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Application of Asymmetric Transformations in the Total Synthesis of Xestospongin Natural Products

A dissertation submitted in partial satisfaction of the requirements for

the degree Doctor of Philosophy in Chemistry

by

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ABSTRACT

Application of Asymmetric Transformations in the Total Synthesis of Xestospongin Natural Products

by

Alana Kim Borum

Asymmetric synthesis is key in the construction of complex natural products, many of which possess chiral centers. Xestospongin compounds are chiral, medicinally intriguing compounds, of which (+)-desmethylxestospongin B has demonstrated potential as a targeted anti-tumor therapeutic. The work conducted and reported here shall discuss the syntheses of (+)-desmethylxestospongin B and (+)-9,9'-difluoroxestospongin C, the latter of which utilizing knowledge gained from our investigation into the synthesis and Ireland-Claisen rearrangement of α-fluoroallylic esters. The production of these materials aimed to support ongoing research regarding the medicinal properties of (+)-desmethylxestospongin B.

Our lab's preexisting synthesis of (+)-desmethylxestospongin B served as a foundation to produce this valuable chemical; the target is distinguished from other compounds in the xestospongin family by its C9 oxidation and lack of C2 symmetry. Herein the execution of synthetic strategies solving scalability issues found within the original route is reported, the updated synthesis yielding this product at a total yield increasing that of the original by 50%. To achieve this, critical analysis was undertaken to elucidate unresolved issues in the published synthesis. A notable restructuring of the route's front-end showed instant results in

increased yield and material efficiency. While the previous synthesis depended on kinetic resolution to make four of the six stereocenters in (+)-desmethylxestospongin B's original synthesis, the improved route features an asymmetric epoxidation step, using novel work performed on terminal alkenes. This method delivered the desired epoxide in high yield and dr while simultaneously increasing material efficiency. Furthermore, different protecting group strategies to avoid problems with their subsequent removal were considered and enacted; to this end, two superfluous protecting/deprotecting steps were discarded. Furthermore, using different protecting groups in the modified synthesis saw retention of material into the route, where the previous strategies lost material in affecting undesired global deprotection. While the late-stage lactam semi-reduction under Birch conditions still requires optimization, the updated synthesis of (+)-desmethylxestospongin B reported increased scalability, affording 0.37 g of this natural product for continued biological studies.

A total synthesis can be adapted to generate analogues, as was the case for (+)-9,9'-difluoroxestospongin C. The results and valuable information obtained from studying the stereoselective Ireland-Claisen rearrangement to afford α-fluorocarboxylic acids supported the proposed synthesis of fluorinated xestospongin analogues. Previously, (–)-9,9'-difluoroaraguspongine B had been afforded within our lab, however this compound's bioactivity could not be studied due to poor solubility. The executed modular synthesis set to investigate if inversion at (–)-9,9'-difluoroaraguspongin B's C9' would decrease crystal packing due to broken symmetry, and thus improve the difluorinated xestospongin's solubility. With (+)-9,9'-difluoroxestospongin C as the proposed target, the modified synthesis of (+)-desmethylxestospongin B was executed to yield 13 mg of this target, which was noted to have improved solubility than its predecessor.

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LIST OF ABBREVIATIONS

acac: acetylacetonate (ligand)

AcO: acetate

AcOH: acetic acid

Bn: benzyl (protecting group)

Br: broad

Bu: butyl

Bz: benzoate

° C: degrees Celsius

Ca^{2+}: calcium ion

Calcd: calculated

δ: chemical shift(s) (ppm)

d: doublet

dmXe B: (+)-desmethylxestospongin B

DIAD: diisopropyl azodicarboxylate

diFAr B: (+)-9,9'-difluoroaraguspongine B

diFXeB: (+)-9,9'-difluoroxestospongin C

DDQ: 2,3-dichloro-5,6-dicyano-*p*-benzoquinone

DMF: dimethylformamide

dr: diastereoseomeric ratio

E: entgegen

EDC·HCl: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

equiv: equivalent

ESI: electrospray ionization

Et: ethyl

g: gram

h: hours

HATU: hexafluorophosphate azabenzotriazole tetramethyl uronium

HMPA: hexamethylphosphoramide

HOBt: hydroxybenzotriazole

HPLC: high performance liquid chromatography

HRMS: high resolution mass spectroscopy

Hz: hertz

ImH: imidazole

i: iso

KHMDS: potassium hexamethyldisilazane

J: coupling constant (NMR)

L: liter(s)

LDA: lithium diisopropylamide

m: multiplet

M: molarity (mol/L)

m/z: mass/charge

[M + Na^+]: molecular weight + sodium

MCPBA: *meta*-chloroperoxybenzoic acid

Me: methyl

mg: milligram(s)

MHz: megahertz

μL: microliter(s)

min: minutes

mL: milliliter(s)

mmol: millimole(s)

mmHg: millimeters of mercury

MS: mass spectrometry

NMR: nuclear magnetic resonance (spectroscopy)

Ph: phenyl

PMB: *para*-methoxybenzyl

ppm: parts per million

R: rectus

rt: room (ambient) temperature

s: singlet

S: sinister

TBAF: tetrabutylammonium fluoride

TBAI: tetrabutylammonium iodide

TBS: *tert*-butyldimethylilyl

THF: tetrahydrofuran

THP: tetrahydropyran

Z: zusammen

Chapter 1

(+)-Modifying the Total Synthesis of (+)-Desmethylxestospongin B

Summary: Modifications to an original synthesis of (+)-desmethylxestospongin B have been applied to generate this compound at a higher total yield. Many similarities exist between this adjusted synthesis and the original as there were many benefits in the latter. However, since this accomplishment of carrying out the published route to completion, careful considerations have been taken (after the author's experience) in every step of the preexisting synthesis with the ultimate goal of improving the scalability and total yield of this important target molecule.

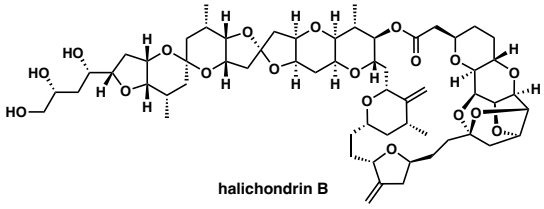
1.1. Introduction

Marine natural products have provided a breadth of compounds which can serve an individual's livelihood. As a singular example, the current number of FDA-approved commodities based on marine natural products exceeds twenty and continues to grow significantly as new marine-sourced compounds are discovered. These compounds behave as chemotherapeutics, provide pain relief, and macular degeneration, and even are found in supplements to reduce triglycerides[1]. While these valuable compounds occur naturally and can be obtained in limited quantities, relying solely on their natural sources may not be the optimal approach to attain them. In such circumstances, attention turns towards organic synthesis chemists who may be able to afford these natural products in appreciable quantities.

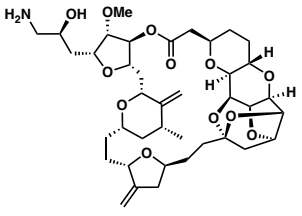
In the case a small amount of natural material is tested and found to be bioactive (or even therapeutic), scalable routes for the syntheses of such compounds are demanded so the product could be more available for what service it could provide – from more biological tests, to development of pharmacophores, to large-scale distribution. One interesting example of this process follows the development of eribulin. After the discovery of marine

natural product halichondrin B, a derivative to this naturally sourced material (norhalichondrin A) was found to have substantial activity against melanoma cells, with a reported IC_{50} of 93 pg/mL. Syntheses were developed in order to attain related (and more simplified) compounds, leading to the route providing eribulin (Figure 1). As this was a complex compound, the original route was 33 steps, which includes the synthesis of a macrocyclic ketone through a Nozaki–Hiyama–Kishi macrocyclization and side chain modification of the intermediate[2]. A process chemistry project was able to target this compound in 67 steps with 33 steps at the longest route, featuring the individual formation of two fragments of the molecule followed by similar macrocyclization strategies as employed on the small scale[3,4]. Through many generations of medicinal, process, and academic chemists making efforts to simplify the route, the synthesis of eribulin was finally shortened to 52 steps in 2023; this final synthesis features a one-pot proline-catalyzed α-chlorination/aldol reaction which accesses an aldehyde intermediate with great efficiency, as well as a key Corey–Chaykovsky step[5].

Figure 1: Halichondrin B and eribulin



halichondrin B



eribulin (Halaven)

Akin to such undertakings to improve known routes to work with higher scales of material to achieve greater amounts of final compound, the synthesis of marine natural product (+)-desmethylxestospongin B has received appreciable scrutiny in accomplishing similar goals. This chapter shall discuss how the published synthesis of (+)-desmethylxestospongin B was improved, and how intermediates were submitted through effective reactions on a hectogram scale.

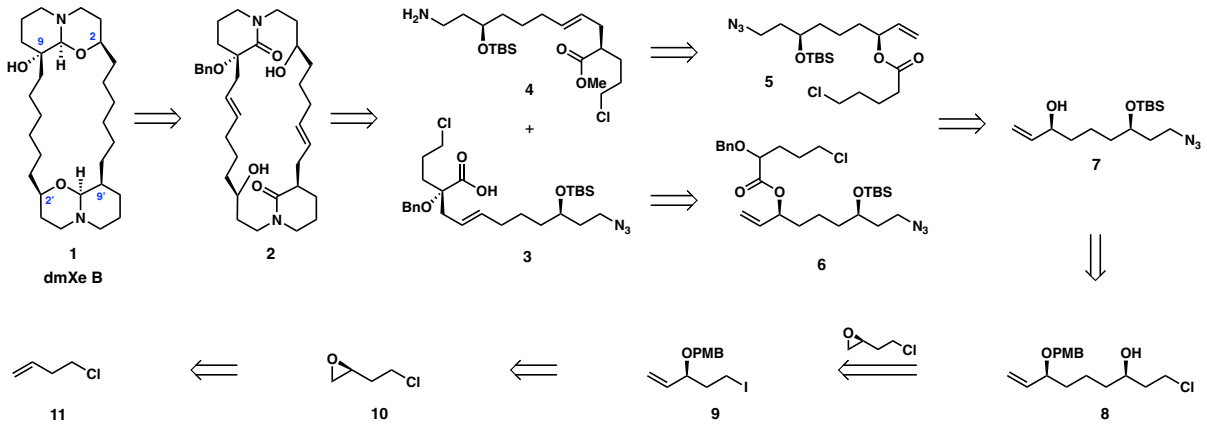
1.1.1 (+)-Desmethylxestospongin B

(+)-Desmethylxestospongin B (dmXe B) is a natural product holding great attention for its structural complexity and bioactivity. Xestospongin and araguspongine compounds were isolated from the species *Xestospongia exigua* and structurally identified[6,7,8] to be comprised of two bis-1-oxaquinolizidine heterocycles bound by two equivalent hexamethylene chains. Some variance does exist between these compounds, including C2-symmetry (or lack thereof) and C9/9' oxidation. Few of these xestospongin compounds – notably dmXe B – were observed to affect mitochondrial respiration by blocking inositol triphosphate receptors in the endoplasmic reticulum, leading to cellular autophagy, and allowing selective tumor cell apoptosis. The mechanism of action for the activation of autophagy can be explained by the blocking of the inositol triphosphate receptors by the xestospongin compound, effectively halting Ca^{2+} transfer from the endoplasmic reticulum to the mitochondria[9]. Under low Ca^{2+} mitochondrial concentrations, the cell's ability to phosphorylate ATP substrates is reduced under these conditions, and to combat this disruption to homeostasis, AMPK is activated within the mitochondria to continue the production of ATP. From here, the cell enters a state of autophagy, which is a pro-survival method evolved in cells to survive reduced ATP

production and turns on in conjunction with AMPK activation[5]. This phenomenon has been observed in treating MDA-MB-231 cell lines with increasing concentrations of dmXe B against normal MCF10A cells[9,10]. While the promise of targeted cancer treatments remains attractive, the natural source of dmXe B has been depleted while biological studies are still ongoing. To provide this material to continue the highly anticipated studies, this lab has developed and reported a 22-step total synthesis for this compound in 2021[10].

The syntheses of other xestospongin compounds have been executed by other groups. Hoye's synthesis[11] of (+)-xestospongin A and Baldwin's biomimetic synthesis[12] of (+)-araguspongine B and (–)-xestospongin A both approach C2-symmetrical targets (lacking C9 and/or 9' hydroxylation, as in the target dmXe B) through dimerization strategies, which has proven useful in the production of these targets. In Baldwin's case, the syntheses of enantiomers to the naturally produced xestospongin compounds were crucial in the assignment of absolute stereochemistry of these molecules. An original route was required in the synthesis of an asymmetric, C9 hydroxylated xestospongin (as is dmXe B) so it could be produced in an efficient, rational manner beginning with simple starting materials[10].

Scheme 1: Retrosynthesis of (+)-desmethylxestospongin B, reported in 2021



The strategy enacted previously in our group is shown in Scheme 1. Preceding the last step requiring hydrogenation to provide the saturated hexamethylene tethers in the xestospongin compound, the final ring closure gives provides the intermediate structure bearing the two bis-1-oxaquinolizidine heterocycles of the target and is affected by the partial reduction of the δ-lactam in **2** to a hemiaminal intermediate. The first six membered rings to close in the construction of the bis-1-oxaquinolizidine heterocycles to give the δ-lactams in **2** occur in tandem under the strongly basic conditions provided by $LiN(SiMe_3)_2$. In functionalizing intermediates **3** and **4** independently, the desired macrolactam is assembled in a stepwise manner with each of the amide bonds formed one at a time with strategic protection of the fragments aimed to completely avoid homodimerization in the synthesis of a macrolactam intermediate. In the case of acid **3** and amine **4**, the established stereochemistry and functionalization at C9 and C9' (of the final bis-1-oxaquinolizidine heterocycles) is translated through separate Ireland Claisen rearrangement reactions, their conditions determined by the α-substitution (or lack thereof) of the corresponding allylic ester substrates **5** and **6**. In the case of **4** the rearrangement is followed by esterification and azide reduction to amine to allow the stepwise formation of the two crucial amide bonds in the macrolactam intermediate preceding **2**. These individual allylic esters **5** and **6** are derived from standard esterification of azido alcohol **7**, which is synthesized through a coupling reaction between chiral epoxide **10** and alkyl-iodide **9** by use of a higher order cuprate. Intermediate **9** itself is given by methylenation and alcohol protection of chiral epoxide **10**, which is furnished through an epoxidation of chloride **11** with MCPBA followed by kinetic resolution[10]. This chiral epoxide – used twice in the synthesis – establishes the stereochemistry of four centers in the final compound. **11** itself is either commercially

available or can be made through chlorodehydroxylation of 3,4-buten-1-ol. Since the published work reported the total yield from commercially available **11**, comparisons in the modified synthesis will not include the first chlorodehydroxylation step in calculations. The chloride and bromide of **11** used in this synthesis are both commercially available.

1.2 Strategies in modifying the original synthesis

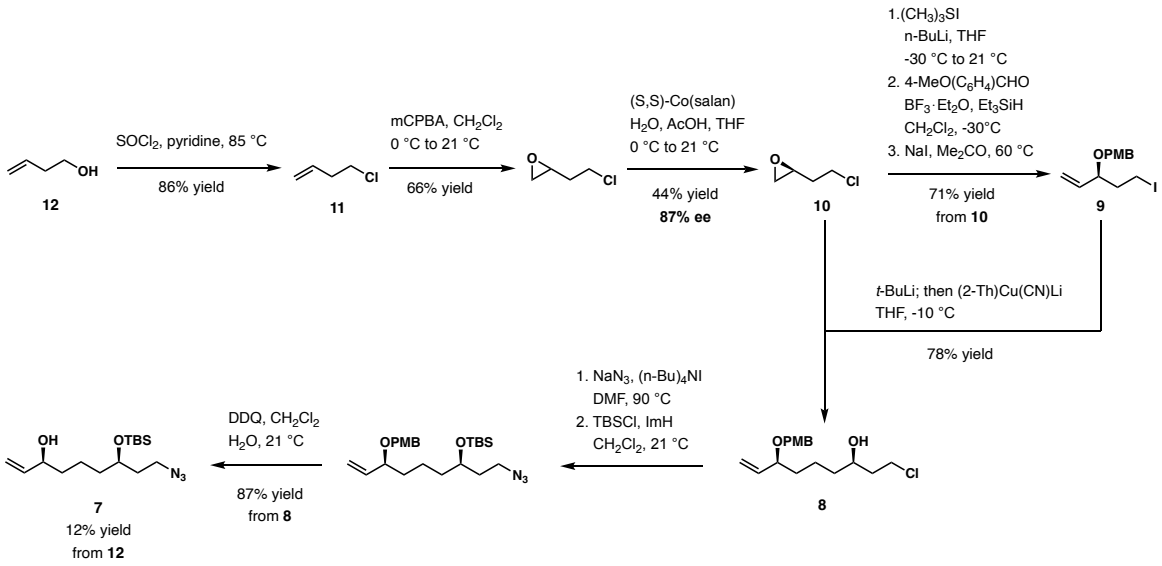
While the original synthesis remains effective in achieving a non-symmetric, functionalized xestospongin molecule, a few outstanding questions remained following the initial completion of the route. The original route delivered enough dmXe B to be studied biologically, however the material would eventually be consumed in the tests. Solving these problems would substantially improve the route's overall efficiency, its scalability, and ultimately providing greater amounts of this biologically remarkable target compound. The opportunity for a new and improved synthesis arose in 2022 when the collaborating biological team ran low on material and asked the lab for one gram of dmXe B. The issues with the original route demanded consideration so it could best suit a gram-scale synthesis of this marine natural product.

1.2.1 Considerations of excessive use of kinetic resolution

The first point to consider was the kinetic resolution step which is performed early in the route. Roughly half the material in making chiral epoxide **10** (which is used twice in the synthesis to establish the four stereocenters at C2, C2', C9, and C9' on the two separate bis-1-oxaquinolizidine heterocycles) had to be discarded after kinetic resolution with Jacobsen's catalyst with effective hydrolysis of the undesired isomer. Reduced dependence on this

material afforded through this inefficient method can be accomplished with a high-yielding, asymmetric transformation to establish at least two of these four aforementioned stereocenters, so long as it could reproduce the high chiral purity given in the preestablished work.

Scheme 2: Original synthesis of common intermediate **7**



1.2.2 Considerations of the challenging PMB protecting group to provide 9, superfluous installation and removal of protecting group steps

In this manner, the first twelve steps of the synthesis demonstrated material inefficiency, which is then furthered by the superfluous alcohol protection to make alkyl iodide **9**, as the para-methoxybenzyl (PMB) group would need to be removed a mere four steps later in a 22-step synthesis. This PMB-protecting group procedure furthermore presented a challenge when our best efforts would see the partial conversion to the protected alcohol, and substrate

had to be recovered and resubmitted to the reaction to save material. For this reaction, the protection is carried forward under $BF_3 \cdot OEt_2$ and triethylsilane, instead of standard conditions using sodium hydride. This former method was chosen for the final route because initial attempts to use the standard conditions saw no conversion. Due to these challenges in making the PMB-protected allylic alcohol **9**, new approaches were explored. A new scheme which could avoid requirement of this protecting group would certainly improve the productivity of these initial steps.

1.2.3 Considerations of a challenging intermediate requiring reaction conditions affecting global deprotection

On a separate note (within a far more advanced stage in the total synthesis), the hydrolysis of methyl ester given by **4** (enacted to access the intermediate for macrolactamization) was accompanied by the unintentional removal of the silyl protecting groups, which must remain on the intermediates until the final stages of the route. This desilylated byproduct was observed upon the rapidly applied acidic workup conditions required, which aimed to circumvent the formation of a six-membered lactone byproduct which could form under the basic conditions of the hydrolysis. There was no feasible way to recover this material by selective re-silylation of the byproduct, so the yield was adversely impacted by this loss in material.

Finally, the Birch reduction of the α-lactam units showed 54% yield of the desired product, as well as 11% yield of the α-dehydroxylation to the araguspongine B (Ar B) precursor. Optimization is still required to suppress this α-dehydroxylation, which perhaps might be possible by the careful selection of a different intermediate expected to be less

impacted by these strong conditions which unfavorably fragmented the intermediate of the preexisting synthesis.

1.2.4 Working strategy in updating the synthesis

To solve these outstanding questions regarding the scalability of this important target, several modifications were proposed and executed in an updated synthesis. Firstly, the original route was significantly adjusted in the first twelve steps to improve its overall efficiency. To achieve this, a unique asymmetric epoxidation method is applied to establish the stereocenter in terminal epoxide **16** and subsequently allylic alcohol **17** (Scheme 2), to be translated to C9/9' stereochemistry and functionalization and to reduce dependence on the production of epoxide **10**. In this manner, the unessential and cumbersome PMB protection to give **9** is no longer required; the coupling step will take place instead by Grignard addition to one equivalent of the chiral epoxide to give the terminal olefin shown in **14** (see Scheme 3). To prevent early-stage desilylation with the acidic workup conditions applied after the hydrolysis of the methyl ester intermediate (given by **4**), this challenging intermediate is replaced instead with an allyl ester, as the conditions for its cleavage do not involve drastic changes to pH and are expected to leave the silyl ether groups unaffected throughout the course of the reaction and its workup.

Finally, in a hypothesis to reduce α-dehydroxylation in the Birch reduction, the protecting group at the C9 hydroxyl group is changed from a benzyl ether to PMB so it is removed selectively before the reduction step instead of the benzyl group's concurrent removal enacted in the previous strategy. Having the free hydroxyl group at C9 was conjectured to suppress loss of this functional group as the rate of α-dehydroxylation was expected to be

slower than α-deoxybenzylation. This hypothesis seemed to hold weight with the reported synthesis of (+)-araguspongine C[10], where this hypothesis saw its initial test. In the synthesis of this natural product, PMB was employed to protect the oxidated sites at C9 and C9' and in its respective Birch reduction, α-dehydroxylation was not reported even though the isolated yield of pre-(+)-araguspongine C was still low at 45%[10]. With these promising results, a new plan was drafted to use PMB instead of Bn to protect the C9 hydroxyl group until just before this crucial reduction step.

1.3. Initial results, failed attempt to bypass the PMB protection to give azidoalcohol 7

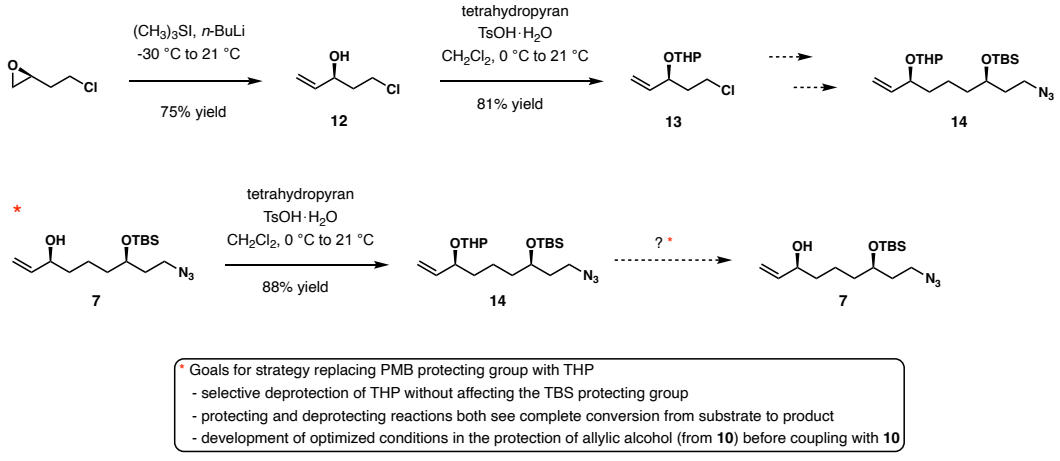
There were multiple attempts undertaken to solve the problem stemming from the PMB protection to give the alkyl iodide **9**. One effort made to accomplish this involved switching the protecting group from PMB to THP. While this strategy would not increase the efficiency of the route by decreasing the number of steps to common intermediate **7**, a complete reaction in the THP protection (of allylic alcohol generated from reaction of **10** with ylide derived from trimethylsulfonium iodide) made this method more attractive than that of the original.

1.3.1 Using THP to protect intermediate 12

After methylene installation upon **10** using ylide chemistry (75% yield, which was believed to be lower yielding due to the volatility of the product and the concentration in vacuo to isolate it after aqueous workup), tetrahydropyran (THP) is installed under standard conditions to protect the free hydroxyl group. This reaction would provide the protected alcohol in yields up to 81%, which already demonstrated an improvement over the original

PMB strategy. Specifically, these improvements were seen in terms of complete conversion to product and isolated yield (without having to re-cycle starting material). Initially, this scheme demonstrated further promise as optimization of product isolation could show significant yield improvements. While these preliminary results were encouraging, there was another major hurdle in enacting this plan: the installation of the THP protecting group was already proving to be higher yielding than that of PMB, but what about the removal of THP? The planned intermediate expecting to be submitted to these deprotecting conditions is compound **14** from Scheme 3. As shown, this intermediate is also protected as a *tert*-butyldimethylsilyl ether, and global deprotection may present an issue (See section 1.3.2 for details).

Scheme 3: An attempt to bypass difficult installation of the PMB protecting group in alkyl iodide **9** given by the original route



1.3.2 The anticipated challenges in selective removal of THP from 14

With intermediate **7** in storage and available for small-scale use at the time, attempts were made to see if the proposed new route was worth the effort of optimizing the THP protecting step of allylic alcohol given by **10**. The underlying question addressed in this work was to determine if there were conditions to selectively remove THP without affecting the *tert*-butyldimethylsilyl (TBS) protecting group. With the TBS group expected to be sensitive to acidic conditions (especially with the experience already gained by enacting the original synthesis of dmXe B), there seemed to be great risk in this endeavor since THP is classically removed by acidic conditions. The same THP-protecting conditions used beforehand on the allylic alcohol intermediate are used again to protect azidoalcohol **7** in reasonably high yield (although this reaction would not be incorporated into the route if the modification was found to be beneficial to the total yield). At this point, efforts were made to immediately remove the THP group to pinpoint conditions which could selectively and completely return to azidoalcohol **7** in high yield.

1.3.3 Other challenges: Finkelstein reaction

At this point in this research, there were already negative results signaling this method may ultimately fail; attempts to convert chloride **13** into an alkyl iodide (resembling intermediate **9** in all manners except the THP protecting group) saw low yields of the iodide at around 52%; there was additionally a 29% yield of prematurely deprotected material, the THP group having been removed in the extended Finkelstein reaction conditions. It is believed either the workup of the Finkelstein reaction or the isolation by column chromatography was the cause behind this undesired result. Information which supports this

claim is in the form of the crude material's proton NMR, which was observed to report only desired iodide product, and the mixture was only noticed after column chromatography. Efforts to explore reactions with **14** were still made in hopes the isolation of iodinated (in place of the chloride) **13** could be optimized later to prevent the THP removal. With the challenges in removing THP from **14**, these optimizations were never carried out as interest was soon lost in this endeavor.

1.3.4 Attempts to remove THP without concurrently hydrolyzing TBS

The first attempt to achieve this was to expose **14** to mild acidic conditions to see how low pH the TBS group could tolerate. This was done using a 0.1 M formic acid solution (in 1:4 DI H_2O in THF). Unfortunately, this method did not work and saw no conversion in terms of either of the hydroxyl groups liberated and returned starting material. Attempts to submit **14** to a more concentrated solution of formic acid (in the same ratio of water in THF) yielded the same results. Changing the organic acid from formic acid to p-toluenesulfonic acid (1.0 equivalents to the substrate) saw disastrous results, with only 27 mol% of the crude material corresponding to the desired alcohol product **7**, and 73 mol% consequent of global deprotection (THP removal in tandem with desilylation). A yield for this reaction was not determined due to the poor results (which at this point seemed a worse method than the PMB strategy enacted in the original synthesis). Reducing the equivalents of p-toluenesulfonic at lower temperatures (0 °C instead of 21 °C) did not improve the reaction. Decreasing the equivalents of the acid ten-fold returned starting material along with the same mixture of products described in the previous case. Decreasing equivalents again to 0.05 equivalents and keeping the reaction temperature at 21 °C returned almost the exact same results as with

1 equivalent of acid (76 mol% diol from global deprotection; 24 mol% being the desired product with TBS intact). Attempts to remove THP by mild acidic conditions were thus abandoned at this point with the inability for selective deprotection.

Another effort made in the selective deprotection of **14** describes the use of magnesium bromide to avoid lowering the pH and compromising the silyl protecting group[13]. Although there was improvement shown in this endeavor with a 65% isolated yield of **7** after isolating components from this reaction, desilylation was still observed on TLC and NMR. Optimization of this reaction could have been undertaken to improve these preliminary results; however the initial profile of this proposed sequence was discouraging due to the concurrent desilylation observed with the intended intermediate, and formulation of a more promising strategy was in progress at this time in the research. Attention was turned towards a more ambitious plan.

1.4 Readjusting the challenging initial twelve steps of the original synthesis to ten productive steps

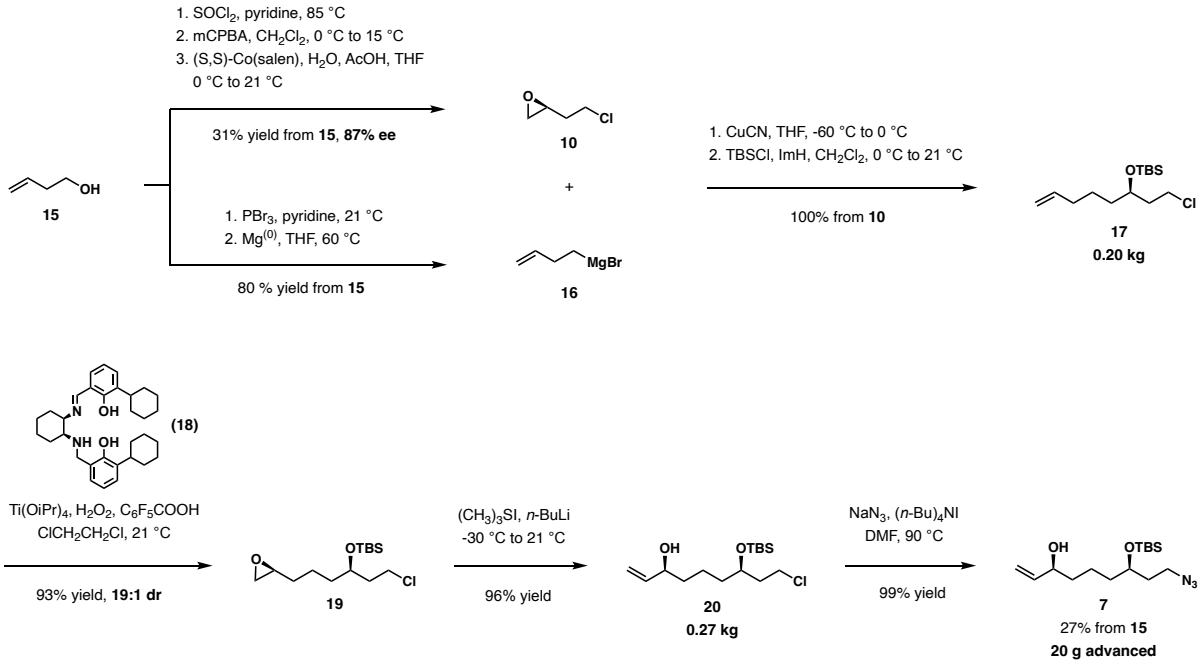
In the first twelve reactions of the original route, the major goals were to bypass the PMB protecting and deprotecting steps, reduce dependence on epoxide **10**, and improve overall efficiency by use of robust reactions. Efforts to exchange the challenging PMB protecting group for THP were proving unproductive at this time, so the new objective was to reach azidoalcohol intermediate **7** by totally avoiding protecting that allylic alcohol, while simultaneously achieving the project goal to reduce dependence on chiral epoxide **10**. The answer to accomplish both these ends was asymmetric catalysis, which could give the C9 and C9' centers the desired stereochemistry after those for C2 and C2' have already been

established. Therefore, the centers for C2 and C2' would be assigned by the original method, while an asymmetric approach could set those for C9 and C9'.

1.4.1 Route start, minor improvements made in the epoxidation by MCPBA

The modified synthesis begins with 3,4-buten-1-ol (**15**), which is distributed to prepare 4-bromo-1,2-butene (which will be converted to Grignard reagent **16**) as well as (S)-2-(2-chloroethyl)oxirane (**10**) as depicted in Scheme 4.

Scheme 4: Modified synthesis of common intermediate **7**



As mentioned in the previous paragraph, the chiral epoxide is generated by the same sequence as in the original synthesis, as this was seen as a reasonable method to bring up material in a short period of time, however these early stages in the route could see even

further improvement in material efficiency with deeper research and careful experimentation (see 1.7 Conclusions). Chlorodehydroxylation of the substrate takes place with thionyl chloride, followed by epoxidation with MCPBA. In an effort to improve the return of this reaction from 65% yield as reported in the original synthesis[10], the epoxidation was performed carefully to suppress the reflux observed when the reaction temperature reached ambient temperature. This reflux was conjectured to decrease the reaction yield because the substrate was volatile and may have evaporated as a mixture with the solvent when the reaction showed formation of gas. To combat this, the temperature of the reaction was decreased so it would not exceed 15 °C. While the reaction took a significantly longer time to reach complete conversion to epoxide product (twelve hours versus four hours), the yield for this step increased from 65% to 81%, confirming a productive strategy in lowering reaction temperature. With this improved procedure, up to 224 g of 4-chlorobut-1-ene have been processed, returning reproducible results in terms of conversion and yield even as the substrate scale increased. Prior to this epoxide's isolation by distillation, the crude solution underwent a quench procedure with dimethylsulfide, and was then carefully checked for presence of peroxides. This was done using potassium iodide, acetic acid, and a small aliquot of the crude solution; a yellow color would indicate presence of peroxides, however if the solution remained colorless, it was safe to heat the crude solution and begin the distillation. The crude racemic epoxide mixture then is submitted to kinetic resolution using Jacobsen's catalyst.

In employing Jacobsen's catalyst to afford chiral epoxide **10**, the reaction was tracked by proton NMR and saw the reaction (expectedly) stalling between 50 – 52% conversion from the epoxide to the oxidized product diol after three days, which signaled a complete kinetic

resolution. The hydrolysis of the undesired enantiomer to give this diol byproduct proved advantageous in the separation of the desired epoxide as **10** was far more volatile than the diol and could be feasibly separated by distillation.

This sequence delivered **10** in 31% yield (62% of the possible yield) over three steps and 87% *ee*. Determining ee was accomplished by derivatization of **10** in the opening of the epoxide and installation of a chromaphore – essentially reconstructing the precursor to compound **9** (chloride instead of iodide) so this compound's enantiopurity could be assessed by HPLC.

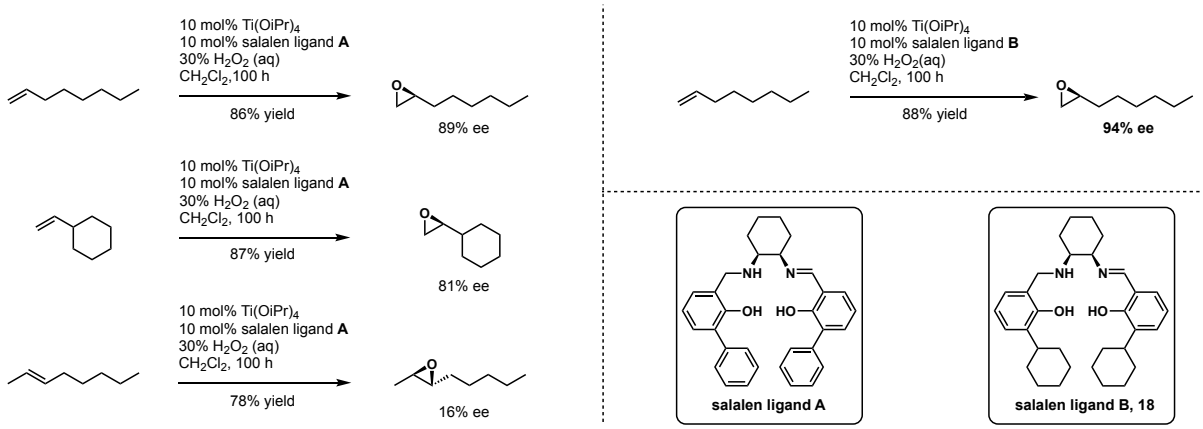
1.4.2 A restructuring of the synthesis's front-end to improve yield of azidoalcohol 7

The Grignard reagent **16** is prepared from 4-bromo-1,2-butene after bromodehydroxylation is performed on **15**, then is immediately submitted to reaction with **10** using a catalytic amount of copper (I) cyanide[14]. This reaction was intended to provide a terminal olefin product which would eventually see asymmetric epoxidation to establish stereochemistry at C9 and C9'. Another goal of this Grignard addition reaction was to afford this terminal olefin product in comparable or higher yields than observed in the coupling reaction from the original route between **9** and **10**. In the amendment to include the copper-catalyzed Grignard addition to the chiral epoxide in this synthesis, the reaction yielded high-purity material in its crude state, with no byproducts observed during the course of the reaction and its subsequent workup. This allowed purification to be postponed until after the ensuing silylation of the product alcohol, which saw 100% yield of olefin intermediate **17** over these two steps. Furthermore, the reaction tolerated adjusted parameters including increasing concentration from 0.18 M to 0.5 M and processing reactions up to 17 g of **10**

with reduced amounts of solvent; these efforts saw no formation of byproducts, reliably providing the alcohol precursor to **17** in quantitative yields and reproducing results from the less concentrated and lower scale renditions of this reaction. It should be noted that scales and concentrations exceeding 17 g and 0.5 M respectively can still be explored to further test the extent of this reaction's scalability, especially if one seeks to generate an even greater mass of this target chemical.

Following the synthesis of olefin **17**, asymmetric epoxidation is employed to increase material efficiency. While numerous, reliable methods to perform asymmetric epoxidations exist, there were few options to allow the transformation to take place on terminal alkenes such as **17** or its alcohol precursor. Initial attempts at remote stereocontrol with desilylated **17** using conditions such as $VO(acac)_2$/*t*-BuOOH proved unproductive, with 6% conversion to the epoxide at best. Even when the literature conditions were reproduced on a reported compound, these conditions would not translate to the proposed substrate **17**. Attention was then turned towards Berkessel's unique work, which describes the asymmetric epoxidation of simple terminal alkenes via the in-situ preparation of a catalyst formed from titanium isopropoxide and salalen ligand **18**[15]. The results and screening studies reported in Berkessel's work (a few examples shown in Figure 2) aided in this optimization for the synthesis of dmXe B. Primarily, the choice of catalyst ligand was dependent on these findings. Although multiple ligands were synthesized and screened for the dmXe B total synthesis project, the same salalen compound **18** provided optimal results as it did for Berkessel's case.

Scheme 5: A brief summary of Berkessel's asymmetric epoxidation of terminal alkenes



After optimizing this reaction to the intermediates of this dmXe B synthesis, it was decided to perform this asymmetric epoxidation on **17** instead of its alcohol precursor. After attempts to isolate this epoxide product, the material afforded was approximately 65 mol% desired epoxide while the remaining 35 mol% corresponded to intramolecular etherification to form a tetrahydropyran byproduct. Since this byproduct was not observed in the crude material, it was strongly believed purification through silica instigated this adverse reaction, which could be easily circumvented by protecting the hydroxyl group as in intermediate **17**. Initial yields of this asymmetric epoxidation with **17** already exceeded those of its alcohol precursor's at 85% yield compared with 60% yield. Further optimization investigated strategies to keep the heterogeneous reaction as homogenous as possible, use of acid additives to increase the reaction's rate (conversion, simply observed as a percent conversion over time), and effects of increased concentration on the reaction. Furthermore, since the salalen ligand was not commercially available, this project was tasked with synthesizing the ligand in house, so efforts were made to see if decreasing the catalyst loading (and thus

amount of ligand) could still reproduce the high yield and chiral purity at 10 mol% catalyst loading. Optimization of this reaction determined the best conditions to carry out this epoxidation; with 5 mol% catalyst, the concentration of the substrate increased to 6.0 M in 1,2-dichloroethane, and the addition of 5 mol% pentafluorobenzoic acid, this reaction would provide epoxide **19** at yields exceeding 90% with an observed 19:1 dr. This measurement was taken through the derivatization of allylic alcohol intermediate **20**. This compound was submitted to reaction with benzoyl chloride to install the chromaphore, then was exposed to mild acidic conditions in order to remove the TBS group. The reason why the silyl ether needed to be cleaved was the alcohol product of this reaction provided better separation by HPLC, which was the instrument utilized to analyze the dr of each batch of epoxide **19** produced. Compared with the 24:1 dr observed in the original route, the newly incorporated asymmetric epoxidation effectively matched stereocontrol from the pre-established synthesis with a more straight-forward, high-yielding method. The decreased catalyst loading was especially accommodating as the reaction was scaled up from 1 g to 50 g to 0.14 kg, and the yield and dr results were reproduced even as substrate mass increased.

Methylene is added into the epoxide by use of an ylide prepared from trimethylsulfonium iodide and *n*-butyllithium. Although trimethylsulfonium iodide is commercially available, at large quantities it was deemed to be more efficient to make this salt in house. The reaction was concentrated from 2.4 M to 5.0 M in ethanol, and methyl iodide was added to the solution of dimethylsulfide at ambient temperature. As the trimethylsulfonium iodide was light sensitive, it had to be shielded from light as the reaction proceeded overnight. Simple filtration would afford the trimethylsulfonium iodide in high yields up to 90%. When the reaction with the ylide was scaled up to 0.10 kg, concentration of the substrate in reaction

increased from 0.2 M to 0.4 M to increase reaction rate and reduce solvent use, and a commercially obtained 10 M *n*-butyllithium in hexanes solution was cannulated to trimethylsulfonium iodide instead of the usual 2.5 M solution to increase material and time efficiency for this singular reaction. To keep the amount of hexanes consistent with the more concentrated *n*-butyllithium solution, HPLC grade hexanes were added to dilute the reaction in an effort to account for the difference in volume from using more concentrated *n*-butyllithium solution. Fortunately, this reaction run on 0.10 kg saw complete conversion and 96% yield.

To reach intermediate **7**, which is in common with the intermediate of the original publication, the epoxide opening step is followed by azide substitution of the chloride in **20**, providing this compound in high purity in its crude state (as what was reported in the original synthesis[5]). This reaction could not be tracked by TLC due to both the product and starting material's same retention factor, so this step required careful monitoring by proton NMR and was only stopped once the reaction reached complete conversion. In re-routing the front-end of the synthesis, the yield of this common intermediate **7** was increased from 13.9% to 30.9% from **11** as compared to the original route, and the number of steps reduced by two in successfully avoiding PMB installation and removal.

1.4.3 A note regarding the advancement of material

As shown in Scheme 4, over 0.2 kg of intermediate **20** was afforded at this stage in the synthesis. One of the initial goals of this undertaking was to synthesize one full gram of dmXe B, and careful analysis indicated 0.2 kg of allylic alcohol **20** would be needed to at least meet (but hopefully exceed) this project aim. At this point in the project, it was decided

bringing up a smaller amount of material would take less time, and it was more crucial for the collaborating biologists to receive this material in a small amount sooner rather than the full gram at a much later date. As **20** was known to be bench-stable, the 0.2 kg of this chemical was stored away at -20 °C so the full gram of dmXe B could be synthesized at a later time, and the new target amount became 0.1 g. 20 g of **20** was thus advanced to make intermediate **7**. Another graduate student may bring this material forward if more of the compound is needed by our collaborators.

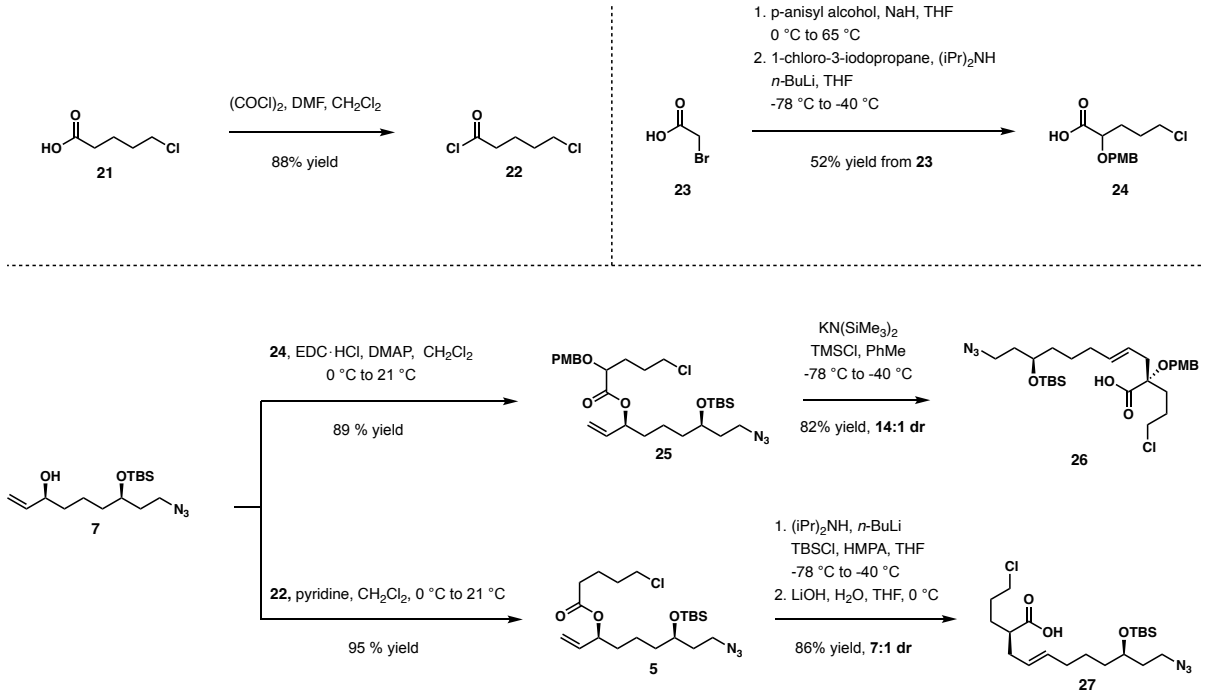
1.5 Other strategies employed to improve scalability of the dmXe B synthesis

Although the front end of the route was significantly modified from the original route, nevertheless many aspects of the published work were retained in the project reported here. Following the synthesis of **7**, much of this synthesis proceeds as such. These compounds were nevertheless new molecules bearing the PMB ether instead of the benzyl intermediates previously employed. Additionally, some of the original synthesis's published procedures differ from the author's in order to account for larger reaction scales, prevention of unwanted byproducts, and the natures of these new intermediates. For the final product mass goals of this project, all 20. g of **7** was used to make the final 0.37 g of synthetic natural product.

1.5.1 Formation of allylic ester fragments, Ireland-Claisen rearrangements

Having successfully achieved intermediate **7**, this compound is then distributed to synthesize the two acid fragments, **26** and **27** (Scheme 6).

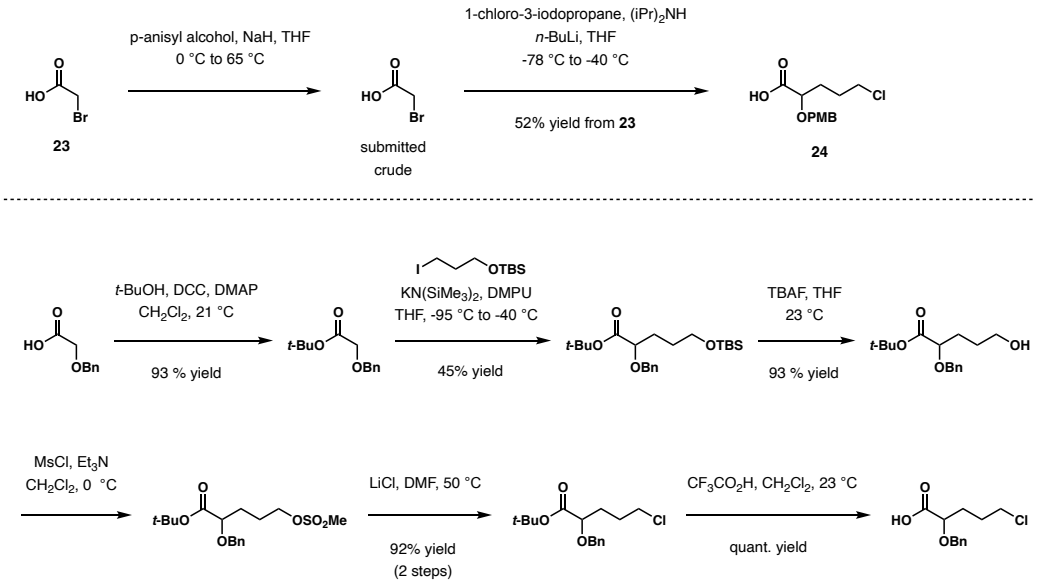
Scheme 6: Synthesis of allylic esters, Ireland Claisen rearrangement



Compound **5** was prepared through the esterification of **7** with prior preparation of 5-chloropentanoyl chloride from 5-chloropentanoic acid. Ester **25** was constructed through the synthesis of carboxylic acid **24,** prepared by substitution of 1-bromoacetic acid with *p*-methoxybenzyl alcohol, then alkylation with 1-chloro-2-iodopropane and lithium diisopropylamine. The procedure to make acid **24** was reported in the literature[16] and is noted for the increased efficiency in providing this fragment which would eventually provide the C9 hydroxylation of the final target. In the previous route to provide the α-OBn substituted acid (Bn instead of PMB in **24**, which would also provide the C9 hydroxylation in dmXe B) took years to optimize in its production and was ultimately a five step route instead of two steps shown in Scheme 7[10]. The shorter and higher yielding route to make this acid fragment served as an added benefit in the primary aim of changing the protecting group

from Bn to PMB, the primary aim standing to remove PMB prior to Birch reduction and potentially suppress the loss of this hydroxylation in the challenging reaction. This sequence to produce **24** was also proven to be scalable to up to 11 g material mass, however higher scales in attempts to make greater amounts of dmXe B could also be explored.

Scheme 7: Synthesis of acid 24 compared with original counterpart



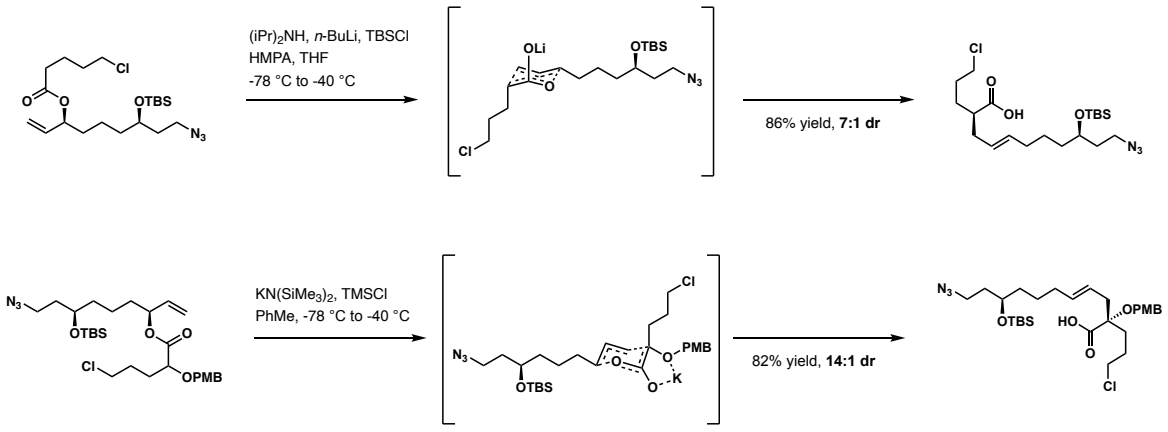
Acid **24** would also require esterification with **7** to continue the route, and vigilant evaporation of contaminant acetic acid (carried over from column chromatography of **24**) was crucial to prevent the acetic ester byproduct (of **7**) which would unnecessarily remove material from the total synthesis. Rotovaping **24** with toluene immediately after isolation by column chromatography effectively avoided this issue. In this synthesis, EDC·HCl conditions are employed instead of converting **24** to an acyl chloride (as was the case for **5**). This was because previous efforts to afford ester **25** by the acyl chloride intermediate of **24**

saw the loss of -OPMB, essentially returning a mixture of **25** and **5** which was unsought and also proved difficulty in separating these two compounds. EDC·HCl conditions were therefore deemed optimal in the synthesis of **25**.

Allylic esters **5** and **25** are then submitted to separate Ireland-Claisen rearrangement conditions depending upon the α-substitution of the substrate. Ester **5** undergoes this rearrangement under standard conditions using lithium diisopropylamine. Preference for the (*E*)-enolate in the intermediate silyl ketene acetal structure gives predictable stereochemistry favoring the desired diastereomer **27** with a 7:1 dr. These conditions were deemed appropriate with an allylic ester lacking α-substitution and were optimized in our studies of this reaction (next paragraph) as well as optimization of the original route.

With **25**, the Ireland-Claisen rearrangement was accomplished with $KN(SiMe_3)_2$ in toluene, which provided optimal conditions for the corresponding transition on the α-substituted allylic ester substrate. Previous work in our lab had demonstrated the stereocontrolled rearrangement of α-alkoxy substituted allylic esters through its preference for the (*Z*)-enolate. This stereocontrol is a result of potassium chelation to the silyl ketene acetal intermediate to the α-substituent (-OPMB) and the (formerly) carbonyl oxygen[17] in the chair-like transition state, which encourages the intermediate to adopt the (*Z*)-enolate geometry. With the execution of these Ireland-Claisen conditions, acid product **26** was afforded at an excellent 14:1 dr.

Figure 2: Chelation control observed in $KN(SiMe_3)_2$ in toluene conditions



1.5.2 Advancing carboxylic acid fragments 26 and 27 to synthesis convergence

Acid **27** is then submitted to allylation followed by azide reduction to give amine **28** in preparation for the stepwise formation of the macrolactam **31** (Scheme 8). It should be noted the conditions for this azide reduction were slightly adjusted from what was previously reported[10] in decreasing the presence of thiophenol from 6 equivalents to 4.5 equivalents as reported in literature[18, 19]. This modification circumvented the previously observed thiophenol substitution of the chloride in **28**. Furthermore, the concentration of the reaction was increased from 0.1 M (to the substrate) to 1.0 M. This prevented excessive concentration of the crude material; in the original procedure, the acetonitrile solvent required removal *in vacuo* before aqueous workup could quench the reducing agent, potentially compromising the crude material and increasing the likelihood of unwanted reactions. Namely, this may have aided in the unwanted thiophenol substitution. At a higher reaction concentration, the solution could be diluted in methylene chloride upon completion

of the reaction and submitted to aqueous workup immediately without concentration *in vacuo* beforehand.

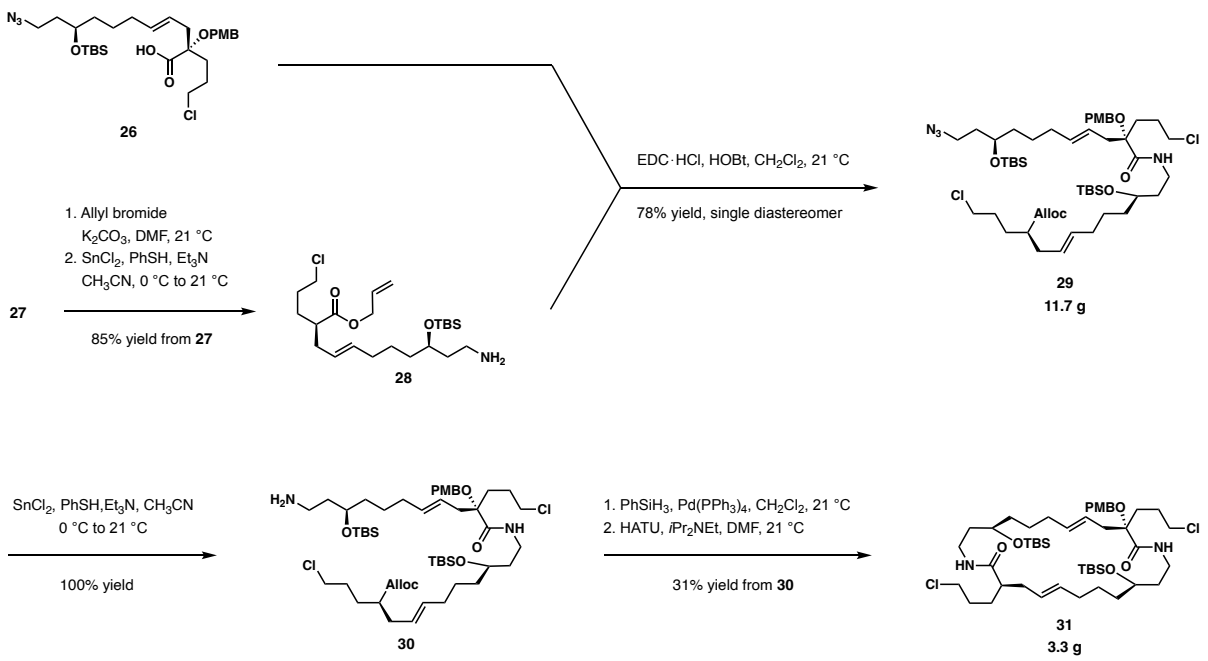
With these procedural adjustments in practice, the initial temperature for the addition of azide substrate was lowered from 21 °C to 0 °C to counteract the exothermic reaction at higher concentrations. In this rendition of the azide reduction with tin (II) chloride, quantitative yields were achieved without any unwanted byproducts observed from the previous procedure at scales up to 7 g, a greater substrate mass than what was ever seen in the original route.

1.5.3 Macrolactamization, completing the synthesis of dmXe B

With carboxylic acid **26** and amine fragment **28** in hand, a convergence step follows in the first amide bond made in the bis(lactam) (**31**) in the formation of **29**. The minor isomers furnished from the Ireland Claisen rearrangements are separable by (painstaking) column chromatography. While the reported synthesis postpones this separation until after macrolactamization, it was envisioned this extra effort could increase the low yield of that cyclization step in removing the undesired isomers beforehand. Following the purification of amide **29**, the azide is reduced using the same tin (II) chloride conditions as previously employed in constructing amine fragment **30**. The acid is liberated with the removal of the allyl group using phenylsilane and palladium tetrakis(triphenylphosphine). This method effectively avoided drastic changes in pH (as was the case with the methyl ester intermediate of the original route), therefore avoiding the unfortunate desilylation issue observed from the previous challenging intermediate, now replaced in this new route. At this stage, the

macrolactamization takes place in high dilution to affect the formation of a 24-membered ring in bis(lactam) **31**.

Scheme 8: Formation of macrolactam **31**



This macrolactamization step proved to be lower yielding than the attempts made in the original synthesis, despite the effort made with amide **29**'s purification. While a reaction with such high dilution (0.003 M substrate in DMF) is expected to give such results, there were efforts made to try and improve this yield. Firstly, by TLC and proton NMR, the crude mixture appeared to still contain unreacted substrate. However, once this material was separated by column chromatography and resubmitted to the macrolactamization reaction, no conversion whatsoever was observed, so unfortunately this material could not be recycled into the route. There was also the consideration of a competing polymerization reaction

(between two or more equivalents of the precursor acid-amine substrate), in which the reaction was diluted by a factor of ten (0.0003 M substrate in DMF) to carry out this reaction on a small amount (84 mg) of substrate in an effort to circumvent this issue. The conversion from substrate to product stalled at ~35%, which replicated the results of the attempts made at higher concentrations and ultimately showed no effect on the reaction's success. No impactful modifications were made in this step of the synthesis, which still begs for optimization as it is one of the lowest-yielding steps in the route. Nevertheless, the 31% yield was deemed to provide an acceptable amount of intermediate **31** to continue the synthesis and deliver dmXe B.

The first six-membered rings to form the two separately functionalized bis-oxaquinolizidine heterocycles are formed in an intramolecular *N*-substitution of amide with the chloride, mediated by $LiN(SiMe_3)_2$. This reaction demanded extreme care as epimerization at the C9' position will take place under the strongly basic environment if too much of the $LiN(SiMe_3)_2$ reagent is added too quickly. Incremental addition of $LiN(SiMe_3)_2$ solution to the substrate solution was therefore required, cautiously titrating the reaction to completion with TLC monitoring after each addition. In this manner, epimerization was thus minimized with the small amount of byproduct easily removed by column chromatography, providing **32** as a single diastereomer.

Following this ring closure, desilylation of **32** is required at this stage in preparation for the final construction of the bis-oxaquinolizidine heterocycles. Standard tetrabutylammonium fluoride conditions were used as in the original synthesis to give the desilylated material in high yield. Purification of this intermediate presented a challenge, as usually mixtures with *tert*-butyldimethylsilanol were observed after compound isolation.

However pure material could be feasibly obtained after the following step. The compound is then submitted to reaction with DDQ in order to remove the PMB group, freeing the hydroxylation at C9.

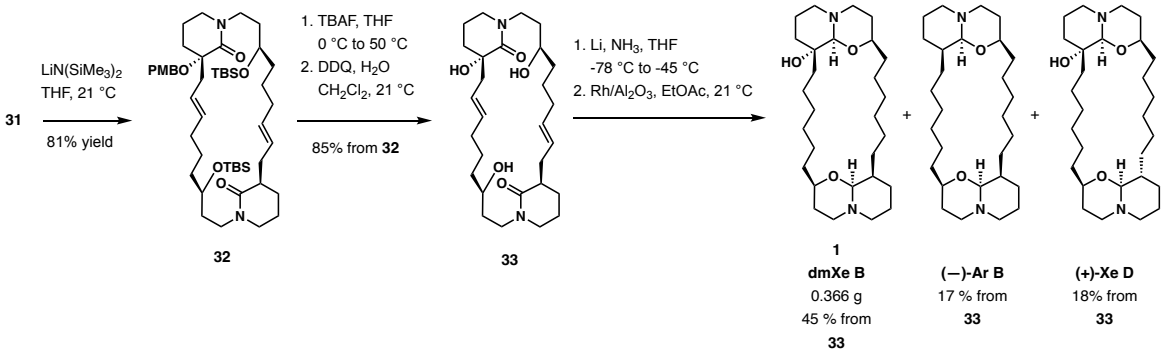
After removal of the PMB group, compound **33** is now prepared for submission to Birch reduction conditions. For this reaction, careful direction was required, not only in matters of safety but also to complete this reaction on an unknown intermediate. It was shortly found that simply following the procedure given in the original synthesis led to an incomplete reaction with only one of the bis-1-oxaquinolizidine rings formed, as observed by scrutiny of the proton NMR.

In efforts to drive the reaction to completion, the partial reduction required extension of the reaction time (30 minutes instead of 15 minutes) as well as an increased reaction temperature (-45 °C instead of -78 °C). Upon completion of these optimization efforts, the reaction saw complete partial reduction with both bis-1-oxaquinolizidine heterocycles closed, however, α-dehydroxylation was unfortunately still observed. Not only that, but the epimerization was also observed. These two byproducts represent the precursor intermediates to (–)-araguspongine B and (+)-xestospongin D, respectively. The only silver lining of this result was the fact the majority of the material (estimated to be between 55 and 60 mol% of the crude) corresponded to the intended product: the precursor to dmXe B. This mixture of three natural product precursors was most likely caused by the extended reaction time required for the Birch reduction to complete so both bis-1-oxaquinolizidine heterocycles could close, while the material remained under the harsh conditions of the reaction.

As the three components could not be separated at this stage (an attempt to do so by reverse-phase column chromatography was fruitlessly made), the mixture was accepted as is

and submitted to hydrogenation with rhodium on alumina. Since the three products and their starting materials were indistinguishable by TLC, monitoring by ^{1}H NMR was required. It was found that the hydrogen needed to be re-introduced into the solution every 30 minutes (otherwise conversion would stall) until the hydrogenation achieved completion. Following filtration over celite to remove the rhodium on alumina, the mixture was finally separated using reverse-phase column chromatography successfully, affording 0.37 g (45% yield from **33**) of dmXe B. The yields shown in Scheme 9 for (–)-araguspongine B and (+)-xestospongin D were determined by ^{1}H NMR as there was coelution observed in this column.

Scheme 9: Concluding the synthesis of dmXe B



1.6 Conclusions

In summary, a successful synthesis of dmXe B was completed with several modifications enhancing scalability issues, which have enabled resumption of biological studies on this natural product. With these adjustments in place, the yield of the common intermediate **7** (following the modified beginning of the synthesis) was increased more than two-fold, in part and also due to the decreased dependence on chiral material obtained by kinetic resolution.

The use of an allyl ester intermediate to replace methyl ester **4** further served to increase the total yield by avoiding premature desilylation prior to the macrolactamization reaction, preventing the loss of material from the total synthesis.

However, it must be said the partial Birch reduction of **33** still requires optimization. Unfortunately, the unsought α-dehydroxylation at C9 was observed at a higher ratio with the free hydroxyl group at C9 compared to the benzyl ether in the same position from the previous synthesis. Further studies are required to continue testing the hypothesis of a more effective bis-1-oxaquinilizidine ring closure with a free hydroxyl group at C9 instead of the benzyl ether. Optimization could have been carried out by the author, however the collaborating biologists needed this material within a week at this point in the project's completion, so such efforts were not given the opportunity for further exploration and this responsibility will probably fall upon another.

There are also other aspects of this synthesis which could be further investigated in a future generation study of this route. There were preliminary efforts to use Berkessel's epoxidation method to synthesize chiral epoxide **10**. The efforts were abandoned at the time due to low conversion in the preliminary reactions, however more time could be spent on this end and might prove beneficial for a chemist with enough salalen ligand **18** on hand. Such efforts, if proven successful, could completely circumvent the production of racemic epoxide (precursor to **10**) and by extension the kinetic resolution step. The author imagines a simplified procedure with isolation carried out by distillation of the crude material from the catalyst (following removal or quenching of peroxides). Even if the enantiomeric purity is decreased from the original method, kinetic resolution could be used instead on enantiomerically enriched material instead of a racemic mixture, increasing material

efficiency. Macrolactamization could also be further optimized in this synthesis; it was never determined why the recovered starting material could not be recycled into this reaction to afford more of the product **31**. Nevertheless, the completion of this project saw achievement of the primary goal, as the total yield of dmXe B (from commercially available **11**) increased from 2.2% to 3.3% in 20 steps.

Chapter 2

Stereocontrol in the Ireland Claisen Rearrangement of α-Fluoro Allylic Esters

Summary: Interesting methods exist to generate α-fluorocarboxylic acids with stereospecificity although they are few. Here, the [3,3]-sigmatropic rearrangement of α-fluoroallylic esters is explored and reported. The high selectivity demonstrated in these reactions supports the rationale of chelation control of potassium (from base $KN(SiMe_3)_2$) encourages the ordered, cyclic silyl ketene acetal intermediate to proceed through the (*Z*)-enolate to provide the corresponding α-fluorocarboxylic acid with predictable stereochemistry.

2.1 Introduction

With the effects of fluorine on bioactive molecules still in exploration, there have been many cases where the known pharmacokinetic properties of bioactive molecules were expanded with the installation of fluorine. Within the last three decades, much progress in the field of medicinal chemistry has been made with the study of fluorinated compounds based on natural product parent compounds, and roughly 25% of all known drugs are fluorinated molecules analogous to natural products – an interesting point when fluorine is found in such a low percentage of naturally sourced compounds[20]. As fluorine is the most electronegative known element, its presence within a structure can meaningfully modulate the medicinal properties of the drug/natural product[20]. In a chemical standpoint, the pKa and pKb of the compound can show a drastic change with the presence of fluorine; considering simple examples of acetic acid and ethanol, the pKa values decrease considerably as more fluorine atoms are present on the molecule. To be specific, the pKa value for acetic acid (4.76) decreases to 2.59 with one fluorine in CH_2FCOOH, then to 0.52 in CF_3COOH. These changes and trends can be rationalized by the electronegativity and inductive effects caused

by presence of fluorine. In some cases of drug-like molecules with amino functional groups (i.e., as what was studied in 2-phenyl-3-piperidylindoles with and without fluorination[21], the bioavailability of the molecule (which was termed as "poor") was increased substantially to 18% with the addition of a single fluorine atom onto the structure, which could be rationalized through the overall decreased basicity of the compound[21].

The trifluoromethyl functional group can also replace methyl groups in a known bioactive target, increasing steric bulk and in some cases, adding to the drug's potency with increased binding forces which favor this steric bulk and the electronegative fluorine. Lipophilicity could also be affected. There were few examples where the lipophilicity of a therapeutic was increased with the installation of fluorine upon the structure, which increased potency of the drug without decreasing the absorption of these compounds by cells. Finally, hydrogen bonding can also be observed between target biomolecules and drugs designed to incorporate fluorine; this is a common consideration made in the current design of new drug-like molecules. The impact of fluorine in the field of medicinal chemistry is quite great and requires further discussion; while these points will not be discussed even close to their entirely within this dissertation, a few notable topics will be expanded upon as mere examples in Chapter 3 which shall discuss the synthesis of a fluorinated analogue to (+)-xestospongin C.

In building these medicinal targets, the fluorine could be installed upon the final molecule itself, however this may present a considerable challenge, since much of these natural products have quite complicated structures and increased functionality, where an issue might be present in the regioselectivity of the fluorination. Not only that, but difluorination is often reported with the use of N-F fluorinating agents. Another method to accomplish these

fluorinated structures is with the methodic development of useful fragments which carry fluorine prior to the fragment's incorporation within the molecule's structure in synthesis. Fluorinated carboxylic acids are remarkable compounds which can be operated as useful fragments to install fluorine into a bioactive target's structure. The carboxylic acid functional group is reactive in itself, and thus can be used as is to access a breadth of related compounds, however a wide range of other functional groups can be accessed. Due to this functionalization's impact in the field of medicinal chemistry, the stereoselective synthesis of such fragments was attractive to the author's goals in a total synthesis project described in Chapter 3.

There are few methods which have been developed in order to synthesize fluorinated carboxylic acids stereoselectively. Tongi and Hintermann report the enantioselective, catalytic, fluorination of β-ketoesters through utility of SelectFluor (known as 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis{tetrafluoroborate}) and a titanium catalyst[22]. The catalytic, enantioselective fluorination was unique as much of these fluorinations were proceeding unselectively through N-F fluorination agents without catalysts. The reported *ee* values for this work exceed 90% *ee* within their substrate scope of seven β-ketoesters except for one outlier (40% *ee*).

Since Tongi and Hintermann's development of this catalytic fluorination, several methods describe enantioselective α-fluorination using various methods, including use of organometallics, phase transfer catalysis, and Lewis acids. Phase transfer catalysis is quite interesting. This process involves the catalytic, enantioselective electrophilic fluorination affected by a quaternary ammonium salt derived from cinchonine, which serves as a phase-transfer catalyst. Under mild reaction conditions, the treatment of β-keto esters with N-

fluorobenzenesulfonimide as the fluorine source yields α-fluoro β-keto esters in excellent yields, accompanied by reasonable *ee*.[23]

Specifically, α-fluorocarboxylic acids can be accessed with predictable stereochemistry via the Ireland-Claisen rearrangement. This reaction is a powerful tool in the formation of new sterocenters in the α-position of the product acid as the rearrangment's selectivity can be deduced from the intermediate silyl ketene acetal, which adopts a highly ordered chair structure. The rearrangement can proceed through the (*E*)-enolate or the (*Z*)-enolate, and a reasonable deduction of which geometry this intermediate may adopt can depend on factors including (but not limited to) steric bulk of substituents and how it affects the chair structure of the silyl ketene acetal intermediate.

The [3,3]-sigmatropic rearrangement with fluorinated allylic esters has been reported[24, 25] with the effect of fluorine in the substrate structure upon this transformation providing insight into this specific reaction with this class of compounds[26, 27]. In the instance of the latter, interesting work has been described in the Ireland-Claisen rearrangement on α-fluoroacetates. Work conducted by Welch and coworkers detail this rearrangement reaction and its stereoselectivity, which is explained by "good internal asymmetric induction[25]." Carrying out this reaction through different conditions demonstrated the sensitivity of the deprotonation and rearrangement when carried out on these fluorinated substrates and was examined such that optimal yield and diastereoselectivity could be realized. They reported an improved procedure for this reaction.[26] In their modified conditions, they report use of triethylamine instead of lithiated organic bases (i.e., lithium diisopropylethylamine or $LiN(SiMe_3)_2$), which was rationalized through the harsh basic conditions causing epimerization and decreasing stereoselectivity, among lowered yield and C-silylation

considerations. Furthermore, Welch and coworkers used a trialkylsilyl triflate reagent to form the silyl ketene acetal intermediate instead of silyl chlorides.[27]

As an extension to our optimized reaction conditions in the Ireland-Claisen rearrangement of α-alkoxy substituted esters[17], we sought to expand this substrate scope to α-fluoro allylic ester substrates. We hypothesized chelation control with potassium in $KN(SiMe_3)_2$ could also be observed with these fluorinated substrates given by the electronegativity of the substituents. In planning substrates in which this rearrangement could be investigated, esters bearing a 2-fluoro-5-chloropentanoic acid fragment were proposed, requiring synthesis of this acid. There were apparent challenges in the direct α-fluorination of ester (compound number) in the initial attempts to synthesize this acid, and thus optimization of this substrate's production was key to the execution of this project. The optimized procedure was adapted to make other substrates within the reported scope.

This investigation aimed to explore this reaction and its stereoselectivity through a demonstration of this reaction over a considerable substrate scope, indicating a preference for the fluorinated silyl ketene acetal to adopt (*Z*)-enolate geometry in the transition from ester to rearranged acid. Through a crystal structure and derivatization, clear selectivity under optimized conditions across the scope was demonstrated to confirm this preference.

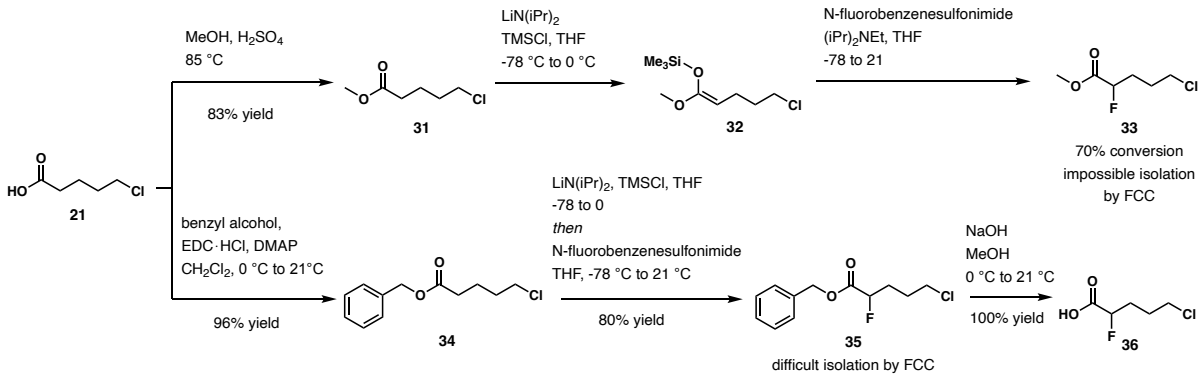
2.2 Substrate preparation – optimizing α-fluorination with N-fluorobenzenesulfonimide

To generate material for the substrate scope, α-fluorination of chlorovaleric acid **21** (prior to esterification to make allylic ester substrates) required optimization. This was material we had in house and was imagined to be converted to an enolate in electrophilic fluorination. The first instinct here was to use N-fluorobenzenesulfonimide as the fluorinating reagent.

2.2.1 Troubleshooting the electrophilic fluorination reaction

The major issue with the reaction using N-fluorobenzenesulfonimide was the incomplete fluorination, leaving crude material which contained starting material and product (It should be noted di-fluorination was never observed in these studies). It was found to be difficult – if not impossible – for the separation between the α-fluoro product with the unreacted starting material in the case of **33**, and furthermore the excess N-fluorobenzenesulfonimide required was observed to be difficult in its removal by aqueous workup and column chromatography. The first attempts were made to try and optimize the reaction to reach completion such that the isolation would be more feasible. For this, we started with the 5-chloropentanoic acid. The acid was converted to an ester under acidic conditions with methanol to give **31**, before it was converted to silyl ketene acetal **32**. In one rendition, the silyl ketene acetal was isolated after aqueous workup and extraction with hexanes, then submitted to solution with N-fluorobenzenesulfonimide in a separate reaction with organic base, however these reactions would not see completion at 70 % conversion of substrate to product.

Scheme 10: α-fluorination of esters originating from acid **21**



From there, a new approach was taken in exchanging methyl ester **31** for benzyl ester **34**, after also finding the methyl ester was volatile and difficult to isolate after column chromatography. With ester **34**, the fluorinated ester showed some separation from the starting material in column chromatography (although major co-elution was observed even with the best attempts made to separate them), so there is less requirement to coax the reaction to go to completion. In this case, the benzyl ester was generated under standard conditions, and the two-pot approach was used to see 31% conversion. In another rendition, a one-pot protocol was used in the addition of N-fluorobenzenesulfonimide solution to the silyl ketene acetal intermediate in its reaction mixture. Under this approach, the reaction reached 77% conversion, however multiple columns were required to fully separate this material. After isolation of **35**, a modest 64% yield was initially observed for this reaction, and optimization efforts continued.

In efforts to try and bring the reaction to complete conversion to simplify product isolation while simultaneously improving the yield, the benzyl ester substrate **34** was submitted to the same reaction conditions as described in the previous paragraph, utilizing a large excess of 4.0 equivalents N-fluorobenzenesulfonimide. This reaction could not be scaled up past 1.0 g and see the same conversion results, however at scales 1.0 g of **34** or less, complete conversion to fluorinated product was observed. Furthermore, because N-fluorobenzenesulfonimide in the crude material also presented an issue with product isolation, optimizing the workup to remove N-fluorobenzenesulfonimide prior to column chromatography would simplify the purification as well. The workup involved adding saturated potassium iodide aqueous solution to the crude solution, filtering the biphasic

mixture through celite, then extraction with ethyl acetate. Here, the N-fluorobenzenesulfonimide was completely removed prior to the column, was not found in any fractions containing the fluorinated product and allowed pure α-fluoro benzyl ester to be isolated at 80% yield and purity exceeding 97% (determined by ^{1}H NMR).

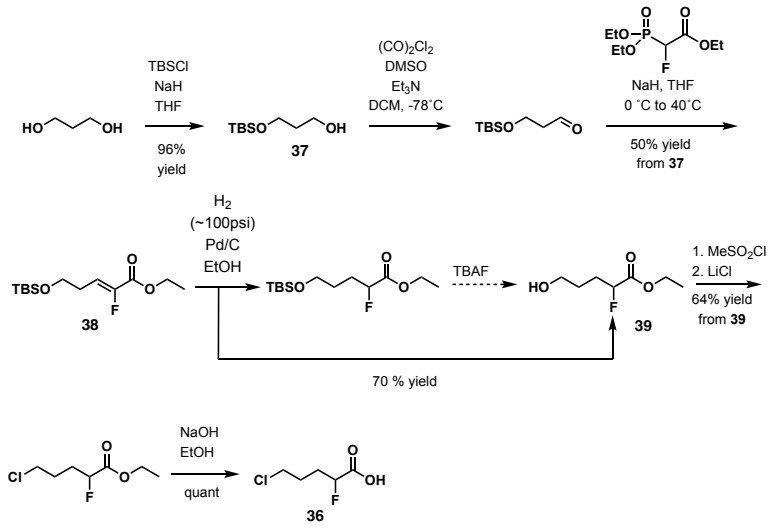
After this, ester would be submitted to hydrolysis under basic conditions to provide 5-chloro-2-fluoropentanoic acid, which has been used to generate a series of α-fluoro allylic esters used in this study of their corresponding Ireland-Claisen rearrangements.

2.2.2 A discontinued route to synthesize 36

Another established (but far less efficient) route developed in this work in attempts to afford **36** was explored when the fluorination of **32** proved a massive challenge and little room for optimization. The strategy for this discontinued synthesis is described in Scheme 11. 1,3-propanediol is mono-protected using *tert*-butyldimethylsilyl chloride at a high yield. After a feasible Swern reduction is enacted, the crude aldehyde material is submitted to a Wittig reaction with commercially available ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate, giving α,β-unsaturated ketone product **38**. The alkene was provided in 50% yield over two steps. Hydrogenation of the alkene returned interesting results. In the initial attempts to afford the following intermediate through hydrogenation, a parr reactor was found to be required for the conversion of this substrate, as the balloon procedure was not providing the sufficient atmosphere for high conversion. In the parr reactor, intermediate **38** saw convenient and simultaneous removal of the *tert*-butyldimethylsilyl protecting group along with hydrogenation; these reactions would go to full conversion in this step with a 70% yield. From there, methanesulfonyl chloride facilitates conversion of alcohol to chloride. Ester

saponification then takes place in order to give acid **36**. This route has been attempted and saw completion with a total yield of 22% over seven steps.

Scheme 11: Discontinued approach to afford **36**

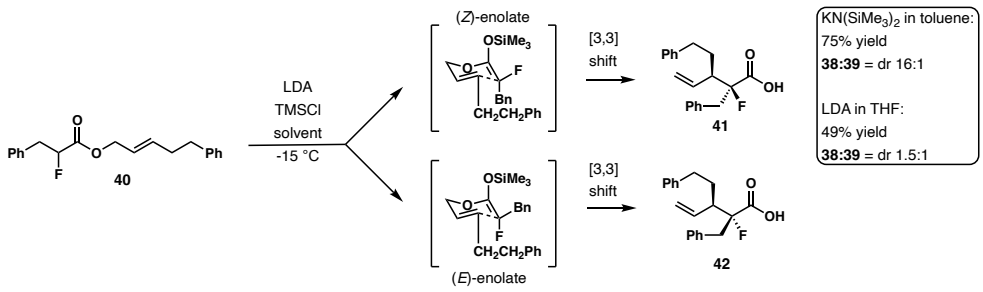


While this tactic was considered successful in affording the α-fluorinated acid **36** to make some of the initial esters for the substrate scope, it slowly lost its appeal in comparison with the direct α-fluorination using N-fluorobenzenesulfonimide. With the eight steps in the former tactic compared with the three employed in the latter, this route featuring the Wittig olefination was deemed inefficient in terms of reactions required for the fragment synthesis. Additionally, the convenient and concurrent TBS removal in the hydrogenation of alkene **38** was not reproducible in every attempt, in some cases giving a mixture of silylated and alcohol material, which would further extend this sequence by another step from seven to eight. With progress made in bringing benzyl ester **34** up to fluorinated acid **36** in terms of complete conversion and increased yield, this route featuring the Wittig olefination was soon abandoned.

2.3 Ireland Claisen rearrangement of α-Fluoro Allylic Esters

A wide substrate scope was investigated in this study[28] and found clear selectivity in the Ireland Claisen rearrangement of α-fluoro allylic esters with $KN(SiMe_3)_2$ in toluene. The optimized conditions for a model substrate shown in Scheme 12, and the substrate scope with their respective dr and yield results shall be shown and discussed in 2.3.1. The substrates can be divided into four distinct classes depending on the ester's alcohol component and include primary alcohols, secondary (*E*)-allylic alcohols, secondary (*Z*)-allylic alcohols, and enantioenriched terminal allylic alcohols. The latter class helped to set precedent work in supporting the research efforts in the total synthesis of analogue target (+)-9, 9' difluoroxestospongin C (Chapter 3). Furthermore, the relative configuration of α-fluorocarboxylic acid product from substrate was confirmed with a crystal structure, and this data allowed comparative conclusions to be made in regard to most of the substrate scope. Derivatization of all acid products to chiral amides was also performed so the diastereomeric ratio could be determined by proton NMR spectroscopy.[28]

Scheme 12: Optimized conditions for the Ireland-Claisen rearrangement on fluorinated allylic ester on a model substrate

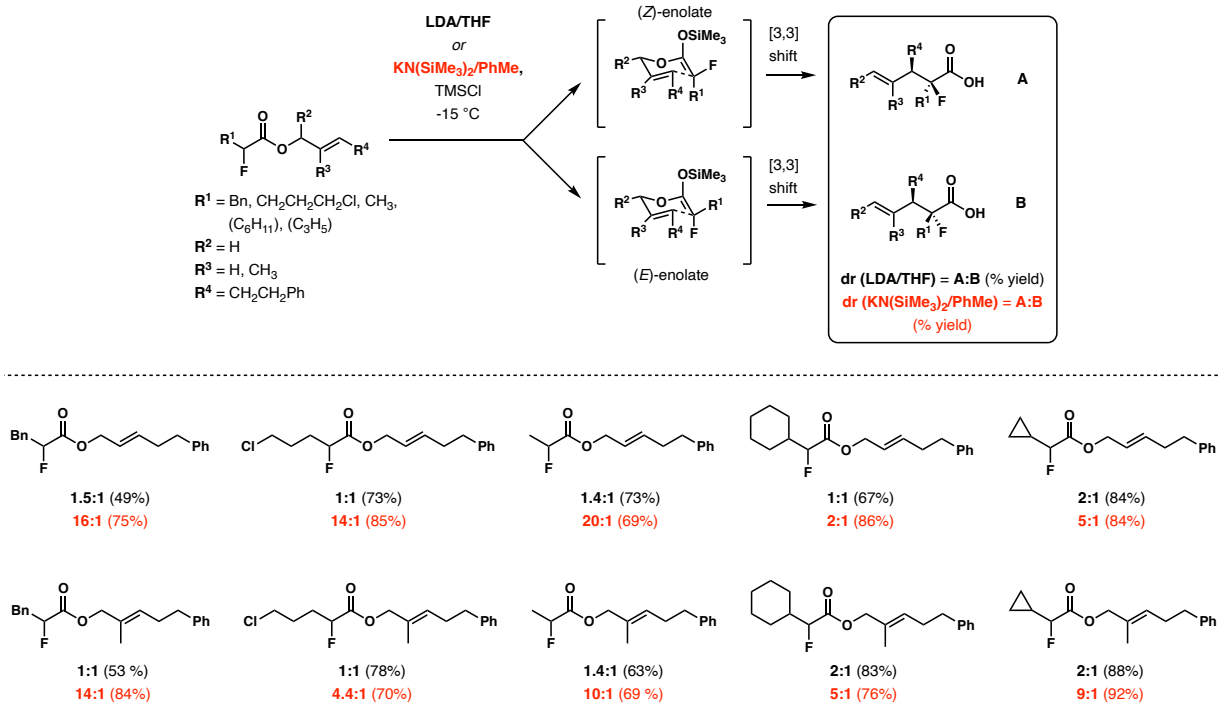


Given the results of optimization studies in the Ireland-Claisen rearrangement reaction of substrate **37** all the substrate allylic esters were submitted to these reactions using the internal quench procedure, in which trimethylsilyl chloride was added before the addition of substrate to the solution of base. This served to prevent enolate fragmentation caused by the endurance of extended time under the strongly basic conditions. Furthermore, in most applications, the rearrangement reaction was accompanied by competitive C-silylation, which saw decreased yield after the reaction. Efforts to convert this C-silylation product back to the allylic ester starting material have not been undertaken by the author of this dissertation, although this conversion is expected to work.

2.3.1 Drawing conclusions, Ireland Claisen rearrangement on α-fluoroallylic esters

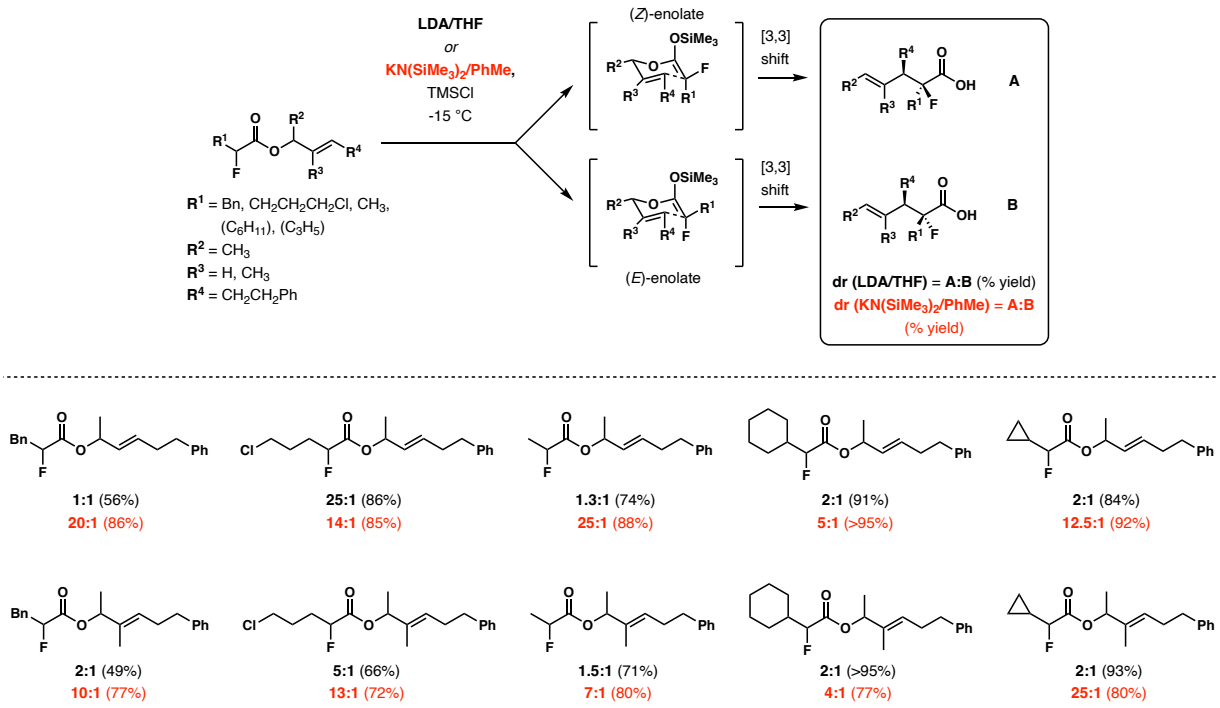
In the case of the α-fluoroallylic esters stemming from primary allylic alcohols showed clear trends in the partiality for the (*Z*)-enolate intermediate, and by the $KN(SiMe_3)_2$ conditions, the product acid could be afforded in yields between 69% and 95%, whereas the yield would drop when the reaction was executed under LDA conditions. In the case of these primary allylic esters bearing methyl substitution on the alkene function (trisubstituted alkenes), a decrease in diastereoselectivity is observed in most cases (except where acid component substituent R^1 was cyclopropane or cyclohexane), which is hypothesized to result from hinderance in the chair-like structure of the silyl ketene acetal intermediate. It is unclear why the cyclic substituent (R^1 of acid component) substrates did not follow this trend. Results for this class of substrates are shown in Figure 3.

Figure 3: Substrate scope, results for α-fluoroallylic esters containing a primary alcohol component



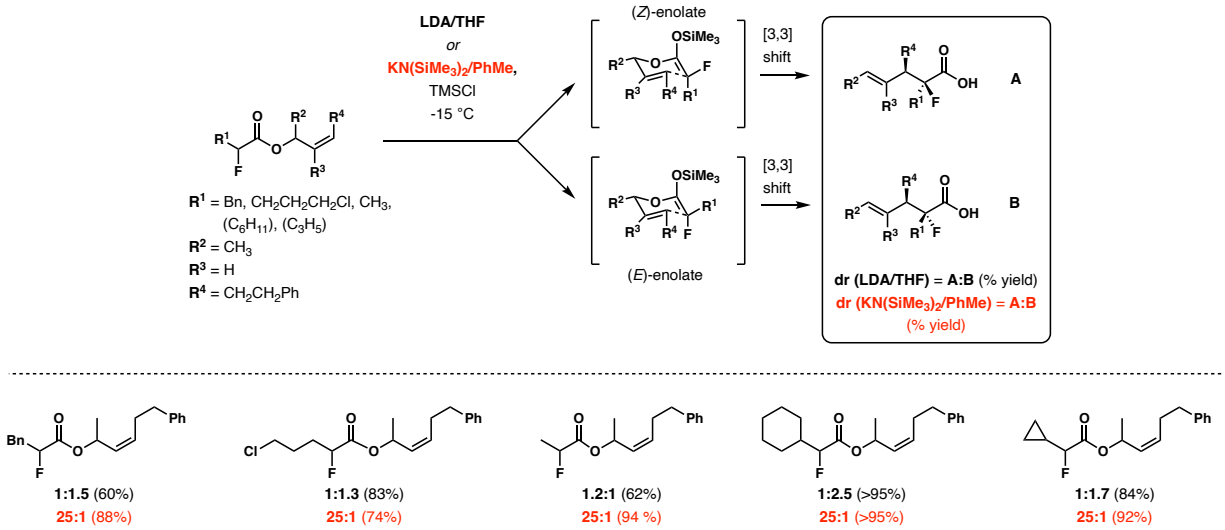
For the esters derived from secondary (*E*)-allylic alcohols (under $KN(SiMe_3)_2$ conditions, similar patterns were identified, while the slightly decreased diastereoselectivity was additionally noted. It should be mentioned however four of these substrates under these conditions (Figure 4) still attained a 25:1 dr. The nature of these four substrates features no methyl substitution at the alkene (while the esters derived from secondary (*E*)-allylic alcohols with this substitution showed decreased diastereoselectivity), thus following the same trends observed in the previously discussed class (esters with a primary allylic alcohol component).

Figure 4: Substrate scope, results for α-fluoroallylic esters containing a secondary (*E*)-allylic alcohol component



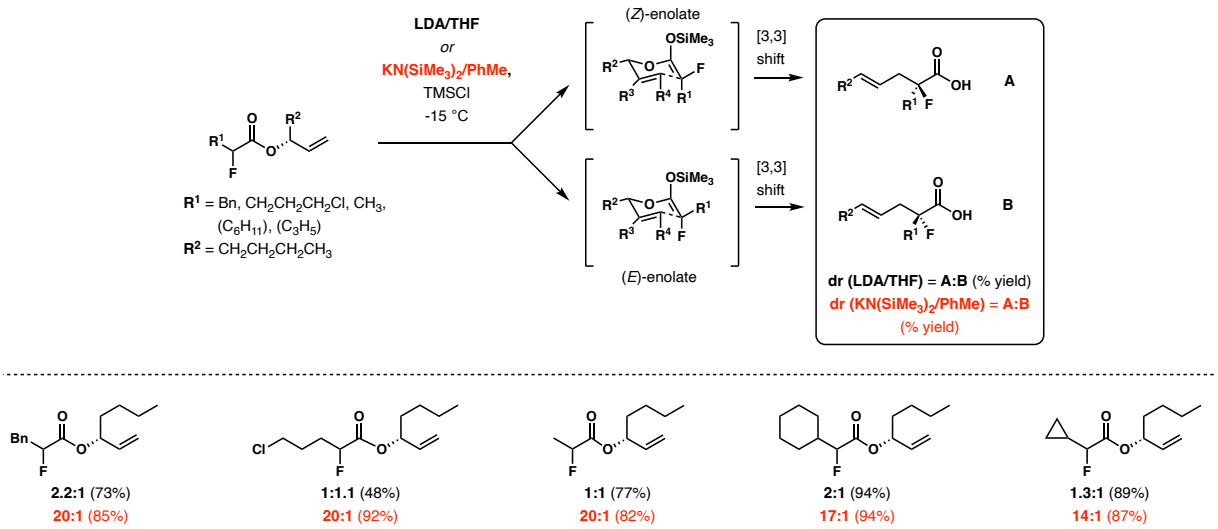
In consideration of the fluorinated esters bearing secondary (*Z*)-allylic alcohols, excellent dr of 25:1 was observed in every rearrangement of these substrates under $KN(SiMe_3)_2$ conditions (see Figure 5).

Figure 5: Substrate scope, results for α-fluoroallylic esters containing a secondary (*Z*)-allylic alcohol component



Finally, for the esters synthesized from enantioenriched terminal allylic alcohol, the same trends as found in the first two compound classes were observed, with dr reaching 20:1 under $KN(SiMe_3)_2$ conditions (Figure 6). It should be mentioned here that the absolute configurations of the acids made from the rearrangement of these enantioenriched substrates were not determined in this study, as there was difficulty in producing a crystal to obtain the crystal structure.

Figure 6: Substrate scope, results for α-fluoroallylic esters containing a secondary enantioenriched allylic alcohol component



In general, under conditions with LiN(*i*Pr)$_2$ in THF, little to no stereoselectivity was observed, the absolute highest dr value reaching 5:1 – a reasonable outcome in demonstrating selectivity, but it pales in comparison to the KN(SiMe$_3$)$_2$ condition results. If there was any preference for enolate geometry demonstrated in the products, results indicated favor for the (*Z*)-enolate as well[27] with the exception of esters with secondary (*Z*)-allylic alcohol components as aforementioned.

2.4 Conclusions

From this study, it can be seen there is good to excellent selectivity for various α-fluoro allylic esters within our published scope to undergo the Ireland Claisen rearrangement via the (*Z*)-enolate intermediate, which could be justified by the chelation control of potassium from KN(SiMe$_3$)$_2$ between the electronegative fluorine atom and an oxygen in the silyl ketene

acetal. This preference can aid in the provision of fluorinated fragments with predictable stereochemistry, which can then be employed in the synthesis of a medicinally intriguing target molecule so fluorine could be installed upon the structure. Application of this work has been adapted for the information described in the following chapter, which reports the construction of (+)-9,9'-difluoroxestospongin C, in both construction of an α-fluoro allylic ester, as well as its subsequent Ireland-Claisen rearrangement in a total synthesis project.

Chapter 3

Modular Synthesis of (+)-Difluoroxestospongin C; a Fluorinated Analogue of a Natural Xestospongin Compound

Summary: As seen with some of the reactions in the route to make dmXe B, epimerization at the C9' center remains a concern at multiple stages within the synthesis plan. Specific substitutions at these stereocenters can provide a convenient mitigation of these issues while simultaneously producing functionalized xestospongin molecule with unexplored medicinal properties. Difluoroxestospongin compounds were proposed within this lab to create a new analogue molecule based on those of the xestospongin family, some of which are known inositol triphosphate inhibitors. For the work reported in this chapter, the modified synthesis of (+)-desmethylxestospongin B was utilized to reach the final target structure, and thus further examines the endurance of this synthesis before it was applied in the increased-scale efforts reported in Chapter 1.

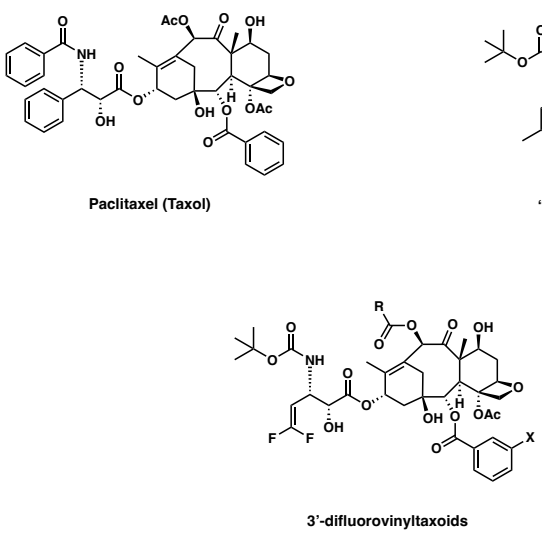
3.1 Introduction

As touched upon in Chapter 2, fluorination upon a bioactive compound with medicinal properties could expand upon the molecule's abilities as a drug. Fluorine is known to augment various properties in bioactive molecules, a synthesis field still in exploration as medicinal chemists continue to generate fluorinated analogues.[28] The small size and high electronegativity of this element can increase binding affinity to a protein scaffold and/or their respective side chains, can illicit conformational changes through hyperconjugation, and additionally increase lipophilicity. Bioavailability was increased in antipsychotic 3-piperdinylindoles by decreasing the basicity of the overall compound[21] as mentioned in Chapter 2.

One very fascinating example of derivatization by fluorination involves the prevalent natural product and chemotherapeutic, Taxol. Some derivative compounds of Taxol were

made (Figure 7) and saw the formation of a new generation of taxoids, based on exhaustive structure activity relationship studies, replacing two of the three phenyl functional groups with isobutenyl or isobutyl substituents[29] (the former case is shown in Figure 7). Although preliminary results of these analogues demonstrated significantly increased potency against MDR cell lines when compared with Taxol, they were readily metabolized by cytochrome P450 3A4 and hydroxylated at isobutenyl and isobutyl substituents[30]. Therefore, in order to counteract this oxidation, new analogues were projected and synthesized so that fluorine atoms replaced the methyl groups in the isobutenyl group, giving rise to 3'-difluorovinyltaxoids.

Figure 7: Taxol and analogous compounds



Not only was the rapid metabolism by CYP 3A4 and successive oxidation thwarted in the case of the fluorinated analogue, but oxidations at other sites of the molecule were mitigated even though they were additionally observed in the "new generation" taxoids. These 3'-difluorovinyltaxoids have shown increased selectivity in treating drug sensitive and drug

resistant cancer cell lines when compared with Taxol, including MCF-7 breast, HCT-29 colon, and PANC-1 pancreatic tumor cell lines. Despite these impressive advances, further studies are being carried out as more fluorinated taxoids are proposed and synthesized, and one of these fluorinated analogues have yet to be approved by the FDA.

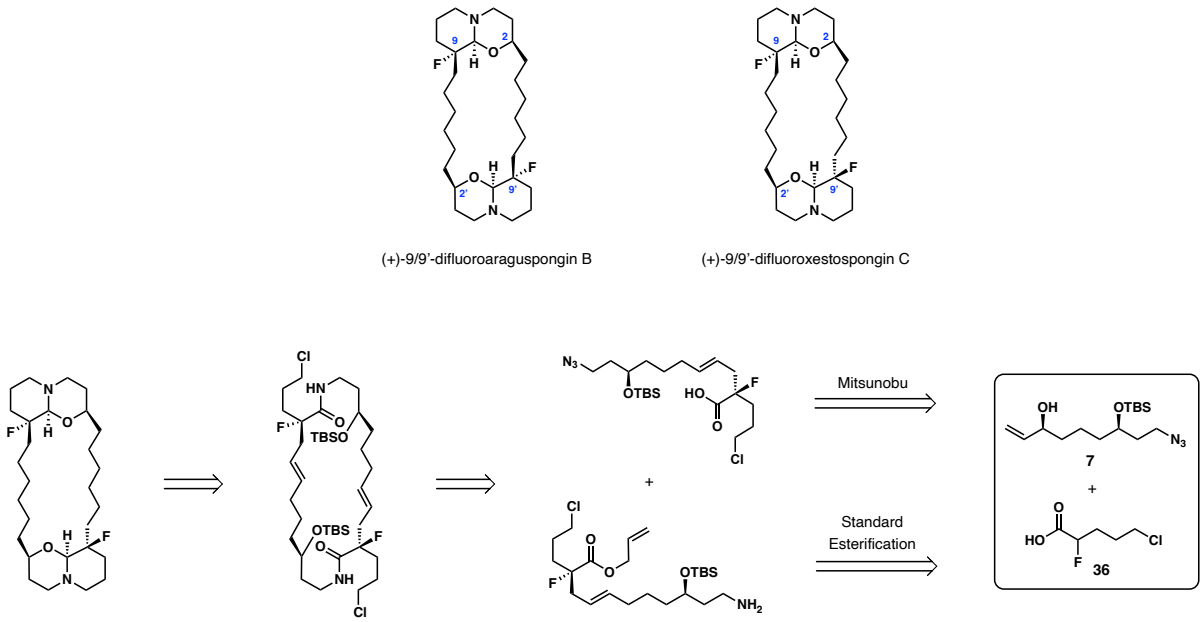
3.1.1 Proposing fluorinated analogues to xestospongin compounds

To carry the xestospongin projects further and to provide new compounds to collaborating biologists, fluorinated analogues of natural xestospongin molecules were proposed so they could be made through the routes developed within our lab. In doing so, we can demonstrate the route's power as a modular synthesis with variance of the substitution at C9. In the production of new xestospongin analogues, (–)-9,9'-difluoroaraguspongine B (Scheme 13) was synthesized using the original method (published in 2021 to make dmXe B)[10] (it should be noted the fluorinated compound was not reported in this publication). To provide the fluorination at C9, acids **21** and **24** (**24** was used in the modified synthesis, another acid with -OBn α- substitution was used in the original route) were replaced with two equivalents of acid **36**. Perhaps a simpler method could have been used to make this C2 symmetric compound, as the two halves are alike, and a dimerization strategy might prove useful without the drawbacks it would have presented for dmXe B and related xestospongin compounds lacking C2 symmetry. However, using the previous syntheses would not help as there is no opportunity for functionalization at C9 and/or C9'. Although (–)-9,9'-difluoroaraguspongine B was a highly anticipated compound – an unnatural analogue compound featuring a fluorinated xestospongin at C9 and C9' – the material was disappointingly found to be insoluble in every solvent to be used for the initial biological

tests. This compound's resistance to leaving the solid state required examination and reconsideration of its structure, and in this manner, a new analogue was proposed with the objective in avoiding this unfortunate solubility issue. As shown, (–)-9,9'-difluoroaraguspongine B (diFAr B) is C2-symmetrical in structure and probably explained the tighter crystal packing of this material. It was hypothesized breaking this symmetry would allow it to be more soluble in the solvents used for the biological studies. Choosing the asymmetric compound (+)-9,9'-difluoroxestospongin C (diFXe C) as a target was expected achieve this end (Scheme 13).

While the insoluble, C2 symmetric diFAr B was generated by the original synthesis, diFXe C was afforded by the modified synthesis of xestospongin compounds reported in Chapter 1. Unlike what was briefly mentioned in the previous paragraph, diFXe C is asymmetric; this target could be best achieved by the synthetic methods developed in this lab between the original or modified routes. Much of this total synthesis proceeds in the same manner as described in the first chapter, and therefore, mainly key differences in the handling and submission of these fluorinated intermediates to make diFXe C shall be addressed in this chapter.

Scheme 13: Fluorinated analogues based on xestospongin/araguspongine compounds; new target



3.2. Synthesis of a fluorinated analogue to (+)-xestospongin C

The azidoalcohol **7** was made in the same manner as described in Chapter 1, key steps being the Grignard addition to chiral epoxide **10** and the asymmetric epoxidation step adapted from Berkessel's work. The results of this undertaking were reproducible and consistent with what was reported in Chapter 1 – although performed on a far smaller scale than for dmXe B – and the details in order to attain this key intermediate shall not be reiterated in this chapter.

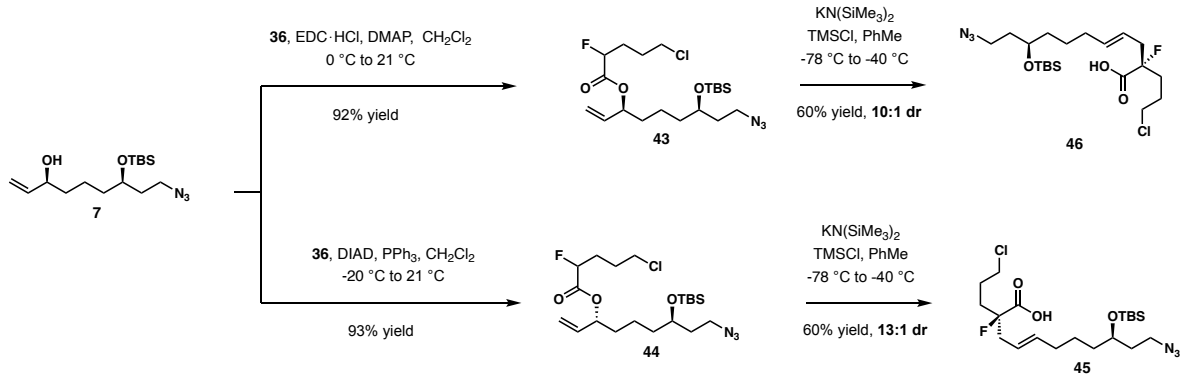
3.2.1 Esterification of intermediate 7, Ireland-Claisen rearrangements

After successfully obtaining the azidoalcohol intermediate **7**, esterification is required to give the fragments providing the functionalization at C9 and C9'. Instead of esterification with 1-chloropentanoyl chloride and α-PMB-oxy chlorovaleric acid **24**, the common intermediate is submitted to reactions with α-fluoro-chlorovaleric acid **36**. This acid was synthesized by α-fluorination of benzyl ester **34** by N-fluorobenzenesulfonimide, as described in Chapter 2[26]. Purification of this fluorinated product was quite difficult in separation from unreacted starting material, so full conversion was required in the α-fluorination reaction (optimization efforts described in Chapter 2).

To consider the stereochemistry for both C9 and inverted C9' centers of the final target molecule, one equivalent of azidoalcohol **7** becomes an ester through EDC·HCl in esterification with **36** to provide **43**. Meanwhile, the second equivalent of **7** to make the other fragment (corresponding to the other half of the target) undergoes a Mitsunobu reaction with **36** to invert the stereocenter established by the asymmetric epoxidation reaction, which executes the C9' inversion in diFAr B to eventually give diFXe C. These esterification reactions experience a 92% and a 93% yield respectively. An effort was undertaken to determine the dr of compound **44** by derivatization and HPLC analysis. Due to the chiral center at the alpha position of this ester where fluorine had been un-stereoselectively added to provide a racemic mixture of the α-fluoro acid **36**, this endeavor was found to be too difficult as the HPLC was only separating isomers furnished at that center. It was therefore determined to postpone this analysis until after the stereoselective Ireland-Claisen rearrangement, which assesses the same centers which eventually give C9 and C9'. In the

next step, the diastereomeric esters undergo their separate Ireland-Claisen rearrangements under the same conditions reported in the alpha substituted ester in the dmXe B synthesis.

Scheme 14: Esterification, Ireland-Claisen rearrangements of the fluorinated fragments in synthesis of diFXe C



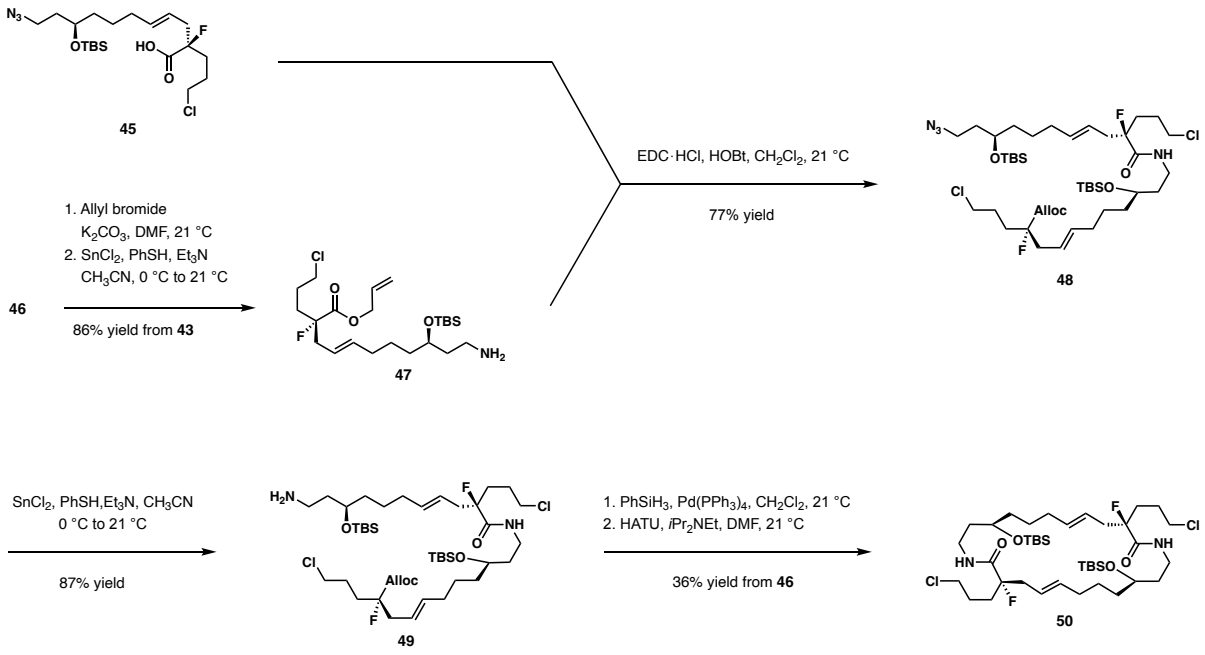
In the Ireland-Claisen rearrangement of α-fluoro allylic esters, the transformation could transpire to give very predictable stereochemistry of the product using optimal conditions. In the study of the Ireland Claisen rearrangement of α-fluoro allylic esters[26] it was found using LiN(*i*Pr)$_2$ gave little to no diastereoselectivity in the rearrangement. However, the potassium in KN(SiMe$_3$)$_2$ allowed chelation control between the cation and the electronegative α-substituent (discussed in Chapter 2). This chelation control encourages the silyl ketene acetal intermediate to adopt (*Z*)-enolate geometry and thus provides expected stereochemistry in the α-fluoro acid product of this rearrangement. Therefore, the stereochemistry of the two α-fluoro allylic esters **44** and **43** is translated from these substrates to their individual acid products **45** and **46** at 13:1 dr and 10:1 dr, respectively.

From there, the substrate is carried forward through the synthesis, with **43** submitted through allylation followed by azide reduction. For these azide reductions, the conditions reported in the original paper were used, with 6.0 equivalents of thiophenol. Substitution at the chloride by thiophenol was rarely observed in these instances taking a fraction of the material. This unintended product was also observed in the original dmXe B synthesis as well, but not by the author. Since the amount was so small, no effort was made to reconvert this material back into an intermediate of the route, however this byproduct was observed, and plans were made to avoid this problem from proceeding on a larger scale. The convergence step progressed as expected.

In the case of compound **47** obtained through a second azide reduction, there was one instance where transesterification was unfortunately observed in the column chromatography of the product amine. The purification of **47** by column chromatography required an eluent of 20% methanol and 1% ammonium hydroxide in methylene chloride, and under these conditions a portion of the allyl ester material was converted to a methyl ester on normal phase silica gel. These two esters were thankfully separable from one another with careful column chromatography and prevented in the future by reduced ammonium hydroxide in the eluent (0.5% instead of 1%). The desired allyl ester intermediate was submitted to de-allylation with palladium tetrakis(triphenylphosphine) and phenylsilane as intended, while the methyl ester underwent hydrolysis with lithium hydroxide as in the original method with the goal of both reactions affording the same intermediate before macrolactamization. Since the amount of material for the methyl ester was so small (approximately 0.1 g), the reaction was diluted by a factor of two from published conditions[5], and the desired acid was produced

in 75% yield with minimal desilylation, allowing partial material recovery into the overall synthesis.

Scheme 15: Using the strategies from the modified route to afford diFXe C



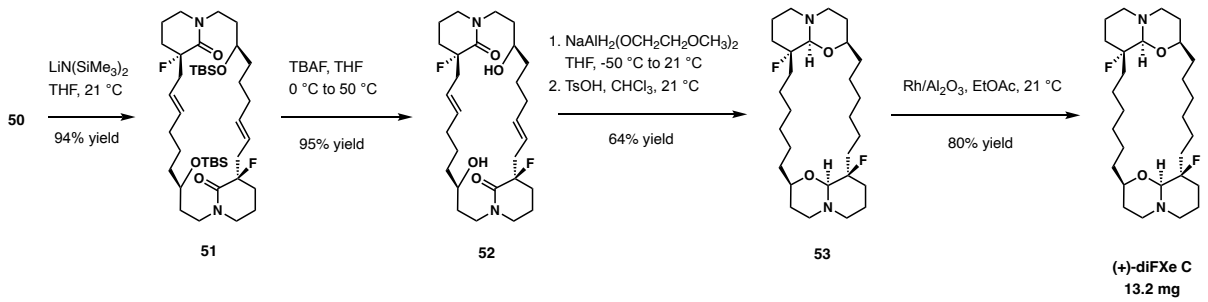
Macrolactamization proceeded with disappointing but unsurprising results (28% yield) when compared with those of the original dmXe B synthesis. There was a desperate effort made to recover material believed to be the pre-lactam substrate (following the deallylation of the ester to free the carboxylic acid), however resubmission into the cyclization reaction saw 0% conversion to product and was ultimately discarded.

Moving forward, since there are no hydrogens acidic enough to facilitate epimerization in the diamide **50** (at the C9 and C9' centers represented in the final product) given by the fluorine substitutions in the amide α-positions, therefore epimerization will not present as

great concern in the cyclization reaction with $LiN(SiMe_3)_2$ as was the case in the synthesis of dmXe B, and gratifyingly, a single product was observed after adding as much as four equivalents of the base to afford **51** as a single diastereomer after product isolation.

Desilylation of **51** proceeded as expected, with a mixture of this compound with *tert*-butyldimethylsilanol as the major impurity. As was the case for dmXe B, pure product was obtained after the partial reduction step.

Scheme 16: Conclusion of the synthesis of diFXe C



Following desilylation of intermediate **48**, partial reduction is required on **49** to close the bis-1-oxaquinolizidine heterocycles in the final target. This step was enacted in a different manner than what was described in the dmXe B synthesis in Chapter 1. Birch reduction conditions were deemed ideal for the desired transformation to hemiaminal then to bis-1-oxaquinolizidine (in the case of dmXe B) because other reductive methods led to over-reduction to the corresponding piperidine[5]. In the case of the fluorinated δ-lactam **49**, over-reduction to piperidine proved over-reduction to piperidine to be a lesser concern than was the case for dmXe B, and other reductive methods with simpler protocols could thus be

employed. In this case, reductive alumina ($NaAlH_2(OCH_2CH_2OCH_3)_2$) was deemed an appropriate reagent to achieve the same partial reduction as in dmXe B.

In practice for diFXe C, the partial reduction carried forward to the hemiaminal intermediate as expected, however, only partial conversion to the bis-1-oxaquinolizidine product was observed, with the crude material comprising of both hemiaminal intermediate as well as the precursor molecule to diFXe C. The two compounds were somewhat separable by column chromatography, however most of the material ended in co-elution. It was accidentally found the ring closure of the remaining hemiaminal material could take effect under mild acidic conditions, and this information was explored in an effort to retain the hemiaminal intermediate material in the synthesis. The accident in question involved the analysis of co-eluted material from column chromatography of the crude from the partial reduction reaction and leaving it in chloroform. The sample had to be re-analyzed the next day, and upon inspection of the proton NMR, only the desired product was observed with no hemiaminal intermediate remaining in solution. No other byproducts were seen in the solution, only the desired bis-1-oxaquinolizidine product. This finding led to the understanding the intermediate converted to product overnight. It was hypothesized the mild acidic conditions given by air-exposed chloroform provided the conditions necessary to complete the transformation with the ring closure.

Instead of optimizing the reduction reaction itself to fully convert the material to bis-1-oxaquinolizidine, it was deemed to be a better use of time and precious late-stage material to instead split this step into two, with immediate submission of the crude mixture from the partial reduction to a 0.025 M solution of p-tolulenesulfonic acid in chloroform. This added step converts the hemiaminal intermediate to the oxaquinolizidine product to completion,

with a reasonable 64% yield over both steps. Although this single reaction was extended to two steps and wasn't particularly high yielding, the two steps nevertheless exceeded the yield by nearly 20% when compared with the single Birch reduction step in the synthesis of dmXe B. Finally, hydrogenation of the unsaturated tethers is carried out using the same catalyst as in dmXe B, rhodium on alumina. Careful monitoring of the reaction and constant re-introduction of hydrogen gas into the reaction solution carried this hydrogenation to completion.

In this synthesis, 13.2 mg of (+)-difluoroxestospongin C were obtained. All of the material had to be used for each NMR analysis to obtain decent spectra, and the material was of course recovered and collected so it could be saved for potential biological testing.

3.3 Conclusions

This work has demonstrated the abilities of the modular synthesis of dmXe B to carry material forward in the development of related natural and analogous xestospongin compounds with substitution at C9 and C9', with an opportunity to invert these centers during an early-stage esterification using Mitsunobu conditions. While there remain several opportunities for optimization with the synthesis of diFXe C, the route still managed to produce this compound at a total yield of 2.8%.

Solubility screenings of this final compound showed noticeably improved results, with complete solubility in chlorinated solvents methylene chloride and chloroform in 13 mg/mL. The same concentration saw partial solubility of diFXe C in ethanol and ethyl acetate, however, was found to be soluble in both at 1 mg/mL. These were all solvents where diFAr B was proven to be completely insoluble. The quick solubility tests performed in this lab

signaled success in the objective of creating a difluorinated xestospongin molecule with increased solvent solubility, and this compound is expected to be tested by collaborating biologists within the near future. Of key importance, the synthesis developed in the Zakarian lab has been proven at this point to serve as a modular synthesis for compounds related to those in the xestospongin family, with control over the chirality and functionality of the centers at C9 and C9' of the bis-1-oxaquinolizidine heterocycles.

Experimental Procedures

General Information. All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and diethylether (Et_2O) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, diisopropylamine, pyridine, triethylamine, and chorotrimethylsilane were distilled from calcium hydride in a continuous still under an atmosphere of argon. Diisopropylethylamine (Hünig's Base) was distilled from calcium hydride under an inert atmosphere of dry argon and stored over calcium hydride. Reaction temperatures were controlled by IKA ETS-D4 fuzzy thermo couples. Room temperature reactions were carried out between 20-22 °C. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F_{254} (EMD no 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganante, and iodine staining. Flash column chromatography was performed using 40-63 mm silica gel (Merck, Geduran, no 11567-1) as the stationary phase. Proton magnetic resonance spectra were recorded at 400, 500, and 600 MHz on Varian Unity Inova spectrometers and Bruker Avance NEO spectrometers. Carbon nuclear magnetic resonance spectra were recorded at 100 MHz, 125 MHz, and 150 MHz on Varian Unity Inova spectrometers and Bruker Avance NEO spectrometers. All chemical shifts were reported in δ units relative to tetramethylsilane. High resolution mass spectral data were obtained by the Materials Research Laboratory at the University of California, Santa Barbara.

Note: *n*-Butyllithium was purchased from Sigma-Aldrich (2.5M solution in hexanes, catalog # 230707-100ml) and used directly as received. The reagent was titrated before use.

Modifying the Total Synthesis of (+)-Desmethylxestospongin B

Procedure 1: chlorodehydroxylation of **15**

To freshly distilled 3,4-buten-1-ol (0.214 kg, 3.0 mol), freshly distilled pyridine (17 mL, 0.21 mol, 0.07 equiv) was added. The mixture was cooled to 0 °C before thionyl chloride (0.217 kg, 3.0 mol, 1.0 equiv) was added dropwise. After 0.5 hours, warmed to 21 °C and assembled a reflux condenser, distillation head, and collection flask over the reaction flask, then increased the temperature to 85 °C. ^{1}H NMR monitoring indicated complete conversion after 2 hours. The collected product was combined with the crude material, and distillation was performed at 95 °C. The distilled product was washed with saturated $NaHCO_3$ aqueous solution and dried with Na_2SO_4 to give 4-chloro-1,2-butene (0.231 kg, 2.6 mol, 86% yield) as a clear, colorless oil. ^{1}H and ^{13}C NMR spectral data matched those reported in the literature.[31]

Procedure 2:

To a solution of 4-chloro-1,2-butene (0.225 kg, 2.5 mol) in 0.60 L CH_2Cl_2 cooled to 0 °C, 75% MCPBA in H_2O (0.628 kg, 2.7 mol, 1.1 equiv) was added in six portions. Allowed the temperature to reach but not exceed 15 °C. The reaction was monitored by ^{1}H NMR; complete conversion was observed after 12 hours. The reaction mixture was filtered, then placed in a -20 °C freezer overnight. Filtered again, cooled to 0 °C, then added Me_2S (0.237 L, 3.2 mol, 1.3 equiv), then increased temperature to 21 °C. The presence of peroxides was checked by combining 0.2 mL solution with 0.2 mL AcOH and 20 mg KI, confirming peroxides were quenched. Removed CH_2Cl_2 by distillation at 65 °C under atmospheric

pressure, then distilled epoxide product under vacuum (35 mmHg) at 85 °C with the collection flask in a -78 °C cold bath (vapor temperature observed between 68 – 70 °C), providing 2-(2-chloroethyl)oxirane (0.214 kg, 81% yield) as a clear, colorless oil. ^{1}H and ^{13}C NMR spectral data matched those reported in the literature.[10]

Procedure 3:

(S)-2-(2-chloroethyl)oxirane (**10**): Freshly distilled 2-(2-chloroethyl)oxirane (59.7 g, 0.56 mol) was added to (S,S)–(salen)Co(II) (1.69 g, 2.80 mmol, 0.005 equiv) under inert atmosphere, followed by 5.6 mL THF, then acetic acid (0.32 mL, 5.6 mmol, 0.01 equiv). The mixture was cooled to 0 °C, then added DI H_2O (5.6 mL, 0.31 mol, 0.55 equiv) dropwise to the reaction. Maintained temperature for 20 min before warming to 21 °C. Monitoring by ^{1}H NMR showed 52% conversion to diol after 96 hours. All volatiles were collected by vacuum distillation at 0.2 mmHg at 70 °C (increasing the temperature up to 95 °C to collect diol) in a vessel cooled to -78 °C. Dried over Na_2SO_4 (rinsing with CH_2Cl_2), then combined rinses with crude product mixture. Distilled under atmospheric pressure to remove CH_2Cl_2 and THF, then distilled the remaining crude product mixture under vacuum (35 mmHg) at 85 °C to isolate (*S*)-2-(2-chloroethyl)oxirane (26.4 g, 0.25 mol, 44% yield) into a flask cooled to -78 °C (vapor temperature observed between 50 °C – 52 °C). ^{1}H and ^{13}C NMR spectral data matched those reported in the literature.[10]

Procedure 4: Derivative of **10**

A solution of Me_3SI (67.2 mg. 0.33 mmol, 3.5 equiv) in 0.20 mL THF was cooled to -30 °C before 2.1 M *n*-BuLi (0.15 mL, 0.32 mmol, 3.4 equiv) was added dropwise. After 0.5 hours,

increased temperature to -10 °C and added (*S*)-2-(2-chloroethyl)oxirane (9.4 mg, 0.088 mmol) in solution with 0.25 mL THF. The reaction was allowed to warm to ambient temperature over the course of 1 hour, then maintained conditions for 1 hour. When the reaction was complete by thin-layer chromatography, cooled to 0 °C and added 1 mL saturated $NH_4Cl_{(aq)}$ solution. Washed with 5 mL brine and extracted with 5 mL Et_2O. Dried with $MgSO_4$, filtered, then concentrated in vacuo (with the bath set to 0 °C to prevent product evaporation). The crude product was submitted to the next reaction in its crude state.

Procedure 5: Derivative of **10**, HPLC results

To a solution of p-anisaldehyde (16 μL, 0.13 mmol, 1.5 equiv) in 0.60 mL CH_2Cl_2, $BF_3{\cdot}OEt$ (17 μL, 0.13 mmol, 1.5 equiv) was added dropwise at -40 °C, then the crude substrate (*S*)-5-Chloropent-1-en-3-ol (0.088 mmol) in solution with 0.24 mL CH_2Cl_2 was added dropwise to the reaction, followed by Et_3SiH (50 μL, 0.31 mmol, 3.5 equiv). The reaction was warmed to -10 °C; these conditions were maintained for 1 hour before quenching with 1 mL DI H_2O (the reaction did not reach completion by TLC analysis). Washed with 2 mL saturated $NaHCO_{3(aq)}$ solution and extracted with 5 mL CH_2Cl_2. Dried with Na_2SO_4, filtered, then concentrated in vacuo. The crude product was then purified by column chromatography (3% EtOAc in hexanes) to obtain (S)-1-(((5-chloropent-1-en-3-yl)oxy)methyl)-4-methoxybenzene (2.2 mg, 0.0091 mmol, 10 % yield) as a pale yellow oil. ^{1}H and ^{13}C NMR spectral data matched those reported in the literature.[5] Er [93.5:6.5] (Chiralcel® OD-H; 1% i-PrOH in hexanes; flow rate = 1.0 mL/min; detection at (230) nm; t1 = 5.18 min (major); t2 = 5.49 min (minor).

Procedure 6: Bromodehydroxylation of **15**

To freshly distilled 3,4-buten-1-ol (28.5 g, 0.40 mol), freshly distilled pyridine (9.0 mL, 0.11 mol, 0.28 equiv) was added at ambient temperature, then the mixture was cooled 0 °C. Phosphorous tribromide (14.9 mL, 0.16 mol, 0.4 equiv) was added dropwise to the reaction, pausing addition if the reaction fumed excessively. Maintained conditions for 0.5 hours after the addition, then warmed the reaction to 21 °C. ^{1}H NMR monitoring showed complete conversion after 2 hours. The product was distilled under atmospheric pressure by heating to 150 °C (vapor temperature 130 °C -132 °C). The distilled product was washed with 40 mL saturated $NaHCO_3$ aqueous solution and dried with Na_2SO_4 (without rinsing the drying agent) to obtain 4-bromobut-1-ene (42.9 g, 0.32 mol, 80% yield) as a clear, colorless oil. ^{1}H and ^{13}C NMR spectral data matched those reported in the literature.

Procedure 7: Grignard reagent **16** formation

To a suspension of Mg turnings (5.47 g, 0.23 mol) and 10 μL 1,2-dibromoethane in THF, 4-bromobut-1-ene (31.98 g, 0.24 mol, 1.05 equiv) was added dropwise at ambient temperature. 0.5 hours after substrate addition, the reaction was heated to 75 °C so reflux was observed. Conditions were maintained for 1 hour until Mg turnings were completely consumed in solution. The solution was utilized immediately after it was cooled back to ambient temperature for the following reaction.

Procedure 8:

To a solution of **10** (16.8 g, 0.16 mol) in 90 mL THF, CuCN (0.678 g, 7.9 mmol, 0.05 equiv) was added. The mixture was cooled to -60 °C before 1.0 M but-3-en-1-ylmagnesium

bromide solution in THF (0.225 L, 0.23 mol, 1.4 equiv) was added dropwise to the reaction. Maintained conditions for 0.5 hours after Grignard reagent addition, then allowed the reaction to warm to -30 °C over the course of 0.75 hours. Maintained temperature conditions for 0.5 hours before allowing the reaction to warm to 0 °C over the course of 0.5 hours. Kept the reaction at 0 °C for 0.75 hours when TLC analysis indicated a complete reaction. Added 0.1 L saturated $NH_4Cl_{(aq)}$ solution to quench at 0 °C, then warmed to 21 °C. Maintained temperature conditions for 1 hour before washing with brine and extracting with EtOAc. Dried with Na_2SO_4, filtered, and concentrated in vacuo. This afforded the crude product (25.9 g) which was submitted to the next reaction without further purification.

Procedure 9: Silylation

The crude product (*R*)-1-chlorooct-7-en-3-ol (25.9 g, ~0.16 mol) from the previous reaction was dissolved in 50 mL CH_2Cl_2; imidazole (32.6 g, 0.48 mol, 3.0 equiv) was added in one portion. The reaction was cooled to 0 °C, then added *tert*-butyldimethylsilyl chloride (31.5 g, 0.21 mol, 1.5 equiv) in three portions. Maintained temperature conditions for 0.5 hours before warming to 21 °C. The reaction was stirred at ambient temperature for 12 hours. Quenched with 50 mL DI H_2O; washed with DI H_2O (2 x 30 mL), then brine (30 mL) while extracting with 50 mL hexanes. Dried with Na_2SO_4, filtered, then concentrated in vacuo. The crude material was purified through use of a silica plug (hexanes) to afford **17** (43.3 g, 0.16 mol, 100 % yield over two steps) as a clear, colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.96 (ddt, *J* = 10.2, 2.3, 1.3 Hz, 1H), 3.87 (p, *J* = 5.7 Hz, 1H), 3.65 – 3.55 (m, 2H), 2.08 – 2.01 (m, 2H), 1.91 – 1.83 (m, 2H), 1.54 – 1.37 (m, 4H), 0.89 (s, 9H), 0.07 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (500

MHz, $CDCl_3$) 138.8, 114.8, 69.2, 42.1, 39.8, 36.8, 33.9, 26.0, 25.9, 24.3, 18.2, -4.2, -4.5. HRMS (ESI) *m/z*: [M+H] calcd for $C_{14}H_{30}ClOSi$ 277.1754; found 277.1779.

Procedure 10: Asymmetric epoxidation of **17**

The salalen ligand **18** was prepared as described according to literature.[15] To a solution of **18** (12.3 g, 25 mmol, 0.05 equiv) in 0.230 L CH_2Cl_2, titanium isopropoxide (7.5 mL, 25 mmol, 0.05 equiv) was added. The color was observed to change slightly from bright yellow/green to dark yellow/gold. After 2 hours, CH_2Cl_2 was removed using vacuum distillation under 35 mmHg at 21 °C (ambient temperature water bath) providing the catalyst as a gold-colored solid.

To the flask containing the catalyst, substrate **17** (0.139 kg, 0.50 mol) was added, followed by 84 mL 1,2-dichloroethane and pentafluorobenzoic acid (5.33 g, 25 mmol, 0.05 equiv). The color changed from dark yellow to red/orange after the addition of the acid additive. Next, 30% $H_2O_{2(aq)}$ (0.103 L, 1.0 mol, 2.0 equiv) was added. The reaction was allowed to stir at ambient temperature for 24 hours before 30% $H_2O_{2(aq)}$ (0.103 L, 1.0 mol, 2.0 equiv) was added, then additional 30% $H_2O_{2(aq)}$ (0.103 L, 1.0 mol, 2.0 equiv) was added again at 48 hours. At 72 hours, ^{1}H NMR shows nearly complete conversion (of over 95 %). Washed with saturated Rochelle salt solution (2 x 0.2 L) and brine (0.2 L) while extracting with 0.2 L CH_2Cl_2. Dried with Na_2SO_4, filtered, then concentrated in vacuo. The crude material was purified through column chromatography (2% EtOAc in hexanes), affording tert-butyl(((*R*)-1-chloro-6-((S)-oxiran-2-yl)hexan-3-yl)oxy)dimethylsilane **19** (0.137 kg, 0.47 mol, 93% yield) as a pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.92 – 3.83 (m, 1H), 3.58 (ddd, *J* = 7.1, 6.1, 1.5 Hz, 2H), 2.93 – 2.85 (m, 1H), 2.73 (dd, *J* = 5.1, 4.0 Hz, 1H), 2.44 (dd, *J* = 5.0,

2.7 Hz, 1H), 1.92 – 1.80 (m, 2H), 1.64 – 1.38 (m, 6H), 0.87 (s, 9H), 0.06 (d, J = 7.4 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 68.9, 52.1, 46.9, 41.7, 39.5, 36.9, 32.5, 25.8, 21.3, 18.0, -4.4, -4.7.

Procedure 11: Epoxide opening of **19**

A mixture of trimethylsulfonium iodide (0.185 kg, 0.91 mol, 2.6 equiv) in 0.720 L THF and 0.260 L hexanes was cooled to -30 °C before 10M *n*-BuLi (87 mL, 0.87 mol, 2.5 equiv) was added dropwise by first cannulating into a marked (flame-dried, inert atmosphere, sealed) Erlenmeyer flask, then cannulating the amount into the reaction. After 0.5 hours and observing the formation of precipitant, the reaction was warmed to -10 °C before substrate **19** (0.102 kg, 0.35 mol) in solution in 0.150 L THF was added dropwise. Maintained conditions for 1 hour before warming to ambient temperature. A complete reaction was observed by TLC after 0.5 hours at 21 °C. Quenched with 0.2 L saturated $NH_4Cl_{(aq)}$ solution and noticed the color change from colorless to a strong yellow hue. Washed with 0.2 L H_2O and 0.2 L brine while extracting with 0.2 L EtOAc. Two back extractions were performed on the combined aqueous layers (2x0.2 L) with EtOAc. The organic layers were dried with Na_2SO_4, filtered, then concentrated in vacuo. The crude product was purified by column chromatography (4% EtOAc in Hexanes) to give (3*S*,7*R*)-7-((tert-butyldimethylsilyl)oxy)-9-chlorononon-1-en-3-ol **20** (0.103 kg, 0.34 mol, 96 % yield) as a pale yellow oil. ^1H and ^{13}C NMR spectral data matched those reported in the literature.[10]

Procedure 12: Derivatization of **20**; benzoylation

A solution of **20** (53 mg, 0.17 mmol) in 1.7 mL CH_2Cl_2 was cooled to 0 °C before pyridine (56 μL, 0.69 mmol, 4.0 equiv), then benzoyl chloride (61 μL, 0.48 mmol, 2.8 equiv), were added dropwise to the reaction in this order. Warmed to ambient temperature and stirred for 1 hour when the reaction was complete by TLC. Quenched with 0.5 mL H_2O before washing with H_2O and extracting with CH_2Cl_2. Dried with Na_2SO_4, filtered, then concentrated in vacuo. The product was submitted in its crude state to the following reaction.

Procedure 13: Synthesis and HPLC analysis of derivative

To a solution of (3*S*,7*R*)-7-((tert-butyldimethylsilyl)oxy)-9-chlorononon-1-en-3-yl benzoate (74 mg, ~0.17 mmol) in 9 mL of THF, 4.5 mL of 1N $HCl_{(aq)}$ were added. The reaction was left to stir at ambient temperature for 16 h and reached completion in this time (confirmed by TLC). Washed with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. Dried with Na_2SO_4, filtered, then concentrated in vacuo. The crude material was purified by column chromatography (10% EtOAc in hexanes to 20% EtOAc in hexanes) to give (3*S*,7*R*)-9-chloro-7-hydroxynon-1-en-3-yl benzoate (49 mg, 0.16 mmol, 97 % yield over two steps) as a pale yellow oil. Dr 92:6:2:0 (Chiralcel® AD-H analytic; 5% i-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 254nm; t1 = 15.6 min (minor); t2 = 20.8 min (major); t3 = 22.3 min (minor); t4 = 29.8 min (minor). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, 2H), 7.56 (td, *J* = 6.9, 1.4 Hz, 1H), 7.45 (td, 2H), 5.90 (ddd, *J* = 17.0, 10.5, 6.2 Hz, 1H), 5.52 (qt, 1H), 5.34 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.22 (dt, *J* = 10.6, 1.3 Hz, 1H), 3.85 (o, *J* = 8.4, 4.3 Hz, 1H), 3.77 – 3.61 (m, 2H), 1.95 – 1.70 (m, 4H), 1.67 – 1.40 (m, 6H).

Procedure 14:

To a solution of **20** (20.3 g, 66 mmol) in 41 mL DMF, sodium azide (6.50 g, 100 mmol, 1.5 equiv) and tetrabutylammonium iodide (2.49 g, 6.7 mmol, 0.1 equiv) were added at 21 °C. The mixture was heated to 90 °C. Monitoring by ^{1}H NMR showed complete conversion after 7 hours. The reaction was cooled to ambient temperature and washed with H_2O (5 x 20 mL) while extracting with 20 mL of a mixture of 20% EtOAc in hexanes. Dried with $MgSO_4$, filtered, and concentrated in vacuo. **7** (20.5 g, 65 mmol, 99% yield) was obtained as a yellow oil. The product was submitted in its crude state to the following esterification reactions without purification.

Procedure 15: synthesis of acid fragment: 2-((4-methoxybenzyl)oxy)acetic acid

To a solution of 2-bromoacetic acid (0.505 g, 3.6 mmol) and para-methoxybenzyl alcohol (0.45 mL, 3.6 mmol, 1.0 equiv) in 6.4 mL THF, 60% sodium hydride in mineral oil (0.354 g, 8.9 mmol, 2.4 equiv) was added in three portions at 0 °C. Observed the mixture become turbid with the addition of sodium hydride. Warmed to 21 °C for 20 minutes before attaching a reflux condenser to the flask (with a drying tube) and heated the reaction to 65 °C, observing the formation of precipitant. Maintained reflux for 20 hours before TLC monitoring indicated a complete reaction. The reaction was quenched with 5 mL methanol at ambient temperature before concentrating in vacuo. Diluted in 5 mL DI H_2O and washed with 5 mL EtOAc, extracting twice from the organic layer with aqueous extractions. 1M HCl was added to the aqueous layer until pH ~4. Extracted with 5 mL CH_2Cl_2 five times from the acidic aqueous layer. Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. The product 2-((4-methoxybenzyl)oxy)acetic acid was submitted in its crude state to the next reaction.

Procedure 16: synthesis of acid fragment **24**

To a solution of diisopropylamine (20.0 mL, 0.14 mol, 2.6 equiv) in 0.180 L THF, 2.5 M *n*-BuLi (54 mL, 0.14 mmol, 2.5 equiv) were added at -78 °C. After 30 minutes, a solution of 2-((4-methoxybenzyl)oxy)acetic acid (10.69 g, 54 mmol) in 70 mL of THF was cannulated dropwise into the LDA solution (rinsing the original vessel with THF with 2x 10 mL). After 1 hour at -78 °C, 1-chloro-3-iodopentane (17.5 mL, 0.16 mol, 3.0 equiv) was added (neat) to the reaction. Maintained temperature conditions for 0.5 hours before increasing temperature bath to -40 °C. TLC monitoring showed complete consumption of starting material after 2 hours. The reaction was quenched with 50 mL 1M HCl before warming to ambient temperature. The product was extracted with 0.1 L EtOAc and washed with 0.1 L 1M HCl. Dried over Na_2SO_4, filtered, then concentrated in vacuo. The crude residue was purified by column chromatography (30% EtOAc in hexanes to 50% EtOAc 1% AcOH in hexanes. Obtained **24** (7.66 g, 28 mmol, 52% yield over two steps) as a yellow oil. ^{1}H and ^{13}C NMR spectral data matched those reported in the literature.[10]

Procedure 17: synthesis of allylic ester **25**

To a solution of **7** (9.12 g, 29 mmol) and **24** (11.9 g, 44 mmol, 1.5 equiv) in 200 mL CH_2Cl_2, 4-dimethylaminopyridine (0.714 g, 5.8 mmol, 0.2 equiv) was added before cooling the reaction to 0 °C. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (11.2 g, 58 mmol, 2.0 equiv) were added in two portions, then the reaction was warmed to 21 °C after 20 minutes. TLC monitoring showed a complete reaction after 1 hour at ambient temperature. The product was extracted with 50 mL CH_2Cl_2 and washed with 50 mL saturated $NaHCO_3$

aqueous solution. Extracted once more from the aqueous layer with 50 mL CH_2Cl_2. The crude product was purified by column chromatography (2.5% EtOAc in hexanes to 5% EtOAc in hexanes) to give **25** (14.7 g, 26 mmol, 89% yield) as a pale yellow oil. ^1H and ^{13}C NMR spectral data matched those reported in the literature.[10]

Procedure 18: Ireland-Claisen rearrangement of allylic ester **25**

A solution of $KN(SiMe_3)_2$ (9.92 g, 50 mmol, 2.2 equiv) in 80 mL distilled toluene was cooled to -78 °C for 0.5 hours before a solution of **25** (12.8 g, 23 mmol) in 80 mL distilled toluene was cannulated dropwise into the reaction. After 0.5 hours, freshly distilled trimethylsilyl chloride (5.7 mL, 45 mmol, 2.0 equiv) was added dropwise into the reaction mixture. After 1 hour, the reaction was warmed to -40 °C; TLC monitoring confirmed a complete reaction after 1 hour at this temperature. The reaction was quenched with 0.1 mL 1M HCl, and the product was extracted with 0.1 L EtOAc three times. Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was isolated by column chromatography (15% EtOAc in hexanes to 25% EtOAc 1% AcOH in hexanes) to give **26** (10.5 g, 18 mmol, 82% yield) as a yellow oil. ^1H and ^{13}C NMR spectral data matched those reported in the literature.[10]

Procedure 19: synthesis of acid fragment, 5-chloropentanoyl chloride **22**

To a solution of 5-chloropentanoic acid (5.90 g, 43 mmol) in 29 mL CH_2Cl_2, oxalyl chloride (4.4mL, 51 mmol, 1.2 equiv) was added dropwise. The argon line was removed and replaced with a drying tube before a catalytic amount (three drops) of dimethylformamide were added to the reaction. Vigorous bubbling observed. The reaction was left stirring at ambient

temperature for 2 hours while monitoring by ^{1}H NMR; complete conversion to 5-chloropentanoyl chloride was observed after 2 hours. The reaction was concentrated in vacuo, and the product was distilled under vacuum at 0.2 mmHg (vapor temperature 52 – 54 °C). **22** (5.87 g, 37 mmol, 88% yield) was obtained as a yellow liquid and submitted to esterification without further purification.

Procedure 20: synthesis of allylic ester **5**

A solution of **7** (10.0 g, 32 mmol) in 40 mL CH_2Cl_2 was cooled to 0 °C before freshly distilled pyridine (5.2 mL, 64 mmol, 2.0 equiv) was added. A solution of 5-chloropentanoyl chloride (5.87 g, 37 mmol, 1.2 equiv) in 14 mL CH_2Cl_2 (additional 2x 5 mL CH_2Cl_2 to rinse original vessel) was added dropwise to the reaction. Observed a color change from a yellow reaction solution to pink. TLC monitoring indicated a complete reaction after 20 minutes. The reaction was quenched with 30 mL 1N HCl, and the product was extracted with 30 mL CH_2Cl_2 twice. The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated under vacuum. The product was purified by column chromatography (Hexanes to 2% EtOAc in hexanes) to provide **5** (13.1 g, 30 mmol, 95% yield) as a pale, yellow oil. ^{1}H and ^{13}C NMR spectral data matched those reported in the literature.[10]

Procedure 21: Ireland-Claisen rearrangement of **5**

A solution of diisopropylamine (7.2 mL, 51 mmol, 2.17 equiv) in 0.140 L THF was cooled to -78 °C for 0.5 hours before 2.3 M *n*-BuLi (20.5 mL, 47 mmol, 2.0 equiv) was added dropwise. After 0.5 hours, a solution of **5** (10.1 g, 23 mmol) in 95 mL THF was added dropwise to the LDA solution at -78 °C. After another 0.5 hours, *tert*-butyldimethylsilyl

chloride (8.24 g, 55 mmol, 2.33 equiv) was added, followed by 42 mL freshly distilled HMPA. The reaction was warmed to -40 °C after 0.5 hours, then warmed again to -15 °C after another 0.5 hours. The reaction mixture was poured over 15 g of ice and 50 mL hexanes; extracted intermediate with 50 mL hexanes twice from the aqueous layer. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude intermediate was then diluted in 94 mL THF and cooled to 0 °C. 33 mL of a prepared 1.8 M aqueous solution of LiOH (cooled to 0 °C for 20 minutes) was added dropwise to the crude intermediate solution at 0 °C. Monitoring by TLC shows conversion of the intermediate to product after 5 minutes. The reaction was quenched with 0.15 L 1N HCl and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by column chromatography (7% EtOAc in hexanes to 20% EtOAc 1% AcOH in hexanes) to provide **27** (8.75 g, 20 mmol, 86% yield) as a yellow oil. ^{1}H and ^{13}C NMR spectral data matched those reported in the literature.[10]

Procedure 22: derivatization of acid **26**

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (12.7 mg, 0.066 mmol, 3 equiv), (R)-(+)-alpha-methylbenzylamine (9 µL, 0.069 mmol, 3 equiv), and HOBt (8.9 mg, 0.053 mmol, 3 equiv) were added sequentially to a solution of acid **26** (12.5 mg, 0.022 mmol) in 0.13 mL CH_2Cl_2. The solution was stirred at room temperature for 1 hour, then diluted with 2 mL CH_2Cl_2 and washed with 2 mL saturated aqueous sodium bicarbonate, then 2 mL brine. Dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc in hexanes) to give (2*S*,9*R*,*E*)-11-azido-9-((*tert*-butyldimethylsilyl)oxy)-2-(3-chloropropyl)-2-((4-methoxybenzyl)oxy)-*N*-((*R*)-1-

phenylethyl)undec-4-enamide (13.6 mg, 0.20 mmol, 92% yield, dr 14:1) as a clear oil. ^{1}H and ^{13}C NMR spectral data matched those reported in the literature.[10]

Procedure 23: derivatization of acid **27**

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (9.8 mg, 0.051 mmol, 3 equiv), (R)-(+)-alpha-methylbenzylamine (7 µL, 0.054 mmol, 3 equiv), and HOBt (6.9 mg, 0.051 mmol, 3 equiv) were added sequentially to a solution of acid **27** (7.4 mg, 0.017 mmol) in 0.10 mL CH_2Cl_2. The solution was stirred at room temperature for 1 hour, then diluted with 2 mL CH_2Cl_2 and washed with 2 mL saturated aqueous sodium bicarbonate, then 2 mL brine. Dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc in hexanes) to give the chiral amide derivative (8.4 mg, 0.16 mmol, 91% yield, dr 7:1) as a clear oil. ^{1}H and ^{13}C NMR spectral data matched those reported in the literature.[10]

Procedure 22: formation of allyl ester intermediate

To a solution of **27** (7.76 g, 18 mmol) in 36 mL distilled dimethylformamide, K_2CO_3 (5.46 g, 39 mmol, 2.2 equiv) was added at 21 °C, then freshly distilled allyl bromide (4.7 mL, 54 mmol, 3.0 equiv) was added dropwise to the reaction. Monitoring by TLC showed a complete reaction after 6 hours. The reaction was diluted in 30 mL hexanes and quenched with slow addition of 10 mL 1N HCl. The product was extracted with 20 mL hexanes and washed with 15 mL DI H_2O three times. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (4% EtOAc in hexanes) to obtain allyl (2*R*,9*R*,*E*)-11-azido-9-((tert-butyldimethylsilyl)oxy)-2-(3-

chloropropyl)undec-4-enoate (7.23 g, 15 mmol, 85% yield) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.89 (ddt, *J* = 17.3, 10.4, 5.8 Hz, 1H), 5.43 (dtt, *J* = 14.6, 6.6, 1.2 Hz, 1H), 5.38 – 5.26 (m, 2H), 5.22 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.56 (dq, *J* = 5.7, 1.4 Hz, 2H), 3.75 (dtd, *J* = 7.2, 5.6, 4.3 Hz, 1H), 3.59 – 3.43 (m, 2H), 3.41 – 3.25 (m, 2H), 2.48 – 2.38 (m, 1H), 2.36 – 2.24 (m, 1H), 2.24 – 2.12 (m, 1H), 1.96 (q, *J* = 6.9 Hz, 2H), 1.88 – 1.59 (m, 6H), 1.49 – 1.26 (m, 4H), 0.87 (d, *J* = 1.4 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 133.0, 132.4, 126.8, 118.3, 118.3, 69.3, 65.0, 48.1, 45.2, 44.7, 36.8, 35.7, 35.4, 32.6, 30.4, 28.9, 26.0, 24.9, 18.1, -4.3, -4.6. HRMS (ESI) *m/z*: [M+Na^+] calcd for ($C_{23}H_{42}ClN_3O_3SiNa^+$) 494.2582; found 494.2577.

Procedure 23: Reduction of azide intermediate, formation of amine **28**

A 100 mL round bottom flask was charged with a stirbar, gas inlet adapter and septum before it was flame dried under vacuum and backfilled with argon. The flask was charged with $SnCl_2$ (4.12 g, 22 mmol, 1.5 equiv) under nitrogen, then reconnected to an argon line. 8.7 mL of distilled acetonitrile were added before the mixture was cooled to 0 °C. Thiophenol (6.6 mL, 65 mmol, 4.5 equiv) was added dropwise to the reaction, followed by dropwise addition of distilled triethylamine (9.1 mL, 65 mmol, 4.5 equiv). Observed the reaction change color from colorless to bright yellow. The reaction was removed from the cold bath to reach ambient temperature for 15 minutes, after which the reaction was cooled back down to 0 °C again. A solution of allyl (2*R*,9*R*,*E*)-11-azido-9-((tert-butyldimethylsilyl)oxy)-2-(3-chloropropyl)undec-4-enoate (6.82 g, 14 mmol) in 2.0 mL of distilled acetonitrile (and 2x 1.9 mL rinses of the original vessel) was added dropwise to the reaction at 0 °C. Once the substrate solution had been completely included in the reaction, the reaction mixture was

removed from the cold bath and allowed to reach ambient temperature. Observed the reaction change color from yellow to orange, as well as gas evolution. The bubbling stopped after 15 minutes, and the reaction was then diluted in 0.1 L CH_2Cl_2 and washed with 50 mL 3M NaOH twice. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Crude ^{1}H NMR shows a complete conversion of the azide substrate to amine product. The crude material was purified by column chromatography to remove thiophenol (20% EtOAc in hexanes to 20% MeOH 1% NH_4OH in CH_2Cl_2) to afford **28** (6.45 g, 14 mmol, 100% yield) as a light brown oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.93 – 5.82 (m, 1H), 5.48 – 5.37 (m, 1H), 5.36 – 5.24 (m, 2H), 5.21 (dt, *J* = 10.3, 1.2 Hz, 1H), 4.55 (dt, *J* = 5.9, 1.4 Hz, 2H), 3.71 (p, *J* = 5.7 Hz, 1H), 3.49 (td, *J* = 6.3, 2.7 Hz, 2H), 2.73 (hept, *J* = 6.3 Hz, 2H), 2.45 – 2.35 (m, 1H), 2.30 (dt, *J* = 14.4, 7.5 Hz, 1H), 2.17 (dt, *J* = 13.8, 6.7 Hz, 1H), 1.94 (t, *J* = 7.0 Hz, 4H), 1.80 – 1.60 (m, 4H), 1.57 (h, *J* = 6.4 Hz, 2H), 1.44 – 1.36 (m, 2H), 1.36 – 1.27 (m, 2H), 0.89 – 0.83 (m, 9H), 0.02 (d, *J* = 4.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 133.2, 132.3, 126.6, 118.3, 70.5, 65.0, 45.2, 44.7, 40.4, 38.7, 36.9, 35.4, 32.7, 30.4, 28.9, 26.0, 25.0, 18.2, -4.3, -4.4. HRMS (ESI) *m/z*: [M+H$^+$] calcd for ($C_{23}H_{45}ClNO_3Si$) 446.2587; found 446.2584.

Procedure 24: Convergence of fragments

To a mixture of **26** (9.04 g, 16 mmol, 1.1 equiv) and **28** (6.45 g, 14 mmol) in 15.2 mL CH_2Cl_2 at 21 °C, HOBt (2.93 g, 22 mmol, 1.5 equiv) was added, followed by 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (4.16 g, 22 mmol, 1.5 equiv). Monitoring by TLC showed consumption of **28** after 0.5 hours. The reaction was diluted in 40 mL 50% EtOAc in hexanes and quenched with 30 mL of saturated $NaHCO_{3(aq)}$, and was washed with 30 mL brine. Back-extraction was performed using 30 mL 50% EtOAc in hexanes to extract from

the combined aqueous layers. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (7.5% EtOAc in hexanes to 20% EtOAc in hexanes) to give **29** (11.2 g, 11 mmol, 78% yield) as a pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (s, 3H), 6.92 – 6.87 (m, 2H), 6.83 (t, *J* = 6.0 Hz, 1H), 5.90 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.56 – 5.48 (m, 1H), 5.47 – 5.39 (m, 1H), 5.35 – 5.27 (m, 3H), 5.23 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.57 (dt, *J* = 5.8, 1.4 Hz, 2H), 4.42 (d, *J* = 9.9 Hz, 1H), 4.34 (d, *J* = 9.9 Hz, 1H), 3.82 (s, 3H), 3.79 – 3.72 (m, 1H), 3.68 – 3.55 (m, 2H), 3.51 (td, *J* = 6.3, 2.4 Hz, 2H), 3.49 – 3.42 (m, 1H), 3.33 (qt, *J* = 10.4, 3.8 Hz, 3H), 3.23 – 3.13 (m, 1H), 2.63 (dd, *J* = 15.0, 6.5 Hz, 1H), 2.54 (dd, *J* = 15.0, 7.4 Hz, 1H), 2.43 (ddd, *J* = 11.5, 7.9, 5.7 Hz, 1H), 2.32 (dt, *J* = 14.3, 7.3 Hz, 1H), 2.18 (dt, *J* = 13.7, 6.7 Hz, 1H), 2.06 – 1.97 (m, 3H), 1.97 – 1.90 (m, 3H), 1.83 – 1.47 (m, 13H), 1.46 – 1.23 (m, 11H), 0.91 – 0.82 (m, 18H), 0.05 (d, *J* = 5.6 Hz, 6H), -0.02 (d, *J* = 15.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 172.8, 159.5, 134.0, 133.2, 132.4, 130.0, 129.6, 126.7, 124.1, 118.4, 114.1, 83.0, 70.1, 69.3, 65.1, 63.9, 55.4, 48.1, 45.2, 45.2, 44.8, 38.3, 36.9, 36.9, 36.8, 35.9, 35.8, 35.4, 32.9, 32.7, 31.8, 30.4, 28.9, 26.9, 26.0, 25.0, 24.9, 18.2, -4.2, -4.2, -4.5, -4.5. HRMS (ESI) *m/z*: [M+Na^+] calcd for ($C_{51}H_{88}Cl_2N_4O_7Si_2Na^+$) 1017.5466; found 1017.5464.

Procedure 25: reduction of azide **29**

A 250 mL round bottom flask was charged with a stirbar, gas inlet adapter and septum before it was flame dried under vacuum and backfilled with argon. The flask was charged with $SnCl_2$ (2.53 g, 13 mmol, 1.19 equiv) under nitrogen, then reconnected to an argon line. 6.7 mL of distilled acetonitrile were added before the mixture was cooled to 0 °C. Thiophenol

(4.1 mL, 40 mmol, 3.57 equiv) was added dropwise to the reaction, followed by dropwise addition of distilled triethylamine (5.6 mL, 40 mmol, 3.57 equiv). Observed the reaction change color from colorless to bright yellow. The reaction was removed from the cold bath to reach ambient temperature for 15 minutes, after which the reaction was cooled back down to 0 °C again. A solution of **29** (11.2 g, 11 mmol) in 4.5 mL of distilled acetonitrile was added dropwise to the reaction at 0 °C. Once the substrate solution had been completely included in the reaction, the reaction mixture was removed from the cold bath and allowed to reach ambient temperature. Observed the reaction change color from yellow to orange, as well as gas evolution. The bubbling stopped after 0.5 hours, and the reaction was then diluted in 100 mL CH_2Cl_2 and washed with 50 mL NaOH twice. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Crude ^1H NMR shows a complete conversion of the azide substrate to amine product. The crude material was purified by column chromatography to remove thiophenol (20% EtOAc in hexanes to 25% MeOH 2% NH_4OH in CH_2Cl_2), affording **30** (10.9 g, 11 mmol, 100% yield) as a light brown oil. ^1H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 6.9 Hz, 2H), 6.92 – 6.87 (m, 2H), 6.84 (t, *J* = 6.0 Hz, 1H), 5.95 – 5.84 (m, 1H), 5.50 (dt, *J* = 14.4, 6.8 Hz, 1H), 5.43 (dt, *J* = 14.0, 6.7 Hz, 1H), 5.37 – 5.26 (m, 3H), 5.23 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.57 (dt, *J* = 5.8, 1.4 Hz, 2H), 4.42 (d, *J* = 10.0 Hz, 1H), 4.34 (d, *J* = 9.9 Hz, 1H), 3.82 (s, 4H), 3.78 – 3.71 (m, 2H), 3.68 – 3.60 (m, 2H), 3.60 – 3.53 (m, 1H), 3.51 (dt, *J* = 6.4, 3.1 Hz, 2H), 3.45 (ddd, *J* = 10.5, 8.5, 5.6 Hz, 1H), 3.34 (ddd, *J* = 13.8, 8.2, 4.2 Hz, 1H), 3.21 – 3.11 (m, 1H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.62 (dd, *J* = 15.0, 6.6 Hz, 1H), 2.54 (dd, *J* = 15.0, 7.4 Hz, 1H), 2.43 (tt, *J* = 7.7, 5.5 Hz, 1H), 2.32 (td, *J* = 14.1, 7.0 Hz, 1H), 2.18 (dt, *J* = 13.7, 6.8 Hz, 1H), 2.03 – 1.91 (m, 8H), 1.82 – 1.58 (m, 11H), 1.51 (dtd, *J* = 13.2, 7.7, 5.4 Hz, 2H), 1.41 (ddt, *J* = 16.0, 10.8, 5.6 Hz, 5H), 1.37 – 1.21

(m, 9H), 0.91 – 0.86 (m, 13H), 0.84 (d, J = 2.8 Hz, 11H), 0.05 (s, 7H), -0.02 (d, J = 16.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 172.7, 159.4, 134.0, 133.1, 133.0, 132.3, 129.9, 129.5, 126.6, 123.9, 118.3, 118.2, 113.9, 82.9, 77.4, 77.4, 77.2, 77.1, 76.9, 70.4, 70.0, 65.0, 65.0, 63.8, 55.3, 55.3, 45.1, 45.1, 45.0, 44.7, 44.6, 39.5, 38.4, 38.2, 36.8, 36.8, 36.6, 35.8, 35.3, 32.9, 32.6, 31.7, 30.3, 28.8, 26.8, 25.9, 25.9, 25.0, 24.9, 18.1, 18.1, 18.1, -4.3, -4.3, -4.5, -4.5. HRMS (ESI) *m/z*: [M+H] calcd for ($C_{51}H_{91}Cl_2N_2O_7Si_2^+$) 969.5742; found 969.5719.

Procedure 26: de-allylation, macrolactamization in synthesis of **31**

To a solution of **30** (2.08 g, 2.1 mmol) in 2.7 mL CH_2Cl_2, $PhSiH_3$ (0.79 mL, 6.4 mmol, 3.0 equiv) was added dropwise. $Pd(PPh_3)_4$ (74.4 mg, 0.064 mmol, 0.03 equiv) was added (charged flame dried dram vial under N_2 environment). The reaction mixture rapidly changed color from a light brown to black. After 0.5 hours, TLC monitoring indicated consumption of starting material and the reaction mixture was concentrated in vacuo, then rapidly performed column chromatography to purify it (25% EtOAc in hexanes to 25% MeOH 1% NH_4OH in CH_2Cl_2) to provide a brown semi-solid. The product was submitted rapidly to the next reaction in the synthesis.

To a solution of (2*R*,9*R*,*E*)-11-((2*S*,9*R*,*E*)-11-amino-9-((*tert*-butyldimethylsilyl)oxy)-2-(3-chloropropyl)-2-((4-methoxybenzyl)oxy)undec-4-enamido)-9-((*tert*-butyldimethylsilyl)oxy)-2-(3-chloropropyl)undec-4-enoic acid (1.97 g, ~2.1 mmol) in 0.7 L DMF, ethyl diisopropylamine (1.5 mL, 8.6 mmol, 4.0 equiv) were added, followed by HATU (1.21 g, 3.2 mmol, 1.5 equiv). The reaction was stirred at ambient temperature for three days with monitoring by ^{1}H NMR. When the reaction had reached its extent, the reaction was quenched with 5 mL DI H_2O, and the DMF was removed by distillation in vacuo (0.2 mmHg,

rotovap bath set to 50 °C). The crude reaction mixture was washed with 0.1L water five times and the product was extracted by 0.1 L EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was isolated by column chromatography (25% EtOAc in hexanes to 40% EtOAc in hexanes) to afford **31** (0.602 g, 0.66 mmol, 31% yield over two steps) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.8 Hz, 4H), 6.93 (dd, *J* = 7.8, 4.4 Hz, 1H), 6.90 (d, 2H), 6.27 (t, *J* = 4.9 Hz, 1H), 5.52 (dt, *J* = 15.3, 6.5 Hz, 1H), 5.44 (dt, *J* = 15.1, 6.4 Hz, 1H), 5.35 – 5.24 (m, 2H), 4.43 (d, *J* = 10.2 Hz, 1H), 4.36 (d, *J* = 10.1 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 1H), 3.73 (dq, *J* = 10.2, 5.5 Hz, 1H), 3.59 (dt, *J* = 11.1, 5.7 Hz, 1H), 3.52 (dt, *J* = 8.1, 6.0 Hz, 2H), 3.50 – 3.47 (m, 1H), 3.47 – 3.35 (m, 2H), 3.21 (dq, *J* = 11.5, 5.3 Hz, 1H), 3.06 – 2.98 (m, 1H), 2.59 (dd, *J* = 14.9, 7.2 Hz, 1H), 2.53 (dd, *J* = 14.8, 6.9 Hz, 1H), 2.27 (ddd, *J* = 13.7, 10.8, 7.5 Hz, 1H), 2.10 (dt, *J* = 13.0, 5.1 Hz, 1H), 2.05 – 1.93 (m, 5H), 1.77 (tq, *J* = 9.2, 4.6 Hz, 3H), 1.74 – 1.64 (m, 4H), 1.58 – 1.51 (m, 2H), 1.51 – 1.35 (m, 6H), 1.32 (p, *J* = 7.8 Hz, 4H), 1.25 (d, *J* = 2.3 Hz, 1H), 0.88 (s, 9H), 0.84 (s, 9H), 0.10 – -0.05 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 172.6, 159.3, 133.8, 132.6, 130.2, 129.4, 127.0, 123.7, 114.1, 83.3, 71.5, 70.7, 63.7, 55.5, 48.1, 45.2, 45.0, 38.3, 37.7, 36.8, 36.6, 36.5, 36.4, 36.2, 35.0, 33.1, 33.0, 31.6, 30.9, 30.3, 26.9, 26.1, 26.0, 26.0, 25.0, 24.8, 18.2, 18.1, -4.2, -4.4, -4.4. HRMS(ESI) *m/z*: [M+H] calcd for ($C_{48}H_{85}Cl_2N_2O_6Si_2^+$) 911.5324; found 911.5339.

Procedure 27: cyclization by $LiN(SiMe_3)_2$

A solution of $LiN(SiMe_3)_2$ was prepared by adding a 2.35M solution of *n*-BuLi (5.3 mL, 12 mmol) to a solution of freshly distilled bis(trimethylsilyl)amine (2.8 mL, 13 mmol) in 25 mL

distilled THF at 0 °C. After 15 minutes, the reaction was removed from the cold bath and allowed to reach ambient temperature.

To a solution of **31** (2.81 g, 3.1 mmol) in 15.5 mL THF, 0.1 equiv of $LiN(SiMe_3)_2$ were added at a time until 2.3 equiv (14.2 mL) of 0.5 M $LiN(SiMe_3)_2$ solution were added to the reaction at 21 °C. TLC analysis showed near-complete conversion of this intermediate at this time. More $LiN(SiMe_3)_2$ solution was not added to prevent epimerization with excess $LiN(SiMe_3)_2$. The reaction was quenched with 10 mL saturated $NH_4Cl_{(aq)}$ solution and the crude product was extracted with 20 mL EtOAc and washed with 20 mL DI H_2O. The crude solution was dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was isolated by column chromatography (17% EtOAc in hexanes to 30% EtOAc in hexanes), to give **32** (2.10 g, 2.5 mmol, 81% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.1 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 2H), 5.55 – 5.36 (m, 3H), 5.27 (dt, *J* = 15.0, 7.3 Hz, 1H), 4.59 (d, *J* = 11.1 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.78 (s, 4H), 3.69 (hept, *J* = 5.6 Hz, 2H), 3.43 (q, *J* = 6.8 Hz, 1H), 3.36 (dt, *J* = 14.0, 7.1 Hz, 1H), 3.29 (td, *J* = 11.2, 4.9 Hz, 1H), 3.21 (dt, *J* = 17.4, 6.3 Hz, 2H), 3.01 (ddd, *J* = 17.2, 13.2, 7.5 Hz, 2H), 2.42 (dt, *J* = 13.2, 6.5 Hz, 1H), 2.38 – 2.28 (m, 2H), 2.19 (dd, *J* = 13.1, 8.3 Hz, 1H), 2.15 – 2.06 (m, 1H), 1.97 (qd, *J* = 14.9, 6.6 Hz, 6H), 1.90 – 1.82 (m, 4H), 1.67 – 1.54 (m, 5H), 1.50 (qd, *J* = 8.9, 4.1 Hz, 1H), 1.40 (ttd, *J* = 15.5, 11.3, 4.5 Hz, 7H), 1.34 – 1.24 (m, 9H), 0.89 (d, *J* = 2.4 Hz, 18H), 0.06 (d, *J* = 2.6 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 168.5, 159.0, 134.6, 132.5, 131.7, 129.2, 129.1, 128.1, 125.2, 113.8, 113.8, 77.5, 70.8, 70.4, 65.8, 65.8, 55.4, 48.8, 48.7, 48.3, 44.1, 44.1, 42.0, 39.1, 36.5, 35.8, 35.2, 34.8, 34.7, 34.2, 33.9, 32.7, 32.2, 32.1, 31.7, 29.8, 29.2, 26.6, 26.0, 25.4, 25.3, 25.2, 22.8, 22.8, 22.3, 20.8, 19.0, 18.2, 14.3, 11.6, -4.2, -4.2, -4.2, -4.3, -4.4, -4.4. HRMS (ESI) *m/z*: [M+Na^+] calcd for ($C_{48}H_{82}N_2O_6Si_2Na^+$) 861.5609; found 861.5635.

Procedure 28: de-silylation of **32**

A 1 M solution of tetrabutylammonium fluoride trihydrate solution (10.1 mL, 10 mmol, 4.0 equiv) was added to **32** (2.10 g. 2.5 mmol) at 0°C. The reaction was then warmed to ambient temperature, then heated to 50 °C for 3 hours. TLC analysis showed complete consumption of starting material. The reaction was quenched with 4 mL of a saturated solution of NH_4Cl, then extracted with 10 mL EtOAc while washing with 10 mL brine (five times). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified using a silica plug (70% acetone in hexanes) to provide (4*R*,8*E*,11*S*,18*R*,22*E*,25*R*)-4,18-dihydroxy-11-((4-methoxybenzyl)oxy)-1,15-diazatricyclo[23.3.1.1^{11,15}]triaconta-8,22-diene-29,30-dione. Submitted to the following reaction as a mixture, *tert*-butyldimethylsilanol the significant impurity.

Procedure 29: PMB removal

To a mixture of (4*R*,8*E*,11*S*,18*R*,22*E*,25*R*)-4,18-dihydroxy-11-((4-methoxybenzyl)oxy)-1,15-diazatricyclo[23.3.1.1^{11,15}]triaconta-8,22-diene-29,30-dione (1.55 g, 2.5 mmol) 25.4 mL distilled CH_2Cl_2, and 2.5 mL DI H_2O, 2,3-dichloro-5,6-dicyano-p-benzoquinone (0.724 g, 3.2 mmol, 1.25 equiv) was added in one portion at ambient temperature. Observed the heterogeneous mixture change color from light yellow to fuchsia. TLC monitoring indicated complete consumption of starting material after 10 minutes. The reaction was quenched with 20 mL of an aqueous mixture of 50% saturated $NaHCO_3$ and 50% brine; the crude product was extracted with 30 mL CH_2Cl_2. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. The product was isolated by column chromatography (30% hexanes

in EtOAc to 10% MeOH in CH_2Cl_2) to obtain **33** (1.07 g, 2.2 mmol, 85% over two steps) as an off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.53 (dt, *J* = 14.1, 6.5 Hz, 1H), 5.45 – 5.38 (m, 2H), 5.36 (dd, *J* = 15.2, 7.6 Hz, 1H), 3.82 (ddd, *J* = 14.1, 9.5, 4.8 Hz, 1H), 3.63 (s, 1H), 3.58 (ddd, *J* = 14.2, 9.0, 5.6 Hz, 1H), 3.46 (s, 1H), 3.42 (s, 1H), 3.37 – 3.29 (m, 3H), 3.26 (dd, *J* = 7.9, 4.3 Hz, 3H), 3.08 (dt, *J* = 13.9, 5.2 Hz, 1H), 2.42 (td, *J* = 12.5, 6.6 Hz, 2H), 2.35 (dd, *J* = 13.2, 7.3 Hz, 2H), 2.29 (dt, *J* = 12.4, 6.0 Hz, 1H), 2.13 – 2.04 (m, 3H), 2.03 – 1.96 (m, 3H), 1.94 (s, 1H), 1.92 – 1.83 (m, 4H), 1.80 – 1.58 (m, 6H), 1.54 – 1.45 (m, 10H). HRMS (ESI) *m/z*: [M+Na^+] calcd for ($C_{28}H_{46}N_2O_5Na^+$) 513.3304; found 513.3298.

Procedure 30: Birch reduction

A 100 mL round bottom flask and a 250 mL round bottom flask (charged with a glass stirbar) was dried under vacuum and backfilled with argon. Both flasks were cooled to -78 °C. NH_3 was condensed from a cylinder into the 100 mL round bottom flask, marked to 50 mL, before it was cannulated into the pre-cooled 250 mL round bottom flask. Lithium metal was added in six portions amounting to 0.373 g (54 mmol, ~30 equiv) in total, and the solution was observed to change from colorless to a deep blue color. The reaction was warmed to -40 °C for 1 hour. After this, the solution was again cooled to -78 °C for 20 minutes, before 2 mL THF were added. The substrate **33** (0.869 g, 1.8 mmol) was prepared as a solution in 30 mL THF (and 3 mL to rinse original container and syringe) which was added dropwise to the reaction at -78 °C. The reaction was kept at -78 °C for 15 minutes before warming to -40 °C and maintaining temperature for 30 minutes. After this time, the reaction was quenched with the addition of 5 g $NH_4Cl_{(s)}$, followed by 30 mL THF and warming to 21 °C for 20 minutes. 5 mL DI H_2O were added before 30 mL CH_2Cl_2 was included. The reaction was washed

with 20 mL 1M $NaOH_{(aq)}$ and extracted with 10 mL CH_2Cl_2. The crude product material was submitted to column chromatography (reverse phase silica gel) (10% DI H_2O in MeOH to 5% DI H_2O in MeOH) and isolated a mixture of three products weighing 0.606 g as a white semi-solid. The material was submitted as a mixture to the final reaction in the synthesis.

Procedure 31: hydrogenation to give (+)-desmethylxestospongin B

The product mixture from the previous reaction (0.606 g) was dissolved in HPLC grade EtOAc. 5 wt. % rhodium on alumina (0.304 g) was added to the solution and the reaction vessel was sealed. A balloon filled with H_2 was fixed to a syringe with needle and was introduced through the septum of the reaction vessel. An outlet needle was introduced, and the H_2 was allowed to bubble through the solution for 5 minutes, after which the outlet needle was removed and the H_2 source needle was placed above the reaction solution. Every 30 minutes, the H_2 was bubbled through the reaction mixture for 5 minutes, and the reaction was monitored by ^1H NMR; after 2 hours, the reaction was deemed complete. The reaction was filtered through celite (filtering agent was rinsed with HPLC-grade EtOAc) and concentrated in vacuo. The product was purified via column chromatography (reverse-phase silica gel) (10% H_2O in MeOH to 5% H_2O in MeOH) to give **1** (0.366 g, 0.79 mmol, 45 % yield over two steps) as a white solid. ^1H and ^{13}C NMR spectral data matched those reported in the literature.[10]

Stereocontrol in the Ireland Claisen Rearrangement of α-Fluoro Allylic Esters

Procedure 32: formation of silyl ketene acetal **32.**

To a solution of $(iPr)_2NH$ (2.0 mL, 14 mmol, 1.4 equiv) in 20 mL THF, 2.23 M *n*-BuLi (5.8 mL, 13 mmol, 1.3 equiv) was added dropwise at -78 °C. After 0.5 hours, **31** (1.50 g, 10.0 mmol) was added in solution with 13 mL THF dropwise to LDA. After 0.5 hours, added freshly distilled TMSCl (2.8 mL, 22 mmol, 2.2 equiv) to the reaction, and after another 0.5 hours the reaction mixture was warmed to 0 °C. Maintained temperature conditions for one hour. The reaction was diluted in 10 mL hexanes and 10 mL DI H_2O was added to quench the reaction. Poured over 10 mL saturated $NaHCO_{3(aq)}$ solution and extracted the product with hexanes. The organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The product **32** was submitted crude to the next reaction.

Procedure 33: fluorination of silyl ketene acetal intermediate **32**

The crude material **32** from the previous reaction (~1.0 mmol) was dissolved in 3.3 mL THF and cooled to -78 °C. $(iPr)_2Net$ (0.17 mL, 1 mmol, 1 equiv) was added dropwise to the solution, before N-fluorobenzenesulfonimide (0.984 g, 3.1 mmol, 3.0 equiv) was added in 3 portion(s). ^1H NMR was used to track conversion after each equivalent of N-fluorobenzenesulfonamide added, with the reaction reaching 70% conversion of starting material to product.

Procedure 34: fluorination of benzyl ester **34**, a one-pot procedure

To a solution of $(iPr)_2NH$ (1.5 mL, 11 mmol, 2.4 equiv) in 11.9 mL THF, 1.96 M *n*-BuLi (5 mL, 9.8 mmol, 2.2 equiv) was added dropwise at -78 °C. After 0.5 hours, **34** (1.00 g, 4.4 mmol) was added in solution with 17.5 mL THF dropwise to LDA. After 0.5 hours, added freshly distilled TMSCl (1.7 mL, 13 mmol, 3.0 equiv) to the reaction, and after another 0.5 hours the reaction mixture was warmed to 0 °C. Maintained temperature conditions for one hour before adding a 1.0 M solution of N-fluorobenzenesulfonimide (17.7 mL, 17.7 mmol, 4.0 equiv) dropwise to the reaction. After 1 hour, the reaction was warmed to 0 °C, then to 21 °C after another hour. After 18 hours at ambient temperature, ^1H NMR showed full conversion. The reaction was quenched with 20 mL saturated $NH_4Cl_{(aq)}$ solution, and the mixture was washed with 10 mL saturated $KI_{(aq)}$ solution and extracted with EtOAc. The heterogeneous mixture was filtered through celite before partitioning. Washed once with 10 mL saturated $Na_2S_2O_3$. Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (Hexanes to 3% EtOAc in hexanes) to provide **35** (0.868 g, 3.5 mmol, 80 % yield) as a pale yellow oil. ^1H NMR (600 MHz, $cdcl_3$) δ 7.42 – 7.32 (m, 5H), 5.24 (d, J = 1.3 Hz, 2H), 5.05 – 4.92 (m, 1H), 3.56 (td, J = 6.4, 1.0 Hz, 2H), 2.19 – 1.99 (m, 2H), 1.99 – 1.86 (m, 2H).

Modular Synthesis of Fluorinated Analogue, (+)-Difluoroxestospongin C

Procedure 35: Esterification, **7** and **36**

To a mixture of **7** (0.651 g, 2.1 mmol) and **36** (0.538 g, 3.5 mmol, 1.65 equiv) in 13.9 mL CH_2Cl_2, DMAP (56 mg, 0.46 mmol, 0.2 equiv) was added in one portion. The reaction was cooled to 0 °C for 0.5 hours before 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (0.607 g, 3.1 mmol, 1.5 equiv) was added to the reaction mixture. The cold bath was removed and the reaction was allowed to reach ambient temperature. TLC monitoring showed a near-complete reaction after 2 hours. The reaction was quenched with 5 mL saturated $NH_4Cl_{(aq)}$ solution before extracting with 10 mL CH_2Cl_2 and washing with 10 mL DI H_2O and 10 mL brine. Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (Hexanes to 3% EtOAc in hexanes) to provide **43** (0.861 g, 1.9 mmol, 92% yield) as a pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (ddddd, *J* = 17.2, 10.3, 6.8, 3.3, 0.9 Hz, 1H), 5.36 – 5.26 (m, 4H), 5.26 – 5.20 (m, 2H), 4.95 (dq, 1H), 3.77 (p, *J* = 5.8 Hz, 1H), 3.59 (td, *J* = 6.0, 2.9 Hz, 2H), 3.35 (h, *J* = 5.5 Hz, 2H), 2.20 – 1.86 (m, 6H), 1.76 – 1.60 (m, 4H), 1.52 – 1.43 (m, 2H), 1.43 – 1.23 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H).

Procedure 36: Mitsunobu conditions, esterification to make **44**

To a mixture of **7** (20.5 mg, 0.065 mmol), **36** (20.2 mg, 0.13 mmol, 2 equiv) in 0.17 mL distilled THF and 0.17 mL distilled CH_2Cl_2, triphenylphosphine (57.9 mg, 0.22 mmol, 3.3 equiv) was added at ambient temperature. Cooled to -20 °C before DIAD (38 μL, 0.19 mmol, 3.0 equiv) was added to the reaction. After 0.5 hours, the cold bath was removed and the reaction was left stirring overnight. TLC analysis showed complete consumption of

starting material and formation of major product. The reaction was quenched with 0.5 mL saturated $NH_4Cl_{(aq)}$ solution and after 10 minutes the product was extracted with 1 mL 20% EtOAc in hexanes and washed with 1 mL DI H_2O. Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (Hexanes to 3% EtOAc in hexanes) to provide **44** (27.3 mg, 0.61 mmol, 93% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (dddd, *J* = 17.3, 10.6, 6.8, 2.6 Hz, 1H), 5.37 – 5.26 (m, 2H), 5.26 – 5.20 (m, 1H), 5.05 – 4.86 (dq, 1H), 3.77 (p, *J* = 5.8 Hz, 1H), 3.59 (td, *J* = 6.2, 2.5 Hz, 2H), 3.40 – 3.28 (m, 2H), 2.19 – 1.89 (m, 4H), 1.77 – 1.57 (m, 4H), 1.46 (tq, *J* = 13.5, 6.9 Hz, 2H), 1.35 (p, *J* = 7.8 Hz, 2H), 0.88 (s, 9H), 0.05 (d, *J* = 3.9 Hz, 6H).

Procedure 37: Ireland-Claisen rearrangement of **43**

A solution of $KN(SiMe_3)_2$ (0.878 g, 4.4 mmol, 2.2 equiv) in 4.3 mL distilled toluene was cooled to -78 °C for 0.5 hours before a solution of **43** (0.861 g, 1.9 mmol) in 8.9 mL distilled toluene was added dropwise into the reaction solution. After 0.5 hours, freshly distilled trimethylsilyl chloride (0.49 mL, 3.9 mmol, 2.0 equiv) was added dropwise into the reaction mixture. After 1 hour, the reaction was warmed to -40 °C for one hour, then warmed to -15 °C for 1 hour. At this time, the reaction was allowed to reach 21 °C, and was left stirring overnight. TLC monitoring confirmed consumption of starting material to the C-silylation product and to the desired product acid. The reaction was quenched with 5 mL 1M HCl, and the product was extracted with 5 mL EtOAc three times. Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was isolated by column chromatography (15% EtOAc in hexanes to 25% EtOAc 1% AcOH in hexanes) to give **46**

(0.514 g, 1.1 mmol, 60% yield) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.57 (dt, *J* = 14.2, 6.8 Hz, 1H), 5.42 (dt, *J* = 15.0, 7.2 Hz, 1H), 3.76 (p, *J* = 5.7 Hz, 1H), 3.56 (dq, *J* = 6.7, 2.4 Hz, 2H), 3.35 (hept, *J* = 6.5 Hz, 2H), 2.62 (td, *J* = 14.3, 7.2 Hz, 1H), 2.57 (dd, *J* = 7.4, 3.8 Hz, 1H), 2.14 – 2.05 (m, 2H), 2.05 – 2.02 (m, 2H), 2.00 (dd, *J* = 12.1, 5.0 Hz, 2H), 1.71 (q, *J* = 6.6 Hz, 2H), 1.43 (tt, *J* = 9.2, 4.1 Hz, 3H), 0.89 (d, *J* = 1.1 Hz, 9H), 0.06 (d, *J* = 1.0 Hz, 6H).

Procedure 37: Ireland-Claisen rearrangement of **44**

A solution of $KN(SiMe_3)_2$ (0.677 g, 3.4 mmol, 2.2 equiv) in 3.5 mL distilled toluene was cooled to -78 °C for 0.5 hours before a solution of **44** (0.689 g, 1.5 mmol) in 7.1 mL distilled toluene was added dropwise into the reaction solution. After 0.5 hours, freshly distilled trimethylsilyl chloride (0.39 mL, 3.1 mmol, 2.0 equiv) was added dropwise into the reaction mixture. After 1 hour, the reaction was warmed to -40 °C for one hour, then warmed to -15 °C for 1 hour. At this time, the reaction was allowed to reach 21 °C, and was left stirring overnight. TLC monitoring confirmed consumption of starting material to the C-silylation product and to the desired product acid. The reaction was quenched with 5 mL 1M HCl, and the product was extracted with 5 mL EtOAc three times. Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was isolated by column chromatography (15% EtOAc in hexanes to 25% EtOAc 1% AcOH in hexanes) to give **45** (0.414 g, 0.92 mmol, 60 % yield) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.57 (dt, *J* = 14.4, 6.8 Hz, 1H), 5.42 (dt, *J* = 15.1, 7.2 Hz, 1H), 3.77 (q, *J* = 5.8 Hz, 1H), 3.58 – 3.52 (m, 2H), 3.36 (t, *J* = 6.9 Hz, 2H), 2.62 (td, *J* = 12.9, 7.2 Hz, 1H), 2.57 (d, *J* = 7.0 Hz, 1H), 2.17 (d, *J* = 1.3 Hz, 1H), 2.14 – 2.05 (m, 2H), 2.01 (td, *J* = 14.4, 7.6 Hz, 4H), 1.82 (s, 1H), 1.77 –

1.72 (m, 1H), 1.72 – 1.67 (m, 2H), 1.47 – 1.36 (m, 5H), 1.26 (s, 2H), 0.89 (s, 9H), 0.06 (d, *J* = 1.5 Hz, 6H).

Procedure 38: derivatization of acid **46**

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (14.7 mg, 0.077 mmol, 3 equiv), (R)-(+)-alpha-methylbenzylamine (11 μL, 0.083 mmol, 3 equiv), and HOBt (11.1 mg, 0.082 mmol, 3 equiv) were added sequentially to a solution of acid **46** (11.4 mg, 0.025 mmol) in 0.14 mL CH_2Cl_2. The solution was stirred at room temperature for 1 hour, then diluted with 2 mL CH_2Cl_2 and washed with 2 mL saturated aqueous sodium bicarbonate, then 2 mL brine. Dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc in hexanes) to give (2*S*,9*R*,*E*)-11-azido-9-((*tert*-butyldimethylsilyl)oxy)-2-(3-chloropropyl)-2-fluoro-*N*-((*R*)-1-phenylethyl)undec-4-enamide (6.4 mg, 0.12 mmol, 46% yield, dr 12:1) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 3H), 6.60 – 6.54 (m, 1H), 5.47 (dt, *J* = 15.1, 6.7 Hz, 1H), 5.29 – 5.20 (m, 1H), 5.18 – 5.09 (m, 1H), 3.80 – 3.70 (m, 1H), 3.54 (qt, *J* = 10.9, 6.5 Hz, 2H), 3.39 – 3.33 (m, 2H), 2.66 – 2.53 (m, 1H), 2.43 (ddd, *J* = 17.3, 14.5, 7.5 Hz, 1H), 2.15 – 2.00 (m, 1H), 1.99 – 1.87 (m, 4H), 1.86 – 1.77 (m, 1H), 1.73 – 1.61 (m, 2H), 1.52 (d, *J* = 6.9 Hz, 3H), 1.46 – 1.36 (m, 2H), 1.31 (s, 1H), 1.31 – 1.24 (m, 4H), 0.88 (s, 9H), 0.05 (s, 6H).

Procedure 39: derivatization of acid **45**

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (7.2 mg, 0.038 mmol, 3 equiv), (R)-(+)-alpha-methylbenzylamine (5 μL, 0.038 mmol, 3 equiv), and HOBt (6.1 mg, 0.045 mmol, 3 equiv) were added sequentially to a solution of acid **45** (5.3 mg, 0.012 mmol) in 0.10 mL

CH_2Cl_2. The solution was stirred at room temperature for 1 hour, then diluted with 2 mL CH_2Cl_2 and washed with 2 mL saturated aqueous sodium bicarbonate, then 2 mL brine. Dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc in hexanes) to give (2*R*,9*R*,*E*)-11-azido-9-((*tert*-butyldimethylsilyl)oxy)-2-(3-chloropropyl)-2-fluoro-*N*-((*R*)-1-phenylethyl)undec-4-enamide (4.1 mg, 0.0074 mmol, 63% yield, dr 16:1) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 6H), 6.56 (t, *J* = 7.0 Hz, 1H), 5.56 (dt, *J* = 14.0, 6.7 Hz, 1H), 5.43 – 5.35 (m, 1H), 5.12 (p, *J* = 7.1 Hz, 1H), 3.78 (dq, *J* = 6.9, 5.4 Hz, 1H), 3.49 – 3.30 (m, 4H), 2.68 – 2.56 (m, 1H), 2.53 – 2.43 (m, 1H), 2.09 – 1.96 (m, 4H), 1.95 – 1.76 (m, 4H), 1.76 – 1.61 (m, 6H), 1.54 – 1.34 (m, 12H), 1.25 (s, 15H), 0.89 (s, 9H), 0.06 (d, *J* = 2.5 Hz, 6H).

Procedure 40: allylation of acid **46**

To a solution of **46** (0.446 g, 0.99 mmol) in 2.0 mL distilled dimethylformamide, K_2CO_3 (0.161 g, 1.2 mmol, 1.1 equiv) was added at 21 °C, then freshly distilled allyl bromide (0.26 mL, 3.0 mmol, 3 equiv) was added dropwise to the reaction. Monitoring by TLC showed a complete reaction after 2 hours. The reaction was diluted in 10 mL hexanes and quenched with slow addition of 10 mL 1N HCl. The product was extracted with 10 mL hexanes and washed with 10 mL DI H_2O three times. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (4% EtOAc in hexanes) to obtain allyl (2*S*,9*R*,*E*)-11-azido-9-((*tert*-butyldimethylsilyl)oxy)-2-(3-chloropropyl)-2-fluoroundec-4-enoate (0.378 g, 0.77 mmol, 78% yield) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.92 (ddtd, *J* = 16.3, 10.4, 5.8, 1.0 Hz, 1H), 5.53 (dt, *J* = 14.1, 6.7 Hz, 1H), 5.43 – 5.33 (m, 2H), 5.32 – 5.26 (m, 1H), 4.67 (dd, *J* = 5.9, 1.5 Hz, 2H), 3.76 (dt, *J*

= 10.9, 5.4 Hz, 1H), 3.61 – 3.49 (m, 2H), 3.34 (hept, *J* = 6.6 Hz, 2H), 2.64 – 2.49 (m, 2H), 2.13 – 2.00 (m, 2H), 2.00 – 1.92 (m, 3H), 1.79 – 1.69 (m, 2H), 1.67 (dd, *J* = 13.9, 7.0 Hz, 1H), 1.49 – 1.31 (m, 4H), 0.88 (d, *J* = 1.0 Hz, 9H), 0.05 (d, *J* = 2.9 Hz, 6H).

Procedure 41: reduction of azide, formation of amine fragment **47**

A 25 mL round bottom flask was charged with a stirbar, gas inlet adapter and septum before it was flame dried under vacuum and backfilled with argon. The flask was charged with $SnCl_2$ (0.2195 g, 1.2 mmol, 1.5 equiv) under nitrogen, then reconnected to an argon line. 4.7 mL of distilled acetonitrile was added before the mixture was cooled to 0 °C. Thiophenol (0.47 mL, 4.6 mmol, 6.0 equiv) was added dropwise to the reaction, followed by dropwise addition of distilled triethylamine (0.49 mL, 3.5 mmol, 4.5 equiv). Observed the reaction change color from colorless to bright yellow. A solution of allyl (2*S*,9*R*,*E*)-11-azido-9-((*tert*-butyldimethylsilyl)oxy)-2-(3-chloropropyl)-2-fluoroundec-4-enoate (0.378 g, 0.77 mmol) in 2.1 mL of distilled acetonitrile (and 2x 0.5 mL rinses of the original vessel) was added dropwise to the reaction at 21 °C. Observed the reaction change color from yellow to orange, as well as gas evolution. The bubbling stopped after 15 minutes, and the reaction was then diluted in 3 mL CH_2Cl_2 and concentrated in vacuo. The crude residue was washed with 2 mL 3M NaOH twice while extracting with 3 mL CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography to remove thiophenol (20% EtOAc in hexanes to 20% MeOH 1% NH_4OH in CH_2Cl_2) to afford **47** (0.327 g, 0.70 mmol, 91% yield) as a light brown oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.96 – 5.87 (m, 1H), 5.53 (dt, *J* = 14.1, 6.7 Hz, 2H), 5.42 – 5.33 (m, 3H), 5.32 – 5.26 (m, 2H), 4.67 (dt, *J* = 5.8, 1.2 Hz, 2H), 3.81 – 3.72 (m, 4H), 3.54 (hd, *J* = 7.2, 2.9

Hz, 4H), 2.79 (d, J = 6.1 Hz, 3H), 2.64 – 2.48 (m, 4H), 2.13 – 1.92 (m, 12H), 1.80 – 1.67 (m, 4H), 1.61 (h, J = 6.8 Hz, 4H), 1.49 – 1.18 (m, 14H), 0.88 (s, 9H), 0.06 (d, 6H).

Procedure 42: convergence of fragments **46** and **47**

To a mixture of **46** (0.219 g, 0.49 mmol, 1.1 equiv) and **47** (0.204 g, 0.44 mmol) in 2.6 mL CH_2Cl_2 at 21 °C, HOBt (0.189 g, 1.4 mmol, 1.5 equiv) was added, followed by 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl (0.255 g, 1.33 mmol, 1.5 equiv). Monitoring by TLC showed consumption of **47** after 0.5 hours. The reaction was diluted in 5 mL 50% EtOAc in hexanes and quenched with 5 mL of saturated $NaHCO_{3(aq)}$, and was washed with 5 mL brine. Back-extraction was performed using 5 mL 50% EtOAc in hexanes to extract from the combined aqueous layers. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (8% EtOAc in hexanes to 15% EtOAc in hexanes) to give **48** (0.287 g, 0.32 mmol, 73% yield) as a pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.76 (q, J = 5.4 Hz, 1H), 5.92 (ddt, J = 16.6, 10.4, 5.9 Hz, 1H), 5.52 (dq, J = 13.0, 6.4 Hz, 2H), 5.43 – 5.31 (m, 3H), 5.29 (dt, J = 10.4, 1.2 Hz, 1H), 4.67 (dt, J = 5.9, 1.4 Hz, 2H), 3.77 (dp, J = 11.7, 5.8 Hz, 2H), 3.59 – 3.46 (m, 4H), 3.34 (ddt, J = 12.0, 9.6, 6.6 Hz, 4H), 2.64 – 2.41 (m, 4H), 2.13 – 1.84 (m, 11H), 1.80 – 1.59 (m, 7H), 1.50 – 1.30 (m, 9H), 1.25 (s, 2H), 0.89 (d, J = 8.1 Hz, 18H), 0.06 (dd, 12H).

Procedure 43: reduction of azide **48,** preparation for macrolactamization

A 10 mL round bottom flask was charged with a stirbar, gas inlet adapter and septum before it was flame dried under vacuum and backfilled with argon. The flask was charged with

$SnCl_2$ (0.103 g, 0.54 mmol, 1.5 equiv) under nitrogen, then reconnected to an argon line. 2.2 mL of distilled acetonitrile was added before the mixture was cooled to 0 °C. Thiophenol (0.21 mL, 2.1 mmol, 6.0 equiv) was added dropwise to the reaction, followed by dropwise addition of distilled triethylamine (0.22 mL, 1.6 mmol, 4.5 equiv). Observed the reaction change color from colorless to bright yellow. A solution of **48** (0.310 g, 0.35 mmol) in 0.7 mL of distilled acetonitrile (and 2x 0.3 mL rinses of the original vessel) was added dropwise to the reaction at 21 °C. Observed the reaction change color from yellow to orange, as well as gas evolution. The bubbling stopped after 15 minutes, and the reaction was then diluted in 3 mL CH_2Cl_2 and concentrated in vacuo. The crude residue was washed with 2 mL 3M NaOH twice while extracting with 3 mL CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography to remove thiophenol (20% EtOAc in hexanes to 20% MeOH 1% NH_4OH in CH_2Cl_2) to afford **49** (0.263 g, 0.30 mmol, 87% yield) as a light brown oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.78 (q, *J* = 5.5 Hz, 1H), 5.92 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.52 (dq, *J* = 13.0, 6.5 Hz, 2H), 5.42 – 5.31 (m, 3H), 5.31 – 5.26 (m, 2H), 4.66 (dq, *J* = 5.9, 1.4 Hz, 2H), 3.78 (dq, *J* = 9.2, 5.7 Hz, 2H), 3.59 – 3.46 (m, 5H), 3.34 (hept, *J* = 6.9 Hz, 2H), 2.81 (s, 1H), 2.64 – 2.41 (m, 5H), 2.13 – 2.00 (m, 4H), 2.00 – 1.97 (m, 5H), 1.96 (dt, *J* = 4.3, 2.3 Hz, 1H), 1.95 – 1.78 (m, 4H), 1.78 – 1.68 (m, 4H), 1.68 – 1.58 (m, 4H), 1.54 – 1.41 (m, 5H), 1.41 – 1.33 (m, 4H), 1.33 – 1.23 (m, 3H), 0.93 – 0.82 (m, 24H), 0.10 – 0.04 (m, 14H).

Procedure 44: de-allylation, macrolactamization to attain **50**

To a solution of **46** (0.108 g, 0.12 mmol) in 0.80 mL CH_2Cl_2, $PhSiH_3$ (61 μL, 0.49 mmol, 4.0 equiv) was added dropwise. $Pd(PPh_3)_4$ (14.3 mg, 0.012 mmol, 0.10 equiv) was added

(charged flame dried dram vial under N_2 environment). The reaction mixture rapidly changed color from a light brown to black. After 0.5 hours, TLC monitoring indicated consumption of starting material and the reaction mixture was concentrated in vacuo, then rapidly performed column chromatography to purify it (25% EtOAc in hexanes to 20% MeOH 1% NH_4OH in CH_2Cl_2) to provide a yellow oil. The product was submitted rapidly to the next reaction in the synthesis.

To a solution of crude material from the de-allylation reaction (0.103 g, ~0.12 mmol) in 41 mL DMF, ethyl diisopropylamine (90 μL, 0.52 mmol, 4.0 equiv) were added, followed by HATU (98.1 mg, 0.26 mmol, 1.5 equiv). The reaction was stirred at ambient temperature for three days under argon with monitoring by ^{1}H NMR. When the reaction had reached its extent, it was quenched with 3 mL DI H_2O and the DMF was removed by distillation in vacuo (0.2 mmHg, oil bath set to 50 °C). The crude reaction mixture was washed with 3 mL DI H_2O five times and the product was extracted by 3 mL EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was isolated by column chromatography (20% EtOAc in hexanes to 30% EtOAc in hexanes) to afford **47** (36.2 mg, 0.045 mmol, 36 % yield over two steps) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.79 (q, *J* = 5.6 Hz, 1H), 6.71 (p, *J* = 5.6 Hz, 1H), 5.49 (dt, *J* = 16.1, 5.7 Hz, 2H), 5.36 – 5.26 (m, 2H), 3.75 (dp, *J* = 12.2, 6.0 Hz, 2H), 3.52 – 3.42 (m, 4H), 3.37 – 3.23 (m, 4H), 2.60 – 2.49 (m, 2H), 2.43 (td, *J* = 17.7, 7.4 Hz, 2H), 2.06 – 1.93 (m, 7H), 1.86 (ddt, *J* = 16.0, 12.1, 4.8 Hz, 4H), 1.68 (s, 4H), 1.59 (tq, *J* = 13.1, 6.3 Hz, 2H), 1.43 (tt, *J* = 13.8, 6.8 Hz, 4H), 1.33 (h, *J* = 6.7 Hz, 4H), 0.86 (s, 18H), 0.09 – -0.03 (m, 12H).

Procedure 45: cyclization of **50** by $LiN(SiMe_3)_2$

A solution of $LiN(SiMe_3)_2$ was prepared by adding a 2.24 M solution of *n*-BuLi (0.22 mL, 0.49 mmol) to a solution of freshly distilled bis(trimethylsilyl)amine (0.11 mL, 0.52 mmol) in 1.0 mL distilled THF at 0 °C. After 15 minutes, the reaction was removed from the cold bath and allowed to reach ambient temperature.

To a solution of **50** (41.4 mg, 0.051 mmol) in 0.21 mL THF, 1.5 equiv of $LiN(SiMe_3)_2$ solution were added, followed by subsequent additions of 1.0 equiv at a time until 4.5 equiv (0.46 mL) of 0.5 M $LiN(SiMe_3)_2$ solution were added to the reaction at 21 °C. TLC analysis showed complete conversion of this intermediate at this time. The reaction was quenched with 1 mL saturated $NH_4Cl_{(aq)}$ solution and the crude product was extracted with 3 mL EtOAc and washed with 3 mL DI H_2O. The crude solution was dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was isolated by column chromatography (hexanes to 20% EtOAc in hexanes), to give **51** (35.4 mg, 0.048 mmol, 94% yield) as a clear oil. ^1H NMR (600 MHz, cdcl$_3$) δ 5.55 (dq, *J* = 14.4, 7.0 Hz, 2H), 5.29 – 5.19 (m, 2H), 3.92 (ddd, *J* = 14.4, 8.8, 6.9 Hz, 1H), 3.80 – 3.68 (m, 2H), 3.65 (p, *J* = 5.4 Hz, 1H), 3.38 (s, 2H), 3.23 (dt, *J* = 11.8, 4.9 Hz, 2H), 3.06 – 2.85 (m, 4H), 2.39 – 2.26 (m, 2H), 2.11 – 1.93 (m, 11H), 1.91 – 1.76 (m, 3H), 1.76 – 1.57 (m, 7H), 1.53 – 1.19 (m, 22H), 1.17 – 1.01 (m, 2H), 0.96 (dd, *J* = 6.7, 1.5 Hz, 2H), 0.88 (q, *J* = 2.8 Hz, 18H), 0.05 (s, 12H).

Procedure 46: de-silylation of protecting groups

A 1 M solution of tetrabutylammonium fluoride trihydrate solution (0.34 mL, 0.34 mmol, 5.0 equiv) was added to **51** (49.0 mg, 0.066 mmol) at 0 °C. The reaction was then warmed to ambient temperature, then heated to 50 °C for 3 hours. TLC analysis showed complete consumption of starting material. The reaction was quenched with 1 mL of a saturated

solution of NH_4Cl, then extracted with 5 mL EtOAc while washing with 5 mL brine (five times). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified using a silica plug (50% acetone in hexanes) to provide **52** (32.3 mg, 0.063 mmol, 95% yield).

Procedure 47: ring closure by partial reduction using $NaAlH_2(OCH_2CH_2OCH_3)_2$

To a solution of **52** (16.9 mg, 0.033 mmol) in 0.66 mL THF, 60 wt. % $NaAlH_2(OCH_2CH_2OCH_3)_2$ in toluene (0.21 mL, 0.65 mmol, 20 equiv) was added dropwise at -50 °C. After 0.5 hours, the reaction was warmed to 0 °C for 1 hour, then warmed to 21 °C for one hour. TLC monitoring at this time shows full conversion of starting material to both hemiaminal intermediate and product. The reaction was quenched with 0.5 mL saturated aqueous Rochelle salt solution, then extracted the crude residue with 3 mL EtOAc and washed with 1 mL brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo.

The crude residue was submitted to a solution of 0.025 M p-toluenesulfonic acid in $CHCl_3$ (2.5 mL, 0.063 mmol) and stirred at 21 °C. TLC monitoring showed conversion of hemiaminal intermediate to desired product after 5 hours. Quenched with 0.5 mL saturated $NaHCO_{3(aq)}$ solution, and extracted with 2 mL EtOAc and washed with 1 mL brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was isolated by column chromatography (50% EtOAc in hexanes to EtOAc) to provide **53** (10.0 mg, 0.021 mmol, 64 % yield) as an off-white solid. ^1H NMR (600 MHz, $CDCl_3$) δ 5.59 (dt, J = 14.2, 6.7 Hz, 1H), 5.56 – 5.45 (m, 2H), 5.28 (ddd, J = 15.0, 8.9, 6.6 Hz, 1H), 4.26 (d, J = 6.2 Hz, 1H), 3.51 (ddt, J = 11.8, 9.4, 2.9 Hz, 1H), 3.33 (t, J = 11.2 Hz, 1H), 3.26 – 3.12 (m,

2H), 3.10 – 2.98 (m, 3H), 2.93 (td, *J* = 13.1, 8.7 Hz, 1H), 2.87 – 2.77 (m, 1H), 2.50 – 2.32 (m, 2H), 2.27 (ddd, *J* = 14.4, 11.2, 4.5 Hz, 1H), 2.22 – 2.12 (m, 2H), 2.09 (dq, *J* = 16.3, 7.2 Hz, 2H), 2.04 – 1.97 (m, 2H), 1.97 – 1.85 (m, 3H), 1.85 – 1.72 (m, 6H), 1.72 – 1.42 (m, 11H), 1.37 (dddd, *J* = 13.8, 9.2, 6.2, 2.7 Hz, 1H), 1.32 – 1.20 (m, 2H), 1.07 (ddt, *J* = 13.4, 3.8, 1.8 Hz, 1H). ^{3}C NMR (126 MHz, $CDCl_3$) δ 135.0, 134.8, 123.2, 123.1, 122.6, 94.4, 94.3, 93.2, 93.1, 93.0, 87.9, 87.6, 77.3, 77.1, 77.0, 76.8, 76.3, 54.2, 53.5, 52.1, 44.3, 40.8, 40.6, 40.0, 39.8, 35.5, 34.9, 32.6, 32.4, 32.1, 31.9, 31.5, 30.7, 30.5, 25.7, 24.9, 20.9, 20.2.

Procedure 48: hydrogenation to give (+)-9,9'-difluoroxestospongin C

To a solution of **50** (16.5 mg, 0.034 mmol) in 3.5 mL HPLC-grade EtOAc, 5 wt. % rhodium on alumina (11.4 mg) was added to the solution and the reaction vessel was sealed. A balloon filled with H_2 was fixed to a syringe with needle and was introduced through the septum of the reaction vessel. An outlet needle was introduced, and the H_2 was allowed to bubble through the solution for 5 minutes, after which the outlet needle was removed and the H_2 source needle was placed above the reaction solution. Every 30 minutes, the H_2 was bubbled through the reaction mixture for 5 minutes, and the reaction was monitored by ^{1}H NMR; after 2 hours, the reaction was deemed complete. The reaction was filtered through celite (filtering agent was rinsed with HPLC-grade EtOAc) and concentrated in vacuo to give **diFXe C** (13.2 mg, 0.027 mmol, 80 % yield) as an off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.33 (d, *J* = 6.5 Hz, 1H), 3.57 (tt, *J* = 11.0, 2.1 Hz, 1H), 3.42 – 3.32 (m, 1H), 3.28 – 3.16 (m, 2H), 3.09 – 2.97 (m, 3H), 2.83 (dt, *J* = 7.7, 2.3 Hz, 1H), 2.46 (dt, *J* = 12.0, 2.8 Hz, 1H), 2.17 (dddd, *J* = 16.4, 14.1, 10.1, 7.7 Hz, 2H), 2.07 – 1.95 (m, 2H), 1.89 (dddd, *J* = 17.5, 13.4, 8.1, 3.9 Hz, 1H), 1.84 – 1.65 (m, 8H), 1.65 – 1.41 (m, 13H), 1.41 – 1.09 (m, 23H), 1.06

(dq, J = 13.5, 1.9 Hz, 2H), 0.99 – 0.75 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 94.9, 94.5, 93.4, 93.4, 93.2, 93.2, 87.7, 87.4, 76.1, 60.5, 54.5, 53.7, 53.6, 52.3, 44.5, 38.2, 38.0, 36.7, 36.5, 36.3, 35.5, 32.6, 32.5, 32.1, 32.0, 31.6, 31.1, 31.1, 31.0, 29.8, 29.8, 29.6, 29.5, 29.4, 26.2, 25.4, 25.3, 25.2, 24.9, 22.8, 22.6, 22.5, 21.2, 21.1, 20.3, 20.3, 14.3, 14.3, 1.2.

NMR Spectra

NMR Spectra 1: 14

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3	Solvent	cdcl3
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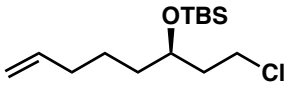
5	Number of Scans	24
6	Relaxation Delay	8.0000
7	Pulse Width	5.3250
8	Acquisition Time	2.5000
9	Acquisition Date	2023-02-04T14:31:32
10	Spectrometer Frequency	599.64



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2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
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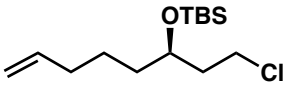
10	Spectrometer Frequency	125.70



NMR Spectra 2: 16

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4	Temperature	25.0
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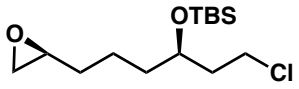
10	Spectrometer Frequency	599.64



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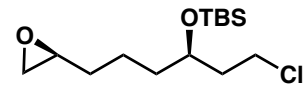
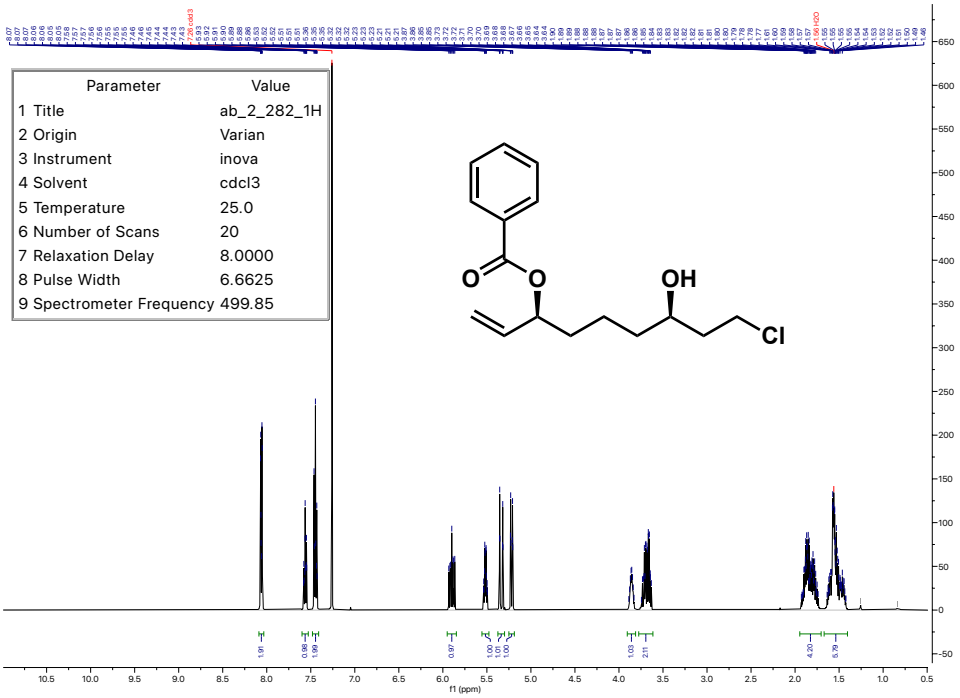
10	Spectrometer Frequency	125.70



NMR Spectra 3: derivative of 16



SHIMADZU LabSolutions

Analysis Report

<Sample Information>

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Batch Filename	:		
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Injection Volume	: 1 uL		
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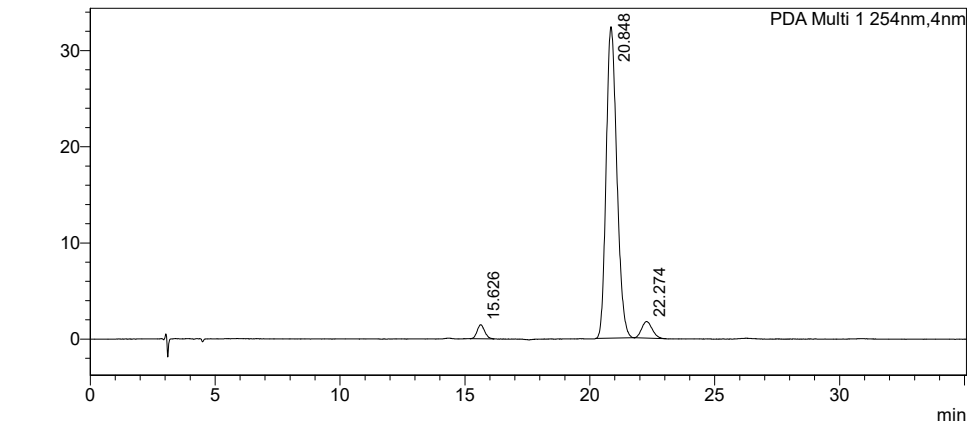

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PDA Ch1 254nm

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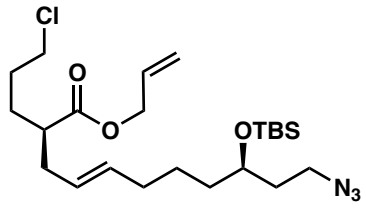

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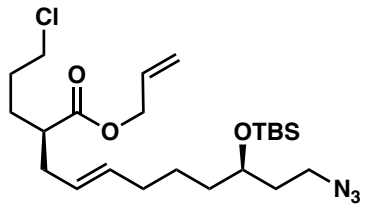
10	Spectrometer Frequency	125.70



NMR Spectra 5: 25

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3	Solvent	cdcl3
4	Temperature	25.0
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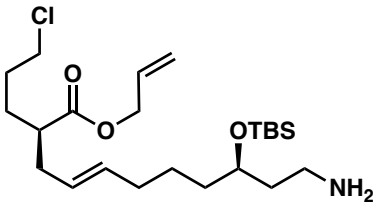
10	Spectrometer Frequency	599.64



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3	Solvent	cdcl3
4	Temperature	25.0
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7	Pulse Width	7.0000
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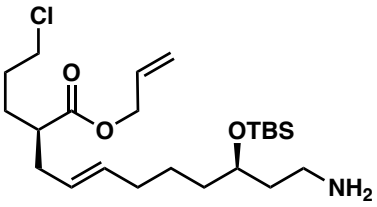
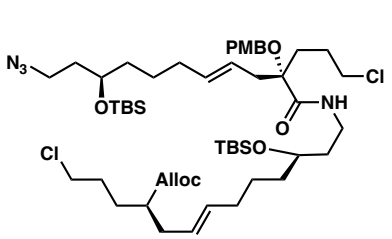
9	Acquisition Date	2023-06-19T18:57:20
10	Spectrometer Frequency	125.70

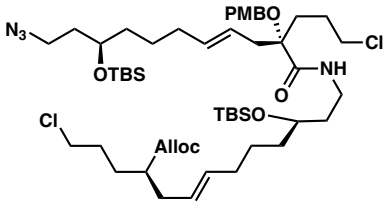


NMR 6: 26

	Parameter	Value
1	Title	akb_3_014_1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	20
6	Relaxation Delay	8.0000
7	Pulse Width	5.4125
8	Acquisition Time	2.5000
9	Acquisition Date	2023-06-19T18:33:02
10	Spectrometer Frequency	599.64

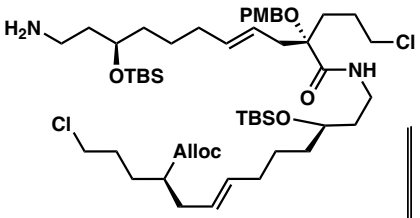


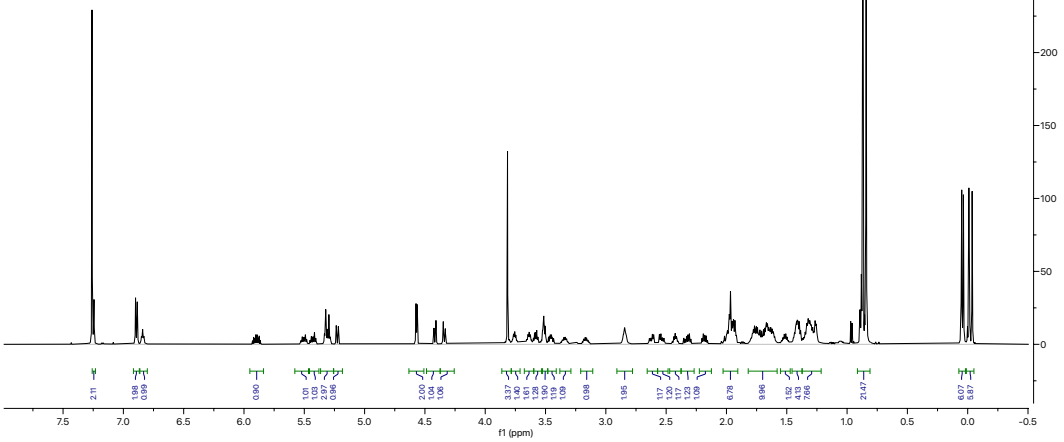
	Parameter	Value
1	Title	akb_3_017_13c
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	120
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2023-06-27T17:42:39
10	Spectrometer Frequency	125.70



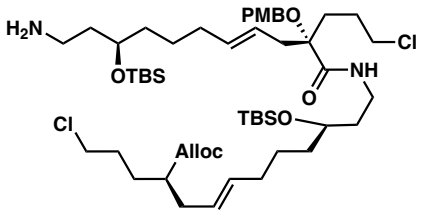
NMR 7: 27

	Parameter	Value
1	Title	akb_3_018_1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	16
6	Relaxation Delay	8.0000
7	Pulse Width	5.4125
8	Acquisition Time	2.5000
9	Acquisition Date	2023-06-20T19:05:31
10	Spectrometer Frequency	599.64



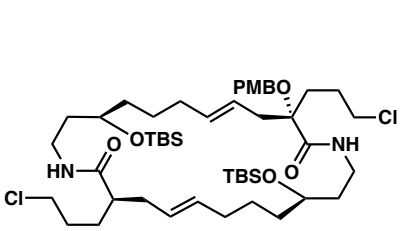


	Parameter	Value
1	Title	akb_3_020_13c
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	124
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2023-06-27T17:34:54
10	Spectrometer Frequency	125.70

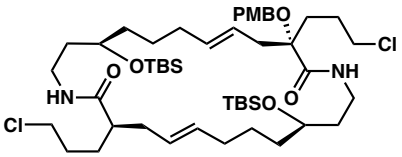


NMR 8: 28

	Parameter	Value
1	Title	akb_3_026_1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	28
6	Relaxation Delay	8.0000
7	Pulse Width	5.4125
8	Acquisition Time	2.5000
9	Acquisition Date	2023-11-13T10:19:40
10	Spectrometer Frequency	599.64

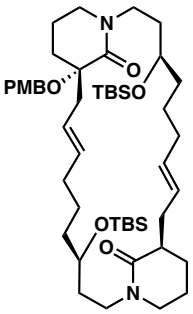


	Parameter	Value
1	Title	akb_3_026_13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	672
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2023-11-13T10:30:16
10	Spectrometer Frequency	125.70

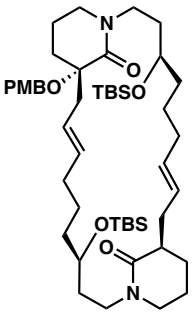


NMR 9: 29

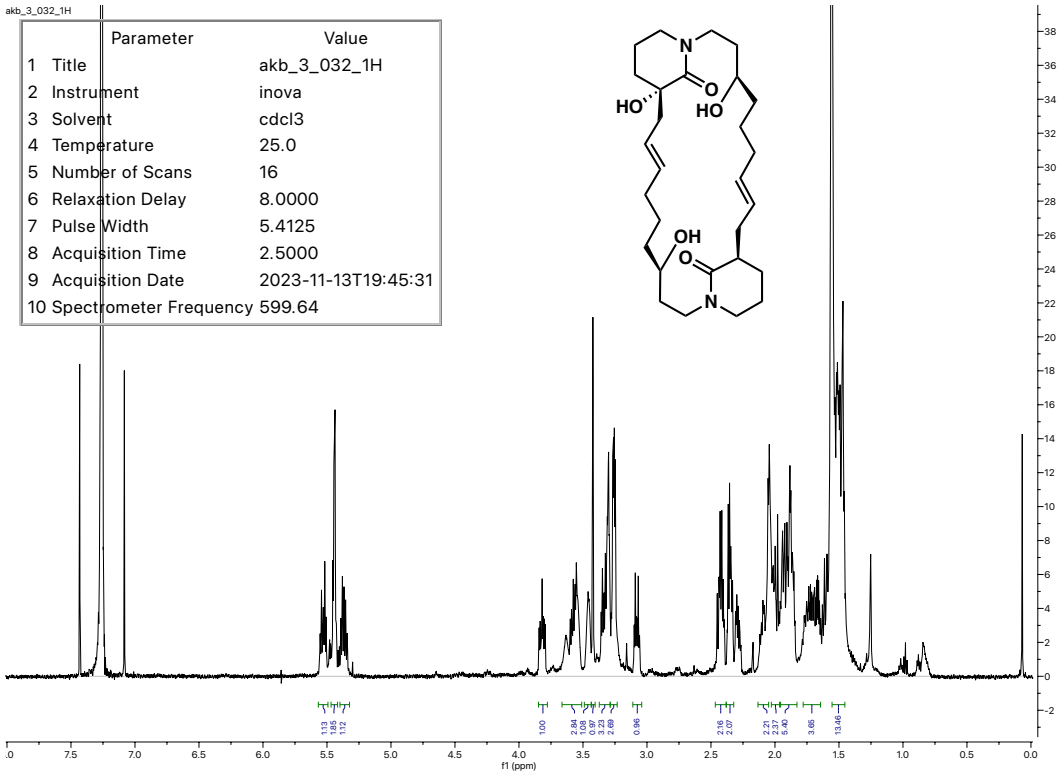
	Parameter	Value
1	Title	akb_3_029_1H_2
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	28
6	Relaxation Delay	8.0000
7	Pulse Width	5.4125
8	Acquisition Time	2.5000
9	Acquisition Date	2023-11-21T11:43:11
10	Spectrometer Frequency	599.64



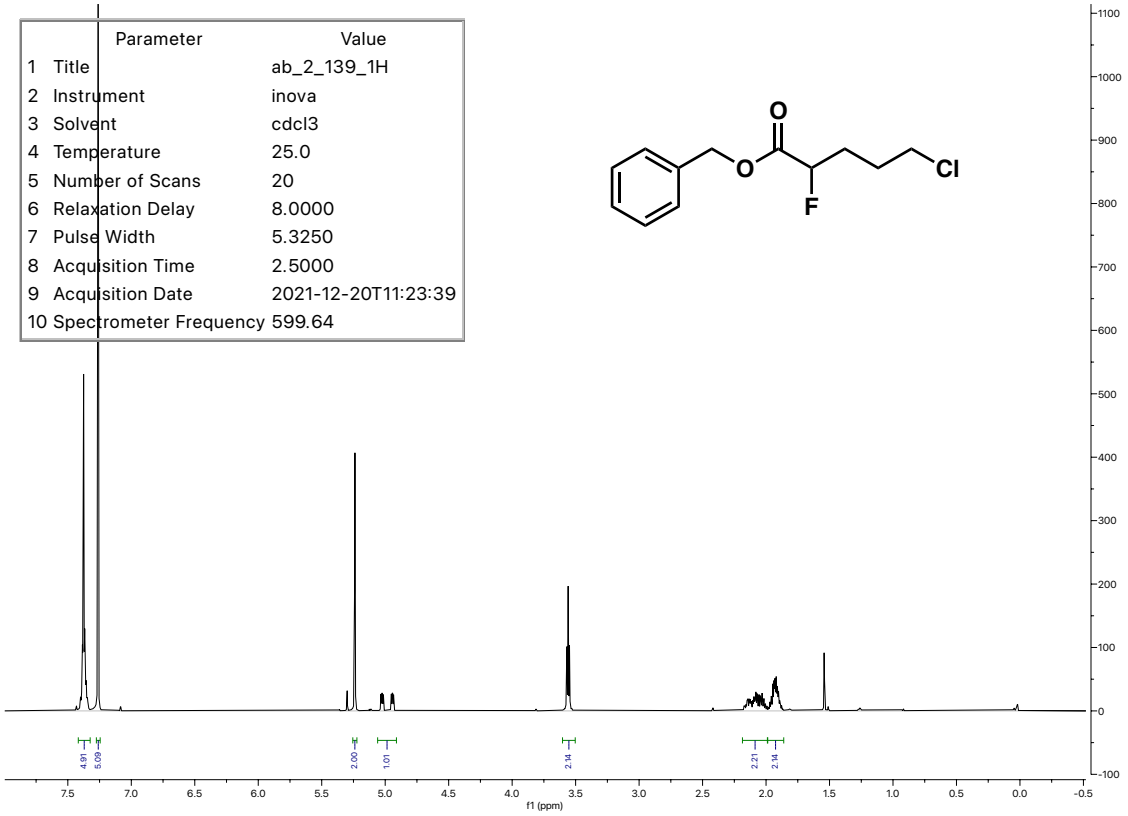
	Parameter	Value
1	Title	akb_3_029_13C_2.10.fid
2	Instrument	NEO500
3	Solvent	CDCl3
4	Temperature	298.2
5	Number of Scans	512
6	Relaxation Delay	2.0000
7	Pulse Width	10.0000
8	Acquisition Time	1.0879
9	Acquisition Date	2023-11-21T12:45:19
10	Spectrometer Frequency	125.78



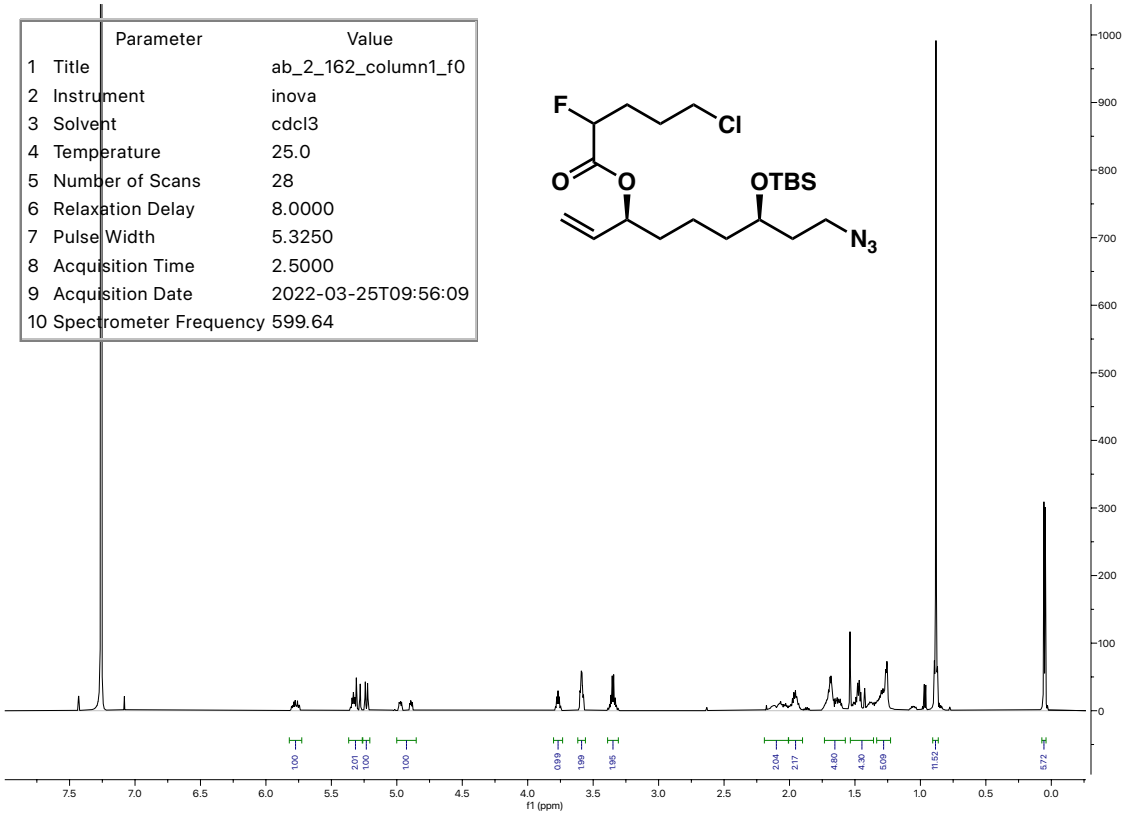
NMR 10: 29


akb_3_032_1H
Parameter Value
1 Title akb_3_032_1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 5.4125
8 Acquisition Time 2.5000
9 Acquisition Date 2023-11-13T19:45:31
10 Spectrometer Frequency 599.64
HO
HO
OH
O
N
f1 (ppm)

NMR 11: 35

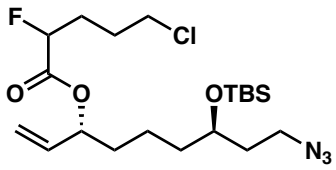

Parameter Value
1 Title ab_2_139_1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 20
6 Relaxation Delay 8.0000
7 Pulse Width 5.3250
8 Acquisition Time 2.5000
9 Acquisition Date 2021-12-20T11:23:39
10 Spectrometer Frequency 599.64
O
O
F
Cl
f1 (ppm)

NMR 12: 40

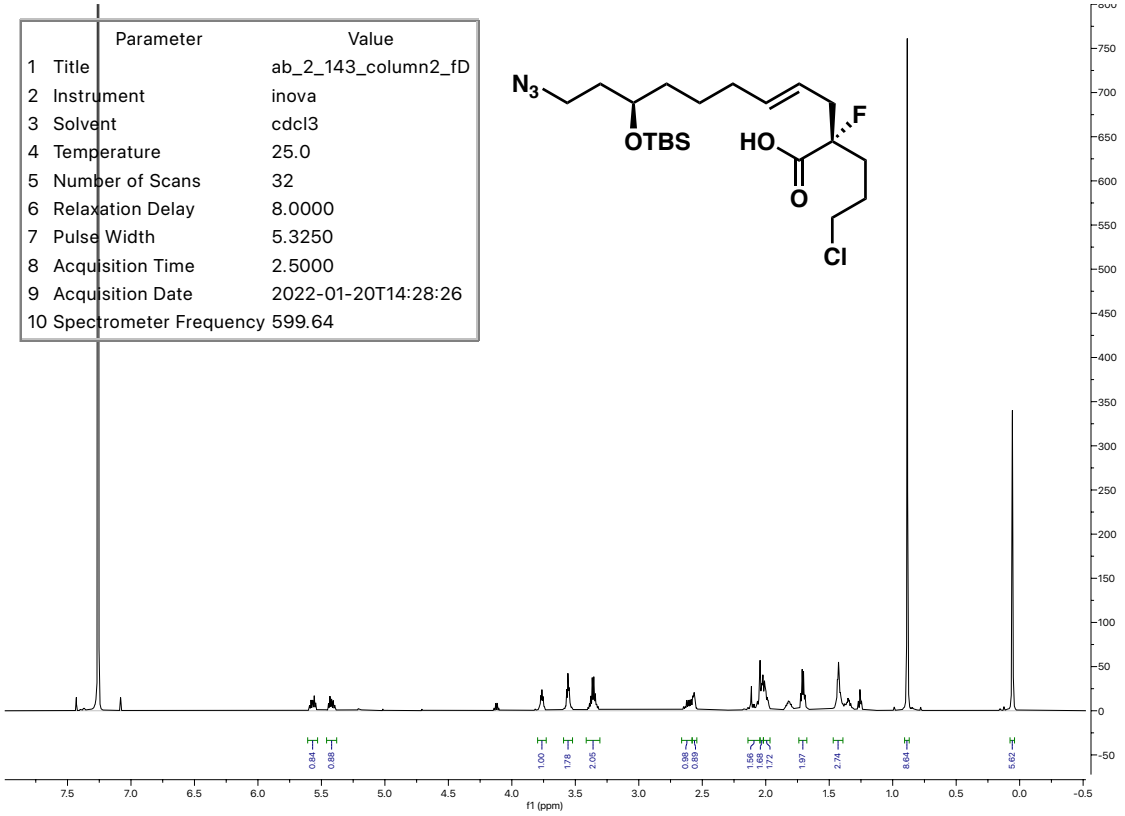

Parameter Value
1 Title ab_2_162_column1_f0
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 28
6 Relaxation Delay 8.0000
7 Pulse Width 5.3250
8 Acquisition Time 2.5000
9 Acquisition Date 2022-03-25T09:56:09
10 Spectrometer Frequency 599.64
F
Cl
O
O
OTBS
N3
f1 (ppm)

NMR 13: 41

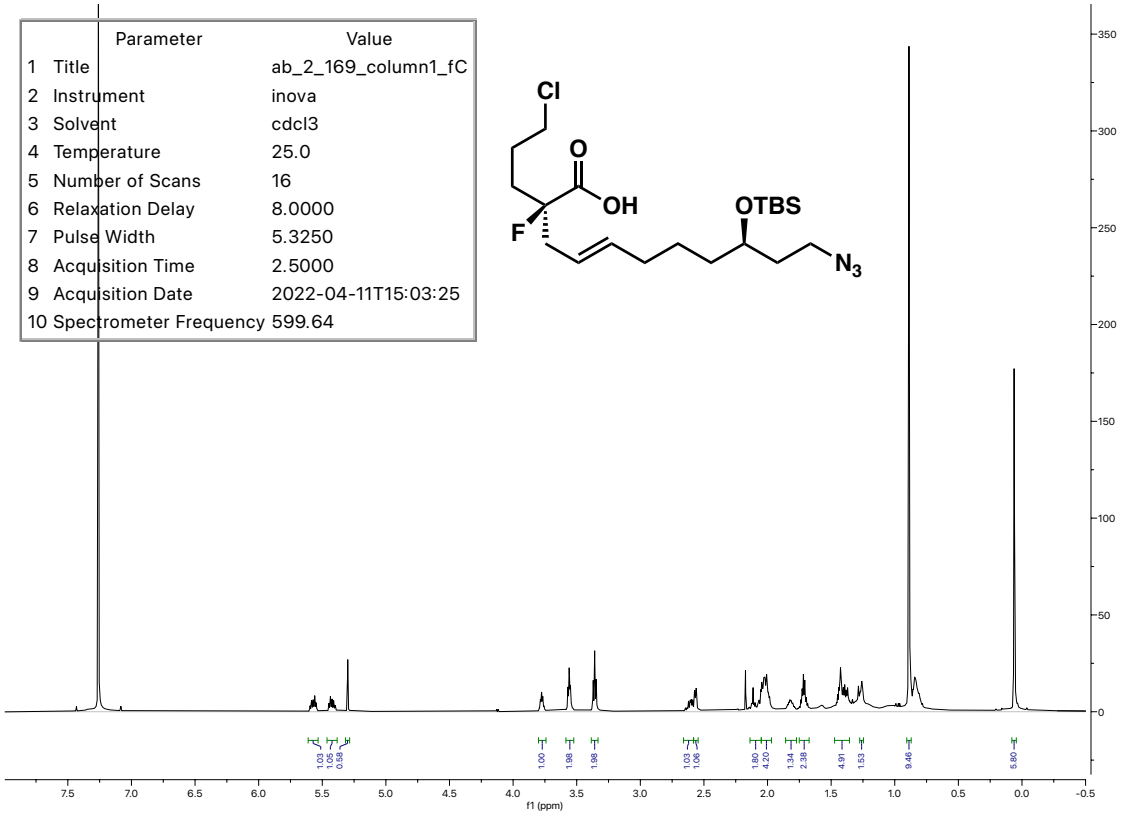
	Parameter	Value
1	Title	ab_2_113_fA
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	16
6	Relaxation Delay	8.0000
7	Pulse Width	6.6625
8	Acquisition Time	2.5001
9	Acquisition Date	2021-09-01T12:58:48
10	Spectrometer Frequency	499.85



NMR 14: 43

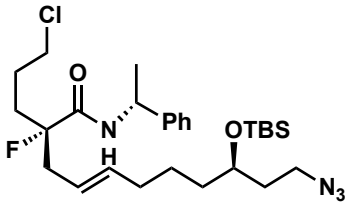

Parameter Value
1 Title ab_2_143_column2_fD
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 32
6 Relaxation Delay 8.0000
7 Pulse Width 5.3250
8 Acquisition Time 2.5000
9 Acquisition Date 2022-01-20T14:28:26
10 Spectrometer Frequency 599.64
N3
OTBS
HO
F
O
Cl
f1 (ppm)

NMR 15: 42


Parameter Value
1 Title ab_2_169_column1_fC
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 5.3250
8 Acquisition Time 2.5000
9 Acquisition Date 2022-04-11T15:03:25
10 Spectrometer Frequency 599.64
Cl
O
OH
F
OTBS
N3
f1 (ppm)

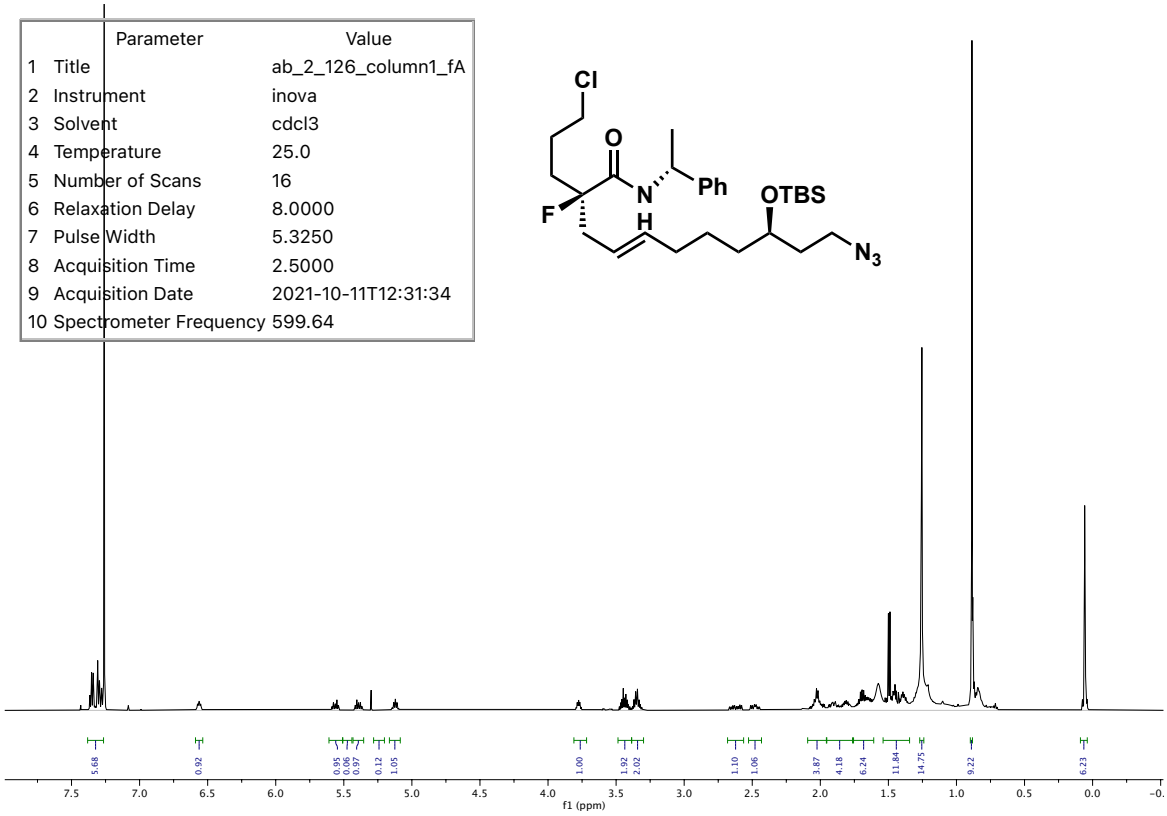
NMR 16: derivative of **43**

	Parameter	Value
1	Title	ab_2_124_column1_fA
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	20
6	Relaxation Delay	8.0000
7	Pulse Width	5.3250
8	Acquisition Time	2.5000
9	Acquisition Date	2021-10-09T16:32:25
10	Spectrometer Frequency	599.64



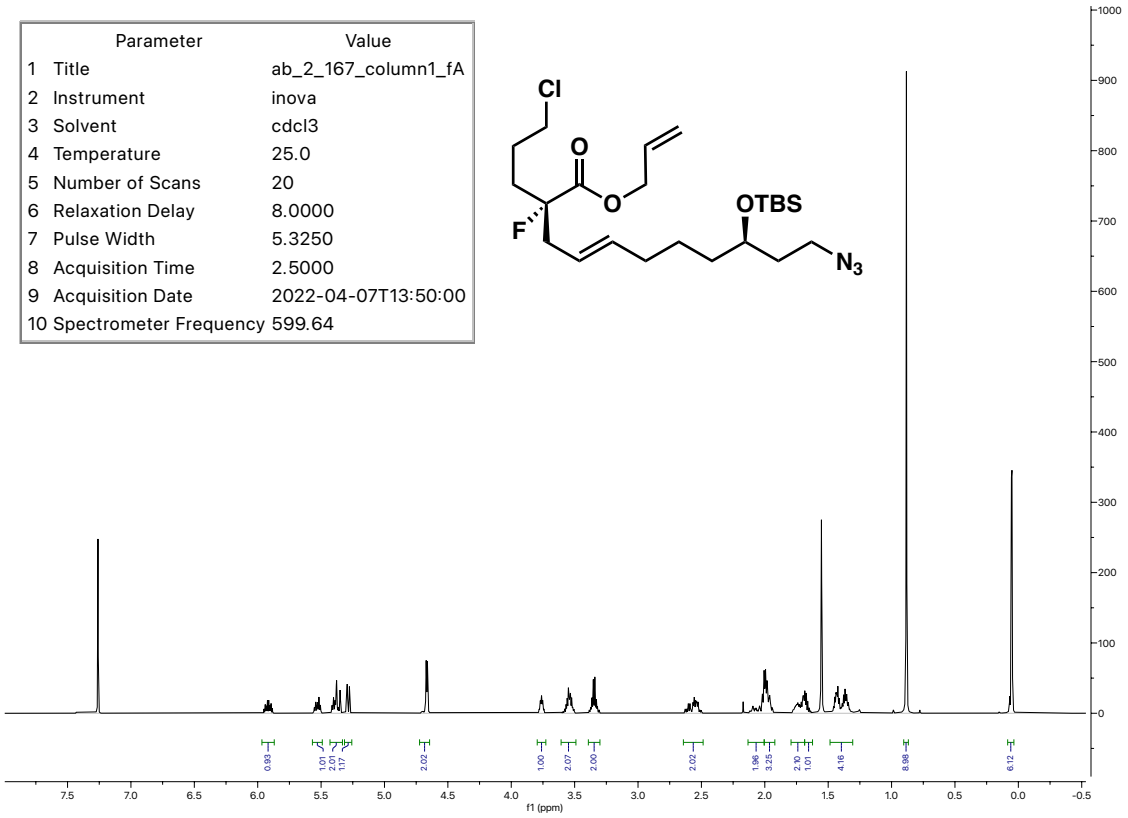
NMR 17: Derivative of **42**

	Parameter	Value
1	Title	ab_2_126_column1_fA
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	16
6	Relaxation Delay	8.0000
7	Pulse Width	5.3250
8	Acquisition Time	2.5000
9	Acquisition Date	2021-10-11T12:31:34
10	Spectrometer Frequency	599.64

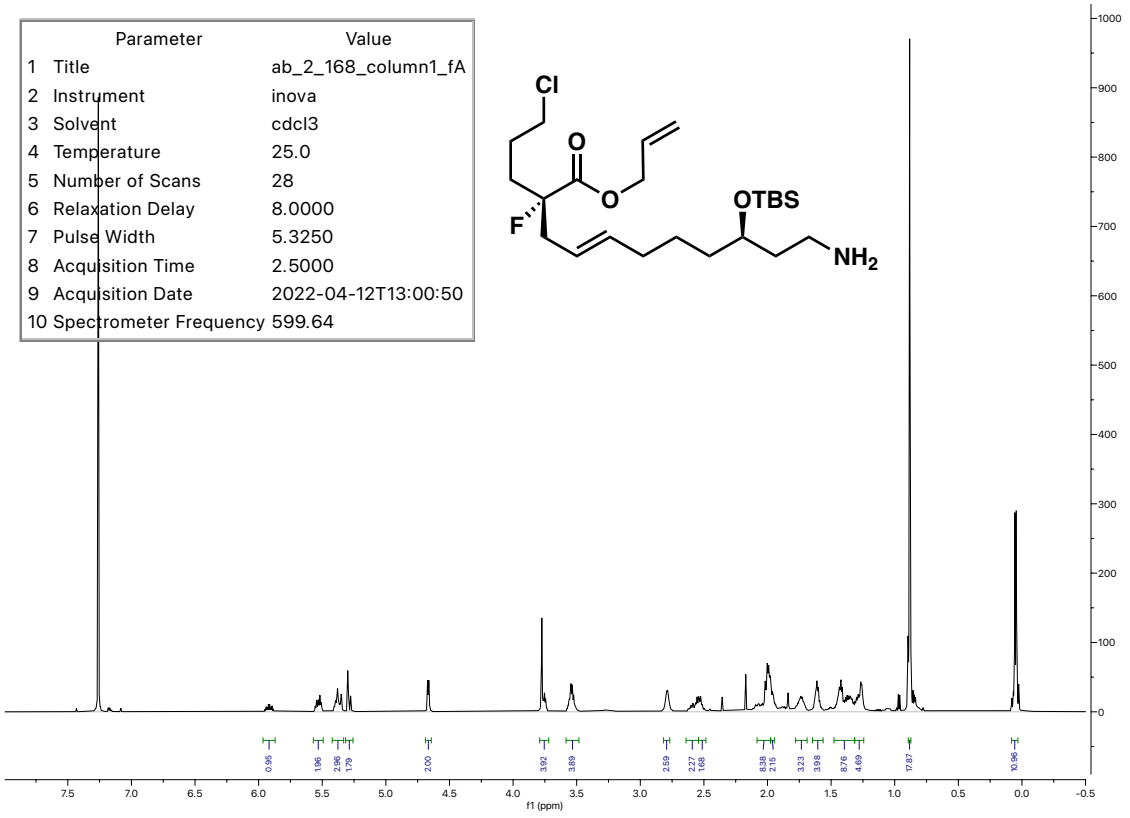


NMR 18: allylation of **42**

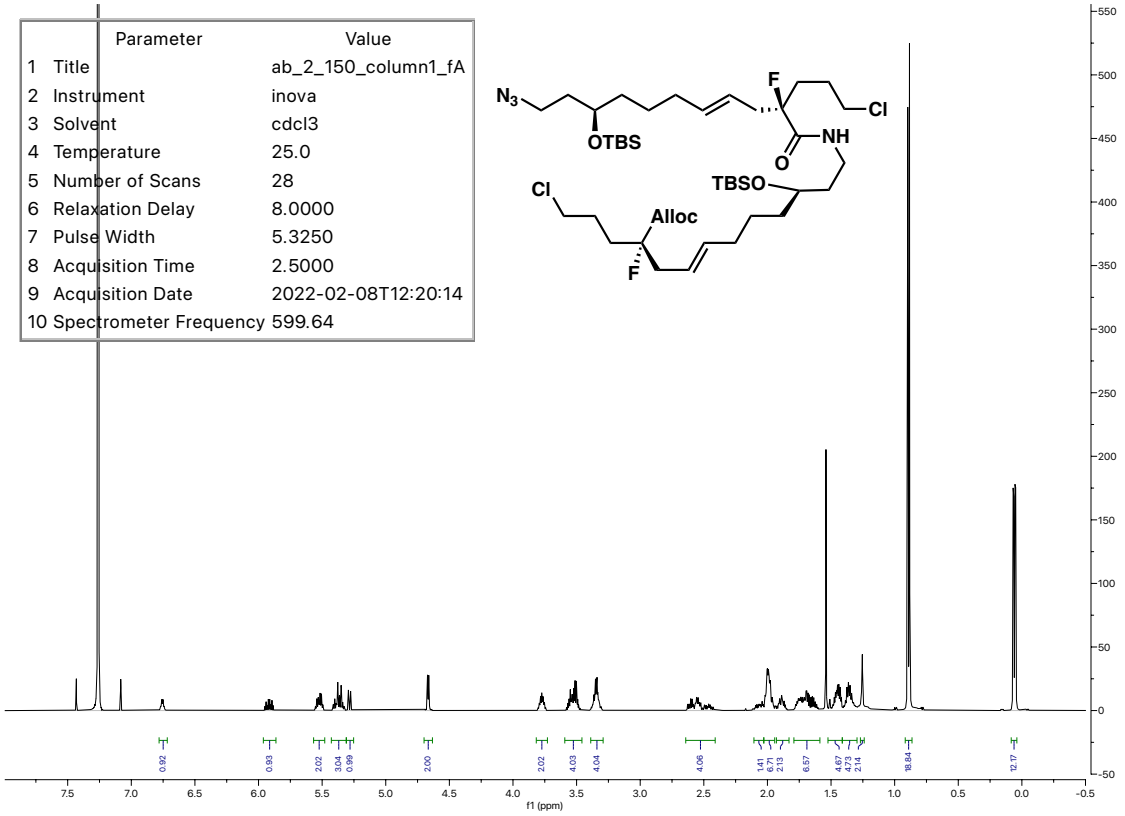
	Parameter	Value
1	Title	ab_2_167_column1_fA
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	20
6	Relaxation Delay	8.0000
7	Pulse Width	5.3250
8	Acquisition Time	2.5000
9	Acquisition Date	2022-04-07T13:50:00
10	Spectrometer Frequency	599.64



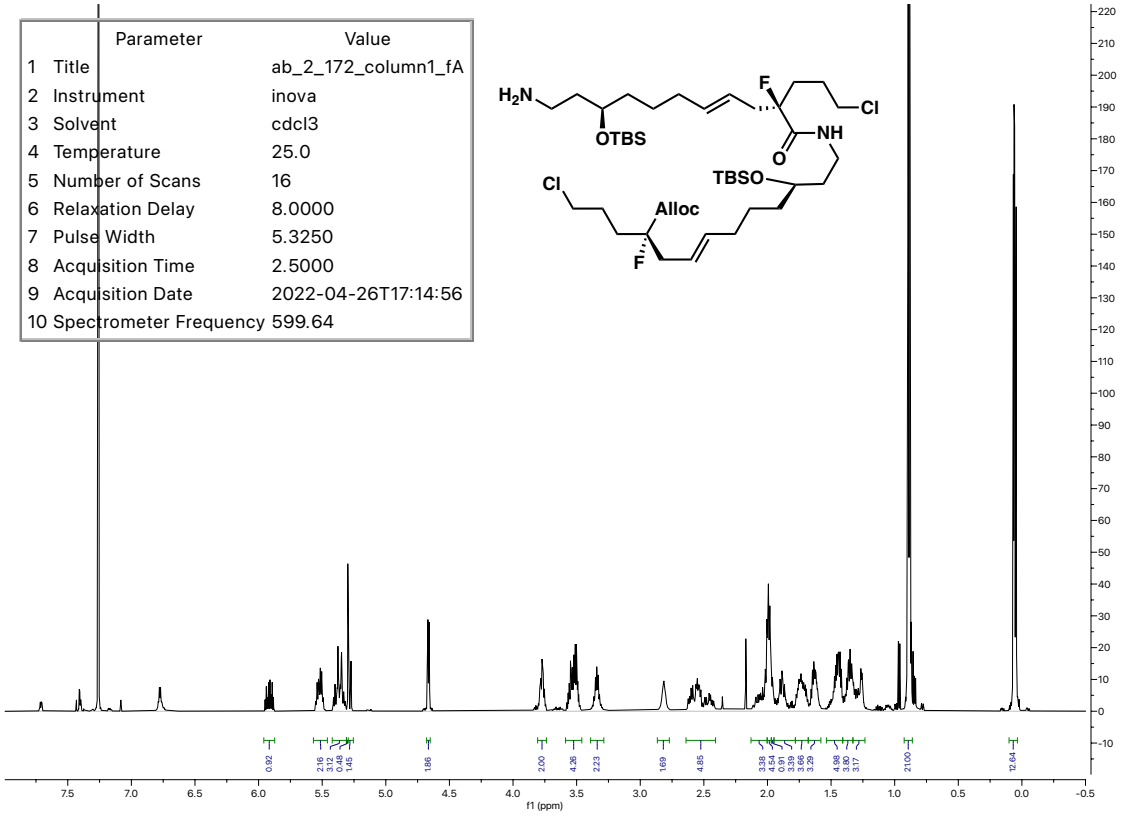
NMR 19: amine **44**



NMR 20: convergence, **45**

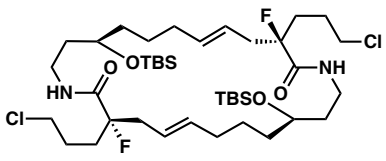


NMR 21: amine **46**



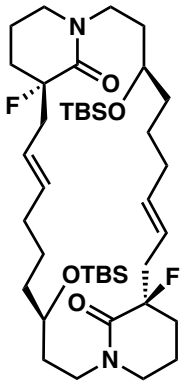
NMR 22: Macrolactam **47**

	Parameter	Value
1	Title	ab_2_176_column1_fB
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	20
6	Relaxation Delay	8.0000
7	Pulse Width	5.3250
8	Acquisition Time	2.5000
9	Acquisition Date	2022-05-09T15:04:44
10	Spectrometer Frequency	599.64



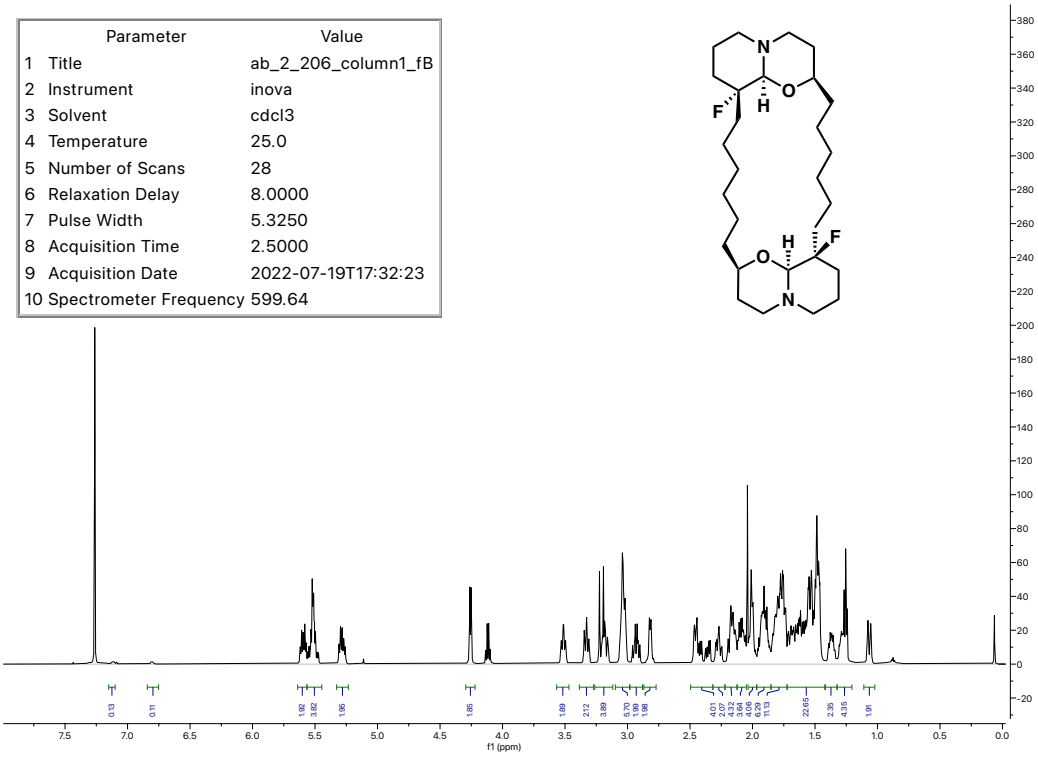
NMR 23: 48

	Parameter	Value
1	Title	ab_2_180_column1_fA
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	20
6	Relaxation Delay	8.0000
7	Pulse Width	5.3250
8	Acquisition Time	2.5000
9	Acquisition Date	2022-05-20T15:12:31
10	Spectrometer Frequency	599.64

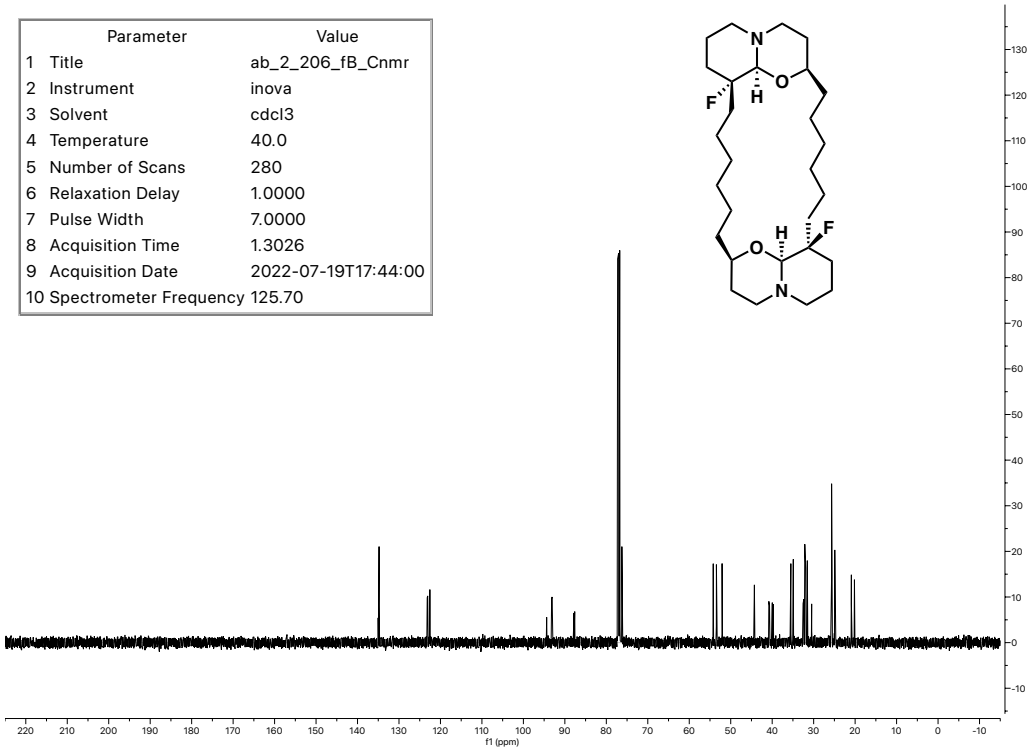


NMR 24: bis-1-oxaquinalizidine **50**

	Parameter	Value
1	Title	ab_2_206_column1_fB
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	28
6	Relaxation Delay	8.0000
7	Pulse Width	5.3250
8	Acquisition Time	2.5000
9	Acquisition Date	2022-07-19T17:32:23
10	Spectrometer Frequency	599.64

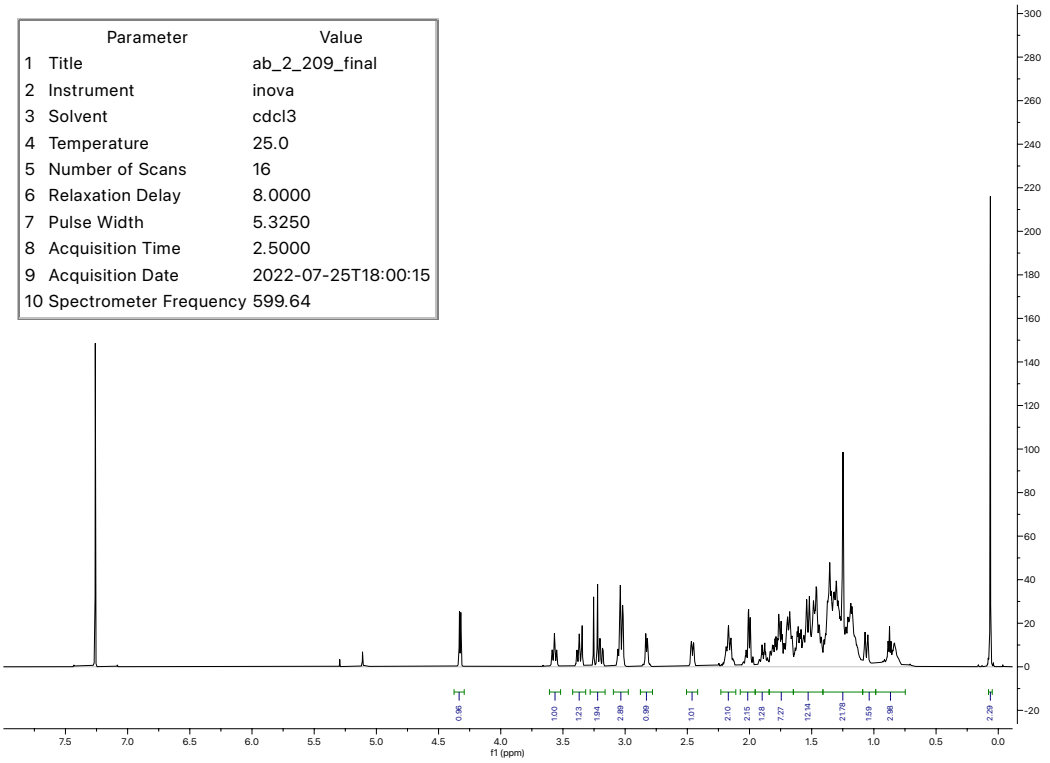


	Parameter	Value
1	Title	ab_2_206_fB_Cnmr
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	40.0
5	Number of Scans	280
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2022-07-19T17:44:00
10	Spectrometer Frequency	125.70

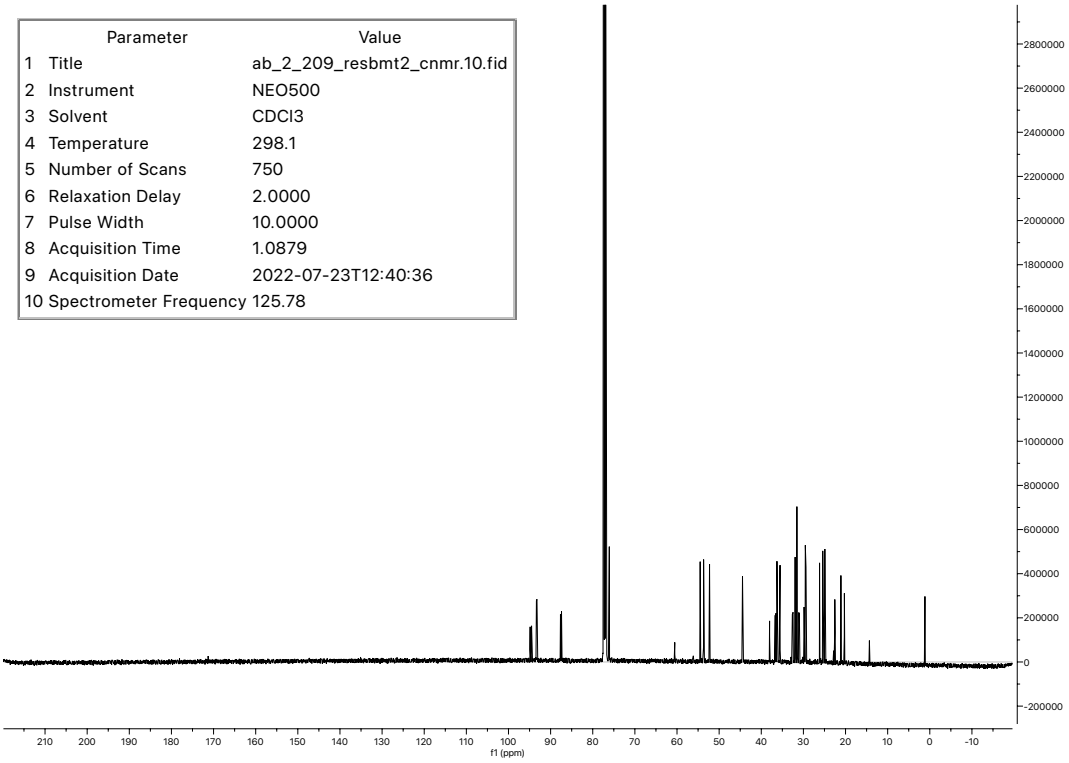


NMR 25: (+)-9,9’-difluoroxestospongin C

	Parameter	Value
1	Title	ab_2_209_final
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	16
6	Relaxation Delay	8.0000
7	Pulse Width	5.3250
8	Acquisition Time	2.5000
9	Acquisition Date	2022-07-25T18:00:15
10	Spectrometer Frequency	599.64



	Parameter	Value
1	Title	ab_2_209_resbmt2_cnmr.10.fid
2	Instrument	NEO500
3	Solvent	CDCl3
4	Temperature	298.1
5	Number of Scans	750
6	Relaxation Delay	2.0000
7	Pulse Width	10.0000
8	Acquisition Time	1.0879
9	Acquisition Date	2022-07-23T12:40:36
10	Spectrometer Frequency	125.78



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