Towards the Total Synthesis of Penostatin Natural Products

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A thesis submitted in partial fulfillment of the
requirements for the Doctorate in Philosophy degree in Chemistry

Department of Chemistry and Biomolecular Science

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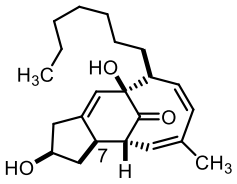
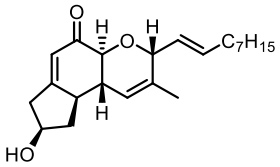
Abstract

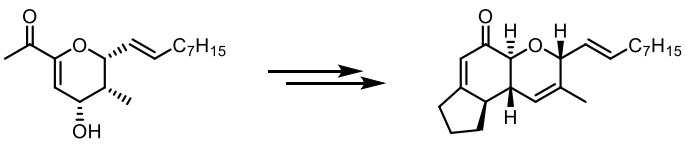


Penostatin F



Penostatin B

The penostatins are a family of polycyclic natural products isolated from marine bacteria. They exhibit unique biological activity and have garnered interest from synthetic organic chemists due to their complex structure. In particular, the complex oxidation pattern combined with either a fused tricyclic or bridged bicyclic core presents significant challenges to synthesis. The lack of a completed total synthesis of the bridged bicyclic congener penostatin F has motivated the pursuit of a strategy for its synthesis based on a Diels-Alder reaction /Claisen rearrangement sequence. In this work, progress and limitations of this approach are presented. A hydroxy-directed Diels-Alder/Claisen Rearrangement cascade was envisioned and explored however a series of roadblocks prevented the elaboration of bridged bicycle intermediates. Through this process, a novel degradation of hydroxy-dienes was uncovered as well as the isolation of a bridged bicycle containing a cyclic anti-Bredt alkene.



5-deoxypenostatin B

The challenges uncovered led to a pivot away from this strategy and ultimately to a new approach for the synthesis of penostatin natural products. In this strategy, a hydroxyl group is used as a tether for an intramolecular Michael addition. Following the optimization of this reaction, an unexpected retro-Dieckman rearrangement of the product forced the development of an alternative route to

an initially envisioned decarboxylation. This approach was employed to yield 5-deoxypenostatin B. Finally, progress towards integrating the cyclopentanol ring of penostatin B as part of this strategy via a Tamao-Fleming reaction is described.

Acknowledgements

The scientific process makes graduate studies often long and difficult, but the positive contributions of people involved along this journey make it possible to find moments of joy, satisfaction, and happiness. I want to start by thanking my supervisor, Prof. Louis Barriault, for mentoring me over my studies and providing essential guidance along the way. I want to also thank Prof. Jeffery Keillor, for encouraging me to pursue a summer internship in Prof. Barriault's lab almost nine years ago! I also want to thank my thesis advisory committee, Prof. André Beauchemin and Prof. Michael Organ, whose teaching have had a lasting impact on my knowledge of organic synthesis and perspective on science as a whole.

I would like to strongly and wholeheartedly thank my fiancée Natalie, for being by my side throughout it all, even with my long and sometimes unpredictable hours in the lab, and especially for her unconditional love and support. I can honestly say I would not have finished this without you. I would also like to thank my family and friends, whose support has also been crucial. From early morning ski trips to late nights at the bar, thank you for keeping me grounded over the years.

My lab mates have also been an important source of help and inspiration. I want to give special thanks to Tegan O'Brien and Avery Morris for reviewing many of my written works over my studies and overall being fantastic lab mates. I want to give a special shout out to Chris Wicks and Sam Rohe for the great conversations when our studies overlapped. I want to also thank Phil, Montse, Huy, Chad, Martin, Lea, and all other Barriault lab members I have encountered over the years. I also want to acknowledge the work from the departmental and faculty support staff, in particular Chloe Lagacée, Peter Pallister and Sharon Curtis.

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Abbreviations

Ac:	Acetyl
BINAP:	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn:	Benzyl
Bz:	Benzoyl
CDI:	1,1'-Carbonyldiimidazole
CN:	Nitrile
DBU:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM:	Dichloromethane
DIBAL:	Diisobutylaluminium hydride
DIPEA:	N,N-Diisopropylethylamine,
DMAP:	4-Dimethylaminopyridine
DMF:	Dimethylformamide
DMP:	Dess-Martin Periodinane
DMSO:	Dimethyl sulfoxide
EDC:	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et:	Ethyl
HDDA:	Hydroxy Directed Diels-Alder
HFIP:	Hexafluoroisopropanol
HMPA:	Hexamethylphosphoramide
iPr:	Isopropyl
KHMDS:	Potassium bis(trimethylsilyl)amide
LDA:	Lithium bis(trimethylsilyl)amide
LiDBB:	Di-tert-butylbiphenylide
MBNA:	2-Methyl-6-nitrobenzoic anhydride
Me:	Methyl
MOM	Methoxymethyl
Ms:	Mesyl
NaHMDS:	Sodium bis(trimethylsilyl)amide
NMO:	N-Methylmorpholine N-oxide
NMP	N-Methyl-2-pyrrolidone
NMR:	Nuclear Magnetic Resonance
NOESY:	Nuclear Overhauser Effect Spectroscopy
Ph:	Phenyl
PPTS:	Pyridinium p-toluenesulfonate
R_f	Retention factor
TBAF:	Tetra-n-butylammonium fluoride
TBS:	tert-Butyldimethylsilyl chloride
tBu:	tert-Butyl
TES:	Triethylsilyl
Tf:	Triflate

TFA:	Trifluoroacetic acid
TFE:	2,2,2-Trifluoroethanol
THF:	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC:	Thin Layer Chromatography
TMS:	Trimethylsilyl
TPAP:	Tetrapropylammonium perruthenate
Ts:	Tosyl

Abbreviations

Ac:	Acetyl
BINAP:	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn:	Benzyl
Bz:	Benzoyl
CDI:	1,1'-Carbonyldiimidazole
CN:	Nitrile
DBU:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM:	Dichloromethane
DIBAL:	Diisobutylaluminium hydride
DIPEA:	N,N-Diisopropylethylamine,
DMAP:	4-Dimethylaminopyridine
DMF:	Dimethylformamide
DMP:	Dess-Martin Periodinane
DMSO:	Dimethyl sulfoxide
EDC:	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et:	Ethyl
HDDA:	Hydroxy Directed Diels-Alder
HFIP:	Hexafluoroisopropanol
HMPA:	Hexamethylphosphoramide
iPr:	Isopropyl
KHMDS:	Potassium bis(trimethylsilyl)amide
LDA:	Lithium bis(trimethylsilyl)amide
LiDBB:	Di-tert-butylbiphenylide
MBNA:	2-Methyl-6-nitrobenzoic anhydride
Me:	Methyl
MOM	Methoxymethyl
Ms:	Mesyl
NaHMDS:	Sodium bis(trimethylsilyl)amide
NMO:	N-Methylmorpholine N-oxide
NMP	N-Methyl-2-pyrrolidone
NMR:	Nuclear Magnetic Resonance
NOESY:	Nuclear Overhauser Effect Spectroscopy
Ph:	Phenyl
PPTS:	Pyridinium p-toluenesulfonate
R_f	Retention factor
TBAF:	Tetra-n-butylammonium fluoride
TBS:	tert-Butyldimethylsilyl chloride
tBu:	tert-Butyl
TES:	Triethylsilyl
Tf:	Triflate

TFA:	Trifluoroacetic acid
TFE:	2,2,2-Trifluoroethanol
THF:	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC:	Thin Layer Chromatography
TMS:	Trimethylsilyl
TPAP:	Tetrapropylammonium perruthenate
Ts:	Tosyl

Chapter 1: Origin and Synthetic Progress Towards the Penostatins

1.1 Isolation of the penostatins

Marine microorganisms have proven to be a rich source of bioactive small molecules.[1] The Penicillium fungal strain OUPS-79, separated from the marine alga *Enteromorpha intestinalis*, was isolated by the group of Numata in the 1990's leading to the identification of multiple families of natural products, including the communesin, penochalasin and penostatin families of molecules.[2,3] Many of these exhibit potentially useful therapeutic properties, such as cancer cell cytoxicity.

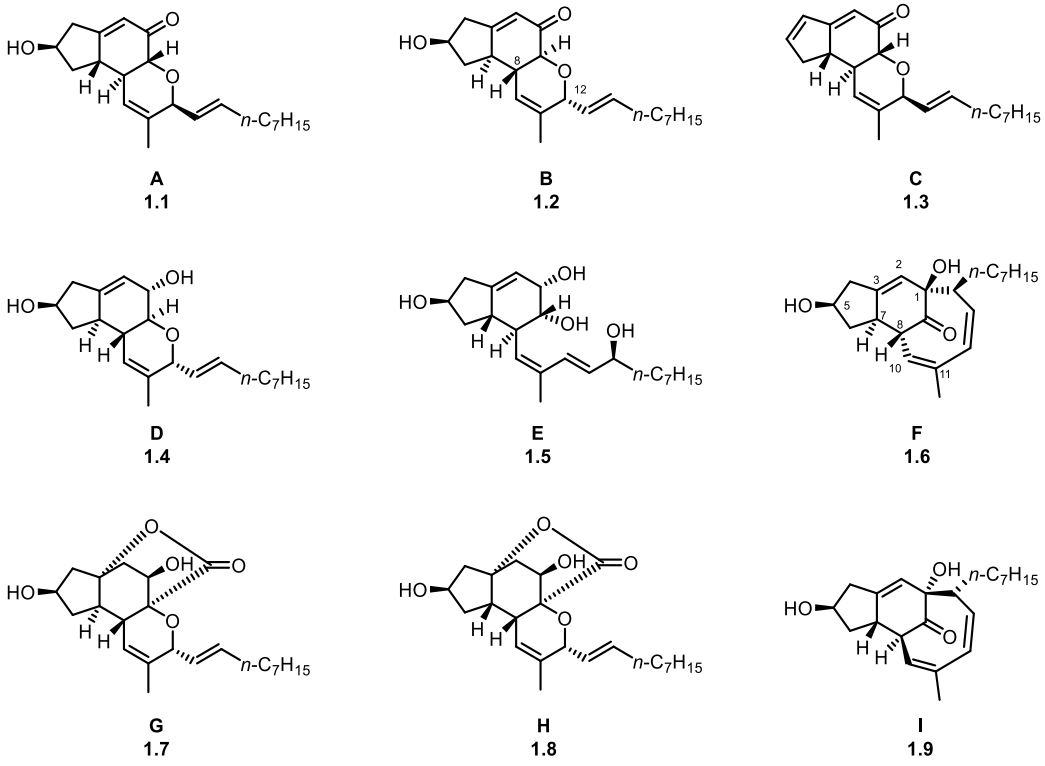
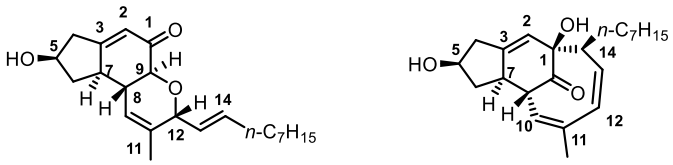


Figure 1.1 Isolated penostatins

The penostatins (Figure 1.1) are composed of constitutionally isomeric polycyclic molecules that can be generally categorized into two subgroups. The first one are characterized by core structures containing a unique [5.6.0] bicycle fused to a pyran ring, such as penostatin B **1.2**, C **1.3** and G **1.7**. The second are distinguished from their congeners through their [5.3.1] bridged bicyclic core structure, such as penostatin F **1.6** and I **1.9**. Many structural features are conserved throughout the family, such as a seven membered alkyl chain and the absolute stereochemistry of the alcohol on the cyclopentanol ring. All the stereogenic sp^3 carbons of the core [4.4.0] bicycle ring system bearing stereocenters are of opposite configuration when comparing penostatin A **1.1** and B **1.2**, with the exception of the carbon bearing the hydroxyl group. The conservation of these structural elements in the penostatin family has spurred the search for a possible common intermediate in the biosynthesis of this family of natural products.



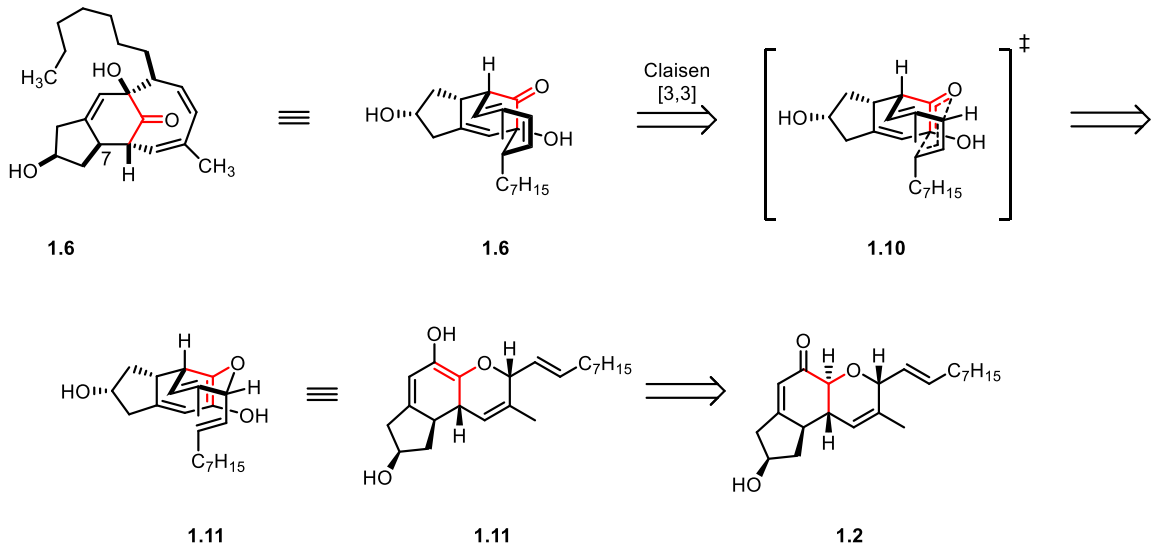
B **1.2** **F** **1.6**

Figure 1.2 Penostatin carbon numbering

1.2 Biosynthetic hypotheses

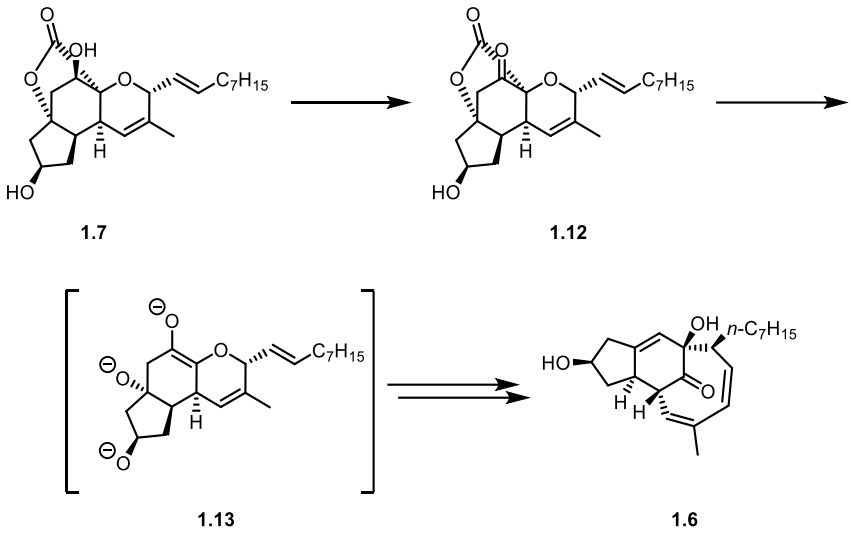
The unique structural features of the penostatins have led the Snider[4] and Hoye[5,6] groups to propose two biosynthetic hypotheses that could explain the conservation of structural elements in the penostatins. In both cases, the bridged ketone found in penostatins F and I are hypothesized to originate from a Claisen rearrangement of an enol tautomer **1.11** of a fused congener (Scheme 1.1).

Of note here, the specific stereochemistry of penostatin B matters; a syn relationship between protons at C8 and C14 is required for the chair like transition state **1.10** of the proposed rearrangement.



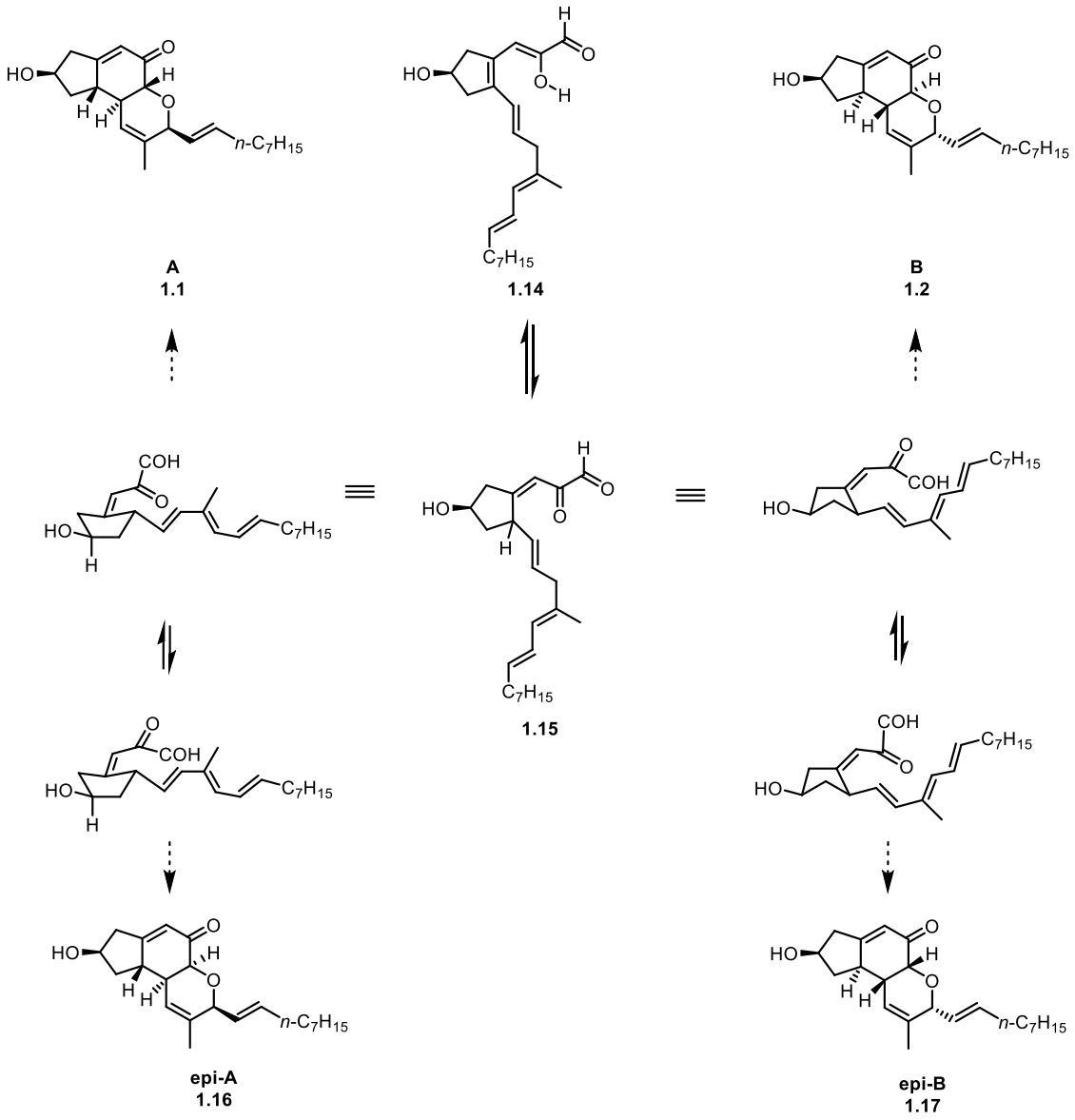
Scheme 1.1 - General biosynthetic hypothesis

Snider suggests a sequence whereby penostatin G **1.7** would undergo an oxidation/decarboxylation sequence to generate the required enolate **1.13** for the Claisen rearrangement (Scheme 1.2). Although no further elaboration or study on this hypothesis was reported by the Snider group, recent isolation of the glycosylated and oxidized product of penostatin G **1.7** supports the possibility of such a biosynthetic pathway.[7]



Scheme 1.2 - Snider's hypothesized biosynthetic Claisen rearrangement sequence

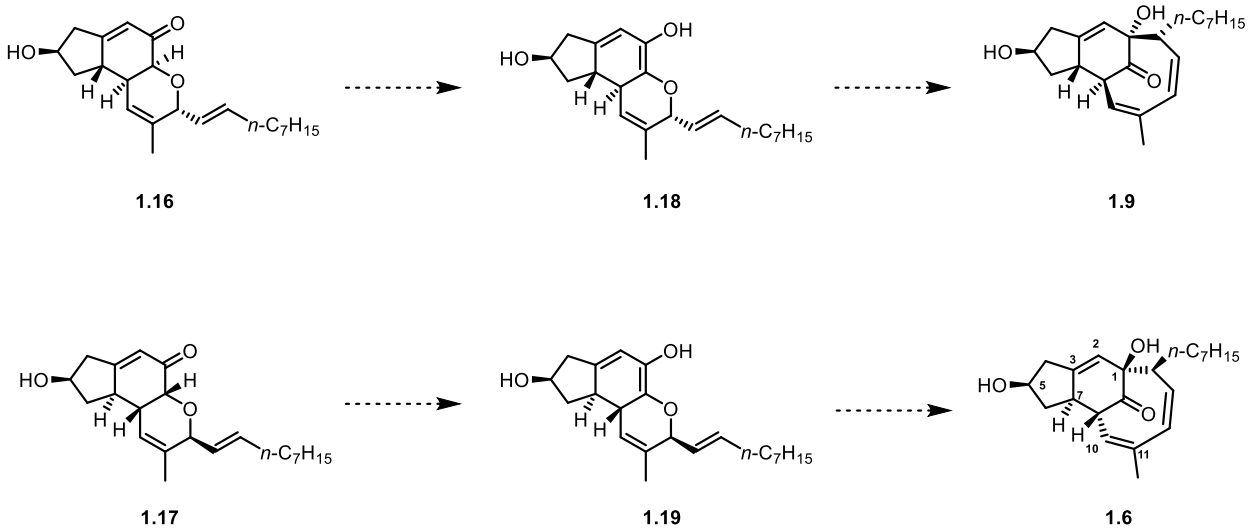
The Hoye group has suggested a biosynthetic pathway based on the polyketide synthetic machinery to explain the origin of this polyoxygenated natural product family (Scheme 1.3).



Scheme 1.3 - Hoye's biosynthetic hypothesis for the [5.6.0] fused bicyclic core of penostatin A and penostatin B

The proposed biosynthesis starts with a 1,5 hydride shift of a substrate **1.14** synthesized via a polyketide pathway. Assuming the 1,5-hydride shift is not stereoselective, the stereochemistry of the hydrogen at C7 of **1.15** should not be controlled and thus the reaction should produce two distinct stereoisomers at this carbon. The resulting polyenes could then undergo an

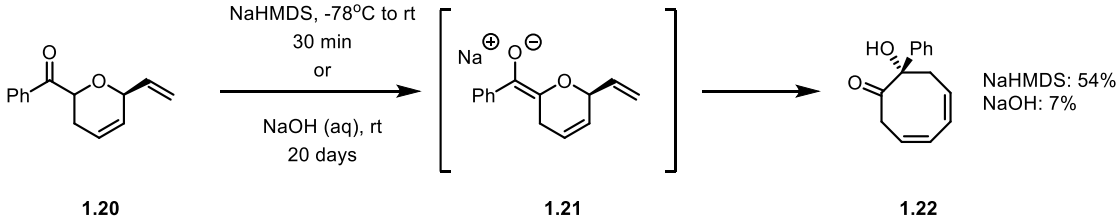
intramolecular hetero Diels-Alder reaction to form the pyran ring. The observed stereochemistry of penostatins A **1.1** and B **1.2** would correspond to the products of the *exo* transition state of such a cycloaddition, whereas their epimers **1.16** and **1.17** stem from the *endo* transition states. Although the *endo* isomer was never directly isolated by the group of Numata, the stereocenter alpha to the ketone formed in this reaction would be ablated in a keto enol tautomerization process prior to the Claisen rearrangement. The bridged bicyclic penostatins would correspond to the products of a Claisen rearrangement of either epimer (Scheme 1.4).



Scheme 1.4 - Hoye's biosynthetic hypothesis for [5.3.1] bridged bicyclic core of penostatin I and F

This hypothesis, linking the family of natural products to one common precursor has been explored through model systems by the Hoye group and the Snider group. The proposed intramolecular Diels-Alder reaction was not studied, as the authors did not make the appropriate precursors to confirm or reject this hypothesis.

The Hoye group had some success in examining the possibility of the suggested anionic Claisen rearrangement.[6] Results obtained on model substrates such as **1.20** indicate that the Claisen rearrangement is extremely rapid even at sub zero temperatures (Scheme 1.5). It is not clear whether the requisite sodium or potassium enolates are accessible in vivo, but the high reactivity of this model substrate supports the possibility of an anion accelerated Claisen rearrangement as the key step biosynthetically.

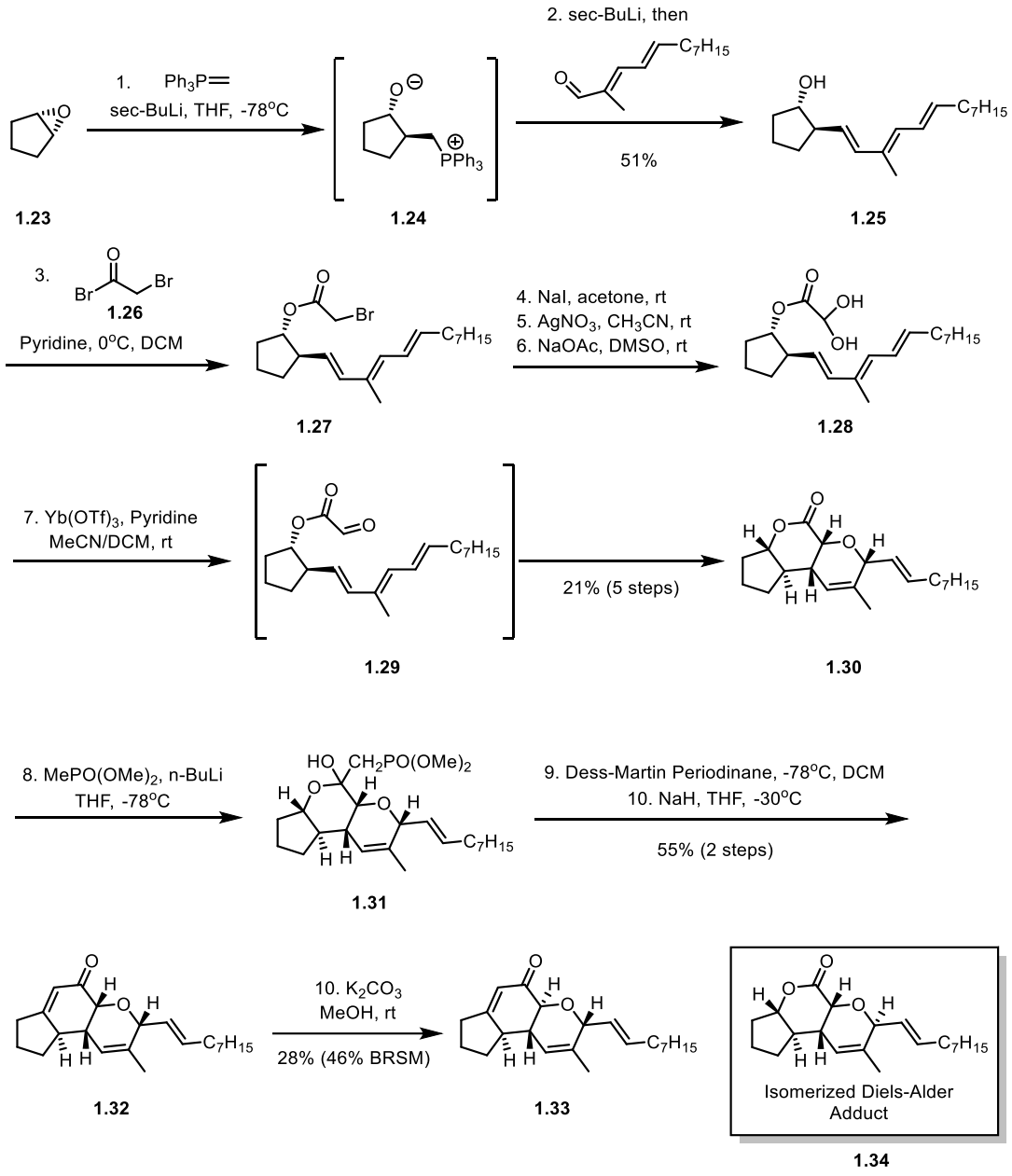


Scheme 1.5 - Anionic Claisen rearrangement of a model substrate

1.3 Total synthesis of 5-deoxypenostatin B

The penostatin family has been the target of total synthesis, however only three members have been synthesized to this date: 5-deoxypenostatin B[4] **1.33**, penostatin B[8] **1.2** and penostatin E[9] **1.5**. 5-deoxypenostatin B **1.33**, a variant of **1.2** missing the oxygen at C5, was synthesized by the group of Prof. Barry Snider (Snider incorrectly names the congener in his paper). A biomimetic strategy employing an intramolecular hetero Diels-Alder reaction from a glyoxylate ester **1.29** was chosen as a key step to assemble the core of the natural product from a polyunsaturated substrate (Scheme 1.6). The glyoxylate ester was chosen as a surrogate of the more obvious alpha keto aldehyde retron due to the presumed instability of this molecule. To determine whether this approach would be successful, the authors synthesized a deoxygenated version of penostatin B **1.33** (Scheme 1.6). The synthesis began by assembling the glyoxylate ester substrate via a convergent synthesis using

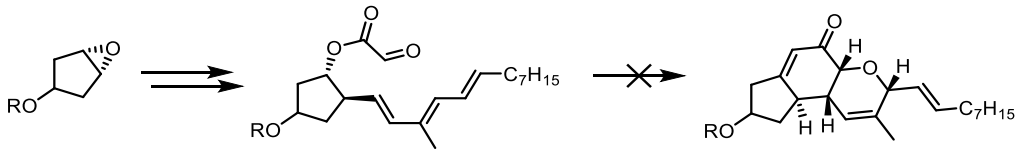
a homologated aldehyde in a Wittig reaction with the γ-oxido ylide derived from a 5 membered cyclic epoxide. The alcohol was then acetylated with bromo acetyl bromide. This substrate proved to be unstable and was therefore converted without chromatographic purification to the glyoxylate hydrate **1.28**, which decomposed upon dehydration. To avoid having to perform a dehydration step, the hydrate of the aldehyde was directly engaged in the hetero-Diels-Alder reaction by submitting the crude material to Lewis acidic conditions. A water stable lanthanide Lewis acid proved to be an effective catalyst for this transformation. In this step, the substrate is dehydrated to **1.29** and undergoes cyclization in one pot, avoiding severe degradation and yielding the cycloadduct **1.30** in 24% yield over 5 steps. Surprisingly, the authors also observed a diastereoisomer **1.34** that stems from an isomerization at the doubly allylic C-12 position. Since scrambling of the other stereocenters resulting from the hetero-Diels-Alder reaction is not observed, the isomerization is presumed to occur via a doubly allylic cation generated by trace amounts of acid following the hetero-Diels-Alder reaction. To suppress this isomerization, pyridine was added to the reaction mixture in order to quench any trace of acid. Lactone **1.30** was then converted to an enone **1.32** by performing a 1,2 addition onto the ester moiety of the lactone with $LiCH_2PO(OMe)_2$ to yield the hydroxy keto phosphonate **1.31** as a hemiacetal. The product was then oxidized and underwent an intramolecular aldol condensation to complete the synthesis of **1.32**, the [4.4.0] bicyclic core of the natural product. Following epimerization, 5-deoxypenostatin B was finally obtained. Although the epimerization presumably operates via an enol intermediate that is set up to undergo a Claisen rearrangement, the presence of a Claisen rearrangement by-product was not reported.



Scheme 1.6 - Snider's total synthesis of 5-Deoxypenostatin B

With a viable strategy towards the model substrate in hand, the authors performed the same sequence of reactions starting from an oxygenated cyclic epoxide **1.35**, which would correspond to the oxygen at C5 in the natural product.[10] However, the Diels-Alder step turned out to be problematic when an oxygenated functionality is present at that position (Scheme 1.7). All efforts

perform the key Diels-Alder reaction in the presence of an ether at C5 were futile, despite attempts to optimize the Lewis acid and other reaction parameters. Hypothesizing that the oxygen at C5 hinders the formation of the Diels-Alder transition state, the protecting group and stereochemistry at the C5 oxygen was modified. Stereochemical inversion of the ether moiety and variation of the protecting group was successful in forming product, albeit in poor yield and poor diastereomeric control. Although the strategy enabled a rapid assembly of the core carbon structure of the penostatins, the sensitivity of intermediates and necessary oxidation and functionalization sequences prevented a successful total synthesis of penostatin A or B.



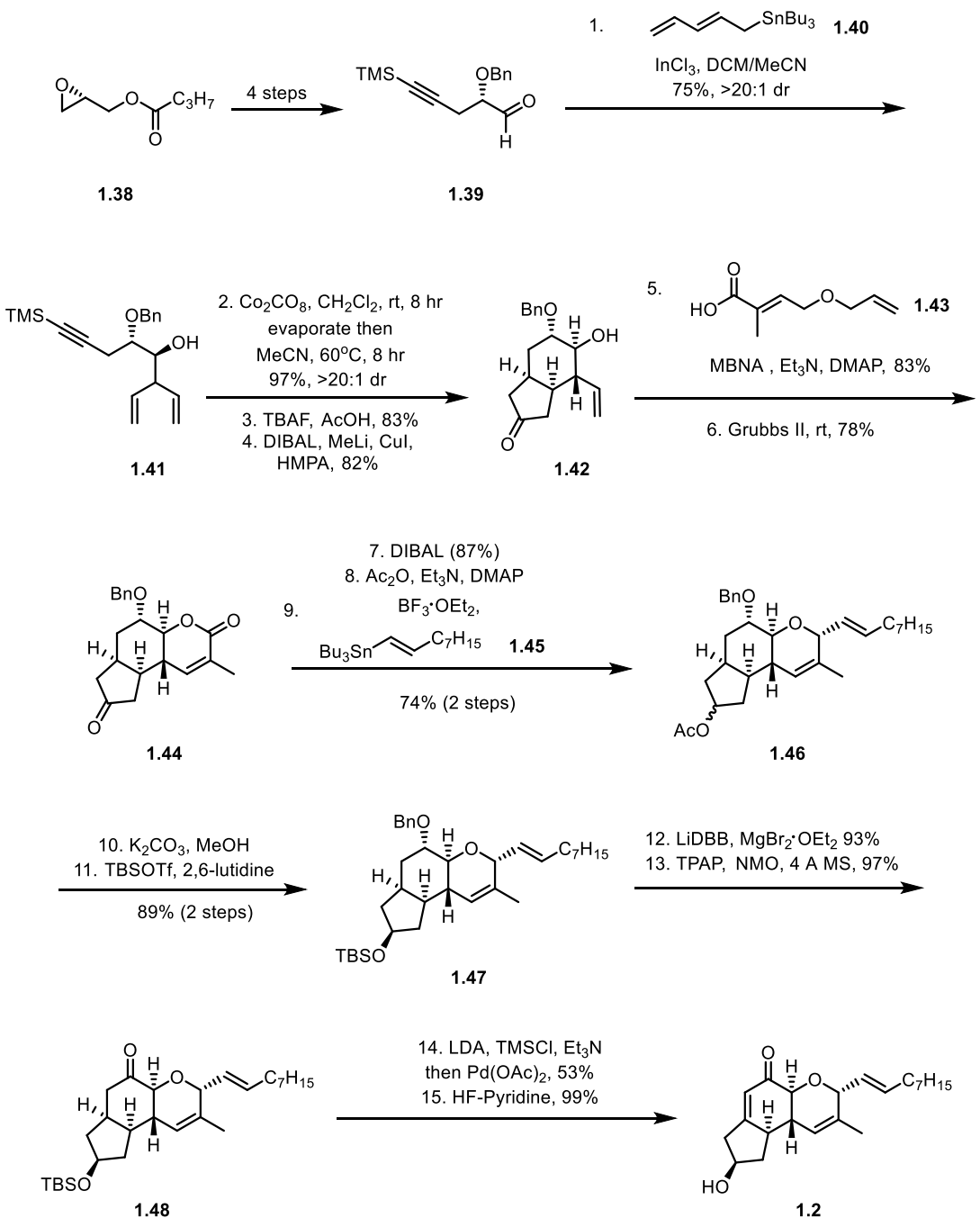
1.35 **1.36** **1.37**

Scheme 1.7 - Challenges in performing the key hetero-Diels-Alder step with C5 oxygenation

1.4 Total synthesis of penostatin B

The first successful total synthesis of penostatins B and E was reported by the group of Prof. Shishido[8,9] (Scheme 1.8). Both penostatins B and E were accessed using the same general strategy. The synthesis relied on an asymmetric Pauson-Khand reaction, setting the stage for a stereochemical relay. The Pauson-Khand substrate **1.41** could be synthesized enantiospecifically from a chiral glycidol ester in six steps via a synthesis previously disclosed by the Trost group. The first stereocenter of the natural product was installed by a directed indium catalyzed addition of **1.40** to an alpha-oxo aldehyde **1.39**. This chiral center can be mapped out onto the core of the natural product at C7. The subsequent Pauson-Khand reaction was diastereoselective, forming a bicyclic product which after treatment with TBAF and enone reduction gave compound **1.42**. This

intermediate contains the fused 5 and 6 membered ring system as well as a pair of vicinal stereocenters that will be at the junction of the [4.4.0] bicycle. From here, **1.42** underwent acylation with an activated methacrylic acid derivative **1.43**. A relay ring closing metathesis concluded the synthesis of the core of the natural product. To finish the synthesis, the alkenyl side chain was added by a Lewis acid catalyzed diastereoselective addition of a vinyl tin reagent **1.45** to a cyclic acetylated lactol formed after DIBAL reduction and acetylation of **1.44**. Of note, the cyclopentanone ring is also reduced in this step to the corresponding alcohol. A decent 10:1 diastereoisomeric ratio at C5 for **1.46** was observed for this reaction, however the two diastereoisomers could not be separated. The desired product was isolated only after exchanging the acetate protecting group for a TBS ether. Finally, the benzyl ether underwent deprotection and oxidation to the ketone **1.48**, followed by dehydrogenation to an enone by Saegusa-Ito oxidation. Finally, deprotection of the silyl ether provided penostatin B. Through a well designed stereochemical relay, penostatin B was thus synthesized in a total of 19 steps.

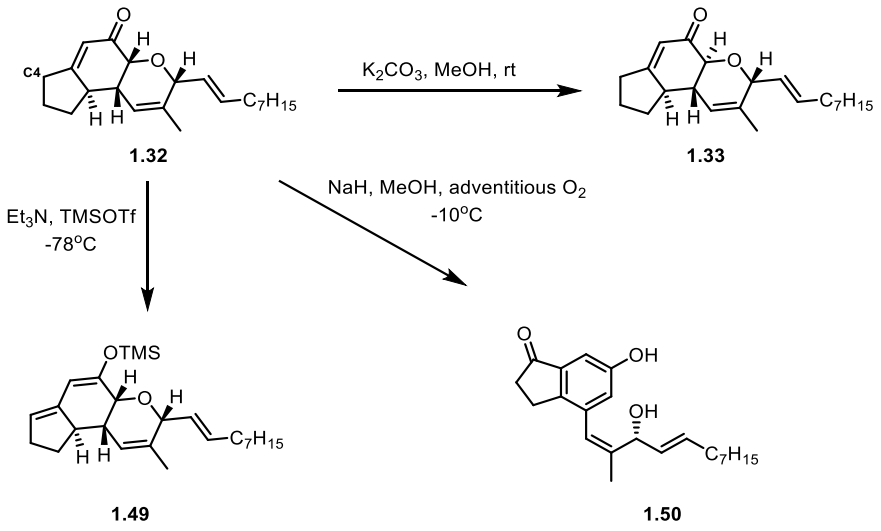


Scheme 1.8 - Shishido's Total Synthesis of penostatin B

1.5 Attempts at applying a biomimetic Claisen rearrangement towards penostatin F

Missing amongst the reported progress on the penostatins is a complete synthesis of the bridged bicycle congeners of this natural product family, namely penostatin F **1.6** or I **1.9**. The biosynthetic

hypothesis has inspired some work towards the completion of the bridged bicyclic natural products, however these efforts were ultimately unsuccessful. The group of Snider attempted to convert a late stage intermediate **1.32** containing the fused tricyclic core into the bridged bicycle via an anion accelerated Claisen Rearrangement mimicking the biosynthetic hypothesis, however the desired product was never isolated.[10] As the stereochemistry of the C2 position was set via an epimerization under basic conditions, the treatment of this intermediate with base was expected to lead to the enolate at C2 and to the hypothesized anion accelerated Claisen rearrangement. However, treatment of intermediate in a variety of basic conditions led to deprotonation at the vinylogous position to yield **1.49** or to undesired products such as the oxidation product **1.50** (Scheme 1.9). This is a strong indicator of the base sensitivity of the enone and of the kinetic preference of deprotonation at C4.

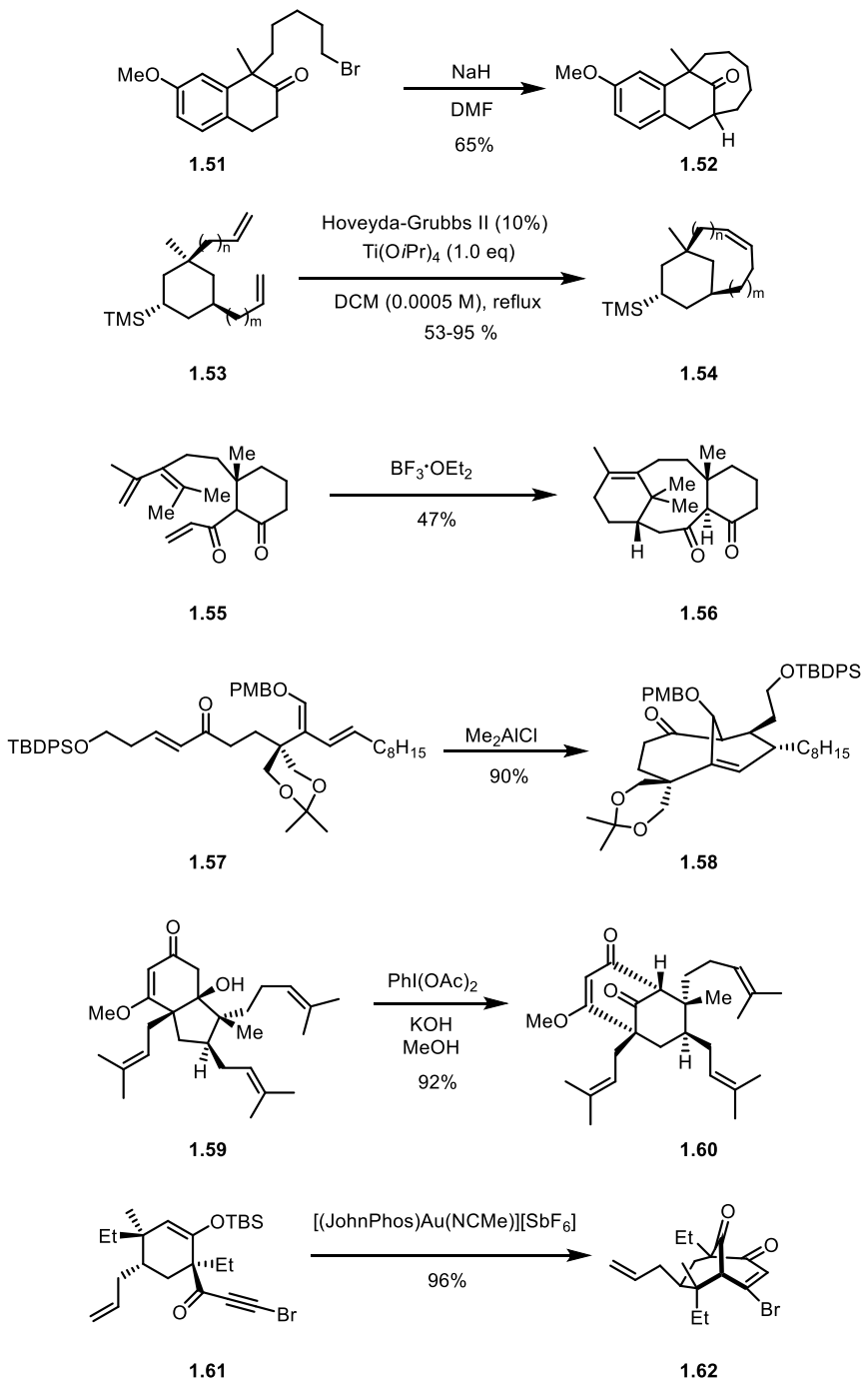


Scheme 1.9 – Attempts at exploiting enolate intermediates towards a biomimetic Claisen rearrangement.

1.6 General approaches in the synthesis of bridged bicycles

The lack of a completed total synthesis of penostatin F presents a fertile ground to develop new efficient methods to access molecular complexity. Beyond the penostatins, bridged bicyclic natural

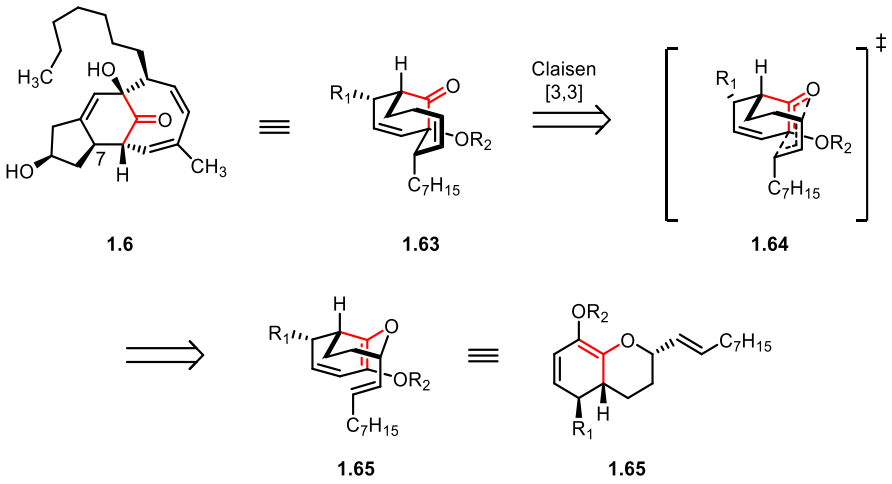
products have garnered a significant amount of interest from organic chemists. General strategic approaches have emerged as highlighted below (Scheme 1.10). For example, the intramolecular Type II Diels-Alder reaction has been a key transformation applied in many syntheses of bridged bicyclic structures, namely in the syntheses of taxol,[11] phomoidride[12,13] and vinigrol.[14] This reaction yields not only the bicyclic core but provides key stereocenters of the natural product as well as unsaturations that would be otherwise difficult to install, such as anti-Bredt alkenes. Another common strategy towards this motif is a double alkylation of cyclic ketones, with electrophiles such as metallated allyl groups, Michael acceptors and alkyl bromides. Rearrangements have also featured prominently as a tactic towards bridged bicycles.[15] Modern methods using transition metal catalysis also feature prominently in accessing these structures.[16,17] Lastly, cross metathesis as a strategy has been explored but has proven difficult in the case of bridged [5.3.1] bicycles as very low concentrations and conformational bias are necessary for the reaction to be productive.[18]



Scheme 1.10 – Selected examples of bridged bicyclic core synthesis

1.7 Barriault's progress towards penostatin F

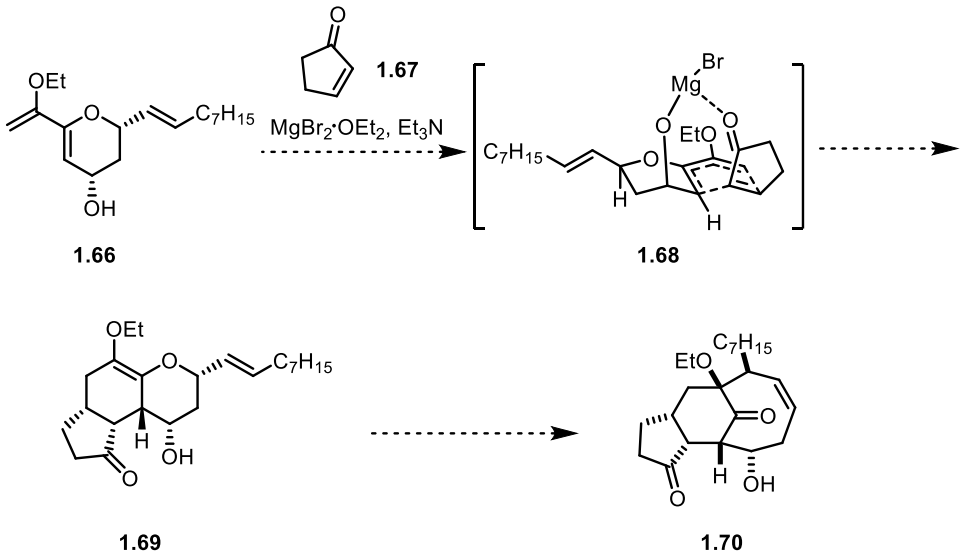
Inspired by the biosynthetic hypotheses for this transformation, the group of Prof. Barriault also sought to employ a Claisen rearrangement to assemble the bridged bicycle.[19] In order to avoid the challenging enolization required to obtain the Claisen rearrangement substrate, the group targeted an alkylated enol ether such as **1.66** as a substrate for this reaction (Scheme 1.11). As explained earlier in the chapter, conformational analysis reveals that the *syn* relative stereochemistry of the carbons at C7 and C12 are crucial to access the Claisen rearrangement's chair like transition state. To assemble a bicyclic substrate containing this particular stereochemistry, the Barriault group explored two strategies. The first involved a hydroxy directed Diels-Alder reaction[19] as a key step and the second one is a conratory 6π electrocyclization.[20] These two approaches have been explored on a series of model substrates and have laid the groundwork for further application towards the completion of the penostatin family of natural products.



Scheme 1.11 - Retrosynthesis of bridged bicycle via a Claisen rearrangement

1.8 Diels-Alder/Claisen cascade synthesis of the bridged bicyclic core of penostatin F

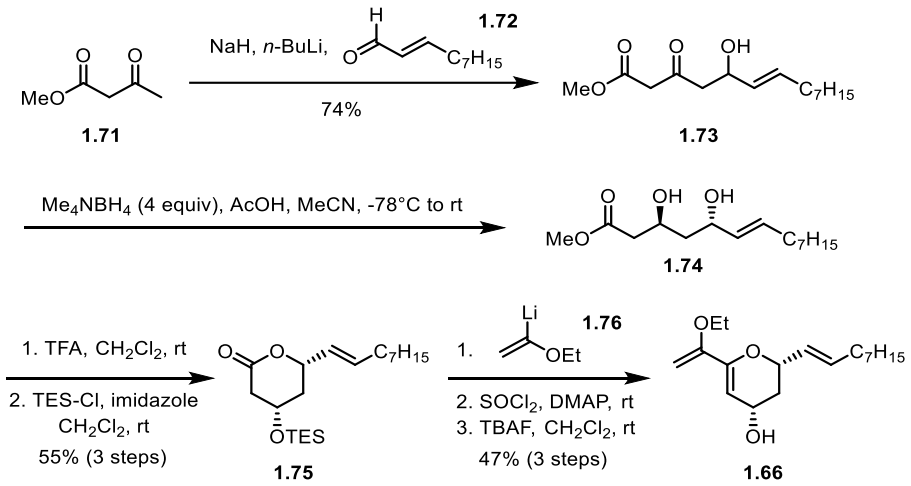
The venerable Diels-Alder reaction has proven fruitful in the synthesis of stereodefined 6 membered rings.[21] In the context of the penostatin synthesis, an approach based on a hydroxy directed Diels-Alder reaction was developed to install the stereocenter at C7 and to assemble the [4.4.0] fused bicyclic substrate for the Claisen rearrangement. In this reaction, the hydroxyl moiety on the diene **1.66** forms a magnesium alkoxide complex that can further bind the dienophile through its carbonyl activating group.



Scheme 1.12 - Diels-Alder approach towards the Claisen Rearrangement substrate. In the proposed transition state for the key Diels-Alder reaction, the approach of the dienophile is syn to the hydroxyl group.

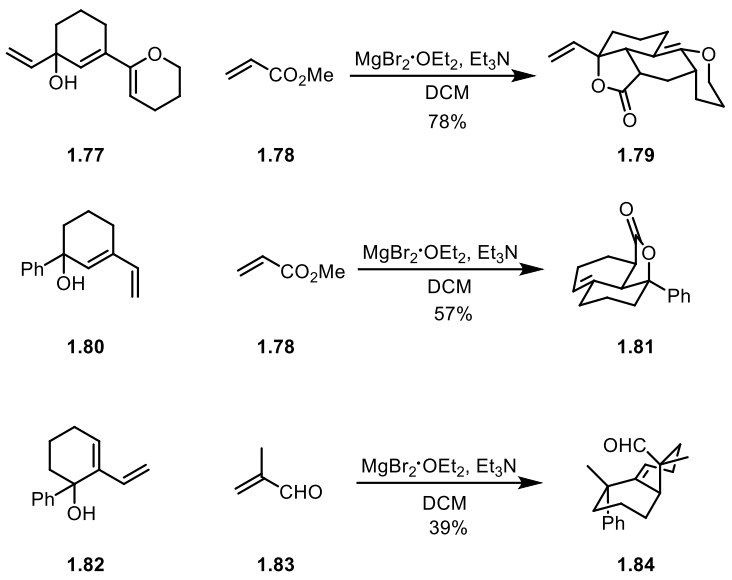
This process activates the dienophile and directs the face of the approach in an endo transition state, thus enabling the stereospecific synthesis of cycloadducts such as **1.69** in high yield and diastereoselectivity. To test this two-step cascade, the necessary diene was prepared starting from methyl acetoacetate **1.71** (Scheme 1.13). Key in the sequence is an *anti* selective reduction of a β-hydroxy ketone **1.72** using the classic triacetoxyborohydride salt method.[22] The

diastereoselective reduction sets the stage for the *syn* stereochemistry of the hydrogen substituent at C8 relative to C14 in the diene, thus securing the stereochemical requirement to access the transition state of the Claisen rearrangement.



*Scheme 1.13 - Synthesis of the first-generation hydroxytriene **1.66***

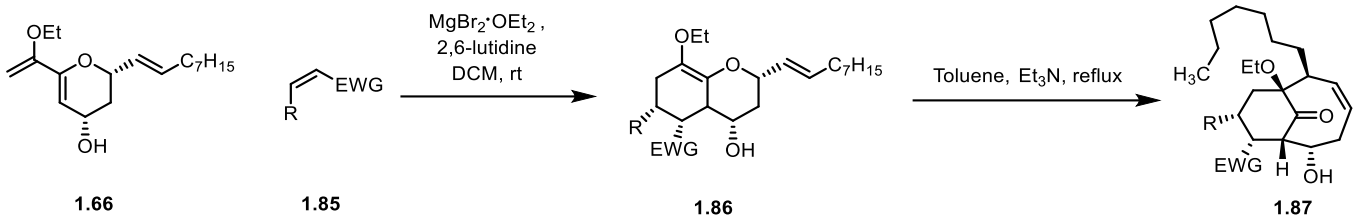
With the synthesis of the diene **1.66** secured, the key Diels-Alder/Claisen sequence could be evaluated. Several factors concerning this sequence were revealed (Figure 1.3). First, only highly activated dienes seemed to effectively produce the Diels-Alder adduct. Cyclopentenone, the only mono activated diene reported, suffered a significant reduction in yield compared to dienophiles activated with two electron withdrawing groups, such as maleimides **1.89** and **1.92**. This is a surprising result since mono activated dienophiles such as methyl acrylate were shown to be competent dienophiles in previous studies on magnesium catalyzed hydroxy directed Diels-Alder reactions reported by the Barriault group[23] (Scheme 1.14).



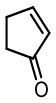
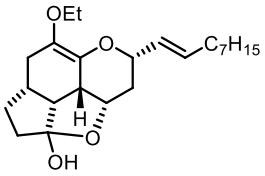
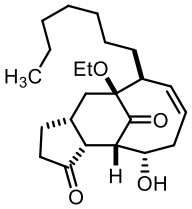
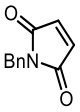
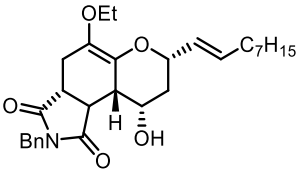
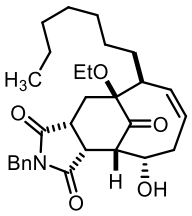
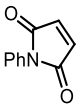
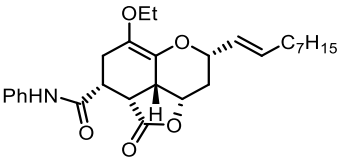
Scheme 1.14 - Magnesium catalyzed hydroxy-directed Diels-Alder reaction (Barriault, 2003)

Further, the activating moiety on the dienophile succumbs to cyclization by the hydroxyl group following the Diels-Alder reaction in certain cases, such as in the case of ester activating groups or *N*-phenyl maleimide. This turned out to be important in the Claisen rearrangement, as lactonized cycloadducts were not able to convert to bridged bicyclic products. Presumably, the strain generated by the lactone ring hinders the formation of the chair like transition state of the Claisen Rearrangement.

Figure 1.3 Scope of the hydroxy directed Diels-Alder/Claisen Rearrangement sequence

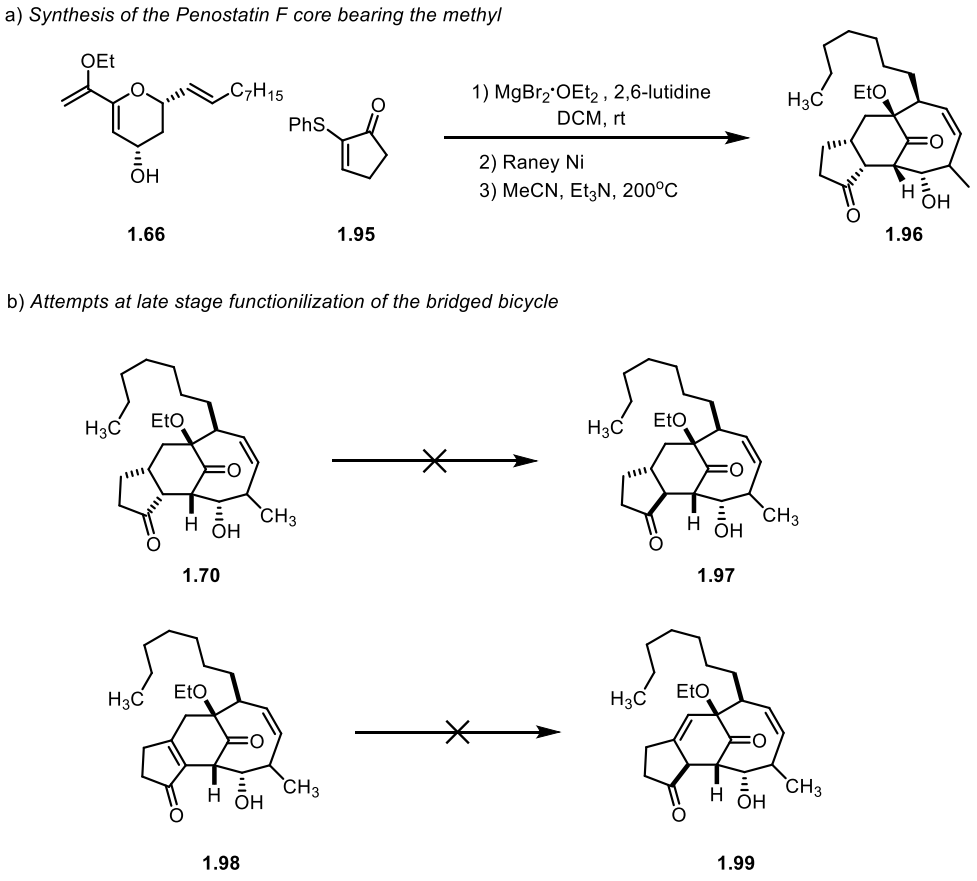


1.66 **1.85** **1.86** **1.87**

Dienophile	Diels-Alder Product (yield)	Claisen Product (yield)
 **1.67**	 (23%) **1.88**	 (70%) **1.89**
 **1.90**	 (72%) **1.91**	 (55%) **1.92**
 **1.93**	 (80%) **1.94**	No Reaction

Although the key steps of this strategy achieved the desired outcome, attempts to complete a total synthesis using were not as successful (Scheme 1.15). For example, conducting the key

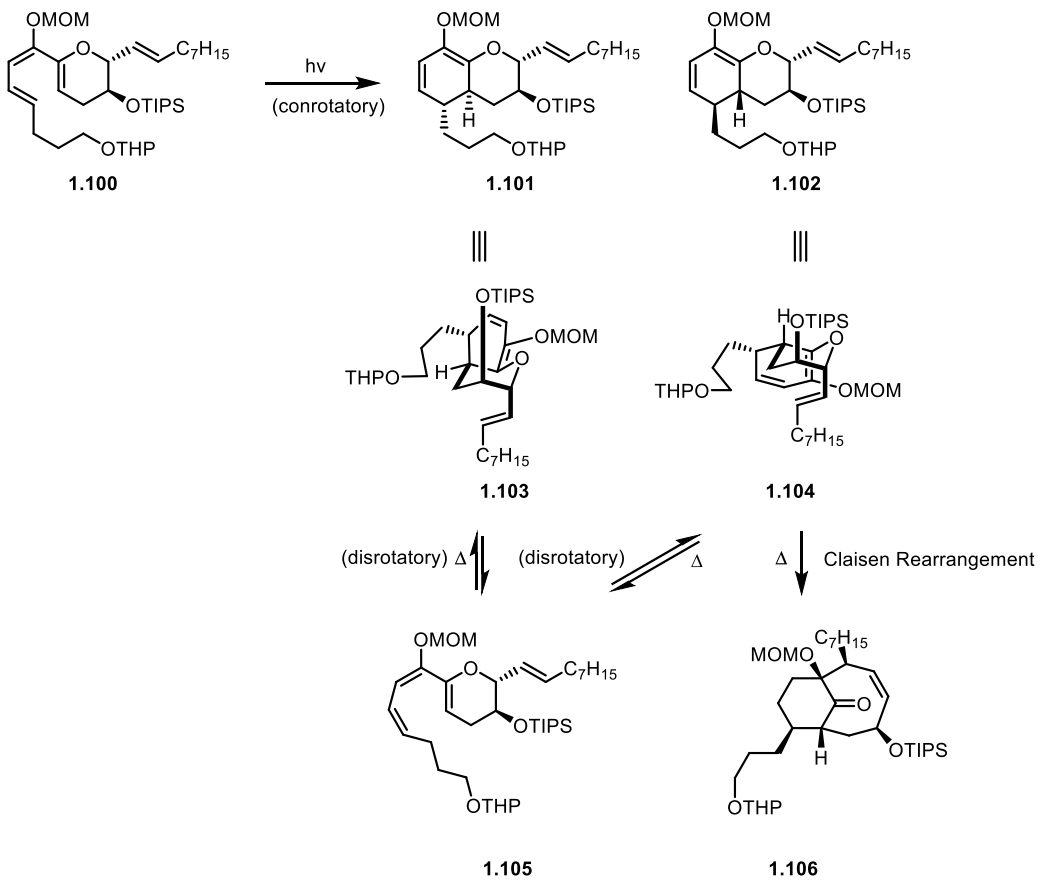
steps with an activated dienophile such as 2-thiophenoxycyclopentenone yielded the core of penostatin F.[20] However, serious issues were encountered upon further functionalization. After reductive desulfurization, the carbon at C8 of **1.88** was expected to epimerize to the required stereoisomer, but attempts to convert the trans ring junction to the *cis* isomer were fruitless. Second, efforts to deconjugate a tetrasubstituted enone **1.98** generated by elimination of the sulfur group were also met with failure. Due to the inability to successfully functionalize the 5 membered ring after the Claisen rearrangement, an alternative to the Diels-Alder reaction was proposed.



Scheme 1.15 - Unsuccessful attempts at further functionalization of the bicyclic core

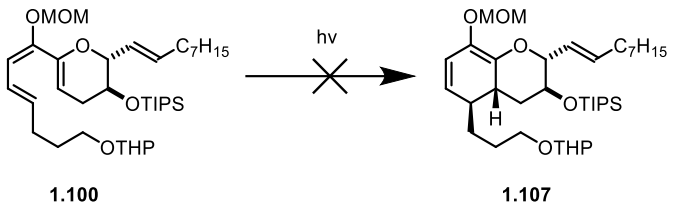
1.9 Electrocyclization/Claisen cascade synthesis of the bridged bicyclic core

The challenges encountered in the installation of cyclopentanol ring of the natural product coupled with the limited scope of the Diels-Alder reaction led to interest in alternatives to bring about a total synthesis of penostatin F. The 6π-electrocyclization was believed to be a particularly direct method to assemble the stereodefined fused bicyclic precursor to the Claisen rearrangement, as this transformation could control the stereochemistry at C7 and C8 through a light enabling conrotatory process following the Woodward Hoffman rules for the cyclization of pericylic systems.[20] In addition, this reaction would install an unsaturation between C2 and C3 that is present in the natural product. Further, the Claisen rearrangement could be performed directly after the electrocyclization in a one pot fashion, thus converting a triene **1.100** to a highly functionalized bridged bicycle in one step. The alkyl substituent at C7 was envisioned to contain a vicinal diol bearing distinguishable protecting groups, enabling an oxidative Heck reaction that would yield the cyclopentanol ring late in the synthesis (Scheme 1.16).



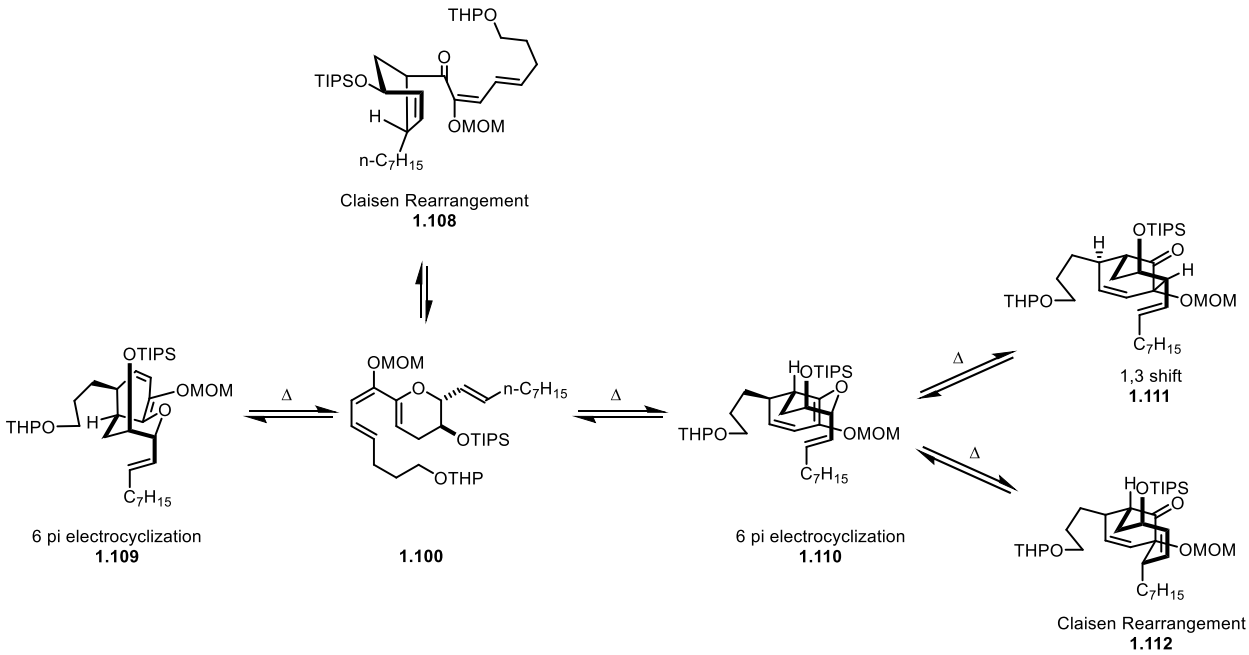
Scheme 1.16 – Tandem electrocyclization/Claisen rearrangement strategy

To explore the feasibility of this approach, a model triene **1.103** was designed. Since the double bond between C3 and C7 is of E stereochemistry, a photochemically enabled conrotatory electrocyclization was necessary to yield a product **1.104** with the correct stereochemistry at C7. Unfortunately, the photochemical cyclization turned out to be unsuccessful after screening for various reaction parameters, including solvent, photon source and additives. All conditions led to either degradation or isolation of the starting material (Scheme 1.17).



Scheme 1.17. Attempt at a photochemical electrocyclization

Met with this disappointment, a thermal disrotatory cyclization was attempted to explore the reactivity of the system (Scheme 1.18). Along with the desired 6π–cyclization/Claisen rearrangement product **1.109**, a product from an undesired Claisen rearrangement **1.105** of the starting material **1.103** was also observed. In addition, ketone **1.108** was also isolated presumably from a 1,3 rearrangement of intermediate **1.107**. Again, screening efforts to improve the selectivity of the transformation proved unfruitful (Table 1.1).



*Scheme 1.18. Attempt at thermal electrocyclization/Claisen Rearrangement sequence. The sequence led to the desired product **1.112**, in addition to a 1,3 shift product **1.111** from the desired electrocyclization product. Notably, the undesired product of electrocyclization **1.109** was also isolated.*

Table 1.1 Optimization of the electrocyclization/Claisen rearrangement cascade

Entry	Solvent	Temp (°C)	Time (h)	Additive (equiv.)	1.112 (%)	1.108 (%)	1.111 (%)	1.100 (%)
1	PhMe	140	5	--	16	3	3	15
2	MeCN	180	0.75	--	12	9	9	0
3	**MeOH**	**160**	**1**	**--**	**16**	**10**	**8**	**0**
4	PhCl	180	0.75	--	6	6	18	0
5	MeCN	180	0.75	$CaCO_3$ (3)	13	7	7	0
6	MeCN	180	0.75	$MgBr_2$-OEt_2 (3)	0	0	0	0
7	**MeCN**	**140**	**5**	**$MgBr_2$-OEt_2 (3)**	**0**	**11**	**0**	**4**

1.10 Lessons learned from the synthetic progress on penostatin F

Penostatin F has proven to be a challenging target for synthesis. Both the Diels-Alder and electrocyclization approaches have enabled the assembly of the bridged bicyclic core, however the completion of the total synthesis has been hampered by the need to further functionalize the core towards the natural product. This challenge presents an opportunity to develop new strategies and methods to fully exploit the key Claisen rearrangement in a completed total synthesis. To this end, an approach was designed to address these limitations by targeting dienophiles with strategically placed handles that can be converted more readily into the challenging cyclopentanol ring.

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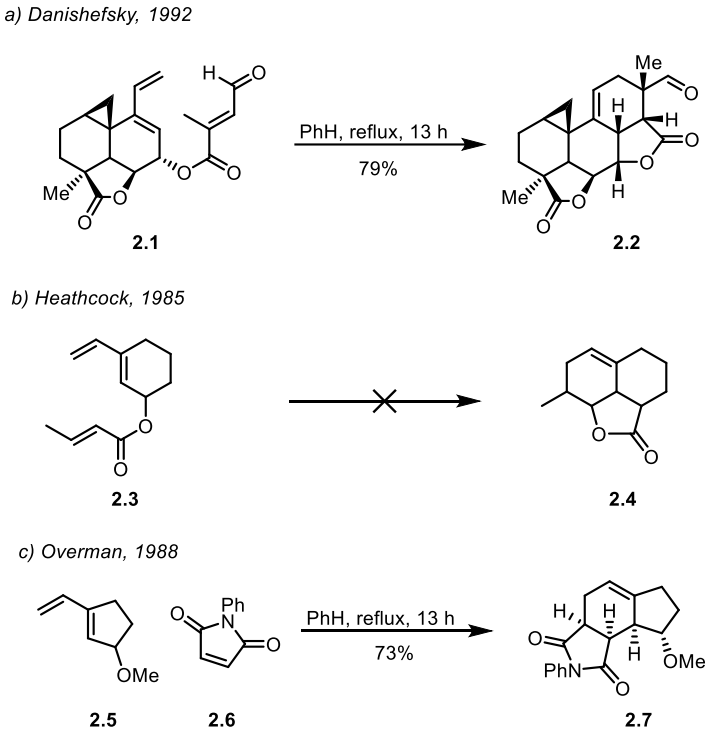
Chapter 2: Advancing The Initial Forays Towards a Hydroxy-Directed Diels-Alder Approach Towards Penostatin F

2.1 Retrosynthetic analysis

Previous work on the total synthesis of penostatin F uncovered a number of challenges in applying a strategy based on a hydroxy directed Diels-Alder/Claisen rearrangement sequence as key steps, however the general approach remained attractive for a few reasons. First, the magnesium catalyzed hydroxy directed Diels-Alder reaction elegantly assembles complex hydroxy dienes with a broad range dienophiles, as shown by the work of Barriault and others[1–3]. Other Diels-Alder reaction based tactics with hydroxy dienes were considered. One such alternative is a covalently tethered intramolecular Diels-Alder reaction (Scheme 2.1), however, this transformation proves to be non trivial due to significant torsional strain at the transition state to form [4.3.0] gamma lactone rings, as demonstrated by Heathcock's attempt (Scheme 2.1b) to convert the tethered system **2.3** into the Diels-Alder product **2.4**.[4,5] In addition, literature precedents suggest a second electron withdrawing group at the terminal position is often necessary[6]

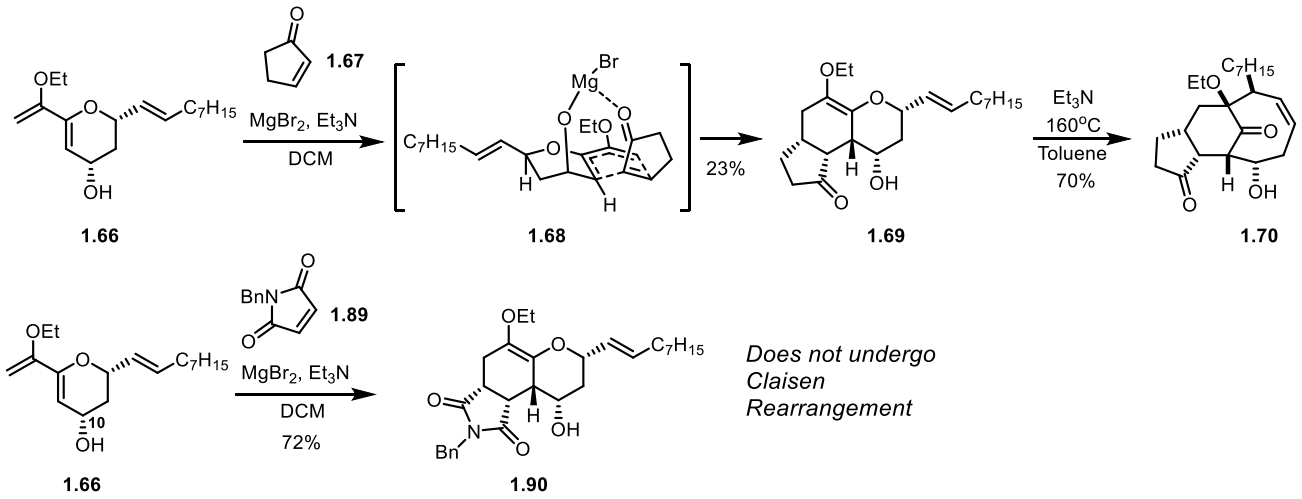
(Scheme 2.1a). Another tactic considered was an undirected intermolecular Diels-Alder reaction, however, these reactions yield the *endo* adduct **2.7** where the *endo* attack is *anti* to the methoxy group[7] (Scheme 2.1c). These outcomes are not desired in our case, since the subsequent Claisen rearrangement requires a *syn* relationship between protons at C8 and C14 for the chair like transition state. This can only be achieved if the Diels-Alder reaction proceeds with facial selectivity *syn* relative to the hydroxyl group (Scheme 1.11).



Scheme 2.1. Selected challenging ester tethered Diels-Alder reactions

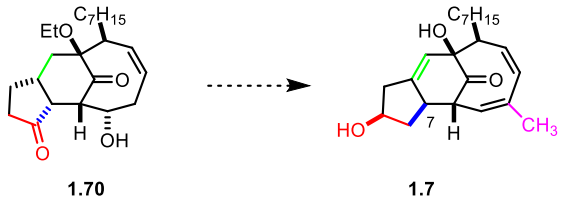
Second, the general hydroxy directed Diels-Alder/Claisen Rearrangement approach remained attractive because of the strategic advantage in converting a fused decalin like system to a relatively more complex [5.3.1] bridged bicycle through a thermal Claisen rearrangement. A previous investigation using a model substrate **1.69** demonstrated success in securing the required stereochemical elements of the core carbocycle **1.70**, as well as the key oxygenation at the

bridgehead position (Scheme 2.2a). Third, the hydroxyl group at C10 used in the directed Diels-Alder reaction presents a handle that could be used to generate the alkene upon elimination.



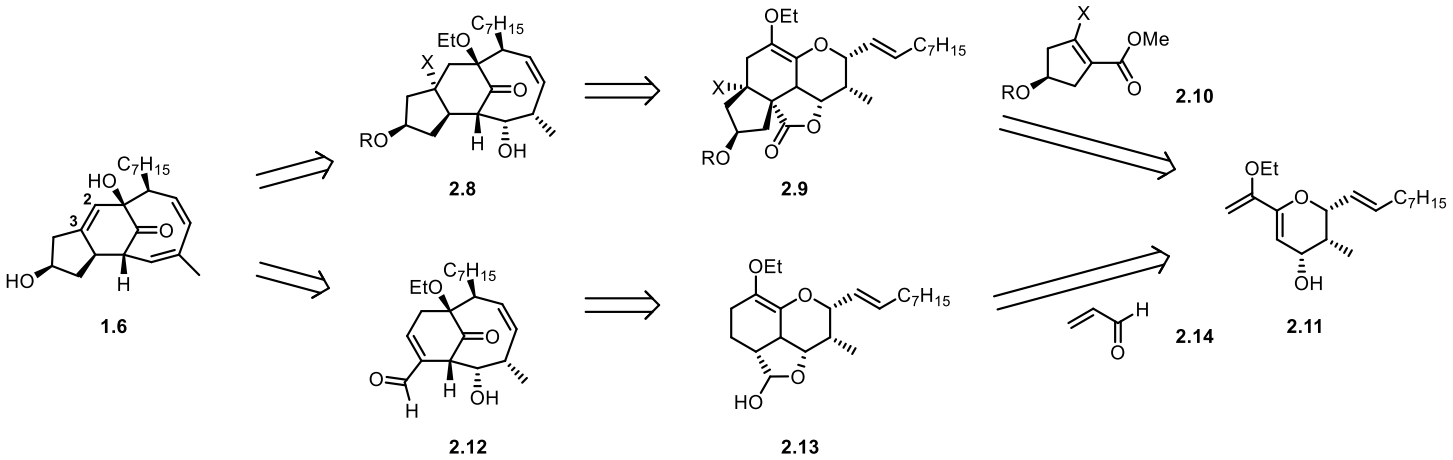
Scheme 2.2. Reported advances in application of HDDA to the synthesis of penostatin F (Barriault, 2004)

The most advanced intermediate **1.70** published as part of this project served as the starting point for this work. Structural analysis of this intermediate reveals the key challenges that need to be overcome in order to build penostatin F **1.6**. The most glaring are the stereochemistry at C7, the absent methyl group at C11, the missing double bond at the junction of the five membered cycle, and the chiral hydroxyl group of the cyclopentanol ring. (Scheme 2.3)



Scheme 2.3. Key challenges identified in advancing the HDDA/Claisen strategy towards the total synthesis of penostatin F

To address these challenges, an improved diene synthesis was desired as well as a potential point of divergence for the Diels-Alder reaction strategy. First, the hydroxy diene **2.11** with a preinstalled methyl group was targeted. Installing the methyl early would avoid the need to add this carbon at a late stage in the synthesis and thus prevent excessive functional group manipulation. Second, two potential approaches for the Diels-Alder reaction were envisioned (Scheme 2.4). The first approach is based on a complex fragment coupling strategy. Following this strategy would require a dienophile **2.10** containing the five membered ring and a handle for the elimination that would reveal the C2-C3 alkene on the natural product. The advantage of such an approach is the reduction of risk of challenging functional group manipulations late in the synthesis. However a significant drawback is the need for a complex dienophile to be compatible in the key hydroxy-directed Diels-Alder step.



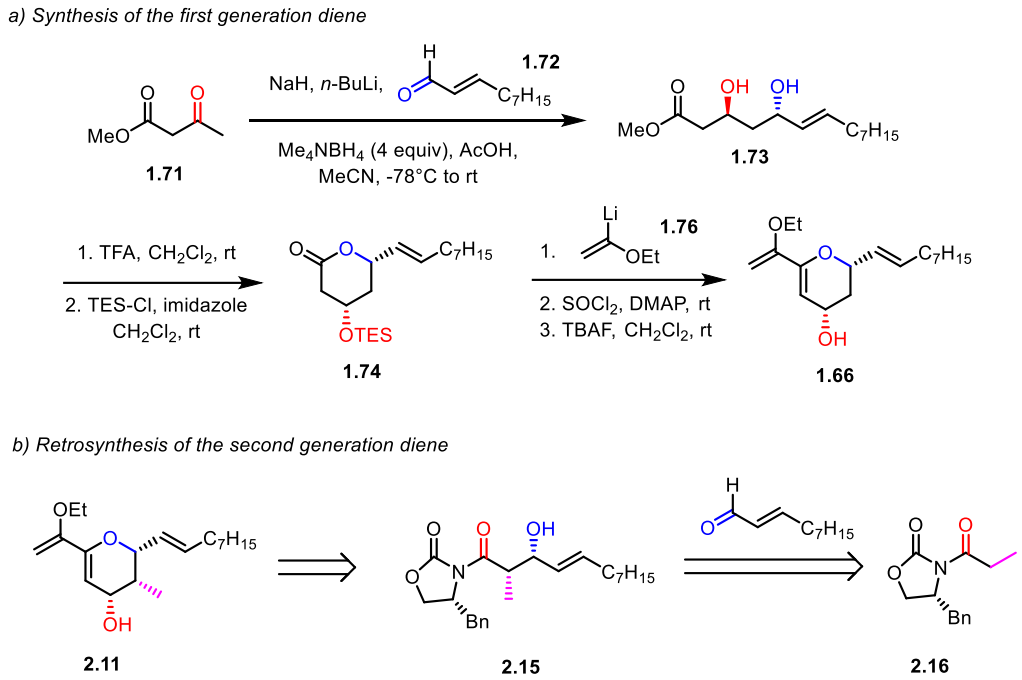
Scheme 2.4. Retrosynthetic approaches from penostatin F to the hydroxy-diene

In a conceptually reversed approach, a simpler and more precedented dienophile such as acrolein **2.14** can be used, reducing the risk of failure in the Diels-Alder step. However, this route

will potentially require extensive functional group manipulation in the later stages of the synthesis in order to assemble to cyclopentanol ring. Previously established work by the Barriault group has revealed the risk of relying on late stage functionalization in this context.[8] However, nearly two decades of progress in synthetic methods development might open avenues that were not previously accessible when this project was last active.

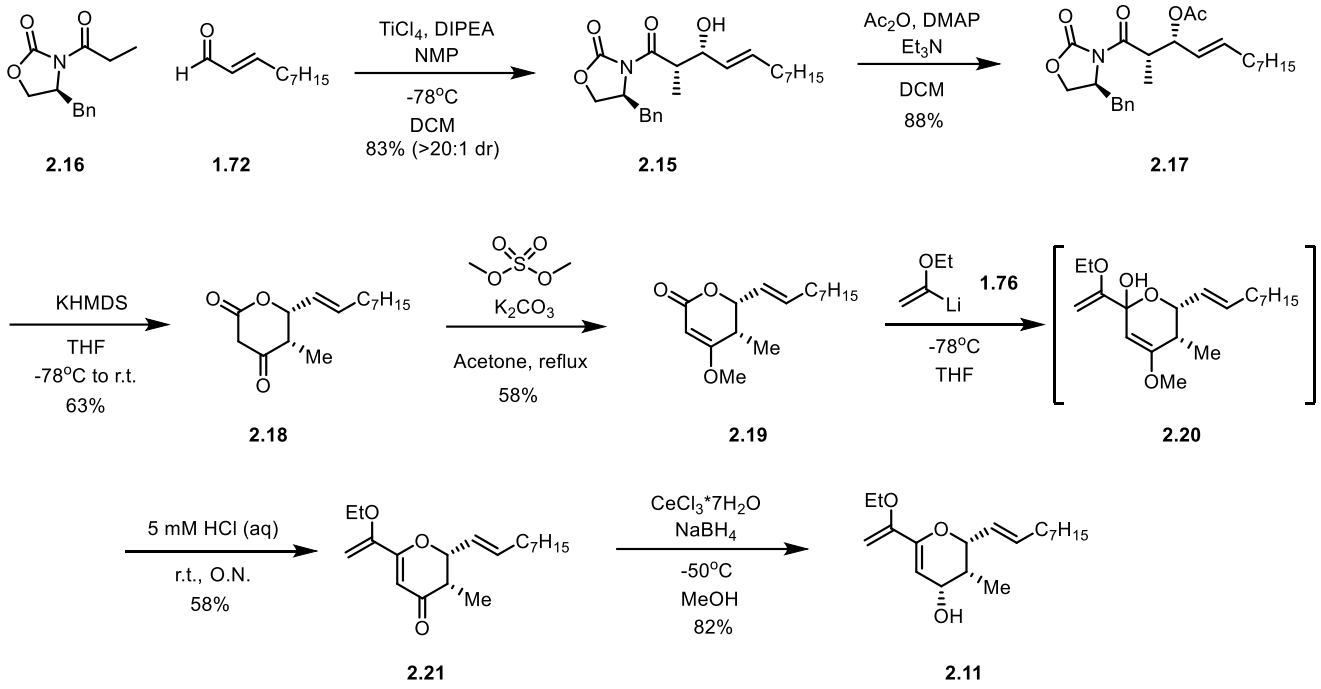
2.2 Enantioselective synthesis of the hydroxy-diene

The targeted diene **2.11** differs from the previously synthesized diene **1.66** only by one methyl group. The synthesis for this first-generation diene[3] **1.66** begins with an aldol reaction between *trans*-2-decenal **1.72** and the "Weiler" dianion, followed by a diastereoselective directed reduction secures the 1,3-oxygenation pattern that translates into the endocyclic oxygen of the ether ring and the exocyclic hydroxy substituent key for the directed Diels-Alder reaction (Scheme 2.5). Following that step, a cyclization and protection sequence is followed by an addition and dehydration step, yielding the desired protected diene **1.66**. In the case of the second-generation diene **2.11** it seemed ideal to install the methyl group in the aldol reaction. Although the stereochemistry of the methyl group is ultimately irrelevant due to the planned elimination of the hydroxyl group, the prospect of carrying through two distinct stereoisomers early in the synthesis seemed disadvantageous. The classic Evans Aldol reaction was thus envisaged as the first step to secure the stereochemistry of the methyl group as well as impart enantioselectivity to the synthesis, as the stereochemistry of this hydroxyl moiety sets the stage for an eventual directed reduction leading to the key directing hydroxyl group of the HDDA.



Scheme 2.5. Synthesis of the first-generation hydroxy-diene and planned approach towards the second-generation hydroxy-diene. The stereochemistry of the directing hydroxy group (red) is set via a reduction directed by the hydroxyl group of the aldol product.

The synthesis of the hydroxy diene proceeded smoothly (Scheme 2.6). The Evans aldol reaction[9,10] between trans-2 decenal **1.72** and (*S*)-4-benzyl-3-propionyl oxazolidin-2-one **2.16** proceeded in 83% yield and >20:1 dr. At this point, a two-carbon building block needs to be added onto the amide position of the aldol fragment to eventually make the key pyran ring **2.18**. A simple Claisen condensation was envisaged to obtain the desired product.[11] To this end,



Scheme 2.6. Second-generation hydroxy-diene synthesis

acetylation of the aldol adduct **2.15** with acetic anhydride gave the desired acetate **2.17** in 88% yield. Then, the treatment with KHMDS generated the corresponding enolate which upon intramolecular cyclization afforded compound **2.18** in 63% yield. Curiously, the use of solid KHMDS dissolved in THF as opposed to the commercial solutions yielded the desired product in higher and more consistent yields. Having the cyclized product in hand, a reduction/protection sequence of the ketone was considered as was done for the previously reported hydroxydiene. Although this type of reduction to generate 3-hydroxy-δ-lactones is precedented, the instability of these compounds make this reaction non trivial.[12] To avoid this potential issue, an alternative route was developed. Protection of the ketone in **2.18** with dimethyl sulphate yields the enol ether **2.19** in 58% yield. This enables a selective addition of the lithiated vinyl enol ether species **1.76** onto the lactone carbonyl. The lithiated vinyl enol ether was prepared via directed lithiation of ethyl vinyl ether with tBuLi. Key to good conversion of this transformation was a large excess of the

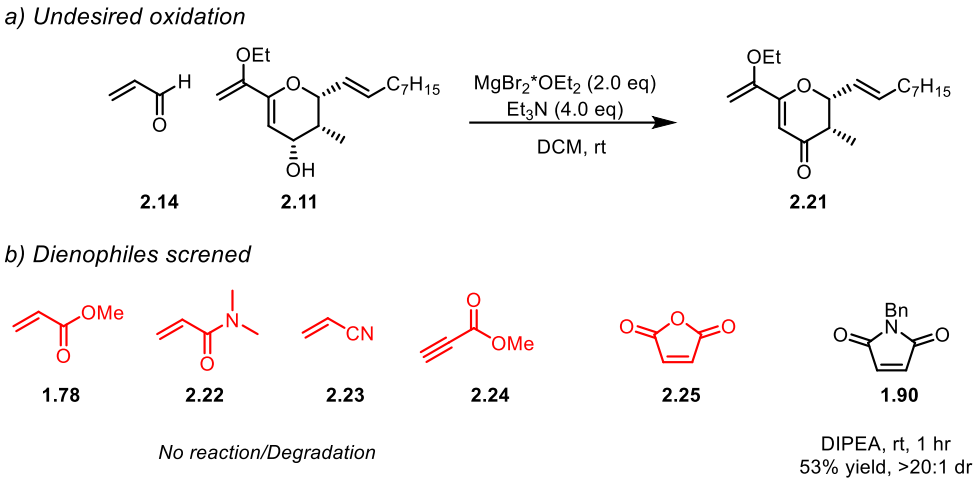
lithiated species **1.76**. Gratifyingly, product of double addition to the lactone ring of the lithiated species was not observed. The crude adduct of addition **2.20** was then dissolved in acetonitrile and subjected to dilute aqueous acidic conditions. The use of dilute conditions allows for the selective hydrolysis of the endocyclic enol ether, producing the desired enone **2.21** in 58% yield. A risk presenting itself here was the potential for over hydrolysis of the enol ether to the enone, however the opportunity to quickly intercept the diene moiety through a simple hydrolysis of the lithiated ethyl vinyl ether adduct seemed too attractive to pass up. Finally, reduction of the ketone under Luche conditions[13] produces the desired hydroxy diene **2.11** in 82% yield and 20:1 diastereoselectivity.

2.3 Limitations of the HDDA/Claisen rearrangement sequence

With a route to the hydroxy diene **2.11** secured, the development of the key Diels-Alder step could begin. The first dienophile to screened was acrolein **2.14**. Not only does it contain a strong electron withdrawing group with precedent in hydroxy directed Diels-Alder reactions, but its Diels-Alder adduct would form a lactol that is able to exist in either a closed or open form. The lability of this ring was hypothesized to be essential for a successful Claisen rearrangement, as previous work demonstrated that Diels-Alder adducts with lactone rings formed via cyclization of the directing hydroxyl group onto the activating group of the dienophile are unreactive (Scheme 2.2b).

Disappointingly, submission of the hydroxy diene **2.11** and acrolein **2.14** to the established hydroxy directed Diels-Alder conditions did not provide any desired adduct, but rather the oxidized diene **2.21** (Scheme 7a). Mechanistically, a magnesium catalyzed Oppenauer oxidation reaction is likely responsible for the formation of the undesired product. The aldehyde of acrolein

is likely reduced and the hydroxyl group of **2.11** is oxidized in a closed transition state via coordination with magnesium.[14] To avoid this issue while maintaining the general carbon-carbon bond forming strategy, we envisaged the use of analogous dienophiles such as methyl acrylate **1.78** (Scheme 7b). Although a lactone ring is usually formed following the Diels-Alder reaction with dienophiles activated by methyl esters, reduction of the lactone ring following the Diels-Alder reaction would provide the same intermediate. Unfortunately, methyl acrylate as well as other dienophiles screened did not provide any Diels-Alder adduct, with the notable exception of N-benzylmaleimide **1.90** (Scheme 7b). A short base screen and prolonged reaction times did not result in improved yields. This result was only partly surprising, as mono activated dienes proved to be less competent dienophiles in previous reports of HDDA reactions as well.

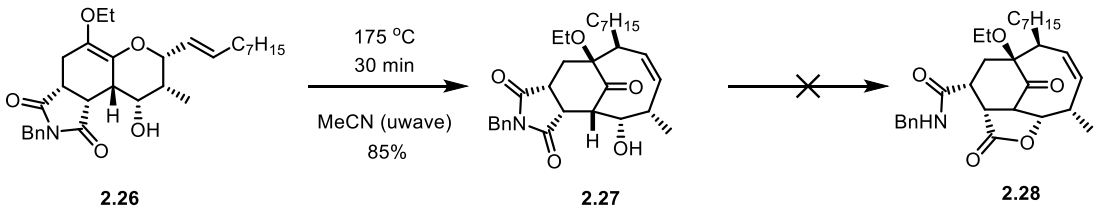


Scheme 2.7. Challenges in finding reactive dienophiles in the HDDA of the functionalized hydroxy diene. The use of acrolein led to an oxidation product, while all other mono activated dienes were also unreactive. N-benzyl maleimide was the only reactive dienophile screened.

2.4 Functionalization of the maleimide HDDA/Claisen rearrangement product

The Diels-Alder adduct of N-Benzylmaleimide **2.26** could be readily converted to the bridged bicycle **2.27** via Claisen rearrangement (Scheme 2.8). This reaction turned out to be more

practical and more consistent when executed in a microwave reactor in acetonitrile as opposed to the precedented high pressure tube conditions in toluene. Although the HDDA/Claisen Rearrangement cascade proceeded well, the product **2.27** would require many functional group manipulations to produce the desired cyclopentanol ring. However, as this was the only substrate able to undergo the desired sequence, we went through the process of thinking how a maleimide ring could be converted to a cyclopentanol ring. A challenge that was expected is the nearly identical reactivity profile of the two carbonyl groups on the maleimide ring. To discriminate between the two, a sequence was envisaged where the Claisen product **2.27** would undergo an intramolecular lactonization of the hydroxyl functionality onto the maleimide and liberate a secondary amide[15] **2.28**. The orthogonal lactone and amide functionalities could then be further converted to the desired cyclopentanol ring of penostatin F.

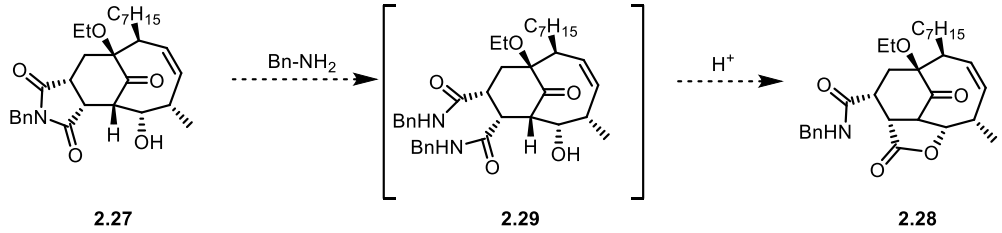


Scheme 2.8. Claisen rearrangement in microwave conditions. The attempted lactonization of the Claisen product to the secondary amide was not successful.

The success of the key Claisen rearrangement was unfortunately followed with failure of the lactonization step. All attempts to perform the lactonization in both acidic and basic conditions resulted in either recovery of starting material **2.27** or degradation. To find answers to this surprising result, a conformational analysis of the reaction was performed. Looking at the three dimensional structure of the molecule, it is clear the hydroxyl group would have difficulty

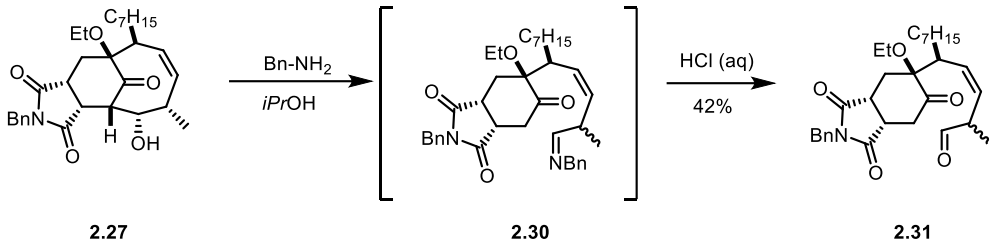
lactonizing, as the vector of the Burgi-Dunitz angle required for the approach onto the carbonyl is fixed and essentially perpendicular to the free orbitals of the oxygen at C10.

A potential solution to this issue was hypothesized to be an opening of the maleimide ring prior to lactonization to yield **2.29**, in order to increase in rotational freedom of the carbonyl group and facilitate lactonization (Scheme 2.9). To this effect, the rearrangement product was treated with an excess of N-benzyl maleimide and the solution acidified.



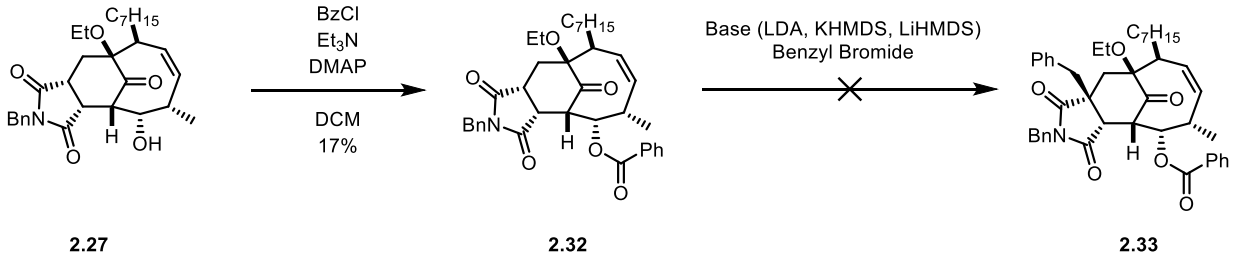
Scheme 2.9. Planned maleimide opening/lactonization sequence

In most cases, no conversion was observed but surprisingly, reaction of benzylamine with the substrate in isopropanol at room temperature yielded a product **2.30** that was not an opening/lactonization sequence, but rather a retro aldol reaction to open the bridged bicycle (Scheme 2.10). A potential mechanism to explain this outcome is a retro aldol reaction followed by condensation of the benzylamine to the liberated aldehyde to yield **2.30**. Condensation of benzylamine to the bridgehead ketone is less likely at room temperature due to its position at a bridging carbon next to a quaternary center. The aqueous acidic conditions that follow likely promote hydrolysis of the condensation product back to the aldehyde.



Scheme 2.10. Retro-aldol fragmentation of the bridged bicyclic core

To sidestep the problematic retro aldol fragmentation, an alternative approach to find differing reactivity in the carbonyl groups was envisaged whereby the local steric environments at the carbons alpha the carbonyls could provide some selectivity in generating an amide enolate regioselectively via deprotonation (Scheme 2.11). The Claisen adduct was thus protected to a benzoyl ester **2.31** in order to avoid retro aldol fragmentation. Screening a variety of strong non-nucleophilic bases was then performed. In this case, no enolate trapping product could be observed following exposure to a trapping agent.



Scheme 2.11. Attempts at functionalization of the fused maleimide ring

2.5 Maleimide functionalization challenges

The limited availability of competent dienophiles with the second-generation diene 2.11 was disappointing. However, it allowed to confirm that the Claisen rearrangement can work in presence of the methyl at C11, the difficulty in lactonizing the hydroxyl group, and the risk of

retro-aldol fragmentation of the Claisen adduct. In the next chapter, an unexpected byproduct motivates the design of a slightly modified diene in order to expand the dienophile scope of the HDDA.

2.6 References

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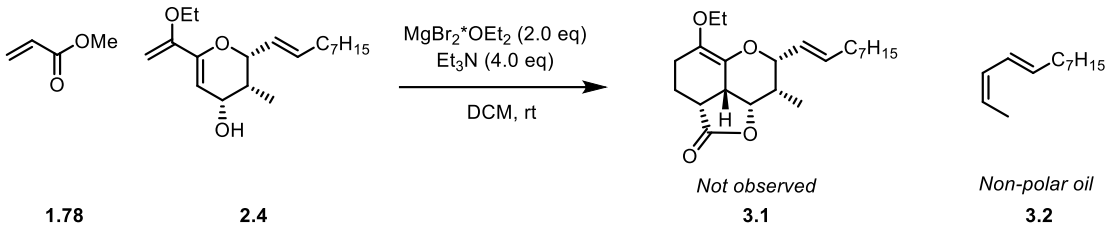
Chapter 3: Elaboration of HDDA Tactics Towards Penostatin F

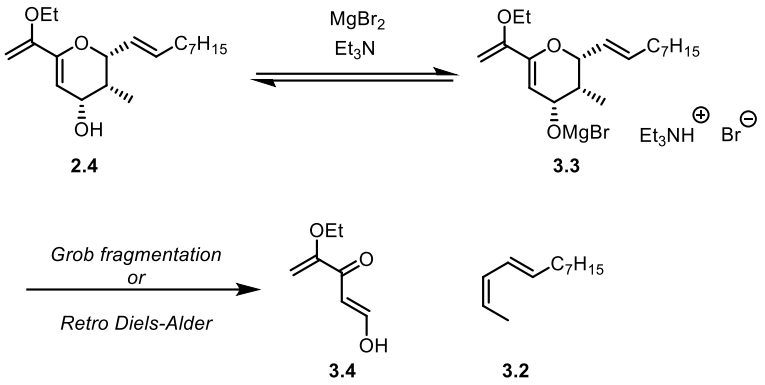
3.1 Identification of a key diene degradation product

The unsuccessful attempts at using an HDDA strategies so far in the project forced the choice to either abandon this general HDDA/Claisen rearrangement strategy or attempt to optimize the reaction. Specifically, the poor scope of reactive dienophiles, even simple unsubstituted mono activated acrylates, limited options to further elaborate the Diels-Alder adducts towards the targeted natural product. To optimize the system, three general approaches were considered. The first was to further optimize the catalyst system, specifically the base, solvent, and Lewis acid. The original publication by the Barriault group reporting the HDDA methodology went through this exercise without finding any improvements, therefore optimization of this part of the system was not further explored. A second option was to optimize the dienophile, however work from the previous chapter showed the limitations of that approach. Using superstoichiometric amounts of unsubstituted mono activated dienophiles proved futile. The third and perhaps least obvious option was to optimize the diene. The challenge in this approach lies in the difficulty to alter the different structural elements of the diene as compared to screening dienophiles or catalysts. However, a serendipitous finding would prove key to motivate the pursuit of this optimization approach.



Scheme 3.1. Identification of a diene byproduct in the HDDA reaction

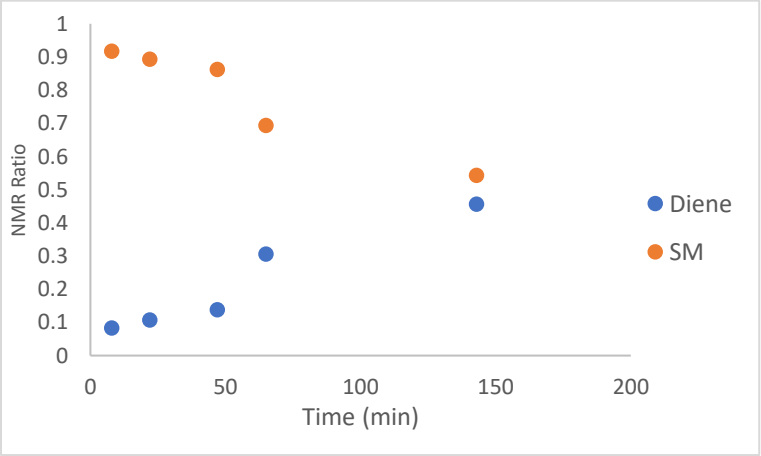
When performing flash chromatography in attempts to identify products in the Diels-Alder reactions with methyl acrylate as a dienophile, an oily product was seen condensing on the first fractions if they were left overnight (Scheme 3.1). These fractions were evaporated and the oil analyzed to elucidate its identity. Interestingly, this oil was found to be (2Z,4E)-dodeca-2,4-diene **3.2**. The seven membered aliphatic carbon chain was a clear sign that this product stemmed from either the diene or a Diels-Alder adduct. Mapping this product onto the dienophile, two mechanistic hypotheses are proposed (Scheme 3.2). In the first hypothesis, formation of the magnesium alkoxide **3.3** leads to a Grob-type fragmentation, pushing electrons from the exocyclic oxygen to break the bonds at C10-C11 and C12-O, while forming the alkene between C11 and C12. Alternatively, one could propose a retro Diels-Alder mechanism, whereby a retro cycloaddition forms the same product **3.4**. A mechanistic study was not undertaken, however the time frame of this degradation in the HDDA system was probed (Figure 3.1). The hydroxydiene **2.11** was submitted to the reaction conditions in the absence of a dienophile, and aliquots taken at time points.



Scheme 3.2. Proposed mechanism for the elimination of the observed diene

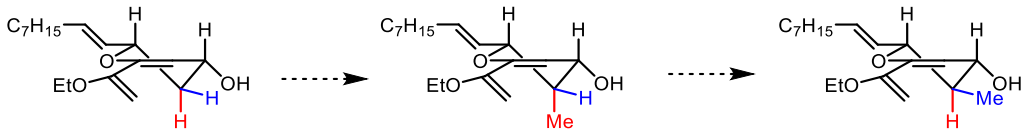
Plotting the relationship between the ^{1}H NMR trace of the hydroxydiene **3.2** and the product of degradation **3.2**, one can observe almost half of the starting material has degraded within 90 minutes. This data in combination with observations made previously suggests that in the case of reactive dienophiles, the desired HDDA reaction occurs quickly relative to degradation. This is supported by the successful HDDA reaction with N-benzylmaleimide. However in the case of less reactive dienophiles, the degradation is faster than the desired HDDA reaction, resulting in a lack of desired product.

Figure 3.1. Time plot of hydroxydiene degradation in standard HDDA conditions in absence of dienophile.



3.2 Design and synthesis of an improved dienophile

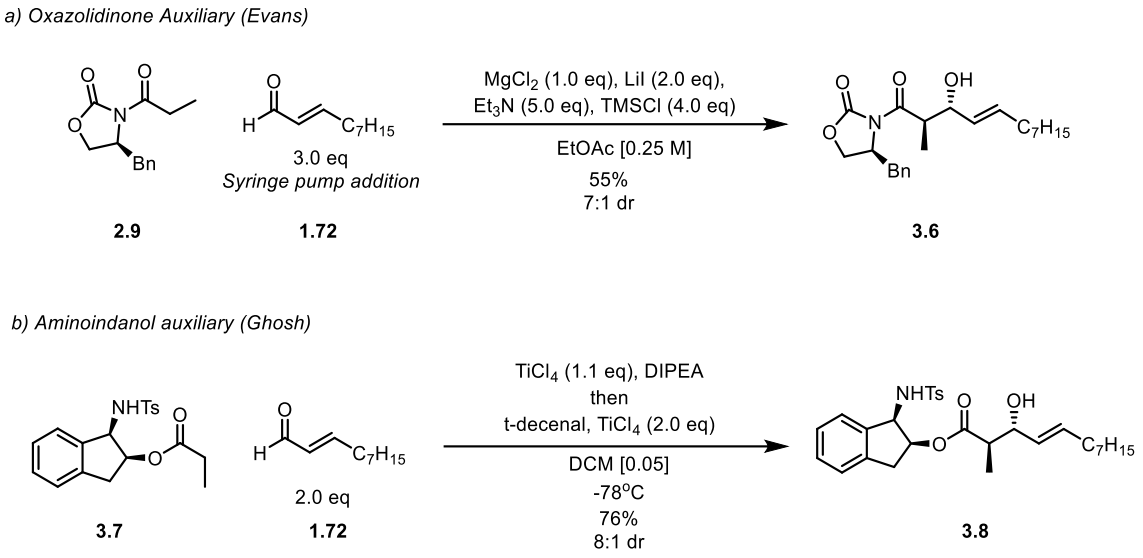
With this problem identified, a potential solution was developed. The degradation pathway was deemed to be likely unavoidable, therefore the solution to this problem was hypothesized to be a system whereby the Diels-Alder reaction is quicker than degradation. As mentioned previously, optimizing the metal was not seen as a viable approach, therefore the diene was examined to find opportunities where reactivity could be improved. Upon conformational analysis, an unappreciated subtlety of the diene was revealed (Scheme 3.3). Modelling the diene using a computational geometry optimization procedure, the ground state conformation suggests the diene **2.11** exists in a half chair with both the alkenyl and hydroxyl groups in an equatorial conformation and the methyl group in an axial position. Notably, this methyl group is pointing directly in the way of the incoming dienophile, likely leading to steric strain and thus reduction in the reactivity of the diene. The solution to reduce steric strain would be to either remove the methyl from the dienophile, effectively going back to dienophile **1.66**, or to flip the stereochemistry at the methyl to ensure it lies in an equatorial conformation as in **3.5**. Since the methyl on this carbon is present in the natural product, a synthesis of the diene with the reversed stereochemistry 3.9 was designed.



Scheme 3.3. Dienophile design process. Axial substituents at C11 (red) are syn to the incoming dienophile, while equatorial substituents (blue) avoid steric clash.

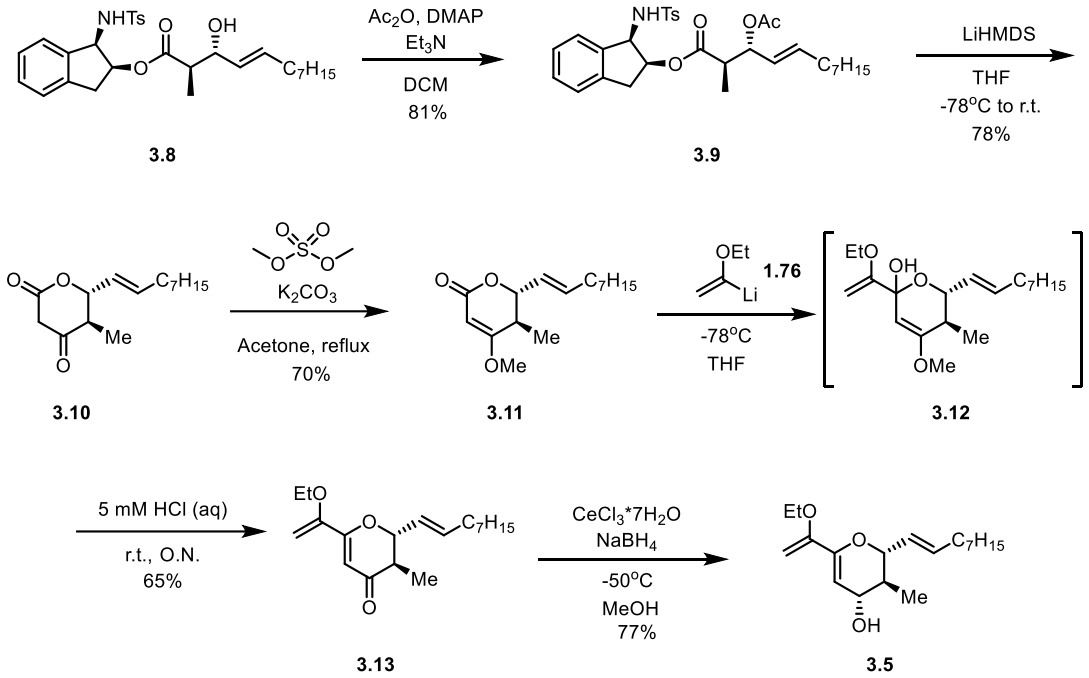
The stereochemistry at this carbon is set in the syn aldol reaction with trans-decenal **1.72**. Therefore, if the anti aldol adduct can be made, the rest of the synthetic sequence can be identical

to the one developed for the dienophile **2.11** in the previous chapter. The literature precedents for anti aldol reactions was thus examined. A report by the group of Evans[2] and another by the group of Ghosh[3] stood out for their broad substrate scope and commercially available ligands. The reports by Masamune[4] were noted, but the difficulty in obtaining large quantities of the norephedrine precursor to the chiral auxiliary prevented the application of this protocol in this project. In the Evans report, a magnesium enolate of the venerable propionyl oxazolidinone **2.16** is used to affect this transformation, whereas Ghosh uses an amino indanol derived auxiliary **3.7** with a titanium Lewis acid. Both protocols were tested and each revealed particularities relevant for scalability of the planned first step of the total synthesis (Scheme 3.4). In the case of the oxazolidinone (Scheme 3.4a), the reaction yields are good however the product **3.12** coelutes with the starting material, making separation at scale quite difficult. In addition, a large excess of trans-decenal **1.72** is necessary and the workup requires multiple filtration steps to remove a gunk formed as a byproduct of this reaction. In the case of the amino indanol derived auxiliary **3.7**, the reaction proceeds in good yield, however concentrations need to be kept low to obtain good anti selectivity (Scheme 3.4b). Though slightly inconvenient at larger scales, the easy separation of the *anti* and *syn* diastereomers and smoother workup made this reaction more practical as a first step of the synthesis.



Scheme 3.4. Development of an anti-aldol reaction with trans-decenal

The anti aldol adduct **3.8** was carried through the identical series of steps as previously developed for **2.11** to obtain the desired dienophile (Scheme 3.5). Protection of the aldol adduct produced the acetate **3.9** in 81% yield and was followed by cyclization to **3.10** in 78% yield. This was followed by protection to **3.11** in 61% yield and an addition elimination sequence to yield the enone **3.13** in 65% yield. Finally, Luche reduction yielded the hydroxydiene **3.5** in 77% yield.

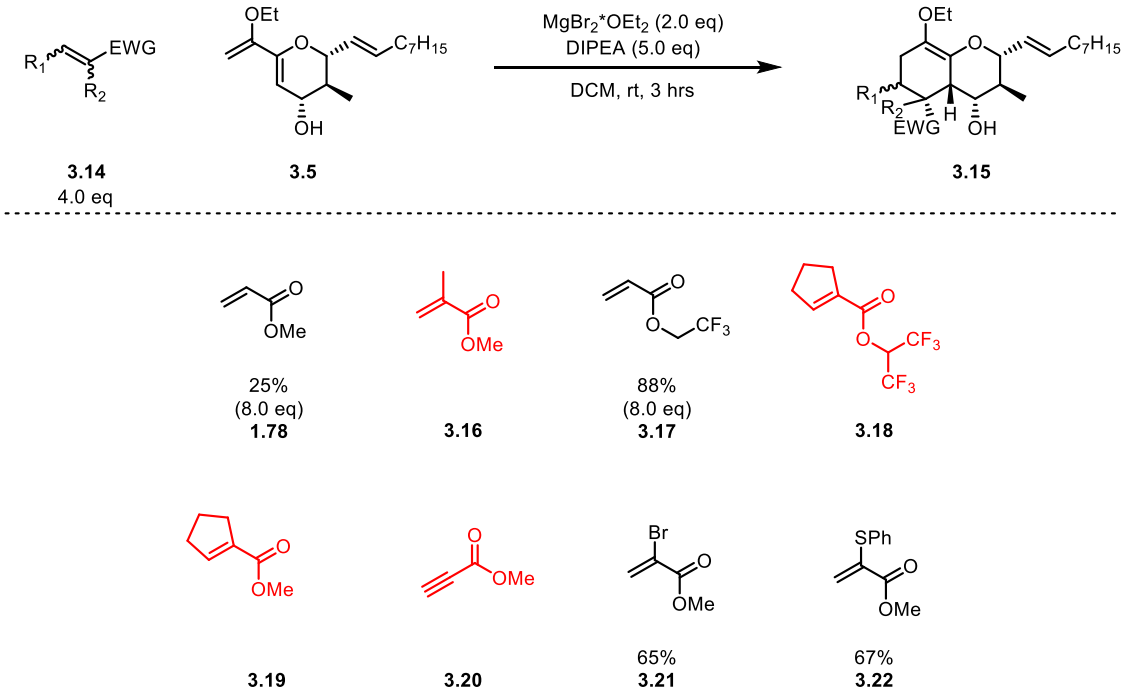


Scheme 3.5. Synthesis of the hydroxy diene bearing the methyl with anti relative stereochemistry

3.3 Dienophile screen

With the hydroxydiene **3.5** in hand, a series of dienophiles were screened to assess the reactivity of the system. Satisfyingly, methyl acrylate **1.78** was found to be a competent, albeit low yielding dienophile for this transformation when used in very large excess. Its analog with a methyl substituent at the 2 position **3.16** was not successful. A complex cyclic dienophile with a methyl ester substituent as an activating group **3.19** was tried for this reaction, but only starting material was observed. To improve the reactivity of the ester moiety, fluorinated ester moieties were explored as better activating groups stronger than their alkyl analogs. [5–7] Cyclopentenecarboxylic acid was thus esterified with hexafluoroisopropanol to yield **3.18** and used as a dienophile. Again, no conversion to the desired product was observed. This disappointing result led to the abandonment of the strategy incorporating complex cyclic dienophiles, and thus all efforts were

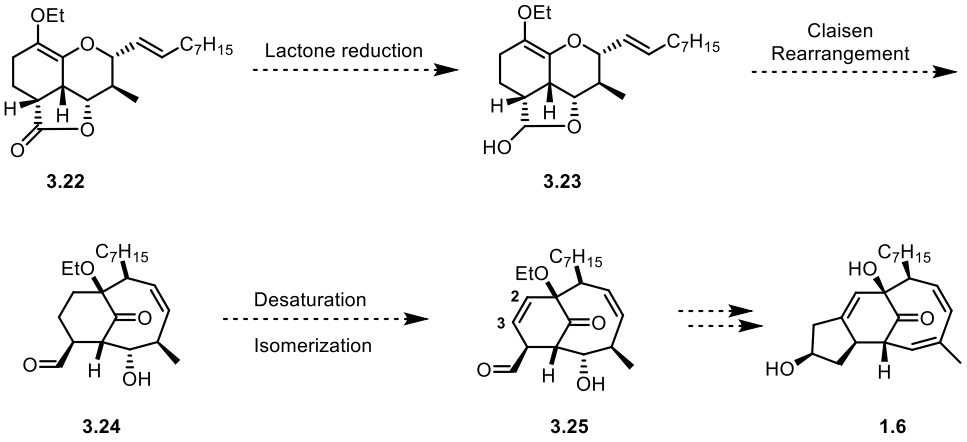
put towards the transform based strategy using less substituted acrylate dienophiles. Of those, trifluoroethyl acrylate **3.17** proved to be a very effective dienophile. As compared to methyl acrylate **1.78**, the reaction produced an identical cycloadduct **3.22** upon lactone ring formation however yields were significantly improved. Another class of reactive dienophiles were acrylates with a heteroatom substitution, namely 2-bromoacrylate **3.28** and 2-thiophenylacrylate **3.29**. Each of these acrylate dienophiles was examined to identify synthetic approaches that could best make use of their specific functional groups. These approaches were then tested as outlined below (Scheme 3.6).



Scheme 3.6. Dienophile screen. Unreactive substrates are highlighted in red.

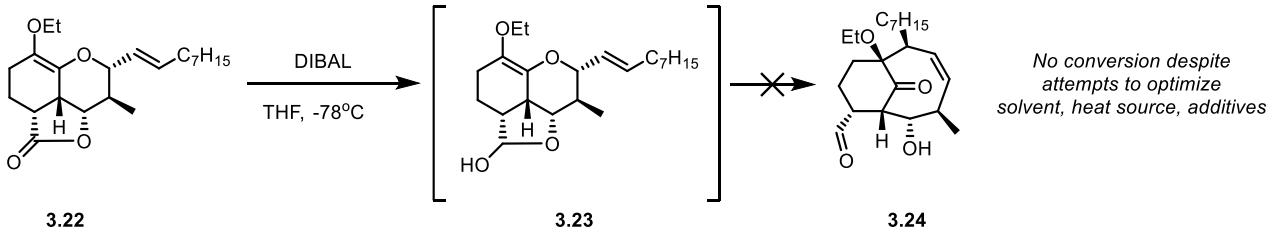
3.4 Derivatization of unsubstituted acrylate HDDA adducts

Starting with the unsubstituted acrylate adduct, two strategic challenges must be overcome (Scheme 3.7). The first challenge is the strain caused by the lactone ring, which prevents the Claisen rearrangement from proceeding, as previously observed for other cycloadducts bearing the lactone ring. However, a reduction of the lactone **3.30** to the lactol **3.31** should enable this molecule to transiently enter a ring open form at the high temperatures required for the Claisen rearrangement, and thus allow the rearrangement to proceed. The second strategic challenge is the installation of the alkene at C2-C3. The solution to this problem must take into consideration the absence of other functional groups on either of these carbons in the Diels-Alder adduct. A hypothesized approach was to perform an alpha beta desaturation of **3.24**, followed by vinyloguous deprotonation and acidic quench at the alpha position to yield the alkene at C2-C3 **3.25**. The carbonyl handle could then be further extended into the cyclopentanol ring.



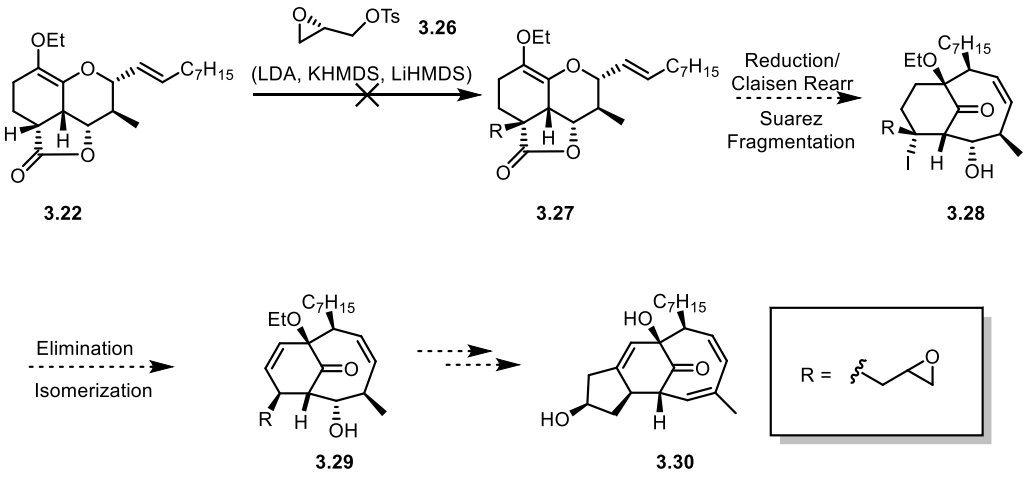
Scheme 3.7. Synthetic approach following the Diels-Alder reaction with trifluoroethyl acrylate.

To test this hypothesis, the lactone **3.22** was reduced to yield the lactol **3.23**. This product turned out be unstable, however change in R_f by TLC of the crude mixture coupled with analysis of its ^{1}H NMR suggested conversion towards a product of lactone reduction. The crude lactol was immediately submitted to the Claisen rearrangement conditions. However, no conversion was observed. Addition of triethylamine and changing reaction time or temperature did not bring about any changes. In all cases, a mix of degradation and leftover starting material **3.31** was observed by NMR analysis of the crude reaction mixture (Scheme 3.8).



Scheme 3.8. Formation of unstable lactol towards the key Claisen rearrangement

An alternative approach was envisaged, whereby the alpha position of the lactone carbonyl could be alkylated to **3.27**. This would be followed by a DIBAL reduction and Claisen rearrangement. The lactol ring could be then fragmented via a Suarez reaction,[8,9] and the resulting alkyl halide **3.28** eliminated and isomerized into the alkene at C2-C3. Tosylated epichlorohydrin **3.26** was chosen as an alkylation partner, as this would provide a valuable moiety for the planned late stage epoxide cyclization. The Diels-Alder adduct **3.22** was subjected to base and subsequently treated with tosylated epichlorohydrin **3.26**. However, no conversion to the desired product was observed (Scheme 3.9).

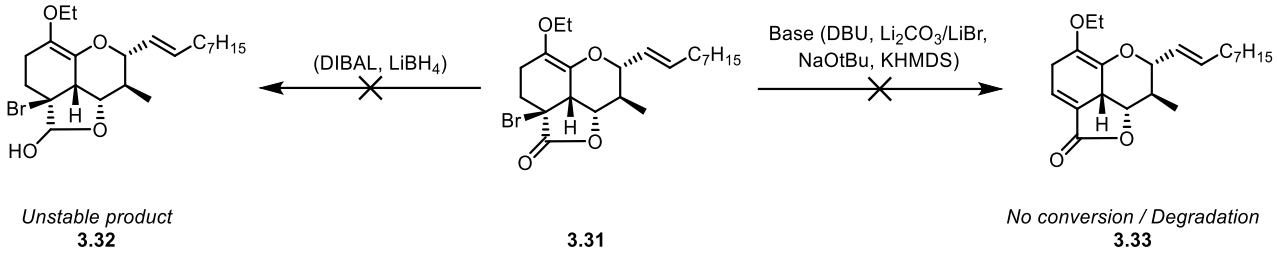


Scheme 3.9. Alternative synthetic approach following the Diels-Alder reaction with trifluoroethyl acrylate.

3.5 Derivatization of heteroatom substituted acrylate HDDA adducts

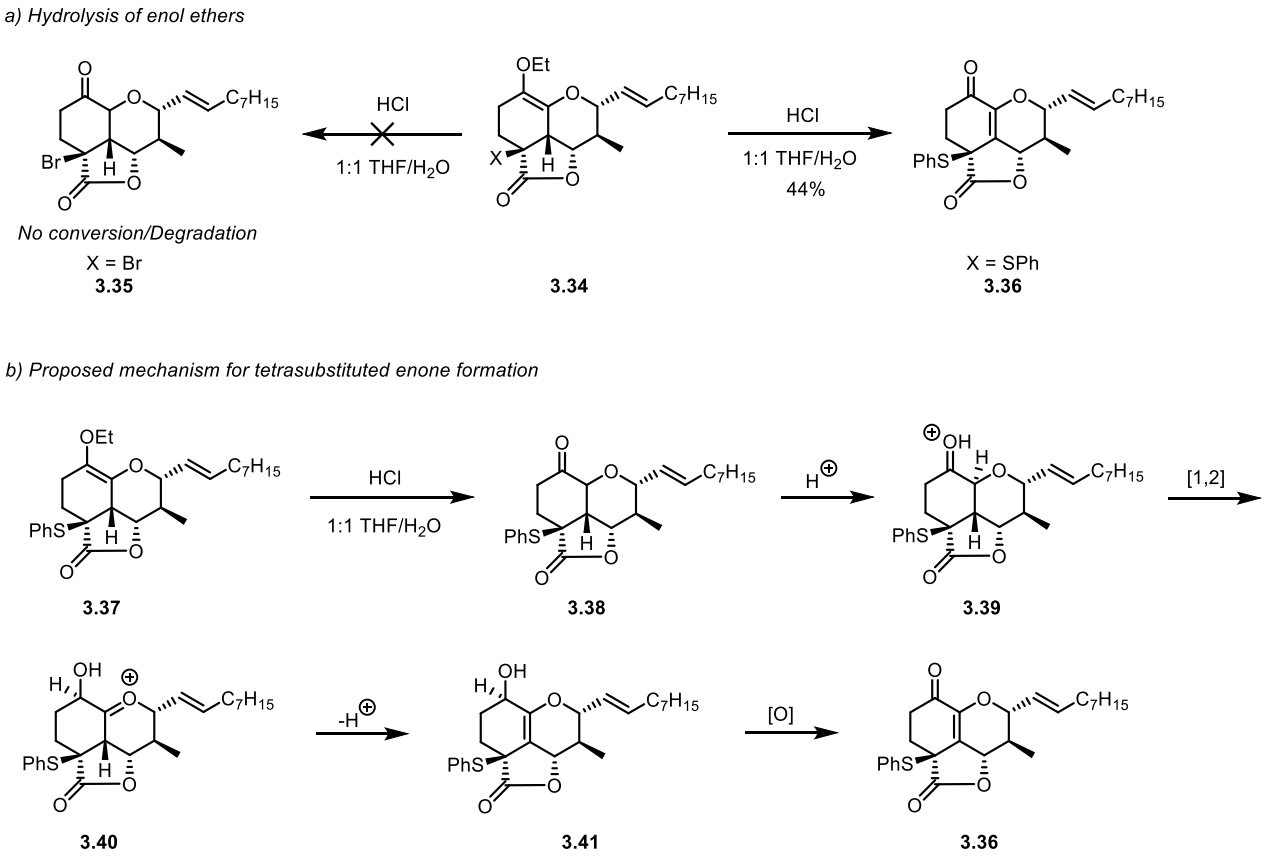
In the case of the heteroatom substituted dienophiles, the bromo or thiophenol functional groups present additional synthetic handles and thus opportunities for derivatization. For example, the installation of an alkene at C2-C3 can be envisioned to proceed via an elimination of the heteroatom functionalities followed by isomerization, either before or after the Claisen rearrangement. To begin, a reduction to the lactol was planned in order to enable the Claisen rearrangement to proceed (Scheme 3.10). In the case of the bromo acrylate Diels-Alder adduct **3.31**, the lactone was treated with DIBAL but this resulted in significant degradation. Similarly to the unsubstituted acrylate Diels-Alder adduct, conversion could be observed by TLC however the product degraded even quicker. Elimination of the bromide proved unsuccessful, as either lack of conversion or degradation was observed regardless of the nature of the base. The elimination is likely rendered difficult in this context by the lack of a proton in anti periplanar configuration, due to the bromide being fixed in an equatorial position. An alternative was hypothesized whereby the ethyl enol could be hydrolyzed and an alpha beta desaturation performed to install the alkene at

C2-C3. However, the tetrasubstituted enol ether of **3.31** proved to be inert at room temperature, and degraded when heated.



Scheme 3.10. Attempted functionalization of the bromo acrylate Diels-Alder adduct

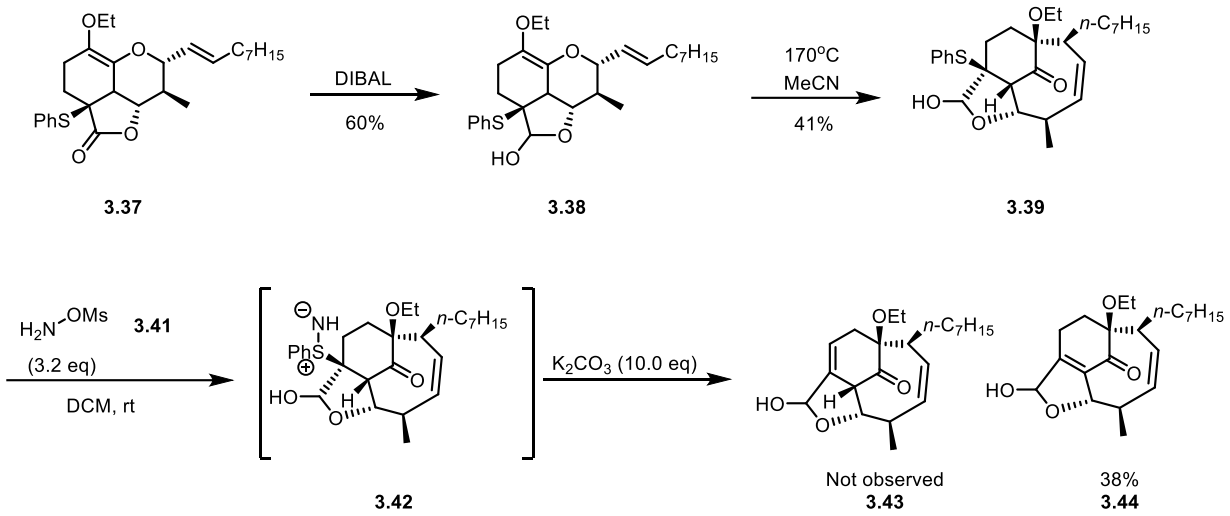
The thiophenyl acrylate cycloadduct **3.37** presents a series of intriguing reactivity differences as compared to the bromo acrylate. First, the attempted hydrolysis of the ethyl enol ether did not yield the ketone. Instead, acidic hydrolysis and aerobic oxidation yielded an enone **3.36**. To account for this result, the following mechanism is proposed (Scheme 3.11). Upon hydrolysis of the enol ether, the resulting ketone **3.38** is protonated and a 1,2 rearrangement leads to **3.40**, an oxonium ion on the endocyclic pyran ring oxygen. From there, elimination of the proton at C8 can quench the oxonium to yield an allylic alcohol **3.41**, which undergoes oxidation with adventitious oxygen to yield the observed enone **3.36**.



Scheme 3.11. Attempted hydrolysis of ethyl enol ether of heterofunctionilized acrylate Diels-Alder adducts.

The reduction of the lactone ring of the Diels-Alder adduct **3.37** was more successful in this case (Scheme 3.12). A stable product could be isolated and characterized. From there, the lactol intermediate **3.38** underwent the desired Claisen rearrangement to **3.39** albeit in low isolated yield of 41%. The stage was thus set for the elimination of the thiophenol substituent. To perform this reaction, an amination of the sulfur to the sulfilimine **3.42** was performed. The sulfilimine is a more reactive analog to the classic sulfoxide handle used in elimination chemistry, allowing for eliminations to occur at room temperature.[10,11] The expected and desired product was the alkene at C3-C7 **3.43**, however the product isolated from this reaction was instead the isomer with a

tetrasubstituted bridgehead alkene **3.44** at C7-C8. The regioselectivity of this transformation could be either kinetic, due to a potentially more accessible proton at C8 versus C3, or thermodynamic, due to the conjugation of the alkene at C7-C8 with the ketone. Regardless, it was not clear at this point how the alkene could be isomerized to the desired position.



Scheme 3.12. Claisen rearrangement/elimination sequence of the thiophenylsubstituted Diels-Alder adduct

3.6 Moving away from the HDDA approach

Through the work described in this chapter, the limitations of the HDDA approach became clear. The limitations stem from the difficulty in finding dienophiles that are both reactive in the HDDA step and contain functional groups that can be functionalized further to penostatin F. Although the challenge of making the bridged bicycle was overcome in the case of the Diels-Alder adduct of the 2-thiophenyl acrylate, the challenge in transforming the enone **3.44** to penostatin F was deemed too much to overcome, and thus led to the abandonment of this route. The other dienophiles screened that have performed well in the HDDA could not even be converted to a bridged bicycle. Due to these challenges, alternative strategies to exploit the hydroxy-diene

intermediates were sought. The following chapter describes such an approach leveraging the hydroxyl moiety of the hydroxy-diene to access the key structural elements of the penostatin family of natural products.

3.7 References

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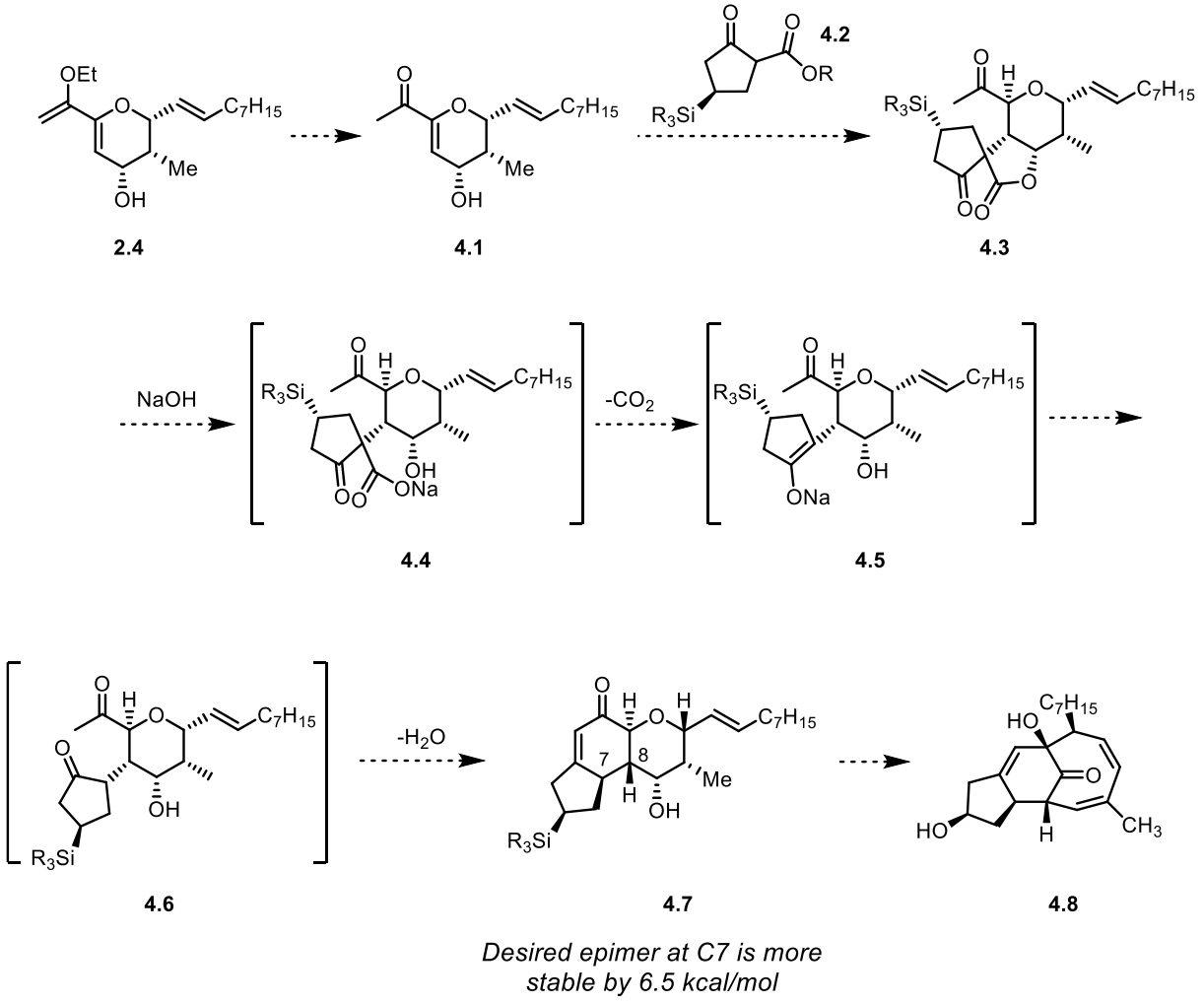
Chapter 4: Total Synthesis of 5-deoxypenostatin B

4.1 Development of a tethered Michael addition strategy towards penostatin B

Although the bridged bicycle of penostatin F was secured, the experiments described in the past two chapters revealed unexpected challenges of the hydroxy directed Diels-Alder approach. Specifically, the endo geometry of the Diels-Alder products forces a cyclization to a lactone with most dienophiles, preventing the necessary Claisen rearrangement to occur in the next step. Attempts to open the ring via reduction proved to be not trivial, due to the instability of the lactol products. Functionalization of C7 via elimination or alkylation also proved difficult, preventing the generation of a handle to install the C2-C3 alkene. Lastly, the sensitivity of the diene to degradation and of the dienophile to steric hindrance also limits the scope of dienophiles that can be employed to complete a successful total synthesis.

However, the hydroxyl directing group proved itself to be exquisitely selective in securing the correct stereochemistry of C8, which is crucial to attain the chair like transition state of the Claisen

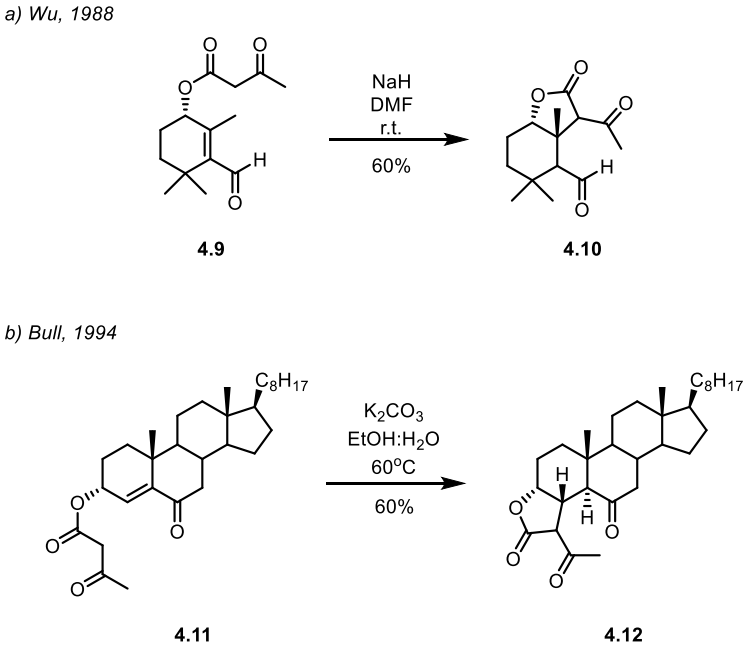
rearrangement. Due to the difficulties encountered with the Diels-Alder approach, other reactions that could exploit the hydroxyl directing group were examined. By considering the ethyl enol ether **2.11** a masked methyl ketone **4.1** that could be revealed upon acidic hydrolysis, a Michael acceptor becomes available as a synthetic handle.



Scheme 4.1. Envisioned Michael addition Approach towards the core of penostatin B

A new approach was thus developed whereby the hydroxyl moiety could direct a Michael addition with a nucleophile onto the enone in a stereospecific fashion (Scheme 4.1). Literature

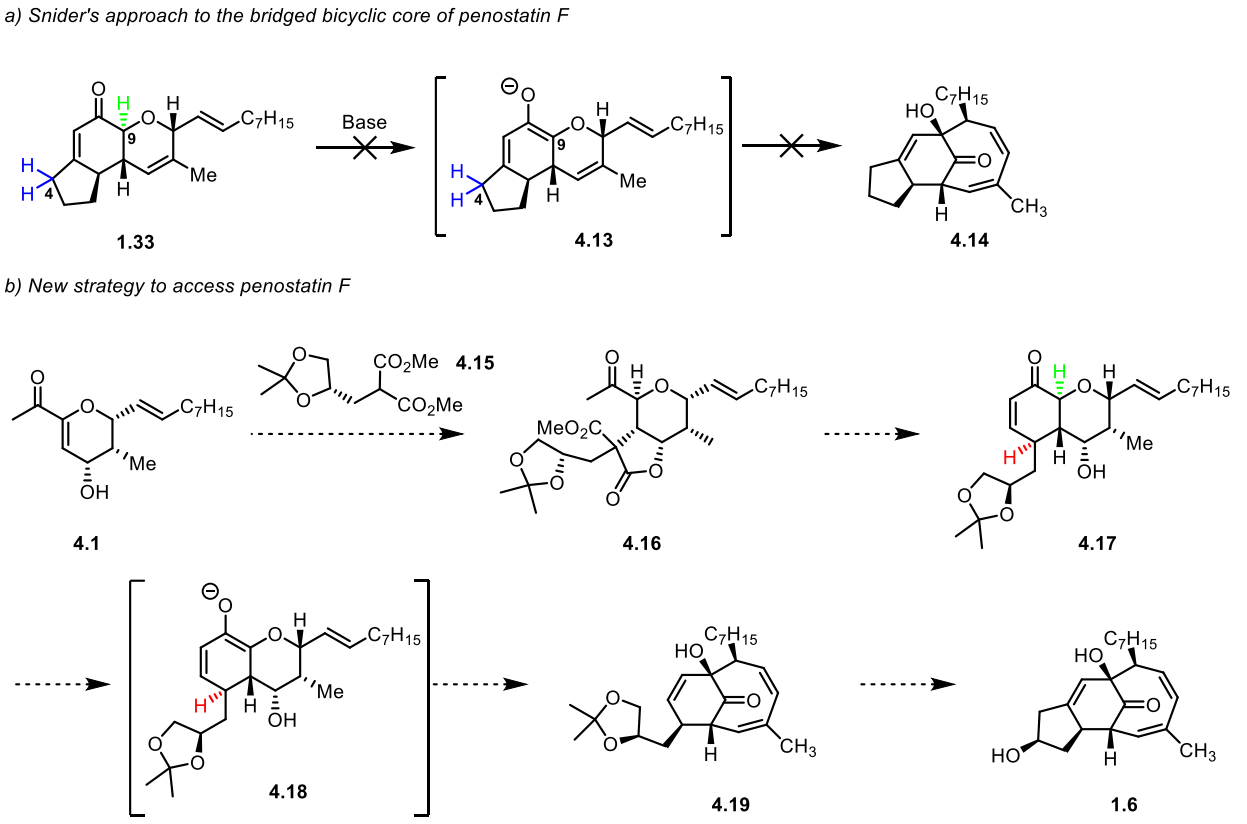
precedent for this kind of tethered Michael addition exists, such as reports in the synthesis of forskolin[1,2] and the synthesis of cholesterol analogs (Scheme 4.2).[3] The product of addition would be a beta-ketoester **4.3** capable of undergoing a saponification/decarboxylation sequence, followed by aldol condensation to form the key C2-C3 alkene, thus yielding the carbocyclic core of penostatin B **4.7**. In this approach, only two carbon-carbon bonds are formed, namely the C7-C8 bond via a Michael addition and the C2-C3 bond via an aldol condensation, in order to build the core of penostatin B. This contrasts positively with the multiple late stage functional group manipulations previously envisioned for the Diels-Alder/Claisen strategy.



Scheme 4.2. Key precedents for a tethered Michael addition using cyclic enones

However, this Michael addition approach is not without risk. A potential issue is the lack of stereocontrol at C7, since the decarboxylation forms an enolate that could presumably be protonated on either face. To examine the thermodynamic difference between the two isomers at C7, free energy calculations of the ground state of each isomer in the product of aldol condensation

shows a large energy gap favoring the product **4.7** with the proton at C7 *anti* to the one at C8. Since this vinyloguous position is enolizable, one could envision a late stage epimerization to drive the strong thermodynamic equilibrium towards the desired product. Another challenge is the lack of a discrete C1-C9 enol intermediate that can undergo a Claisen rearrangement as is the case in the Diels-Alder approach. One could envision an optimization campaign to deprotonate C9, however Snider's work demonstrating the base instability of the starting material and kinetic preference for deprotonation at C4 are not suggestive that such a campaign would be successful (Scheme 4.3a). A workaround to this problem would be to install the cyclopentanol ring at a late stage, via a linear nucleophile **4.14** (Scheme 4.3b). The addition adduct would possess a protected diol handle that can be converted into an epoxide and then cyclized to install the cyclopentanol ring.[4]

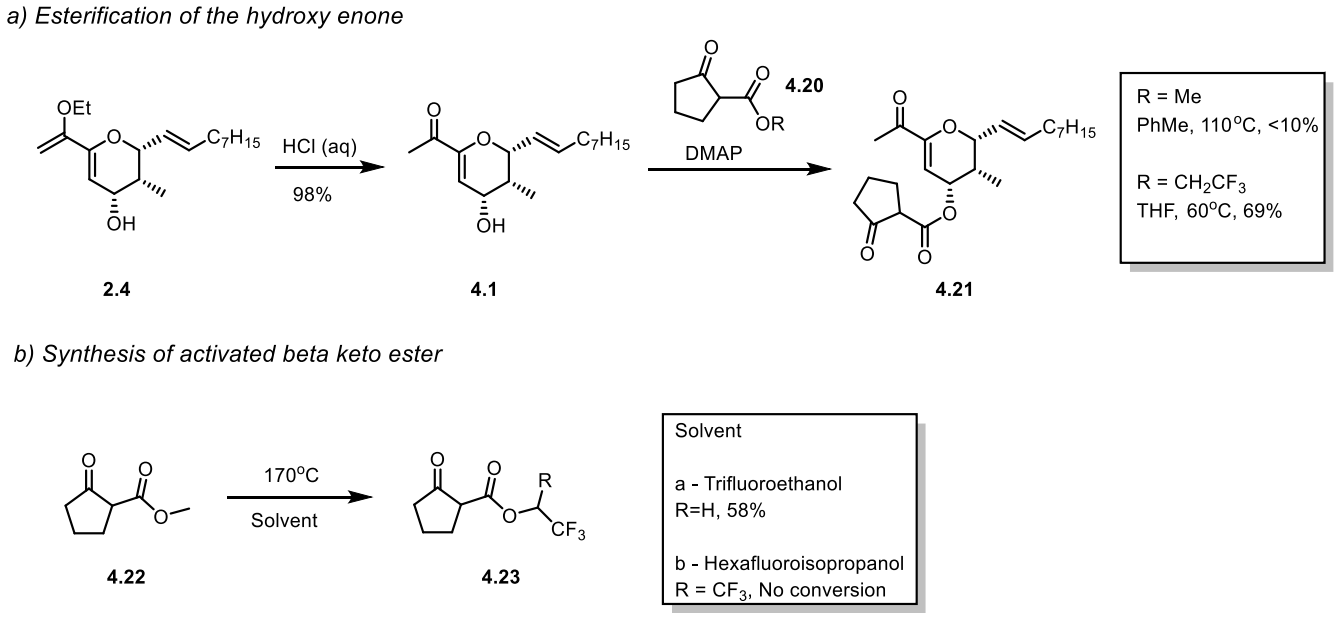


Scheme 4.3. Development of a new strategy to access the enolate required for the Claisen Rearrangement

4.2 Synthesis of the tethered Michael addition substrate

Following the elaboration of this strategy, the synthesis of the intramolecular addition substrate began (Scheme 4.4). First, the ethyl enol ether was smoothly hydrolyzed under acidic conditions to generate the enone **4.1**. The hydroxyl group was then esterified using classical conditions[5–7] with commercially available methyl 2-oxocyclopentane-1-carboxylate **4.20**. However, this required high temperatures, leading to significant degradation and low yields. Due to the success in increasing the electron withdrawing strength of esters with fluorinated alcohol substituents in the Diels-Alder chemistry, the corresponding fluorinated beta-ketoesters **4.23a** and **4.23b** were hypothesized to be more reactive and would therefore reduce the temperature required

for the esterification, thus lowering the degradation of the hydroxy enone **4.1**. To test this, the commercial methylated cyclopentanone beta-ketoester **4.20** underwent a transesterification by heating a solution of this substrate in fluorinated solvent using microwaves. Using trifluoroethanol, the corresponding fluorinated beta-ketoester **4.23a** was obtained in 58% yield, however using hexafluoroisopropanol as a solvent led to no conversion towards product **4.23b**. Presumably the oxygen of hexafluoroisopropanol is less nucleophilic to perform the transesterification. Gratifyingly, heating **4.23a** with the hydroxy enone at 60°C led to much better yields of the desired product **4.21**.



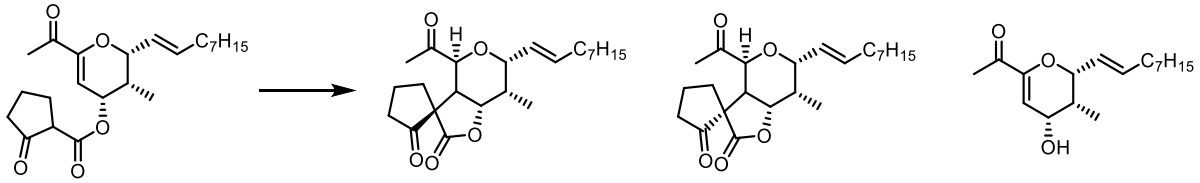
Scheme 4.4. Optimization of the Michael addition substrate synthesis

4.3 Optimization of the tethered Michael addition

With the beta-ketoester **4.21** in hand, optimization of the intramolecular Michael addition could begin (Table 4.1). The first set of conditions tried were literature precedented conditions

using carbonate bases in mixtures of alcohol solvents and water (Table 4.1, Entry 1-4). Disappointingly, this led to mostly saponification of the starting material to the hydroxy enone **4.1**. To reduce saponification, polar non protic solvents were screened (Table 4.1, Entry 5-8). In the case of DMF and acetonitrile, trace amounts of water also led to saponification. In the case of dry THF, toluene or acetone, no conversion was observed.

Table 4.1. Michael Addition Optimization

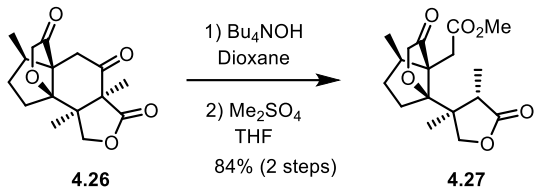


4.21 **4.24** **4.25** **4.1**

Entry	Conditions	Result
1	K_2CO_3, tBuOH, ON, 65ºC	**4.25 (29%)** Complex mixture of saponification, addition, starting material.
2	Na_2CO_3, tBuOH, ON, 65ºC	Saponification
3	K_2CO_3, 60ºC, HFIP, ON	Complex mixture
4	K_2CO_3 aq (1M), 1:10 in iPrOH	**4.28 (84%)**
5	K_2CO_3, 60ºC, DMF, ON	Saponification
6	Cs_2CO_3, THF, ON, 65ºC	No conversion
7	Cs_2CO_3, MeCN, ON, 65ºC	Saponification
8	K_2CO_3, acetone 2 hrs, rt	SM with trace saponification
9	NaHMDS, THF, 0ºC to rt, ON	No conversion
10	KHMDS, THF, 0ºC to 50ºC, ON	No conversion
11	$Cu(OTf)_2$ (2 eq), DCE, rt, 30 min	Degradation
12	**Piperidine, Bu_4NHSO_4, MeCN**	**4.24 (61%)**

Interestingly, sodium carbonate in *tert*-butanol (Table 4.1, Entry 1) led to saponification, however potassium carbonate in the same solvent (Table 4.1, Entry 2) led to a modest yield of addition adduct **4.25**. Isopropanol led to full conversion of the starting material to a product which at first glance seemed to be the addition adduct, but after careful NMR analysis turned out to be a

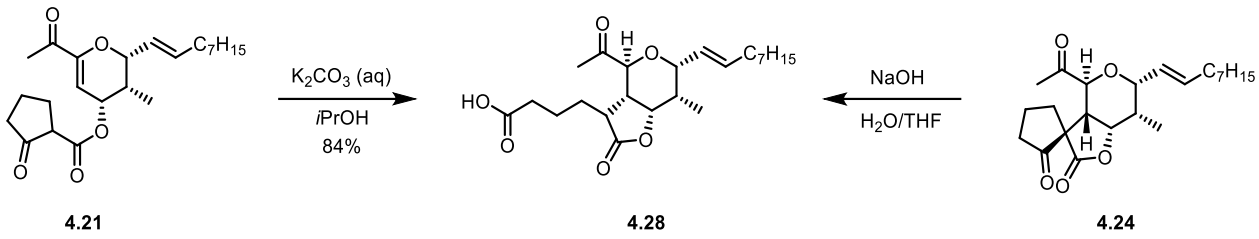
product of retro-Dieckman fragmentation **4.28** of the addition adduct. Upon examination of the literature, the issue of retro-Dieckman fragmentation of substituted beta-ketoesters has been observed in other total synthesis work, such as a report by Shenvi in the synthesis of (−)-11-O-debenzoyltashironin.[8]



Scheme 4.5 Retro-Dieckman product observed during attempted lactone saponification in Shenvi's synthesesis of (−)-11-O-debenzoyltashironin

Since the product of saponification of **4.19** is not observed, the Michael addition is presumably relatively quick. The addition adduct **4.23** then undergoes hydration at the ketone, retro-Dieckman fragmentation. This result is particularly interesting as it augurs poorly for the planned saponification/decarboxylation sequence (Scheme 4.1). For this sequence to be possible, hydroxide needs to cleave the lactone ring first. If the more electrophilic ketone is hydrated and undergoes fragmentation, then the sequence is not feasible as planned.

Due to the lack of success with carbonate bases, attention was turned towards stronger bases. Potassium bis(trimethylsilyl)amide was screened was screened as a possible alternative to potassium *tert*-butoxide. The absence of water and alkoxide base was hypothesized to tame the competing saponification. Addition of KHMDS to a solution of starting material led to a clear colour change, however no conversion was observed, even after heating the solution at 50°C overnight. This result is interesting in the context of the moderate success with potassium tert-butoxide at similar temperatures.

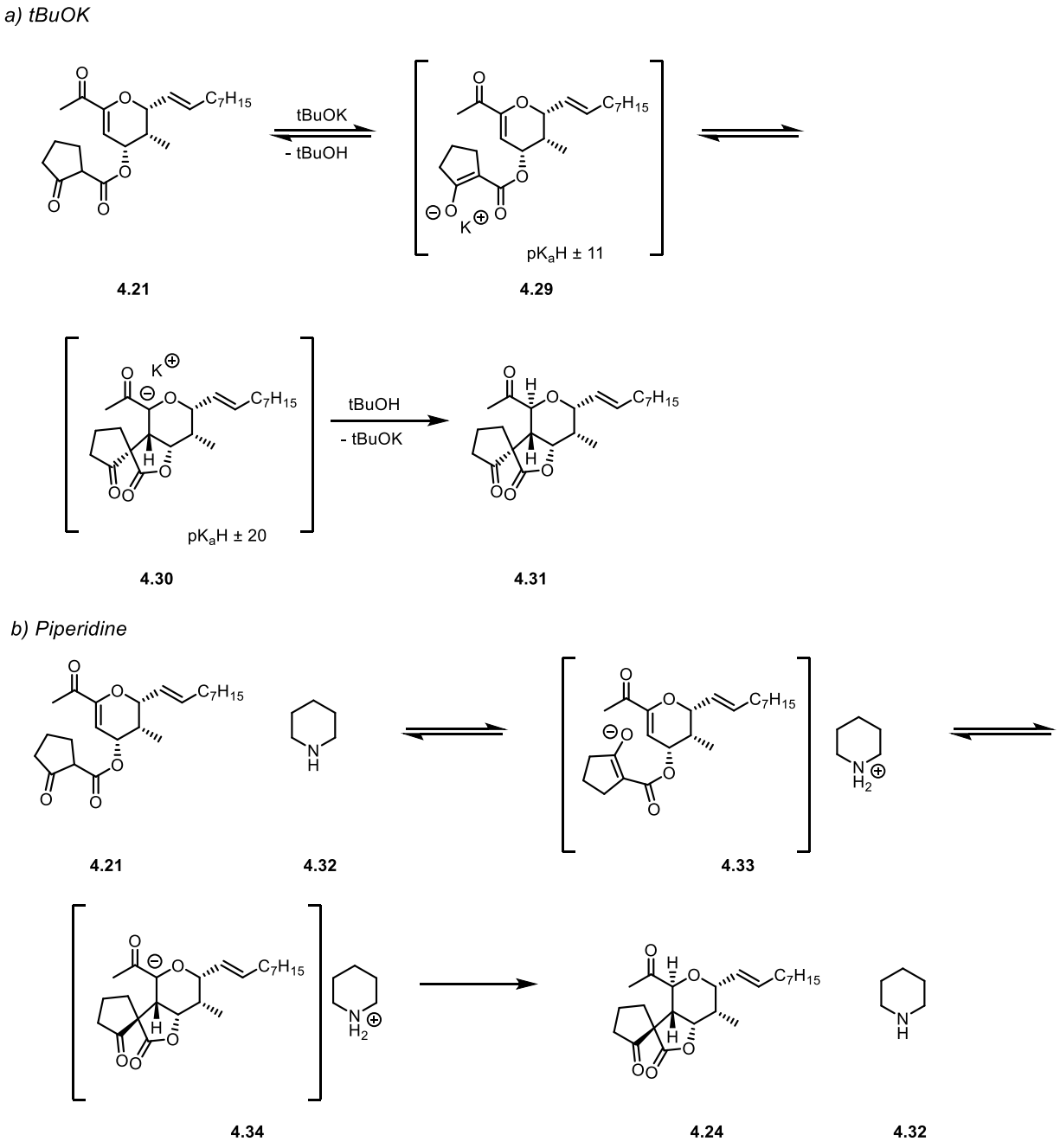


Scheme 4.6. Retro-Dieckman fragmentation observed during the optimization of the Michael addition. The product is also accessible by subjecting the addition adduct to hydroxide.

Following the lack of success with the classic approach, further examination of the literature uncovered a report of an intramolecular Michael addition with a very similar substrate.[9] The authors reported the use of piperidine as a base with tetrabutylammonnium hydrogen sulfate additive in acetonitrile. Gratifyingly, the use of these conditions resulted in the formation of product **4.25** in 61% yield. The addition product turns out to be a diastereoisomer of the product **4.24** obtained using potassium *tert*-butoxide as a base. The stereochemistry of the products was assigned by NOESY relations between key proton signals (Scheme 9). The stereochemistry at C7 differs between the two products, with all other stereocenters remaining the same. One can account for this difference by considering the different nature of the counterions in the deprotonated beta-ketoester (Scheme 4.6).[10] When using potassium *tert*-butoxide, the beta-ketoester anion **4.25** is likely coordinating the potassium cation via both carbonyl oxygens, forcing both carbonyls to be coplanar during the addition step. In the case of piperidine, the protonated amine can not coordinate both carbonyls, therefore dipole minimization forces the carbonyls of the anion **4.28** in an anti configuration. The divergence in geometry of the beta-ketoester anion likely leads to a difference in stereochemistry of the product at C7.

The success with piperidine was initially perplexing as it is the weakest base screened, with a conjugate acid of comparable pKa to that of the beta-ketoester. In addition, a catalytic amount of

acid is present in solution, reducing further the basicity of the system. To explain the success of the reaction in the weakly basic system and lack thereof with stronger bases, the mechanism of this reaction was examined. The intramolecular Michael addition consists of three steps: deprotonation of the beta-ketoester **4.21**, addition to form the C7-C8 bond, and protonation of the C9 enolate intermediates. Thermodynamically, the energy difference between the starting material and product favours the formation of the latter as a pi bond is transformed into two sigma bonds. However, the same can not be necessarily said for the two intermediates. Relatively stable beta-ketoester enolates **4.29** and **4.33** are converted into a less stable enolate at C9 **4.30** and **4.34**. The difference in pKa of the conjugate acids of the beta-ketoester enolate and the enolate resulting from the Michael addition is of approximately 9 orders of magnitude. (pKa of approximately 11 to 20 respectively). Until the C9 enolate is quenched by the conjugate acid of the base, every step is reversible. Therefore, the ideal base will be one that is best able to quench the enolate resulting from Michael addition. This explains why the most success was found with bases having the strongest conjugate acid, or in other words the weakest base. This likely explains why piperidine, the weakest base screened, was found to provide the desired addition adduct in the highest yield. In the case of potassium carbonate, the *tert*-butanol solvent likely assists in the protonation of the C9 enolate **4.30**.

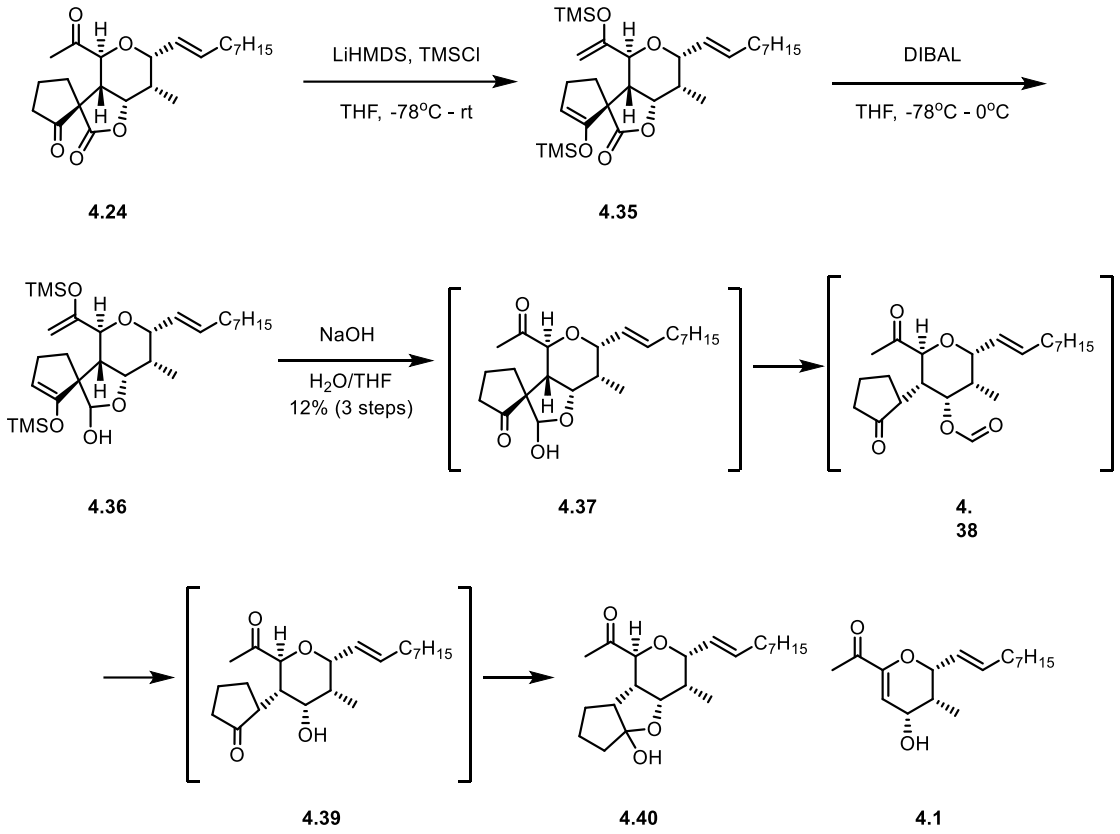


Scheme 4.7. Proposed mechanism for the intramolecular Michael addition

4.4 Troubleshooting the planned decarboxylation

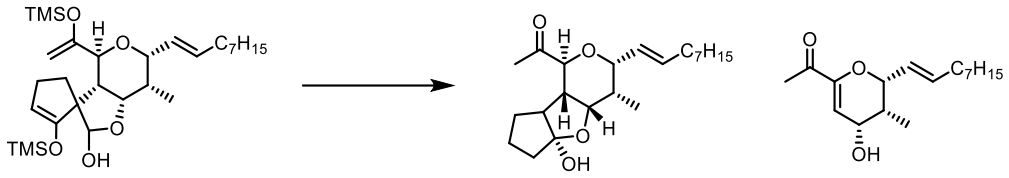
With the addition adduct **4.24** secured, the stage was set for the decarboxylation/aldol addition sequence. The original plan involved a saponification step followed by decarboxylation. Disappointingly, submitting the addition product to sodium or potassium hydroxide yielded solely the retro-Dieckman condensation product **4.28**, much like in the attempted 1,4 addition in isopropanol. The key observation made here is that saponification of the lactone moiety of **4.24** is slower than the hydration/fragmentation of the ketone. Protection of the ketone prior to lactone functionalization seemed necessary to solve this problem, however the ketone at C3 is essential for the stabilization of the anionic charge as an enolate following decarboxylation.

An alternative transform to the decarboxylation was thus sought. To this end, a sequence consisting of lactone reduction and retro aldol was envisaged (Scheme 4.7). Moving forward with this plan, the protection of the two ketones was conducted. This reaction was initially quite sluggish using the usual sequence of deprotonation at -78°C followed by enolate trapping. Three modifications were essential to obtain consistent full conversions. The first was an order of addition switch, whereby the trimethylsilyl chloride was added to a solution of the base at -78°C, followed by immediate addition of a solution of substrate **4.24**. The second was an increase in temperature. Removing the flask from the dry ice/acetone bath after all reagents were added and letting the mixture warm to room temperature followed by stirring for two hours ensured full conversion. Third, addition of triethylamine to the mixture at the end of the reaction prior to quenching with saturated aqueous sodium bicarbonate helped to achieve consistent yields. The crude oil following workup of the protection reaction was used without purification in the following step.



Scheme 4.8. Retro-aldol approach towards lactone opening. A protection/reduction sequence allows for a tandem deprotection and retro-aldol step.

Table 4.2. Optimization of the tandem deprotection/retro-aldol reaction



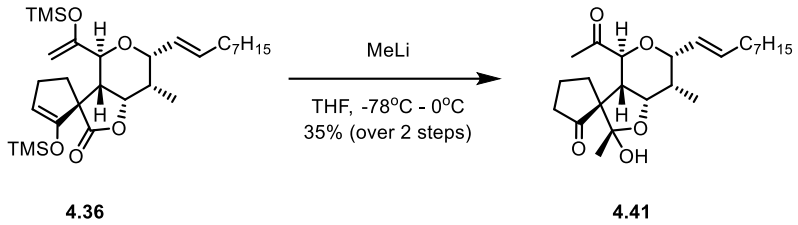
4.36 **4.40** **4.1**

Conditions	**Result**
THF: 1M NaOH (10:1), r.t. ON	2:1 Retro-Michael:Deformylation, other byproducts by NMR
TBAF, r.t., 1 hr	Retro-Michael
THF: 0.01 M NaOH (10:1), rt, ON	No conversion
THF: 1M HCl (10:1), rt. 1hr	Retro-Michael and other byproducts
K_2CO_3 in Toluene (0.1M)	No conversion

Reduction of the lactone ring of **4.35** to the lactol **4.36** with DIBAL proceeded without issue, however the planned one pot deprotection/retro-aldol step turned out to be problematic (Table 4.2). Although some retro aldol product **4.37** was isolated in 12% yield over 3 steps, analysis of the crude mixture by NMR showed the major product was surprisingly the hydroxy enone **4.1**. Presumably, basic hydrolysis of the silyl enol ethers is followed by a retro-Michael reaction, and then hydrolysis of the hemiacetal to yield the hydroxy enone. To avoid this problem, the first hypothesized solution was to perform a deprotection of the silyl enol ether prior to the retro-aldol fragmentation. A solution of TBAF was added to a solution of the lactol **4.36**, and disappointingly only the retro-Michael product **4.1** was observed. This result could be due to the trace amounts of water that are often present is commercial TBAF solutions. Performing the deprotection under acidic conditions was also not successful as a mix of degradation and retro-

Michael product was obtained. Reducing the concentration of sodium hydroxide led to a lack of conversion entirely. The same outcome was observed if the reaction was performed in absence of water.

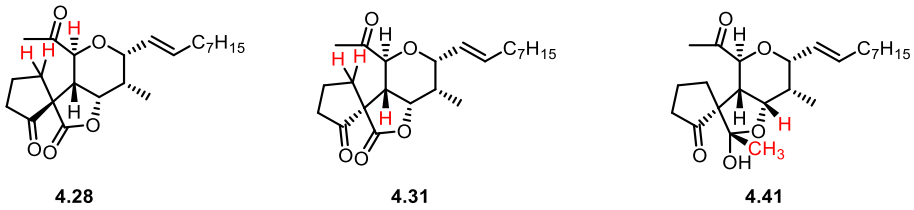
Despite these setbacks, deprotection of the silyl enol ethers in between lactone functionalization and fragmentation steps remained an attractive strategy. The central issue with the approach at this point is the need for protic solvent to deprotect the enol ethers into the ketone. Alternative conditions that could deprotect the enol ethers under non protic conditions were therefore sought.



Scheme 4.9. Addition of MeLi on the lactone ring in and tandem deprotection of the silyl enol ethers. Base catalyzed retro-aldol reaction followed by aldol condensation completes the synthesis of the tricyclic core of penostatin B.

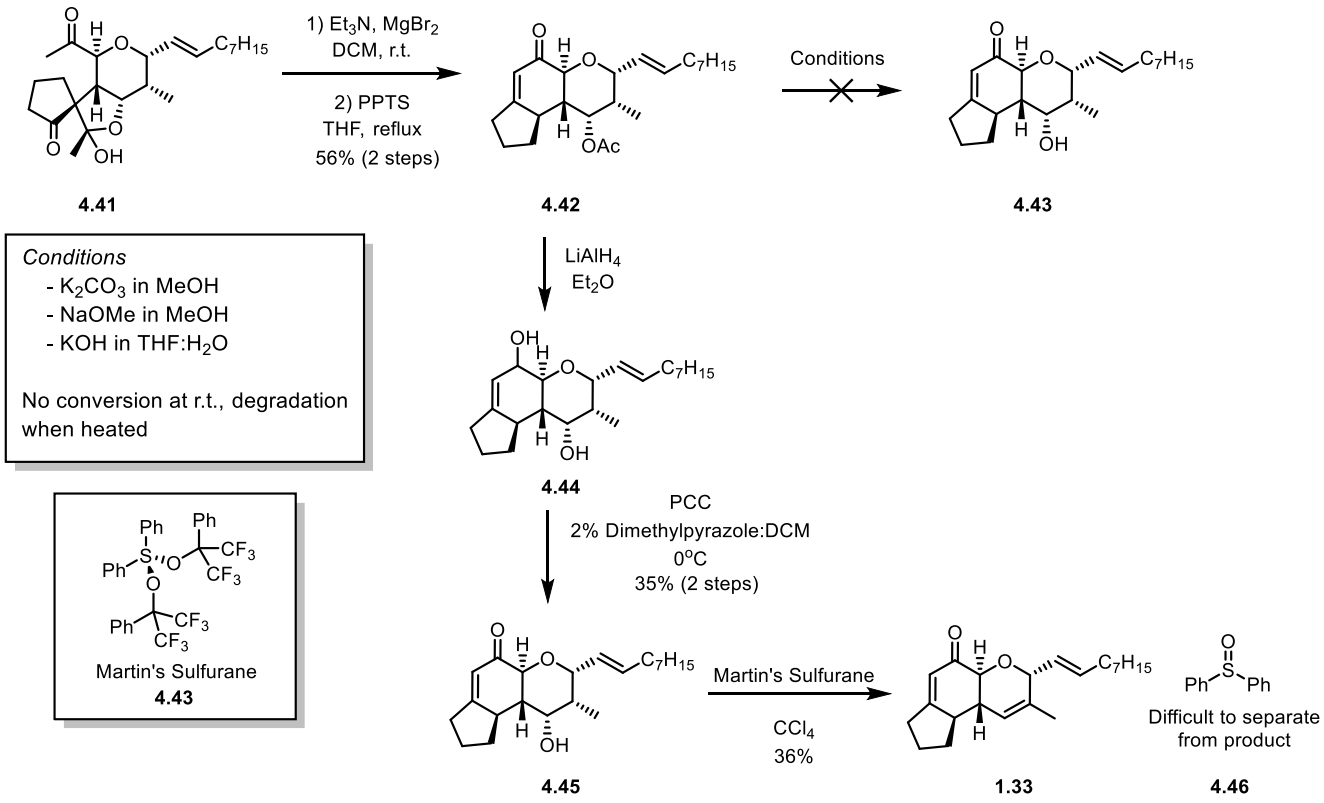
An idea that was developed in this process was to use methyl lithium, as this reagent is known to convert trimethylsilyl enol ethers to the lithium enolate at room temperature (Scheme 4.8).[11] Additionally, this could present an opportunity for a one pot reaction with addition of MeLi onto the lactone to generate a hemiacetal. If the silylated Michael addition adduct **4.36** is used as substrate, methyl lithium could perform an addition onto the lactone carbonyl at -78°C and subsequently warming the solution would lead to deprotection of the silyl enol ethers, assuming an excess of methyl lithium is present. This idea was somewhat risky however, as each reaction with methyl lithium increases the charge on the molecule, ultimately leading to a triply anionic

intermediate. Gratifyingly, a large excess of methyl lithium added to a solution of the protected Michael addition adduct **4.36** in THF provided the desired product **4.41** in 35% yield. The stereochemistry of the addition adduct **4.41** was determined via a NOESY correlation between the methyl added in this step and the proton at C10, showing the addition to be adding on the more accessible top face of the molecule (Scheme 9). Key to this reaction was the large excess of methyl lithium and warming to room temperature. Modifying reaction time or temperature did not result in improved yields. Importantly, hydroxy enone **4.1** was not observed in any of the crude mixtures.



Scheme 4.10. Key NOESY correlations used to identify the stereochemistry of the addition adducts. Relevant proton signals highlighted in red.

The stage was thus set for the retro aldol fragmentation reaction of **4.41** (Scheme 4.10). The first attempt was made with a potassium tert-butoxide solution, however only degradation was observed. The combination of triethylamine base with a magnesium bromide Lewis acid used for the hydroxy directed Diels-Alder reaction was screened next. This led to conversion of starting material to a complex mixture with seemingly much less degradation based off the crude NMR. Satisfyingly, heating this mixture in THF with PPTS led to the isolation of the aldol condensation product **4.42** in 56% yield, completing the synthesis of the carbocyclic core of penostatin B.



Scheme 4.11 Completion of the synthesis of 5-deoxypenostatin B

To complete the synthesis of 5-deoxypenostatin B (**1.33**), the acetate effectively needed to be eliminated to an alkene at C10-C11 (Scheme 4.9). A better leaving group than the acetate was sought, therefore a saponification followed by elimination with Martin's sulfurane was planned. However, subjecting **4.42** to either carbonate base in methanol, sodium methoxide or potassium hydroxide did not lead to any product. Presumably, the position of the acetate, situated in the more sterically hindered bottom face of the molecule leads to steric strain and thus hampers saponification. Heating the reaction to accelerate this reaction led to degradation. The base sensitivity of this substrate mimics the reports of Snider in his attempts to perform the biosynthetically hypothesized Claisen rearrangement with base on very similar substrates. To

circumvent saponification, a global reduction of the substrate was performed, yielding the diol **4.44**. Selective oxidation of the allylic alcohol performed using chromium oxide with a dimethylpyrazole additive effectively led to the desired deprotected product **4.45** in 36% yield (over 2 steps). The elimination with Martins sulfurane was not converting at room temperature, however upon stirring the reaction overnight at 45°C and increasing the equivalent of Martins sulfurane, the starting material could be fully converted to the desired product **1.33** in 36% yield. A significant issue encountered was chromatographic separation of the sulfoxide byproduct **4.46**. Additional separation allowed for a relatively clean spectrum to be obtained and for full characterization of 5-deoxypenostatin B.

4.6 Perspectives on the Michael addition strategy

In this chapter, a Michael addition based strategy delivered the core of penostatin B. The hydroxyl group was effectively used as a tether to direct the addition of a beta-ketoester nucleophile onto the desired face of the hydroxy enone. However, removing the resulting lactone ring turned out to be more difficult than planned. Although an effective workaround was found by protecting the ketones as silyl enol ethers, the low yields of the methyl lithium deprotection/addition reaction will likely limit the potential scalability of this strategy. In addition, the challenging installation of the cyclopentanol ring needed to be solved. We chose to prioritize the latter of the two challenges. Efforts towards the installation of the cyclopentanol ring are described in the next chapter.

4.7 References

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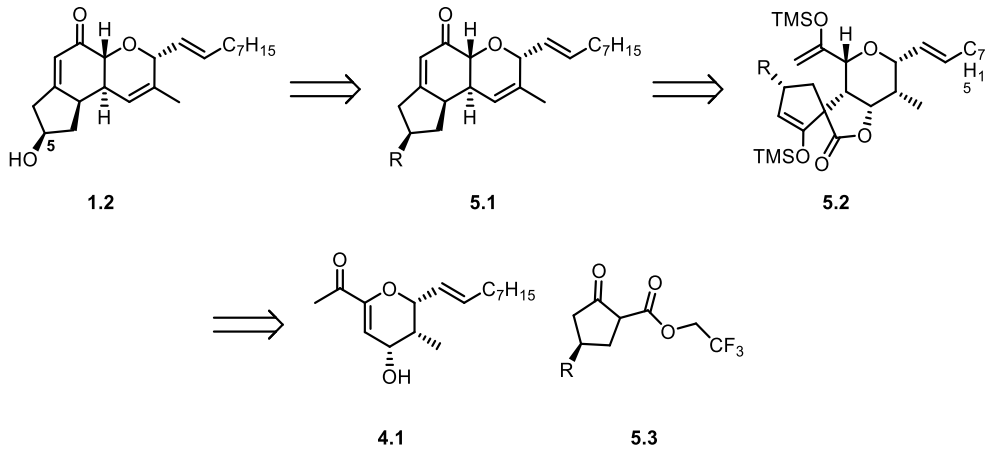
Chapter 5: Deriving a strategy towards the cyclopentanol ring of penostatin B

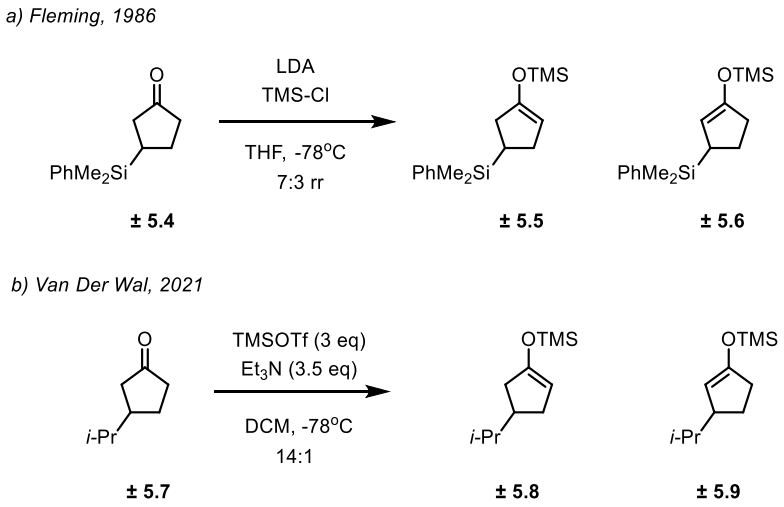
5.1 Design of a beta-ketoester fragment with a masked oxygen at C5

In the previous chapter, 5-deoxypenostatin B was synthesized through an intramolecular Michael addition strategy. With the general carbon-carbon bond forming strategy developed, efforts to install the hydroxyl functionality at C5 began. The plan was to find a beta-ketoester fragment **5.1** with a masked hydroxyl group, as opposed to a more obvious protected hydroxyl group (Scheme 1). The principal reason for this choice is the presence of an enolate intermediate **5.2** in the ketone protection/methyl lithium addition sequence. If an oxygenated functionality is present at this position in this step, there is a high risk of E1cb elimination to yield the enone. The masked hydroxyl group selected was the dimethylphenyl silane, as it is inert to most redox chemistry and not labile under basic or acidic conditions. The dimethylphenyl silane can undergo a stereospecific Tamao-Fleming oxidation and convert to the required hydroxyl functional group. This allows for the design of a strategy whereby the silane would be installed enantioselectively on the beta-ketoester fragment early in the synthesis and would be converted to the desired hydroxyl group at a later stage.



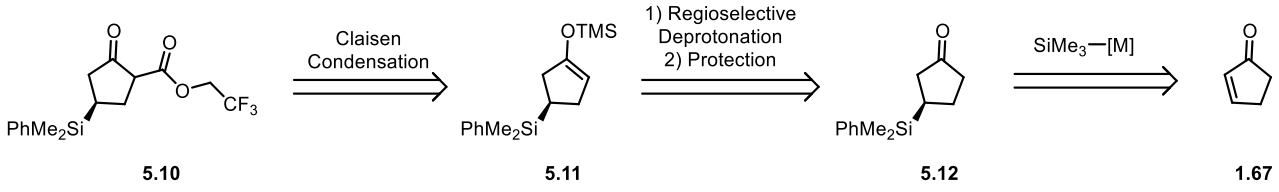
Scheme 5.1. Retrosynthetic analysis of the cyclopentanol ring of penostatin B. A functional group R capable of acting as an oxygen surrogate while withstanding the synthetic sequence is desired.

With this strategy in mind, the first step would be the enantioselective synthesis at the beta-ketoester fragment **5.3** (R = ($PhMe_2Si$). The classic approaches towards beta-ketoesters usually involve Claisen condensation or Dieckman condensation chemistry.[1,2] In either case, the condensation would be done late in the synthesis, and therefore require a substrate bearing the silane. Thankfully, the enantioselective synthesis of **5.4**, the substrate required for the Claisen condensation, had been already reported using a variety of approaches.[3] A Claisen condensation using this approach would require a selective deprotonation at the less hindered enolizable methylene, however this deprotonation has proven to be not trivial (Scheme 2a).[4] Previous work from Fleming showed that deprotonation of substrate 5.6 with LDA a mixture of regioisomer **5.5**/**5.6** (7:3) favoring the desired enolate **5.5**. The presence of moderate regioselectivity for the desired enolate was encouraging, and thus other similar cases were sought in order to find methods that could improve on the existing precedent. The Van Der Wal group reported (Scheme 2b) the use of trimethyl silyl triflate and DIPEA to synthesize silyl enol ethers with very good regioselectivity for the less hindered enolizable methylene.[5]



Scheme 5.2. Precedented functionalization of the less hindered enolizable position of beta substituted cyclopentanones.

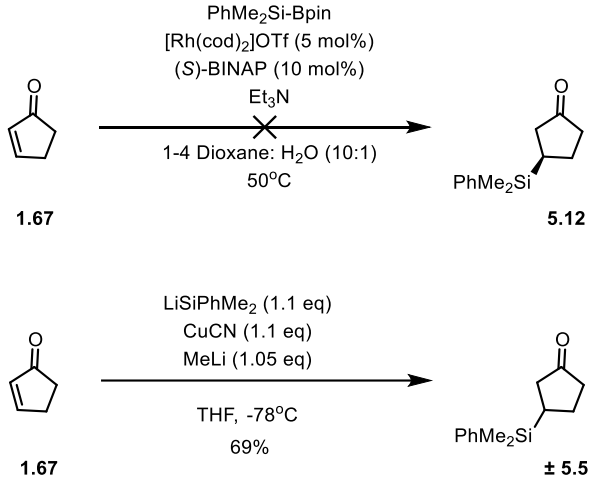
Although the substrate scope did not include silanes such as **5.4**, the success with sterically similar alkane substituents such as **5.7** was hypothesized to be interchangeable to the silylated cyclopentanone (Scheme 3). The silyl enol ether product **5.11** could then be used as a nucleophile in a Claisen condensation.



Scheme 5.3. Retrosynthetic analysis of the beta keto ester fragment

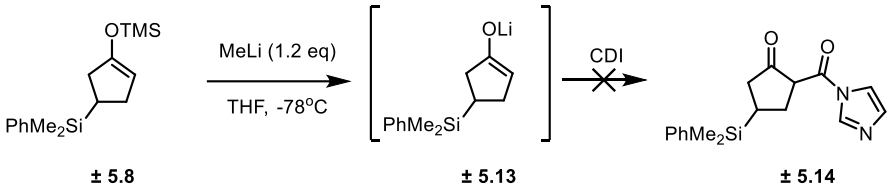
5.2 Synthesis of the silyl fragment 5.12

The synthesis of the beta keto ester fragment began with the 1,4-addition of a silyl nucleophile onto cyclopentenone **1.67** (Scheme 4). The first conditions screened were the rhodium catalyzed protocol reported by Oesterreich.[3] The use of a commercially available BINAP ligand and rhodium catalyst seemed particularly attractive. Surprisingly, only isolation of the starting material was observed (Scheme 4a). Reattempting the reaction with increased care to ensure an inert atmosphere and raising the equivalents of the silyl-boron ester reagent did not lead to a better outcome. Due to our failure in reproducing these conditions, the enantioselective route towards the beta-ketoester fragment was abandoned. A racemic approach using **5.5** was chosen as an alternative, as it would still allow for the validation of the general synthetic approach. The drawback of this alternative is the need to carry a pair of diastereomers after the ester coupling onwards until the end of the synthesis. At this stage, the plan was to revisit the enantioselective 1,4-addition later in the project.



Scheme 5.4. Attempted silylation of cyclopentenone.

The synthesis of the ester **5.16** began with a 1,4 addition of a silyl cuprate reagent onto cyclopentenone **1.67**, to afford **5.5** in 69% yield (Scheme 4b). This intermediate was then subjected to the enolization conditions reported by Vanderwal (Scheme 5). Based on the ^{1}H NMR of the crude reaction mixture after workup, it is clear the silyl enol ether **5.7** had formed with good 5:1 regioselectivity. The synthesis moved forward at this point under the assumption that the silylenol ether **5.8** was the desired isomer. Treatment of **5.8** with methyl lithium gave the corresponding lithium enolate **5.13** which could be trapped by a carbonyl electrophile. In terms of the electrophile, the classical approach is to use cyanoformate reagents, as these softer electrophiles ensure good C-alkylation of the enolate as opposed to O-alkylation.[6] The drawback is the generation of a stoichiometric amount of lithium cyanide, which under acidic conditions can be converted to toxic cyanide gas.

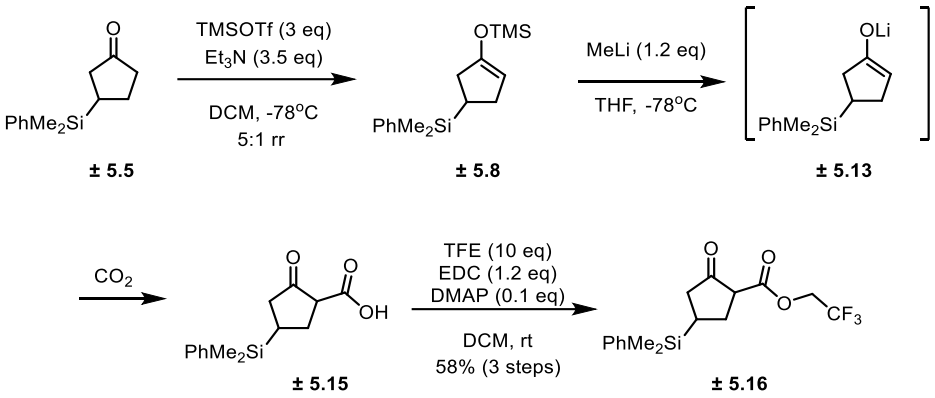


± 5.8 **± 5.13** **± 5.14**

Scheme 5.5. Unsuccessful approach towards the fluorinated beta keto ester bearing the dimethylphenylsilane

Alternatively, literature precedents exist for the use of carbonyldiimidazole as a cyanoformate equivalent.[7] The resulting carbamate could then be esterified to generate a desired beta-ketoester. However in our hands, this chemistry was not very successful as no carbamate product **5.14** could be isolated (Scheme 6a). Another alternative was explored whereby the lithium enolate could undergo addition with carbon dioxide under the form of dry ice added to mixture, to yield a beta-ketoacid **5.15**. This avoids the generation of toxic cyanide byproducts. The downside however is the instability of the keto acid, as these are known to decarboxylate readily.[8] When performing the addition, TLC clearly indicated a full conversion of the starting material to a very

polar product, assumed to be the beta keto acid **5.15**. After acidic workup, the beta keto acid was immediately subjected to a Steglich esterification with a large excess of trifluoroethanol, to yield the desired fluorinated beta keto ester **5.16** in 58% yield over 3 steps.



Scheme 5.6. Synthesis of the fluorinated beta keto ester bearing the dimethylphenylsilane.

5.3 Coupling and Michael addition of the silylated beta keto ester fragment

As shown in Scheme 5.7, the coupling of the hydroxy enone **4.1** and the fluorinated beta keto ester **5.16** was performed using the same conditions as previously employed, however significant amounts of starting material remained. Switching the solvent to toluene and increasing the temperature of the reaction improved the yield significantly, to give the desired product **5.16** in 57% yield as a mixture of diastereomers (1:1). The direct coupling of the hydroxy enone **4.1** with **5.15** was attempted. The reaction provide **5.16** in trace amounts and significant decarboxylation was observed as evidenced by the presence of the silylated cyclopentanone **5.4** by TLC and crude NMR.

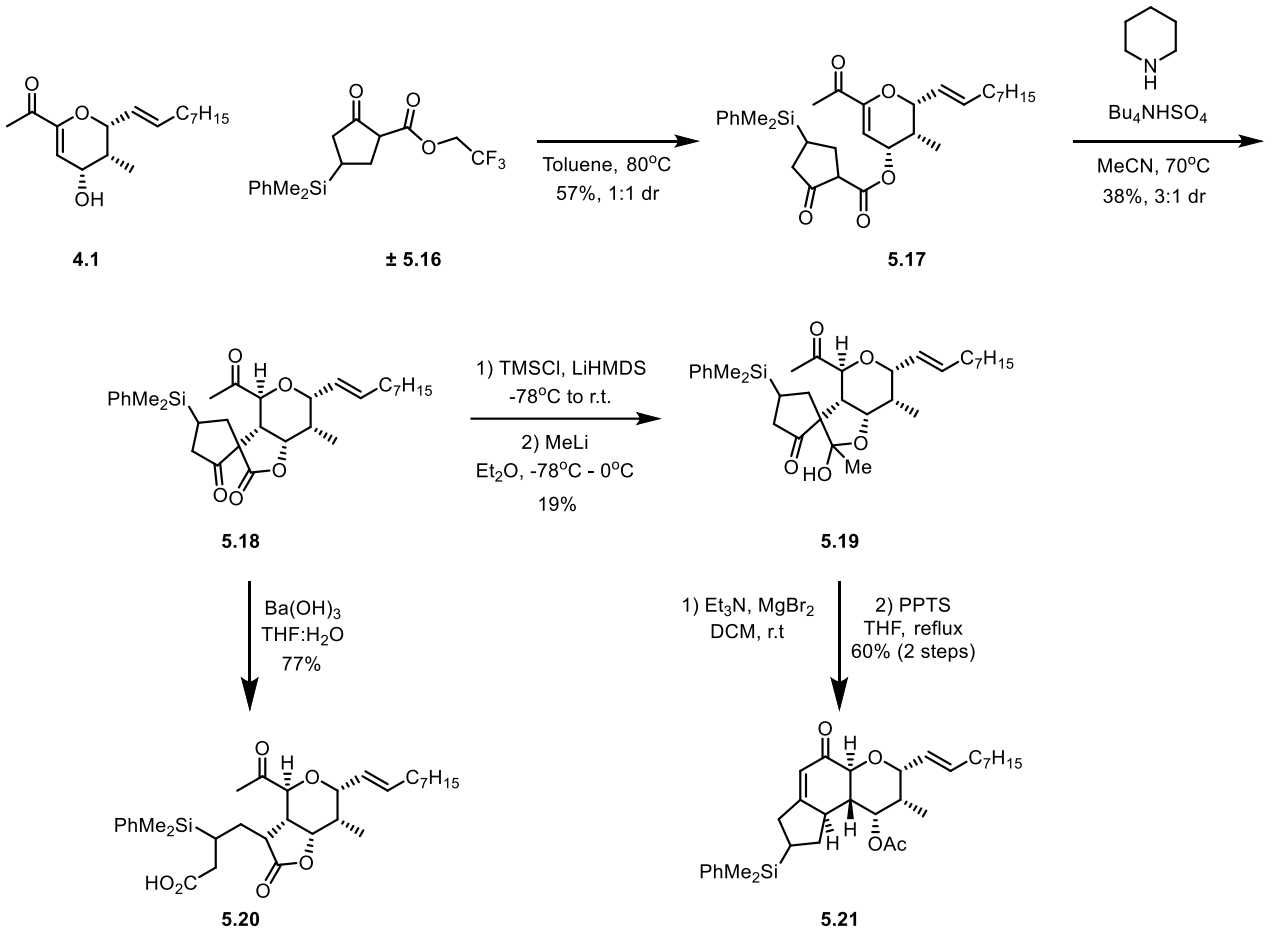
The next step consisted of the key intramolecular Michael addition. Previous work in this project has shown that the intramolecular addition gave one of the two possible diastereomers with respect to the stereocenter at C7 when using piperidine. Therefore, having a racemic stereocenter

at C5 and all other stereocenters controlled, a pair of diastereomers were expected for the intramolecular Michael reaction of **5.17**. To our surprise, when using piperidine, compound **5.18** was isolated in 38% yield as mixture of diastereomers in a ratio of 3:1. The diastereomers correspond to a pair of molecules with opposite stereochemistry on the C5 carbon bearing the dimethylphenyl silane. The yield of the reaction was also much lower than of the substrate without the silane group used in Chapter 4. To explain this outcome, one can postulate that the stereocenter at C5 is somehow affecting the rate of the addition, assuming the reaction is under kinetic control. Alternatively, if the reaction is under thermodynamic control due to the reversibility of the addition step, one could postulate that the diastereomeric ratio is simply a reflection of the energy difference between the two diastereomers. A remaining challenge is the assignment of the stereochemistry at C5 of the silane group in the major addition product.

5.4 Functionalization of the Michael addition adduct towards penostatin B

Moving forward with the enriched diastereomeric mixture of **5.18**, the next steps consisted of the ketone protection via the silyl enol ether followed by methyl lithium addition. The protection step was not problematic, however the methyl lithium addition turned out to be challenging. Using the same conditions as for the unsubstituted substrate led to degradation. Changing the solvent from THF to diethylether led to the isolation of desired product **5.19**, however yields were consistently low. An option that was considered was the transmetallation with cerium chloride,[9,10] in order to generate more nuclophilic organocerate species from methyl lithium. However, no conversion was observed when cerium chloride was added to the reaction. The low yields of this step have plagued the scalability of the synthesis. The combined yield of the intramolecular Michael addition and ketone protection/methyl lithium addition step are of 7%, severely hampering efforts to obtain enough material to complete the last steps of the synthesis. In addition,

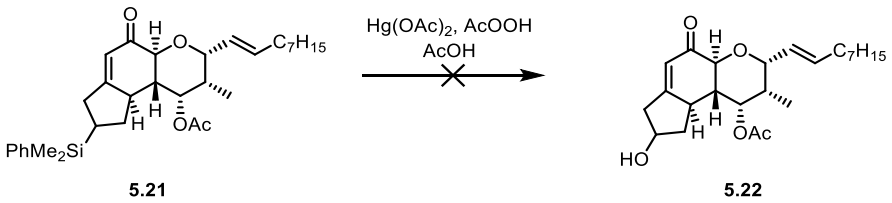
the addition substrate **5.18** suffers from the same retro-Dieckman fragmentation as in the case with no heteroatom at C5.



Scheme 5.7. Synthesis of the carbocyclic core of penostatin B

Although the amount of material at this stage was limited to a few milligrams, enough was pushed through to try a few more preliminary experiments in order to evaluate the feasibility of the last steps. First, the enone **5.21** was successfully synthesized via the previously established sequence of retro-aldol fragmentation followed by aldol condensation. At this stage, the two diastereomers were moderately separable and the major diastereomer was characterized. The Tamao-Fleming oxidation was attempted at this stage (Scheme 5.8). Ideally, this oxidation would

be performed as the last step of the synthesis, however the conditions for this reaction usually include a peroxide, which could epoxidize the endocyclic alkene at C10-C11 of **5.1**. Therefore, the intermediate **5.24** was deemed as an adequate alternative. Another consideration was the presence of an enone, which can undergo epoxidation with nucleophilic epoxidizing agents, such as hydrogen or alkyl peroxides in basic conditions. Conditions for the Tamao-Fleming oxidations were therefore limited to acidic media. The mildest condition found in the literature was the use of mercury acetate and peracetic acid in acetic acid.[11] These conditions were attempted, however, only starting material was recovered.



5.21 **5.22**

Scheme 5.8. Attempted Tamao-Fleming oxidation

5.5 Analyzing the current state of the project

In this chapter, the final efforts towards penostatin B revealed the impact of the silyl group on the diastereospecificity of the Michael addition when a silane group is present at C5. It is worth mentioning that the importance of the stereochemistry at C5 to the addition step was uncovered due to the racemic nature of the beta-ketoester **5.5**, which was used as a substrate due to our inability to produce the substrate **5.12** with stereocontrol at C5. Had we been successful in reproducing Oestereich's conditions, we might not have been able to identify this effect. The complications encountered in the Michael addition step coupled with the low yielding process to functionalize the lactone ring suggest that the route described in this chapter is likely not suited to

complete a total synthesis of penostatin B. In the conclusion of the thesis, an alternative route will be proposed, taking into account the lessons learned in the project so far.

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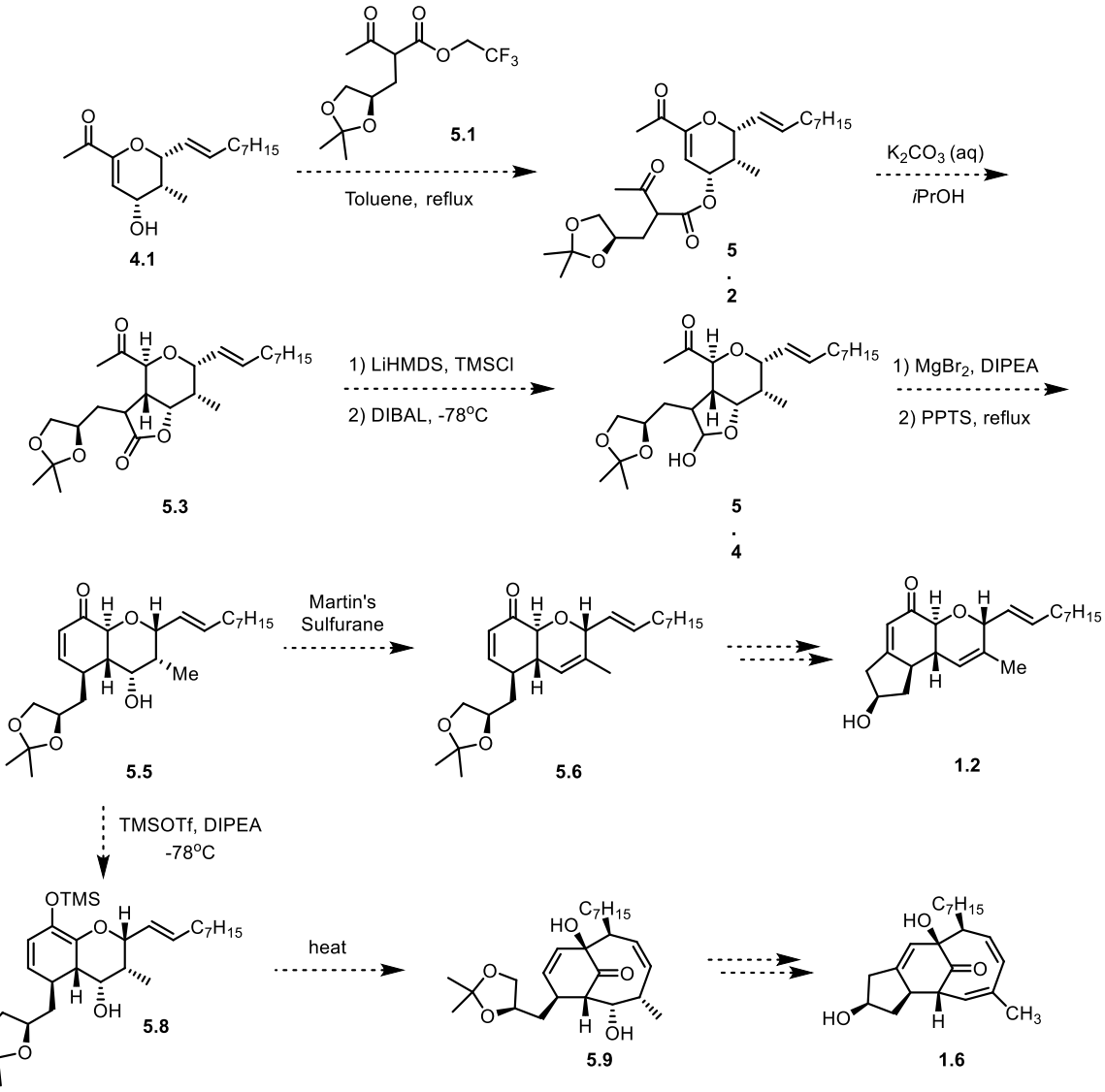
Chapter 6: Conclusion

Penostatin F remains unconquered as of the writing of this text. The work described in this thesis has deepened the understanding of the key hydroxy-directed Diels-Alder reaction and intramolecular Michael addition reactions in the context of the total synthesis of the penostatin family of natural products. In Chapter 2, the methylated hydroxy diene **2.34** was prepared. Applying the HDDA reaction led to the identification of limitations with this dienophile. Trying to exploit the HDDA/Claisen rearrangement adduct with N-benzyl maleimide was not successful in our hands. Taking the lessons from these failures led to Chapter 3, where the stereochemistry of the methyl group on the dienophile was flipped to expand the scope of potential dienophiles. However, the functional groups on Diels-Alder/Claisen Rearrangement products could not be converted towards handles that could yield penostatin F. In Chapter 4, we pivoted towards the fused bicyclic congeners of the penostatins, where a tethered Michael addition was developed to assemble the key C7-C8 bond with the appropriate stereochemistry at C8. This led to the synthesis of 5-deoxypenostatin B in 16 steps. In Chapter 5, early efforts towards the application of this strategy to penostatin B were presented. In this chapter, the peculiar role of the silane group on the diastereospecificity of the Michael addition was identified.

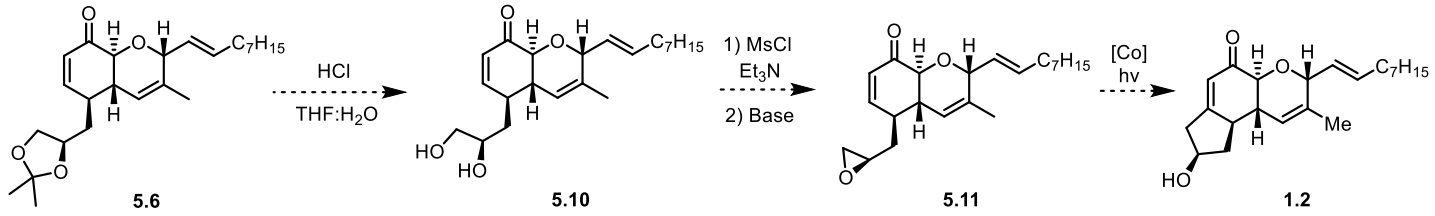
The lessons of this project lay a foundation to better routes towards the penostatin natural products. To achieve a complete total synthesis of penostatin B, the remaining challenges can be solved through different approaches. A simple although not very elegant solution would to be scale up enough material to push through the low yielding Michael addition and lactone functionalization steps. From there, conditions for the Tamao-Fleming oxidation could be

identified and complete the total synthesis of penostatin B. A better option would be to integrate the lessons learned over the course of the project and follow the alternative synthetic strategy suggested in Scheme 4.3 (Scheme 5.1a). For example, a fragment such as **5.1** could be esterified to the hydroxy enone **4.1** to yield **5.2**. In a one pot fashion, the Michael addition could be followed by a retro-Dieckman to yield intermediate **5.3** using the conditions identified in the optimization campaign for the tethered Michael addition in Chapter 4. This strategy applies the conditions that yielded the undesired retro-Dieckman product **4.23** on an intermediate for which the retro-Dieckman fragmentation cleaves a handle that is no longer necessary for the rest of the synthesis. From there, the methyl ketone could be protected, and the lactone reduced to the lactol **5.4**. The lactol could then be condensed to the methyl ketone to yield intermediate **5.5**. Elimination of the hydroxyl at C10 and cyclization of the diol handle onto the enone could generate penostatin B (Scheme 6.1b). This cyclization would require hydrolysis of the diol protecting group followed intramolecular substitution to generate the epoxide **5.11**. The epoxide could be cyclized via a radical process onto the enone to generate penostatin B. Importantly, intermediate **5.5** would a strategic point to diverge to penostatin F. A silyl enol ether intermediate **5.8** can be made via kinetic deprotonation and then undergo the Claisen rearrangement. The generation of such an enol species should be easier than in Snider's case, as there is no vinyloguous methylene position that is more sterically accessible than the enolizable position alpha to the ketone. From there, a similar endgame to penostatin B would complete the total synthesis of penostatin F.

a) Proposed route to complete a divergent synthesis of penostatin natural products.



b) Proposed endgame for the total synthesis of penostatin natural products



Scheme 6.1. Proposed route to complete a divergent synthesis of penostatin natural products.

Claims to original research:

- Development of a concise enantioselective routes towards complex cyclic hydroxy dienes.
- Elucidation of byproducts of the hydroxy directed Diels-Alder reaction.
- Identification of the effect of a remote methyl substituent in the hydroxy directed Diels-Alder reaction.
- Synthesis of an anti-Bredt enone via sulfilimine elimination
- Completion of a synthesis of 5-deoxypenostatin B via an intramolecular Michael Addition reaction
- Identification of the effect of a remote stereocenter in the intramolecular Michael Addition reaction.

Oral presentation

104th Canadian Chemistry Conference and Exhibition (CCCE) "*Towards the total synthesis of penostatin natural products*", **2022**

Ottawa-Carleton Chemistry Symposium (OCCI), "*Towards the total synthesis of penostatin F*", **2019**

Poster presentations

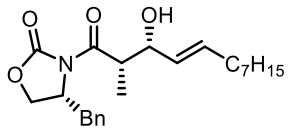
Gordon Research Conferences: Natural product and Bioactive compound (GRC) "*Towards the total synthesis of penostatin natural products*", **2022**

102nd Canadian Chemistry Conference and Exhibition (CCCE) "*Towards the total synthesis of penostatin F*", **2019**

Chapter 7: Experimental Procedures and Spectra

All reactions were performed under argon atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. All other commercial reagents were used without purification, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) analysis of aliquots using glass sheets pre-coated (0.2 mm layer thickness) with silica gel 60 F254 (E. Merck). Thin layer chromatography plates were viewed under UV light and stained with phosphomolybdic acid or p-anisaldehyde staining solution. Column chromatography was carried out with silica gel 60 (230-400 mesh, Merck). ^{1}H and ^{13}C NMR spectra were recorded in deuterated solvents, on Bruker AMX 300 MHz, Bruker AMX 600 MHz and Bruker AMX 400 MHz spectrometers. IR spectra were recorded with a Bomem Michaelson 100 FTIR spectrometer. HRMS were obtained on a Kratos Analytical Concept instrument (University of Ottawa Mass Spectrum Centre).

2.15



Name: (R)-4-benzyl-3-((2S,3R,E)-3-hydroxy-2-methyldodec-4-enoyl)oxazolidin-2-one

Procedure: To a round bottom flask containing (R)-4-benzyl-3-propionyloxazolidin-2-one (11.1 g, 48 mmol) was added DCM (400 mL). The mixture was cooled to 0°C. Titanium tetrachloride (1M in DCM, 50 mL, 50 mmol) was added and stirred for 15 min. Diisopropylethylamine (9.4 mL, 53 mmol) was added and stirred for 40 min, followed by addition of N-methylpyrollidone (4.8 mL, 48 mmol). After stirring for 10 min, the mixture was cooled to -20°C. Trans-decenal (9.7 mL, 53 mmol) was added and the mixture stirred for 1.5 hours at -20°C. The reaction was quenched with an aqueous saturated solution of NH_4Cl. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel (10-20 % EtOAc:Hex) to provide the desired product in 83% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.17 (m, 3H), 7.14 – 7.04 (m, 2H), 5.65 (dtd, *J* = 15.1, 6.8, 1.3 Hz, 1H), 5.38 (ddt, *J* = 15.4, 6.3, 1.4 Hz, 1H), 4.60 (ddt, *J* = 9.4, 6.9, 3.4 Hz, 1H), 4.34 (ddd, *J* = 6.3, 3.7, 1.1 Hz, 1H), 3.77 (qd, *J* = 7.0, 3.7 Hz, 1H), 3.16 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.69 (dd, *J* = 13.4, 9.5 Hz, 1H), 1.94 (q, *J* = 7.0 Hz, 2H), 1.27 (t, *J* = 6.9 Hz, 2H), 1.16 (m, *J* = 3.2 Hz, 11H), 0.85 – 0.69 (m, 3H).

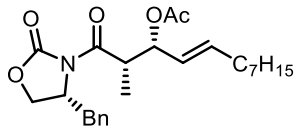
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 153.6, 135.5, 134.2, 129.9, 129.5, 129.2, 127.9, 73.3, 66.6, 55.7, 43.3, 38.3, 32.8, 32.3, 29.6 (3), 23.1, 14.6, 11.7.

HRMS: HRMS (EI) m/z calculated for $C_{23}H_{33}NO_4$ [M^+] 387.2410; found 387.2374

FTIR: 3499 (m), 2923 (s), 1775 (s), 1700 (s), 1208 (s)

$[\alpha_D]^{25}$: +76.6 (*c* 0.048, MeCN)

2.17



Name: (2S,3R,E)-1-((R)-4-benzyl-2-oxooxazolidin-3-yl)-2-methyl-1-oxododec-4-en-3-yl acetate

Procedure: To a round bottom flask containing **2.15** (11.43 g, 30 mmol) in 250 mL of DCM was added triethylamine (8.3 mL, 60 mmol), DMAP (183 mg, 1.5 mmol), and acetic anhydride (3.6 mL, 36 mmol). The mixture was stirred overnight and quenched with saturated $NaHCO_3$. The layers were separated and extracted with DCM three times. The combined organic layers were dried with magnesium sulfate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the acetylated product. (11.3 g, 26.4, 88%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.04 (m, 5H), 5.83 – 5.58 (m, 1H), 5.47 (ddd, *J* = 6.0, 4.8, 1.0 Hz, 1H), 5.35 (ddt, *J* = 15.4, 6.8, 1.5 Hz, 1H), 4.57 – 4.40 (m, 1H), 4.17 – 4.02 (m, 2H), 3.97 (qd, *J* = 6.9, 4.8 Hz, 1H), 3.17 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.66 (dd, *J* = 13.4, 9.7 Hz, 1H), 1.95 (s, 3H), 1.96 – 1.87 (m, 2H), 1.25 (t, *J* = 7.3 Hz, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.77 (t, *J* = 7.1 Hz, 3H).

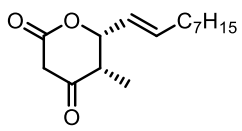
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 170.4, 153.7, 135.6, 135.5, 129.6, 129.1, 127.5, 125.6, 74.5, 66.4, 55.9, 42.1, 38.1, 32.4, 31.9, 29.3, 29.2, 29.1, 22.8, 21.2, 14.2, 11.4.

HRMS: HRMS (EI) m/z calculated for $C_{25}H_{35}NO_5$ [M^+] 429.25; found 429.2450

FTIR: 2922 (s), 1775 (s), 1699 (s), 1228 (s)

$[\alpha_D]^{25}$: +55.5 (*c* 0.020, MeCN)

2.18



Name: (5S,6R)-5-methyl-6-((E)-non-1-en-1-yl)dihydro-2H-pyran-2,4(3H)-dione

Procedure: In a round bottom flask, KHMDS (24g, 120 mmol) was dissolved in THF (300 mL), then cooled to -78ºC. The acetylated aldol adduct **2.17** (15.5g, 40 mmol) was dissolved in THF, and added slowly to the KHMDS solution. The solution was stirred for 20 min at -78ºC, upon which the reaction showed full conversion by TLC. The reaction was quenched by adding acetic acid (13.3 mL, 239 mmol), water and warmed to room temperature. The layers were separated, the aqueous layer checked by pH paper to ensure a pH of approximately 4, and the mixture was extracted with diethyl ether three times. The combined organic layers were dried with magnesium sulfate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10%-50% EtOAc:Hex) to yield the cyclized product **2.18**. (6.4 g, 25 mmol, 63%)

^{1}H NMR (400 MHz, C_6D_6) δ 5.54 (dtd, *J* = 15.2, 6.9, 1.4 Hz, 1H), 4.96 (ddt, *J* = 15.3, 6.4, 1.5 Hz, 1H), 4.24 (t, *J* = 5.3 Hz, 1H), 3.89 – 2.51 (m, 2H), 1.87 (qd, *J* = 7.1, 4.4 Hz, 1H), 1.80 – 1.66 (m, 2H), 1.39 – 1.05 (m, 10H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.70 (d, *J* = 7.1 Hz, 3H).

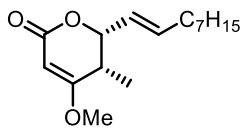
^{13}C NMR (101 MHz, C_6D_6) δ 201.7, 166.6, 137.4, 123.6, 78.8, 46.6, 45.8, 32.7, 32.4, 29.7, 29.6, 29.4, 23.3, 14.6, 9.7.

HRMS: HRMS (ESI) m/z calculated for $C_{15}H_{24}O_3$ [$M^+ + Na^+$] 275.1623; found 275.1632

FTIR: 2923 (s), 1653 (s), 1608 (s), 1211 (s)

$[\alpha_D]^{25}$: +29.8 (*c* 0.013, MeCN)

2.19



Name: (5S,6R)-4-methoxy-5-methyl-6-((E)-non-1-en-1-yl)-5,6-dihydro-2H-pyran-2-one

Procedure: In a dry round bottom flask , **2.18** (4.3 g, 17 mmol) was dissolved in acetone (85 mL). Potassium carbonate (4.7 g, 34 mmol) and dimethyl sulphate (1.8 mL, 18.7 mmol) were added [*the syringe and needle used for dimethyl sulphate was quenched with a saturated solution of aqueous sodium bicarbonate*]. The suspension was stirred at reflux for 3 hours. After cooling the suspension to room temperature, the reaction was quenched with water. After stirring for 15 min at room temperature, diethyl ether was added, and the phases separated. The aqueous phase was extracted three times. The combined organic layers were washed with brine, dried with magnesium sulfate, and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (20% EtOAc:Hex) to yield the methylated product **2.19**. (2.6 g, 9.9 mmol, 58%)

^{1}H NMR (400 MHz, C_6D_6) δ 5.73 (dtd, *J* = 15.3, 6.8, 1.4 Hz, 1H), 5.29 (ddt, *J* = 15.5, 6.1, 1.4 Hz, 1H), 4.95 (d, *J* = 1.1 Hz, 1H), 4.50 (ddt, *J* = 4.9, 2.6, 1.3 Hz, 1H), 3.06 – 2.67 (m, 3H), 1.99 – 1.84 (m, 3H), 1.37 – 1.14 (m, 12H), 1.06 – 0.83 (m, 6H).

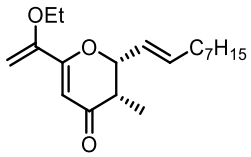
^{13}C NMR (101 MHz, C_6D_6) δ 177.0, 165.4, 135.0, 125.3, 90.2, 78.5, 55.2, 37.5, 32.7, 32.2, 29.6, 29.5, 29.3, 23.1, 14.4, 11.3.

HRMS: (ESI) m/z calculated for $C_{16}H_{26}O_3$ [M^++Na^+] 289.1792 ; found 289.1780

FTIR: 2922 (s), 1707 (s), 1619 (s), 1216 (s)

$[\alpha_D]^{25}$: -59.7 (*c* 0.020, DCM)

2.20



Name: (2R,3S)-6-(1-ethoxyvinyl)-3-methyl-2-((E)-non-1-en-1-yl)-2,3-dihydro-4H-pyran-4-one

Procedure: To a dry round bottom flask was added ethyl vinyl ether (7.1 mL. 75 mmol) and THF (40 mL). The solution was cooled to -78ºC. A solution of tBuLi (1.7 M in hexanes, 25 mL, 43 mmol) was added to the round bottom flask at -78ºC. The mixture was warmed to 0ºC and stirred until the suspended tBuLi dissolved and the color changed from yellow to nearly colour-less. The solution was cooled to -78ºC. The enol ether **2.19** (3.92 g, 15 mmol) dissolved in THF (20 mL) and added to the solution. After stirring at -78ºC for 30 min, the reaction was quenched with a saturated solution of aqueous ammonium chloride. After warming to room temperature, diethyl ether was added and the phases separated. The aqueous phase was extracted twice. The combined organic layers dried with magnesium sulfate and filtered. The dried organic layers were evaporated under reduced pressure and dissolved in acetonitrile (150 mL). A 4 mM solution of HCl (150 mL) was added and the mixture stirred overnight. After TLC indicated full conversion, diethyl ether was added, and the phases separated. The aqueous phase was extracted three times. The combined organic layers were washed with brine, dried with magnesium sulfate, and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the desired product. (2.3 g, 7.5 mmol, 58%)

^{1}H NMR (400 MHz, C_6D_6) δ 6.34 (s, 1H), 5.59 (dtd, *J* = 15.4, 6.6, 1.0 Hz, 1H), 5.51 – 5.31 (m, 1H), 5.18 (d, *J* = 2.2 Hz, 1H), 4.57 (ddd, *J* = 6.9, 3.9, 1.0 Hz, 1H), 4.14 (d, *J* = 2.2 Hz, 1H), 3.51 – 3.10 (m, 2H), 2.38 (qd, *J* = 7.3, 3.9 Hz, 1H), 1.84 (q, *J* = 6.7 Hz, 2H), 1.28 (t, *J* = 7.5 Hz, 1H), 1.24 – 1.14 (m, 8H), 1.03 (d, *J* = 7.3 Hz, 3H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H).

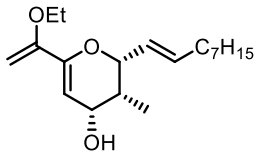
^{13}C NMR (101 MHz, C_6D_6) δ 195.6, 163.3, 154.0, 136.0, 124.0, 101.5, 88.1, 82.9, 63.4, 44.1, 32.4, 32.0, 29.2, 29.2, 29.0, 22.8, 14.1, 13.9, 9.7.

HRMS: HRMS (ESI) m/z calculated for C19H30O3 [$M^+ + Na^+$] 329.2093; found 329.2110

IR: 2923 (s), 1675 (s), 1232 (s)

$[\alpha_D]^{25}$: +71.5 (*c* 0.019, DCM)

2.11



Name: (2R,3R,4S)-6-(1-ethoxyvinyl)-3-methyl-2-((E)-non-1-en-1-yl)-3,4-dihydro-2H-pyran-4-ol

Procedure: The dienone **2.20** (2.28 g, 7.45 mmol, 1.0 eq) was dissolved in methanol and cooled to -50°C. Cerium trichloride heptahydrate (279 mg, 0.75 mmol, 0.1 eq) was added. Upon dissolution, sodium tetraborohydride (570 mg, 15 mmol, 2.0 eq) was added. The mixture was stirred for 1 hour, after which the solution was quenched with slow addition of NH_4Cl. The solution was stirred for 20 min and warmed to room temperature. Diethyl ether was added and the phases were separated. The aqueous phase was extracted three times, the organic phases combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The amorphous solid residue was purified by flash chromatography on silica gel using 10% EtOAc in hexanes to provide the desired product **2.11** (1.9 g, 0.21, 82% yield).

^{1}H NMR (400 MHz, C_6D_6): δ 5.76 (dtd, *J* = 15.0, 6.7, 1.4 Hz, 1H), 5.66 – 5.51 (m, 2H), 5.12 (d, *J* = 1.7 Hz, 1H), 4.41 – 4.34 (m, 1H), 4.34 – 4.25 (m, 1H), 4.14 (d, *J* = 1.7 Hz, 1H), 3.47 (q, *J* = 7.0 Hz, 2H), 1.95 (q, *J* = 7.0 Hz, 2H), 1.88 – 1.77 (m, 1H), 1.38 – 1.18 (m, 10H), 1.07 (t, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 2H), 0.90 (t, *J* = 7.0 Hz, 2H).

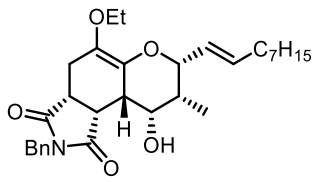
^{13}C NMR (101 MHz, C_6D_6) δ 155.3, 148.2, 133.0, 127.4, 101.2, 83.5, 78.9, 66.4, 63.1, 36.9, 32.8, 32.2, 29.6, 29.6, 29.5, 23.1, 14.5, 14.4, 7.5.

HRMS: HRMS (EI) m/z calculated for $C_{19}H_{32}O_3$ [M^+] 308.2351; found 308.2340

FTIR: 2924 (s), 1595 (s), 1105 (s)

$[\alpha_D]^{25}$: + 61.4 (*c* 0.0078, DCM)

2.26



Name: (3aR,7R,8R,9S,9aS,9bS)-5-ethoxy-9-hydroxy-8-methyl-7-((E)-non-1-en-1-yl)-3a,7,8,9,9a,9b-hexahydropyrano[3,2-e]isoindole-1,3(2H,4H)-dione

Procedure: Magnesium bromide diethyl etherate (206 mg, 0.8 mmol, 2.0 eq) was suspended in 2 mL of DCM. To the suspension DIPEA (0.36 mL, 2.0 mmol, 5.0 eq) was added to the suspension and stirred at room temperature for 30 min, upon which the suspension turned to a dark pink. N-benzylmaleimide (300 mg, 1.6 mmol, 4.0 eq) was added followed by addition of the hydroxy diene **2.11** (120 mg, 0.4 mmol, 1.0 eq) in 2 mL of DCM. The solution was stirred at room temperature for 30 min. The reaction was quenched with an aqueous saturated solution of NH_4Cl. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel using 1% MeOH in DCM to provide the desired product **2.26** (105 mg, 0.21 mmol, 53% yield).

^{1}H NMR (400 MHz, C_6D_6) δ 7.48 – 7.41 (m, 2H), 7.10 – 6.95 (m, 3H), 5.94 (ddt, *J* = 15.5, 8.5, 1.4 Hz, 1H), 5.53 (dtd, *J* = 15.2, 6.9, 0.9 Hz, 1H), 4.48 (d, *J* = 13.9 Hz, 1H), 4.43 (d, *J* = 14.0 Hz, 1H), 4.21 (dd, *J* = 8.5, 6.0 Hz, 1H), 4.05 (dq, *J* = 9.7, 7.0 Hz, 1H), 3.95 – 3.83 (m, 2H), 2.78 (ddd, *J* = 16.5, 3.7, 1.4 Hz, 1H), 2.69 (d, *J* = 5.9 Hz, 1H), 2.48 (t, *J* = 8.7 Hz, 1H), 2.42 – 2.33 (m, 1H), 2.26 (td, *J* = 8.8, 3.7 Hz, 1H), 2.14 (ddd, *J* = 16.5, 8.8, 1.6 Hz, 1H), 2.02 – 1.85 (m, 2H), 1.75 (ddd, *J* = 7.2, 6.1, 2.7 Hz, 1H), 1.42 – 1.19 (m, 15H), 1.16 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H), 0.72 (d, *J* = 7.2 Hz, 3H).

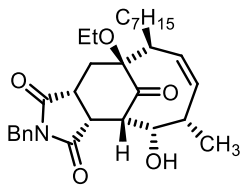
^{13}C NMR (101 MHz, C_6D_6) δ 178.2, 177.8, 136.3, 135.2, 133.5, 129.2, 129.1, 128.6, 128.1, 127.9, 81.7, 69.6, 66.3, 42.3, 41.2, 40.6, 39.1, 38.5, 32.4, 32.0, 29.6, 29.3, 29.2, 25.5, 23.0, 15.7, 14.1, 13.4.

HRMS: (ESI) m/z calculated for $C_{30}H_{41}NO_5$ [M^++Na^+] 518.2868; found 518.2882

IR: 2923 (s), 1689 (s), 1166 (s)

[α_D]^{25}: +33 (*c* 0.0041, DCM)

2.27



Name: (3aS,4S,5S,6S,10S,11aR,Z)-2-benzyl-10-ethoxy-9-heptyl-5-hydroxy-6-methyl-3a,4,5,6,9,10,11,11a-octahydro-1H-4,10-methanocyclodeca[c]pyrrole-1,3,12(2H)-trione

Procedure: To a microwave vial, **2.26** (90 mg, 0.18 mmol) was dissolved in acetonitrile (1.5 mL) and degassed with argon. The solution was stirred for 175ºC in a microwave reactor for 25 min. The solvent was removed in vacuo and the oily residue was purified by flash chromatography on silica gel using 1% MeOH in DCM to provide the desired product **2.27**. (54 mg, 85% yield).

^{1}H NMR (400 MHz, C_6D_6) δ 7.70 – 7.45 (m, 2H), 7.14 – 6.85 (m, 3H), 5.38 (ddd, *J* = 12.1, 8.8, 1.5 Hz, 1H), 4.97 (dd, *J* = 12.1, 6.1 Hz, 1H), 4.71 – 4.27 (m, 2H), 3.93 (d, *J* = 7.5 Hz, 1H), 3.39 (q, *J* = 6.9 Hz, 2H), 3.27 – 3.18 (m, 1H), 3.06 – 2.92 (m, 2H), 2.54 (t, *J* = 9.5 Hz, 1H), 2.40 – 2.24 (m, 2H), 2.04 (t, *J* = 6.9 Hz, 1H), 1.97 (q, *J* = 7.1 Hz, 2H), 1.62 – 1.51 (m, 1H), 1.34 – 1.27 (m, 8H), 1.23 (t, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 6.2 Hz, 4H), 0.51 (d, *J* = 7.2 Hz, 3H).

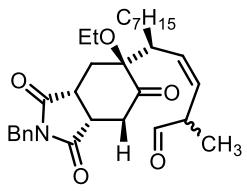
^{13}C NMR (101 MHz, C_6D_6) δ 209.3, 177.6, 176.5, 136.4, 132.7, 132.5, 129.3, 128.7, 128/0, 83.9, 70.3, 59.9, 54.2, 43.7, 42.4, 41.8, 37.3, 33.7, 32.1, 29.9, 29.5, 29.4, 28.5, 22.8, 16.0, 14.1.

HRMS: (ESI) m/z calculated for $C_{30}H_{41}NO_5$ [M^++Na^+] 518.2878; found 518.2882

IR: 2922 (s), 1690 (s), 1395 (s), 1169 (s)

$[\alpha_D]^{25}$: +5.2 (*c* 0.0050, DCM)

2.31



Name: (Z)-5-((3aR,5S,7aS)-2-benzyl-5-ethoxy-1,3,6-trioxooctahydro-1H-isoindol-5-yl)-2-methyldodec-3-enal

Procedure: In a round bottom flask **2.27** (10 mg, 0.02 mmol) was dissolved in 0.2 mL of isopropanol. The solution was stirred overnight. The solution was diluted with dichloromethane and extracted twice with 2 M HCl (eq). The organic phases were combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel using 20% EtOAc in DCM to provide the aldehyde product **2.31** (4.2 mg, 0.008 mmol, 42% yield).

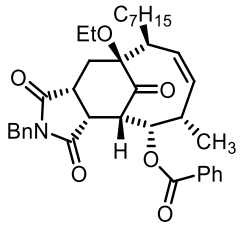
^{1}H NMR (600 MHz, C_6D_6) δ 9.30 (d, *J* = 1.6 Hz, 1H), 9.14 (d, *J* = 1.7 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 2H), 7.15 – 7.01 (m, 3H), 5.30 (t, *J* = 11.2 Hz, 1H), 5.28 (t, *J* = 11.2 Hz, 1H), 5.12 (t, *J* = 10.8 Hz, 1H), 5.04 (t, *J* = 10.9 Hz, 1H), 4.64 (d, *J* = 3.2 Hz, 2H), 4.62 (s, 2H), 3.19 (td, *J* = 10.6, 5.2 Hz, 1H), 3.15 (dd, *J* = 8.6, 7.0 Hz, 0H), 3.02 – 2.94 (m, 2H), 2.91 – 2.78 (m, 2H), 2.46 (dd, *J* = 17.7, 14.8 Hz, 1H), 2.25 – 2.17 (m, 1H), 2.17 – 2.07 (m, 1H), 1.86 – 1.73 (m, 1H), 1.36 – 1.15 (m, 12H), 0.94 (t, *J* = 7.0 Hz, 4H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 1H), 0.82 (t, *J* = 7.0 Hz, 1H), 0.79 (d, *J* = 6.8 Hz, 1H), 0.74 (t, *J* = 7.0 Hz, 2H).

^{13}C NMR (151 MHz, C_6D_6) δ 202.9, 202.7, 199.8, 199.5, 178.9, 178.9, 178.5, 178.5, 137.1, 137.1, 130.9, 130.6, 129.6, 129.6, 129.1, 129.0, 129.0, 129.0, 128.4, 128.4, 128.3, 128.2, 81.4, 81.4, 58.8, 58.5, 46.3, 46.1, 42.8 (2), 36.7, 36.7, 36.3, 36.2, 35.3, 35.3, 34.6, 32.3, 32.3, 31.4, 31.4, 30.1, 30.1, 29.7, 29.6, 28.5, 28.1, 28.0, 23.1, 23.1, 15.1, 14.7, 14.4, 14.4, 14.4, 14.2.

HRMS: (ESI) m/z calculated for $C_{30}H_{41}NO_5$ [M^++Na^+] 518.2882; found 518.2889

FTIR: 2924 (s), 1700, (s), 1397 (s)

2.32



Name: (3aS,4S,5S,6S,10S,11aR,Z)-2-benzyl-10-ethoxy-9-heptyl-6-methyl-1,3,12-trioxo-2,3,3a,4,5,6,9,10,11,11a-decahydro-1H-4,10-methanocyclodeca[c]pyrrol-5-yl benzoate

Procedure: Starting material **2.31** (54 mg, 0.1 mmol) was dissolved in DCM (2 mL). To the flask was added triethylamine (0.12 mL, 0.88 mmol), benzoyl chloride (0.05 ml, 0.44 mmol) and DMAP (20 mg, 0.02 mmol). The reaction was quenched with an aqueous saturated solution of NH_4Cl. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel using 1% MeOH in DCM to provide the desired product **2.32** (10 mg, 0.016 mmol, 17% yield).

^{1}H NMR (600 MHz, C_6D_6) δ 7.69 – 7.50 (m, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 7.08 – 7.00 (m, 1H), 6.92 (t, *J* = 7.8 Hz, 2H), 6.81 (d, *J* = 7.7 Hz, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 5.38 (m, 1H), 5.36 (m, 1H), 5.21 – 5.07 (m, 1H), 4.46 (d, *J* = 8.9 Hz, 1H), 4.31 (d, *J* = 14.9 Hz, 1H), 3.71 (m, 1H), 3.53 (m, 2H), 3.04 (s, 1H), 2.97 (m, 2H), 2.86 (d, *J* = 14.4 Hz, 1H), 2.46 (m, 1H), 2.04 (m, 1H), 1.99 – 1.92 (m, 1H), 1.62 (q, *J* = 12.9 Hz, 1H), 1.52 (m, 2H), 1.40 – 1.34 (m, 2H), 1.27 – 1.23 (m, 6H), 1.14 (d, *J* = 7.4 Hz, 3H), 0.92 – 0.77 (m, 3H).

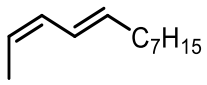
^{13}C NMR (151 MHz, C_6D_6) δ 208.0, 174.5 (2), 164.6, 133.5, 133.2, 130.8, 129.9, 129.2, 128.46, 128.4, 128.2, 127.3, 85.2, 60.2, 54.2, 46.0, 44.6, 38.2, 37.7, 37.7, 37.0, 32.3, 30.8, 30.7, 30.2, 29.9, 28.8, 28.7, 23.1, 21.05, 16.5, 14.4.

HRMS: (ESI) m/z calculated for $C_{37}H_{45}NO_6$ [M^++Na^+] 622.3145; found 622.3137

FTIR: 2925 (s), 1707 (s), 1175 (s)

$[\alpha_D]^{25}$: +6.8 (*c* 0.0044, DCM)

3.2



Name: (2Z,4E)-dodeca-2,4-diene

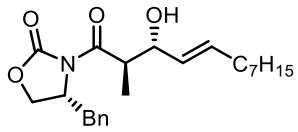
^{1}H NMR (400 MHz, C_6D_6) δ 6.46 (ddd, *J* = 15.1, 10.9, 1.3 Hz, 1H), 6.18 – 6.03 (m, 1H), 5.65 (dt, *J* = 14.6, 7.1 Hz, 1H), 5.37 (dd, *J* = 10.8, 7.0 Hz, 1H), 2.06 (q, *J* = 7.4 Hz, 2H), 1.64 (dd, *J* = 7.1, 1.8 Hz, 3H), 1.36 (m, 6H), 1.28 – 1.14 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ 134.7, 130.3, 126.1, 123.8, 33.3, 32.2, 30.2, 29.9, 29.6, 29.6, 23.1, 14.4.

HRMS (EI) m/z calculated for $C_{12}H_{22}$ [M^+] 166.1722; found 166.1714

IR: 1462 (s), 2850 (s), 2921 (s)

3.6



Name: (R)-4-benzyl-3-((2R,3R,E)-3-hydroxy-2-methyldodec-4-enoyl)oxazolidin-2-one

Procedure: To a round bottom flask was added magnesium chloride (1.26 g, 13.2 mmol), LiI (3.48 g, 26 mmol), (R)-4-benzyl-3-propionyloxazolidin-2-one (3 g, 12.9 mmol) and EtOAc (23 mL). After the exotherm subsided, triethylamine (9 mL, 66.0 mmol) was added. After the exotherm subsided, trimethylsilyl chloride (6.6 mL, 51.0 mmol). The mixture was stirred for 10 min at room temperature. Trans-decenal (7 mL, 38.4 mmol) dissolved in EtOAc (23 mL) was added via syringe pump over 3 hours, and stirred for an additional hour. The mixture was then filtered through cotton then through a silica plug. The solvent was evaporated in vacuo. The residue was dissolved in MeOH (120 mL) after which para-toluene sulfonic acid hydrate (750 mg) was added. After 20 min, the solvent was removed in vacuo and the residue purified by flash chromatography (20% EtOAc:Hex) to yield the desired product **3.6** (3g, 55% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 3H), 7.25 – 7.19 (m, 2H), 5.75 (dt, *J* = 14.3, 6.8 Hz, 1H), 5.50 (dd, *J* = 15.3, 7.3 Hz, 1H), 4.73 – 4.63 (m, 1H), 4.36 – 4.09 (m, 3H), 3.94 (p, *J* = 7.1 Hz, 1H), 3.29 (dt, *J* = 13.6, 2.8 Hz, 1H), 2.76 (ddd, *J* = 13.6, 9.4, 1.6 Hz, 1H), 2.05 (td, *J* = 8.5, 4.2 Hz, 2H), 1.37 (q, *J* = 7.6 Hz, 2H), 1.27 (dt, *J* = 14.7, 8.0 Hz, 9H), 1.16 (dd, *J* = 7.0, 1.7 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H).

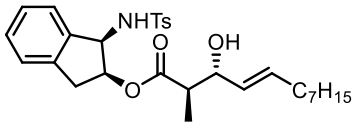
^{13}C NMR (151 MHz, $CDCl_3$) δ 176.5, 153.6, 135.4, 134.6, 130.2, 129.6, 129.0, 127.4, 76.0, 75.9, 66.1, 55.6, 43.4, 37.9, 32.3, 31.9, 29.2, 29.2, 29.2, 22.7, 14.6, 14.6, 14.2.

FTIR: 3509 (w), 2923 (s), 1777 (s), 1696 (s), 1383 (s)

HRMS: HRMS (ESI) m/z calculated for $C_{23}H_{33}NO_4$ [M^++Na^+] 410.2307; found 387.2299

$[\alpha_D]^{25}$: +10 (*c* 0.032, DCM)

3.8



Name: (1R,2S)-1-((4-methylphenyl)sulfonamido)-2,3-dihydro-1H-inden-2-yl (2R,3R,E)-3-hydroxy-2-methyldodec-4-enoate

Procedure: To a round bottom flask containing **3.7** (7.6 g, 21 mmol) was added DCM (300 mL). The mixture was cooled to 0°C. Titanium tetrachloride (1M in DCM, 24 mL, 24 mmol) was added and stirred for 5 min. Diisopropylethylamine (11 mL, 63 mmol) was added and stirred for 20 min. In a separate flask, the trans-decenal (7.6 mL, 42 mmol) was dissolved in DCM (400 mL) and the solution cooled to -78°C. To this cooled solution was added $TiCl_4$ (1M in DCM, 46 mL, 46 mmol). After stirring for 5 min, acetonitrile (2.5 mL, 46 mmol) was added. After stirring for 5 min, the enolate solution is added over 15 min. The solution is further stirred for 2 hours at -78°C. The reaction was quenched with an aqueous saturated solution of NH_4Cl. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel (10-20 % EtOAc:Hex) to provide the desired product **3.8** (8.2 g, 76% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.48 – 7.40 (m, 1H), 7.36 – 7.30 (m, 2H), 7.27 (d, *J* = 1.9 Hz, 1H), 7.20 – 7.13 (m, 1H), 6.39 (d, *J* = 9.5 Hz, 1H), 5.90 – 5.52 (m, 1H), 5.50 – 5.19 (m, 2H), 4.84 (dd, *J* = 9.2, 5.1 Hz, 1H), 4.00 (t, *J* = 8.5 Hz, 1H), 3.08 (dd, *J* = 17.2, 5.0 Hz, 1H), 2.86 (d, *J* = 17.1 Hz, 1H), 2.54 – 2.34 (m, 5H), 2.00 (q, *J* = 7.1 Hz, 2H), 1.36 – 1.20 (m, 10H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.94 – 0.81 (m, 3H).

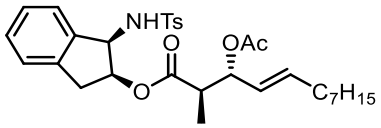
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 143.6, 140.5, 138.5, 137.8, 136.7, 129.9, 129.3, 128.5, 127.5, 127.4, 124.9, 124.9, 75.4, 74.6, 59.9, 46.7, 37.4, 32.3, 31.9, 29.2, 29.2, 29.1, 22.8, 21.7, 14.4, 14.2.

HRMS: (ESI) m/z calculated for $C_{29}H_{39}NO_5S$ [M^++Na^+] 536.2455; found 536.2447

FTIR: 3266 (m), 1734 (s), 1156 (s)

$[\alpha_D]^{25}$: +6.6 (*c* 0.013, DCM)

3.9



Name: (1R,2S)-1-((4-methylphenyl)sulfonamido)-2,3-dihydro-1H-inden-2-yl (2R,3R,E)-3-acetoxy-2-methyldodec-4-enoate

Procedure: To a round bottom flask containing **3.8** (7.1 g, 13.5 mmol) in 65 mL of DCM was added triethylamine (2.3 mL, 16 mmol), DMAP (165 mg, 1.35 mmol), and acetic anhydride (1.5 mL, 16 mmol). The mixture was stirred overnight and quenched with saturated $NaHCO_3$. The layers were separated and extracted with DCM three times. The combined organic layers were dried with magnesium sulfate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the acetylated product **3.9**. (10.9 g, 81%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 1.6 Hz, 3H), 7.18 – 7.12 (m, 1H), 5.65 (dt, *J* = 13.7, 6.8 Hz, 1H), 5.29 – 5.09 (m, 3H), 4.99 (dd, *J* = 10.2, 5.1 Hz, 1H), 3.08 (dd, *J* = 17.3, 4.8 Hz, 1H), 2.83 (d, *J* = 17.2 Hz, 1H), 2.57 (t, *J* = 7.3 Hz, 1H), 2.45 (s, 3H), 1.94 (q, *J* = 7.1 Hz, 2H), 1.91 (s, 3H), 1.56 (s, 3H), 1.24 (s, 10H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H).

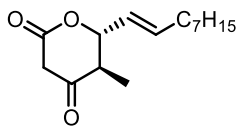
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 170.1, 143.9, 139.9, 138.6, 138.1, 137.9, 130.0, 128.7, 127.6, 127.2, 125.0, 124.9, 124.4, 76.0, 75.9, 59.7, 43.9, 37.6, 32.3, 31.9, 29.2(2), 28.9, 22.8, 21.7, 21.2, 14.2, 13.3.

HRMS: (ESI) m/z calculated for $C_{31}H_{41}NO_6S$ [M^++Na^+] 578.2535; found 578.2552

$[\alpha_D]^{25}$: +42.7 (*c* 0.043, DCM)

FTIR: 3275 (s), 2924 (s), 1734 (s), 1157 (s)

3.10



Name: (5R,6R)-5-methyl-6-((E)-non-1-en-1-yl)dihydro-2H-pyran-2,4(3H)-dione

Procedure: In a round bottom flask, the acetylated aldol adduct **3.9** (15.0 g, 27 mmol) was dissolved in THF. The solution was cooled to -20ºC. To this solution LiHMDS was added (86 mL, 86 mmol). The reaction was quenched by adding acetic acid (9.2 mL, 161 mmol), water and warmed to room temperature. The layers were separated, the aqueous layer checked by pH paper to ensure a pH of approximately 4, and the mixture was extracted with diethyl ether three times. The combined organic layers were dried with magnesium sulfate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10%-50% EtOAc:Hex) to yield the cyclized product **3.10**. (5.3 g, 21 mmol, 78%)

^{1}H NMR (400 MHz, C_6D_6) δ 5.49 (dt, *J* = 14.5, 6.9 Hz, 1H), 5.08 (ddd, *J* = 15.3, 7.8, 1.7 Hz, 1H), 3.94 – 3.60 (m, 1H), 3.22 – 2.92 (m, 1H), 2.90 – 2.58 (m, 1H), 1.92 – 1.81 (m, 2H), 1.64 – 1.50 (m, 1H), 1.34 – 1.13 (m, 10H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.69 (dd, *J* = 7.1, 1.6 Hz, 3H).

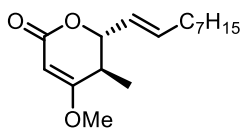
^{13}C NMR (151 MHz, C_6D_6) δ 201.3, 165.9, 137.5, 125.9, 80.9, 46.6, 45.9, 32.4, 32.2, 29.5, 29.5, 29.2, 23.1, 14.3, 10.9.

HRMS: (ESI) m/z calculated for $C_{15}H_{24}O_3$ [M^++Na^+] 275.1629; found 275.1623

FTIR: 2922 (s), 1725 (s), 1263 (s)

$[\alpha_D]^{25}$: -19.2 (*c* 0.032, DCM)

3.11



Name: (5R,6R)-4-methoxy-5-methyl-6-((E)-non-1-en-1-yl)-5,6-dihydro-2H-pyran-2-one

Procedure: In a dry round bottom flask , **3.10** (1.3 g, 5 mmol) was dissolved in acetone (25 mL). Potassium carbonate (1.4 g, 10 mmol) and dimethyl sulphate (0.52 mL, 5.5 mmol) were added [*the syringe and needle used for dimethyl sulphate was quenched with a saturated solution of aqueous sodium bicarbonate*]. The suspension was stirred at reflux for 3 hours. After cooling the suspension to room temperature, the reaction was quenched with water. After stirring for 15 min at room temperature, diethyl ether was added, and the phases separated. The aqueous phase was extracted three times. The combined organic layers were washed with brine, dried with magnesium sulfate, and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (20% EtOAc:Hex) to yield the methylated product **3.11**. (1 g, 3.5 mmol, 70%)

^{1}H NMR (300 MHz, C_6D_6) δ 5.64 (dtd, *J* = 15.4, 6.8, 1.0 Hz, 1H), 5.36 (ddt, *J* = 15.4, 7.1, 1.4 Hz, 1H), 5.02 (d, *J* = 1.0 Hz, 1H), 4.64 – 3.87 (m, 1H), 3.33 – 2.73 (m, 3H), 2.11 (tt, *J* = 7.5, 6.5 Hz, 1H), 1.99 – 1.72 (m, 2H), 1.47 – 1.10 (m, 10H), 0.94 – 0.84 (m, 6H).

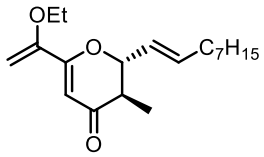
^{13}C NMR (151 MHz, C_6D_6) δ 174.2, 165.0, 136.3, 127.5, 90.8, 81.9, 55.3, 37.1, 32.6, 32.2, 29.5, 29.5, 29.3, 23.1, 14.4, 13.7.

HRMS: (ESI) m/z calculated for $C_{16}H_{26}O_3$ [M^++Na^+]289.1799; found 289.1780

$[\alpha_D]^{25}$: +18.6 (*c* 0.0078, DCM)

FTIR: 2923 (s), 1706 (s), 1219 (s)

3.13



Name: (2R,3R)-6-(1-ethoxyvinyl)-3-methyl-2-((E)-non-1-en-1-yl)-2,3-dihydro-4H-pyran-4-one

Procedure: To a dry round bottom flask was added ethyl vinyl ether (1.8 mL. 18 mmol) and THF (7 mL). The solution was cooled to -78ºC. A solution of tBuLi (1.7 M in hexanes, 6.2 mL, 10.5 mmol) was added to the round bottom flask at -78ºC. The mixture was warmed to 0ºC and stirred until the suspended tBuLi dissolved and the color changed from yellow to nearly colour-less. The solution was cooled to -78ºC. Enol ether **3.11** (1 g, 3.5 mmol) dissolved in THF (7 mL) and added to the solution. After stirring at -78ºC for 30 min, the reaction was quenched with a saturated solution of aqueous ammonium chloride. After warming to room temperature, diethyl ether was added and the phases separated. The aqueous phase was extracted twice. The combined organic layers dried with magnesium sulfate and filtered. The dried organic layers were evaporated under reduced pressure and dissolved in acetonitrile (35 mL). A 4 mM solution of HCl (35 mL) was added and the mixture stirred overnight. After TLC indicated full conversion, diethyl ether was added, and the phases separated. The aqueous phase was extracted three times. The combined organic layers were washed with brine, dried with magnesium sulfate, and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the desired product **3.13**. (650 mg, 2.11 mmol, 65%)

^{1}H NMR (300 MHz, C_6D_6) δ 6.37 (s, 1H), 5.53 (dt, *J* = 15.4, 6.5 Hz, 1H), 5.38 (ddt, *J* = 15.3, 7.8, 1.2 Hz, 1H), 5.17 (d, *J* = 2.2 Hz, 1H), 4.22 – 4.09 (m, 2H), 3.31 (q, *J* = 7.0 Hz, 2H), 2.23 (dq, *J* = 12.0, 7.0 Hz, 1H), 1.87 (q, *J* = 7.0 Hz, 2H), 1.36 – 1.14 (m, 10H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 6.9 Hz, 3H).

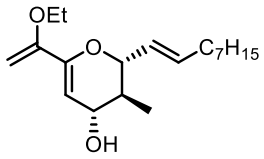
^{13}C NMR (151 MHz, C_6D_6) δ 194.2, 164.0, 154.3, 137.3, 127.2, 102.2, 88.3, 86.0, 63.6, 44.1, 32.5, 32.2, 29.5, 29.4, 29.2, 23.1, 14.4, 14.2, 11.0.

HRMS: (ESI) m/z calculated for $C_{19}H_{30}O_3$ [M^++Na^+] 329.2106; found 329.2093

$[\alpha_D]^{25}$: +13.7 (*c* 0.014, DCM)

FTIR: 2922 (s), 1680 (s), 1246 (s)

3.5



Name: (2R,3S,4S)-6-(1-ethoxyvinyl)-3-methyl-2-((E)-non-1-en-1-yl)-3,4-dihydro-2H-pyran-4-ol

Procedure: Dienone **3.13** (650 g, 2.11 mmol, 1.0 eq) was dissolved in methanol and cooled to -50°C. Cerium trichloride heptahydrate (74 mg, 0.2 mmol, 0.1 eq) was added. Upon dissolution, sodium tetraborohydride (160 mg, 4.22 mmol, 2.0 eq) was added. The mixture was stirred for 1 hour, after which the solution was quenched with slow addition of NH_4Cl. The solution was stirred for 20 min and warmed to room temperature. Diethyl ether was added and the phases were separated. The aqueous phase was extracted three times, the organic phases combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The amorphous solid residue was purified by flash chromatography on silica gel using 10% EtOAc in hexanes to provide the desired product (500 mg, 1.62, 77% yield).

^{1}H NMR (300 MHz, C_6D_6) δ 5.69 (d, *J* = 2.7 Hz, 1H), 5.64 (dt, *J* = 15.4, 6.6 Hz, 1H), 5.51 (ddt, *J* = 15.4, 7.5, 1.1 Hz, 1H), 5.11 (d, *J* = 1.7 Hz, 1H), 4.14 (d, *J* = 1.8 Hz, 1H), 3.94 (dd, *J* = 9.8, 7.5 Hz, 1H), 3.85 (td, *J* = 8.2, 2.7 Hz, 1H), 3.48 (q, *J* = 7.0 Hz, 2H), 1.95 (q, *J* = 6.8 Hz, 2H), 1.55 (ddd, *J* = 9.7, 8.1, 6.7 Hz, 1H), 1.40 – 1.15 (m, 10H), 1.08 (td, *J* = 7.0, 1.4 Hz, 3H), 0.97 – 0.81 (m, 6H).

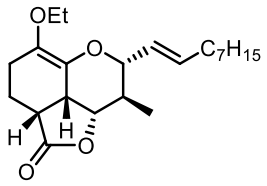
^{13}C NMR (151 MHz, C_6D_6) δ 155.4, 148.8, 135.2, 128.7, 102.2, 83.6, 81.9, 70.0, 63.1, 40.9, 32.6, 32.2, 29.5, 29.5, 29.4, 23.1, 14.9, 14.5, 14.4.

HRMS: (ESI) m/z calculated for $C_{19}H_{32}O_3$ [M^++Na^+] 331.2269; found 331.2249

FTIR: 3445 (m), 2924 (s), 1734 (s), 1070 (s)

$[\alpha_D]^{25}$: +18.6 (*c* 0.0086, DCM)

3.22



Name: (2R,3R,3aS,3a1S,5aR)-8-ethoxy-3-methyl-2-((E)-non-1-en-1-yl)-3,3a,3a1,5a,6,7-hexahydrofuro[2,3,4-de]chromen-5(2H)-one

Procedure: Magnesium bromide diethyl etherate (619 mg, 2.4 mmol, 2.0 eq) was suspended in 6 mL of DCM. DIPEA (1.25 mL, 6.0 mmol, 5.0 eq) was added to the suspension and stirred at room temperature for 30 min, upon which the suspension turned to a dark pink. Trifluoroethylacrylate (1.2 mL, 9.6 mmol, 8.0 eq) was added followed by addition of **3.5** (370 mg, 1.2 mmol, 1.0 eq) in 6 mL of DCM. The solution was stirred at room temperature for 2 hours. The reaction was quenched with an aqueous saturated solution of NH_4Cl. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel using 20% EtOAc:Hex to provide the desired product **3.22** (764 mg, 2.1 mmol, 88% yield).

^{1}H NMR (600 MHz, C_6D_6) δ 5.64 (dtd, *J* = 15.3, 6.8, 0.8 Hz, 1H), 5.31 (ddt, *J* = 15.3, 8.1, 1.5 Hz, 1H), 3.96 (dq, *J* = 9.7, 7.0 Hz, 1H), 3.80 (dq, *J* = 9.7, 7.0 Hz, 1H), 3.74 (ddd, *J* = 10.6, 8.1, 0.8 Hz, 1H), 3.51 (dd, *J* = 7.3, 6.2 Hz, 1H), 2.50 (dddd, *J* = 7.9, 6.2, 3.3, 1.6 Hz, 1H), 2.41 (dddd, *J* = 16.6, 11.9, 6.3, 3.3 Hz, 1H), 2.21 (ddd, *J* = 7.8, 4.8, 2.9 Hz, 1H), 2.07 (dddd, *J* = 13.4, 6.1, 3.1, 1.4 Hz, 1H), 1.95 (dtdd, *J* = 14.3, 7.1, 4.9, 1.6 Hz, 3H), 1.64 (dp, *J* = 10.5, 7.0 Hz, 1H), 1.35 – 1.26 (m, 4H), 1.23 (td, *J* = 5.0, 3.0 Hz, 6H), 1.14 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H).

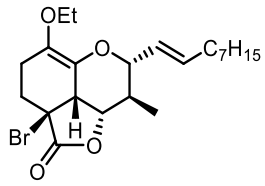
^{13}C NMR (151 MHz, C_6D_6) δ 175.8, 135.7, 135.7, 129.8, 128.5, 81.6, 78.9, 65.6, 40.4, 38.9, 36.8, 32.5, 32.2, 29.5, 29.5 (2), 23.5, 23.1, 19.8, 16.2, 16.0, 14.4.

HRMS: (ESI) m/z calculated for $C_{22}H_{34}O_4$ [M^++Na^+] 385.2327; found 385.2355

$[\alpha_D]^{25}$: -18.4 (*c* 0.0074, DCM)

FTIR: 2925 (s), 1756 (s), 1167 (s)

3.31



Name: (2R,3R,3aS,3a1S,5aS)-5a-bromo-8-ethoxy-3-methyl-2-((E)-non-1-en-1-yl)-3,3a,3a1,5a,6,7-hexahydrofuro[2,3,4-de]chromen-5(2H)-one

Procedure: Magnesium bromide diethyl etherate (52 mg, 0.2 mmol, 2.0 eq) was suspended in 1 mL of DCM. DIPEA (0.1 mL, 0.5 mmol, 5.0 eq) was added to the suspension and stirred at room temperature for 30 min, upon which the suspension turned to a dark pink. Methyl 2-bromoacrylate (66 mg, 0.4 mmol, 4.0 eq) was added followed by addition of **3.5** (30 mg, 1.2 mmol, 1.0 eq) in 0.2 mL of DCM. The solution was stirred at room temperature for 2 hours. The reaction was quenched with an aqueous saturated solution of NH_4Cl. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel using 10% EtOAc:Hex to provide the desired product **3.31** (29 mg, 0.065 mmol, 65% yield).

^{1}H NMR (600 MHz, C_6D_6) δ 5.58 (dt, *J* = 15.4, 6.9 Hz, 1H), 5.21 (ddt, *J* = 15.3, 8.2, 1.5 Hz, 1H), 4.20 (dd, *J* = 7.0, 5.5 Hz, 1H), 3.84 (dq, *J* = 9.7, 7.0 Hz, 1H), 3.70 (dq, *J* = 9.7, 7.0 Hz, 1H), 3.57 (dd, *J* = 10.3, 8.1 Hz, 1H), 3.04 (ddd, *J* = 5.1, 3.4, 1.2 Hz, 1H), 2.55 (ddd, *J* = 13.0, 6.3, 1.4 Hz, 1H), 2.29 (dddd, *J* = 16.6, 11.6, 6.3, 3.4 Hz, 1H), 1.99 – 1.88 (m, 3H), 1.83 (ddt, *J* = 16.7, 6.8, 1.3 Hz, 1H), 1.59 (dp, *J* = 10.3, 7.0 Hz, 1H), 1.32 – 1.16 (m, 10H), 1.08 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.68 (d, *J* = 6.9 Hz, 3H).

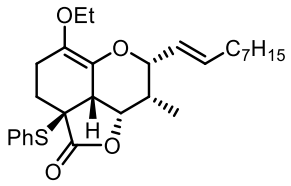
^{13}C NMR (151 MHz, C_6D_6) δ 171.9, 136.2, 135.1, 128.4, 128.2, 81.1, 78.9, 65.6, 56.1, 46.9, 39.9, 32.5, 32.2, 31.4, 29.5, 29.5, 29.4, 24.7, 23.1, 15.9, 15.8, 14.4.

HRMS: (EI) m/z calculated for $C_{22}H_{33}BrO_4$ [M^+] 440.1562; found 440.1540

$[\alpha_D]^{25}$: -59.5 (*c* 0.0026, DCM)

FTIR: 2925 (s), 1671 (s), 1268 (s)

3.37



Name: (2R,3S,3aS,3a1S,5aS)-8-ethoxy-3-methyl-2-((E)-non-1-en-1-yl)-5a-(phenylthio)-3,3a,3a1,5a,6,7-hexahydrofuro[2,3,4-de]chromen-5(2H)-one

Procedure: Magnesium bromide diethyl etherate (104 mg, 0.4 mmol, 2.0 eq) was suspended in 1.6 mL of DCM. DIPEA (0.2 mL, 1.0 mmol, 5.0 eq) was added to the suspension and stirred at room temperature for 30 min, upon which the suspension turned to a dark pink. Methyl 2-thiophenyl acrylate (155 mg, 0.8 mmol, 4.0 eq) was added followed by addition of **3.5** (60 mg, 0.2 mmol, 1.0 eq) in 0.4 mL of DCM. The solution was stirred at room temperature for 2 hours. The reaction was quenched with an aqueous saturated solution of NH_4Cl. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel using 10% EtOAc:Hex to provide the desired product **3.37** (63 mg, 0.13 mmol, 67% yield).

^{1}H NMR (600 MHz, C_6D_6) δ 7.64 – 7.54 (m, 2H), 7.10 – 6.98 (m, 3H), 5.60 (dt, *J* = 15.1, 6.8 Hz, 1H), 5.26 (ddt, *J* = 15.2, 8.1, 1.5 Hz, 1H), 4.36 (dd, *J* = 7.6, 6.0 Hz, 1H), 3.94 (dq, *J* = 9.7, 7.0 Hz, 1H), 3.75 (dq, *J* = 9.7, 7.0 Hz, 1H), 3.67 (dd, *J* = 10.7, 8.1 Hz, 1H), 2.96 (ddd, *J* = 6.0, 3.2, 1.3 Hz, 1H), 2.31 – 2.19 (m, 1H), 2.16 (ddd, *J* = 13.2, 6.0, 1.5 Hz, 1H), 1.97 – 1.86 (m, 3H), 1.77 – 1.64 (m, 2H), 1.35 – 1.26 (m, 4H), 1.25 – 1.21 (m, 6H), 1.11 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H).

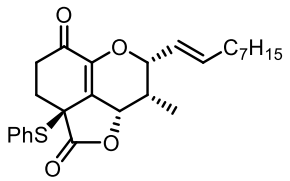
^{13}C NMR (151 MHz, C_6D_6) δ 173.1, 137.8, 136.0, 135.8, 130.3, 129.2, 129.2, 128.9, 128.2, 80.8, 79.0, 65.7, 53.2, 44.1, 40.3, 32.5, 32.2, 29.5, 29.5, 29.4, 28.1, 24.3, 23.1, 16.0 (2), 14.4.

HRMS: (ESI) m/z calculated for $C_{28}H_{38}O_4S$ [M^++Na^+] 493.2389; found 493.2383

FTIR: 2921 (s), 2851 (s), 1773 (s), 1700 (s), 1182 (s)

$[\alpha_D]^{25}$: +67 (*c* 0.00063, DCM)

3.36



Name: (2R,3S,3aS,5aS)-3-methyl-2-((E)-non-1-en-1-yl)-5a-(phenylthio)-3,3a,6,7-tetrahydrofuro[2,3,4-de]chromene-5,8(2H,5aH)-dione

Procedure: In a round bottom flask was dissolved **3.37** (4 mg, 0.0085 mmol) in THF (0.1 mL). A solution of HCl (1M, 0.1 mL) was added and the mixture stirred for 3 hours. The mixture was diluted with water and diethyl ether. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel using 10% EtOAc:Hex to provide the desired product **3.36** (1.6 mg, 0.0037 mmol, 44% yield).

^{1}H NMR (600 MHz, C_6D_6) δ 7.69 – 7.43 (m, 2H), 7.04 – 6.96 (m, 4H), 5.57 (dt, *J* = 15.5, 6.8 Hz, 1H), 5.22 (ddt, *J* = 15.3, 8.3, 1.5 Hz, 1H), 4.17 (d, *J* = 9.3 Hz, 1H), 3.44 (dd, *J* = 10.8, 8.3 Hz, 1H), 2.88 (ddd, *J* = 16.7, 14.2, 4.5 Hz, 1H), 2.11 (ddd, *J* = 16.7, 3.9, 2.5 Hz, 1H), 1.95 – 1.85 (m, 2H), 1.51 (td, *J* = 14.4, 3.9 Hz, 1H), 1.35 – 1.15 (m, 17H), 0.92 (t, *J* = 7.2 Hz, 4H), 0.71 (d, *J* = 6.6 Hz, 3H).

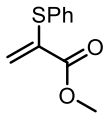
^{13}C NMR (151 MHz, C_6D_6) δ 189.5, 172.1, 144.7, 138.1, 137.6, 130.4, 129.8, 129.3, 125.8, 123.9, 80.7, 77.8, 53.3, 36.7, 34.3, 32.6, 32.2, 29.5 (2), 29.2, 29.1, 23.1, 14.6, 14.4.

HRMS: HRMS (ESI) m/z calculated for $C_{26}H_{32}O_4S$ [$M^+ + Na^+$] 463.1919; found 463.1916

FTIR: 2923 (s), 2851 (s), 1777 (s), 1699 (s), 1130 (s)

$[\alpha_D]^{25}$: +91 (*c* 0.0019, DCM)

3.22



Name: Methyl 2-(phenylthio)acrylate

Procedure: In a round bottom flask, methyl 2-bromoacrylate (3.3 g, 20 mmol) was dissolved in DCM (60 mL). Thiophenol (2.6 g, 24 mmol) was subsequently dissolved followed by DBU (3.6 mL, 24 mmol). The mixture stirred for 36 hours. The reaction was quenched with an aqueous saturated solution of NH_4Cl. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel using 5% EtOAc:Hex to provide the desired product **3.22** (63 mg, 11 mmol, 55% yield).

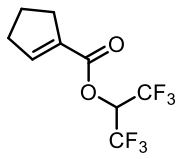
^{1}H NMR (400 MHz, CDCl3) δ 7.62 – 7.46 (m, 2H), 7.44 – 7.34 (m, 3H), 6.33 (d, J = 0.5 Hz, 1H), 5.23 (d, J = 0.5 Hz, 1H), 3.81 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.9, 138.8, 134.5, 131.3, 129.8, 129.1, 122.8, 52.9.

HRMS: (EI) m/z calculated for $C_{10}H_{10}O_2S$ [M^+] 194.0402; found 194.0394

Matches literature data

3.18



Name: 1,1,1,3,3,3-hexafluoropropan-2-yl cyclopent-1-ene-1-carboxylate

Procedure: To a round bottom flask was added cyclopent-1-ene-1-carboxylic acid (112 mg, 1 mmol), DMAP (36 mg, 0.3 mmol), EDC (192 mg, 1 mmol), DCM (2 mL) and hexafluoroisopropanol (1 mL). The solution was stirred at room temperature for 3 hours. Water was added and the phases separated. The aqueous phase was extracted twice. The organic phases were combined, dried with magnesium sulphate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (5% EtOAc:Hex) to yield the desired product **3.18** (157 mg, 0.60 mmol, 60%). *(caution: Product is very volatile*).

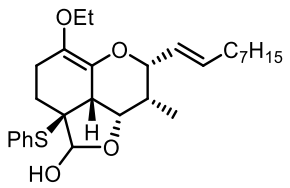
^{1}H NMR (600 MHz, C_6D_6) δ 6.55 (ddd, *J* = 4.6, 2.6, 1.9 Hz, 1H), 5.82 (p, *J* = 6.2 Hz, 1H), 2.35 – 2.17 (m, 2H), 1.83 (tq, *J* = 7.8, 2.7 Hz, 2H), 1.37 (p, *J* = 7.7 Hz, 2H).

^{13}C NMR (151 MHz, C_6D_6) δ 161.0, 149.5, 133.3, 124.5 – 117.6 (m), 66.6 (dt, *J* = 68.9, 34.4 Hz), 33.7, 31.2, 22.7.

FTIR: 1745 (s), 1193 (s), 1096 (s)

HRMS: HRMS (EI) m/z calculated for $C_9H_8F_6O_2$ [M^+] 262.0428; found 262.0400

3.38



Name : (2R,3S,3aS,3a1S,5aS)-8-ethoxy-3-methyl-2-((E)-non-1-en-1-yl)-5a-(phenylthio)-2,3,3a,3a1,5,5a,6,7-octahydrofuro[2,3,4-de]chromen-5-ol

Procedure: In a round bottom flask was dissolved **3.37** (10 mg, 0.021 mmol) and cooled to -78ºC. To this solution was added DIBAL (1.5 M, 0.07 mL, 0.1 mmol) and stirred further at -78ºC for 2 hours. Acetone (1 mL) was added to quench the reaction. The mixture was warmed to 0ºC, followed by the addition of Rochelle salt. The mixture was warmed to room temperature and left to stir until two phases could be separated. The aqueous phase was extracted twice. The organic phases were combined, dried with magnesium sulphate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the desired product **3.38** (6 mg, 0.0126 mmol, 60%).

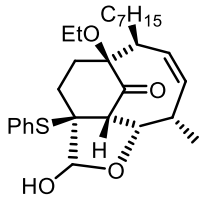
^{1}H NMR (600 MHz, C_6D_6) δ 7.54 – 7.48 (m, 2H), 6.98 – 6.90 (m, 3H), 5.64 (dt, *J* = 15.5, 6.7 Hz, 1H), 5.40 (ddt, *J* = 15.2, 7.9, 1.5 Hz, 1H), 5.06 (d, *J* = 6.2 Hz, 1H), 4.20 (d, *J* = 6.1 Hz, 1H (OH)), 4.21 – 4.13 (m, 1H), 4.06 – 4.01 (m, 1H), 3.85 (dd, *J* = 9.7, 8.3 Hz, 1H), 3.71 (dd, *J* = 10.8, 8.2 Hz, 1H), 2.75 (ddd, *J* = 8.5, 2.9, 1.4 Hz, 1H), 2.60 (dddd, *J* = 16.1, 10.0, 4.7, 2.7 Hz, 1H), 2.04 – 1.89 (m, 3H), 1.88 – 1.77 (m, 1H), 1.61 – 1.44 (m, 2H), 1.35 – 1.26 (m, 4H), 1.24 – 1.21 (m, 6H), 0.94 (d, *J* = 6.6 Hz, 2H), 0.90 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ 137.5, 136.2, 136.1, 135.2, 129.3, 129.3, 129.2, 129.2, 100.9, 80.8, 80.4, 66.5, 64.4, 45.5, 39.3, 32.6, 32.2, 29.6, 29.5, 29.5, 29.3, 24.8, 23.1, 16.2, 15.2, 14.4.

HRMS: (ESI) m/z calculated for $C_{28}H_{40}O_4S$ [M^++Na^+] 495.2538; found 495.2538

FTIR: 3415 (m), 2923 (s), 1093 (s)

3.39



Name: (2R,3S,3aS,5S,9S,9aS,Z)-5-ethoxy-6-heptyl-2-hydroxy-9-methyl-3-(phenylthio)-3,3a,5,6,9,9a-hexahydro-3,5-ethanocycloocta[b]furan-4(2H)-one

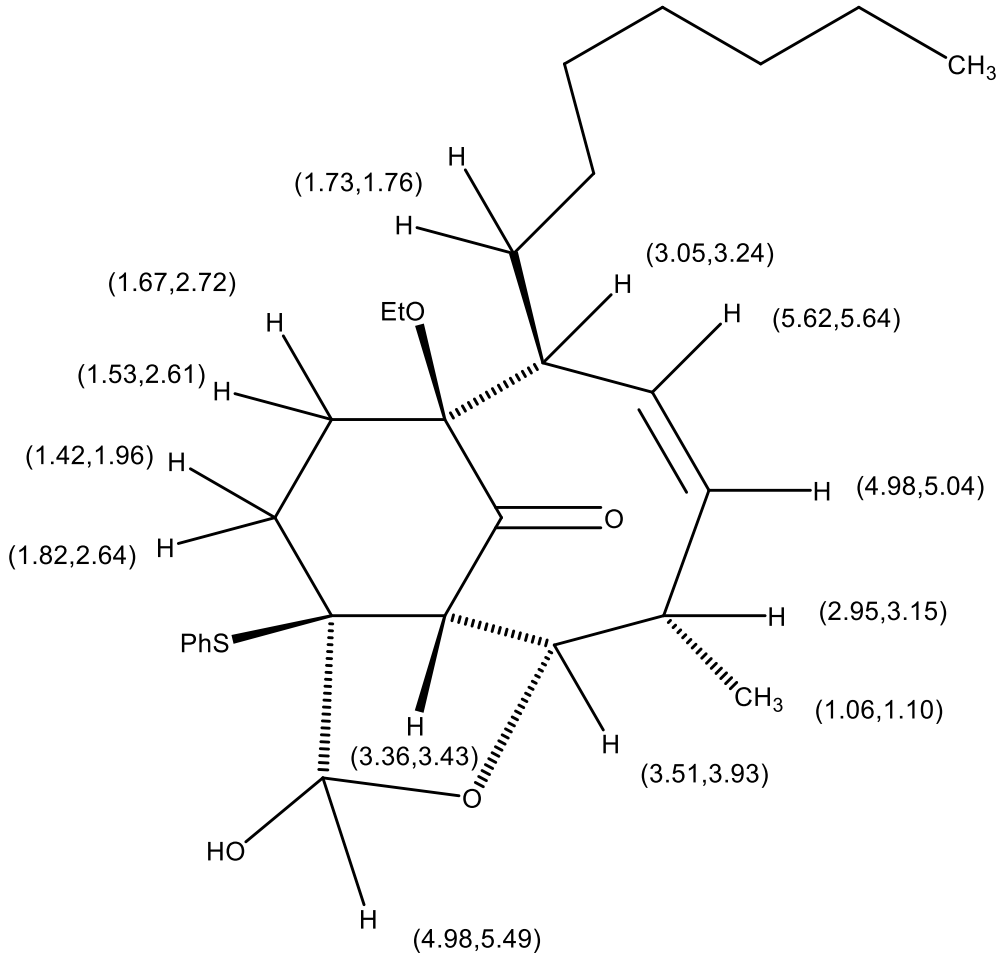
Procedure: To a microwave vial, **3.38** (34 mg, 0.072 mmol) was dissolved in acetonitrile (1.5 mL) and degassed with argon. The solution was stirred for 180°C in a microwave reactor for 25 min. The solvent was removed in vacuo and the oily residue was purified by flash chromatography on silica gel (10% EtOAc:Hex) to provide the desired product **3.39**. (14 mg, 0.036 mmol, 41% yield).

^{1}H NMR (600 MHz, C_6D_6) δ 7.49 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.44 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.09 – 7.01 (m, 3H), 7.00 – 6.91 (m, 3H), 5.64 (dtd, *J* = 10.1, 9.9, 1.5 Hz, 1H(2)), 5.49 (s, 1H), 5.04 (ddd, *J* = 10.0, 8.5, 1.2 Hz, 1H), 4.99 (ddd, *J* = 10.1, 8.7, 1.3 Hz, 1H), 4.98 (s, 1H), 3.93 (dd, *J* = 10.8, 9.9 Hz, 1H), 3.89 – 3.84 (m, 1H), 3.84 – 3.79 (m, 1H), 3.71 – 3.65 (m, 1H), 3.66 – 3.59 (m, 1H), 3.52 (dd, *J* = 10.8, 9.8 Hz, 1H), 3.43 (dd, *J* = 9.7, 2.4 Hz, 1H), 3.36 (dd, *J* = 10.8, 2.7 Hz, 1H), 3.24 (td, *J* = 10.3, 3.1 Hz, 1H), 3.20 – 3.11 (m, 1H), 3.09 – 3.01 (m, 1H), 2.99 – 2.89 (m, 1H), 2.81 – 2.54 (m, 3H), 1.96 (ddd, *J* = 15.2, 13.6, 3.7 Hz, 1H), 1.85 – 1.73 (m, 2H), 1.73 – 1.62 (m, 2H), 1.53 (dt, *J* = 13.5, 3.4 Hz, 1H), 1.40 (ddt, *J* = 15.3, 4.1, 2.9 Hz, 1H), 1.34 (t, *J* = 6.9 Hz, 3H), 1.31 (t, *J* = 6.9 Hz, 3H), 1.29 – 1.19 (m, 8H (2)), 1.10 (d, *J* = 6.3 Hz, 3H), 1.06 (d, *J* = 6.2 Hz, 2H), 0.88 (t, *J* = 7.1 Hz, 3H (2)).

^{13}C NMR (151 MHz, C_6D_6) δ 205.0, 204.0, 137.8, 137.7, 136.5, 135.5, 132.7, 132.3, 131.6, 130.7, 129.4, 129.3 (2), 129.3, 107.1, 105.0, 101.1, 88.6, 88.5, 81.6, 81.0, 66.5, 62.0, 61.6, 60.8, 60.7, 59.6, 41.8, 41.3, 39.2, 38.7, 32.2, 30.2, 29.7, 29.1, 28.9, 28.7, 28.6, 28.3, 26.9, 24.6, 23.1, 20.3, 19.5, 16.5 (2), 14.3 (2).

HRMS: (ESI) m/z calculated for $C_{28}H_{40}O_4S$ [M^++Na^+] 495.2531; found 495.2545

FTIR: 2921 (s), 1700 (s), 1024 (s)


CH3
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(1.73,1.76)
H
(3.05,3.24)
(1.67,2.72)
H
H
(5.62,5.64)
EtO
H
(1.53,2.61)
H
(1.42,1.96)
H
H
(4.98,5.04)
O
(1.82,2.64)
H
H
(2.95,3.15)
PhS
CH3
(1.06,1.10)
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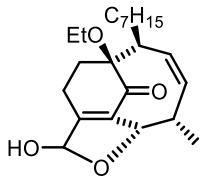
(3.36,3.43)
(3.51,3.93)
O
HO
H
(4.98,5.49)

3.44



Name: (5S,9S,9aS,Z)-5-ethoxy-6-heptyl-2-hydroxy-9-methyl-5,6,9,9a-tetrahydro-3,5-ethanocycloocta[b]furan-4(2H)-one

Procedure: 4 from 17

In a round bottom flask was dissolved **3.39** (24 mg, 0.05 mmol) in DCM (0.5 mL) and the solution cooled to 0ºC. To this solution was added MSH (24 mg, 0.11 mmol). After stirring for 45 min at 0ºC, K_2CO_3 (70 mg, 0.5 mmol) was added. The mixture was stirred overnight. The reaction was quenched with aqueous sodium bicarbonate and diluted with DCM. The aqueous phase was extracted twice. The organic phases were combined, dried with magnesium sulphate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the desired product **3.44** (7 mg, 0.019 mmol, 38%).

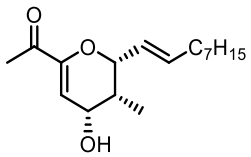
^{1}H NMR (600 MHz, C_6D_6) δ 5.69 (ddd, *J* = 12.1, 10.4, 2.0 Hz, 1H, M), 5.61 (ddd, *J* = 11.8, 10.2, 1.9 Hz, 1H, m), 5.53 (dd, *J* = 11.0, 3.4 Hz, 1H, m), 5.49 (d, *J* = 3.9 Hz, 1H, M), 5.29 (ddd, *J* = 11.2, 7.3, 1.1 Hz, 1H, M), 5.23 (ddd, *J* = 11.2, 7.4, 1.2 Hz, 1H, m), 4.75 (ddd, *J* = 8.3, 3.1, 1.6 Hz, 1H, mix), 3.92 (tq, *J* = 8.8, 7.0 Hz, 1H, mix), 3.64 (dqd, *J* = 8.7, 6.9, 4.5 Hz, 1H, mix), 2.96 (td, *J* = 9.7, 4.5 Hz, 1H, M), 2.72 (dpd, *J* = 8.6, 6.8, 2.0 Hz, 1H, M), 2.55 (dt, *J* = 10.1, 6.9 Hz, 1H, m), 2.40 – 2.20 (m, 1H, M), 2.19 (d, *J* = 4.0 Hz, OH, M), 2.14 – 2.00 (m, 2H, mix), 1.99 – 1.90 (m, 2H, mix), 1.83 (d, *J* = 11.0 Hz, OH, m), 1.84 – 1.73 (m, 1H, M), 1.67 – 1.53 (m, 2H), 1.38 – 1.33 (m, 2H), 1.31 (td, *J* = 6.9, 1.2 Hz, 3H, M), 1.28 – 1.18 (m, 10H, mix), 1.15 (d, *J* = 6.6 Hz, 3H, M), 1.12 (d, *J* = 6.6 Hz, 3H, m), 0.87 (t, *J* = 7.2 Hz, 3H, mix).

^{13}C NMR (151 MHz, C_6D_6) δ 199.7 (m), 199.5 (M), 144.2 (M), 144.0 (m), 143.6 (m), 142.1 (M), 137.6 (M), 137.3 (m), 134.8 (M), 134.6 (m), 104.2 (m), 102.5 (M), 89.8 (M), 88.0 (m), 86.3 (M), 85.7 (m), 60.9 (m), 60.9 (M), 46.1 (M), 45.3 (m), 44.3 (M), 44.3 (m), 32.2 (mix), 30.3 (m), 30.1 (M), 29.7 (m), 29.6 (M), 28.6 (m), 28.5 (m), 28.5 (M), 28.4 (M), 26.1 (mix), 23.1 (m), 23.0 (M), 20.7 (m), 20.1 (M), 18.4 (m), 18.3 (M), 16.6 (M), 16.6 (m), 14.3 (mix).

HRMS: (ESI) m/z calculated for $C_{22}H_{34}O_4$ [M^++Na^+] 385.2355; found 385.2337

FTIR: 2923 (s), 1714 (s), 1087 (s)

4.1



Name: 1-((2R,3R,4S)-4-hydroxy-3-methyl-2-((E)-non-1-en-1-yl)-3,4-dihydro-2H-pyran-6-yl)ethan-1-one

Procedure: To a round bottom flask was added hydroxy-diene **4.1** (900 mg, 2.9 mmol) and THF (20 mL). After dissolution, 2M HCl (5 mL). The solution was stirred at room temperature for 30 min. The mixture was diluted with water and ether. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel using 20% EtOAc in hexanes to provide the desired product (740 mg, 2.85 mmol, 98% yield).

^{1}H NMR (400 MHz, C_6D_6) δ 5.80 (dd, *J* = 3.0, 1.2 Hz, 1H), 5.69 (dtd, *J* = 15.1, 6.7, 1.3 Hz, 1H), 5.60 – 5.47 (m, 1H), 4.20 (dd, *J* = 5.9, 1.2 Hz, 1H), 4.17 (dd, *J* = 5.9, 2.9 Hz, 1H), 2.05 (s, 3H), 2.01 – 1.90 (m, 2H), 1.73 (dddd, *J* = 7.1, 6.0, 2.5, 1.3 Hz, 1H), 1.36 – 1.17 (m, 10H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 4H).

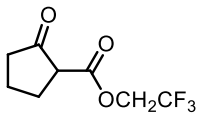
^{13}C NMR (101 MHz, C_6D_6) δ 193.8, 150.5, 133.7, 126.9, 109.1, 79.4, 66.1, 36.1, 32.7, 32.2, 29.5, 29.5, 25.7, 23.1, 14.4, 6.9.

$[\alpha_D]^{25}$: +54.8 (*c* 0.017, DCM)

HRMS: (ESI) m/z calculated for $C_{17}H_{28}O_3$ [M^++Na^+] 303.1936; found 303.1943

FTIR: 3446 (m), 2922 (s), 1713 (s)

4.23a



Name: 2,2,2-trifluoroethyl 2-oxocyclopentane-1-carboxylate

Procedure: Methyl 2-oxocyclopentane-1-carboxylate (1.2 mL, 7.5 mmol) was dissolved in a 20 mL microwave vial with trifluoroethanol (17 mL). The mixture was stirred at 170 °C for 90 min in a microwave reactor. The solvent was removed in vacuo and the residue purified with flash chromatography (10-20% EtOAc:Hex) to yield the desired product **4.23a** (910 mg, 4.33 mmol, 58%)

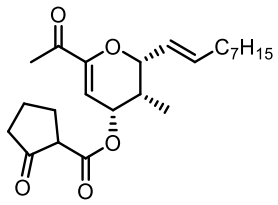
^{1}H NMR (600 MHz, C_6D_6) δ 4.05 (dq, *J* = 12.4, 8.5 Hz, 1H), 3.89 (dq, *J* = 12.7, 8.6 Hz, 1H), 2.60 (dd, *J* = 10.2, 8.4 Hz, 1H), 1.81 (dtd, *J* = 12.9, 10.2, 6.9 Hz, 1H), 1.62 (ddd, *J* = 9.7, 6.3, 4.0 Hz, 2H), 1.48 (ddq, *J* = 15.5, 9.0, 3.3 Hz, 1H), 1.33 (tdd, *J* = 12.3, 5.7, 2.6 Hz, 1H), 0.93 (dqd, *J* = 12.8, 9.5, 6.6 Hz, 1H).

^{13}C NMR (151 MHz, C_6D_6) δ 209.3, 168.0, 123.5 (q, *J* = 277.2 Hz), 60.4 (q, *J* = 36.4 Hz), 54.2, 37.3, 27.2, 20.7.

HRMS: (ESI) m/z calculated for $C_8H_9F_3O_3$ [M^++Na^+] 233.0401; found 233.0391

FTIR: 2979 (s), 1763 (s), 1734 (s), 1154 (s)

4.21



Name: (2R,3S,4S)-6-acetyl-3-methyl-2-((E)-non-1-en-1-yl)-3,4-dihydro-2H-pyran-4-yl 2-oxocyclopentane-1-carboxylate

Procedure: In a screw capped vial, **4.1** (1.12 g, 4.33 mmol) and **4.23a** (1 g, 4.76 mmol) were dissolved in THF (18 mL), followed by the addition of DMAP (61 mg, 0.43 mmol). The solution was stirred overnight at 60°C. The mixture was diluted with diethyl ether and aqueous ammonium chloride. The aqueous phase was extracted twice. The organic phases were combined, dried with magnesium sulphate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the desired product **4.21** (1.1g , 3.0 mmol, 69%).

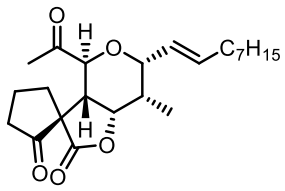
^{1}H NMR (400 MHz, C_6D_6) δ 6.03 – 5.94 (m, 1H), 5.72 – 5.58 (m, 2H), 5.58 – 5.42 (m, 2H), 4.19 (t, *J* = 6.8 Hz, 1H), 2.76 (td, *J* = 10.5, 8.5 Hz, 1H), 2.22 – 2.11 (m, 1H), 2.08 – 2.02 (m, 1H), 2.01 – 2.00 (m, 2H), 1.99 (s, 3H), 1.97 (s, 3H, minor), 1.94 – 1.87 (m, 1H), 1.72 (dt, *J* = 9.2, 6.9 Hz, 2H), 1.67 – 1.57 (m, 1H), 1.51 – 1.40 (m, 1H), 1.38 – 1.20 (m, 10H), 1.10 (d, *J* = 7.0 Hz, 3H, minor), 1.08 – 0.95 (m, 1H), 0.95 – 0.88 (m, 6H).

^{13}C NMR (101 MHz, C_6D_6) δ 210.7 (M), 210.4 (m), 193.3 (M), 193.1 (m), 169.2 (M), 169.1 (m), 152.1 (M), 152.0 (m), 134.5 (m), 134.4 (M), 126.1 (M), 126.0 (m), 104.4 (m), 104.2 (M), 79.2 (M), 79.2 (m), 69.7 (M), 69.5 (m), 55.0 (m), 54.9 (M), 37.7 (M), 37.7 (m), 33.3 (mix), 32.8 (mix), 32.2 (mix), 29.6 (M), 29.6 (M), 29.5 (m), 29.4 (m), 27.6 (m), 27.3 (M), 25.6 (M), 25.5 (m), 23.1 (mix), 21.0 (m), 20.9 (M), 14.4 (mix).

HRMS: (EI) m/z calculated for $C_{23}H_{34}O_5$ [M^+] 390.2406; found 390.2374

IR: 2924 (s), 1727 (s), 1107 (s)

4.24



Name: (1R,3a'S,4'S,6'R,7'S,7a'S)-4'-acetyl-7'-methyl-6'-((E)-non-1-en-1-yl)tetrahydro-2'H,4'H-spiro[cyclopentane-1,3'-furo[3,2-c]pyran]-2,2'-dione

Procedure: In a screw capped vial was dissolved **4.21** (1.1 g, 3 mmol) in dry acetonitrile, followed by addition of piperidine (128 mg, 1.5 mmol) and tetrabutylammonium sulfate (100 mg, 0.3 mmol). The mixture was stirred at 65 ºC overnight. The mixture was diluted with diethyl ether, followed by addition of a saturated aqueous ammonium chloride solution. The phases were separated and the aqueous phase extracted 3 times with ether. The organic phases were combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel using 20% EtOAc in hexanes to provide the desired product **4.24** (657 mg, 1.8 mmol, 60% yield).

^{1}H NMR (400 MHz, C_6D_6) δ 5.92 (ddt, *J* = 15.3, 8.3, 1.5 Hz, 1H), 5.63 (dtd, *J* = 15.1, 6.9, 1.0 Hz, 1H), 5.08 (dd, *J* = 5.4, 3.3 Hz, 1H), 4.28 – 4.00 (m, 1H), 3.88 (d, *J* = 9.0 Hz, 1H), 3.02 (dd, *J* = 9.1, 5.4 Hz, 1H), 2.20 – 2.04 (m, 1H), 1.98 (s, 3H), 1.97-1.90 (m, 2H), 1.87 – 1.74 (m, 3H), 1.65 – 1.56 (m, 1H), 1.56 – 1.47 (m, 1H), 1.46 – 1.36 (m, 1H), 1.34 – 1.16 (m, 10H), 0.91 (t, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 7.3 Hz, 3H).

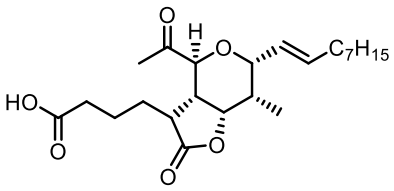
^{13}C NMR (101 MHz, C_6D_6) δ 212.4, 204.2, 173.6, 138.9, 125.3, 77.7, 77.5, 71.1, 61.8, 40.1, 37.2, 34.1, 32.8, 32.3, 29.5, 29.5, 29.4, 29.2, 27.0, 23.1, 19.5, 14.4, 13.8.

HRMS: (ESI) m/z calculated for $C_{23}H_{34}O_5$ [M^++Na^+] 413.2308; found 413.2304

$[\alpha_D]^{25}$: -25.3 (*c* 0.013, DCM)

FTIR: 2927 (s), 1772 (s), 1730 (s), 1111 (s)

4.28



Name: (S)-2-((2S,3S,4S,5R,6R)-2-acetyl-4-hydroxy-5-methyl-6-((E)-non-1-en-1-yl)tetrahydro-2H-pyran-3-yl)hexanedioic acid

Procedure:

A: In a round bottom flask was dissolved compound **4.24** (3.6 mg, 0.01 mmol) in THF (0.1 mL). Aqueous sodium hydroxide (1 M, 0.1 mL, 0.1 mmol) was added and the mixture stirred at room temperature for 1 hour. The reaction was quenched with quenched with a saturated solution of aqueous ammonium chloride. The aqueous phase was extracted twice. The combined organic layers dried with magnesium sulfate and filtered. The combined organic layers were washed with brine, dried with magnesium sulfate and filtered. The dried organic layers were evaporated under reduced pressure to yield the observed crude product.

B: In a round bottom flask was dissolved compound **4.21** (205 mg, 0.53 mmol) in isopropanol (5 mL). A solution of potassium carbonate (1 M (aq), 0.5 mL) was added and the mixture stirred overnight at 50ºC. The reaction was quenched with quenched with a saturated solution of aqueous ammonium chloride. The layers were separated and the aqueous phase was extracted twice. The combined organic layers dried with magnesium sulfate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (2% MeOH:DCM) to yield the observed product (194 mg, 0.445 mmol, 84% yield)

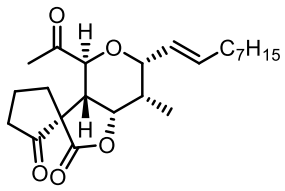
^{1}H NMR (400 MHz, C_6D_6) δ 6.10 – 5.85 (m, 1H), 5.71 – 5.53 (m, 1H), 4.18 – 4.02 (m, 1H), 3.93 (d, *J* = 9.7 Hz, 1H), 3.72 (d, *J* = 9.6 Hz, 0H), 3.69 – 3.59 (m, 1H), 2.53 (ddd, *J* = 9.6, 6.6, 4.5 Hz, 1H), 2.04 (t, *J* = 7.1 Hz, 2H), 1.99 (s, 3H), 1.96 (d, *J* = 8.9 Hz, 3H), 1.80 – 1.66 (m, 1H), 1.66 – 1.52 (m, 3H), 1.37 – 1.18 (m, 12H), 1.16 – 1.04 (m, 1H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, C_6D_6) δ 203.2, 177.7, 175.8, 138.5, 125.2, 77.5 (2), 70.7, 44.9, 37.0, 33.9, 33.2, 32.5, 32.0, 29.2, 29.2, 29.1, 26.5, 24.8, 23.0, 22.8, 14.1, 13.72.

HRMS: HRMS (ESI) m/z calculated for $C_{23}H_{36}O$ [$M^+ + Na^+$] 431.2396; found 431.2410

IR: v = 2856(w), 1762(s), 1696(s), 1133(s), 884(s),

4.25



Name: (1S,3a'S,4'S,6'R,7'S,7a'S)-4'-acetyl-7'-methyl-6'-((E)-non-1-en-1-yl)tetrahydro-2'H,4'H-spiro[cyclopentane-1,3'-furo[3,2-c]pyran]-2,2'-dione

Procedure: To a screw capped vial containing **4.21** (10 mg, 0.025 mmol) was added tertbutanol (0.25 mL) and K_2CO_3 (35 mg, 0.25 mmol). The mixture was stirred overnight at 80°C. The mixture was diluted with diethyl ether, followed by addition of a saturated aqueous ammonium chloride solution. The phases were separated and the aqueous phase extracted 3 times with ether. The organic phases were combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel using 20% EtOAc in hexanes to provide the desired product **4.25** (3.5 mg, 0.0073 mmol, 29% yield).

^{1}H NMR (400 MHz, C_6D_6) δ 6.05 (ddt, *J* = 15.3, 8.4, 1.4 Hz, 1H), 5.73 (dtd, *J* = 15.2, 7.1, 1.2 Hz, 1H), 4.91 (d, *J* = 10.6 Hz, 1H), 4.29 – 4.03 (m, 1H), 3.83 (t, *J* = 4.0 Hz, 1H), 2.33 (dd, *J* = 10.6, 4.6 Hz, 1H), 2.25 – 2.17 (m, 1H), 2.13 (s, 3H), 2.08 – 2.04 (m, 2H), 1.88 (t, *J* = 7.3 Hz, 2H), 1.85 – 1.77 (m, 1H), 1.67 – 1.60 (m, 1H), 1.36 – 1.28 (m, 10H), 0.97 – 0.91 (m, 7H), 0.86 (d, *J* = 7.3 Hz, 3H).

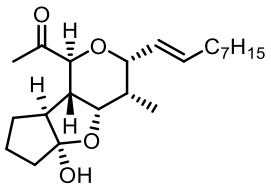
^{13}C NMR (151 MHz, C_6D_6) δ 213.5, 206.0, 175.2, 139.9, 124.6, 78.1, 77.8, 68.9, 60.1, 44.8, 39.2, 34.8, 34.0, 32.7, 32.3, 29.6, 29.5, 29.4, 27.2, 23.1, 20.6, 14.4, 13.9.

HRMS: HRMS (ESI) m/z calculated for 413.2304 [M^+ + Na^+]; found 413.2285

$[\alpha_D]^{25}$: -40 (*c* 0.0021, DCM)

FTIR : 1762 (s), 1734 (s), 1161 (s)

4.40



Name: 1-((1S,3R,4S,4aS,5aS,8aS,8bS)-5a-hydroxy-4-methyl-3-((E)-non-1-en-1-yl)octahydro-1H,3H-cyclopenta[4,5]furo[3,2-c]pyran-1-yl)ethan-1-one

Procedure: In a round bottom flask, LiHMDS (1M in THF, 0.14 mL, 0.14 mmol) was further dissolved in THF (0.5 mL). The solution was cooled to -78ºC, followed by addition of TMSCl (0.3 mL, 0.23 mmol) and **4.24** (14 mg, 0.035 mmol) dissolved in THF (0.4 mL). The mixture was stirred for 30 min at -78ºC then warmed to room temperature and stirred for 2 hours. The mixture was quenched with addition of a few drops of triethylamine followed by satured aqueous sodium bicarbonate and diethyl ether. The phases were separated and the aqueous phase extracted 3 times with ether. The organic phases were combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The crude mixture was directly taken to the next step.

The crude mixture was dissolved in DCM (1 mL) and cooled to -78ºC. To this solution was added DIBAL (1.5 M, 0.07 mL, 0.105 mmol) and stirred further at -78ºC for 2 hours. Acetone (1 mL) was added to quench the reaction. The mixture was warmed to 0ºC, followed by the addition of Rochelle salt. The mixture was warmed to room temperature and left to stir until two phases could be separated. The aqueous phase was extracted twice. The organic phases were combined, dried with magnesium sulphate and filtered. The dried organic layers were evaporated under reduced pressure.

The crude mixture was dissolved in THF (1 mL). Aqueous sodium hydroxide (1.0 M, 0.1 mL, 0.1 mmol) was added and the mixture stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride. The phases were separated and the aqueous phase extracted 3 times with ether. The organic phases were combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The oily residue was purified by flash chromatography on silica gel using 20% EtOAc in hexanes to provide the desired product **4.40** (1.5 mg, 0.0041 mmol, 12% yield).

^{1}H NMR (400 MHz, C_6D_6) δ 6.54 (dd, *J* = 15.3, 8.8 Hz, 1H), 6.03 – 5.64 (m, 1H), 4.42 (d, *J* = 10.5 Hz, 1H), 4.26 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.96 – 3.67 (m, 1H), 2.52 (dd, *J* = 9.6, 7.5 Hz, 1H), 2.11 (s, 3H), 2.16 – 2.06 (m, 2H), 1.96 – 1.79 (m, 2H), 1.76 – 1.57 (m, 2H), 1.45 – 1.34 (m, 6H), 1.25 (s, 5H), 1.17 – 1.10 (m, 1H), 1.00 (d, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H).

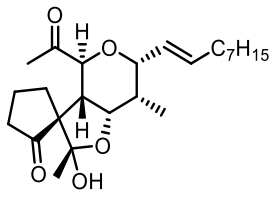
^{13}C NMR (151 MHz, C_6D_6) δ 207.7, 137.2, 127.3, 116.6, 78.9, 78.6, 74.5, 52.0, 45.0, 41.5, 34.7, 33.1, 32.3, 31.1, 30.2, 29.7, 29.6, 26.3, 25.3, 23.1, 14.9, 14.4.

HRMS: HRMS (ESI) m/z calculated for $C_{22}H_{36}O_4$ [$M^+ + Na^+$] 387.2511; found 387.2492

$[\alpha_D]^{25}$: -45 (*c* 0.00063, DCM)

FTIR: 2918 (s), 1719 (s), 1080 (s)

4.41



Name: (1R,2'S,3a'S,4'S,6'R,7'S,7a'S)-4'-acetyl-2'-hydroxy-2',7'-dimethyl-6'-((E)-non-1-en-1-yl)tetrahydro-2'H,4'H-spiro[cyclopentane-1,3'-furo[3,2-c]pyran]-2-one

Procedure: In a round bottom flask, LiHMDS (1M in THF, 5 mL, 5 mmol) was further dissolved in THF (15 mL). The solution was cooled to -78ºC, followed by addition of TMSCl (1 mL, 8 mmol) and **4.24** (720 mg, 2 mmol) dissolved in THF (5 mL). The mixture was stirred for 30 min at -78ºC then warmed to room temperature and stirred for 2 hours. The mixture was quenched with addition of a few drops of triethylamine followed by saturated aqueous sodium bicarbonate and diethyl ether. The phases were separated and the aqueous phase extracted 3 times with ether. The organic phases were combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The crude mixture was directly taken to the next step.

The crude mixture was dissolved in THF (20 mL) and cooled to -78ºC. To this solution was added methyl lithium (1.6 M in diethyl ether, 6 mL, 9.6 mmol). The mixture was warmed to room temperature over 30 minutes. The solution was cooled to 0ºC, followed by addition of saturated aqueous ammonium chloride to quench the reaction. The layers were separated and the aqueous phase was extracted twice. The combined organic layers dried with magnesium sulfate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (20% EtOAc:Hex) to yield the desired product **4.41** (273 mg, 0.72 mmol, 35% yield)

^{1}H NMR (400 MHz, C_6D_6) δ 6.10 – 5.75 (m, 1H), 5.50 (dt, *J* = 14.4, 6.7 Hz, 1H), 5.14 (t, *J* = 2.7 Hz, 1H), 4.52 (d, *J* = 11.1 Hz, 1H), 4.06 (dd, *J* = 8.9, 6.1 Hz, 1H), 2.64 (dt, *J* = 11.1, 2.3 Hz, 1H), 2.27 (s, 3H), 2.22 (dd, *J* = 11.8, 6.6 Hz, 1H), 2.14 – 1.84 (m, 4H), 1.77 (dd, *J* = 6.9, 2.7 Hz, 1H), 1.74 (s, 3H), 1.66 (dt, *J* = 12.4, 7.9 Hz, 2H), 1.36 – 1.17 (m, 10H), 1.16 – 1.02 (m, 1H), 0.90 (t, *J* = 6.9 Hz, 3H), 0.59 (d, *J* = 7.1 Hz, 3H), 0.51 (s, 1H).

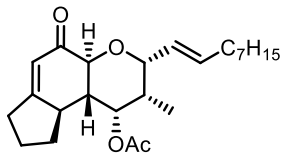
^{13}C NMR (101 MHz, C_6D_6) δ 216.7, 209.5, 169.6, 136.0, 126.4, 78.1, 74.6, 73.3, 51.7, 40.8, 37.5, 36.8, 32.9, 32.2, 29.5, 29.5, 29.5, 25.9, 25.2, 23.1, 21.0, 20.8, 14.3, 13.9.

HRMS: (ESI) m/z calculated for $C_{24}H_{38}O_5$ [M^++Na^+] 429.2598; found 429.2617

FTIR: 2924 (s), 1737 (s), 1228 (s)

$[\alpha_D]^{25}$: -23.4 (*c* 0.0056, DCM)

4.42



Name: (1S,2S,3R,4aS,9aR,9bS)-2-methyl-3-((E)-non-1-en-1-yl)-5-oxo-1,2,3,4a,5,7,8,9,9a,9b-decahydrocyclopenta[f]chromen-1-yl acetate

Procedure: Magnesium bromide diethyl etherate (371 mg, 1.44 mmol) was suspended in 4 mL of DCM. DIPEA (0.5 mL, 2.88 mmol) was added to the suspension and stirred at room temperature for 30 min, upon which the suspension turned to a dark pink. The hemiacetal **4.41** (273 mg, 0.72 mmol) dissolved in DCM (4 mL) was added to the suspension. The mixture was stirred for 3 hours at room temperature. The reaction was quenched with an aqueous saturated solution of NH_4Cl. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. The dried organic layers were evaporated under reduced pressure and taken to the next step directly.

The crude material was dissolved in THF (4 mL). To the solution was added PPTS (181 mg, 0.72 mmol). The mixture was stirred at reflux for 3 hours. The mixture was diluted with water and diethyl ether. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the condensation product **4.42** (140 mg, 0.4 mmol, 56% yield)

^{1}H NMR (600 MHz, C_6D_6) δ 5.93 (ddt, *J* = 15.3, 8.0, 1.5 Hz, 1H), 5.85 (q, *J* = 2.2 Hz, 1H), 5.70 (dtd, *J* = 15.0, 6.7, 1.1 Hz, 1H), 5.19 (t, *J* = 2.8 Hz, 1H), 4.30 (d, *J* = 8.0 Hz, 1H), 4.27 (d, *J* = 12.1 Hz, 1H), 2.09 – 2.00 (m, 3H), 1.97 (dt, *J* = 13.1, 6.9 Hz, 1H), 1.90 – 1.84 (m, 1H), 1.84-1.79 (m, 1H), 1.74 (d, *J* = 1.2 Hz, 3H), 1.65 (dddd, *J* = 11.9, 10.6, 2.9, 1.2 Hz, 1H), 1.41 – 1.32 (m, 2H), 1.31 – 1.21 (m, 8H), 1.20 – 1.12 (m, 1H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.81 (qd, J = 11.5, 7.7 Hz, 1H), 0.65 (d, *J* = 7.1 Hz, 3H).

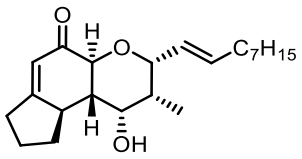
^{13}C NMR (151 MHz, C_6D_6) δ 193.8, 169.8, 169.4, 135.4, 126.2, 122.0, 78.1, 71.0, 70.2, 49.1, 42.8, 37.2, 33.1, 32.2, 31.2, 30.5, 29.6, 29.6, 29.5, 23.6, 23.1, 20.4, 14.3, 13.9.

FTIR: 2928 (s), 1738 (s), 1684 (s), 1230 (s)

HRMS: (EI) m/z calculated for $C_{24}H_{36}O_4$ [M^+] 388.2614; found 388.2629

$[\alpha_D]^{25}$: +47.5 (*c* 0.014, DCM)

4.45



Name: (1S,2R,3R,4aS,9aR,9bS)-1-hydroxy-2-methyl-3-((E)-non-1-en-1-yl)-2,3,4a,7,8,9,9a,9b-octahydrocyclopenta[f]chromen-5(1H)-one

Procedure: In a round bottom flask, **4.42** (140 mg, 0.4 mmol) was dissolved in diethyl ether (4 mL). To the solution was added lithium aluminium hydride (46 mg, 1.2 mmol). The suspension was stirred for one hour, then quenched with Rochelle's salt at 0°C. The mixture was warmed to room temperature and left to stir until two phases could be separated. The aqueous phase was extracted twice. The organic phases were combined, dried with magnesium sulphate and filtered. The dried organic layers were evaporated under reduced pressure and taken directly to the next step.

In a round bottom flask, the crude oil was dissolved in DCM containing 2% of 3,5-dimethylpyrazole (4 mL). The solution was cooled to 0°C. To the solution was added celite and PCC (260 mg, 1.2 mmol). The suspension was stirred for an hour. The solution was then filtered through a celite plug. The filtrate was evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the desired product **4.45** (46 mg, 0.14 mmol, 35% yield)

^{1}H NMR (600 MHz, C_6D_6) δ 6.15 (ddt, *J* = 15.3, 7.6, 1.5 Hz, 1H), 5.88 (q, *J* = 2.2 Hz, 1H), 5.79 (dtd, *J* = 15.2, 6.8, 1.3 Hz, 1H), 4.47 (d, *J* = 12.2 Hz, 1H), 4.37 (t, *J* = 6.8 Hz, 1H), 3.41 (dt, *J* = 5.2, 2.6 Hz, 1H), 2.64 – 2.41 (m, 1H), 2.12 – 1.99 (m, 3H), 1.95 – 1.84 (m, 1H), 1.81 – 1.70 (m, 2H), 1.61 (ddd, *J* = 12.1, 10.6, 2.8 Hz, 1H), 1.52 – 1.41 (m, 1H), 1.41 – 1.32 (m, 3H), 1.31 – 1.20 (m, 10H), 0.90 (t, *J* = 7.1 Hz, 3H), 0.74 (d, *J* = 7.3 Hz, 3H).

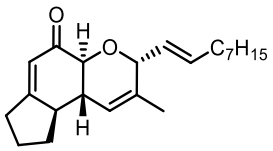
^{13}C NMR (151 MHz, C_6D_6) δ 195.1, 170.8, 135.5, 127.1, 121.8, 78.3, 69.9, 69.9, 51.5, 42.8, 38.5, 33.3, 32.4, 31.4, 30.0, 29.8, 29.8, 29.7, 23.8, 23.2, 14.5, 14.4.

HRMS: (EI) m/z calculated for $C_{22}H_{34}O_3$ [M^+] 346.2508; found 346.2522

$[\alpha_D]^{25}$: +57.6 (*c* 0.0028, DCM)

FTIR: 2930 (s), 1735 (s), 1246 (s)

1.33



Name: (3R,4aS,9aR,9bR)-2-methyl-3-((E)-non-1-en-1-yl)-4a,7,8,9,9a,9b-hexahydrocyclopenta[f]chromen-5(3H)-one

Procedure: In a round bottom flask **4.45** (3.2 mg, 0.0086 mmol) was dissolved in chloroform (0.2 mL). Martins sulfurane (27 mg, 0.04 mmol) was added. The solution was stirred at 45ºC overnight. The mixture was diluted with water and DCM. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. The dried organic layers were evaporated under reduced pressure. Crude NMR indicated full conversion. The crude mixture was purified with flash chromatography (5% EtOAc:Hex) to yield a mixture of the dehydration product **1.33** and dimethyl sulfoxide. The mixture was purified with flash chromatography (5% EtOAc:Hex) a second time to yield desired product **1.33** (1.1 mg, 0.003 mmol, 36% yield) with trace amounts of sulfoxide.

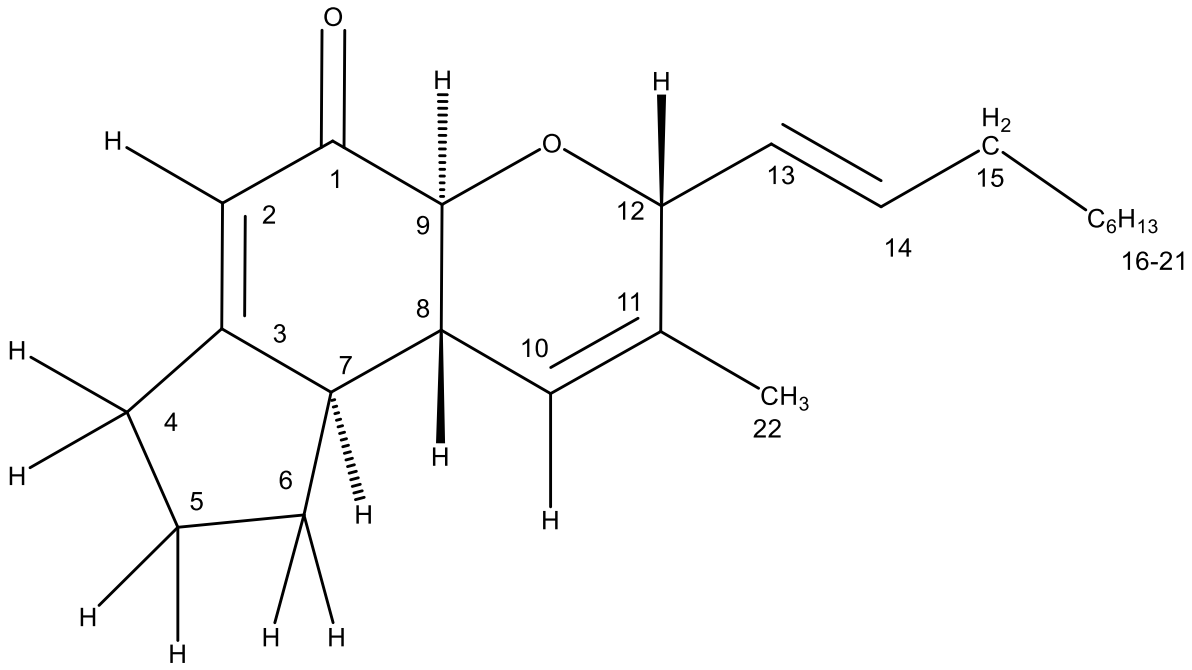
^{1}H NMR (600 MHz, C_6D_6) δ 5.85 (q, *J* = 2.3 Hz, 1H), 5.77 (dtd, *J* = 15.2, 6.8, 1.3 Hz, 1H), 5.61 (ddt, *J* = 15.4, 6.1, 1.4 Hz, 1H), 5.35 (q, *J* = 1.6 Hz, 1H), 4.64 (d, *J* = 6.0 Hz, 1H), 4.06 (d, *J* = 11.5 Hz, 1H), 2.28 (tq, *J* = 11.0, 2.1 Hz, 1H), 2.08 – 1.93 (m, 3H), 1.90 – 1.74 (m, 2H), 1.73 – 1.62 (m, 1H), 1.51 (t, *J* = 2.1 Hz, 3H), 1.41 – 1.34 (m, 1H), 1.34 – 1.20 (m, 10H), 1.18 – 1.07 (m, 1H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.76 (qd, *J* = 11.7, 7.3 Hz, 1H).

^{13}C NMR (151 MHz, C_6D_6) δ 193.9, 169.7, 136.4, 135.0, 127.3, 122.9, 122.6, 77.4, 74.4, 47.7, 45.1, 32.8, 32.2, 31.0, 30.0, 29.6 (3), 23.8, 23.1, 20.0, 14.4.

HRMS: (ESI) m/z calculated for $C_{22}H_{32}O_2$ [M^++Na^+] 351.2280; found 351.2300

$[\alpha_D]^{25}$: +66 (*c* 0.00075, DCM)

FTIR: 2924 (s),1684 (s), 1091 (s)



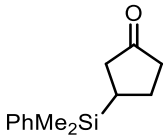
Assignment of peaks (C_6D_6 spectra)

^{13}C	^{1}H	Assignment
193.87	--	C1
169.70	--	C3
136.44	--	C11
134.97	5.77	C14
127.30	5.61	C13
122.85	5.35	C10
122.59	5.85	C2
77.38	4.64	C12
74.35	4.06	C9
47.68	1.90 – 1.74	C7
45.07	2.28	CC8
32.81	2.08 – 1.93	C15
32.22	1.34 – 1.20	C16-C20
31.02	1.90 – 1.74, 2.08 – 1.93	C4
30.03	1.73 – 1.62, 0.76	C6
29.56 (3)	1.34 – 1.20	C16-C20
23.81	1.41 – 1.34, 1.18 – 1.07	C5
23.06	1.34 – 1.20	C16-C20
20.00	1.51	C22
14.35	0.89	C21

Comparison of 1H NMR peaks between Snider's synthesis of 5-deoxypenostatin B and this work

Snider (300 MHz)	600 MHz (This work)
5.94 (d, J=1.8 Hz, 1H)	5.94 (d, *J* = 2.0 Hz, 1H)
5.67 (dt, J= 15.3, 6.7 Hz, 1H)	5.67 (dd, *J* = 15.3, 6.8 Hz, 1H)
5.57 (s, 1H)	5.57 (s, 1H)
5.56 (dd, J=15.3, 6.1 Hz, 1H)	5.60 – 5.52 (m, 1H)
4.59 (d, J= 6.1 Hz, 1H)	4.59 (d, *J* = 6.2 Hz, 1H)
4.02 (d, J= 11 Hz, 1H)	4.02 (d, *J* = 11.3 Hz, 1H)
2.7-2.6 (m, 1H)	2.73 – 2.55 (m, 1H)
2.54-2.44 (m, 1H)	2.55 – 2.45 (m, 1H)
2.44-2.30 (m, 1H)	2.45 – 2.30 (m, 2H)
2.29-2.21 (m, 1H)	2.25 (dt, *J* = 12.4, 6.7 Hz, 1H)
2.05 (q, J= 7.9, 2H)	2.05 (dt, *J* = 13.3, 6.7 Hz, 2H)
2.02-1.92 (m, 1H)	2.00 – 1.91 (m, 1H)
1.8-1.66 (m, 1H)	1.80 – 1.69 (m, 1H)
1.66 (s, 3H)	1.66 (s, 3H)
1.42-1.32 (m, 2H)	1.40 – 1.33 (m, 2H)
1.32-1.2 (m, 10H)	1.30 – 1.18 (m, 10H)
0.87 (t, J= 6.4 Hz, 3H)	0.87 (t, *J* = 7.0 Hz, 3H)

5.5



Name: 3-(dimethyl(phenyl)silyl)cyclopentan-1-one

Procedure: In a dry round bottom flask, lithium granules (275 mg, 40 mmol) were suspended in THF (10 mL). Dimethylphenylsilylchloride (1.67 mL, 10 mmol) was added and the mixture stirred at room temperature overnight to generate the dimethylphenylsilyl lithium reagent.

In a separate dry round bottom flask, copper cyanide (900 mg, 10 mmol) was suspended in THF (16 mL). The mixture was cooled to -50ºC. A solution of MeLi (1.6 M in diethyl ether, 6 mL, 9.5 mmol) was added. The mixture was stirred for 20 min at -50ºC, then cooled to -78ºC. The previously prepared lithium reagent was added and the mixture stirred for 30 min at -78ºC. Cyclopentenone (0.76 mL. 9.1 mmol) was added to the mixture and stirred for 30 min at -78ºC. The reaction was then quenched with a saturated solution of aqueous ammonium chloride. The mixture was warmed to room temperature and stirred for 30 min, upon which the aqueous phase turned blue. The aqueous phase was extracted three times [*significant emulsion present*]. The combined organic layers dried with magnesium sulfate and filtered. The combined organic layers were washed with brine, dried with magnesium sulfate and filtered. [*All aqueous phases and washings were disposed of in a separate copper cyanide waste container*] The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the observed product **4.41**. (1.51 g, 69%)

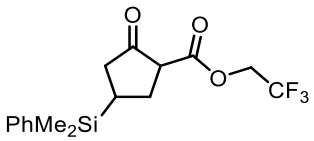
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.46 (m, 2H), 7.45 – 7.33 (m, 3H), 2.38 – 2.17 (m, 2H), 2.16 – 2.00 (m, 2H), 1.95 – 1.77 (m, 1H), 1.78 – 1.61 (m, 1H), 1.62 – 1.45 (m, 2H), 0.33 (d, *J* = 1.1 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 221.2, 137.1, 134.0, 129.5, 40.3, 39.5, 25.1, 24.1, -4.79, -4.84.

HRMS: HRMS (EI) m/z calculated for $C_{13}H_{18}OSi$ [M^+] 218.1127; found 218.1104

FTIR: 2952 (s), 1735 (s), 1248 (s)

5.16



Name: 2,2,2-trifluoroethyl 4-(dimethyl(phenyl)silyl)-2-oxocyclopentane-1-carboxylate

Procedure: In a round bottom flask **4.41** (3.0 g, 14 mmol) was dissolved in 30 mL of DCM, followed by addition of DIPEA (8.8 mL, 49 mmol). The solution was cooled to -78ºC. To the solution was added trimethylsilyl triflate (7.7 mL, 42 mmol). The solution was stirred at -78ºC for 2 hours. The reaction was quenched by addition of 1 mL of triethylamine followed by a solution of saturated aqueous sodium bicarbonate. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. The dried organic layers were evaporated under reduced pressure and taken directly to the next step. Crude NMR indicates 5:1 regioisomeric ratio based on the enol ether alkene peak.

In a round bottom flask, the crude mixture was dissolved in THF (140 mL) and cooled to -78ºC. To the solution was added MeLi (1.6 M in THF, 9.6 mL, 15.4 mmol) and the solution warmed to room temperature over 30 min. The solution was cooled back down to -78ºC, followed by slow addition of dry ice (6 g). The mixture was stirred for 30 min after addition, after which the reaction was quenched by slow addition of aqueous 1M HCl. The mixture was diluted with diethyl ether. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. The dried organic layers were evaporated under reduced pressure and taken directly to the next step.

The crude mixture was dissolved in DCM (70 mL). To the solution was added EDC (2.94 g, 15.4 mmol), DMAP (256 mg, 2.1 mmol), and trifluoroethanol (10 mL, 140 mmol). The solution was stirred overnight, then diluted with water and DCM. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. The dried organic layers were filtered, evaporated under reduced pressure and purified with flash chromatography (5% EtOAc:Hex) to yield the desired product **5.16** (2.8 g, 8.12 mmol, 58% yield)

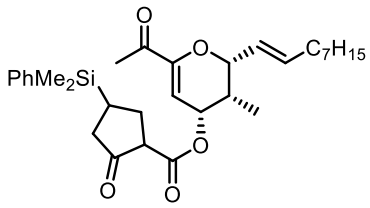
^{1}H NMR (600 MHz, C_6D_6) δ 7.39 – 7.17 (m, 5H, mix), 4.15 – 3.80 (m, 2H, mix), 2.80 – 2.67 (m, 1H, mix), 2.14 – 2.01 (m, 1H, minor), 1.94 – 1.84 (m, 1H, mix), 1.77 (td, *J* = 13.3, 6.2 Hz, 1H, minor), 1.73 – 1.56 (m, 2H, mix), 1.38 (dddd, *J* = 13.3, 10.0, 7.1, 3.6 Hz, 1H, major), 1.01 – 0.89 (m, 1H, major), 0.70 (tdd, *J* = 13.5, 7.7, 5.7 Hz, 1H, minor), 0.15 – -0.08 (m, 6H, mix).

^{13}C NMR (151 MHz, C_6D_6) δ 210.7, 209.9, 209.6, 168.7, 168.23, 168.0, 137.4, 136.7, 136.5, 135.9, 134.3, 134.1, 134.0, 129.8, 129.8, 129.7, 123.5 (q, *J* = 277.5 Hz), 60.6 (q, *J* = 36.4 Hz), 57.0, 56.0, 53.0, 40.1, 40.0, 39.8, 39.0, 38.2, 29.6, 29.1, 28.5, 25.0, 23.8, 22.9, 21.9, 21.5, -5.1, -5.2, -5.2, -5.6.

HRMS: (ESI) m/z calculated for $C_{16}H_{19}F_3O_3Si$ [M^++Na^+] 367.0953; found 367.0924

FTIR: 2959 (s), 1763 (s), 1736 (s), 1161 (s)

5.17



Name: (2R,3S,4S)-6-acetyl-3-methyl-2-((E)-non-1-en-1-yl)-3,4-dihydro-2H-pyran-4-yl 4-(dimethyl(phenyl)silyl)-2-oxocyclopentane-1-carboxylate

Procedure: In a screw capped vial, **4.1** (740 mg, 2.8 mmol) and **4.16** (1.65 g, 4.8 mmol) were dissolved in toluene (18 mL). The solution was stirred overnight at 80ºC. The mixture was diluted with diethyl ether and aqueous ammonium chloride. The aqueous phase was extracted twice. The organic phases were combined, dried with magnesium sulphate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the desired product **5.17** (800 mg, 1.6 mmol, 57%).

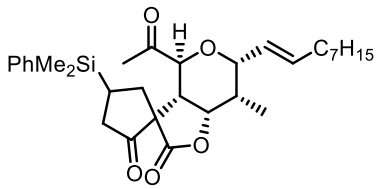
^{1}H NMR (600 MHz, C_6D_6) δ 7.46 – 7.18 (m, 5H), 6.08 – 5.88 (m, 1H), 5.78 – 5.61 (m, 1H), 5.59 (dt, *J* = 5.9, 2.6 Hz, 1H), 5.54 – 5.44 (m, 1H), 4.19 (dd, *J* = 17.6, 9.2 Hz, 1H), 2.94 – 2.79 (m, 1H), 2.21 – 2.13 (m, 1H), 2.13 – 2.04 (m, 1H), 2.02 – 1.94 (m, 6H), 1.91 – 1.81 (m, 1H), 1.79 – 1.73 (m, 2H), 1.40 – 1.28 (m, 4H), 1.25 (d, *J* = 3.2 Hz, 6H), 0.91 (tt, *J* = 7.2, 2.4 Hz, 6H), 0.04 (d, *J* = 14.3 Hz, 6H).

^{13}C NMR (151 MHz, C_6D_6) δ 210.9, 192.9, 169.3, 152.0, 136.8, 134.2, 134.0, 129.7, 126.1, 106.0, 104.5, 79.1, 56.7, 40.0, 33.3, 32.8, 32.2, 29.9, 29.6, 29.5, 25.6, 25.5, 23.1, 21.6, 14.4, -5.0, -5.1, -5.2, -5.5.

HRMS: (ESI) m/z calculated for $C_{31}H_{44}O_5Si$ [M^++Na^+] 547.2856; found 547.2845

FTIR: 2924 (s), 1723 (s), 1250 (s)

5.18



Name: (1R,3a'S,4'S,6'R,7'S,7a'S)-4'-acetyl-4-(dimethyl(phenyl)silyl)-7'-methyl-6'-((E)-non-1-en-1-yl)tetrahydro-2'H,4'H-spiro[cyclopentane-1,3'-furo[3,2-c]pyran]-2,2'-dione

Procedure: The starting material **5.17** (470 mg, 0.9 mmol) was dissolved in dry acetonitrile (10 mL), after which piperidine (0.047 mL, 0.5 mmol) and tetrabutylammonium hydrogen sulfate (31 mg, 0.1 mmol) was added. The mixture was stirred at 65 °C overnight. The reaction was quenched with quenched with a saturated solution of aqueous ammonium chloride. The aqueous phase was extracted twice. The combined organic layers dried with magnesium sulfate and filtered. The combined organic layers were dried with magnesium sulfate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield **5.18** as a mixture of diastereomers. (180 mg, 0.34 mmol, 38%).

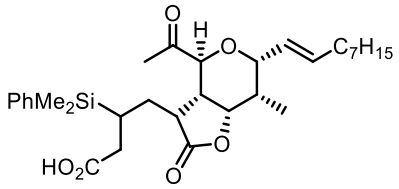
^{1}H NMR (400 MHz, C_6D_6) δ 7.46 – 7.38 (m, 2H, major), 7.37 – 7.27 (m, 2H, minor), 7.23 – 7.17 (m, 3H, mix), 6.05 – 5.83 (m, 1H, mix), 5.81 – 5.47 (m, 1H, mix), 5.20 (dd, *J* = 5.6, 3.3 Hz, 1H, minor), 5.10 (dd, *J* = 4.9, 3.5 Hz, 1H), 4.05 (dd, *J* = 8.6, 5.8 Hz, 1H, mix), 3.95 (d, *J* = 8.9 Hz, 1H, minor), 3.84 (d, *J* = 9.9 Hz, 1H, major), 3.14 (dd, *J* = 8.9, 5.5 Hz, 1H, minor), 2.96 (dd, *J* = 10.0, 4.9 Hz, 1H, major), 2.35 (t, *J* = 14.0 Hz, 1H, major), 2.30 – 2.19 (m, 1H, minor), 2.20 – 2.11 (m, 1H, major), 2.00 – 1.93 (m, 2H, mix), 1.92 (s, 3H, minor), 1.88 (s, 3H, major), 1.87 – 1.79 (m, 1H, mix), 1.79 – 1.54 (m, 2H, mix), 1.42 – 1.16 (m, 10H, mix), 0.91 (t, *J* = 7.0 Hz, 3H, mix), 0.82 (d, *J* = 7.3 Hz, 3H, major), 0.79 (d, *J* = 7.3 Hz, 3H, minor), 0.11 (s, 3H, minor), 0.10 (s, 3H, major), 0.08 (s, 3H, minor), 0.06 (s, 3H, major).

^{13}C NMR (101 MHz, C_6D_6) δ 212.7, 203.0, 174.2, 139.5, 137.0, 134.1, 129.6, 128.3, 124.9, 77.7, 77.2, 70.3, 62.3, 40.2, 39.1, 34.4, 32.9, 32.3, 31.7, 29.5, 29.5, 29.4, 29.4, 27.1, 23.1, 20.0, 14.4, 13.8, -4.53, -6.38.

HRMS: HRMS (EI) m/z calculated for $C_{31}H_{44}O_5Si$ [M^+-CH_3] 509.2723; found 509.2708

FTIR: 2924 (s), 1771 (s), 1727 (s), 1108 (s)

5.20



Name: (2S)-2-((2S,3S,4S,5R,6R)-2-acetyl-4-hydroxy-5-methyl-6-((E)-non-1-en-1-yl)tetrahydro-2H-pyran-3-yl)-4-(dimethyl(phenyl)silyl)hexanedioic acid

Procedure: In a round bottom flask was dissolved compound **5.18** (15 mg, 0.028 mmol) in 1:1 THF:H_2O (1 mL). Barium hydroxide was added and the mixture stirred at room temperature for 1 hour. The reaction was quenched with quenched with a saturated solution of aqueous ammonium chloride. The aqueous phase was extracted twice. The combined organic layers dried with magnesium sulfate and filtered. The combined organic layers were washed with brine, dried with magnesium sulfate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (2% MeOH:DCM) to yield the observed product **5.20**. (12 mg, 77%).

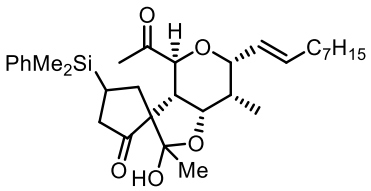
^{1}H NMR (600 MHz, C_6D_6) δ 7.60 – 7.42 (m, 2H), 7.24 – 7.17 (m, 4H), 5.98 (ddt, *J* = 15.2, 8.6, 1.5 Hz, 1H), 5.70 – 5.52 (m, 1H), 4.11 (dt, *J* = 8.4, 5.5 Hz, 1H), 3.91 (d, *J* = 9.2 Hz, 1H), 3.79 (dd, *J* = 4.5, 2.9 Hz, 1H), 2.89 (dddd, *J* = 9.2, 6.6, 4.5, 2.5 Hz, 1H), 2.61 (ddd, *J* = 9.5, 6.5, 4.6 Hz, 1H), 2.43 (dd, *J* = 16.7, 5.1 Hz, 1H), 2.20 (dd, *J* = 16.8, 6.9 Hz, 1H), 1.97 (s, 2H), 1.96 – 1.84 (m, 3H), 1.80 – 1.73 (m, 1H), 1.64 (dq, *J* = 11.0, 3.5 Hz, 1H), 1.57 – 1.50 (m, 1H), 1.33 – 1.26 (m, 5H), 1.26 – 1.16 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 4H), 0.84 (d, *J* = 7.2 Hz, 3H), 0.25 (s, 4H), 0.25 (s, 4H).

^{13}C NMR (151 MHz, C_6D_6) δ 203.8, 179.2, 177.0, 138.6, 137.5, 134.5, 133.5, 129.5, 125.8, 78.1, 77.8, 71.4, 37.3, 34.3, 34.1, 32.8, 32.3, 29.5 (3C), 29.4, 26.9, 26.2, 23.1, 19.5, 14.4, 14.1, -4.6, -4.8.

IR: 2923 (s), 1772 (s), 1728 (s), 1163 (s)

HRMS: HRMS (ESI) m/z calculated for $C_{31}H_{48}O_7Si$ [$M^+ + Na^+$] 565.2961; found 565.2954

5.19



Name: (1R,3a'S,4'S,6'R,7'S,7a'S)-4'-acetyl-4-(dimethyl(phenyl)silyl)-2'-hydroxy-2',7'-dimethyl-6'-((E)-non-1-en-1-yl)tetrahydro-2'H,4'H-spiro[cyclopentane-1,3'-furo[3,2-c]pyran]-2-one

Procedure: In a round bottom flask, LiHMDS (1M in THF, 0.9 mL, 0.9 mmol) was further dissolved in THF (2 mL). The solution was cooled to -78ºC, followed by addition of TMSCl (0.18 mL, 1.4 mmol) and **5.18** (180 mg, 0.34 mmol) dissolved in THF (2 mL). The mixture was stirred for 30 min at -78ºC then warmed to room temperature and stirred for 2 hours. The mixture was quenched with addition of a few drops of triethylamine followed by saturated aqueous sodium bicarbonate and diethyl ether. The phases were separated and the aqueous phase extracted 3 times with ether. The organic phases were combined and dried with magnesium sulphate. After filtration, the solvent was removed in vacuo. The crude mixture was directly taken to the next step.

The crude mixture was dissolved in diethyl ether (2 mL) and cooled to -78ºC. To this solution was added methyl lithium (1.6 M in diethyl ether, 2.3 mL, 3.6 mmol). The mixture was warmed to room temperature over 45 minutes. The solution was cooled to 0ºC, followed by addition of saturated aqueous ammonium chloride to quench the reaction. The layers were separated and the aqueous phase was extracted twice. The combined organic layers dried with magnesium sulfate and filtered. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the desired product **5.19** (44 mg, 0.081 mmol, 24% yield)

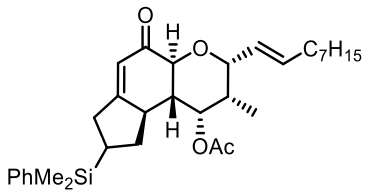
^{1}H NMR (400 MHz, C_6D_6) δ 7.42 – 7.33 (m, 2H), 7.27 – 7.18 (m, 3H), 5.94 (ddd, *J* = 16.5, 15.1, 8.7 Hz, 1H), 5.50 (dt, *J* = 16.4, 7.2 Hz, 1H), 5.36 (t, *J* = 2.6 Hz, 1H, maj), 5.17 (t, *J* = 2.6 Hz, 1H, minor), 4.66 (d, *J* = 10.6 Hz, 1H, major), 4.59 (d, *J* = 11.1 Hz, 1H, minor), 4.07 (dt, *J* = 9.0, 6.0 Hz, 1H, mix), 2.62 (dt, *J* = 11.1, 2.4 Hz, 1H, mix), 2.30 (ddd, *J* = 10.7, 5.0, 2.5 Hz, 1H, mix), 2.26 (s, 3H, minor), 2.22 (s, 3H, maj), 2.26 – 2.15 (m, 2H, mix), 2.17 – 2.02 (m, 1H, mix), 2.02 – 1.95 (m, 2H, mix), 1.91 (m, 2H, mix), 1.81 – 1.77 (m, 1H, mix), 1.74 (s, 3H, minor), 1.71 (s, 3H, major), 1.70 – 1.61 (m, 1H, mix), 1.34 – 1.17 (m, 10H), 0.95 – 0.87 (m, 3H, mix), 0.60 (d, *J* = 7.1 Hz, 3H, min), 0.60 (d, *J* = 7.1 Hz, 3H, maj), 0.35 – 0.09 (m, 6H, mix).

^{13}C NMR (101 MHz, C_6D_6) δ 217.7 (M), 217.5 (m), 209.4 (m), 207.6 (M), 169.8 (M), 169.6 (m), 138.2 (m), 137.4 (M), 136.3 (m), 135.5 (M), 134.2 (M,2), 134.1 (m,2), 129.5 (M), 129.3 (m), 126.7 (M), 126.4 (m), 78.4 (M), 78.2 (m), 75.1 (M), 74.5 (m), 73.3 (m), 71.7 (M), 53.1 (m), 50.4 (M), 41.4 (M), 41.2 (m), 39.8 (M), 38.7 (m), 37.8 (M), 37.5 (m), 32.9 (M), 32.8 (m), 32.2 (M), 32.2 (m), 29.9 (m), 29.5 (M), 29.5 (M), 29.4 (m), 27.5 (m), 26.0 (M), 26.0 (m), 23.1 (mix), 21.7 (M), 21.4 (m), 20.9 (M), 20.8 (m), 14.3 (M), 13.9 (m), -4.5 (m), -4.9 (M), -5.0 (M), -5.8 (m).

HRMS: HRMS (ESI) m/z calculated for $C_{32}H_{48}O_5Si$ [M + Na^+] 563.3169; found 563.3180

FTIR: 2924 (s), 1739 (s), 1230 (s)

5.21



Name: (1R,3a'S,4'S,6'R,7'S,7a'S)-4'-acetyl-4-(dimethyl(phenyl)silyl)-2'-hydroxy-2',7'-dimethyl-6'-((E)-non-1-en-1-yl)tetrahydro-2'H,4'H-spiro[cyclopentane-1,3'-furo[3,2-c]pyran]-2-one

Procedure: 10 mg to 6 mg, 20% EtOAc:Hex. Major diastereomer isolated

Magnesium bromide diethyl etherate (10 mg, 0.038 mmol) was suspended DCM (0.3 mL). DIPEA (0.01 mL, 0.076 mmol) was added to the suspension and stirred at room temperature for 30 min, upon which the suspension turned to a dark pink. The hemiacetal **5.19** (10 mg, 0.019 mmol) dissolved in DCM (0.3 mL) was added to the suspension. The mixture was stirred for 3 hours at room temperature. The reaction was quenched with an aqueous saturated solution of NH_4Cl. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. The dried organic layers were evaporated under reduced pressure and taken to the next step directly.

The crude material was dissolved in THF (0.4 mL). To the solution was added PPTS (10 mg, 0.04 mmol). The mixture was stirred at reflux for 3 hours. The mixture was diluted with water and diethyl ether. The phases were separated. The aqueous phase was extracted twice, the organic phases combined and dried with magnesium sulphate. The dried organic layers were evaporated under reduced pressure and purified with flash chromatography (10% EtOAc:Hex) to yield the condensation product (6 mg, 0.011 mmol, 60% yield) as a mixture of diastereomers. The major diastereomer of **5.21** was isolated and characterized.

^{1}H NMR (600 MHz, C_6D_6) δ 7.50 – 7.35 (m, 2H), 7.26 – 7.18 (m, 3H), 5.93 (ddt, *J* = 15.4, 8.1, 1.6 Hz, 1H), 5.86 (d, *J* = 2.2 Hz, 1H), 5.70 (dt, *J* = 14.5, 6.6 Hz, 1H), 5.17 (t, *J* = 2.7 Hz, 1H), 4.30 (dd, *J* = 7.2, 6.8 Hz, 1H), 4.28 (d, *J* = 12.1 Hz, 1H), 2.29 – 2.13 (m, 3H), 2.09 – 1.93 (m, 3H), 1.81 – 1.76 (m, 1H), 1.75 (s, 3H), 1.59 – 1.52 (m, 1H), 1.38 – 1.32 (m, 2H), 1.31 – 1.21 (m, 10H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.65 (d, *J* = 7.2 Hz, 3H), 0.15 (s, 6H).

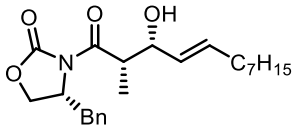
^{13}C NMR (151 MHz, C_6D_6) δ 193.7, 170.5, 169.5, 137.5, 135.3, 134.2 (2), 129.6, 128.2 (2), 126.3, 122.1, 78.1, 71.1, 70.1, 48.8, 45.0, 37.2, 33.5, 33.2, 33.1, 32.2, 29.6, 29.6, 29.5, 24.4, 23.1, 20.3, 14.3, 13.9, -4.2, -5.1.

HRMS: HRMS (ESI) m/z calculated for $C_{32}H_{46}O_4Si$ [$M^+ + Na^+$] 545.3063; found 545.3071

FTIR: 2926 (s), 1742 (s), 1683 (s), 1233 (s)

$[\alpha_D]^{25}$: +52 (*c* 0.0010, DCM)

2.15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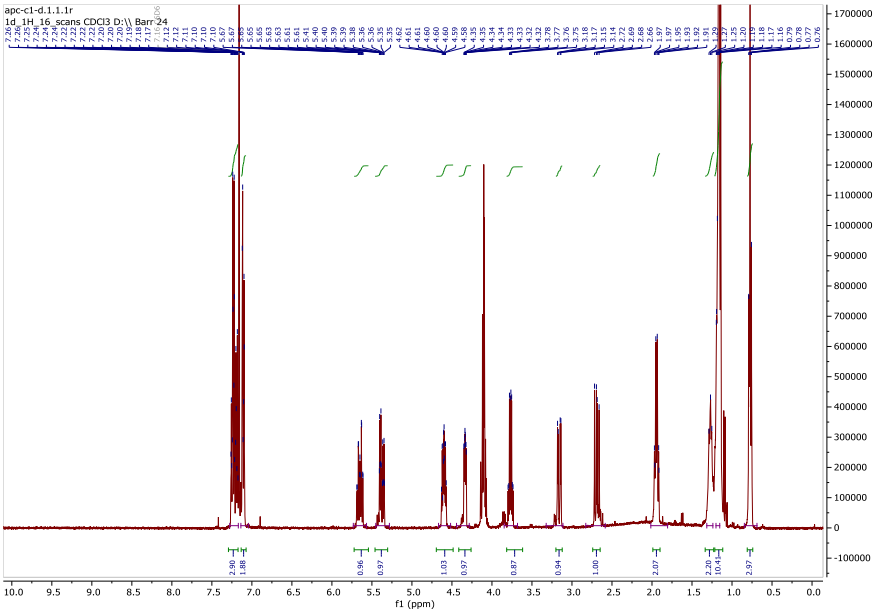
Bn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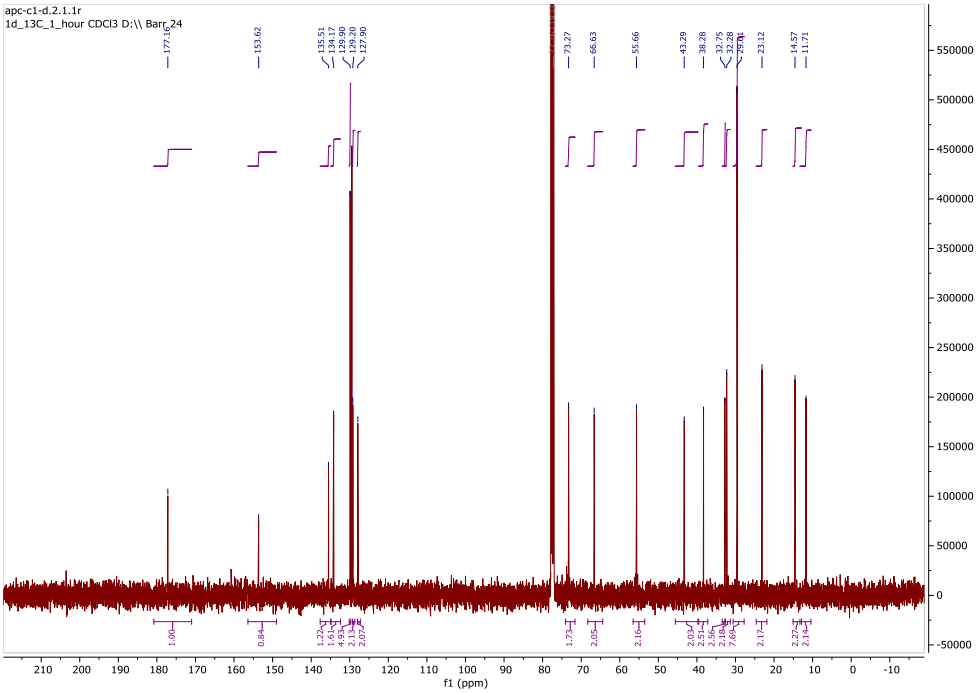
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127.90
73.27
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14.57
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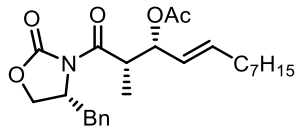
f1 (ppm)

2.17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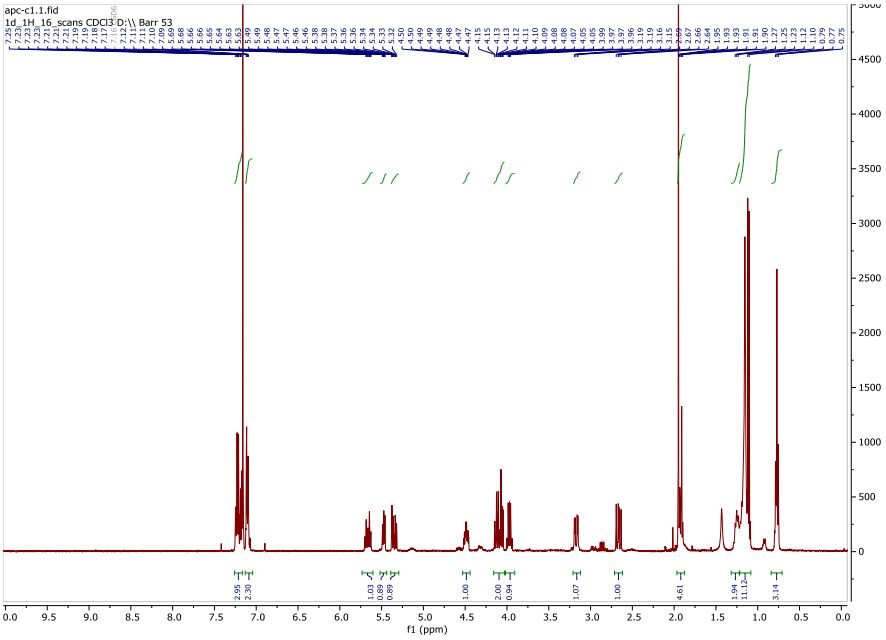
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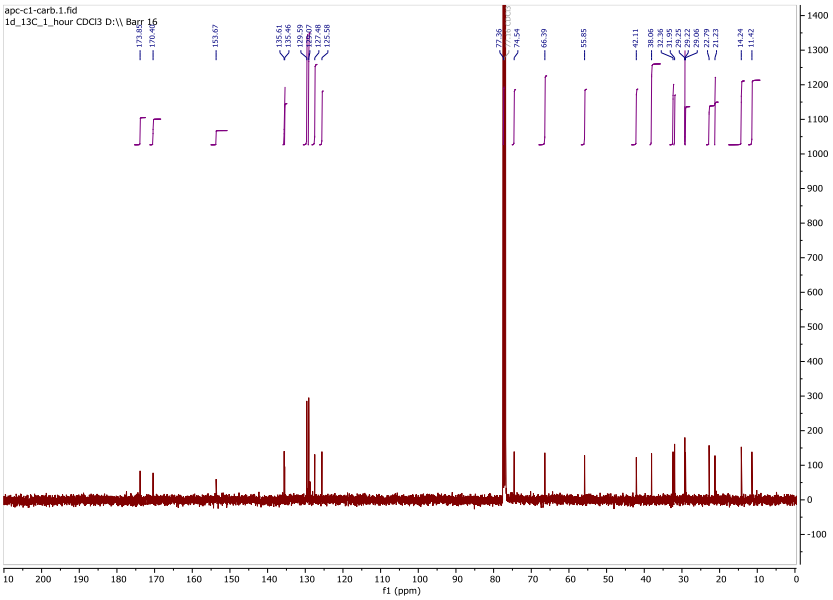
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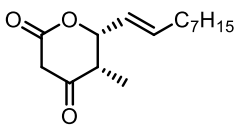
f1 (ppm)

2.18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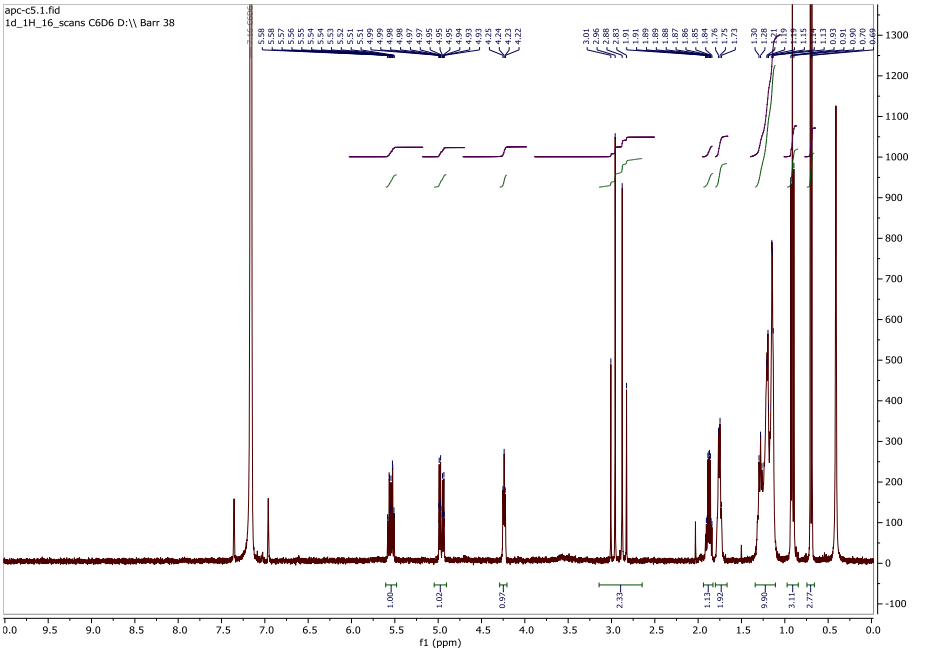
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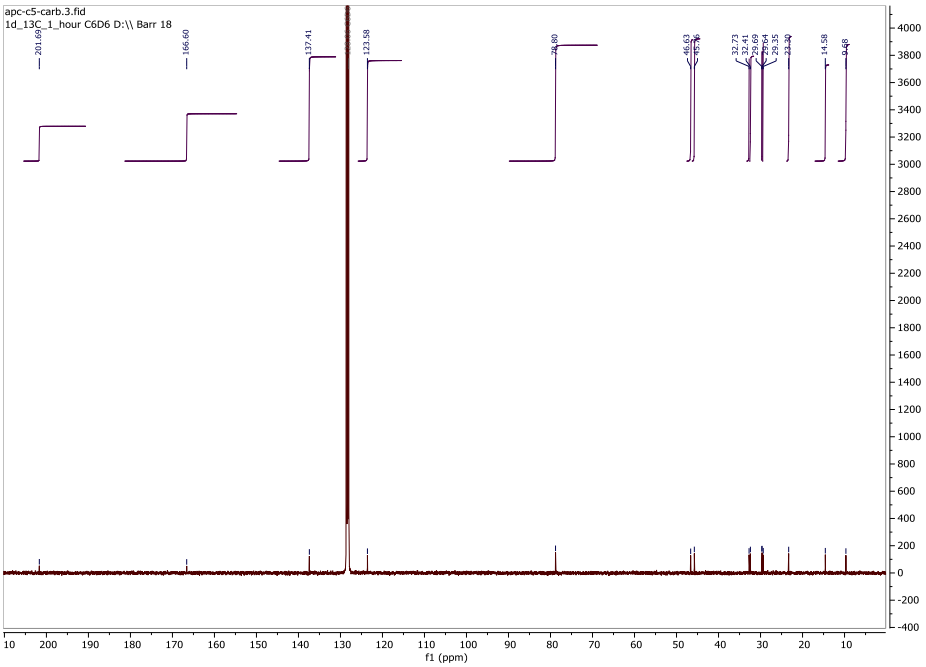
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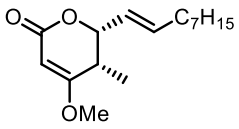
2.19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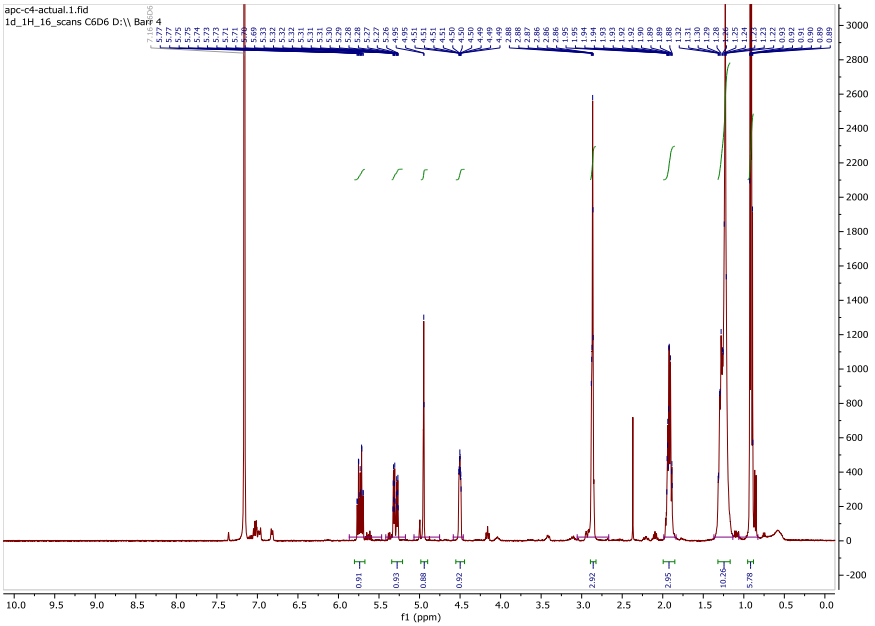
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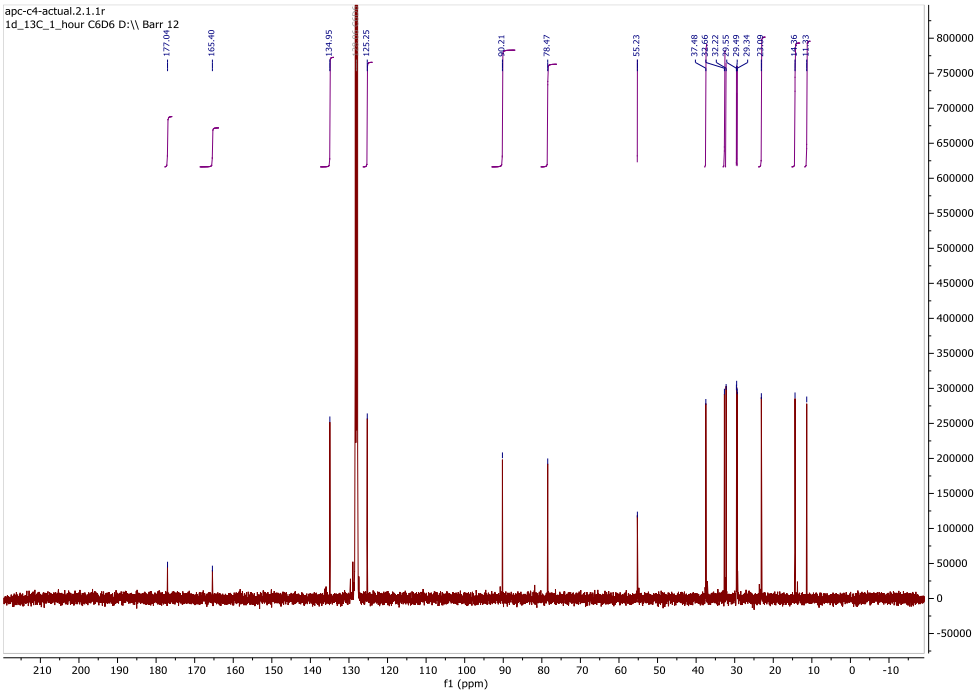
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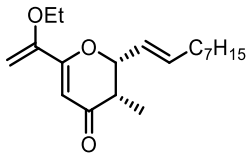
14.26
11.23
f1 (ppm)

2.20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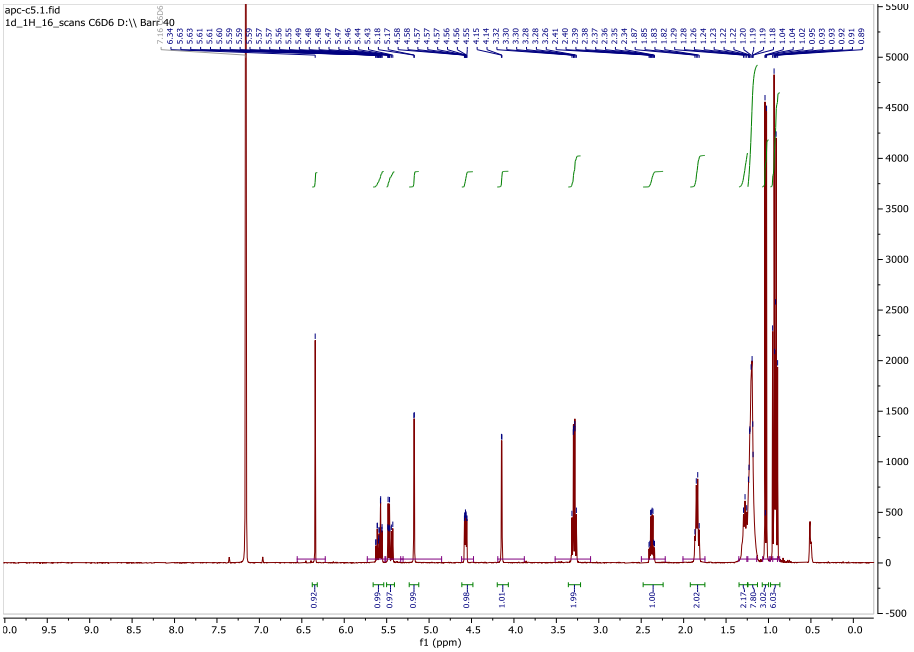
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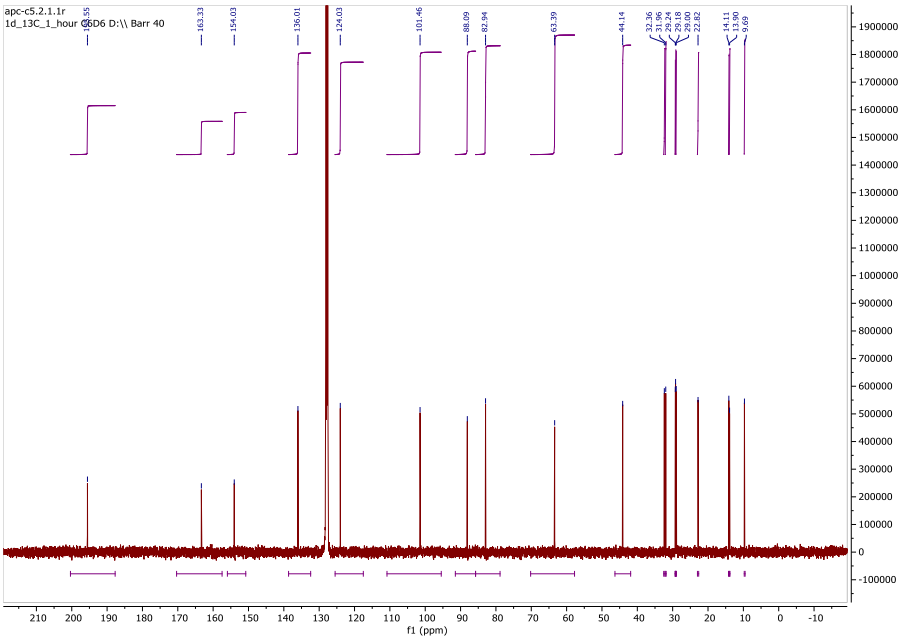
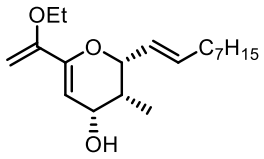
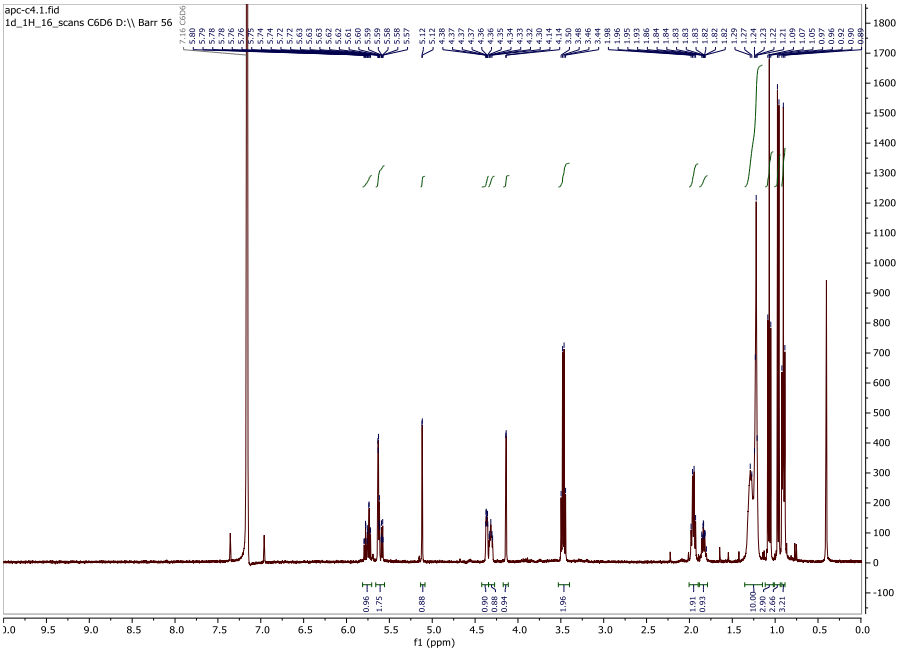
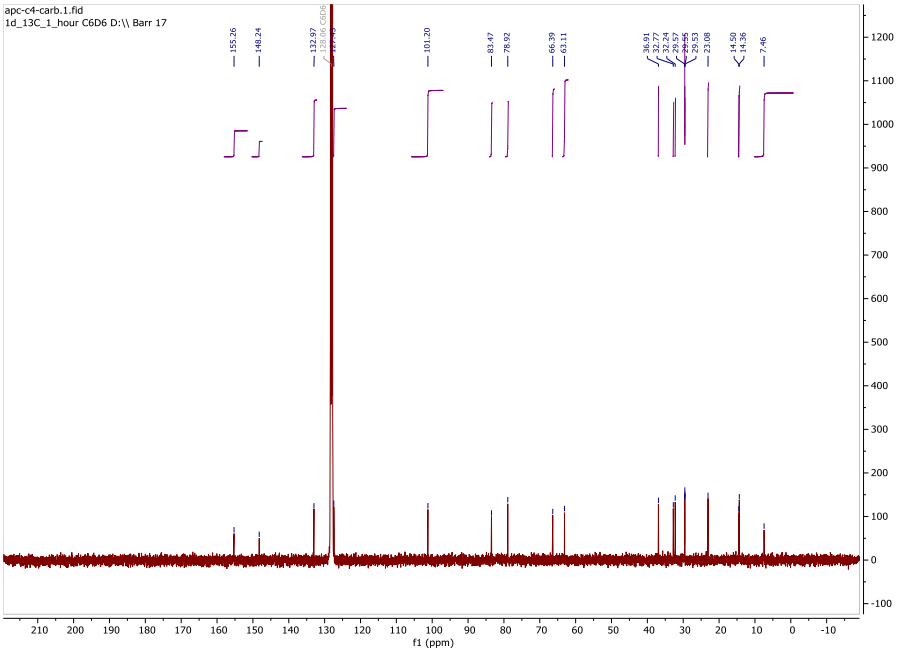
1d_1H_16_scans C6D6 D:\\ Barr 40
f1 (ppm)


apc-c5.2.1.1r
1d_13C_1_hour C6D6 D:\\ Barr 40
f1 (ppm)

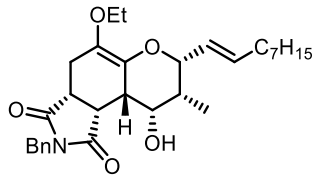
2.11

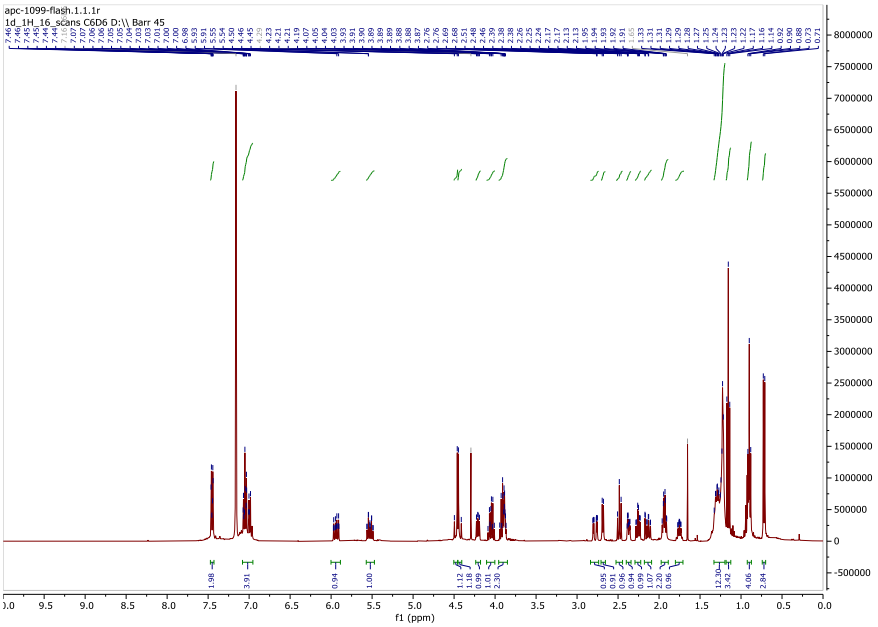

OEt
O
C_7H_{15}
OH

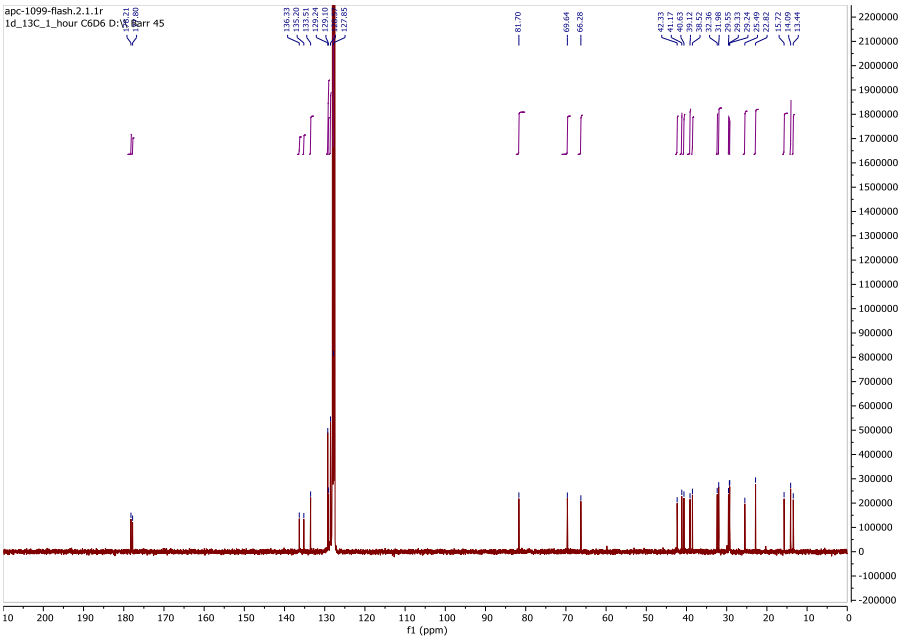

apc-c4.1.fid
1d_1H_16_scans C6D6 D:\\ Barr 56
f1 (ppm)

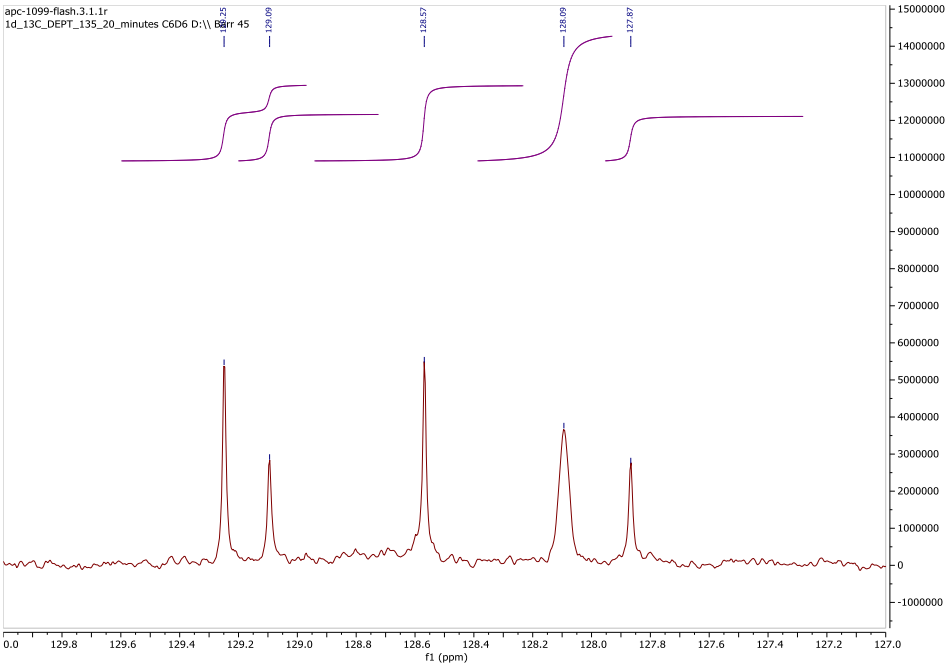

apc-c4-carb.1.fid
1d_13C_1_hour C6D6 D:\\ Barr 17
155.26
148.24
132.97
128.06 C6D6
101.20
83.47
78.92
66.39
63.11
36.91
32.77
32.74
29.57
29.55
29.53
23.08
14.50
14.36
7.46
f1 (ppm)

2.26

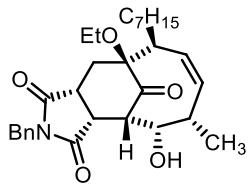

OEt
O
C_7H_{15}
O
H
OH
BnN
O

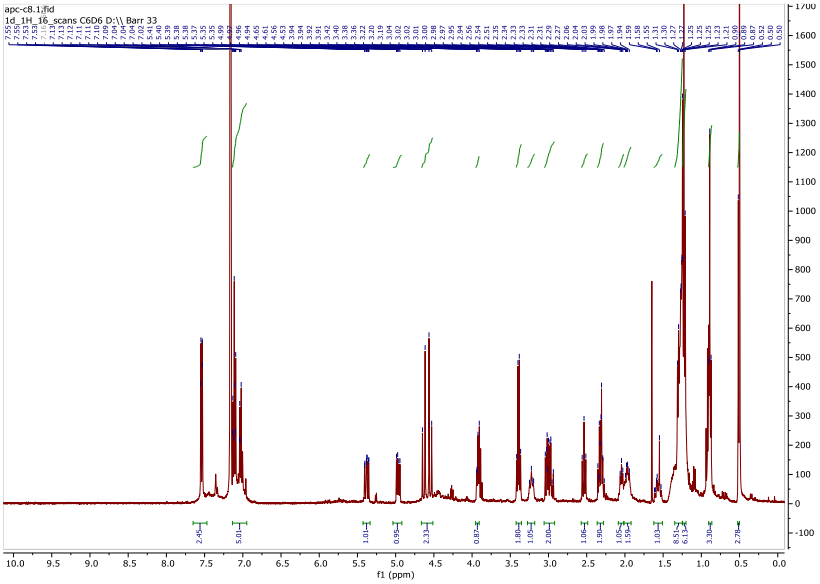

apc-1099-flash.1.1.1r
1d_1H_16_scans C6D6 D:\\ Barr 45
f1 (ppm)

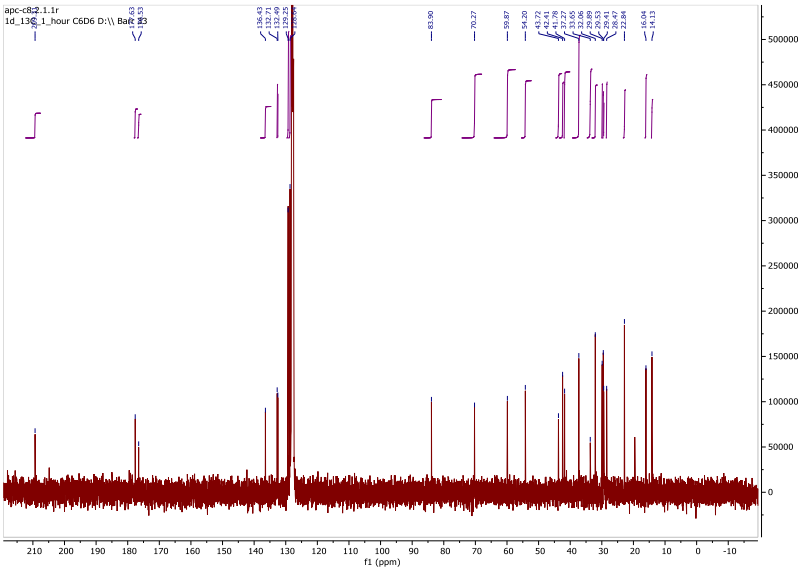

apc-1099-flash.2.1.1r
1d_13C_1_hour C6D6 D:\\ Barr 45
f1 (ppm)

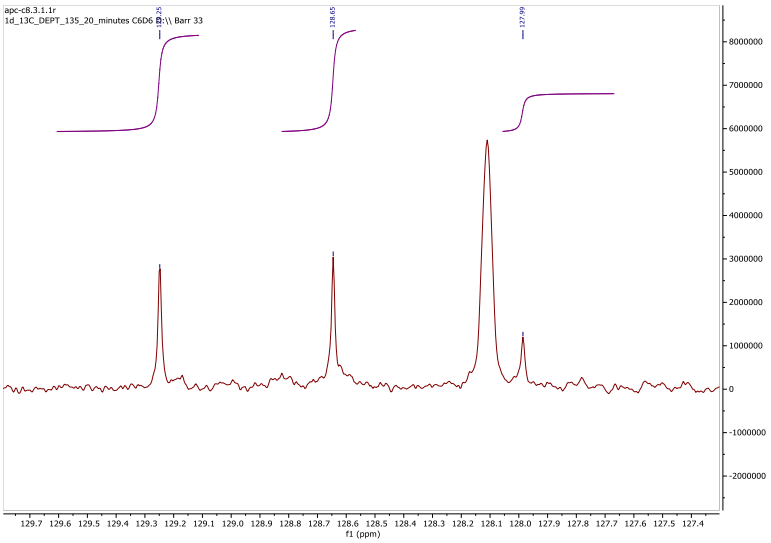

apc-1099-flash.3.1.1r
1d_13C_DEPT_135_20_minutes C6D6 D:\\ Barr 45
129.09
128.57
128.09
127.87
15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
0.0
129.8
129.6
129.4
129.2
129.0
128.8
128.6
128.4
128.2
128.0
127.8
127.6
127.4
127.2
127.0
f1 (ppm)

2.27

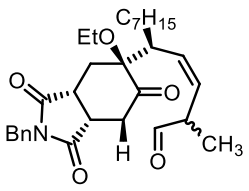


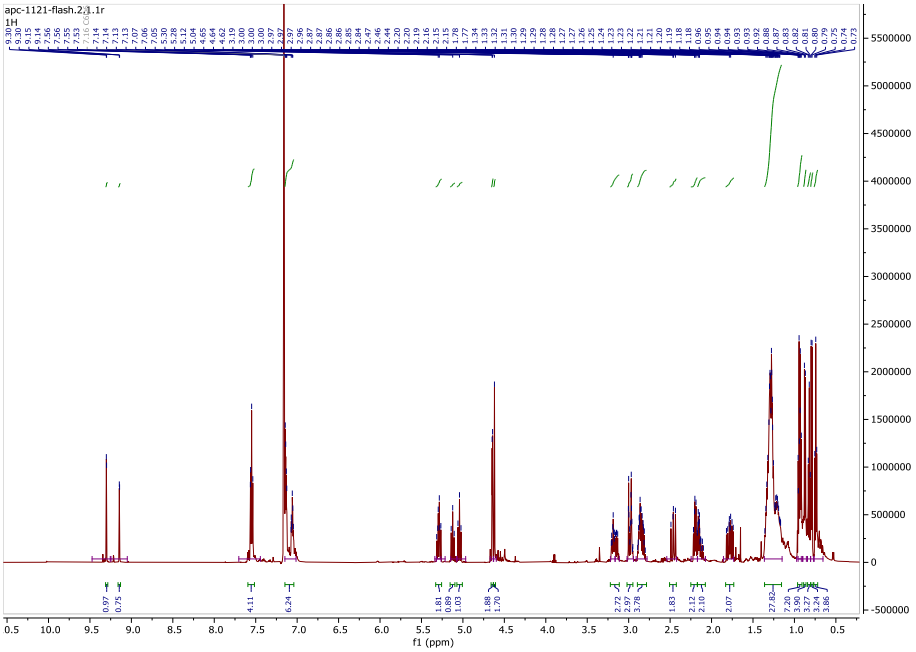


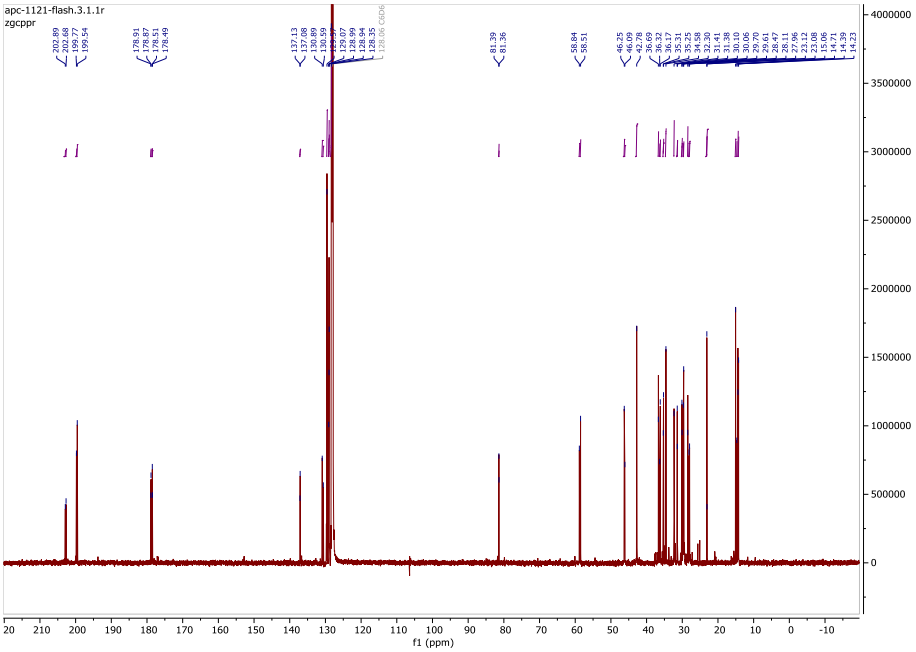



apc-c8.3.1.1r
1d_13C_DEPT_135_20_minutes C6D6 D:\\ Barr 33
129.35
128.65
127.99
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
-2000000
129.7 129.6 129.5 129.4 129.3 129.2 129.1 129.0 128.9 128.8 128.7 128.6 128.5 128.4 128.3 128.2 128.1 128.0 127.9 127.8 127.7 127.6 127.5 127.4
f1 (ppm)

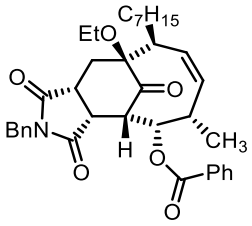
2.31

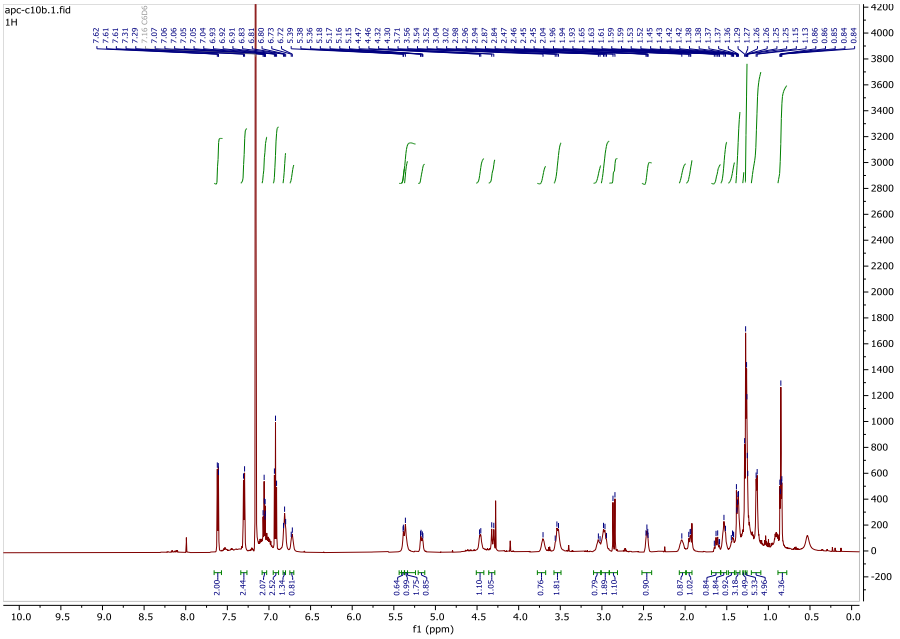

C7H15
EtO
O
O
BnN
H
O
O
CH3

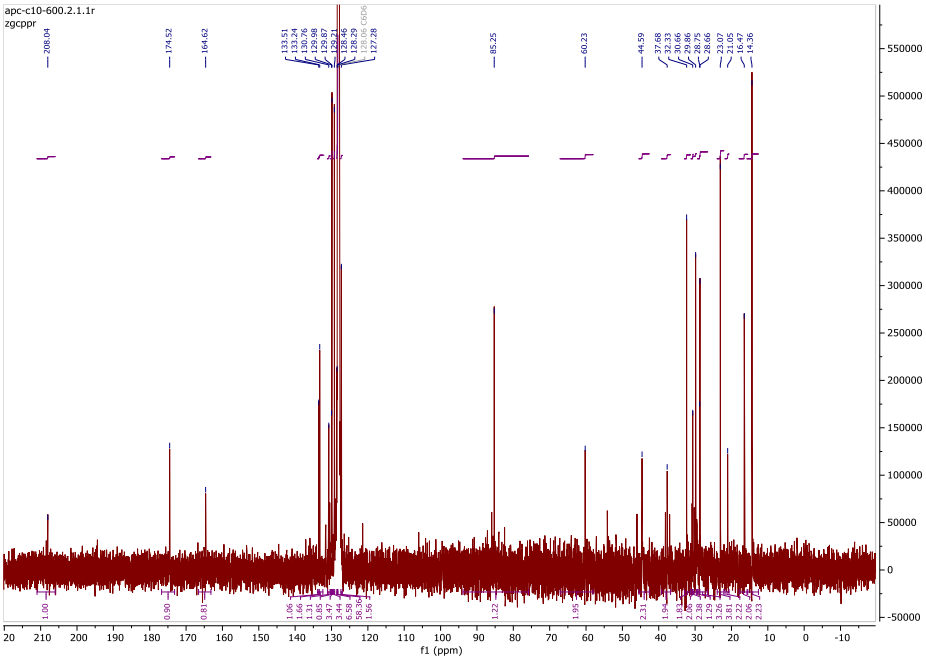

apc-1121-flash.2.1.1r
1H
f1 (ppm)

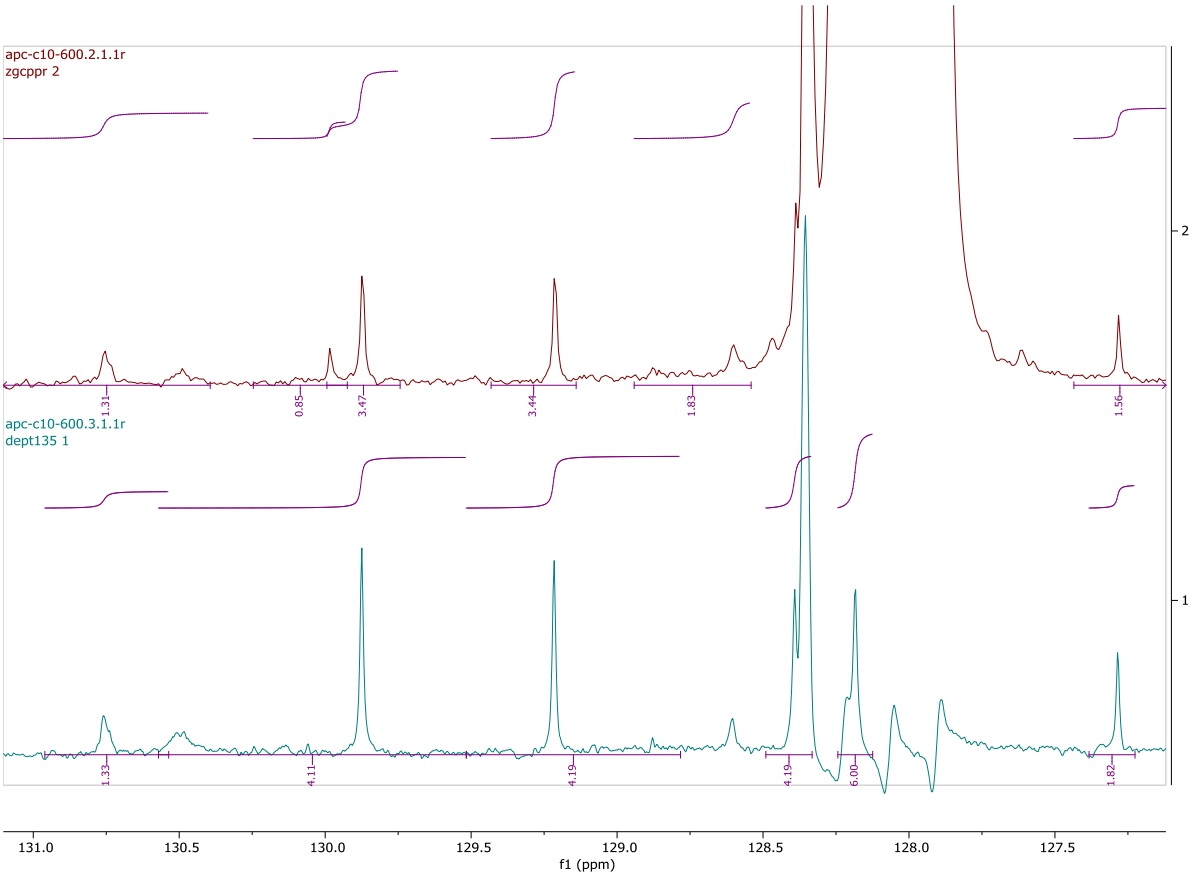

apc-1121-flash.3.1.1r
zgcppr
f1 (ppm)

2.32

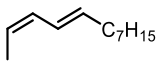

C7H15
EtO
O
O
BnN
O
H
O
CH3
Ph
O

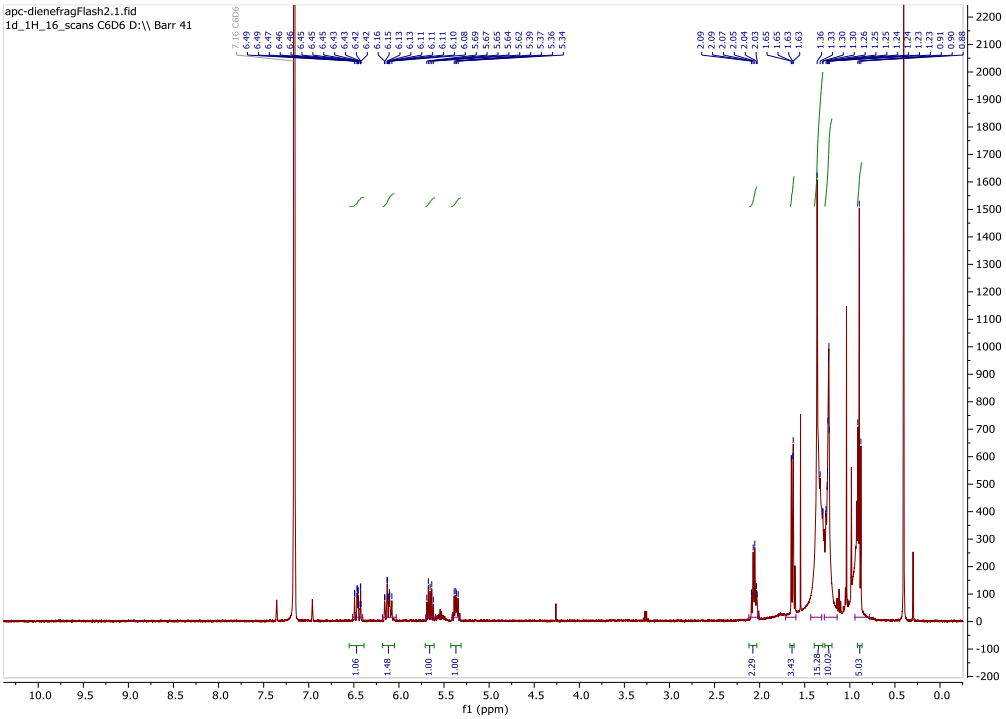

apc-c10b.1.fid
1H
f1 (ppm)

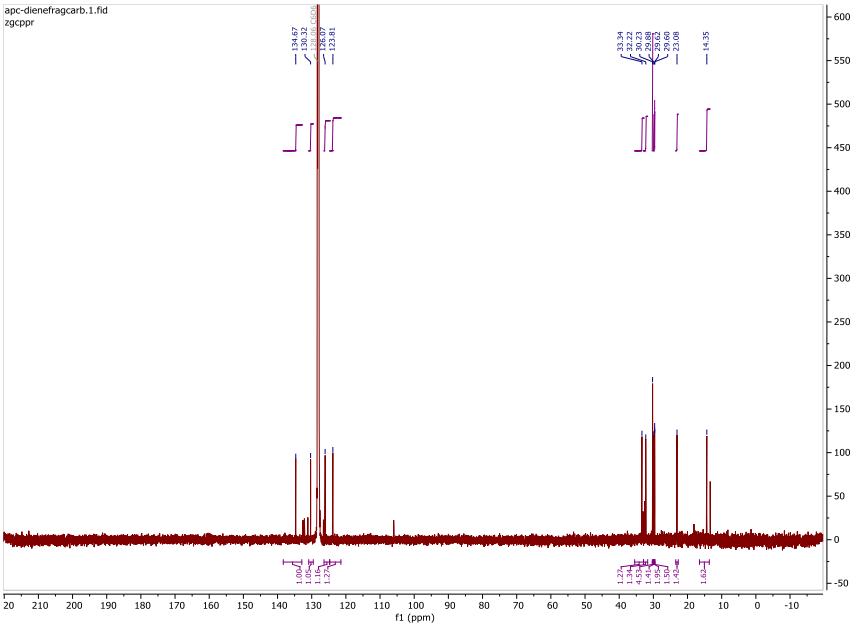

apc-c10-600.2.1.1r
zgcppr
f1 (ppm)


apc-c10-600.2.1.1r
zgcppr 2
1.31
0.85
3.47
3.44
1.83
1.56
2
apc-c10-600.3.1.1r
dept135 1
1.33
4.11
4.19
4.19
6.00
1.82
1
131.0
130.5
130.0
129.5
129.0
128.5
128.0
127.5
f1 (ppm)

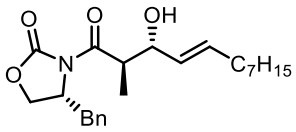
3.2

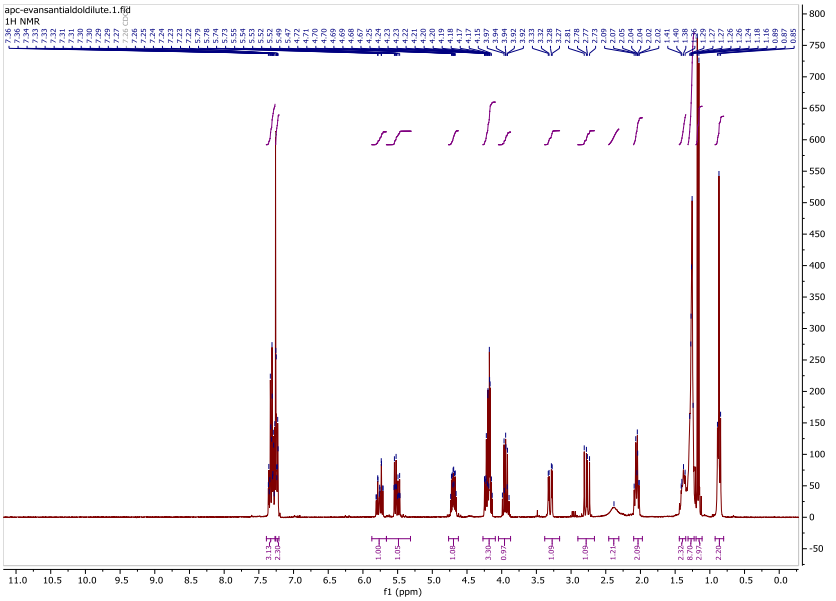

C_7H_{15}

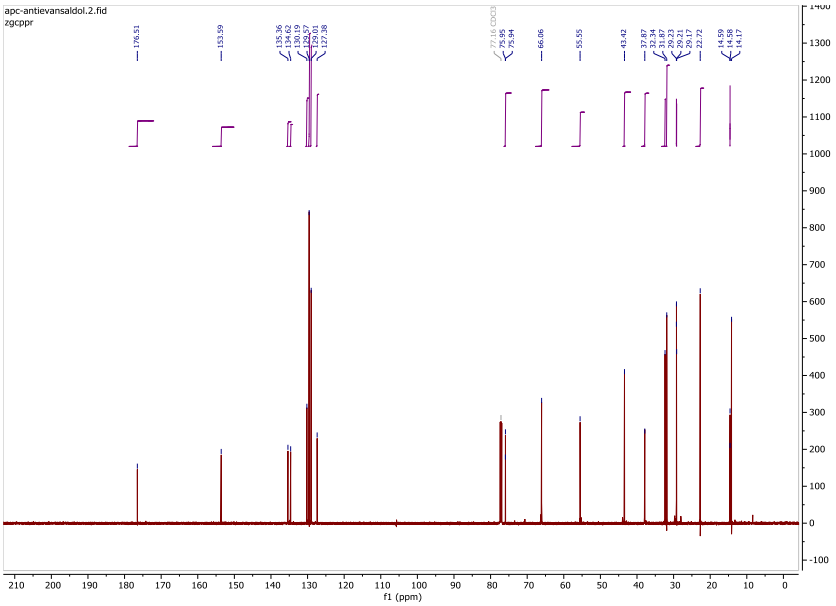

apc-dienefragFlash2.1.fid
1d_1H_16_scans C6D6 D:\\ Barr 41
f1 (ppm)


apc-dienefragcarb.1.fid
zgcppr
f1 (ppm)

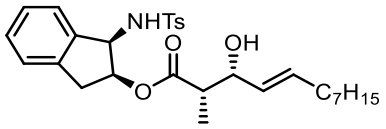
3.6

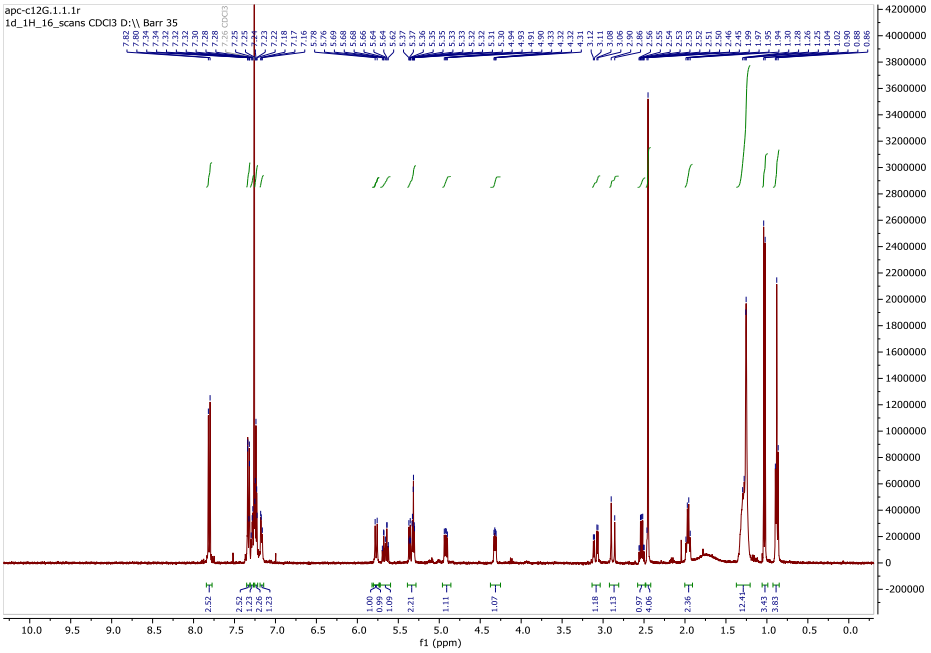

O
O
OH
N
O
C7H15
Bn

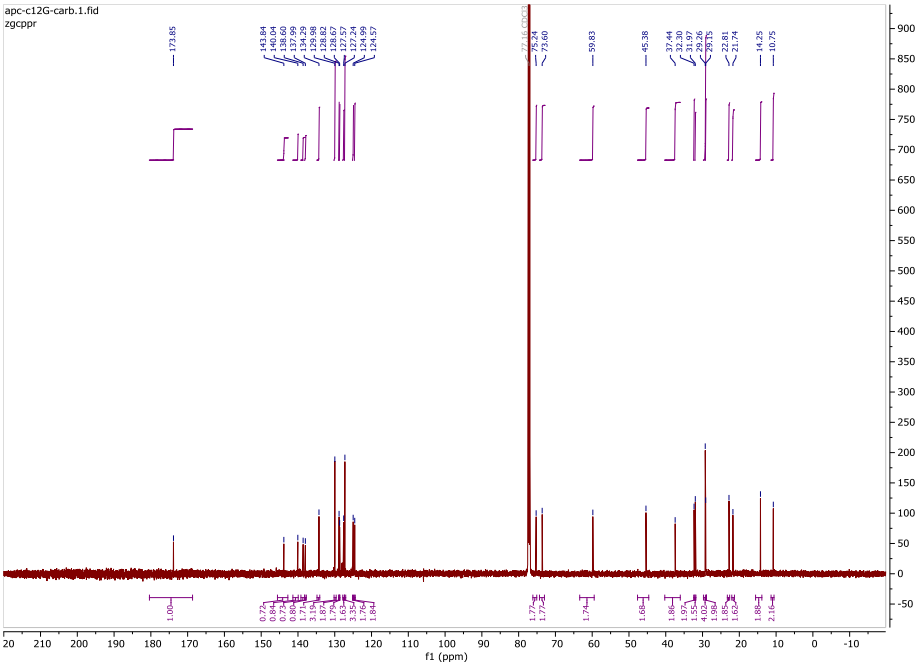

apc-evansantialdoldilute.1.fid
1H NMR
f1 (ppm)


apc-antievansaldol.2.fid
zgcppr
f1 (ppm)

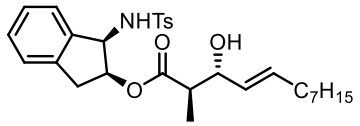
3.8-syn

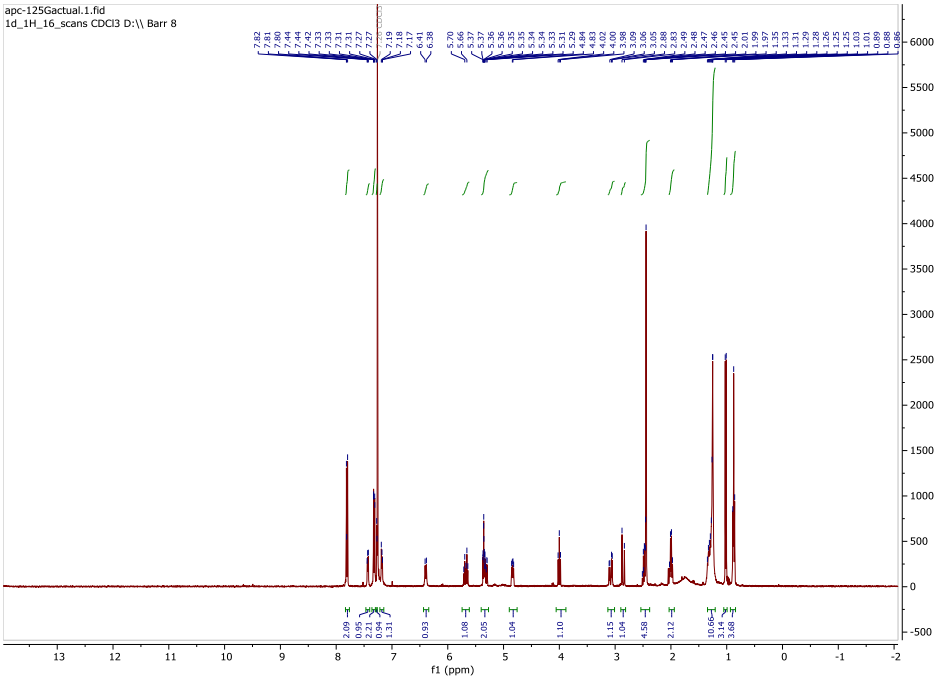

NHTs
O
OH
O
C_7H_{15}

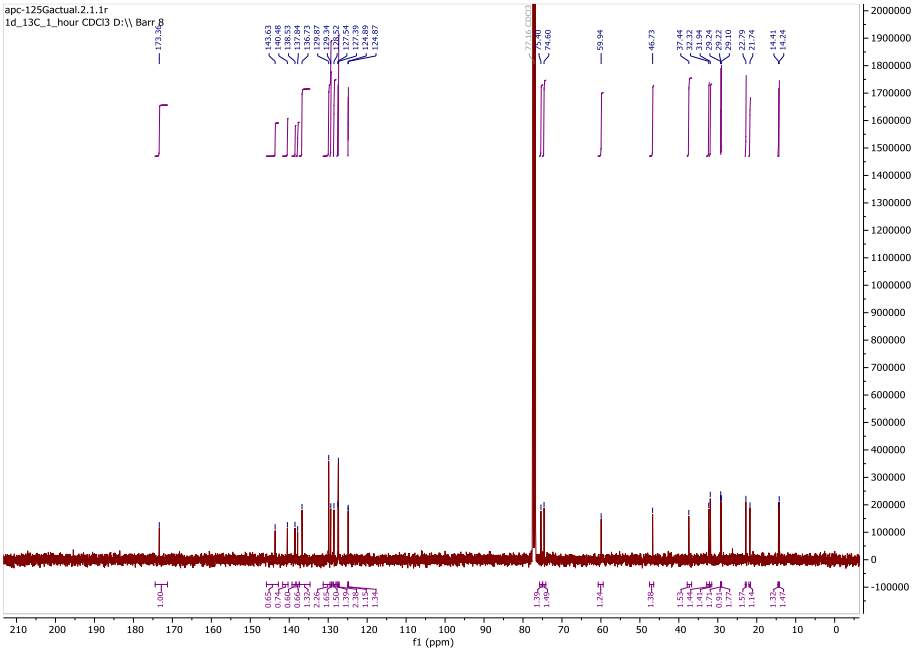

apc-c12G.1.1.1r
1d_1H_16_scans CDCl3 D:\\ Barr 35
f1 (ppm)


apc-c12G-carb.1.fid
zgcppr
f1 (ppm)

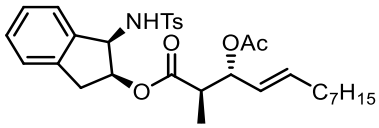
3.8

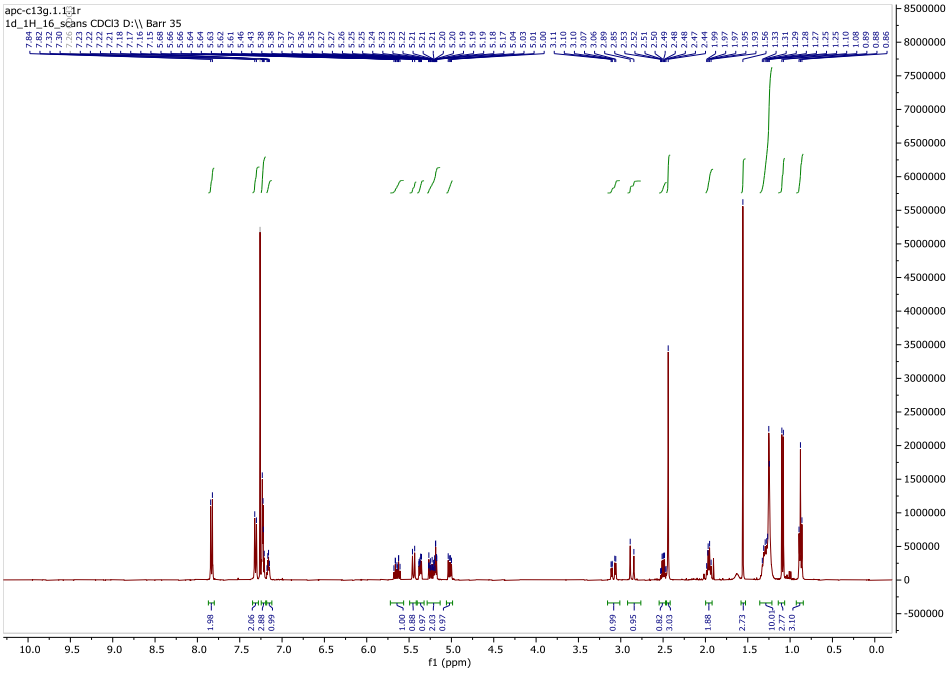

NHTs
O
OH
O
C_7H_{15}

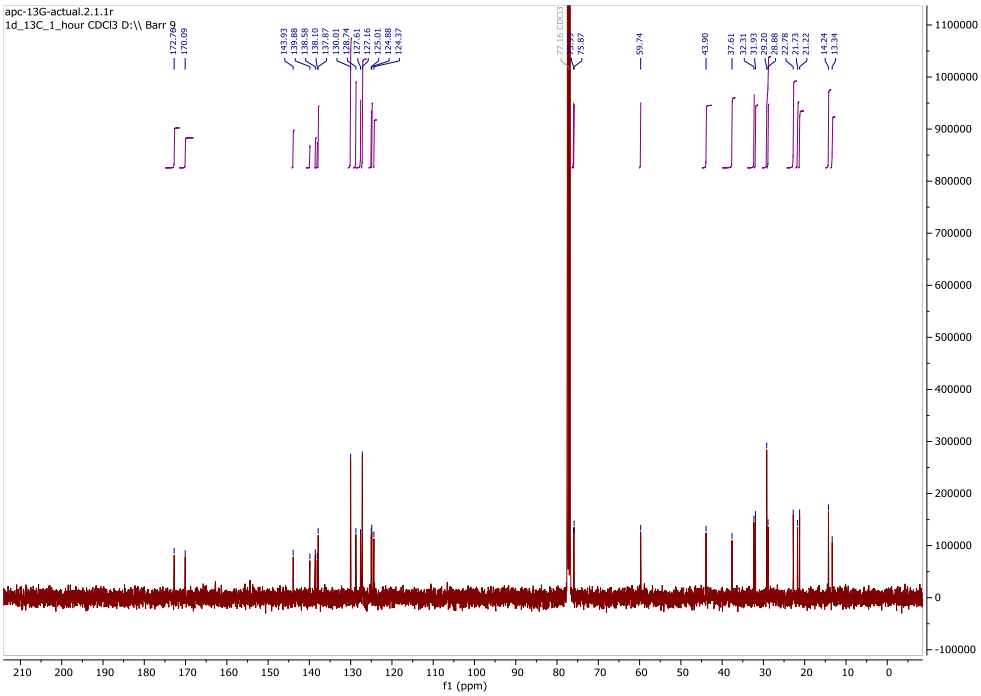

apc-125Gactual.1.fid
1d_1H_16_scans CDCl3 D:\\ Barr 8
f1 (ppm)


apc-125Gactual.2.1.1r
1d_13C_1_hour CDCl3 D:\\ Barr 8
f1 (ppm)

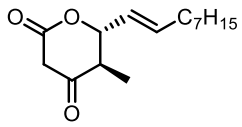
3.9

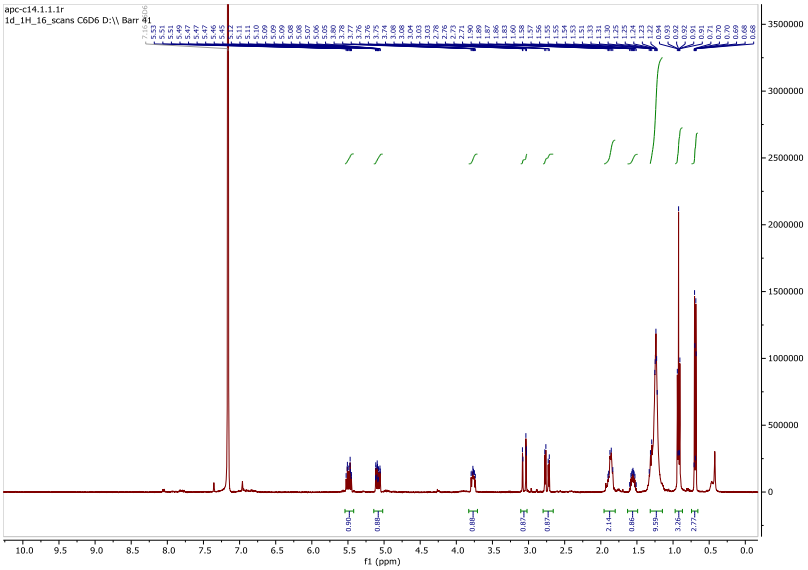

NHTs
O
OAc
O
C_7H_{15}

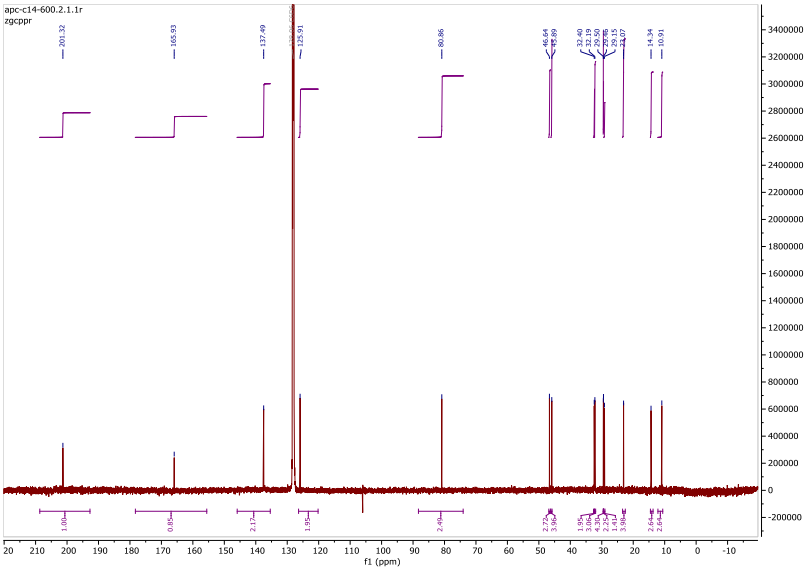

apc-c13g.1.1.1r
1d_1H_16_scans CDCl3 D:\\ Barr 35
f1 (ppm)


apc-13G-actual.2.1.1r
1d_13C_1_hour CDCl3 D:\\ Barr 9
f1 (ppm)

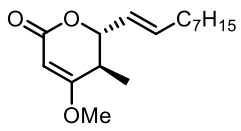
3.10

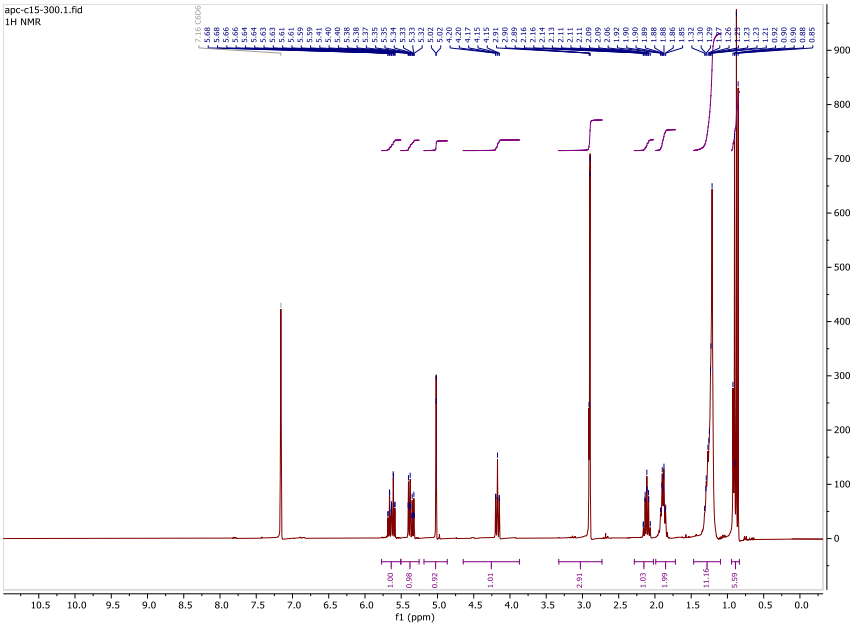

O
O
O
C_7H_{15}

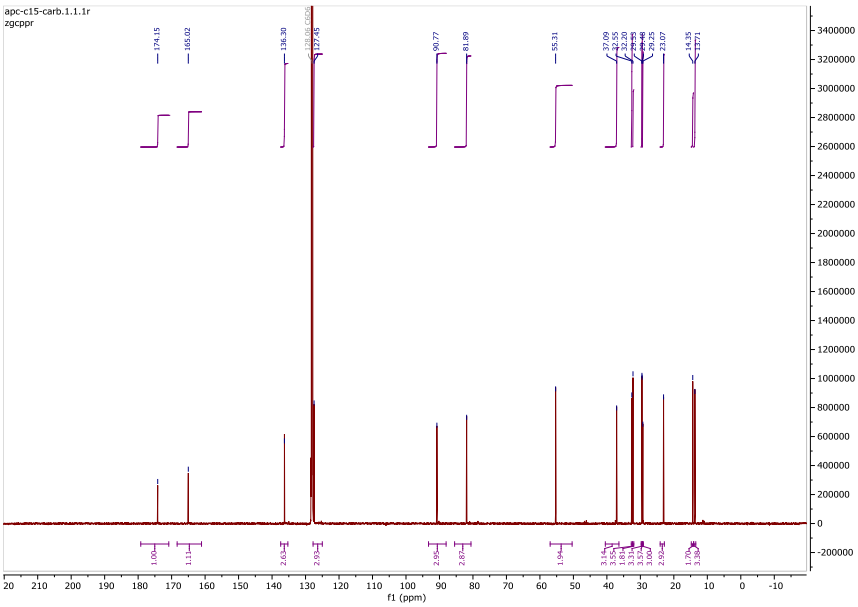

apc-c14.1.1.1r
1d_1H_16_scans C6D6 D:\\ Barr 41
f1 (ppm)


apc-c14-600.2.1.1r
zgcppr
201.32
165.93
137.49
128.91
80.86
46.64
45.89
32.40
32.19
29.50
29.36
29.15
23.07
14.34
10.91
f1 (ppm)

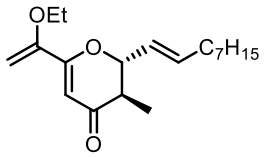
3.11

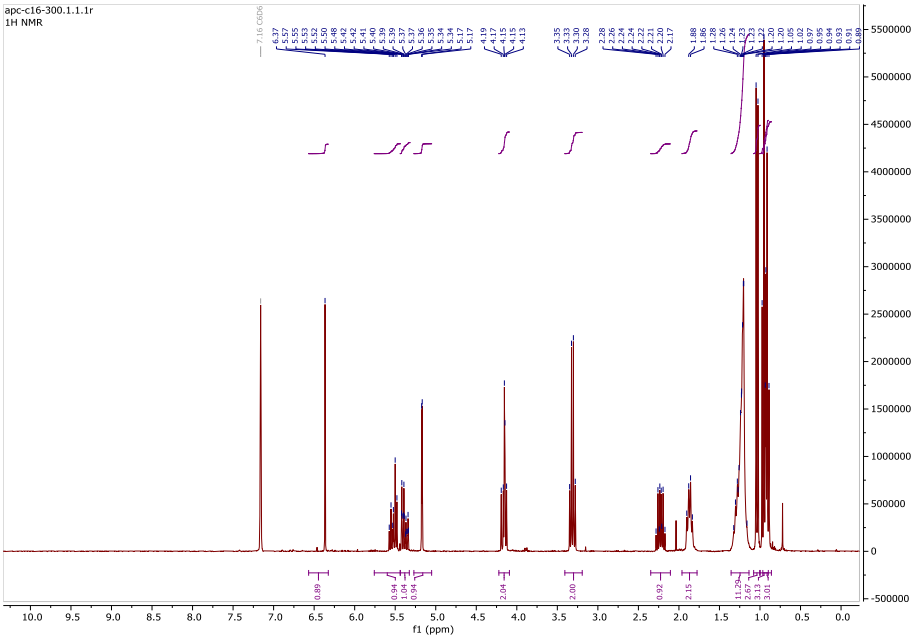

O
O
C7H15
OMe

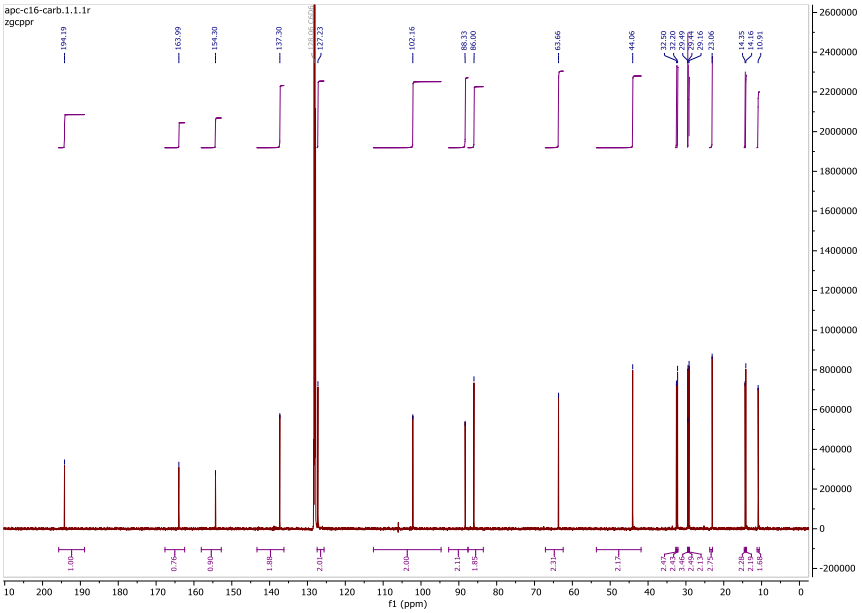

apc-c15-300.1.fid
1H NMR
f1 (ppm)


apc-c15-carb.1.1.1r
zgcppr
f1 (ppm)

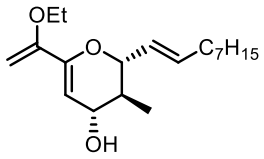
3.13

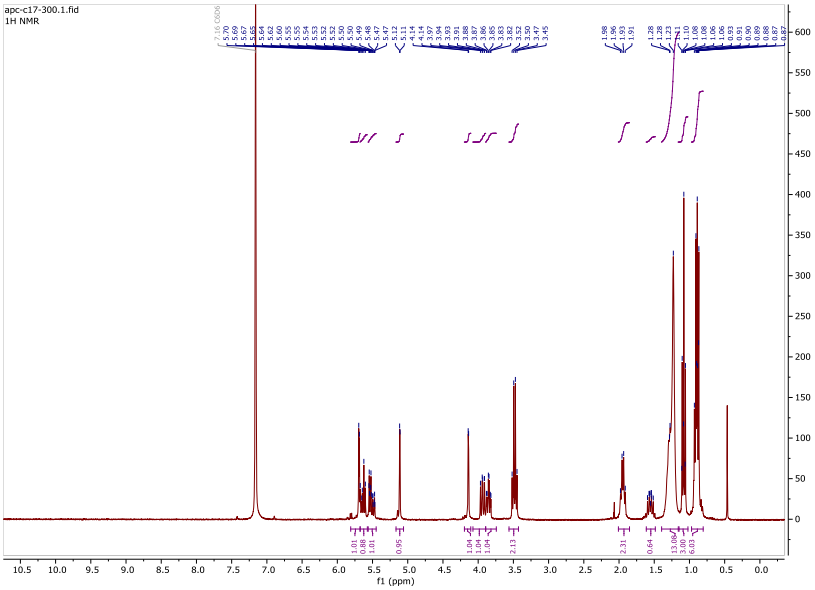

OEt
O
C_7H_{15}
O

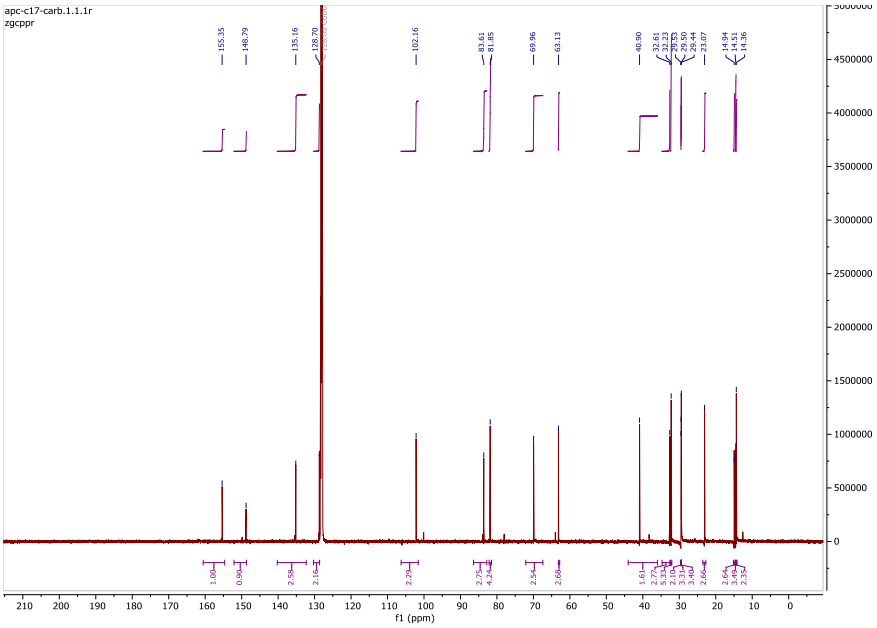

apc-c16-300.1.1.1r
1H NMR
f1 (ppm)


apc-c16-carb.1.1.1r
zgcppr
f1 (ppm)

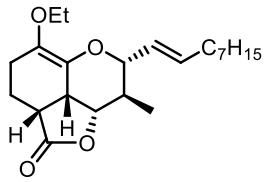
3.5

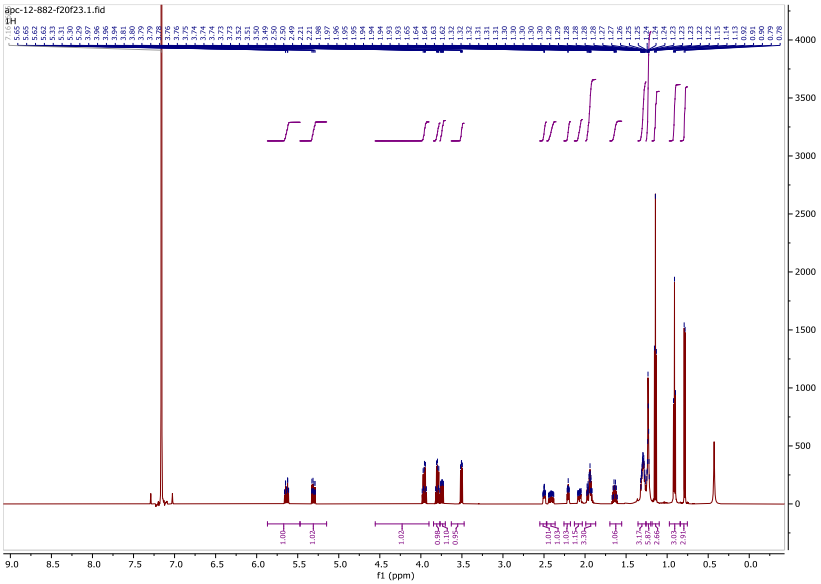

OEt
O
C_7H_{15}
OH

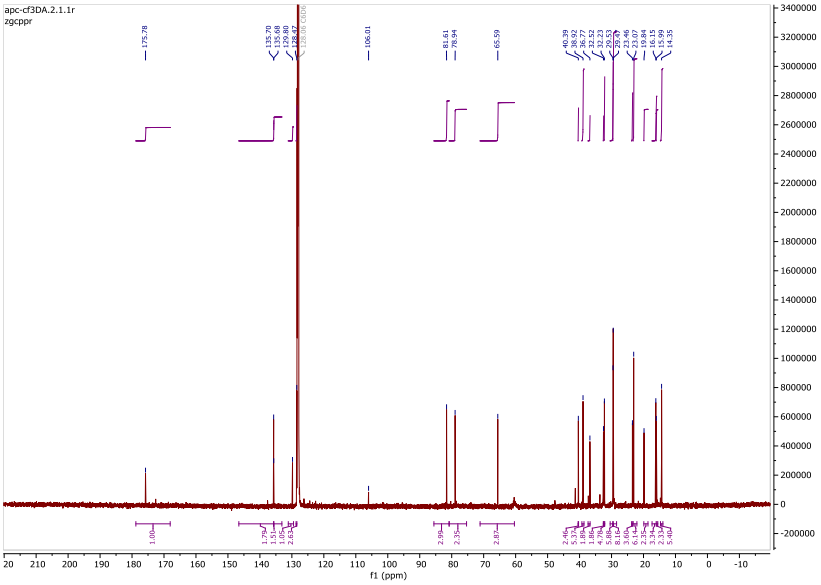

apc-c17-300.1.fid
1H NMR
f1 (ppm)


apc-c17-carb.1.1.1r
zgcppr
155.35
148.79
135.16
128.70
102.16
83.61
81.85
69.86
63.13
40.90
32.61
29.73
29.53
29.50
29.04
23.07
14.94
14.15
14.36
f1 (ppm)

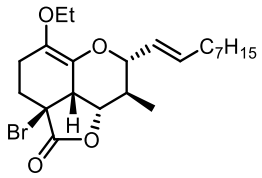
3.22

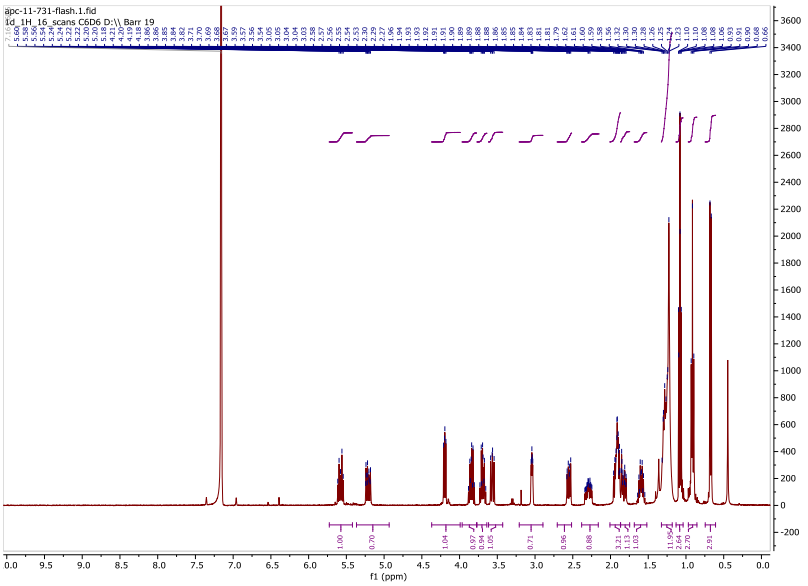

OEt
O
C_7H_{15}
H
H
O
O

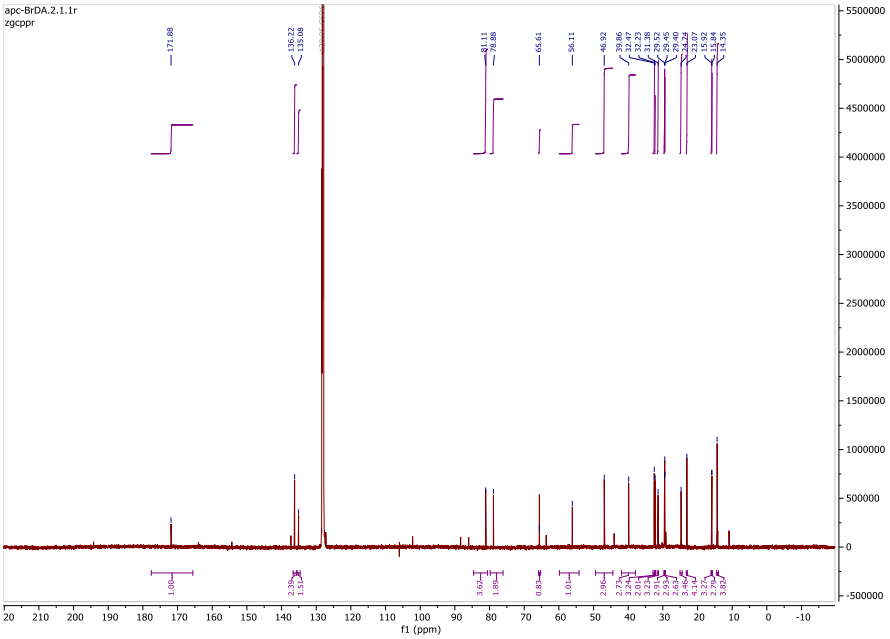

apc-12-882-f20f23.1.fid
1H
f1 (ppm)


apc-cf3DA.2.1.1r
zgcppr
f1 (ppm)

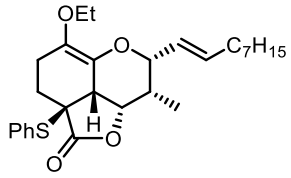
3.31

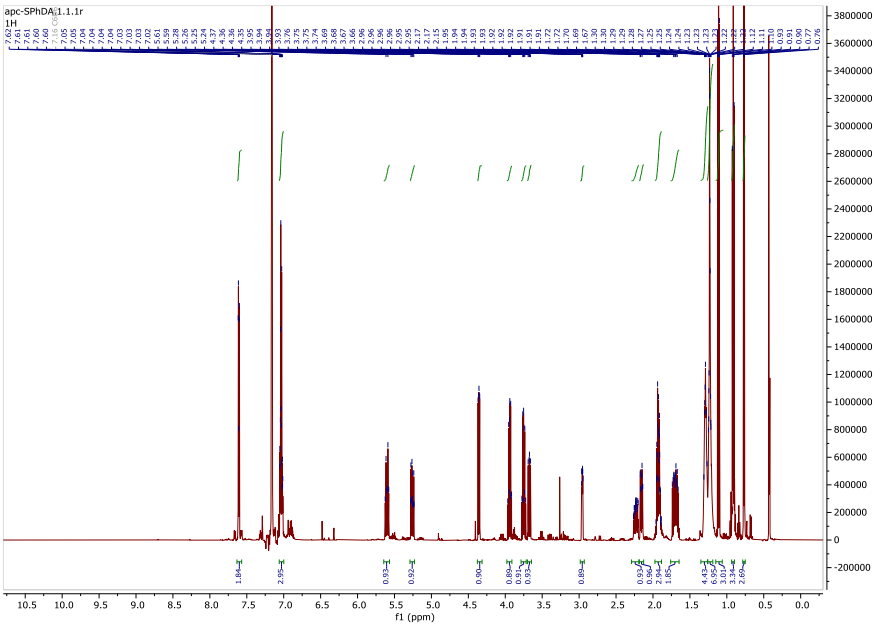

OEt
O
C_7H_{15}
Br
H
O
O

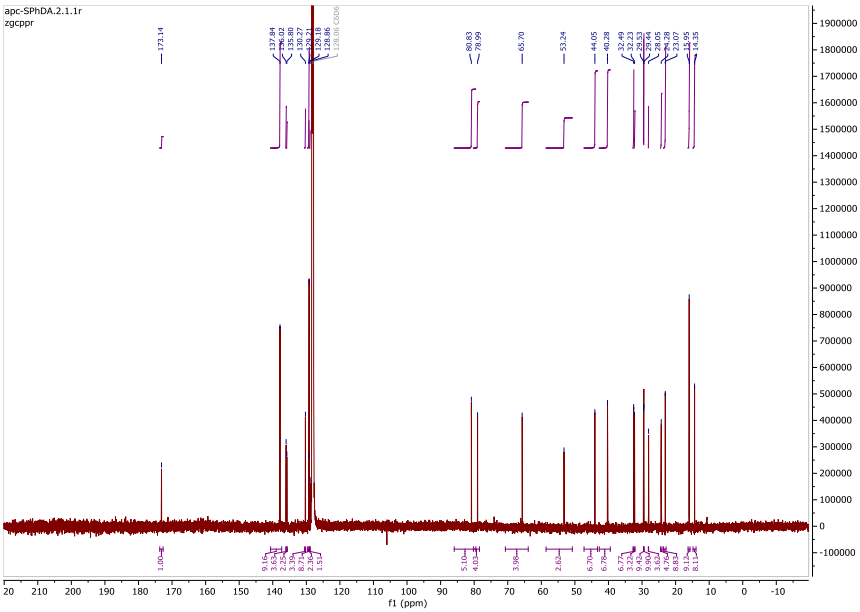

apc-11-731-flash.1.fid
1d_1H_16_scans C6D6 D:\\ Barr 19
f1 (ppm)


apc-BrDA.2.1.1r
zgcppr
171.88
136.22
135.08
81.11
78.48
65.61
56.11
46.92
39.86
32.47
32.23
31.38
29.62
29.45
29.40
24.29
23.97
23.92
15.84
14.35
f1 (ppm)

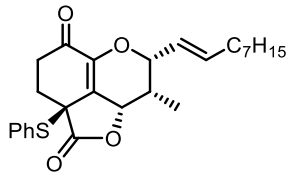
3.37

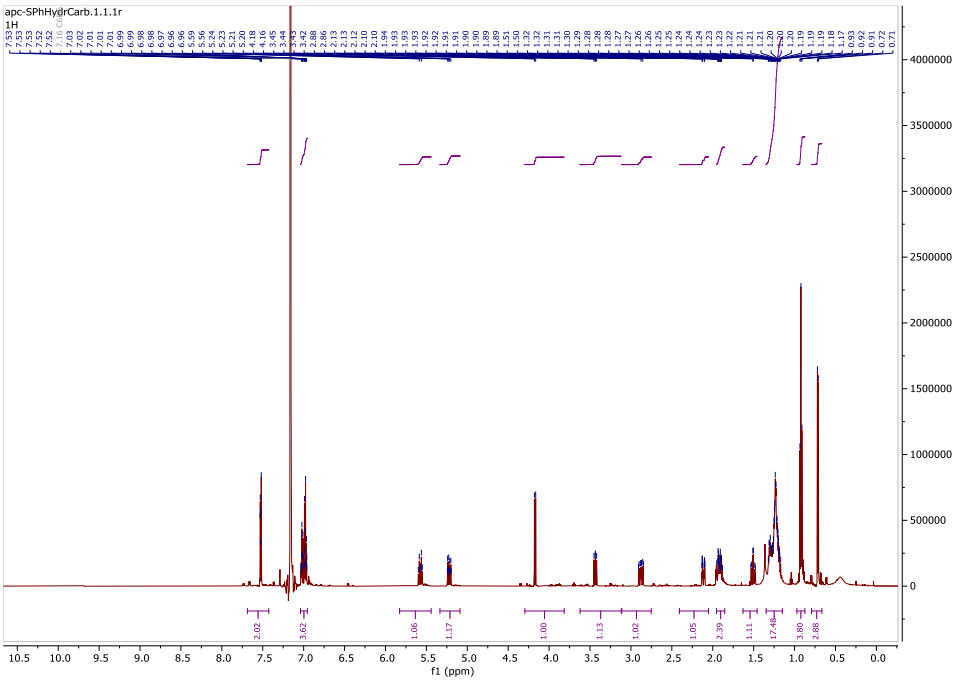

OEt
O
C_7H_{15}
PhS
H
O
O

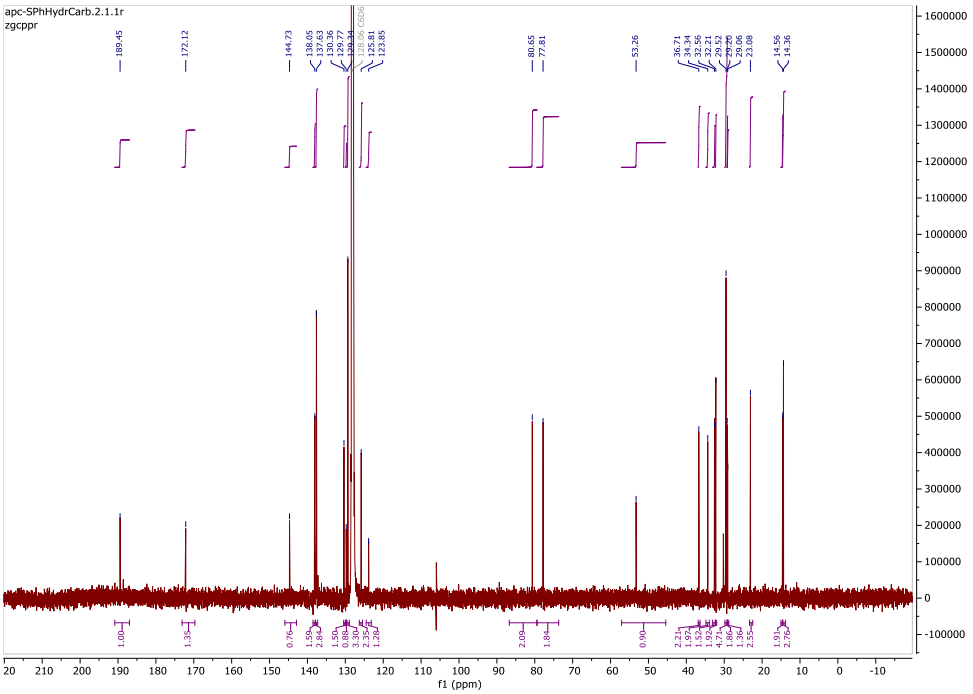

apc-SPhDA.1.1.1r
1H
f1 (ppm)


apc-SPhDA.2.1.1r
zgcppr
f1 (ppm)

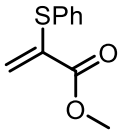
3.36

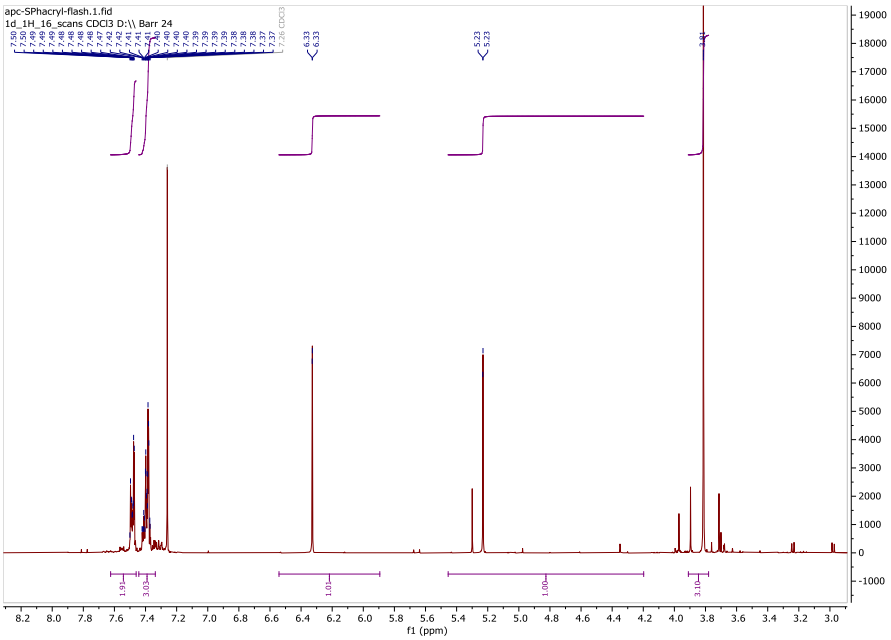

O
O
C_7H_{15}
PhS
O
O

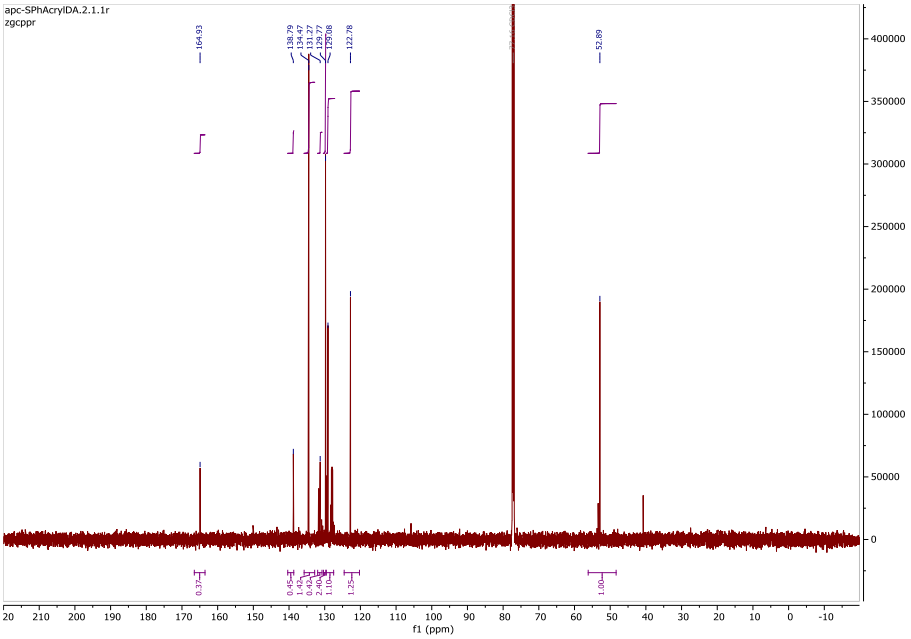

apc-SPhHydrCarb.1.1.1r
1H
f1 (ppm)


apc-SPhHydrCarb.2.1.1r
zgcppr
f1 (ppm)

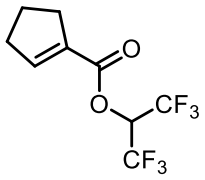
3.22

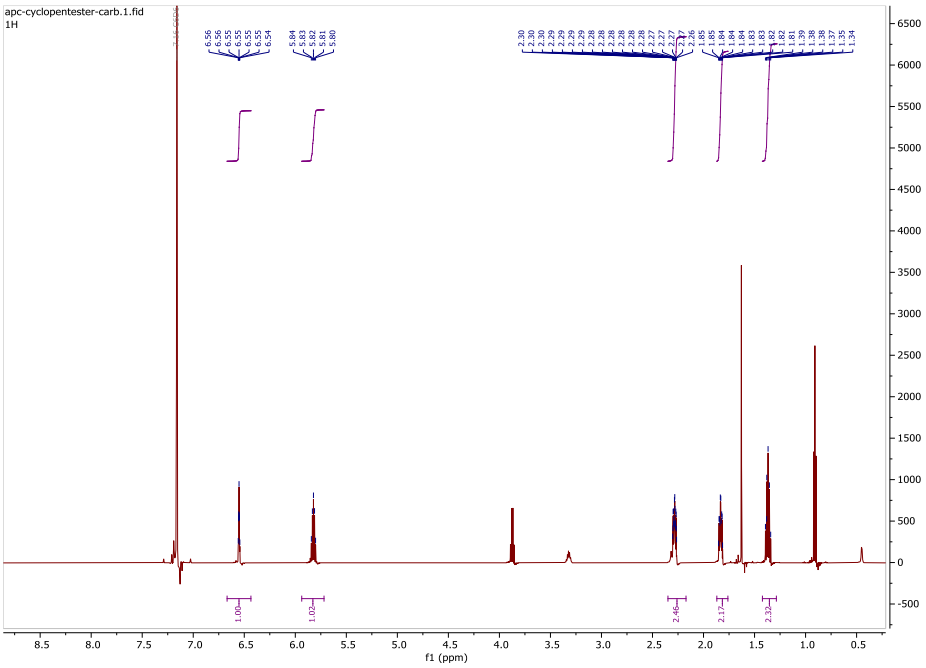

SPh
O
O

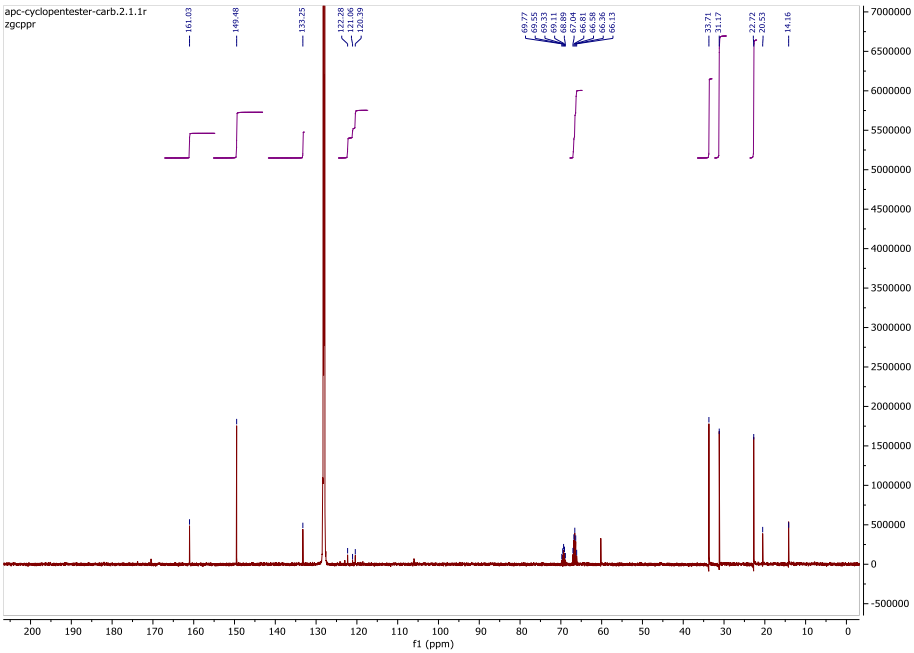

apc-SPhacryl-flash.1.fid
1d_1H_16_scans CDCl3 D:\\ Barr 24
6.33
5.23
2.91
f1 (ppm)


apc-SPhAcrylDA.2.1.1r
zgcppr
164.93
138.79
134.47
131.27
129.77
129.08
122.78
52.89
f1 (ppm)

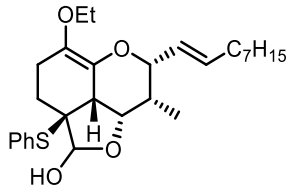
3.18

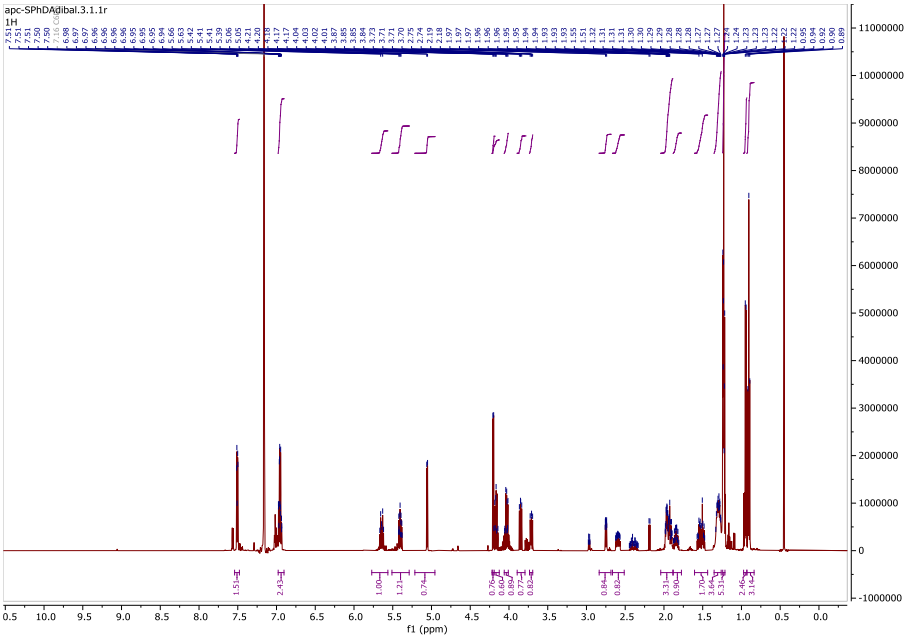

O
O
CF3
CF3

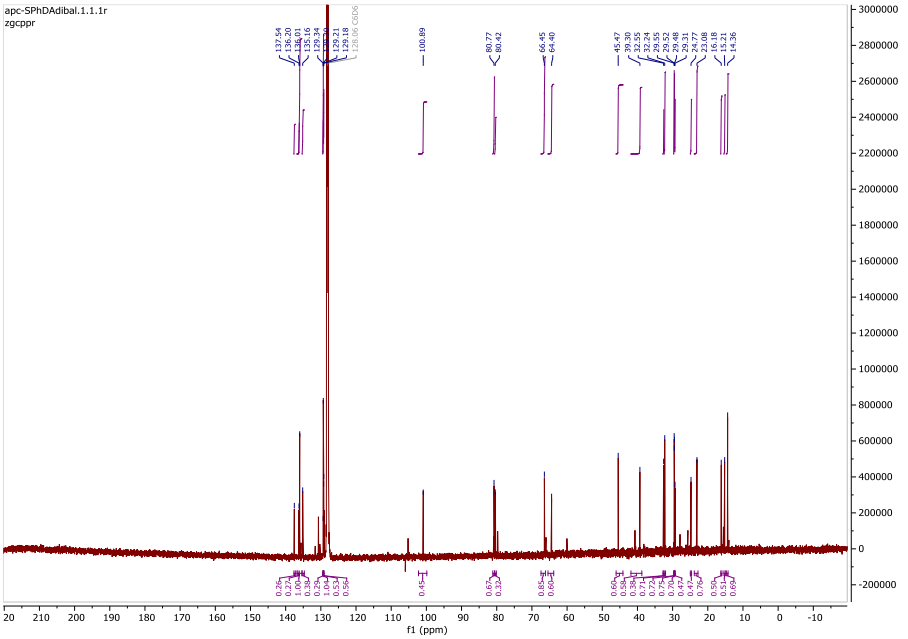

apc-cyclopentester-carb.1.fid
1H
f1 (ppm)


apc-cyclopentester-carb.2.1.1r
zgcppr
f1 (ppm)

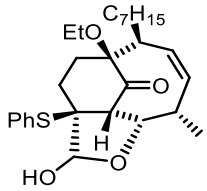
3.38

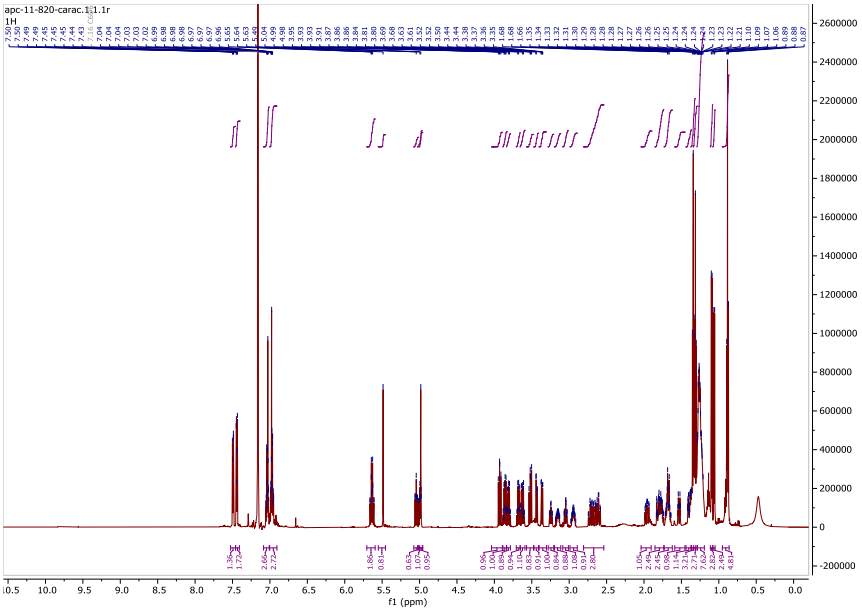

OEt
O
C_7H_{15}
PhS
H
O
HO

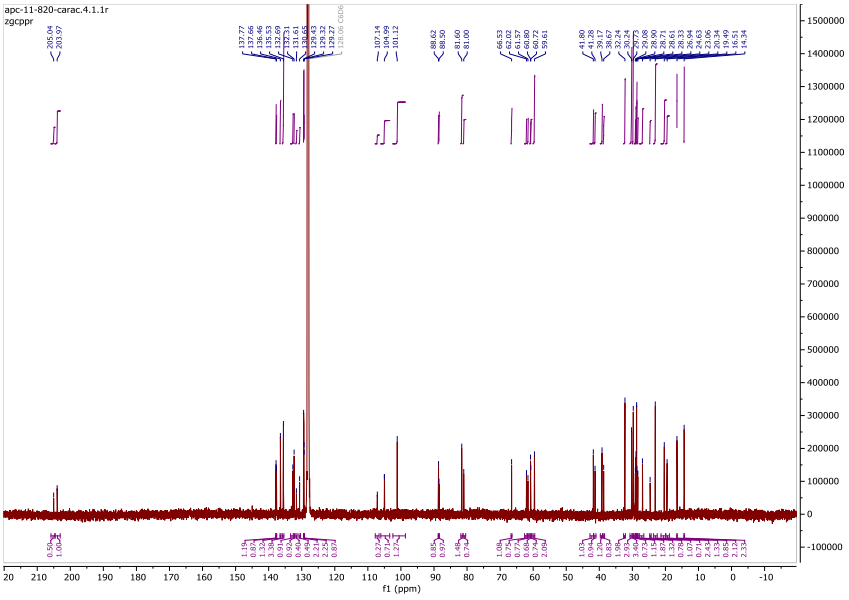

apc-SPhDAdibal.3.1.1r
1H
f1 (ppm)


apc-SPhDAdibal.1.1.1r
zgcppr
f1 (ppm)

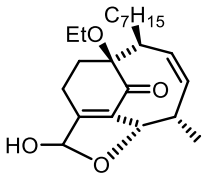
3.39

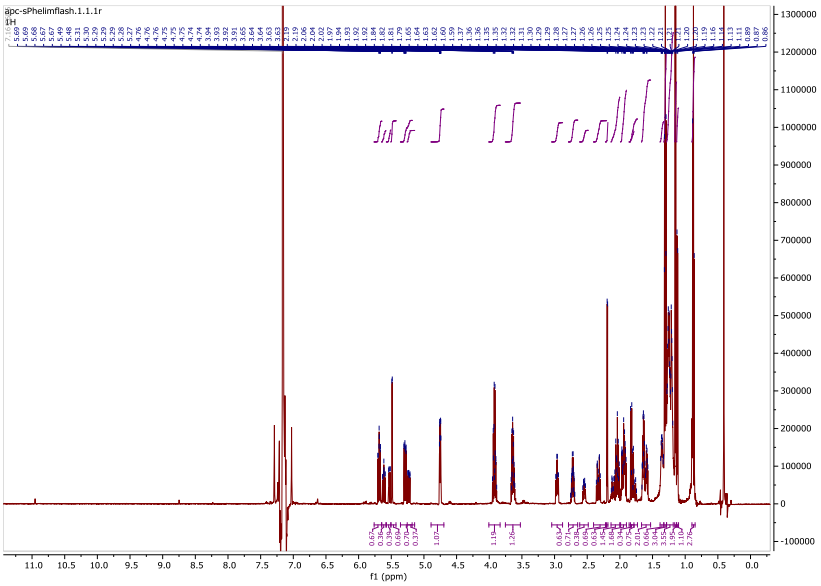

C7H15
EtO
O
PhS
H
HO
O

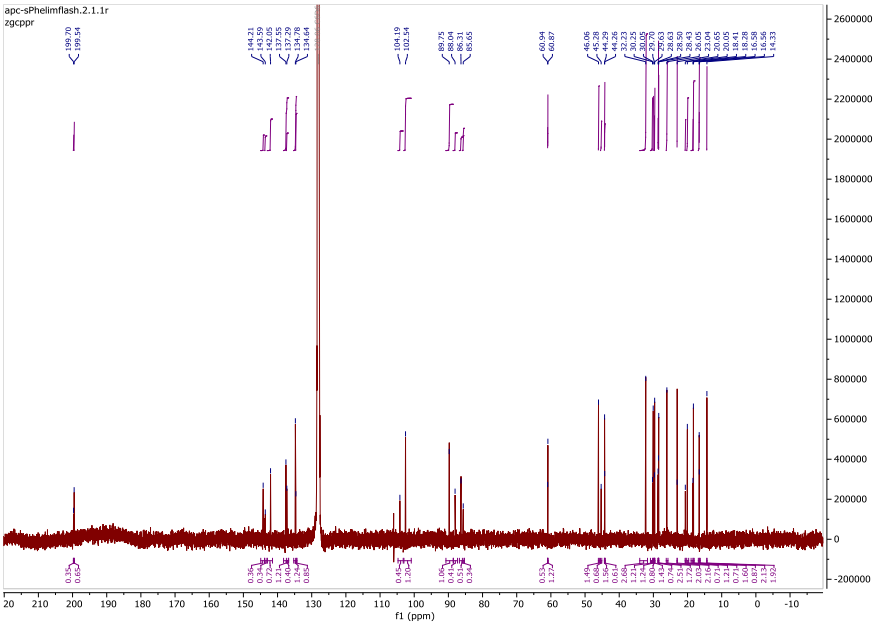

apc-11-820-carac.1.1.1r
1H
f1 (ppm)


apc-11-820-carac.4.1.1r
zgcppr
f1 (ppm)

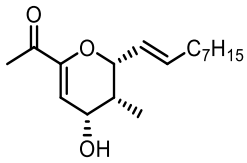
3.44

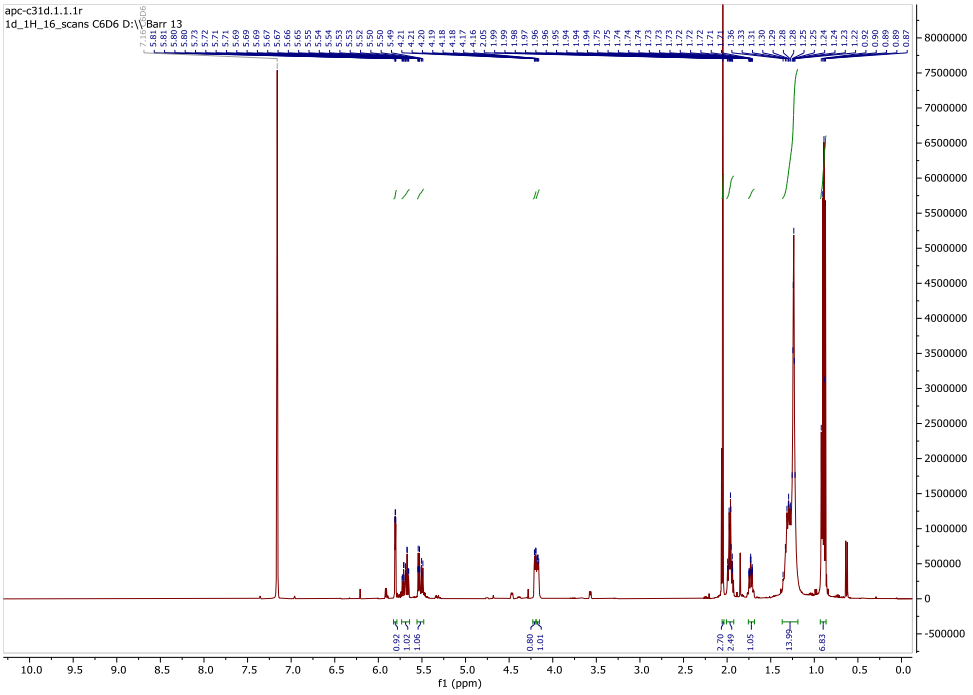

C7H15
EtO
O
HO
O

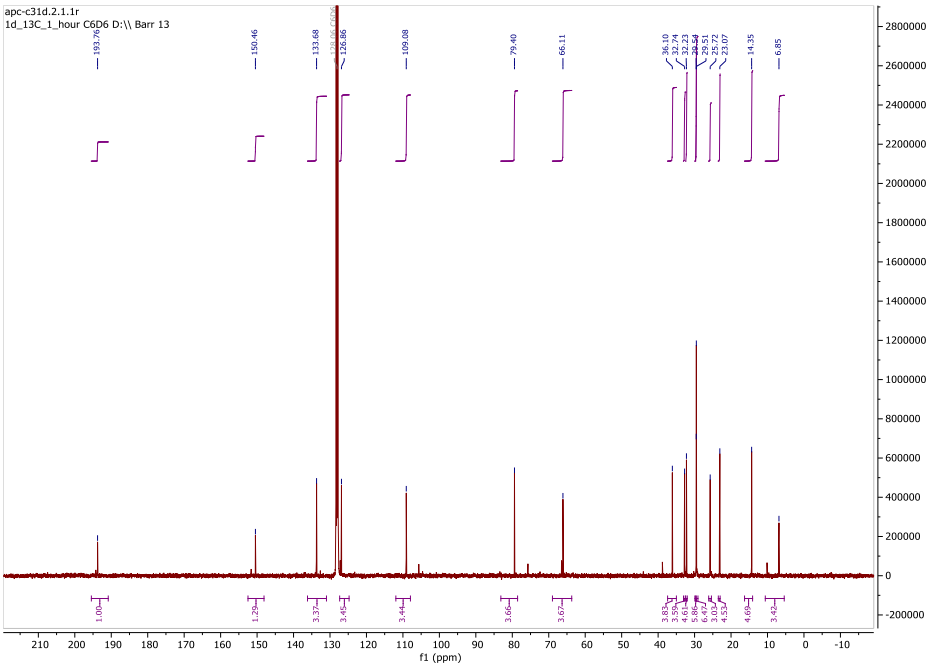

apc-sPhelimflash.1.1.1r
1H
f1 (ppm)


apc-sPhelimflash.2.1.1r
zgcppr
f1 (ppm)

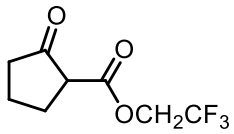
4.1

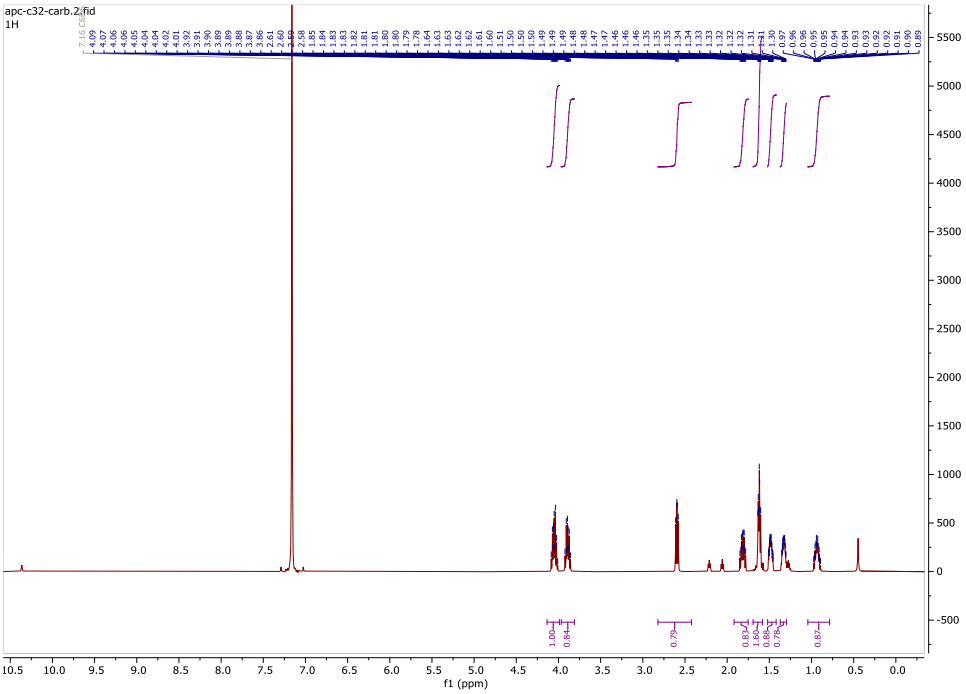

O
O
C_7H_{15}
OH

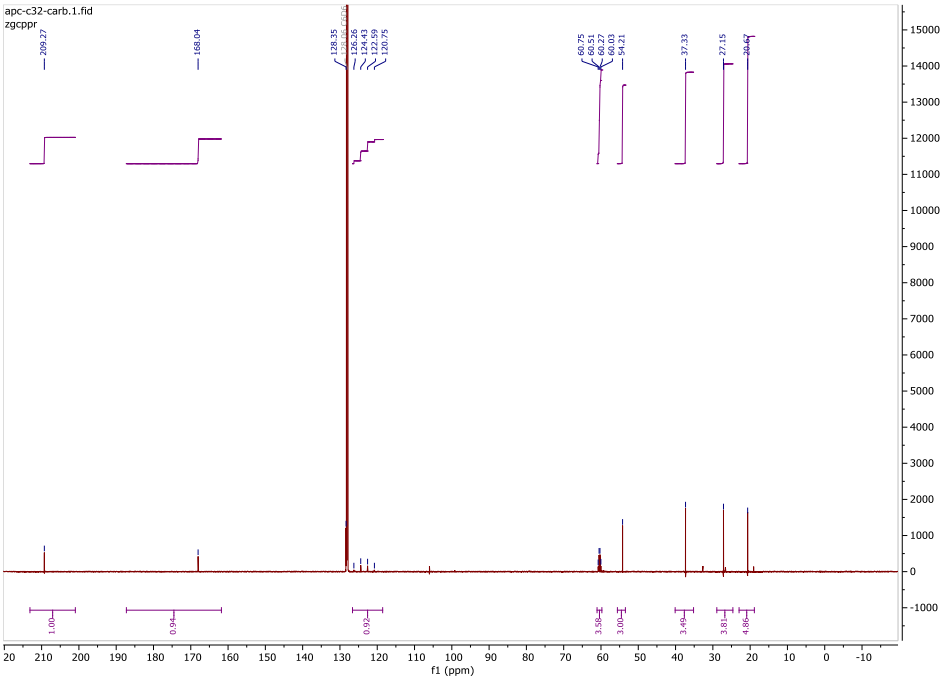

apc-c31d.1.1.1r
1d_1H_16_scans C6D6 D:\\ Barr 13
f1 (ppm)


apc-c31d.2.1.1r
1d_13C_1_hour C6D6 D:\\ Barr 13
193.76
150.46
133.68
128.66
109.08
79.40
65.11
36.10
32.74
32.23
28.54
28.51
25.72
23.07
14.35
6.85
f1 (ppm)

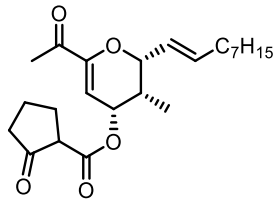
4.23a

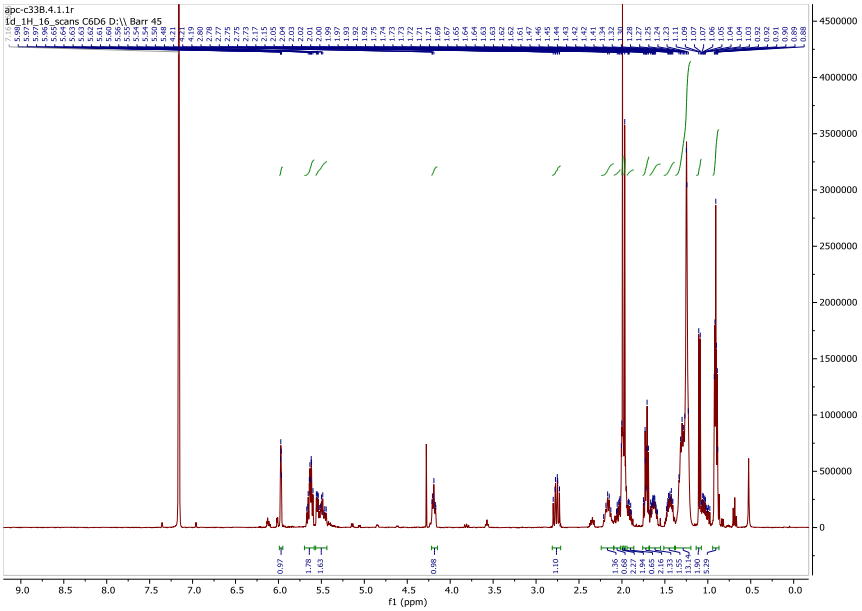

O
O
OCH2CF3

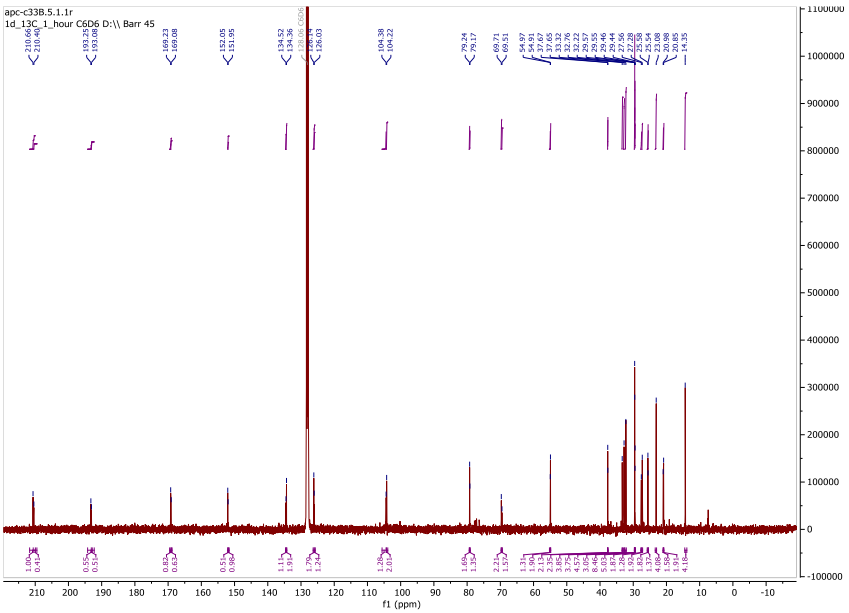

apc-c32-carb.2.fid
1H
f1 (ppm)


apc-c32-carb.1.fid
zgcppr
209.27
168.04
128.35
126.26
124.43
122.59
120.75
60.75
60.51
60.27
60.03
54.21
37.33
27.15
20.47
f1 (ppm)

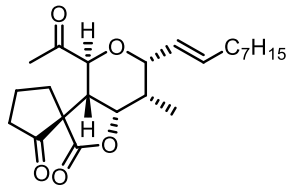
4.21

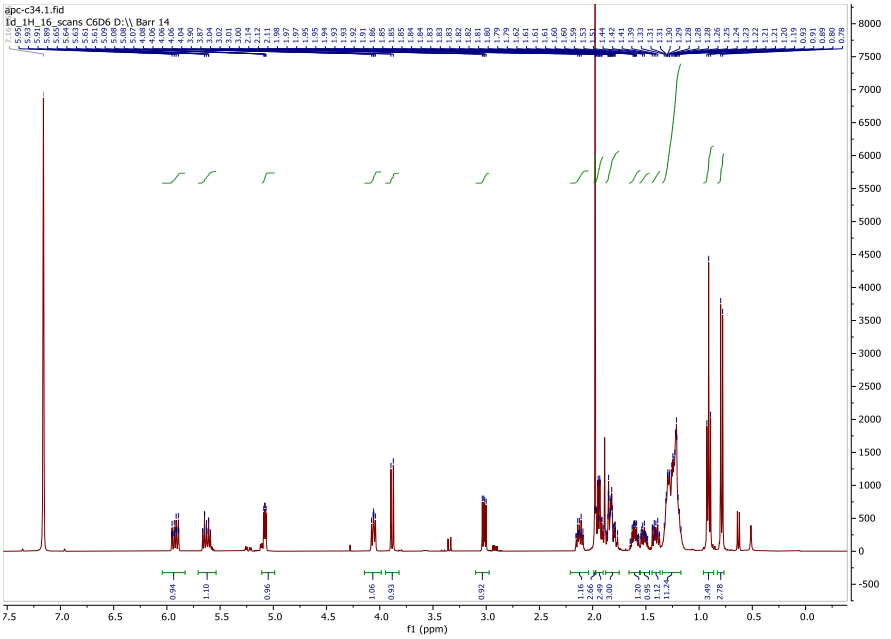

O
O
C_7H_{15}
O
O
O

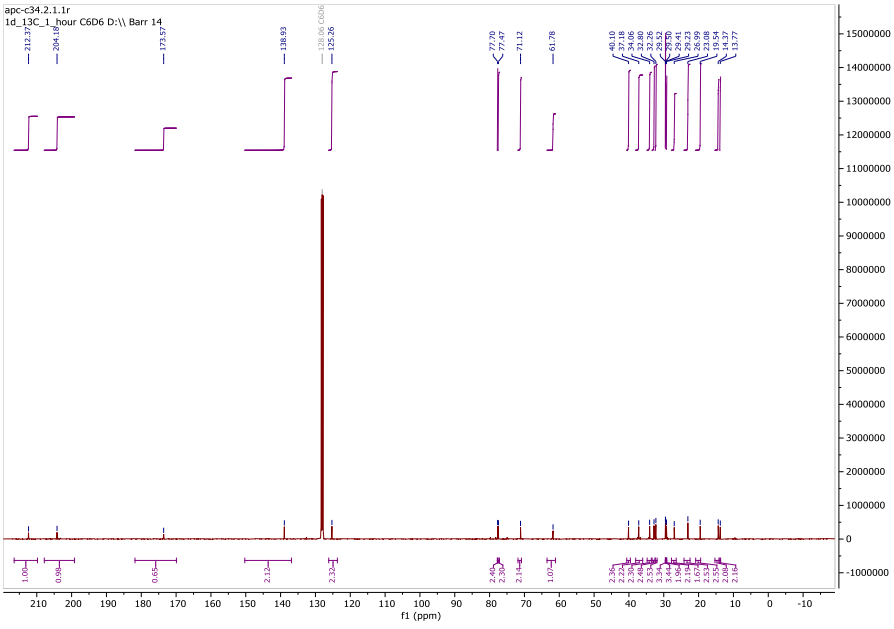

apc-c33B.4.1.1r
1d_1H_16_scans C6D6 D:\\ Barr 45
f1 (ppm)

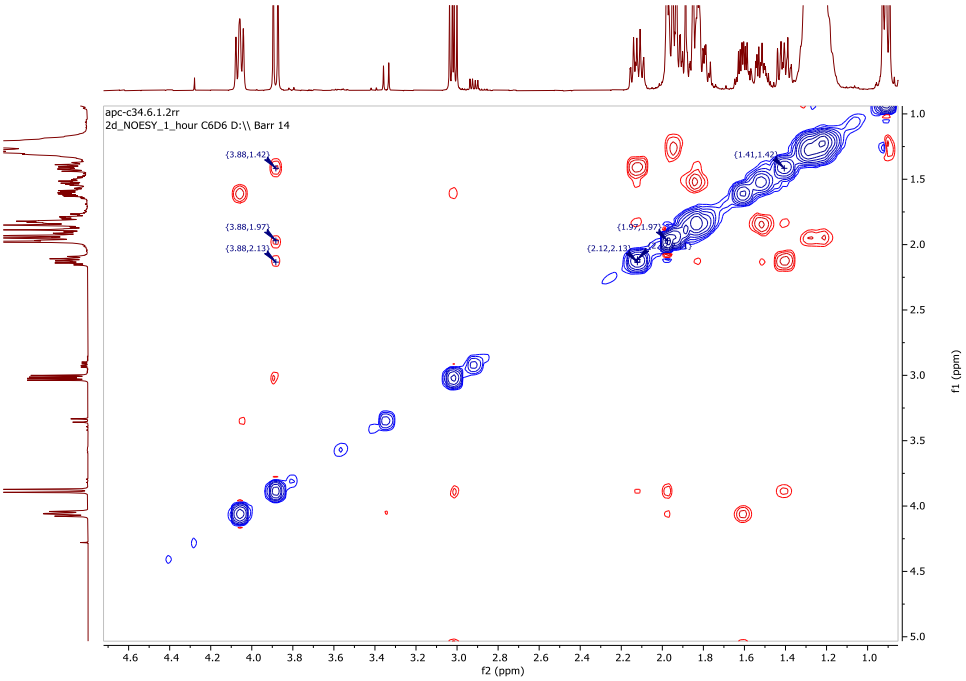

apc-c33B.5.1.1r
1d_13C_1_hour C6D6 D:\\ Barr 45
f1 (ppm)

4.24

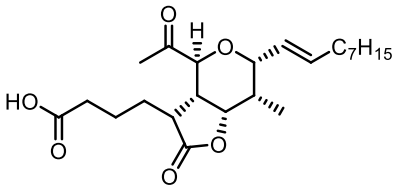

O
H
O
C_7H_{15}
H
O
O
O

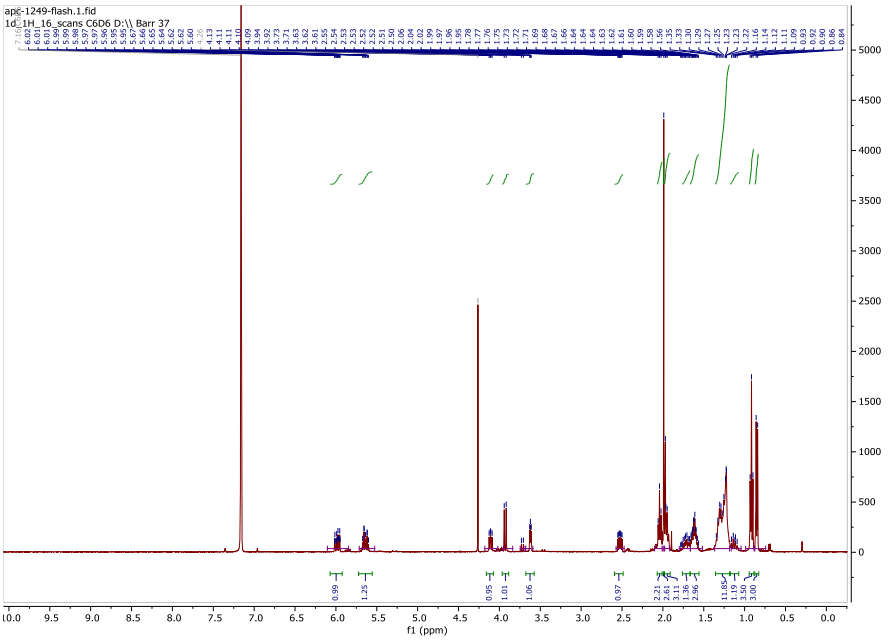

apc-c34.1.fid
1d_1H_16_scans C6D6 D:\\ Barr 14
f1 (ppm)

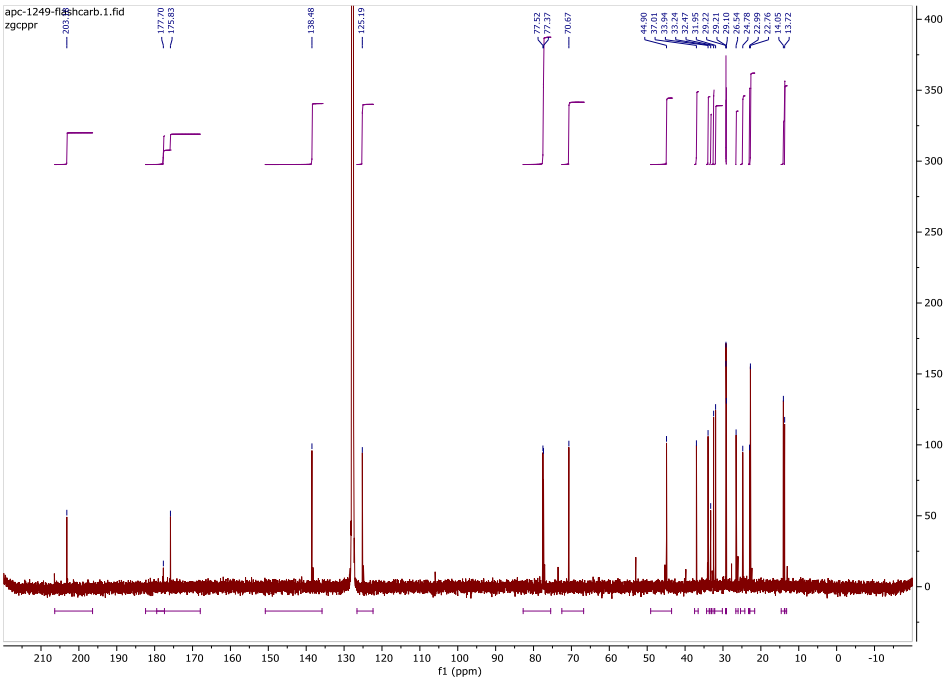

apc-c34.2.1.1r
1d_13C_1_hour C6D6 D:\\ Barr 14
212.37
204.18
173.57
138.93
128.06
125.26
77.70
77.47
71.12
61.78
40.10
37.14
34.06
32.80
32.26
29.52
29.30
29.23
26.99
21.08
19.54
14.37
13.77
f1 (ppm)


apc-c34.6.1.2rr
2d_NOESY_1_hour C6D6 D:\\ Barr 14
{3.88,1.42}
{3.88,1.97}
{3.88,2.13}
{1.41,1.42}
{1.97,1.97}
{2.12,2.13}
f2 (ppm)
f1 (ppm)

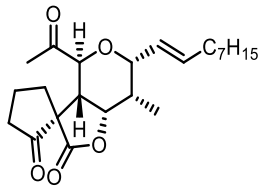
4.28

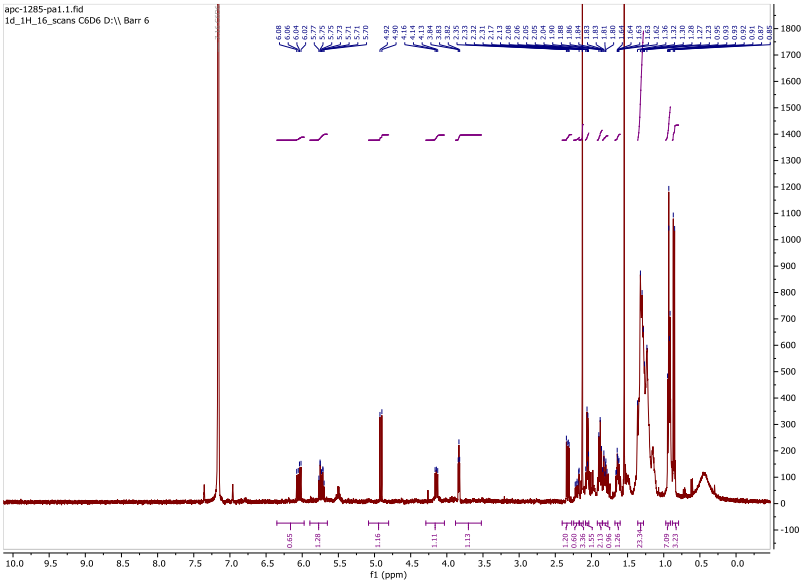

O
H
O
C7H15
HO
O
O
O

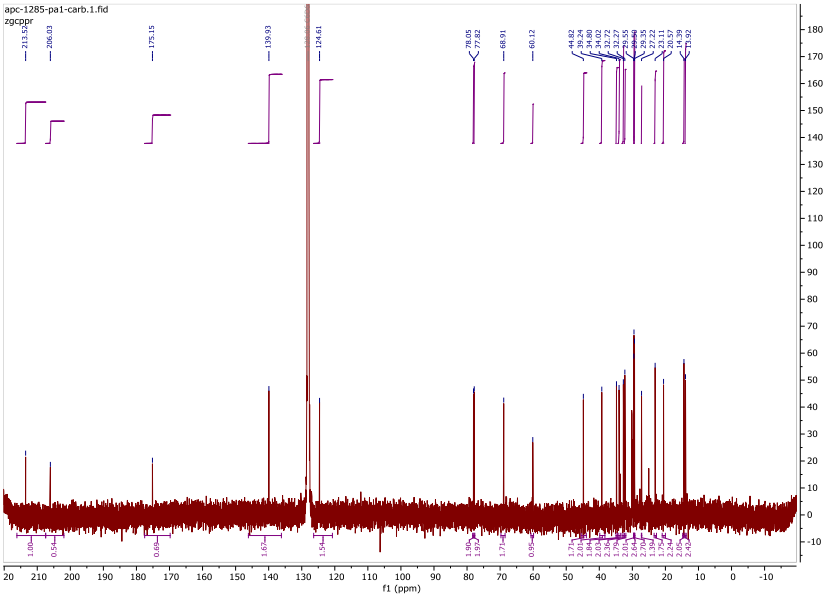

apc-1249-flash.1.fid
1d_1H_16_scans C6D6 D:\\ Barr 37
f1 (ppm)

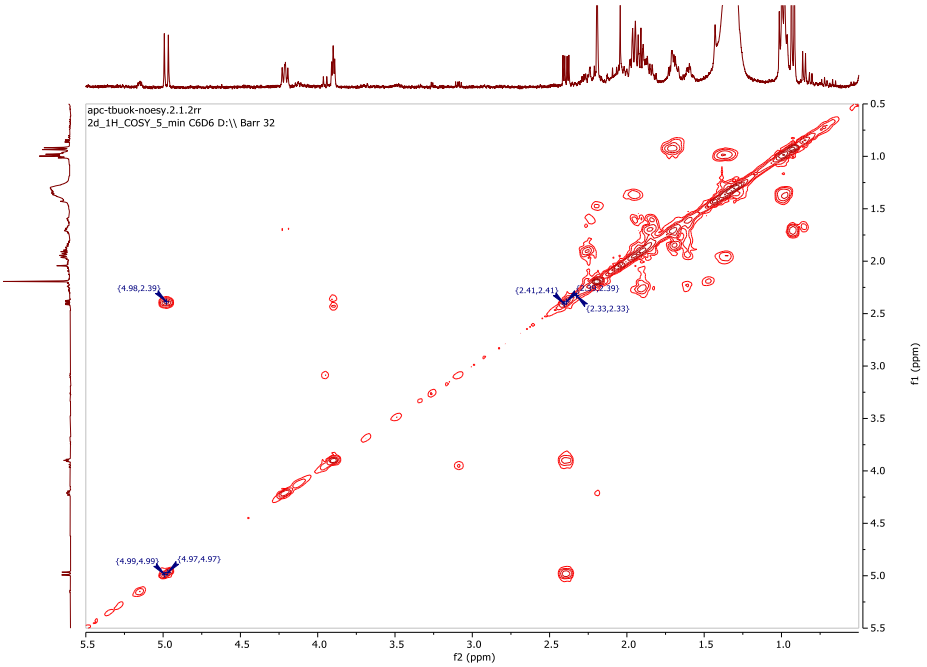

apc-1249-flashcarb.1.fid
zgcppr
f1 (ppm)

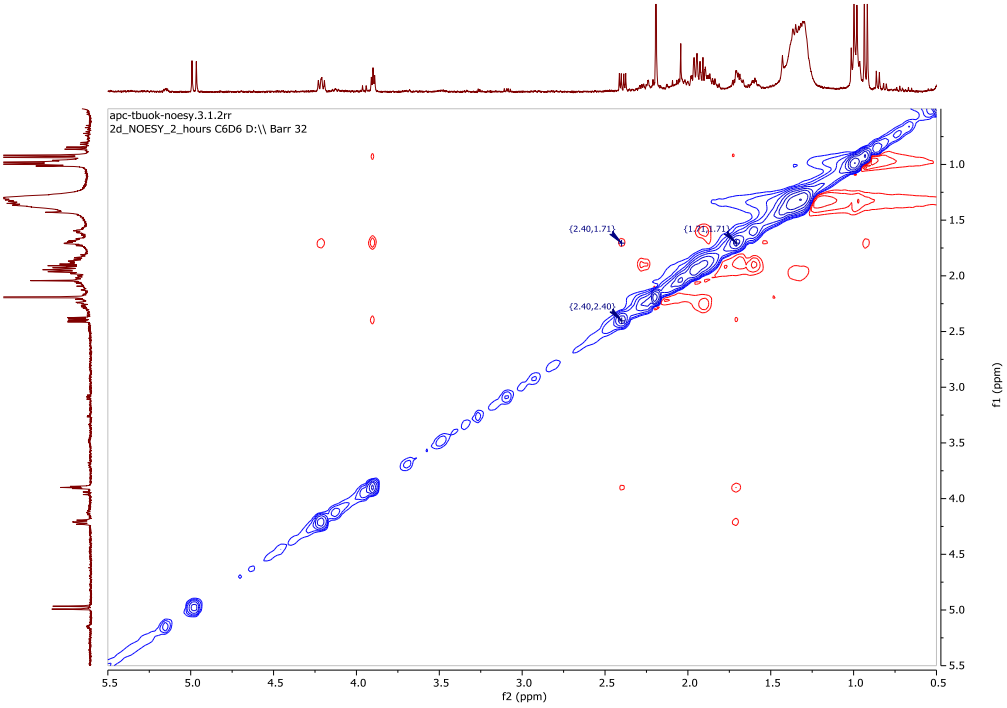
4.25


O
H
O
C_7H_{15}
H
O
O
O

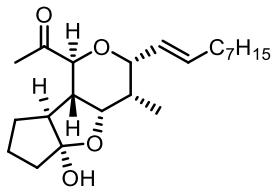

apc-1285-pa1.1.fid
1d_1H_16_scans C6D6 D:\\ Barr 6
f1 (ppm)

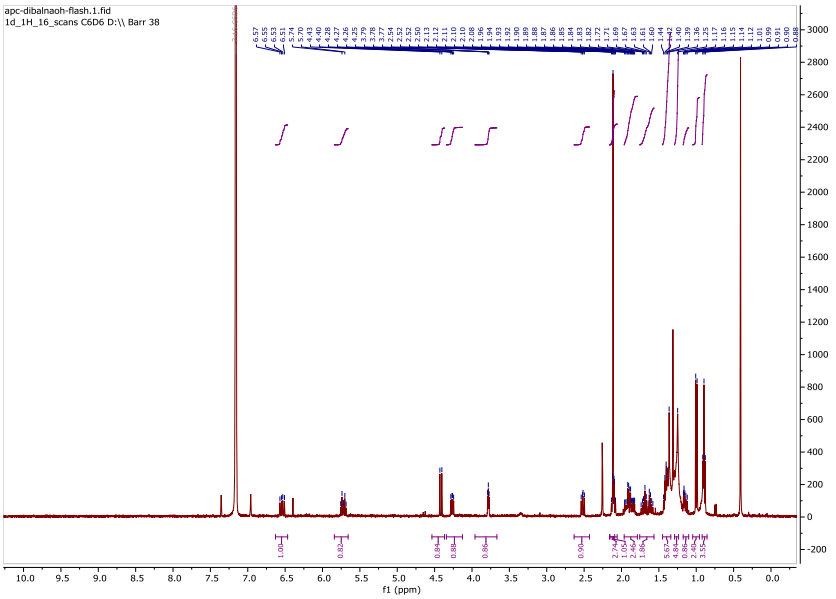

apc-1285-pa1-carb.1.fid
zgcppr
213.50
206.03
175.15
139.93
124.61
78.05
77.82
68.91
60.12
f1 (ppm)

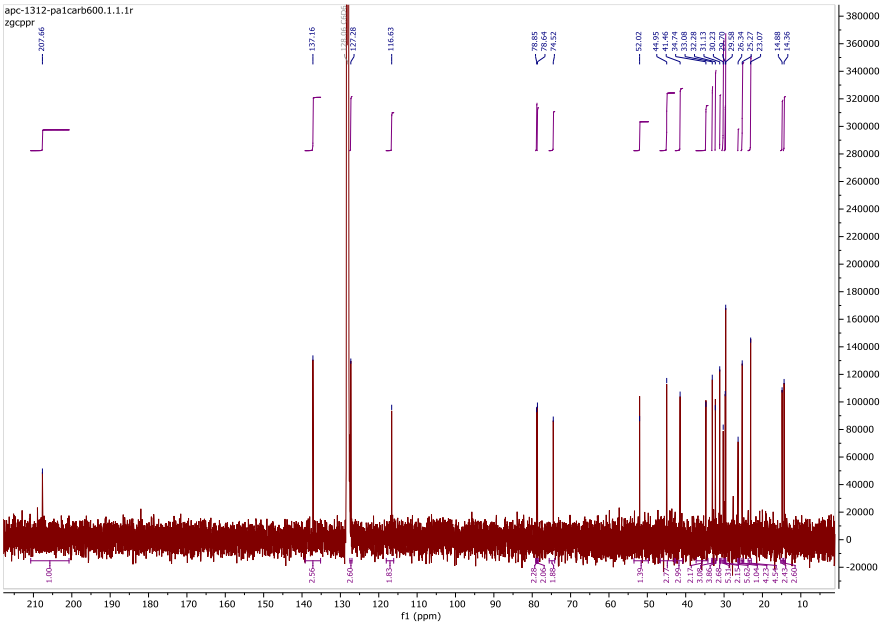

apc-tbuok-noesy.2.1.2rr
2d_1H_COSY_5_min C6D6 D:\\ Barr 32
{4.98,2.39}
{2.41,2.41}
{2.39,2.39}
{2.33,2.33}
{4.99,4.99}
{4.97,4.97}
f1 (ppm)
f2 (ppm)

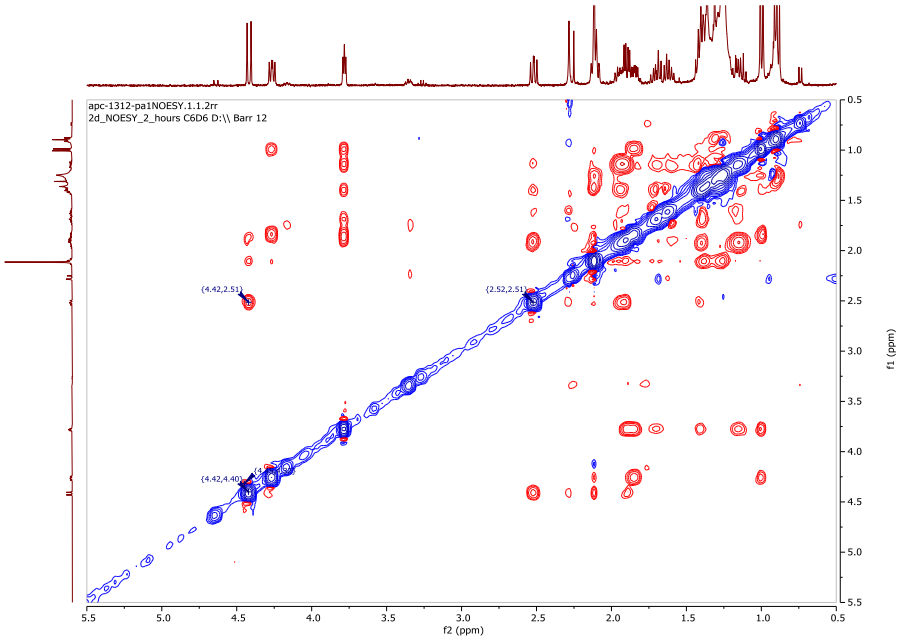

apc-tbuok-noesy.3.1.2rr
2d_NOESY_2_hours C6D6 D:\\ Barr 32
{2.40,1.71}
{1.71,1.71}
{2.40,2.40}
f1 (ppm)
f2 (ppm)

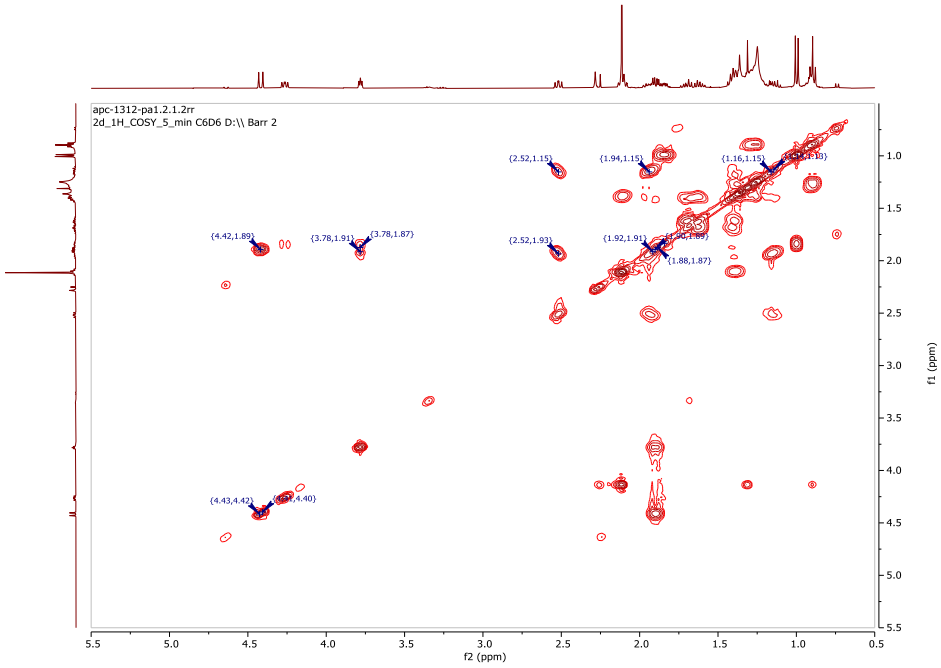
4.40


O
H
O
C7H15
H
H
O
OH

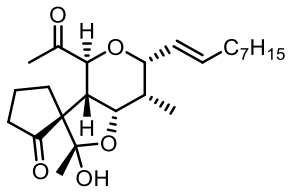

apc-dibalnaoh-flash.1.fid
1d_1H_16_scans C6D6 D:\\ Barr 38
f1 (ppm)

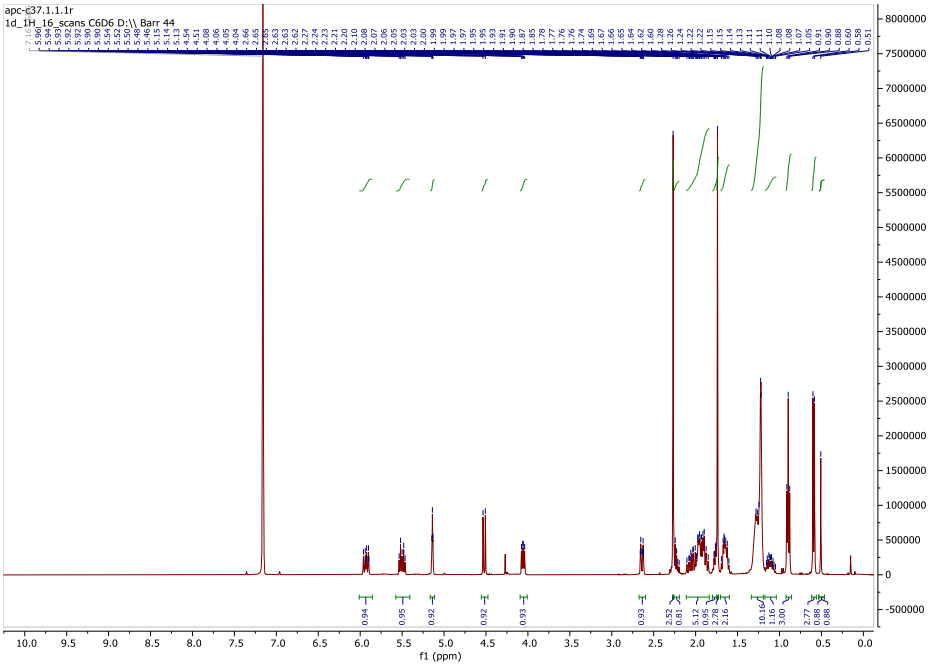

apc-1312-pa1carb600.1.1.1r
zgcppr
f1 (ppm)

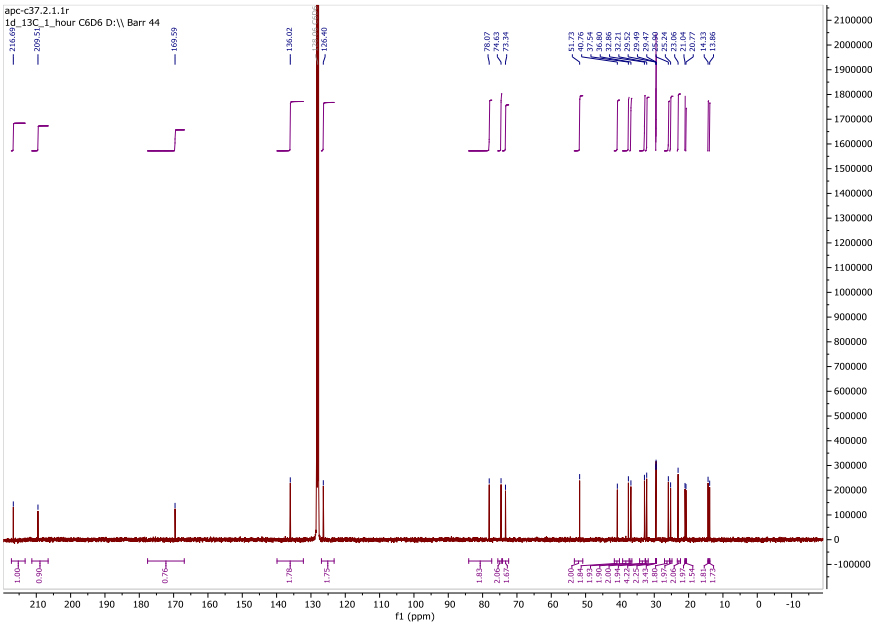

apc-1312-pa1NOESY.1.1.2rr
2d_NOESY_2_hours C6D6 D:\\ Barr 12
{4.42,2.51}
{2.52,2.51}
{4.42,4.40}
f2 (ppm)
f1 (ppm)

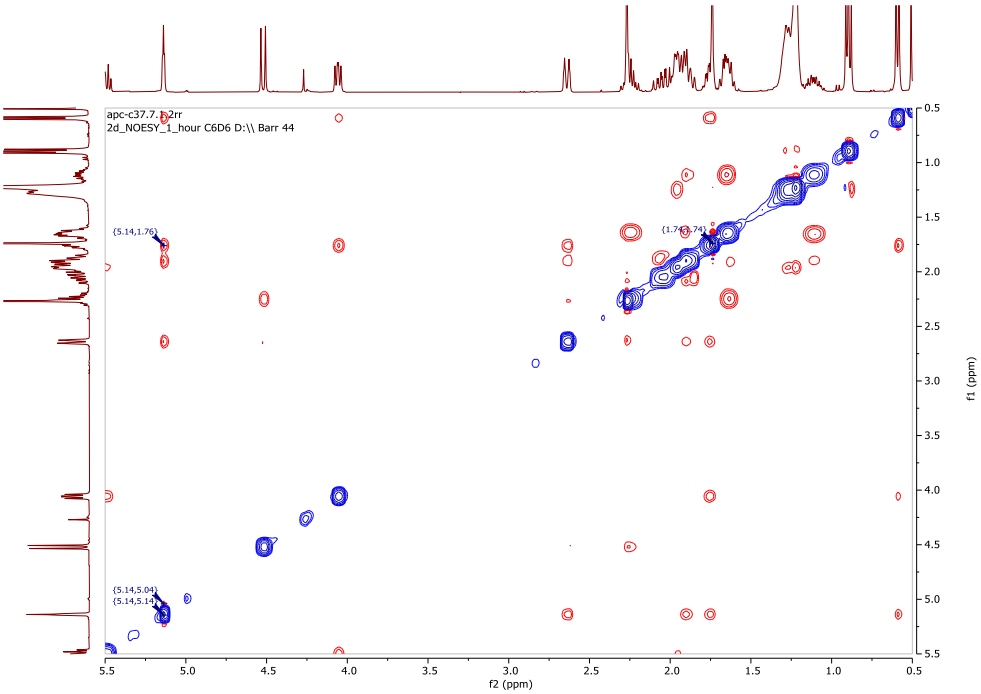

apc-1312-pa1.2.1.2rr
2d_1H_COSY_5_min C6D6 D:\\ Barr 2
{2.52,1.15}
{1.94,1.15}
{1.16,1.15}
{4.42,1.89}
{3.78,1.91}
{3.78,1.87}
{2.52,1.93}
{1.92,1.91}
{1.88,1.87}
{4.43,4.42}
{4.42,4.40}
f2 (ppm)
f1 (ppm)

4.41

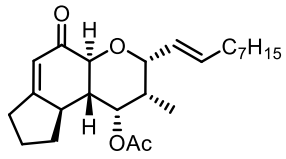

O
H
O
C_7H_{15}
H
O
O
OH

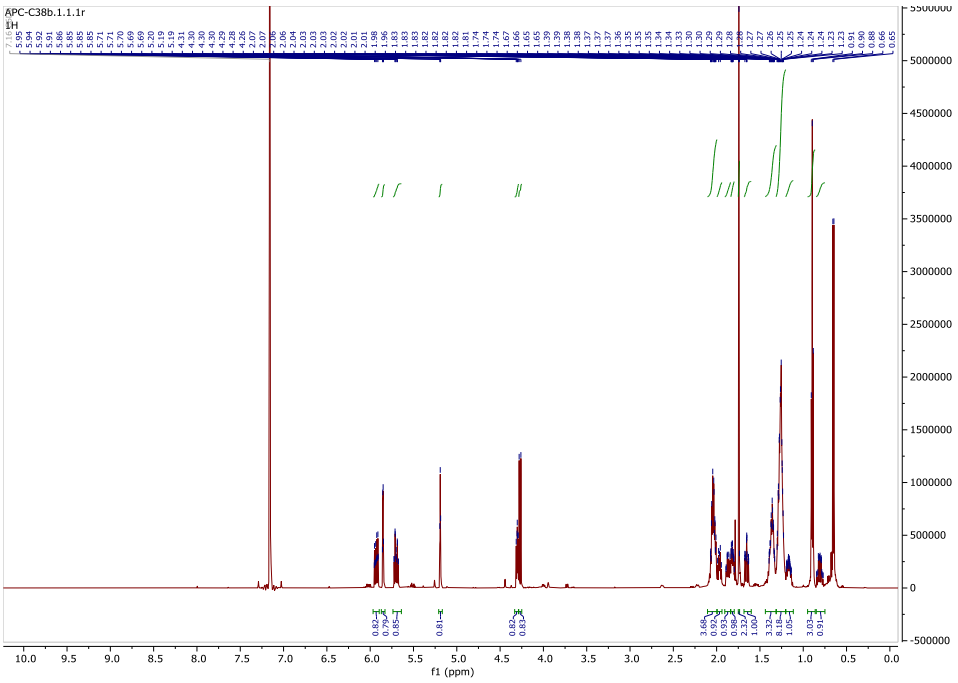

apc-c37.1.1.1r
1d_1H_16_scans C6D6 D:\\ Barr 44
f1 (ppm)

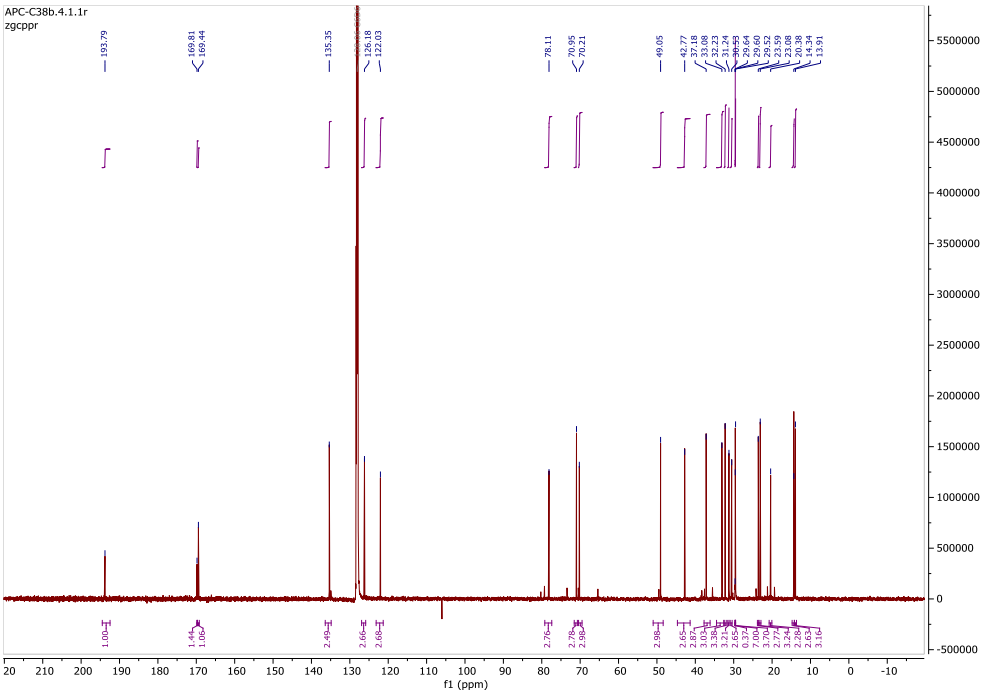

apc-c37.2.1.1r
1d_13C_1_hour C6D6 D:\\ Barr 44
f1 (ppm)


apc-c37.7.12rr
2d_NOESY_1_hour C6D6 D:\\ Barr 44
{5.14,1.76}
{5.14,5.04}
{5.14,5.14}
f2 (ppm)
f1 (ppm)

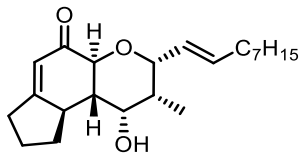
4.42

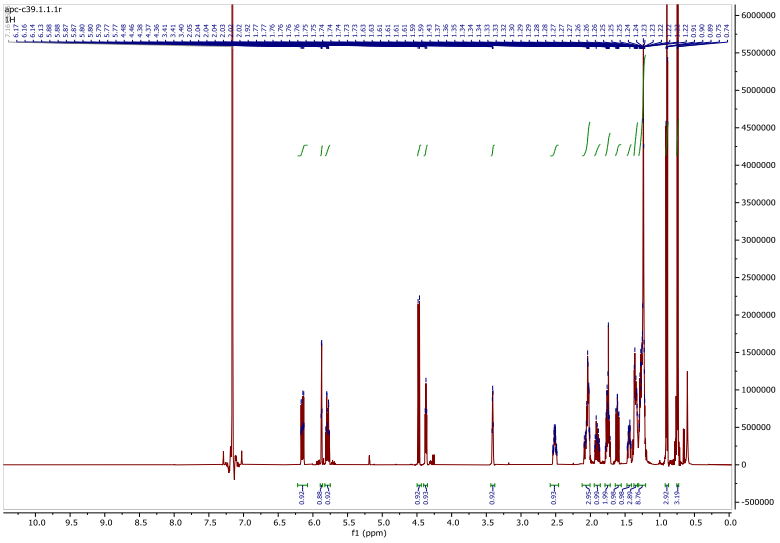

O
H
O
C_7H_{15}
H
OAc

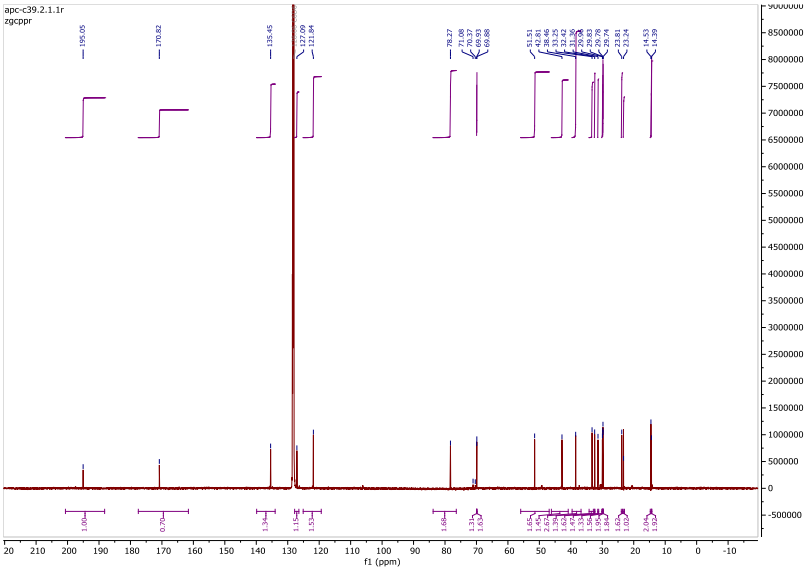

APC-C38b.1.1.1r
1H
f1 (ppm)


APC-C38b.4.1.1r
zgcppr
193.79
169.81
169.44
135.35
126.18
122.03
78.11
70.95
70.21
49.05
42.77
37.48
35.08
32.23
31.24
30.83
29.64
29.60
29.52
23.59
23.08
20.38
14.34
13.91
f1 (ppm)

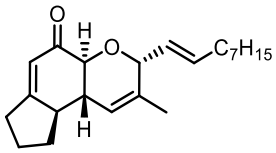
4.45

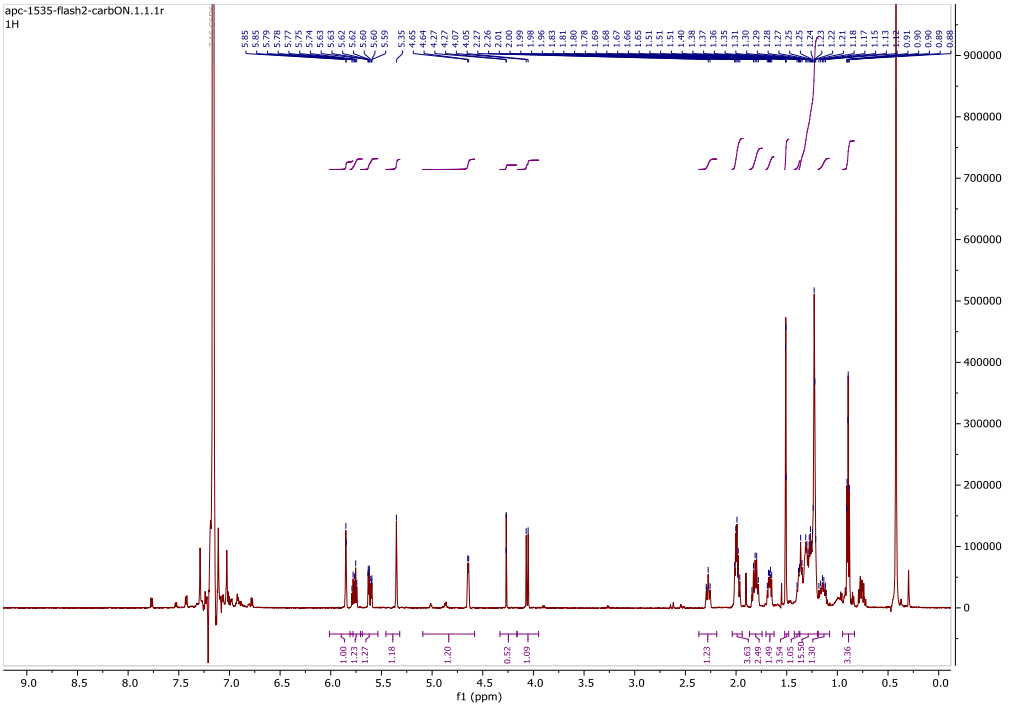


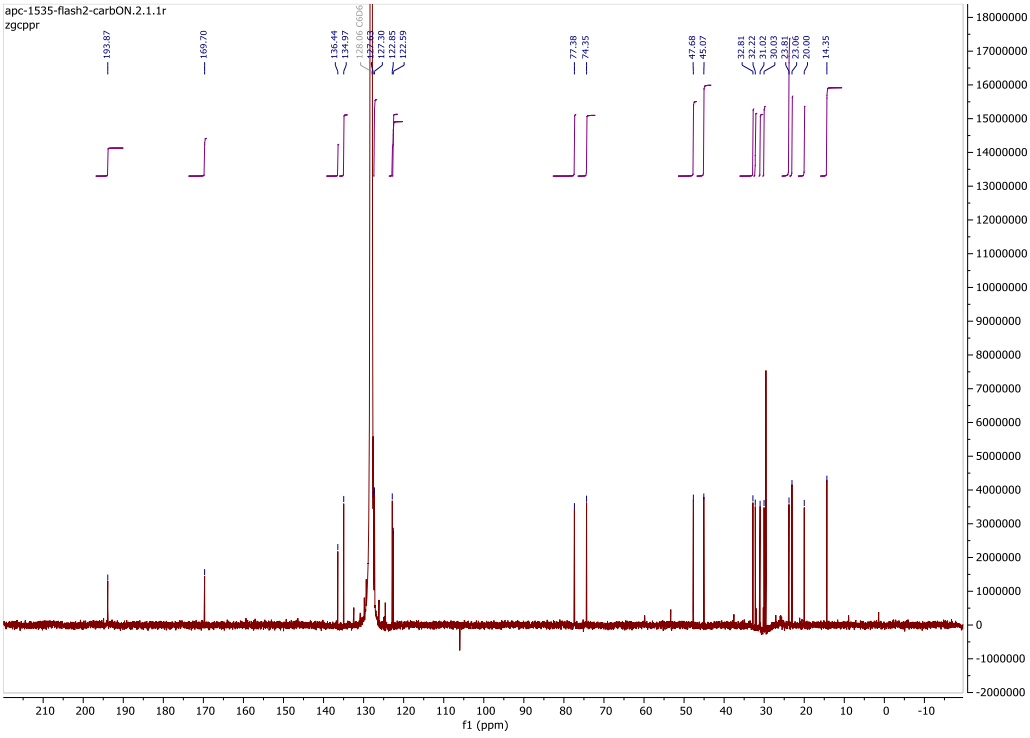


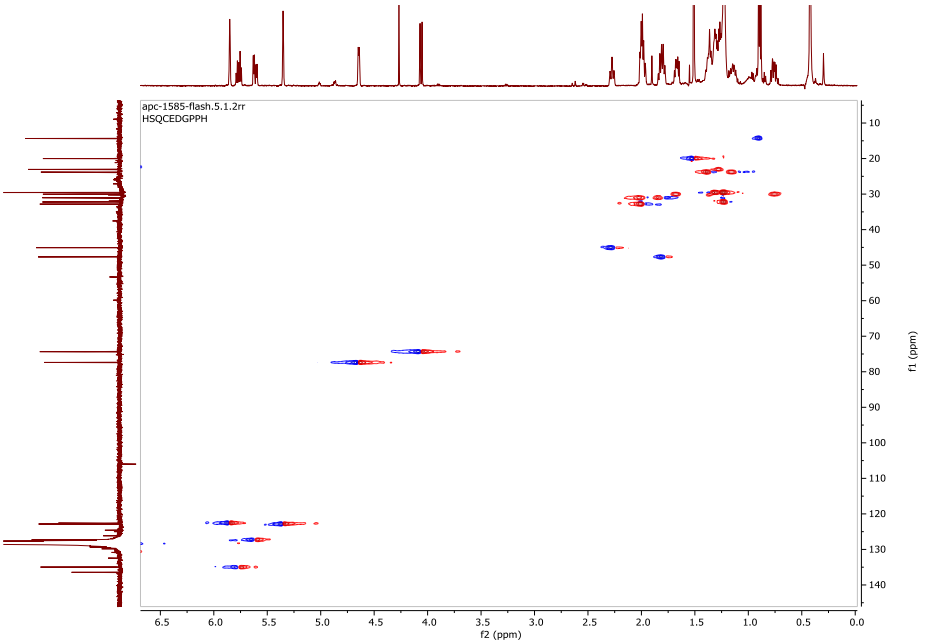


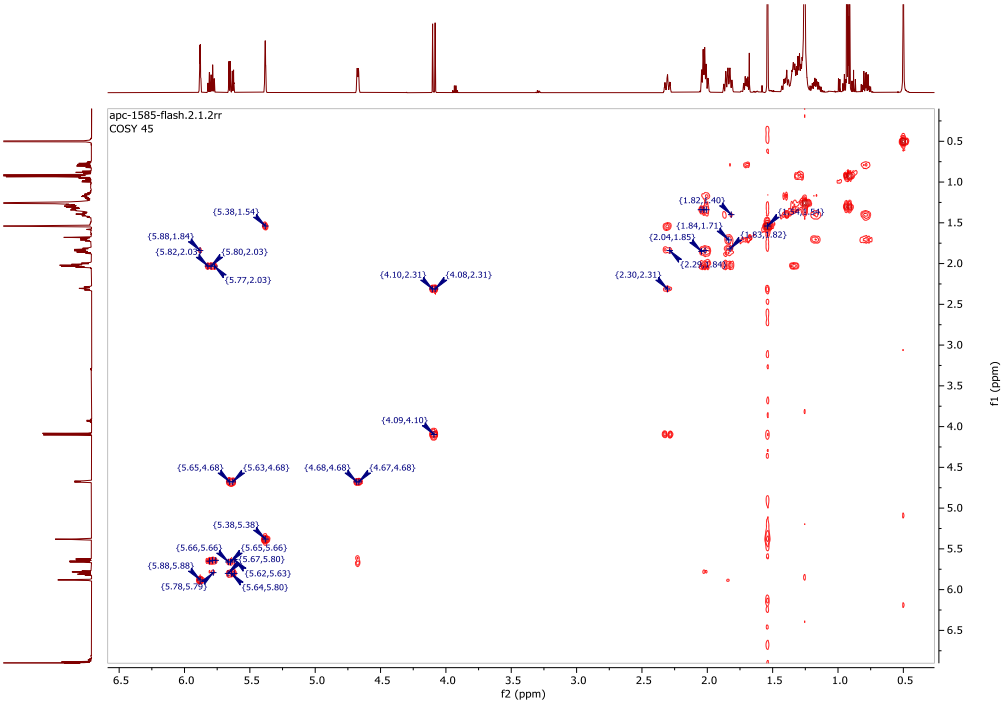
1.33

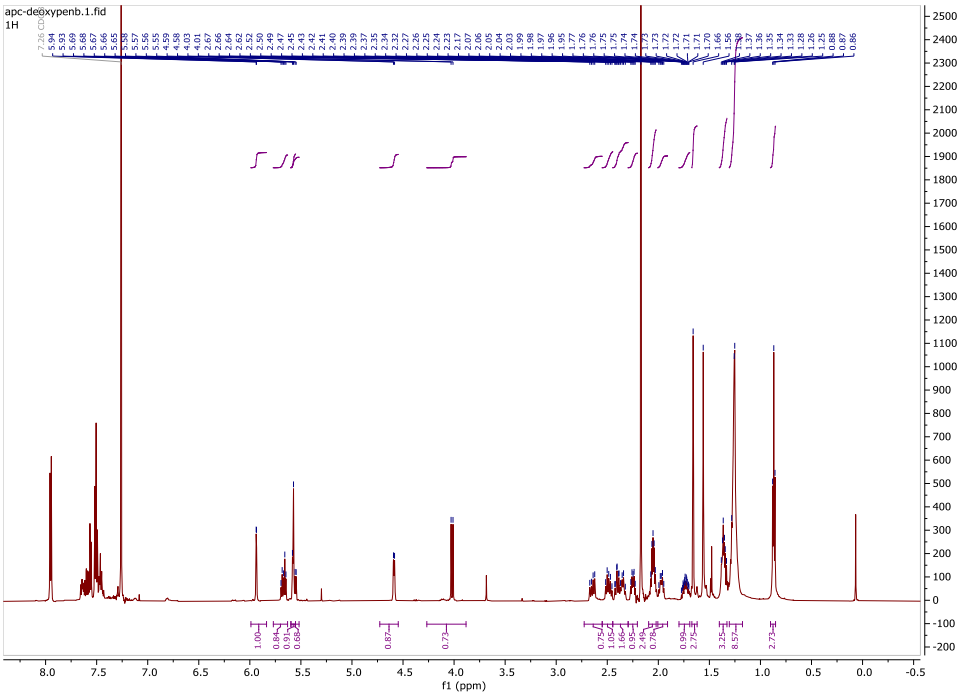

O
H
O
C_7H_{15}
H


apc-1535-flash2-carbON.1.1.1r
1H
f1 (ppm)


apc-1535-flash2-carbON.2.1.1r
zgcppr
193.87
169.70
136.44
134.97
127.30
122.85
122.59
77.38
74.35
47.68
45.07
32.81
32.22
31.03
30.03
23.81
23.06
20.00
14.35
f1 (ppm)

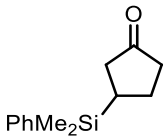

apc-1585-flash.5.1.2rr
HSQCEDGPPH
f2 (ppm)
f1 (ppm)

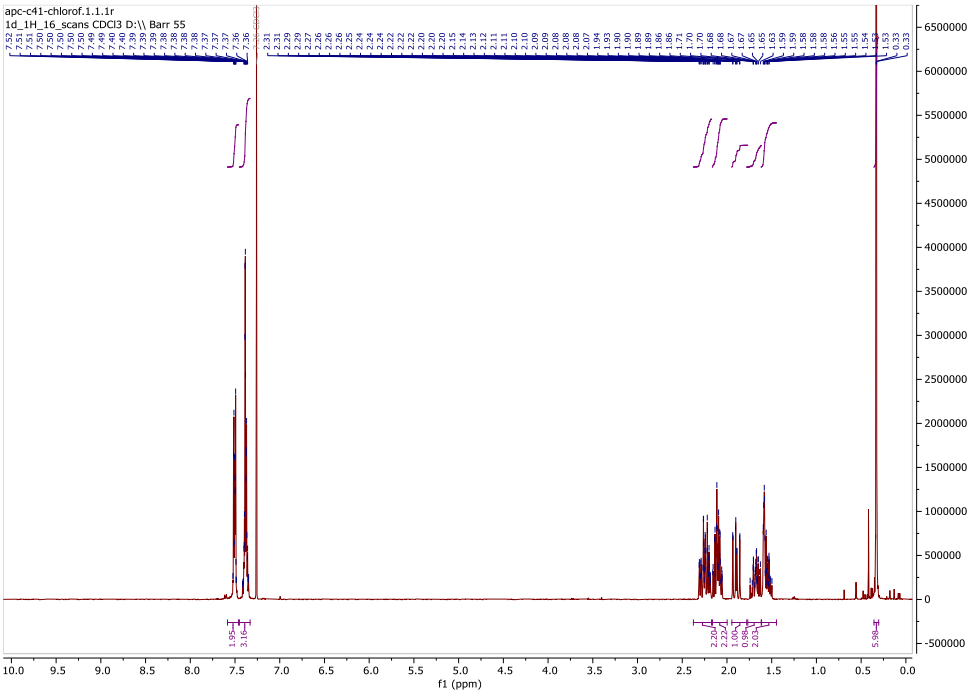

apc-1585-flash.2.1.2rr
COSY 45
{5.38,1.54}
{5.88,1.84}
{5.82,2.03}
{5.80,2.03}
{5.77,2.03}
{4.10,2.31}
{4.08,2.31}
{2.30,2.31}
{4.09,4.10}
{5.65,4.68}
{5.63,4.68}
{4.68,4.68}
{4.67,4.68}
{5.38,5.38}
{5.66,5.66}
{5.67,5.80}
{5.88,5.88}
{5.62,5.63}
{5.78,5.79}
{5.64,5.80}
f2 (ppm)
f1 (ppm)

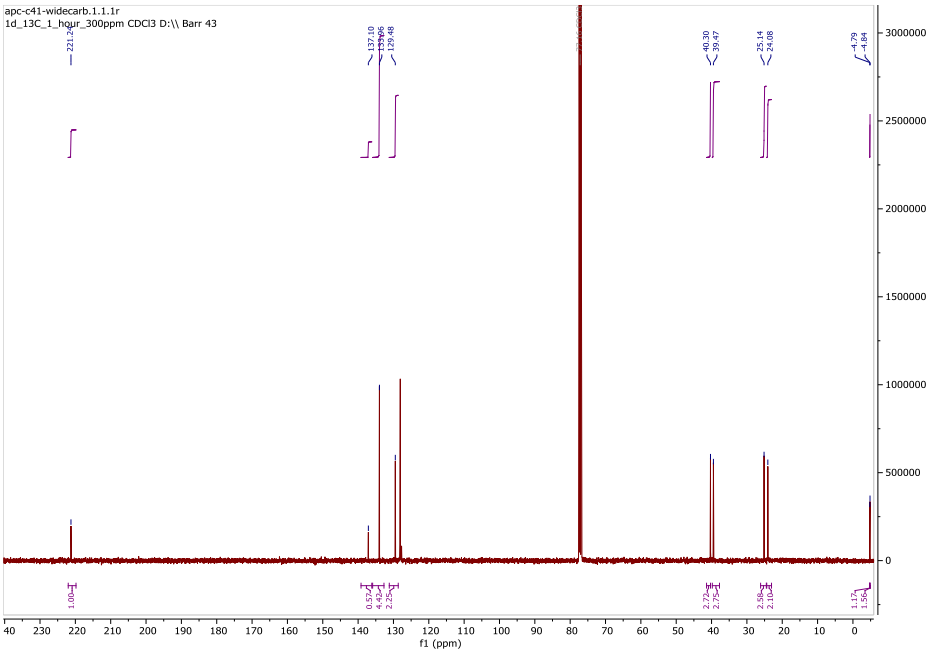


^{1}H NMR spectrum of 1.33 in chloroform. Significant presence of diphenyl sulfoxide impurity (7.3-8 ppm).

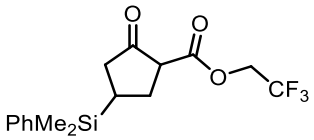
5.5

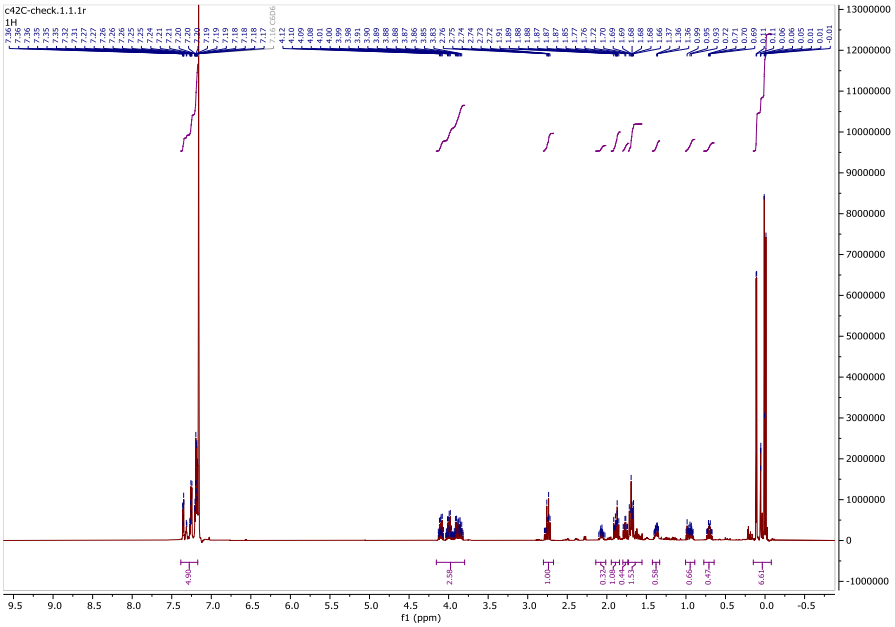

O
PhMe2Si

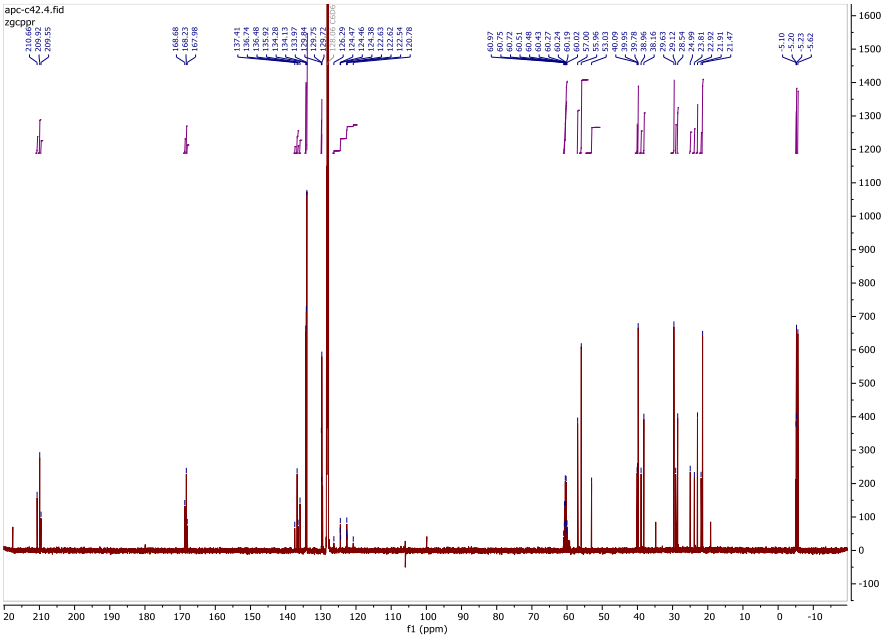

apc-c41-chlorof.1.1.1r
1d_1H_16_scans CDCl3 D:\\ Barr 55
f1 (ppm)


apc-c41-widecarb.1.1.1r
1d_13C_1_hour_300ppm CDCl3 D:\\ Barr 43
f1 (ppm)

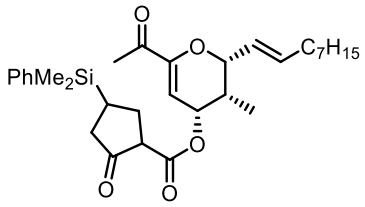
5.16

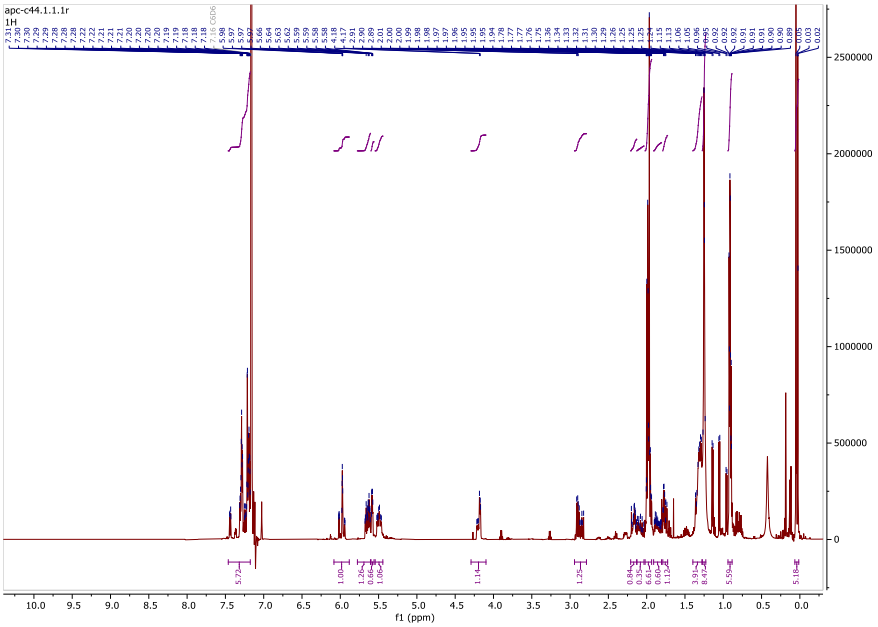

O
O
O
CF3
PhMe2Si

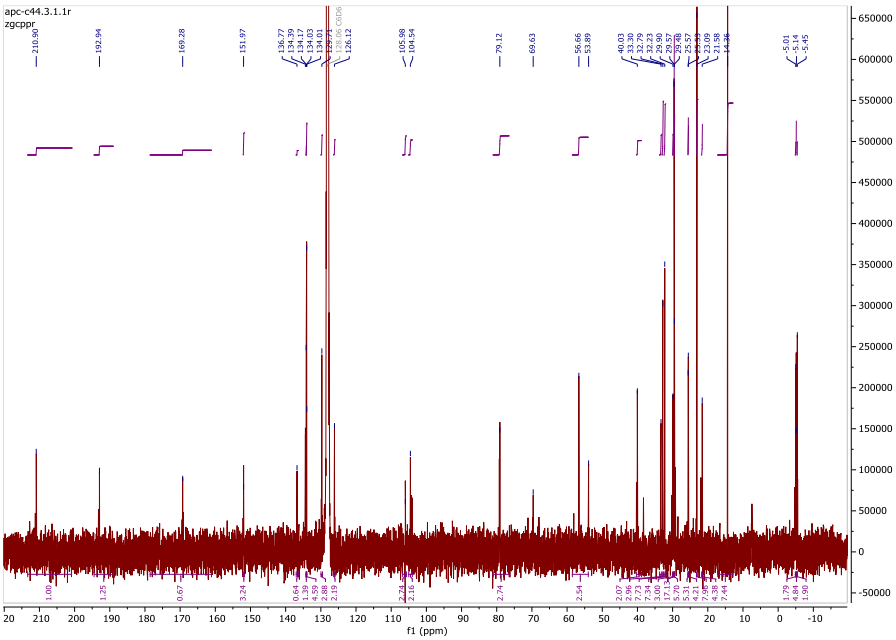

c42C-check.1.1.1r
f1 (ppm)


apc-c42.4.fid
zgcppr
f1 (ppm)

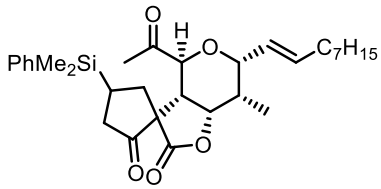
5.17

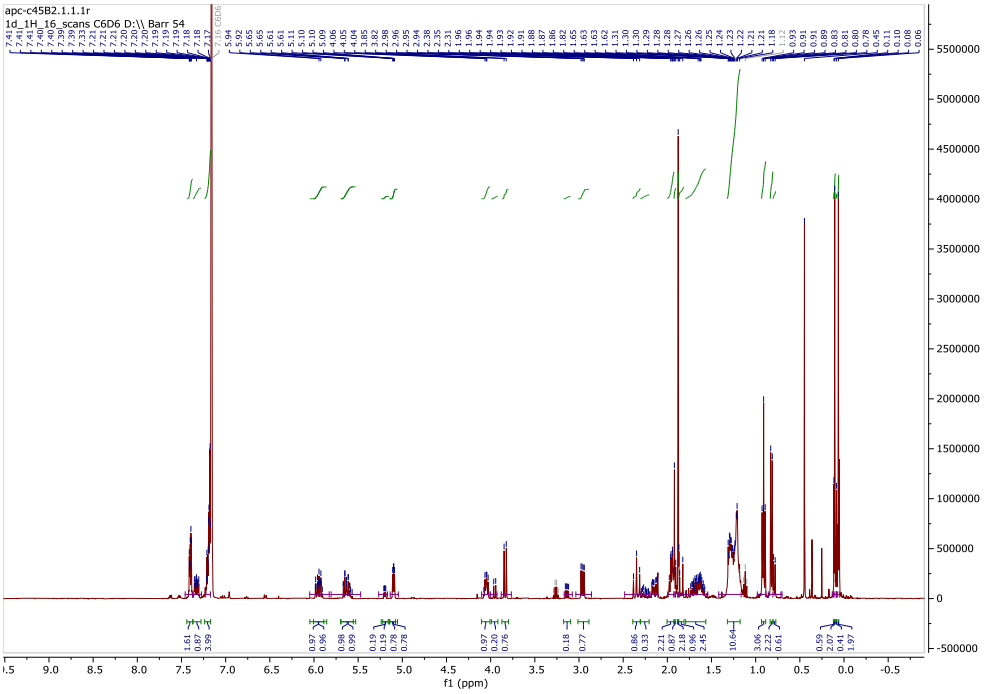

O
O
C7H15
PhMe2Si
O
O
O

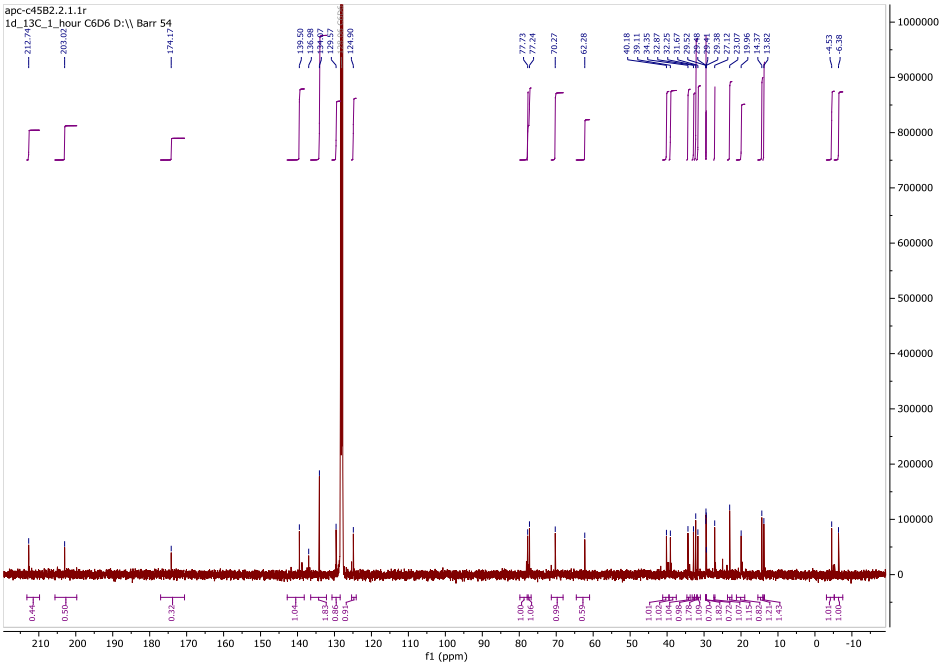

apc-c44.1.1.1r
1H
f1 (ppm)


apc-c44.3.1.1r
zgcppr
f1 (ppm)

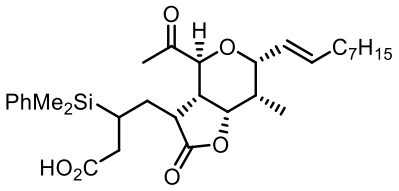
5.18

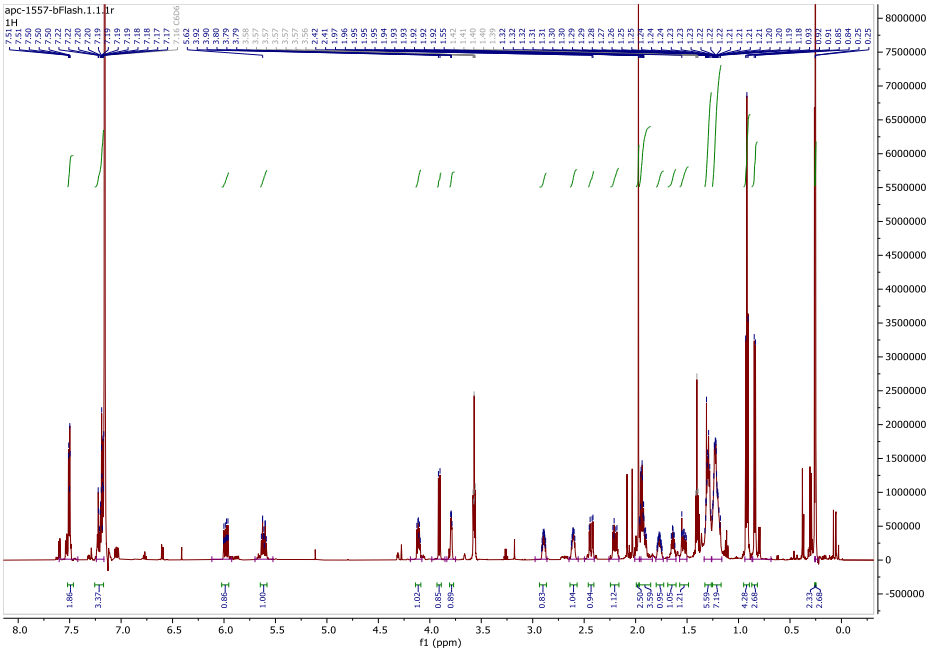

PhMe2Si
C7H15
O
H
O
O
O
O

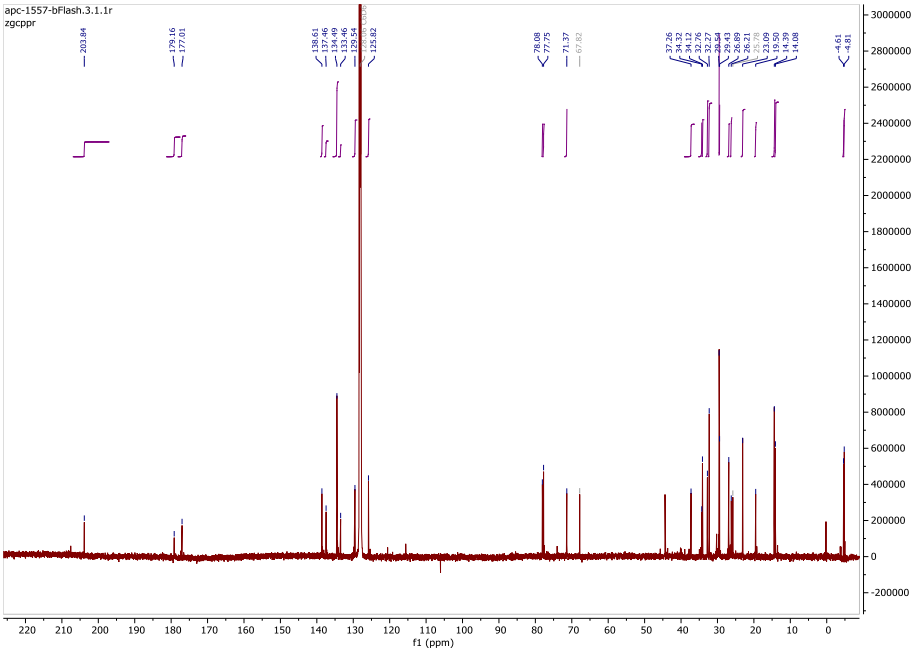

apc-c45B2.1.1.1r
1d_1H_16_scans C6D6 D:\\ Barr 54
f1 (ppm)


apc-c45B2.2.1.1r
1d_13C_1_hour C6D6 D:\\ Barr 54
f1 (ppm)

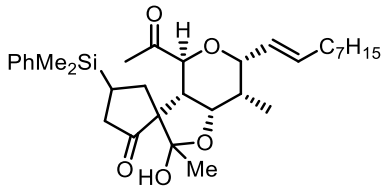
5.20

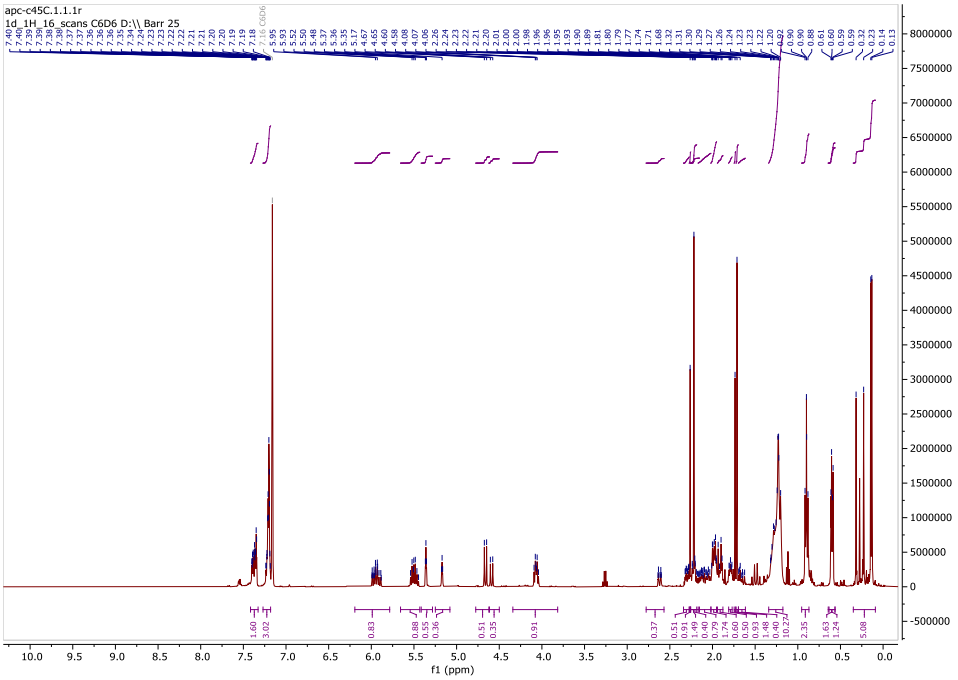

O
H
O
C_7H_{15}
$PhMe_2Si$
HO_2C
O
O

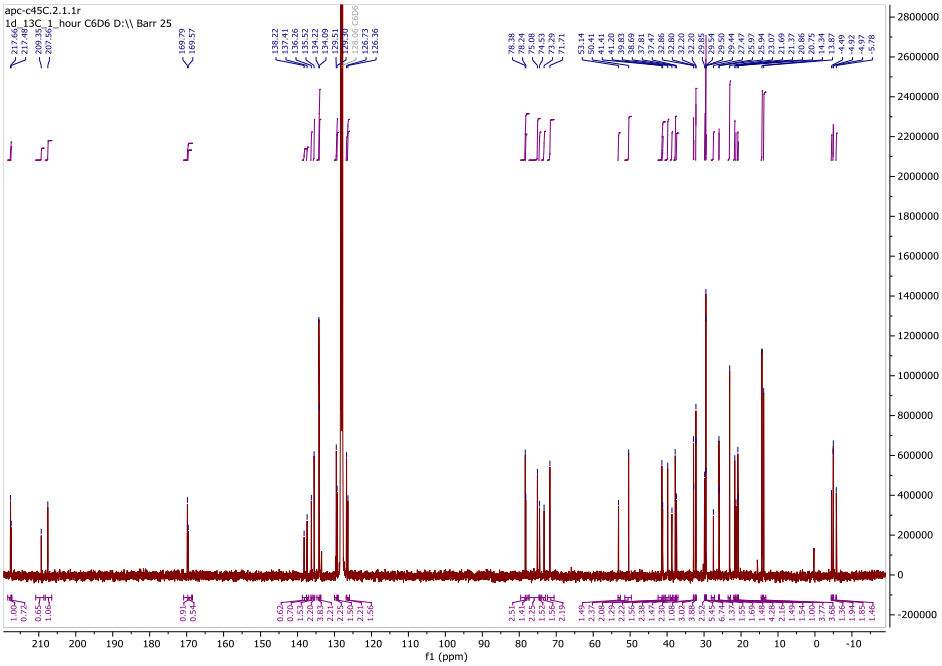

apc-1557-bFlash.1.1.1r
1H
f1 (ppm)


apc-1557-bFlash.3.1.1r
zgcppr
f1 (ppm)

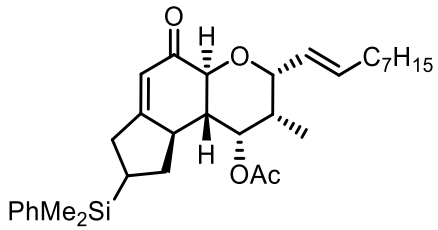
5.19

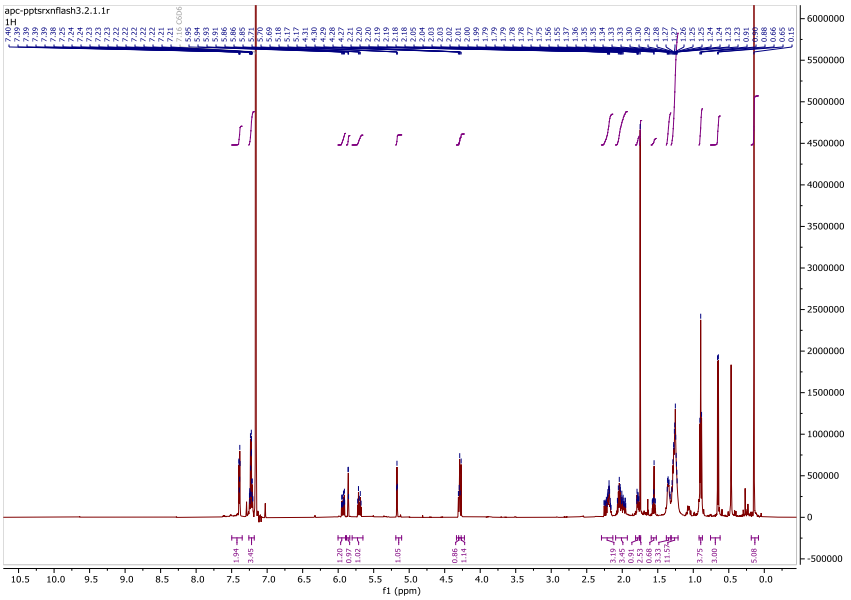

O
H
O
C7H15
PhMe2Si
O
O
HO
Me

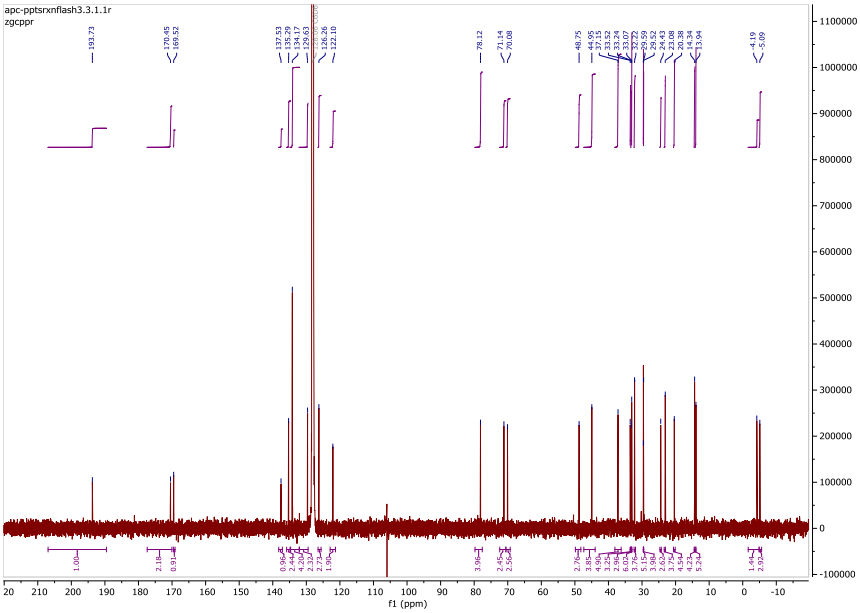

apc-c45C.1.1.1r
1d_1H_16_scans C6D6 D:\\ Barr 25
f1 (ppm)


apc-c45C.2.1.1r
1d_13C_1_hour C6D6 D:\\ Barr 25
f1 (ppm)

5.21


O
H
O
C_7H_{15}
H
OAc
$PhMe_2Si$


apc-pptsrxnflash3.2.1.1r
f1 (ppm)


apc-pptsrxnflash3.3.1.1r
zgcppr
f1 (ppm)