# NEW REACTIONS AND STRATEGIES IN

# DIVERGENT SYNTHESES OF MACROLIDE ANTIBIOTICS

by

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And approved by

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ABSTRACT OF THE DISSERTATION

New Reactions and Strategies in Divergent Syntheses of Macrolide Antibiotics

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Professor Lawrence J. Williams

From the microbial world, antibiotics are structurally complex and highly potent chemical weapons that co-evolved with bacteria. Macrolide (glycosylated cyclic polyketides) antibiotics have been used extensively as first-line antibacterial agents since the discovery of the broad-spectrum antibiotic erythromycin A in 1952. However wide-spread use of antibiotics has led pathogens to develop drug resistance. Therefore new and enhanced antibiotics are constantly in need.

Described in this dissertation is my effort to emulate the synthetic capabilities of erythromycin-producing bacteria by accessing novel erythromycin-inspired polyketides via divergent total synthesis. New allene oxidation methods have been developed and implemented in a modular and divergent route to produce a diversified portfolio of cyclic polyketides and their glycoconjugates. I will disclose a total synthesis of 4,10-didesmethyl-(9*S*)-dihydroerythronolide A (Chapter 2), preparation of glycosylated erythromycin analogs (Chapter 3) and progress towards synthesis of 9(*S*)-dihydroerythronolide A (Chapter 4).

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## Dedication

This dissertation is dedicated to my family

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## List of Abbreviations

| | |
|---|---|
| ºC | degrees Celsius |
| Ac | acetate |
| ADMB | 4-allyl-1,2-dimethoxybenzene |
| Bu | butyl |
| Bn | benzyl |
| BP | biphenyl |
| cat. | catalytic |
| CoA | coenzyme A |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DCE | dichloroethane |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEBS | 6-deoxyerythronolide B synthase |
| DMAP | 4-(*N,N*-dimethylamino) pyridine |
| dr | diastereomeric ratio |
| DTBMP | 2,6-di-tert-butyl-4-methylpyrdidine |
| E | eletrophile |
| Et | ethyl |
| $Et_2O$ | diethyl ether |
| FCC | flash column chromatography |
| h | hour(s) |
| LLS | longest linear sequence |

| | |
|---|---|
| *m*- | *meta*- |
| M | molar (moles/liter) |
| *m*CPBA | *m*-chloroperbenzoic acid |
| Me | methyl |
| MeOH | methanol |
| mL | milliliters |
| min | minutes |
| mol | moles |
| mmol | micromole |
| Ms | methanesulfonyl |
| MS | molecular sieves |
| NBS | *N*-bromosuccinimide |
| NIS | *N*-iodosuccinimide |
| NMO | *N*-methylmorpholine-*N*-oxide |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser effect |
| Nu | nucleophile |
| *p*- | *para*- |
| Ph | phenyl |
| Pr | propyl |
| *R* | rectus (Cahn-Inglod-Prelog system) |
| rt | room temperature |
| *S* | sinister (Cahn-Inglod-Prelog system) |

| | |
|---|---|
| S | Svedberg unit (for sedimentation rate) |
| TBAF | tetrabutylammonium fluoride |
| TBS | *tert*-butyldimethylsilyl |
| *t*- | *tert*- |
| TE | thioesterase |
| TES | triethylsilyl |
| TMS | trimethylsilyl |
| Tf | triflate |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TLC | thin-layer chromatography |
| TMS | trimethylsilyl |
| Ts | *p*-toluenesulfonyl |

# Chapter 1 Antibiotics of the Erythromycin Class

## 1.1. Discovery and applications of erythromycin A

Life is challenging in the microbial world. Stimulated by the constant competition for limited resources, many bacteria have evolved capabilities of synthesizing structurally complex and highly potent chemical weapons – the antibiotics (Figure 1.1). Macrolide (glycosylated cyclic polyketides) antibiotics have been used extensively as first-line antibacterial agents since the discovery of broad-spectrum antibiotic erythromycin A **1.1** in 1952.[1-3] Erythromycin A was initially isolated as a secondary metabolite from soil-dwelling bacteria *Streptomyces erythraea*. Despite the availability of other major classes of antibiotics[2] (Figure 1.1, β-lactams, quinolones and tetracyclines), the erythromycin class remains the modality of choice for the treatment of many infections, especially those of the respiratory tract.

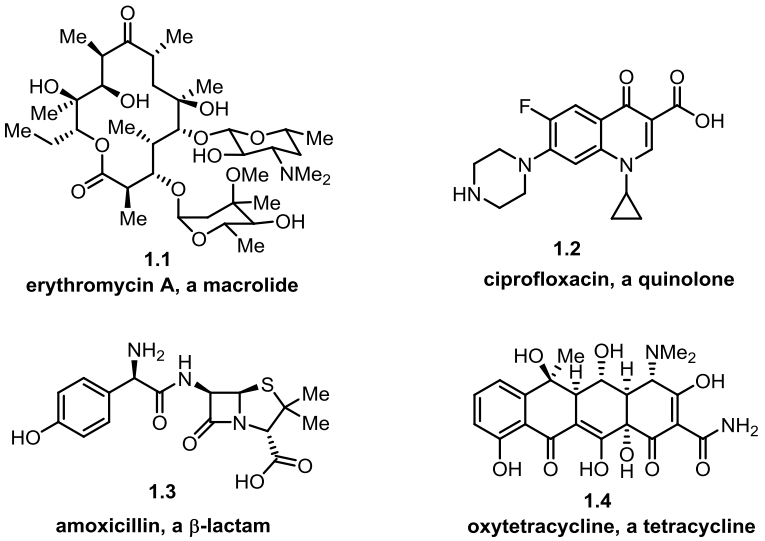
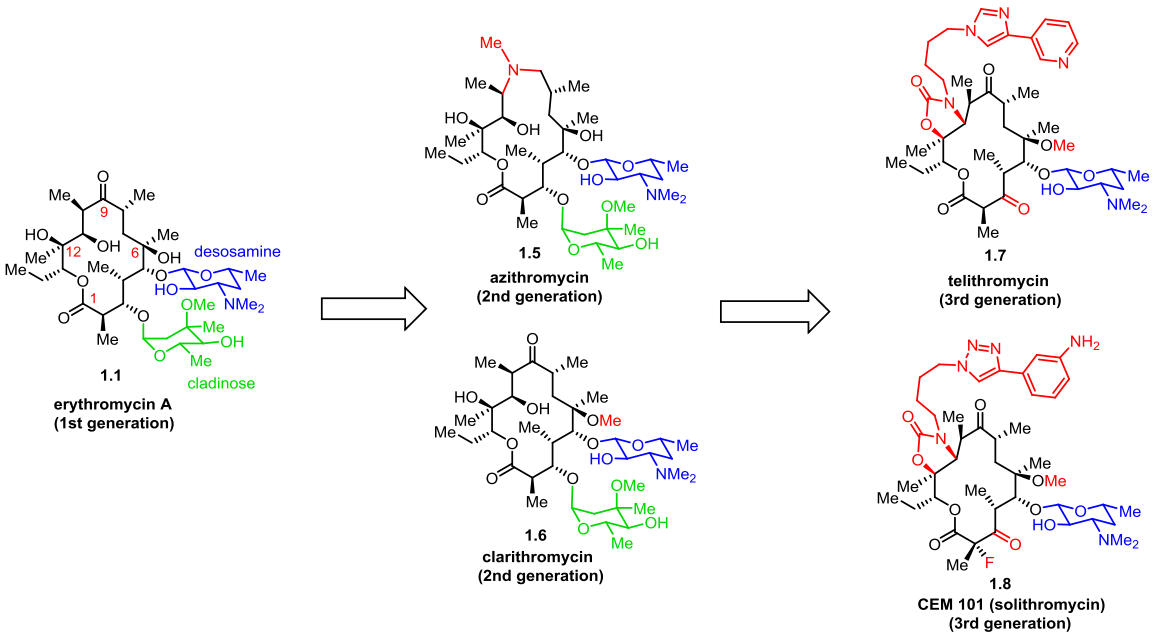



**Figure 1.1** Erythromycin A and other major classes of antibiotics.

The selection pressure associated with wide-spread use of antibiotics has prompted pathogens to rapidly develop resistance to existing antibiotics. Therefore new and enhanced erythromycin derivatives are constantly needed.[4,5] On top of this seemingly inescapable resistance problem, erythromycin A suffers instability in the stomach due to acid-catalyzed hemiketal formation between the C-6 alcohol and C-9 ketone. Aiming to address these limitations, medicinal chemists developed two generations of improved erythromycin-derived antibiotics (Scheme 1.1).[6]




**Scheme 1.1.** Development of antibiotics derived from erythromycin A.

The second-generation erythromycinoids (e.g. azithromycin **1.5** and clarithromycin **1.6**) were prepared in the 1980s semi-synthetically from erythromycin A. While the deoxy-sugars desosamine and cladinose were both retained, the acid-labile groups were masked by methylating the C-6 alchohol in clarithromycin **1.6** or replacing the C-9 ketone with a tertiary amine in azithromycin **1.5**. Hence, the second-generation compounds are more

stable in the acidic environment of stomach and therefore enjoy a longer half-life and lower dosages. Despite improvements in pharmacokinetic properties, however this generation failed to address emerging resistance to antibiotics.[4,5]

The third-generation derivatives (telithromycin **1.7** and CEM-101 **1.8**) were developed to tackle resistant pathogens. Several distinct modifications were introduced: (1) The deoxysugar cladinose was deleted and the C-3 alcohol oxidized to a ketone, (2) A biaryl side chain, which presumably binds to a secondary pocket in the target, was installed via an oxazolidinone at C-11 and C-12, and (3) The C-6 alcohol was methylated to avoid hemiketal formation with the C-3 ketone. Despite effectiveness against many pathogens that eluded previous erythromycin derivatives, the third-generation is not perfect, adverse effects (notably hepatotoxicity) have been reported for telithromycin, and susceptible pathogens eventually develop resistance.

### 1.2. Structural basis for antibacterial activity and for antibiotic resistance

Decades of studies have suggested that the macrolide antibiotics inhibit protein synthesis in bacteria by binding to the ribosome - the protein factory in all branches of life. Atomic-resolution crystal structures of bacterial ribosomes complexed with macrolide antibiotics have been elucidated in the past decade[7-11] (Figure 1.2). These detailed structures not only provide unprecedented opportunities of structure-based approaches to design superior antibiotics, but also shed light on the origin of antibiotic resistance. In recognition of these watershed structural studies, the 2009 Nobel Prize in Chemistry was awarded to Venkatraman Ramakrishnan, Thomas Steitz and Ada Yonath "*for studies of the structure and function of the ribosome*".

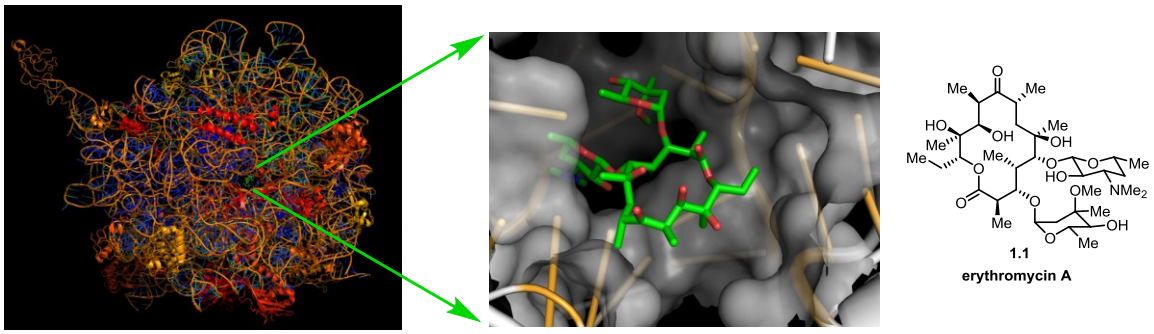



**Figure 1.2** Left: erythromycin A (green, center) bound in the nascent peptide exit channel of *E. coli* 50S ribosomal subunit. Right: detailed structure of erythromycin A bound in the tunnel. Figure rendered with PyMol (PDB ID: 3OFQ).[8]

Based on crystal structures and biochemical experiments, erythromycin A and several other macrolides are believed to bind in the nascent peptide exit tunnel in the 50S ribosomal subunit, blocking the extension of peptide chains and triggering premature termination of protein synthesis (Figure 1.2). Structural data suggest the desosamine sugar is pivotal in binding to the ribosome tunnel, forming multiple hydrogen bonds and

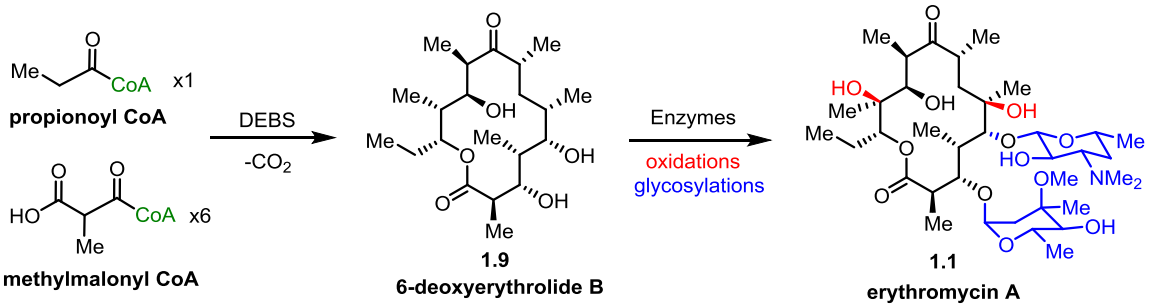
electrostatic interactions, while the macrolactone of erythromycin contacts the tunnel wall mainly via van der Waals interactions. The cladinose moiety does not seem to directly contact the ribosome, which is in accord with the finding that removal of cladinose does not abrogate antibiotic activity (e.g. Scheme1.1, telithromycin **1.7** and CEM 101 **1.8**).

The most common mechanism of antibiotic resistance is through the modification of the target – the ribosome. The A2058G mutation (adenine at position 2058 of 23S ribosomal RNA is mutated to guanine) is the most prevalent mutation that confers resistance to erythromycin. Guided by crystal structures, Steitz *et al.* suggest the A2058G mutation induces a steric clash between the ribosome tunnel wall and the C-4 methyl group of erythromycin, leading to greatly reduced binding affinity and potency.[7-11] Other resistant pathogens employ Erm methyltransferase to di-methylate the amino-group of the 2058 adenine residue. The resulting bulky dimethyl-amino group is believed to compromise the binding between the ribosome and desosamine of erythromycin. Unlike the endogenously expressed A2058G mutation, this methylation mechanism is activated by recognition of antibiotics and the ribosome remains un-methylated in their absence.

Other mechanisms of resistance include 1) the expression of efflux pumps that export antibiotics (often responsible for self-resistance in erythromycin-producing bacteria); 2) enzymatic inactivation of erythromycin (hydrolysis, phosphorylation and glucosylation). Taken together, an effective new antibiotic entails structural features that enable binding to the mutated ribosome, evading the efflux pumps and ideally surviving the onslaught of neutralizing enzymes.

### 1.3. Biosynthesis of erythromycin and engineering of biosynthesis machinery

Polyketide synthase is the key player in the biosynthesis of macrolide antibiotics.[1] Studies on the biogenesis of erythromycin A constitute the majority of current understanding of macrolide biosynthesis (Scheme 1.2), and available data on other macrolides (methymycin, pikromycin, tylosin *etc.*) suggest the mechanism of erythromycin biosynthesis is indeed representative of the macrolide class. Briefly, the algycon 6-deoxyerythronolide B **1.9** is assembled by the DEBS (6-deoxyerythonolide B synthase), and subsequent oxidations and glycosylations furnish erythromycin A.




**Scheme 1.2** Biosynthesis of erythromycin A. DEBS: 6-deoxyerythronolide B synthase.

Considering the structural complexity and glut of stereocenters in 6-deoxyerythrolide B **1.9**, the starting materials for its construction are elegantly simple: one molecule of propionyl CoA and 6 molecules of methylmalonyl CoA. Summarized in Figure 1.3 is the basic organization of the DEBS (6-deoxyerythronolide B synthase) and the proposed intermediates tethered to this enzyme complex.

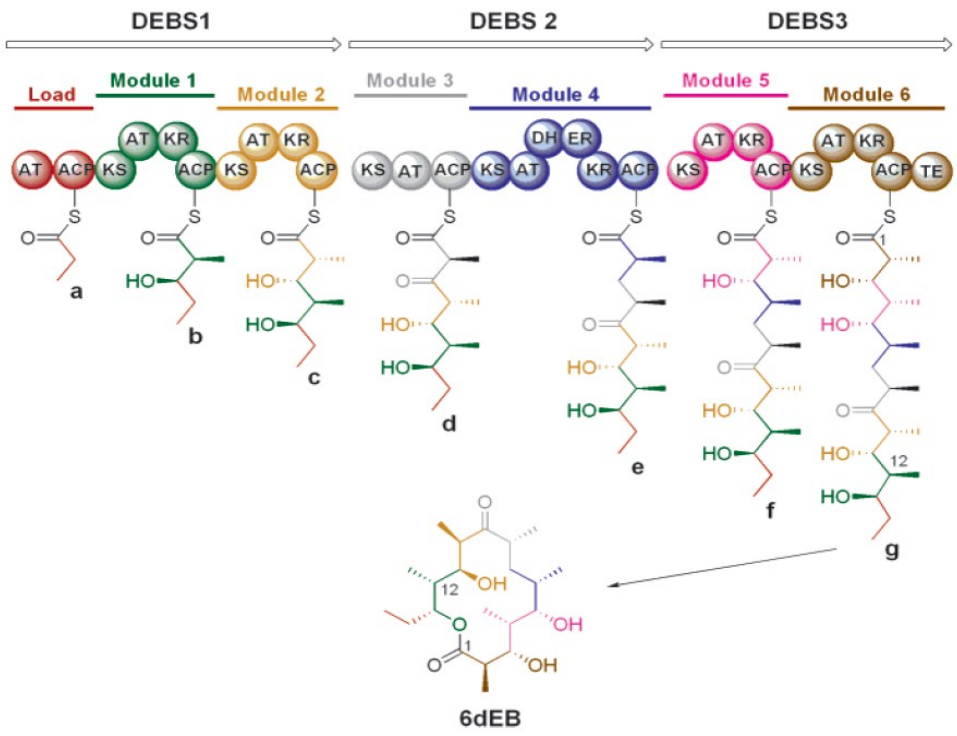
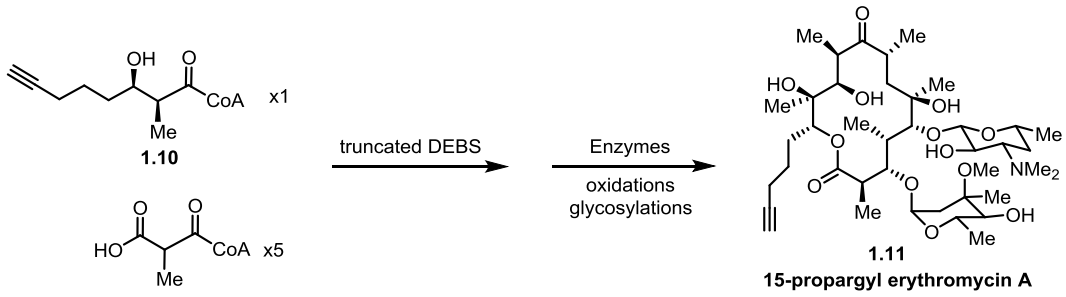



**Figure 1.3** Biosynthesis of 6-deoxyerythronolide B by DEBS (6-deoxyerythronolide synthase). Domains of DEBS are abbreviated as: ACP, acyl carrier protein; AT, acyltransferase; DH, dehydratase; ER, enoylreducase; KR, *β*-ketoreductase; KS, *β*-keto acyl-CoA synthase; TE, thioesterase. Figure adapted from reference 1.

The catalyst DEBS is a mega-dalton three-protein complex that synthesizes polyketides in a modular fashion. The assembly line commences with loading of a propionyl CoA via forming a thioester linkage (**a**), 6 consecutive decarboxylative thio-Claisen condensation reactions between methylmalonyl CoA and enzyme-tethered thioesters extend the polyketide chain (**b-g**). In between the condensation events, domains responsible for modifications (stereoselective reduction, dehydration etc.) set the correct stereochemistry and oxidation state. Finally the TE (thioesterase) domain at the end of the assembly line catalyzes the cyclization and 6-deoxyerythronolide B **1.9** is released from the synthase.

Manufacturing and maintenance of this massive biosynthesis machinery entails large energy and material expenditures, as evidenced by the fact that bacteria in competition-free environment usually do not express the enzymes for antibiotic synthesis. Another testament to the complexity of this biosynthesis machinery is the tremendous effort required to recapitulate its function *in vitro*. Despite decades of research on 6-deoxyerythronolide B synthase (DEBS), it was not until 2013 that researchers successfully reconstituted a functional assembly line *in vitro* from purified protein components.[12]

Nevertheless, great strides in understanding of the erythromycin biosynthesis machinery have opened the door to creating new macrolides by genetic engineering. The Khosla lab reported a series of modified erythromycin A analogs (e.g. **1.11**) biosynthesized by tailored synthases (Scheme 1.3). [13]

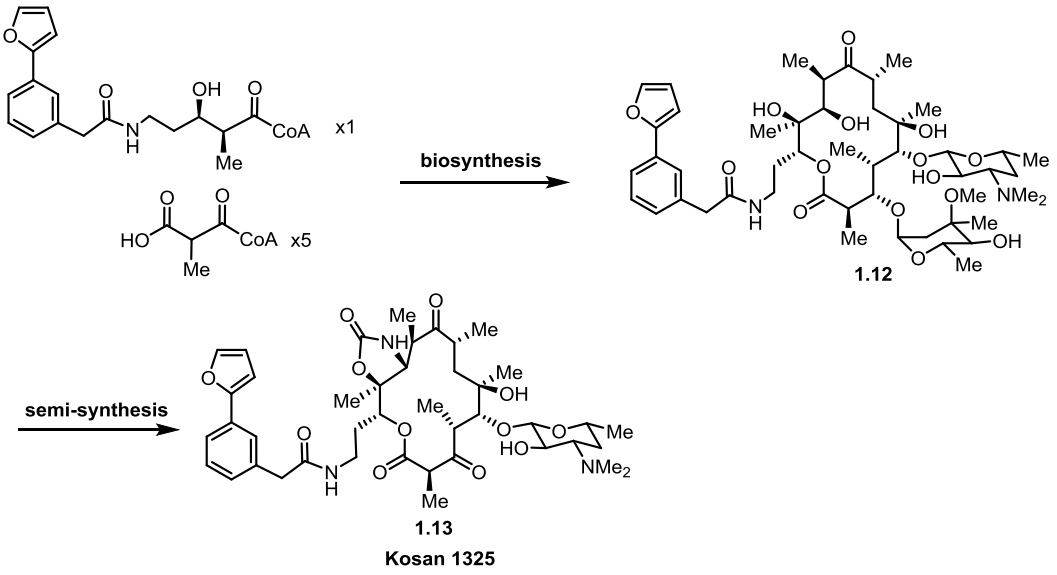



**Scheme 1.3** Biosynthesis of 15-propargyl erythromycin A. Bacteria that express truncated DEBS incorporate unnatural starting material **1.10** to deliver a modified erythromycin A **1.11**.

The 15-propargyl erythromycin A **1.11** is found to inhibit protein synthesis with potency equal to erythromycin A in a cell-free translation assay, and harbors a terminal alkyne that could be used for bioorthogonal functionalization. In the fermenting bacteria, the

loading module and the first module of the 6-deoxyerythronolide B synthase were truncated; therefore the biosynthesis was able to start with artificially supplemented material **1.10**. The rest of the biosynthetic machinery remained intact and **1.11**, containing an unnatural alkyne, was obtained at the end of the assembly line.

Kosan 1325 (**1.13**, Scheme 1.4) resulted from a hybrid discovery approach combining polyketide synthase engineering and conventional medicinal chemistry.[14] In light of the aforementioned technology, intermediate **1.12** was biosynthesized from unnatural building blocks and further modified via semi-synthesis to afford **1.13**.




**Scheme 1.4** Production of Kosan 1325 by combining biosynthetic engineering and semi-synthetic medicinal chemistry.

## 1.4 Total synthesis of erythromycin and erythronolides

In the field of natural product synthesis, erythromycin A and its aglycon erythronolides have long been deemed the benchmarks for state of the art. Over 20 syntheses in this class have been reported[15] (Figure 1.4). Powerful methods of acyclic stereocontrol, especially the Evans aldol reaction and crotylation reactions, have been rapidly advanced to install the plethora of stereocenters (Figure 1.5).

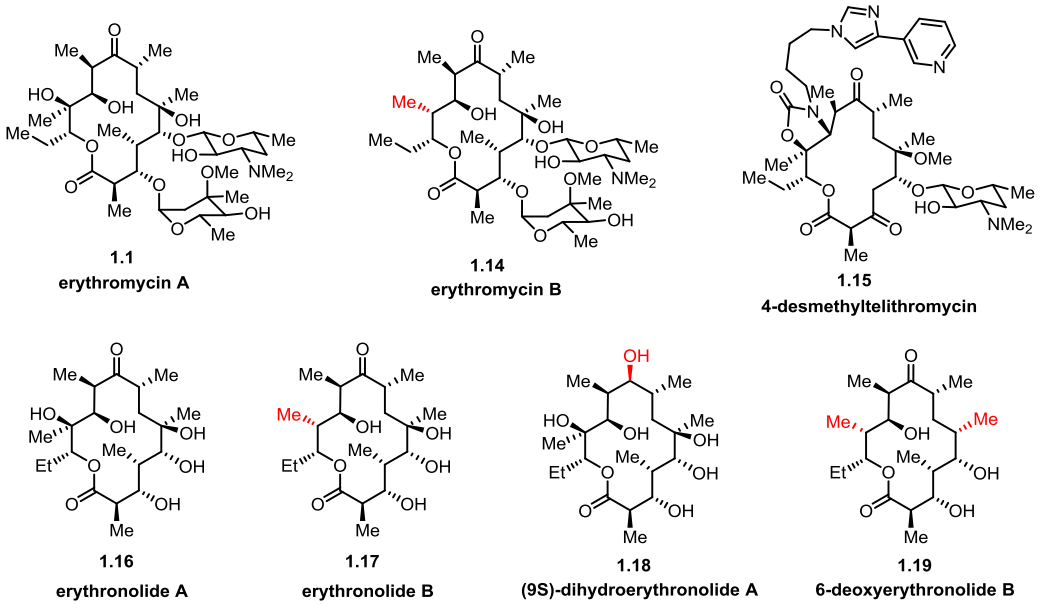



**Figure 1.4** Erythromycin A related glycosides and algycons prepared by total synthesis.

While most reports focus on the synthesis of the aglycons (**1.16-1.19**), there are only scattered reports on the synthesis of glycosylated erythromycins: two of erythromycin A, one of erythromycin B **1.14** and several of desmethyl telithromycins (eg **1.15**). Syntheses of the aglycons, mostly carried out to test new methods and strategies of stereocontrol, have been reviewed extensively elsewhere[16-19] (Figure 1.5). Here I will review the

syntheses of glycosylated erythromycin analogs (erythromycin A **1.1**, erythromycin B **1.14** and 4-desmethyl telithromycin **1.15**), with a focus on the glycosylation reactions.

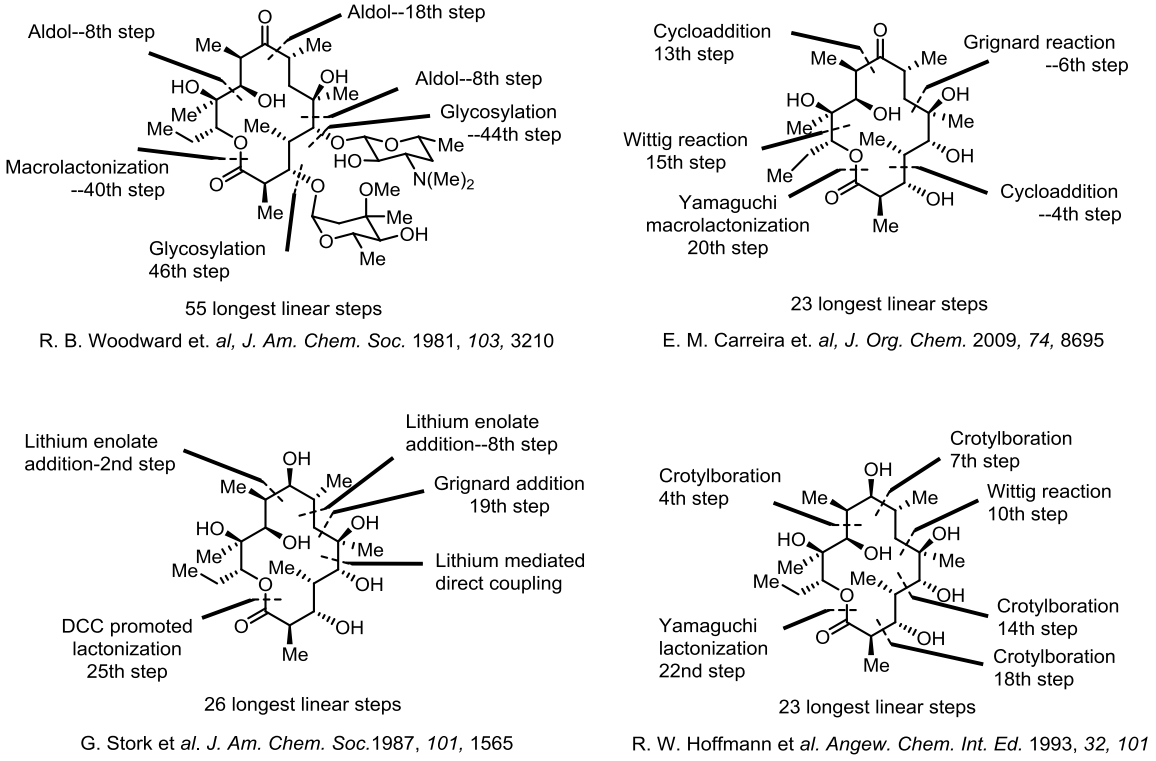
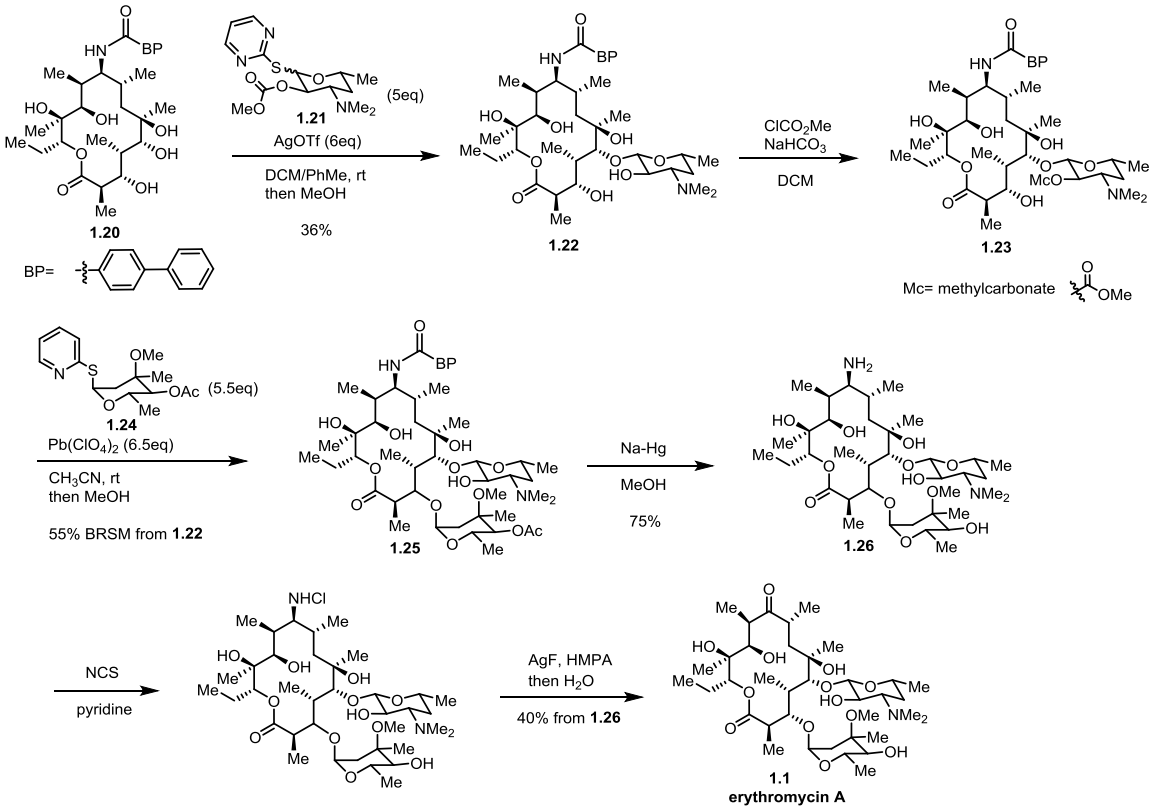



**Figure 1.5** Selected total syntheses of erythromycin A and erythronolides. Aldol and crotylation reactions were employed extensively. Adapted from Kai Liu's Ph.D. thesis.[16]

## The Woodward synthesis of erythromycin A (1981)

Over two decades of effort culminated in the first and the only total synthesis of erythromycin A.[20] (Figure 1.5) Synthesis of the aglycon featured a proline-catalyzed aldol reaction, and used the Corey-Nicolaou condition for the macrolactonization. Cyclic intermediate **1.20** was glycosylated with a thiopyrimidyl desosamine donor **1.21** with excellent β selectivity (Scheme 1.5), and silver (I) triflate was found to be the best promoter among many other metal salts (Hg (II), Cu(II) and Pb(II)). Although the

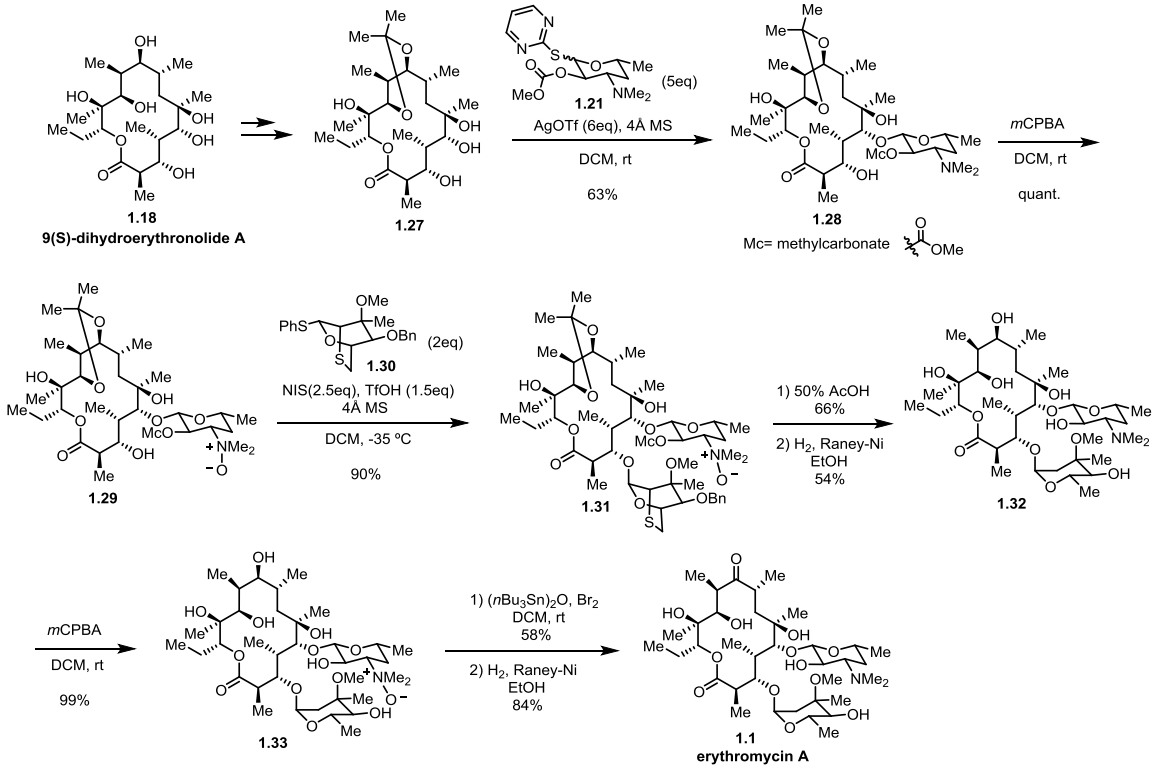
glycosyl acceptor **1.20** has five alcohols, the site-selectivity was remarkable: the desired C-5 glycoside **1.22** was isolated as the major product in 36% yield; three minor glycosides were isolated in a combined yield of 29%. The 2'-OH of desosamine was masked as methylcarbonate to afford the second glycosyl acceptor **1.23**. Glycosylation of **1.23** with thiopyridyl cladinose donor **1.24** furnished, after methanolysis, the glycoside **1.25** (37% conversion, 55% yield based on consumed **1.23**). The erythromycylamine **1.26** was then converted to erythromycin A in three steps (chlorination of amine, dehydrochlorination followed by hydrolysis of immine).




**Scheme 1.5** The Woodward synthesis of erythromycin A (glycosylation and endgame).

**The Toshima synthesis of erythromycin A (1995)**

In order to demonstrate highly efficient glycosylation reactions, Toshima *et al.* reported a synthesis of erythromycin A from its algycon (9*S*)-dihydroerythronolide A **1.18**[21] (Scheme 1.6), in which glycosylation steps were improved from the original Woodward synthesis.[20] Cyclic ketal protected tetraol **1.27** was glycosylated with 63% yield under a modified Woodward glycosylation condition (*c.f.* Scheme 1.5), in which molecule sieves (4Å) were indispensable for high yield. Prior to introduction of cladinose, the dimethylamino group in **1.28** was oxidized to the *N*-oxide (tertiary amine were found to interfere with subsequent glycosylation). Various cladinose donors (glycosyl fluorides, glycals, etc.) including the Woodward cladinose donor (**1.24**) failed at appending the cladinose. Nevertheless the 2,6-anhydro-2-thio donor **1.30** was eventually employed at

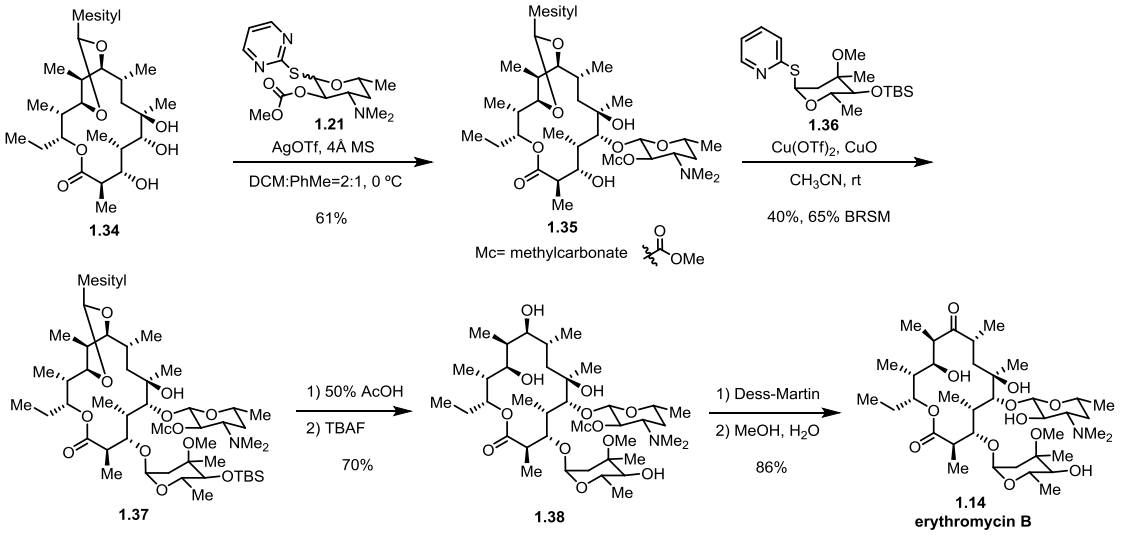



**Scheme 1.6** The Toshima synthesis of erythromycin A from its aglycon **1.18**.

low temperature to delivered glycoside **1.31** in 90% yield. Treatment with acid and Raney-nickel removed the cyclic ketal and revealed the latent cladinose to furnish (9*S*)-dihydroerythromycin A **1.32**. After extensive experimentation, a three-step procedure was identified to selectively oxidize the C-9 alcohol of **1.32**, hence concluding the synthesis of erythromycin A.

**The Martin synthesis of erythromycin B (1997)**

The total synthesis of erythromycin B (12-deoxyerythromycin A), a minor metabolite isolated from erythromycin A producing bacteria, was accomplished by the Martin lab (Scheme 1.7).[22] The Evans aldol reaction was instrumental for introducing stereocenters in the aglycon synthesis, and a slightly modified Toshima condition (*c.f.* Scheme 1.6) was employed to install the desosamine in 61% yield. Subsequent introduction of cladinose **1.36** under the Woodward condition (promoted by lead (II) perchlorate, *c.f.* Scheme 1.5)

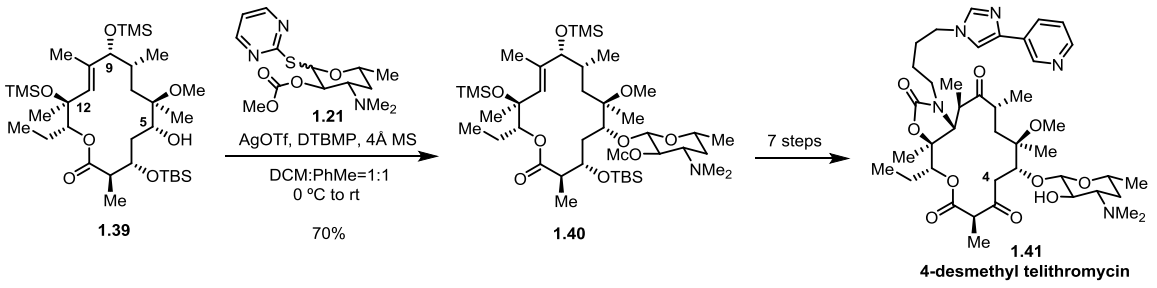



**Scheme 1.7** The Martin synthesis of erythromycin B (glycosylation and endgame).

was not fruitful, although a mixture of copper (II) triflate and copper (II) oxide was identified to effect the glycosylation in 40% yield. Removal of the cyclic mesitylene acetal and TBS ether in **1.37** afforded the 9-dihydroerythronolide **1.38**. One equivalent of Dess-Martin periodinane exclusively oxidized the C-9 alcohol, in the presence of other alcohols (C-11 and C-4') and an unprotected tertiary amine. Thus erythromycin B **1.14** was obtained in 30 longest linear steps (the Woodward synthesis of erythromycin A required 55 longest linear steps).

**The Andrade synthesis of 4-desmethyltelithromycin (2014)**

In search of telithromycin analogs that are active against resistant pathogens, the Andrade group reported total syntheses of a series of desmethyl telithromycins.[23] The Martin's glycosylation condition was successfully applied to all these cases (e.g. Scheme 1.8). However in contrast to the excellent site selectivity observed in the Woodward, Toshima and Martin syntheses (Scheme 1.5-1.7), C-9 and C-12 alcohols of **1.39**, if not protected, were preferentially glycosylated over the desired C-5 alcohol. Eventually all alcohols in **1.39**, except the C-5 alcohol, were protected to secure exclusive site selectivity, and a bulky base DTBMP (2,6-di-tert-butyl-4-methylpyrdidine) was included to suppress any




**Scheme 1.8** The Andrade synthesis of 4-desmethyl telithromycin.

undesired acid-promoted reactions. The 4-desmethyl telithromycin **1.41** was constructed in 26 steps (longest linear sequence), however its antibacterial activity is inferior to the parent telithromycin.

## 1.5 Conclusion

I have described three approaches to produce erythromycin analogs (Figure 1.6):

1) Semi-synthesis starting from fermentation-produced erythromycin A;

2) Biosynthesis with engineered biosynthetic machinery;

3) Total synthesis.

These approaches have limitations, as discussed below.

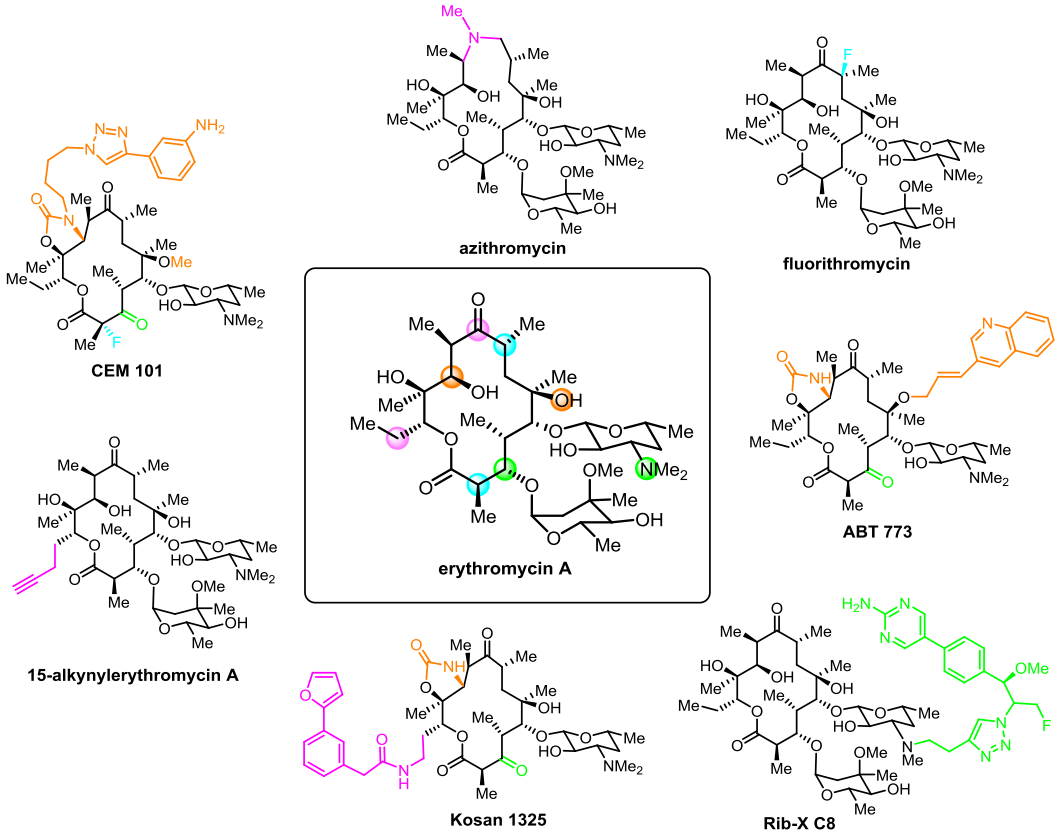
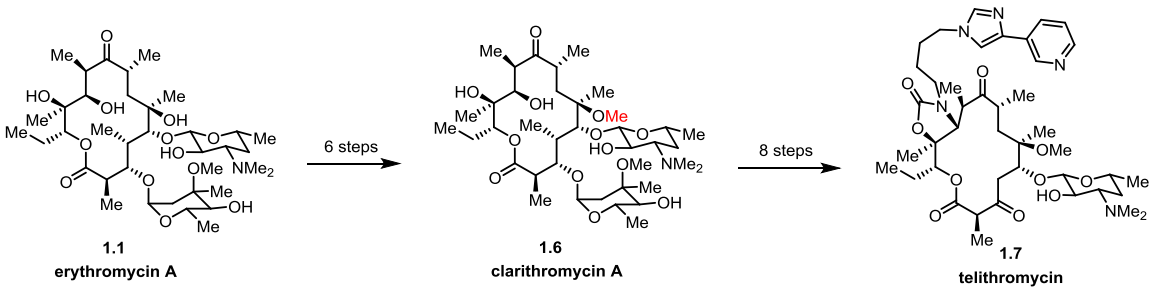



**Figure 1.6** Selected examples of erythromycin derivatives. Sites of modifications are color-coded in the central erythromycin A molecule and in the corresponding analogs.

**Semi-synthesis approach**

Semi-synthesis starting from erythromycin A is the conventional and the most fruitful approach for producing focused libraries of erythromycin analogs. To date, all commercial erythromycin antibiotics were developed using this approach. The benefit of a structurally complex starting material is that many steps can be saved.




**Scheme 1.9** Semi-synthesis of clarithromycin and telithromycin from erythromycin A.

Although the starting material can be obtained on large scale from fermentation, this approach is limited by the complex structure and reactivity of erythromycin A. Selective modifications pose formidable challenges because the natural product is riddled with reactive functionalities. For instance, the conversion of erythromycin A to clarithromycin **1.6** (mere methylation at the C-6 alcohol) requires 6 steps and further conversation to telithromycin **1.7** requires 8 steps[6] (Scheme 1.9). Unfortunately, most of the steps involved are protecting group manipulations. Using a structurally complex natural product as starting material also curbs the scope of target selection. Although various sites have been modified (Figure 1.6), structural editing at many additional sites (e.g. removal/addition of methyl group) cannot be feasibly achieved.

**Biosynthetic engineering approach**

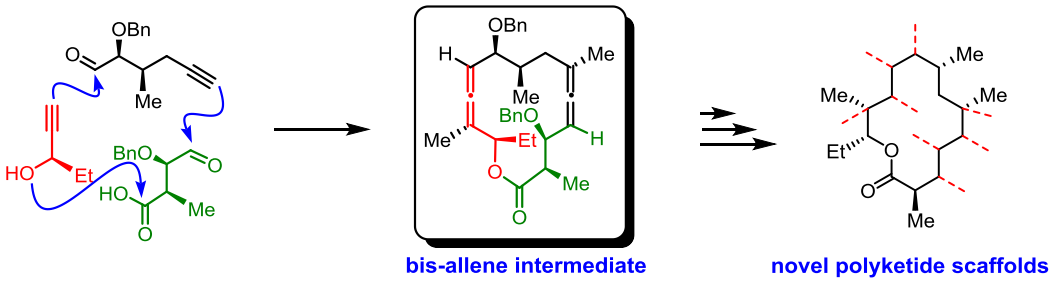
Engineered biosynthesis machinery has delivered distinct erythromycin derivatives (e.g. 15-alkynylerythromycin A and Kosan 1325, Figure 1.6) that cannot be accessed from semi-synthesis, except, perhaps, after great effort. Nevertheless this approach is severely limited by the stringent substrate tolerance of the enzymes involved in the biosynthesis. In order to expand the substrate scope, extensive and tedious engineering of multiple enzymes may be required. Moreover, limited throughput of the engineered biosynthesis system can restrict production on a manufacturing scale required for drug development.

**Total synthesis**

Total synthesis is a highly flexible approach that promises virtually unlimited modifications. However, most of the previous synthetic routes are not relevant to drug discovery since they are long (most over 30 steps) and lack flexibility (aimed to exclusively prepare the natural product). If the activity of the target was found to be suboptimal, which is likely, a synthesis would have to be devised anew to prepare another single target. For instance, the Andrade group prepared a series of closely related desmethyl-telithromycin analogs, yet each requiring a different route (most over 30 longest linear steps).[23] The primary challenge for the total synthesis approach is to simultaneously target many, rather than just one molecule.

Our lab has developed a convergent-divergent synthesis strategy to prepare a library of erythronolides, from a single cyclic bis-allene intermediate (Scheme 1.10). This approach

could potentially lead to multiple active erythromycin derivatives and provide much-needed insight into the full structure-activity profile of macrolide antibiotics.




**Scheme 1.10** Convergent-divergent total synthetic approach. A cyclic bis-allene, assembled from sequential coupling of three modules, was subsequently converted to diverse novel scaffolds within 5 steps.

My graduate work is based on this multi-target approach. I will describe a total synthesis of 4,10-didesmethyl-(9*S*)-dihydroerythronolide A (Chapter 2), preparation of glycosylated erythromycin analogs (Chapter 3) and progress towards synthesis of 9(*S*)-dihydroerythronolide A (Chapter 4).

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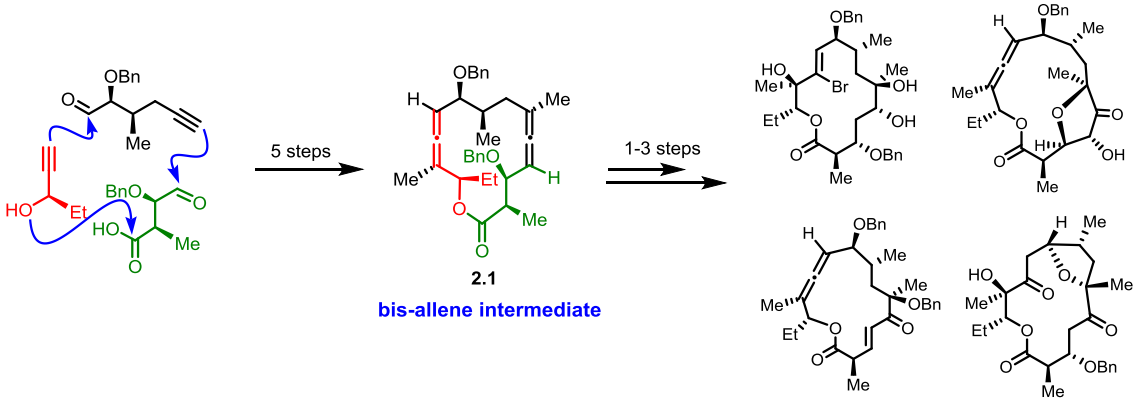
# Chapter 2 Total Synthesis of 4,10-Didesmethyl-(9*S*)-dihydroerythronolide A

## 2.1. Introduction

Emerging resistant pathogens create the urgent need for novel antibiotics with enhanced properties. Unfortunately, the complexity of erythromycin A and its biosynthetic pathways limit our ability to use bioengineering and conventional semi-synthetic approaches to search this macrolide structural space. Although total synthesis can, in principle, exhaustively evaluate this space, previous synthetic routes of erythromycin A and erythronolides are not readily applicable to drug discovery since they are long (over 20 steps) and/or inflexible.

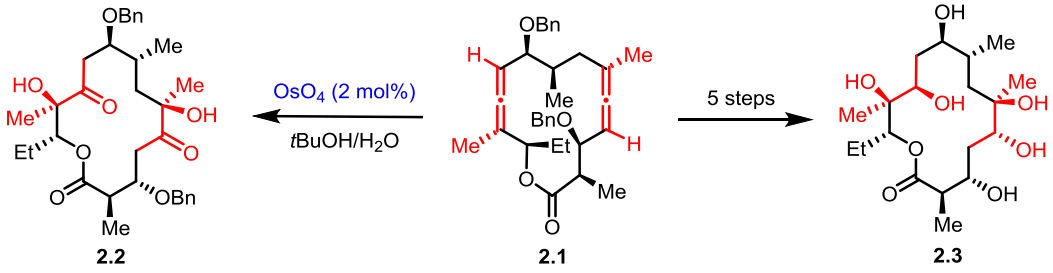
Our lab has previously devised a multi-target synthetic strategy to expeditiously access cyclic polyketide scaffolds related to erythromycin (Scheme 2.1).[1-4] Branching from a common bis-allenic intermediate **2.1**, a diverse collection of analogs have been prepared, each within 3 steps.




**Scheme 2.1** Convergent assembly of key intermediate **2.1** and divergent derivatizations.

I have further exploited the potential of this strategy by preparing a diversified portfolio of aglycons and glycosides related to erythromycin. In this chapter, I will relate a 16-step total synthesis of a cyclic polyketide 4,10-didesmethyl-(9*S*)-dihydroerythronolide A **2.3** (Scheme 2.2). Deletion of the methyl groups at C4 and C10 represent potential means to overcome antibiotic resistance, such as the A2058G ribosomal RNA mutation resistance mechanism (described in Chapter 1.2).

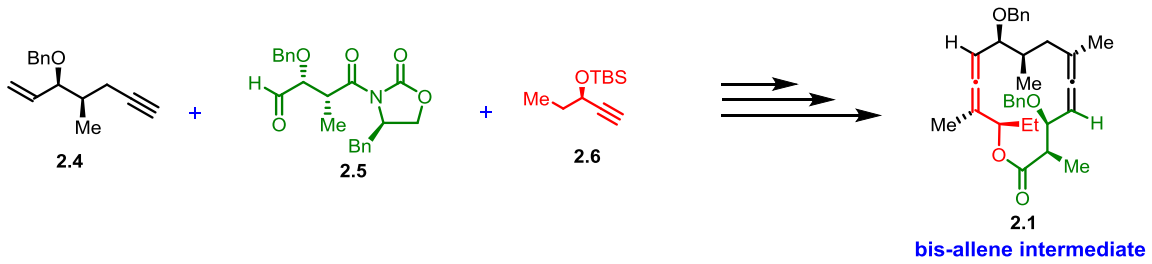
I will disclose an improved route to the common intermediate **2.1** (chapter 2.2), completion of target **2.3** (chapter 2.3), a catalytic allene osmylation reaction to prepare diketone **2.2** (chapter 2.4) and a nonconventional macrolactonization with a (9*R*)-seco acid (Chapter 2.5).




**Scheme 2.2** A catalytic osmylation reaction to **2.2** and a 5-step synthesis of **2.3**.

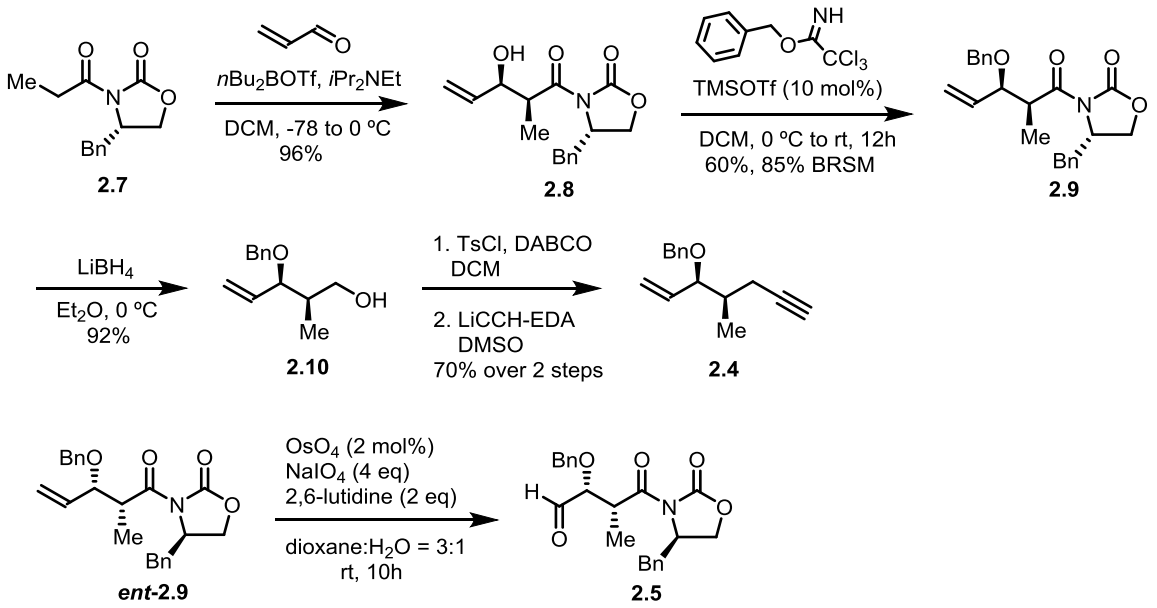
## 2.2. Synthesis of cyclic bis-allene intermediate

The orginal route to the pivotal intermediate **2.1** was published by our lab in 2011.[1] Reported here is an improved synthesis which increases the number of crystallizable intermediates and therefore streamlines purifications on large scale. The bis-allenic macrolactone **2.1** is constructed in a modular fashion via sequential coupling of alkyne **2.4**, aldehyde **2.5** and alkyne **2.6** (Scheme 2.3).



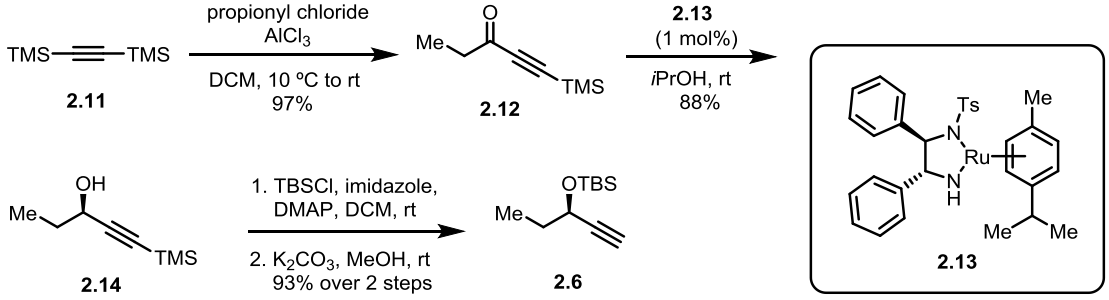

**Scheme 2.3** Construction of cyclic bis-allene **2.1** from three modules **2.4-2.6**.

Commercially available oxazolidinone **2.7** and acrolein were coupled with the Evans aldol reaction (Scheme 2.4),[5,6] from which a single isomer was isolated in over 95% yield. Catalyzed by trimethylsilyl triflate, allylic alcohol **2.8** was alkylated with benzyl trichloroacetimide, and the chiral auxiliary of **2.9** was reductively cleaved to give primary alcohol **2.10**. Tosylation of the newly formed alcohol and substitution with lithium acetylide yielded the first alkyne module **2.4**. The enantiomer of **2.9**, which was prepared with the same two-step sequence, was subjected to the Johnson-Lemieux condition to afford aldehyde module **2.5**.[7] Since **2.5** epimerizes during silica gel chromatography, the crude material was used for the subsequent coupling reaction without purification.



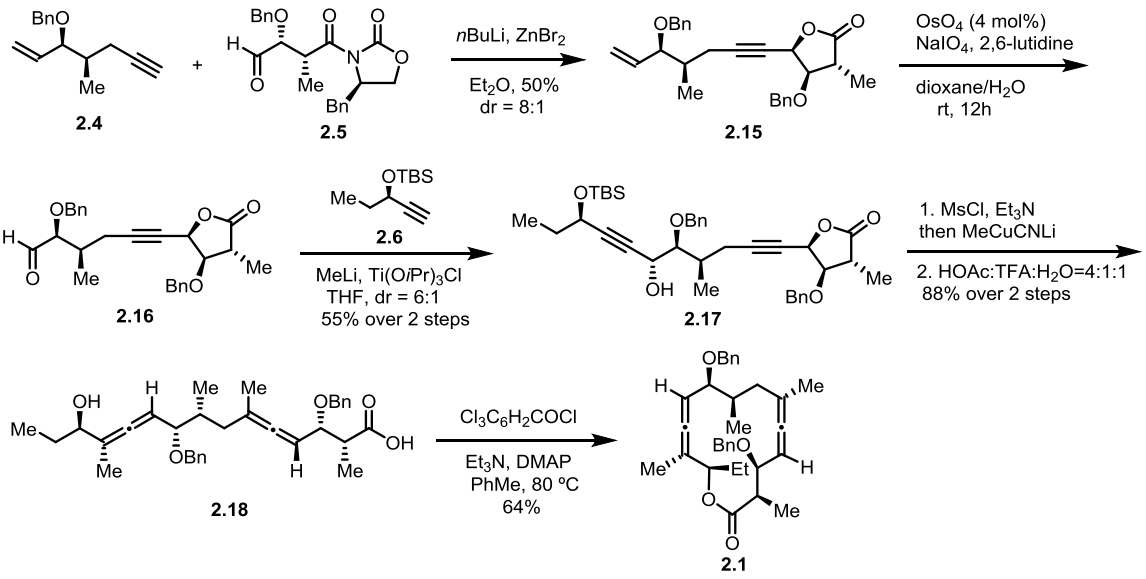

**Scheme 2.4** Synthesis of coupling components alkyne **2.4** and aldehyde **2.5**.

The third coupling component alkyne **2.6** was prepared according to a known procedure (Scheme 2.5).[8] Bis-trimethylsilyl alkyne **2.11** was acylated to afford ynone **2.12**, which was hydrogenated with (*R, R*)-Noyori catalyst **2.13**.[9] Protection of the resulting alcohol and cleavage of trimethylsilyl group furnished the third module **2.6**. Exposure to high-vacuum was avoided for this molecule due to its volatile nature.




**Scheme 2.5** Synthesis of alkyne **2.6**.

Availability of the three components set the stage for construction of **2.1**. Zinc bromide mediated addition of alkyne **2.4** to aldehyde **2.5** proceeded under chelation control (dr=8:1), concomitant with cleavage of the chiral auxiliary by the nascent alkoxide.[10] Oxidative cleavage of the terminal alkene revealed aldehyde **2.16**, which was then coupled with alkyne **2.6**. Titanium-mediated coupling yielded the desired polar Felkin-Anh product **2.17** with 6:1 dr.[11] A single flask mesylation/cuprate-addition procedure converted diyne **2.17** to the corresponding bis-allene,[12] the crude material from which was treated with a mild aqueous acid to yield bis-allenic seco-acid **2.18**. Yamaguchi lactonization condition[13] smoothly furnished cyclic bis-allene **2.1**, although high-dilution (3 mM) was required for obtaining reproducible yield and for suppressing intermolecular esterification. To this end the activated ester was slowly added (in 2 hours via syringe pump) to a large volume of toluene.

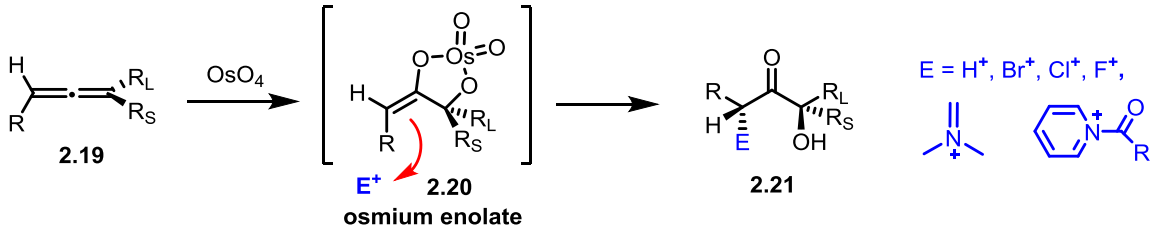



**Scheme 2.6** Construction of the key intermediate **2.1** from three modules.

As previously shown, bis-allene **2.1** was constructed in 11 longest linear steps. The seco acid **2.18** is routinely prepared on gram-scale and **2.1** is prepared on 500 mg scale. This route is amenable to further scale-up.

## 2.3. Completion of total synthesis

From the bis-allenic intermediate **2.1**, a 5-step sequence was implemented to prepare 4,10-didesmethyl-(9*S*)-dihydroerythronolide A **2.3**. Central to this route are novel allene osmylation reactions developed in our laboratory (Scheme 2.7).[2,3,14]

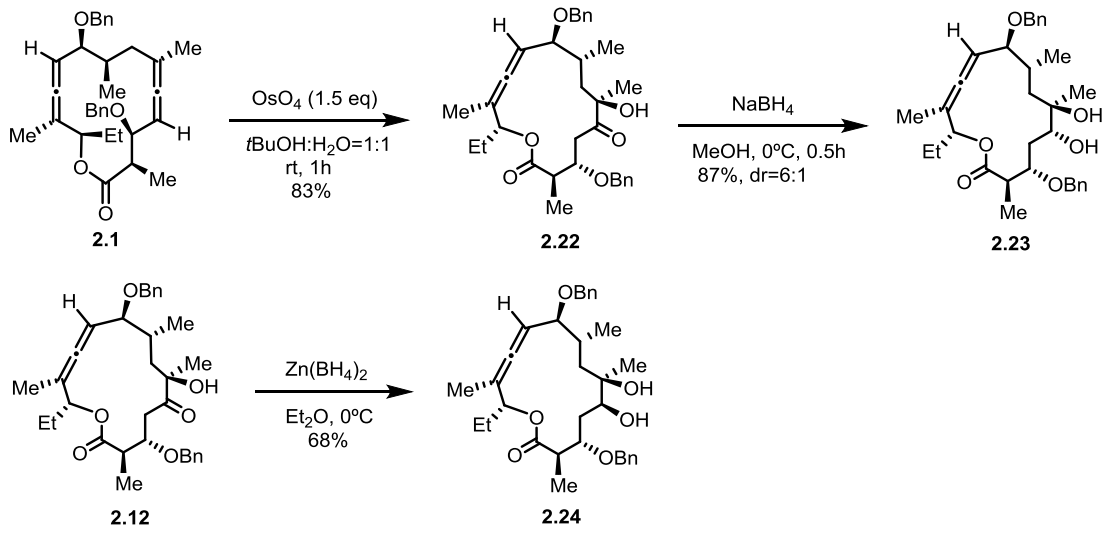



**Scheme 2.7** Allene osmylation/electrophile capture cascade to α-hydroxyketones.

The osmate ester intermediate **2.20**, related to other metal enolates, was derived from osmium tetroxide addition to the more substituted and the more electron-rich end of allene **2.19**. Osmium tetroxide approaches from the more accessible face (the side opposite to the R substituent), and the addition typically proceeds with excellent selectivity. The osmium enolate intermediate **2.20** recruits a variety of reactive electrophiles (proton, electrophilic halogen sources, ammonium salts, *etc.*) to furnish, after hydrolysis, α'-functionalized α-hydroxyketones **2.21**. Face selectivity of the electrophile addition seems to be governed by $A^{1,3}$-strain, with selectivity typically lower

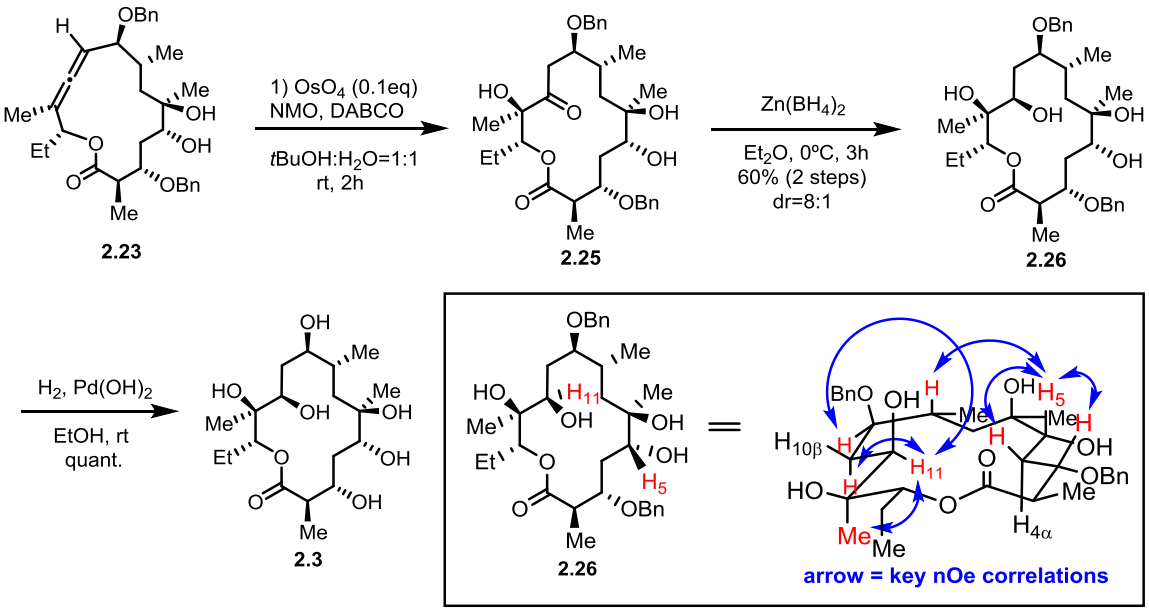
than that of osmium tetroxide addition. This reaction cascade has been rendered catalytic in osmium by using co-oxidants, such as NMO (*N*-methylmorpholine-*N*-oxide).

Treatment of **2.1** with stoichiometric osmium tetroxide furnished α-hydroxyketone **2.22** with complete regioselectivity for the C4-C6 allene (Scheme 2.8).[1] This selectivity can be ascribed to the C13 ester that attenuates the reactivity of the C10-C12 allene. Catalytic osmylation condition with NMO was found to give a complex mixture.[2] The newly formed C5 ketone was then reduced with sodium borohydride to yield diol **2.23** stereoselectively (dr=6:1). Zinc borohydride reduction gives the C5 epimer **2.24**, the structure of which has been assigned unambiguously with comprehensive NMR studies.[1]




**Scheme 2.8** Synthesis of 4,10-didesmethyl-(9*S*)-dihydroerythronolide A **2.3**.

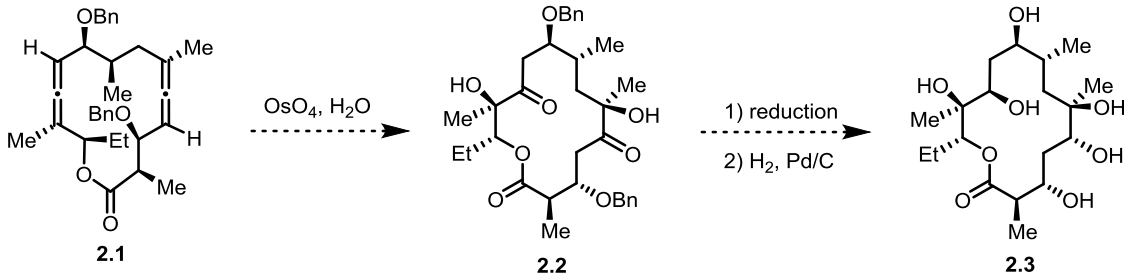
The C10-C12 allene was oxidized under catalytic osmylation condition, for which DABCO (1,4-diazabicyclo[2.2.2]octane) was identified to be a crucial additive (Scheme 2.9). C11 ketone **2.25** was reduced with zinc borohydride to afford tetraol **2.26**, the structure of which was confirmed by comprehensive NMR studies (see Scheme 2.9 for a graphic summary of key nOe correlations focusing on H5 and H11). Heterogeneous hydrogenolysis furnished the target (9*S*)-dihydro-4,10-didesmethylerythronolide A **2.3**, in 16 longest linear steps or 5 steps from intermediate **2.1**.




**Scheme 2.9** Synthesis of 4,10-didesmethyl-(9*S*)-dihydroerythronolide A **2.3** (continued).

## 2.4. Catalytic double-osmylation of a cyclic bis-allene

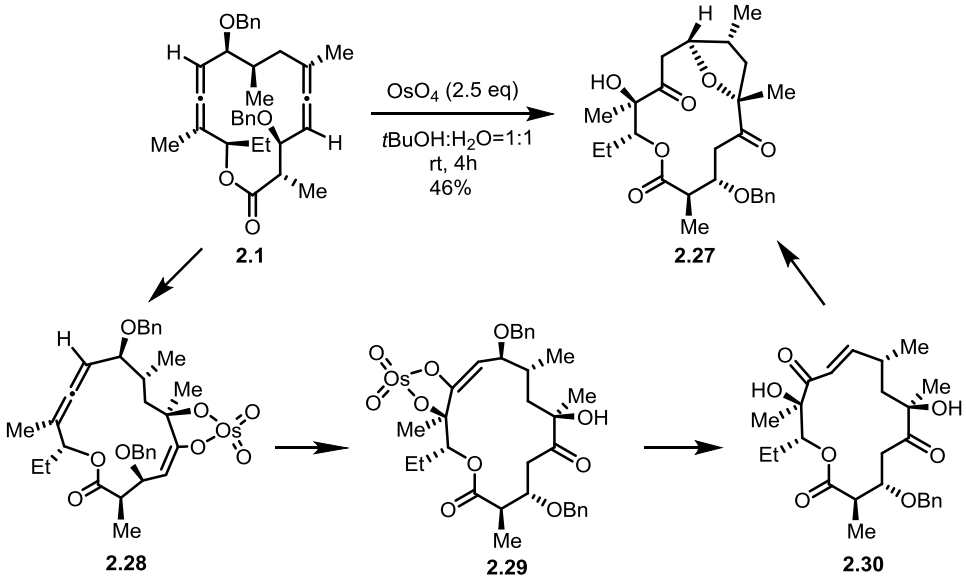
Aiming at maximum brevity, we initially envisaged a 14-step synthesis of **2.3** (3 steps from bis-allenic intermediate **2.1**) (Scheme 2.10).




**Scheme 2.10** Proposed 3-step preparation of **2.3** from bis-allene **2.1**.

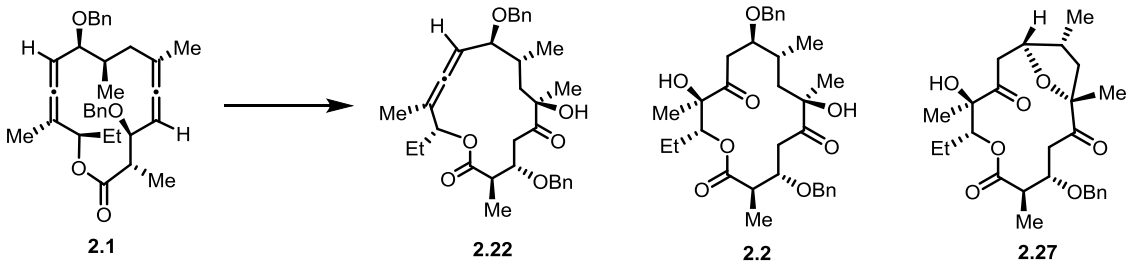
Diketone **2.2**, derived from double-osmylation of the central intermediate **2.1**, was proposed to be selectively reduced and then deprotected to afford **2.3**. This sequence poses significant challenges: 1) as delineated in Scheme 2.11, the proposed double-osmylation is problematic; 2) stereoselectivity of reductions in a macrolactone system cannot be reliable predicted with existing models (e.g. the Felkin-Anh model).

When treated with excess (2.5 equivalents) of osmium tetroxide, bis-allene **2.1** was converted to a bicycle **2.27**, concomitant with loss of a benzyl alcohol (Scheme 2.11).[1] The mechanistic rationale is as follows: osmium tetroxide first adds to the most electron-rich double bond at C5-C6; while the first osmium enolate **2.28** hydrolyzes without complication, the second osmium enolate **2.29** undergoes β-elimination of the C9 benzyl ether to give enone **2.30**; intramolecular conjugate addition of the C6 alcohol results in the bicycle **2.27**. Elimination of β-ethers has not been observed for linear allenes, hence this phenomenon is likely traceable to the stereoelectronics of the osmate intermediates derived from cyclic allenes.




**Scheme 2.11** Attempted double-osmylation of **2.1** resulted in bicycle **2.27**.

**Table 2.1** Optimization of double-osmylation reaction.




| entry | eq. of $OsO_4$ | additive (eq) | time | yields (%) of 2.22 | 2.2 | 2.27 |
|---|---|---|---|---|---|---|
| 1 | 2.5 | none | 4h | 0 | 0 | 46 |
| 2 | 2.5 | quinuclidine (4) | 20min | 0 | 40 | 20 |
| 3 | 2.5 | DABCO (4) | 20min | 0 | 44 | 20 |
| 4 | 1.5 | none | 1h | 83 | 0 | 0 |
| 5 | 1.5 | AcOH (3) | 1h | 40 | 0 | 0 |
| 6 | 1.5 | DABCO (1) | 15min | 68 | 0 | 0 |
| 7 | 0.3 | DABCO (4) | 40min | 0 | 60 | 20 |
| 8 | 0.1 | DABCO (4) | 2h | 0 | 60 | 15 |
| 9 | 0.1 | DABCO (1) | 2h | 0 | 77 | 15 |
| 10[a] | 0.1 | DABCO (1) | 2h | 0 | 76 | 15 |
| 11 | 0.1 | quinuclidine (1) | 6h | 30 | 32 | 35 |
| 12[b] | 0.1 | pyridine (1) | 2h | 0 | 0 | 0 |
| 13 | 0.1 | DABCO (0.2) | 3h | 0 | 48 | 45 |
| 14 | 0.05 | DABCO (0.5) | 4h | 0 | 74 | 15 |
| **15** | **0.02** | **DABCO (0.2)** | **20h** | **0** | **75** | **15** |

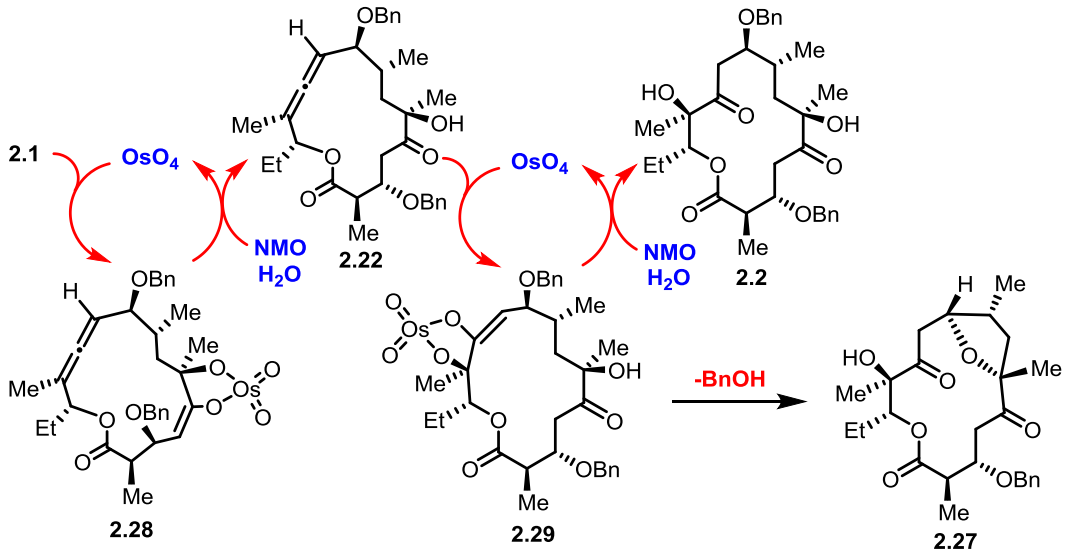
a. pH = 7.4 phosphate buffer used instead of water. b. no reaction observed after 2h.

After extensive experimentation, the desired transformation to **2.2** was realized and the data gleaned during the course of reaction optimization are compiled in Table 2.1. General reaction conditions involve 0.02-0.04 mmol of bis-allene **2.1** in 1:1 mitxure of *tert*-butanol and water (0.03M) at room temperature. Under catalytic conditions (entries 7-15), *N*-methylmorpholine-*N*-oxide (2 equivalents) was used as co-oxidant. Yields were determined based on purified products after flash column chromatography.

During preliminary screening with additives that are known to promote osmylation reactions,[2,3,14] quinuclidine and DABCO were found to yield the desired diketone **2.2** (entries 2 and 3). Tertiary amine additives markedly accelerated the reactions (entries 2, 3 and 6, compared with entry 1 and 4), whereas acid additives resulted in diminished yield (entry 5).

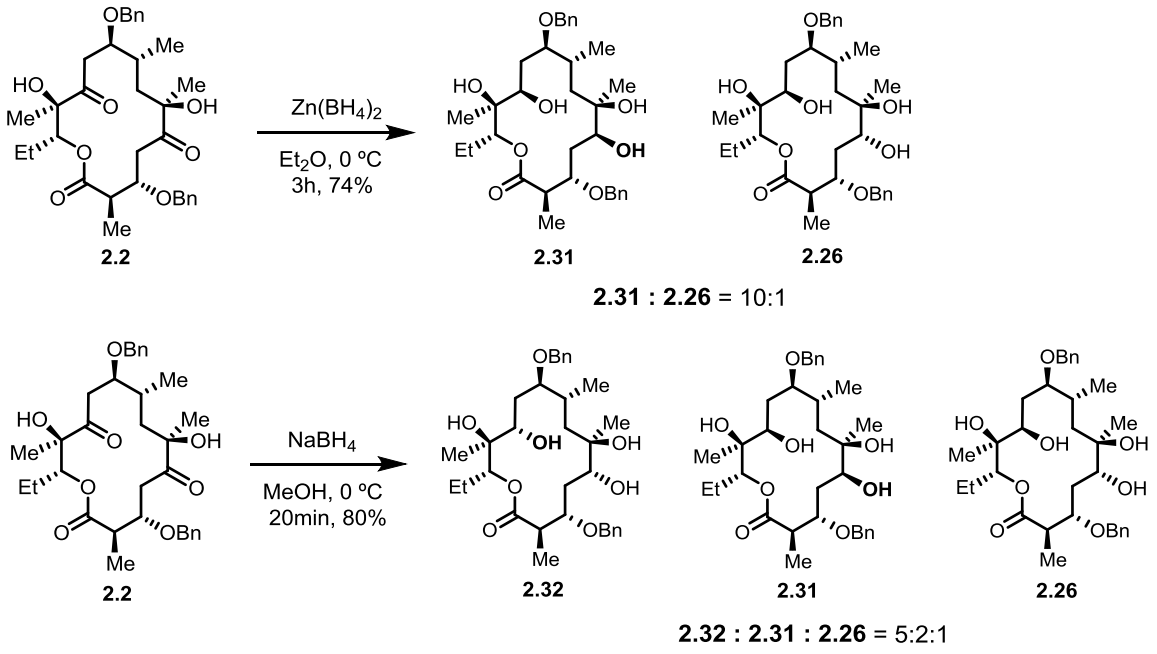
In the presence of tertiary amine additives, osmylation was rendered catalytic with NMO as co-oxidant (entries 7-15). This catalytic procedure minimizes use of hazardous osmium tetroxide. DABCO outperformed other additives in terms of yield and enhancement of reaction rate (entries 9-12). The optimal ratio of DABCO and osmium tetroxide appeared to be 10:1 (entries 8, 9 and 13); deviation from this ratio resulted in lower yields. Catalyst loading can be lowered to 2 mol% while maintaining good yields and convenient reaction rates (entries 14 and 15). Under this optimized condition the desired diketone **2.2** was obtainted in 75% yield along with bicycle **2.27** in 15% yield.

The mechanistic framework for formation of mono-ketone **2.22**, diketone **2.2** and bicycle **2.27** is summarized in Scheme 2.12. Osmium tetroxide adds to the most reactive double bond (C5-C6) of **2.1**, yielding osmium enolate **2.28**. Hydrolysis of this osmium enolate affords α-hydroxyketone **2.22**, while the co-oxidant NMO regenerates osmium tetroxide. Osmium tetroxide addition to **2.22** gives a second osmium enolate **2.29**, which hydrolyzes to diketone **2.2**. Alternatively, β-elimination of the C9 benzyl ether from **2.29** delivers enone **2.30**, which undergoes intramolecular conjugate addition to furnish bicycle **2.27**. In the absence of DABCO, bicycle **2.27** is the major product (entry 1, Table 2.1), implying the possibility that DABCO facilitates hydrolysis of osmium enolate intermediate **2.29** and, hence, shunts the pathway towards formation of diketone **2.2**.




**Scheme 2.12** Proposed catalytic cycle accounting for formation of **2.2** and bicycle **2.27**.

With an efficient catalytic reaction to prepare diketone **2.2**, we turned to focus on selective reductions. Various attempts, however, failed to yield **2.26** as the major product (Scheme 2.13). For instance, the C5 epimer **2.31** was obtained predominantly with zinc borohydride; the C11 epimer **2.32** was obtained as the major product with sodium borohydride. The stereochemistry of these isomers was assigned unambiguously by comprehensive NMR experiments (see NMR spectra in appendix) and by comparison with minor products isolated from reduction steps in the original route (Scheme 2.9). A one-step stereoselective reduction of diketone **2.2** was not pursued further.




**Scheme 2.13** Reduction of diketone **2.2**.

## 2.5. Cyclization using a (9*R*)-seco acid

In the first synthesis of erythromycin A, Woodward *et al.* formulated two guidelines for successful macrolactonization[15]: 1) *S* configuration at C9 and 2) cyclic protecting groups at C3-C5 and C9-C11. These features have been recapitulated in virtually all synthesis of erythronolides (Figure 2.1).[16,17] Presumably the two six-member ring cyclic protecting groups rigidify and pre-organize the linear substrates while the (9*S*) stereocenter contributes to a favorable conformation for lactonization.

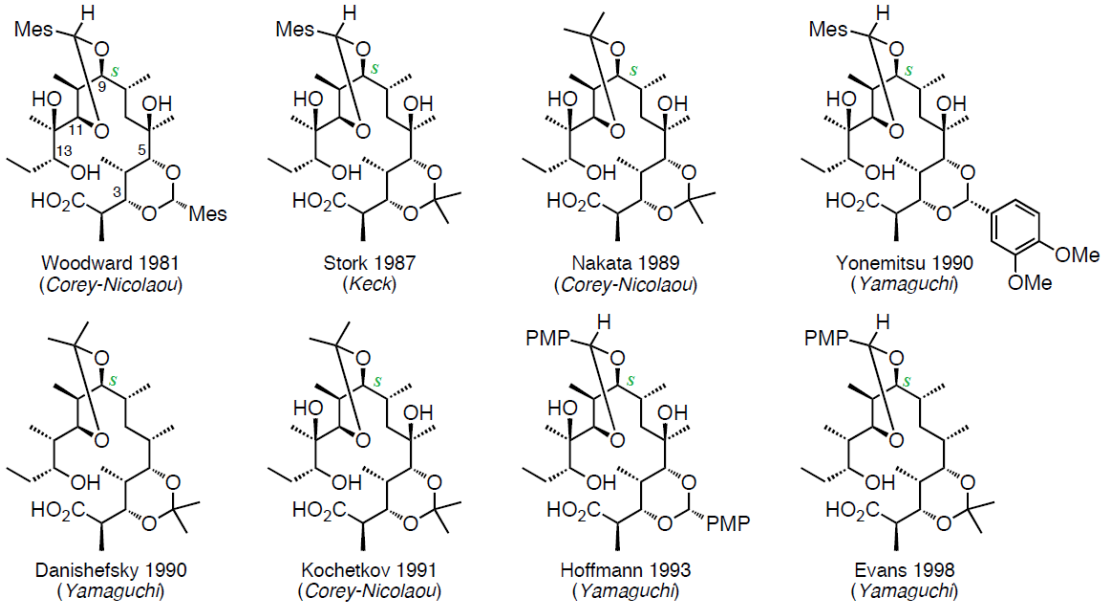
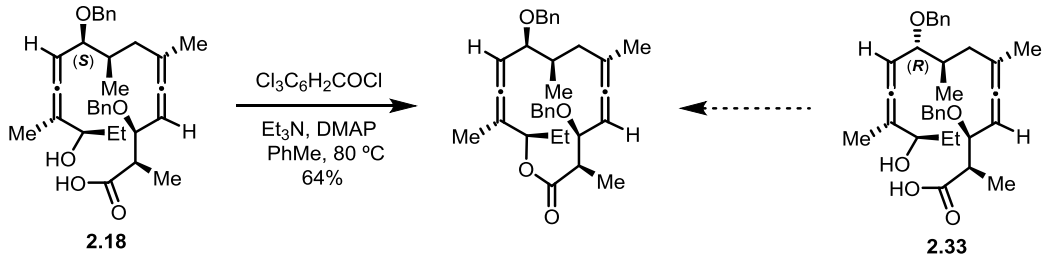



**Figure 2.1** Selected pre-cyclizaiton intermediates. Notice Cyclic protecting groups spanning C3-C5 and C9-C11, as well as the (9*S*) configuration. Figure adapted from reference 17.

As described previously, the central intermediate **2.1** was prepared by cyclizing a (9*S*) substrate **2.18** (Scheme 2.6).[1] The two embeded allenes likely served as counterparts of

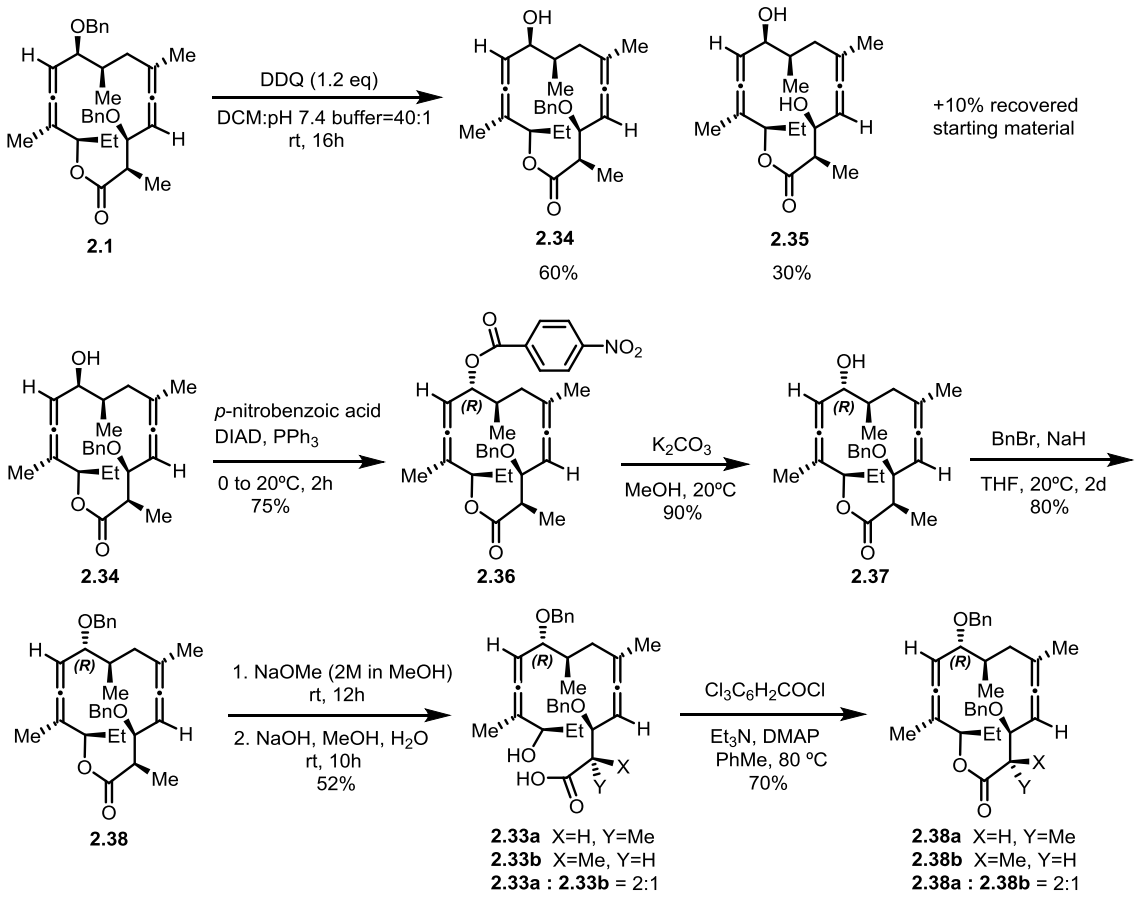
the prevalent cyclic protecting groups. To test the flexibility of our route, we examined the feasibility of cyclizing the (9*R*) seco-acid (**2.33**, Scheme 2.14).




**Scheme 2.14** Cyclization using (9*S*) and (9*R*) seco-acids.

In order to prepare the (9*R*) seco-acid, the C9 stereocenter of **2.1** was inverted using the Mitsunobu reaction (Scheme 2.15).[18] DDQ oxidatively cleaved the benzyl ether at C9 with good selectivity, providing the C9 alcohol **2.34** in 60% yield,[19] and the Mitsunobu reaction afforded para-nitrobenzoate bearing the desired (9*R*) stereocenter. The C9 alcohol **2.37**, derived from methanolysis of **2.36**, was alkylated with benzyl bromide to furnish the (9*R*) cyclic bis-allene **2.38**.

As known for other macrolactones, **2.38** resisted various hydrolysis conditions (e.g. LiOOH, 5 M KOH in $H_2O$/MeOH). Nevertheless concentrated sodium methoxide was found to open the macrolactone, albeit the seco acid **2.33** was obtained as a mixture of inseparable epimers at C2 (dr=2:1). This finding is reminiscent of the findings of Martin *et al.* where the hydrolysis of a 14-member lactone derived from erythromycin B proved stubbornly resistant to cleavage under a wide variety of reaction conditions.[20]




**Scheme 2.15** Synthesis of (9*R*) seco-acid **2.33** and successful cyclization.

The mixture of seco-acids **2.33** was smoothly cyclized under the Yamaguchi condition (dr=2:1),[13] and the minor isomer obtained was found to be identical to previously prepared (9*R*) macrolactone **2.38**. Therefore, as I have demonstrated in our bis-allenic system, cyclization is compatible with both (9*S*) and (9*R*) stereochemistry.

## 2.6. Conclusion

I achieved the first total synthesis of (9*S*)-dihydro-4,10-didesmethylerythronolide A **2.3** and deployed novel allene osmylation reactions in a complex context. Catalytic osmylation conditions bypass stoichiometric use of hazardous osmium tetroxide. In contrast to most of the previous routes to erythronolides, where the cyclization step was at the penultimate stage, our route features early cyclization of a minimally functionalized bis-allene **2.1**. This post-cyclization editing strategy is reminiscent of the biogenesis pathways of macrolides and offers versatility in late-stage diversifications.

An illustration of the flexibility of this strategy is the success in executing the macrolactonization step with both (9*S*) and (9*R*) substrates, whereas previous strategies were strictly limited to the (9*S*) configuration. Our flexible *de novo* synthesis strategy could potentially provide entry into otherwise inaccessible novel macrolide antibiotic derivatives.

Branching from the central intermediate **2.1**, syntheses of glycosylated erythronolide analogs and (9*S*)-dihydroerythronolide A will be discussed in the following chapters.

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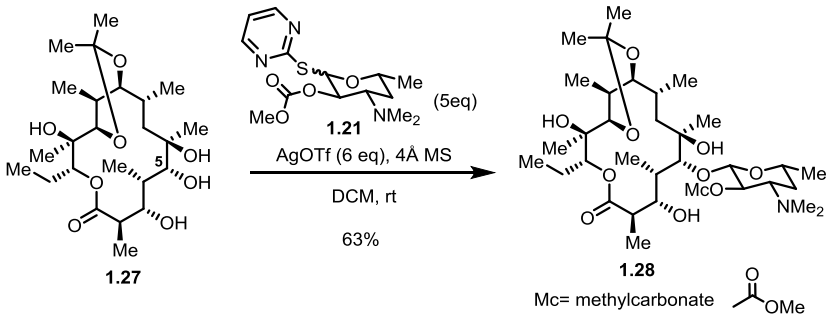
# Chapter 3 Glycosylation of Erythronolides

## 3.1. Introduction

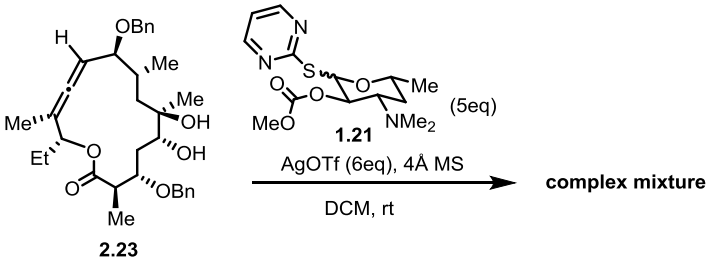
As discussed in chapter 1, the desosamine moiety is central to multiple interactions with the target ribosome and, consequently, is indispensible to conferring antimicrobial activity. Chemical means to append this crucial glycan will be delineated in this chapter.




**Scheme 3.1** Glycosylation with a thioglycoside donor **1.21**.[2]

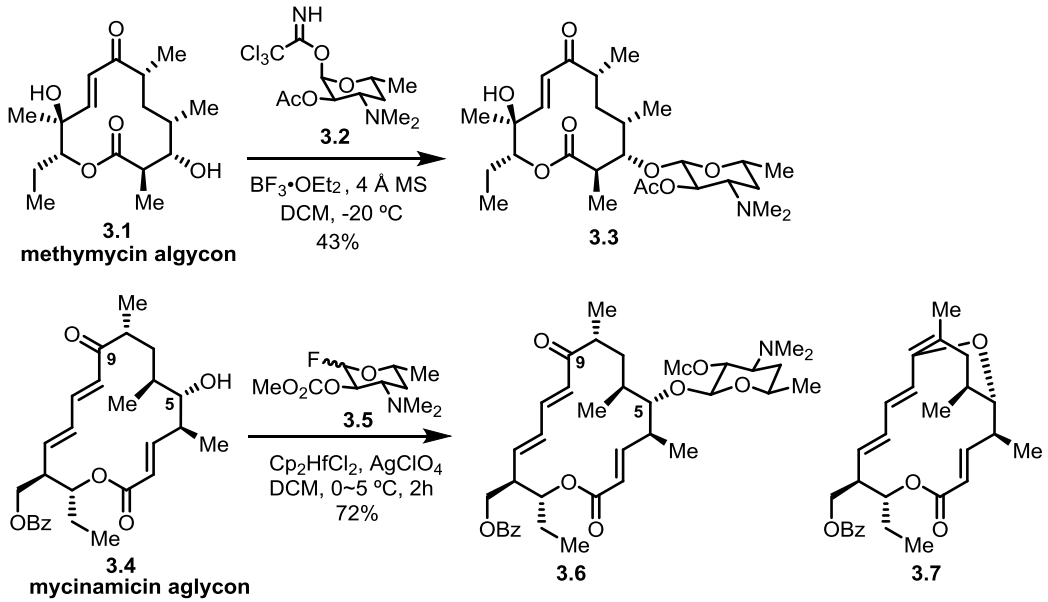
Inspired by the pioneering work from the Woodward group,[1] all reported syntheses of erythromycins rely on thioglycoside donor **1.21** (Scheme 3.1, *c.f.* summary of the Woodward, Toshima, Martin and Andrade syntheses in Chapter 1.4), which exhibited excellent site-selectivity for C5 glycosides and formed the β-glycosidic bonds exclusively.

Encouraged by these successful precedents, my colleague Dr. Kai Liu attempted glycosylation of allenic diol **2.23** under the Toshima condition (Scheme 3.2).[2,5] Unfortunately, despite the tuning of various reaction parameters, complex mixtures were invariably obtained. Moreover, silver (I) triflate alone in DCM was found to trigger decomposition of **2.23**, implicating silver Lewis acid-promoted reactions of allenes.




**Scheme 3.2** Attempted glycosylation of macrocyclic allene **2.23**.[5]

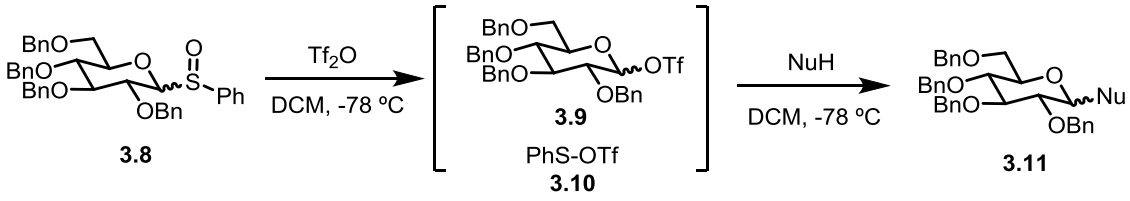
Alternatives to the canonical desososamine donor **1.21**, including trichloroacetimidate **3.2** and glycosyl fluoride **3.5,** were successfully deployed in syntheses of other macrolide antibiotics (Scheme 3.3).[6,7] Nevertheless, activation of these glycosyl donors require strong Lewis acids, which may not be compatible with labile substrates. Indeed, in a synthesis of mycinamicin the Suzuki group identified a fused bicycle **3.7**, which presumably arised from Lewis acid-promoted addition of C5 alcohol to C9 ketone followed by dehydration.[7] When the reaction was carried out below 0 ºC, glycosylation




**Scheme 3.3** Glycosylations with trichloroacetimide **3.2** and glycosyl fluoride **3.5**.

was relatively slow, the competing bicycle (**3.7**) was found to be the major product.

In view of the general sensitivity of polyketides, especially our allenic analogs, to Lewis acids, we aimed for mild glycosylation conditions that would minimize competing pathways and permit broad substrate scope. A survey of available glycosylation methods suggested that Kahne conditions may well be ideal (Scheme 3.4).[8] Triflic anhydride activates sulfoxide glycosyl donors (e.g. **3.8**) to give a highly reactive glycosyl triflate intermediate (e.g. **3.9**),[9] which is then captured by a nucleophile to yield glycoside (e.g. **3.11**).

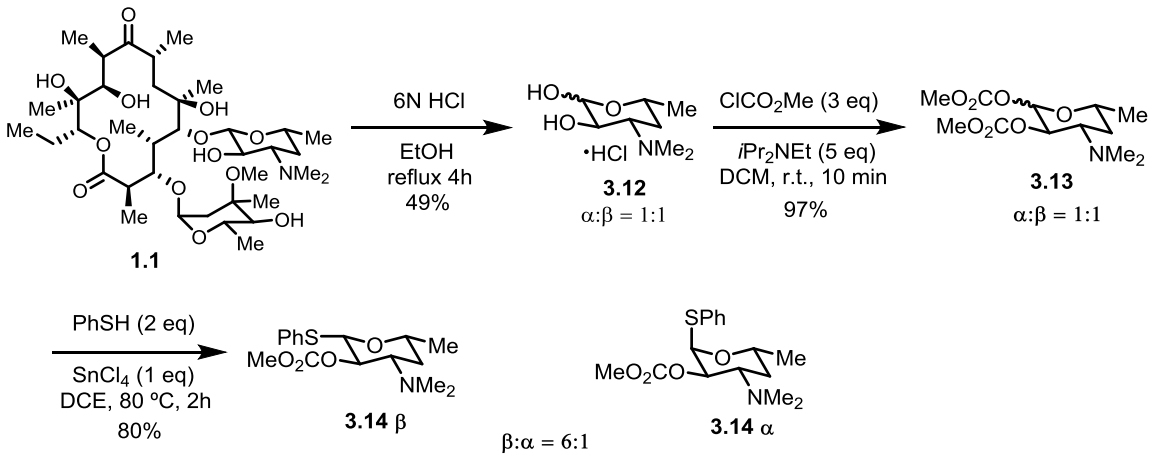



**Scheme 3.4** The Kahne glycosylation method.[8]

This method is Lewis acid-free and is typically performed at low temperature (-78 ºC in most cases). The high reactivity of the activated glycosyl donor and the mild reaction conditions have enabled glycosylations of many most challenging substrates (e.g. vancomycin).[10] One caveat of this method is associated with phenylsulfenyl triflate **3.10**, a potent electrophile generated during activation of the sulfoxide donor. Problems caused by **3.10** and the corresponding solutions will be discussed in Chapter 3.3.

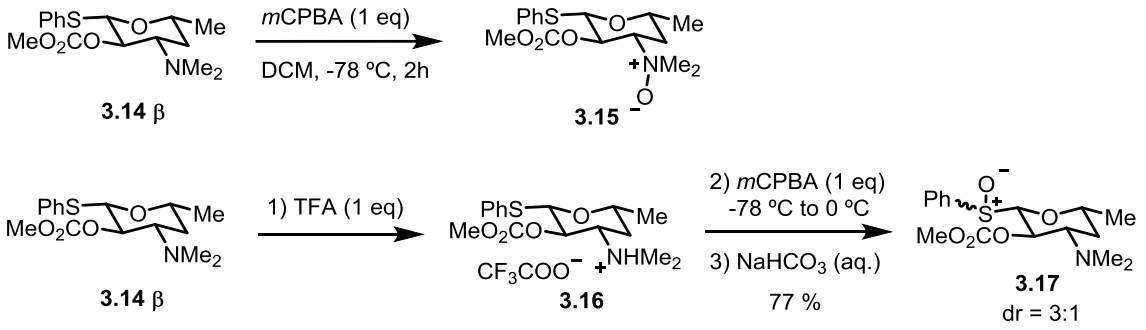
### 3.2. Synthesis of a sulfoxide desosamine donor

To apply the Kahne glycosylation method, a sulfoxide deosamine donor is needed. A concise route to this novel desosamine donor is designed based on a known synthesis of thioglycoside **3.14** (Scheme 3.5).[11]



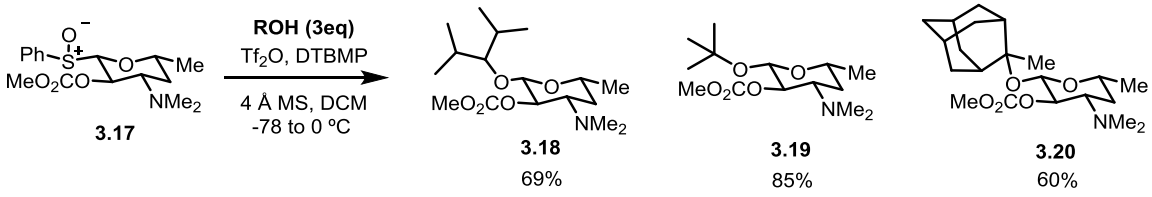

**Scheme 3.5** Synthesis of a sulfoxide desosamine donor.

Desosamine hydrochloride **3.12** (as a mixture of anomers) was obtained from commercial erythromycin A by acid-promoted degradation (Scheme 3.5).[12] Methyl chloroformate was then used to mask the two alcohols of **3.12** as methyl carbonates. Tin (IV)-mediated displacement of anomeric methyl carbonate by thiophenol afforded thioglycoside **3.14** (β:α=6:1). To sidestep manipulation of mixtures composed of isomeric α,β and *R,S* sulfoxides, the β isomer was isolated and used for the following steps.




**Scheme 3.6** Synthesis of a sulfoxide desosamine donor (continued).

Exposure of **3.14** to one equivalent of *m*CPBA resulted in clean formation of *N*-oxide **3.15**, without oxidation of the sulfide (Scheme 3.6). Oxidation of the tertiary amine was suppressed by protonation with trifluoroacetic acid and the desired sulfoxide **3.17** was obtained as a mixture of readily separable diastereomers (dr=3:1). One equivalent of *m*CPBA was required - excess oxidant resulted in over-oxidation to the sulfone. The major isomer was a crystalline solid which could be stored at -20ºC for two years without erosion in activity. For ease of handling, the major isomer is preferred over the minor isomer, which appears as viscous oil. The C2 methyl carbonate group is expected to dictate formation of β-glycosides through anchimeric assistance.



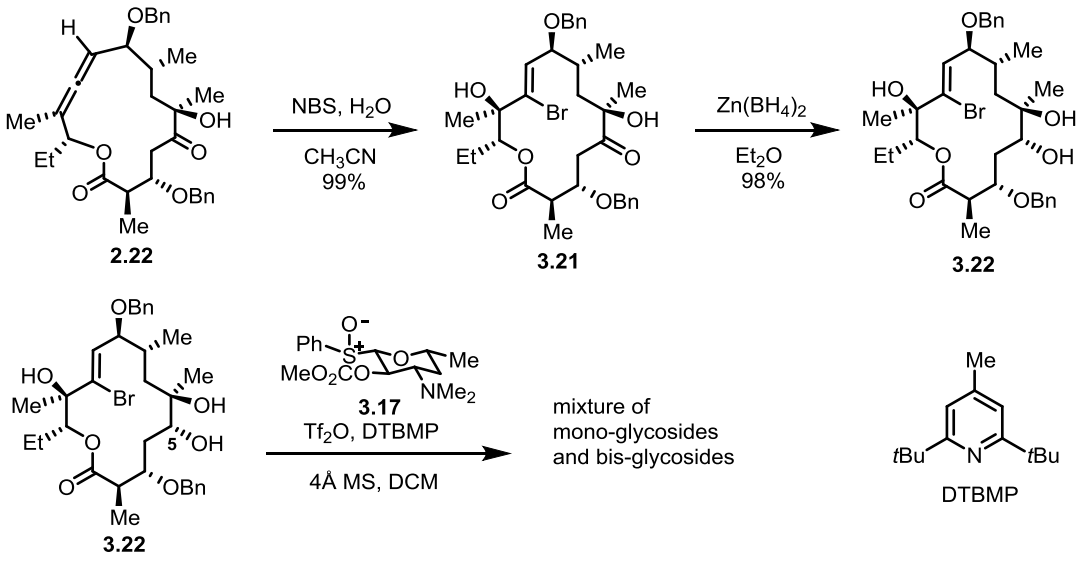

**Scheme 3.7** Glycosylation of hindered alcohols with sulfoxide desosamine donor **3.17**.

Upon activation with triflic anhydride, sulfoxide **3.17** was successfully employed to glycosylate hindered alcohols (Scheme 3.7). For instance, glycosides of 2,4-dimethyl-3-

pentanol (**3.18**), *tert*-butanol (**3.19**) and 2-methyl-2-adamantanol (**3.20**) were prepared with excellent selectivity (β:α>15:1) at low temperature.

### 3.3. Glycosylation of erythronolides

Disclosed here is our foray into glycosylation of erythronolides, in order to discovery bioactive analogs. The first substrate I examined, a cyclic vinyl bromide **3.22**, was prepared in a high-yielding two-step sequence from **2.22** (Scheme 3.8).[13]

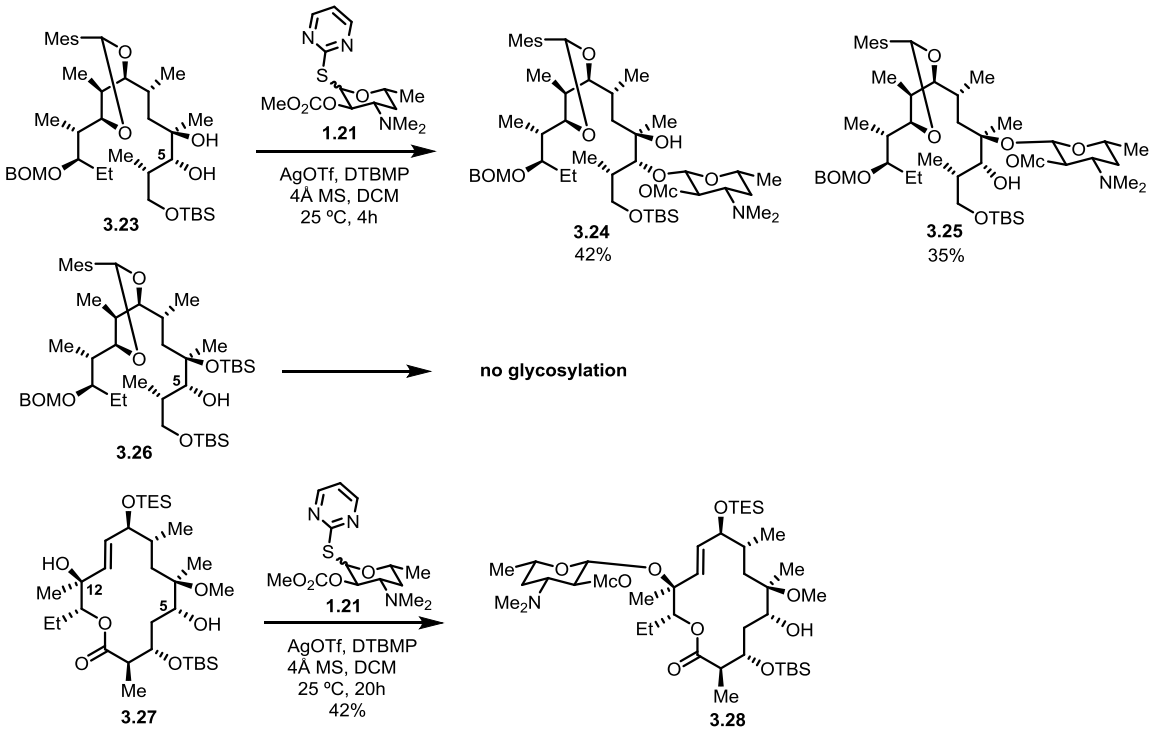



**Scheme 3.8** Glycosylation of erythronolide triol **3.22**.

Site-selectivity was found to be poor. When triol **3.22** was treated with sulfoxide donor **3.17**, a mixture of glycosides resulted. Data from mass spectrometry suggest presence of both mono-glycosylated and bis-glycosylated species, meaning that in addition to the desired C5 alcohol, C6 and/or C12 alcohols were also attached with desosamine. This finding is in contrast to reports by Woodward[1], Toshima[2] and Martin[3] (e.g. Scheme 3.1),

which described excellent site-selectivity when tetraols and triols were glycosylated with thioglycoside **1.21**.

Nevertheless, poor site-selectivities have been reported with the classic thioglycoside (**1.21**) in other related systems (Scheme 3.9).[14,15] According to Martin *et al.*, C5 glycoside **3.24** and C6 glycoside **3.25** were obtained in approximately 1:1 ration from diol **3.23** (Scheme 3.9).[14] Other glycosylation methods resulted in similar ratio of products, implying the poor selectivity is intrinsic to the substrate and is independent of methods of glycosylation. Protection of C6 alcohol with TBS ether (**3.26**), an attempt to improve selectivity, was found to prevent any glycosylation at C5.

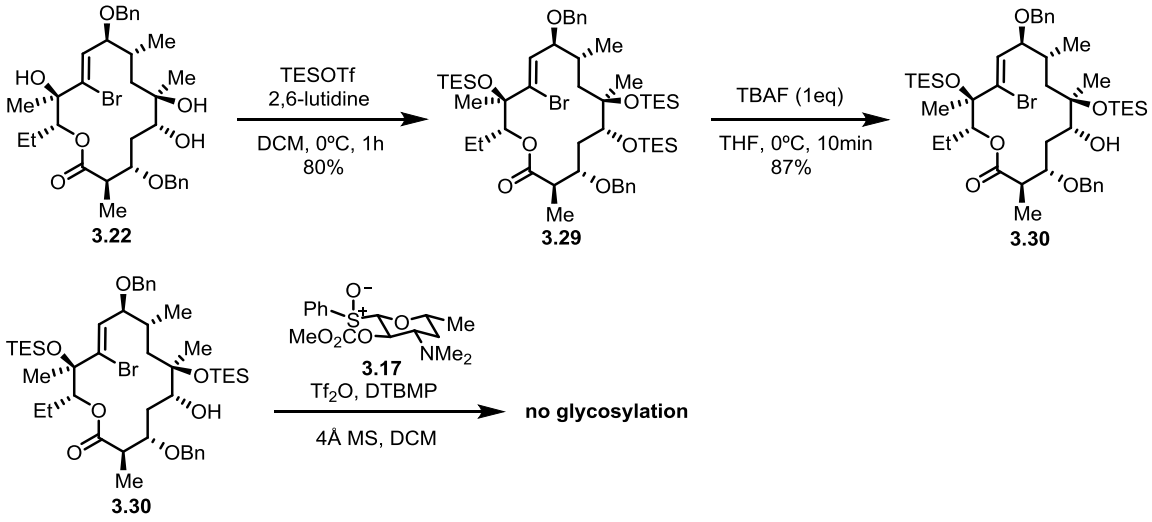



**Scheme 3.9** Poor site-selectivity with thioglycoside donor **1.21**.

In a synthesis of modified telithromycin,[15] the Andrade group reported exclusive glycosylation of a tertiary alcohol (C12) in the presence of a secondary alcohol (C5). This

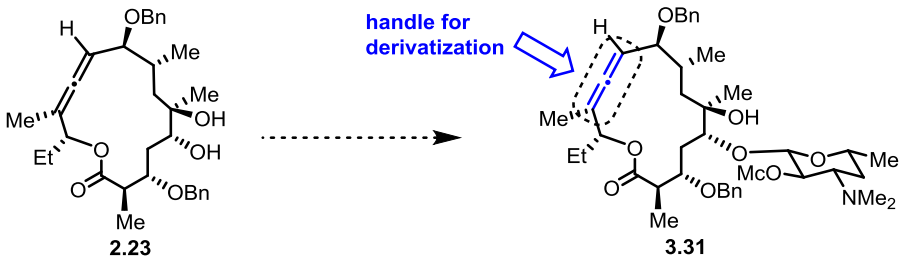
perplexing selectivity can be attributed to steric hindrance around C5 alcohol (C3 TBS ether and C6 methyl ether) and to relatively high nucleophilicity of allylic alcohol at C12.

To achieve exclusive glycosylation at C5, alcohols at C6 and C12 were protected (Scheme 3.10). To accomplish this, all three alcohols of **3.22** were initially masked as triethylsilyl ether. Selective cleavage of the C5 TES ether, which was derived form a secondary alcohol, delivered mono-alcohol **3.30** in excellent yield. However no glycosylation was observed for **3.30**, possibly due to hindrance posed by the neighboring C6 TES ether.



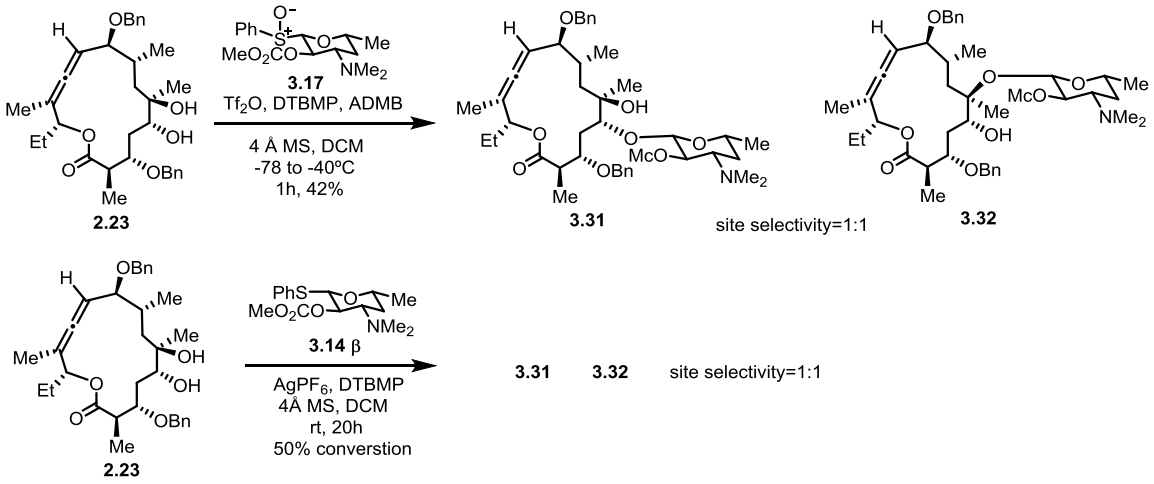

**Scheme 3.10** Attempted glycosylation of C5 alcohol **3.30**.

Our attention next turned to **2.23**, which was previously shown to elude glycosylation under the classic thioglycoside condition (possibly due to Lewis acid-promoted decompositions, see discussion in Scheme 3.2).[2,5] The resulting glycoside **3.31** would be an invaluable intermediate since the embedded allene could serve as a branching point to access various analogs (Scheme 3.11).



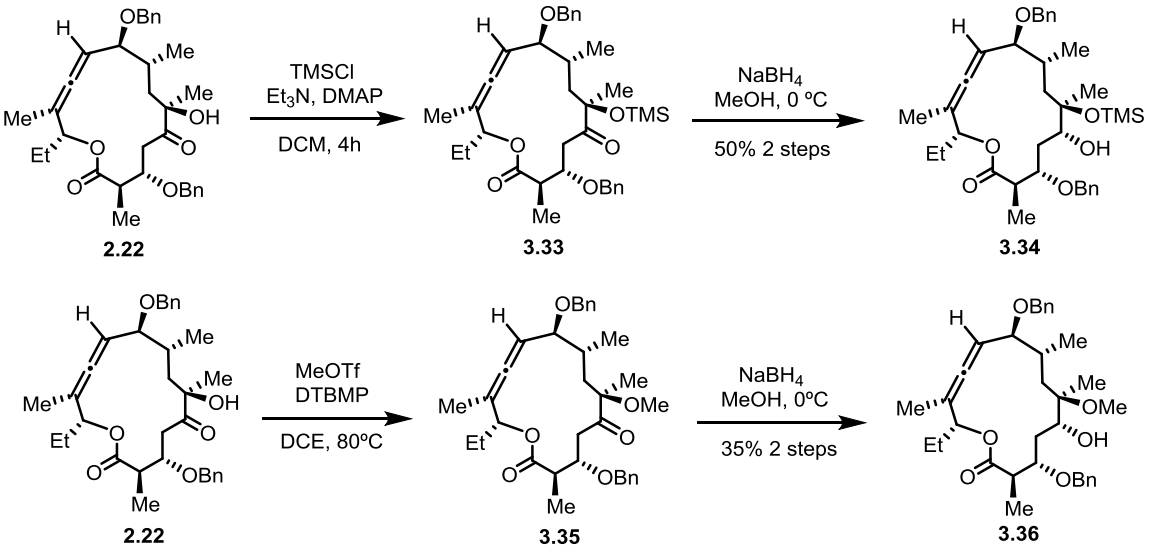

**Scheme 3.11** Glycoside **2.31**, housing a versatile allene, could be readily derivatized.

Glycosylation of diol **2.23** with sulfoxide **3.17** afforded a 1:1 mixture of C5 and C6 glycosides (Scheme 3.12, c.f. Scheme 3.9). Glycosylation with thioglycoside **3.14**, albeit slower and stopped prior to full-conversion, resulted in essentially the same site-selectivity.




**Scheme 3.12** Glycosylation of allenic diol **2.23** resulted in poor site-selectivity.

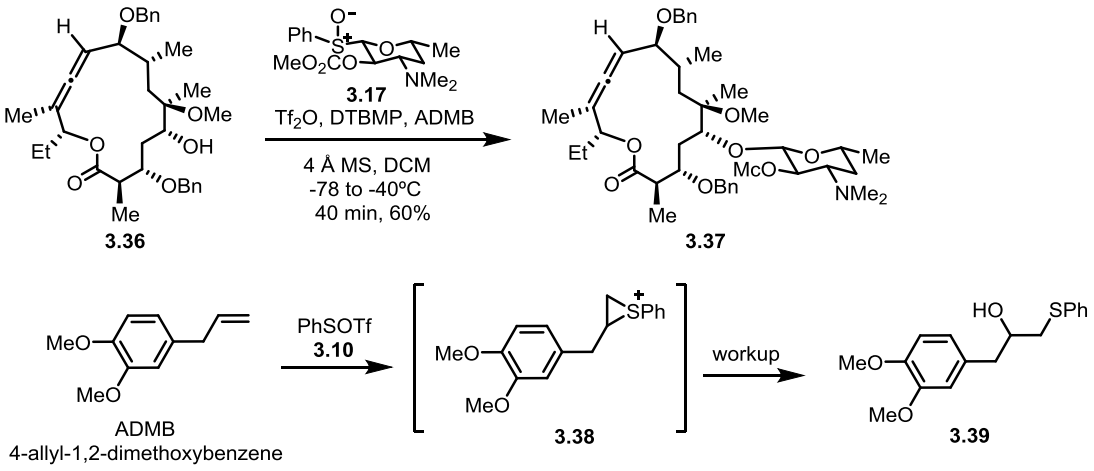
To tackle the problem of poor site-selectivity, I prepared two analogs with protected C6 alcohols (Scheme 3.13). The first compound C6 TMS ether **3.34** required protection with trimethylsilyl cholride followed by reduction with sodium borohydride.[16] The methylation at C6, used to synthesize the second desired analog, required forcing reaction conditions (excess amount of methyl triflate at 80 ºC). Formation of multiple minor products was observed during methylation and the desired C5 alcohol **3.36** was obtained, after reduction, in a moderate yield (35%). Other methylating reagents (methyl iodide, dimethyl sulfate and Meerwein's salt[17]) failed to alkylate this inert tertiary alcohol. Methylation at C6 may be advantageous, as this modification is known to enhance pharmacokinetic properties of erythromycin-derived antibiotics (Chapter 1.1).




**Scheme 3.13** Protection of C6 alcohol with TMS ether (**3.34**) and methyl ether (**3.36**).

Whereas the TMS ether **3.34** resisted glycosylation (likely due to steric hindrance), gratifyingly the methyl ether **3.36** was converted to a single glycoside **3.37** in 60% yield (Scheme 3.14). ADMB (4-allyl-1,2-dimethoxybenzene) was identified as a crucial

additive, as in its absence, **3.37** was isolated in lower yield (30%) and accompanied by formation of several side-products. ADMB, a non-volatile alkene that can be azeotroped prior to use, was employed by Kahne *et al.* as an efficient scavenger of the reactive phenylsulfenyl triflate **3.10** (see Scheme 3.4 for origin of **3.10**).[18]




**Scheme 3.14** Efficient glycosylation of cyclic allene **3.36**.

Pleasingly, this valuable intermediate (**3.37**) was selectively fashioned in 15 steps (LLS) from commercial reagents and in only 4 steps from our common intermediate **2.1**.

### 3.4. Conclusion

In summary, a novel sulfoxide desosamine donor **2.17** was prepared and successfully deployed to glycosylate erythronolides under mild conditions at low temperature. Major hurdles associated with labile substrates (those that react with strong Lewis acids) and with poor site-selectivity have been circumvented. Glycosylated cyclic allenes (e.g. **3.37**), derived in 4 steps from common intermediate **2.1**, should be well-poised for further

elaboration by exploiting rich reactivity of the embedded allene. As a general tool for incorporation of desosamine, sulfoxide donors **3.17** should aid synthesis of other macrolides and glycoconjugates.

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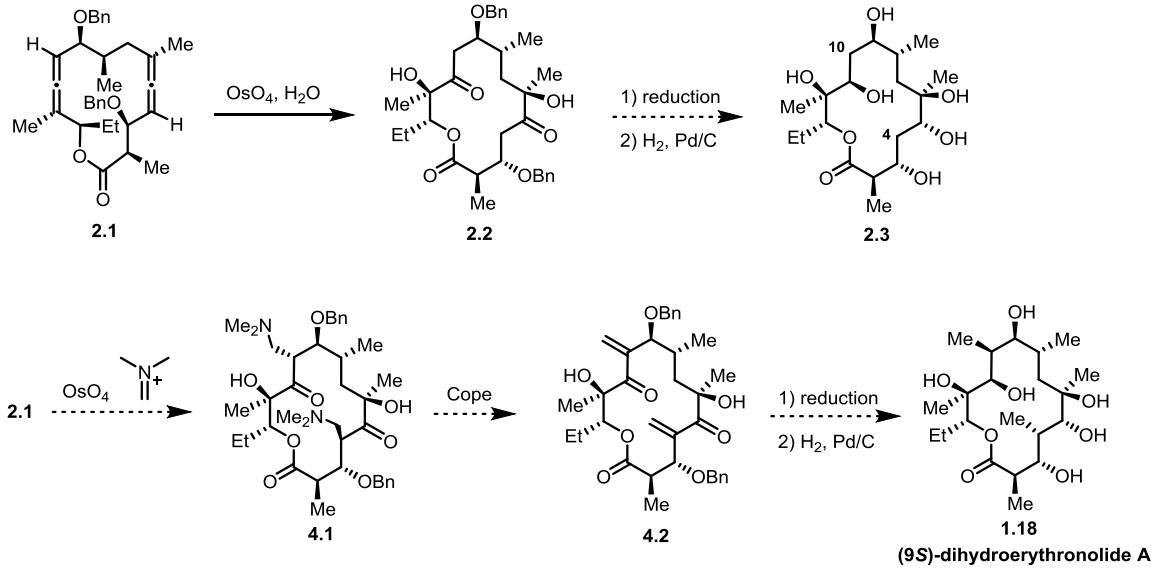
# Chapter 4 Progress Towards Synthesis of (9*S*)-Dihydroerythronolide A

## 4.1. Introduction

Chapter 2 includes a description of a concise total synthesis of cyclic polyketide 4,10-didesmethyl-(9*S*)-dihydroerythronolide A (**2.3**). According to the original plan, diketone **2.2**, derived from double-osmylation of the versatile intermediate **2.1**, would lead to target **2.3** (Scheme 4.1). At the same time, it had not escaped our attention that (9*S*)-dihydroerythronolide A (**1.18**), a most popular synthetic target among the erythronolides, could potentially be accessed expeditiously from bis-allene **2.1** (Scheme 4.1).

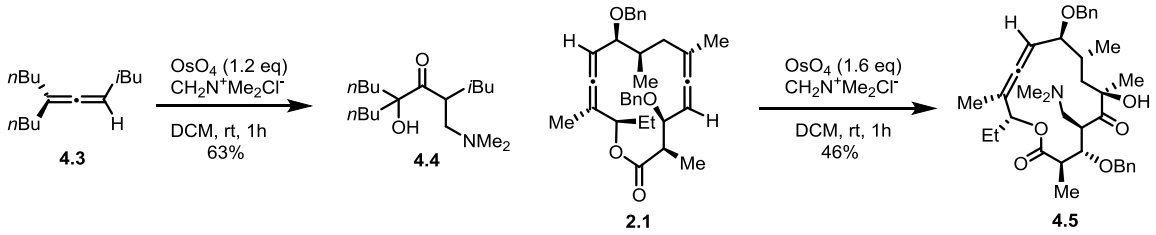



**Scheme 4.1** Outline for a proposed total synthesis of (9*S*)-dihydroerythronolide A (**1.18**).

As proposed in Scheme 4.1, bis-allene **2.1** would be oxidized with osmium tetroxide, and the resulting intermediate would trap Eschenmoser's salt to afford diamine **4.1**. *N*-oxidation and the Cope elimination[2] would provide bis-enone **4.2**, which would be

selectively reduced and deprotected to furnish the target (**1.18**). This concise sequence could culminate in the shortest, and the only flexible route to this classic target.

Partial feasibility of the proposed synthesis has been established by my colleague Dr. Kai Liu (Scheme 4.2).[1] In his studies pertaining to the allene osmylation/electrophile capture cascade methods (*c.f.* Scheme 2.7), Kai successfully incorporated immium salts into linear allenes (e.g. **4.3**) to give tertiary amines **4.4**. Under the same conditions, cyclic bis-allene **2.1** was found to yield mono-amine **4.5**; the site-selectivity is in accord with the previous finding that the C4-C6 allene is more reactive than the C10-C12 allene (*c.f.* Scheme 2.8). To advance this route, the next step aimed to oxidizing the less reactive allene at C10-C12.

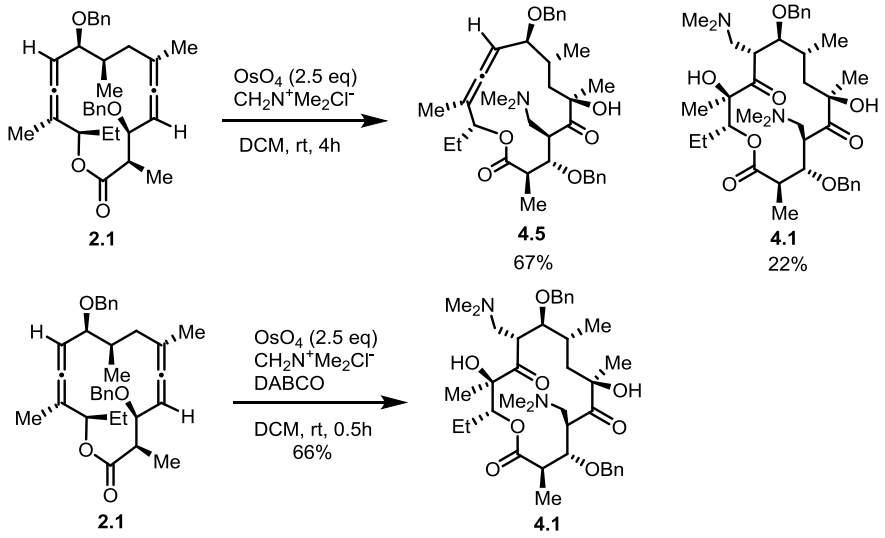



**Scheme 4.2** Osmylation/electrophile capture cascade to tertiary amines.

## 4.2. Preliminary efforts towards (9*S*)-dihydroerythronolide A

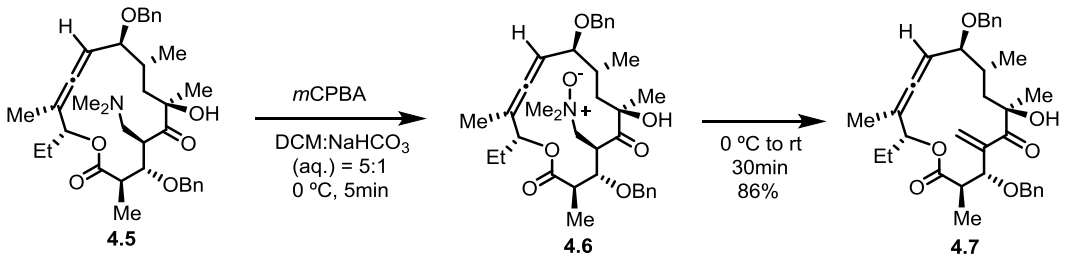
In view of the available data, the immediate task was to oxidize the C10-C12 allene of **2.1**, therefore to access the desired diamine (**4.1**). To this end, bis-allene **2.1** was treated with excess $OsO_4$ (2.5 equiv) in presence of immium salts (Scheme 4.3). Although mono-amine **4.5** (67% yield) was again found to be the major product, the desired diamine (**4.1**) was isolated (22% yield). DABCO was found to drastically accelerate the reaction,

offering diamine **4.1** as the major product (66% yield). Using the same conditions, mono-amine **4.5** was converted to diamine **4.1** with ease.



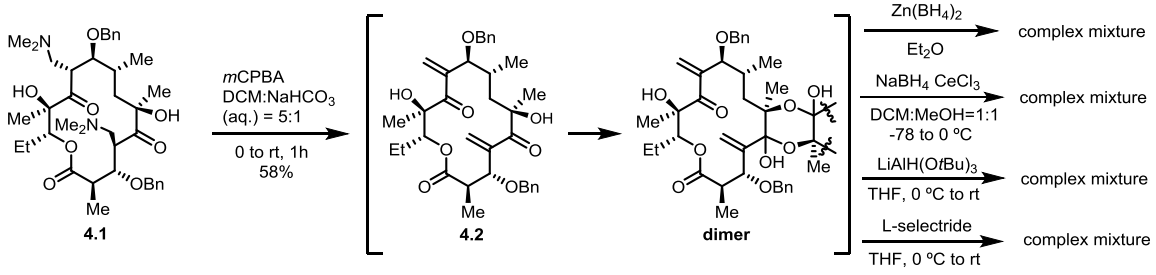

**Scheme 4.3** Osmylation/electrophile capture cascade to give diamine **4.1**.

To our delight, the subsequent Cope elimination of the macrocyclic amines was facile (Scheme 4.4). When tertiary amine **4.5** was exposed to *m*CPBA at 0 ºC, clean conversion to the corresponding *N*-oxide (**4.6**) was observed, followed by smooth eliminations as the reaction mixture warmed to room temperature. The resulting enone (**4.7**) appeared to deviate from canonical conjugated enones, as evidenced by chemical shifts of $^{1}$H NMR (enone H 5.7-5.8 ppm) and infrared spectroscopy (ketone frequency at 1698 cm$^{-1}$). We surmised the conformational constraints imparted by the cyclic allene rendered the enone partially out of conjugation.



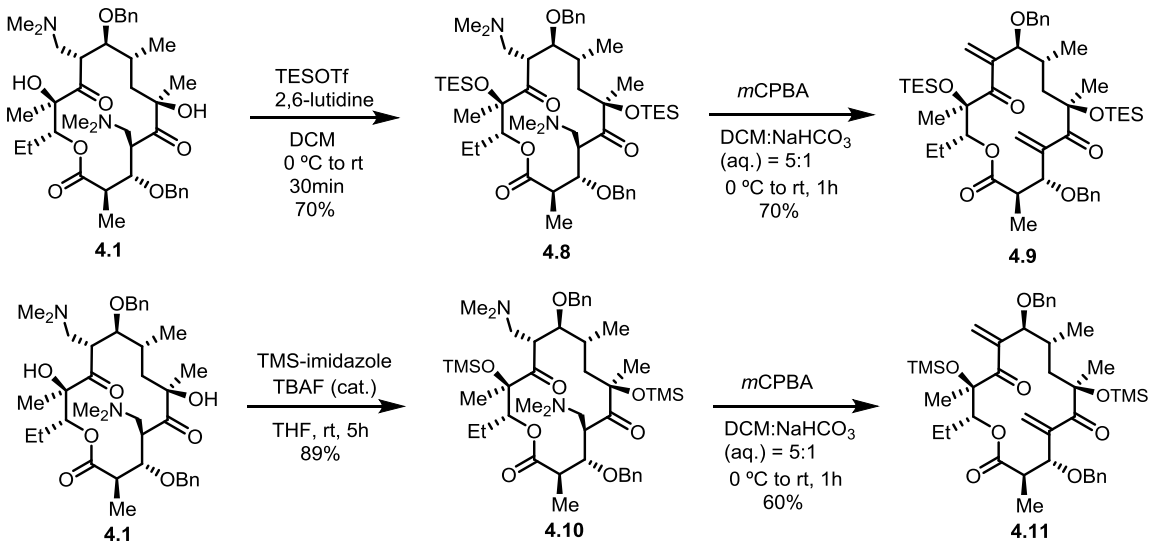

**Scheme 4.4** Facile Cope elimination to give enone **4.7**.

Surprisingly, when diamine **4.1** was subjected to the Cope elimination conditions, the corresponding enone (**4.2**) was isolated in an apparent dimeric form (apparently as hemiketals), the presence of which is supported by mass spectrometry (a dominant peak indicating the dimer) and $^{13}C$ NMR (only one ketone signal observed). $^{1}H$ NMR chemical shifts (enone H 6.1-6.2 ppm) and infrared spectroscopy (ketone frequency 1657 $cm^{-1}$) implicated a canonical conjugate enone. Interestingly, when **4.2** was treated with TMS chloride, monomeric **4.11** (see Scheme 4.6) was obtained; this suggested the dimerization is reversible and the dimeric form served as a reservoir for the monomeric form. However, even after extensive study, complex mixtures were invariably obtained under reducing conditions, led us to abandon **4.2** as a possible synthetic intermediate *en route* to the erythronolide target.




**Scheme 4.5** Bis-enone **4.2** was in a dimeric form that eluded selective reductions.

The elusive behavior **4.2** exhibited under various reduction conditions is possibly associated with complications caused by the dimeric form. To suppress formation of dimers, the two tertiary alcohols of **4.1** were protected as triethylsilyl (TES) ethers, and Cope elimination followed to give protected enone **4.9** with no evidence of dimer formation (Scheme 4.6). In anticipation of the likely hindrance to reductions caused by the bulky TES ethers, a smaller trimethylsilyl analog (**4.11**) was fashioned in a similar sequence. However **4.9** and **4.11** turned out to be nearly identical based on spectroscopy data and reactivity towards various reducing reagents. The following discussions will focus on TES protected bis-enone **4.9**.



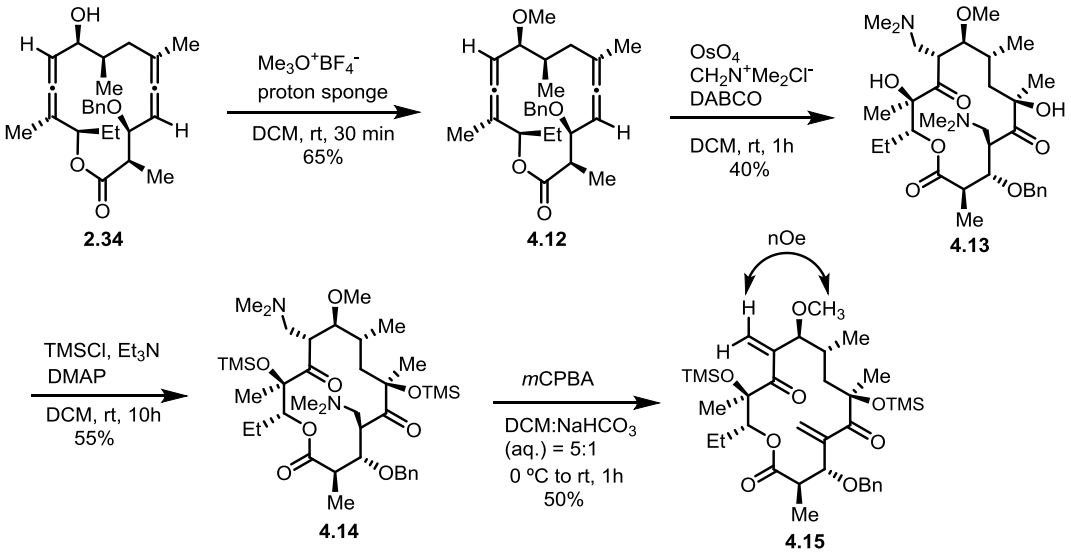

**Scheme 4.6** Synthesis of silyl ether protected bis-enone **4.9** and **4.11**.

### 4.3. NMR assignment of a key bis-enone intermediate

Before embarking on reductions of bis-enone **4.9**, additional information was required to preempt any problems caused by the highly symmetrical structure of **4.9**. For instance, if

only one ketone was found to be reduced, it could be very difficult to identify unambiguously the site of reduction. However by previously assigning the enone NMR signals to their respective positions in **4.9**, the reaction sites should be assigned based on which signals were consumed after the reduction.

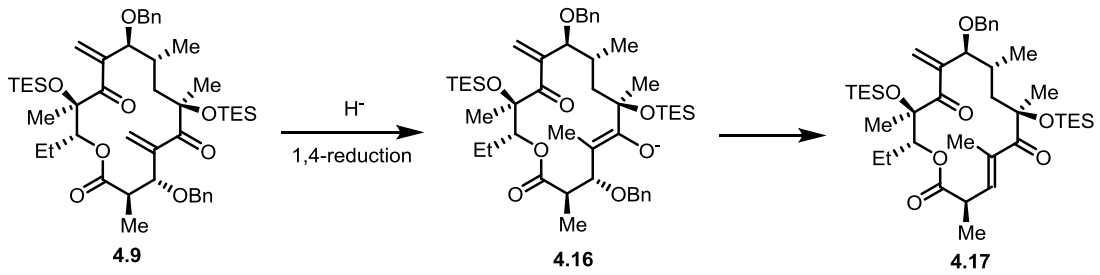
We reasoned a C9 methylether (**4.15**) would facilitate assignment of the NMR signals. The C9 alcohol **2.34**, prepared from DDQ oxidation of **2.1** (Scheme 2.14), was smoothly methylated with Meerwein's salt.[3] The resulting methyl ether (**4.12**) was converted to diamine **4.13**, which was then protected and treated with *m*CPBA to afford **4.15**. The C9 methyl group was selectively irradiated in an 1D nOe experiment; the enone signals that exhibited enhancement were assigned to the C10 alkene; the signals that remained silent were assigned to the C4 alkene. These assignments were corroborated by other nOe correlations, such as the one between the C4 enone proton and the C2 proton.




**Scheme 4.7** Synthesis of 9-methoxy bis-enone **4.15** and a key nOe correlation.

### 4.4. Progress towards (9*S*)-dihydroerythronolide A

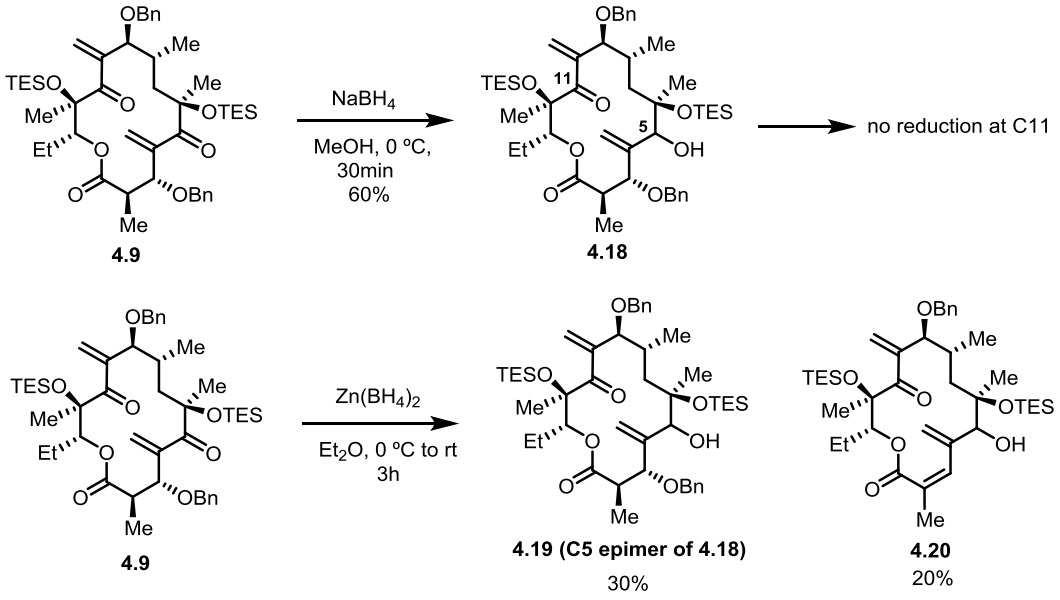
The stage was thus set for reductions of bis-enone **4.9**. Preliminary results obtained with 1,4-reducing reagents (e.g. L-selectride) were not encouraging (Scheme 4.8). β-elimination of the benzyl ethers was a liability via enolate intermediate **4.16** (yield of enone **4.17** was not determined due to difficulty of purification). Moreover, preliminary experiments with catalytic hydrogenation conditions also led to complex mixtures that included, for example, diastereomeric mixtures that lacked the benzyl ether group. Therefore my efforts were focused on 1,2-hydride reduction conditions. Even with these reductants, major obstacles arose.




**Scheme 4.8** Delivery of hydride in a conjugate fashion led to β-elimination.

The first obstacle was associated with low reactivity of the C11 ketone (Scheme 4.9). For instance, when bis-enone **4.9** was treated with sodium borohydride at 0 ºC the C5 ketone was rapidly reduced to alcohol **4.18** (dr > 5:1); however, excess reducing reagents did not result in any noticeable further conversion of **4.18** at room temperature, whereas at elevated temperature a complex mixture was obtained. Zinc borohydride converted bis-enone **4.9** to the C5-anomer (**4.19**), accompanied by formation of a side product **4.20**, which lost the benzyl ether at C3. To date the C11 ketone remains intact under multiple

reducing conditions (e.g. $NaBH_4$, $NaBH_4/CeCl_3$, $Zn(BH_4)_2$, $LiAlH(OtBu)_3$); its inert reactivity is likely traceable to the conformational constraints within this cyclic bis-enone.

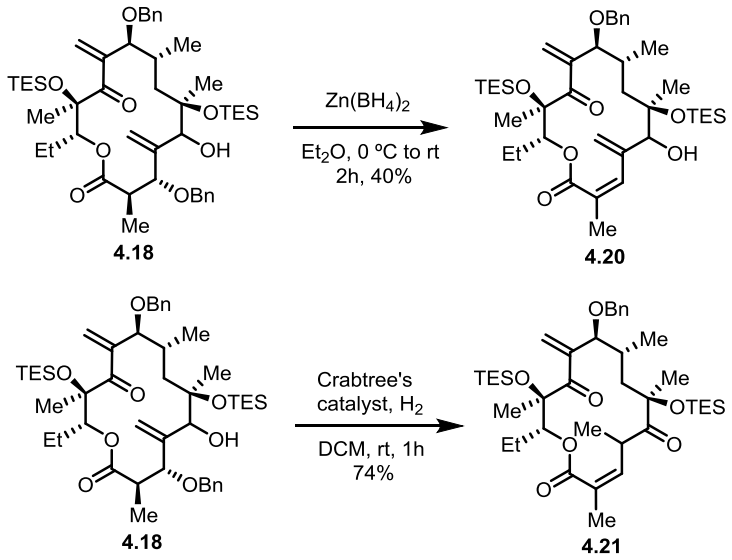



**Scheme 4.9** Reduction of bis-enone **4.9** only took place at C5.

The stereochemistry of C5 was not determined at this stage because the proton at C5 is an isolated spin-system flanked by the C6 quaternary center and the alkene at C4. Without additional information, unequivocal determination of stereochemistry at C5 is difficult. Nevertheless, the stereochemistry could be elucidated in later stages by comparison with spectra available in literature or by correlation with degradation products of commercial erythromycin A.

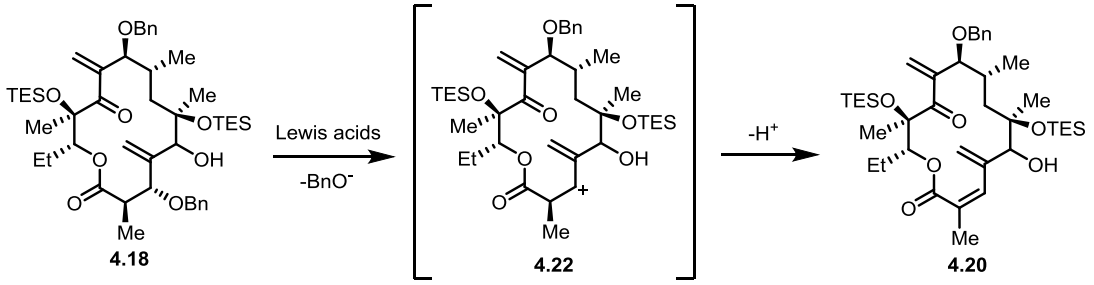
As shown in the reduction using zinc borohydride (Scheme 4.9), we found a second major hurdle: the C3 benzyl ether is highly prone to elimination. This hurdle was made apparent when **4.18**, the initial product from sodium borohydride reduction, was treated with zinc borohydride. Enone **4.20** was isolated as the main product (Scheme 4.10).

Moreover, in an attempt to hydrogenate **4.18** with the Crabtree's catalyst,[4] rapid conversion to a single enone species **4.21** was observed. Again the C3 benzyl ether was eliminated, and the C5 alcohol was isomerized back into the C-5 ketone. The Crabtree's catalyst is known to catalyze isomerization of allylic alcohols to ketones or aldehydes, as well as to convert exocyclic alkenes to endocyclic alkenes.[5,6]



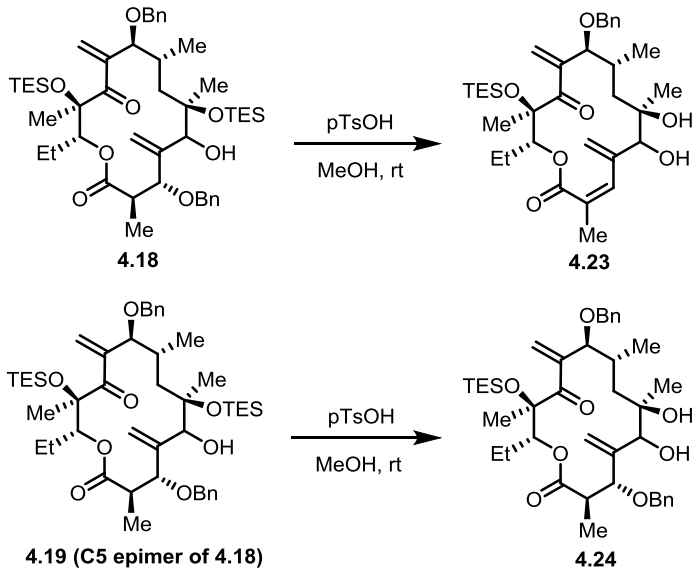

**Scheme 4.10** Elimination of benzyl ether at C3.

A suitable mechanistic framework for the formation of **4.20** is to consider a Lewis acid-mediated pathway (Scheme 4.11). Lewis acids, e.g. zinc and iridium salts in the aforementioned cases, could promote ionization of **4.18** to allylic carbocation **4.22**, which upon deprotonation gives the product (**4.20**). Intriguingly, the tendency to eliminate appears linked to the stereochemistry of the C5 alcohol. Under zinc borohydride conditions, whereas **4.18** readily underwent elimination; its C5 epimer (**4.19**) remained intact.



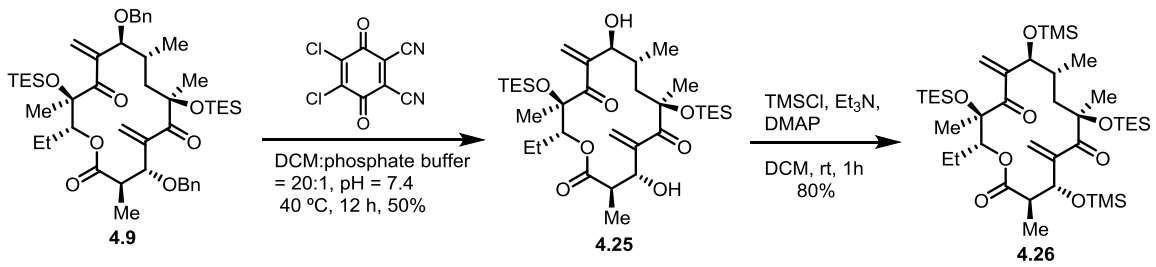

**Scheme 4.11** Elimination of benzyl ether promoted by Lewis acid.

Elimination of the benzyl ether was also observed in the presence of a Bronsted acid (Scheme 4.12). Toluenesulfonic acid was found to effect elimination and cleavage of the TES ether at C6 of **4.18**. The presence of the TES group at C12 of **4.23** was supported by nOe correlations between the methylene protons of TES and the C10 alkene protons. The apparent dependence of elimination propensity on the C5 stereochemistry was recapitulated as the C5 epimer (**4.19**) lost a TES group while eluded elimination at C3.



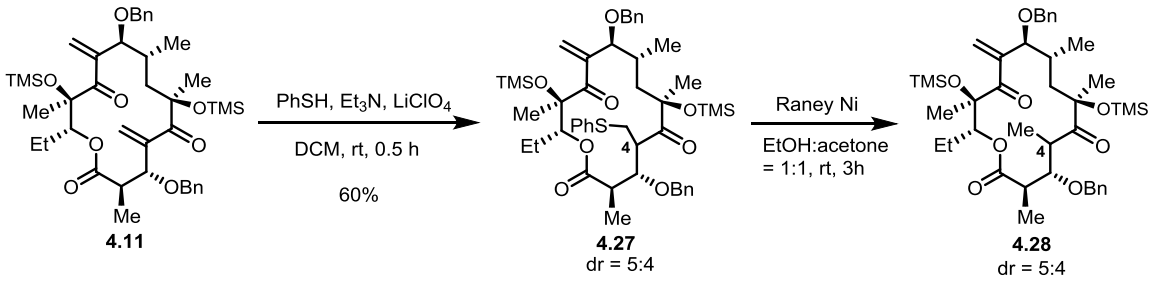

**Scheme 4.12** Elimination of benzyl ether promoted by a Bronsted acid.

We posited that conversion of the benzyl ether to an alcohol or silyl ether could prevent the elimination, as these changes are expected to dampen acid-induced ionization (Scheme 4.13). To this end, the benzyl groups of **4.9** were removed with DDQ to afford 3,9 diol **4.25**, which was masked with TMS chloride to yield **4.26**. Unfortunately, both of the newly prepared analogs invariably resulted in complex mixtures under standard reduction conditions, for example $NaBH_4$ and $Zn(BH_4)_2$.




**Scheme 4.13** Preparation of 3,9-diol **4.25** and bis-TMS ether **4.26**.

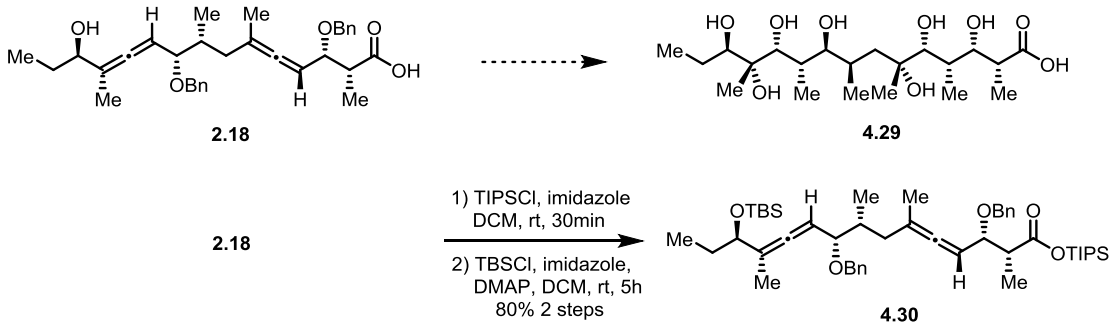
As illustrated in Scheme 4.14, a formal conjugate-reduction approach was also pursued. Lithium perchlorate promoted thiophenol addition to **4.11** to yield sulfide **4.27** as an inseparable mixture of epimers at C4 (dr=5:4), whereas conditions employing thio-radicals did not result in any conversion of **4.11**. As another testament to the inert nature of the C10 enone, addition of a second thiophenol was not observed, even under harsh conditions that induced rapid decomposition. Raney Nickel desulfurized **4.27** to afford the formal 1,4-reduction product (**4.28**), again as an inseparable mixture of C4 epimers.




**Scheme 4.14** A formal conjugate-reduction with thiol-addtion/desulfurization sequence.

## 4.5. Alternative route using a linear bis-allene

An alternative route has been tested using linear bis-allene **2.18**, which could be elaborated with osmylation and reductions to give **4.29**, the seco-acid of (9*S*)-dihydroerythronolide A (Scheme 4.15). A doubly protected bis-allene **4.30**, prepared expeditiously from **2.18**, was used for subsequent studies.

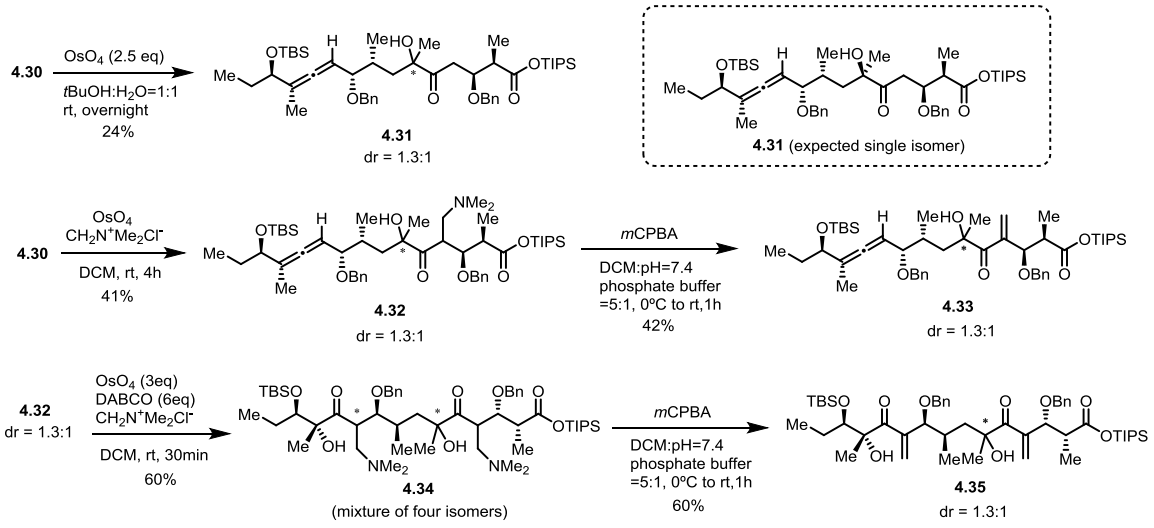



**Scheme 4.15** Synthesis of erythronolide seco-acid **4.29** from linear bis-allene **4.18**.

Studies on the linear allene **4.30** were summarized in Scheme 4.16. When **4.30** was exposed to OsO4 in *t*BuOH/$H_2O$, a mixture of epimers at C6 (dr=1.3:1) was obtained (24% yield). The poor stereoselectivity was surprising in view of our previous studies (*c.f.* Scheme 2.7), in which $OsO_4$ addition to linear allenes exhibited excellent face-selectivity.

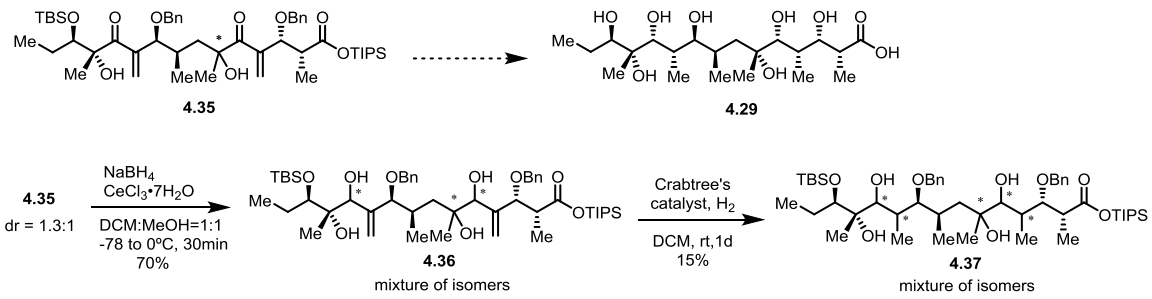
While we suspect the directing effect of the ester may influence face-selectivity of $OsO_4$ addition, we have not arrived at a satisfactory explanation. Under the same condition (Scheme 2.8), osmylation of the cyclic bis-allene **2.1** gave a single isomer in one hour (84% yield). We surmise the reactivity of **2.1** was elevated by ring-strain of the macrolactone, whereas the intrinsic stereoinduction of the allene in **2.1** was reinforced by the ring.

Amine **4.32** was isolated as a mixture of isomers (dr=1.3:1), and *N*-oxidation followed by Cope elimination afforded the enone **4.33** (dr=1.3:1). DABCO was found to promote osmylation of **4.32** to yield diamine **4.34** as a mixture of four stereoisomers, which were converted to bis-enone **4.35** (dr=1.3:1).




**Scheme 4.16** Reactions of linear bis-allene **4.30**.

Preliminary experiments with bis-enone **4.35** (dr=1.3:1) established partial feasibility of preparing seco-acid **4.29** (Scheme 4.17). Both of the ketones in **4.35** were rapidly reduced with $NaBH_4/CeCl_3$ to the tetraol **4.36**, which was hydrogenated with Crabtree's catalyst to give protected seco-acid **4.37**.




**Scheme 4.17** Further steps to seco-acid **4.29**.

These preliminary results bode well for completion of synthesis. One hurdle remained - most of the intermediates were mixtures of inseparable isomers. Fortunately, the two C6 epimers of amine **4.32** were separable by standard silica gel flash chromatography; therefore each purified epimer could then be converted to bis-enone **4.35** (as a single isomer). The stereochemistry of **4.37** could be elucidated by comparison with samples derived from natural sources.

## 4.6. Conclusion

A novel C-C bond forming osmylation-electrophile capture method was successfully implemented in complex settings (*e.g.* bis-allene **2.1**). The synthesis of (9*S*)-dihydroerythronolide A (**1.18**) was pursued; advanced intermediates (*e.g.* **4.18** and **4.28**) were fashioned from common bis-allene intermediate **2.1** within 5 steps.

The remaining challenges include (1) the low reactivity of the C11 ketone of **4.9** and (2) the facile elimination of benzyl ether at C3. Based on the osmylation-electrophile capture cascade, a synthesis of seco-acid **4.29** has been initiated from linear bis-allene **4.30**.

**References:**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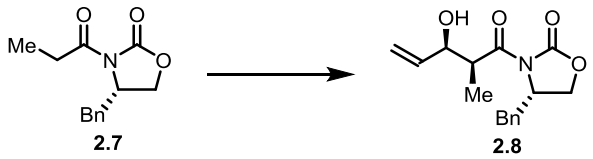
2. Cope, A. C.; Ciganek, E. "Methylenecyclohexane and *N,N*-Dimethylhydroxylamine Hydrochloride". *Organic Syntheses*, **1963**, *4*, 612.
3. Meerwein, H.; Hinz, G.; Hofmann, P.; Kroning, E.; Pfeil, E. *Journal für Praktische Chemie* **1937**, *147*, 257.
4. Crabtree, R.; Felkin, H.; Morris, G. *J. Organomet. Chem.* **1977**, *141*, 205.
5. Crabtree, R. (1,5-Cyclooctadiene)(tricyclohexylphosphine)(pyridine)iridium(I) Hexafluorophosphate. *e-EROS Encyclopedia of Reagents for Organic Synthesis* **2001** doi:10.1002/047084289X.rc290m
6. Krel, M.; Lallemand, J. Y.; Guillou, C. *Synlett* **2005**, 2043.

# Chapter 5 Experimental Data

## 5.1. General Procedure

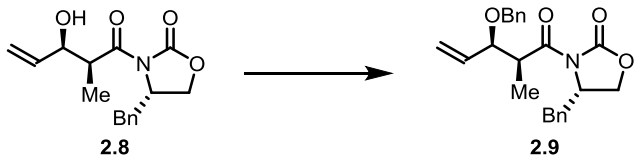
Starting materials, reagents and solvents were purchased from commercial suppliers (Aldrich, Alfa-Aesar, Acros, Strem) and used without further purification unless otherwise stated. All reactions were conducted under an inert atmosphere of argon. The progress of reactions was monitored by silica gel thin layer chromatography (TLC) plates (thickness 250 μm with F-254 indicator), visualized under UV and charred using anisaldehyde, potassium permanganate or ceric ammonium molybdate (CAM) stain. Products were purified by flash column chromatography (FCC) on 60 Å, 230-400 mesh silica gel (Aldrich). Infrared (FTIR) spectra were recorded on an ATI Mattson Genesis Series FTIR spectrophotometer. 1D-proton nuclear magnetic resonance spectra ($^{1}$H NMR) and 1D-carbon nuclear magnetic resonance spectra ($^{13}$C NMR) were recorded on either a Varian-500 instrument (500 MHz) or a Varian-400 instrument (400MHz). Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) as the internal standard. Data is reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet) and coupling constant (Hz). 1D-NOE and 2D-Nuclear magnetic resonance spectra were recorded on a Varian-600 instrument (600 MHz). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. Optical rotations were recorded at room temperature using the sodium D line (589 nm), on a JASCO P-2000 Polarimeter.

## 5.2. Chapter 2



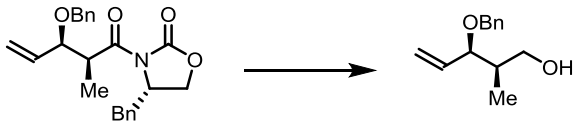

**2.7** **2.8**

The oxazolidinone **2.7** (10.13 g, 43.4 mmol) was dissolved in 120 mL anhydrous DCM cooled to 0 ºC. *n*$Bu_2$BOTf (52 mL of 1M solution in DCM) was added slowly followed by slow addition of *i*$Pr_2$NEt (10.5 mL, 60.1 mmol). After stirring for 10 min, the solution was cooled to -78 ºC before a solution of acrolein in DCM (5 mL acrolein dissolved in 15 mL anhydrous DCM, 67.4 mmol) was added over 5 min. The solution was stirred at -78 ºC for 30 min, then changed to ice bath and stirred for 1h before pH = 7.4 aqueous phosphate buffer (60 mL) and MeOH (200 mL) were added. 200 mL 2 : 1 mixture of MeOH and 35% aq. $H_2O_2$ was then added slowly over 10 min. The stirring was continued at 0 ºC for a further 20 min before the mixture was concentrated under reduced pressure to remove most of the $CH_2Cl_2$ and MeOH. The residue was partitioned between $Et_2O$ (300 mL) and water (300 mL). The aqueous layer was extracted with $Et_2O$ (2 × 300 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (200 mL), brine (200 mL), then dried with $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel (30% EtOAc in hexanes) to afford product **2.8** as white solid (12.1 g, 96% yield). For characterization data of this compound, refer to: Nicolaou, K. C. , et al. *Org. Biomol. Chem*. **2006**, *4*, 2119.



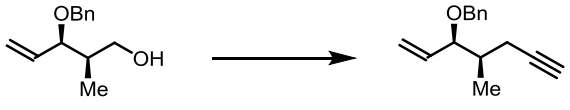

**2.8** **2.9**

Alcohol **2.8** (4.0 g, 13.8 mmol) and benzyl 2,2,2-trichloroacetimidate (5.0 g, 19.8 mmol) were dissolved in 70 mL anhydrous DCM. TMSOTf (0.25 mL, 1.38 mmol, 0.1 eq) was added slowly at 0 ºC. The reaction was stirred at 0 ºC for 2 h and was allowed to stir at room temperature for 2 h before quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with DCM (2 x 30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (10% ethyl acetate in hexanes) to afford **2.9** as white solid (3.14 g, 60 % yield) and recovered alcohol **2.8** (1.17 g). Melting point: 92-93 ºC (colorless crystal recrystallized from pentane/ether); $[\alpha]^{23}_{D}$ = +19.7 (c = 1.0, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 1780, 1699, 1384, 1210, 1096, 700; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.11 (10H, m), 5.84 (1H, ddd, *J* = 17.0, 10.7, 7.6 Hz), 5.35 – 5.23 (2H, m), 4.60 (1H, d, *J* = 12.1 Hz), 4.55 – 4.34 (1H, m), 4.32 (1H, d, *J* = 12.1 Hz), 4.17 – 3.91 (3H, m), 3.90 (1H, d, *J* = 8.6 Hz), 3.23 (1H, dd, *J* = 13.3, 3.1 Hz), 2.72 (1H, dd, *J* = 13.3, 9.7 Hz), 1.29 – 1.18 (3H, m) ; $^{13}$C NMR (126 MHz, $CDCl_3$) δ 174.6, 153.4, 138.6, 136.2, 135.6, 129.7, 129.2, 128.5, 128.2, 127.8, 127.5, 119.2, 81.0, 70.5, 66.2, 55.8, 42.5, 38.0, 12.9; MS (ESI+) calculated for $[C_{23}H_{25}NO_4 + Na]^+$: 402.2, found: 402.2.




**2.9** **2.10**

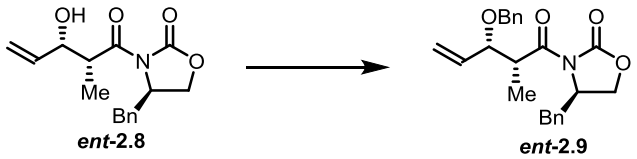
To a solution of **2.9** (4.10 g, 10.81 mmol) in anhydrous diethyl ether (75 mL) was added methanol (1.3 mL). $LiBH_4$ was added slowly under argon at 0 ºC. The solution was stirred at 0 ºC for 2 h then quenched with saturated aqueous $NH_4Cl$ (50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified with FCC (10% ethyl acetate in hexanes) to afford **2.10** as colorless oil (2.05 g, 92 % yield). $[\alpha]^{23}_D$ = -28.7 (c = 2.0, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 3384 (broad), 2930, 2876, 1454, 1029, 699; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.25 (5H, m), 5.86 (1H, ddd, *J* = 17.3, 10.4, 7.7 Hz), 5.39 – 5.25 (2H, m), 4.64 (1H, d, *J* = 11.9 Hz), 4.35 (1H, d, *J* = 11.9 Hz), 3.91 (1H, dd, *J* = 7.7, 4.4 Hz), 3.68 (1H, ddd, *J* = 11.3, 7.7, 4.3 Hz), 3.54 (1H, ddd, *J* = 10.9, 6.6, 4.4 Hz), 2.44 (1H, dd, *J* = 6.5, 4.6 Hz), 2.08 – 1.99 (1H, m), 0.91 (3H, d, *J* = 7.1 Hz). $^{13}$C NMR (126 MHz, CDCl3) δ 138.5, 136.0, 128.6, 127.9, 127.8, 119.0, 83.7, 70.6, 66.0, 39.8, 12.3; MS (ESI+) calculated for $[C_{13}H_{18}O_2 + Na]^+$: 229.1, found: 229.1.



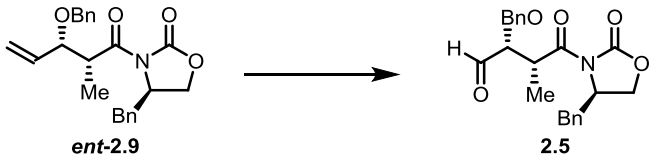

**2.10** **2.4**

Alcohol **2.10** (900 mg, 4.36 mmol) and DABCO (590 mg, 5.10 mmol) was dissolved in anhydrous DCM (20 mL). Tosyl chloride (920 mg, 4.83 mmol) was added in one portion

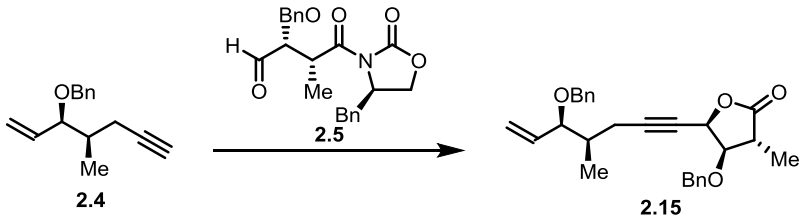
at 0 ºC. The ice bath was removed and the reaction was allowed to warm to rt over 30 min. The reaction was then diluted with DCM (30 mL) and washed with saturated $NH_4Cl$ (2 x 20 mL) and water (20 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude tosylate was dissolved in anhydrous DMSO (10 mL) under argon and the solution was cooled to 10 ºC. lithium acetylide-ethylenediamine (1.35 g, 13.2 mmol) was added slowly as a slurry in anhydrous DMSO (10 mL). The reaction was allowed to warm to rt and stirred 2.5 h at rt. The reaction was cooled to 10 ºC before carefully quenched with saturated aqueous $NH_4Cl$ (maintaining reaction internal temperature below 20 ºC). The quenched solution was diluted with ethyl acetate (150 mL), washed with water (3 x 80 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified with FCC (1.5 % ethyl acetate in hexanes) to afford **2.4** as colorless oil (654 mg, 70 % yield over 2 steps). $[\alpha]^{23}_D$ = -25.7 (c = 2.0, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 3305, 2972, 2931, 2869, 1090, 1028; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.23 (5H, m), 5.74 (1H, ddd, *J* = 18.0, 10.4, 7.7 Hz), 5.33 – 5.23 (2H, m), 4.59 (1H, d, *J* = 11.8 Hz), 4.34 (1H, d, *J* = 11.8 Hz), 3.78 – 3.71 (1H, m), 2.36 (1H, ddd, *J* = 16.7, 5.5, 2.7 Hz), 2.09 (1H, ddd, *J* = 16.7, 7.8, 2.6 Hz), 1.96 – 1.83 (2H, m), 1.07 (3H, d, *J* = 6.8 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 139.0, 137.1, 128.5, 127.9, 127.6, 118.6, 83.5, 83.2, 70.8, 69.6, 37.7, 22.5, 15.1; MS (ESI+) calculated for $[C_{15}H_{18}O + Na]^+$: 237.1, found: 237.1.




***Ent*-2.8** and ***ent*-2.9** were prepared following the same procedure used for the synthesis of **2.8** and **2.9** respectively. The observed optical rotation for *ent*-**2.9** is $[\alpha]^{23}_{D}$ = -19.7 (c = 1.0, $CHCl_3$).

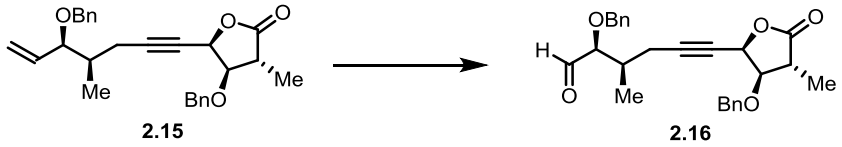



*Ent*-**2.9** (2.41 g, 6.35 mmol) was dissolved in 50 mL 3:1 mixture of dioxane and water. To this solution was added sequentially 2,6-lutine (1.50 mL, 13.0 mmol), osmium tetroxide (0.80 mL of 4% w/w water solution, 0.126 mmol) and sodium periodate (5.40 g, 25.3 mmol). The mixture was stirred at rt for 10 h then quenched with saturated aqueous $Na_2SO_3$ solution (20 mL) before diluted with DCM (100 mL) and water (100 mL). The organic layer was washed with 1 M aqueous $CuSO_4$ solution (3 x 50 mL) and then water (50 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure to afford the crude product as colorless oil. The crude product was used for next step in the synthesis without further purification. For complete characterization of the product **2.5**, refer to: Liu, K.; Kim, H.; Ghosh, P.; Akhmedov, N. G.; Williams, L. J. *J. Am. Chem. Soc.* **2011***, 133*, 14968.

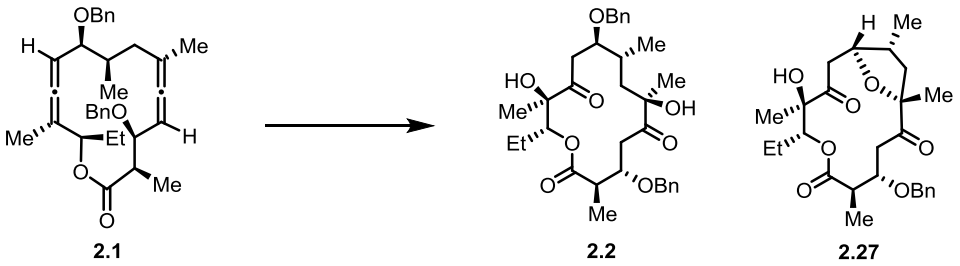



A solution of alkyne **2.4** (600 mg, 2.80 mmol) in anhydrous diethyl ether (20 mL) was cooled to -78 ºC and *n*BuLi (1.1 mL, 2.75 mmol) was added slowly. The reaction was stirred at -78 ºC for 1 h and then a solution of zinc bromide (700 mg, 3.10 mmol, dried at 160 ºC *in vacuo* overnight to obtain white $ZnBr_2$ powder ) in anhydrous diethyl ether (9 mL) was added. The resulting solution was stirred at -78 ºC for 10 min and then warmed to 0 ºC. A solution of aldehyde **2.5** (530 mg, 1.40 mmol, theoretical yield from *ent*-**2.9**) in anhydrous diethyl ether (10 mL) was added via syringe pump over 2 h. The solution was then stirred for 3 h before quenched with saturated aqueous $NH_4Cl$ (20 mL). The organic layer was diluted with ethyl acetate (100 mL) and washed with water (2 x 30 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product (dr = 8:1 by $^1H$ NMR) was purified with FCC (10 % ethyl acetate in hexanes) to afford major isomer of **2.15** as colorless oil (277 mg, 47 % yield over 2 steps from *ent*-**2.9**). $[\alpha]^{23}_D$ = +26.3 (c = 2.0, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2957, 2870, 1790, 1457, 1365; 1H NMR (500 MHz, CDCl3) δ 7.41 – 7.23 (10H, m), 5.77 – 5.66 (1H, m), 5.35 – 5.20 (2H, m), 5.13 (1H, dt, J = 6.3, 1.9 Hz), 4.74 – 4.46 (3H, m), 4.36 – 4.25 (1H, m), 3.88 (1H, dd, J = 9.5, 6.4 Hz), 3.79 – 3.66 (1H, m), 2.80 (1H, dq, J = 9.5, 7.1 Hz), 2.44 (1H, ddd, J = 16.8, 5.3, 2.1 Hz), 2.18 (1H, ddd, J = 16.8, 7.9, 2.0 Hz), 1.86 (1H, dd, J = 12.4, 6.8 Hz), 1.42 – 1.19 (3H, m), 1.05 (3H, d, J = 6.8 Hz); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 176.0, 138.9, 137.2, 136.9, 128.8, 128.7, 128.5, 128.4, 128.1, 127.8,

127.6, 118.8, 90.3, 83.2, 81.0, 72.3, 70.6, 70.6, 39.4, 37.6, 22.8, 15.2, 12.7; MS (ESI+) calculated for $[C_{27}H_{30}O_4 + Na]^+$: 441.2, found: 441.2.

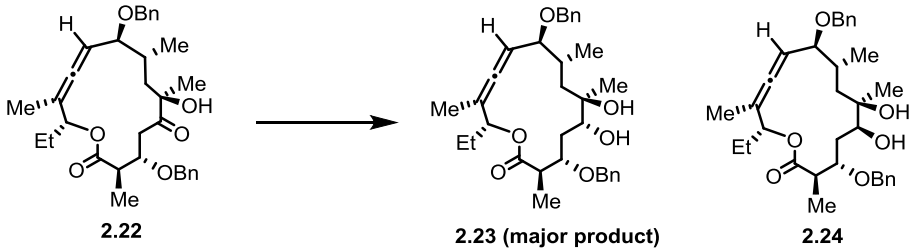



Alkene **2.15** (130 mg, 0.31 mmol) was dissolved in 4 mL 3:1 mixture of dioxane and water. To this solution was added sequentially 2,6-lutine (80 μL, 0.69 mmol), osmium tetroxide (80 μL of 4% w/w water solution, 12.6 μmol) and sodium periodate (270 mg, 1.26 mmol). The mixture was stirred at rt for 6 h then quenched with saturated aqueous $Na_2SO_3$ solution (5 mL) before diluted with DCM (20 mL) and water (20 mL). The organic layer was washed with 1 M aqueous $CuSO_4$ solution (3 x 10 mL) and then water (20 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure to afford the crude product as colorless oil. The crude product was used for next step in the synthesis without further purification. For complete characterization of the product **2.16** and subsequent conversion to **2.1**, refer to: Liu, K.; Kim, H.; Ghosh, P.; Akhmedov, N. G.; Williams, L. J. *J. Am. Chem. Soc.* **2011***, 133*, 14968.



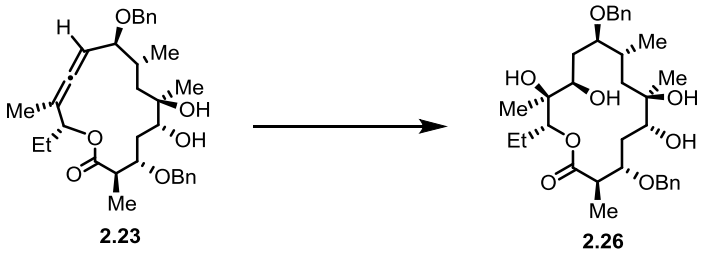

**2.1** was prepared in 4 steps from **2.16** (Liu, K.; Kim, H.; Ghosh, P.; Akhmedov, N. G.; Williams, L. J. *J. Am. Chem. Soc.* **2011***, 133*, 14968). Bis-allene **2.1** (11 mg, 0.022 mmol) was dissolved in 0.7 mL 1:1 mixture of *t*BuOH and water. NMO (5.2 mg, 0.043 mmol) and DABCO (0.5 mg, 4.4 μmol, added as 50 μL of 10 mg/mL stock solution in *t*BuOH) was added. The mixture was stirred for 5 min followed by addition of $OsO_4$ (3 μL of 4 % w/w solution in water, 0.47 μmol). The reaction was stirred at rt for 24 h before quenched with saturated aqueous $Na_2SO_3$ solution (1 mL) and diluted with water (5 mL). The mixture was extracted with diethyl ether (3 x 5 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified with FCC (15 % to 20% ethyl acetate in hexanes) to afford **2.2** as colorless oil (9.4 mg, 75 % yield) and bicycle **2.27** as colorless oil (1.5 mg, 15 % yield). **2.2**: $[\alpha]^{23}_{D}$ = +2.89 (c = 0.9, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2957, 2871, 1707, 1456, 1365, 1069; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (10H, m), 4.76 (1H, dd, *J* = 9.8, 2.7 Hz), 4.56 (2H, dd, *J* = 11.2, 8.3 Hz), 4.45 (2H, dd, *J* = 11.2, 5.9 Hz), 4.23 (1H, s), 3.97 (1H, ddd, *J* = 2.9, 3.8, 7.7 Hz), 3.90 (1H, ddd, *J* = 3.7, 4.5, 9.2 Hz), 3.47 (1H, s), 3.34 (1H, dq, *J* = 7.1, 9.2 Hz), 3.03 (1H, dd, *J* = 19.0, 4.5 Hz), 2.78 (1H, dd, *J* = 19.0, 3.7 Hz), 2.73 (1H, dd, *J* = 18.7, 7.7 Hz), 2.63 (1H, dd, *J* = 18.7, 3.9 Hz), 2.17 (1H, dd, *J* = 14.7, 9.3 Hz), 1.99 (2H, m), 1.55 (2H, m), 1.39 (3H, s), 1.30 (3H, d, *J* = 7.1 Hz), 1.19 (3H, s), 0.95-0.82 (6H, m); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 214.0, 212.9, 175.0, 138.1, 137.0, 128.6, 128.5, 128.3,

128.2, 127.9, 127.7, 78.9 (2), 78.7, 76.9, 75.8, 73.6, 72.4, 44.1, 42.0, 39.8, 39.1, 32.9, 28.1, 22.7, 18.3, 18.2, 16.0, 10.7; MS (ESI+) calculated for $[C_{33}H_{44}O_8 + Na]^+$: 591.3, found: 591.3. For complete characterization of the minor product bicycle **2.27**, refer to: Liu, K.; Kim, H.; Ghosh, P.; Akhmedov, N. G.; Williams, L. J. *J. Am. Chem. Soc.* **2011***, 133*, 14968.




**2.22** was prepared from **2.1** with osmium tetroxide (Liu, K.; Kim, H.; Ghosh, P.; Akhmedov, N. G.; Williams, L. J. *J. Am. Chem. Soc.* **2011***, 133*, 14968). Ketone **2.22** (24 mg, 0.045 mmol) was dissolved in 1.5 mL anhydrous MeOH. The solution was cooled to 0 ºC before sodium borohydride (5 mg, 0.13 mmol) was added. The reaction was stirred at 0 ºC for 30 min and quenched with saturated aqueous $NH_4Cl$ (2 mL). The mixture was extracted with DCM (3 x 5 mL) and the resulting organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product (dr = 6:1 by $^1$H NMR) was purified with FCC (20 % ethyl acetate in hexanes) to afford major product **2.23** as colorless oil (17 mg, 71 % yield) and minor product **2.24** as colorless oil (2.8 mg, 12% yield). Major product **2.23**: $[\alpha]^{23}_D$ = -32.2 (c = 0.5, $CHCl_3$); IR $\nu_{max}$ (neat)/cm$^{-1}$ 2967, 2933, 1728, 1455, 1064; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.24 (10H, m), 5.21 (1H, t, *J* = 6.7 Hz), 5.09 (1H, dd, *J* = 7.3, 3.3 Hz), 4.71 – 4.58 (3H, m), 4.46 (1H, d, *J* = 12.0 Hz),

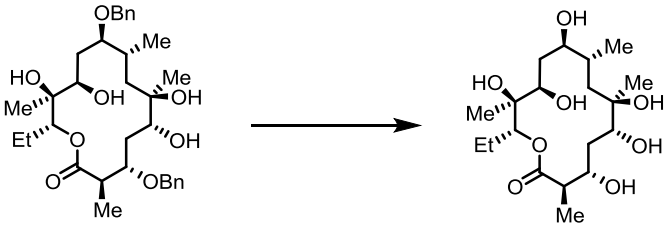
3.65 – 3.53 (3H, m), 3.15 (1H, s), 2.92 (1H, s), 2.65 (1H, dt, *J* = 15.2, 6.9 Hz), 2.06 (1H, m), 1.94 (1H, dd, *J* = 15.2, 4.0 Hz), 1.78 (3H, d, *J* = 3.0 Hz), 1.77 – 1.55 (5H, m), 1.29 (3H, d, *J* = 7.0 Hz), 1.08 (3H, d, *J* = 6.8 Hz), 1.06 (3H, s), 0.89 (3H, t, *J* = 6.8 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 204.1, 174.3, 138.5, 137.8, 128.8, 128.6, 128.4, 128.2, 128.0, 127.8, 99.8, 90.7, 81.6, 81.3, 77.0, 76.4, 74.2, 72.8, 70.3, 46.9, 40.4, 37.3, 33.1, 25.8, 21.3, 19.6, 14.8, 14.8, 9.9; MS (ESI+) calculated for $[C_{33}H_{44}O_6 + Na]^+$: 559.3, found: 559.3. For an alternative preparation and characterization details of minor product **2.24**, refer to: Liu, K.; Kim, H.; Ghosh, P.; Akhmedov, N. G.; Williams, L. J. J. Am. Chem. Soc. 2011, *133*, 14968.



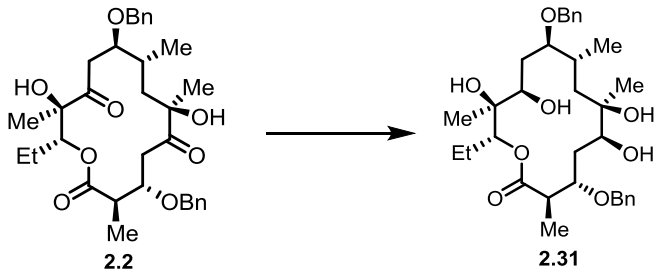

**2.23** **2.26**

Macrolactone **2.23** (5.0 mg, 9.3 μmol) was dissolved in 0.6 mL 1:1 mixture of *t*BuOH and water. NMO (2.2 mg, 0.019 mmol) and DABCO (1.0 mg, 9.0 μmol, added as 100 μL of 10 mg/mL stock solution in *t*BuOH) was added. The mixture was stirred for 5 min followed by addition of $OsO_4$ (6 μL of 4 % w/w solution in water, 0.094 μmol, 10 mol%). The reaction was stirred at rt for 3 h before quenched with saturated aqueous $Na_2SO_3$ solution (1 mL) and diluted with water (5 mL). The mixture was extracted with diethyl ether (3 x 5 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was briefly purified with FCC (30 % ethyl acetate in hexanes) and then dissolved in 0.8 mL anhydrous diethyl ether.

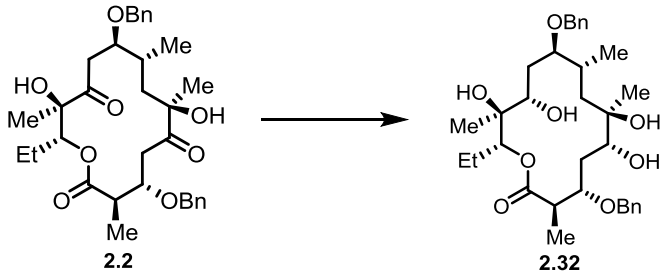
The solution was cooled to 0 ºC before addition of zinc borohydride (0.5 mL of 0.1 M diethyl ether solution, 0.05 mmol). The reaction was warmed to rt over 1 h and quenched with saturated aqueous $NH_4Cl$ (2 mL) and extracted with diethyl ether (2 x 5 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product (dr = 8:1 by $^1H$ NMR) was purified with FCC (40 % ethyl acetate in hexanes) to afford major product **2.26** as colorless oil (3.5 mg, 60 % yield over 2 steps). $[\alpha]^{20}_D$ = -1.73 (c = 0.3, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 3444 (broad), 2968, 2931, 1729, 1456, 1070; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.24 (10H, m), 5.12 – 5.06 (1H, m), 4.72 – 4.64 (2H, m), 4.61 (1H, d, *J* = 10.9 Hz), 4.49 (1H, d, *J* = 10.6 Hz), 3.90 (1H, m), 3.75 (1H, m), 3.66 (1H, s), 3.62 (1H, m), 3.35 (1H, m), 2.96 (1H, d, *J* = 2.9 Hz), 2.72 (1H, s), 2.65 – 2.59 (1H, m), 2.49 (1H, s), 1.91 – 1.82 (2H, m), 1.68 – 1.42 (7H, m), 1.35 (3H, d, *J* = 7.2 Hz), 1.24 (3H, s), 1.17 (3H, d, *J* = 6.8 Hz), 1.14 (3H, s), 0.90 (3H, t, *J* = 7.5 Hz). $^{13}C$ NMR (126 MHz, $C_6D_6$) δ 175.0, 138.6, 138.3, 128.7 (2), 128.4, 127.6, 127.5, 127.3, 86.0, 79.6, 77.6, 76.2, 75.0, 74.9, 74.8, 73.1, 72.4, 47.2, 44.4, 38.2, 35.8, 34.9, 25.3, 23.9, 19.9, 18.0, 15.6, 11.2; MS (ESI+) calculated for $[C_{33}H_{48}O_8 + Na]^+$: 595.3, found: 595.3.



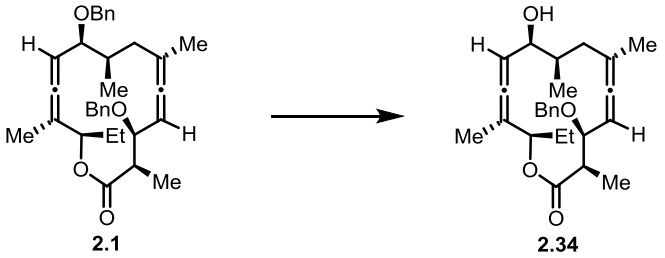

To a solution of macrolactone **2.26** (3.0 mg, 5.2 μmol) in ethanol was added $Pd(OH)_2$ (8.0 mg, 20 % w/w on carbon, < 50% water). The solution was purged with hydrogen for 5 min and then maintained under positive pressure (with a hydrogen balloon). The mixture was stirred at rt for 3 h before concentrated under reduced pressure. The crude product was was purified with FCC (10 % ethyl acetate in hexanes) to afford product **2.3** as colorless oil (2.0 mg, quantitative yield). $[\alpha]^{22}_{D}$ = -9.4 (c = 0.2, MeOH); IR $\nu_{max}$ (neat)/$cm^{-1}$ 3393 (broad), 2968, 2973, 2933, 1716, 1075; $^{1}$H NMR (500 MHz, $CD_3OD$) δ 5.08 (1H, m), 3.84 (2H, m), 3.58 (1H, m), 3.34 (1H, m), 2.45 (1H, m), 1.87 (2H, m), 1.68 (1H, d, *J* = 14.3 Hz), 1.61 – 1.49 (3H, m), 1.49 – 1.25 (3H, m), 1.24 (3H, d, *J* = 6.9 Hz), 1.21 (3H, s), 1.12 (3H, s), 1.07 (3H, d, *J* = 6.5 Hz), 0.86 (3H, t, *J* = 7.4 Hz). $^{13}$C NMR (126 MHz, $CD_3OD$) δ 177.1, 78.4, 77.6, 77.4, 77.3, 76.3, 76.2, 74.5, 49.3, 43.6, 39.4, 38.5, 36.8, 24.8, 24.7, 19.8, 18.6, 15.6, 11.4; MS (ESI+) calculated for $[C_{19}H_{36}O_8 + Na]^+$: 415.2, found: 415.2.



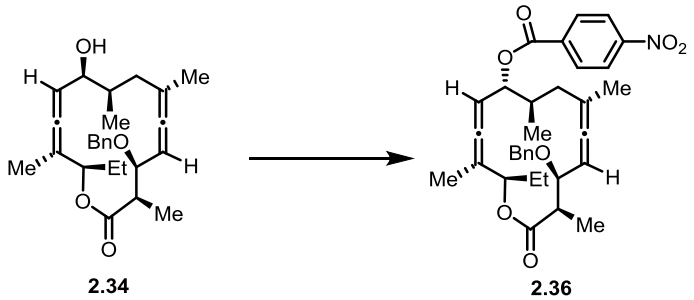

A solution of zinc borohydride (0.9 mL of 0.1 M diethyl ether solution, 0.09 mmol) was added to a solution of macrolactone **2.2** (15.5 mg, 0.027 mmol) in diethyl ether (0.5 mL) at 0 ºC. The reaction was stirred at 0 ºC for 3.5 h before quenched with saturated aqueous $NH_4Cl$ (2 mL) and extracted with diethyl ether (2 x 5 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product (dr = 10:1 by $^1H$ NMR) was purified with FCC (40 % ethyl acetate in hexanes) to afford major product **2.31** as colorless oil (10.0 mg, 65 % yield). $[\alpha]^{23}_D$ = -2.34 (c = 0.9, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 3446 (broad), 2957, 2930, 1729, 1456, 1069; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (10H, m), 5.03 (1H, dd, *J* = 10.0, 2.8 Hz), 4.70 – 4.55 (3H, m), 4.46 (1H, d, *J* = 10.9 Hz), 4.14 (1H, ddd, *J* = 9.1, 7.1, 2.6 Hz), 3.63 (1H, dd, *J* = 9.2, 1.6 Hz), 3.56 (2H, m), 3.38 (1H, d, *J* = 2.7 Hz), 3.03 (1H, d, *J* = 5.3 Hz), 2.77 (1H, dq, *J* = 7.1, 6.7 Hz), 2.62 (1H, s), 2.53 (1H, s), 2.11 (1H, m), 1.96 – 1.72 (6H, m), 1.56 (1H, m), 1.36 – 1.27 (4H, m), 1.25 (3H, s), 1.20 (3H, s), 1.07 (3H, d, *J* = 7.0 Hz), 0.92 (3H, t, *J* = 7.4 Hz); $^{13}C$ NMR (126 MHz, $C_6D_6$) δ 175.3, 137.8, 137.4, 128.6, 128.5 (2), 128.1, 128.0 (2), 84.4, 78.5, 77.8, 75.6, 75.0, 74.2, 74.0, 72.7 (2), 44.0, 43.9, 34.8, 34.6, 33.7, 27.0, 23.5, 20.0, 18.6, 14.2, 11.0; MS (ESI+) calculated for $[C_{33}H_{48}O_8 + Na]^+$: 595.3, found: 595.2.



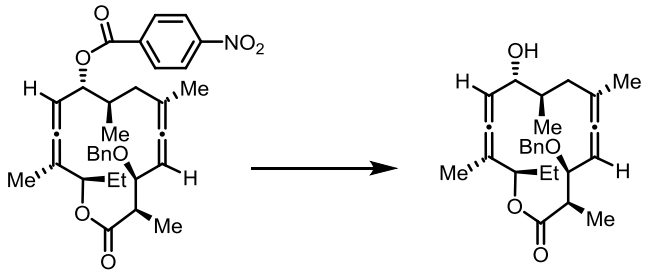

**2.2** (9.0 mg, 15.9 μmol) was dissolved in 1.8 mL anhydrous MeOH. The solution was cooled to 0 ºC before sodium borohydride (5 mg, 0.13 mmol) was added. The reaction was stirred at 0 ºC for 40 min and quenched with saturated aqueous $NH_4Cl$ (2 mL). The mixture was extracted with DCM (3 x 5 mL) and the resulting organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified with FCC (30 % ethyl acetate in hexanes) to afford major product **2.32** as colorless oil (4.5 mg, 50 % yield) and mixture of minor products **2.26** and **2.31** as colorless oil (2.7 mg, 30% yield, F:D = 2:1 approximately by $^1$H NMR). Major product **2.32**: $[\alpha]^{24}_D$ = -14.4 (c = 0.6, $CHCl_3$); IR $\nu_{max}$ (neat)/cm$^{-1}$ 3448 (broad), 2969, 2930, 1732, 1165, 1071; $^1$H NMR (500 MHz, C6D6) δ 7.20 – 6.98 (10H, m), 5.57 (1H, dd, *J* = 10.9, 2.6 Hz), 4.66 (1H, s), 4.37 (1H, d, *J* = 10.8 Hz), 4.26 (1H, d, *J* = 11.1 Hz), 4.18 (1H, d, *J* = 10.8 Hz), 4.01 (1H, d, *J* = 11.1 Hz), 3.85 (1H, m), 3.76 – 3.65 (2H, m), 3.33 (1H, s), 2.88 (1H, m), 2.85 (1H, s), 2.68 (1H, s), 2.43 (1H, dq, *J* = 9.8, 6.9 Hz), 2.03 (1H, m), 1.95 (1H, m), 1.81 (1H, m), 1.66 (1H, m), 1.49 (3H, m), 1.42 (3H, d, *J* = 6.2 Hz), 1.27 (3H, d, *J* = 7.0 Hz), 1.21 – 1.15 (2H, m), 1.06 (3H, s), 1.04 (3H, s), 0.91 (3H, t, J = 7.5 Hz). $^{13}$C NMR (126 MHz, $C_6D_6$) δ 174.4, 137.6 (2), 128.7, 128.6, 128.3, 128.2 (2), 128.1, 85.0, 82.6, 76.6, 75.0, 74.6, 74.0, 73.8, 72.8, 69.0, 48.2, 40.1, 37.7, 32.2, 26.8, 25.3, 21.9, 17.5, 16.5, 14.8, 11.5; MS (ESI+) calculated for $[C_{33}H_{48}O_8 + Na]^+$: 595.3, found: 595.2.



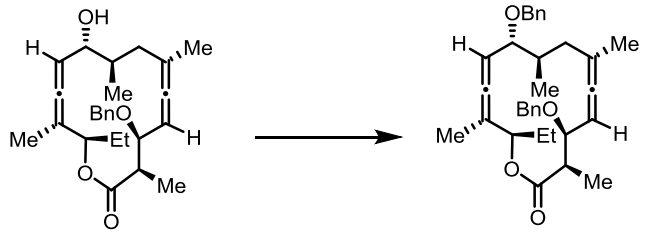

To a solution of macrolactone **2.1** (80 mg, 0.16 mmol) in DCM (2 mL) was added 50 μL pH = 7.4 phosphate buffer. The mixture was cooled to 0 ºC before the addition of DDQ (45 mg, 0.19 mmol). The ice bath was removed after 10 min and the mixture was stirred at rt for 16 h. To the reaction was added saturated aqueous $NaHCO_3$ solution (5 mL) and the resulting mixture was stirred at rt for 30 min. The aqueous layer was extracted with DCM (3 x 8 mL) and the combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (10 % to 20 % ethyl acetate in hexanes) to afford **2.34** as colorless oil (40 mg, 60 % yield), diol **2.35** (20 mg, 30% yield). Major product **2.34**: $[\alpha]^{23}_{D}$ = +15.1 (c = 0.5, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 3435, 2968, 2917, 2848, 1963, 1729, 1453, 1376, 1177, 1069. For detailed NMR data, see Hiyun Kim's thesis Page 504 (Kim, H. Allene-Based Approach to the Synthesis of *De Novo* Erythromycinoids. Ph.D. dissertation, Rutgers, The State University of New Jersey, 2012). MS (ESI+) calculated for $[C_{26}H_{34}O_4 + Na]^+$: 433.3, found: 433.2.




To a solution of alcohol **2.34** (37 mg, 0.09 mmol) in anhydrous THF (2 mL) was added triphenyl phosphine (190 mg, 0.72 mmol) and *p*-nitrobenzoic acid (120 mg, 0.72 mmol). DIAD (0.15 mL, 0.73 mmol) was added at 0 ºC. The ice bath was removed and the reaction was stirred at rt for 3h before concentrated under reduced pressure. The crude product was purified with FCC (5 % ethyl acetate in hexanes) to afford **2.36** as colorless oil (38 mg, 76 % yield). $[\alpha]^{23}_{D}$ = +76.0 (c = 0.5, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2969, 2930, 1727, 1530, 1270; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.30 (2H, d, *J* = 8.3 Hz), 8.20 (2H, d, *J* = 8.3 Hz), 7.40 – 7.24 (5H, m), 5.59 (1H, d, *J* = 4.3 Hz), 5.53 – 5.48 (1H, m), 5.39 – 5.20 (2H, m), 4.64 (1H, d, *J* = 11.4 Hz), 4.56 (1H, d, *J* = 11.4 Hz), 4.14 (1H, dd, *J* = 8.6, 3.5 Hz), 2.79 (1H, dt, *J* = 15.3, 7.4 Hz), 2.53 (1H, dd, *J* = 16.8, 4.1 Hz), 2.26 (1H, dd, *J* = 16.9, 6.5 Hz), 1.85 – 1.58 (6H, m), 1.46 – 1.37 (1H, m), 1.29 (6H, dd, *J* = 19.8, 7.7 Hz), 1.03 (3H, d, *J* = 6.7 Hz), 0.89 (3H, q, *J* = 8.5, 7.3 Hz); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.2, 199.5, 174.1, 164.8, 150.7, 138.6, 136.2, 130.9, 128.6, 128.1, 127.9, 123.8, 105.0, 102.8, 101.2, 92.2, 78.1, 70.8, 43.3, 35.3, 32.3, 24.8, 21.8, 21.1, 18.7, 16.2, 15.5, 12.1, 10.1; MS (ESI+) calculated for $[C_{33}H_{37}NO_7 + Na]^+$: 582.3, found: 582.3.



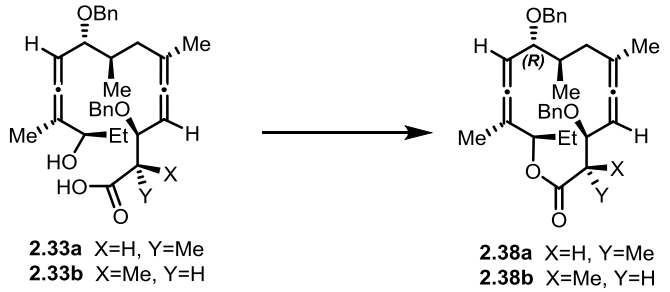

To a solution of macrolactone **2.36** (33 mg, 0.046 mmol) in methanol (2 mL) was added potassium carbonate (30 mg, 0.22 mmol). The reaction was stirred at rt for 20 min and diluted with ethyl acetate (20 mL). The mixture was washed with saturated aqueous $NH_4Cl$ (10 mL) and water (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (20 % ethyl acetate in hexanes) to afford **2.37** as colorless oil (24 mg, quantitative yield). $[\alpha]^{23}_D$ = +27.9 (c = 0.2, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 3445 (broad), 2970, 2931, 1732, 1173, 1070; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.22 (5H, m), 5.45 – 5.40 (1H, m), 5.33 – 5.24 (2H, m), 4.62 (1H, d, *J* = 11.7 Hz), 4.54 (1H, d, *J* = 11.7 Hz), 4.08 (2H, dd, *J* = 8.4, 3.5 Hz), 2.78 (1H, dt, *J* = 15.6, 7.2 Hz), 2.20 (1H, m), 1.96 – 1.88 (1H, m), 1.76 – 1.60 (9H, m), 1.26 (3H, d, *J* = 7.2 Hz), 1.03 (3H, d, *J* = 6.8 Hz), 0.96 – 0.85 (3H, m) (alcohol OH not observed); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 202.7, 199.9, 174.0, 138.6, 128.5, 128.1, 127.8, 103.5, 100.8, 93.5, 91.5, 77.1, 74.2, 70.6, 43.3, 35.0, 34.6, 29.9, 24.9, 21.0, 18.9, 15.3, 12.7, 10.1; MS (ESI+) calculated for $[C_{26}H_{34}O_4 + Na]^+$: 433.3, found: 433.3.




**2.37** **2.38**

To a solution of alcohol **2.37** (22 mg, 0.054 mmol) in anhydrous THF (2 mL) was added sodium hydride (50 mg, 1.25 mmol, 60 % w/w in mineral oil) in one portion. The suspension was stirred at rt before benzyl bromide (0.15 mL, 1.26 mmol) was added dropwise. The reaction was stirred at rt for 2.5 d and cooled to – 78 ºC before quenched with pH = 7.4 phosphate buffer (2 mL). The mixture was diluted with diethyl ether (10 mL) and washed with water (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (3 % ethyl acetate in hexanes) to afford **2.38** as colorless oil (22 mg, 80 % yield). $[\alpha]^{23}_{D}$ = +60.8 (c = 0.8, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2970, 2933, 1731, 1455, 1070, 735, 679; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.24 (10H, m), 5.45 – 5.40 (1H, m), 5.35 – 5.20 (2H, m), 4.70 (1H, dd, *J* = 21.2, 11.8 Hz), 4.66 – 4.44 (3H, m), 4.10 (1H, dd, *J* = 8.7, 3.7 Hz), 4.00 – 3.85 (1H, m), 2.81 – 2.71 (1H, m), 2.36 (1H, m), 2.02 – 1.90 (1H, m), 1.76 – 1.53 (9H, m), 1.28 (3H, d, *J* = 7.2 Hz), 1.01 (3H, dd, *J* = 16.4, 6.8 Hz), 0.87 (3H, t, *J* = 7.4 Hz); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.2, 199.5, 174.1, 150.7, 138.6, 136.2, 130.9, 129.4, 128.6, 128.1, 127.9, 123.8, 105.0, 102.8, 101.2, 92.2, 78.1, 70.8, 43.3, 35.3, 32.3, 29.9, 24.8, 21.8, 21.1, 18.7, 15.5, 12.1, 10.1; MS (ESI+) calculated for $[C_{33}H_{40}O_4 + Na]^+$: 523.3, found: 523.3.

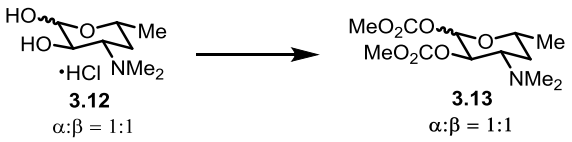

To the macrolactone **2.38** (10 mg, 0.02 mmol) in 1 mL methanol was added 1 mL sodium methoxide solution (25 % w/w in MeOH, 4.6 mmol). After stirring at rt for 1d, distilled water (1 mL) was added and the mixture was stirred at rt for 12 h. The mixture was diluted with diethyl ether (15 mL) and washed with saturated aqueous $NH_4Cl$ solution (2 x 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (30 % ethyl acetate in hexanes) to afford **2.33** (5.4 mg, 52 % yield) as inseparable mixture of diastereomers (**2.33a**:**2.33b** = 2:1).



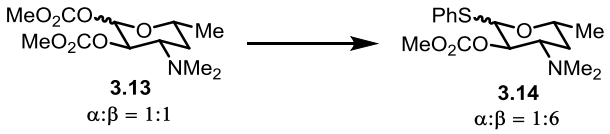

The seco acid **2.33** (mixture of diastereomers, 5.4 mg, 0.01 mmol) was dissolved in 1.5 mL anhydrous toluene. Triethylamine (10 μL, 0.071 mmol) and trichlorobenzoyl chloride (10 μL, 0.064 mmol) was added and the mixture was stirred at rt for 4 h. The mixture was then delivered via syringe pump over 1 h to a 80 ºC solution of DMAP (12 mg, 0.099

mmol in 5 mL anhydrous toluene). The solution was allowed to cool to rt and was quenched with saturated aqueous $NH_4Cl$ solution (5 mL). The aqueous layer was extracted with ethyl acetate (5 mL) and the combined organic phase was washed with water (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (3 % ethyl acetate in hexanes) to afford **2.38** (3.6 mg, 70 % yield, **2.38a**:**2.38b** = 2:1).

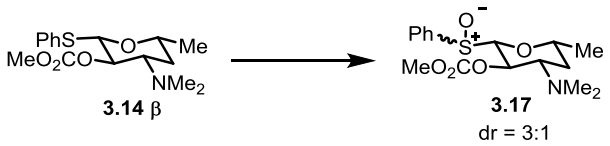
## 5.3. Chapter 3




To a suspension of desoamine hydrochloride **3.12** (4.87 g, 23.0 mmol, prepared according to *J. Am. Chem. Soc.* **1954***, 76*, 3121) in DCM (120 mL) was added *i*$Pr_2$NEt (20 mL, 114 mmol). The mixture was stirred at rt for 20 min to yield a clear solution. Methyl chloroformate (5.3 mL, 69.0 mmol) was added slowly over 5 min (reaction is exothermic). The reaction was stirred at rt for 10 min before washed with water (2 x 100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (20 % acetone in hexanes) to afford **3.13** as light yellow oil (6.36 g, 95 % yield, α:β = 1:1 by $^1$H NMR). IR $\nu_{max}$ (neat)/cm$^{-1}$ 2974, 2937, 1751, 1444, 1270, 1049; $^1$H NMR (400 MHz, $CDCl_3$) δ 6.06 (1H, d, *J* = 3.6 Hz), 5.36 (1H, d, *J* = 7.9 Hz), 4.73 (1H, dd, *J* = 11.1, 3.6 Hz), 4.61 (1H, dd, *J* = 10.5, 7.9 Hz), 3.99 (1H, m), 3.75 – 3.69 (12H, m), 3.69 – 3.59 (1H, m), 3.09 (1H, td, *J* = 12.0, 4.0 Hz), 2.74 (1H, ddd, *J* = 12.2, 10.6, 4.3 Hz), 2.21 (12H, two singlets), 1.75 (2H, m), 1.33 (2H, m), 1.20 (3H, d, *J* = 6.2 Hz), 1.13 (3H, d, *J* = 6.2 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 155.2, 155.1, 154.6, 154.5, 97.1, 97.0, 94.6, 94.5, 73.5, 72.7, 72.6, 70.7, 70.6, 67.6, 67.4, 63.4, 55.0, 40.8, 40.7, 40.6, 31.6, 30.1, 21.1 (2); MS (ESI+) calculated for $[C_{12}H_{21}NO_7 + H]^+$: 292.1, found: 292.1.

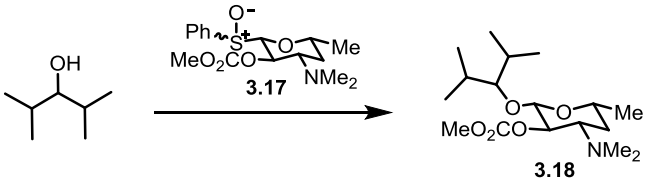



To a solution of **3.13** (2.50 g, 8.58 mmol) in anhydrous DCE (80 mL) was added thiophenol (1.70 mL, 16.5 mmol) followed by tin (IV) chloride (1.0 mL, 8.56 mmol). The reaction was heated and stirred at 80 ºC for 2h before cooled to rt. The reaction was washed with saturated aqueous solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with DCM (2 x 40 mL) and the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (10 % acetone in hexanes) to afford **3.14** as colorless oil (2.23 g, 80 % yield; α:β = 1:6 by $^1$H NMR). Major (β) isomer: $[\alpha]^{23}_D$ = +37.9 (c = 1.0, $CHCl_3$); IR $\nu_{max}$ (neat)/cm$^{-1}$ 2972, 2865, 1751, 1440, 1263; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.50 (2H, m), 7.28 (3H, m), 4.66 (2H, m), 3.83 (3H, s), 3.58 (1H, m), 2.80 (1H, m), 2.28 (6H, s), 1.81 (1H, ddd, *J* = 13.2, 4.2, 1.8 Hz), 1.49 – 1.37 (1H, m), 1.29 (3H, d, *J* = 6.1 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 155.3, 134.0, 132.3, 129.0, 127.7, 87.8, 73.8, 73.5, 64.9, 55.2, 40.9, 31.2, 21.6; MS (ESI+) calculated for $[C_{16}H_{23}NO_4S + H]^+$: 326.1, found: 326.1.

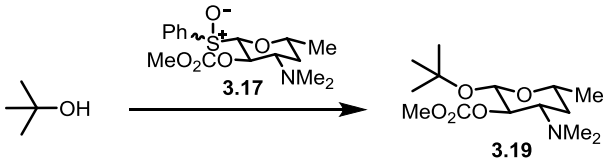



Phenyl sulfide **3.14** (β anomer, 630 mg, 1.94 mmol) was mixed with trifluoroacetic acid (1 mL) and concentrated under reduced pressure to afford the amine salt. To the salt in DCM (20 mL) was added *m*CPBA (334 mg, 1.94 mmol) at -78 ºC. The reaction was

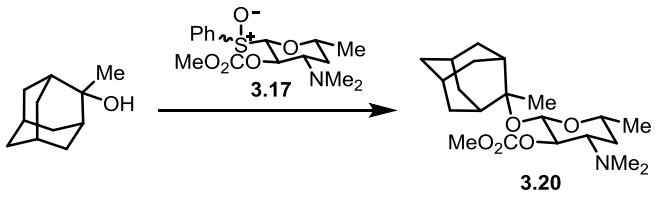
stirred at -78 ºC for 1 h then was allowed the warm to 0 ºC over 30 min. The reaction was washed with saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with DCM (2 x 20 mL) and the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (30 % acetone in hexanes) to afford **3.17** (510 mg, 77 % yield, dr = 3:1 by $^1$H NMR). Major isomer is a crystalline solid, whereas minor isomer is colorless oil. **Major isomer:** melting point = 123-124 ºC; $[\alpha]^{23}_D$ = -95.3 (c = 1.0, $CHCl_3$); IR $\nu_{max}$ (neat)/cm$^{-1}$ 2939, 2868, 1752, 1443, 1262, 1089; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.60 (2H, m), 7.51 – 7.45 (3H, m), 5.09 (1H, t, *J* = 9.8 Hz), 3.97 (1H, d, *J* = 9.5 Hz), 3.83 (3H, s), 3.47 – 3.38 (1H, m), 2.81 (1H, ddd, *J* = 12.4, 10.3, 4.1 Hz), 2.27 (6H, s), 1.78 – 1.71 (1H, m), 1.43 (1H, m), 1.13 (3H, d, *J* = 6.1 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 154.7, 140.2, 131.3, 128.9, 125.7, 93.2, 75.0, 69.9, 65.1, 55.5, 40.9, 30.1, 20.9; MS (ESI+) calculated for $[C_{16}H_{23}NO_5S + H]^+$: 342.1, found: 342.1. **Minor isomer:** $[\alpha]^{23}_D$ = +39.2 (c = 1.0, $CHCl_3$); IR $\nu_{max}$ (neat)/cm$^{-1}$ 2954, 2868, 1754, 1443, 1264, 1048; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, m), 7.50 (3H, m), 4.91 (1H, t, *J* = 9.7 Hz), 4.35 (1H, d, *J* = 9.4 Hz), 3.76 (3H, s), 3.59 (1H, m), 2.81 (1H, ddd, *J* = 12.5, 10.1, 4.2 Hz), 2.25 (6H, s), 1.74 (1H, ddd, *J* = 13.2, 4.1, 1.8 Hz), 1.29 – 1.23 (1H, m), 1.20 (3H, d, *J* = 6.1 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 154.8, 140.0, 131.3, 128.7, 125.8, 94.7, 74.7, 70.0, 64.6, 55.2, 40.8, 30.5, 21.1; MS (ESI+) calculated for $[C_{16}H_{23}NO_5S + H]^+$: 342.1, found: 342.1.



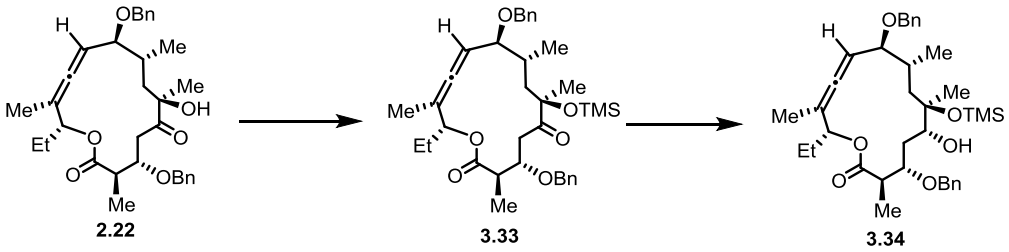

DTBMP (70 mg, 0.34 mmol) was azeotroped with toluene (3 x 2 mL), dissolved in 1 mL anhydrous DCM and added to a 10 mL flask with 100 mg 4 Å MS (activated by flame-drying). 2,4-dimethyl-3-pentanol (0.38 mL of 0.7 M solution in DCM, 0.26 mmol, dried with 4 Å MS overnight) was added. The suspension was stirred at rt for 1 h before cooled to -78 ºC. Triflic anhydride (0.15 mL of 0.6 M solution in DCM, 0.09 mmol) was added over 1 min followed by addition of sulfoxide **3.17** (30 mg, 0.088 mmol) in 1 mL DCM over 10 min via a syringe pump. The reaction was stirred at –78 ºC for 20 min and warmed to -40 ºC over 20 min. The reaction was filtered through a short pad of celite (in a Pasteur pipette) into saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with DCM (2 x 5 mL) and the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (15 % acetone in hexanes) to afford glycoside **3.18** as colorless oil (20 mg, 69 % yield). $[\alpha]^{23}_D$ = 3.68 (c = 1.0, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 3444, 2959, 2873, 1755, 1442, 1266, 1111, 995; $^1$H NMR (500 MHz, $CDCl_3$) δ 4.62 (1H, dd, *J* = 10.6, 7.6 Hz), 4.34 (1H, d, *J* = 7.5 Hz), 3.77 (3H, s), 3.47 (1H, m), 3.07 (1H, dd, *J* = 5.8, 4.4 Hz), 2.76 (1H, ddd, *J* = 12.4, 10.6, 4.5 Hz), 2.30 (6H, s), 1.82 (2H, m), 1.75 – 1.70 (1H, m), 1.43 – 1.30 (1H, m), 1.23 (3H, d, *J* = 6.1 Hz), 0.94 – 0.89 (10H, m), 0.86 (2H, d, *J* = 6.8 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 155.5, 102.8, 89.3, 76.0, 69.0, 63.4, 54.8 (2), 40.9, 31.1, 30.9, 30.5, 21.3, 20.4 (2), 19.1, 17.2; MS (ESI+) calculated for $[C_{17}H_{33}NO_5 + H]^+$: 332.2, found: 332.1.




DTBMP (70 mg, 0.34 mmol) was azeotroped with toluene (3 x 2 mL), dissolved in 1 mL anhydrous DCM and added to a 10 mL flask with 100 mg 4 Å MS (activated by flame-drying). *Tert*-butanol (0.26 mL of 1.0 M solution in DCM, 0.26 mmol, dried with 4 Å MS overnight) was added. The suspension was stirred at rt for 1 h before cooled to -78 ºC. Triflic anhydride (0.15 mL of 0.6 M solution in DCM, 0.09 mmol) was added over 1 min followed by addition of sulfoxide **3.17** (30 mg, 0.088 mmol) in 1 mL DCM over 10 min via a syringe pump. The reaction was stirred at –78 ºC for 20 min and warmed to -40 ºC over 20 min. The reaction was filtered through a short pad of celite (in a Pasteur pipette) into saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with DCM (2 x 5 mL) and the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (15 % acetone in hexanes) to afford glycoside **3.19** as colorless oil (21 mg, 85 % yield). $[\alpha]^{23}_{D}$ = 1.72 (c = 1.0, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2975, 2776, 1750, 1443, 1270, 1050, 991; $^1$H NMR (400 MHz, $CDCl_3$) δ 4.57 (1H, dd, *J* = 10.3, 7.6 Hz), 4.49 (1H, d, *J* = 7.6 Hz), 3.79 (3H, s), 3.53 (1H, m), 2.80 (1H, m), 2.30 (6H, s), 1.74 (1H, m), 1.38 (1H, m), 1.25 (3H, d, *J* = 6.2 Hz), 1.23 (9H, s); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 155.4, 96.7, 75.8, 75.3, 69.1, 63.3, 54.9 (2), 40.9, 31.1, 28.8, 21.5; MS (ESI+) calculated for $[C_{14}H_{27}NO_5 + H]^+$: 290.2, found: 290.1.

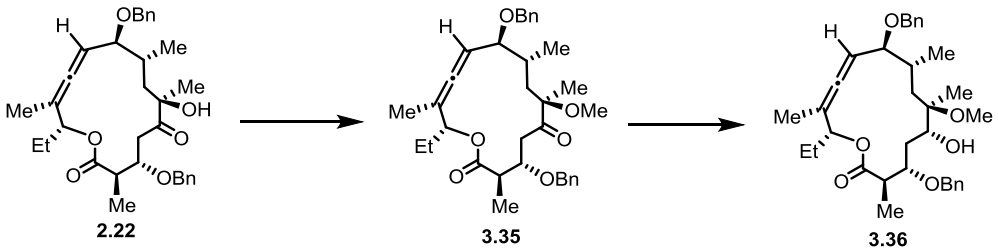



DTBMP (70 mg, 0.34 mmol) and 2-methyl-2-adamantanol (44 mg, 0.265 mmol) was combined and azeotroped with toluene (3 x 2 mL), then dissolved in 1 mL anhydrous DCM and added to a 10 mL flask with 100 mg 4 Å MS (activated by flame-drying). The suspension was stirred at rt for 1 h before cooled to -78 ºC. Triflic anhydride (0.15 mL of 0.6 M solution in DCM, 0.09 mmol) was added over 1 min followed by addition of sulfoxide **3.17** (30 mg, 0.088 mmol) in 1 mL DCM over 10 min via a syringe pump. The reaction was stirred at –78 ºC for 20 min and warmed to -40 ºC over 20 min. The reaction was filtered through a short pad of celite (in a Pasteur pipette) into saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with DCM (2 x 5 mL) and the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (10 % acetone in hexanes) to afford **3.20** as colorless oil (20 mg, 60 % yield). IR $_{max}$ (neat)/$cm^{-1}$ 2903, 2860, 1754, 1441, 1267, 1160, 1109, 994; $^1$H NMR (500 MHz, $CDCl_3$) δ 4.61 (1H, dd, $J$ = 7.5, 1.6 Hz), 4.70 – 4.65 (1H, m), 3.76 (3H, s), 3.50 (1H, m), 2.80 (1H, m), 2.30 (6H, s), 2.22 (1H, m), 1.85 (3H, m), 1.82 – 1.76 (4H, m), 1.76 – 1.68 (4H, m), 1.44 – 1.38 (4H, m), 1.37 (3H, s), 1.23 (3H, d, $J$ = 6.1Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 155.5, 96.1, 81.2, 75.6, 69.0, 63.5, 54.9, 40.9, 38.9, 38.5, 36.1, 35.3, 35.1, 32.8, 32.3, 31.0, 28.0, 27.3, 23.7, 21.5; MS (ESI+) calculated for $[C_{21}H_{35}NO_5 + H]^+$: 382.3, found: 382.2.



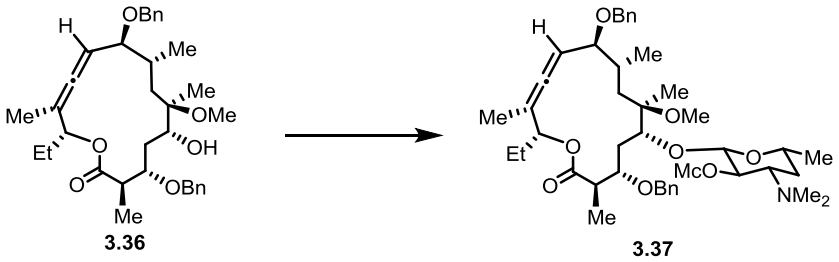

To a solution of **2.22** (12 mg, 22 μmol) and DMAP (5 mg, 44 μmol) in anhydrous DCM (1 mL) was added triethylamine (50 μL, 0.35 mmol) and TMSCl (30 μL, 0.23 mmol) at rt. The reaction was stirred at rt for 3 h before diluted with DCM (5 mL), washed with saturated aqueous $NaHCO_3$ (5 mL) and water (5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was briefly purified with FCC (5 % ethyl acetate in hexanes) to afford **3.33** as colorless oil (13 mg, not pure). **3.33** (10 mg) was dissolved in 1 mL anhydrous MeOH. The solution was cooled to 0 ºC before sodium borohydride (2 mg, 0.05 mmol) was added. The reaction was stirred at 0 ºC for 20 min and allowed to warm to rt. After 30 min at rt, the reaction was quenched with saturated aqueous $NH_4Cl$ (2 mL). The mixture was extracted with DCM (3 x 3 mL) and the resulting organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified with FCC (5 % ethyl acetate in hexanes) to afford **3.34** as colorless oil (5.0 mg, 50 % yield over 2 steps). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.23 (10H, m), 5.41 (1H, m), 5.19 (1H, m), 4.72 (1H, d, $J$ = 12.0 Hz), 4.66 (1H, d, $J$ = 11.4 Hz), 4.52 (1H, d, $J$ = 12.0 Hz), 4.45 (1H, d, $J$ = 11.4 Hz), 3.79 (1H, m), 3.69 – 3.59 (2H, m), 2.69 (1H, s), 2.58 – 2.48 (1H, m), 2.12 (1H, m), 1.86 (1H, dd, $J$ = 14.8, 3.2 Hz), 1.78 – 1.63 (7H, m), 1.35 – 1.21 (4H, m), 1.06 (6H, m), 0.94 – 0.82 (3H, m), 0.12 (9H, s); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 205.0, 174.6, 139.1, 138.5, 128.6, 128.5, 128.1, 127.8, 127.8, 127.6,

105.0, 98.7, 79.4, 78.0, 76.1, 74.7, 72.2, 70.6, 47.6, 40.9, 33.1, 32.3, 25.3, 23.0, 19.3, 14.9, 13.6, 9.7, 1.1, 0.2; MS (ESI+) calculated for $[C_{36}H_{52}O_6Si+ H]^+$: 631.4, found: 631.4.




Macrolactone **2.22** (10 mg, 0.019 mmol) and DTBMP (220 mg, 1.07 mmol) was dissolved in 1.2 mL anhydrous dichloroethane. Methyl triflate (0.1 mL, 0.91 mmol) was added to the solution at rt. The reaction was heated to 80 ºC and was stirred for 6 h. The reaction was allowed to cool to rt before quenched with saturated aqueous solution of $NaHCO_3$ (3 mL). The aqueous layer was extracted with DCM (2 x 5 mL) and the combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (10 % ethyl acetate in hexanes) to afford **3.35** as colorless oil (8 mg, not pure). **3.35** (8 mg) was dissolved in 1 mL anhydrous MeOH. The solution was cooled to 0 ºC before sodium borohydride (2 mg, 0.05 mmol) was added. The reaction was stirred at 0 ºC for 20 min and quenched with saturated aqueous $NH_4Cl$ (2 mL). The mixture was extracted with DCM (3 x 3 mL) and the resulting organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified with FCC (10 % ethyl acetate in hexanes) to afford **3.36** as colorless oil (3.6 mg, 35 % yield over 2 steps). $[\alpha]^{23}_D$ = -3.74 (c = 0.5, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2956, 2870, 1729, 1464, 1365, 1189; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.22 (10H, m), 5.38 (1H, m), 5.14 (1H,

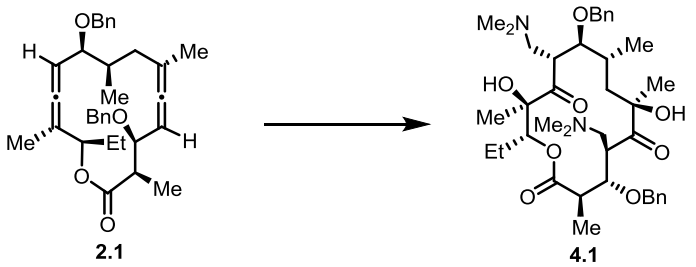
dd, *J* = 7.1, 3.0 Hz), 4.76 (1H, d, *J* = 11.3 Hz), 4.60 (1H, d, *J* = 12.1 Hz), 4.53 (1H, d, *J* = 11.3 Hz), 4.44 (1H, m), 3.79 (1H, m), 3.72 (1H, dt, *J* = 8.9, 4.4 Hz), 3.62 (1H, dd, *J* = 7.1, 4.3 Hz), 3.20 (3H, s), 2.67 (1H, s), 2.63 – 2.53 (1H, m), 1.88 (1H, m), 1.72 (3H, d, *J* = 2.8 Hz), 1.71 – 1.55 (5H, m), 1.42 (1H, m), 1.27 (3H, d, *J* = 7.0 Hz), 1.08 (3H, d, *J* = 6.8 Hz), 1.03 (3H, s), 0.87 (3H, t, *J* = 7.4 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 204.1, 174.7, 139.0, 138.9, 128.5 (2), 128.4, 127.9, 127.7, 127.6, 99.0, 91.2, 83.0, 79.8, 79.6, 76.7, 73.4, 71.7, 70.3, 49.2, 47.3, 38.0, 36.3, 33.4, 25.1, 18.6, 16.0, 15.4, 13.4, 9.9; MS (ESI+) calculated for $[C_{34}H_{46}O_6 + Na]^+$: 573.3, found: 573.3.




Alcohol **3.36** (4.5 mg, 8.2 mol), DTBMP (20 mg, 0.096 mmol), and 4-Allyl-1,2-dimethoxybenzene (ADMB, 20 mg, 0.11 mmol) were combined in a vial and azeotroped with toluene (2 x 1 mL), dissolved in 1.5 mL anhydrous DCM and added to a 10 mL flask with 100 mg 4 Å MS (activated by flame-drying). The suspension was stirred at rt for 1 h before cooled to -78 ºC. Triflic anhydride (40 μL of 1 M solution in DCM, 0.04 mmol) was added over 1 min followed by addition of sulfoxide (16 mg, 0.047 mmol) in 1.5 mL DCM over 15 min via a syringe pump. The reaction was stirred at –78 ºC for 10 min and warmed to -40 ºC over 30 min. The reaction was filtered through a short pad of celite (in a Pasteur pipette) into saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with DCM (2 x 5 mL) and the organic layer was dried over

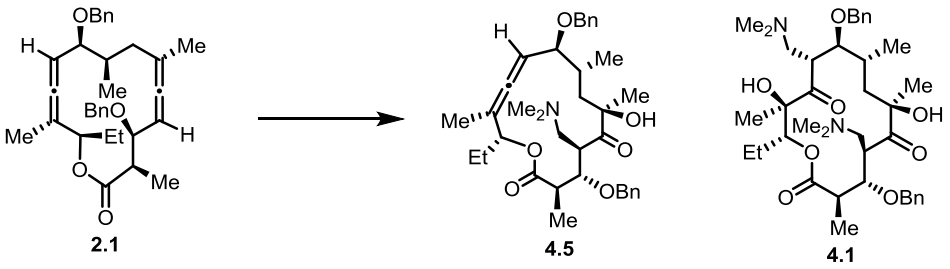
anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (40 % ethyl acetate in hexanes followed by 25 % acetone in hexanes) to afford glycoside **3.37** as colorless oil (4.0 mg, 63 % yield). $[\alpha]^{23}_{D}$ = -22.8 (c = 0.25, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2936, 1754, 1442, 1267, 1056; $^{1}H$ NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.26 (10H, m), 5.23 (1H, m), 5.16 (1H, m), 4.66 (1H, d, J = 11.8 Hz), 4.52 (2H, m), 4.43 – 4.37 (1H, m), 4.37 – 4.32 (1H, m), 4.29 (1H, m), 3.92 – 3.85 (1H, m), 3.82 (1H, m), 3.73 (3H, s), 3.46 (1H, m), 3.38 (1H, m), 3.12 (3H, s), 2.74 (1H, m), 2.44 (1H, m), 2.28 (6H, s), 1.94 – 1.82 (2H, m), 1.82 – 1.76 (3H, m), 1.70 (1H, s), 1.64 (2H, m), 1.38 (1H, dd, J = 11.4, 1.9 Hz), 1.37 – 1.27 (3H, m), 1.27 – 1.24 (3H, m), 1.22 (6H, d, J = 6.4 Hz), 1.11 (3H, dd, J = 6.6, 1.6 Hz), 0.91 – 0.78 (3H, m); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 203.3, 175.3, 155.4, 139.0 (2), 128.5, 128.4, 128.2, 127.8, 127.6 (2), 100.5, 98.2, 93.8, 85.1, 79.3, 76.4, 75.4, 74.0, 71.3, 70.3, 69.2, 63.4, 54.8, 50.4, 45.5, 40.9, 38.0, 37.8, 33.7, 30.8, 29.9, 25.0, 21.3, 20.5, 19.7, 16.8, 14.3, 8.4; MS (ESI+) calculated for $[C_{44}H_{63}NO_{10} + Na]^{+}$: 783.4, found: 783.3.

## 5.4. Chapter 4

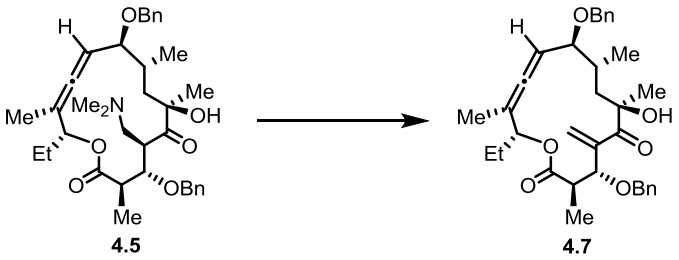



Macrolactone **2.1** (10 mg, 0.02 mmol), DABCO (10 mg, 0.089 mmol) and imminium salt (15 mg, 0.16 mmol) was dissolved in anhydrous DCM (1 mL) and stirred at rt for 5 min. Osmium tetroxide (0.25 mL of 0.2 M solution is DCM, 0.05 mmol) was added. The reaction was stirred at rt for 40 min before quenched with saturated aqueous solution of $Na_2SO_3$ (2 mL). The aqueous layer was extracted with DCM (2 x 5 mL) and the combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (20 % acetone in hexanes) to afford diketone **4.1** as colorless oil (9 mg, 66 % yield). $[\alpha]^{23}_{D}$ = +21.1 (c = 0.5, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2937, 1737, 1701, 1457, 1090; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.25 (10H, m), 5.05 (1H, d, *J* = 10.9 Hz), 4.97 (1H, dd, *J* = 9.5, 2.8 Hz), 4.88 (2H, d, *J* = 11.0 Hz), 4.57 (1H, d, *J* = 10.8 Hz), 4.47 (1H, d, *J* = 10.9 Hz), 4.06 (1H, d, *J* = 10.6 Hz), 3.29 (1H, d, *J* = 9.6 Hz), 3.17 – 3.09 (1H, m), 3.09 – 3.00 (1H, m), 2.78 (1H, d, *J* = 13.0 Hz), 2.64 – 2.55 (1H, m), 2.47 (1H, dd, *J* = 11.6, 6.8 Hz), 2.39 (6H, d, *J* = 10.4 Hz), 2.26 (1H, m), 2.16 (6H, s), 2.10 (2H, m), 1.91 – 1.80 (3H, m), 1.41 (2H, dd, *J* = 15.3, 7.7 Hz), 1.35 (3H, s), 1.33 – 1.26 (3H, m), 1.24 (3H, d, *J* = 6.7 Hz), 1.17 (3H, d, *J* = 6.7 Hz), 0.91 (3H, t, *J* = 7.4 Hz); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 219.8, 217.8, 175.4, 139.2, 138.8, 128.6, 128.5, 128.4, 127.9, 127.8, 127.6, 105.0, 83.1, 81.8,

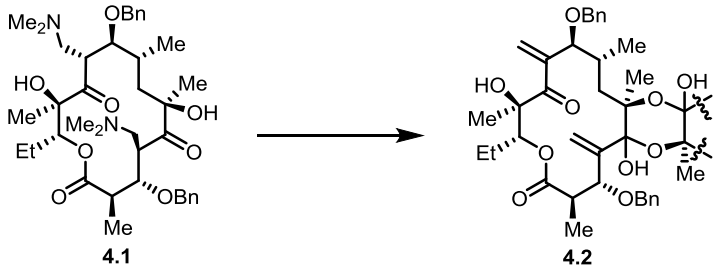
81.5, 79.9, 79.1, 75.1, 74.5, 60.4, 60.0, 59.5, 48.6, 45.8, 42.5, 42.1, 32.4, 26.0, 25.6, 23.9, 20.8, 11.5, 9.4; MS (ESI+) calculated for $[C_{39}H_{58}N_2O_8 + H]^+$: 683.4, found: 683.4.



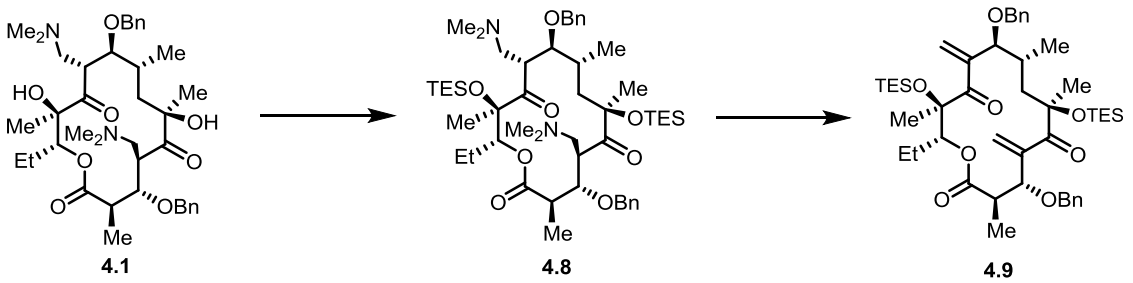

Macrolactone **2.1** (10 mg, 0.02 mmol) and imminium salt (15 mg, 0.16 mmol) was dissolved in anhydrous DCM (1 mL) and stirred at rt for 5 min. Osmium tetroxide (0.25 mL of 0.2 M solution is DCM, 0.05 mmol) was added. The reaction was stirred at rt for 4 h before quenched with saturated aqueous solution of $Na_2SO_3$ (2 mL). The aqueous layer was extracted with DCM (2 x 5 mL) and the combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (10% to 20 % acetone in hexanes) to afford **4.5** as colorless oil (7.9 mg, 67 % yield) and **4.1** (3.0 mg, 22 % yield) as colorless oil. Major product **4.5**: $[\alpha]^{23}_D$ = -2.38 (c = 0.8, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2936, 1737, 1696, 1456, 1369, 1183, 1059; MS (ESI+) calculated for $[C_{36}H_{49}NO_6 + H]^+$: 592.4, found: 592.4. For detailed NMR characterization, refer to Kai Liu's thesis (Liu, K. Accessing Erythronolide Structure Space: New Reactions and Applications. Ph.D. dissertation, Rutgers, The State University of New Jersey, 2012).




To a solution of amine **4.5** (5.0 mg, 8.5 μmol) in DCM (1 mL) and saturated aqueous $NaHCO_3$ (0.2 mL) was added *m*CPBA (10 mg, 0.043 mmol) at 0 ºC. The reaction was stirred at 0 ºC for 10 min then warmed to rt over 20 min. The reaction was diluted with DCM (5 mL), washed with saturated aqueous $Na_2SO_3$ (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (15 % ethyl acetate in hexanes) to afford enone **4.7** as colorless oil (4.0 mg, 86 % yield). $[\alpha]^{26}_D$ = -7.3 (c = 0.3, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2967, 2933, 1742, 1698, 1456; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.23 (10H, m), 5.78 (1H, s), 5.73 (1H, s), 5.20 (1H, m), 5.01 (1H, d, *J* = 6.5 Hz), 4.84 (1H, m), 4.64 (1H, d, *J* = 11.9 Hz), 4.45 (1H, d, *J* = 12.1 Hz), 4.37 – 4.30 (2H, m), 3.72 (1H, s), 3.40 (1H, dd, *J* = 8.1, 5.0 Hz), 2.50 – 2.43 (1H, m), 2.07 (1H, d, *J* = 15.0 Hz), 1.73 (1H, m), 1.69 (3H, d, *J* = 1.5 Hz), 1.61 (2H, dd, *J* = 14.4, 7.2 Hz), 1.40 (3H, s), 1.26 (3H, d, *J* = 6.9 Hz), 1.09 (3H, d, *J* = 6.7 Hz), 0.79 (3H, t, *J* = 7.3 Hz); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 204.0, 173.1, 148.8, 138.5(2), 128.5, 128.4, 128.3, 127.9, 127.8, 98.5, 93.4, 91.5, 83.2, 80.3, 75.6, 75.1, 70.7, 70.4, 45.2, 34.7, 29.9, 28.2, 24.5, 17.7, 14.6, 9.1, 1.2 (ketone carbonyl peak not observed); MS (ESI+) calculated for $[C_{34}H_{42}O_6 + Na]^+$: 569.3, found: 569.3.

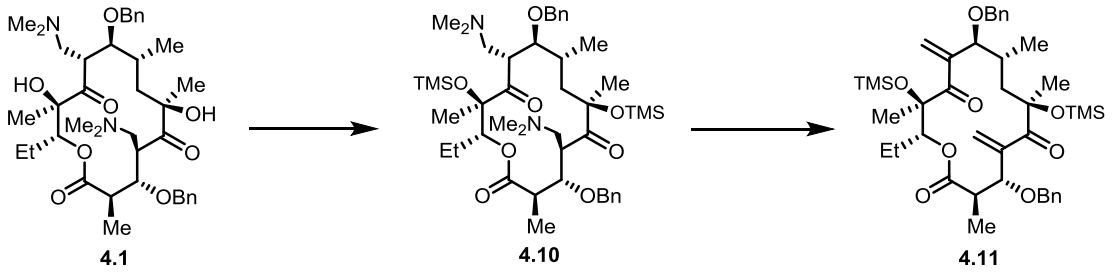



To a solution of **4.1** (8.0 mg, 0.012 mmol) in DCM (1.5 mL) and saturated aqueous $NaHCO_3$ (0.3 mL) was added *m*CPBA (10 mg, 0.043 mmol) at 0 ºC. The reaction was stirred at 0 ºC for 10 min then was allowed to warm to rt. The reaction was stirred at rt for 7 h before diluted with DCM (5 mL), washed with saturated aqueous $Na_2SO_3$ (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (20 % ethyl acetate in hexanes) to afford **4.2** as colorless oil (4.0 mg, 58 % yield). $[\alpha]^{26}_D$ = +52.7 (c = 0.8, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2974, 2937, 1735, 1657, 1456, 1178, 1069; $^1$H NMR (500 MHz, $C_6D_6$) δ 7.11 (10H, s), 6.17 (1H, s), 6.12 (1H, s), 5.15 – 5.08 (1H, m), 5.00 (1H, d, *J* = 10.1 Hz), 4.47 (1H, s), 4.37 – 4.17 (5H, m), 2.84 – 2.75 (1H, m), 2.24 (1H, s), 1.99 (1H, d, *J* = 12.7 Hz), 1.68 – 1.51 (3H, m), 1.34 (3H, s), 1.31 (3H, d, *J* = 7.0 Hz), 1.30 – 1.22 (3H, m), 1.21 (3H, d, *J* = 6.7 Hz), 1.15 (3H, s), 0.70 (3H, t, *J* = 7.4 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 204.5, 173.9, 144.5, 138.3, 131.2, 128.5, 128.0, 127.8, 107.3, 78.8, 71.7, 71.0, 46.8, 34.3, 31.1, 21.6, 20.5, 16.6, 10.6; MS (ESI+) calculated for $[C_{35}H_{44}O_8 + Na]^+$: 615.3, found: 1207.6 ($2M + Na^+$).




To a solution of **4.1** (11 mg, 16 μmol) in anhydrous DCM (2 mL) was added 2,6-lutidine (30 μL, 0.26 mmol) and TESOTf (40 μL, 0.17 mmol) at 0 ºC. The reaction was stirred at 0 ºC for 15 min then was warmed to rt over 20 min. The mixture was diluted with DCM (5 mL), washed with saturated aqueous $NaHCO_3$ (5 mL) and water (5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (10 % acetone in hexanes) to afford **4.8** as colorless oil (10 mg, 70 % yield). To a solution of **4.8** (8.0 mg, 8.8 μmol) in DCM (1.5 mL) and saturated aqueous $NaHCO_3$ (0.3 mL) was added *m*CPBA (10 mg, 0.043 mmol) at 0 ºC. The reaction was stirred at 0 ºC for 10 min then was allowed to warm to rt. The reaction was stirred at rt for 30 min before diluted with DCM (5 mL), washed with saturated aqueous $Na_2SO_3$ (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (3 % ethyl acetate in hexanes) to afford bis-enone **4.9** as colorless oil (5.0 mg, 70 % yield). $[\alpha]^{26}_D$ = +14.4 (c = 0.5, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2955, 2877, 1739, 1674, 1456, 1164, 1073; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.23 (10H, m), 7.05 (1H, s), 6.17 (1H, s), 6.13 (1H, s), 6.04 (1H, s), 5.14 (1H, d, *J* = 9.7 Hz), 4.65 (1H, d, *J* = 8.9 Hz), 4.46 – 4.34 (3H, m), 4.23 – 4.13 (2H, m), 2.75 (1H, m), 2.01 (1H, dd, *J* = 13.1, 7.4 Hz), 1.94 (2H, d, *J* = 7.2 Hz), 1.54 (3H, d, *J* =

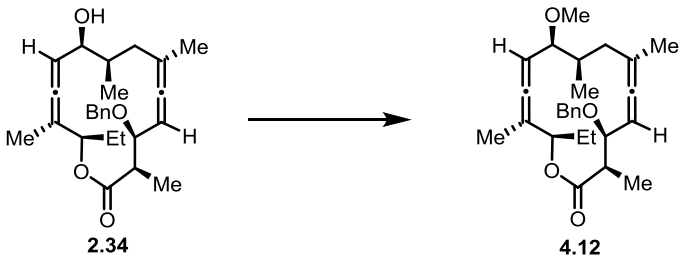
1.7 Hz), 1.50 (3H, s), 1.49 – 1.40 (2H, m), 1.38 (3H, s), 1.32 (3H, d, $J$ = 7.0 Hz), 0.96 (18H, m), 0.88 (3H, t, $J$ = 6.8 Hz), 0.75 – 0.58 (12H, m); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 203.9, 201.7, 173.6, 145.9, 142.6, 139.1, 138.7, 128.5, 128.4, 128.2, 127.9, 127.6 (2), 127.6, 126.2, 84.2, 83.3, 80.5, 75.7, 71.1 (2), 48.9, 45.2, 34.9, 30.5, 21.9, 19.3, 15.7, 11.9, 10.9, 7.7, 7.6, 7.5, 7.3, 7.2, 6.8; MS (ESI+) calculated for $[C_{47}H_{72}O_8Si_2 + Na]^+$: 843.5, found: 843.6.



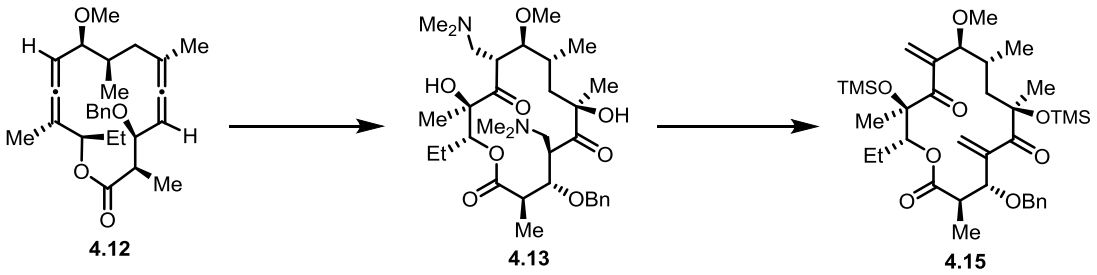

To a solution of **4.1** (13 mg, 20 μmol) in anhydrous THF (1.2 mL) was added TMS-imidazole (0.15 mL, 1.0 mmol) and TBAF (10 μL of 1M solution in THF, 0.01 mmol) at rt. The reaction was stirred rt for 14 h then partitioned between diethyl ether (5 mL) and water (5 mL). The aqueous layer was extracted with diethyl ether (2 x 5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (20 % ethyl acetate in hexanes) to afford **4.10** as colorless oil (14 mg, 89 % yield). Alternatively, to a solution of **4.1** (9.0 mg, 13 μmol) and DMAP (3 mg, 0.024 mmol) in anhydrous DCM (2 mL) was added triethylamine (70 μL, 0.49 mmol) and TMSCl (50 μL, 0.39 mmol) at rt. The reaction was stirred at rt for 4 h before diluted with DCM (5 mL), washed with saturated aqueous $NaHCO_3$ (5 mL) and water (5 mL). The organic layer was dried over anhydrous sodium

sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (20 % ethyl acetate in hexanes) to afford **4.10** as colorless oil (8.6 mg, 80 % yield).

To a solution of **4.10** (14 mg, 17 μmol) in DCM (1.5 mL) and saturated aqueous $NaHCO_3$ (0.3 mL) was added *m*CPBA (14 mg, 62 μmol) at 0 ºC. The reaction was stirred at 0 ºC for 10 min then was allowed to warm to rt. The reaction was stirred at rt for 50 min before diluted with DCM (5 mL), washed with saturated aqueous $Na_2SO_3$ (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (3 % ethyl acetate in hexanes) to afford bis-enone **4.11** as colorless oil (7.5 mg, 60 % yield). $[\alpha]^{26}_D$ = +10.7 (c = 0.5, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2957, 1739, 1675, 1455, 1254, 1086, 842; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.26 (1H, m), 7.04 (1H, s), 6.16 (1H, s), 5.90 (1H, s), 5.88 (1H, s), 5.10 (1H, dd, *J* = 10.3, 2.4 Hz), 4.70 (1H, d, *J* = 7.2 Hz), 4.49 – 4.38 (3H, m), 4.26 – 4.16 (2H, m), 2.66 (1H, m), 2.00 – 1.88 (4H, m), 1.51 (3H, s), 1.49 (1H, d, *J* = 3.2 Hz), 1.39 (3H, s), 1.37 – 1.22 (3H, m), 0.90 (6H, dd, *J* = 15.4, 7.9 Hz), 0.17 (9H, s), 0.12 (9H, s); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 201.8, 173.8, 147.3, 142.6, 139.1, 138.8, 128.5, 128.4, 128.3, 128.1, 127.8, 127.6 (2), 127.5, 84.3 (2), 81.1, 77.6, 75.3, 71.4, 71.2, 48.8, 44.6, 35.0, 30.3, 24.9, 21.8, 19.5, 14.3, 11.7, 10.9, 3.0, 2.1; MS (ESI+) calculated for $[C_{41}H_{60}O_8Si_2 + Na]^+$: 759.4, found: 759.4.

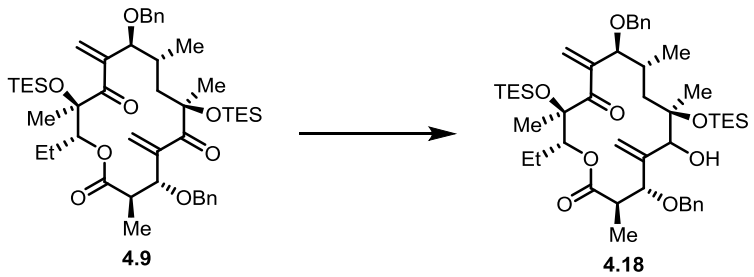



Alcohol **2.34** (12 mg, 0.029 mmol) in 2 mL anhydrous DCM was added to 10 mL round bottom flask containing 100 mg flamed activated 4Å molecular sieves. Proton sponge (40 mg, 0.18 mmol) and Meerwein's salt (27 mg, 0.18 mmol) was added at rt. The reaction was stirred at rt for 30 min before filtered through a pad of celite in a Pasteur pipette. The reaction was washed with $CuSO_4$ aqueous solution (1 M) to remove proton sponge and was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (5 % ethylacetate in hexanes) to afford **4.12** as colorless oil (8.0 mg, 65 % yield). IR $\nu_{max}$ (neat)/$cm^{-1}$ 2967, 2931, 1732, 1455, 1372, 1172, 1070, 735, 697; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.28 (5H, m), 5.35 (1H, m), 5.26 (1H, m), 5.05 (1H, m), 4.66 (1H, d, *J* = 11.7 Hz), 4.51 (1H, d, *J* = 11.7 Hz), 3.98 (1H, dd, *J* = 8.3, 4.0 Hz), 3.56 (1H, dd, *J* = 7.9, 6.8 Hz), 3.23 (3H, s), 2.78 (1H, m), 2.14 (1H, ddd, *J* = 15.5, 4.9, 2.9 Hz), 1.96 – 1.82 (1H, m), 1.72 (3H, d, *J* = 2.9 Hz), 1.69 (1H, m), 1.67 (3H, d, *J* = 2.8 Hz), 1.59 (1H, m), 1.58 – 1.54 (1H, m), 1.26 (3H, d, *J* = 7.1 Hz), 1.00 (3H, d, *J* = 6.6 Hz), 0.91 (3H, t, *J* = 7.4 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 203.8, 201.1, 174.0, 138.8, 128.5, 127.9, 127.7, 102.6, 99.2, 91.3, 90.8, 83.0, 75.9, 70.8, 54.4, 44.9, 37.9, 35.3, 25.1, 20.5, 17.4, 15.5, 13.8, 9.9; MS (ESI+) calculated for $[C_{27}H_{36}O_4 + Na]^+$: 447.3, found: 447.3.



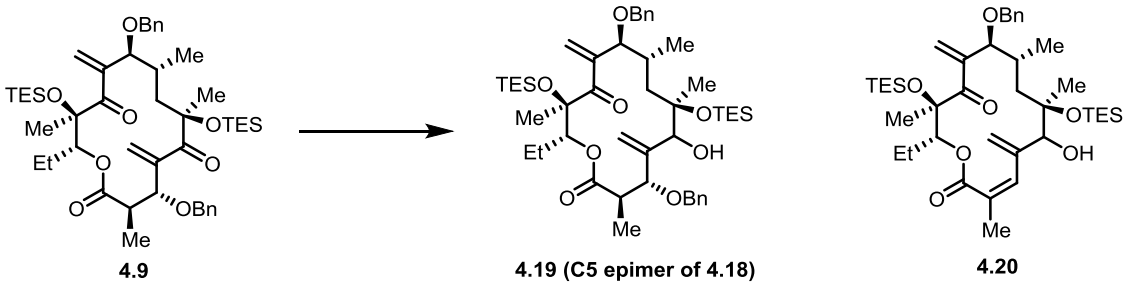

Macrolactone **4.12** (6 mg, 0.014 mmol), DABCO (8 mg, 0.071 mmol) and imminium salt (10 mg, 0.11 mmol) was dissolved in anhydrous DCM (1 mL) and stirred at rt for 5 min. Osmium tetroxide (0.2 mL of 0.2 M solution is DCM, 0.04 mmol) was added. The reaction was stirred at rt for 50 min before quenched with saturated aqueous solution of $Na_2SO_3$ (2 mL). The aqueous layer was extracted with DCM (2 x 5 mL) and the combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (20 % acetone in hexanes) to afford **4.13** as colorless oil (3 mg, 40 % yield). To a solution of **4.13** (3 mg, 5 μmol) and DMAP (5 mg, 0.045 mmol) in anhydrous DCM (1.5 mL) was added triethylamine (70 μL, 0.49 mmol) and TMSCl (50 μL, 0.39 mmol) at rt. The reaction was stirred at rt for 10 h before diluted with DCM (5 mL), washed with saturated aqueous $NaHCO_3$ (5 mL) and water (5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (20 % ethyl acetate in hexanes) to afford TMS-ether as colorless oil (2 mg, 55 % yield). To a solution of TMS-ether (2 mg, 2.5 μmol) in DCM (1 mL) and saturated aqueous $NaHCO_3$ (0.2 mL) was added *m*CPBA (5 mg, 20 μmol) at 0 ºC. The reaction was stirred at 0 ºC for 10 min then was allowed to warm to rt over 1h before diluted with DCM (5 mL), washed with saturated aqueous $Na_2SO_3$ (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The organic layer was dried over anhydrous sodium sulfate,

filtered and concentrated under reduced pressure. The crude product was purified with FCC (4 % ethyl acetate in hexanes) to afford **4.15** as colorless oil (1 mg, 50 % yield). IR $\nu_{max}$ (neat)/cm$^{-1}$ 2957, 1739, 1456, 1254, 1165, 1027, 842; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.31 (5H, m), 7.02 (1H, s), 6.02 (1H, s), 5.88 (2H, d, *J* = 4.6 Hz), 5.09 (1H, m), 4.72 (1H, m), 4.50 – 4.41 (2H, m), 4.01 (1H, s), 3.16 (3H, s), 2.64 (1H, m), 2.06 (1H, m), 1.96 – 1.91 (1H, m), 1.55 (3H, s), 1.49 (3H, m), 1.38 (3H, s), 1.28 (3H, m), 0.91 – 0.83 (6H, m), 0.17 (9H, s), 0.11 (9H, s); MS (ESI+) calculated for $[C_{35}H_{56}O_8Si_2 + Na]^+$: 683.4, found: 683.4.



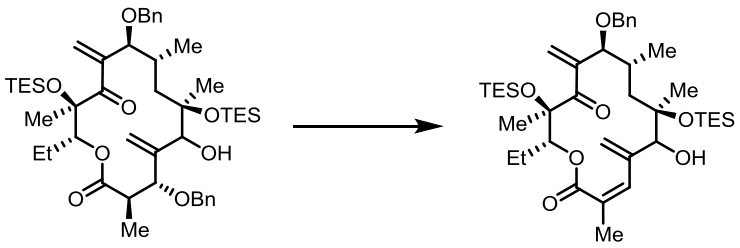

Bis-enone **4.9** (10 mg, 0.012 mmol) was dissolved in 1.5 mL anhydrous MeOH. The solution was cooled to 0 ºC before sodium borohydride (8 mg, 0.21 mmol) was added. The reaction was stirred at 0 ºC for 15 min and quenched with saturated aqueous $NH_4Cl$ (2 mL). The mixture was extracted with DCM (3 x 3 mL) and the resulting organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified with FCC (3 % ethyl acetate in hexanes) to afford alcohol **4.18** as colorless oil (6.5 mg, 65 %). IR $\nu_{max}$ (neat)/cm$^{-1}$ 2957, 2877, 1742, 1669, 1456, 1160, 1070, 1026. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.19 (10H, m), 6.99 (1H, s), 6.07 (1H, s), 5.16 (1H, m), 4.76 (1H, d, *J* = 10 Hz), 4.46 – 4.36 (2H, m), 4.31 (1H, d, *J* = 10

Hz), 4.16 (1H, d, *J* = 10 Hz), 2.67 (1H, m), 2.08 – 1.93 (2H, m), 1.83 (1H, m), 1.54 (4H, d, *J* = 14.7 Hz), 1.48 – 1.36 (4H, m), 1.36 – 1.21 (5H, m), 1.08 (3H, m), 0.98 (17H, m), 0.92 – 0.83 (5H, m), 0.83 – 0.60 (14H, m); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 202.0, 173.6, 151.9, 142.6, 139.8, 139.2, 128.4, 128.3, 128.2, 127.6, 127.5, 127.3, 127.2, 98.4, 84.2, 80.6, 79.1, 76.3, 71.0, 69.6, 46.6, 43.2, 34.8, 29.9, 29.4, 22.5, 19.0, 17.2, 10.9, 10.3, 10.3, 7.3, 7.2, 7.1, 6.8; MS (ESI+) calculated for $[C_{47}H_{74}O_8Si_2 + Na]^+$: 845.5, found: 845.4.



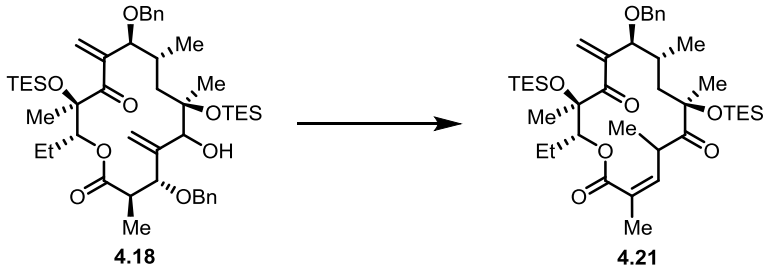

A solution of zinc borohydride (0.4 mL of 0.2 M diethyl ether solution, 0.08 mmol) was added to a solution of macrolactone **4.9** (10 mg, 0.012 mmol) in diethyl ether (0.5 mL) at 0 ºC. The reaction was stirred at 0 ºC for 0.5 h before ice bath was removed. The reaction was stirred at rt for 3 h before quenched with saturated aqueous $NH_4Cl$ (2 mL) and extracted with diethyl ether (2 x 5 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified with FCC (3 % ethyl acetate in hexanes) to afford product **4.19** as colorless oil (3 mg, 30 % yield) and LY2-52 (1.7 mg, 20 % yield). **4.19**: IR $\nu_{max}$ (neat)/cm$^{-1}$ 2955, 2876, 1738, 1456, 1159, 1072, 1023, 732. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.17 (10H, m), 7.12 (1H, s), 6.09 (1H, s), 5.40 (1H, s), 5.35 (1H, s), 5.18 (1H, m), 4.53 – 4.31 (2H, m), 4.14 (1H, m), 2.81 (1H, m), 2.54 (1H, m), 2.00 (1H, m), 1.83 (2H, m), 1.69 (3H, m), 1.53

– 1.28 (9H, m), 1.27 – 1.17 (3H, m), 1.05 – 0.84 (24H, m), 0.71 – 0.50 (12H, m); **74H** MS (ESI+) calculated for $[C_{47}H_{74}O_8Si_2 + Na]^+$: 845.5, found: 845.4.

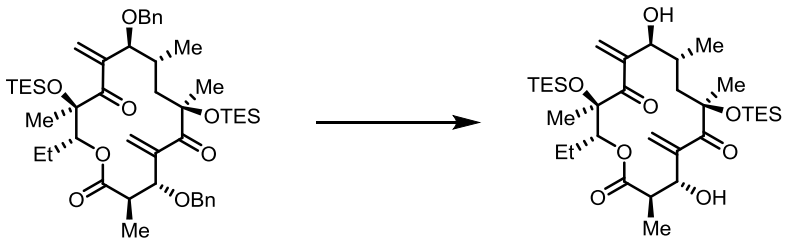



A solution of zinc borohydride (0.4 mL of 0.2 M diethyl ether solution, 0.08 mmol) was added to a solution of macrolactone alcohol **4.18** (3 mg, 3.6 μmol) in diethyl ether (0.5 mL) at 0 ºC. The reaction was stirred at 0 ºC for 0.5 h before ice bath was removed. The reaction was stirred at rt for 2 h before quenched with saturated aqueous $NH_4Cl$ (2 mL) and extracted with diethyl ether (2 x 5 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified with FCC (3 % ethyl acetate in hexanes) to afford product **4.20** as colorless oil (1.2 mg, 40 % yield). $[\alpha]^{24}_D$ = +5.0 (c = 0.1, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2956, 2877, 1741, 1455, 1157, 1024, 1000, 744; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.15 (10H, m), 7.07 (1H, s), 6.05 (1H, s), 5.52 (1H, d, *J* = 12 Hz), 5.23 (1H, dd, *J* = 7.6, 4.1 Hz), 4.54 (1H, s), 4.43 (1H, d, *J* = 11.6 Hz), 4.18 (1H, d, *J* = 11.6 Hz), 3.76 (1H, s), 3.27 (1H, m), 3.21 (1H, s), 2.00 (2H, m), 1.83 – 1.73 (3H, m), 1.51 – 1.41 (5H, m), 1.27 – 1.17 (4H, m), 1.02 – 0.85 (20H, m), 0.69 – 0.50 (12H, m); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 202.5, 173.1, 142.4, 138.6, 136.6, 128.5, 128.1, 127.8, 124.5, 83.7, 83.5, 80.7, 79.0, 78.8, 71.5, 41.5,

38.6, 32.2, 29.9, 25.8, 23.5, 19.2, 18.2, 17.7, 14.5, 11.8, 7.3, 7.2, 7.0, 6.7; MS (ESI+) calculated for $[C_{40}H_{66}O_7Si_2 + Na]^+$: 737.4, found: 737.5.

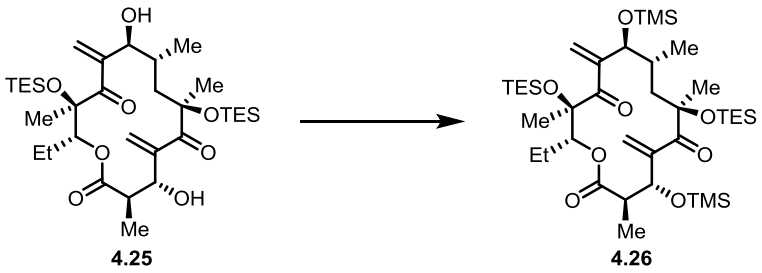



To flame-dried flask filled with argon was added macrolactone **4.18** (7 mg, 8.5 μmol) in 2 mL anhydrous DCM. Crabtree's catalyst (Aldrich BARF salt) was added as 10 mg/mL solution in DCM (0.2 mL, 1.3 μmol). The solution was purged with argon for 1 min then $H_2$ for 2 min then was stirred under positive pressure of $H_2$ (balloon). After 1 h, the mixture was concentrated under reduced pressure. The crude product was purified with FCC (3 % ethyl acetate in hexanes) to afford product **4.21** as colorless oil (4.5 mg, 74 % yield). $[\alpha]^{24}_D$ = +9.2 (c = 0.45, $CHCl_3$); $\nu_{max}$ (neat)/$cm^{-1}$ 2957, 2877, 1740, 1662, 1456, 1164, 743; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.12 (10H, m), 7.04 (1H, s), 6.16 (1H, s), 5.18 (1H, m), 4.37 (1H, d, *J* = 10 Hz), 4.25 – 4.12 (2H, m), 3.49 (1H, m), 1.95 (1H, ddd, *J* = 14.3, 7.6, 3.2 Hz), 1.86 (1H, s), 1.55 – 1.23 (14H, m), 0.93 (23H, m), 0.67 – 0.51 (10H, m); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 204.2, 201.0, 172.7, 143.3, 142.9, 139.0, 138.9, 131.1, 129.0, 128.5, 127.6, 127.5, 85.9, 84.1, 82.3, 79.6, 71.2, 49.9, 40.9, 33.8, 28.8, 23.0, 20.5, 16.7, 14.3, 13.3, 11.4, 7.3, 7.2, 6.9, 6.7, 0.2; MS (ESI+) calculated for $[C_{40}H_{66}O_7Si_2 + Na]^+$: 737.4, found: 737.3.

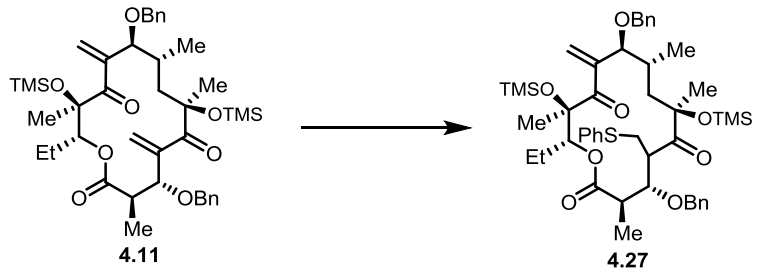



**4.9** **4.25**

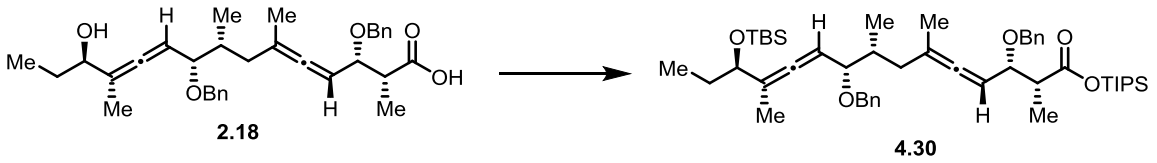
To a solution of macrolactone **4.9** (5 mg, 6.1 μmol) in DCM (2 mL) was added 50 μL pH = 7.4 phosphate buffer. DDQ (26 mg, 0.12 mmol) was added at rt. The reaction was heated to 40 ºC and then stirred for 12 h. To the reaction was added saturated aqueous $NaHCO_3$ solution (5 mL) and the resulting mixture was stirred at rt for 30 min. The aqueous layer was extracted with DCM (3 x 5 mL) and the combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (30 % to 40 % ethyl acetate in hexanes) to afford diol **4.25** as colorless oil (1.5 mg, 40 % yield). IR $\nu_{max}$ (neat)/$cm^{-1}$ 3445 (broad), 2957, 2934, 2878, 1738, 1660, 1456, 1374, 1165, 1026; $^1$H NMR (500 MHz, $CDCl_3$) δ 6.94 (1H, s), 6.40 (1H, s), 6.26 (1H, s), 6.13 (1H, s), 5.30 (1H, m), 5.13 (1H, d, *J* = 10 Hz), 4.73 (1H, m), 4.30 (1H, m), 4.13 (1H, s), 2.74 (1H, m), 2.16 (1H, m), 2.10 – 1.97 (3H, m), 1.44 – 1.36 (10H, m), 1.26 (2H, s), 0.90 (22H, m), 0.74 – 0.69 (3H, m), 0.59 (10H, m); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 206.1, 201.9, 173.9, 145.8, 145.2, 129.3, 127.1, 84.0, 78.9, 77.7, 73.4, 69.2, 46.3, 44.6, 34.4, 31.4, 29.9, 21.6, 19.4, 16.5, 10.8, 10.8, 7.2, 6.7 (2); MS (ESI+) calculated for $[C_{33}H_{60}O_8Si_2 + Na]^+$: 663.4, found: 663.3.




To a solution of diol **4.25** (4 mg, 6.3 μmol) and DMAP (3 mg, 0.024 mmol) in anhydrous DCM (1.5 mL) was added triethylamine (70 μL, 0.49 mmol) and TMSCl (50 μL, 0.39 mmol) at rt. The reaction was stirred at rt for 1 h before diluted with DCM (5 mL), washed with saturated aqueous $NaHCO_3$ (5 mL) and water (5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (3 % ethyl acetate in hexanes) to afford **4.26** as colorless oil (4 mg, 82 % yield). IR $\nu_{max}$ (neat)/$cm^{-1}$ 3445 (broad), 2957, 2879, 1739, 1659, 1457, 1374, 1075, 876.8, 842.3; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.01 (1H, s), 6.44 (1H, s), 6.38 (1H, s), 6.11 (1H, s), 5.02 (1H, d, *J* = 10.5 Hz), 4.96 (1H, d, *J* = 10.4 Hz), 4.49 (1H, s), 4.42 (1H, s), 2.68 (1H, m), 2.08 – 2.00 (2H, m), 1.50 (3H, m), 1.38 – 1.23 (11H, m), 0.88 (22H, m), 0.64 – 0.55 (11H, m), 0.06 – 0 (18H, m); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 203.3, 201.3, 173.5, 146.2, 145.6, 131.3, 128.2, 84.4, 79.0, 76.5, 73.6, 67.7, 48.0, 47.5, 34.6, 31.3, 21.6, 19.1, 17.0, 10.6, 9.9, 7.2 (2), 6.8 (2), 0.3 (2); MS (ESI+) calculated for $[C_{39}H_{76}O_8Si_4 + Na]^+$: 807.5, found: 807.4.

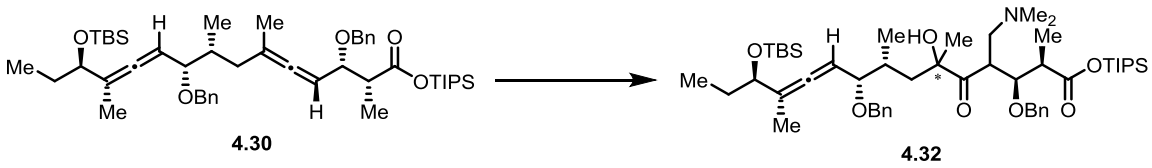



Macrolactone **4.11** (2.4 mg, 3.3 μmol) and triethylamine (50 μL, 0.35 mmol) was dissolved in 0.5 mL DCM. Lithium perchlorate (20 mg, 0.2 mmol) was added followed by thiophenol (75 μL, 0.72 mmol). Reaction was stirred at rt for 30 min before washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (2 % ethyl acetate in hexanes) to afford **4.27** as colorless oil (1 mg, 40 % yield, mixture of epimers at C4, dr = 5:4 by $^1$H NMR). $^1$H NMR (mixture of diastereomers) 500 MHz, $CDCl_3$) δ 7.41 (7H, m), 7.37 – 7.20 (20H, m), 7.20 – 7.05 (3H, m), 6.14 (1H, m), 6.08 (1H, m), 5.13 (2H, m), 5.03 (1H, m), 4.88 (1H, m), 4.76 (1H, m), 4.67 (1H, m), 4.59 (1H, m), 4.52 (1H, m),4.45 – 4.26 (4H, m), 4.20 (1H, m), 4.03 (1H, m), 3.68 (3H, m), 3.56 (1H, m), 3.48 (3H, m), 3.36 (5H, m), 3.13 – 2.99 (1H, m), 2.80 (1H, m), 2.42 (1H, m), 2.11 (2H, m), 1.91 (4H, m), 1.72 (4H, m), 1.63 (4H, m),1.58 – 1.09 (28H, m), 1.07 – 0.82 (10H, m), 0.24 – 0.05 (16H, m); MS (ESI+) calculated for $[C_{47}H_{66}O_8SSi_2+ Na]^+$: 869.4, found: 869.3.




To a solution of **2.18** (100 mg, 0.193 mmol) in DCM (4 mL) was added TIPSCl (50 μL, 0.233 mmol) and imidazole (18 mg, 0.264 mmol) at rt. The reaction was stirred at rt for 30 min then before diluted with DCM (10 mL), washed with water (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was dissolved in 4 mL DCM followed by the addition of DMAP (4 mg, 0.03 mmol) and imidazole (18 mg, 0.264 mmol). TBSCl (80 mg, 0.53 mmol) was added at rt and the reaction was stirred for 4 h before diluted with DCM (10 mL) and washed with water (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (2 % ethyl acetate in hexanes) to afford protected bis-allene **4.30** as colorless oil (114 mg, 75 % yield). $[\alpha]^{26}_{D}$ = +24.0 (c = 1.0, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2946, 2868, 1716, 1455, 1250, 1066, 841; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.19 (10H, m), 5.05 (1H, m), 4.95 (1H, m), 4.72 – 4.63 (2H, m), 4.43 – 4.33 (2H, m), 4.16 (1H, dd, *J* = 8.0, 5.6 Hz), 4.00 (1H, t, *J* = 6.5 Hz), 3.64 (1H, dd, *J* = 9.1, 5.7 Hz), 2.76 – 2.66 (1H, m), 2.35 (1H, m), 1.88 (1H, m), 1.86 – 1.75 (1H, m), 1.72 (3H, d, *J* = 2.8 Hz), 1.66 (3H, d, *J* = 2.8 Hz), 1.63 – 1.47 (5H, m), 1.36 – 1.22 (3H, m), 1.07 (18H, d, *J* = 7.5 Hz), 1.00 (3H, d, *J* = 6.6 Hz), 0.91 – 0.82 (12H, m), 0.02 – 0 (6H, d, *J* = 8.3 Hz); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 203.5, 202.8, 174.3, 139.1, 138.9, 128.4, 128.3, 127.9, 127.7, 127.5, 127.4, 102.3, 99.0, 89.9, 88.9, 82.3, 79.9, 75.8, 70.7, 70.1, 47.2, 38.3, 36.7, 29.5, 26.1, 18.6, 18.4, 18.0, 15.5,

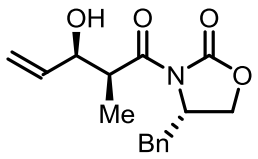
13.7, 12.8, 12.1, 10.3, -4.3, -4.8; (TBS group exhibits two methyl peaks at -4.3 ppm and -4.8 ppm); MS (ESI+) calculated for $[C_{48}H_{76}O_5Si_2 + Na]^+$: 811.5, found: 811.4.



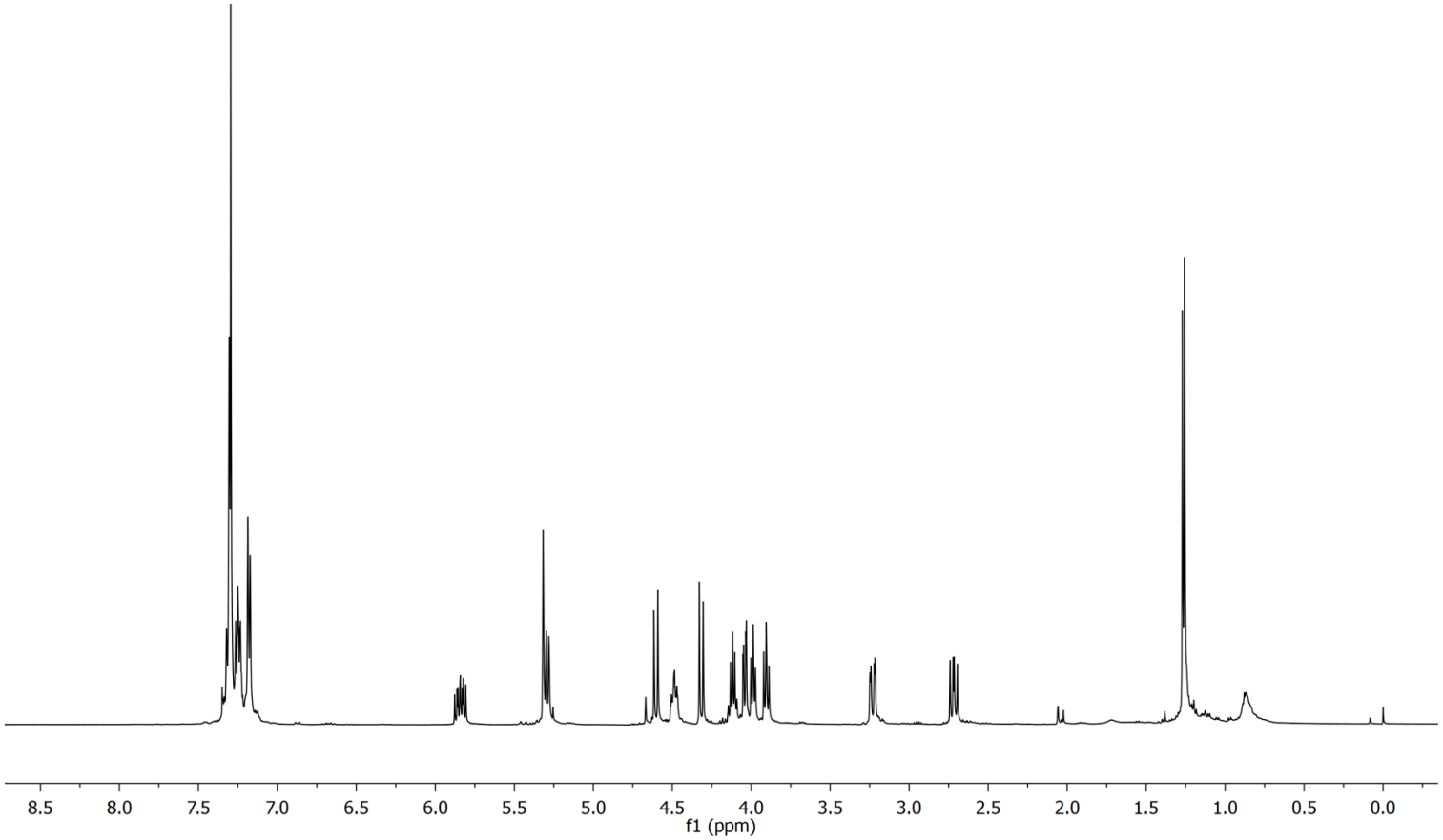

Bis-allene **4.30** (17 mg, 0.022 mmol) and imminium salt (20 mg, 0.21 mmol) was dissolved in anhydrous DCM (0.7 mL) and stirred at rt for 5 min. Osmium tetroxide (0.32 mL of 0.2 M solution is DCM, 0.064 mmol) was added. The reaction was stirred at rt for 4 h before quenched with saturated aqueous solution of $Na_2SO_3$ (2 mL). The aqueous layer was extracted with DCM (2 x 5 mL) and the combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified with FCC (20 % ethyl acetate in hexanes) to afford major stereoisomer **4.32a** (5.2 mg, 28 % yield) and minor stereoisomer **4.32b** (2.5 mg, 13 % yield), both as colorless oil. **4.32a**: $[\alpha]^{23}_D$ = -2.73 (c = 1.0, $CHCl_3$); IR $\nu_{max}$ (neat)/$cm^{-1}$ 2953, 2867, 1713, 1463, 1257, 1066; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.19 (10H, m), 4.97 (1H, dd, *J* = 9.1, 2.8 Hz), 4.64 (3H, m), 4.40 (1H, d, *J* = 12.0 Hz), 4.25 (1H, m), 4.01 (1H, m), 3.70 (2H, m), 2.63 (1H, d, *J* = 11.0 Hz), 2.58 – 2.48 (2H, m), 2.15 (6H, s), 2.08 – 1.98 (1H, m), 1.95 (1H, s), 1.71 (3H, d, *J* = 2.7 Hz), 1.53 (4H, m), 1.31 (2H, m), 1.26 (3H, d, *J* = 7.1 Hz), 1.21 (3H, s), 1.15 – 1.02 (21H, m), 0.92 – 0.80 (12H, m), 0.06 – -0.02 (6H, m); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 219.6, 202.9, 175.0, 139.1, 138.9, 128.4 (2), 127.9, 127.6 (2), 127.4, 102.0, 82.8, 79.2, 78.5, 75.8, 74.3, 69.9, 59.9, 48.9, 45.6, 44.7,

41.6, 34.0, 29.6, 26.8, 26.1, 18.4, 18.1, 18.0, 17.9, 13.6, 12.2, 10.5, -4.4, -4.8; MS (ESI+) calculated for $[C_{51}H_{85}NO_7Si_2 + H]^+$: 880.6, found: 880.5.

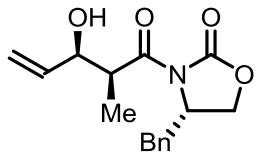
$^1$H NMR (500 MHz, $CDCl_3$)



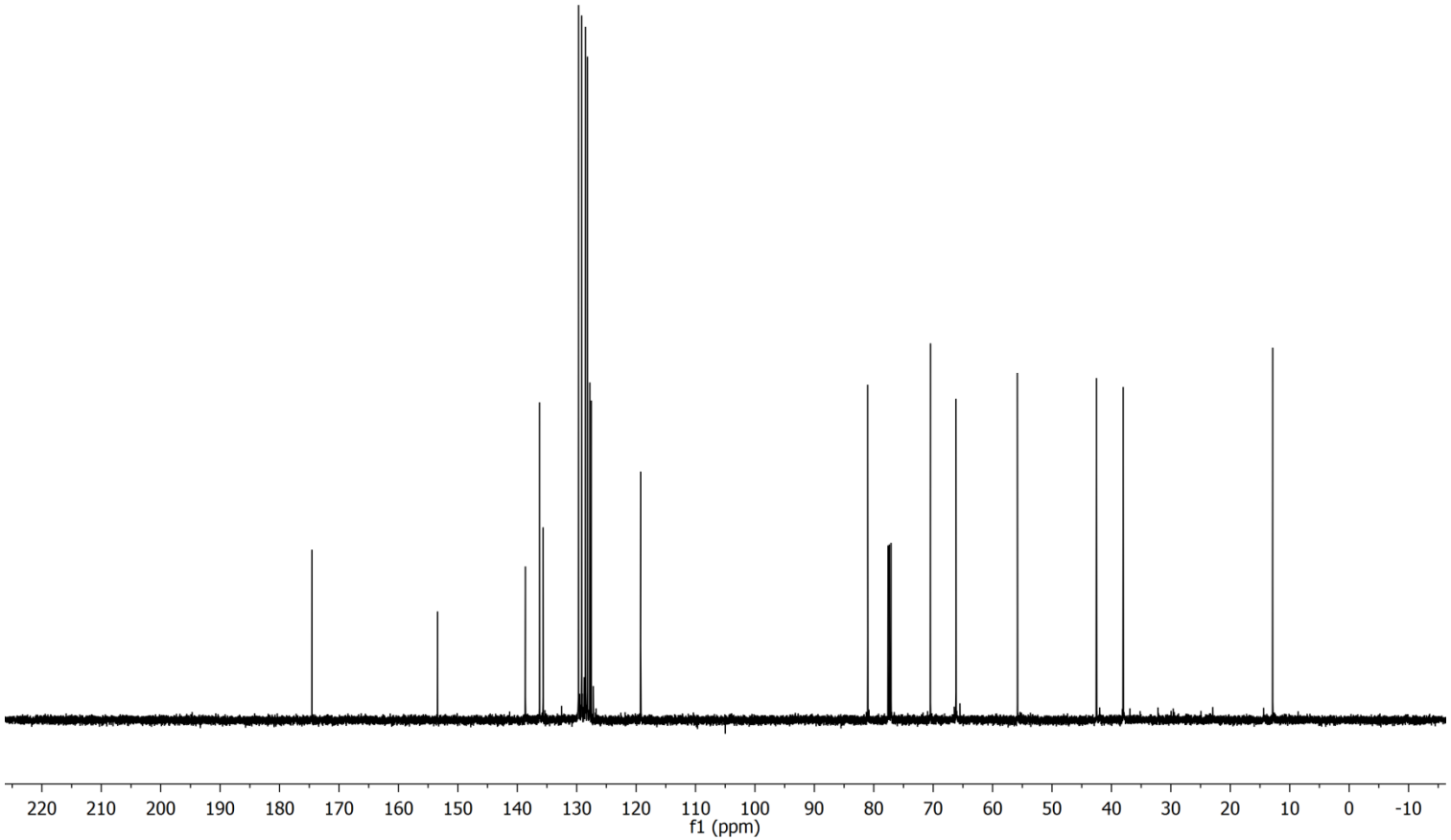

**2.9**



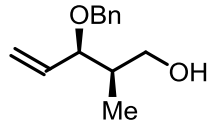
$^{13}$C NMR (126 MHz, $CDCl_3$)



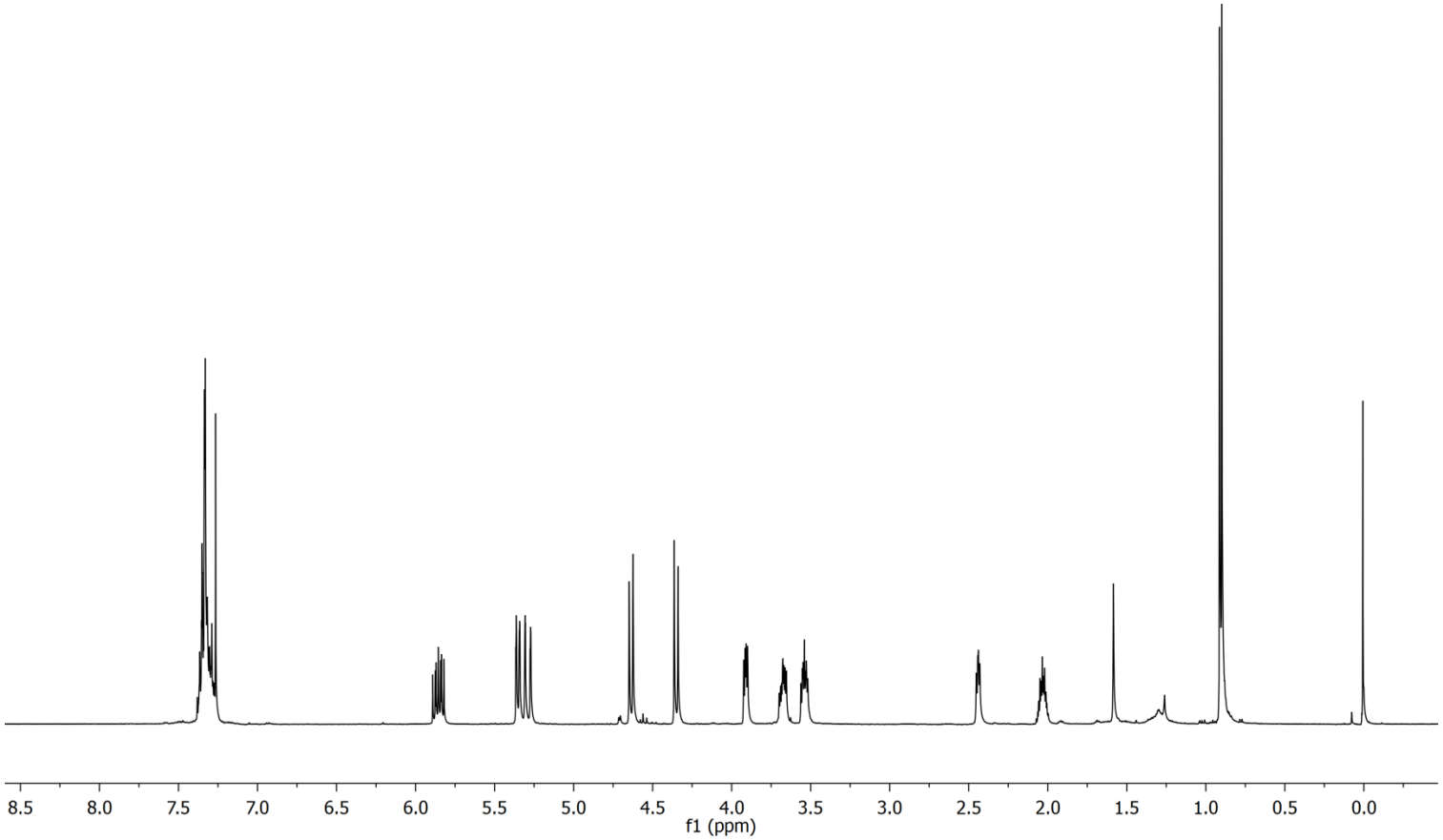

**2.9**



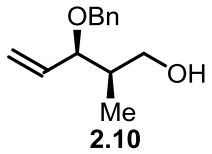
$^1$H NMR (500 MHz, $CDCl_3$)




**2.10**

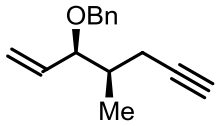


$^{13}$C NMR (126 MHz, $CDCl_3$)

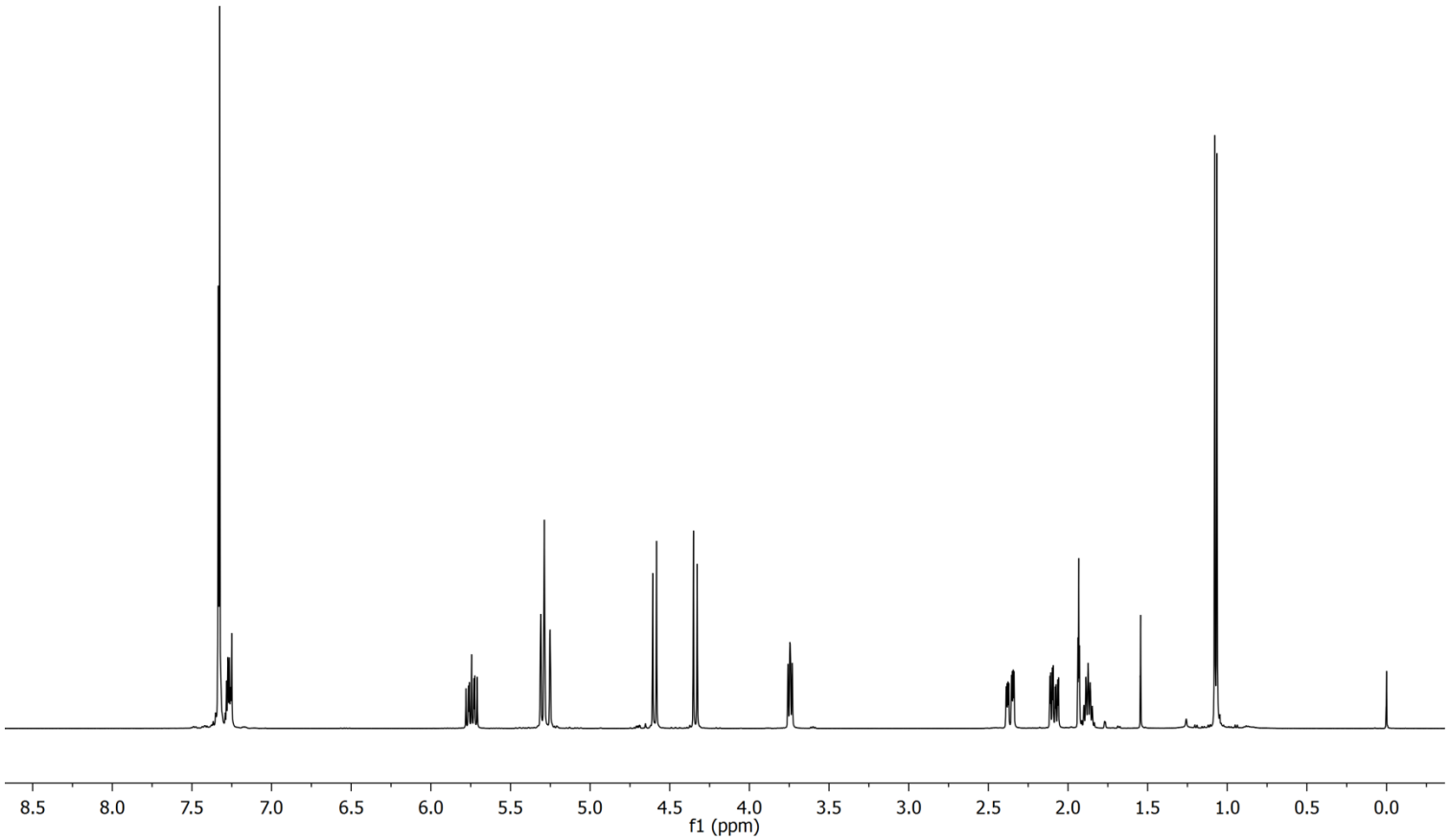



**2.10**

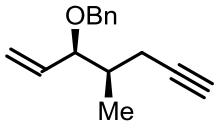
$^1$H NMR (500 MHz, $CDCl_3$)



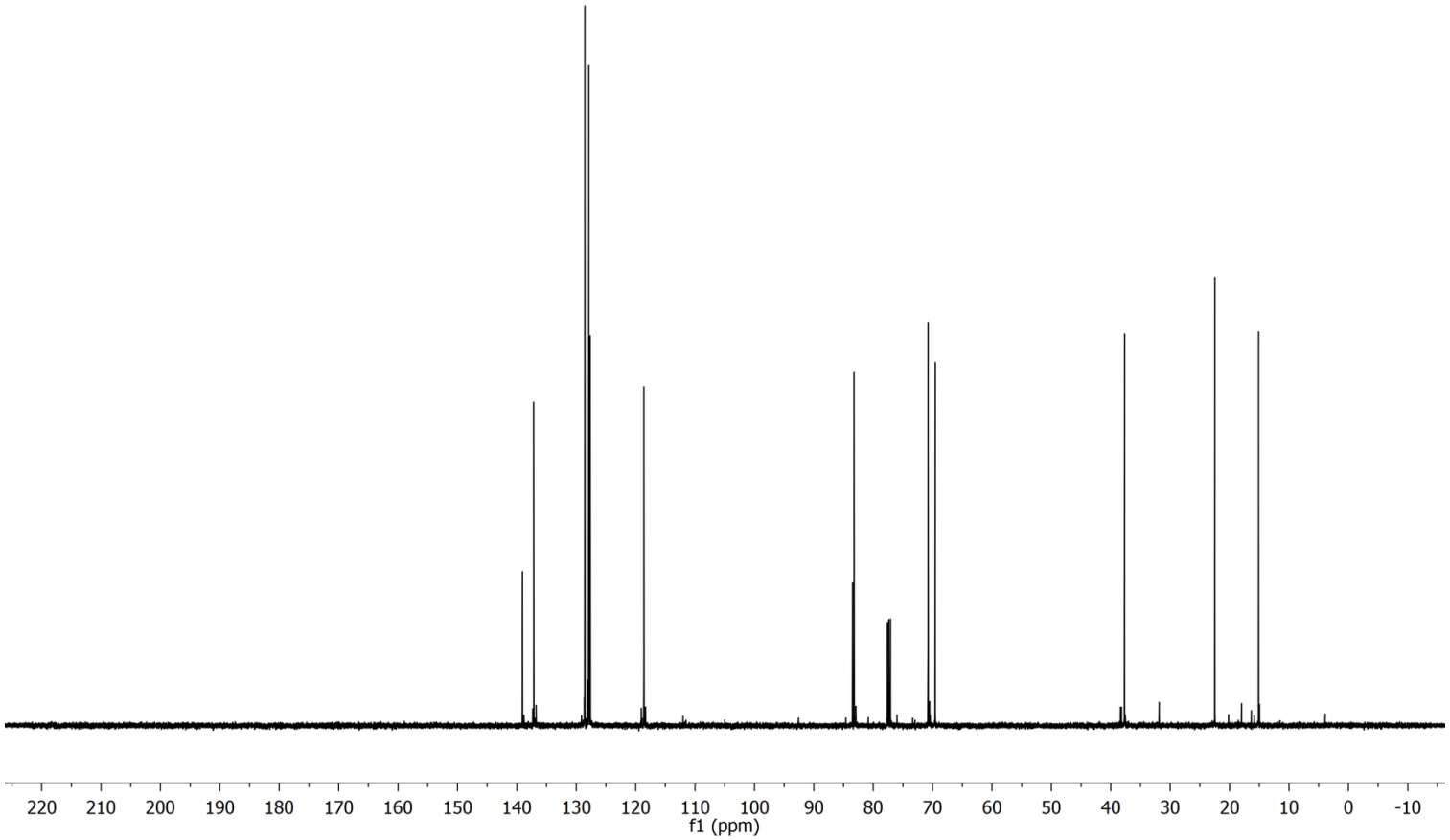

**2.4**



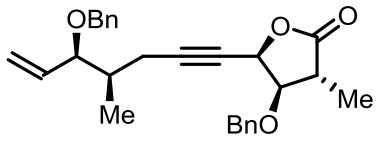
$^{13}C$ NMR (126 MHz, $CDCl_3$)



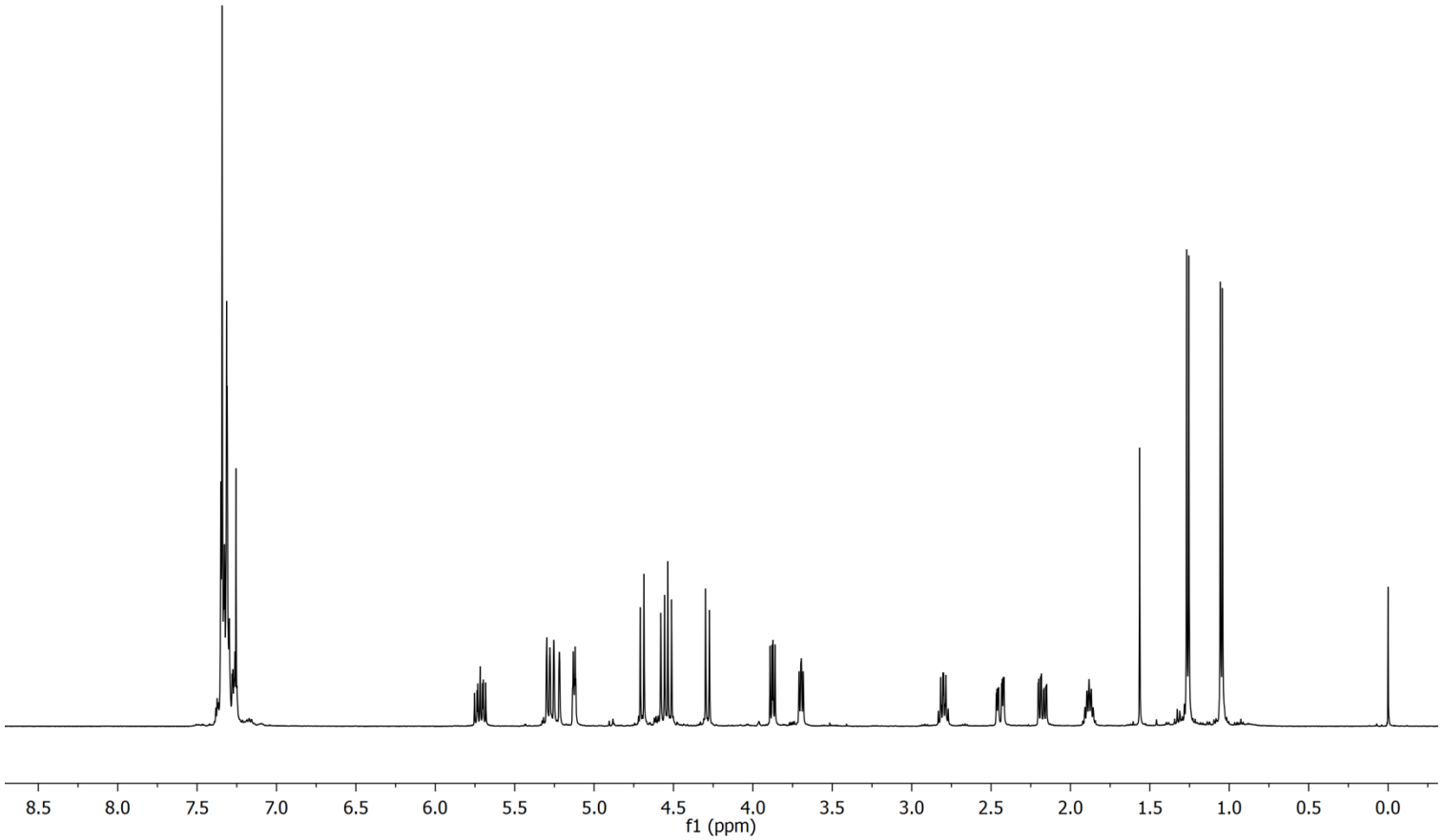

**2.4**



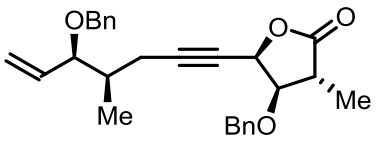
$^1$H NMR (500 MHz, $CDCl_3$)




**2.15**

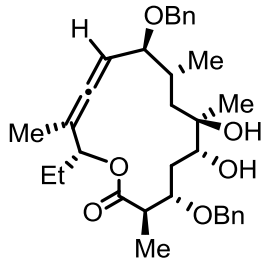


$^{13}$C NMR (126 MHz, $CDCl_3$)



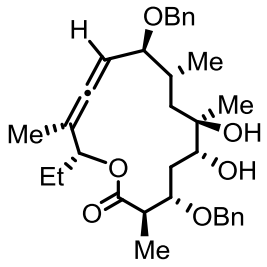

**2.15**

$^1$H NMR (500 MHz, $CDCl_3$)



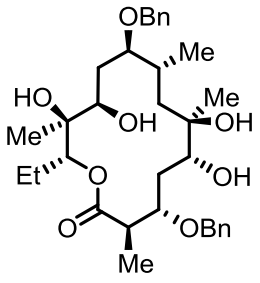

**2.23**

$^{13}$C NMR (126 MHz, $CDCl_3$)



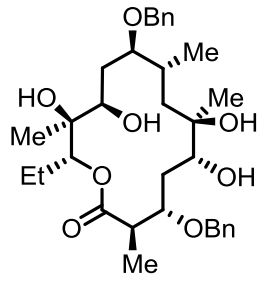

**2.23**

$^1$H NMR (500 MHz, $CDCl_3$)



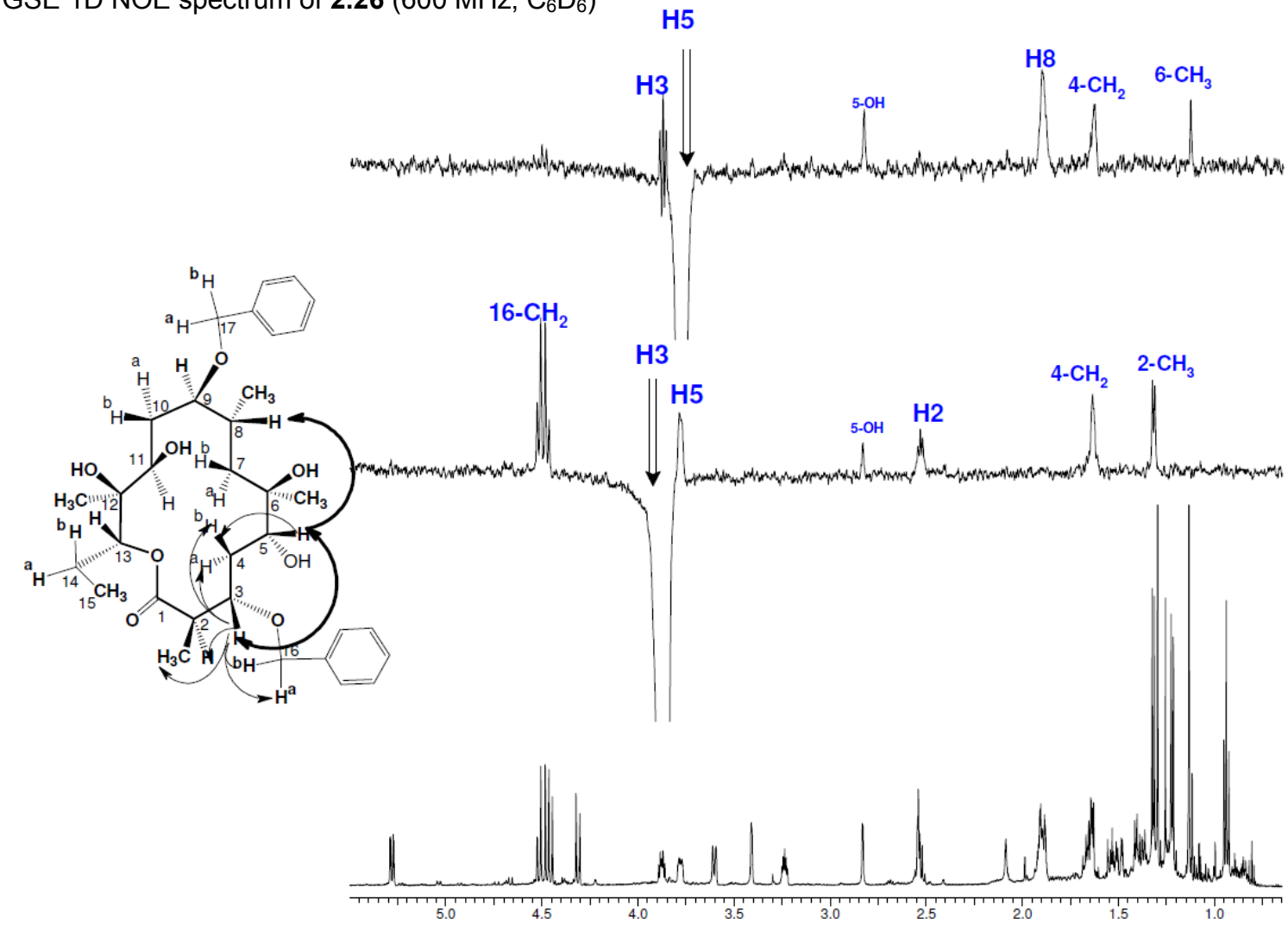

**2.26**

$^{13}$C NMR (126 MHz, $C_6D_6$)

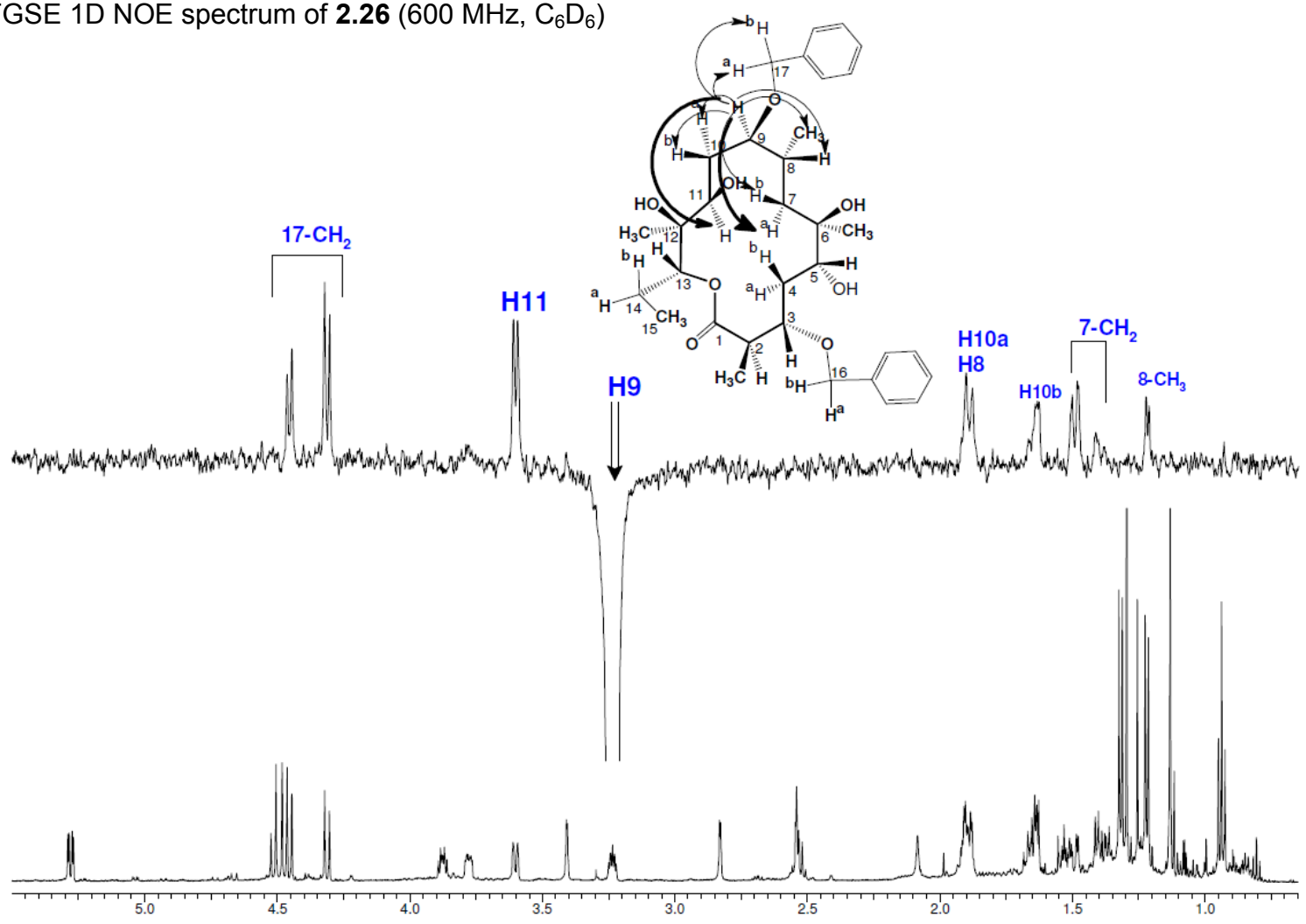



**2.26**

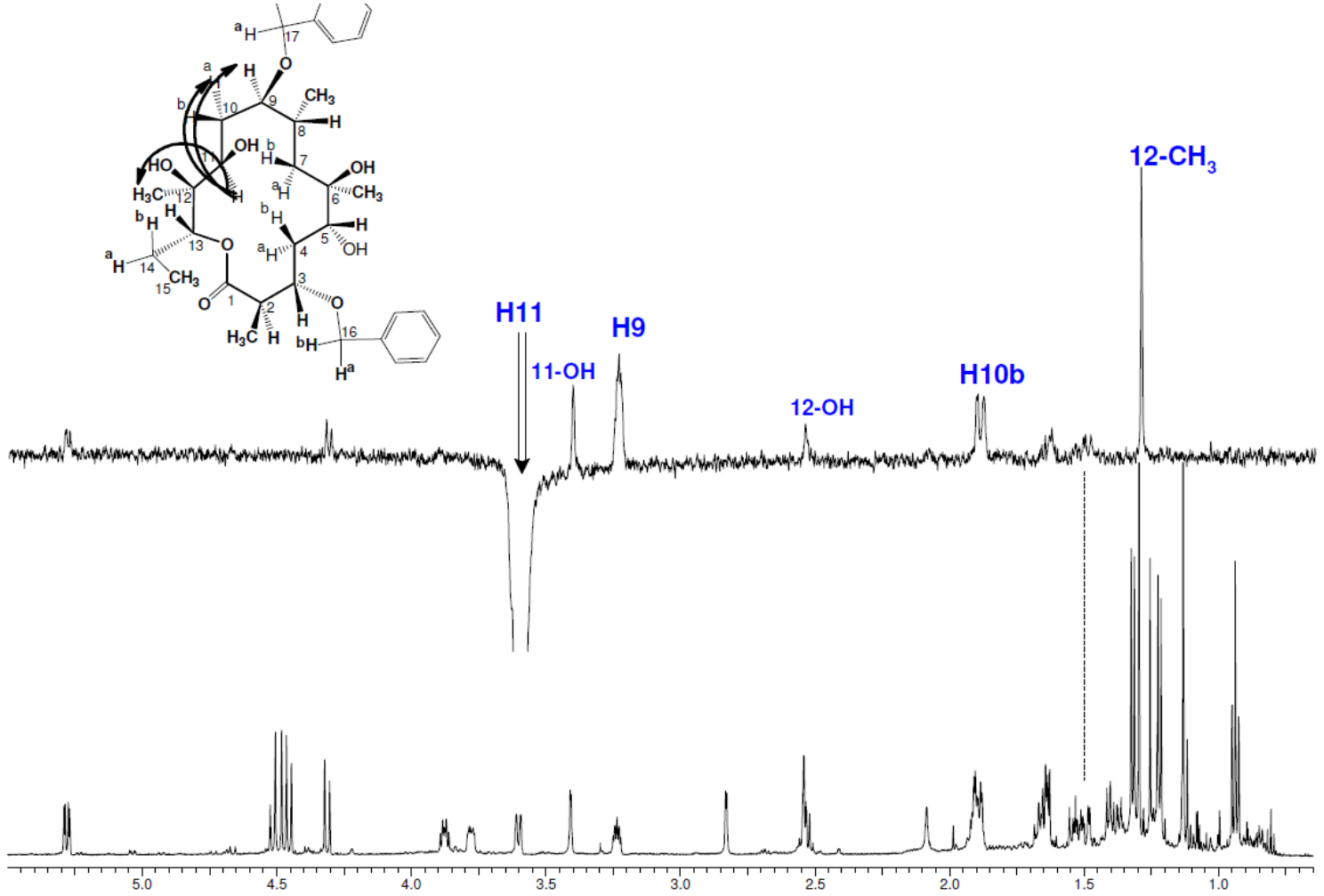
DPFGSE 1D NOE spectrum of **2.26** (600 MHz, $C_6D_6$)

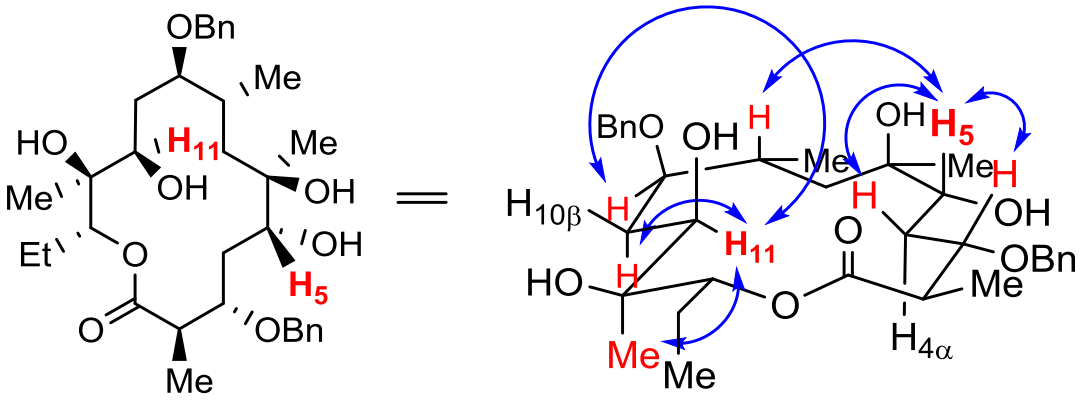


DPFGSE 1D NOE spectrum of **2.26** (600 MHz, $C_6D_6$)



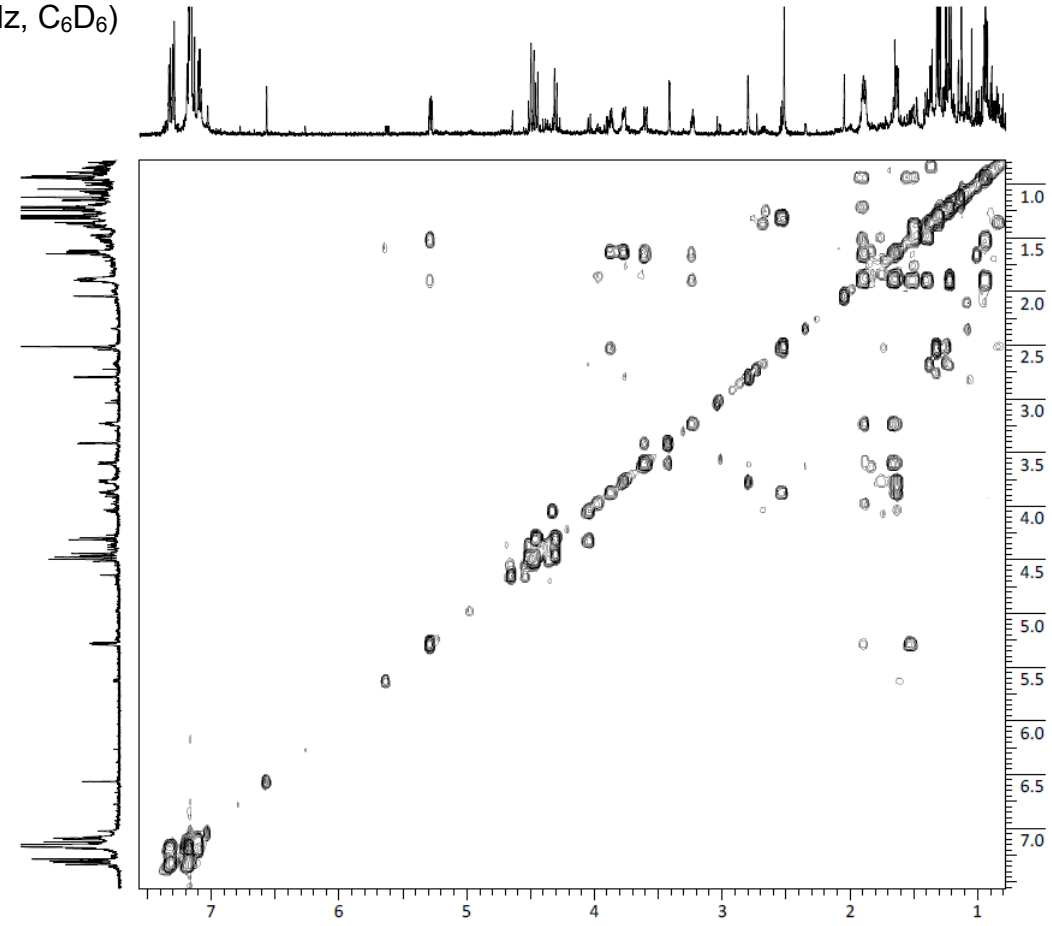
DPFGSE 1D NOE spectrum of **2.26** (600 MHz, $C_6D_6$)



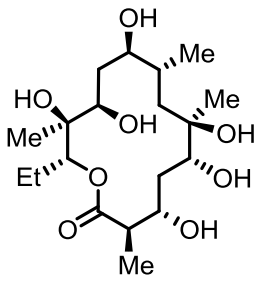



key nOe signals of **2.26** (600 MHz, $C_6D_6$)

gCOSY spectrum of **2.26** (600 MHz, $C_6D_6$)

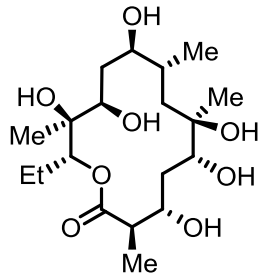


$^1$H NMR (500 MHz, $CD_3OD$)



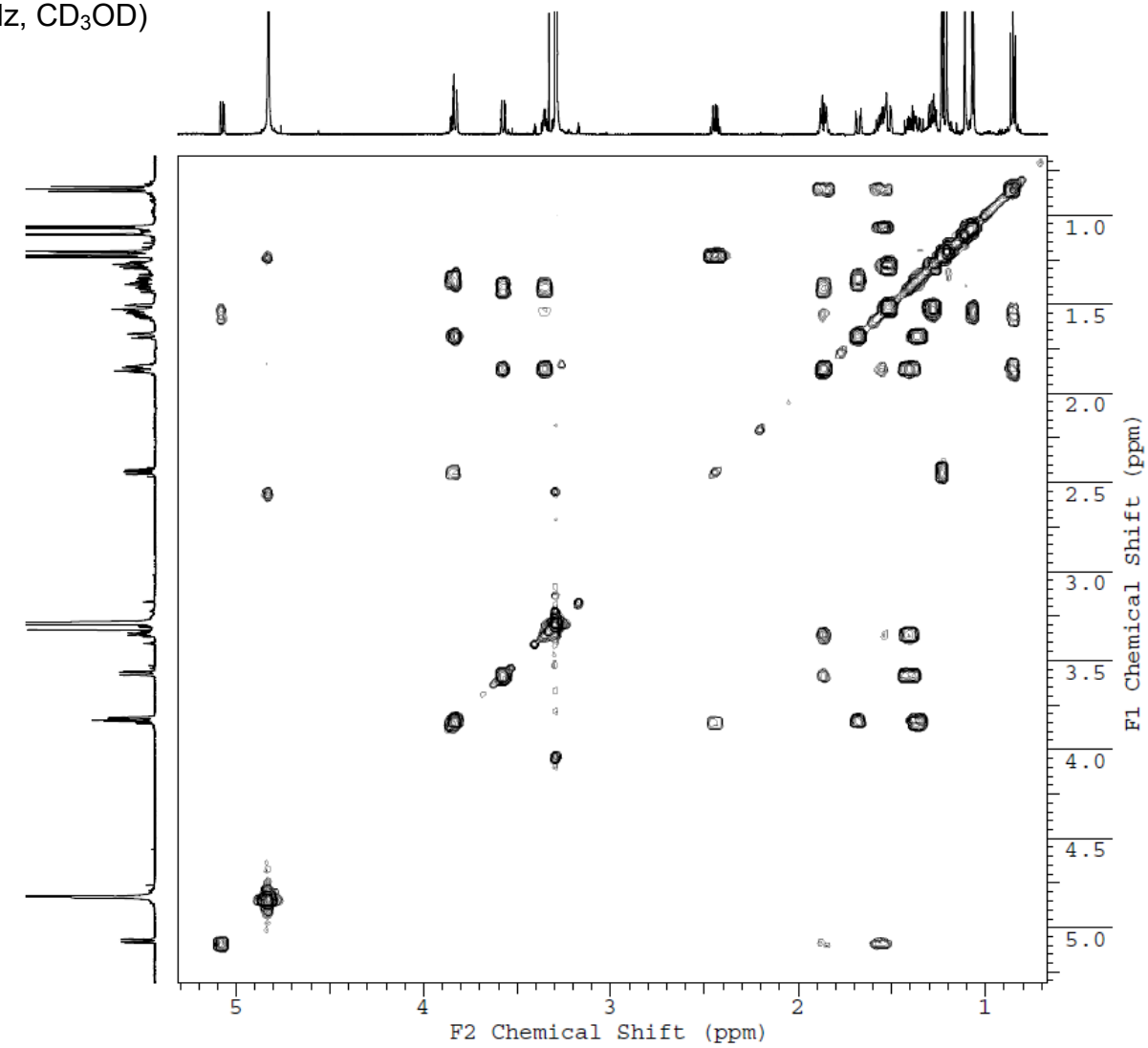

**2.3**

$^{13}$C NMR (126 MHz, $CD_3OD$)

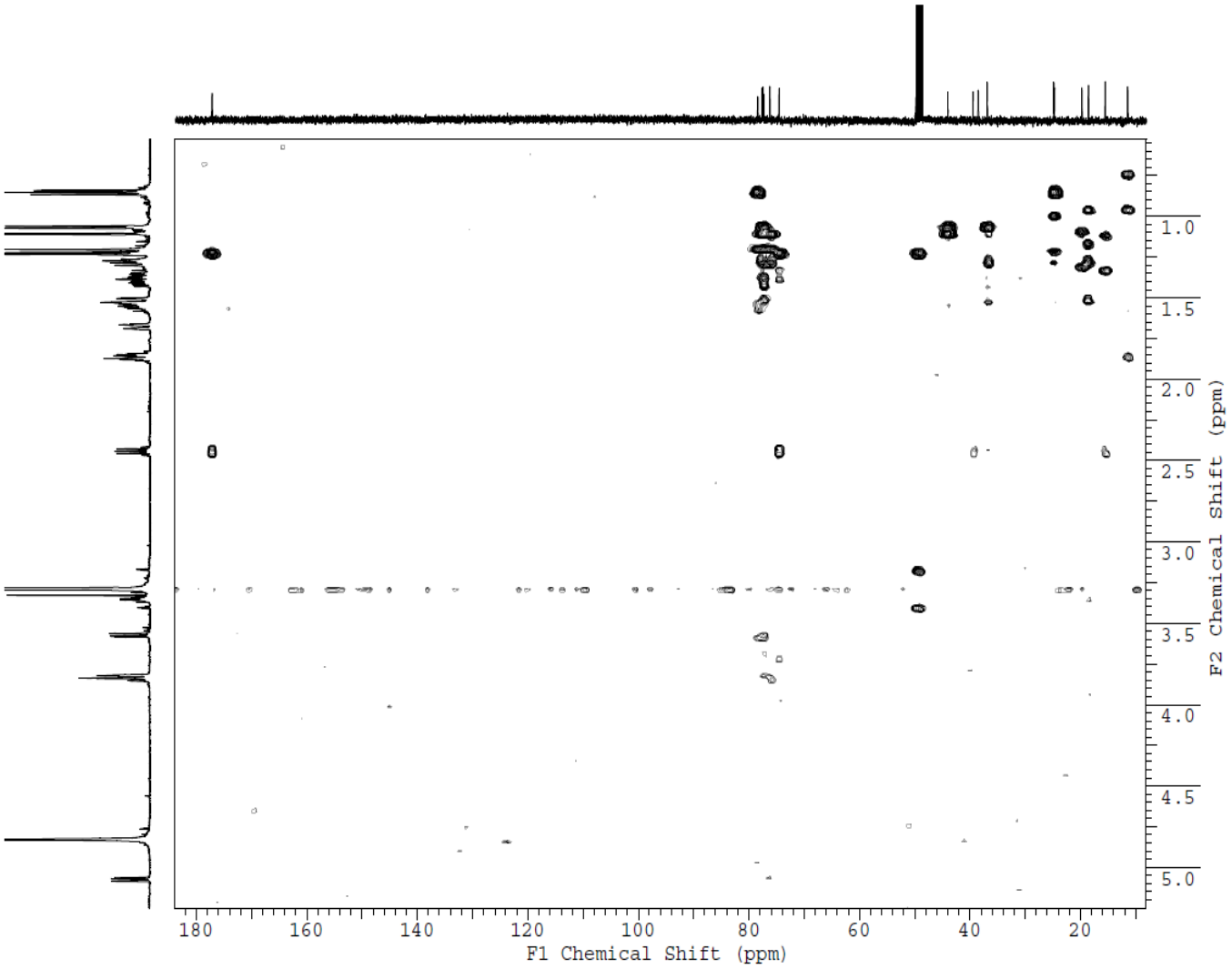



**2.3**

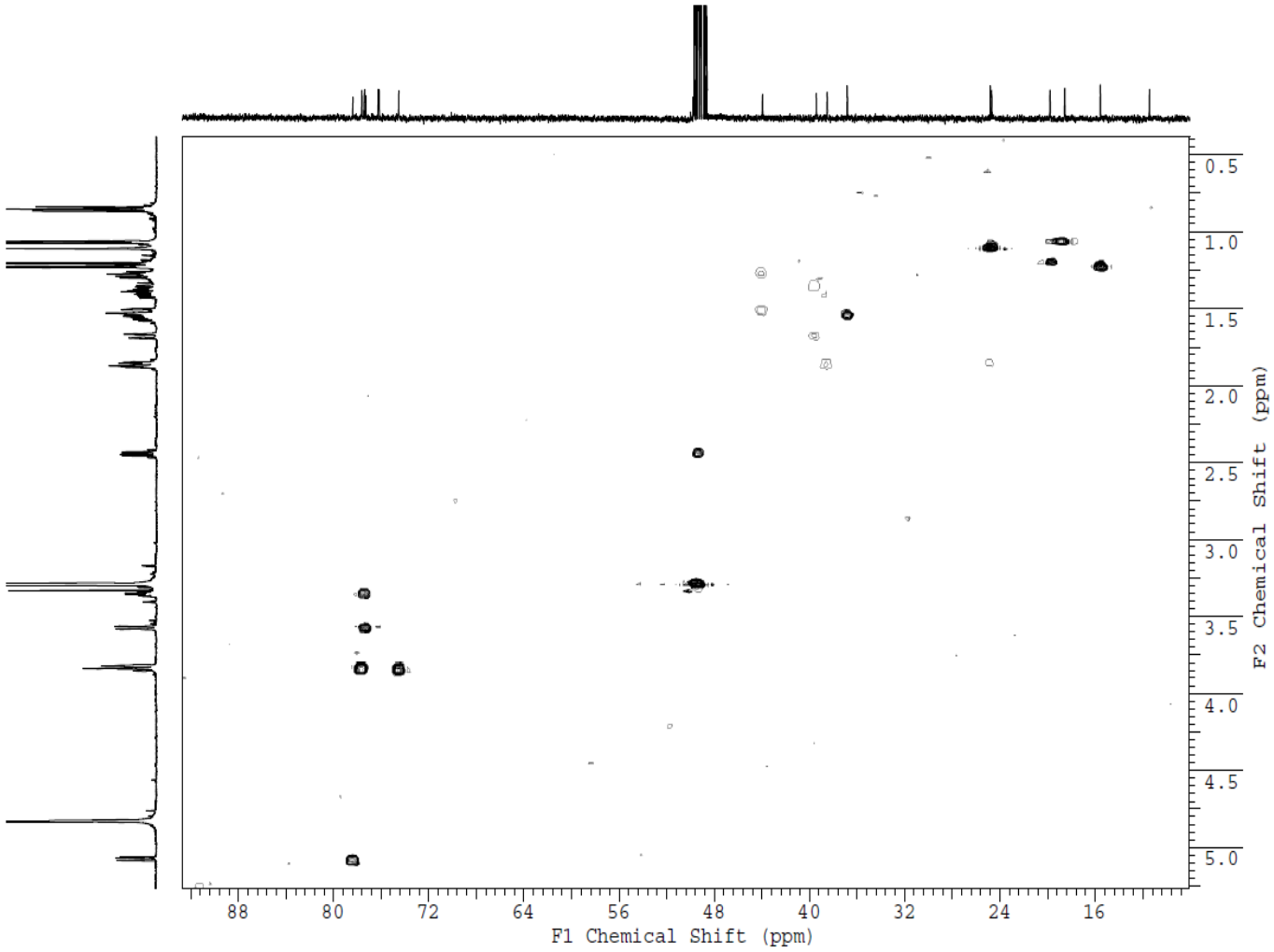
gCOSY spectrum of **2.3** (600 MHz, $CD_3OD$)



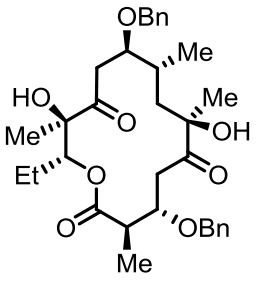
gHMBC spectrum of **2.3** (600 MHz, $CD_3OD$)



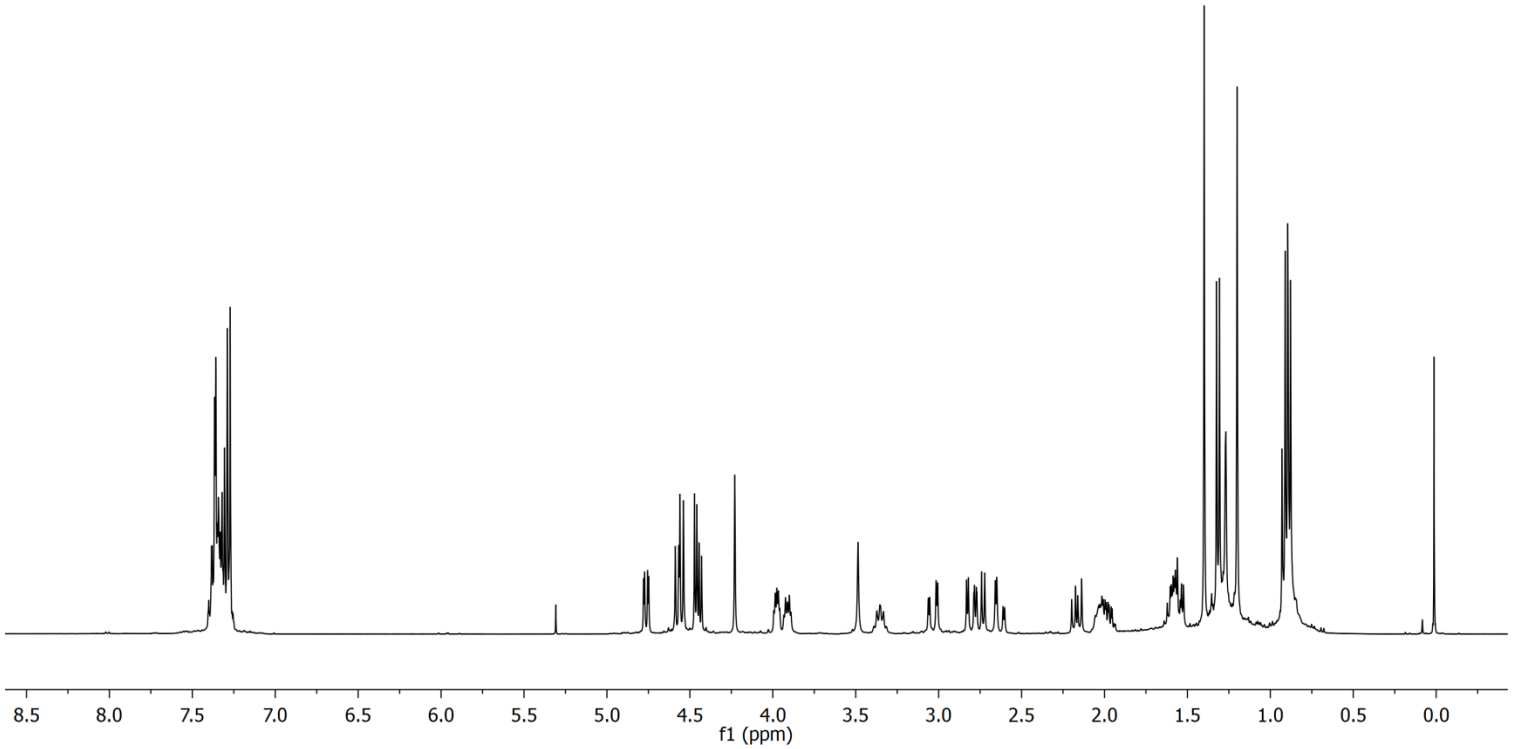
gHSQC spectrum of **2.3** (600 MHz, $CD_3OD$)



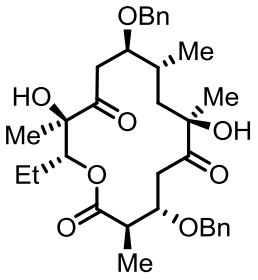
$^1$H NMR (400 MHz, $CDCl_3$)




**2.2**

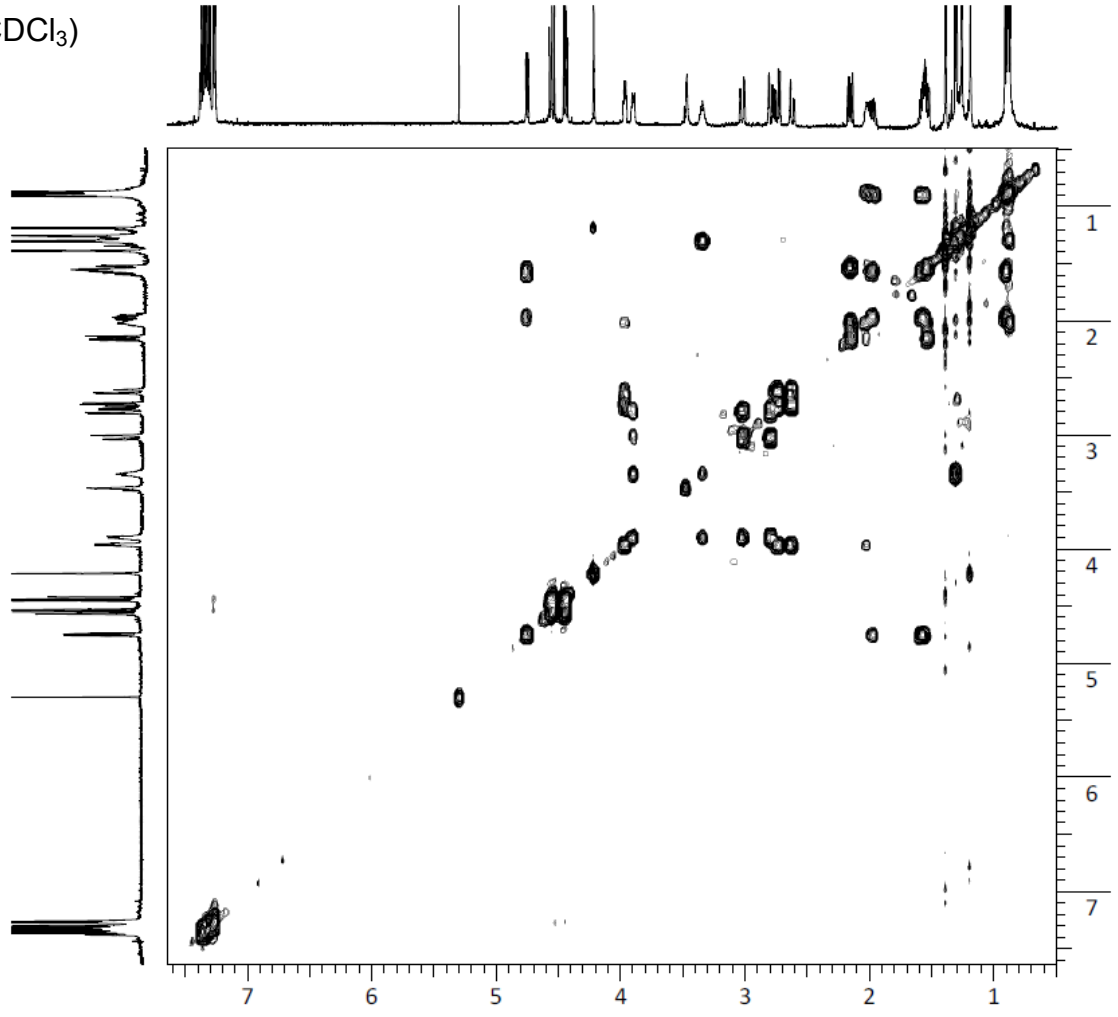


$^{13}$C NMR (126 MHz, $CDCl_3$)

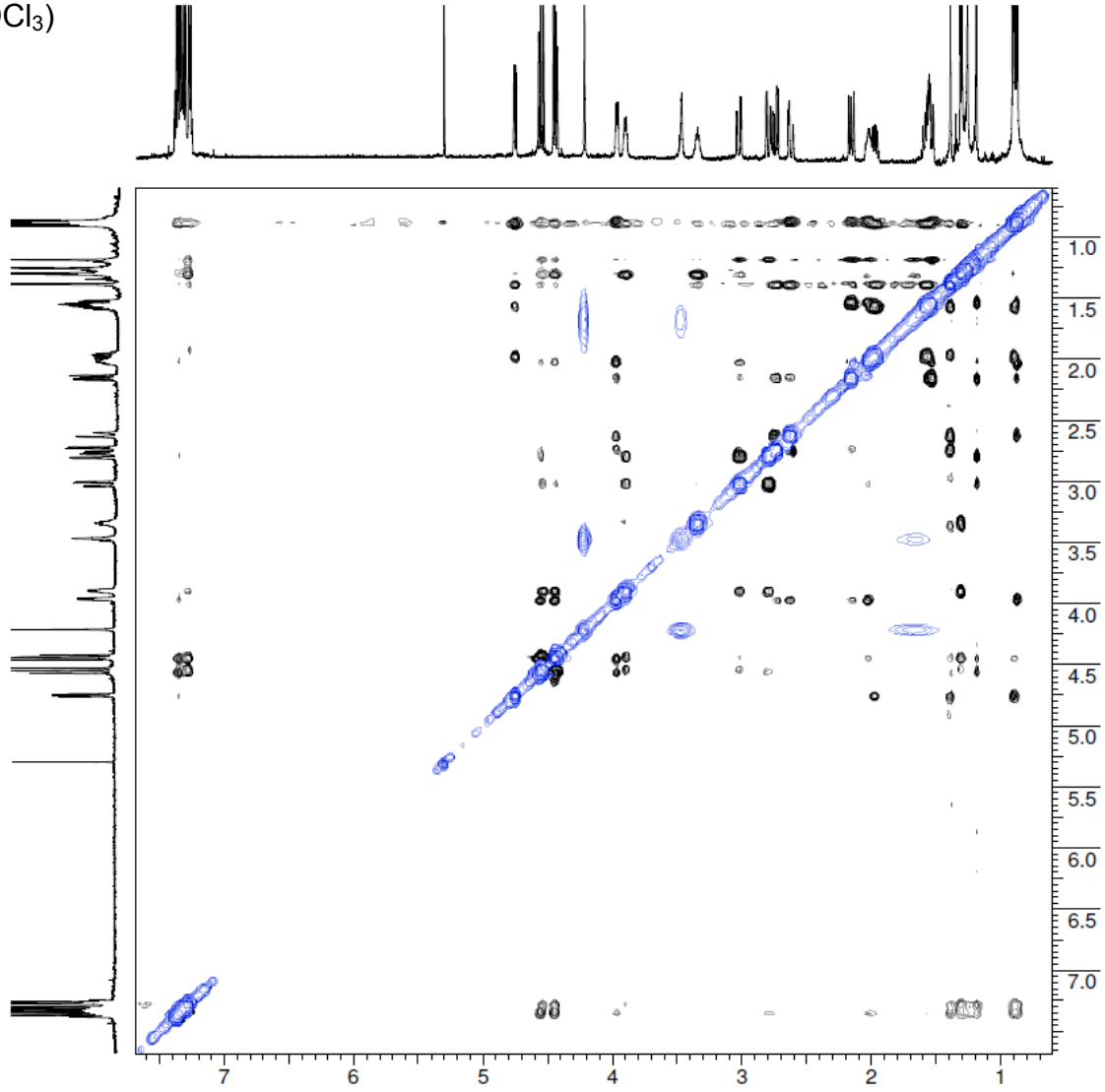



**2.2**

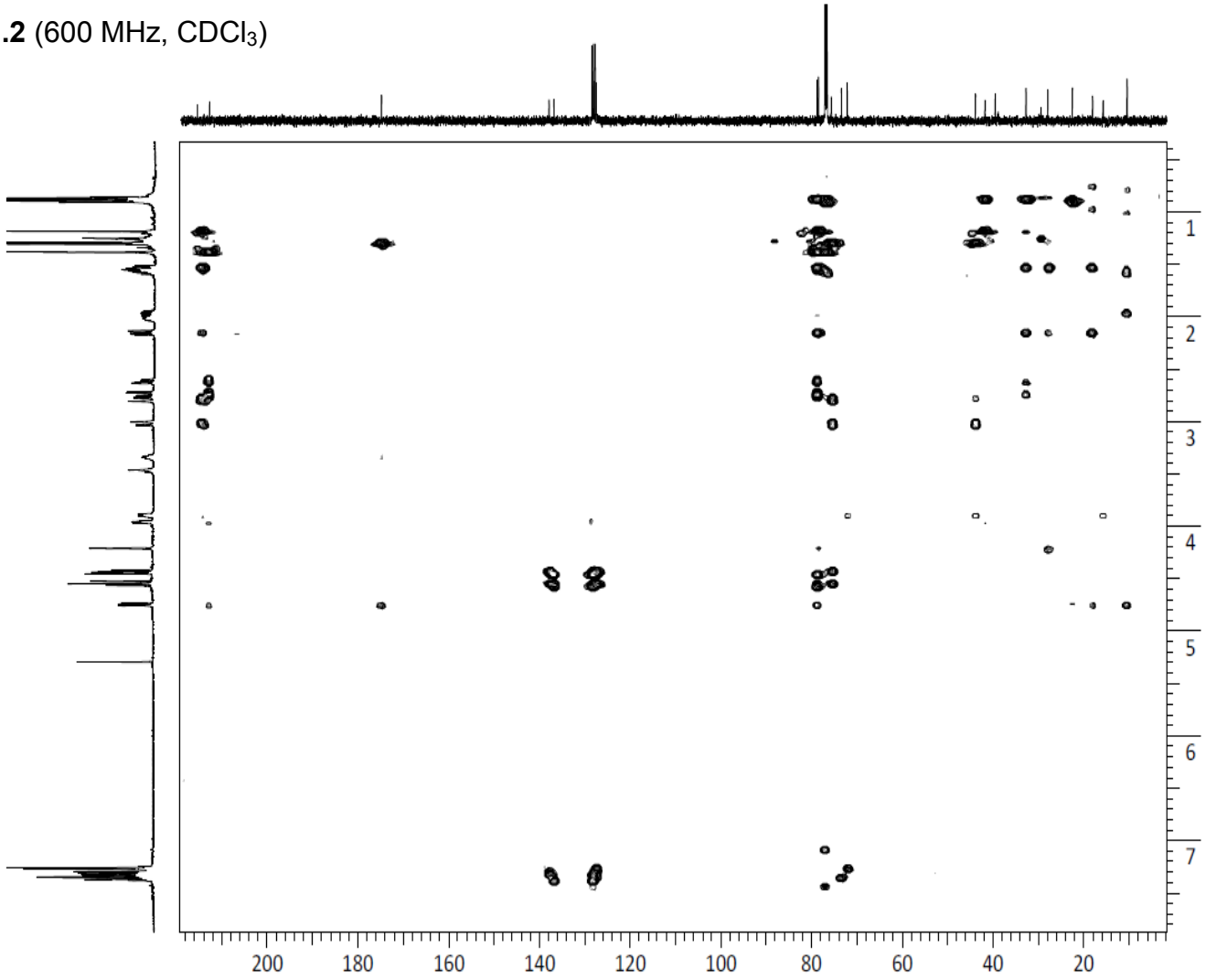
gCOSY spectrum of **2.2** (600 MHz, $CDCl_3$)



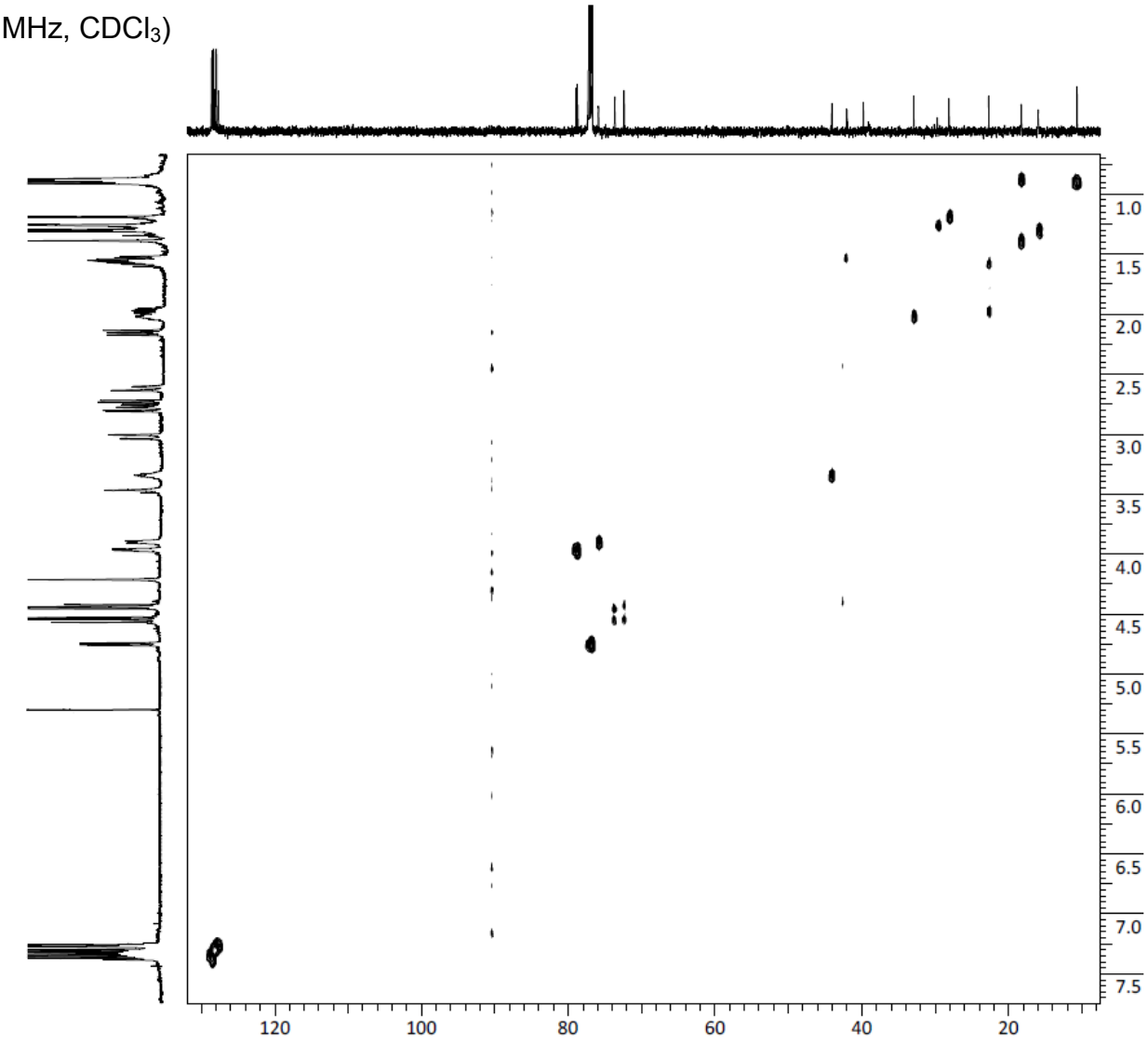
NOESY spectrum of **2.2** (600 MHz, $CDCl_3$)



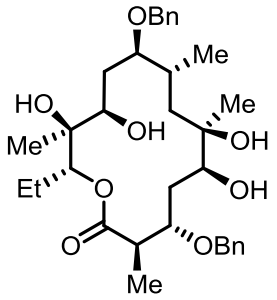
gHMBC spectrum of **2.2** (600 MHz, $CDCl_3$)



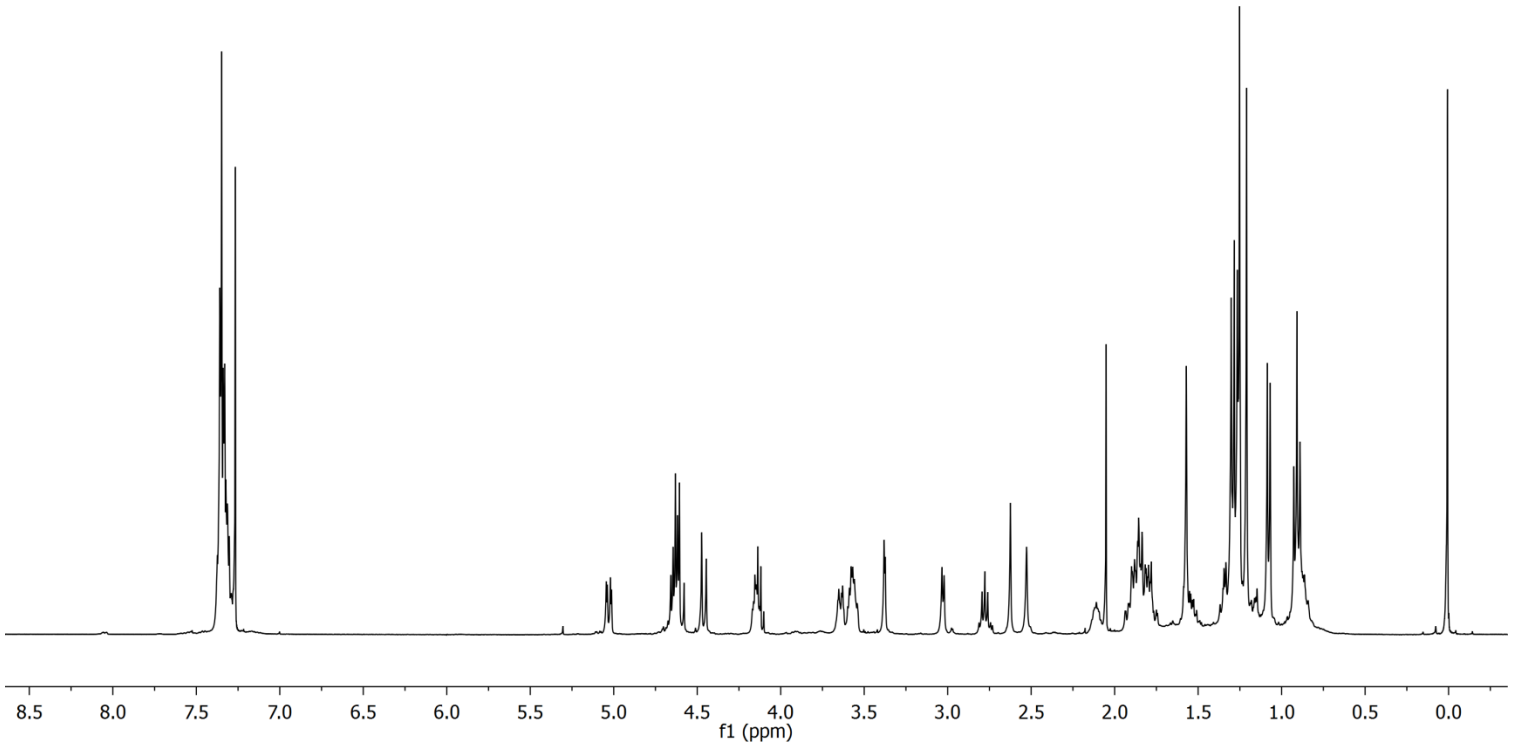
HETCOR spectrum of **2.2** (600 MHz, $CDCl_3$)



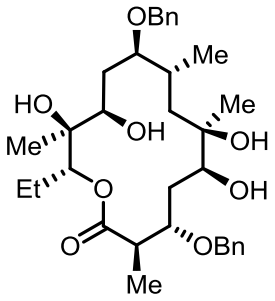
$^1$H NMR (400 MHz, $CDCl_3$)




**2.31**

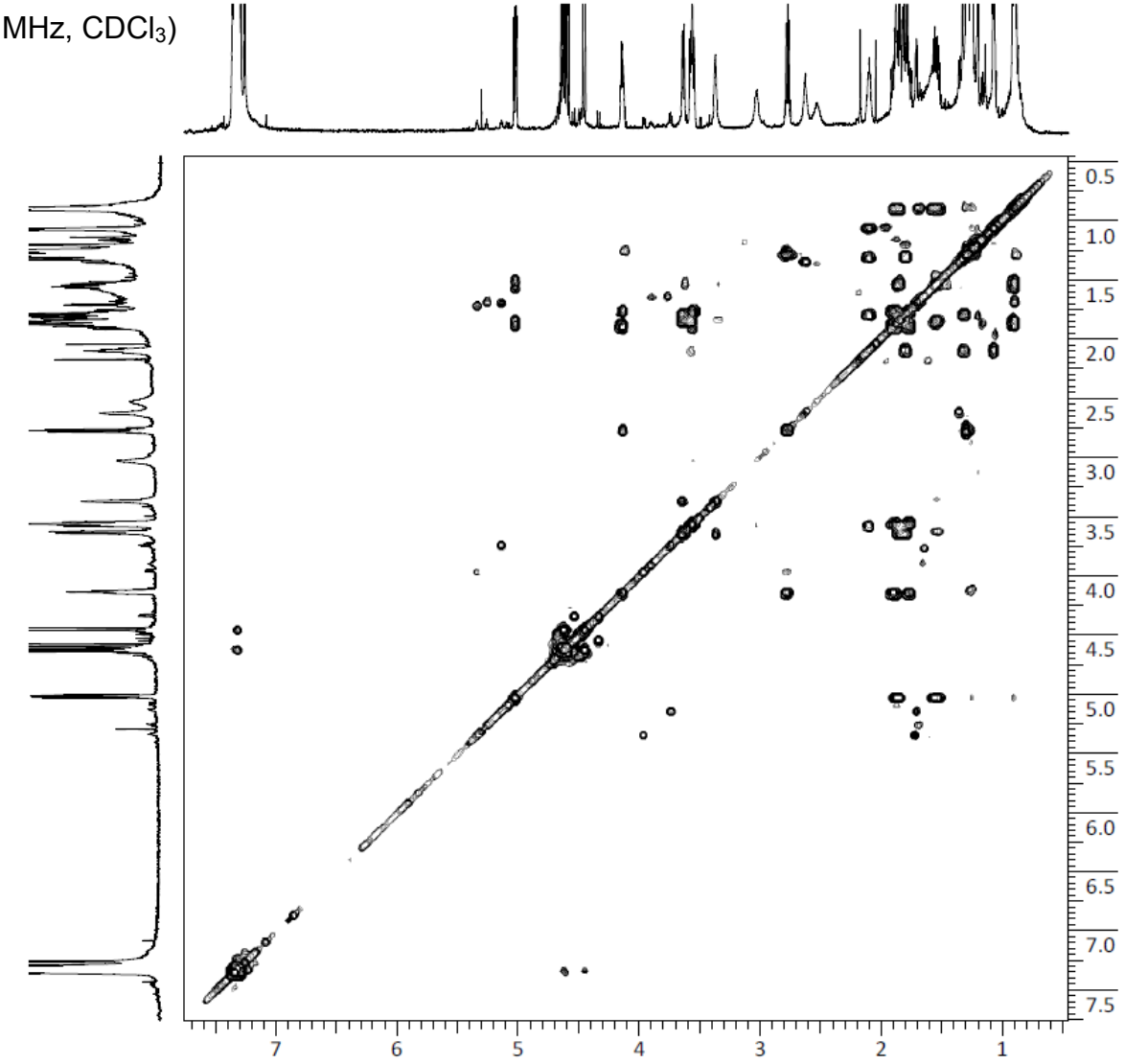


$^{13}$C NMR (126 MHz, $CDCl_3$)

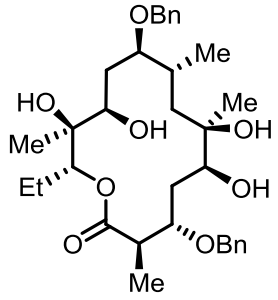



**2.31**

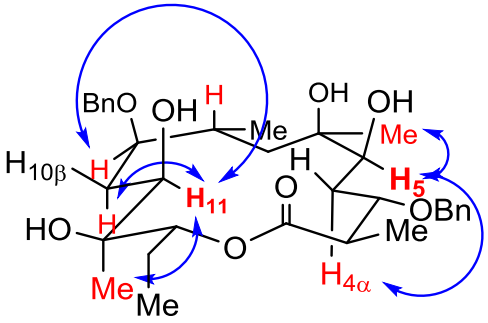
gCOSY spectrum of **2.31** (600 MHz, $CDCl_3$)



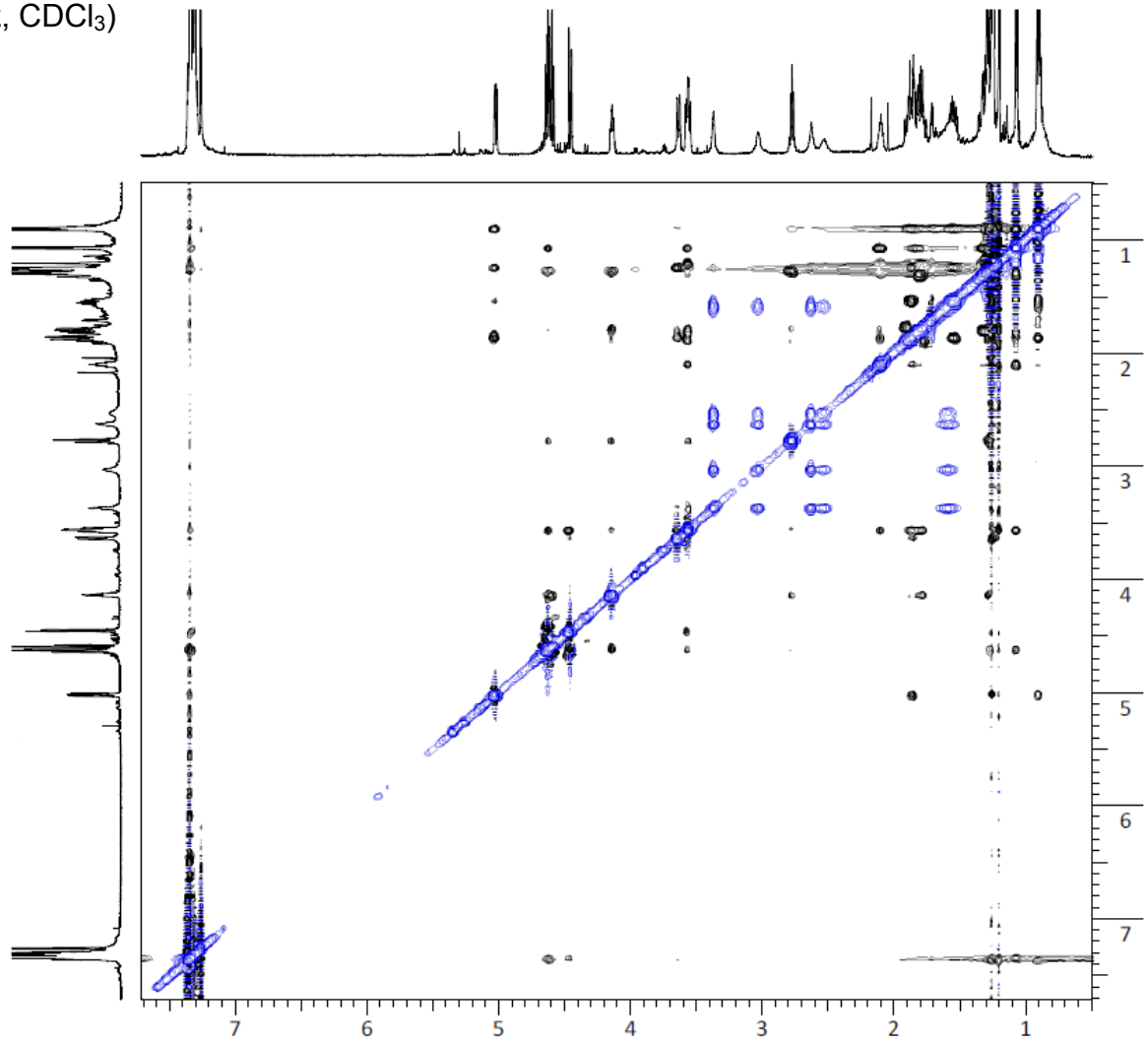
NOESY spectrum of **2.31** (600 MHz, $CDCl_3$)



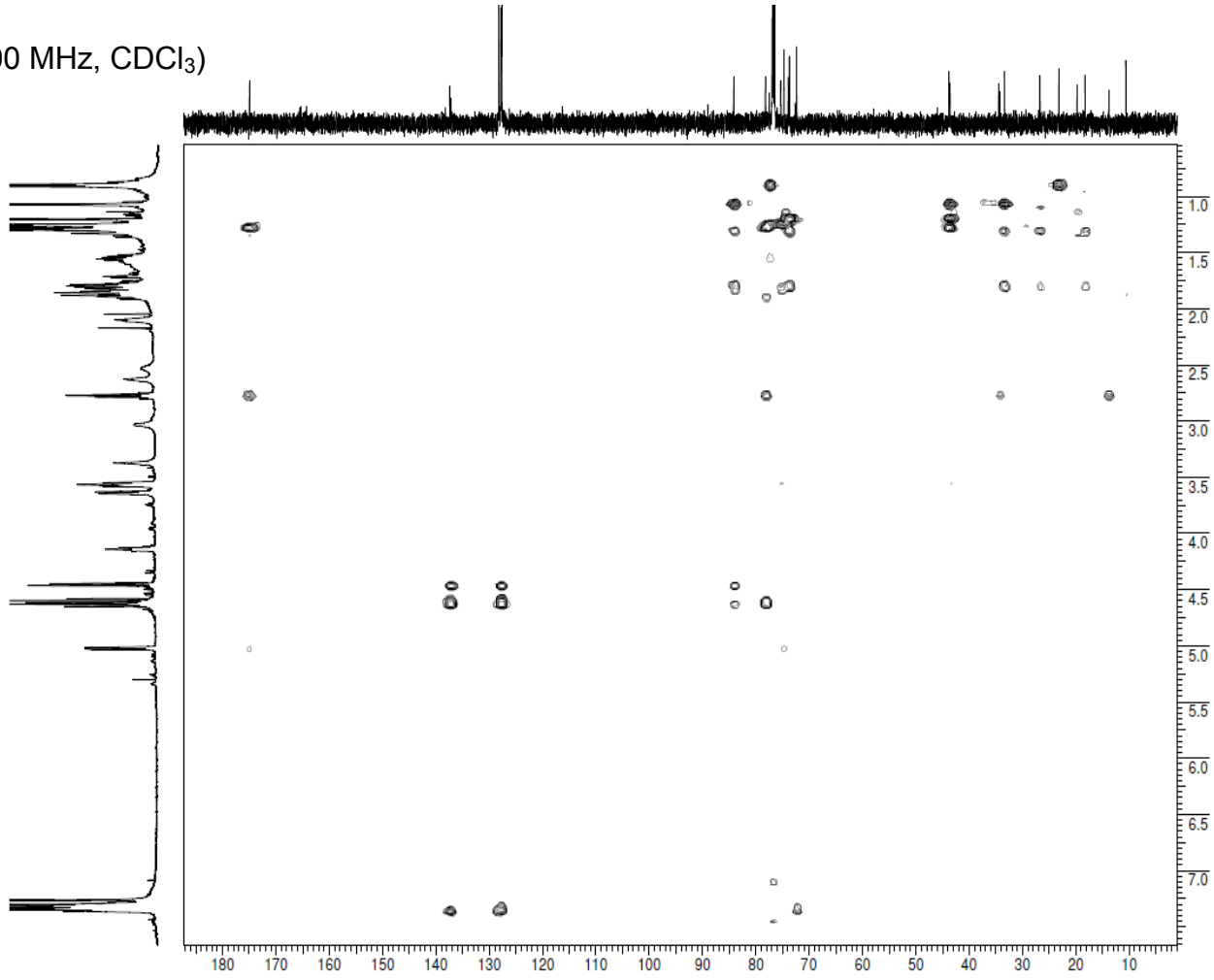

**2.31**



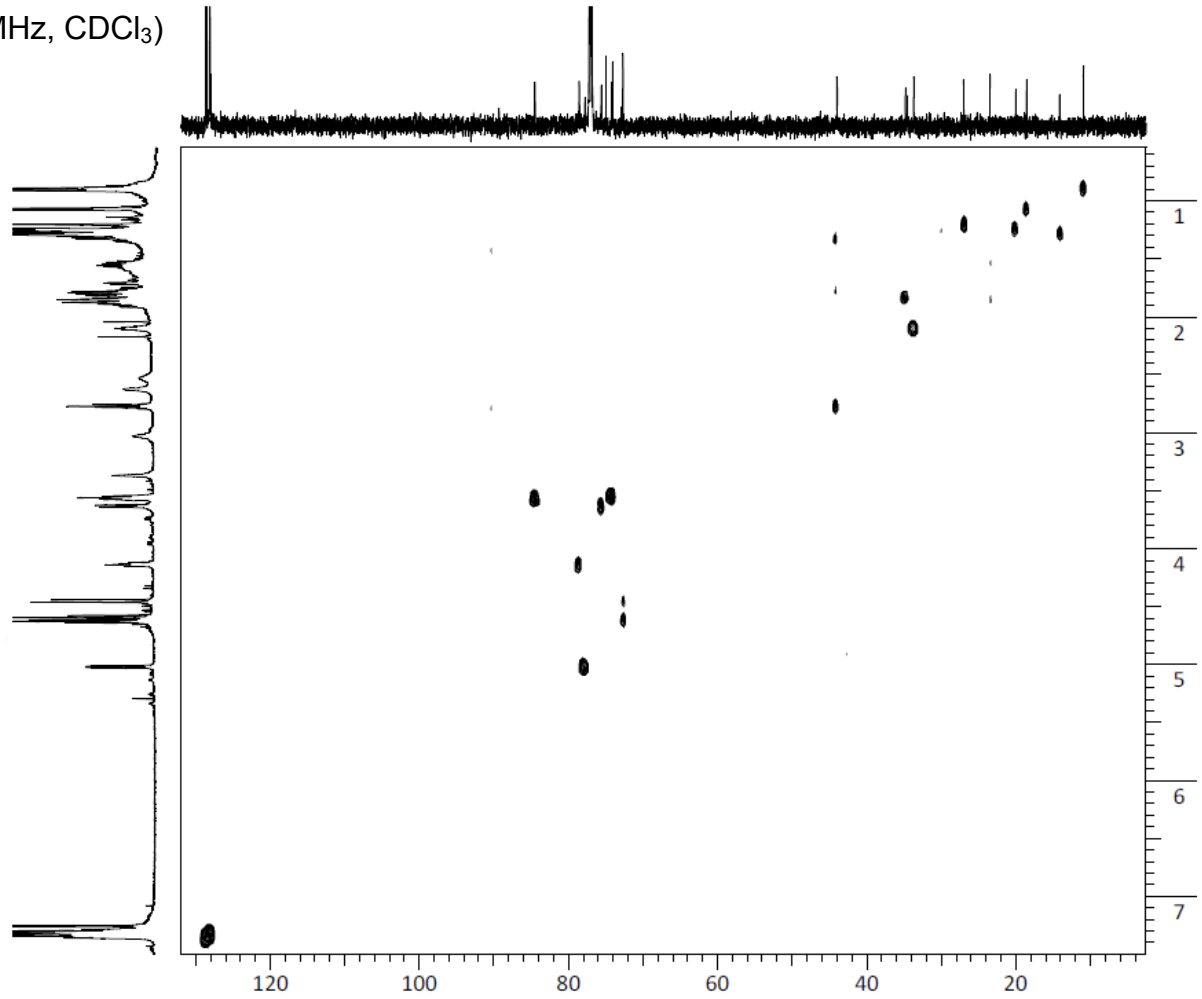

Key nOe signals of **2.31**



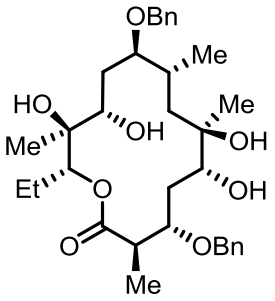
gHMBC spectrum of **2.31** (600 MHz, $CDCl_3$)



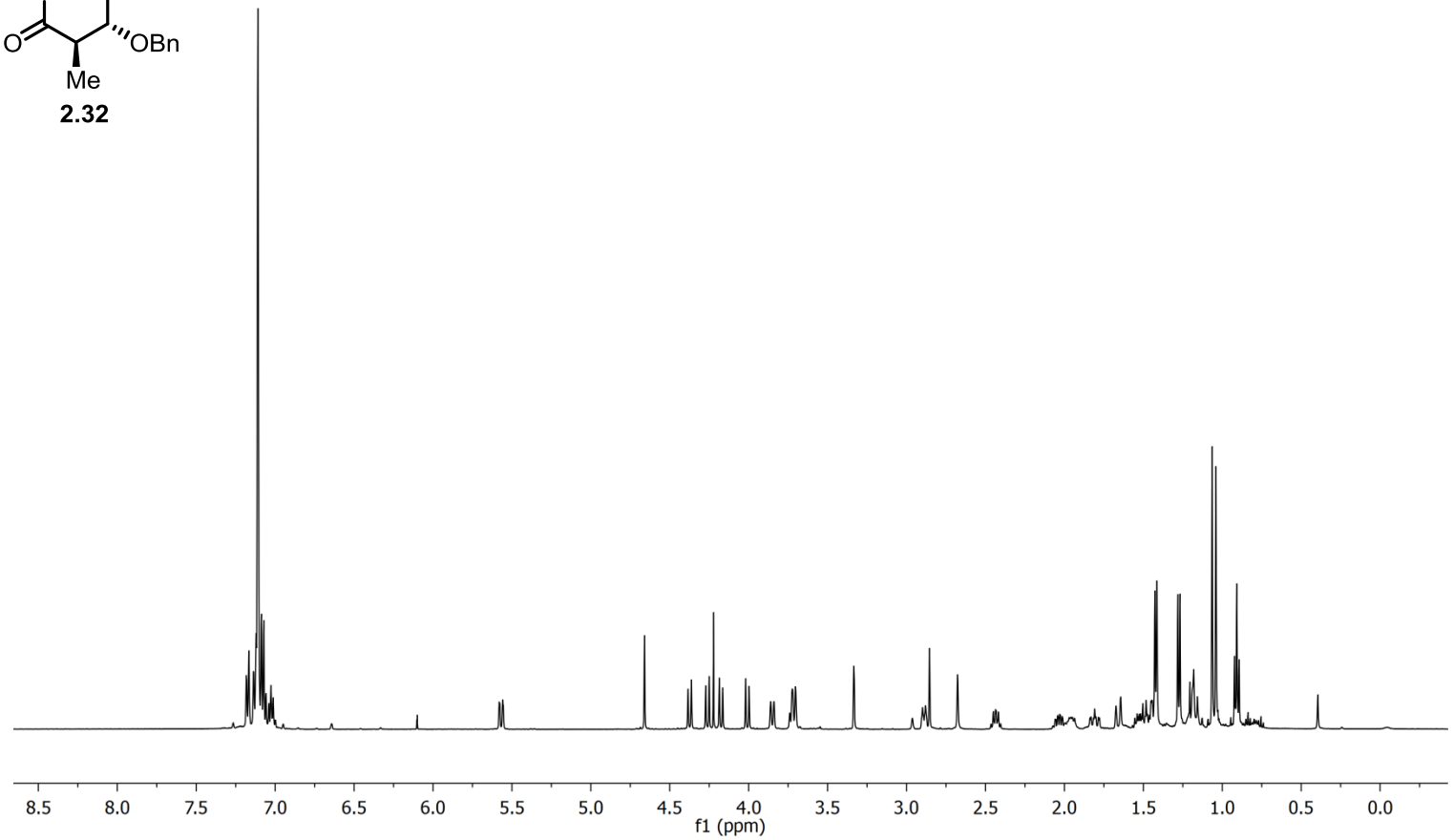
HETCOR spectrum of **2.31** (600 MHz, $CDCl_3$)



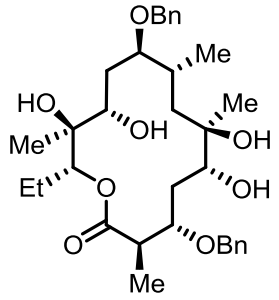
$^1$H NMR (500 MHz, $C_6D_6$)




**2.32**

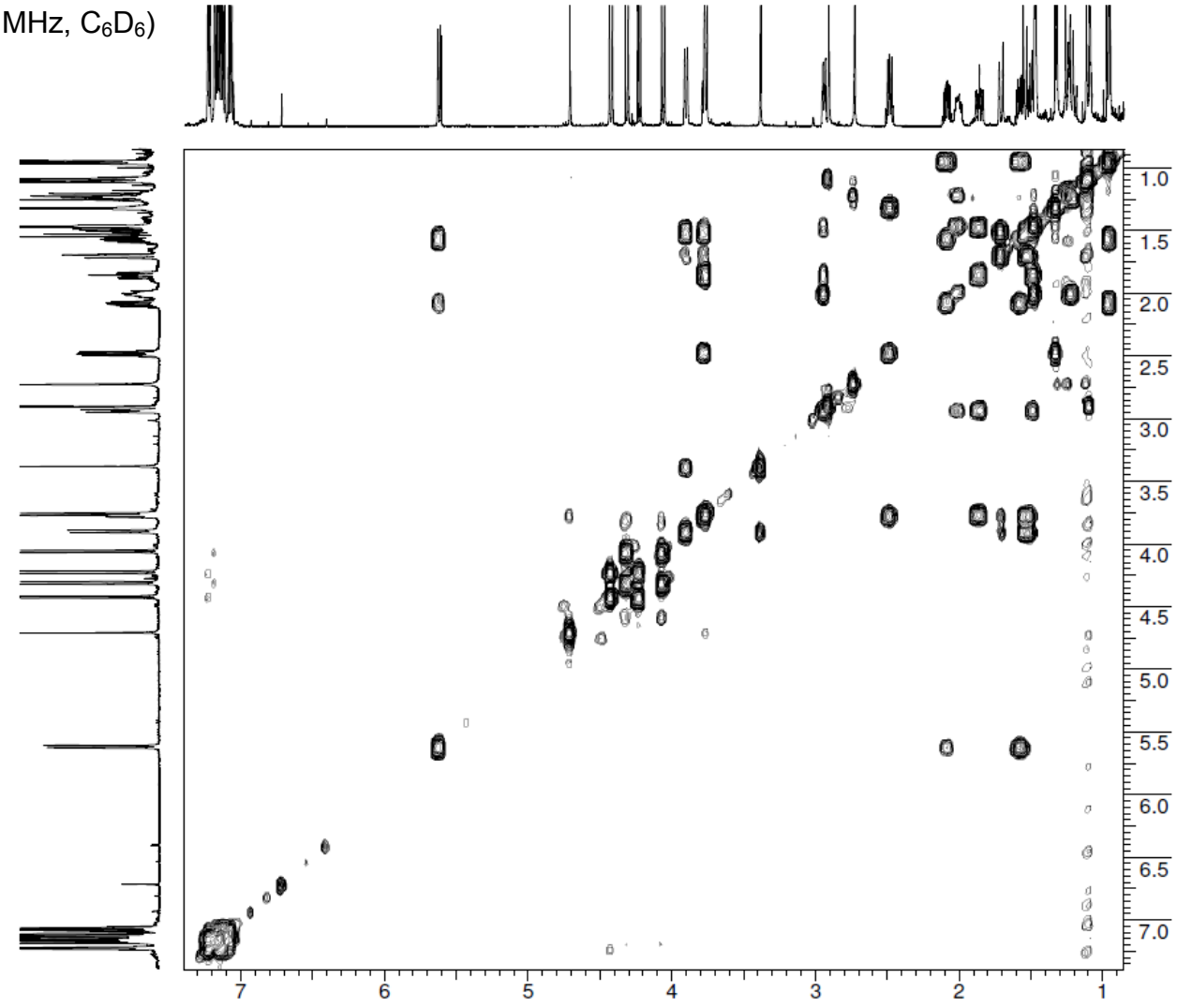


$^{13}$C NMR (126 MHz, $C_6D_6$)

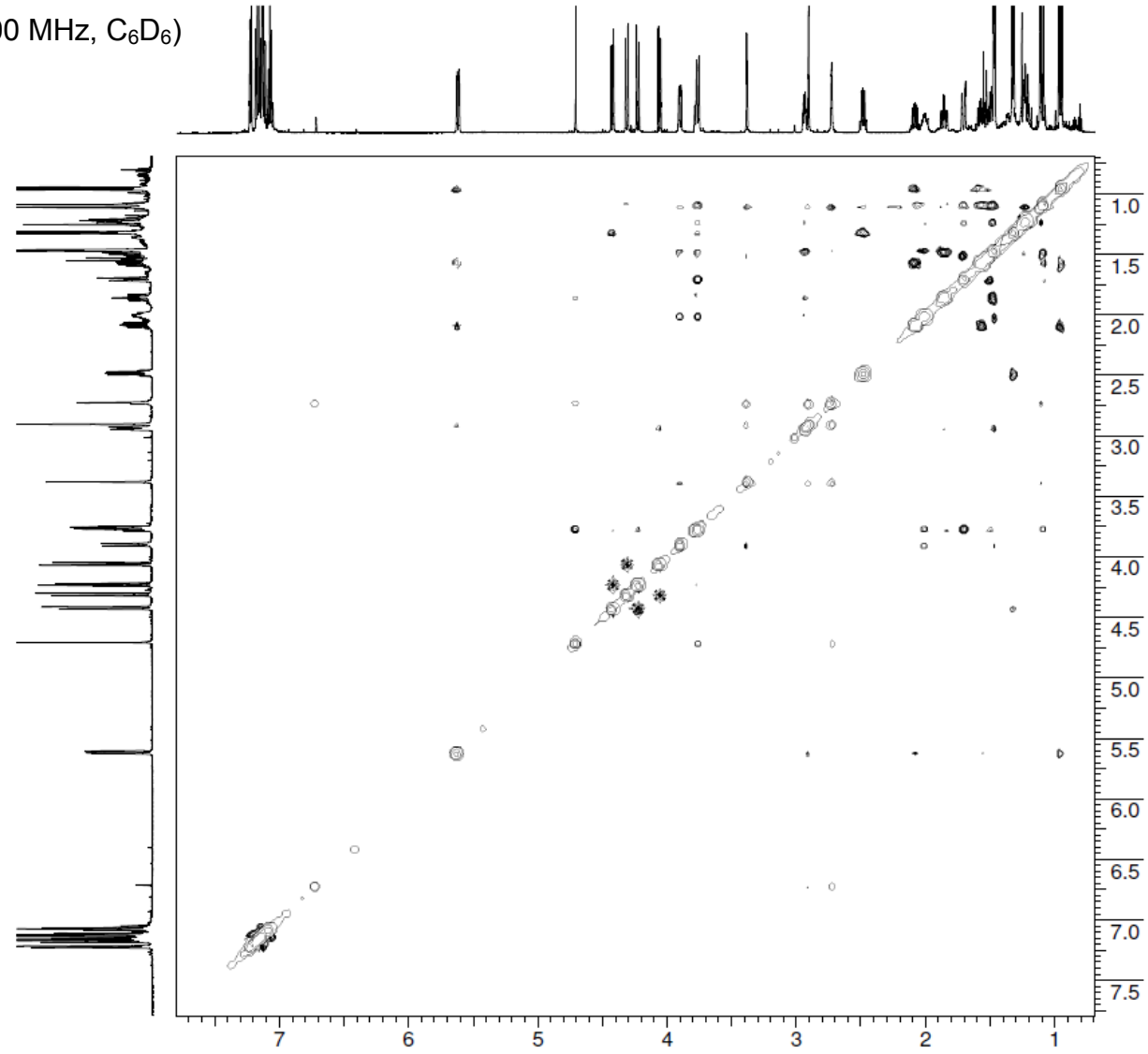



**2.32**

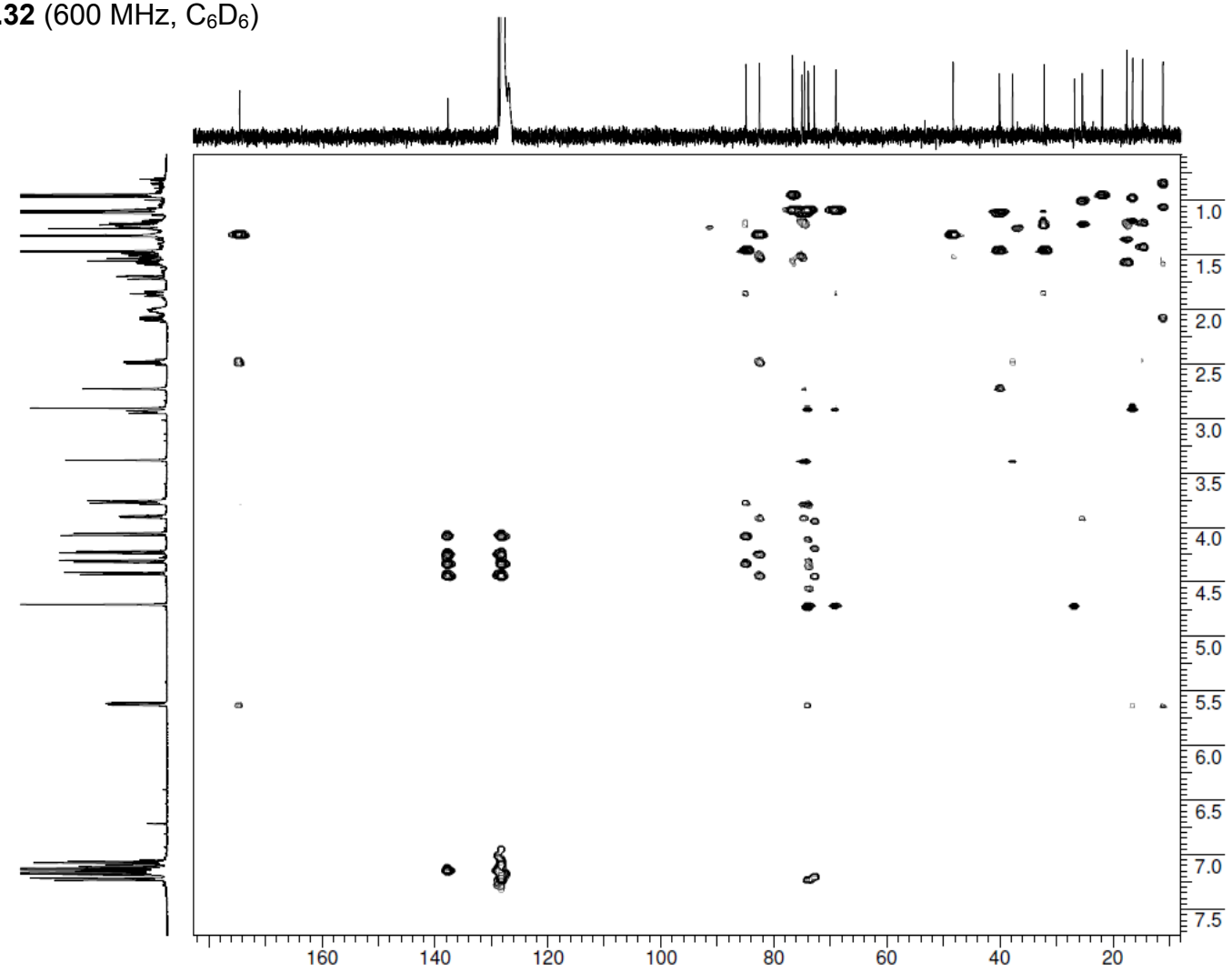
gCOSY spectrum of **2.32** (600 MHz, $C_6D_6$)



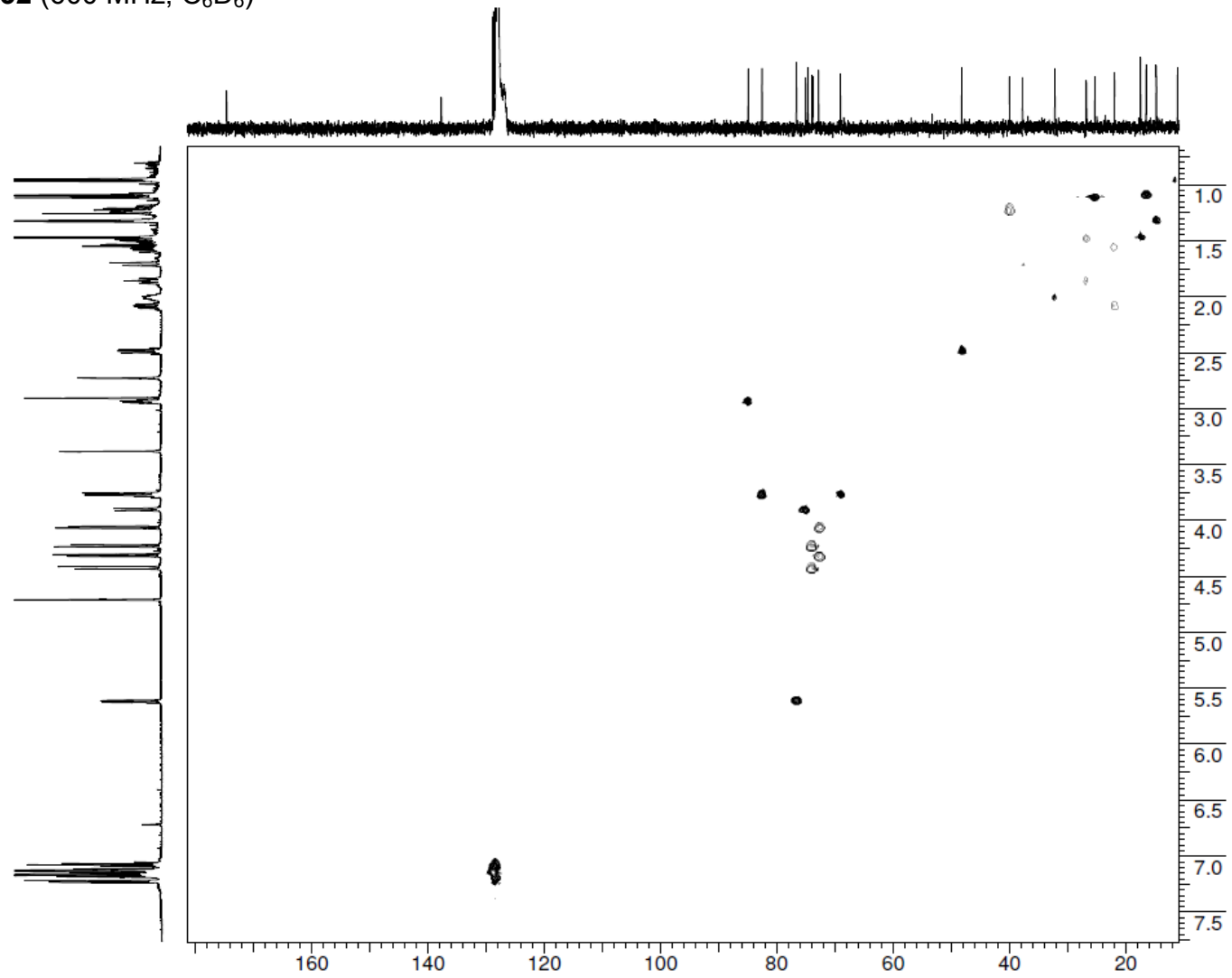
NOESY spectrum of **2.32** (600 MHz, $C_6D_6$)



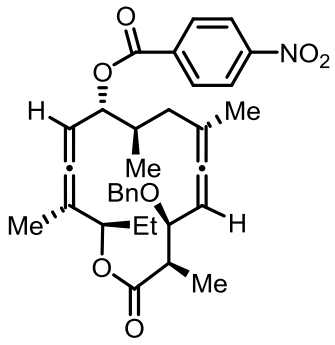
gHMBC spectrum of **2.32** (600 MHz, $C_6D_6$)



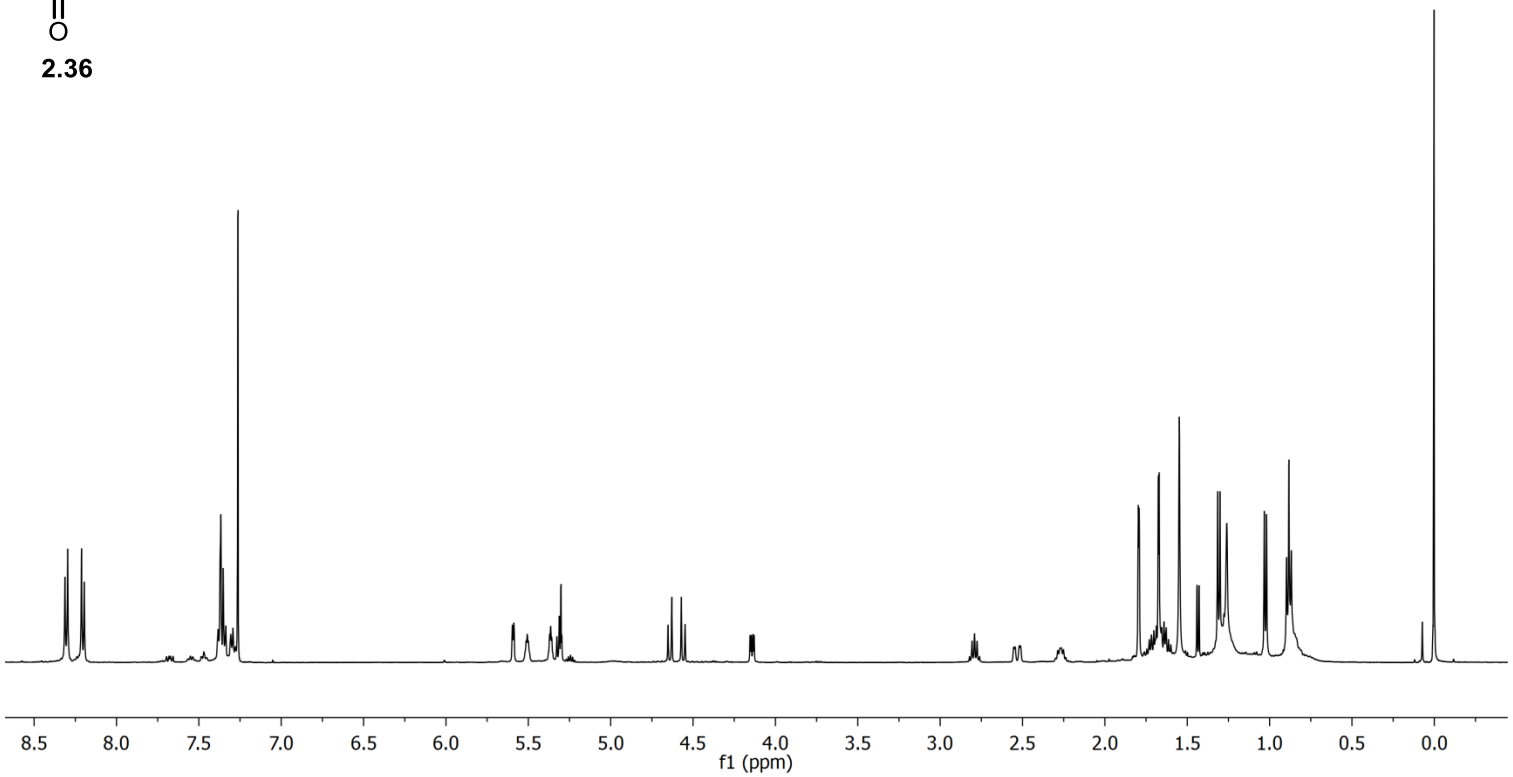
gHSQC spectrum of **2.32** (600 MHz, $C_6D_6$)



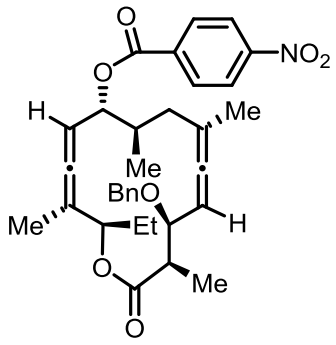
$^1$H NMR (500 MHz, $CDCl_3$)




**2.36**

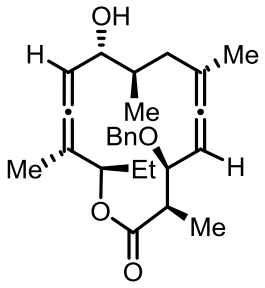


$^{13}$C NMR (100 MHz, $CDCl_3$)



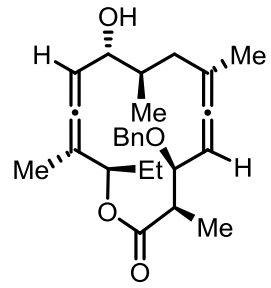

**2.36**

$^1$H NMR (500 MHz, $CDCl_3$)



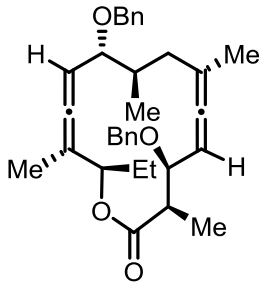

**2.37**

$^{13}$C NMR (100 MHz, $CDCl_3$)

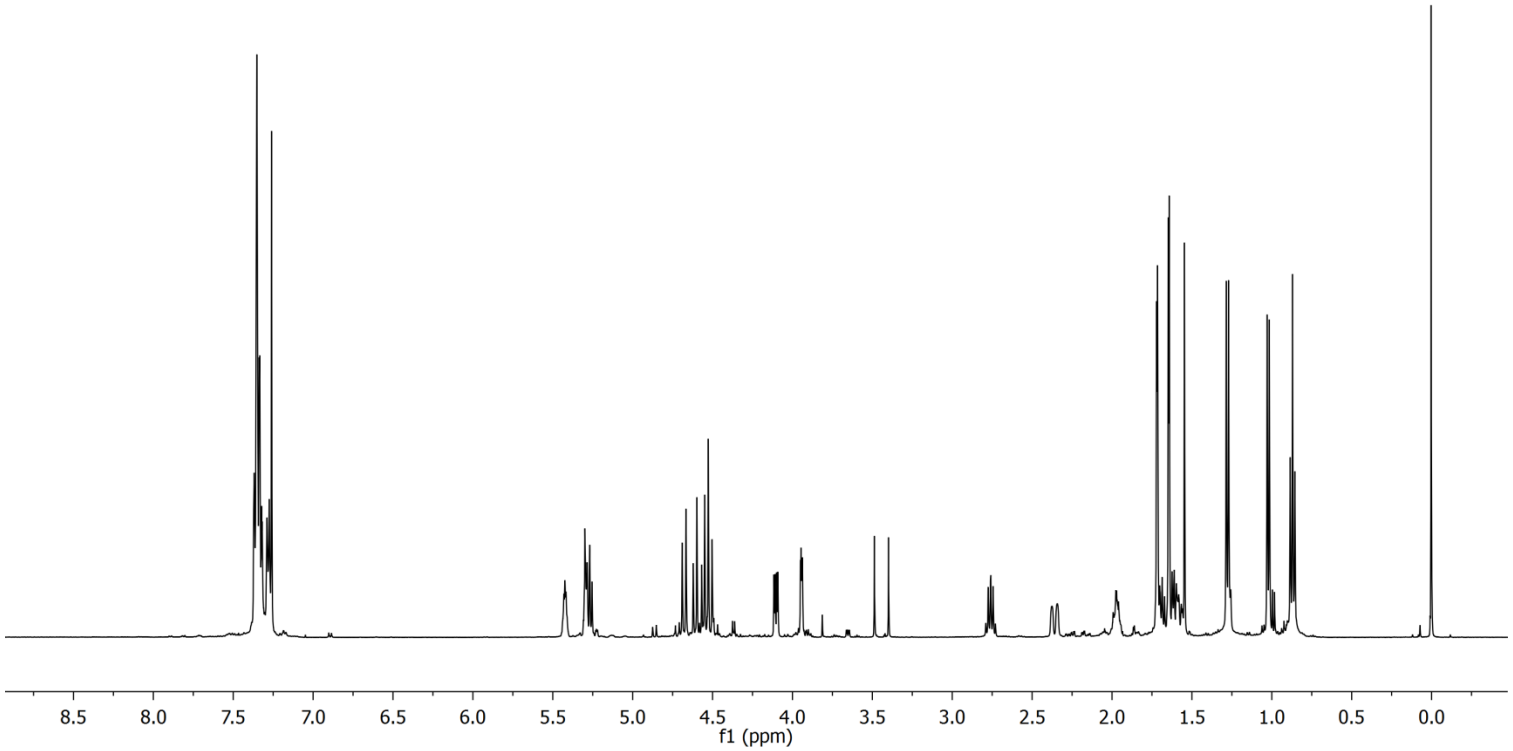



**2.37**

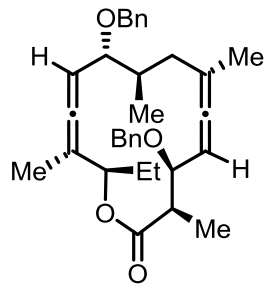
$^1$H NMR (500 MHz, $CDCl_3$)




**2.38**

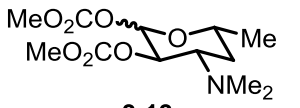


$^{13}$C NMR (100 MHz, $CDCl_3$)



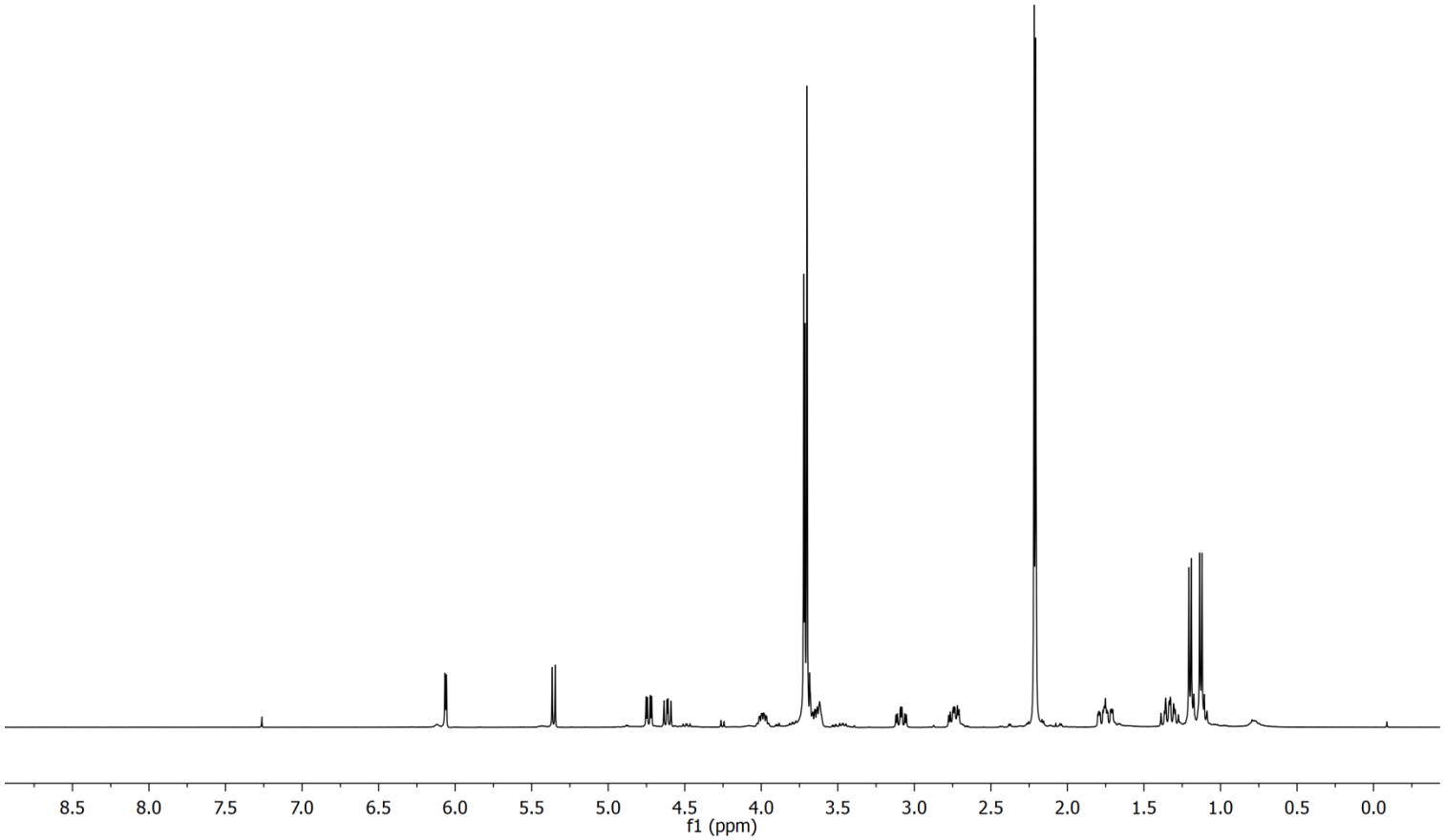

**2.38**

$^1$H NMR (400 MHz, $CDCl_3$)

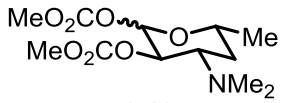



**3.13**

α:β = 1:1

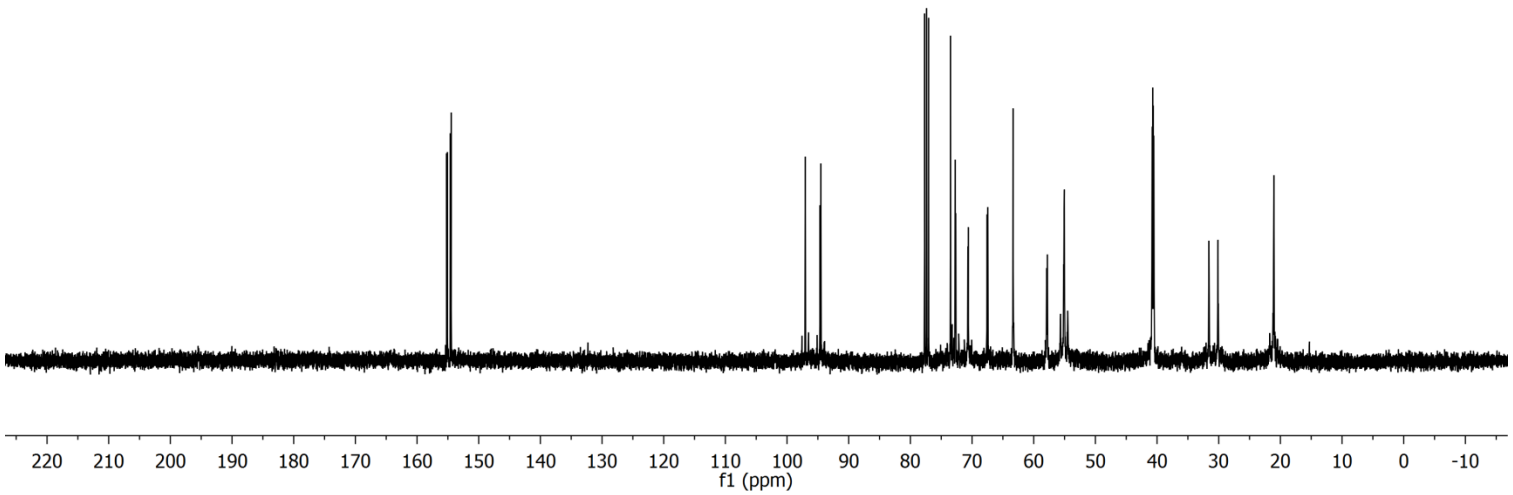


$^{13}$C NMR (100 MHz, $CDCl_3$)

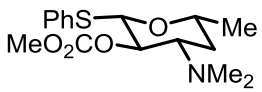



**3.13**

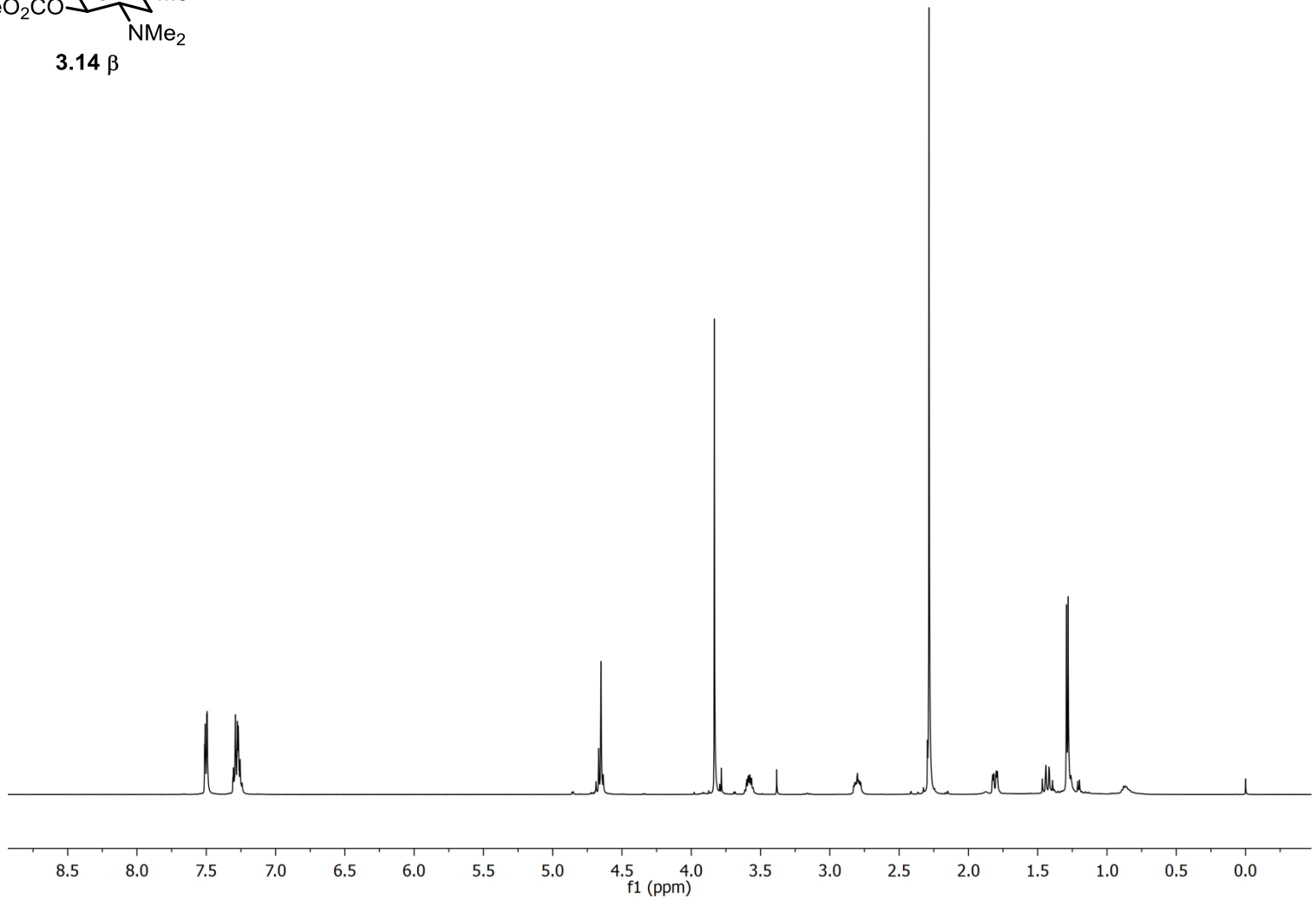
α:β = 1:1



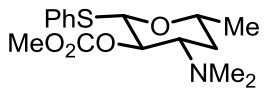
$^1$H NMR (500 MHz, $CDCl_3$)



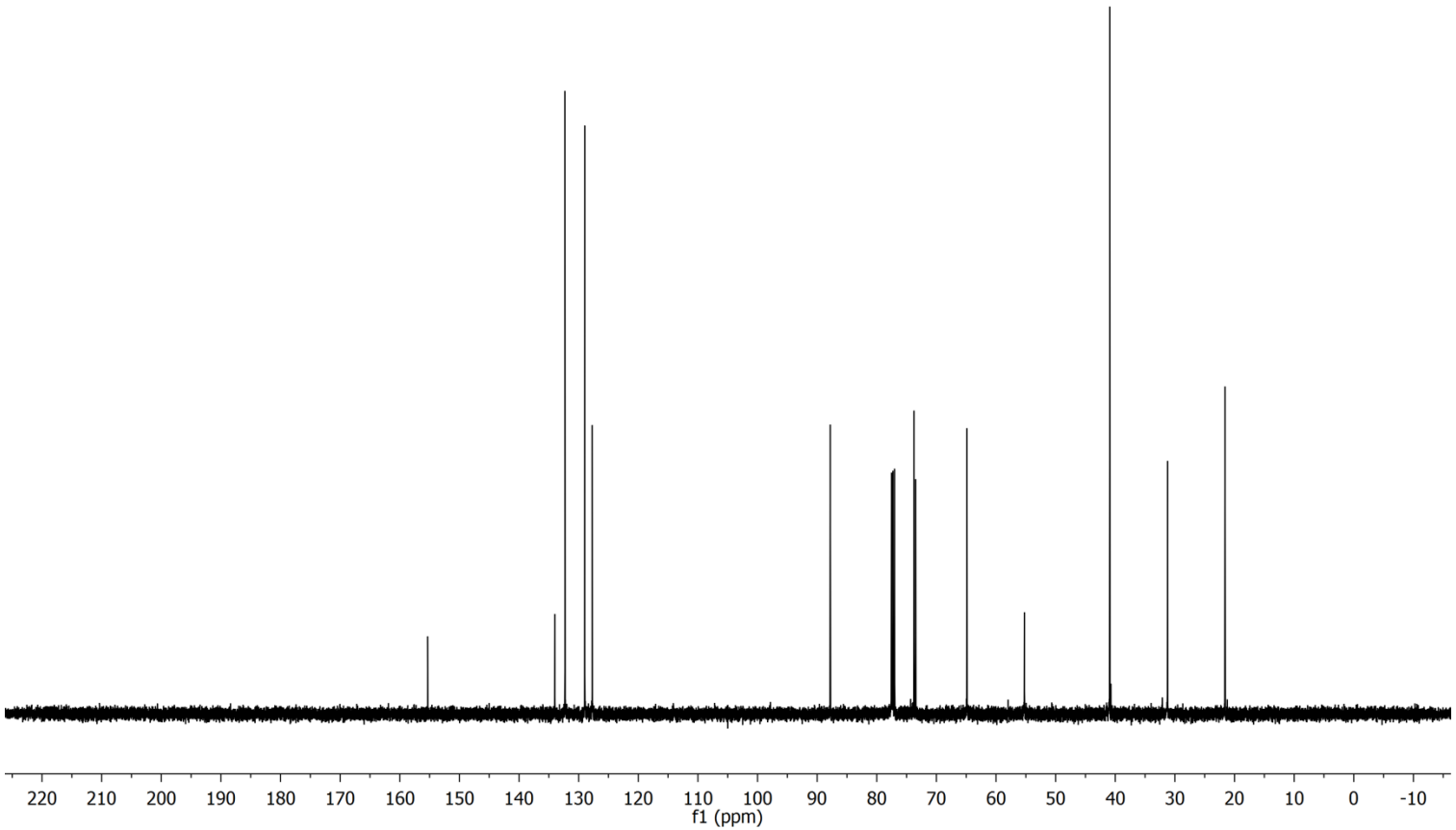

**3.14** β



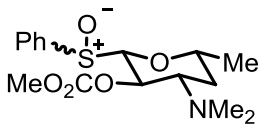
$^{13}$C NMR (126 MHz, $CDCl_3$)




**3.14** β

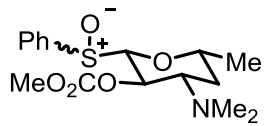


$^1$H NMR (500 MHz, $CDCl_3$)

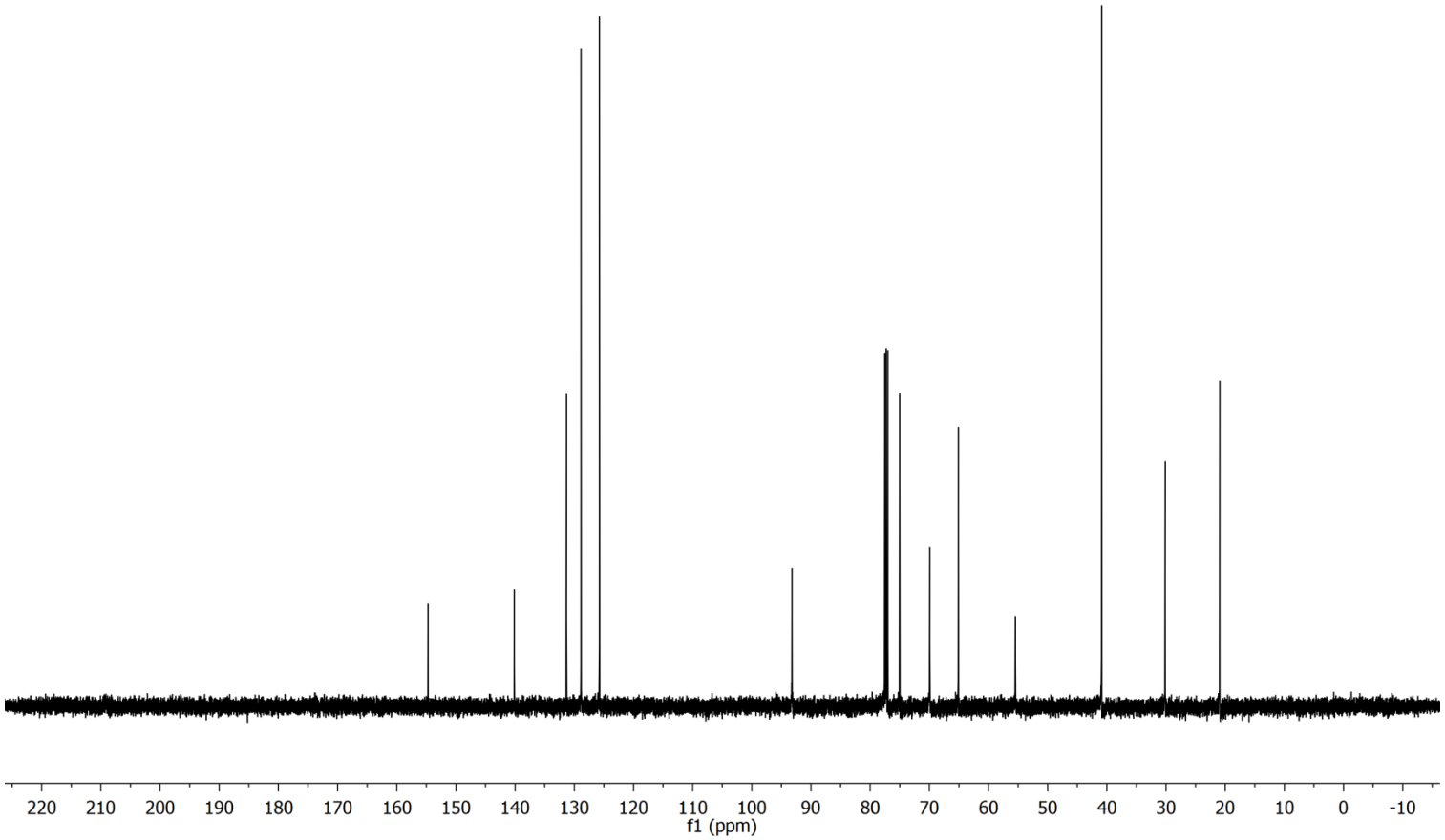



**3.17 major isomer**

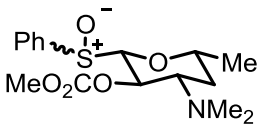
$^{13}$C NMR (126 MHz, $CDCl_3$)




**3.17 major isomer**

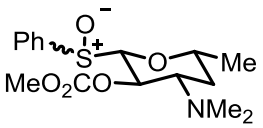


$^1$H NMR (400 MHz, $CDCl_3$)

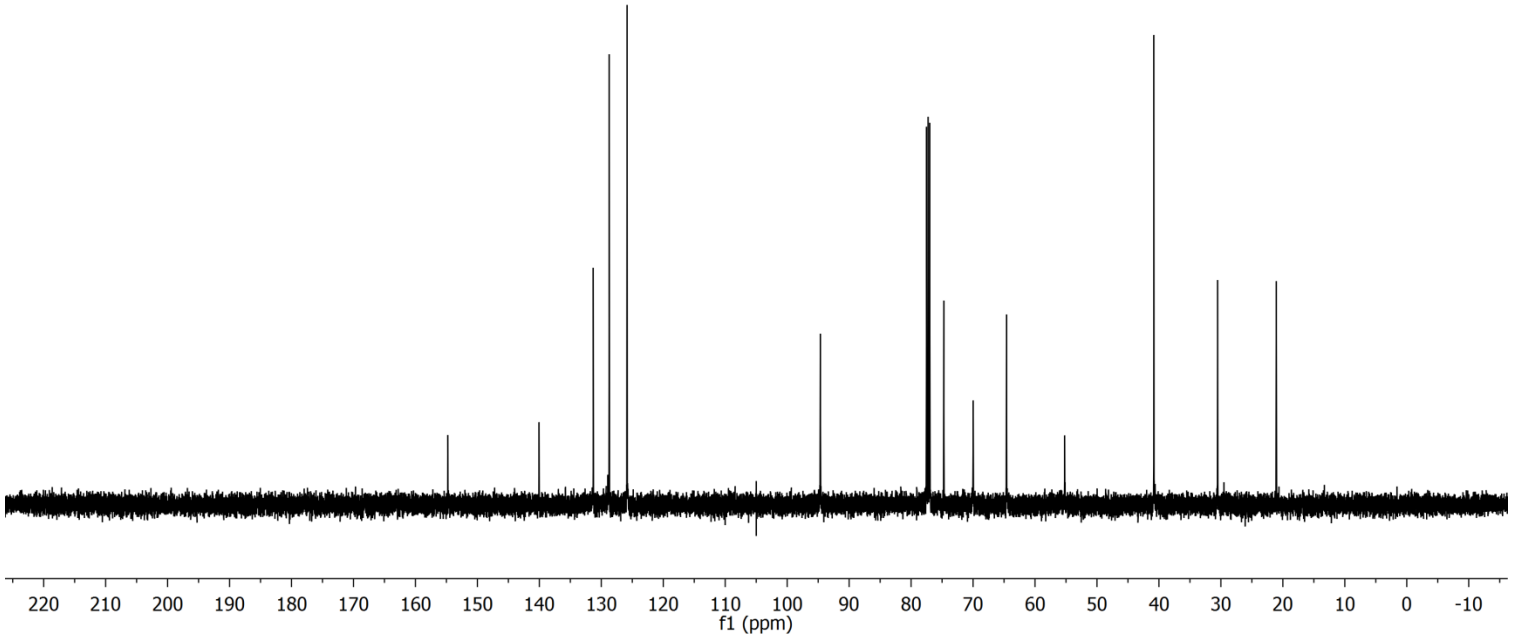



**3.17 minor isomer**

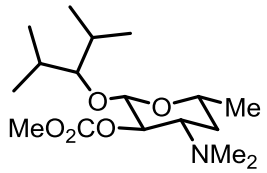
$^{13}$C NMR (126 MHz, $CDCl_3$)




**3.17 minor isomer**

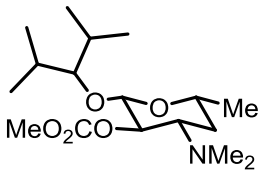


$^1$H NMR (500 MHz, $CDCl_3$)

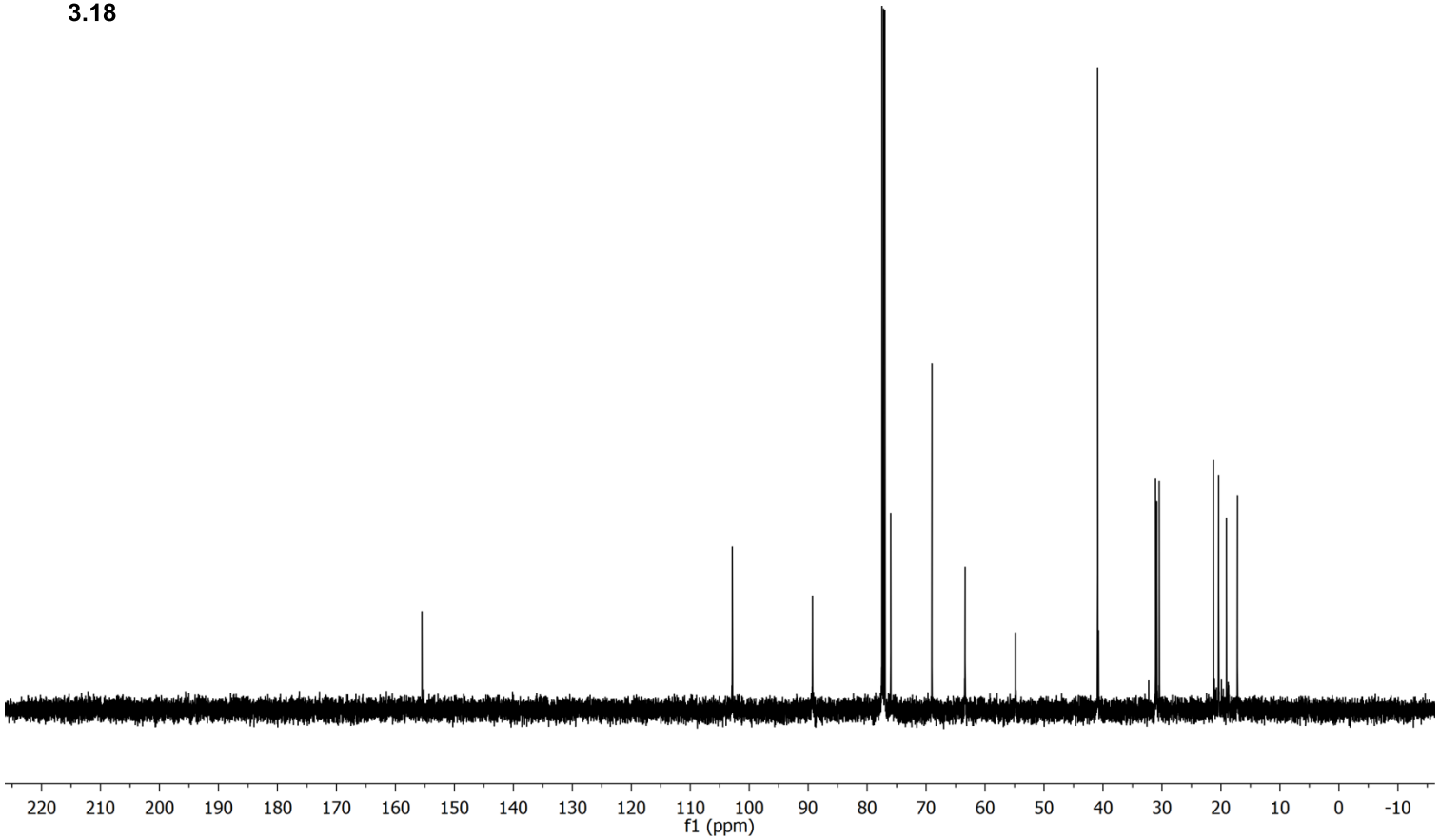



**3.18**

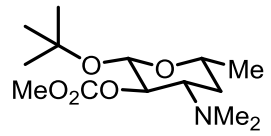
$^{13}$C NMR (126 MHz, $CDCl_3$)




**3.18**

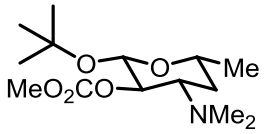


$^1$H NMR (400 MHz, $CDCl_3$)

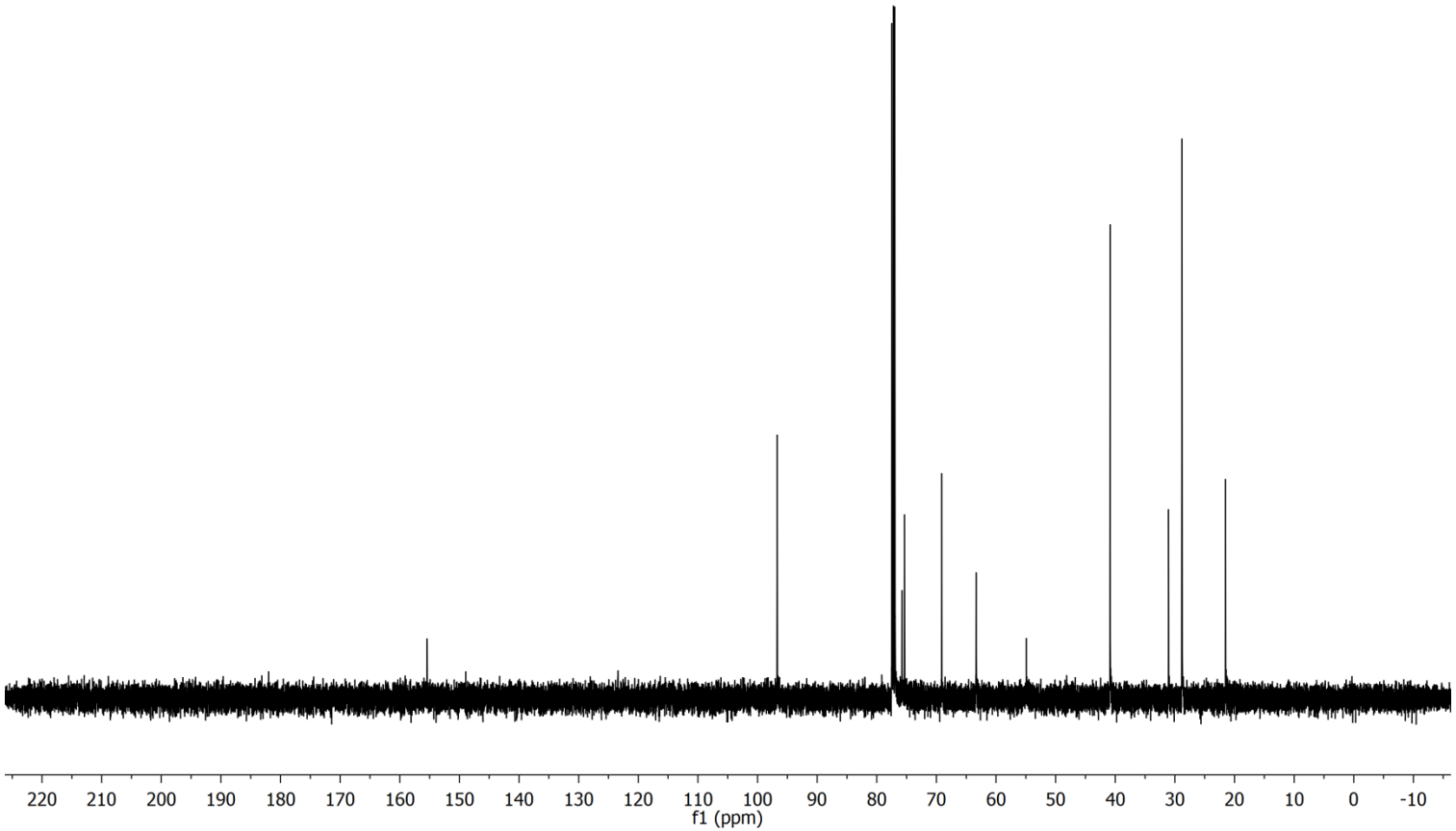



**3.19**

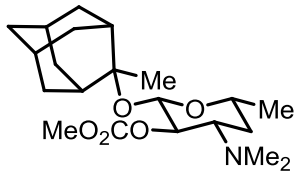
$^{13}$C NMR (126 MHz, $CDCl_3$)



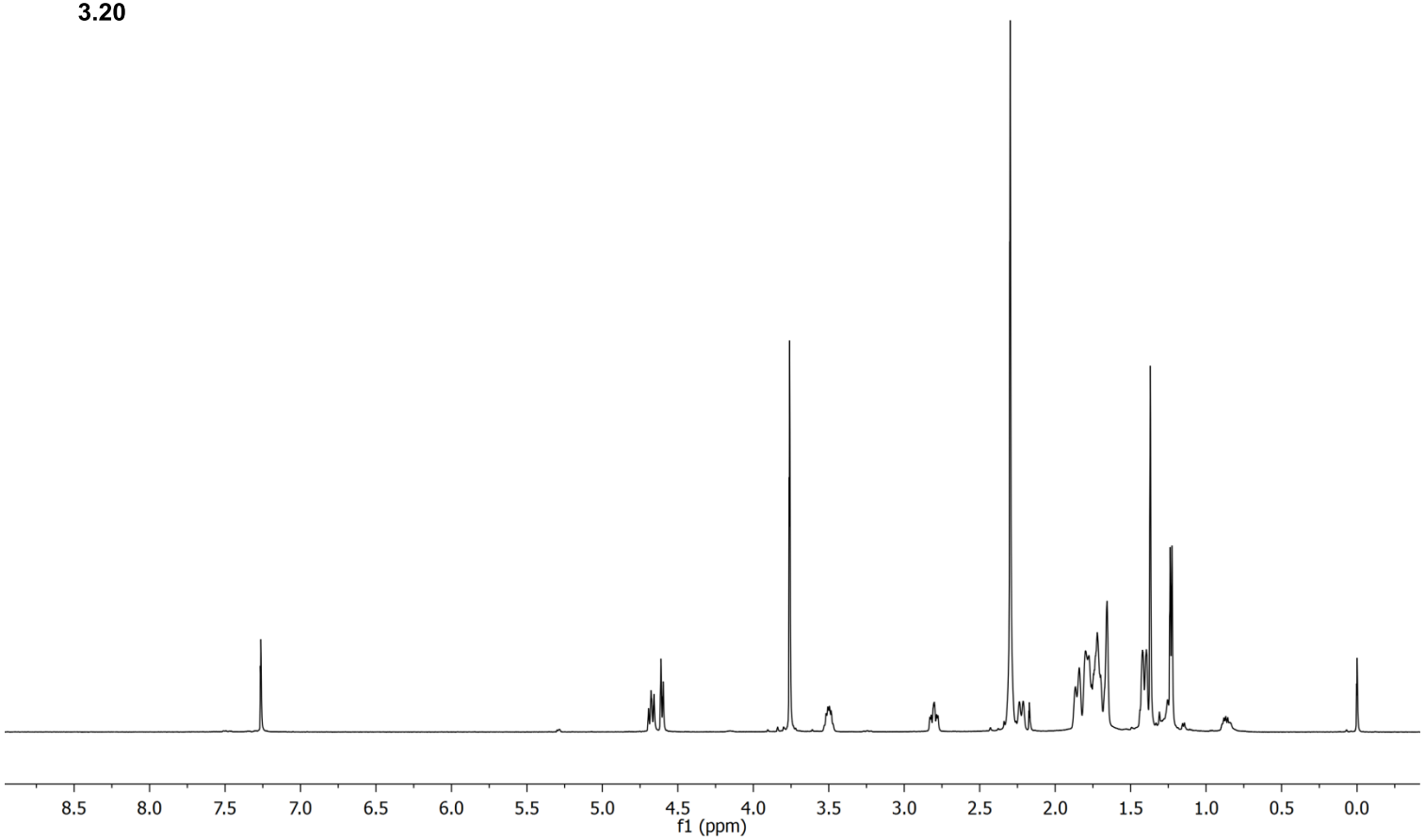

**3.19**



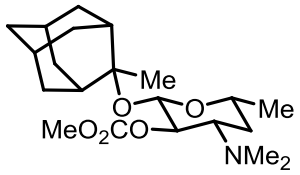
$^1$H NMR (500 MHz, $CDCl_3$)



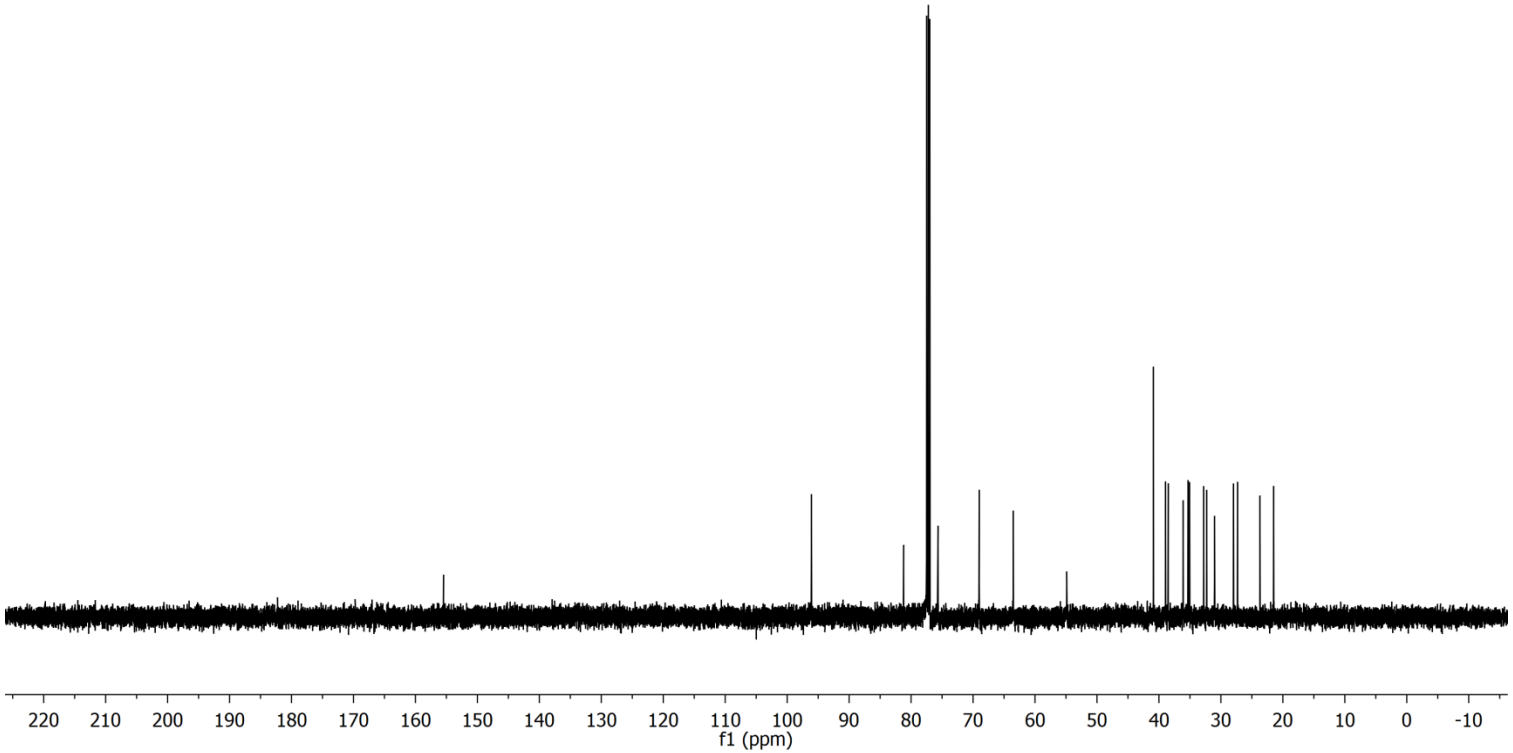

**3.20**



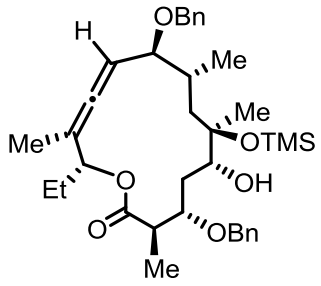
$^{13}$C NMR (126 MHz, $CDCl_3$)




**3.20**

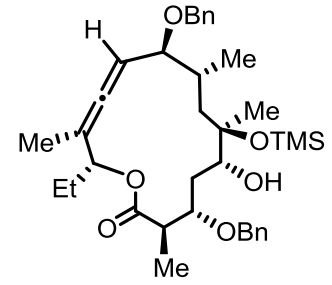


$^1$H NMR (500 MHz, $CDCl_3$)



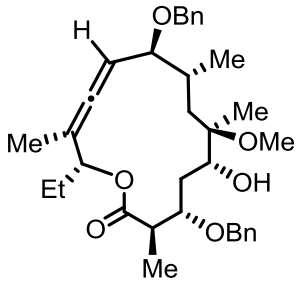

**3.34**

$^{13}$C NMR (126 MHz, $CDCl_3$)

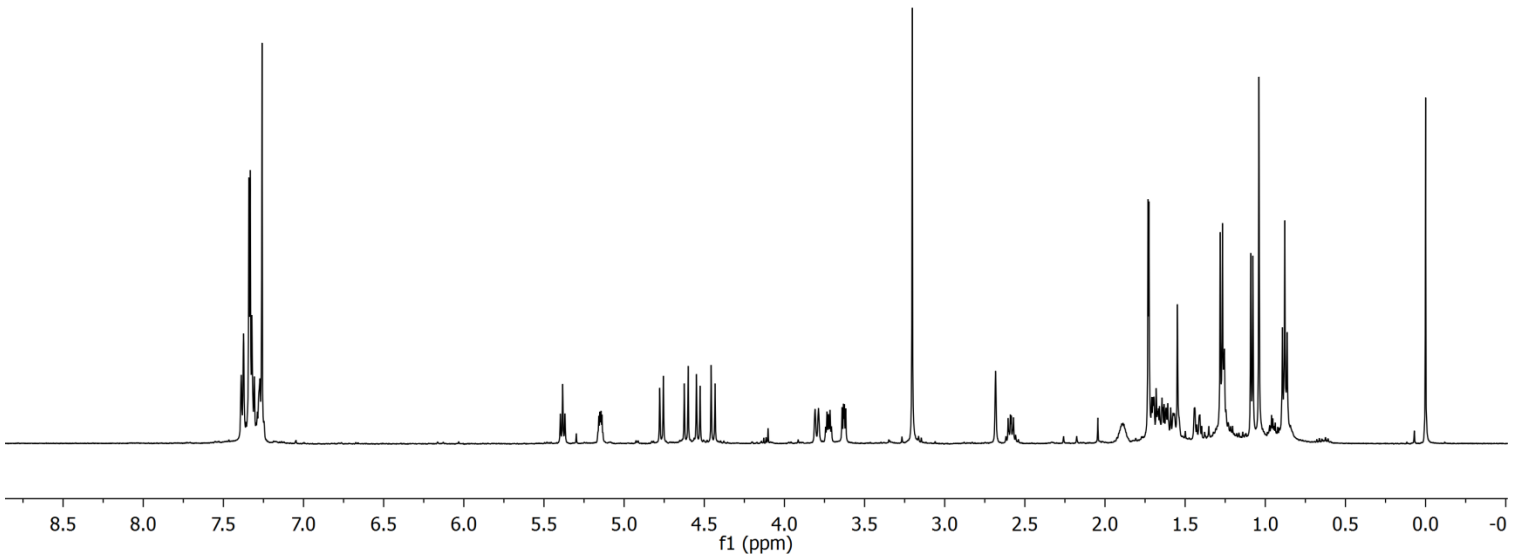



**3.34**

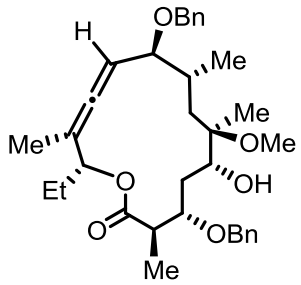
$^1$H NMR (500 MHz, $CDCl_3$)



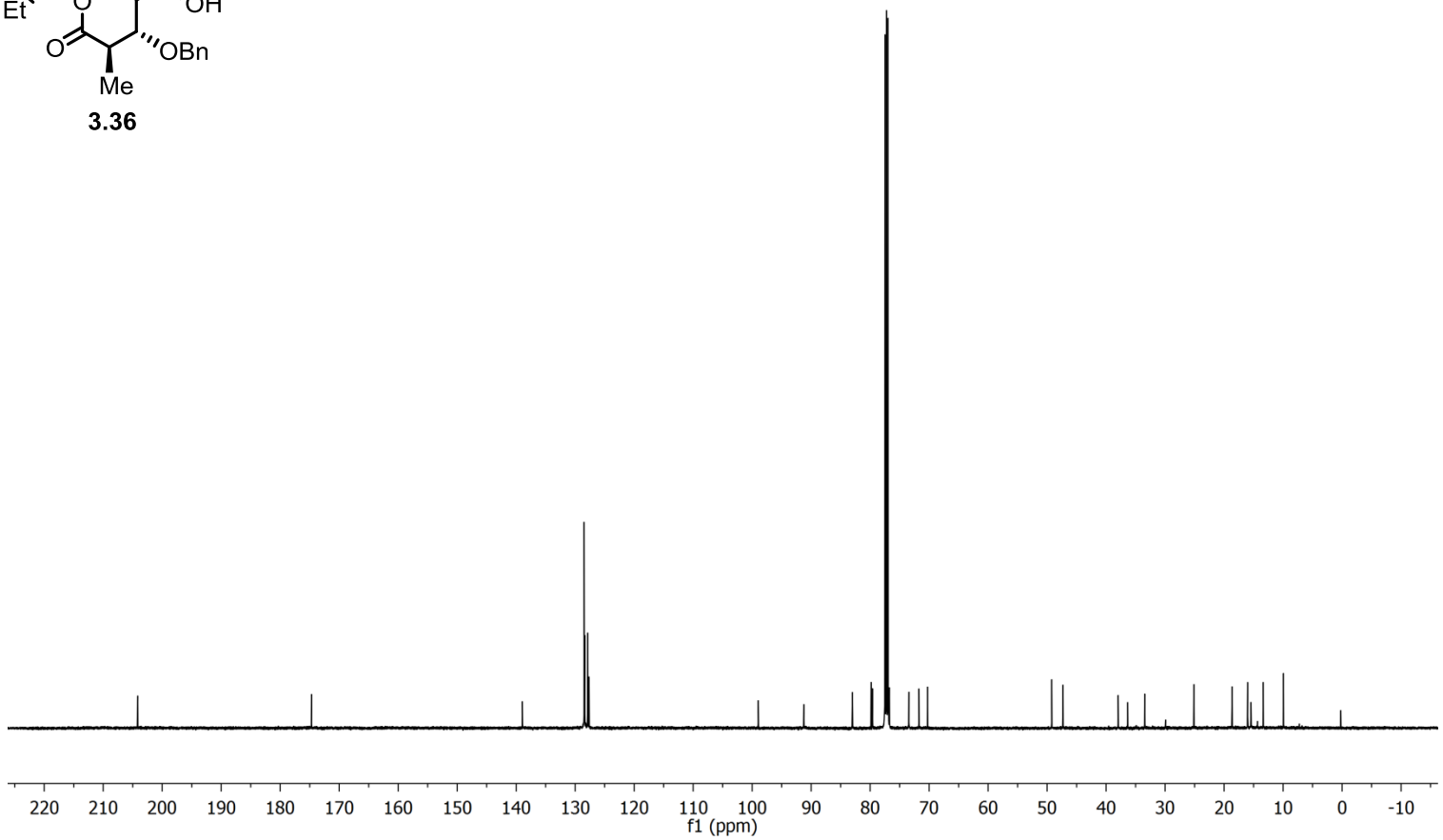

**3.36**



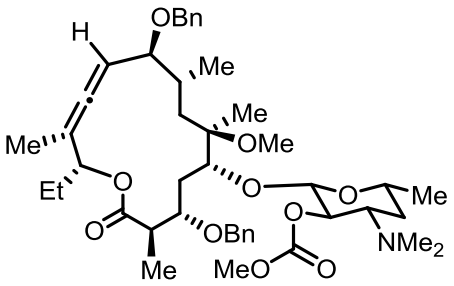
$^{13}$C NMR (126 MHz, $CDCl_3$)




**3.36**

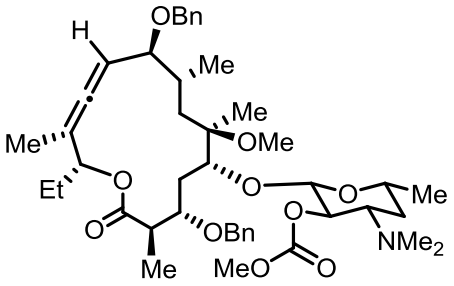


$^1$H NMR (500 MHz, $CDCl_3$)



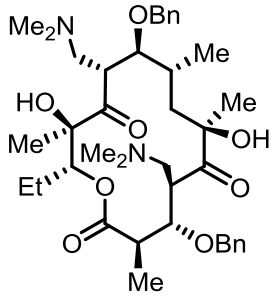

**3.37**

$^{13}$C NMR (126 MHz, $CDCl_3$)

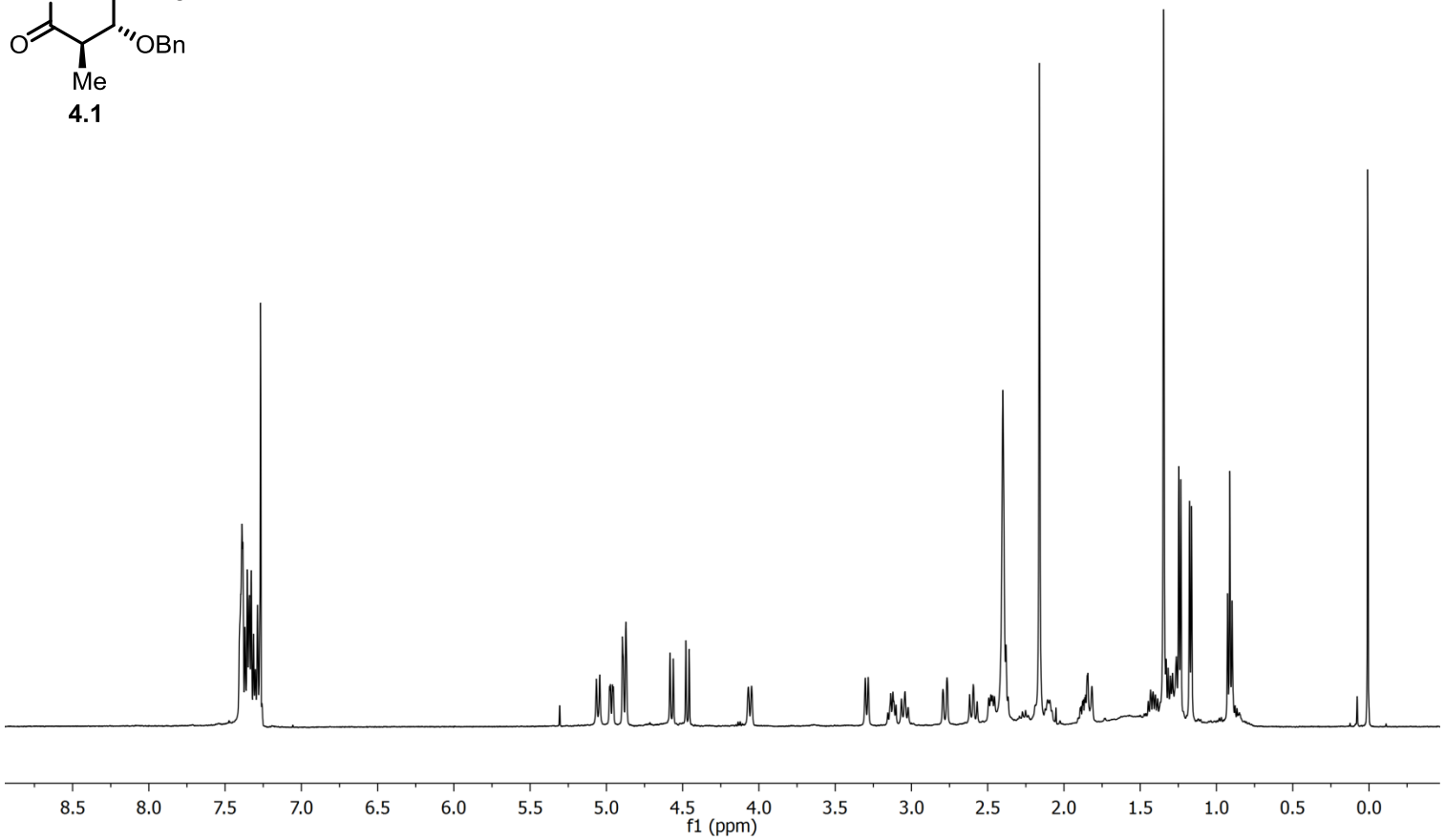



**3.37**

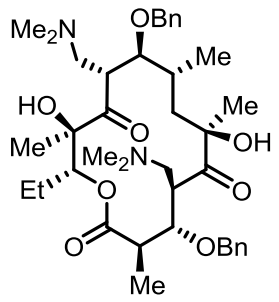
$^1$H NMR (500 MHz, $CDCl_3$)




**4.1**

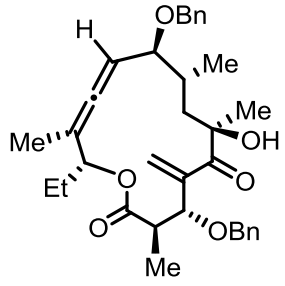


$^{13}$C NMR (100 MHz, $CDCl_3$)



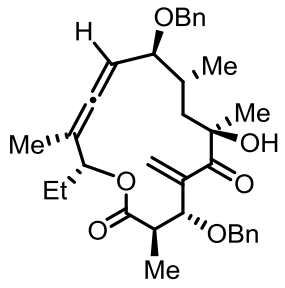

**4.1**

$^1$H NMR (500 MHz, $CDCl_3$)



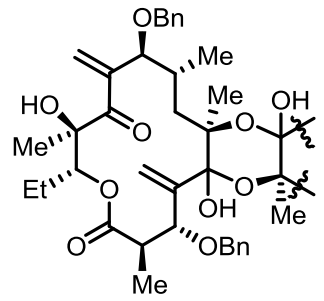

**4.7**

$^{13}$C NMR (126 MHz, $CDCl_3$)



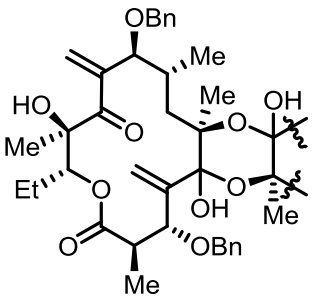

**4.7**

$^1$H NMR (500 MHz, $C_6D_6$)



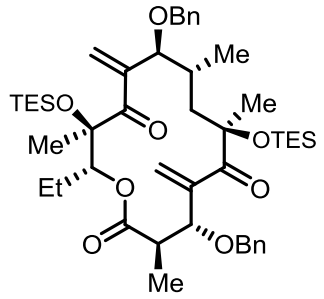

**4.2**

$^{13}$C NMR (100 MHz, $CDCl_3$)

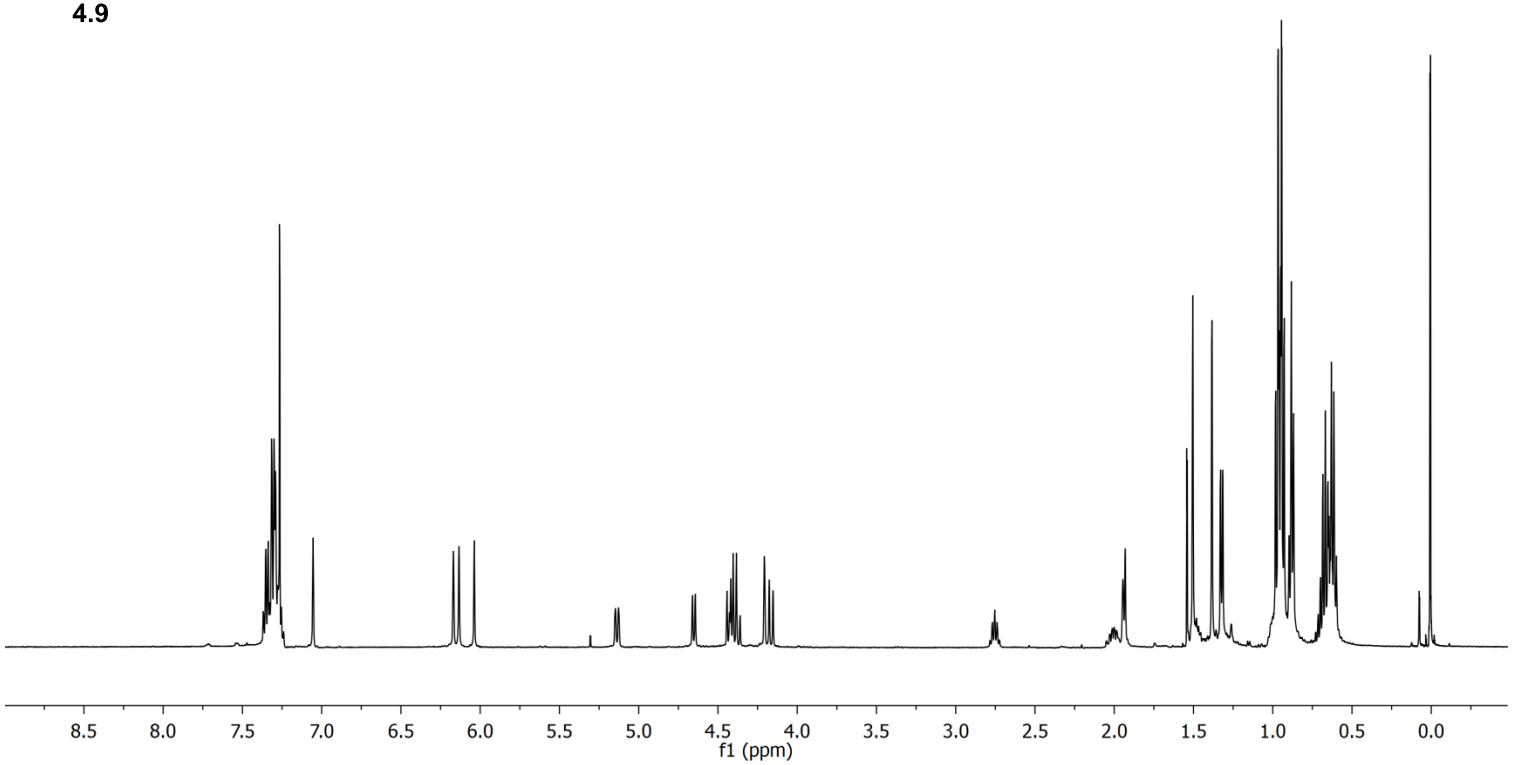



**4.2**

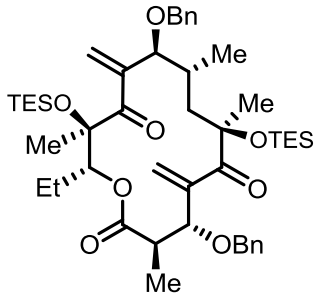
$^1$H NMR (500 MHz, $CDCl_3$)




**4.9**

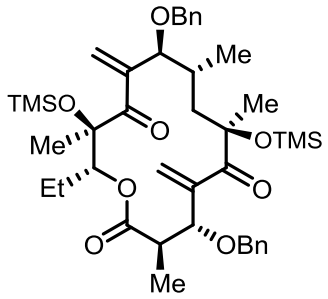


$^{13}$C NMR (126 MHz, $CDCl_3$)



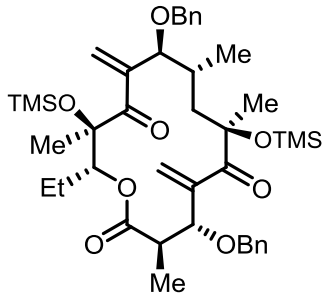

**4.9**

$^1$H NMR (500 MHz, $CDCl_3$)



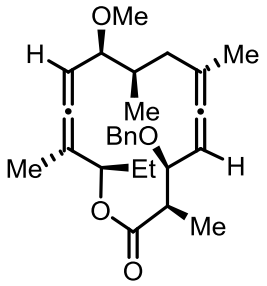

**4.11**

$^{13}$C NMR (126 MHz, $CDCl_3$)

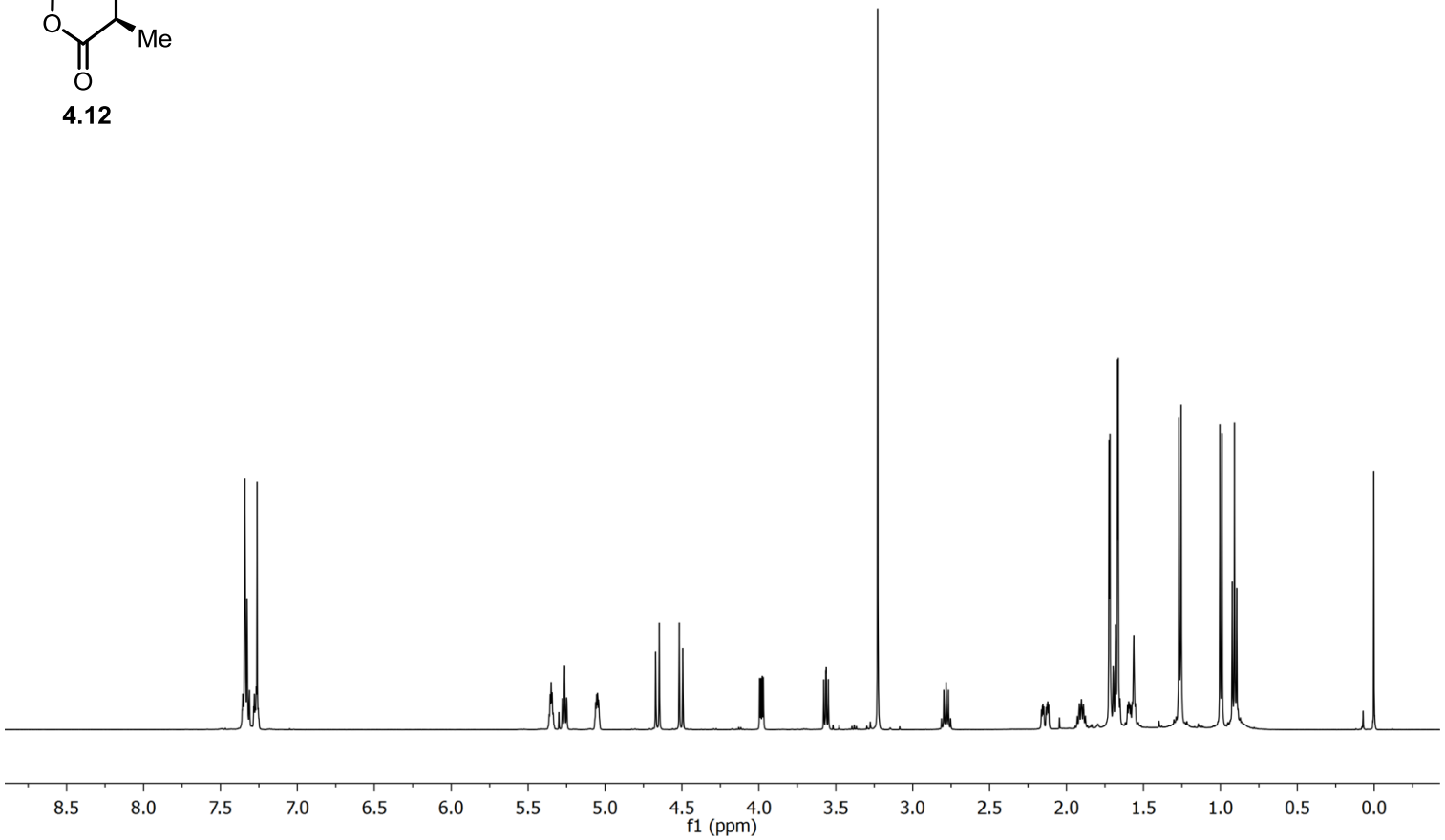



**4.11**

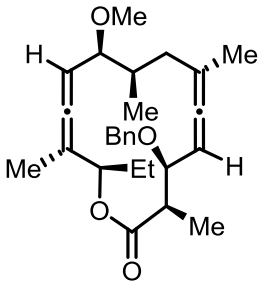
$^1$H NMR (500 MHz, $CDCl_3$)



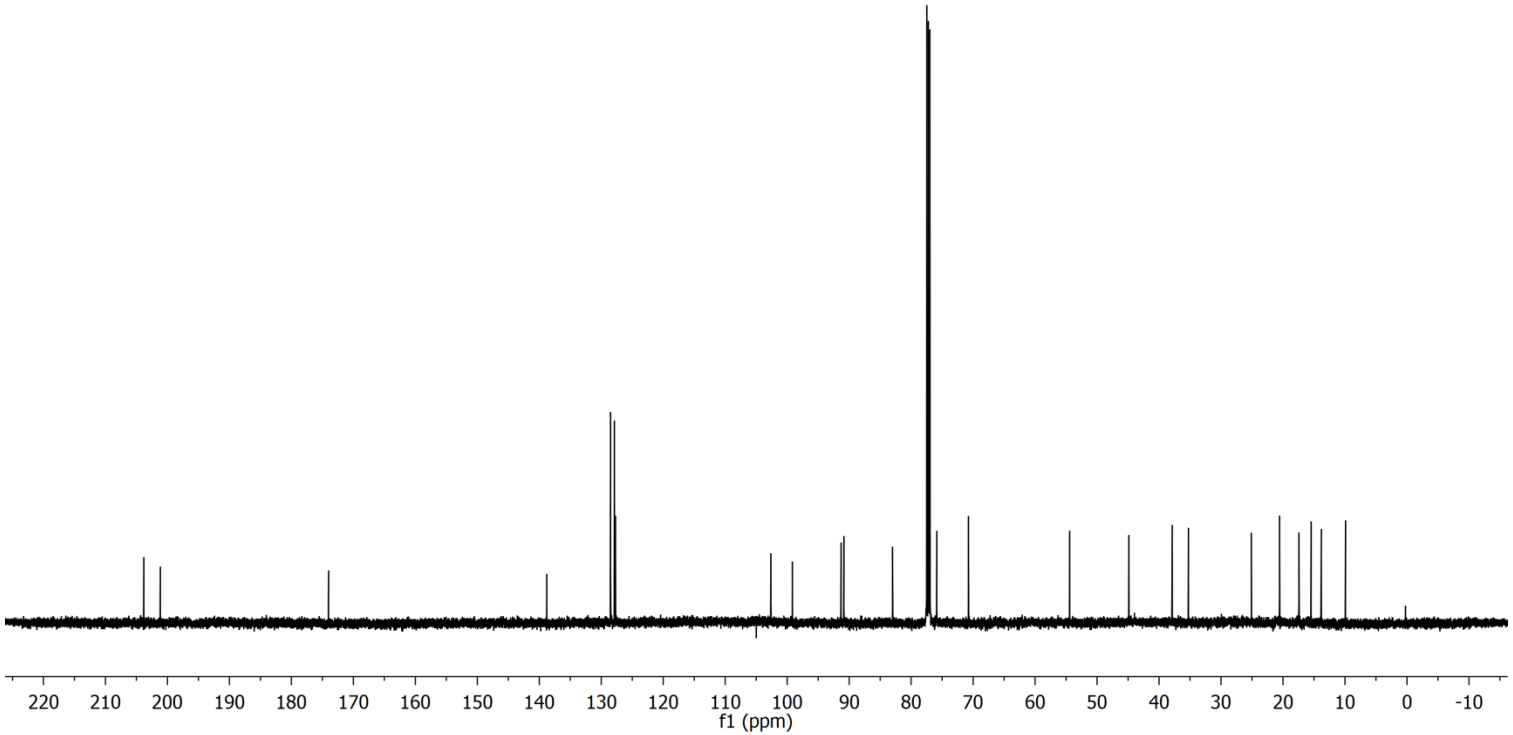

**4.12**



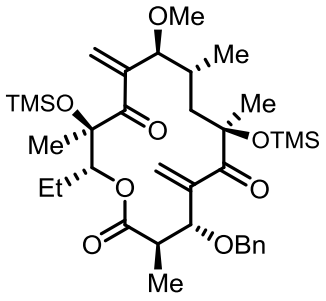
$^{13}$C NMR (126 MHz, $CDCl_3$)




**4.12**

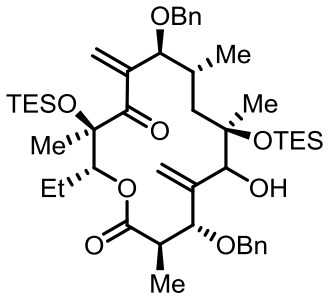


$^1$H NMR (500 MHz, $CDCl_3$)

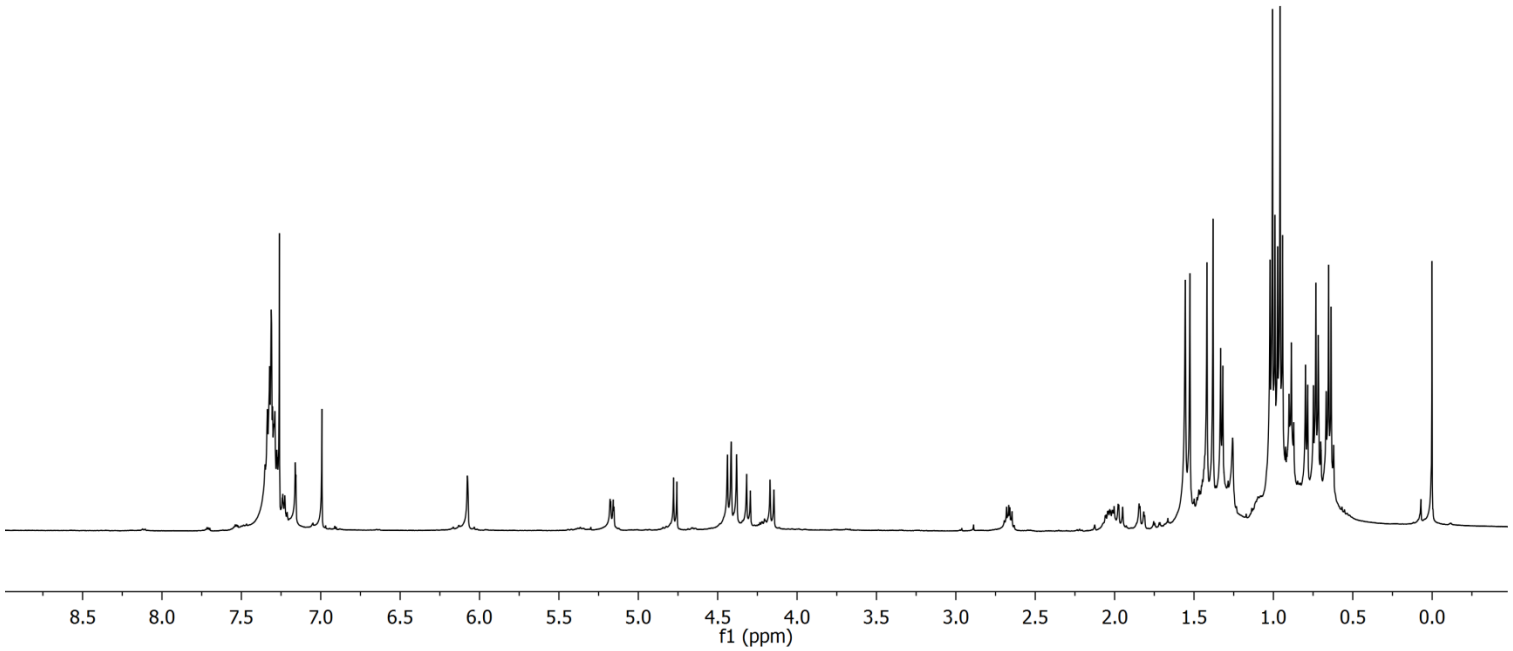



**4.15**

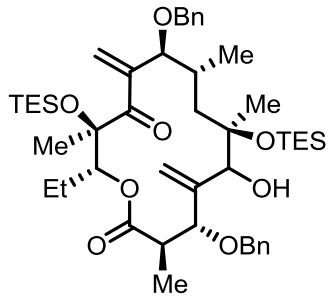
$^1$H NMR (500 MHz, $CDCl_3$)




**4.18**

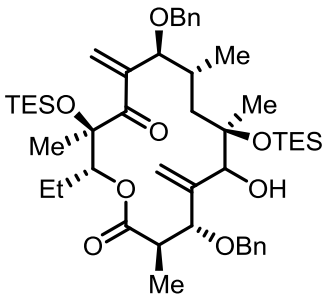


$^{13}$C NMR (126 MHz, $CDCl_3$)



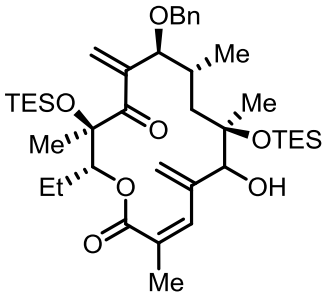

**4.18**

$^1$H NMR (400 MHz, $CDCl_3$)



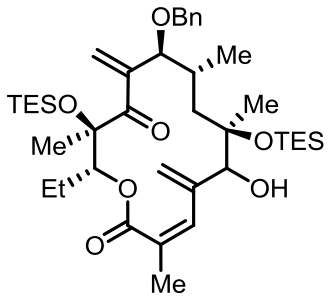

**4.19 (C5 epimer of 4.18)**

$^1$H NMR (400 MHz, $CDCl_3$)



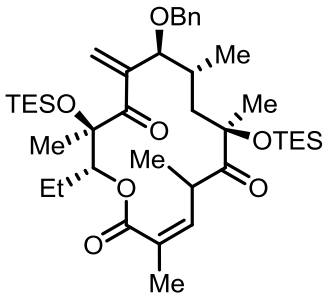

**4.20**

$^{13}$C NMR (126 MHz, $CDCl_3$)



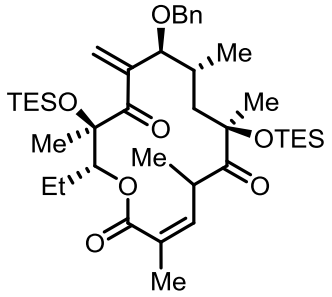

**4.20**

$^1$H NMR (500 MHz, $CDCl_3$)



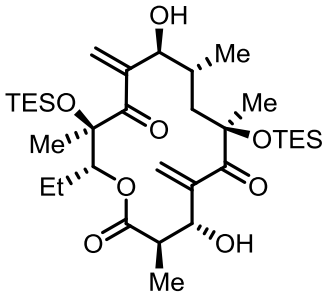

**4.21**

$^{13}$C NMR (126 MHz, $CDCl_3$)

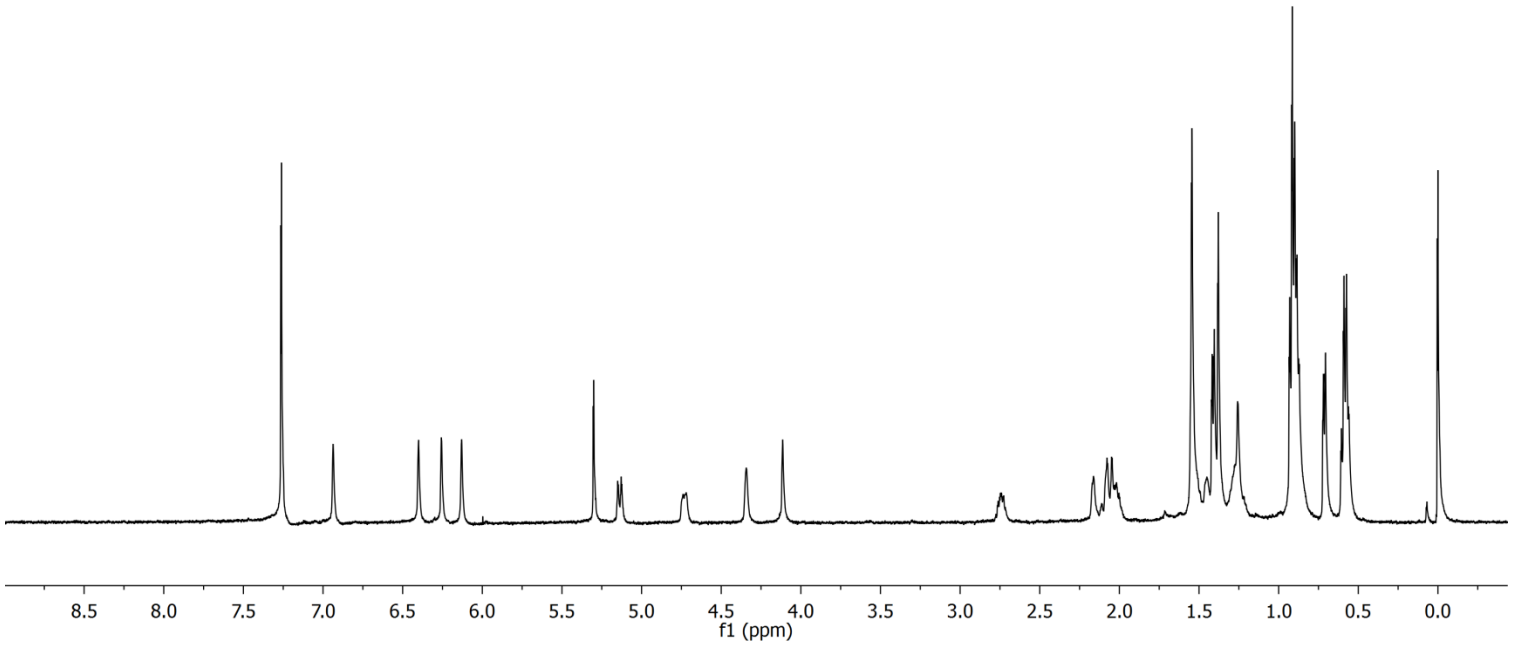



**4.21**

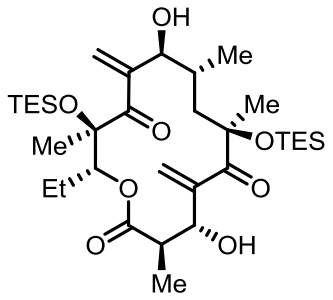
$^1$H NMR (500 MHz, $CDCl_3$)




**4.25**

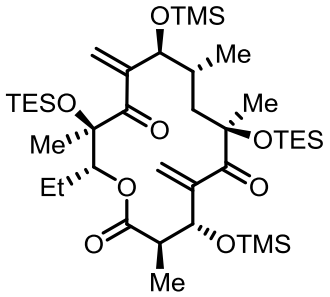


$^{13}$C NMR (126 MHz, $CDCl_3$)



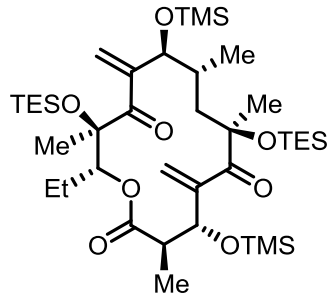

**4.25**

$^1$H NMR (500 MHz, $CDCl_3$)



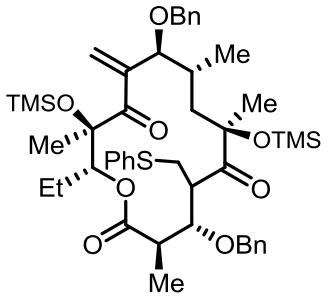

**4.26**

$^{13}$C NMR (126 MHz, $CDCl_3$)



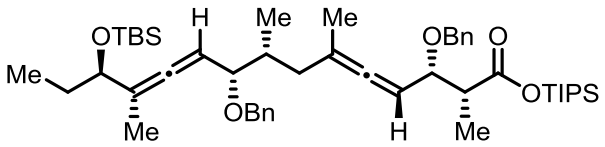

**4.26**

$^1$H NMR (500 MHz, $CDCl_3$)



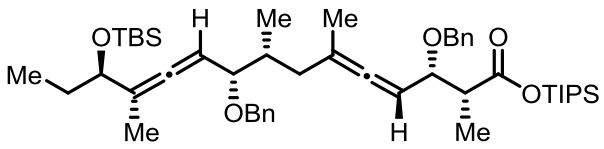

**4.27**

$^1$H NMR (500 MHz, $CDCl_3$)



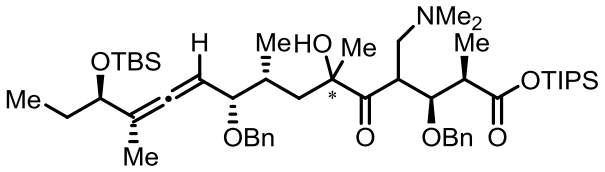

**4.30**

$^{13}$C NMR (126 MHz, $CDCl_3$)



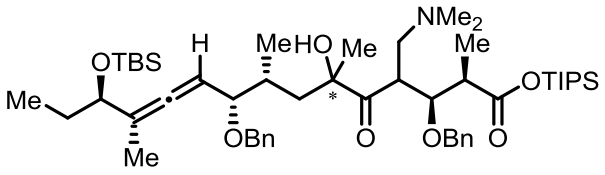

**4.30**

$^1$H NMR (500 MHz, $CDCl_3$)

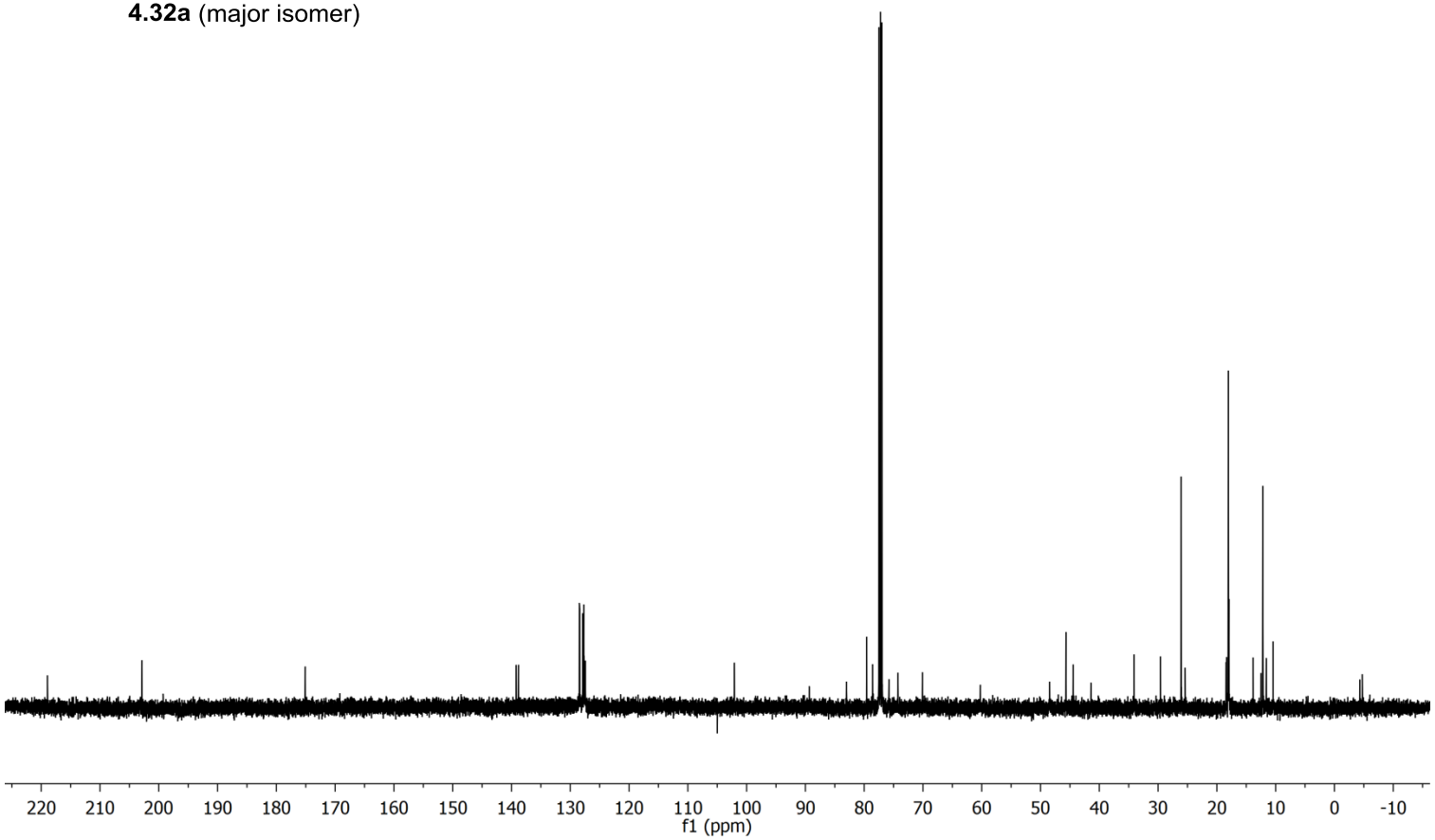



**4.32a** (major isomer)

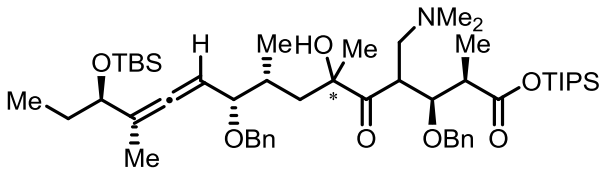
$^{13}$C NMR (126 MHz, $CDCl_3$)




**4.32a** (major isomer)

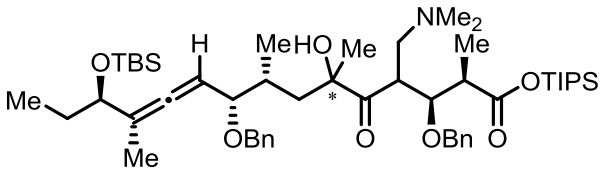


$^1$H NMR (500 MHz, $CDCl_3$)




**4.32b** (minor isomer)

$^{13}$C NMR (126 MHz, $CDCl_3$)




**4.32b** (minor isomer)