, 1726, 1700 cm^{-1}
HRMS (EI): calcd. for $[C_{13}H_{14}O_3]$ (M): m/z 218.0941, found 218.0943

Compound 179. Following general procedure B (1.0 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (50% EtOAc in hexanes) as a brown oil (97 mg, 44% yield).
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.18 (d, *J* = 3.0 Hz, 1H), 5.93 (d, *J* = 3.0 Hz, 1H), 3.50 (s, 2H), 3.28 (d, *J* = 16.0 Hz, 1H), 3.14 (q, *J* = 6.8 Hz, 1H), 2.90 (d, *J* = 16.0 Hz, 1H), 2.70 (bs, 1H), 2.28 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H) ppm
^{13}C NMR (100 MHz, $CDCl_3$): δ 203.1, 201.9, 153.5, 152.5, 107.2, 106.6, 73.3, 57.1, 53.4, 52.3, 13.7, 8.7 ppm
IR (neat): 3357, 2985, 2925, 1707, 1603, 1451 cm^{-1}

HRMS (ESI): calcd. for $[C_{12}H_{13}O_4]^-$ $(M-H)^-$: m/z 221.0819, found 221.0830.

Compound 180. Following general procedure B (1.0 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (20%→60% EtOAc in hexanes) as a orange solid (184 mg, 62% yield).
mp: 155-158 °C
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 3.58 (d, *J* = 20.0 Hz, 1H), 3.53 (dd, *J* = 20.0, 1.9 Hz, 1H), 3.22 (d, *J* = 15.7 Hz, 1H), 3.13 (q, *J* = 6.8 Hz, 1H), 2.85 (dd, *J* = 15.8, 1.9 Hz, 1H), 2.38 (bs, 1H), 0.93 (d, *J* = 6.8 Hz, 3H) ppm
^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 201.4, 142.5, 132.2, 126.4, 122.0, 76.0, 57.3, 55.5, 53.3, 8.4 ppm
IR (neat): 3569, 3368, 2985, 2903, 1700, 1588 cm^{-1}
HRMS (ESI): calcd. for $[C_{13}H_{12}BrO_3]^-$ $(M-H)^-$: m/z 294.9975, found 294.9991

Compound 181. Following general procedure B (3.6 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (20%→50% EtOAc in hexanes) as a light brown solid (697 mg, 65% yield).
mp: 180-183 °C
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.78 (m, 2H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.40 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.20 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 3.94 (s, 3H), 3.61 (d, *J* = 3.3 Hz, 2H), 3.35 (d, *J* = 15.8 Hz, 1H), 3.28 (q, *J* = 6.8 Hz, 1H), 2.93 (d, *J* = 15.8 Hz, 1H), 2.16 (bs, 1H), 0.96 (d, *J* = 6.8 Hz, 3H) ppm
^{13}C NMR (150 MHz, $CDCl_3$): δ 203.0, 201.6, 158.4, 138.4, 133.9, 129.8, 128.8, 127.9, 123.4, 122.8, 119.8, 105.8, 76.4, 57.4, 55.8, 55.6, 53.3, 8.6 ppm
IR (neat): 3357, 3003, 2907, 1704, 1626, 1611 cm^{-1}
HRMS (ESI): calcd for $[C_{18}H_{17}O_4]^-$ $(M-H)^-$: m/z 297.1132, found 297.1133.

Compound 182. Following general procedure B (1.0 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (20%→50% EtOAc in hexanes) as a white crystalline solid (160 mg, 68% yield).
mp: 154-158 °C
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (td, *J* = 8.1, 1.8 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.23 (td, *J* = 7.7, 1.3 Hz, 1H), 7.10 (ddd, *J* = 12.2, 8.2, 1.2 Hz, 1H), 3.67 – 3.44 (m, 4H), 2.81 (dd, *J* = 15.8, 2.3 Hz, 1H), 2.42 (bs, 1H), 0.92 (d, *J* = 6.9 Hz, 3H) ppm
^{13}C NMR (100 MHz, $CDCl_3$): δ 202.64, 201.81, 158.69 (d, *J* = 244.4 Hz), 130.32 (d, *J* =

8.6 Hz), 130.01 (d, *J* = 12.4 Hz), 127.00 (d, *J* = 3.7 Hz), 125.00 (d, *J* = 3.6 Hz), 116.46 (d, *J* = 23.4 Hz), 74.94 (d, *J* = 4.4 Hz), 57.43, 53.27 (d, *J* = 3.6 Hz), 51.45 (d, *J* = 4.1 Hz), 8.54 ppm

^{19}F NMR (376 MHz, $CDCl_3$): δ -112.55 ppm

IR (neat): 3391, 2925, 2854, 1730, 1700, 1488 cm^{-1}

HRMS (ESI): calcd. for $[C_{13}H_{12}FO_3]^-$ $(M-H)^-$: m/z 235.0776, found 235.0792

Compound 183. Following general procedure A (0.80 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (50%→ 100% EtOAc in hexanes) as a white solid (40 mg, 27% yield). The remaining column fractions were concentrated and re-purified by silica gel column chromatography (5%→ 7.5% MeOH in CH_2Cl_2) affording the *cis* diastereomer as a yellow solid (27 mg, 19% yield).

Compound 183 trans isomer.

mp: 145-147 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.43 (dd, *J* = 18.0, 1.6 Hz, 1H), 3.40 (d, *J* = 18.0 Hz, 1H), 2.77 (d, *J* = 15.5 Hz, 1H), 2.72 (dd, *J* = 15.5, 1.5 Hz, 1H), 2.51 (dd, *J* = 12.1, 4.2 Hz, 1H), 2.03 – 1.96 (m, 1H), 1.93 – 1.87 (m, 1H), 1.80 (ddt, *J* = 13.4, 4.0, 1.7 Hz, 1H), 1.72 (bs, 1H), 1.71 – 1.66 (m, 1H), 1.63 – 1.56 (m, 2H), 1.56 – 1.49 (m, 1H), 1.28 (qt, *J* = 13.3, 3.7 Hz, 1H) ppm

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.4, 202.4, 70.8, 57.5, 55.2, 55.1, 38.9, 24.6, 21.3, 21.0 ppm

IR (neat): 3383, 2981, 2936, 2854, 1726, 1700 cm^{-1}

HRMS (ESI): calcd. for $[C_{10}H_{13}O_3]^-$ $(M-H)^-$: m/z 181.0870, found 181.0872

Compound 183 cis isomer.

mp: 148-150 °C

In MeOD-d_4, there are no ^{1}H NMR resonances from the protons at the 2-position of the 1,3-diketone due to proton exchange with the deuterated solvent. Also, the compound exists as a mixture of tautomers and the ^{13}C NMR spectrum shows broadening for multiple resonances.

^{1}H NMR (600 MHz, MeOD-d_4): δ 2.84 (d, *J* = 17.6 Hz, 1H), 2.25 – 2.12 (m, 2H), 1.97 (d, *J* = 13.0 Hz, 1H), 1.77 (d, *J* = 10.0 Hz, 2H), 1.69 (d, *J* = 13.0 Hz, 1H), 1.53 – 1.38 (m, 2H), 1.37 – 1.24 (m, 2H) ppm

^{13}C NMR (150 MHz, MeOD-d_4): δ 73.1, 39.4, 25.5, 24.5 ppm

IR (neat): 3171, 2936, 2858, 1707, 1573, 1451 cm^{-1}

HRMS (ESI): calcd. for $[C_{10}H_{13}O_3]^-$ $(M-H)^-$: m/z 181.0870, found 181.0900

Compound 184. Following general procedure B (1.0 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (30%→40% EtOAc in hexanes) as a brown solid (61 mg, 31% yield). The remaining column fractions were concentrated and re-purified by silica gel column chromatography (0%→ 7.5% MeOH in CH_2Cl_2) to give the *cis* diastereomer as a yellow solid (42 mg, 21% yield).

Compound 184 trans isomer.

mp: 116-118 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41 (dd, *J* = 18.3, 1.9 Hz, 1H), 3.31 (d, *J* = 18.2 Hz, 1H), 2.89 (d, *J* = 16.2 Hz, 1H), 2.71 – 2.58 (m, 2H), 2.37 – 2.24 (m, 1H), 2.10 (bs, 1H), 2.08 – 1.96 (m, 2H), 1.88 – 1.76 (m, 2H), 1.72 (dd, *J* = 14.3, 10.1 Hz, 1H), 1.53 – 1.41 (m, 2H), 1.41 – 1.21 (m, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.3, 203.3, 74.4, 60.4, 56.0, 55.3, 42.6, 29.5, 28.1, 22.1, 20.6 ppm

IR (neat): 3391, 2925, 2862, 1726, 1700, 1451 cm^{-1}

HRMS (ESI): calcd. for $[C_{11}H_{15}O_3]^-$ $(M-H)^-$: m/z 195.1027, found 195.1055

Compound 184 cis isomer.

mp: 133-135 °C

^{1}H NMR (400 MHz, CD_2Cl_2): δ 3.38 (d, *J* = 16.0 Hz, 1H), 3.35 (d, *J* = 16.0 Hz, 1H), 2.84 (d, *J* = 15.8 Hz, 1H), 2.62 – 2.50 (m, 2H), 2.03 – 1.86 (m, 3H), 1.86 – 1.70 (m, 3H), 1.70 – 1.56 (m, 2H), 1.56 – 1.36 (m, 2H), 1.26 (bs, 1H) ppm

^{13}C NMR (100 MHz, CD_2Cl_2): δ 206.4, 202.4, 74.9, 60.9, 54.9, 49.9, 43.0, 28.8, 28.6, 27.3, 21.1 ppm

IR (neat): 3361, 3160, 2929, 2862, 1700, 1633 cm^{-1}

HRMS (ESI): calcd. for $[C_{11}H_{15}O_3]^-$ $(M-H)^-$: m/z 195.1027, found 195.1029

Compound 185. Following general procedure A (0.82 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (50%→ 100% EtOAc in hexanes) as a white solid (67 mg, 35% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.50 (s, 1H), 4.84 (s, 1H), 4.79 (s, 1H), 3.49 (d, J = 16.5 Hz, 1H), 3.31 (d, J = 16.4, 1H), 2.99 – 2.86 (m, 2H), 2.85 – 2.77 (m, 1H), 2.29 (ddt, J = 15.6, 10.4, 2.6 Hz, 1H), 2.22 – 2.08 (m, 1H), 1.77 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 201.0, 145.2, 136.5, 123.7, 114.2, 73.3, 60.8, 56.5, 48.5, 45.6, 30.3, 17.5, 16.8 ppm.

Compound 186. Following general procedure A (1.0 mmol scale) using Et_2O as solvent, the title compound was isolated by silica gel column chromatography (100% EtOAc) as a white solid (121 mg, 40% yield).

mp: 164-166 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.35 (s, 1H), 4.73 (s, 1H), 4.69 (s, 1H), 3.43 (d, *J* = 16.2 Hz, 1H), 3.36 (d, *J* = 16.2 Hz, 1H), 2.91 (d, *J* = 15.4 Hz, 1H), 2.72 (d, *J* = 15.4 Hz, 1H), 2.61 (d, *J* = 12.2 Hz, 1H), 2.39 – 2.32 (m, 1H), 2.28 (t, *J* = 12.4 Hz, 1H), 2.17 – 2.11 (m, 1H), 2.05 – 1.99 (m, 1H), 1.97 (d, *J* = 12.7 Hz, 1H), 1.88 (d, *J* = 12.8 Hz, 1H), 1.72 (s, 3H), 1.30 – 1.18 (m, 1H), 1.08 (s, 3H), 1.02 (t, *J* = 12.7 Hz, 1H), 0.91 (d, *J* = 6.9 Hz, 3H) ppm

^{13}C NMR (150 MHz, $CDCl_3$): δ 205.5, 200.7, 149.4, 145.7, 125.1, 109.3, 71.5, 59.8, 56.9, 50.3, 44.8, 41.8, 40.7, 40.1, 32.8, 32.3, 21.0, 18.3, 12.6 ppm

IR (neat): 3346, 2974, 2933, 2854, 1596, 1529 cm^{-1}

HRMS (ESI): calcd. for $[C_{19}H_{25}O_3]^-$ $(M-H)^-$: m/z 301.1809, found 301.1822

Nitrile SI-2. Propionitrile (0.26 mL, 3.64 mmol, 1.06 equiv) was added dropwise to a freshly prepared solution of lithium diisopropylamide (0.61 M in THF, 5.9 mL, 3.60 mmol, 1.05 equiv) at -78 °C. The reaction mixture was stirred for 1 hour at -78 °C and then warmed to 0 °C and stirred for an additional 30 minutes. The reaction mixture was re-cooled to -78 °C, dry Hexamethylphosphoramide (1.0 mL) added, warmed to 0 °C and stirred for 15 minutes, and then re-cooled to -78 °C. *trans*,*trans*-farnesyl bromide (977 mg, 3.42 mmol, 1.0 equiv) was added rapidly at -78 °C and the resulting solution stirred vigorously at this temperature for 30 minutes. The reaction mixture was warmed to 0 °C, stirred 30 minutes, and then quenched with saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with ether (20 mL), and the organic layer washed with water (2 x 10 mL). The combined aqueous layers were extracted with ether (2 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0.5% → 2% Et_2O in hexanes) to afford nitrile **SI-2** (696 mg, 78% yield) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.17 (t, *J* = 7.3 Hz, 1H), 5.13 – 5.04 (m, 2H), 2.60 (m, 1H), 2.33 (dt, *J* = 14.6, 7.3 Hz, 1H), 2.26 (dt, *J* = 14.3, 7.1 Hz, 1H), 2.14 – 1.94 (m, 8H), 1.67 (s, 3H), 1.64 (s, 3H), 1.60 (s, 6H), 1.29 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.7, 135.4, 131.3, 124.4, 123.9, 123.1, 119.0, 39.8, 39.8, 32.3, 26.8, 26.5, 26.0, 25.8, 17.8, 17.5, 16.4, 16.1; IR (thin film) 2966, 2914, 2854, 2240, 1669, 1453, 1380, 1108, 835 cm^{-1}; HRMS (EI) calcd. for $[C_{18}H_{29}N]$: m/z 259.2300, found 259.2302.

Nitrile 216. To a cooled solution (0 °C) of the nitrile **SI-2** (1.00 g, 3.85 mmol, 1.0 equiv) in THF/H_2O (150 mL, 2:1 v:v) was added NBS (0.75 g, 4.21 mmol, 1.1 equiv) as a solution in THF/H_2O (8 mL, 2:1 v:v) over a period of 1 hour. The reaction mixture was stirred at this temperature for 1 hour and then a solution of saturated aqueous $Na_2S_2O_3$ (10 mL) was added. K_2CO_3 (2.67 g, 19.32 mmol, 5 equiv) and MeOH (20 mL) were

added and the resulting mixture warmed to room temperature and stirred for an additional 3 hours. The majority of methanol and THF was removed under reduced pressure and the residue extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by silica gel flash chromatography (Et_2O/hexane, 1:10) affording **216** (639 mg, 60%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.12 (dt, *J* = 14.6, 7.6 Hz, 2H), 2.66 (t, *J* = 6.2 Hz, 1H), 2.57 (m, *J* = 7.0 Hz, 1H), 2.29 (dt, *J* = 14.6, 7.4 Hz, 1H), 2.22 (dt, *J* = 14.2, 6.9 Hz, 1H), 2.14-1.99 (m, 6H), 1.63-1.53 (m, 2H), 1.60 (s, 3H), 1.58 (s, 3H), 1.28-1.23 (m, 6H), 1.22 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.5, 134.4, 124.4, 122.9, 119.1, 64.1, 58.2, 39.6, 36.3, 32.2, 27.5, 26.4, 25.9, 24.9, 18.8, 17.5, 16.3, 16.0; IR (thin film) 2961, 2923, 2849, 2239, 1168, 1456, 1379, 1121, 874 cm^{-1}; HRMS (EI) calcd. for [$C_{18}H_{29}NO$]: m/z 275.2249, found 275.2245.

Ketone 217. *i.* A mixture of Cp_2TiCl_2 (1.0 g, 4.2 mmol, 2.3 equiv) and activated Zn (0.54 g, 8.3 mmol, 4.6 equiv) in rigorously deoxygenated THF (16 mL) was stirred at room temperature under N_2. The resulting green solution was then added dropwise over 1 hour *via* syringe pump to a solution of epoxy nitrile **216** (0.50 g, 1.8 mmol, 1.0 equiv) in deoxygenated THF (50 mL) at 60 °C. After 30 minutes of stirring at 60 °C, the reaction mixture was cooled to room temperature and quenched with 10% aqueous KH_2PO_4 solution (20 mL). The mixture was stirred for an additional 30 minutes and then filtered to remove insoluble titanium salts. The filtered solid was washed with ether (80 mL) and the filtrate was washed with saturated aqueous $NaHCO_3$ (40 mL), and the aqueous layer was extracted with ether (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. *ii.* The crude material was dissolved in DMF (5 mL) and imidazole (1.1 g, 16.2 mmol, 9.0 equiv) and TBSCl (1.2 g, 8.0 mmol, 4.4 equiv) added at room temperature. After stirring for 16 hours, the mixture was diluted with ether (100 mL) and quenched with deionized water (25 mL). The organic layer was washed with deionized H_2O (2 x 25 mL). The combined aqueous layers were further extracted with ether (2 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting crude residue was purified by column chromatography utilizing $AgNO_3$ (10 wt%) impregnated silica gel (0.5% Et_2O in hexanes) affording ketone **217** (297 mg, 42% yield) as a white solid and an inconsequential mixture of methyl diastereomers: Major isomer (mp = 100-103 °C), Minor isomer (mp = 144-147 °C); ^{1}H NMR (600 MHz, $CDCl_3$) major isomer: δ 3.18 (dd, *J* = 11.6, 4.2 Hz, 1H), 2.55-2.47 (m, 1H), 2.05 (td, *J* = 12.8, 9.6 Hz, 1H), 1.77 (dt, *J* = 13.1, 3.2 Hz, 1H), 1.71-1.33 (m, 6H), 1.32-1.15 (m, 3H), 1.08 (d, *J* = 7.6 Hz, 3H),1.09 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.80-0.75 (m, 1H), 0.77 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H); minor isomer: δ 3.18 (dd, *J* = 11.4, 4.4 Hz, 1H), 2.16-2.06 (m, 1H), 2.03-1.93 (m, 1H), 1.81 (dt, *J* = 13.0, 3.3 Hz, 1H), 1.73-1.32 (m, 6H), 1.31-1.15 (m, 3H), 1.19 (d, *J* = 7.4 Hz, 3H),0.95 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.81-0.69 (m, 1H), 0.77 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) major isomer: δ 222.9, 79.7, 56.3, 55.7, 48.9, 39.6, 39.2, 37.5, 37.3, 33.9, 28.7, 27.5, 26.6, 26.1, 18.7, 18.3, 17.6, 16.9, 16.4, 15.8, -3.6, -4.8; minor isomer: δ 223.8, 79.6, 57.2, 56.2, 48.8, 43.7, 39.6, 37.7, 37.3, 34.0, 28.7, 27.6, 27.5, 26.1, 18.7, 18.3, 17.6, 17.3, 16.9, 15.8, -3.6, -4.8; IR (thin film) 2930, 2850, 1735, 1464, 1383, 1362,

1252, 1103, 1065, 1022, 1004, 912, 878, 834, 772, 677 cm^{-1}; HRMS (EI) calcd. for [$C_{24}H_{44}O_2Si$]: m/z 392.3111, found 392.3108.

Diketone 218. A 20 mL flame-dried reaction tube was charged with ketone **217** (50.0 mg, 0.127 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of degassed THF (2.5 mL) and Et_2O (2.5 mL). The reaction vessel was cooled to -78 °C and freshly prepared lithium 2,2,6,6-tetramethylpiperidide (0.45 M in THF, 0.34 mL, 0.153 mmol, 1.2 equiv) was added dropwise resulting in a light yellow colored solution. The reaction mixture was stirred for 30 minutes at -78 °C and then 30 minutes at 0 °C. After this period, the reaction mixture was cooled to -40 °C and freshly distilled diketene (0.14 mL, 10% solution in THF, 1.3 equiv) was added rapidly in resulting in a bright yellow colored solution. The reaction vessel was maintained at this temperature for 30 minutes and then quenched with saturated *aq*. NH_4Cl (5 mL) at this temperature. The reaction mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (2% EtOAc in hexanes → 20% EtOAc in hexanes) to afford recovered **217** (18.0 mg) and diketone **218** (18.0 mg, 30% yield, 47% BRSM) as a white solid: mp = 205-207 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.68 (d, *J* = 18.7 Hz, 1H), 3.14 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.11 (d, *J* = 18.5 Hz, 1H), 2.63 (d, *J* = 15.0 Hz, 1H), 2.58 (dd, *J* = 12.9, 6.3 Hz, 1H), 2.43 (d, *J* = 14.9 Hz, 1H), 1.89 (s, 1H), 1.68-1.56 (m, 2H), 1.54-1.42 (m, 4H), 1.40-1.35 (m, 1H), 1.34 (s, 3H), 1.22-1.14 (m, 1H), 1.08 (s, 3H), 1.02-0.93 (m, 2H), 0.92 (s, 3H), 0.88 (s, 12H), 0.76 (s, 3H), 0.66 (dd, *J* = 12.2, 2.3 Hz, 1H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9, 204.2, 82.1, 79.5, 57.8, 56.4, 54.5, 51.1, 50.8, 48.8, 39.5, 38.6, 36.7, 34.6, 30.2, 28.6, 27.6, 26.1, 24.9, 19.0, 18.3, 16.3, 16.3, 15.9, -3.6, -4.8; IR (thin film) 3406, 2927, 2854, 1726, 1701, 1468, 1387, 1362, 1305, 1254, 1104, 1088, 1062, 1045, 1006, 984, 912, 880, 832, 772; HRMS (ESI) calcd. for [$C_{28}H_{47}O_4Si$]$^-$ $(M-H)^-$: m/z 475.3249, found 475.3242.

Vinylogous ester SI-3. A flame-dried 50 mL flask was charged with 1,3-diketone **218** (168 mg, 0.35 mmol, 1 equiv) and the reaction vessel evacuated and backfilled with nitrogen (three times in total). Diethyl ether (45 mL) and methanol (4.5 mL) were added followed by the dropwise addition of trimethylsilyldiazomethane (2.0 M solution in hexane, 0.70 mL, 1.40 mmol, 4.0 equiv). The resulting yellow solution was stirred for 24 hours and then carefully quenched by the addition of aqueous acetic acid (1M solution, 20 mL). The reaction mixture was extracted with ether (3 x 20 mL) and the combined organic layers were washed with saturated sodium carbonate, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0.5% → 5% MeOH in DCM) to afford vinylogous ester **SI-3** (84 mg, 49%) as a white solid: mp = 248-250 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.68 (s, 3H), 3.14 (dd, *J* = 11.4, 4.4 Hz, 1H), 2.70 (d, *J* = 15.5 Hz, 1H), 2.34 (d, *J* = 15.5 Hz, 1H), 2.03 (dd, *J* = 13.1, 6.9 Hz, 1H), 1.83 (s, 1H), 1.68-1.56 (m, 3H), 1.55-1.40 (m, 4H), 1.38 (s, 3H), 1.31-1.16 (m, 2H), 1.10 (s, 3H), 1.04-0.96 (m, 1H), 0.89 (s, 3H), 0.88 (s, 3H), 0.88 (s, 9H), 0.76 (s, 3H), 0.71-0.65 (m, 1H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6, 181.4, 99.9, 82.0, 79.6, 56.6, 56.2, 54.7, 49.1, 48.1,

48.0, 39.5, 38.6, 36.8, 34.5, 33.3, 28.7, 27.6, 26.7, 26.1, 18.9, 18.3, 16.2, 15.9, 15.8, -3.7, -4.8; IR (neat) 3420, 2941, 2855, 1648, 1609, 1457, 1384, 1363, 1220, 1167, 1103,1087, 1056, 1005, 879, 835, 775 cm^{-1}; HRMS (ESI) calcd. for $[C_{29}H_{50}O_4NaSi]^+$ $(M+Na)^+$: m/z 513.3371, found 513.3368.

Polycycle 219. A 50 mL flame-dried flask was charged with compound **SI-3** (167 mg, 0.34 mmol, 1.0 equiv), (Diacetoxyiodo)benzene (286 mg, 0.89 mmol, 2.6 equiv), and potassium hydroxide (1.42 g, 25.3 mmol, 74 equiv). The reaction vessel was evacuated and backfilled with nitrogen (a total of three times) and then MeOH (20 mL) added. The reaction mixture was stirred at room temperature for 2 hours. The resulting orange solution was concentrated *in vacuo*, diluted with EtOAc (25 mL), and washed with saturated *aq*. NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10% EtOAc in hexanes) to afford **219** (139 mg, 84% yield) as a white solid: mp = 183-185 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (s, 1H), 3.76 (s, 3H), 3.13 (dd, *J* = 11.1, 4.6 Hz, 1H), 2.70 (s, 1H), 1.82 (dd, *J* = 13.4, 3.8 Hz, 1H), 1.72-1.43 (m, 8H), 1.40 (dd, *J* = 13.0, 3.7 Hz, 1H), 1.28 (s, 3H), 0.93 (s, 3H), 0.87 (s, 9H), 0.87 (s, 3H), 0.85 (s, 3H), 0.83-0.70 (m, 2H), 0.72 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.6, 194.4, 177.8, 106.2, 79.1, 75.5, 57.2, 55.4, 53.2, 50.2, 43.5, 39.6, 38.5, 37.4, 37.0, 34.8, 28.4, 27.6, 26.0, 21.0, 18.6, 18.2, 17.2, 16.6, 16.0, -3.6, -4.8; IR (neat) 2932, 2851, 1730, 1644, 1588, 1464, 1388, 1346, 1255, 1229, 1209, 1095, 1064, 989, 913, 879, 835, 771 cm^{-1}; HRMS (EI) calcd. for $[C_{29}H_{48}O_4Si]$: m/z 488.3322, found 488.3315.

Vinylogous ester SI-4. To a suspension of methyltriphenylphosphonium bromide (320 mg, 0.896 mmol, 2.2 equiv) in THF (10 mL) at 0 °C was added *n*-butyllithium (0.33 mL, 2.5 M solution in hexane, 0.825 mmol, 2.0 equiv). After 30 minutes of stirring, the reaction mixture was warmed to room temperature, stirred for 15 minutes, and then cooled to -78 °C. A solution of **219** (198 mg, 0.405 mmol, 1.0 equiv) in THF (5 mL) was added dropwise at -78 °C. The reaction mixture was warmed to room temperature, and then heated to reflux. After 2 hours of heating, the reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl solution (15 mL), and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (hexane/EtOAc = 15:1) affording **SI-4** (168 mg, 85%) as a light colored foam: ^1H NMR (600 MHz, $CDCl_3$) δ 5.45 (s, 1H), 4.79 (s, 1H), 4.68 (s, 1H), 3.69 (s, 3H), 3.12 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.45 (s, 1H),1.62-1.40 (m, 7H), 1.34-1.24 (m, 3H), 1.32 (s, 3H), 0.91 (s, 3H), 0.87 (s, 9H), 0.85 (s, 3H), 0.83 (s, 3H), 0.77-0.68 (m, 2H), 0.72 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6, 180.3, 150.2, 106.6, 104.4, 79.3, 69.5, 56.6, 55.6, 50.8, 44.6, 39.7, 38.5, 38.2, 37.6, 36.9, 32.9, 28.4, 27.8, 26.1, 21.7, 20.1, 18.8, 18.3, 17.3, 16.0, -3.6, -4.8; IR (neat) 2927, 2854, 1663, 1643, 1594, 1461, 1387, 1340, 1254, 1214, 1168, 1096, 1070, 1001, 889, 834, 772 cm^{-1}; HRMS (EI) calcd. for $[C_{30}H_{50}O_3Si]$: m/z 486.3529, found 486.3520.

Chloride 220. A 50 mL flame-dried reaction flask was charged with compound **SI-4** (117 mg, 0.24 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (10 mL). After cooling the reaction vessel to -78 °C, a solution of freshly prepared lithium 2,2,6,6-tetramethylpiperidide (0.445 M in THF, 1.24 mL, 0.55 mmol, 2.3 equiv) was added dropwise resulting in a light yellow colored solution. The reaction mixture was stirred for 60 minutes at -78 °C and then *p*-toluenesulfonyl chloride (105 mg, 0.55 mmol, 2.3 equiv) added as a solution in THF. The reaction mixture was maintained at -78 °C for 15 minutes, warmed to 0 °C and stirred for 15 minutes, and then quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with EtOAc (3 x 20mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10% CH_2Cl_2 in hexanes → 2% Et_2O in hexanes) affording **220** (105 mg, 84% yield) as a white solid: mp = 247-249 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.85 (s, 1H), 4.72 (s, 1H), 4.17 (s, 3H), 3.12 (dd, *J* = 11.3, 4.7 Hz, 1H), 2.67 (s, 1H),1.65-1.54 (m, 4H), 1.50-1.41 (m, 4H), 1.36 (s, 3H), 1.32 (t, *J* = 13.1 Hz, 1H), 1.15 (dd, *J* = 12.9, 3.4 Hz, 1H), 0.91 (s, 3H), 0.87 (s, 9H), 0.86 (s, 3H), 0.84 (s, 3H), 0.78-0.66 (m, 2H), 0.71 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4, 174.9, 147.6, 114.7, 108.1, 79.1, 69.2, 62.6, 55.5, 51.2, 47.8, 39.7, 38.7, 38.4, 37.5, 37.0, 32.6, 28.3, 27.7, 26.1, 21.5, 20.7, 18.7, 18.3, 17.2, 16.0, -3.6, -4.8; IR (neat) 2936, 2855, 1669, 1651, 1574, 1459, 1382, 1285, 1259, 1234, 1094, 1057, 999, 903, 876, 771, 731, 670 cm^{-1}; HRMS (EI) calcd. for [$C_{30}H_{49}O_3SiCl$]: m/z 520.3140, found 520.3133.

Ester SI-5. A 50 mL flame-dried reaction flask was charged with chloride **220** (93 mg, 0.18 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (10 mL). The reaction mixture was cooled to -78 °C and a freshly prepared solution of lithium diisopropylamide (0.45 M in THF, 2.0 mL, 0.90 mmol, 5 equiv) was added dropwise resulting in a light brown colored solution. The reaction mixture was stirred for 90 minutes at -78°C, warmed to 0 °C and stirred 30 minutes, and then re-cooled to -78 °C. Methyl chloroformate (0.14 mL, 1.81 mmol, 10 equiv) was then added dropwise to the cooled reaction mixture. The reaction mixture was stirred for 1 hour at -78 °C and then slowly warmed to -25 °C over the course of 1 hour at which point it was quenched with saturated aqueous NH_4Cl solution (10 mL). The reaction mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (2% Et_2O in hexanes → 3% Et_2O in hexanes) to afford recovered **220** (17 mg, 18% yield) and ester **SI-5** (58 mg, 56% yield) as a white solid: mp = 174-176 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.09 (d, *J* = 1.0 Hz, 1H), 4.52 (d, *J* = 1.0 Hz, 1H), 4.20 (s, 3H), 3.64 (s, 3H), 3.11 (dd, *J* = 11.1, 4.6 Hz, 1H), 2.24 (dt, *J* = 13.6, 3.3 Hz, 1H), 1.69 (td, *J* = 13.3, 4.1 Hz, 1H), 1.65-1.50 (m, 4H), 1.48-1.36 (m, 3H), 1.40 (s, 3H), 1.13 (s, 3H), 1.02 (dd, *J* = 12.7, 3.5 Hz, 1H), 0.87 (s, 9H), 0.86 (s, 3H), 0.85 (s, 3H), 0.74-0.66 (m, 2H), 0.70 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1, 173.4, 169.8, 147.3, 114.3, 109.4, 78.9, 73.6, 62.6, 54.9, 51.8, 51.5, 47.0, 43.2, 39.6, 38.7, 37.5, 33.8, 32.5, 28.2, 27.7, 26.1, 21.5, 18.7, 18.2, 17.3, 16.3, 16.1, -3.7, -4.8; IR (neat) 2951, 2926, 2851, 1742, 1678, 1645, 1593, 1460,

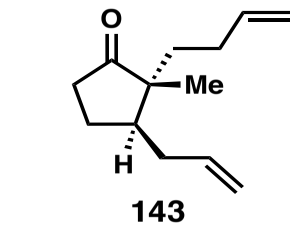
1387, 1289, 1262, 1216, 1188, 1130, 1097, 1068, 1029, 1006, 877, 834, 778 cm^{-1}; HRMS (ESI) calcd. for $[C_{32}H_{52}ClO_5Si]^+$ $(M+H)^+$: m/z 579.3267, found 579.3266.

Ester SI-6. A flame-dried reaction tube was charged with $Pd(OAc)_2$ (4.0 mg, 0.018 mmol, 0.20 equiv), SPhos (**2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) (14 mg, 0.036 mmol, 0.4 equiv),** ester **SI-5** (52 mg, 0.089 mmol, 1.0 equiv), methylboronic acid (32 mg, 0.53 mmol, 6.0 equiv) and powdered anhydrous potassium phosphate (76 mg, 0.36 mmol, 4.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of degassed toluene (1.0 mL) and H_2O (10% solution in THF, 0.06 mL, 4 equiv). The sealed vessel was stirred for 5 minutes, then heated at 100 °C and stirred vigorously at this temperature for 20 hours. Upon cooling to room temperature, the mixture was diluted with ethyl ether (10 mL) and filtered through a short plug of celite which was further rinsed with additional ether (20 mL). The solvent was removed *in vacuo* and the crude material purified by silica gel column chromatography (5% EtOAc in hexanes) to afford ester **SI-6** (44 mg, 88% yield) as a white foam: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.44 (s, 1H), 3.88 (s, 3H), 3.62 (s, 3H), 3.10 (dd, *J* = 11.4, 4.6 Hz, 1H), 2.25 (dt, *J* = 13.6, 3.3 Hz, 1H), 1.91 (s, 3H), 1.67 (td, *J* = 13.3, 4.1 Hz, 1H), 1.61-1.51 (m, 4H), 1.46-1.34 (m, 3H),1.38 (s, 3H), 1.12 (s, 3H), 0.98 (dd, *J* = 12.7, 3.5 Hz, 1H), 0.87 (s, 12H), 0.85 (s, 3H), 0.72-0.61 (m, 2H), 0.71 (s, 3H), 0.01 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 175.5, 170.7, 149.5, 120.9, 107.7, 79.1, 73.4, 62.0, 55.1, 51.6, 51.5, 45.1, 43.0, 39.6, 38.8, 37.5, 33.7, 32.7, 28.3, 27.8, 26.0, 21.2, 18.7, 18.2, 17.3, 16.2, 16.1, 10.5, -3.6, -4.8; IR (neat) 2952, 2928, 2853, 1743, 1663, 1620, 1462, 1388, 1303, 1253, 1209, 1112, 1071, 1007, 980, 885, 835, 774 cm^{-1}; HRMS (ESI) calcd. for $[C_{33}H_{55}O_5Si]^+$ $(M+H)^+$: m/z 559.3813, found 559.3808.

Ester 221. To the solution of compound **SI-6** (31 mg, 0.055 mmol, 1.0 equiv) in MeOH (3.0 mL) was added *p*-Toluenesulfonic acid monohydrate (10 mg, 1.0 equiv). The reaction mixture was heated to 60 °C, stirred for 1 hour at this temperature, cooled to room temperature, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (30% EtOAc in hexanes) affording ester **221** (22 mg, 86% yield) as a white foam: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.44 (s, 1H), 3.88 (s, 3H), 3.62 (s, 3H), 3.14 (dd, *J* = 11.3, 4.8 Hz, 1H), 2.26 (dt, *J* = 13.6, 3.4 Hz, 1H), 1.90 (s, 3H), 1.68 (td, *J* = 13.3, 4.1 Hz, 1H), 1.64-1.49 (m, 5H), 1.47-1.34 (m, 2H), 1.38 (s, 3H), 1.12 (s, 3H), 1.00 (dd, *J* = 12.7, 3.5 Hz, 1H), 0.94 (s, 3H), 0.87 (s, 3H), 0.77-0.65 (m, 2H), 0.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 175.5, 170.7, 149.3, 120.8, 107.8, 78.6, 73.3, 62.0, 55.0, 51.6, 51.5, 45.1, 42.9, 39.0, 38.7, 37.6, 33.6, 32.6, 27.9, 27.2, 21.2, 18.5, 17.3, 16.2, 15.6, 10.5; IR (neat) 3507, 2947, 2874, 2845, 1742, 1661, 1616, 1461, 1386, 1304, 1211, 1189, 1112, 1007, 894 cm^{-1}; HRMS (ESI) calcd. for $[C_{27}H_{40}O_5Na]^+$ $(M+Na)^+$: m/z 467.2768, found 467.2771.

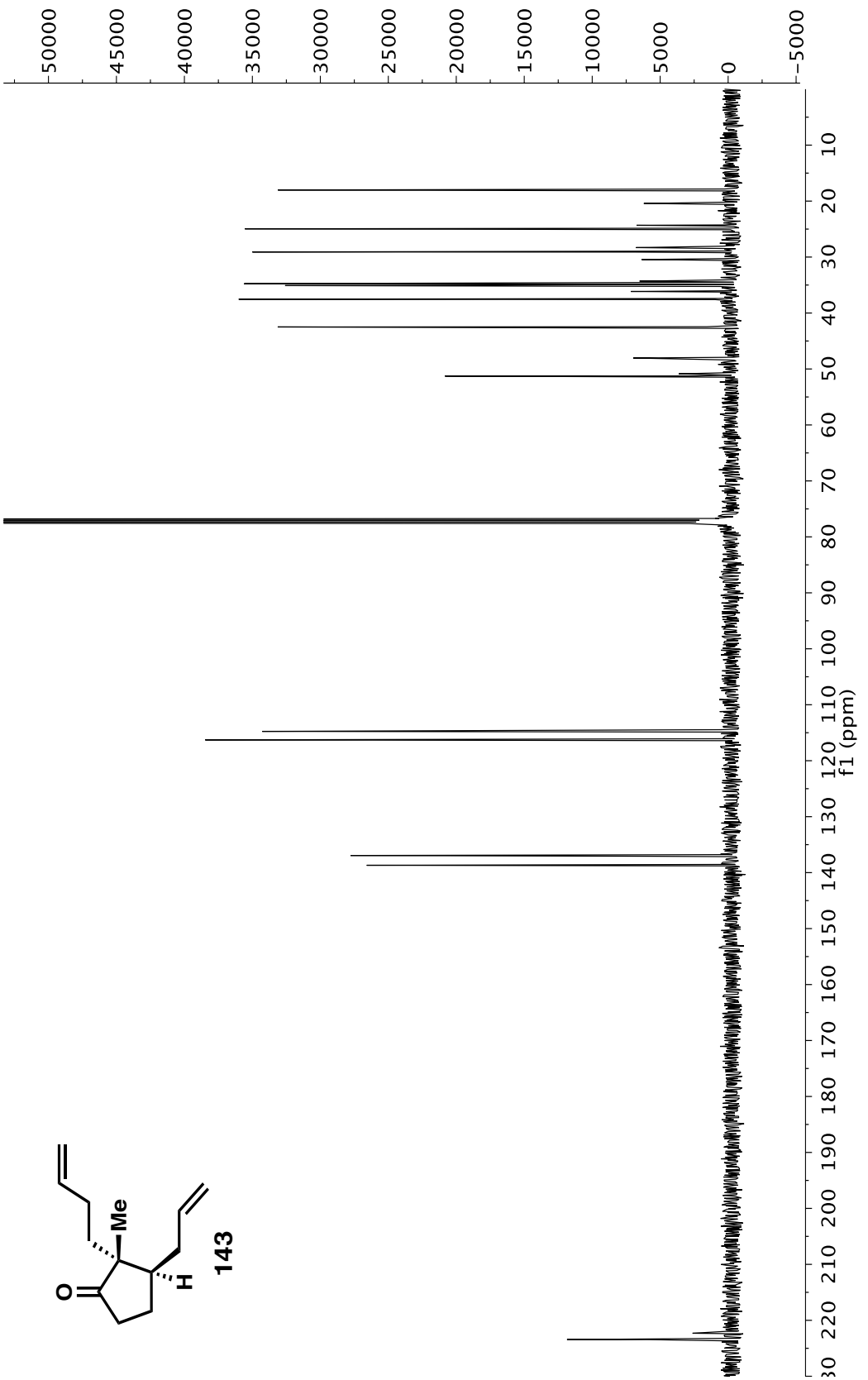
Berkeleyone A (187). [Note: Solvents were purged with argon for 10 minutes prior to use]. A flame-dried reaction tube was charged with ester **221** (30 mg, 0.067 mmol, 1.0 equiv) and previously flame-dried lithium chloride (115 mg, 2.7 mmol, 40 equiv). The reaction vessel was evacuated and backfilled with nitrogen and this process repeated an additional two times. Dry DMSO (1.2 mL) was added and the reaction mixture heated to

120 °C and kept at this temperature for 2 hours. The reaction mixture was then cooled to room temperature, DCM (1.0 mL) was added, and the solution cooled to 0 °C. *m*-CPBA (≤77% purity, 23 mg, 1.5 equiv) was added as a solution in DCM (0.3 mL) to the 0 °C mixture. After 30 minutes of stirring, the reaction was quenched by the addition of a mixture of saturated aqueous $Na_2S_2O_3$ (1.0 mL) and saturated aqueous $NaHCO_3$ (1.0 mL). After stirring for 30 minutes, the reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic layers extracts were washed with H_2O (3 x 5 mL), brine (5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (15%→30% EtOAc in hexanes) to afford Berkeleyone A (**187**) (13 mg, 43% yield) as a white solid: mp = 194-196 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.36 (s, 1H), 4.85 (s, 1H), 3.71 (s, 3H), 3.10 (dd, *J* = 11.7, 4.1 Hz, 1H), 2.20 (dt, *J* = 13.6, 3.5 Hz, 1H), 2.02 (td, *J* = 13.3, 4.3 Hz, 1H), 1.92 (dd, *J* = 13.1, 3.1 Hz, 1H), 1.63-1.53 (m, 4H), 1.52-1.34 (m, 3H), 1.46 (s, 3H), 1.37 (s, 3H), 1.21 (s, 3H), 0.94 (s, 3H), 0.78 (s, 3H), 0.73 (s, 3H), 0.65-0.58 (m, 1H), 0.54-0.47 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.0, 204.2, 168.8, 145.8, 112.5, 80.1, 78.4, 72.7, 54.9, 52.9, 52.6, 51.2, 48.1, 39.1, 38.9, 38.6, 37.9, 33.1, 28.0, 27.0, 22.2, 18.4, 17.4, 16.0, 15.7, 15.4; IR (neat) 3506, 2930, 2846, 1725, 1706, 1643, 1456, 1436, 1389, 1367,1236, 1186, 1127, 1086, 1039, 1024, 999, 891 cm^{-1}; HRMS (ESI) calcd. for $[C_{26}H_{38}O_6Na]^+$ $(M+Na)^+$: m/z 469.2561, found 469.2564.


O
Me
H

143

1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)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40000
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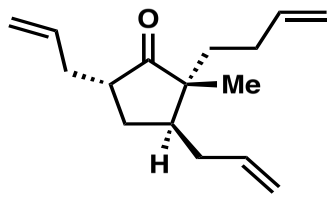
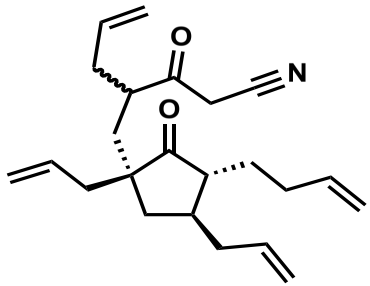
30000
25000
20000
15000
10000
5000
0
−5000
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
f1 (ppm)
O
Me
H
143


O
Me
H

144

1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
N
O

148

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1500
1000
500
0
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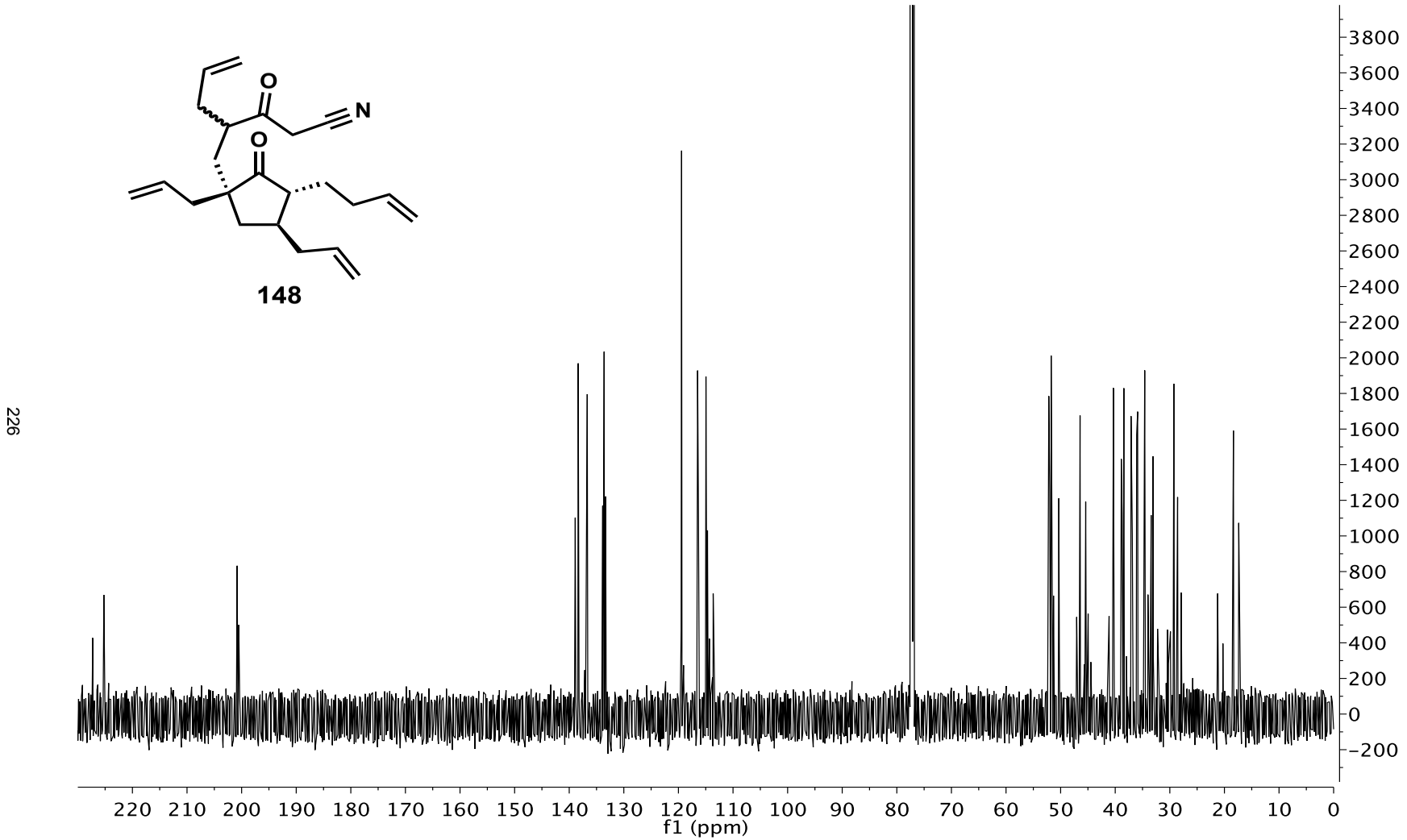
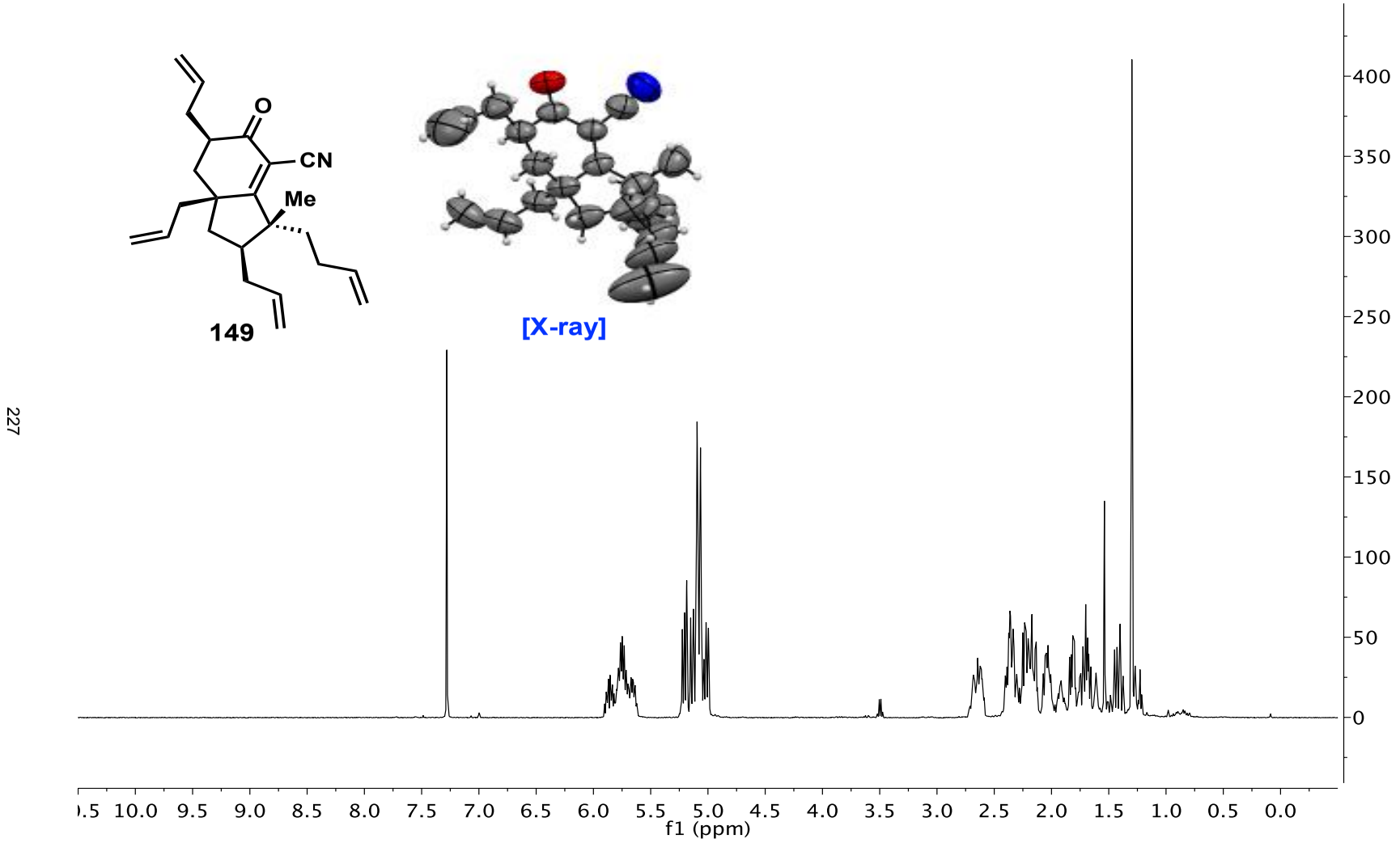
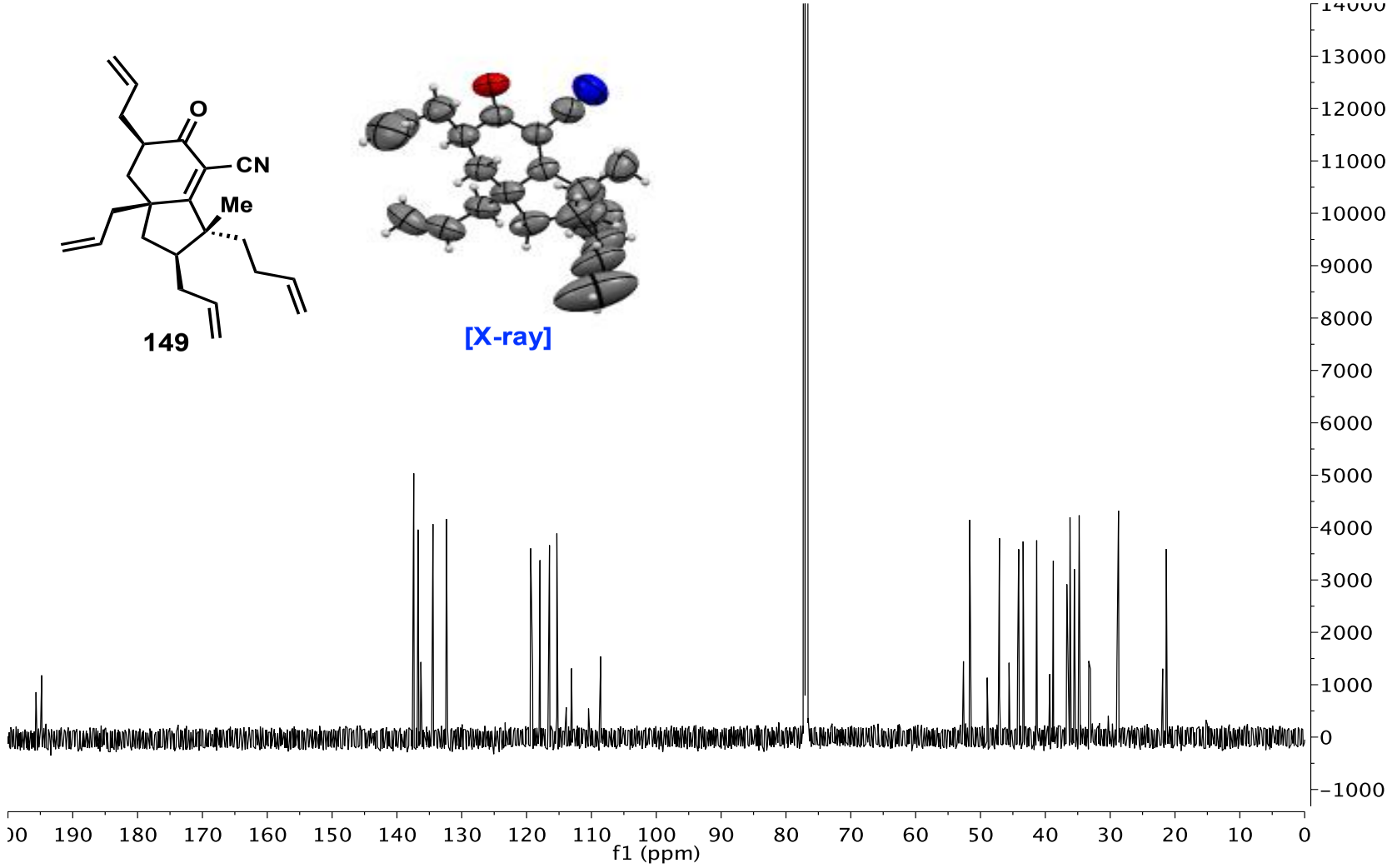
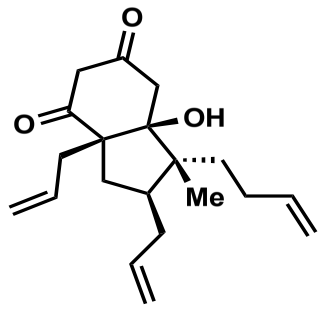
f1 (ppm)


O
N
O
148
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

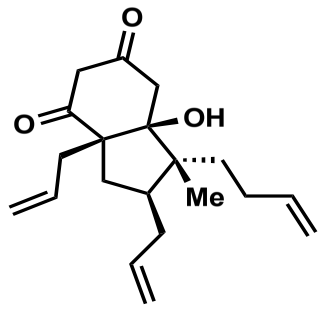

O
CN
Me
149
[X-ray]
227
400
350
300
250
200
150
100
50
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


O
CN
Me
149
[X-ray]
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
OH
Me

155

1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
O
OH
Me

155

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21000
20000
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17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
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4000
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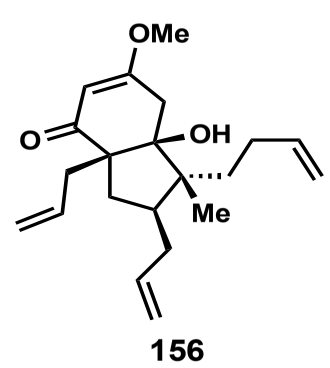
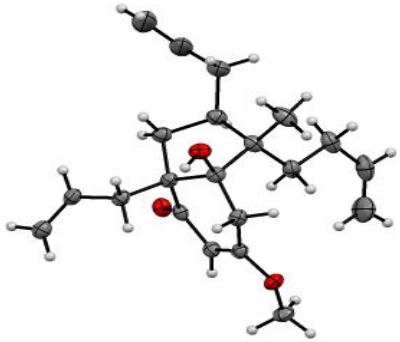
2000
1000
0
-1000
-2000
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OMe
O
OH
Me

156



[X-ray]

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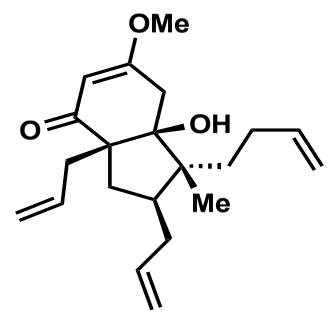
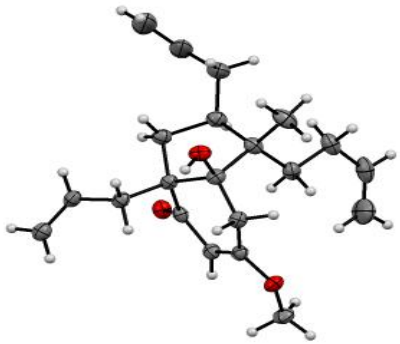
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

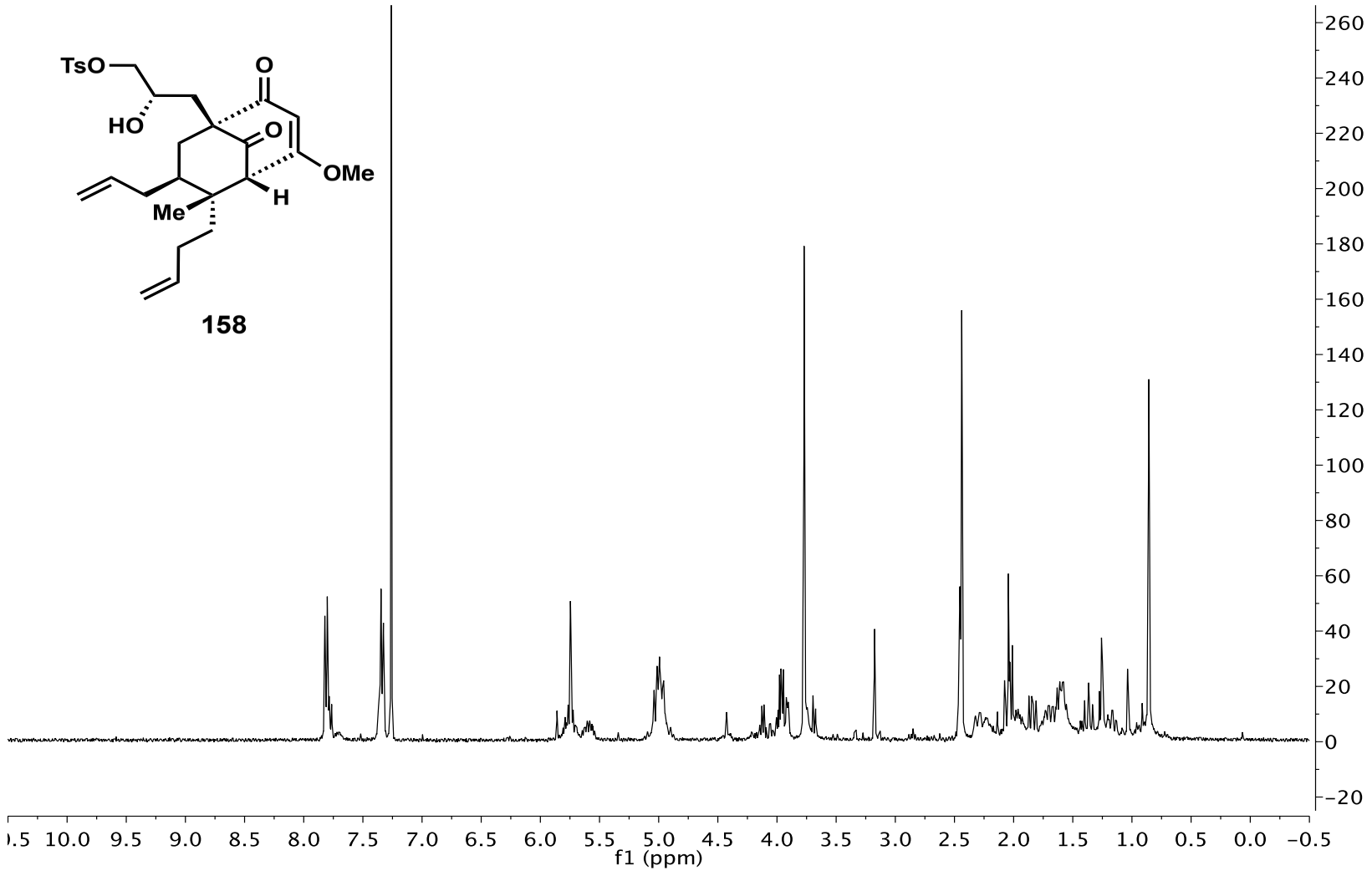

OMe
O
OH
Me

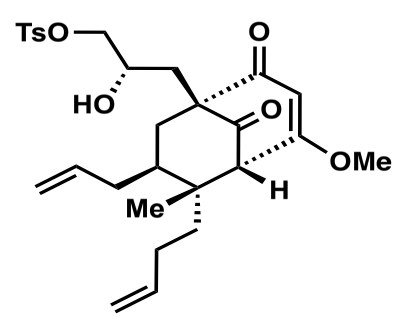
156



[X-ray]

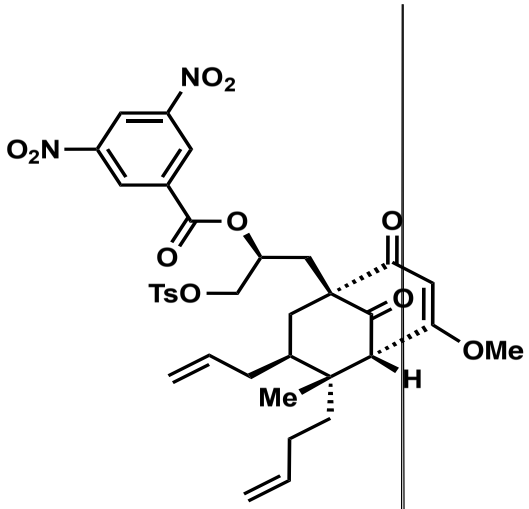
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
−2000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


TsO
HO
O
O
OMe
H
Me
158
260
240
220
200
180
160
140
120
100
80
60
40
20
0
−20
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

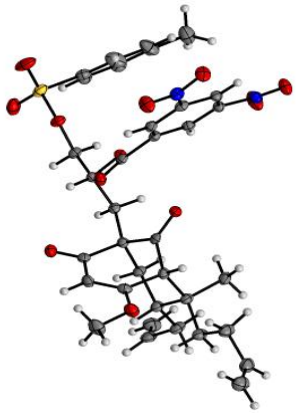

TsO
HO
O
O
OMe
H
Me

158

12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


NO2
O2N
O
O
TsO
O
O
OMe
H
Me

160



[X-ray]

100
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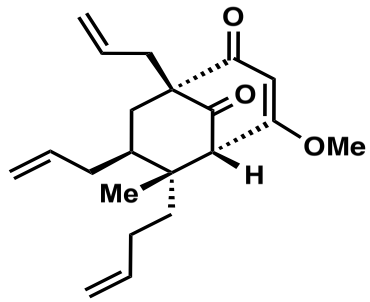
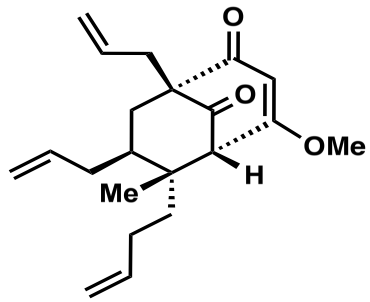
80
70
60
50
40
30
20
10
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
O
OMe
H
Me

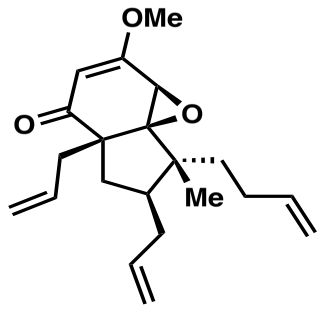
161

450
400
350
300
250
200
150
100
50
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
O
OMe
H
Me

161

3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
−400
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OMe
O
O
Me

162

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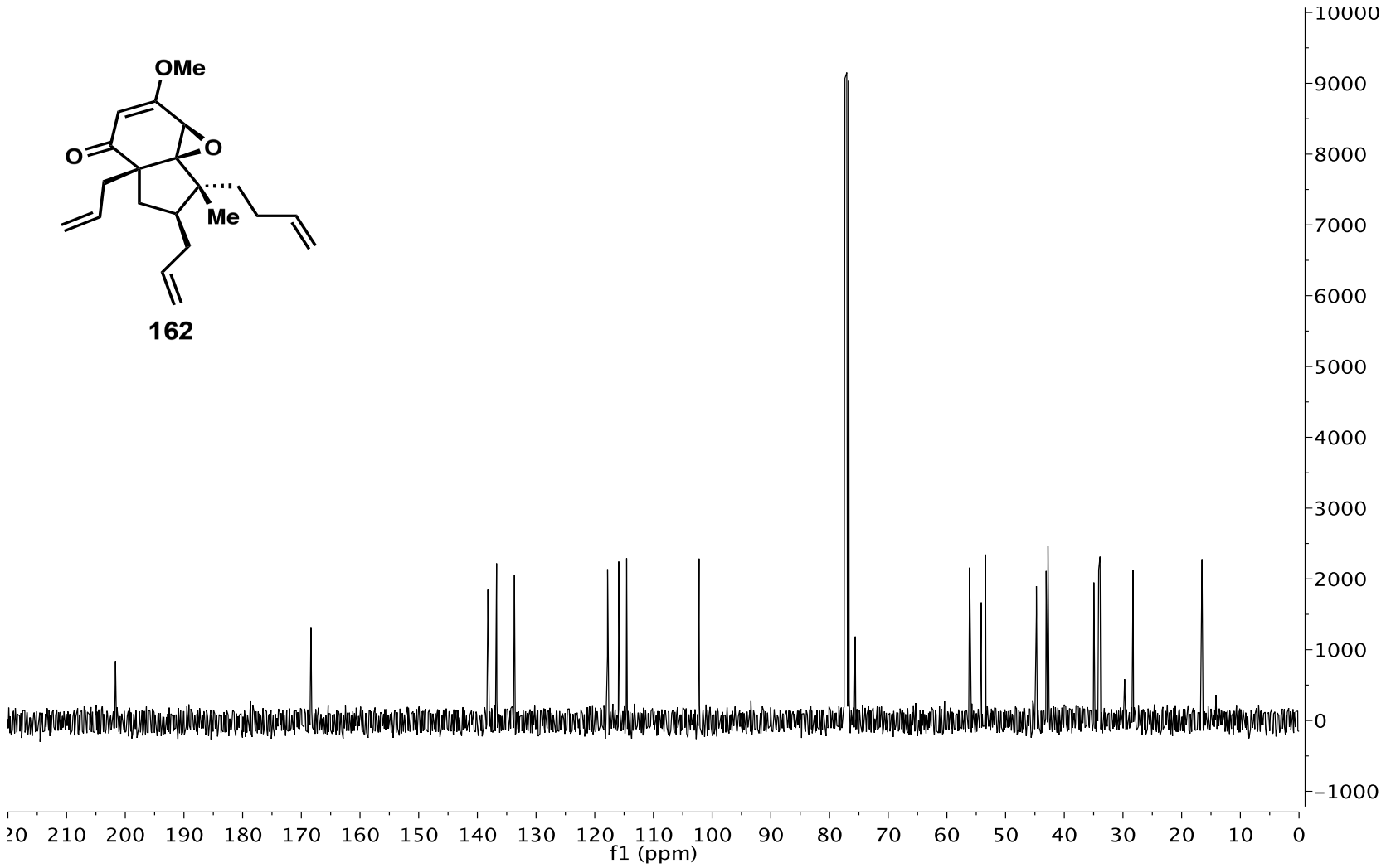
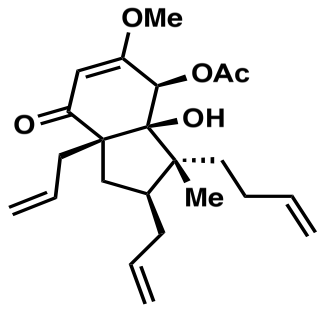
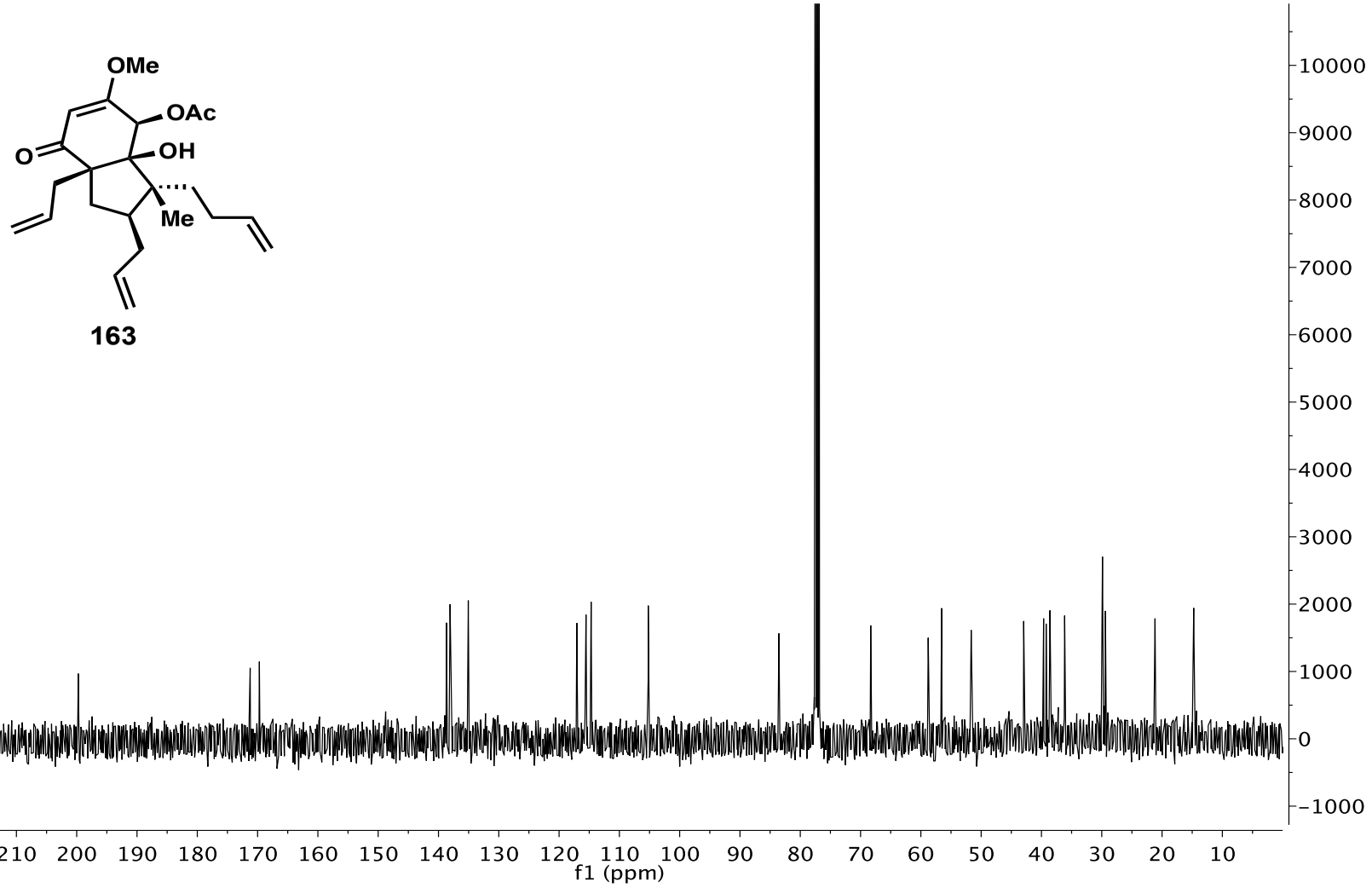
350
300
250
200
150
100
50
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

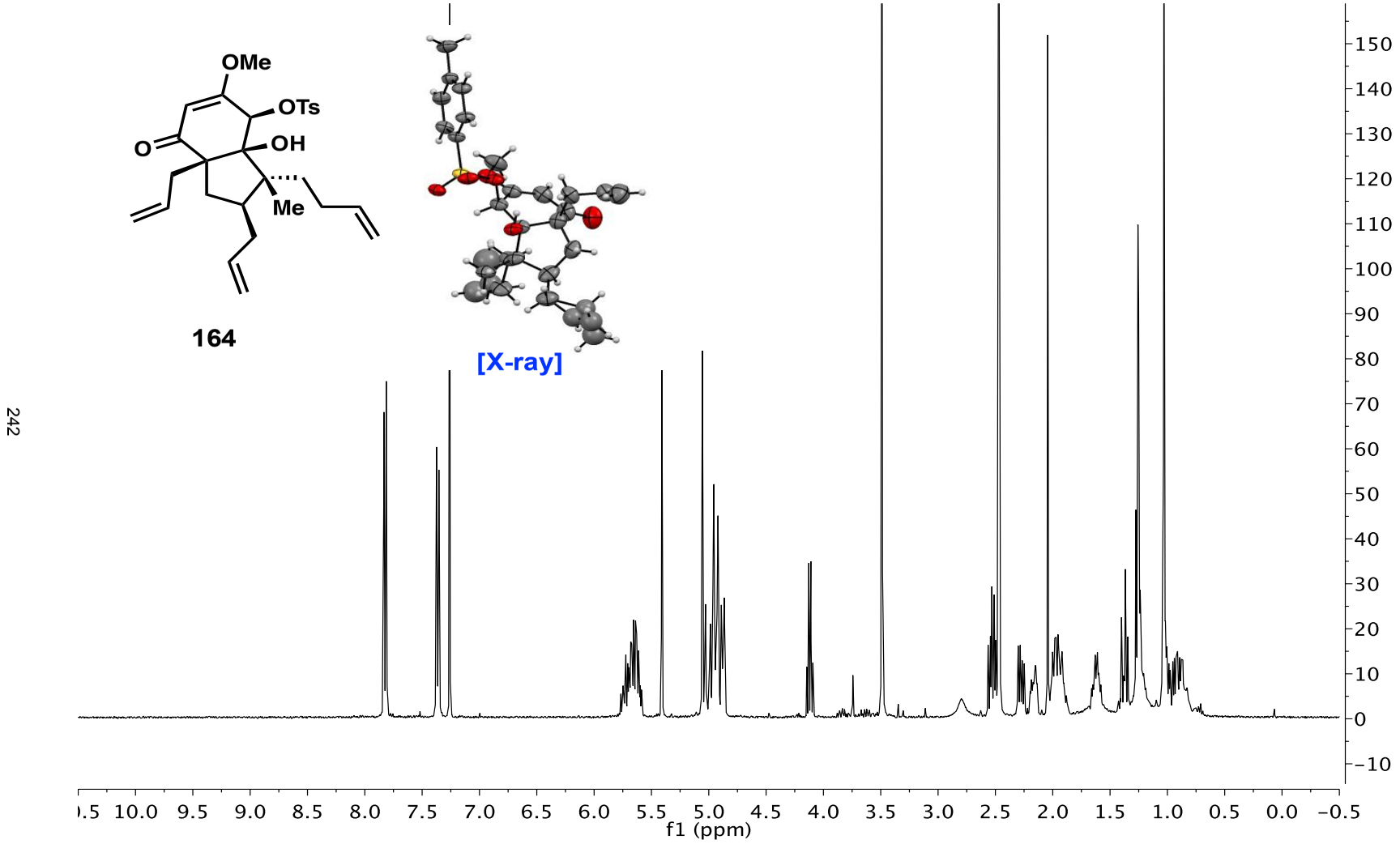

OMe
O
O
Me
162
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

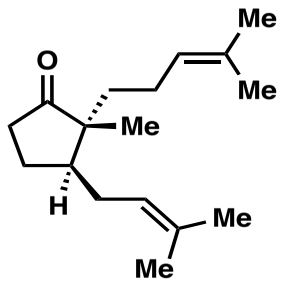

OMe
OAc
O
OH
Me

163

550
500
450
400
350
300
250
200
150
100
50
0
−50
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

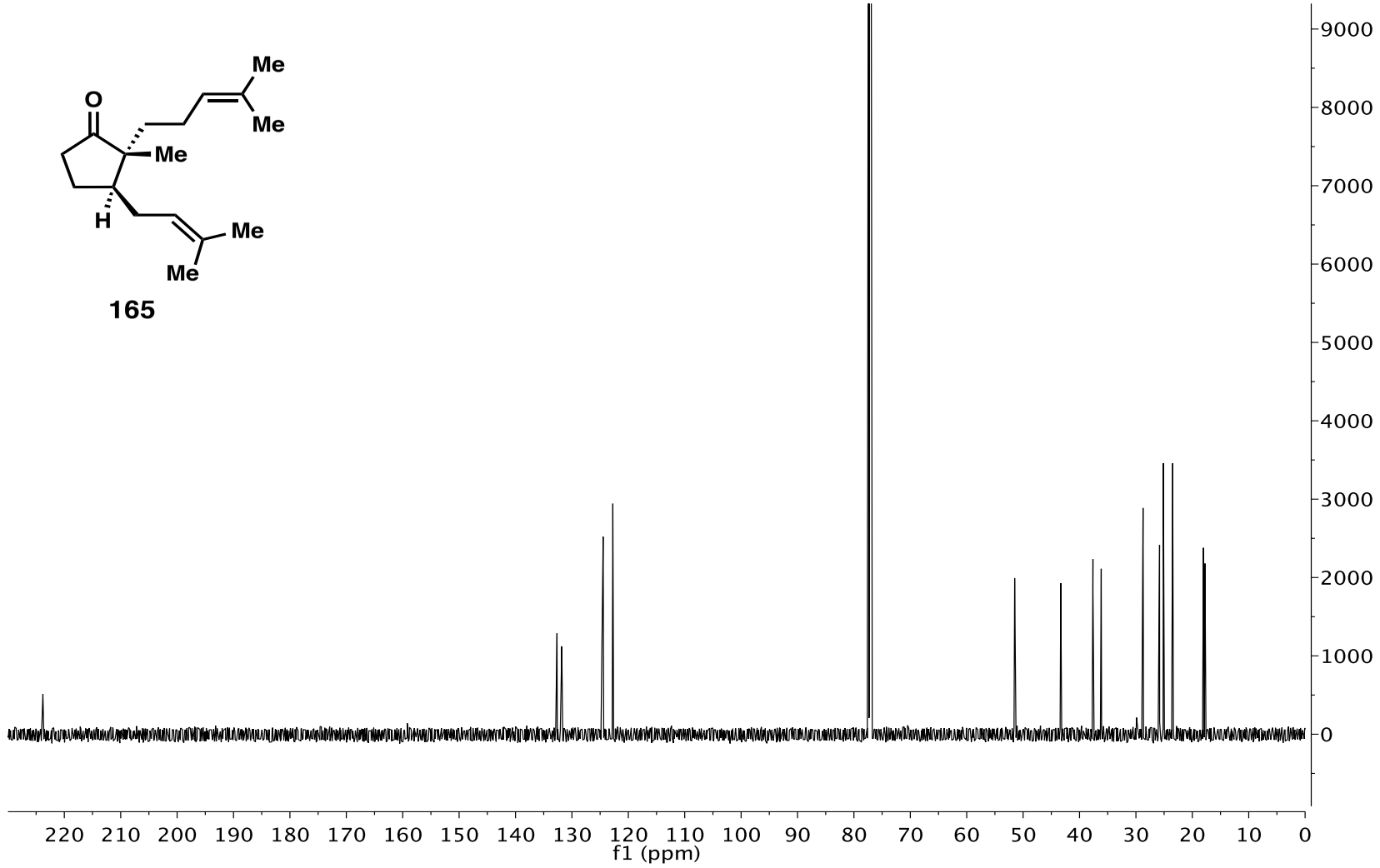

OMe
OAc
O
OH
Me
163
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

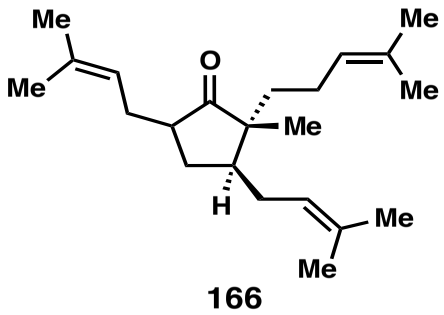

OMe
OTs
O
OH
Me
164
[X-ray]
f1 (ppm)


O
Me
Me
Me
H
Me
Me

165

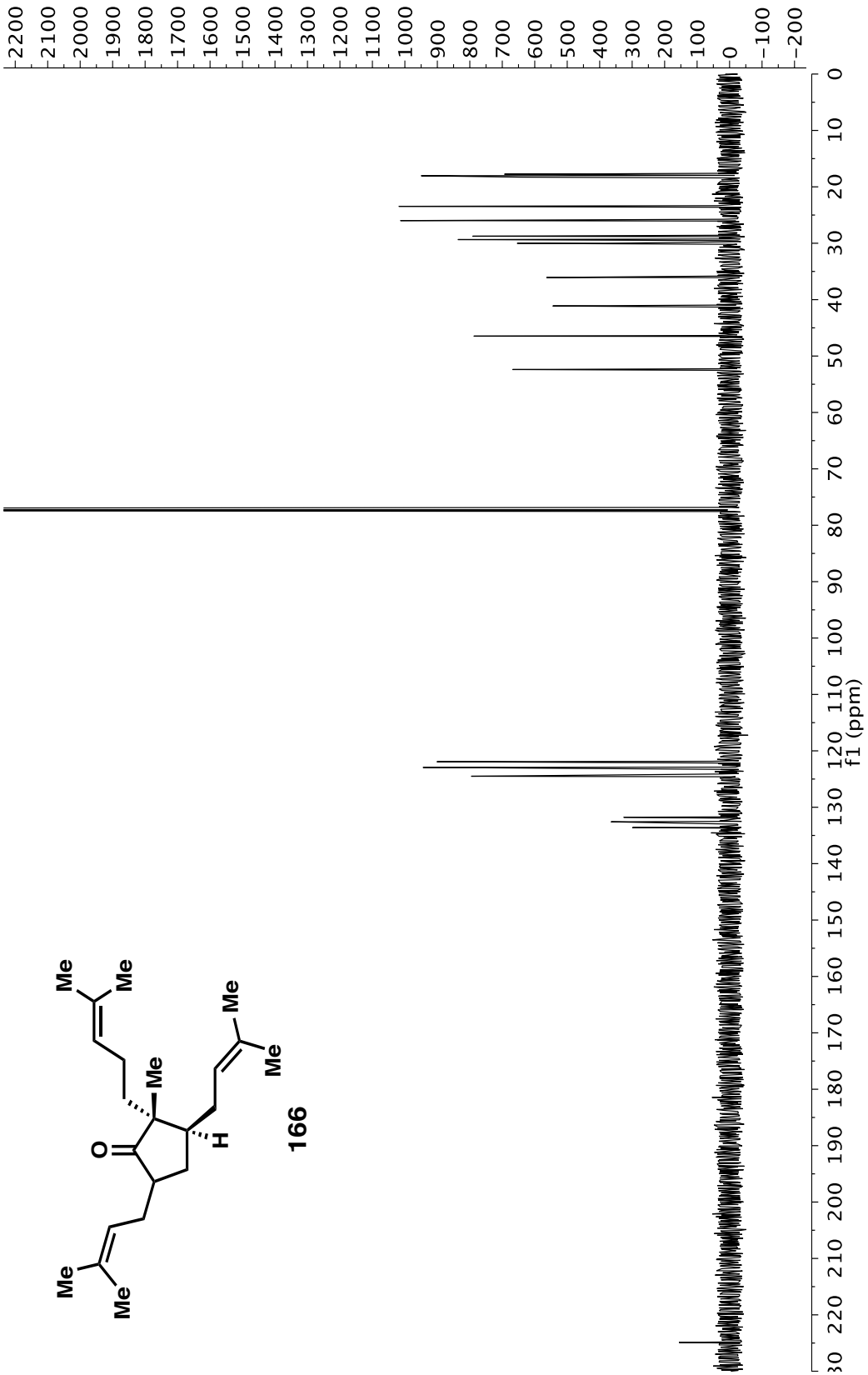
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

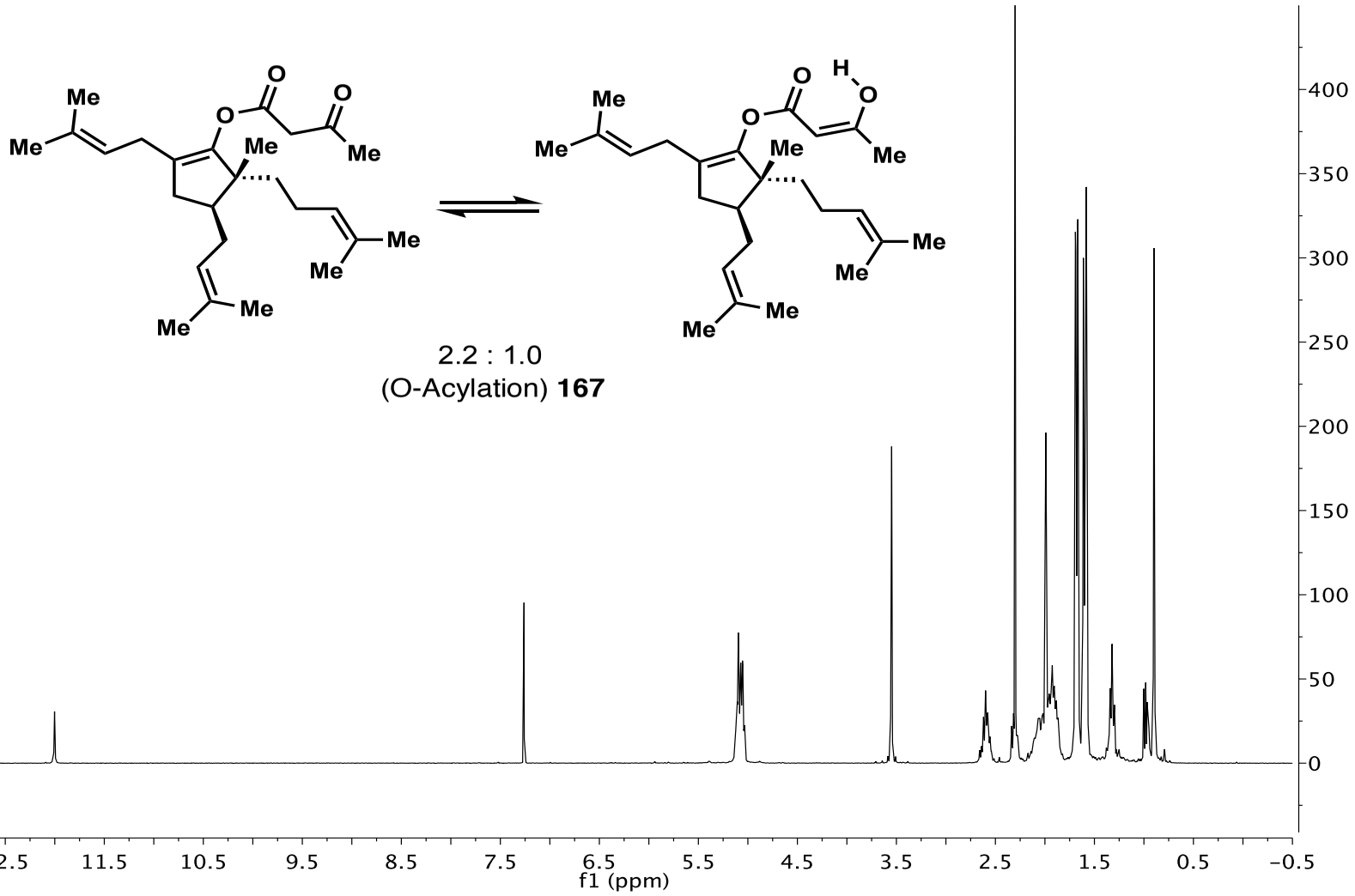

O
Me
Me
Me
H
Me
Me
165
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

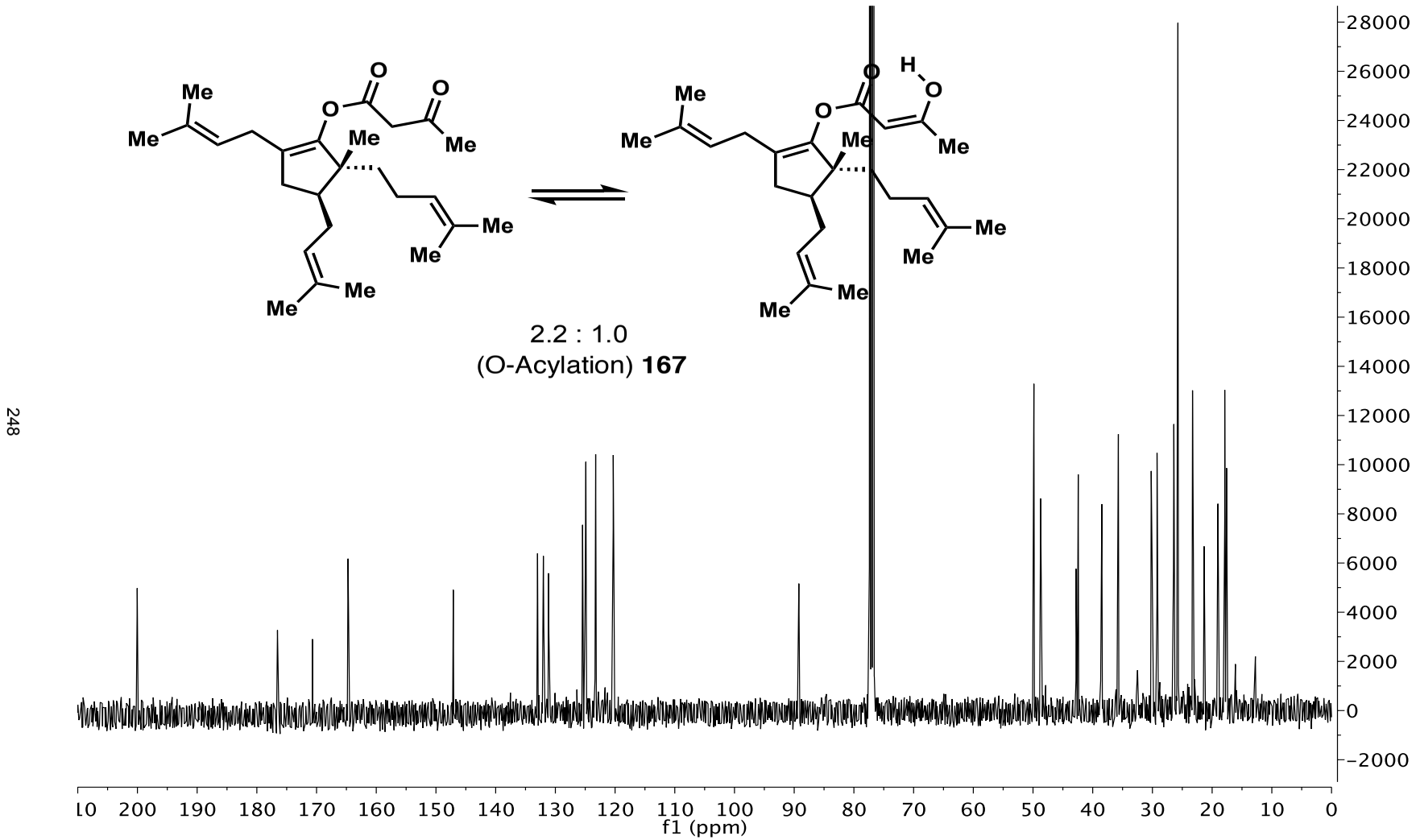

Me
Me
O
Me
Me
Me
H
Me
Me

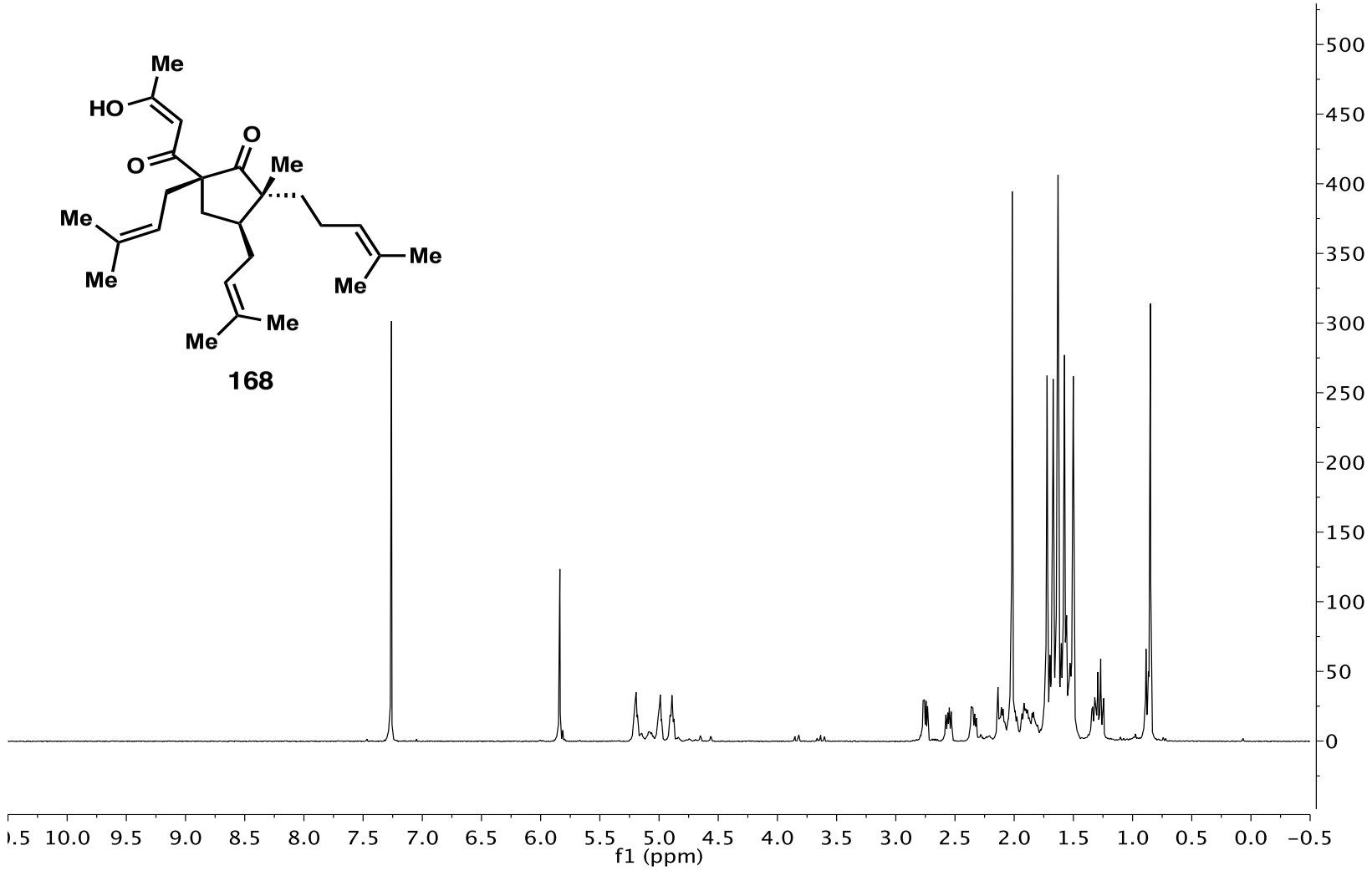
166

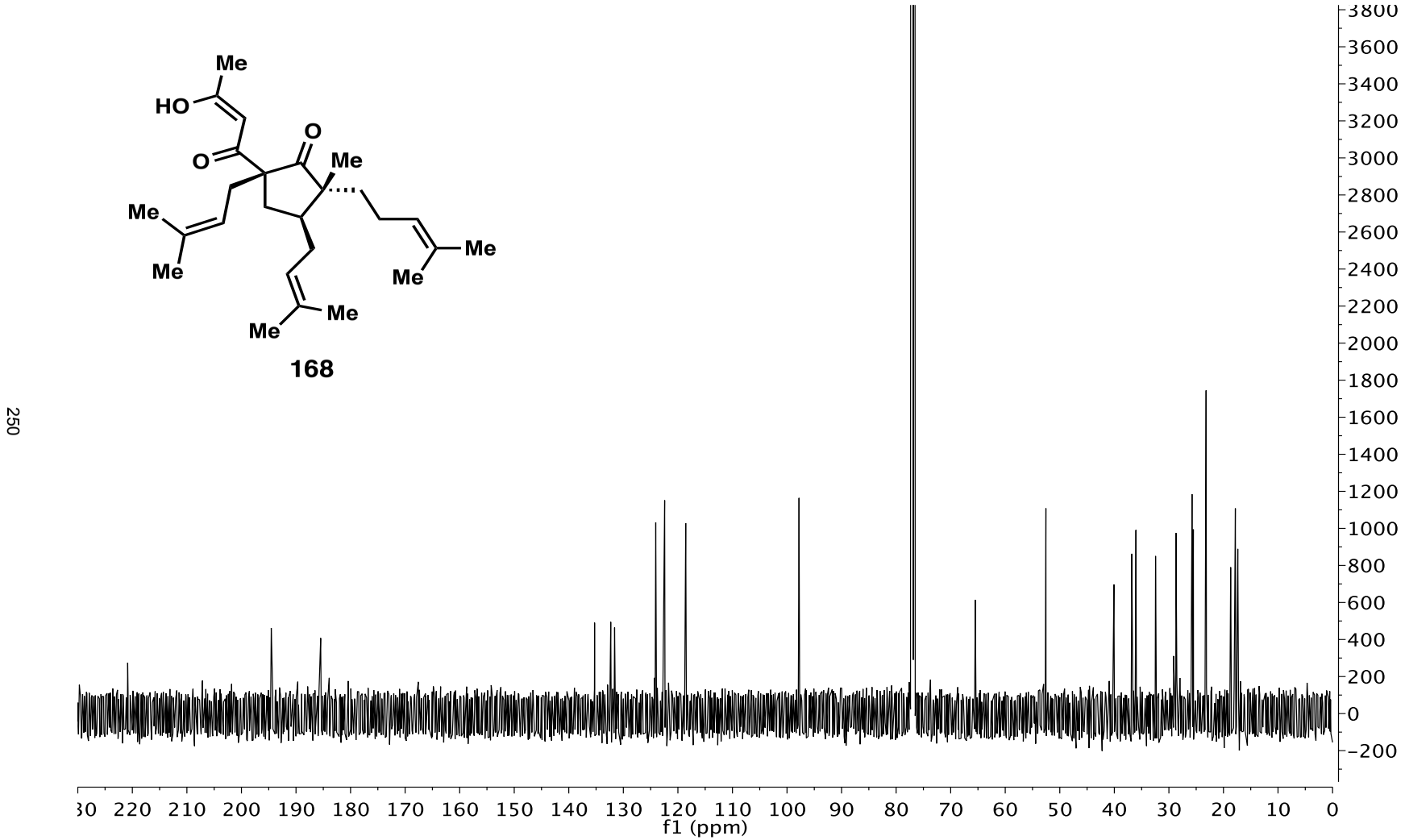
3500
3000
2500
2000
1500
1000
500
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

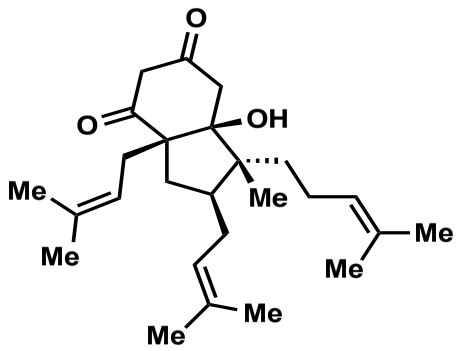

Me
Me
Me
Me
Me
Me
O
H
166
f1 (ppm)


Me
Me
O
O
O
Me
Me
Me
Me
Me
Me
Me
Me
H
O
2.2 : 1.0
(O-Acylation) 167
400
350
300
250
200
150
100
50
0
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
−0.5
f1 (ppm)


Me
Me
O
O
O
Me
Me
Me
Me
Me
Me
Me
Me
H
O
2.2 : 1.0
(O-Acylation) 167
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
−2000
f1 (ppm)

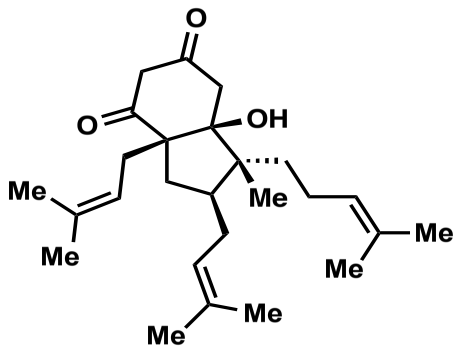

Me
HO
O
O
Me
Me
Me
Me
Me
Me
Me
168
500
450
400
350
300
250
200
150
100
50
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


Me
HO
O
O
Me
Me
Me
Me
Me
Me
Me
168
250
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
OH
Me
Me
Me
Me
Me
Me
Me

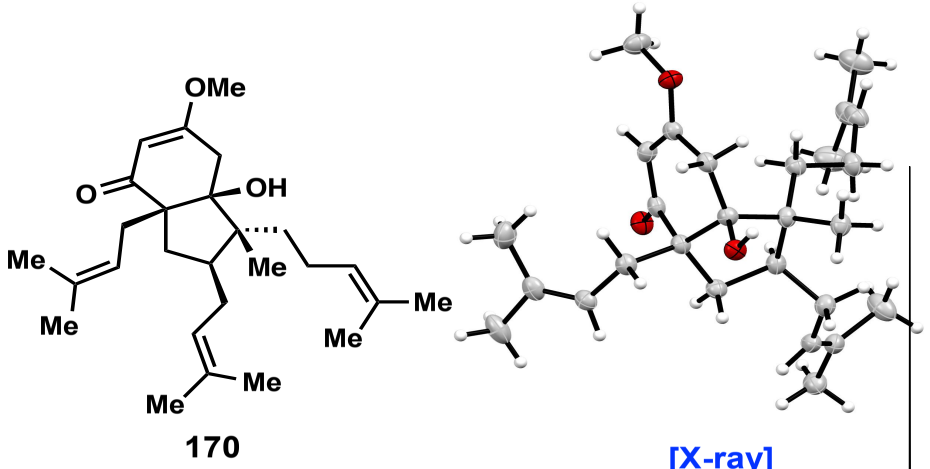
169

550
500
450
400
350
300
250
200
150
100
50
0
−50
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
O
OH
Me
Me
Me
Me
Me
Me
Me

169

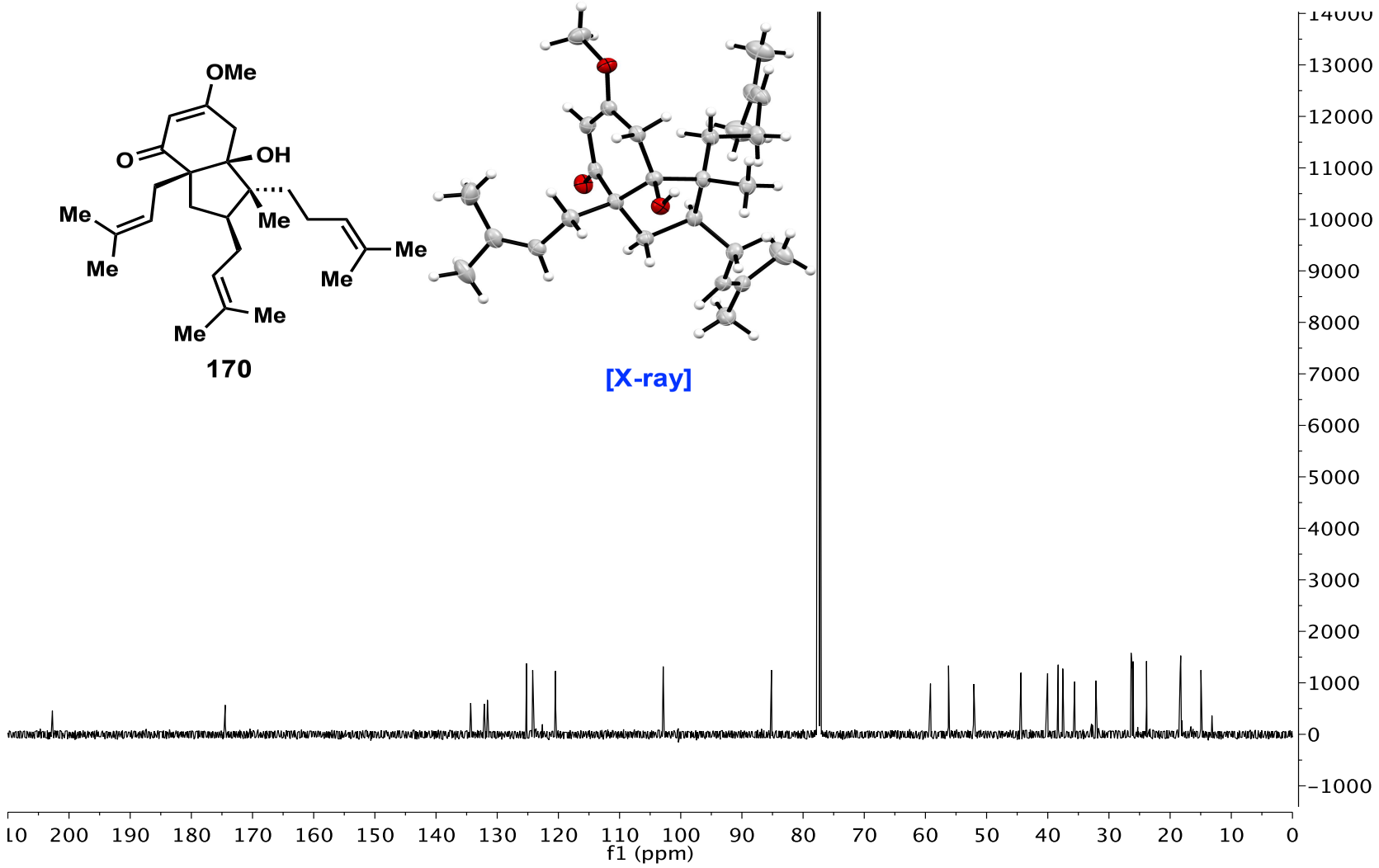
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

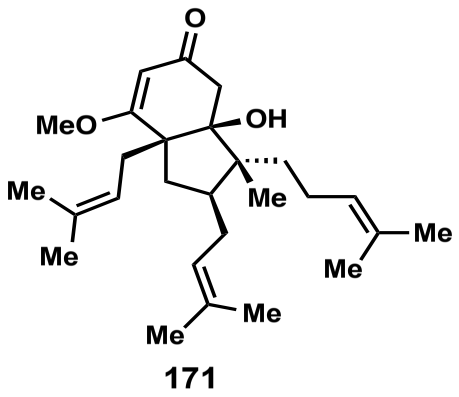

OMe
O
OH
Me
Me
Me
Me
Me
Me
Me

170

[X-ray]

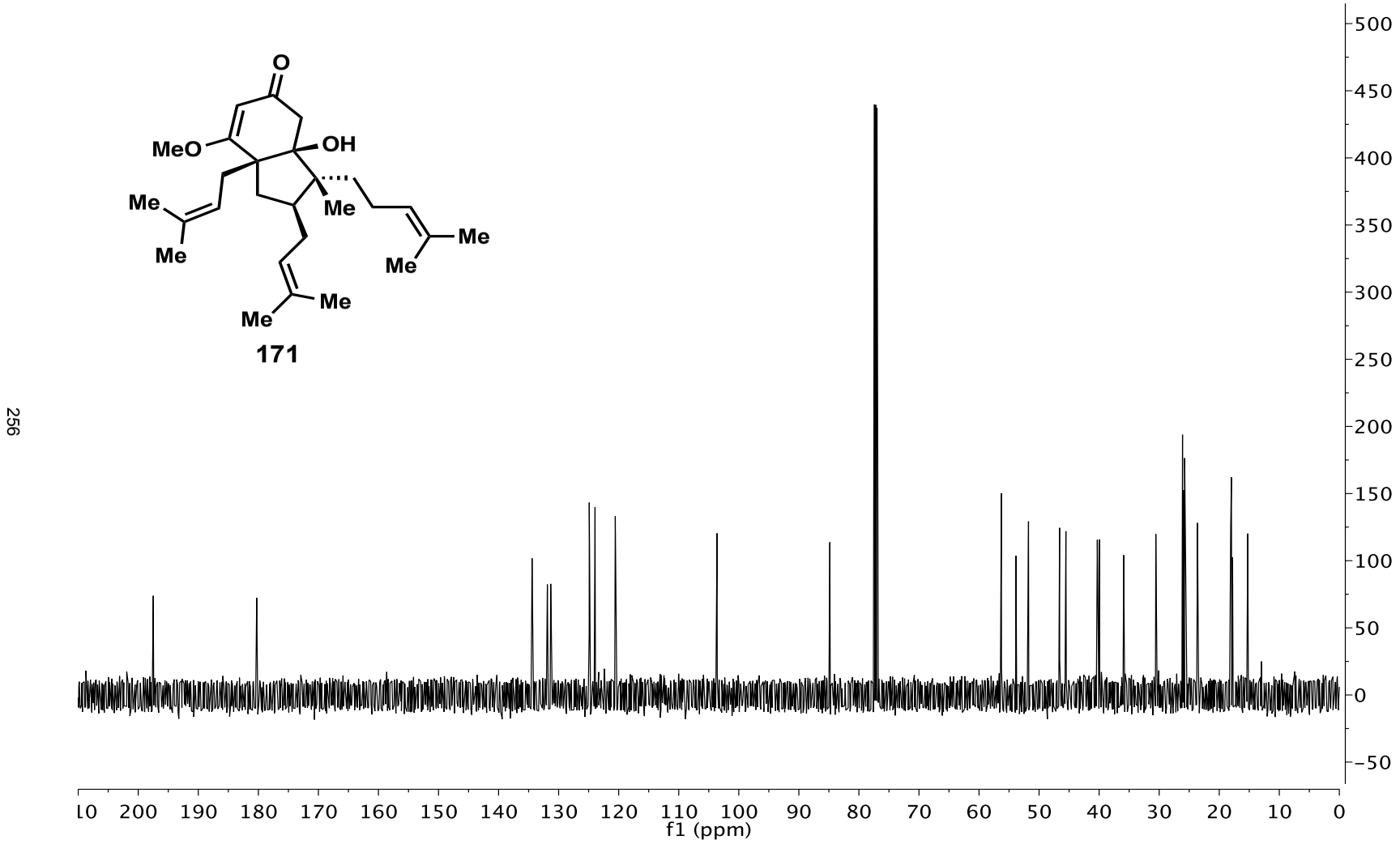
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

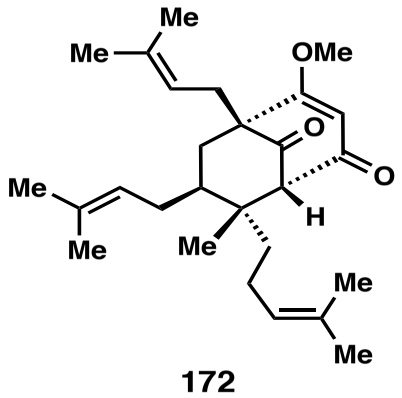

OMe
O
OH
Me
Me
Me
Me
Me
Me
Me
170
[X-ray]
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
MeO
OH
Me
Me
Me
Me
Me
Me
Me

171

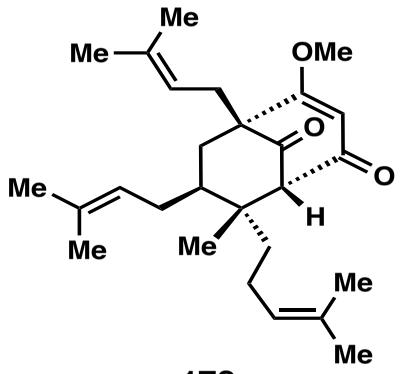
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
MeO
OH
Me
Me
Me
Me
Me
Me
Me
171
256
500
450
400
350
300
250
200
150
100
50
0
−50
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
Me
OMe
O
O
Me
H
Me
Me
Me
Me

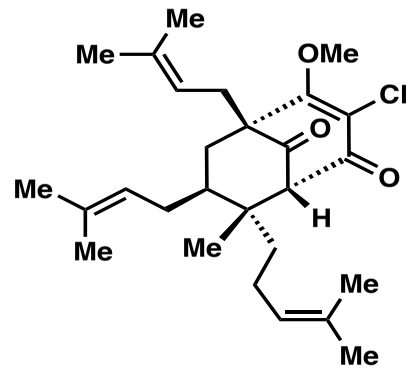
172

1000
900
800
700
600
500
400
300
200
100
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


Me
Me
OMe
O
O
Me
H
Me
Me
Me
Me

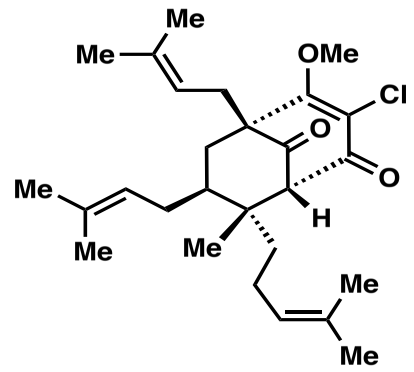
172

75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
−5000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
Me
OMe
Cl
O
O
Me
H
Me
Me
Me
Me

174

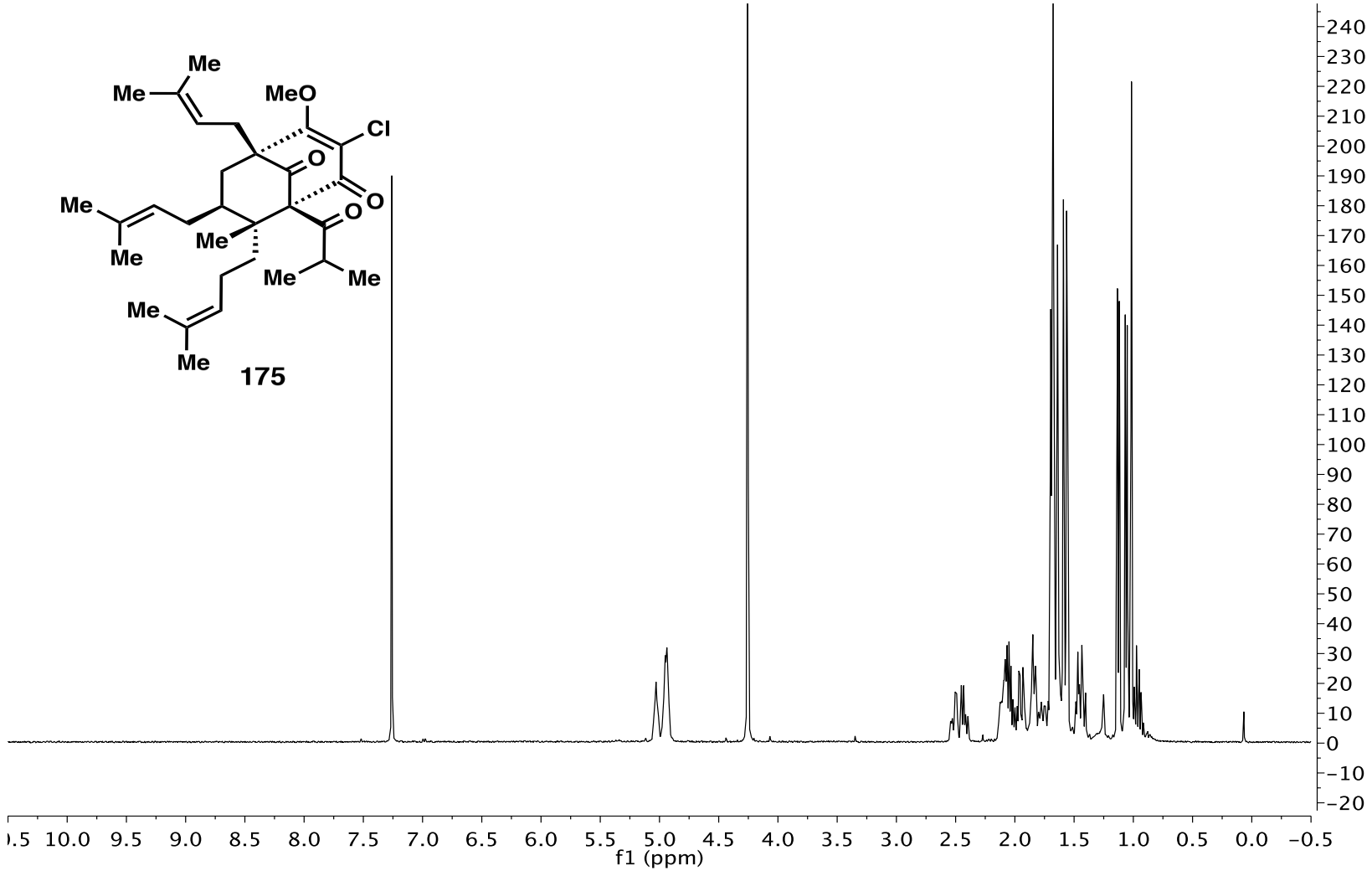
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

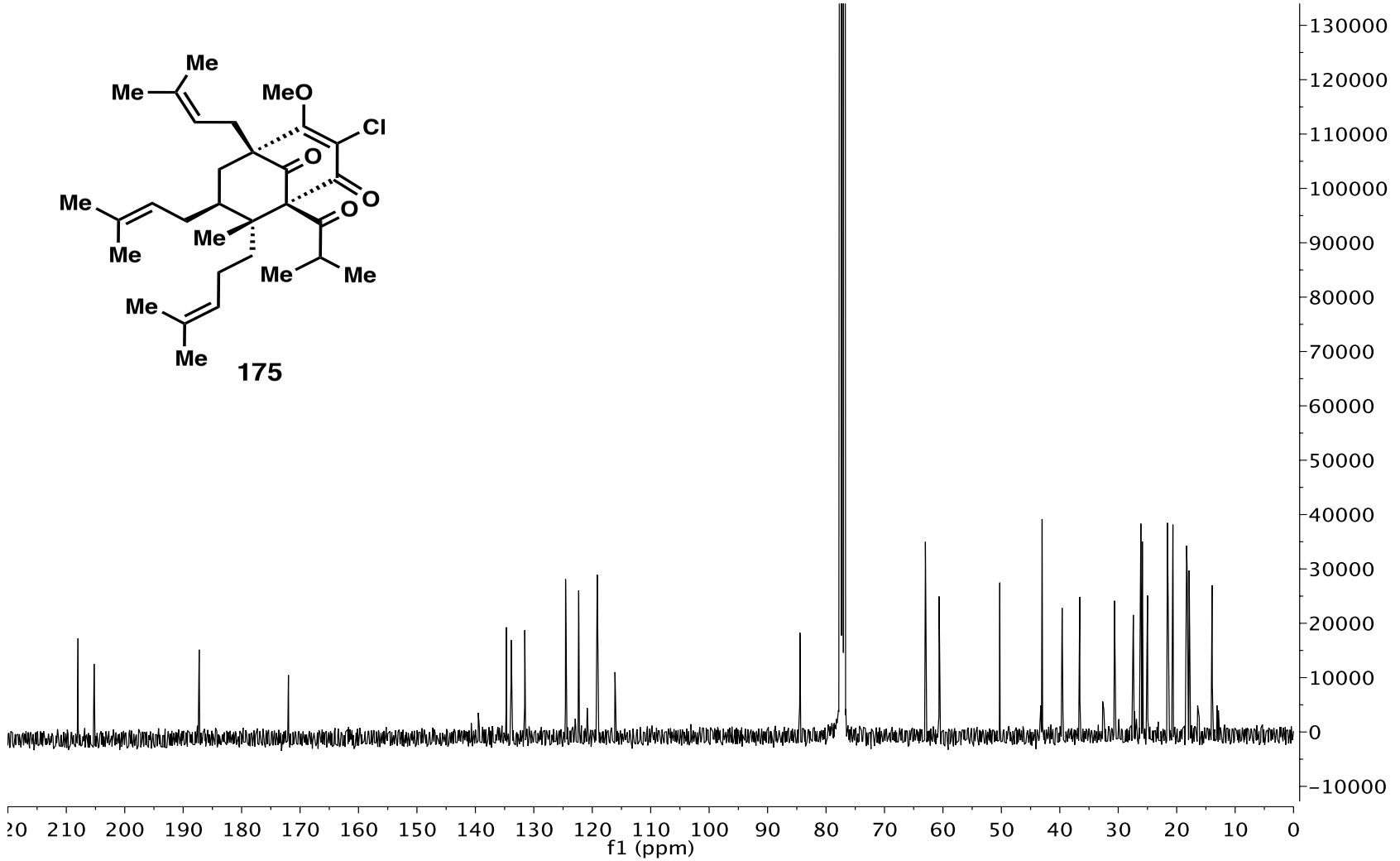

Me
Me
OMe
Cl
O
O
Me
H
Me
Me
Me
Me

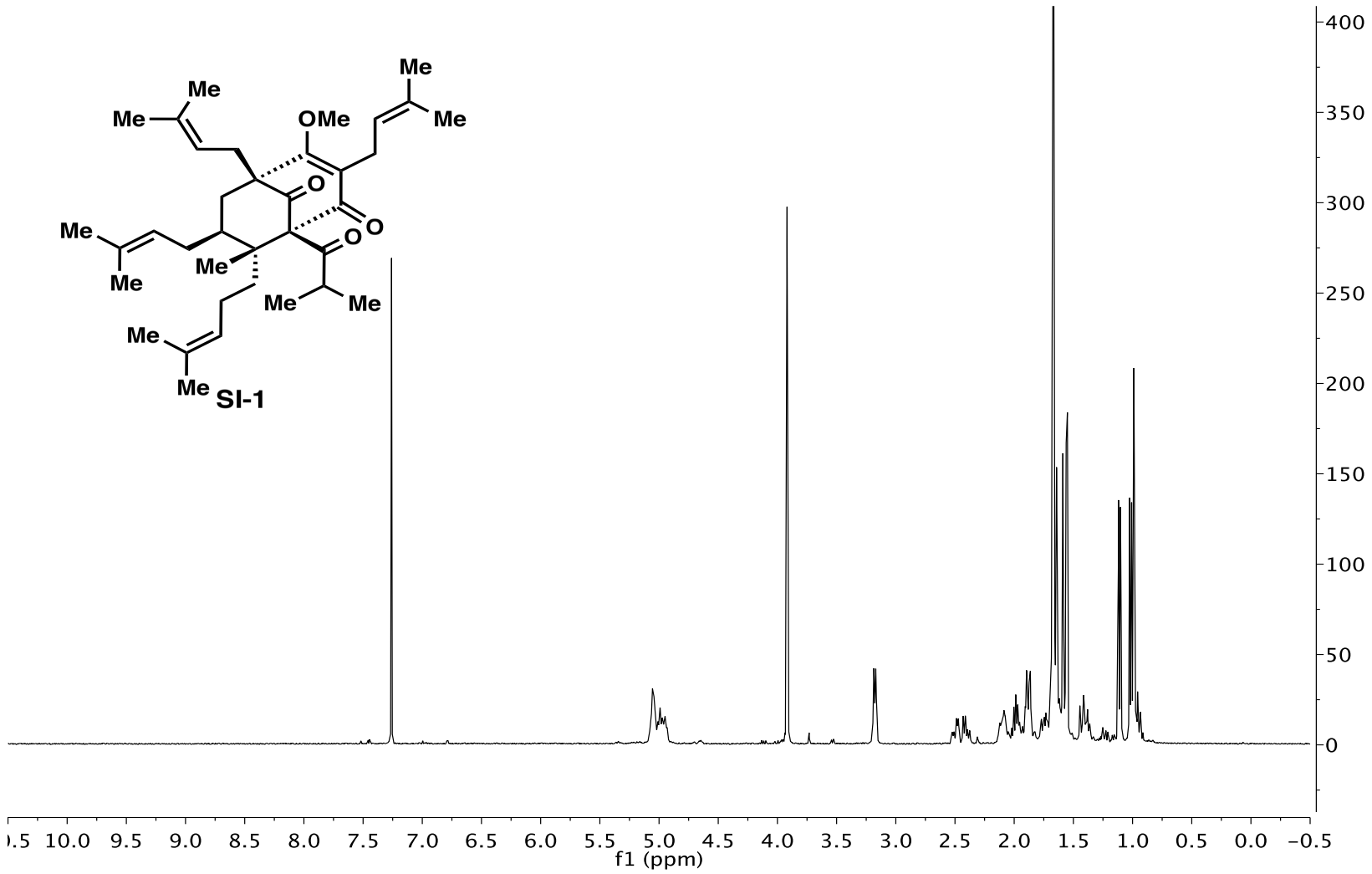
174

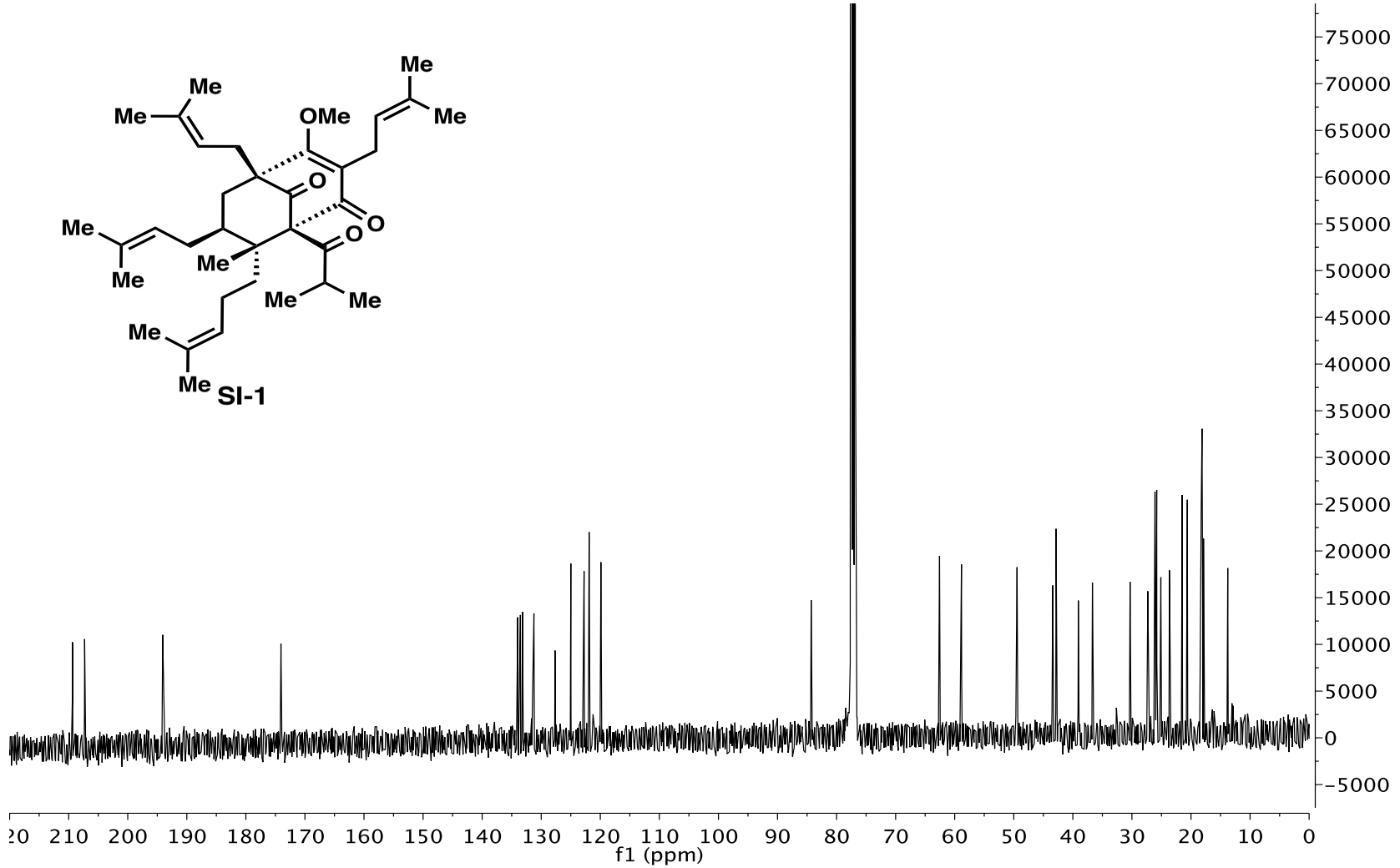
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

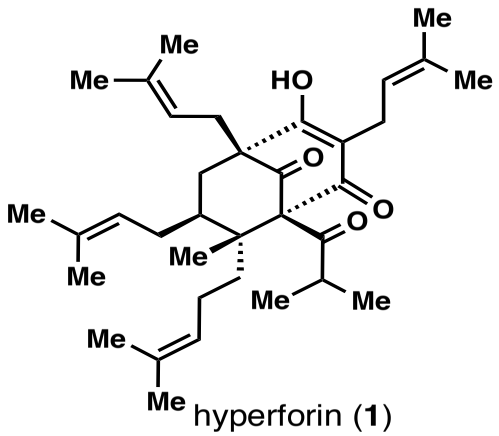
260


Me
Me
MeO
Cl
O
O
O
Me
Me
Me
Me
Me
Me
Me
Me
175
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
f1 (ppm)

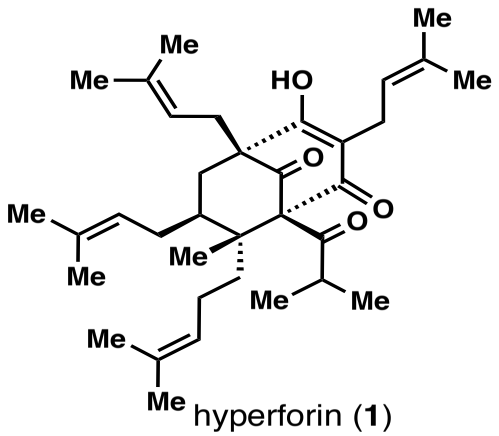

Me
Me
MeO
Cl
O
O
O
Me
Me
Me
Me
Me
Me
Me
Me
175
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
−10000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
Me
Me
OMe
Me
O
O
O
Me
Me
Me
Me
Me
Me
Me
SI-1
400
350
300
250
200
150
100
50
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

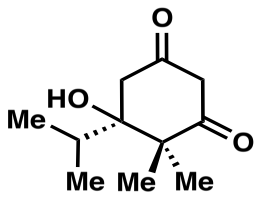

Me
Me
Me
OMe
Me
O
O
O
Me
Me
Me
Me
Me
Me
Me
Me
SI-1
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
−5000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



hyperforin (**1**)

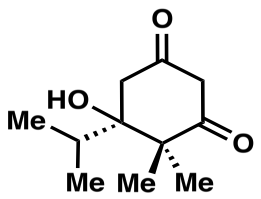


hyperforin (**1**)


O
HO
Me
O
Me Me Me

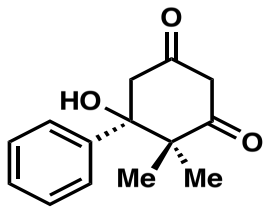
176

1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
HO
Me
O
Me Me Me

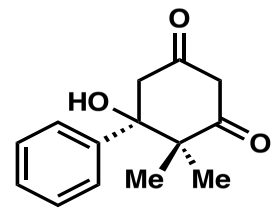
176

5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
HO
O
Me
Me

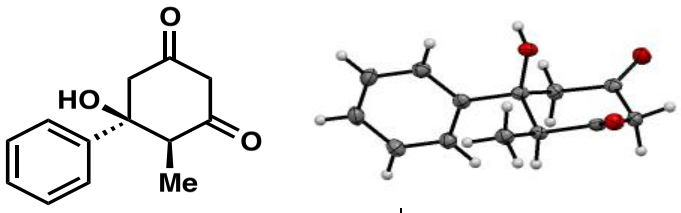
177

1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


O
HO
O
Me
Me

177

270
24000
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
−2000
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

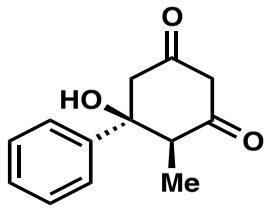

O
HO
O
Me

178

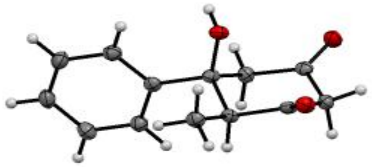
[X-ray]

1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

271

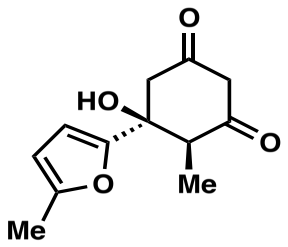

O
HO
O
Me

178



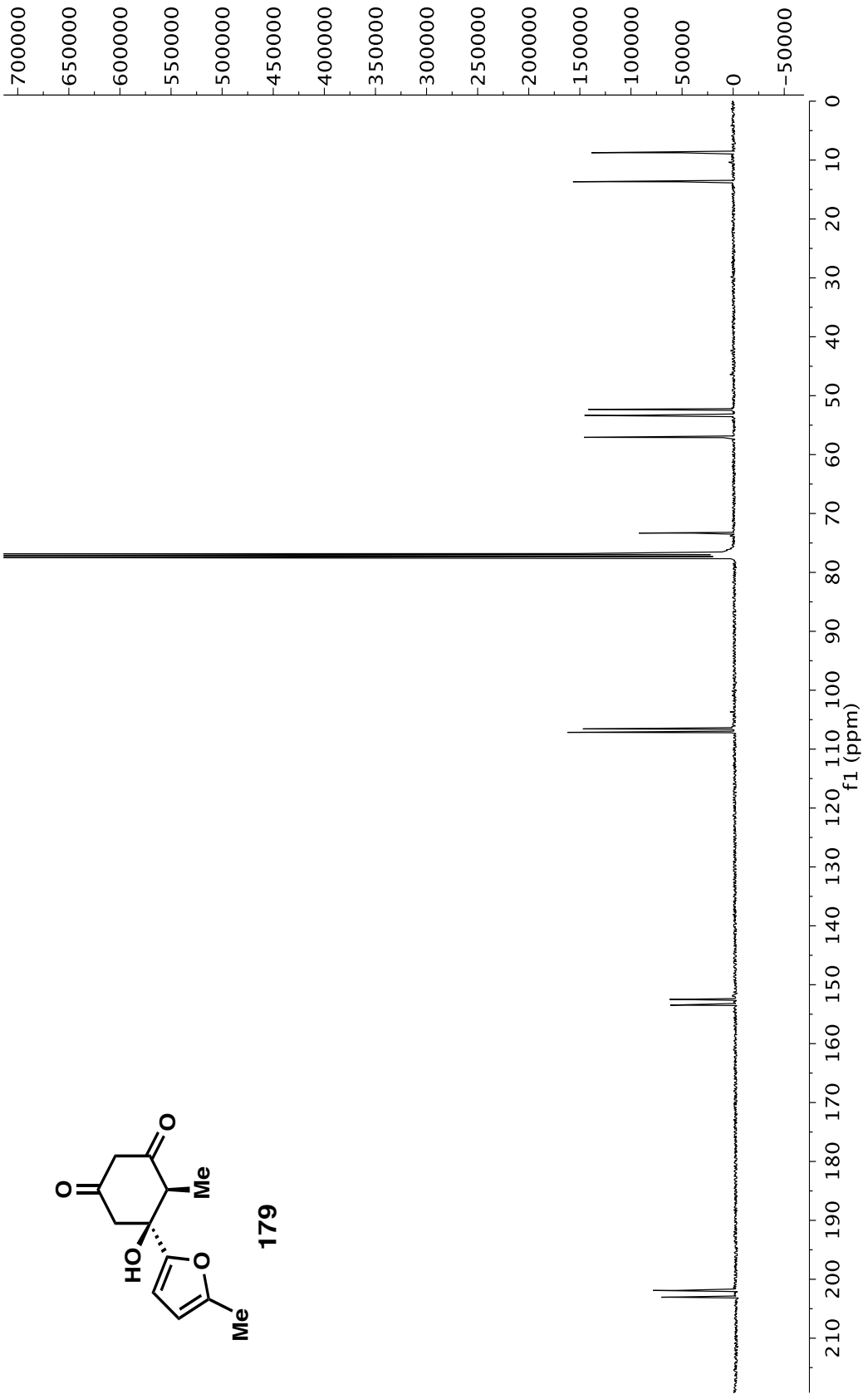
[X-ray]

272
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

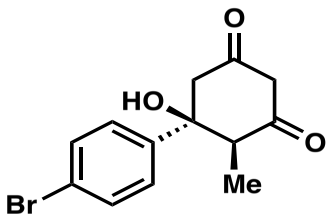

O
HO
O
O
Me
Me

179

1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

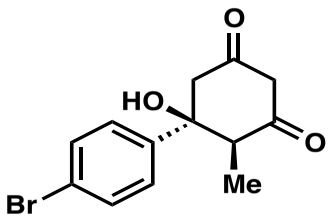

700000
650000
600000
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
−50000
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210
f1 (ppm)
O
O
Me
HO
O
Me

179


O
HO
O
Me
Br

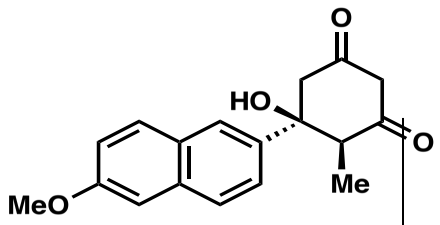
180

275
1000
900
800
700
600
500
400
300
200
100
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
HO
O
Me
Br

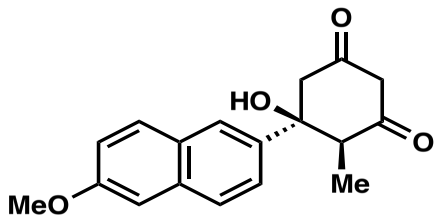
180

400000
350000
300000
250000
200000
150000
100000
50000
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
HO
O
Me
MeO

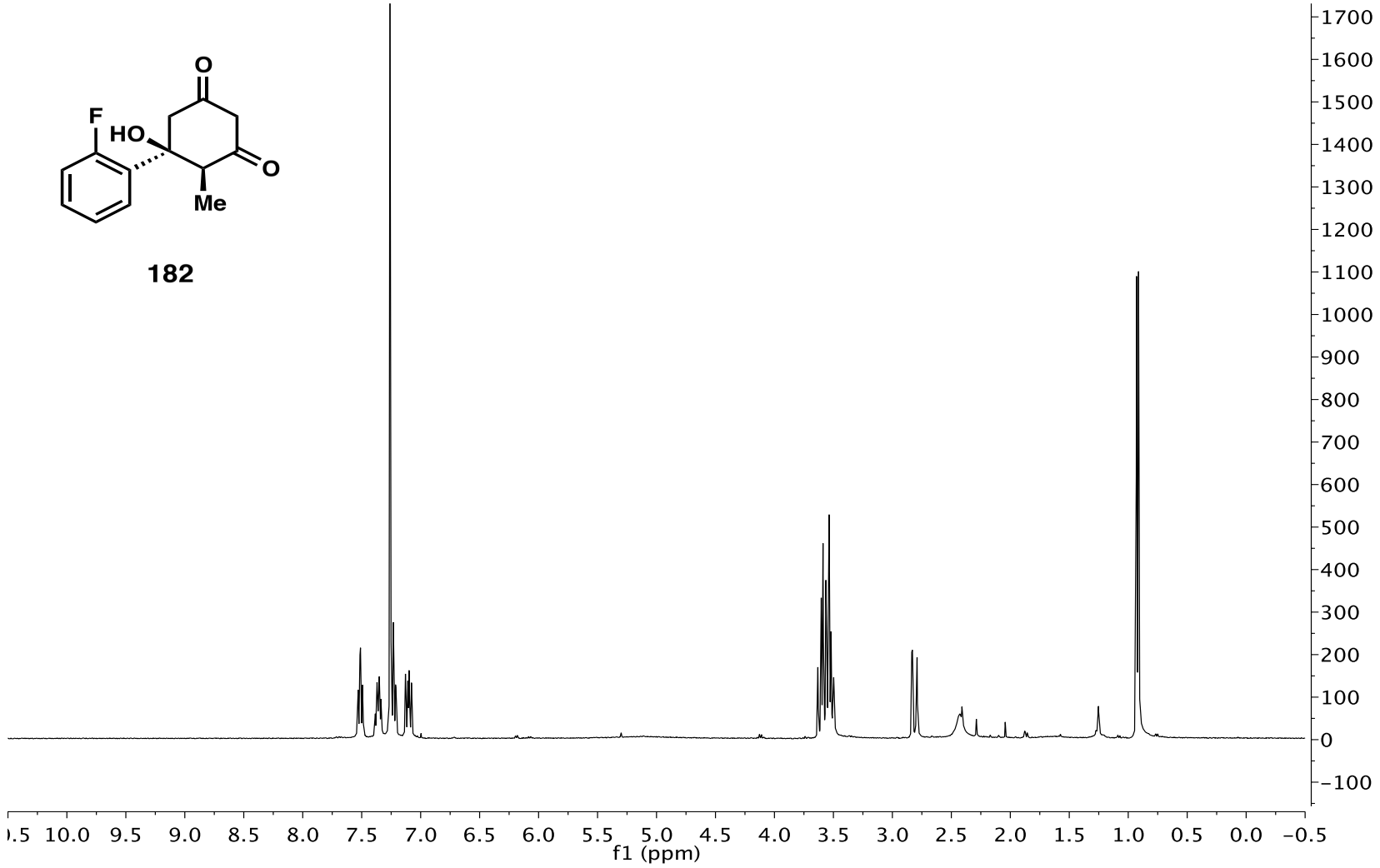
181

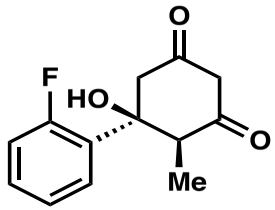
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
HO
O
Me
MeO

181

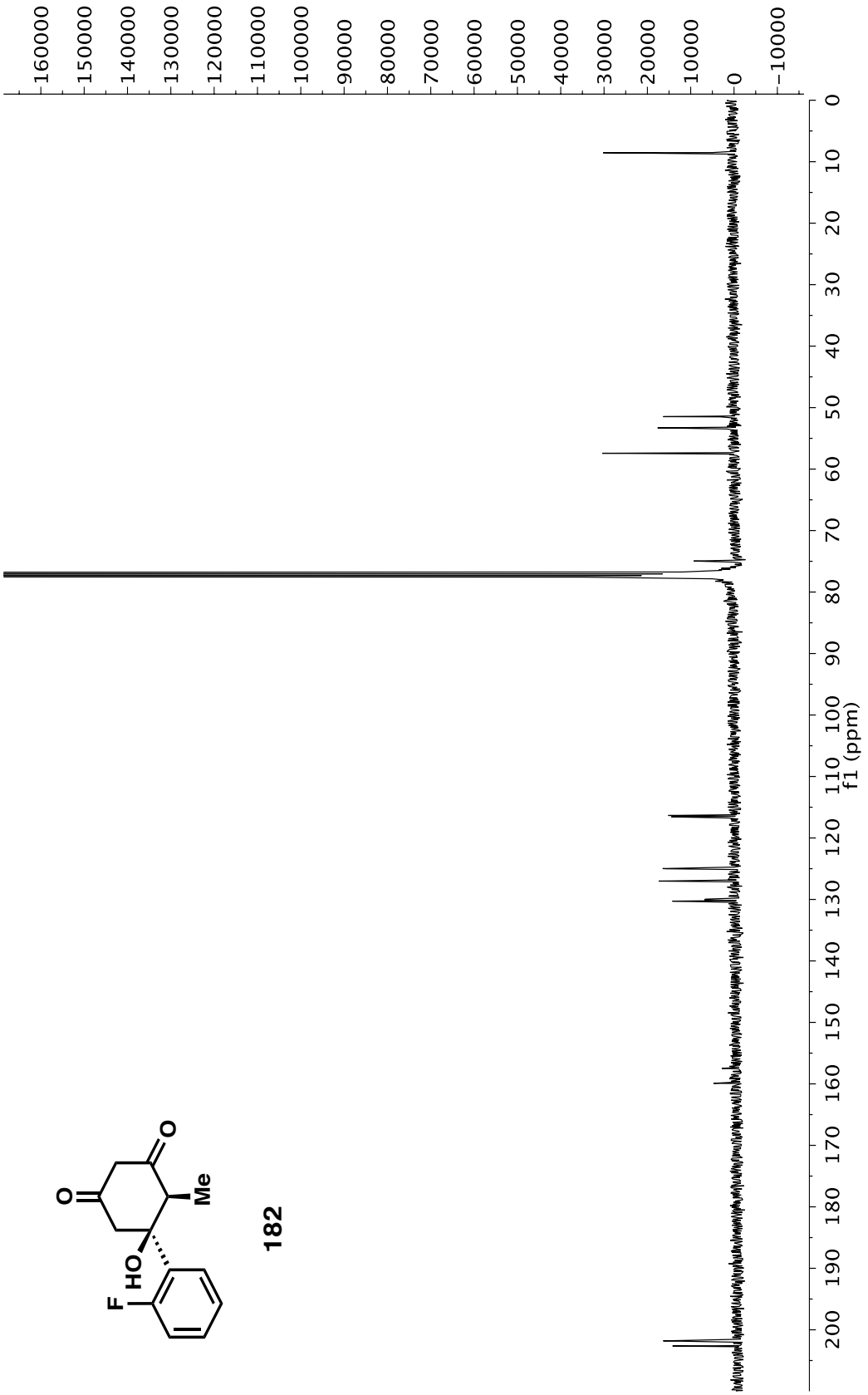
24000
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
−2000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
F
HO
O
Me
182
279
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

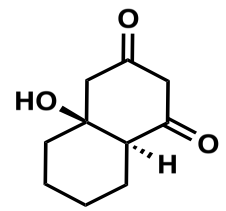

O
F
HO
O
Me

182

320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
−20
−40
−60
110
90
70
50
30
10
−10
−30
−50
−70
−90
−110
f1 (ppm)


160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
−10000
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)
O
O
Me
HO
F

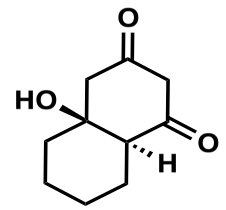
182


O
HO
O
H

183

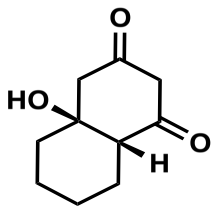
282

1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
HO
O
H

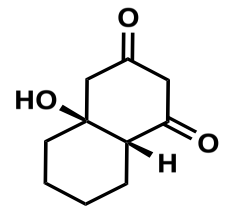
183

45000
40000
35000
30000
25000
20000
15000
10000
5000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
HO
O
H

183

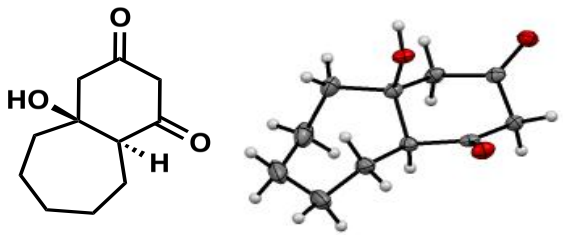
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
−50
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
HO
O
H

183

285

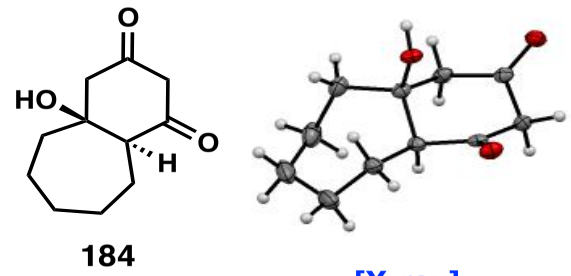
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
HO
O
H

184

[X-ray]

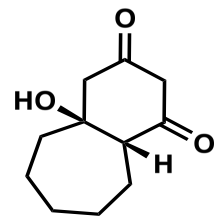
1000
900
800
700
600
500
400
300
200
100
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
HO
O
H

184

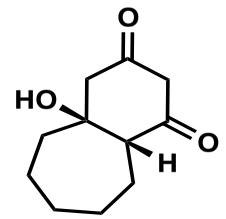
[X-ray]

8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
−1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
HO
O
H

184

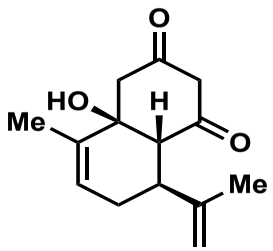
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
−20
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


O
HO
O
H

184

289

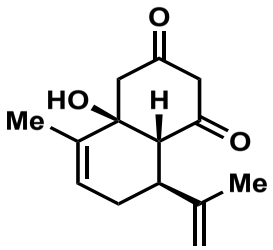
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
−5000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



185

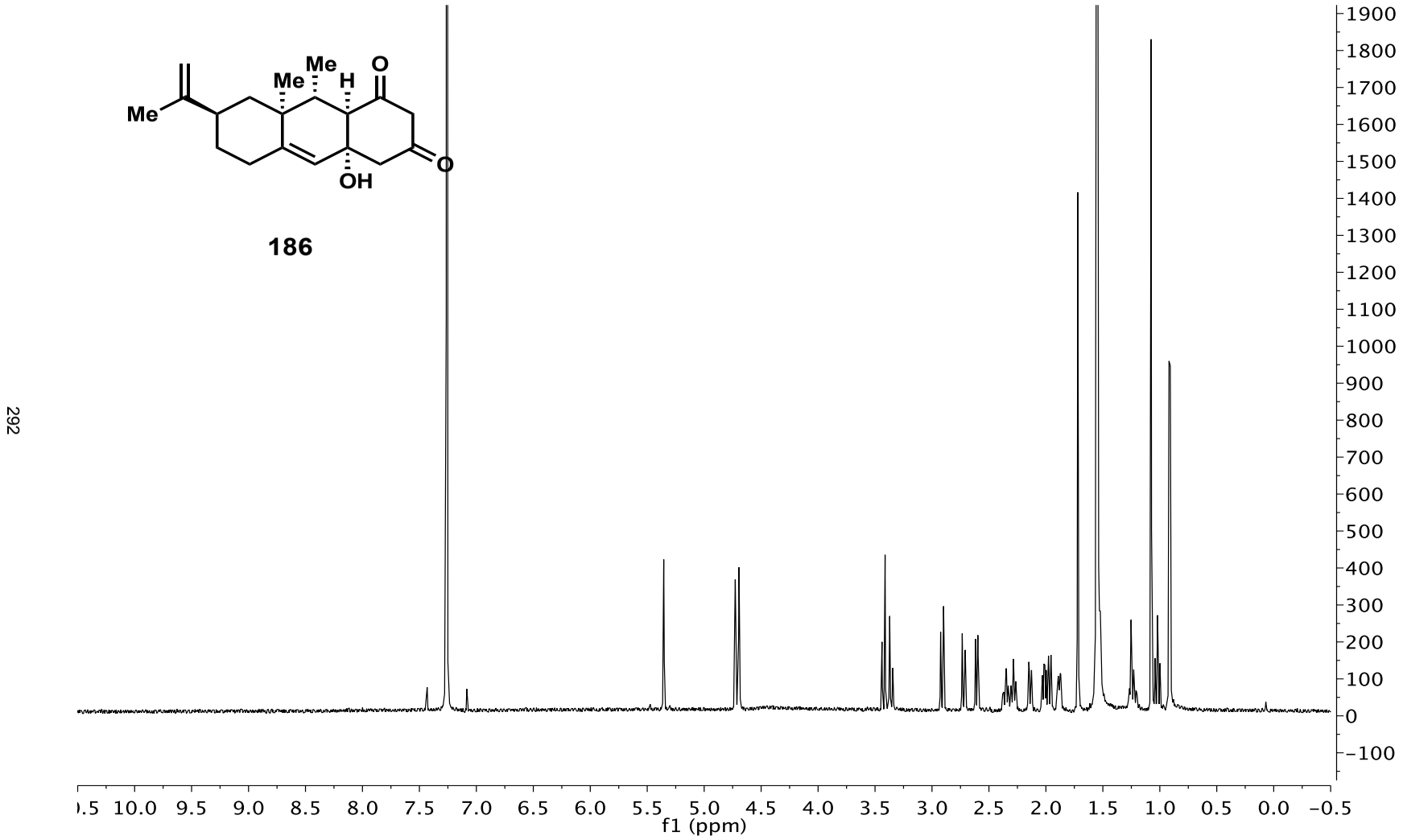
290

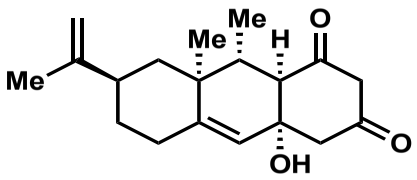
f1 (ppm)


O
HO
H
Me
O
Me

185

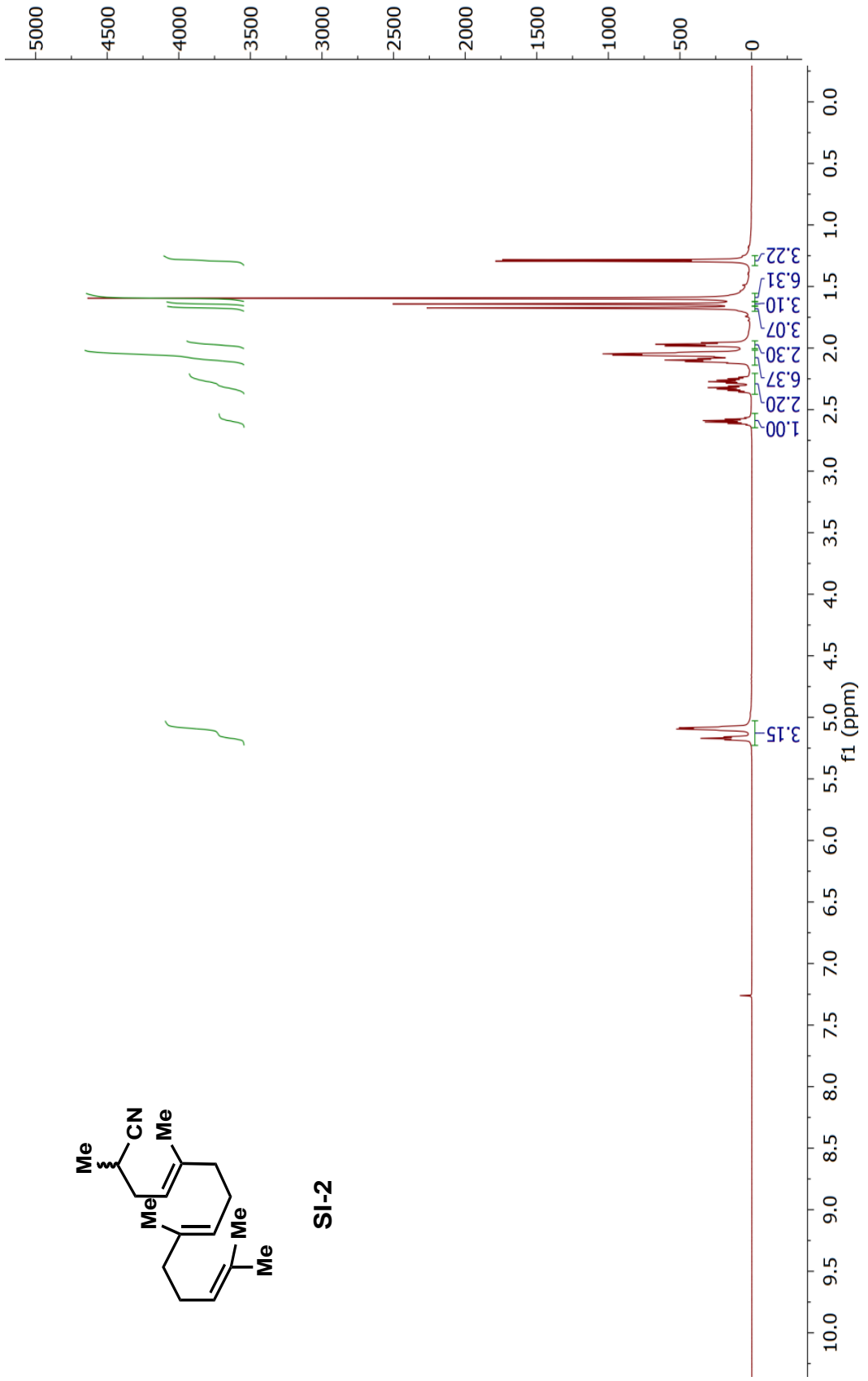
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
−5000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −20
f1 (ppm)

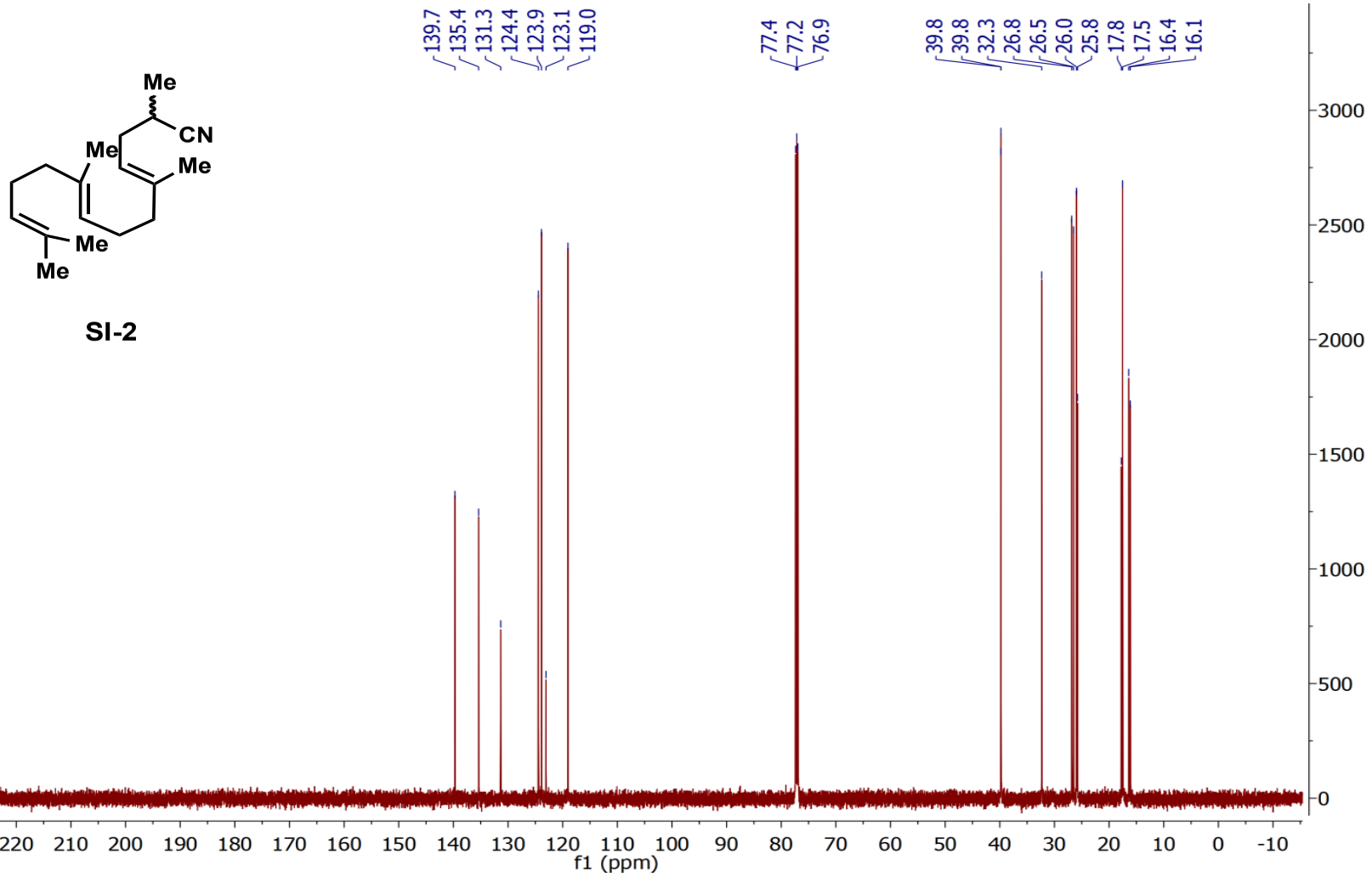

Me
Me
Me
H
O
O
OH
186
292
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

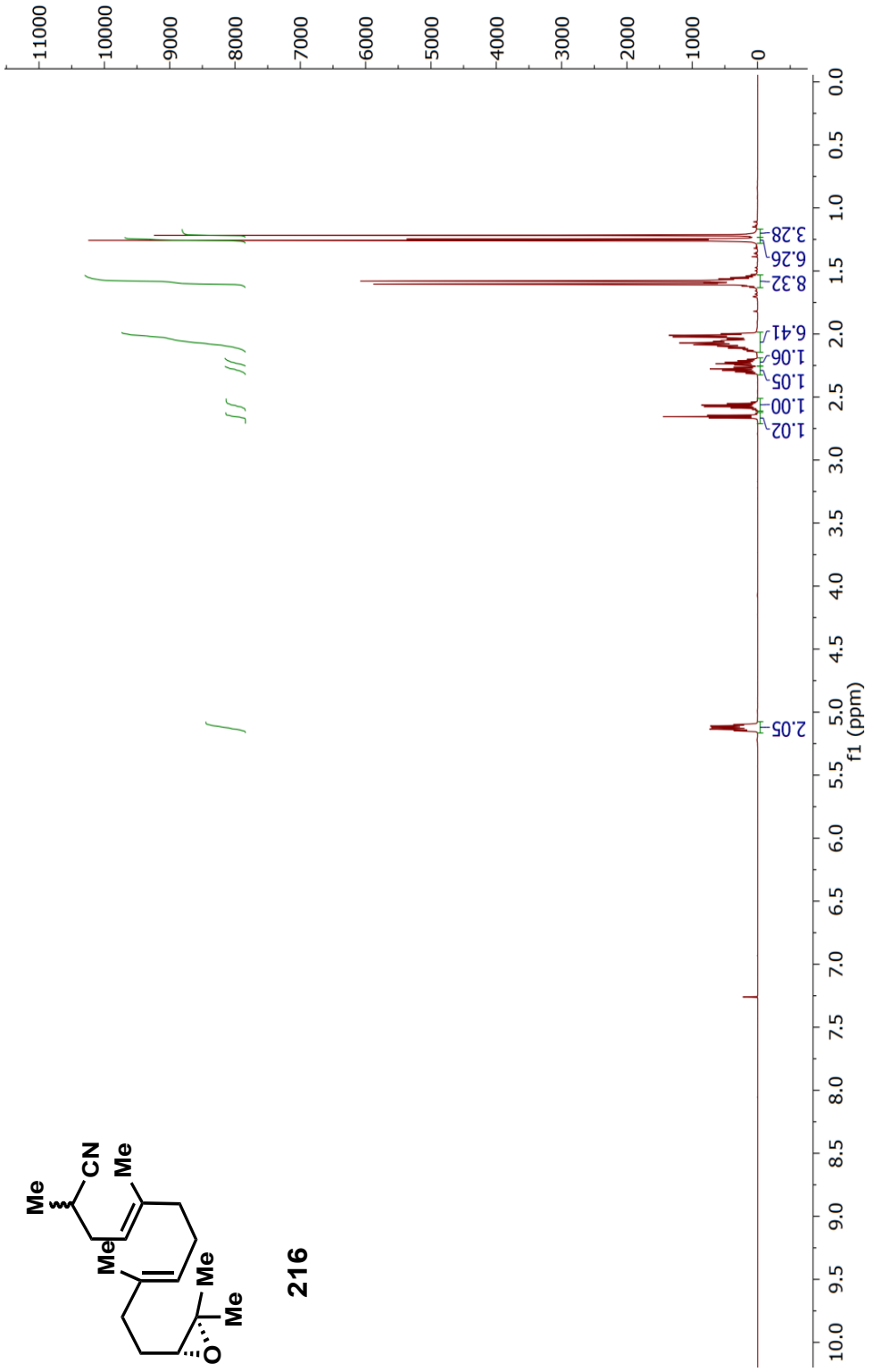

Me
Me
Me
H
O
O
OH

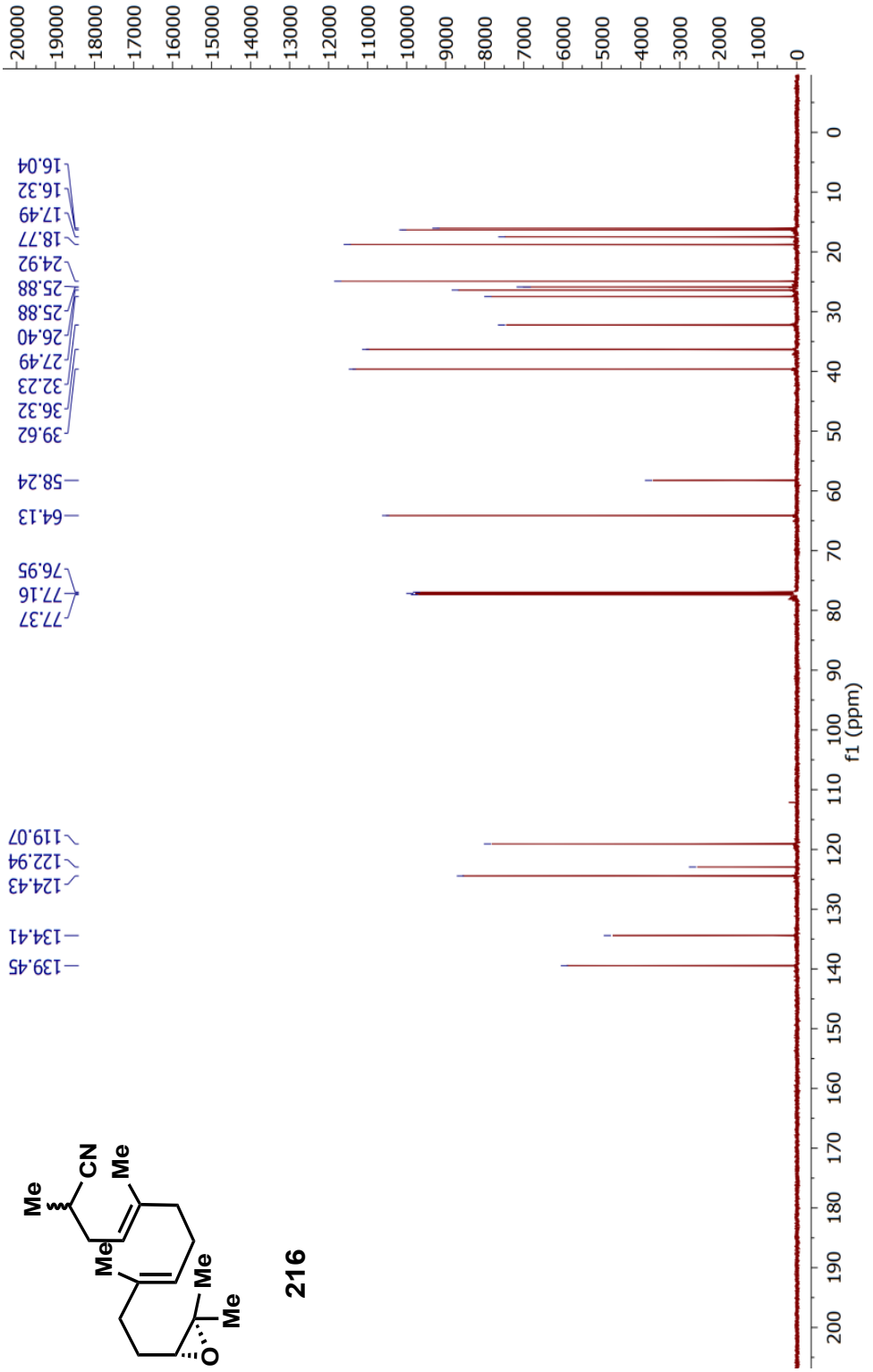
186

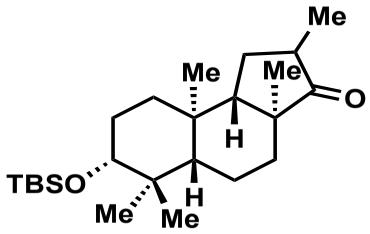
293
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
CN
Me
Me
Me
Me
SI-2
3.22
6.31
3.10
3.07
2.30
6.37
2.20
1.00
3.15
f1 (ppm)

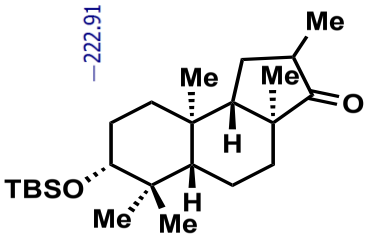

Me
CN
Me
Me
Me
Me
SI-2
139.7
135.4
131.3
124.4
123.9
123.1
119.0
77.4
77.2
76.9
39.8
39.8
32.3
26.8
26.5
26.0
25.8
17.8
17.5
16.4
16.1
3000
2500
2000
1500
1000
500
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
CN
Me
Me
Me
O
Me
Me
216
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
3.28
6.26
8.32
6.41
1.06
1.05
1.00
1.02
2.05
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
f1 (ppm)

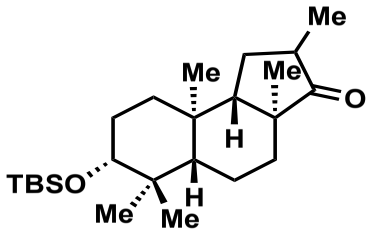

Me
CN
Me
Me
Me
O
Me
216
139.45
134.41
124.43
122.94
119.07
77.37
77.16
76.95
64.13
58.24
39.62
36.32
32.23
27.49
26.40
25.88
25.88
24.92
18.77
17.49
16.32
16.04
f1 (ppm)



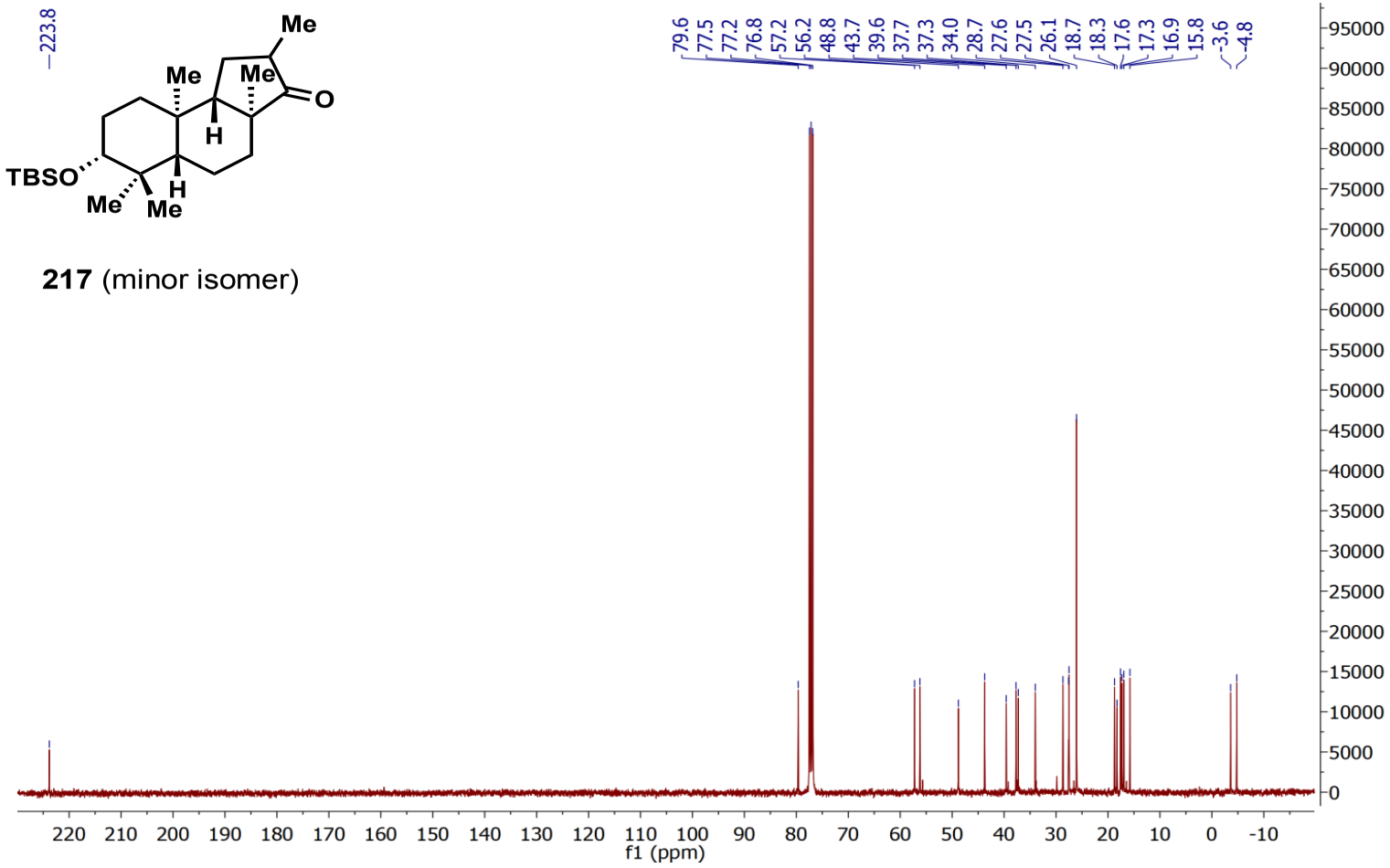
217 (major isomer)



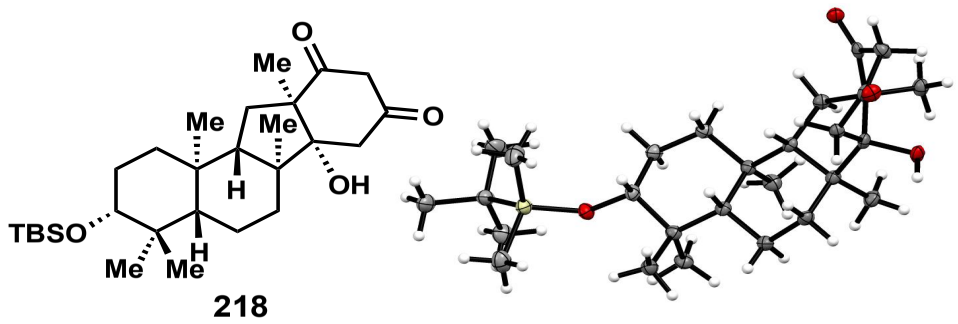
217 (major isomer)



217 (minor isomer)



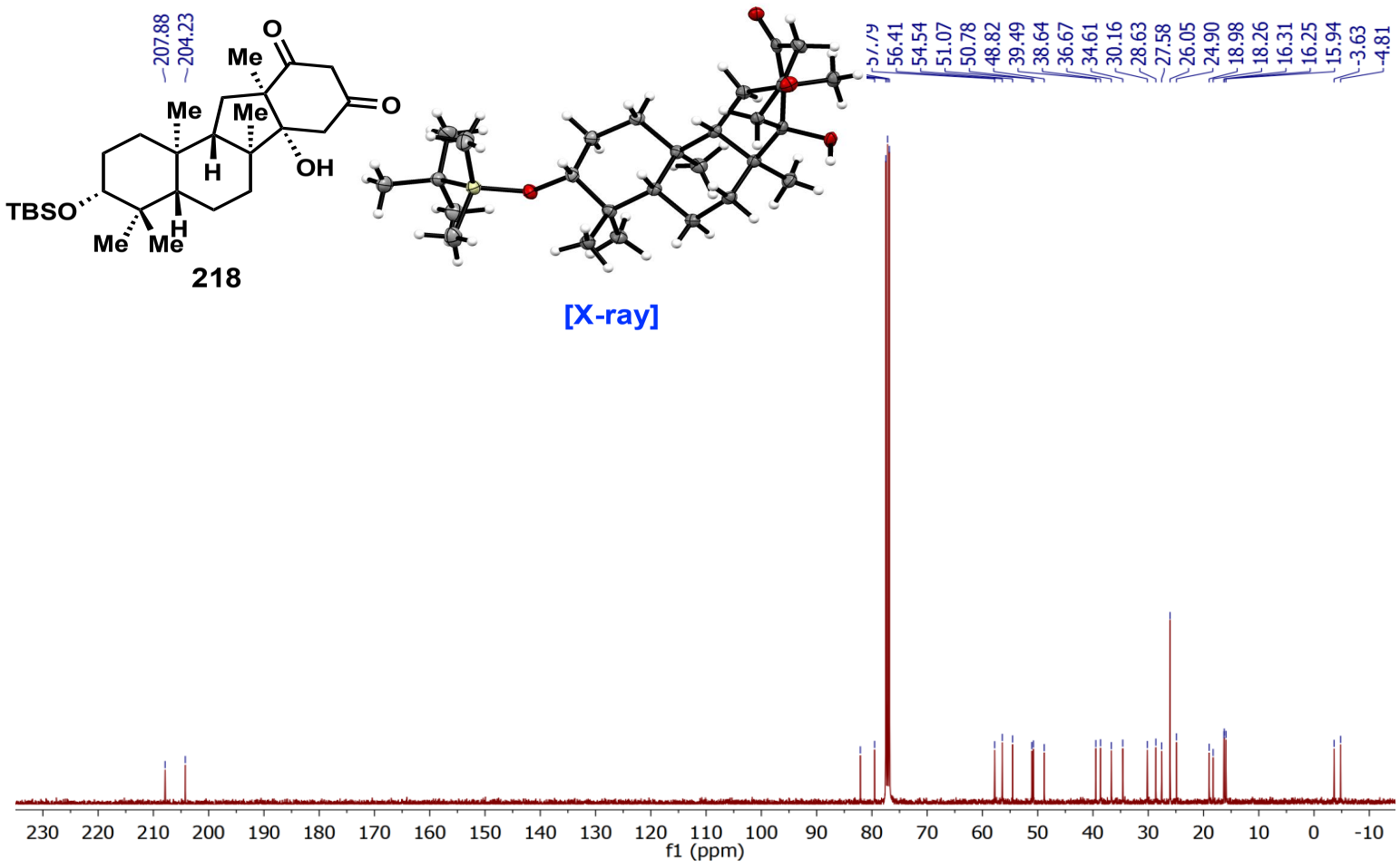
217 (minor isomer)

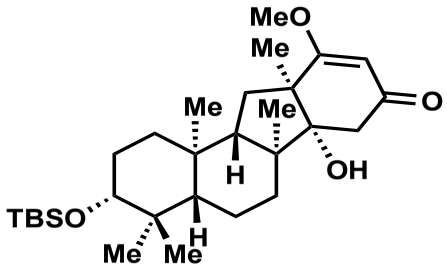

O
Me
O
Me
Me
H
OH
TBSO
Me
Me
H

218

[X-ray]

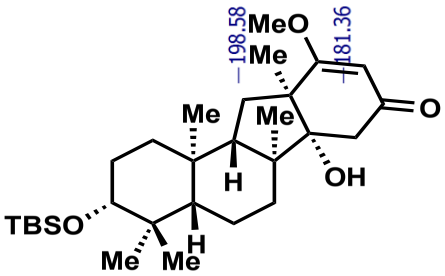
1.02
2.04
2.03
1.01
1.00
2.34
4.16
4.10
1.04
3.07
5.34
12.32
3.16
1.05
6.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


207.88
204.23
57.79
56.41
54.54
51.07
50.78
48.82
39.49
38.64
36.67
34.61
30.16
28.63
27.58
26.05
24.90
18.98
18.26
16.31
16.25
15.94
-3.63
-4.81
O
Me
Me
Me
H
OH
O
TBSO
Me
Me
H
218
[X-ray]
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


MeO
Me
Me
Me
O
H
OH
TBSO
Me
Me
H

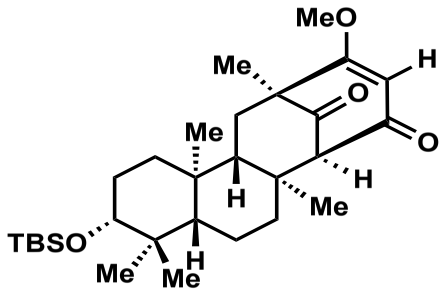
SI-3

1.00
3.18
1.03
1.03
1.06
1.06
1.02
3.77
4.27
3.20
2.78
3.18
1.28
3.45
12.54
3.20
1.07
6.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


198.58
MeO
Me
181.36
Me
Me
O
H
OH
TBSO
Me
Me
H

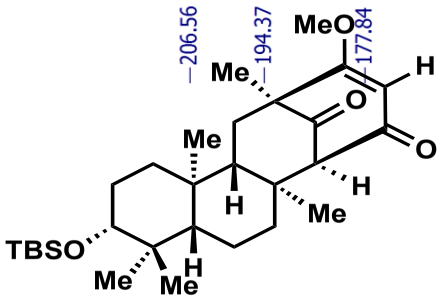
SI-3

99.91
81.99
79.63
77.48
77.16
76.84
56.58
56.23
54.74
49.07
48.14
48.00
39.52
38.60
36.80
34.48
33.32
28.68
27.62
26.67
26.06
18.87
18.26
16.18
15.92
15.78
-3.66
-4.78
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


MeO
H
Me
O
O
Me
H
H
Me
TBSO
Me
Me
H

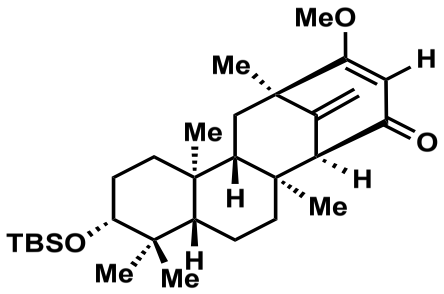
219

1.00
3.11
1.04
1.01
1.03
8.64
1.20
3.03
3.11
12.27
3.60
5.34
6.22
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


MeO
H
Me
O
O
Me
H
H
Me
TBSO
Me
Me
H

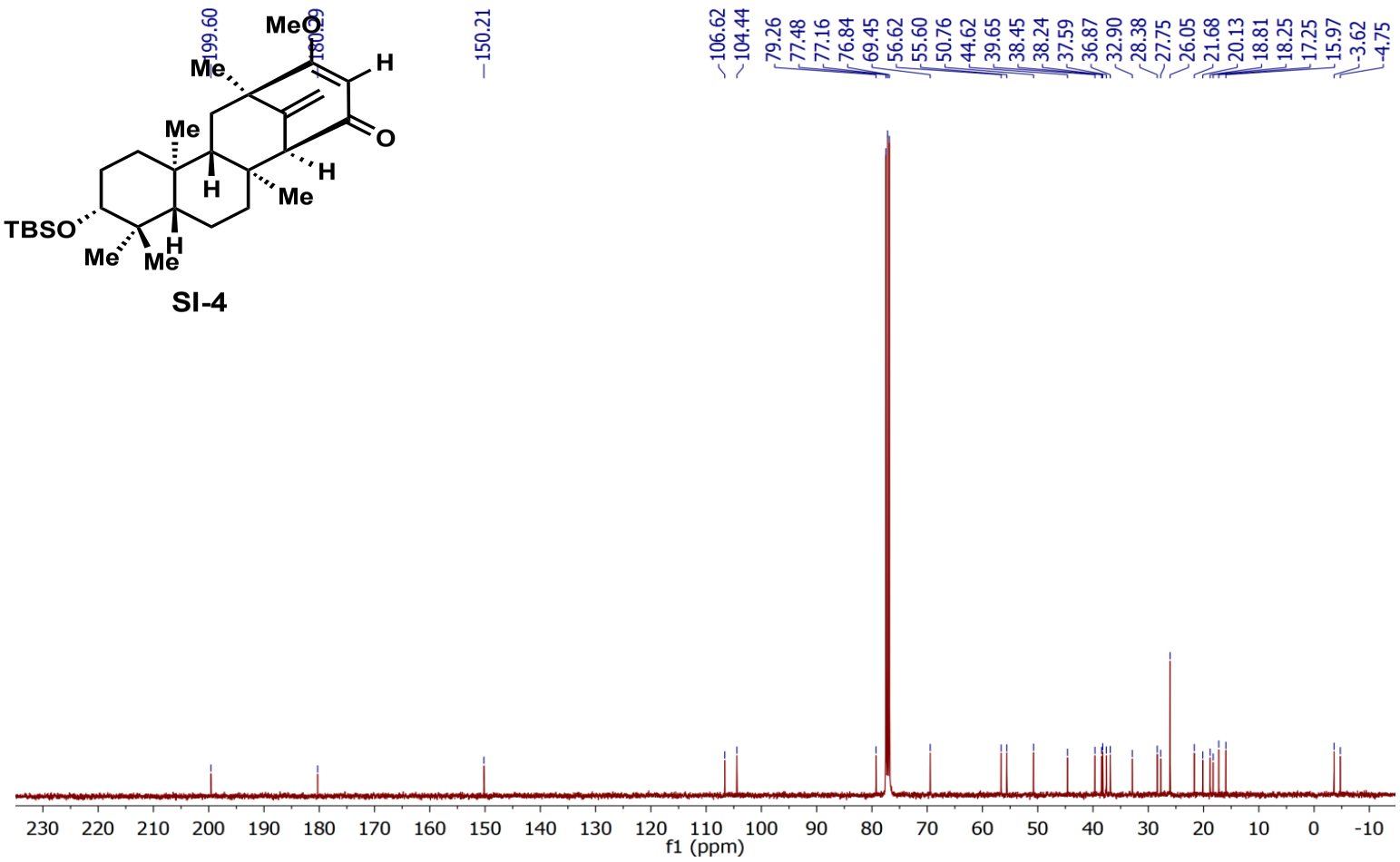
219

206.56
194.37
177.84
106.19
79.08
77.48
77.16
76.84
75.47
57.23
55.40
53.21
50.19
43.47
39.62
38.45
37.44
36.99
34.75
28.40
27.63
26.03
21.03
18.61
18.24
17.18
16.60
15.96
-3.64
-4.76
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

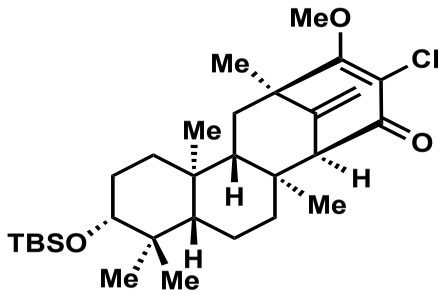

MeO
Me
H
Me
O
H
H
Me
TBSO
Me
Me
H

SI-4

1.00
1.02
1.04
3.15
1.05
1.03
2.08
2.85
3.30
6.43
3.20
9.50
3.26
3.23
5.56
6.22
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

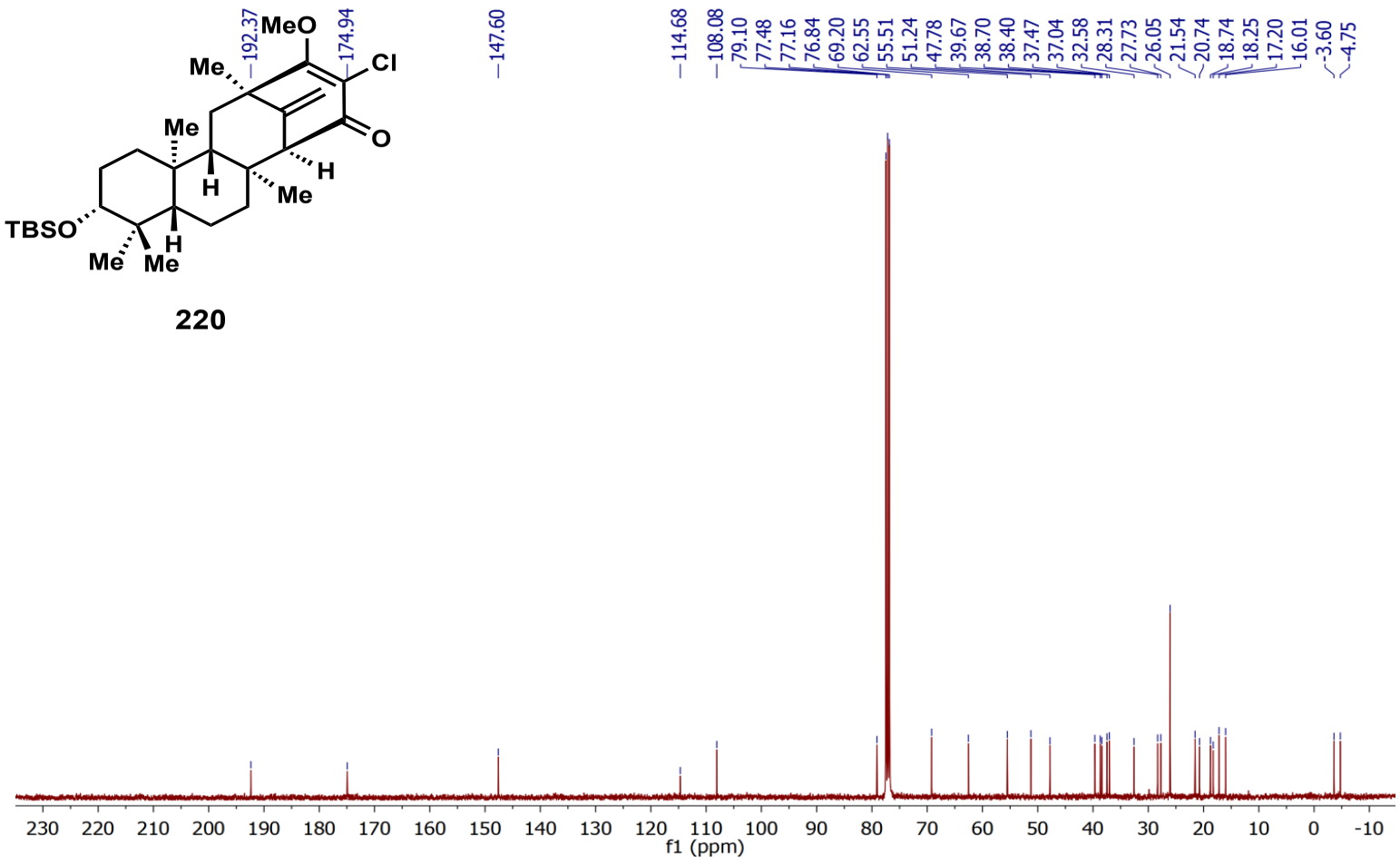

199.60
180.99
150.21
106.62
104.44
79.26
77.48
77.16
76.84
69.45
56.62
55.60
50.76
44.62
39.65
38.45
38.24
37.59
36.87
32.90
28.38
27.75
26.05
21.68
20.13
18.81
18.25
17.25
15.97
-3.62
-4.75
MeO
Me
H
Me
O
H
H
Me
TBSO
Me
Me
H
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

SI-4

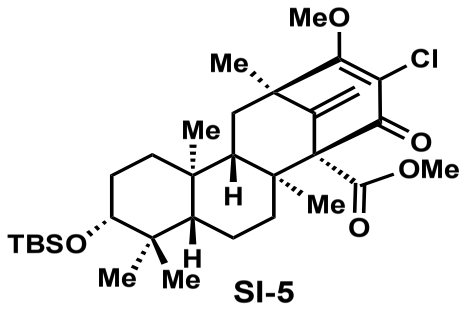

MeO
Cl
Me
Me
O
H
H
Me
TBSO
H
Me
Me

220

1.06
1.07
3.00
1.05
1.03
4.71
4.28
3.09
1.17
1.06
3.22
9.49
3.17
3.17
5.47
6.25
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

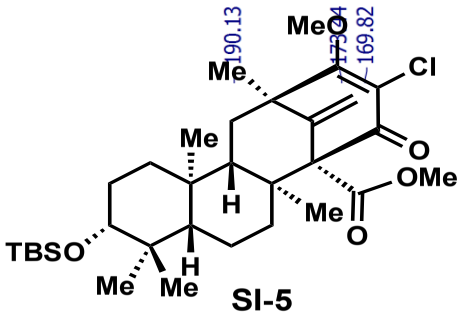

MeO
Cl
O
Me
Me
H
H
Me
TBSO
Me
Me
H
192.37
174.94
147.60
114.68
108.08
79.10
77.48
77.16
76.84
69.20
62.55
55.51
51.24
47.78
39.67
38.70
38.40
37.47
37.04
32.58
28.31
27.73
26.05
21.54
20.74
18.74
18.25
17.20
16.01
-3.60
-4.75
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

220


MeO
Cl
Me
Me
O
OMe
H
Me
O
TBSO
H
Me
Me

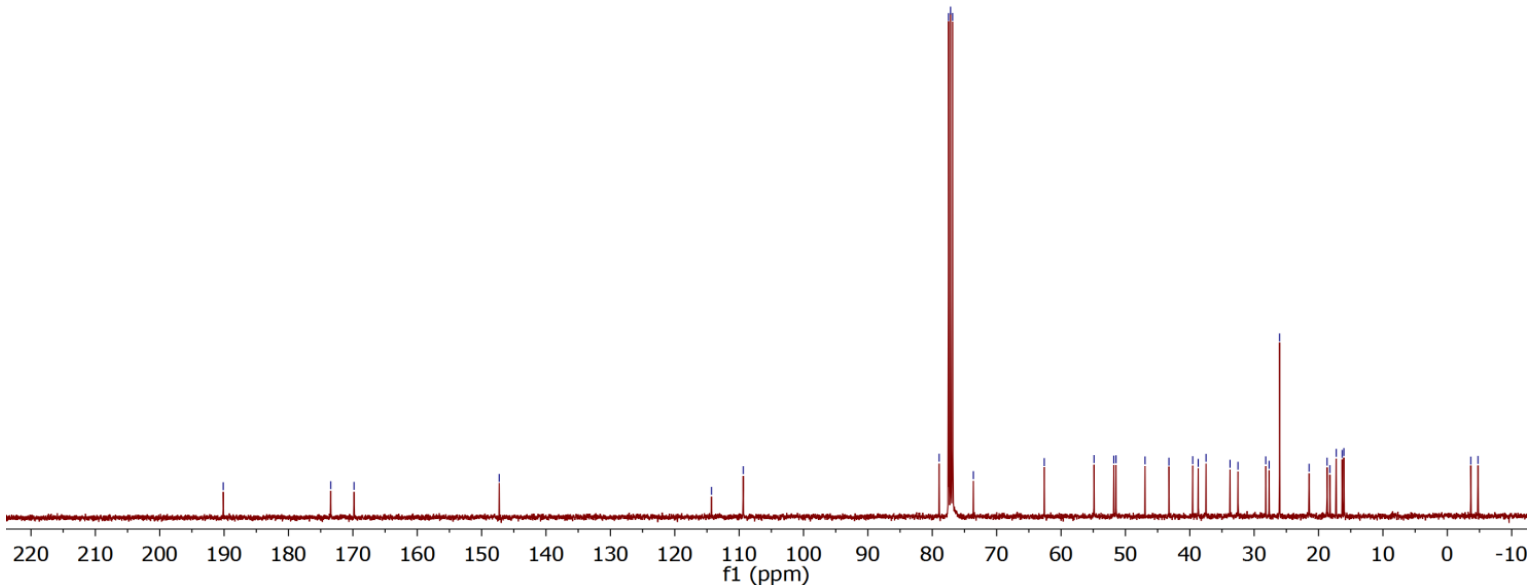
SI-5

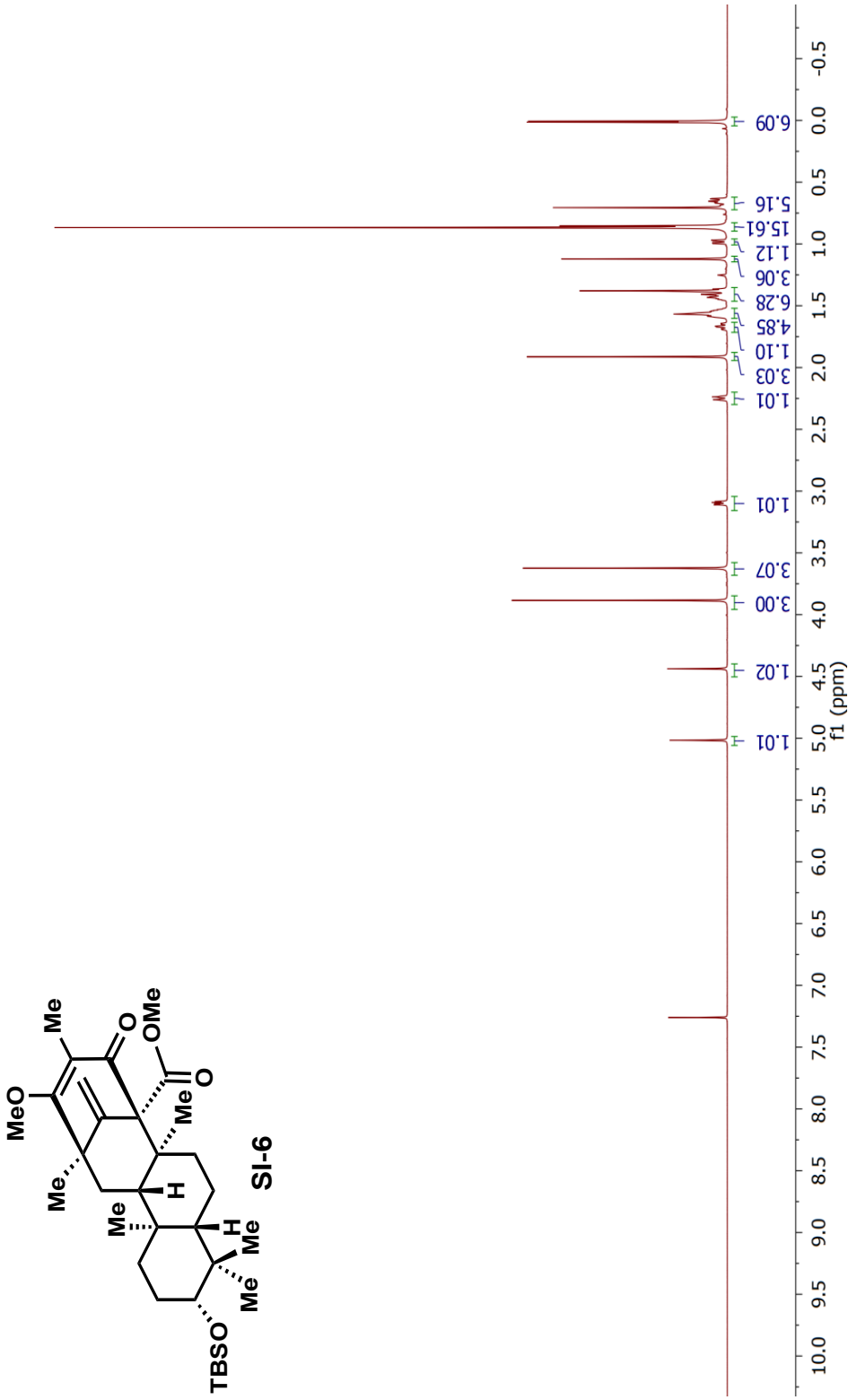
1.05
1.03
3.00
3.07
1.01
1.02
1.07
4.65
6.14
3.07
1.06
15.51
5.17
6.11
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

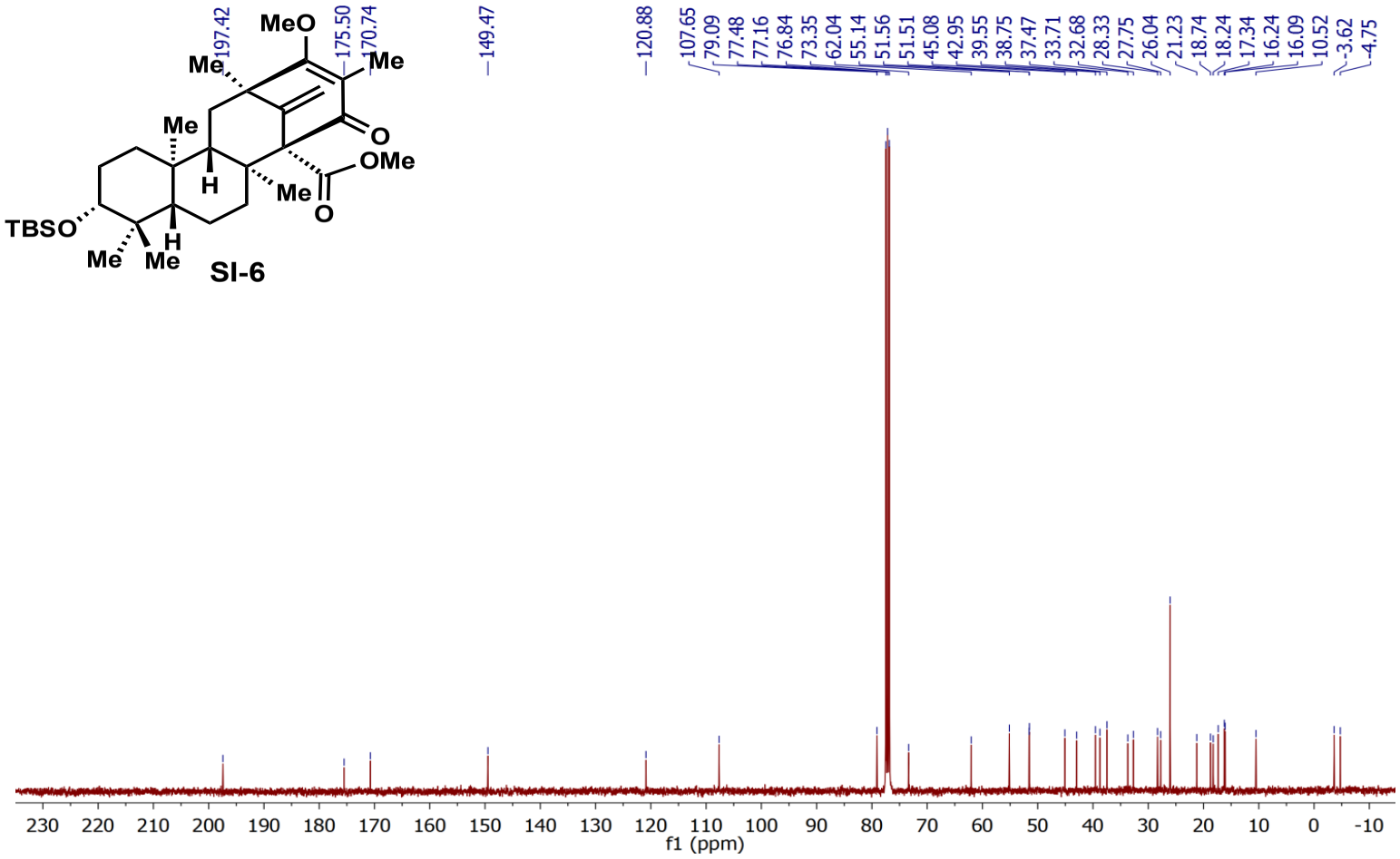


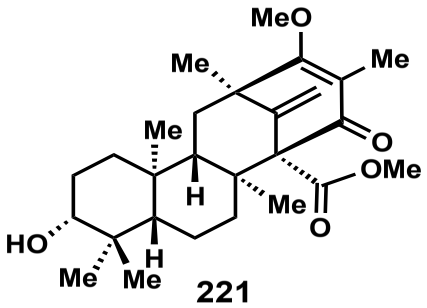
SI-5

190.13
173.04
169.82
147.27
114.29
109.36
78.93
77.48
77.16
76.84
73.62
62.60
54.88
51.80
51.46
46.95
43.24
39.55
38.69
37.47
33.75
32.52
28.20
27.68
26.05
21.47
18.67
18.24
17.25
16.33
16.07
-3.65
-4.77



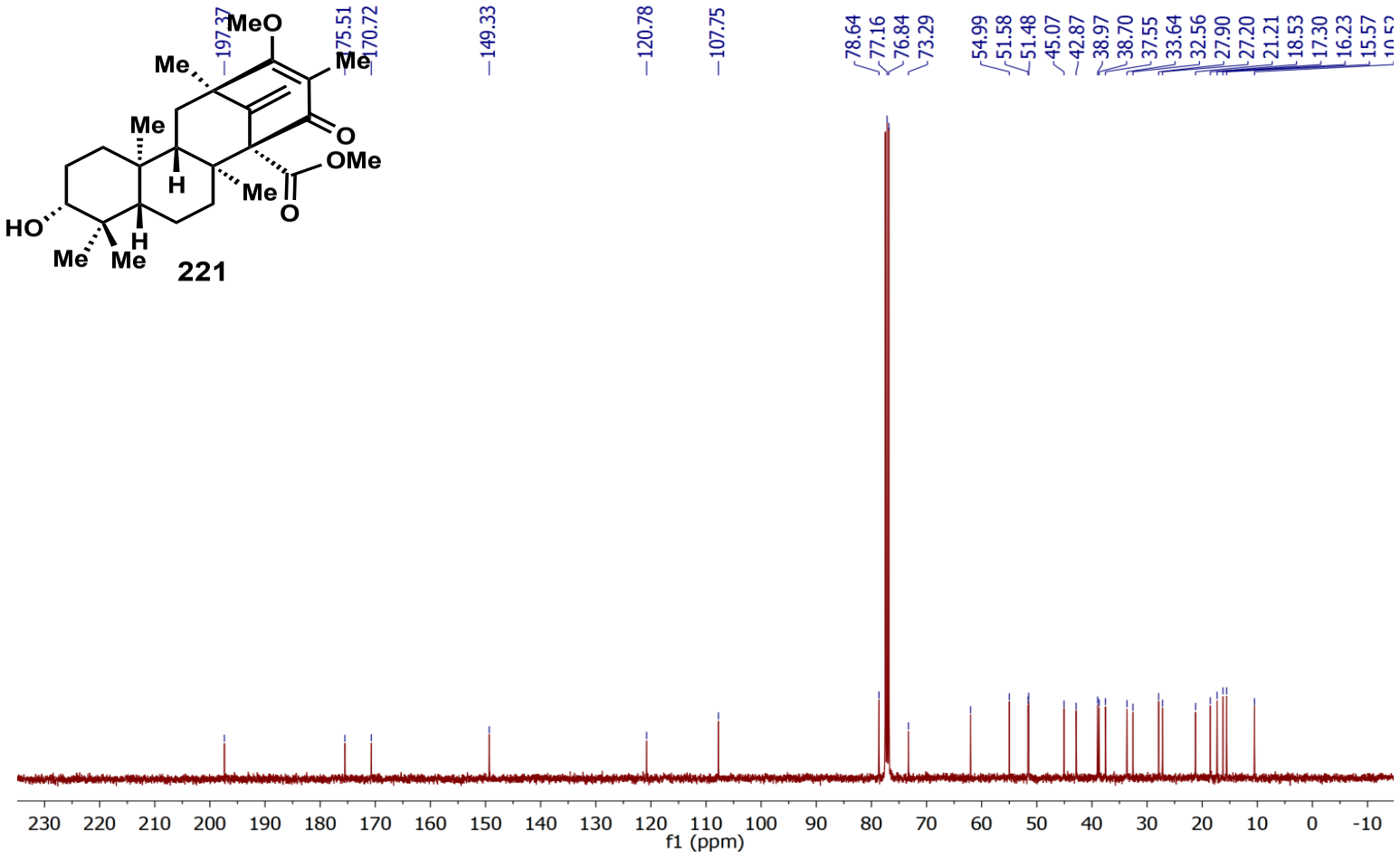

MeO
Me
O
OMe
Me
O
Me
H
Me
H
Me
Me
TBSO
Me
SI-6
6.09
5.16
15.61
1.12
3.06
6.28
4.85
1.10
3.03
1.01
1.01
3.07
3.00
1.02
1.01
f1 (ppm)

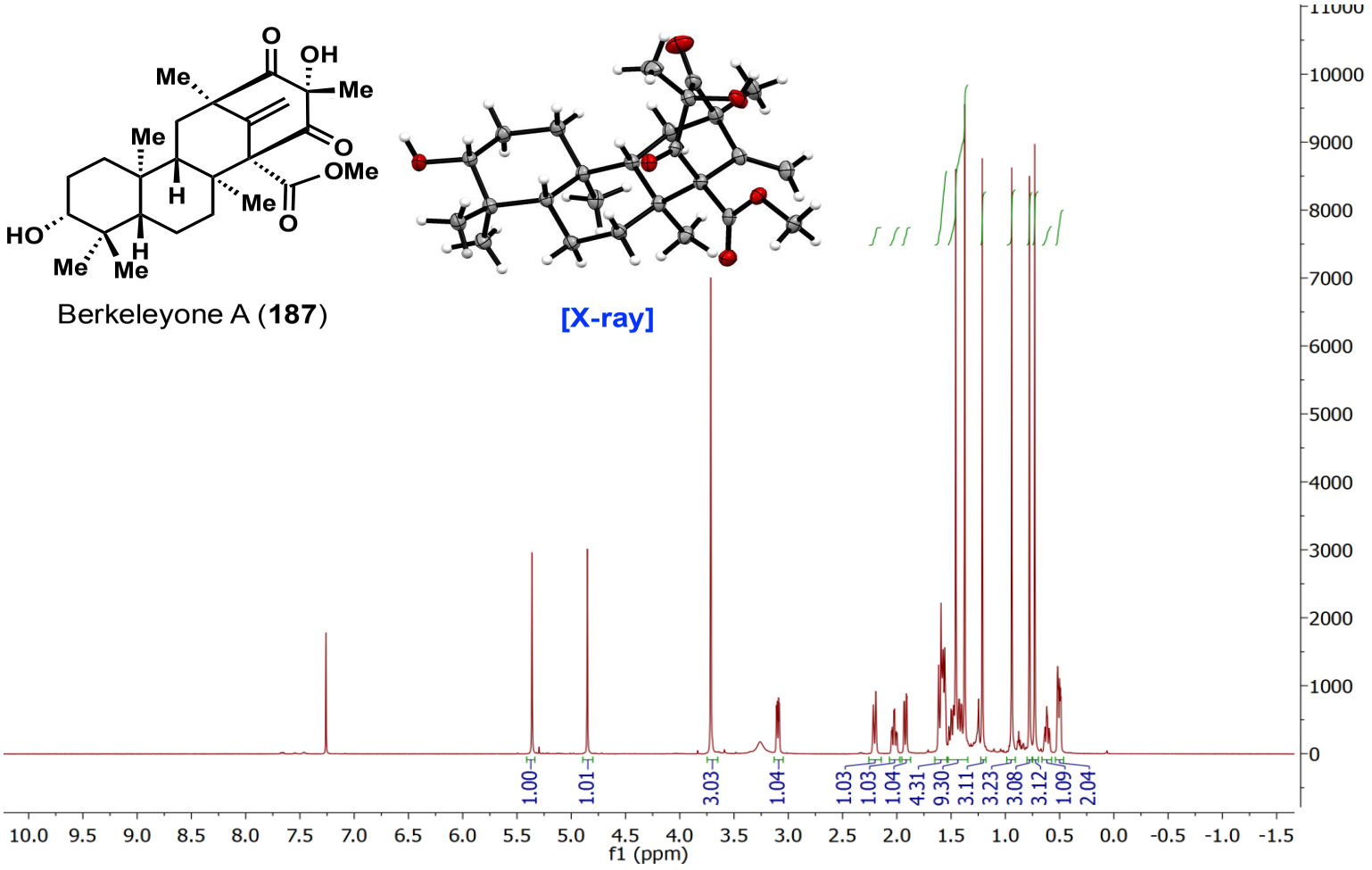

MeO
Me
Me
Me
O
OMe
Me
O
H
Me
TBSO
H
Me
Me
SI-6
197.42
175.50
170.74
149.47
120.88
107.65
79.09
77.48
77.16
76.84
73.35
62.04
55.14
51.56
51.51
45.08
42.95
39.55
38.75
37.47
33.71
32.68
28.33
27.75
26.04
21.23
18.74
18.24
17.34
16.24
16.09
10.52
-3.62
-4.75
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

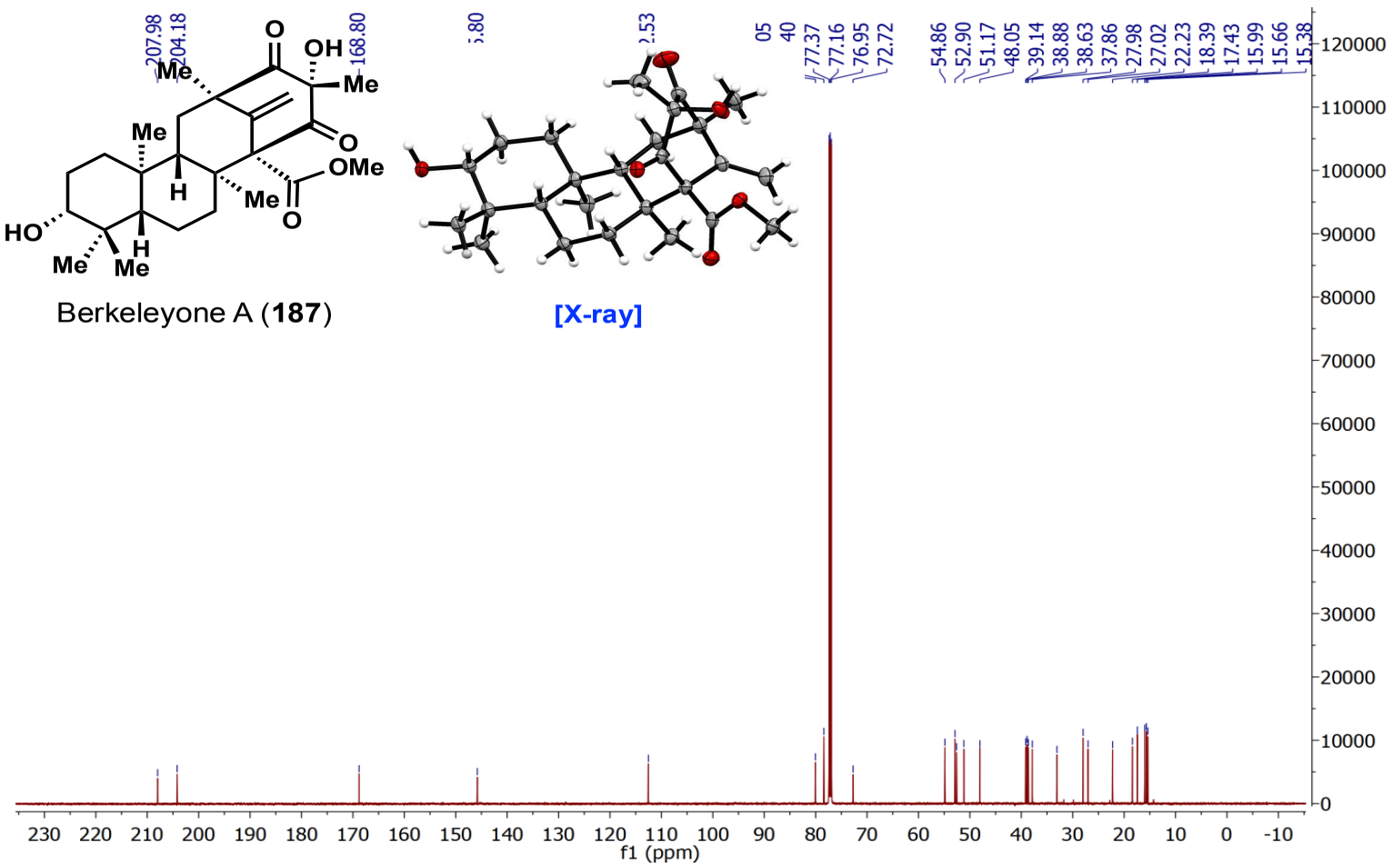

MeO
Me
Me
Me
O
OMe
H
Me
O
HO
H
Me
Me

221

1.03
1.03
3.00
3.12
1.03
1.03
3.09
1.15
5.64
5.82
3.08
1.08
3.23
3.17
5.36
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


MeO
Me
Me
Me
H
HO
Me
Me
H
O
OMe
Me
O
221
197.37
170.72
175.51
149.33
120.78
107.75
78.64
77.16
76.84
73.29
54.99
51.58
51.48
45.07
42.87
38.97
38.70
37.55
33.64
32.56
27.90
27.20
21.21
18.53
17.30
16.23
15.57
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Berkeleyone A (187)
[X-ray]
f1 (ppm)


Me
O
OH
Me
Me
O
OMe
H
Me
O
HO
H
Me
Me
Berkeleyone A (187)
[X-ray]
207.98
204.18
168.80
77.37
77.16
76.95
72.72
54.86
52.90
51.17
48.05
39.14
38.88
38.63
37.86
27.98
27.02
22.23
18.39
17.43
15.99
15.66
15.38
f1 (ppm)

Crystal Structure Determination of Compound 149

A colorless prism 0.070 x 0.040 x 0.040 mm in size was mounted on a Cryoloop with epoxy. Data were collected at 293(2) K using phi 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°. Data collection was 99.5% complete to 50.000° in q. A total of 12194 reflections were collected covering the indices, -7<=*h*<=7, -11<=*k*<=12, -12<=*l*<=10. 2293 reflections were found to be symmetry independent, with an R_{int} of 0.0280. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P -1 (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) 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.

Table 1. Crystal data and structure refinement for compound **149**.

X-ray ID	Compound **149**	
Sample/notebook ID	CT-04050-Pure	
Empirical formula	C24 H31 N O	
Formula weight	349.50	
Temperature	293(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.5112(4) Å	a= 95.972(3)°.
	b = 12.0900(7) Å	b= 97.780(3)°.
	c = 12.5602(6) Å	g = 102.322(3)°.
Volume	1093.60(10) $Å^3$	
Z	2	
Density (calculated)	1.061 Mg/m^3	
Absorption coefficient	0.486 mm^{-1}	
F(000)	380	
Crystal size	0.070 x 0.040 x 0.040 mm^3	
Crystal color/habit	colorless prism	
Theta range for data collection	3.586 to 50.701°.	
Index ranges	-7<=h<=7, -11<=k<=12, -12<=l<=10	
Reflections collected	12194	
Independent reflections	2293 [R(int) = 0.0280]	
Completeness to theta = 50.000°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.819	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2293 / 0 / 235	
Goodness-of-fit on F^2	1.068	
Final R indices [I>2sigma(I)]	R1 = 0.0697, wR2 = 0.2038	
R indices (all data)	R1 = 0.0813, wR2 = 0.2236	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.309 and -0.168 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **149**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8179(4)	9561(3)	5770(3)	94(1)
C(2)	7949(4)	10756(3)	5871(3)	90(1)
C(3)	8375(4)	11442(3)	6819(3)	91(1)
C(4)	7918(5)	12597(3)	7102(3)	112(1)
C(5)	7440(6)	12460(3)	8254(4)	128(1)
C(6)	8760(7)	11802(4)	8763(3)	127(1)
C(7)	9242(5)	11035(3)	7828(2)	96(1)
C(8)	8346(5)	9770(3)	7780(3)	98(1)
C(9)	8648(5)	9058(3)	6781(3)	97(1)
C(10)	7235(5)	11081(4)	4861(4)	112(1)
C(11)	6270(6)	12812(4)	6367(4)	147(2)
C(12)	9639(6)	13577(3)	7151(3)	127(1)
C(13)	10559(6)	13568(4)	6150(4)	138(2)
C(14)	12081(12)	14566(7)	6190(6)	225(4)
C(15)	13017(13)	15071(8)	5953(8)	259(5)
C(16)	7371(9)	13539(5)	8954(5)	173(2)
C(17)	6597(11)	13335(6)	9916(7)	222(3)
C(18)	7070(20)	13745(13)	10781(12)	429(12)
C(19)	11361(5)	11216(3)	7868(3)	106(1)
C(20)	12245(7)	10742(5)	8799(3)	133(2)
C(21)	13158(7)	9949(6)	8701(4)	154(2)
C(22)	7644(6)	7799(3)	6663(3)	123(1)
C(23)	8463(10)	7216(5)	7513(6)	173(2)
C(24)	7720(15)	6718(7)	8180(7)	244(4)
N(1)	6696(6)	11286(4)	4029(3)	153(2)
O(1)	7975(3)	9016(2)	4870(2)	117(1)

Table 3. Bond lengths [Å] and angles [°] for compound **149**.

C(1)-O(1)	1.221(4)
C(1)-C(2)	1.485(5)
C(1)-C(9)	1.495(5)
C(2)-C(3)	1.336(4)
C(2)-C(10)	1.436(6)
C(3)-C(7)	1.522(5)
C(3)-C(4)	1.526(5)
C(4)-C(11)	1.526(6)
C(4)-C(12)	1.546(5)
C(4)-C(5)	1.554(6)
C(5)-C(16)	1.510(6)
C(5)-C(6)	1.515(6)
C(5)-H(5)	0.9800
C(6)-C(7)	1.550(5)
C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700
C(7)-C(8)	1.525(5)
C(7)-C(19)	1.552(5)
C(8)-C(9)	1.518(5)
C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
C(9)-C(22)	1.530(5)
C(9)-H(9)	0.9800
C(10)-N(1)	1.140(5)
C(11)-H(11A)	0.9600
C(11)-H(11B)	0.9600
C(11)-H(11C)	0.9600
C(12)-C(13)	1.514(6)
C(12)-H(12A)	0.9700
C(12)-H(12B)	0.9700
C(13)-C(14)	1.466(8)
C(13)-H(13A)	0.9700
C(13)-H(13B)	0.9700
C(14)-C(15)	0.931(8)

C(14)-H(14)	0.9300
C(15)-H(15A)	0.9300
C(15)-H(15B)	0.9300
C(16)-C(17)	1.432(9)
C(16)-H(16A)	0.9700
C(16)-H(16B)	0.9700
C(17)-C(18)	1.122(12)
C(17)-H(17)	0.9300
C(18)-H(18A)	0.9300
C(18)-H(18B)	0.9300
C(19)-C(20)	1.493(6)
C(19)-H(19A)	0.9700
C(19)-H(19B)	0.9700
C(20)-C(21)	1.297(7)
C(20)-H(20)	0.9300
C(21)-H(21A)	0.9300
C(21)-H(21B)	0.9300
C(22)-C(23)	1.477(7)
C(22)-H(22A)	0.9700
C(22)-H(22B)	0.9700
C(23)-C(24)	1.210(9)
C(23)-H(23)	0.9300
C(24)-H(24A)	0.9300
C(24)-H(24B)	0.9300

O(1)-C(1)-C(2)	119.5(3)
O(1)-C(1)-C(9)	121.8(3)
C(2)-C(1)-C(9)	118.7(3)
C(3)-C(2)-C(10)	124.4(3)
C(3)-C(2)-C(1)	122.2(3)
C(10)-C(2)-C(1)	113.3(3)
C(2)-C(3)-C(7)	120.1(3)
C(2)-C(3)-C(4)	128.7(3)
C(7)-C(3)-C(4)	110.9(3)
C(3)-C(4)-C(11)	115.1(3)
C(3)-C(4)-C(12)	110.4(3)

C(11)-C(4)-C(12)	110.4(3)
C(3)-C(4)-C(5)	99.3(3)
C(11)-C(4)-C(5)	110.1(4)
C(12)-C(4)-C(5)	111.0(3)
C(16)-C(5)-C(6)	114.3(4)
C(16)-C(5)-C(4)	116.4(4)
C(6)-C(5)-C(4)	105.8(3)
C(16)-C(5)-H(5)	106.6
C(6)-C(5)-H(5)	106.6
C(4)-C(5)-H(5)	106.6
C(5)-C(6)-C(7)	107.2(3)
C(5)-C(6)-H(6A)	110.3
C(7)-C(6)-H(6A)	110.3
C(5)-C(6)-H(6B)	110.3
C(7)-C(6)-H(6B)	110.3
H(6A)-C(6)-H(6B)	108.5
C(3)-C(7)-C(8)	107.5(2)
C(3)-C(7)-C(6)	102.9(3)
C(8)-C(7)-C(6)	113.2(3)
C(3)-C(7)-C(19)	110.5(2)
C(8)-C(7)-C(19)	110.5(3)
C(6)-C(7)-C(19)	111.8(3)
C(9)-C(8)-C(7)	112.1(3)
C(9)-C(8)-H(8A)	109.2
C(7)-C(8)-H(8A)	109.2
C(9)-C(8)-H(8B)	109.2
C(7)-C(8)-H(8B)	109.2
H(8A)-C(8)-H(8B)	107.9
C(1)-C(9)-C(8)	111.8(3)
C(1)-C(9)-C(22)	110.9(3)
C(8)-C(9)-C(22)	113.5(3)
C(1)-C(9)-H(9)	106.8
C(8)-C(9)-H(9)	106.8
C(22)-C(9)-H(9)	106.8
N(1)-C(10)-C(2)	175.9(4)
C(4)-C(11)-H(11A)	109.5

C(4)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(4)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(13)-C(12)-C(4)	115.3(3)
C(13)-C(12)-H(12A)	108.5
C(4)-C(12)-H(12A)	108.5
C(13)-C(12)-H(12B)	108.5
C(4)-C(12)-H(12B)	108.5
H(12A)-C(12)-H(12B)	107.5
C(14)-C(13)-C(12)	113.5(4)
C(14)-C(13)-H(13A)	108.9
C(12)-C(13)-H(13A)	108.9
C(14)-C(13)-H(13B)	108.9
C(12)-C(13)-H(13B)	108.9
H(13A)-C(13)-H(13B)	107.7
C(15)-C(14)-C(13)	158.6(11)
C(15)-C(14)-H(14)	100.7
C(13)-C(14)-H(14)	100.7
C(14)-C(15)-H(15A)	120.0
C(14)-C(15)-H(15B)	120.0
H(15A)-C(15)-H(15B)	120.0
C(17)-C(16)-C(5)	113.6(5)
C(17)-C(16)-H(16A)	108.9
C(5)-C(16)-H(16A)	108.9
C(17)-C(16)-H(16B)	108.9
C(5)-C(16)-H(16B)	108.9
H(16A)-C(16)-H(16B)	107.7
C(18)-C(17)-C(16)	131.2(10)
C(18)-C(17)-H(17)	114.4
C(16)-C(17)-H(17)	114.4
C(17)-C(18)-H(18A)	120.0
C(17)-C(18)-H(18B)	120.0
H(18A)-C(18)-H(18B)	120.0
C(20)-C(19)-C(7)	112.2(3)

C(20)-C(19)-H(19A)	109.2
C(7)-C(19)-H(19A)	109.2
C(20)-C(19)-H(19B)	109.2
C(7)-C(19)-H(19B)	109.2
H(19A)-C(19)-H(19B)	107.9
C(21)-C(20)-C(19)	124.3(5)
C(21)-C(20)-H(20)	117.9
C(19)-C(20)-H(20)	117.9
C(20)-C(21)-H(21A)	120.0
C(20)-C(21)-H(21B)	120.0
H(21A)-C(21)-H(21B)	120.0
C(23)-C(22)-C(9)	111.2(4)
C(23)-C(22)-H(22A)	109.4
C(9)-C(22)-H(22A)	109.4
C(23)-C(22)-H(22B)	109.4
C(9)-C(22)-H(22B)	109.4
H(22A)-C(22)-H(22B)	108.0
C(24)-C(23)-C(22)	128.4(8)
C(24)-C(23)-H(23)	115.8
C(22)-C(23)-H(23)	115.8
C(23)-C(24)-H(24A)	120.0
C(23)-C(24)-H(24B)	120.0
H(24A)-C(24)-H(24B)	120.0

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for compound **149**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	81(2)	99(2)	89(2)	-6(2)	19(2)	-2(2)
C(2)	83(2)	95(2)	85(2)	6(2)	14(2)	5(2)
C(3)	85(2)	85(2)	94(2)	4(2)	27(2)	-3(2)
C(4)	110(3)	94(2)	123(3)	2(2)	30(2)	1(2)
C(5)	138(3)	95(3)	143(3)	-12(2)	56(3)	1(2)
C(6)	160(4)	107(3)	97(3)	-5(2)	43(2)	-10(3)
C(7)	103(2)	92(2)	78(2)	1(2)	22(2)	-6(2)
C(8)	95(2)	96(2)	94(2)	17(2)	20(2)	-2(2)
C(9)	93(2)	92(2)	94(2)	4(2)	12(2)	3(2)
C(10)	101(3)	127(3)	102(3)	10(2)	15(2)	17(2)
C(11)	127(3)	128(3)	186(4)	5(3)	23(3)	37(3)
C(12)	145(3)	88(2)	138(3)	9(2)	42(3)	0(2)
C(13)	148(4)	111(3)	146(3)	24(3)	46(3)	-10(3)
C(14)	253(8)	170(6)	211(6)	21(5)	101(6)	-75(6)
C(15)	220(8)	223(9)	290(10)	105(8)	11(7)	-64(6)
C(16)	210(5)	137(4)	168(5)	-26(3)	85(4)	18(4)
C(17)	247(7)	190(6)	201(6)	-84(5)	94(6)	5(5)
C(18)	430(20)	393(19)	359(16)	-182(14)	211(14)	-104(15)
C(19)	106(3)	111(3)	81(2)	10(2)	5(2)	-15(2)
C(20)	115(3)	168(4)	91(3)	16(3)	-2(2)	-9(3)
C(21)	107(3)	211(6)	125(4)	52(4)	-10(3)	-3(3)
C(22)	141(3)	91(3)	125(3)	12(2)	12(2)	6(2)
C(23)	210(6)	106(4)	193(6)	31(4)	33(5)	12(4)
C(24)	308(11)	158(6)	236(8)	57(6)	1(7)	-1(6)
N(1)	160(3)	194(4)	112(3)	26(3)	6(2)	62(3)
O(1)	129(2)	112(2)	94(2)	-11(1)	21(1)	3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **149**.

	x	y	z	U(eq)
H(5)	6202	11958	8152	154
H(6A)	8185	11336	9263	152
H(6B)	9870	12326	9160	152
H(8A)	8857	9493	8424	118
H(8B)	7030	9679	7778	118
H(9)	9972	9081	6865	116
H(11A)	5215	12195	6342	221
H(11B)	6558	12859	5649	221
H(11C)	6002	13517	6648	221
H(12A)	9282	14299	7275	152
H(12B)	10540	13542	7770	152
H(13A)	11027	12881	6063	166
H(13B)	9640	13538	5519	166
H(14)	12167	14912	6898	269
H(15A)	13255	14936	5250	311
H(15B)	13712	15711	6420	311
H(16A)	8614	14011	9160	208
H(16B)	6645	13963	8530	208
H(17)	5519	12762	9805	267
H(18A)	8133	14326	10963	515
H(18B)	6387	13505	11315	515
H(19A)	11603	10848	7196	128
H(19B)	11909	12027	7928	128
H(20)	12134	11034	9496	160
H(21A)	13294	9638	8015	185
H(21B)	13676	9691	9315	185
H(22A)	6351	7745	6712	148
H(22B)	7715	7422	5955	148
H(23)	9712	7234	7540	207
H(24A)	6472	6669	8196	293
H(24B)	8397	6383	8676	293

Crystal Structure Determination of Compound 156

A colorless plate 0.060 x 0.050 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 2.0°. Data collection was 99.9% complete to 67.000° in q. A total of 46194 reflections were collected covering the indices, -20<=*h*<=20, -7<=*k*<=7, -22<=*l*<=22. 3460 reflections were found to be symmetry independent, with an R_{int} of 0.0390. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/n (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) 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.

Table 1. Crystal data and structure refinement for compound **156**.

X-ray ID	Compound **156**	
Sample/notebook ID	CT-04111	
Empirical formula	C21 H30 O3	
Formula weight	330.45	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 16.7903(4) Å	a= 90°.
	b = 6.3161(2) Å	b= 109.1210(10)°.
	c = 18.8239(5) Å	g = 90°.
Volume	1886.12(9) $Å^3$	
Z	4	
Density (calculated)	1.164 Mg/m^3	
Absorption coefficient	0.598 mm^{-1}	
F(000)	720	
Crystal size	0.060 x 0.050 x 0.020 mm^3	
Theta range for data collection	3.066 to 68.444°.	
Index ranges	-20<=h<=20, -7<=k<=7, -22<=l<=22	
Reflections collected	46194	
Independent reflections	3460 [R(int) = 0.0390]	
Completeness to theta = 67.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.780	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3460 / 0 / 220	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2sigma(I)]	R1 = 0.0397, wR2 = 0.1020	
R indices (all data)	R1 = 0.0470, wR2 = 0.1078	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.399 and -0.277 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **156**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2638(1)	5595(2)	4849(1)	23(1)
C(2)	3486(1)	4887(2)	5403(1)	24(1)
C(3)	4142(1)	6590(2)	5619(1)	23(1)
C(4)	4111(1)	8371(2)	5218(1)	24(1)
C(5)	3378(1)	8864(2)	4575(1)	23(1)
C(6)	2744(1)	7109(2)	4233(1)	22(1)
C(7)	1850(1)	7945(2)	3874(1)	26(1)
C(8)	1505(1)	8299(2)	4528(1)	28(1)
C(9)	2027(1)	6828(2)	5192(1)	26(1)
C(10)	5384(1)	7696(2)	6587(1)	31(1)
C(11)	3096(1)	5949(2)	3671(1)	24(1)
C(12)	3075(1)	7229(2)	2992(1)	27(1)
C(13)	3721(1)	7546(2)	2758(1)	30(1)
C(14)	544(1)	8052(3)	4273(1)	45(1)
C(15)	116(1)	9481(4)	3631(1)	58(1)
C(16)	-382(1)	8814(6)	2978(1)	84(1)
C(17)	1497(1)	5245(3)	5468(1)	39(1)
C(18)	2526(1)	8227(2)	5863(1)	29(1)
C(19)	1999(1)	9446(2)	6250(1)	35(1)
C(20)	2506(1)	10855(3)	6872(1)	44(1)
C(21)	3324(1)	11150(4)	7092(1)	61(1)
O(1)	2175(1)	3765(2)	4493(1)	27(1)
O(2)	4749(1)	6111(2)	6266(1)	27(1)
O(3)	3284(1)	10651(2)	4294(1)	27(1)

Table 3. Bond lengths [Å] and angles [°] for compound **156**.

C(1)-O(1)	1.4307(16)
C(1)-C(2)	1.5302(19)
C(1)-C(6)	1.5580(18)
C(1)-C(9)	1.5831(18)
C(2)-C(3)	1.4975(19)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-O(2)	1.3425(17)
C(3)-C(4)	1.346(2)
C(4)-C(5)	1.4495(19)
C(4)-H(4)	0.9500
C(5)-O(3)	1.2350(16)
C(5)-C(6)	1.5247(19)
C(6)-C(7)	1.5243(19)
C(6)-C(11)	1.5536(18)
C(7)-C(8)	1.5392(19)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-C(14)	1.534(2)
C(8)-C(9)	1.5728(19)
C(8)-H(8)	1.0000
C(9)-C(17)	1.539(2)
C(9)-C(18)	1.544(2)
C(10)-O(2)	1.4431(17)
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-C(12)	1.5024(19)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.314(2)
C(12)-H(12)	0.9500
C(13)-H(13A)	0.9500
C(13)-H(13B)	0.9500

C(14)-C(15)	1.490(3)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(16)	1.309(3)
C(15)-H(15)	0.9500
C(16)-H(16A)	0.9500
C(16)-H(16B)	0.9500
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-C(19)	1.5258(19)
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-C(20)	1.496(2)
C(19)-H(19A)	0.9900
C(19)-H(19B)	0.9900
C(20)-C(21)	1.311(3)
C(20)-H(20)	0.9500
C(21)-H(21A)	0.9500
C(21)-H(21B)	0.9500
O(1)-H(1)	0.8400

O(1)-C(1)-C(2)	108.89(11)
O(1)-C(1)-C(6)	108.95(10)
C(2)-C(1)-C(6)	112.24(11)
O(1)-C(1)-C(9)	105.29(11)
C(2)-C(1)-C(9)	116.63(11)
C(6)-C(1)-C(9)	104.41(10)
C(3)-C(2)-C(1)	114.36(11)
C(3)-C(2)-H(2A)	108.7
C(1)-C(2)-H(2A)	108.7
C(3)-C(2)-H(2B)	108.7
C(1)-C(2)-H(2B)	108.7
H(2A)-C(2)-H(2B)	107.6
O(2)-C(3)-C(4)	125.11(13)
O(2)-C(3)-C(2)	110.95(12)

C(4)-C(3)-C(2)	123.93(13)
C(3)-C(4)-C(5)	120.90(13)
C(3)-C(4)-H(4)	119.5
C(5)-C(4)-H(4)	119.5
O(3)-C(5)-C(4)	120.55(13)
O(3)-C(5)-C(6)	120.66(12)
C(4)-C(5)-C(6)	118.73(12)
C(7)-C(6)-C(5)	112.62(11)
C(7)-C(6)-C(11)	113.58(11)
C(5)-C(6)-C(11)	105.23(10)
C(7)-C(6)-C(1)	101.89(11)
C(5)-C(6)-C(1)	111.46(11)
C(11)-C(6)-C(1)	112.28(11)
C(6)-C(7)-C(8)	105.63(11)
C(6)-C(7)-H(7A)	110.6
C(8)-C(7)-H(7A)	110.6
C(6)-C(7)-H(7B)	110.6
C(8)-C(7)-H(7B)	110.6
H(7A)-C(7)-H(7B)	108.7
C(14)-C(8)-C(7)	111.58(12)
C(14)-C(8)-C(9)	116.35(13)
C(7)-C(8)-C(9)	106.97(11)
C(14)-C(8)-H(8)	107.2
C(7)-C(8)-H(8)	107.2
C(9)-C(8)-H(8)	107.2
C(17)-C(9)-C(18)	108.27(12)
C(17)-C(9)-C(8)	114.79(13)
C(18)-C(9)-C(8)	108.88(11)
C(17)-C(9)-C(1)	109.98(11)
C(18)-C(9)-C(1)	111.41(11)
C(8)-C(9)-C(1)	103.51(10)
O(2)-C(10)-H(10A)	109.5
O(2)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
O(2)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5

H(10B)-C(10)-H(10C)	109.5
C(12)-C(11)-C(6)	114.64(11)
C(12)-C(11)-H(11A)	108.6
C(6)-C(11)-H(11A)	108.6
C(12)-C(11)-H(11B)	108.6
C(6)-C(11)-H(11B)	108.6
H(11A)-C(11)-H(11B)	107.6
C(13)-C(12)-C(11)	125.12(13)
C(13)-C(12)-H(12)	117.4
C(11)-C(12)-H(12)	117.4
C(12)-C(13)-H(13A)	120.0
C(12)-C(13)-H(13B)	120.0
H(13A)-C(13)-H(13B)	120.0
C(15)-C(14)-C(8)	111.80(16)
C(15)-C(14)-H(14A)	109.3
C(8)-C(14)-H(14A)	109.3
C(15)-C(14)-H(14B)	109.3
C(8)-C(14)-H(14B)	109.3
H(14A)-C(14)-H(14B)	107.9
C(16)-C(15)-C(14)	123.8(3)
C(16)-C(15)-H(15)	118.1
C(14)-C(15)-H(15)	118.1
C(15)-C(16)-H(16A)	120.0
C(15)-C(16)-H(16B)	120.0
H(16A)-C(16)-H(16B)	120.0
C(9)-C(17)-H(17A)	109.5
C(9)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(9)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(19)-C(18)-C(9)	115.83(13)
C(19)-C(18)-H(18A)	108.3
C(9)-C(18)-H(18A)	108.3
C(19)-C(18)-H(18B)	108.3
C(9)-C(18)-H(18B)	108.3

H(18A)-C(18)-H(18B)	107.4
C(20)-C(19)-C(18)	113.83(14)
C(20)-C(19)-H(19A)	108.8
C(18)-C(19)-H(19A)	108.8
C(20)-C(19)-H(19B)	108.8
C(18)-C(19)-H(19B)	108.8
H(19A)-C(19)-H(19B)	107.7
C(21)-C(20)-C(19)	126.90(16)
C(21)-C(20)-H(20)	116.6
C(19)-C(20)-H(20)	116.6
C(20)-C(21)-H(21A)	120.0
C(20)-C(21)-H(21B)	120.0
H(21A)-C(21)-H(21B)	120.0
C(1)-O(1)-H(1)	109.5
C(3)-O(2)-C(10)	117.47(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for compound **156**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	25(1)	18(1)	25(1)	0(1)	7(1)	-1(1)
C(2)	28(1)	19(1)	24(1)	1(1)	7(1)	0(1)
C(3)	24(1)	24(1)	21(1)	-3(1)	7(1)	2(1)
C(4)	26(1)	22(1)	24(1)	-4(1)	10(1)	-3(1)
C(5)	29(1)	19(1)	23(1)	-1(1)	14(1)	1(1)
C(6)	24(1)	20(1)	22(1)	1(1)	6(1)	1(1)
C(7)	25(1)	25(1)	28(1)	3(1)	8(1)	2(1)
C(8)	28(1)	25(1)	31(1)	1(1)	10(1)	4(1)
C(9)	28(1)	22(1)	31(1)	3(1)	13(1)	2(1)
C(10)	27(1)	33(1)	29(1)	-5(1)	3(1)	-4(1)
C(11)	26(1)	23(1)	22(1)	-2(1)	5(1)	2(1)
C(12)	29(1)	28(1)	21(1)	-1(1)	3(1)	5(1)
C(13)	33(1)	29(1)	27(1)	1(1)	7(1)	1(1)
C(14)	27(1)	68(1)	39(1)	1(1)	12(1)	7(1)
C(15)	36(1)	99(2)	39(1)	2(1)	12(1)	29(1)
C(16)	50(1)	158(3)	43(1)	-2(2)	14(1)	37(2)
C(17)	42(1)	28(1)	57(1)	6(1)	29(1)	1(1)
C(18)	35(1)	28(1)	26(1)	2(1)	13(1)	6(1)
C(19)	48(1)	29(1)	37(1)	4(1)	26(1)	6(1)
C(20)	69(1)	37(1)	36(1)	-4(1)	31(1)	7(1)
C(21)	68(1)	72(1)	43(1)	-28(1)	20(1)	-1(1)
O(1)	26(1)	20(1)	35(1)	-3(1)	7(1)	-2(1)
O(2)	26(1)	28(1)	23(1)	0(1)	2(1)	-2(1)
O(3)	36(1)	19(1)	29(1)	2(1)	14(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **156**.

	x	y	z	U(eq)
H(2A)	3393	4350	5864	28
H(2B)	3703	3698	5177	28
H(4)	4576	9318	5359	29
H(7A)	1500	6904	3512	31
H(7B)	1855	9290	3605	31
H(8)	1637	9796	4700	33
H(10A)	5702	7971	6243	46
H(10B)	5769	7188	7069	46
H(10C)	5113	9007	6667	46
H(11A)	3687	5530	3940	29
H(11B)	2766	4637	3500	29
H(12)	2553	7857	2710	32
H(13A)	4254	6945	3025	36
H(13B)	3656	8378	2322	36
H(14A)	393	6566	4120	53
H(14B)	342	8376	4699	53
H(15)	209	10961	3700	69
H(16A)	-487	7342	2893	101
H(16B)	-638	9801	2590	101
H(17A)	1869	4392	5878	58
H(17B)	1188	4315	5052	58
H(17C)	1096	6020	5650	58
H(18A)	2926	7313	6242	35
H(18B)	2862	9257	5684	35
H(19A)	1580	10319	5870	42
H(19B)	1685	8421	6455	42
H(20)	2203	11616	7137	53
H(21A)	3656	10427	6846	73
H(21B)	3583	12086	7496	73
H(1)	2502	2914	4385	41

Crystal Structure Determination of Compound 160

A colorless prism 0.120 x 0.060 x 0.040 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi 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°. Data collection was 98.6% complete to 67.000° in q. A total of 55760 reflections were collected covering the indices, -10<=*h*<=10, -14<=*k*<=14, -21<=*l*<=20. 6171 reflections were found to be symmetry independent, with an R_{int} of 0.0235. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P -1 (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) 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.

Table 1. Crystal data and structure refinement for compound **160**.

X-ray ID	Compound **160**	
Sample/notebook ID	CT-04125-Bot	
Empirical formula	C35 H38 N2 O12 S	
Formula weight	710.73	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.0393(2) Å	a= 71.6060(10)°.
	b = 12.1104(3) Å	b= 75.7210(10)°.
	c = 17.7713(5) Å	g = 69.6650(10)°.
Volume	1710.34(8) $Å^3$	
Z	2	
Density (calculated)	1.380 Mg/m^3	
Absorption coefficient	1.419 mm^{-1}	
F(000)	748	
Crystal size	0.120 x 0.060 x 0.040 mm^3	
Theta range for data collection	4.223 to 68.289°.	
Index ranges	-10<=h<=10, -14<=k<=14, -21<=l<=20	
Reflections collected	55760	
Independent reflections	6171 [R(int) = 0.0235]	
Completeness to theta = 67.000°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.807	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6171 / 0 / 454	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2sigma(I)]	R1 = 0.0331, wR2 = 0.0860	
R indices (all data)	R1 = 0.0350, wR2 = 0.0877	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.347 and -0.356 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **160**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2548(2)	7804(1)	2757(1)	16(1)
C(2)	3932(2)	8319(1)	2639(1)	17(1)
C(3)	5218(2)	8186(1)	1901(1)	17(1)
C(4)	6320(2)	6908(1)	1943(1)	17(1)
C(5)	7610(2)	6831(1)	1220(1)	18(1)
C(6)	8810(2)	7457(1)	1301(1)	20(1)
C(7)	7880(2)	8816(1)	1260(1)	20(1)
C(8)	6317(2)	8968(1)	1861(1)	19(1)
C(9)	4502(2)	8692(1)	1117(1)	19(1)
C(10)	5431(2)	8247(1)	426(1)	21(1)
C(11)	6869(2)	7401(1)	467(1)	21(1)
C(12)	7274(2)	7410(2)	-906(1)	33(1)
C(13)	9391(2)	6799(1)	2114(1)	23(1)
C(14)	10253(2)	7349(1)	623(1)	25(1)
C(15)	11206(2)	6047(1)	552(1)	29(1)
C(16)	12810(2)	5992(1)	45(1)	31(1)
C(17)	13269(2)	5675(1)	-641(1)	35(1)
C(18)	8877(2)	9509(1)	1417(1)	26(1)
C(19)	8019(2)	10836(1)	1339(1)	26(1)
C(20)	7600(2)	11371(1)	1931(1)	33(1)
C(21)	1194(2)	8409(1)	3324(1)	19(1)
C(22)	-766(2)	7800(1)	5034(1)	24(1)
C(23)	-891(2)	8683(1)	5404(1)	26(1)
C(24)	-280(2)	8330(1)	6112(1)	28(1)
C(25)	460(2)	7120(1)	6456(1)	28(1)
C(26)	598(2)	6251(1)	6062(1)	37(1)
C(27)	-11(2)	6581(2)	5358(1)	35(1)
C(28)	1094(2)	6761(2)	7233(1)	39(1)
C(29)	3369(2)	5726(1)	2706(1)	17(1)
C(30)	3895(2)	4446(1)	3202(1)	17(1)
C(31)	4563(2)	4174(1)	3890(1)	18(1)

C(32)	5124(2)	2964(1)	4288(1)	18(1)
C(33)	5004(2)	2015(1)	4055(1)	19(1)
C(34)	4283(2)	2333(1)	3384(1)	19(1)
C(35)	3758(2)	3522(1)	2941(1)	18(1)
N(1)	5911(1)	2666(1)	4991(1)	21(1)
N(2)	4070(1)	1356(1)	3132(1)	21(1)
O(1)	6277(1)	6046(1)	2516(1)	22(1)
O(2)	3201(1)	9470(1)	1090(1)	24(1)
O(3)	7821(1)	6944(1)	-140(1)	26(1)
O(4)	-46(1)	7811(1)	3509(1)	22(1)
O(5)	-2137(1)	9540(1)	3914(1)	34(1)
O(6)	-2545(1)	7528(1)	4181(1)	41(1)
O(7)	2977(1)	6513(1)	3158(1)	17(1)
O(8)	3310(1)	5985(1)	1999(1)	21(1)
O(9)	5768(2)	3492(1)	5281(1)	35(1)
O(10)	6676(1)	1610(1)	5240(1)	29(1)
O(11)	4445(1)	323(1)	3556(1)	28(1)
O(12)	3498(1)	1645(1)	2514(1)	30(1)
S(1)	-1552(1)	8243(1)	4136(1)	27(1)

Table 3. Bond lengths [Å] and angles [°] for compound **160**.

C(1)-O(7)	1.4539(15)
C(1)-C(21)	1.5115(18)
C(1)-C(2)	1.5258(17)
C(1)-H(1)	1.0000
C(2)-C(3)	1.5317(17)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.5121(18)
C(3)-C(9)	1.5376(18)
C(3)-C(8)	1.5696(17)
C(4)-O(1)	1.2105(16)
C(4)-C(5)	1.5104(18)
C(5)-C(11)	1.5012(19)
C(5)-C(6)	1.5782(18)
C(5)-H(5)	1.0000
C(6)-C(13)	1.535(2)
C(6)-C(14)	1.5420(18)
C(6)-C(7)	1.5537(18)
C(7)-C(8)	1.5394(18)
C(7)-C(18)	1.5469(19)
C(7)-H(7)	1.0000
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-O(2)	1.2254(17)
C(9)-C(10)	1.4495(19)
C(10)-C(11)	1.348(2)
C(10)-H(10)	0.9500
C(11)-O(3)	1.3411(17)
C(12)-O(3)	1.4393(18)
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800

C(13)-H(13C)	0.9800
C(14)-C(15)	1.540(2)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(16)	1.499(2)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-C(17)	1.318(2)
C(16)-H(16)	0.9500
C(17)-H(17A)	0.9500
C(17)-H(17B)	0.9500
C(18)-C(19)	1.500(2)
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-C(20)	1.318(2)
C(19)-H(19)	0.9500
C(20)-H(20A)	0.9500
C(20)-H(20B)	0.9500
C(21)-O(4)	1.4557(16)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-C(23)	1.384(2)
C(22)-C(27)	1.391(2)
C(22)-S(1)	1.7583(15)
C(23)-C(24)	1.382(2)
C(23)-H(23)	0.9500
C(24)-C(25)	1.387(2)
C(24)-H(24)	0.9500
C(25)-C(26)	1.393(2)
C(25)-C(28)	1.504(2)
C(26)-C(27)	1.378(2)
C(26)-H(26)	0.9500
C(27)-H(27)	0.9500
C(28)-H(28A)	0.9800
C(28)-H(28B)	0.9800
C(28)-H(28C)	0.9800

C(29)-O(8)	1.2051(16)
C(29)-O(7)	1.3360(16)
C(29)-C(30)	1.4961(18)
C(30)-C(35)	1.3906(18)
C(30)-C(31)	1.3918(19)
C(31)-C(32)	1.3824(19)
C(31)-H(31)	0.9500
C(32)-C(33)	1.3826(19)
C(32)-N(1)	1.4732(17)
C(33)-C(34)	1.383(2)
C(33)-H(33)	0.9500
C(34)-C(35)	1.3828(19)
C(34)-N(2)	1.4753(17)
C(35)-H(35)	0.9500
N(1)-O(9)	1.2190(16)
N(1)-O(10)	1.2207(15)
N(2)-O(11)	1.2181(15)
N(2)-O(12)	1.2279(16)
O(4)-S(1)	1.5795(10)
O(5)-S(1)	1.4267(12)
O(6)-S(1)	1.4219(12)

O(7)-C(1)-C(21)	105.55(10)
O(7)-C(1)-C(2)	110.92(10)
C(21)-C(1)-C(2)	107.91(10)
O(7)-C(1)-H(1)	110.8
C(21)-C(1)-H(1)	110.8
C(2)-C(1)-H(1)	110.8
C(1)-C(2)-C(3)	118.05(11)
C(1)-C(2)-H(2A)	107.8
C(3)-C(2)-H(2A)	107.8
C(1)-C(2)-H(2B)	107.8
C(3)-C(2)-H(2B)	107.8
H(2A)-C(2)-H(2B)	107.1
C(4)-C(3)-C(2)	114.58(11)
C(4)-C(3)-C(9)	110.06(11)

C(2)-C(3)-C(9)	112.09(11)
C(4)-C(3)-C(8)	105.37(10)
C(2)-C(3)-C(8)	106.77(10)
C(9)-C(3)-C(8)	107.46(10)
O(1)-C(4)-C(5)	122.37(12)
O(1)-C(4)-C(3)	124.66(12)
C(5)-C(4)-C(3)	112.71(11)
C(11)-C(5)-C(4)	109.66(11)
C(11)-C(5)-C(6)	114.51(11)
C(4)-C(5)-C(6)	106.23(10)
C(11)-C(5)-H(5)	108.8
C(4)-C(5)-H(5)	108.8
C(6)-C(5)-H(5)	108.8
C(13)-C(6)-C(14)	109.38(11)
C(13)-C(6)-C(7)	111.33(11)
C(14)-C(6)-C(7)	110.42(11)
C(13)-C(6)-C(5)	107.45(11)
C(14)-C(6)-C(5)	110.81(11)
C(7)-C(6)-C(5)	107.39(10)
C(8)-C(7)-C(18)	108.03(11)
C(8)-C(7)-C(6)	112.19(11)
C(18)-C(7)-C(6)	112.61(11)
C(8)-C(7)-H(7)	107.9
C(18)-C(7)-H(7)	107.9
C(6)-C(7)-H(7)	107.9
C(7)-C(8)-C(3)	117.25(11)
C(7)-C(8)-H(8A)	108.0
C(3)-C(8)-H(8A)	108.0
C(7)-C(8)-H(8B)	108.0
C(3)-C(8)-H(8B)	108.0
H(8A)-C(8)-H(8B)	107.2
O(2)-C(9)-C(10)	122.35(13)
O(2)-C(9)-C(3)	119.68(12)
C(10)-C(9)-C(3)	117.95(11)
C(11)-C(10)-C(9)	121.37(13)
C(11)-C(10)-H(10)	119.3

C(9)-C(10)-H(10)	119.3
O(3)-C(11)-C(10)	125.74(13)
O(3)-C(11)-C(5)	110.73(12)
C(10)-C(11)-C(5)	123.53(12)
O(3)-C(12)-H(12A)	109.5
O(3)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
O(3)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(6)-C(13)-H(13A)	109.5
C(6)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(6)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(15)-C(14)-C(6)	115.87(12)
C(15)-C(14)-H(14A)	108.3
C(6)-C(14)-H(14A)	108.3
C(15)-C(14)-H(14B)	108.3
C(6)-C(14)-H(14B)	108.3
H(14A)-C(14)-H(14B)	107.4
C(16)-C(15)-C(14)	112.10(12)
C(16)-C(15)-H(15A)	109.2
C(14)-C(15)-H(15A)	109.2
C(16)-C(15)-H(15B)	109.2
C(14)-C(15)-H(15B)	109.2
H(15A)-C(15)-H(15B)	107.9
C(17)-C(16)-C(15)	124.91(16)
C(17)-C(16)-H(16)	117.5
C(15)-C(16)-H(16)	117.5
C(16)-C(17)-H(17A)	120.0
C(16)-C(17)-H(17B)	120.0
H(17A)-C(17)-H(17B)	120.0
C(19)-C(18)-C(7)	113.00(12)
C(19)-C(18)-H(18A)	109.0

C(7)-C(18)-H(18A)	109.0
C(19)-C(18)-H(18B)	109.0
C(7)-C(18)-H(18B)	109.0
H(18A)-C(18)-H(18B)	107.8
C(20)-C(19)-C(18)	124.48(15)
C(20)-C(19)-H(19)	117.8
C(18)-C(19)-H(19)	117.8
C(19)-C(20)-H(20A)	120.0
C(19)-C(20)-H(20B)	120.0
H(20A)-C(20)-H(20B)	120.0
O(4)-C(21)-C(1)	107.56(10)
O(4)-C(21)-H(21A)	110.2
C(1)-C(21)-H(21A)	110.2
O(4)-C(21)-H(21B)	110.2
C(1)-C(21)-H(21B)	110.2
H(21A)-C(21)-H(21B)	108.5
C(23)-C(22)-C(27)	120.67(14)
C(23)-C(22)-S(1)	119.00(12)
C(27)-C(22)-S(1)	120.32(12)
C(24)-C(23)-C(22)	118.80(14)
C(24)-C(23)-H(23)	120.6
C(22)-C(23)-H(23)	120.6
C(23)-C(24)-C(25)	121.79(14)
C(23)-C(24)-H(24)	119.1
C(25)-C(24)-H(24)	119.1
C(24)-C(25)-C(26)	118.29(15)
C(24)-C(25)-C(28)	120.60(14)
C(26)-C(25)-C(28)	121.12(14)
C(27)-C(26)-C(25)	120.93(15)
C(27)-C(26)-H(26)	119.5
C(25)-C(26)-H(26)	119.5
C(26)-C(27)-C(22)	119.52(14)
C(26)-C(27)-H(27)	120.2
C(22)-C(27)-H(27)	120.2
C(25)-C(28)-H(28A)	109.5
C(25)-C(28)-H(28B)	109.5

H(28A)-C(28)-H(28B)	109.5
C(25)-C(28)-H(28C)	109.5
H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5
O(8)-C(29)-O(7)	125.92(12)
O(8)-C(29)-C(30)	123.55(12)
O(7)-C(29)-C(30)	110.53(11)
C(35)-C(30)-C(31)	120.52(12)
C(35)-C(30)-C(29)	118.15(12)
C(31)-C(30)-C(29)	121.27(12)
C(32)-C(31)-C(30)	118.17(12)
C(32)-C(31)-H(31)	120.9
C(30)-C(31)-H(31)	120.9
C(31)-C(32)-C(33)	123.38(13)
C(31)-C(32)-N(1)	118.43(12)
C(33)-C(32)-N(1)	118.19(12)
C(32)-C(33)-C(34)	116.33(12)
C(32)-C(33)-H(33)	121.8
C(34)-C(33)-H(33)	121.8
C(35)-C(34)-C(33)	122.99(12)
C(35)-C(34)-N(2)	118.74(12)
C(33)-C(34)-N(2)	118.26(12)
C(34)-C(35)-C(30)	118.52(12)
C(34)-C(35)-H(35)	120.7
C(30)-C(35)-H(35)	120.7
O(9)-N(1)-O(10)	124.28(12)
O(9)-N(1)-C(32)	117.91(11)
O(10)-N(1)-C(32)	117.81(11)
O(11)-N(2)-O(12)	124.45(12)
O(11)-N(2)-C(34)	118.04(11)
O(12)-N(2)-C(34)	117.50(11)
C(11)-O(3)-C(12)	117.24(11)
C(21)-O(4)-S(1)	116.71(8)
C(29)-O(7)-C(1)	117.70(10)
O(6)-S(1)-O(5)	120.29(8)
O(6)-S(1)-O(4)	103.89(6)

O(5)-S(1)-O(4)	109.11(6)
O(6)-S(1)-C(22)	110.64(7)
O(5)-S(1)-C(22)	108.12(7)
O(4)-S(1)-C(22)	103.44(6)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for compound **160**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	17(1)	15(1)	16(1)	-3(1)	-3(1)	-5(1)
C(2)	17(1)	19(1)	17(1)	-6(1)	-3(1)	-6(1)
C(3)	16(1)	18(1)	18(1)	-4(1)	-2(1)	-6(1)
C(4)	15(1)	20(1)	19(1)	-5(1)	-6(1)	-7(1)
C(5)	17(1)	17(1)	21(1)	-5(1)	-3(1)	-4(1)
C(6)	16(1)	19(1)	24(1)	-6(1)	-1(1)	-6(1)
C(7)	18(1)	20(1)	23(1)	-5(1)	-1(1)	-8(1)
C(8)	18(1)	19(1)	23(1)	-6(1)	-1(1)	-8(1)
C(9)	19(1)	18(1)	20(1)	-1(1)	-3(1)	-8(1)
C(10)	24(1)	24(1)	16(1)	-3(1)	-6(1)	-7(1)
C(11)	24(1)	21(1)	18(1)	-6(1)	-1(1)	-9(1)
C(12)	41(1)	36(1)	19(1)	-10(1)	-4(1)	-5(1)
C(13)	18(1)	24(1)	29(1)	-6(1)	-7(1)	-6(1)
C(14)	20(1)	24(1)	29(1)	-7(1)	3(1)	-8(1)
C(15)	23(1)	25(1)	34(1)	-9(1)	2(1)	-6(1)
C(16)	23(1)	29(1)	36(1)	-9(1)	-4(1)	-4(1)
C(17)	32(1)	30(1)	36(1)	-10(1)	2(1)	-5(1)
C(18)	20(1)	25(1)	35(1)	-10(1)	1(1)	-11(1)
C(19)	24(1)	24(1)	32(1)	-5(1)	1(1)	-14(1)
C(20)	36(1)	25(1)	37(1)	-8(1)	-1(1)	-11(1)
C(21)	16(1)	20(1)	23(1)	-7(1)	-2(1)	-7(1)
C(22)	21(1)	29(1)	22(1)	-8(1)	4(1)	-11(1)
C(23)	25(1)	23(1)	29(1)	-7(1)	-3(1)	-5(1)
C(24)	30(1)	26(1)	31(1)	-12(1)	-4(1)	-7(1)
C(25)	27(1)	28(1)	25(1)	-7(1)	1(1)	-7(1)
C(26)	53(1)	22(1)	28(1)	-5(1)	-3(1)	-6(1)
C(27)	52(1)	26(1)	30(1)	-12(1)	1(1)	-14(1)
C(28)	44(1)	36(1)	31(1)	-9(1)	-10(1)	0(1)
C(29)	12(1)	21(1)	20(1)	-7(1)	-3(1)	-5(1)
C(30)	14(1)	20(1)	17(1)	-6(1)	-1(1)	-6(1)
C(31)	18(1)	20(1)	18(1)	-7(1)	-1(1)	-8(1)

C(32)	17(1)	22(1)	16(1)	-5(1)	-2(1)	-7(1)
C(33)	17(1)	18(1)	19(1)	-4(1)	-1(1)	-5(1)
C(34)	17(1)	21(1)	21(1)	-10(1)	0(1)	-7(1)
C(35)	15(1)	23(1)	17(1)	-7(1)	-2(1)	-6(1)
N(1)	25(1)	21(1)	19(1)	-4(1)	-6(1)	-9(1)
N(2)	21(1)	20(1)	25(1)	-10(1)	-3(1)	-6(1)
O(1)	18(1)	20(1)	24(1)	1(1)	-4(1)	-6(1)
O(2)	20(1)	24(1)	23(1)	-2(1)	-5(1)	-2(1)
O(3)	29(1)	28(1)	19(1)	-9(1)	-2(1)	-4(1)
O(4)	17(1)	30(1)	23(1)	-11(1)	2(1)	-11(1)
O(5)	24(1)	41(1)	31(1)	-13(1)	-5(1)	4(1)
O(6)	28(1)	73(1)	36(1)	-24(1)	8(1)	-30(1)
O(7)	19(1)	16(1)	16(1)	-4(1)	-2(1)	-6(1)
O(8)	22(1)	24(1)	18(1)	-7(1)	-6(1)	-3(1)
O(9)	57(1)	26(1)	32(1)	-8(1)	-24(1)	-11(1)
O(10)	36(1)	22(1)	28(1)	-2(1)	-15(1)	-3(1)
O(11)	32(1)	20(1)	36(1)	-8(1)	-10(1)	-8(1)
O(12)	42(1)	30(1)	28(1)	-11(1)	-14(1)	-12(1)
S(1)	17(1)	41(1)	24(1)	-13(1)	2(1)	-10(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **160**.

	x	y	z	U(eq)
H(1)	2201	7952	2232	20
H(2A)	4464	7926	3121	21
H(2B)	3477	9197	2618	21
H(5)	8186	5954	1242	22
H(7)	7599	9213	707	24
H(8A)	5685	9836	1730	23
H(8B)	6593	8772	2403	23
H(10)	5018	8556	-66	26
H(12A)	6256	7253	-854	50
H(12B)	8067	7005	-1297	50
H(12C)	7128	8288	-1090	50
H(13A)	9715	5917	2180	35
H(13B)	8525	7017	2547	35
H(13C)	10304	7042	2135	35
H(14A)	9866	7823	106	30
H(14B)	10989	7730	704	30
H(15A)	11351	5508	1095	34
H(15B)	10590	5743	315	34
H(16)	13551	6201	231	37
H(17A)	12561	5460	-846	42
H(17B)	14308	5662	-929	42
H(18A)	9157	9132	1964	31
H(18B)	9885	9425	1032	31
H(19)	7758	11324	826	31
H(20A)	7842	10910	2451	40
H(20B)	7057	12217	1839	40
H(21A)	1575	8325	3821	23
H(21B)	769	9286	3069	23
H(23)	-1389	9517	5177	32
H(24)	-368	8933	6371	34

H(26)	1120	5419	6282	44
H(27)	84	5981	5097	42
H(28A)	1243	7472	7321	59
H(28B)	2120	6124	7208	59
H(28C)	332	6452	7676	59
H(31)	4632	4802	4080	21
H(33)	5396	1191	4340	22
H(35)	3314	3704	2469	22

Crystal Structure Determination of Compound 164

A colorless rod 0.120 x 0.100 x 0.100 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 1.0°. Data collection was 99.9% complete to 67.000° in q. A total of 37094 reflections were collected covering the indices, -23<=*h*<=34, -11<=*k*<=11, -24<=*l*<=18. 4776 reflections were found to be symmetry independent, with an R_{int} of 0.0324. Indexing and unit cell refinement indicated a C-centered, monoclinic lattice. The space group was found to be C 2/c (No. 15). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) 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.

Table 1. Crystal data and structure refinement for compound **164**.

X-ray ID	Compound **164**	
Sample/notebook ID	Cpting-OTs	
Empirical formula	C28 H35 O6 S	
Formula weight	499.62	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 28.8584(12) Å	a= 90°.
	b = 9.7386(4) Å	b= 115.629(2)°.
	c = 20.6270(9) Å	g = 90°.
Volume	5226.7(4) $Å^3$	
Z	8	
Density (calculated)	1.270 Mg/m^3	
Absorption coefficient	1.429 mm^{-1}	
F(000)	2136	
Crystal size	0.120 x 0.100 x 0.100 mm^3	
Theta range for data collection	3.397 to 68.256°.	
Index ranges	-23<=h<=34, -11<=k<=11, -24<=l<=18	
Reflections collected	37094	
Independent reflections	4776 [R(int) = 0.0324]	
Completeness to theta = 67.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.836	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4776 / 0 / 318	
Goodness-of-fit on F^2	1.069	
Final R indices [I>2sigma(I)]	R1 = 0.0963, wR2 = 0.2734	
R indices (all data)	R1 = 0.1024, wR2 = 0.2809	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.540 and -0.570 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **164**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5935(2)	2243(5)	4771(2)	53(1)
C(2)	5716(2)	845(6)	4473(3)	63(1)
C(3)	5832(2)	-143(6)	5115(3)	67(1)
C(4)	6242(2)	618(5)	5799(2)	50(1)
C(5)	6415(2)	1847(4)	5470(2)	46(1)
C(6)	6648(2)	3049(4)	5987(2)	44(1)
C(7)	6264(2)	4079(5)	6004(2)	50(1)
C(8)	5769(2)	4115(5)	5515(3)	56(1)
C(9)	5561(2)	3141(6)	4935(3)	60(1)
C(10)	6072(2)	3119(5)	4246(2)	58(1)
C(11)	5658(2)	3247(5)	3506(3)	61(1)
C(12)	5741(3)	2800(8)	2955(4)	90(2)
C(13)	5986(2)	-1620(6)	4950(3)	70(1)
C(14)	5614(4)	-2481(12)	4465(7)	79(3)
C(15)	5596(4)	-2983(12)	3872(6)	90(4)
C(14A)	5503(7)	-2060(20)	4191(11)	73(5)
C(15A)	5280(9)	-3220(20)	4121(12)	97(7)
C(16)	6710(2)	-279(5)	6257(3)	58(1)
C(17)	5998(2)	1090(5)	6298(3)	57(1)
C(18)	5854(2)	-50(6)	6691(3)	73(2)
C(19)	5549(4)	409(11)	7021(7)	48(3)
C(20)	5717(7)	455(19)	7714(10)	105(6)
C(19A)	5668(6)	656(19)	7264(9)	86(4)
C(20A)	5653(7)	1920(20)	7436(11)	136(8)
C(21)	7749(1)	5540(4)	6280(2)	37(1)
C(22)	7676(2)	6358(4)	6780(2)	44(1)
C(23)	7783(2)	7733(4)	6810(2)	45(1)
C(24)	7960(1)	8324(4)	6356(2)	42(1)
C(25)	8031(2)	7495(4)	5856(2)	49(1)
C(26)	7928(2)	6107(4)	5814(2)	44(1)
C(27)	8069(2)	9843(4)	6386(3)	57(1)

C(28)	6179(2)	5944(6)	6692(3)	69(1)
O(1)	6801(1)	1270(3)	5292(2)	46(1)
O(2)	6988(1)	3843(3)	5757(2)	44(1)
O(3)	7708(1)	3241(3)	6906(2)	45(1)
O(4)	7794(1)	3136(3)	5771(2)	50(1)
O(5)	6492(1)	4915(3)	6584(2)	54(1)
O(6)	5101(1)	3075(5)	4550(2)	78(1)
S(1)	7601(1)	3791(1)	6218(1)	41(1)

Table 3. Bond lengths [Å] and angles [°] for compound **164**.

C(1)-C(2)	1.514(7)
C(1)-C(9)	1.537(6)
C(1)-C(5)	1.555(6)
C(1)-C(10)	1.557(6)
C(2)-C(3)	1.551(8)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.582(7)
C(3)-C(13)	1.585(8)
C(3)-H(3)	1.0000
C(4)-C(16)	1.540(6)
C(4)-C(17)	1.548(6)
C(4)-C(5)	1.560(6)
C(5)-O(1)	1.431(4)
C(5)-C(6)	1.529(6)
C(6)-O(2)	1.481(4)
C(6)-C(7)	1.506(6)
C(6)-H(6)	1.0000
C(7)-C(8)	1.346(7)
C(7)-O(5)	1.359(6)
C(8)-C(9)	1.440(7)
C(8)-H(8)	0.9500
C(9)-O(6)	1.219(6)
C(10)-C(11)	1.482(7)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.332(8)
C(11)-H(11)	0.9500
C(12)-H(12A)	0.9500
C(12)-H(12B)	0.9500
C(13)-C(14)	1.388(12)
C(13)-C(14A)	1.639(19)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900

C(14)-C(15)	1.297(15)
C(14)-H(14)	0.9500
C(15)-H(15A)	0.9500
C(15)-H(15B)	0.9500
C(14A)-C(15A)	1.28(3)
C(14A)-H(14A)	0.9500
C(15A)-H(15C)	0.9500
C(15A)-H(15D)	0.9500
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(17)-C(18)	1.533(6)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(18)-C(19)	1.398(11)
C(18)-C(19A)	1.645(18)
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-C(20)	1.30(2)
C(19)-H(19)	0.9500
C(20)-H(20A)	0.9500
C(20)-H(20B)	0.9500
C(19A)-C(20A)	1.28(3)
C(19A)-H(19A)	0.9500
C(20A)-H(20C)	0.9500
C(20A)-H(20D)	0.9500
C(21)-C(26)	1.387(5)
C(21)-C(22)	1.390(5)
C(21)-S(1)	1.748(4)
C(22)-C(23)	1.370(6)
C(22)-H(22)	0.9500
C(23)-C(24)	1.374(6)
C(23)-H(23)	0.9500
C(24)-C(25)	1.391(6)
C(24)-C(27)	1.508(5)
C(25)-C(26)	1.379(6)

C(25)-H(25)	0.9500
C(26)-H(26)	0.9500
C(27)-H(27A)	0.9800
C(27)-H(27B)	0.9800
C(27)-H(27C)	0.9800
C(28)-O(5)	1.430(5)
C(28)-H(28A)	0.9800
C(28)-H(28B)	0.9800
C(28)-H(28C)	0.9800
O(1)-H(1)	0.8400
O(2)-S(1)	1.605(3)
O(3)-S(1)	1.420(3)
O(4)-S(1)	1.418(3)

C(2)-C(1)-C(9)	113.0(4)
C(2)-C(1)-C(5)	101.6(4)
C(9)-C(1)-C(5)	111.5(4)
C(2)-C(1)-C(10)	113.4(4)
C(9)-C(1)-C(10)	104.8(4)
C(5)-C(1)-C(10)	112.9(3)
C(1)-C(2)-C(3)	108.3(4)
C(1)-C(2)-H(2A)	110.0
C(3)-C(2)-H(2A)	110.0
C(1)-C(2)-H(2B)	110.0
C(3)-C(2)-H(2B)	110.0
H(2A)-C(2)-H(2B)	108.4
C(2)-C(3)-C(4)	105.8(4)
C(2)-C(3)-C(13)	110.9(4)
C(4)-C(3)-C(13)	116.4(4)
C(2)-C(3)-H(3)	107.8
C(4)-C(3)-H(3)	107.8
C(13)-C(3)-H(3)	107.8
C(16)-C(4)-C(17)	106.9(4)
C(16)-C(4)-C(5)	110.0(3)
C(17)-C(4)-C(5)	112.6(4)
C(16)-C(4)-C(3)	113.6(4)

C(17)-C(4)-C(3)	110.6(3)
C(5)-C(4)-C(3)	103.2(4)
O(1)-C(5)-C(6)	108.9(3)
O(1)-C(5)-C(1)	109.8(3)
C(6)-C(5)-C(1)	113.8(3)
O(1)-C(5)-C(4)	103.9(3)
C(6)-C(5)-C(4)	114.2(3)
C(1)-C(5)-C(4)	105.7(3)
O(2)-C(6)-C(7)	104.9(3)
O(2)-C(6)-C(5)	109.2(3)
C(7)-C(6)-C(5)	114.9(3)
O(2)-C(6)-H(6)	109.3
C(7)-C(6)-H(6)	109.3
C(5)-C(6)-H(6)	109.3
C(8)-C(7)-O(5)	126.8(4)
C(8)-C(7)-C(6)	123.6(4)
O(5)-C(7)-C(6)	109.7(4)
C(7)-C(8)-C(9)	122.1(4)
C(7)-C(8)-H(8)	119.0
C(9)-C(8)-H(8)	119.0
O(6)-C(9)-C(8)	121.3(4)
O(6)-C(9)-C(1)	120.0(5)
C(8)-C(9)-C(1)	118.6(4)
C(11)-C(10)-C(1)	115.4(4)
C(11)-C(10)-H(10A)	108.4
C(1)-C(10)-H(10A)	108.4
C(11)-C(10)-H(10B)	108.4
C(1)-C(10)-H(10B)	108.4
H(10A)-C(10)-H(10B)	107.5
C(12)-C(11)-C(10)	119.3(5)
C(12)-C(11)-H(11)	120.3
C(10)-C(11)-H(11)	120.3
C(11)-C(12)-H(12A)	120.0
C(11)-C(12)-H(12B)	120.0
H(12A)-C(12)-H(12B)	120.0
C(14)-C(13)-C(3)	120.1(7)

C(3)-C(13)-C(14A)	103.9(8)
C(14)-C(13)-H(13A)	107.3
C(3)-C(13)-H(13A)	107.3
C(14)-C(13)-H(13B)	107.3
C(3)-C(13)-H(13B)	107.3
H(13A)-C(13)-H(13B)	106.9
C(15)-C(14)-C(13)	127.6(10)
C(15)-C(14)-H(14)	116.2
C(13)-C(14)-H(14)	116.2
C(14)-C(15)-H(15A)	120.0
C(14)-C(15)-H(15B)	120.0
H(15A)-C(15)-H(15B)	120.0
C(15A)-C(14A)-C(13)	121(2)
C(15A)-C(14A)-H(14A)	119.4
C(13)-C(14A)-H(14A)	119.4
C(14A)-C(15A)-H(15C)	120.0
C(14A)-C(15A)-H(15D)	120.0
H(15C)-C(15A)-H(15D)	120.0
C(4)-C(16)-H(16A)	109.5
C(4)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(4)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(18)-C(17)-C(4)	116.2(4)
C(18)-C(17)-H(17A)	108.2
C(4)-C(17)-H(17A)	108.2
C(18)-C(17)-H(17B)	108.2
C(4)-C(17)-H(17B)	108.2
H(17A)-C(17)-H(17B)	107.4
C(19)-C(18)-C(17)	113.4(6)
C(17)-C(18)-C(19A)	108.9(8)
C(19)-C(18)-H(18A)	108.9
C(17)-C(18)-H(18A)	108.9
C(19)-C(18)-H(18B)	108.9
C(17)-C(18)-H(18B)	108.9

H(18A)-C(18)-H(18B)	107.7
C(20)-C(19)-C(18)	122.2(12)
C(20)-C(19)-H(19)	118.9
C(18)-C(19)-H(19)	118.9
C(19)-C(20)-H(20A)	120.0
C(19)-C(20)-H(20B)	120.0
H(20A)-C(20)-H(20B)	120.0
C(20A)-C(19A)-C(18)	131.3(17)
C(20A)-C(19A)-H(19A)	114.4
C(18)-C(19A)-H(19A)	114.4
C(19A)-C(20A)-H(20C)	120.0
C(19A)-C(20A)-H(20D)	120.0
H(20C)-C(20A)-H(20D)	120.0
C(26)-C(21)-C(22)	120.5(3)
C(26)-C(21)-S(1)	119.4(3)
C(22)-C(21)-S(1)	120.1(3)
C(23)-C(22)-C(21)	119.3(4)
C(23)-C(22)-H(22)	120.3
C(21)-C(22)-H(22)	120.3
C(22)-C(23)-C(24)	121.5(4)
C(22)-C(23)-H(23)	119.3
C(24)-C(23)-H(23)	119.3
C(23)-C(24)-C(25)	118.6(4)
C(23)-C(24)-C(27)	121.0(4)
C(25)-C(24)-C(27)	120.4(4)
C(26)-C(25)-C(24)	121.3(4)
C(26)-C(25)-H(25)	119.4
C(24)-C(25)-H(25)	119.4
C(25)-C(26)-C(21)	118.8(4)
C(25)-C(26)-H(26)	120.6
C(21)-C(26)-H(26)	120.6
C(24)-C(27)-H(27A)	109.5
C(24)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5
C(24)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5

H(27B)-C(27)-H(27C)	109.5
O(5)-C(28)-H(28A)	109.5
O(5)-C(28)-H(28B)	109.5
H(28A)-C(28)-H(28B)	109.5
O(5)-C(28)-H(28C)	109.5
H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5
C(5)-O(1)-H(1)	109.5
C(6)-O(2)-S(1)	120.5(2)
C(7)-O(5)-C(28)	117.2(4)
O(4)-S(1)-O(3)	120.19(18)
O(4)-S(1)-O(2)	105.69(17)
O(3)-S(1)-O(2)	108.20(15)
O(4)-S(1)-C(21)	109.43(16)
O(3)-S(1)-C(21)	110.76(18)
O(2)-S(1)-C(21)	100.65(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for compound **164**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	41(2)	66(3)	60(2)	-2(2)	29(2)	2(2)
C(2)	40(2)	77(3)	69(3)	-8(2)	21(2)	-1(2)
C(3)	53(3)	81(3)	84(3)	-14(3)	46(3)	-21(2)
C(4)	39(2)	50(2)	69(3)	2(2)	31(2)	-5(2)
C(5)	37(2)	47(2)	62(2)	4(2)	30(2)	2(2)
C(6)	42(2)	44(2)	57(2)	8(2)	33(2)	2(2)
C(7)	56(2)	47(2)	62(2)	9(2)	41(2)	5(2)
C(8)	55(3)	63(3)	67(3)	10(2)	42(2)	17(2)
C(9)	46(2)	80(3)	64(3)	7(2)	34(2)	11(2)
C(10)	53(2)	65(3)	63(3)	8(2)	32(2)	18(2)
C(11)	63(3)	66(3)	60(3)	0(2)	33(2)	7(2)
C(12)	82(4)	107(5)	80(4)	-1(4)	34(3)	-13(4)
C(13)	74(3)	63(3)	89(4)	0(3)	50(3)	-10(3)
C(16)	57(3)	43(2)	82(3)	9(2)	37(2)	-5(2)
C(17)	50(2)	62(3)	71(3)	15(2)	39(2)	1(2)
C(18)	60(3)	81(4)	95(4)	18(3)	50(3)	-10(3)
C(21)	44(2)	27(2)	51(2)	3(1)	30(2)	2(1)
C(22)	54(2)	38(2)	51(2)	5(2)	36(2)	6(2)
C(23)	52(2)	37(2)	56(2)	-6(2)	31(2)	6(2)
C(24)	39(2)	31(2)	60(2)	1(2)	23(2)	1(2)
C(25)	58(2)	40(2)	65(2)	2(2)	42(2)	-6(2)
C(26)	56(2)	35(2)	58(2)	-2(2)	41(2)	-5(2)
C(27)	58(3)	33(2)	87(3)	-3(2)	38(2)	-3(2)
C(28)	90(4)	56(3)	81(3)	10(2)	55(3)	22(3)
O(1)	40(1)	41(2)	70(2)	2(1)	35(1)	0(1)
O(2)	45(2)	41(2)	57(2)	7(1)	31(1)	-1(1)
O(3)	46(2)	37(1)	60(2)	12(1)	30(1)	3(1)
O(4)	60(2)	33(1)	76(2)	-6(1)	49(2)	-4(1)
O(5)	66(2)	46(2)	66(2)	5(1)	43(2)	10(1)
O(6)	45(2)	110(3)	85(2)	-2(2)	33(2)	19(2)
S(1)	45(1)	30(1)	61(1)	4(1)	36(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **164**.

	x	y	z	U(eq)
H(2A)	5876	493	4167	75
H(2B)	5341	914	4177	75
H(3)	5509	-242	5180	80
H(6)	6853	2685	6483	52
H(8)	5550	4805	5555	67
H(10A)	6170	4051	4451	69
H(10B)	6377	2707	4219	69
H(11)	5337	3644	3426	73
H(12A)	6062	2404	3038	108
H(12B)	5478	2878	2478	108
H(13A)	6254	-1490	4777	84
H(13B)	6150	-2117	5413	84
H(14)	5341	-2732	4581	95
H(15A)	5859	-2768	3728	108
H(15B)	5320	-3566	3582	108
H(14A)	5388	-1440	3797	87
H(15C)	5393	-3843	4512	117
H(15D)	5001	-3453	3677	117
H(16A)	6954	261	6661	87
H(16B)	6877	-597	5960	87
H(16C)	6595	-1074	6441	87
H(17A)	6241	1721	6663	68
H(17B)	5683	1621	6007	68
H(18A)	5667	-781	6342	88
H(18B)	6173	-458	7061	88
H(19)	5207	697	6727	57
H(20A)	6058	171	8015	126
H(20B)	5500	773	7920	126
H(19A)	5551	21	7510	104
H(20C)	5763	2621	7216	163

H(20D)	5532	2144	7784	163
H(22)	7552	5967	7097	52
H(23)	7733	8291	7153	54
H(25)	8152	7894	5538	58
H(26)	7979	5549	5472	53
H(27A)	7887	10239	5904	86
H(27B)	8440	9990	6559	86
H(27C)	7951	10287	6715	86
H(28A)	6053	6578	6283	104
H(28B)	6384	6453	7134	104
H(28C)	5887	5506	6733	104
H(1)	6904	1869	5091	69

Crystal Structure Determination of Compound 170

A colorless plate 0.060 x 0.040 x 0.010 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi 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°. Data collection was 99.8% complete to 67.000° in θ. A total of 36801 reflections were collected covering the indices, -7<=*h*<=8, -24<=*k*<=24, -18<=*l*<=20. 4502 reflections were found to be symmetry independent, with an R_{int} of 0.0657. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/n (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) 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.

Table 1. Crystal data and structure refinement for compound **170**.

X-ray ID	compound **170**	
Sample/notebook ID	Cpting-05280-Major-P1	
Empirical formula	C27 H42 O3	
Formula weight	414.60	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 6.9326(2) Å	α= 90°.
	b = 20.5641(5) Å	β= 94.577(2)°.
	c = 17.2667(5) Å	γ = 90°.
Volume	2453.74(12) $Å^3$	
Z	4	
Density (calculated)	1.122 Mg/m^3	
Absorption coefficient	0.549 mm^{-1}	
F(000)	912	
Crystal size	0.060 x 0.040 x 0.010 mm^3	
Theta range for data collection	3.348 to 68.975°.	
Index ranges	-7<=h<=8, -24<=k<=24, -18<=l<=20	
Reflections collected	36801	
Independent reflections	4502 [R(int) = 0.0657]	
Completeness to theta = 67.000°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.860	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4502 / 0 / 280	
Goodness-of-fit on F^2	1.019	
Final R indices [I>2sigma(I)]	R1 = 0.0437, wR2 = 0.1054	
R indices (all data)	R1 = 0.0678, wR2 = 0.1166	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.232 and -0.190 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **170**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5312(2)	7285(1)	6547(1)	22(1)
C(2)	5177(2)	6576(1)	6910(1)	24(1)
C(3)	3575(2)	6648(1)	7502(1)	24(1)
C(4)	2984(2)	7366(1)	7492(1)	25(1)
C(5)	3343(2)	7606(1)	6683(1)	22(1)
C(6)	1767(2)	7377(1)	6077(1)	23(1)
C(7)	2256(2)	7274(1)	5285(1)	25(1)
C(8)	4105(2)	7221(1)	5115(1)	23(1)
C(9)	5784(2)	7319(1)	5699(1)	23(1)
C(10)	7177(2)	6374(1)	7286(1)	28(1)
C(11)	4495(3)	6056(1)	6302(1)	27(1)
C(12)	4360(3)	5363(1)	6619(1)	33(1)
C(13)	3527(3)	4886(1)	6031(1)	33(1)
C(14)	1763(3)	4624(1)	5981(1)	36(1)
C(15)	241(3)	4774(1)	6522(2)	52(1)
C(16)	1167(3)	4131(1)	5365(1)	50(1)
C(17)	4041(3)	6394(1)	8333(1)	28(1)
C(18)	2288(3)	6426(1)	8789(1)	27(1)
C(19)	1146(3)	5938(1)	8962(1)	26(1)
C(20)	-590(3)	6048(1)	9412(1)	33(1)
C(21)	1467(3)	5245(1)	8755(1)	46(1)
C(22)	3379(2)	8360(1)	6623(1)	25(1)
C(23)	1618(3)	8686(1)	6899(1)	27(1)
C(24)	146(3)	8946(1)	6469(1)	30(1)
C(25)	-59(3)	8947(1)	5598(1)	42(1)
C(26)	-1500(3)	9267(1)	6834(1)	41(1)
C(27)	3295(3)	6996(1)	3773(1)	36(1)
O(1)	6732(2)	7657(1)	7002(1)	25(1)
O(2)	85(2)	7310(1)	6248(1)	28(1)
O(3)	4727(2)	7084(1)	4412(1)	28(1)

Table 3. Bond lengths [Å] and angles [°] for compound **170**.

C(1)-O(1)	1.431(2)	C(14)-C(15)	1.495(3)
C(1)-C(9)	1.528(2)	C(14)-C(16)	1.504(3)
C(1)-C(5)	1.551(2)	C(15)-H(15A)	0.9800
C(1)-C(2)	1.593(2)	C(15)-H(15B)	0.9800
C(2)-C(10)	1.539(2)	C(15)-H(15C)	0.9800
C(2)-C(11)	1.546(2)	C(16)-H(16A)	0.9800
C(2)-C(3)	1.576(2)	C(16)-H(16B)	0.9800
C(3)-C(4)	1.532(2)	C(16)-H(16C)	0.9800
C(3)-C(17)	1.536(2)	C(17)-C(18)	1.502(2)
C(3)-H(3)	1.0000	C(17)-H(17A)	0.9900
C(4)-C(5)	1.521(2)	C(17)-H(17B)	0.9900
C(4)-H(4A)	0.9900	C(18)-C(19)	1.327(3)
C(4)-H(4B)	0.9900	C(18)-H(18)	0.9500
C(5)-C(6)	1.527(2)	C(19)-C(21)	1.491(3)
C(5)-C(22)	1.554(2)	C(19)-C(20)	1.501(2)
C(6)-O(2)	1.234(2)	C(20)-H(20A)	0.9800
C(6)-C(7)	1.451(2)	C(20)-H(20B)	0.9800
C(7)-C(8)	1.342(2)	C(20)-H(20C)	0.9800
C(7)-H(7)	0.9500	C(21)-H(21A)	0.9800
C(8)-O(3)	1.350(2)	C(21)-H(21B)	0.9800
C(8)-C(9)	1.491(2)	C(21)-H(21C)	0.9800
C(9)-H(9A)	0.9900	C(22)-C(23)	1.503(2)
C(9)-H(9B)	0.9900	C(22)-H(22A)	0.9900
C(10)-H(10A)	0.9800	C(22)-H(22B)	0.9900
C(10)-H(10B)	0.9800	C(23)-C(24)	1.325(3)
C(10)-H(10C)	0.9800	C(23)-H(23)	0.9500
C(11)-C(12)	1.533(3)	C(24)-C(25)	1.499(3)
C(11)-H(11A)	0.9900	C(24)-C(26)	1.500(3)
C(11)-H(11B)	0.9900	C(25)-H(25A)	0.9800
C(12)-C(13)	1.495(3)	C(25)-H(25B)	0.9800
C(12)-H(12A)	0.9900	C(25)-H(25C)	0.9800
C(12)-H(12B)	0.9900	C(26)-H(26A)	0.9800
C(13)-C(14)	1.332(3)	C(26)-H(26B)	0.9800
C(13)-H(13)	0.9500	C(26)-H(26C)	0.9800

C(27)-O(3)	1.435(2)	C(27)-H(27C)	0.9800
C(27)-H(27A)	0.9800	O(1)-H(1)	0.8400
C(27)-H(27B)	0.9800		

O(1)-C(1)-C(9)	108.11(13)	C(7)-C(6)-C(5)	118.89(14)
O(1)-C(1)-C(5)	105.28(13)	C(8)-C(7)-C(6)	121.11(15)
C(9)-C(1)-C(5)	112.55(14)	C(8)-C(7)-H(7)	119.4
O(1)-C(1)-C(2)	109.49(13)	C(6)-C(7)-H(7)	119.4
C(9)-C(1)-C(2)	116.32(14)	C(7)-C(8)-O(3)	126.31(16)
C(5)-C(1)-C(2)	104.53(13)	C(7)-C(8)-C(9)	123.34(16)
C(10)-C(2)-C(11)	108.44(14)	O(3)-C(8)-C(9)	110.35(14)
C(10)-C(2)-C(3)	114.19(14)	C(8)-C(9)-C(1)	115.22(14)
C(11)-C(2)-C(3)	108.22(14)	C(8)-C(9)-H(9A)	108.5
C(10)-C(2)-C(1)	109.46(14)	C(1)-C(9)-H(9A)	108.5
C(11)-C(2)-C(1)	112.95(14)	C(8)-C(9)-H(9B)	108.5
C(3)-C(2)-C(1)	103.62(13)	C(1)-C(9)-H(9B)	108.5
C(4)-C(3)-C(17)	111.96(15)	H(9A)-C(9)-H(9B)	107.5
C(4)-C(3)-C(2)	106.57(14)	C(2)-C(10)-H(10A)	109.5
C(17)-C(3)-C(2)	117.87(14)	C(2)-C(10)-H(10B)	109.5
C(4)-C(3)-H(3)	106.6	H(10A)-C(10)-H(10B)	109.5
C(17)-C(3)-H(3)	106.6	C(2)-C(10)-H(10C)	109.5
C(2)-C(3)-H(3)	106.6	H(10A)-C(10)-H(10C)	109.5
C(5)-C(4)-C(3)	105.11(14)	H(10B)-C(10)-H(10C)	109.5
C(5)-C(4)-H(4A)	110.7	C(12)-C(11)-C(2)	115.08(15)
C(3)-C(4)-H(4A)	110.7	C(12)-C(11)-H(11A)	108.5
C(5)-C(4)-H(4B)	110.7	C(2)-C(11)-H(11A)	108.5
C(3)-C(4)-H(4B)	110.7	C(12)-C(11)-H(11B)	108.5
H(4A)-C(4)-H(4B)	108.8	C(2)-C(11)-H(11B)	108.5
C(4)-C(5)-C(6)	111.62(14)	H(11A)-C(11)-H(11B)	107.5
C(4)-C(5)-C(1)	102.16(13)	C(13)-C(12)-C(11)	113.48(16)
C(6)-C(5)-C(1)	110.76(14)	C(13)-C(12)-H(12A)	108.9
C(4)-C(5)-C(22)	113.00(14)	C(11)-C(12)-H(12A)	108.9
C(6)-C(5)-C(22)	106.07(13)	C(13)-C(12)-H(12B)	108.9
C(1)-C(5)-C(22)	113.36(13)	C(11)-C(12)-H(12B)	108.9
O(2)-C(6)-C(7)	120.46(16)	H(12A)-C(12)-H(12B)	107.7
O(2)-C(6)-C(5)	120.55(16)	C(14)-C(13)-C(12)	127.68(19)

C(14)-C(13)-H(13)	116.2	C(19)-C(21)-H(21B)	109.5
C(12)-C(13)-H(13)	116.2	H(21A)-C(21)-H(21B)	109.5
C(13)-C(14)-C(15)	124.5(2)	C(19)-C(21)-H(21C)	109.5
C(13)-C(14)-C(16)	121.10(19)	H(21A)-C(21)-H(21C)	109.5
C(15)-C(14)-C(16)	114.37(18)	H(21B)-C(21)-H(21C)	109.5
C(14)-C(15)-H(15A)	109.5	C(23)-C(22)-C(5)	113.98(14)
C(14)-C(15)-H(15B)	109.5	C(23)-C(22)-H(22A)	108.8
H(15A)-C(15)-H(15B)	109.5	C(5)-C(22)-H(22A)	108.8
C(14)-C(15)-H(15C)	109.5	C(23)-C(22)-H(22B)	108.8
H(15A)-C(15)-H(15C)	109.5	C(5)-C(22)-H(22B)	108.8
H(15B)-C(15)-H(15C)	109.5	H(22A)-C(22)-H(22B)	107.7
C(14)-C(16)-H(16A)	109.5	C(24)-C(23)-C(22)	127.66(18)
C(14)-C(16)-H(16B)	109.5	C(24)-C(23)-H(23)	116.2
H(16A)-C(16)-H(16B)	109.5	C(22)-C(23)-H(23)	116.2
C(14)-C(16)-H(16C)	109.5	C(23)-C(24)-C(25)	124.70(18)
H(16A)-C(16)-H(16C)	109.5	C(23)-C(24)-C(26)	121.28(19)
H(16B)-C(16)-H(16C)	109.5	C(25)-C(24)-C(26)	114.01(17)
C(18)-C(17)-C(3)	110.88(14)	C(24)-C(25)-H(25A)	109.5
C(18)-C(17)-H(17A)	109.5	C(24)-C(25)-H(25B)	109.5
C(3)-C(17)-H(17A)	109.5	H(25A)-C(25)-H(25B)	109.5
C(18)-C(17)-H(17B)	109.5	C(24)-C(25)-H(25C)	109.5
C(3)-C(17)-H(17B)	109.5	H(25A)-C(25)-H(25C)	109.5
H(17A)-C(17)-H(17B)	108.1	H(25B)-C(25)-H(25C)	109.5
C(19)-C(18)-C(17)	127.39(17)	C(24)-C(26)-H(26A)	109.5
C(19)-C(18)-H(18)	116.3	C(24)-C(26)-H(26B)	109.5
C(17)-C(18)-H(18)	116.3	H(26A)-C(26)-H(26B)	109.5
C(18)-C(19)-C(21)	124.46(18)	C(24)-C(26)-H(26C)	109.5
C(18)-C(19)-C(20)	121.36(17)	H(26A)-C(26)-H(26C)	109.5
C(21)-C(19)-C(20)	114.16(16)	H(26B)-C(26)-H(26C)	109.5
C(19)-C(20)-H(20A)	109.5	O(3)-C(27)-H(27A)	109.5
C(19)-C(20)-H(20B)	109.5	O(3)-C(27)-H(27B)	109.5
H(20A)-C(20)-H(20B)	109.5	H(27A)-C(27)-H(27B)	109.5
C(19)-C(20)-H(20C)	109.5	O(3)-C(27)-H(27C)	109.5
H(20A)-C(20)-H(20C)	109.5	H(27A)-C(27)-H(27C)	109.5
H(20B)-C(20)-H(20C)	109.5	H(27B)-C(27)-H(27C)	109.5
C(19)-C(21)-H(21A)	109.5	C(1)-O(1)-H(1)	109.5

C(8)-O(3)-C(27)	117.81(14)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for compound **170**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	20(1)	22(1)	24(1)	0(1)	2(1)	-2(1)
C(2)	20(1)	24(1)	27(1)	3(1)	1(1)	1(1)
C(3)	20(1)	23(1)	29(1)	3(1)	1(1)	-1(1)
C(4)	23(1)	25(1)	26(1)	1(1)	4(1)	1(1)
C(5)	19(1)	23(1)	26(1)	1(1)	3(1)	-1(1)
C(6)	20(1)	18(1)	32(1)	4(1)	3(1)	1(1)
C(7)	22(1)	24(1)	27(1)	2(1)	-3(1)	-2(1)
C(8)	26(1)	18(1)	26(1)	1(1)	2(1)	-3(1)
C(9)	18(1)	22(1)	28(1)	0(1)	3(1)	-1(1)
C(10)	22(1)	29(1)	33(1)	6(1)	2(1)	1(1)
C(11)	27(1)	24(1)	30(1)	2(1)	4(1)	1(1)
C(12)	34(1)	25(1)	38(1)	4(1)	3(1)	0(1)
C(13)	36(1)	24(1)	42(1)	-1(1)	12(1)	1(1)
C(14)	37(1)	28(1)	43(1)	-1(1)	9(1)	-1(1)
C(15)	39(1)	63(2)	57(1)	-14(1)	11(1)	-5(1)
C(16)	49(1)	42(1)	61(2)	-14(1)	15(1)	-13(1)
C(17)	27(1)	26(1)	30(1)	4(1)	1(1)	-1(1)
C(18)	34(1)	24(1)	24(1)	2(1)	4(1)	3(1)
C(19)	28(1)	25(1)	26(1)	3(1)	1(1)	2(1)
C(20)	35(1)	32(1)	33(1)	5(1)	9(1)	1(1)
C(21)	48(1)	29(1)	64(2)	0(1)	23(1)	-3(1)
C(22)	20(1)	23(1)	32(1)	1(1)	1(1)	-2(1)
C(23)	29(1)	20(1)	32(1)	-1(1)	6(1)	-3(1)
C(24)	25(1)	20(1)	43(1)	-2(1)	2(1)	-5(1)
C(25)	37(1)	40(1)	46(1)	5(1)	-10(1)	3(1)
C(26)	29(1)	25(1)	69(2)	-5(1)	6(1)	1(1)
C(27)	33(1)	45(1)	29(1)	-4(1)	-3(1)	-3(1)
O(1)	18(1)	28(1)	29(1)	-3(1)	-1(1)	-2(1)
O(2)	19(1)	30(1)	37(1)	2(1)	4(1)	-1(1)
O(3)	27(1)	33(1)	23(1)	-1(1)	1(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **170**.

	x	y	z	U(eq)
H(3)	2423	6398	7280	29
H(4A)	1602	7413	7589	30
H(4B)	3777	7613	7894	30
H(7)	1251	7244	4879	29
H(9A)	6362	7750	5606	27
H(9B)	6774	6986	5612	27
H(10A)	7091	5939	7514	42
H(10B)	7600	6686	7693	42
H(10C)	8112	6368	6889	42
H(11A)	3205	6184	6062	32
H(11B)	5399	6055	5886	32
H(12A)	5671	5216	6812	39
H(12B)	3548	5368	7066	39
H(13)	4353	4754	5647	40
H(15A)	677	5134	6864	78
H(15B)	10	4389	6836	78
H(15C)	-960	4897	6220	78
H(16A)	2183	4093	5004	75
H(16B)	-41	4270	5080	75
H(16C)	972	3708	5609	75
H(17A)	4496	5938	8313	33
H(17B)	5093	6658	8595	33
H(18)	1958	6843	8975	33
H(20A)	-402	5827	9915	50
H(20B)	-1744	5873	9119	50
H(20C)	-758	6515	9496	50
H(21A)	2628	5211	8469	69
H(21B)	345	5084	8430	69
H(21C)	1640	4984	9230	69
H(22A)	4539	8525	6933	30

H(22B)	3499	8483	6075	30
H(23)	1552	8709	7445	32
H(25A)	1075	8738	5401	63
H(25B)	-157	9396	5409	63
H(25C)	-1229	8707	5414	63
H(26A)	-1310	9224	7400	62
H(26B)	-2719	9058	6647	62
H(26C)	-1546	9729	6694	62
H(27A)	2442	6634	3887	54
H(27B)	3937	6899	3301	54
H(27C)	2529	7394	3696	54
H(1)	7834	7580	6854	38

Crystal Structure Determination of Compound 178

A colorless plate 0.050 x 0.040 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using and scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 2.0°. Data collection was 100.0% complete to 67.000° in q. A total of 30022 reflections were collected covering the indices, -12<=*h*<=12, -9<=*k*<=9, -16<=*l*<=16. 2024 reflections were found to be symmetry independent, with an R_{int} of 0.0497. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/c (No. 14). 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.

Table 1. Crystal data and structure refinement for compound **178**.

X-ray ID	Compound **178**	
Sample/notebook ID	Cpting-07281-Pure	
Empirical formula	C13 H14 O3	
Formula weight	218.24	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 10.6286(6) Å	a= 90°.
	b = 8.0267(4) Å	b= 110.892(3)°.
	c = 13.8441(7) Å	g = 90°.
Volume	1103.43(10) $Å^3$	
Z	4	
Density (calculated)	1.314 Mg/m^3	
Absorption coefficient	0.758 mm^{-1}	
F(000)	464	
Crystal size	0.050 x 0.040 x 0.020 mm^3	
Theta range for data collection	4.453 to 68.365°.	
Index ranges	-12<=h<=12, -9<=k<=9, -16<=l<=16	
Reflections collected	30022	
Independent reflections	2024 [R(int) = 0.0497]	
Completeness to theta = 67.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.751	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2024 / 0 / 147	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0360, wR2 = 0.0913	
R indices (all data)	R1 = 0.0434, wR2 = 0.0961	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.324 and -0.171 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **178**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6561(1)	8035(2)	4228(1)	18(1)
C(2)	6431(1)	7365(2)	3146(1)	18(1)
C(3)	5125(2)	8016(2)	2363(1)	19(1)
C(4)	3861(1)	7715(2)	2599(1)	20(1)
C(5)	4038(1)	8139(2)	3702(1)	19(1)
C(6)	5326(1)	7550(2)	4505(1)	20(1)
C(7)	7639(1)	7777(2)	2844(1)	22(1)
C(8)	7833(1)	7350(2)	5053(1)	19(1)
C(9)	7925(2)	5650(2)	5287(1)	21(1)
C(10)	9050(2)	5008(2)	6055(1)	25(1)
C(11)	10101(2)	6053(2)	6604(1)	27(1)
C(12)	10027(2)	7731(2)	6361(1)	27(1)
C(13)	8904(2)	8382(2)	5588(1)	23(1)
O(1)	6575(1)	9807(1)	4129(1)	21(1)
O(2)	5076(1)	8762(1)	1585(1)	24(1)
O(3)	3173(1)	8892(1)	3906(1)	26(1)

Table 3. Bond lengths [Å] and angles [°] for compound **178**.

C(1)-O(1)	1.4298(17)
C(1)-C(8)	1.5275(19)
C(1)-C(6)	1.5435(19)
C(1)-C(2)	1.5511(18)
C(2)-C(3)	1.5170(19)
C(2)-C(7)	1.5214(19)
C(2)-H(2)	1.0000
C(3)-O(2)	1.2175(18)
C(3)-C(4)	1.510(2)
C(4)-C(5)	1.5094(19)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-O(3)	1.2153(18)
C(5)-C(6)	1.4992(19)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800
C(7)-H(7C)	0.9800
C(8)-C(13)	1.389(2)
C(8)-C(9)	1.397(2)
C(9)-C(10)	1.386(2)
C(9)-H(9)	0.9500
C(10)-C(11)	1.387(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.384(2)
C(11)-H(11)	0.9500
C(12)-C(13)	1.390(2)
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
O(1)-H(1)	0.8400
O(1)-C(1)-C(8)	113.16(11)
O(1)-C(1)-C(6)	108.32(11)

C(8)-C(1)-C(6)	109.14(11)
O(1)-C(1)-C(2)	104.62(10)
C(8)-C(1)-C(2)	110.36(11)
C(6)-C(1)-C(2)	111.19(11)
C(3)-C(2)-C(7)	112.08(11)
C(3)-C(2)-C(1)	108.34(11)
C(7)-C(2)-C(1)	113.36(11)
C(3)-C(2)-H(2)	107.6
C(7)-C(2)-H(2)	107.6
C(1)-C(2)-H(2)	107.6
O(2)-C(3)-C(4)	120.61(13)
O(2)-C(3)-C(2)	122.75(13)
C(4)-C(3)-C(2)	116.63(12)
C(5)-C(4)-C(3)	112.51(12)
C(5)-C(4)-H(4A)	109.1
C(3)-C(4)-H(4A)	109.1
C(5)-C(4)-H(4B)	109.1
C(3)-C(4)-H(4B)	109.1
H(4A)-C(4)-H(4B)	107.8
O(3)-C(5)-C(6)	123.41(13)
O(3)-C(5)-C(4)	121.07(13)
C(6)-C(5)-C(4)	115.52(12)
C(5)-C(6)-C(1)	111.62(11)
C(5)-C(6)-H(6A)	109.3
C(1)-C(6)-H(6A)	109.3
C(5)-C(6)-H(6B)	109.3
C(1)-C(6)-H(6B)	109.3
H(6A)-C(6)-H(6B)	108.0
C(2)-C(7)-H(7A)	109.5
C(2)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(2)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(13)-C(8)-C(9)	118.87(13)
C(13)-C(8)-C(1)	121.47(13)

C(9)-C(8)-C(1)	119.66(13)
C(10)-C(9)-C(8)	120.70(14)
C(10)-C(9)-H(9)	119.6
C(8)-C(9)-H(9)	119.6
C(9)-C(10)-C(11)	120.12(15)
C(9)-C(10)-H(10)	119.9
C(11)-C(10)-H(10)	119.9
C(12)-C(11)-C(10)	119.38(14)
C(12)-C(11)-H(11)	120.3
C(10)-C(11)-H(11)	120.3
C(11)-C(12)-C(13)	120.78(15)
C(11)-C(12)-H(12)	119.6
C(13)-C(12)-H(12)	119.6
C(8)-C(13)-C(12)	120.11(14)
C(8)-C(13)-H(13)	119.9
C(12)-C(13)-H(13)	119.9
C(1)-O(1)-H(1)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for compound **178**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(1)	16(1)	17(1)	0(1)	8(1)	1(1)
C(2)	22(1)	16(1)	18(1)	-1(1)	9(1)	2(1)
C(3)	25(1)	17(1)	17(1)	-5(1)	8(1)	0(1)
C(4)	20(1)	19(1)	19(1)	-1(1)	5(1)	2(1)
C(5)	20(1)	16(1)	21(1)	0(1)	9(1)	-1(1)
C(6)	21(1)	22(1)	17(1)	2(1)	7(1)	2(1)
C(7)	23(1)	25(1)	20(1)	0(1)	9(1)	2(1)
C(8)	20(1)	22(1)	16(1)	0(1)	9(1)	2(1)
C(9)	21(1)	22(1)	21(1)	1(1)	7(1)	0(1)
C(10)	25(1)	24(1)	26(1)	4(1)	9(1)	5(1)
C(11)	21(1)	34(1)	24(1)	1(1)	4(1)	7(1)
C(12)	20(1)	32(1)	28(1)	-7(1)	5(1)	-3(1)
C(13)	23(1)	22(1)	24(1)	-1(1)	10(1)	0(1)
O(1)	29(1)	15(1)	18(1)	-1(1)	10(1)	2(1)
O(2)	30(1)	25(1)	17(1)	2(1)	8(1)	4(1)
O(3)	22(1)	31(1)	24(1)	-4(1)	9(1)	5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **178**.

	x	y	z	U(eq)
H(2)	6359	6124	3164	22
H(4A)	3120	8397	2126	24
H(4B)	3600	6529	2468	24
H(6A)	5296	6323	4569	24
H(6B)	5416	8043	5182	24
H(7A)	7512	7287	2167	33
H(7B)	8457	7320	3362	33
H(7C)	7726	8989	2809	33
H(9)	7208	4927	4915	26
H(10)	9102	3850	6206	30
H(11)	10864	5621	7143	33
H(12)	10753	8447	6726	33
H(13)	8868	9535	5425	27
H(1)	6658	10252	4697	31

Crystal Structure Determination of Compound 184

A colorless prism 0.070 x 0.050 x 0.040 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using and scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 2.0°. Data collection was 99.9% complete to 67.000° in q. A total of 38424 reflections were collected covering the indices, -12<=*h*<=13, -22<=*k*<=22, -10<=*l*<=11. 1871 reflections were found to be symmetry independent, with an R_{int} of 0.0308. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P b c n (No. 60). 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.

Table 1. Crystal data and structure refinement for compound **184**.

X-ray ID	Compound **184**	
Sample/notebook ID	Cpting-07262-Pure1	
Empirical formula	C11 H16 O3	
Formula weight	196.24	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P b c n	
Unit cell dimensions	a = 11.4542(9) Å	a= 90°.
	b = 18.7790(15) Å	b= 90°.
	c = 9.4302(7) Å	g = 90°.
Volume	2028.4(3) $Å^3$	
Z	8	
Density (calculated)	1.285 Mg/m^3	
Absorption coefficient	0.754 mm^{-1}	
F(000)	848	
Crystal size	0.070 x 0.050 x 0.040 mm^3	
Theta range for data collection	4.522 to 68.365°.	
Index ranges	-12<=h<=13, -22<=k<=22, -10<=l<=11	
Reflections collected	38424	
Independent reflections	1871 [R(int) = 0.0308]	
Completeness to theta = 67.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.858	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1871 / 0 / 128	
Goodness-of-fit on F^2	1.076	
Final R indices [I>2sigma(I)]	R1 = 0.0336, wR2 = 0.0903	
R indices (all data)	R1 = 0.0343, wR2 = 0.0911	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.282 and -0.175 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **184**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7979(1)	4122(1)	5357(1)	19(1)
C(2)	8257(1)	3343(1)	5728(1)	27(1)
C(3)	7423(1)	2971(1)	6761(2)	37(1)
C(4)	6370(1)	2629(1)	6034(2)	42(1)
C(5)	5472(1)	3135(1)	5396(2)	36(1)
C(6)	5965(1)	3719(1)	4441(1)	25(1)
C(7)	6658(1)	4271(1)	5290(1)	19(1)
C(8)	6516(1)	5027(1)	4755(1)	18(1)
C(9)	7123(1)	5588(1)	5654(1)	20(1)
C(10)	8375(1)	5391(1)	5950(1)	20(1)
C(11)	8572(1)	4634(1)	6409(1)	21(1)
O(1)	8403(1)	4284(1)	3960(1)	21(1)
O(2)	5972(1)	5191(1)	3706(1)	25(1)
O(3)	9159(1)	5817(1)	5775(1)	27(1)

Table 3. Bond lengths [Å] and angles [°] for compound **184**.

C(1)-O(1)	1.4367(13)
C(1)-C(2)	1.5368(15)
C(1)-C(11)	1.5390(15)
C(1)-C(7)	1.5402(15)
C(2)-C(3)	1.5323(18)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.529(2)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.524(2)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.5275(18)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.5313(15)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.5154(15)
C(7)-H(7)	1.0000
C(8)-O(2)	1.2094(14)
C(8)-C(9)	1.5197(15)
C(9)-C(10)	1.5069(15)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-O(3)	1.2140(14)
C(10)-C(11)	1.5040(16)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
O(1)-H(1)	0.8400
O(1)-C(1)-C(2)	109.92(9)
O(1)-C(1)-C(11)	108.01(9)

C(2)-C(1)-C(11)	110.87(9)
O(1)-C(1)-C(7)	104.80(8)
C(2)-C(1)-C(7)	112.71(9)
C(11)-C(1)-C(7)	110.26(9)
C(3)-C(2)-C(1)	116.67(10)
C(3)-C(2)-H(2A)	108.1
C(1)-C(2)-H(2A)	108.1
C(3)-C(2)-H(2B)	108.1
C(1)-C(2)-H(2B)	108.1
H(2A)-C(2)-H(2B)	107.3
C(4)-C(3)-C(2)	113.44(12)
C(4)-C(3)-H(3A)	108.9
C(2)-C(3)-H(3A)	108.9
C(4)-C(3)-H(3B)	108.9
C(2)-C(3)-H(3B)	108.9
H(3A)-C(3)-H(3B)	107.7
C(5)-C(4)-C(3)	116.61(11)
C(5)-C(4)-H(4A)	108.1
C(3)-C(4)-H(4A)	108.1
C(5)-C(4)-H(4B)	108.1
C(3)-C(4)-H(4B)	108.1
H(4A)-C(4)-H(4B)	107.3
C(4)-C(5)-C(6)	115.51(11)
C(4)-C(5)-H(5A)	108.4
C(6)-C(5)-H(5A)	108.4
C(4)-C(5)-H(5B)	108.4
C(6)-C(5)-H(5B)	108.4
H(5A)-C(5)-H(5B)	107.5
C(5)-C(6)-C(7)	111.71(10)
C(5)-C(6)-H(6A)	109.3
C(7)-C(6)-H(6A)	109.3
C(5)-C(6)-H(6B)	109.3
C(7)-C(6)-H(6B)	109.3
H(6A)-C(6)-H(6B)	107.9
C(8)-C(7)-C(6)	113.87(9)
C(8)-C(7)-C(1)	106.82(9)

C(6)-C(7)-C(1)	114.06(9)
C(8)-C(7)-H(7)	107.2
C(6)-C(7)-H(7)	107.2
C(1)-C(7)-H(7)	107.2
O(2)-C(8)-C(7)	124.45(10)
O(2)-C(8)-C(9)	121.07(10)
C(7)-C(8)-C(9)	114.49(9)
C(10)-C(9)-C(8)	111.65(9)
C(10)-C(9)-H(9A)	109.3
C(8)-C(9)-H(9A)	109.3
C(10)-C(9)-H(9B)	109.3
C(8)-C(9)-H(9B)	109.3
H(9A)-C(9)-H(9B)	108.0
O(3)-C(10)-C(11)	123.50(10)
O(3)-C(10)-C(9)	121.14(10)
C(11)-C(10)-C(9)	115.31(9)
C(10)-C(11)-C(1)	109.85(9)
C(10)-C(11)-H(11A)	109.7
C(1)-C(11)-H(11A)	109.7
C(10)-C(11)-H(11B)	109.7
C(1)-C(11)-H(11B)	109.7
H(11A)-C(11)-H(11B)	108.2
C(1)-O(1)-H(1)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for compound **184**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	19(1)	21(1)	16(1)	0(1)	0(1)	2(1)
C(2)	30(1)	22(1)	28(1)	0(1)	1(1)	7(1)
C(3)	53(1)	24(1)	34(1)	8(1)	8(1)	8(1)
C(4)	54(1)	22(1)	51(1)	2(1)	18(1)	-7(1)
C(5)	35(1)	27(1)	47(1)	-8(1)	11(1)	-12(1)
C(6)	21(1)	25(1)	29(1)	-7(1)	2(1)	-3(1)
C(7)	17(1)	21(1)	18(1)	-1(1)	2(1)	-1(1)
C(8)	12(1)	24(1)	18(1)	-1(1)	4(1)	1(1)
C(9)	18(1)	19(1)	24(1)	0(1)	0(1)	2(1)
C(10)	18(1)	24(1)	18(1)	-5(1)	1(1)	0(1)
C(11)	17(1)	25(1)	20(1)	-2(1)	-3(1)	3(1)
O(1)	16(1)	29(1)	18(1)	0(1)	2(1)	2(1)
O(2)	21(1)	32(1)	21(1)	1(1)	-3(1)	4(1)
O(3)	19(1)	27(1)	34(1)	-5(1)	3(1)	-4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **184**.

	x	y	z	U(eq)
H(2A)	8272	3065	4835	32
H(2B)	9053	3325	6136	32
H(3A)	7859	2599	7283	44
H(3B)	7141	3324	7463	44
H(4A)	6662	2315	5269	51
H(4B)	5968	2323	6735	51
H(5A)	5036	3363	6180	44
H(5B)	4907	2851	4838	44
H(6A)	5315	3959	3941	30
H(6B)	6480	3502	3718	30
H(7)	6357	4259	6285	22
H(9A)	7098	6051	5154	24
H(9B)	6700	5642	6563	24
H(11A)	8245	4561	7370	25
H(11B)	9420	4533	6446	25
H(1)	9133	4244	3944	32

Crystal Structure Determination of Compound 186

A colorless prism 0.060 x 0.050 x 0.030 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using and scans. Crystal-to-detector distance was 60 mm and exposure time was 2 seconds per frame using a scan width of 2.0°. Data collection was 100.0% complete to 67.000° in q. A total of 16472 reflections were collected covering the indices, -8<=*h*<=7, -10<=*k*<=10, -32<=*l*<=31. 2907 reflections were found to be symmetry independent, with an R_{int} of 0.0323. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P 21 21 21 (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.

Table 1. Crystal data and structure refinement for compound **186**.

X-ray ID	Compound **186**	
Sample/notebook ID	maimone92	
Empirical formula	C19 H26 O3	
Formula weight	302.40	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.6836(2) Å	a= 90°.
	b = 8.7479(3) Å	b= 90°.
	c = 27.3717(8) Å	g = 90°.
Volume	1600.35(9) $Å^3$	
Z	4	
Density (calculated)	1.255 Mg/m^3	
Absorption coefficient	0.659 mm^{-1}	
F(000)	656	
Crystal size	0.060 x 0.050 x 0.030 mm^3	
Theta range for data collection	3.229 to 68.244°.	
Index ranges	-8<=h<=7, -10<=k<=10, -32<=l<=31	
Reflections collected	16472	
Independent reflections	2907 [R(int) = 0.0323]	
Completeness to theta = 67.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.832	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2907 / 0 / 204	
Goodness-of-fit on F^2	1.072	
Final R indices [I>2sigma(I)]	R1 = 0.0334, wR2 = 0.0822	
R indices (all data)	R1 = 0.0348, wR2 = 0.0829	
Absolute structure parameter	-0.29(9)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.182 and -0.174 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **186**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5410(3)	8039(2)	3172(1)	18(1)
C(2)	4198(3)	9455(2)	3324(1)	20(1)
C(3)	2362(3)	9717(2)	3028(1)	19(1)
C(4)	1610(3)	8660(2)	2715(1)	20(1)
C(5)	2493(3)	7185(2)	2673(1)	18(1)
C(6)	4056(3)	6701(2)	3040(1)	17(1)
C(7)	3087(3)	6001(2)	3503(1)	18(1)
C(8)	4723(3)	5346(2)	3849(1)	19(1)
C(9)	3741(3)	5133(3)	4357(1)	22(1)
C(10)	5178(4)	4751(3)	4772(1)	24(1)
C(11)	6758(4)	6013(3)	4803(1)	28(1)
C(12)	7880(3)	6164(3)	4318(1)	27(1)
C(13)	6474(3)	6450(3)	3895(1)	21(1)
C(14)	6779(3)	7610(2)	3588(1)	21(1)
C(15)	1466(3)	4837(2)	3371(1)	21(1)
C(16)	5499(4)	3794(3)	3659(1)	25(1)
C(17)	4128(4)	4468(3)	5257(1)	30(1)
C(18)	2168(4)	4537(3)	5321(1)	35(1)
C(19)	5465(5)	4077(4)	5678(1)	49(1)
O(1)	6517(2)	8345(2)	2736(1)	23(1)
O(2)	1561(2)	11083(2)	3107(1)	23(1)
O(3)	1930(2)	6262(2)	2351(1)	21(1)

Table 3. Bond lengths [Å] and angles [°] for compound **186**.

C(1)-O(1)	1.428(2)
C(1)-C(14)	1.509(3)
C(1)-C(6)	1.523(3)
C(1)-C(2)	1.538(3)
C(2)-C(3)	1.488(3)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-O(2)	1.327(3)
C(3)-C(4)	1.357(3)
C(4)-C(5)	1.424(3)
C(4)-H(4)	0.9500
C(5)-O(3)	1.253(2)
C(5)-C(6)	1.509(3)
C(6)-C(7)	1.549(3)
C(6)-H(6)	1.0000
C(7)-C(15)	1.530(3)
C(7)-C(8)	1.556(3)
C(7)-H(7)	1.0000
C(8)-C(13)	1.523(3)
C(8)-C(16)	1.543(3)
C(8)-C(9)	1.551(3)
C(9)-C(10)	1.525(3)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(17)	1.522(3)
C(10)-C(11)	1.530(3)
C(10)-H(10)	1.0000
C(11)-C(12)	1.531(3)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.513(3)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.333(3)

C(14)-H(14)	0.9500
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(17)-C(18)	1.323(4)
C(17)-C(19)	1.497(3)
C(18)-H(18A)	0.9500
C(18)-H(18B)	0.9500
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
O(1)-H(1)	0.8400
O(2)-H(2)	0.8400

O(1)-C(1)-C(14)	111.31(17)
O(1)-C(1)-C(6)	104.70(16)
C(14)-C(1)-C(6)	110.35(17)
O(1)-C(1)-C(2)	110.42(17)
C(14)-C(1)-C(2)	108.36(17)
C(6)-C(1)-C(2)	111.71(17)
C(3)-C(2)-C(1)	114.27(17)
C(3)-C(2)-H(2A)	108.7
C(1)-C(2)-H(2A)	108.7
C(3)-C(2)-H(2B)	108.7
C(1)-C(2)-H(2B)	108.7
H(2A)-C(2)-H(2B)	107.6
O(2)-C(3)-C(4)	124.5(2)
O(2)-C(3)-C(2)	112.50(18)
C(4)-C(3)-C(2)	122.97(19)
C(3)-C(4)-C(5)	120.99(19)
C(3)-C(4)-H(4)	119.5
C(5)-C(4)-H(4)	119.5
O(3)-C(5)-C(4)	121.06(19)

O(3)-C(5)-C(6)	119.69(19)
C(4)-C(5)-C(6)	119.18(18)
C(5)-C(6)-C(1)	110.70(17)
C(5)-C(6)-C(7)	111.43(16)
C(1)-C(6)-C(7)	111.02(16)
C(5)-C(6)-H(6)	107.8
C(1)-C(6)-H(6)	107.8
C(7)-C(6)-H(6)	107.8
C(15)-C(7)-C(6)	111.50(16)
C(15)-C(7)-C(8)	113.32(17)
C(6)-C(7)-C(8)	110.48(17)
C(15)-C(7)-H(7)	107.1
C(6)-C(7)-H(7)	107.1
C(8)-C(7)-H(7)	107.1
C(13)-C(8)-C(16)	109.10(17)
C(13)-C(8)-C(9)	109.10(17)
C(16)-C(8)-C(9)	109.81(18)
C(13)-C(8)-C(7)	110.90(17)
C(16)-C(8)-C(7)	110.85(17)
C(9)-C(8)-C(7)	107.05(17)
C(10)-C(9)-C(8)	115.38(18)
C(10)-C(9)-H(9A)	108.4
C(8)-C(9)-H(9A)	108.4
C(10)-C(9)-H(9B)	108.4
C(8)-C(9)-H(9B)	108.4
H(9A)-C(9)-H(9B)	107.5
C(17)-C(10)-C(9)	113.26(19)
C(17)-C(10)-C(11)	112.81(19)
C(9)-C(10)-C(11)	108.50(18)
C(17)-C(10)-H(10)	107.3
C(9)-C(10)-H(10)	107.3
C(11)-C(10)-H(10)	107.3
C(10)-C(11)-C(12)	110.63(18)
C(10)-C(11)-H(11A)	109.5
C(12)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5

C(12)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	108.1
C(13)-C(12)-C(11)	112.00(18)
C(13)-C(12)-H(12A)	109.2
C(11)-C(12)-H(12A)	109.2
C(13)-C(12)-H(12B)	109.2
C(11)-C(12)-H(12B)	109.2
H(12A)-C(12)-H(12B)	107.9
C(14)-C(13)-C(12)	120.9(2)
C(14)-C(13)-C(8)	123.25(19)
C(12)-C(13)-C(8)	115.84(18)
C(13)-C(14)-C(1)	124.9(2)
C(13)-C(14)-H(14)	117.5
C(1)-C(14)-H(14)	117.5
C(7)-C(15)-H(15A)	109.5
C(7)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(7)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(8)-C(16)-H(16A)	109.5
C(8)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(8)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(18)-C(17)-C(19)	120.0(2)
C(18)-C(17)-C(10)	124.3(2)
C(19)-C(17)-C(10)	115.6(2)
C(17)-C(18)-H(18A)	120.0
C(17)-C(18)-H(18B)	120.0
H(18A)-C(18)-H(18B)	120.0
C(17)-C(19)-H(19A)	109.5
C(17)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(17)-C(19)-H(19C)	109.5

H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(1)-O(1)-H(1)	109.5
C(3)-O(2)-H(2)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for compound **186**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	18(1)	19(1)	19(1)	0(1)	2(1)	0(1)
C(2)	22(1)	17(1)	21(1)	-2(1)	-1(1)	-2(1)
C(3)	22(1)	16(1)	19(1)	2(1)	4(1)	4(1)
C(4)	21(1)	19(1)	19(1)	2(1)	-4(1)	2(1)
C(5)	19(1)	20(1)	15(1)	1(1)	4(1)	-4(1)
C(6)	18(1)	14(1)	18(1)	-1(1)	0(1)	2(1)
C(7)	19(1)	18(1)	17(1)	-1(1)	1(1)	1(1)
C(8)	21(1)	17(1)	18(1)	1(1)	-2(1)	3(1)
C(9)	26(1)	22(1)	19(1)	1(1)	0(1)	0(1)
C(10)	29(1)	22(1)	22(1)	1(1)	-4(1)	4(1)
C(11)	29(1)	31(1)	22(1)	0(1)	-9(1)	4(1)
C(12)	22(1)	31(1)	27(1)	-2(1)	-5(1)	3(1)
C(13)	18(1)	24(1)	20(1)	-4(1)	-1(1)	5(1)
C(14)	14(1)	24(1)	24(1)	-6(1)	-1(1)	0(1)
C(15)	23(1)	23(1)	18(1)	1(1)	0(1)	-2(1)
C(16)	30(1)	21(1)	23(1)	-1(1)	-4(1)	7(1)
C(17)	47(2)	23(1)	20(1)	1(1)	-5(1)	2(1)
C(18)	47(2)	37(2)	21(1)	5(1)	4(1)	1(1)
C(19)	57(2)	63(2)	27(1)	13(1)	-9(1)	4(2)
O(1)	25(1)	21(1)	22(1)	1(1)	6(1)	-5(1)
O(2)	25(1)	20(1)	25(1)	-2(1)	-5(1)	2(1)
O(3)	24(1)	20(1)	19(1)	-3(1)	-2(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **186**.

	x	y	z	U(eq)
H(2A)	3807	9344	3671	24
H(2B)	5067	10368	3298	24
H(4)	478	8908	2521	23
H(6)	4903	5895	2884	20
H(7)	2414	6855	3682	21
H(9A)	3020	6086	4442	27
H(9B)	2735	4306	4334	27
H(10)	5885	3784	4681	29
H(11A)	7719	5772	5067	33
H(11B)	6103	6997	4883	33
H(12A)	8846	7019	4341	32
H(12B)	8646	5215	4256	32
H(14)	7945	8213	3635	25
H(15A)	2004	4098	3136	32
H(15B)	321	5368	3225	32
H(15C)	1034	4300	3667	32
H(16A)	5927	3902	3318	37
H(16B)	4428	3032	3680	37
H(16C)	6636	3463	3859	37
H(18A)	1609	4338	5633	42
H(18B)	1320	4785	5054	42
H(19A)	6173	4997	5786	74
H(19B)	6439	3304	5575	74
H(19C)	4658	3674	5948	74
H(1)	6908	9257	2738	34
H(2)	514	11175	2940	35

Crystal Structure Determination of Compound 218

A colorless plate 0.080 x 0.060 x 0.030 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using and scans. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame using a scan width of 1.0°.

Data collection was 100.0% complete to 25.000° in \. A total of 56781 reflections were collected covering the indices, -23<=*h*<=21, -8<=*k*<=8, -23<=*l*<=23. 5031 reflections were found to be symmetry independent, with an R_{int} of 0.0819. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/c (No. 14). 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.

Table 1. Crystal data and structure refinement for compound **218**

X-ray ID	maimone74	
Sample/notebook ID	XG-I-41	
Empirical formula	C28 H48 O4 Si	
Formula weight	476.75	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 19.3720(12) Å	⟨= 90°.
	b = 7.4505(5) Å	®= 99.679(2)°.
	c = 19.2839(11) Å	© = 90°.
Volume	2743.6(3) $Å^3$	
Z	4	
Density (calculated)	1.154 Mg/m^3	
Absorption coefficient	0.115 mm^{-1}	
F(000)	1048	
Crystal size	0.080 x 0.060 x 0.030 mm^3	
Theta range for data collection	1.066 to 25.399°.	
Index ranges	-23<=h<=21, -8<=k<=8, -23<=l<=23	
Reflections collected	56781	
Independent reflections	5031 [R(int) = 0.0819]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.928 and 0.785	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5031 / 0 / 309	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2sigma(I)]	R1 = 0.0459, wR2 = 0.1079	
R indices (all data)	R1 = 0.0609, wR2 = 0.1161	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.318 and -0.265 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **218**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2082(1)	4727(3)	2716(1)	20(1)
C(2)	1876(1)	5012(3)	1914(1)	19(1)
C(3)	2559(1)	5574(2)	1644(1)	17(1)
C(4)	2496(1)	5622(3)	838(1)	20(1)
C(5)	3220(1)	5713(3)	609(1)	20(1)
C(6)	3633(1)	7348(2)	928(1)	18(1)
C(7)	4438(1)	7355(2)	904(1)	18(1)
C(8)	4770(1)	5476(2)	1016(1)	17(1)
C(9)	5550(1)	5555(3)	1062(1)	18(1)
C(10)	5917(1)	7086(3)	1483(1)	23(1)
C(11)	5445(1)	8005(2)	1923(1)	18(1)
C(12)	4749(1)	8676(2)	1523(1)	18(1)
C(13)	4182(1)	8805(3)	2002(1)	19(1)
C(14)	3654(1)	7333(2)	1735(1)	16(1)
C(15)	2944(1)	7254(2)	2001(1)	17(1)
C(16)	3094(1)	6897(3)	2802(1)	19(1)
C(17)	2442(1)	6346(3)	3099(1)	21(1)
C(18)	1618(1)	3211(3)	1584(1)	23(1)
C(19)	1265(1)	6335(3)	1743(1)	23(1)
C(20)	3305(1)	9046(3)	549(1)	24(1)
C(21)	4934(1)	10540(3)	1253(1)	23(1)
C(22)	2537(1)	9028(3)	1867(1)	22(1)
C(23)	820(1)	820(3)	2992(1)	34(1)
C(24)	2200(1)	1562(3)	3934(1)	38(1)
C(25)	855(1)	3504(3)	4203(1)	25(1)
C(26)	569(1)	1962(3)	4598(1)	32(1)
C(27)	1346(1)	4667(3)	4728(1)	38(1)
C(28)	243(1)	4661(3)	3841(1)	33(1)
O(1)	4623(1)	8028(2)	267(1)	21(1)
O(2)	5887(1)	4449(2)	795(1)	23(1)
O(3)	5636(1)	8249(2)	2548(1)	21(1)

O(4)	1477(1)	4295(2)	3019(1)	22(1)
Si(1)	1349(1)	2578(1)	3519(1)	22(1)

Table 3. Bond lengths [Å] and angles [°] for compound **218**.

C(1)-O(4)	1.432(2)	C(13)-C(14)	1.529(2)
C(1)-C(17)	1.521(3)	C(13)-H(13A)	0.9900
C(1)-C(2)	1.546(2)	C(13)-H(13B)	0.9900
C(1)-H(1)	1.0000	C(14)-C(15)	1.549(2)
C(2)-C(18)	1.533(3)	C(14)-H(14)	1.0000
C(2)-C(19)	1.534(3)	C(15)-C(22)	1.538(3)
C(2)-C(3)	1.558(2)	C(15)-C(16)	1.545(2)
C(3)-C(4)	1.539(2)	C(16)-C(17)	1.527(2)
C(3)-C(15)	1.557(3)	C(16)-H(16A)	0.9900
C(3)-H(3)	1.0000	C(16)-H(16B)	0.9900
C(4)-C(5)	1.541(2)	C(17)-H(17A)	0.9900
C(4)-H(4A)	0.9900	C(17)-H(17B)	0.9900
C(4)-H(4B)	0.9900	C(18)-H(18A)	0.9800
C(5)-C(6)	1.529(3)	C(18)-H(18B)	0.9800
C(5)-H(5A)	0.9900	C(18)-H(18C)	0.9800
C(5)-H(5B)	0.9900	C(19)-H(19A)	0.9800
C(6)-C(20)	1.543(3)	C(19)-H(19B)	0.9800
C(6)-C(14)	1.549(2)	C(19)-H(19C)	0.9800
C(6)-C(7)	1.567(2)	C(20)-H(20A)	0.9800
C(7)-O(1)	1.427(2)	C(20)-H(20B)	0.9800
C(7)-C(8)	1.541(3)	C(20)-H(20C)	0.9800
C(7)-C(12)	1.586(2)	C(21)-H(21A)	0.9800
C(8)-C(9)	1.500(2)	C(21)-H(21B)	0.9800
C(8)-H(8A)	0.9900	C(21)-H(21C)	0.9800
C(8)-H(8B)	0.9900	C(22)-H(22A)	0.9800
C(9)-O(2)	1.218(2)	C(22)-H(22B)	0.9800
C(9)-C(10)	1.508(3)	C(22)-H(22C)	0.9800
C(10)-C(11)	1.512(2)	C(23)-Si(1)	1.857(2)
C(10)-H(10A)	0.9900	C(23)-H(23A)	0.9800
C(10)-H(10B)	0.9900	C(23)-H(23B)	0.9800
C(11)-O(3)	1.214(2)	C(23)-H(23C)	0.9800
C(11)-C(12)	1.520(3)	C(24)-Si(1)	1.867(2)
C(12)-C(21)	1.546(3)	C(24)-H(24A)	0.9800
C(12)-C(13)	1.552(2)	C(24)-H(24B)	0.9800

C(24)-H(24C)	0.9800	C(27)-H(27A)	0.9800
C(25)-C(26)	1.534(3)	C(27)-H(27B)	0.9800
C(25)-C(28)	1.534(3)	C(27)-H(27C)	0.9800
C(25)-C(27)	1.536(3)	C(28)-H(28A)	0.9800
C(25)-Si(1)	1.8856(19)	C(28)-H(28B)	0.9800
C(26)-H(26A)	0.9800	C(28)-H(28C)	0.9800
C(26)-H(26B)	0.9800	O(1)-H(1A)	0.8400
C(26)-H(26C)	0.9800	O(4)-Si(1)	1.6458(14)

O(4)-C(1)-C(17)	108.66(14)	C(6)-C(5)-H(5B)	109.4
O(4)-C(1)-C(2)	110.38(14)	C(4)-C(5)-H(5B)	109.4
C(17)-C(1)-C(2)	113.40(15)	H(5A)-C(5)-H(5B)	108.0
O(4)-C(1)-H(1)	108.1	C(5)-C(6)-C(20)	108.44(14)
C(17)-C(1)-H(1)	108.1	C(5)-C(6)-C(14)	108.69(14)
C(2)-C(1)-H(1)	108.1	C(20)-C(6)-C(14)	114.90(15)
C(18)-C(2)-C(19)	106.73(15)	C(5)-C(6)-C(7)	116.58(15)
C(18)-C(2)-C(1)	107.82(15)	C(20)-C(6)-C(7)	108.41(15)
C(19)-C(2)-C(1)	111.26(14)	C(14)-C(6)-C(7)	99.89(13)
C(18)-C(2)-C(3)	109.48(14)	O(1)-C(7)-C(8)	106.24(13)
C(19)-C(2)-C(3)	115.15(15)	O(1)-C(7)-C(6)	114.98(14)
C(1)-C(2)-C(3)	106.20(13)	C(8)-C(7)-C(6)	112.75(14)
C(4)-C(3)-C(15)	112.26(14)	O(1)-C(7)-C(12)	108.11(14)
C(4)-C(3)-C(2)	114.48(14)	C(8)-C(7)-C(12)	111.19(14)
C(15)-C(3)-C(2)	116.01(14)	C(6)-C(7)-C(12)	103.56(13)
C(4)-C(3)-H(3)	104.1	C(9)-C(8)-C(7)	111.45(15)
C(15)-C(3)-H(3)	104.1	C(9)-C(8)-H(8A)	109.3
C(2)-C(3)-H(3)	104.1	C(7)-C(8)-H(8A)	109.3
C(3)-C(4)-C(5)	111.60(14)	C(9)-C(8)-H(8B)	109.3
C(3)-C(4)-H(4A)	109.3	C(7)-C(8)-H(8B)	109.3
C(5)-C(4)-H(4A)	109.3	H(8A)-C(8)-H(8B)	108.0
C(3)-C(4)-H(4B)	109.3	O(2)-C(9)-C(8)	123.71(16)
C(5)-C(4)-H(4B)	109.3	O(2)-C(9)-C(10)	120.07(16)
H(4A)-C(4)-H(4B)	108.0	C(8)-C(9)-C(10)	116.20(15)
C(6)-C(5)-C(4)	111.14(15)	C(9)-C(10)-C(11)	111.65(15)
C(6)-C(5)-H(5A)	109.4	C(9)-C(10)-H(10A)	109.3
C(4)-C(5)-H(5A)	109.4	C(11)-C(10)-H(10A)	109.3

C(9)-C(10)-H(10B)	109.3	C(1)-C(17)-C(16)	111.84(14)
C(11)-C(10)-H(10B)	109.3	C(1)-C(17)-H(17A)	109.2
H(10A)-C(10)-H(10B)	108.0	C(16)-C(17)-H(17A)	109.2
O(3)-C(11)-C(10)	120.82(16)	C(1)-C(17)-H(17B)	109.2
O(3)-C(11)-C(12)	123.44(16)	C(16)-C(17)-H(17B)	109.2
C(10)-C(11)-C(12)	115.65(14)	H(17A)-C(17)-H(17B)	107.9
C(11)-C(12)-C(21)	103.39(14)	C(2)-C(18)-H(18A)	109.5
C(11)-C(12)-C(13)	111.98(14)	C(2)-C(18)-H(18B)	109.5
C(21)-C(12)-C(13)	111.84(15)	H(18A)-C(18)-H(18B)	109.5
C(11)-C(12)-C(7)	111.74(14)	C(2)-C(18)-H(18C)	109.5
C(21)-C(12)-C(7)	112.55(14)	H(18A)-C(18)-H(18C)	109.5
C(13)-C(12)-C(7)	105.54(14)	H(18B)-C(18)-H(18C)	109.5
C(14)-C(13)-C(12)	104.84(14)	C(2)-C(19)-H(19A)	109.5
C(14)-C(13)-H(13A)	110.8	C(2)-C(19)-H(19B)	109.5
C(12)-C(13)-H(13A)	110.8	H(19A)-C(19)-H(19B)	109.5
C(14)-C(13)-H(13B)	110.8	C(2)-C(19)-H(19C)	109.5
C(12)-C(13)-H(13B)	110.8	H(19A)-C(19)-H(19C)	109.5
H(13A)-C(13)-H(13B)	108.9	H(19B)-C(19)-H(19C)	109.5
C(13)-C(14)-C(15)	119.77(14)	C(6)-C(20)-H(20A)	109.5
C(13)-C(14)-C(6)	103.62(14)	C(6)-C(20)-H(20B)	109.5
C(15)-C(14)-C(6)	117.35(14)	H(20A)-C(20)-H(20B)	109.5
C(13)-C(14)-H(14)	104.8	C(6)-C(20)-H(20C)	109.5
C(15)-C(14)-H(14)	104.8	H(20A)-C(20)-H(20C)	109.5
C(6)-C(14)-H(14)	104.8	H(20B)-C(20)-H(20C)	109.5
C(22)-C(15)-C(16)	108.70(14)	C(12)-C(21)-H(21A)	109.5
C(22)-C(15)-C(14)	111.76(15)	C(12)-C(21)-H(21B)	109.5
C(16)-C(15)-C(14)	108.05(13)	H(21A)-C(21)-H(21B)	109.5
C(22)-C(15)-C(3)	115.05(14)	C(12)-C(21)-H(21C)	109.5
C(16)-C(15)-C(3)	107.39(14)	H(21A)-C(21)-H(21C)	109.5
C(14)-C(15)-C(3)	105.60(14)	H(21B)-C(21)-H(21C)	109.5
C(17)-C(16)-C(15)	113.08(14)	C(15)-C(22)-H(22A)	109.5
C(17)-C(16)-H(16A)	109.0	C(15)-C(22)-H(22B)	109.5
C(15)-C(16)-H(16A)	109.0	H(22A)-C(22)-H(22B)	109.5
C(17)-C(16)-H(16B)	109.0	C(15)-C(22)-H(22C)	109.5
C(15)-C(16)-H(16B)	109.0	H(22A)-C(22)-H(22C)	109.5
H(16A)-C(16)-H(16B)	107.8	H(22B)-C(22)-H(22C)	109.5

Si(1)-C(23)-H(23A)	109.5	C(7)-O(1)-H(1A)	109.5
Si(1)-C(23)-H(23B)	109.5	C(1)-O(4)-Si(1)	128.94(11)
H(23A)-C(23)-H(23B)	109.5	O(4)-Si(1)-C(23)	110.55(8)
Si(1)-C(23)-H(23C)	109.5	O(4)-Si(1)-C(24)	110.94(8)
H(23A)-C(23)-H(23C)	109.5	C(23)-Si(1)-C(24)	108.32(11)
H(23B)-C(23)-H(23C)	109.5	O(4)-Si(1)-C(25)	105.61(8)
Si(1)-C(24)-H(24A)	109.5	C(23)-Si(1)-C(25)	110.07(9)
Si(1)-C(24)-H(24B)	109.5	C(24)-Si(1)-C(25)	111.35(9)
H(24A)-C(24)-H(24B)	109.5		
Si(1)-C(24)-H(24C)	109.5		
H(24A)-C(24)-H(24C)	109.5		
H(24B)-C(24)-H(24C)	109.5		
C(26)-C(25)-C(28)	109.35(16)		
C(26)-C(25)-C(27)	109.26(16)		
C(28)-C(25)-C(27)	109.18(18)		
C(26)-C(25)-Si(1)	110.00(14)		
C(28)-C(25)-Si(1)	109.38(12)		
C(27)-C(25)-Si(1)	109.66(13)		
C(25)-C(26)-H(26A)	109.5		
C(25)-C(26)-H(26B)	109.5		
H(26A)-C(26)-H(26B)	109.5		
C(25)-C(26)-H(26C)	109.5		
H(26A)-C(26)-H(26C)	109.5		
H(26B)-C(26)-H(26C)	109.5		
C(25)-C(27)-H(27A)	109.5		
C(25)-C(27)-H(27B)	109.5		
H(27A)-C(27)-H(27B)	109.5		
C(25)-C(27)-H(27C)	109.5		
H(27A)-C(27)-H(27C)	109.5		
H(27B)-C(27)-H(27C)	109.5		
C(25)-C(28)-H(28A)	109.5		
C(25)-C(28)-H(28B)	109.5		
H(28A)-C(28)-H(28B)	109.5		
C(25)-C(28)-H(28C)	109.5		
H(28A)-C(28)-H(28C)	109.5		
H(28B)-C(28)-H(28C)	109.5		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for compound **218**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	18(1)	23(1)	20(1)	3(1)	7(1)	1(1)
C(2)	17(1)	20(1)	20(1)	1(1)	4(1)	1(1)
C(3)	15(1)	18(1)	18(1)	1(1)	4(1)	3(1)
C(4)	18(1)	23(1)	19(1)	0(1)	2(1)	-2(1)
C(5)	21(1)	24(1)	15(1)	-3(1)	3(1)	-1(1)
C(6)	18(1)	19(1)	16(1)	1(1)	4(1)	1(1)
C(7)	22(1)	19(1)	13(1)	3(1)	6(1)	-1(1)
C(8)	20(1)	16(1)	16(1)	-2(1)	5(1)	-2(1)
C(9)	22(1)	20(1)	13(1)	4(1)	6(1)	1(1)
C(10)	19(1)	24(1)	25(1)	-4(1)	8(1)	-4(1)
C(11)	22(1)	13(1)	20(1)	-1(1)	8(1)	-6(1)
C(12)	22(1)	16(1)	17(1)	0(1)	6(1)	-1(1)
C(13)	21(1)	18(1)	18(1)	-2(1)	5(1)	0(1)
C(14)	19(1)	14(1)	15(1)	1(1)	3(1)	3(1)
C(15)	17(1)	17(1)	17(1)	1(1)	4(1)	1(1)
C(16)	19(1)	21(1)	18(1)	-3(1)	4(1)	0(1)
C(17)	21(1)	27(1)	18(1)	-2(1)	6(1)	0(1)
C(18)	21(1)	26(1)	21(1)	-1(1)	4(1)	-2(1)
C(19)	17(1)	26(1)	26(1)	1(1)	4(1)	3(1)
C(20)	25(1)	26(1)	21(1)	7(1)	3(1)	3(1)
C(21)	29(1)	18(1)	22(1)	0(1)	7(1)	-3(1)
C(22)	19(1)	22(1)	26(1)	-1(1)	6(1)	4(1)
C(23)	40(1)	33(1)	32(1)	-4(1)	16(1)	-6(1)
C(24)	28(1)	51(2)	36(1)	15(1)	10(1)	5(1)
C(25)	20(1)	35(1)	19(1)	-3(1)	5(1)	-5(1)
C(26)	29(1)	49(2)	21(1)	0(1)	9(1)	-7(1)
C(27)	38(1)	51(2)	27(1)	-12(1)	11(1)	-14(1)
C(28)	28(1)	40(1)	33(1)	-4(1)	12(1)	1(1)
O(1)	29(1)	22(1)	14(1)	0(1)	8(1)	-4(1)
O(2)	25(1)	24(1)	21(1)	-4(1)	7(1)	4(1)
O(3)	25(1)	21(1)	18(1)	-2(1)	3(1)	-3(1)

O(4)	17(1)	29(1)	22(1)	2(1)	8(1)	0(1)
Si(1)	18(1)	29(1)	20(1)	2(1)	6(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **218**.

	x	y	z	U(eq)
H(1)	2412	3688	2795	24
H(3)	2891	4562	1792	20
H(4A)	2216	6681	652	24
H(4B)	2246	4534	635	24
H(5A)	3486	4607	761	24
H(5B)	3158	5779	90	24
H(8A)	4656	4951	1454	21
H(8B)	4569	4687	620	21
H(10A)	6073	7971	1159	27
H(10B)	6338	6624	1796	27
H(13A)	4390	8597	2500	22
H(13B)	3955	10000	1959	22
H(14)	3895	6185	1899	19
H(16A)	3449	5935	2901	23
H(16B)	3293	7997	3046	23
H(17A)	2577	6058	3604	26
H(17B)	2110	7366	3056	26
H(18A)	2011	2369	1622	34
H(18B)	1419	3390	1087	34
H(18C)	1257	2721	1832	34
H(19A)	1201	6660	1244	35
H(19B)	1366	7418	2031	35
H(19C)	835	5774	1846	35
H(20A)	3451	9145	87	36
H(20B)	3463	10108	831	36
H(20C)	2794	8962	487	36
H(21A)	5104	11321	1654	34
H(21B)	4515	11072	972	34
H(21C)	5299	10407	961	34
H(22A)	2867	10034	1913	33

H(22B)	2222	9162	2212	33
H(22C)	2262	9018	1392	33
H(23A)	373	1333	2766	51
H(23B)	733	-170	3300	51
H(23C)	1076	369	2630	51
H(24A)	2416	960	3573	57
H(24B)	2116	686	4290	57
H(24C)	2513	2506	4157	57
H(26A)	956	1185	4809	49
H(26B)	232	1262	4269	49
H(26C)	335	2454	4970	49
H(27A)	1540	5635	4476	57
H(27B)	1729	3923	4973	57
H(27C)	1084	5184	5072	57
H(28A)	-15	5140	4196	49
H(28B)	-71	3926	3504	49
H(28C)	426	5657	3593	49
H(1A)	4480	7316	-64	32

Crystal Structure Determination of Compound 187

A colorless prism 0.050 x 0.040 x 0.030 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using and scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 2.0°. Data collection was 100.0% complete to 67.000° in q. A total of 67277 reflections were collected covering the indices, -11<=*h*<=11, -29<=*k*<=29, -13<=*l*<=13. 4304 reflections were found to be symmetry independent, with an R_{int} of 0.0366. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/c (No. 14). 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.

Table 1. Crystal data and structure refinement for compound **187**.

X-ray ID	maimone82	
Sample/notebook ID	XG-I-186-1	
Empirical formula	C26 H38 O6	
Formula weight	446.56	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 9.2723(6) Å	a= 90°.
	b = 24.6156(16) Å	b= 110.088(3)°.
	c = 10.9526(7) Å	g = 90°.
Volume	2347.8(3) $Å^3$	
Z	4	
Density (calculated)	1.263 Mg/m^3	
Absorption coefficient	0.713 mm^{-1}	
F(000)	968	
Crystal size	0.050 x 0.040 x 0.030 mm^3	
Theta range for data collection	3.591 to 68.338°.	
Index ranges	-11<=h<=11, -29<=k<=29, -13<=l<=13	
Reflections collected	67277	
Independent reflections	4304 [R(int) = 0.0366]	
Completeness to theta = 67.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.797	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4304 / 0 / 298	
Goodness-of-fit on F^2	1.048	
Final R indices [I>2sigma(I)]	R1 = 0.0370, wR2 = 0.0921	
R indices (all data)	R1 = 0.0387, wR2 = 0.0937	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.280 and -0.220 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **187**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3600(1)	6107(1)	7434(1)	19(1)
C(2)	4482(1)	5644(1)	7032(1)	18(1)
C(3)	6132(2)	5756(1)	7074(1)	23(1)
C(4)	6293(2)	6333(1)	6613(1)	26(1)
C(5)	5362(2)	6790(1)	6939(1)	24(1)
C(6)	4047(2)	6925(1)	5646(1)	24(1)
C(7)	2844(1)	6472(1)	5154(1)	19(1)
C(8)	1649(1)	6590(1)	3767(1)	20(1)
C(9)	2545(2)	6662(1)	2822(1)	22(1)
C(10)	1508(2)	6645(1)	1397(1)	23(1)
C(11)	590(1)	6122(1)	1072(1)	22(1)
C(12)	-425(1)	6022(1)	1906(1)	21(1)
C(13)	641(1)	6069(1)	3360(1)	19(1)
C(14)	-168(1)	5949(1)	4339(1)	22(1)
C(15)	1000(1)	5830(1)	5687(1)	21(1)
C(16)	2159(1)	6297(1)	6214(1)	19(1)
C(17)	4646(1)	6600(1)	7917(1)	21(1)
C(18)	4806(2)	6859(1)	9015(1)	25(1)
C(19)	3164(2)	5880(1)	8564(1)	20(1)
C(20)	4228(2)	5516(1)	10682(1)	25(1)
C(21)	6703(2)	5334(1)	6355(2)	34(1)
C(22)	6399(2)	7289(1)	7379(1)	32(1)
C(23)	724(2)	7115(1)	3728(1)	24(1)
C(24)	-1826(2)	6401(1)	1519(1)	25(1)
C(25)	-1017(2)	5433(1)	1653(1)	25(1)
C(26)	1348(2)	6769(1)	6647(1)	24(1)
O(1)	1917(1)	5899(1)	8678(1)	27(1)
O(2)	4392(1)	5669(1)	9459(1)	23(1)
O(3)	3945(1)	5193(1)	6795(1)	22(1)
O(4)	6906(1)	5731(1)	8448(1)	33(1)
O(5)	7129(1)	6424(1)	6000(1)	44(1)

O(6)	-334(1)	6129(1)	-290(1)	29(1)

Table 3. Bond lengths [Å] and angles [°] for compound **187**.

C(1)-C(17)	1.5306(17)
C(1)-C(19)	1.5348(17)
C(1)-C(2)	1.5525(16)
C(1)-C(16)	1.6000(16)
C(2)-O(3)	1.2065(15)
C(2)-C(3)	1.5401(18)
C(3)-O(4)	1.4287(15)
C(3)-C(21)	1.5057(19)
C(3)-C(4)	1.5310(18)
C(4)-O(5)	1.2077(17)
C(4)-C(5)	1.5335(19)
C(5)-C(17)	1.5147(18)
C(5)-C(22)	1.5318(17)
C(5)-C(6)	1.5550(17)
C(6)-C(7)	1.5391(17)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(16)	1.5634(17)
C(7)-C(8)	1.5701(16)
C(7)-H(7)	1.0000
C(8)-C(23)	1.5436(17)
C(8)-C(9)	1.5439(17)
C(8)-C(13)	1.5591(16)
C(9)-C(10)	1.5262(17)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.5168(17)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-O(6)	1.4432(15)
C(11)-C(12)	1.5392(17)
C(11)-H(11)	1.0000
C(12)-C(24)	1.5369(17)
C(12)-C(25)	1.5406(17)

C(12)-C(13)	1.5639(16)
C(13)-C(14)	1.5336(17)
C(13)-H(13)	1.0000
C(14)-C(15)	1.5299(17)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(16)	1.5439(17)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-C(26)	1.5455(17)
C(17)-C(18)	1.3231(18)
C(18)-H(18A)	0.9500
C(18)-H(18B)	0.9500
C(19)-O(1)	1.2059(16)
C(19)-O(2)	1.3259(15)
C(20)-O(2)	1.4489(15)
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(26)-H(26A)	0.9800
C(26)-H(26B)	0.9800

C(26)-H(26C)	0.9800
O(4)-H(4)	0.8400
O(6)-H(6)	0.8400

C(17)-C(1)-C(19)	108.76(10)
C(17)-C(1)-C(2)	110.36(10)
C(19)-C(1)-C(2)	105.72(9)
C(17)-C(1)-C(16)	107.80(9)
C(19)-C(1)-C(16)	113.84(10)
C(2)-C(1)-C(16)	110.35(9)
O(3)-C(2)-C(3)	120.24(11)
O(3)-C(2)-C(1)	121.16(11)
C(3)-C(2)-C(1)	118.33(10)
O(4)-C(3)-C(21)	112.38(11)
O(4)-C(3)-C(4)	108.52(10)
C(21)-C(3)-C(4)	112.09(11)
O(4)-C(3)-C(2)	99.07(9)
C(21)-C(3)-C(2)	112.63(11)
C(4)-C(3)-C(2)	111.41(10)
O(5)-C(4)-C(3)	120.59(13)
O(5)-C(4)-C(5)	120.93(12)
C(3)-C(4)-C(5)	118.48(11)
C(17)-C(5)-C(22)	113.86(11)
C(17)-C(5)-C(4)	110.96(10)
C(22)-C(5)-C(4)	108.56(11)
C(17)-C(5)-C(6)	108.26(10)
C(22)-C(5)-C(6)	109.00(10)
C(4)-C(5)-C(6)	105.88(10)
C(7)-C(6)-C(5)	114.23(10)
C(7)-C(6)-H(6A)	108.7
C(5)-C(6)-H(6A)	108.7
C(7)-C(6)-H(6B)	108.7
C(5)-C(6)-H(6B)	108.7
H(6A)-C(6)-H(6B)	107.6
C(6)-C(7)-C(16)	111.71(10)
C(6)-C(7)-C(8)	112.92(10)

C(16)-C(7)-C(8)	116.01(10)
C(6)-C(7)-H(7)	105.0
C(16)-C(7)-H(7)	105.0
C(8)-C(7)-H(7)	105.0
C(23)-C(8)-C(9)	107.92(10)
C(23)-C(8)-C(13)	114.07(10)
C(9)-C(8)-C(13)	108.11(10)
C(23)-C(8)-C(7)	112.54(10)
C(9)-C(8)-C(7)	107.84(10)
C(13)-C(8)-C(7)	106.13(9)
C(10)-C(9)-C(8)	112.75(10)
C(10)-C(9)-H(9A)	109.0
C(8)-C(9)-H(9A)	109.0
C(10)-C(9)-H(9B)	109.0
C(8)-C(9)-H(9B)	109.0
H(9A)-C(9)-H(9B)	107.8
C(11)-C(10)-C(9)	111.65(10)
C(11)-C(10)-H(10A)	109.3
C(9)-C(10)-H(10A)	109.3
C(11)-C(10)-H(10B)	109.3
C(9)-C(10)-H(10B)	109.3
H(10A)-C(10)-H(10B)	108.0
O(6)-C(11)-C(10)	108.59(10)
O(6)-C(11)-C(12)	110.38(10)
C(10)-C(11)-C(12)	113.91(10)
O(6)-C(11)-H(11)	107.9
C(10)-C(11)-H(11)	107.9
C(12)-C(11)-H(11)	107.9
C(24)-C(12)-C(11)	111.72(10)
C(24)-C(12)-C(25)	107.86(10)
C(11)-C(12)-C(25)	107.32(10)
C(24)-C(12)-C(13)	114.42(10)
C(11)-C(12)-C(13)	106.92(10)
C(25)-C(12)-C(13)	108.35(10)
C(14)-C(13)-C(8)	110.41(10)
C(14)-C(13)-C(12)	114.10(10)

C(8)-C(13)-C(12)	117.35(10)
C(14)-C(13)-H(13)	104.5
C(8)-C(13)-H(13)	104.5
C(12)-C(13)-H(13)	104.5
C(15)-C(14)-C(13)	111.00(10)
C(15)-C(14)-H(14A)	109.4
C(13)-C(14)-H(14A)	109.4
C(15)-C(14)-H(14B)	109.4
C(13)-C(14)-H(14B)	109.4
H(14A)-C(14)-H(14B)	108.0
C(14)-C(15)-C(16)	112.90(10)
C(14)-C(15)-H(15A)	109.0
C(16)-C(15)-H(15A)	109.0
C(14)-C(15)-H(15B)	109.0
C(16)-C(15)-H(15B)	109.0
H(15A)-C(15)-H(15B)	107.8
C(15)-C(16)-C(26)	108.98(10)
C(15)-C(16)-C(7)	109.61(10)
C(26)-C(16)-C(7)	112.67(10)
C(15)-C(16)-C(1)	111.67(9)
C(26)-C(16)-C(1)	108.55(9)
C(7)-C(16)-C(1)	105.36(9)
C(18)-C(17)-C(5)	123.76(12)
C(18)-C(17)-C(1)	123.75(12)
C(5)-C(17)-C(1)	112.26(10)
C(17)-C(18)-H(18A)	120.0
C(17)-C(18)-H(18B)	120.0
H(18A)-C(18)-H(18B)	120.0
O(1)-C(19)-O(2)	123.34(11)
O(1)-C(19)-C(1)	126.65(11)
O(2)-C(19)-C(1)	109.96(10)
O(2)-C(20)-H(20A)	109.5
O(2)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
O(2)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5

H(20B)-C(20)-H(20C)	109.5
C(3)-C(21)-H(21A)	109.5
C(3)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
C(3)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(5)-C(22)-H(22A)	109.5
C(5)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(5)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(8)-C(23)-H(23A)	109.5
C(8)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(8)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(12)-C(24)-H(24A)	109.5
C(12)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(12)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(12)-C(25)-H(25A)	109.5
C(12)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(12)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
C(16)-C(26)-H(26A)	109.5
C(16)-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26B)	109.5
C(16)-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26C)	109.5

H(26B)-C(26)-H(26C)	109.5
C(19)-O(2)-C(20)	116.69(10)
C(3)-O(4)-H(4)	109.5
C(11)-O(6)-H(6)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for compound **187**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(1)	18(1)	16(1)	0(1)	4(1)	1(1)
C(2)	21(1)	21(1)	11(1)	2(1)	2(1)	2(1)
C(3)	21(1)	27(1)	18(1)	0(1)	2(1)	0(1)
C(4)	23(1)	32(1)	19(1)	0(1)	5(1)	-5(1)
C(5)	27(1)	22(1)	19(1)	1(1)	3(1)	-6(1)
C(6)	28(1)	21(1)	18(1)	2(1)	2(1)	-5(1)
C(7)	21(1)	16(1)	17(1)	1(1)	4(1)	-1(1)
C(8)	23(1)	18(1)	16(1)	1(1)	3(1)	-1(1)
C(9)	24(1)	21(1)	19(1)	1(1)	5(1)	-4(1)
C(10)	26(1)	25(1)	18(1)	2(1)	6(1)	-2(1)
C(11)	21(1)	26(1)	17(1)	-2(1)	3(1)	-1(1)
C(12)	20(1)	22(1)	18(1)	-1(1)	3(1)	-1(1)
C(13)	19(1)	17(1)	18(1)	0(1)	3(1)	1(1)
C(14)	20(1)	23(1)	20(1)	1(1)	4(1)	-1(1)
C(15)	21(1)	22(1)	18(1)	2(1)	5(1)	-2(1)
C(16)	21(1)	18(1)	15(1)	1(1)	3(1)	1(1)
C(17)	22(1)	18(1)	18(1)	2(1)	2(1)	1(1)
C(18)	31(1)	20(1)	21(1)	-1(1)	4(1)	1(1)
C(19)	26(1)	17(1)	17(1)	-3(1)	5(1)	-1(1)
C(20)	32(1)	27(1)	16(1)	4(1)	8(1)	2(1)
C(21)	28(1)	35(1)	42(1)	-4(1)	16(1)	3(1)
C(22)	34(1)	30(1)	24(1)	0(1)	2(1)	-13(1)
C(23)	31(1)	19(1)	20(1)	2(1)	4(1)	3(1)
C(24)	21(1)	31(1)	20(1)	1(1)	3(1)	3(1)
C(25)	25(1)	26(1)	21(1)	-2(1)	3(1)	-5(1)
C(26)	28(1)	24(1)	19(1)	1(1)	6(1)	5(1)
O(1)	26(1)	35(1)	21(1)	3(1)	8(1)	1(1)
O(2)	27(1)	25(1)	17(1)	4(1)	7(1)	4(1)
O(3)	26(1)	18(1)	19(1)	0(1)	5(1)	1(1)
O(4)	24(1)	49(1)	20(1)	7(1)	-1(1)	-7(1)
O(5)	49(1)	44(1)	52(1)	7(1)	33(1)	-3(1)

O(6)	26(1)	45(1)	16(1)	-5(1)	5(1)	-7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **187**.

	x	y	z	U(eq)
H(6A)	3522	7260	5772	28
H(6B)	4502	7002	4968	28
H(7)	3436	6148	5035	22
H(9A)	3093	7015	3000	26
H(9B)	3324	6371	2982	26
H(10A)	794	6958	1212	28
H(10B)	2145	6678	838	28
H(11)	1332	5814	1221	26
H(13)	1397	5767	3483	22
H(14A)	-804	6265	4391	26
H(14B)	-856	5632	4037	26
H(15A)	1569	5494	5644	25
H(15B)	445	5764	6301	25
H(18A)	5397	7183	9227	30
H(18B)	4329	6720	9592	30
H(20A)	3860	5828	11046	37
H(20B)	5225	5398	11292	37
H(20C)	3489	5217	10535	37
H(21A)	7791	5398	6496	51
H(21B)	6110	5356	5424	51
H(21C)	6579	4972	6678	51
H(22A)	5792	7596	7504	47
H(22B)	6845	7382	6714	47
H(22C)	7224	7208	8199	47
H(23A)	1407	7396	4255	37
H(23B)	-99	7041	4076	37
H(23C)	276	7242	2828	37
H(24A)	-1490	6776	1479	38
H(24B)	-2335	6376	2167	38
H(24C)	-2546	6294	666	38

H(25A)	-1512	5376	716	38
H(25B)	-1763	5368	2090	38
H(25C)	-154	5181	1992	38
H(26A)	303	6811	6024	36
H(26B)	1923	7106	6682	36
H(26C)	1303	6690	7510	36
H(4)	7771	5879	8638	50
H(6)	227	6070	-736	44