Title
Synthetic studies toward complex Schisandraceae and zoanthamine natural products

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Synthetic Studies Toward Complex Schisandraceae and Zoanthamine Natural Products

A Dissertation submitted in partial satisfaction of the requirements for the degree

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in

Chemistry

by

Derek A. Fischer

Committee in charge:

Professor Emmanuel Theodorakis, Chair
Professor William Gerwick
Professor Joseph O’Connor
Professor Susan Taylor
Professor Michael VanNieuwenhze

2008
The dissertation of Derek A Fischer is approved, and is acceptable in quality and form for publication on microfilm:

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Chair

University of California, San Diego

2008
DEDICATION

To my family and Beth; thank you for the unconditional love, support, and encouragement.
EPIGRAPH

The end of the road is a true beginning.
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LIST OF ABBREVIATIONS

Ac                  acetyl
AcOH                acetic acid
Boc                 tert-butoxycarbonyl
Bu                  butyl
\textit{t}-Bu        \textit{tert}-butyl
Bn                  benzyl
\degree C           degrees celsius
calcd               calculated
CDCl$_3$            deuterated chloroform
CHCl$_3$            chloroform
CD$_2$Cl$_2$        deuterated methylene chloride
C$_6$D$_6$          deuterated benzene
CCDC                Cambridge Crystallographic Data Center
CI                  chemical ionization
DBU                 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC                 1,3-dicyclohexylcarbodiimide
DCM                 dichloromethane
DIBAL-H             diisobutylaluminum hydride
DIEA                diisopropylethylamine
DMA                 \textit{N},\textit{N}-dimethylacetamide
DMAP  $N,N$-4-dimethylaminopyridine
DMF  $N,N$-dimethylformamide
DMP  Dess–Martin periodinane
DMS  dimethylsulfide
DMSO  dimethylsulfoxide
DMSO-$d_6$  deuterated dimethylsulfoxide
Et  ethyl
EtOAc  ethyl acetate
FAB  fast atom bombardment
FT-IR  Fourier transform-infrared
h  hours
HCl  hydrogen chloride
hv  irradiation with light
HMPA  hexamethylphosphoramide
KHMDS  potassium bis(trimethylsilyl)amide
HRMS  high-resolution mass spectrometry
IBX  o-iodoxybenzoic acid
IC$_{50}$  mean inhibitory concentration
IR  infrared
LHMDS  lithium bis(trimethylsilyl)amide
m-CPBA  m-chloroperoxybenzoic acid
Me  methyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>MeI</td>
<td>methyl iodide</td>
</tr>
<tr>
<td>MEM</td>
<td>methoxy ethoxy methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
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<tr>
<td>mL</td>
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<tr>
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</tr>
<tr>
<td>Mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
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<tr>
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</tr>
<tr>
<td>NOE</td>
<td>nuclear overhauser effect</td>
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<td>ORTEP</td>
<td>Oak Ridge thermal ellipsoid plot</td>
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<td>Pd(PPh₃)₄</td>
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<td>phosphomolybdic acid</td>
</tr>
<tr>
<td>PPh₃</td>
<td>triphenylphosphine</td>
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<tr>
<td>ppm</td>
<td>part per million</td>
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<tr>
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<td>-----------</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
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<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
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<td>TBS</td>
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<td>triethylsilyl</td>
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<tr>
<td>Tf</td>
<td>trifluoromethanesulfonate</td>
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</tr>
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<td>trifluoroethanol</td>
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<tr>
<td>TFAAA</td>
<td>trifluoroacetic anhydride</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
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<td>TLC</td>
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</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
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Spectrum 2.290 $^1$H NMR (CD$_2$Cl$_2$, 400 MHz) of compound 668 ........................................ 653
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Spectrum 2.292 $^1$H NMR (CD$_2$Cl$_2$, 400 MHz) of compound 668 ........................................ 655
Spectrum 2.293 $^{13}$C NMR (CD$_2$Cl$_2$, 125 MHz) of compound 668 ........................................ 656
Spectrum 2.294 $^{13}$C NMR (CD$_2$Cl$_2$, 125 MHz) of compound 668 ........................................ 657
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My family and friends deserve the deepest of gratitude. Thank you for your support and encouragement. For the support and encouragement of the last year I am most thankful to Dr. Beth Wilson.
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PUBLICATIONS

Ghosh, Subhash; Rivas, Fatima; Fischer, Derek; Gonzalez, Miguel A.; Theodorakis, Emmanuel A. Stereoselective synthesis of the ABC ring system of norzoanthamine. Organic Letters. 2004, 6(6), 941-944.

Gonzalez, Miguel A.; Ghosh, Subhash, Rivas, Fatima; Fischer, Derek; Theodorakis, Emmanuel A.; Synthesis of (+) and (-)-isocarvone. Tetrahedron Letters. 2004, 45(26), 5039-5041.


ABSTRACT OF THE DISSERTATION

Synthetic Studies Toward Complex Schisandraceae and Zoanthamine Natural Products

by

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Doctor of Philosophy in Chemistry

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Natural products, or secondary metabolites of plants and animals, have proven invaluable to humanity. We have used them for myriad reasons throughout history, including non-essential purposes such as dyes for textiles and paints. Less trivial uses, such as those related to food and health better demonstrate the importance of natural products. We have made use of toxic natural products to bolster hunting efficiency (e.g. poison tipped darts), and insect pheromones and natural products with antifeedant properties have assisted agricultural growth. Therapeutic natural products have long been used as dietary supplements and medicines. The ubiquitous nature of
natural products and their derivatives in current health care validates continued laboratory work in all areas of natural product research.

We (The Theodorakis Lab) have viewed natural product synthesis as a tool for expanding our understanding of organic chemistry. Of particular interest, are natural products which contain rare or novel architectural features. The synthetic study of these natural products therefore inspires creative solutions to complicated synthetic challenges, and often necessitates the development of new methodologies. Unique structural characteristics of two natural product families, Schisandraceae dilactones and zoanthamine alkaloids, caught our interest for the stated reasons.

Research herein describes work directed towards synthesis of the unprecedented micrandilactone A ABC ring system and a distinctive approach to the zoanthamine alkaloids. Chapter I narrates research related to the micrandilactone A ABC ring motif which culminated in an interesting multi-step one pot acid mediated reaction for AC ring formation. Chapter II reports attempts at poly-cyclization cascade reactions directed toward zoanthamine alkaloid synthesis.
Chapter I

Studies Toward Schisandraceae Natural Products

Section 1.1 Introduction to Schisandraceae and Related Natural Products

The plant family Schisandraceae belongs to the order Austrobaileyales and contains the genera Schisandra and Kadsura. This family is composed of flowering plants, typically vines and shrubs indigenous to many regions of the world. Fruits and extracts from the plant family Schisandraceae have been used since antiquity (Schisandra chinensis was referenced in 2697 BC)\(^1\) in Chinese culture for their astringent, anti-hepatotoxic, anti-asthmatic, antitussive, anti-fatigue, antioxidant, anti-cancer, sedative, immunostimulant, and liver protecting properties.\(^2\) Dried berries of the plants belonging to the genus Schisandra, often referred to as Wu-Wei-Zi or Schisandra, are currently marketed as dietary supplements with healing properties. Schisandra is now commonly found in U.S. health stores and is even prominently displayed as an ingredient in the 2008 spring beer, Springboard Ale brewed by New Belgium Brewing.

The long history of natural product use as medicinal remedies and/or treatments of human disease has been the impetus for the study of their pharmacological properties. The quest for new natural products that possess biological activity has been facilitated by technological advancements and has prompted researchers to examine
other components of *Schisandra* plants, less abundant in molecules of interest, in addition to the traditionally studied fruits. In recent years new compounds have been discovered from stem, branch, root, and leaf extracts. Investigations into the chemical components of Schisandraceae plants, specifically of the *Schisandra* and *Kadsura* genera, have led to the identification of a large volume of natural products. Many of these natural products exhibit interesting biological properties. For example, nigranoic acid (*S. sphaerandra*)\(^3\), lancelactone C (*K. lancilimba* How)\(^4\), rubriflordilactones A and B (*S. rubriflora*)\(^5\), and micrandilactone C (*S. micrantha*)\(^6\) have all demonstrated anti-HIV activity.

Although limited biological activity has been displayed by many of the Schisandraceae compounds, our interests lie in the unprecedented structural arrangements. A number of architecturally unique and complex naturally products have been isolated from this family in recent years. Of particular interest is the dilactone group, which includes: micrandilactones\(^6,7\), lancifodilactones\(^8\), henridilactones\(^9\), sphenadilactones\(^10\), schindilactones\(^11\), wuweizidilactones\(^12\), and propindilactone A\(^13\) (Fig 1.0). This group of natural products is characterized by a heavily modified and highly oxygenated cycloartane core. With the exception of lancifodilactone F, all natural products of this group thus reported contain a unique fused cycloheptyl-hydrofuran-butyrolactone motif. To date, this unique moiety has only been reported in the Schisandraceae class of natural products. The structure of micrandilactone A, the first reported member of the dilactone family, was initially disclosed in 2003.\(^7\)
Interestingly, several of the compounds in Figure 1.0 are not species specific. For example, micrandilactone A (1) has been isolated from *S. micrantha*, *S. propinque* var. *propinqua*, *S. lancifolia*, and *S. rubriflora*. It is conceivable that these compounds share a similar biosynthetic pathway, although they are produced by unique plant species.

A series of less densely functionalized compounds, some thought to be important biogenetic precursors to the dilactone group, have also been isolated from the same plant specimens as many of the dilactones (Fig. 1.1). The cycloartane core is more
obvious in this group of compounds. Accordingly, the cyclopropane ring is conserved in each structure. Other structural similarities are also observed within this group of compounds. The tetracyclic steroidal core is conserved in schizandronic acid\(^{15}\) (11) and kadsulactone\(^{16}\) (12). kadsudilactone\(^{16}\) (13) contains an oxidized A ring (steroid assignment) while schisanlactone B\(^{17}\) (13b) contains an unsaturated and oxidized A ring. Micranoic acid B\(^{18}\) (9) and nigranoic acid\(^{3}\) (10) have abbreviated cores in which the A ring has presumably been oxidatively opened.

Figure 1.1 Selected Schisandraceae cycloartane natural products.

Some members of this group of compounds are found in different species and genera. For instance, schizandronic acid (11) has been found in at least four Schisandra species (\(S. \text{ nigra} \) Max,\(^{15}\) \(S. \text{ micrantha},^{18}\) and \(S. \text{ henryi} \) var. yunnanensis\(^9\)) and within a
species that shares the same family but has been classified outside the genus, *Illicium verum* Hook f.\(^\text{19}\) Moreover, they share structural similarities with natural products isolated from *Buxus papillosa*.

**Figure 1.2** Natural products of *Buxus papillosa*.

Buxatenone (14), buxaheptalactone (15), and buxapentalactone (16) have been isolated from root extracts of *Buxus papillosa* (Fig. 1.2). Buxatenone\(^\text{20}\) had previously been reported when Clardy and coworkers disclosed the structures of buxaheptalactone (15) and buxapentalactone (16) in 1992.\(^\text{21}\) In the isolation paper, Clardy’s group recognized a potential biogenetic relationship between the 3 *Buxus* natural products. It was postulated that a combination of olefin reduction and ketone oxidation of buxatenone (14) would give rise to buxaheptalactone (15). Ring opening of the cyclopropane ring and rearrangement of the heptalactone (15) could lead directly to buxapentalactone (16). Notably, buxatenone (14) bares a strong resemblance to micranoic acid B (9).

The combination of novel structural scaffolds and putative pharmacological profiles contained within the Schisandraceae natural products makes them attractive
targets for synthetic chemists. Indeed, several synthetic efforts have been published for these complex natural products.

Section 1.2 Synthetic Studies Toward Schisandraceae Natural Products

Section 1.2.1 Reported Synthetic Studies

The size (octacyclic skeleton) and many stereochemical complexity (13 stereocenters) of micrandilactone A (1) make it an imposing synthetic target. Other structural highlights include: the high level of oxygenation, 3 hydroxy groups, 2 butyrolactones, 2 ketones, a hydrofuran, and a fused 7,5,6 ketal forming the DEG ring system. Any successful synthetic attempt of this molecule would necessitate great effort or incredible foresight.

The published synthetic work will be briefly reviewed. It should be noted that the structure of micrandilactone A (1) was originally incorrectly reported as its enantiomer and the correct structure was published in 2006.22 Prior to the correction, the published studies depict the structure with the enantiomeric stereochemistry. However, the studies presented herein were performed with racemic materials. Original micrandilactone A (1) numbering, which was unchanged by the structural revision, will be used throughout this manuscript (Fig. 1.3).
Zhen Yang and coworkers have published approaches directed at the western, central, and eastern fragments of micrandilactone A. Yang’s approach to the eastern fragment focused on a Pauson-Khand reaction and palladium mediated carbonylation as the key steps in forming the FGH ring fragment (Scheme 1.0). Diels-Alder, a Horner-Wadsworth-Emmons cascade, and ring-closing metathesis reactions were integral to the formation of the reported western fragment, rings ABC. A [3+3] sigmatropic rearrangement has been used to develop a 7,8 fused ring system potentially applicable to the fused CD ring system.
**Scheme 1.0** Yang’s approach to the FGH ring system of micrandilactone A.

The FGH ring study began with a two step sequence from butene-diol, which provided enyne 17. When reacted under Pauson-Khand conditions, 17 gave the bicyclic system (18). The ketone was stereoselectively reduced under Luche conditions and the resultant allylic alcohol protected as the TBS ether. The lactone functionality was reduced to the corresponding diol and the resultant allylic alcohol oxidized to aldehyde 20 in excellent yields. Addition of vinyl magnesium bromide to 20 resulted in a mixture of allylic alcohols. After collection of the desired alcohol, 21, the undesired diastereomer was converted to 21 by oxidation and Luche reduction. Carbonylative
annulations of diol 21 were achieved only in low yields. It was speculated that an intermediate allylic arrangement, involving the terminal olefin hindered the carbonylative annulation. This side reaction was mitigated by converting the olefin to an epoxide. The epoxide gave an excellent yield (95%) of the desired tricycle 22 when treated under carbonylation conditions. Protecting group manipulation and oxidation provided 24, which upon treatment with silica decomposed to 25 in good yield. With the exception of 3 stereocenters, 25 represents the fully functionalized FGH ring system. This work stands as an impressive entry into the Micrandilactone A (1) synthetic effort.

Yang has also addressed formation of the unique 7,8 (CD) ring system of micrandilactone A (1) via a model system (Scheme 1.1). The addition-elimination of 26 and 27 provided allylic alcohol 28, which was then deprotected and oxidized to give lactone 29. It is worth noting that the oxidation reaction involves selective oxidation of a primary alcohol over a secondary and subsequent oxidation of the resultant lactol in one pot with catalytic TEMPO. Lactone 29 was alkylated without selectivity, providing a 1:1 mixture of methylated lactones, 30a, and 30b. The lactones were homologated with the Petasis reagent and treated with Lewis acid at low temperature to instigate the [3+3] sigmatropic rearrangement. Subsequent oxidation provided 32a and 32b.
Scheme 1.1 Yang’s approach to the CD ring system of micrandilactone A.

Although Yang’s model system is simple, the good stereocontrol of the Claisen is an important observation that may allow its strategic use in future synthetic efforts. Also, it appears that C14 substitution may not significantly affect the Claisen stereoselectivity. This will potentially allow a fully, or mostly, functionalized eastern fragment to be formed prior to formation of the central CE ring system. Taken together, this work has given the researchers important insight into synthetic strategies.

Of particular interest to us is the reported work toward the western fragment. Yang has utilized a very interesting Horner-Wadsworth-Emmons cascade reaction to form the butyrolactone A ring and an enyne RCM reaction to fuse ring C to the B ring (Scheme 1.2).
Scheme 1.2 Yang’s approach to the ABC ring system of micrandilactone A.

A regioselective Diels-Alder reaction provided cyclohexene 33, which was treated with a methyl Grignard reagent at low temperature to install the second C4 methyl. The resultant tertiary alcohol cyclized to form the butyrolactone B ring, and oxygen was installed at C10. Stereoselective reduction gave lactol 34. Treatment of 34 with phosphonate 35 and excess base provided 38. The mechanism is speculated to involve a Michael addition to the α,β unsaturated ester (36-37) followed by lactonization (37-38) involving the C10 alkoxy anion. A yield of 50% for this reaction is impressive as it involves multiple anionic manipulations and provides the fully functionalized A ring with the correct stereochemistry.
Reductive ozonolysis and selective reduction of the resultant aldehyde followed by TBS protection provided ketone 39 in 66% yield over 3 steps. Treatment of 39 with lithium TMS acetylide gave propargyl alcohol 40 with good selectivity (72% yield). The free alcohol was protected as the acetate and the primary alcohol revealed by TBAF treatment. Oxidation and single-carbon Wittig homologation provided the enyne RCM substrate 41. The enyne RCM reaction worked extremely well, yielding 84% of 42. This fragment contains the fully functionalized AB ring system, with a nearly fully functionalized C ring. C9 has the necessary oxygen and alkyl substituents, while the C7 hydroxy group could potentially be inserted across the C8-C7 olefin through hydroboration.

More recently, Qiaoling Wang and Chuo Chen have published an approach to the lancifodilactone F (3) and buxapentalactone (16) cores (Scheme 1.3).26 Their approach is focused on an interesting arene-olefin meta-photocycloaddition used to build the 7 and 6 membered rings simultaneously. A 7-step sequence provided a mixture of separable alcohols which were protected to provide the photocycloaddition substrate(s). Studies on the individual diastereomers suggested it was unnecessary to separate them. The individual hydroxyl centers did not affect the cycloaddition and were subsequently destroyed by oxidation, converging to enantiomers.
Scheme 1.3 Chen’s approach to the lancifodilactone F and buxapentalactone cores.

Photocycloaddition of 43 gave the exo isomers 44a and 44b exclusively as a 1:1.2 mixture in yields over 90%. Epoxidation using mCPBA and acid treatment opened the cyclopropane ring, revealing the 7 membered ring, and allylic isomerization occurred when 45a was treated with Pd/C under a hydrogen atmosphere. Treatment of ketone 46 with isopropenyl Grignard and IBX oxidation provided 48. While 48 contains the desired 7,6,5 core, it is not clear how the researchers plan to cleave and functionalize the two 5-membered rings surrounding the methylketal.

In summary, the Chen group has outlined an approach to the 7,6,5 ring system present in lancifodilactone F (3) and and buxapentalactone (16). While the use of an arene-olefin photocycloaddition allows the rapid development of multiple rings and stereochemical complexity, additional research will be necessary if this approach is applied to the total synthesis of the specified natural products.
The Yang group has developed three unique approaches to the western, central, and eastern fragments of micrandilactone A (1). They have synthesized highly functionalized western and eastern fragments in the course of this investigation and each approach appears to be amenable to their plan for total synthesis (Fig. 1.8).

**Section 1.2.2 Retrosynthesis of Western Fragment and Abbreviated Biosynthetic Proposal**

Our interest was focused on the western fragment of the Schisandraceae natural products. With the exception of lancifodilactone F (3), the micrandilactone A (1) tricyclic moiety is ubiquitous within the dilactone group of natural products, making it an ideal scaffold for initial studies. A general approach to building the lancifodilactone F (3) western fragment and the tricyclic micrandilactone A (1) moiety was desirable (Fig. 1.4).

![Figure 1.4 Fragments targeted for synthesis.](image)

With the idea that the compounds of interest may arise from a cycloartane steroidal intermediate, we recognized the diversity of isolated compounds containing differing ring A (steroid ring assignment) oxidation (Figures 1.0 and 1.1). For example,
kadsulactone (12), kadsudilactone (13), and schisanlactone B (13b) differ structurally only in the A ring. The A ring of kadsulactone (12) is a standard cyclohexanone cycloartane motif, the A ring of kadsudilactone (12) is a heptalactone, while the A ring of schisanlactone B (13b) is an unsaturated heptalactone. The cycloartane cyclopropyl ring remains intact for each and imagining a ring expansion arising from cyclopropyl cleavage is academic. Lancifodilactone F (3) and buxapentanone (14) contain a rearranged A,C (micrandilactone A numbering) ring system in the form of spirolactones connected to substituted heptane rings. The spirolactone (A ring) of lancifodilactone F (3) and buxapentalactone (16) was recognized as a potential intermediate in a path of increasing oxidation, culminating in formation of the B ring of the dilactones.

Guided by the observations discussed, we decided on a route which incorporated the structural clues from natural A (steroid) ring modifications (Scheme 1.4). Our plan was centered on a cascade reaction involving cyclopropyl cleavage/ring expansion, spirolactone formation, and B ring cyclization. A model system simple in nature yet a scaffold applicable to the complex Schisandraceae natural products was the main criteria for our decision.
We felt ketone 48 to be a sufficient model for ABC ring formation (47). It also contains a handle, C9 ketone, for potential functionalization. To that end, we felt the penultimate cyclization event may be a Michael addition from the C4 hydroxy group to the C1 olefin. Synthetic studies by Yang and coworkers have supported this Michael addition proposal as a 1,4 addition is likely taking place on the conversion of 34 to 38 (Scheme 1.2). The stereoselectivity would likely be substrate controlled and is expected to provide the desired Schisandraceae stereocenter through attack from the most accessible face. We expected the spirolactone 48 to arise from a carbocation intermediate such as 49. The planar nature of carbocations often limits stereocontrol in synthetic reactions, and with a minimally-substituted model we expected little stereoselectivity. There are alternative mechanisms based on this carbocation intermediate that may provide 48. For instance, the cyclopropyl ring may cleave prior to lactone opening. However, under acidic conditions all mechanisms considered
involve a cyclopropyl ring expansion through a tertiary cation. It is conceivable that a
carbocation such as 48, could arise from a bicyclic lactone such as 51.

The lactone 51 could presumably be a direct product of Baeyer-Villiger oxidation
on a bicyclic system such as 52. Simple manipulations were expected to provide 52
from the reported acetate 53, which has been synthesized from Robinson annulation
adduct 54. We began the study with this potentially biomimetic proposal as a guide.

Section 1.2.3 Literature Background of Key Rearrangement

Cyclopropylcarbinol ring expansions, or related variations, have been used in
natural product synthesis as a means of ring expansion. Although the reaction is
typically performed under acidic conditions, several reports indicate good
stereoselectivity. Of particular interest to us were the reactions used by Corey in the
synthesis of Glycinoeclepin28 and by Matsumoto in the conversion of Humulene to
Dactylo129. The epoxide functionality conjugated to the cyclopropane ring provides a
bond activated for cleavage through a push-pull concept, and rearrangement occurs
without loss of the oxygen. This mechanism resembles our proposed route where a
conjugated keto-cyclopropyl system expands to form an enol expected to tautomerize to
the ketone.

An additional feature of the Glycinoeclepin synthesis is the fact that Corey and
Hong used a cycloartane scaffold (Scheme 1.5). The rearrangement of cyclopropyl
epoxide 55 was achieved by treatment with boron trifluoride. The Lewis acid
presumably forms cation 56, which is trapped by the C4 hydroxy to form the ether
bridge of 57. Features of note are the fact that a cycloartane skeleton applicable to our proposal was used, the cyclopropane was activated by a “non-cleavable” withdrawing group, the internal nucleophile apparently controlled the stereoselectivity, and the carbocation was trapped by an internal nucleophile to form an additional small ring.

Scheme 1.5 Cyclopropyl ring expansion in Corey’s glycinoeclepin synthesis.

Matsumoto and coworkers took advantage of a similar reaction in their Dactylol synthesis (Scheme 1.6). Epoxide-activated cyclopropane (58) was converted to tertiary alcohol 61 and ketone 64 was obtained upon low temperature treatment with boron trifluoride. It is presumed that the cyclopropane opening was preceded by epoxide activation and a cyclopropyl shift leading to the cation 59. Additional events, proposed in Figure 1.11, would potentially lead to the reported products. No additional reaction products were reported, leaving us to speculate the low yields may result from alternative initial cyclopropane ring expansion pathways. While not directly related to our studies, this work demonstrates a cyclopropylcarbinol like ring-expansion utilizing a non-cleavable withdrawing group and demonstrates the unpredictable nature of cations.
Scheme 1.6  Cyclopropyl ring expansion in Matsumoto’s dactylol synthesis.

Examples of true cyclopropylcarbinol ring modifications in total synthesis have been provided by Wender through the total synthesis of Hirsutene\(^{30}\) and in the total synthesis of Confertin\(^{31}\) by Marshall. In contrast to the epoxide activated cyclopropanes, the cyclopropylcarbinol system uses a hydroxyl group to activate the cyclopropane ring. In this strategy the hydroxyl group is lost through elimination under acidic conditions, resulting in an unsaturated ring system.

Wender and Howbert built the highly strained cyclopropyl compound \(65\) through an arene-olefin cycloaddition (Scheme 1.7). When treated with Bronsted acid camphorsulfonic acid, \(65\) rearranged to form the Hirsutene skeleton (\(66\)) in good yield. This appears to be an E1 mechanism as the departing hydroxyl group and the fragile cyclopropane bond are not periplanar.
Scheme 1.7 Cyclopropylcarbinol ring expansion in Wender’s hirsutene synthesis.

Marshall and Ellison have also taken advantage of the relative fragility associated with a hydroxyl activated cyclopropane (Scheme 1.8). Synthetic work towards Confertin yielded cyclopropane 68. Treatment of 68 with perchloric acid initiated a cascade of events. Ring expansion and elimination likely occurred to provide carbocation 69, prior to cyclization by the internal nucleophile. Trans fused lactone 70 was produced in 80% yield with no diastereomers reported. The manuscript contained no speculation as to the source stereoselectivity, however earlier studies by Marshall’s group may have predicted the outcome of this reaction.

Scheme 1.8 Cyclopropylcarbinol ring expansion in Marshall’s confertin synthesis.

Marshall and Ellsion reported results of a series of relevant cyclopropylcarbinol studies prior to the Confertin synthesis (Scheme 1.9). Work with methyl esters 71 and 72 gave impressive yields of single isomers 73 and 74. Worthy of note, is the
observation that carboxylic acid 75 gave a high yield of 73. The fact that 71 and 75, epimeric at the hydroxyl carbon, gave the same reaction product suggested alcohol stereochemistry was not critical and supports an E1 mechanism. Marshall also found that the butyrolactones 73 and 74 could be formed from lactones 76 and 77. The study showed cyclopropane stereochemistry to be the most important predictor for the reaction outcome. Marshall commented that the acid or ester side chain might have played an anchimeric role. However, an explanation for the surprising stereoselectivity was not provided.

Scheme 1.9  Cyclopropylcarbinol ring expansion studies by Marshall and Ellison.

Section 1.2.4 Synthesis of Isomeric Fragment

Without a clear understanding of expected stereoselectivity from the key ring expansion step, we required a route amenable to controlling cyclopropane
stereochemistry. We sought to test the reaction on compounds resembling 78 and 79, which are diastereomeric at the decalin ring junction (Fig. 1.15). We felt the reported compound 80\(^\text{27}\) (Fig. 1.5) matched our synthetic design and intermediates within its synthesis could allow for stereochemical diversity at the ring junction.

![Figure 1.5 Targeted synthetic intermediates.](image)

We targeted diol 87 as an intermediate capable of synthetic divergence (Scheme 1.10). Our route began with protection of 1,4 cyclohexanonedione as the mono dioxolane. Slow addition of ethylene glycol to an acidic solution of the dione 81 provided monodioxolane 83 in acceptable yields, but separation from the di-dioxolane (82) proved difficult. Accordingly, a literature procedure was followed for the preparation of dioxolane 82.\(^\text{33}\) Di-dioxolane was prepared by refluxing ethylene glycol with 1,4-cyclohexanedione (81) in benzene with pTSOH under dehydrating conditions (Dean-Stark trap). The di-dioxolane (82) was refluxed in an acidic (pTSOH) toluene solution with 1.5 eq. 1,4-cyclohexanedione, which allowed equilibration to dioxolane 83 in excellent yield. The mono ketal (83) was easily separated from the excess 81 through chromatography.

Acylation methodology developed by Mander and Sethi allowed for acylation of dioxolane 83 by enolization with LDA and treatment with methyl cyanoformate.\(^\text{34}\)
Robinson annelations of 84 with methyl vinyl ketone worked best when performed under conditions developed for the analogous ethyl ester by Tsuda and coworkers. In addition, conditions use by Kabuto and coworkers (MeOH, NaOMe) also produced the reported enone (85). Treatment of keto-ester 84 with triethylamine and methyl vinyl ketone in methanol for several days followed by refluxing with a solution of pyrrolidine and acetic acid in benzene (Dean-Stark dehydrating conditions) provided Robinson adduct 85 in 65% yield. Uncyclized intermediates were often isolated from this reaction after chromatography and could generally be converted to the cyclized product by retreatment.

Scheme 1.10 Synthetic route to diol 87.

Dimethylation of 85 was achieved through the extended enolate by treatment with excess methyl iodide over extended time periods. Di-methylated keto-ester 86 was reduced to diol 87 with lithium aluminum hydride. The bulky reducing agent approached the cyclohexanol axially, from the face opposite the methyl ester, to provide the equatorial alcohol in 82% yield. Analyses of the crude mixture suggested a
significant amount of the epimeric alcohol was produced. However, an amount of sufficient purity for characterization was not obtained.

With diol 87 in hand, cyclopropyl diketone 97 became the immediate goal (Scheme 1.11). Diol 87 was stirred in ethanol with pTSOH to provide ethyl ketal 88. This ketal was reduced under standard hydrogenation conditions with 10% Pd/C. Reduction occurred from the less hindered α-face to provide 89 in excellent yield. Acetylation preceded pTSOH treatment to form the hemiketal 91.

Scheme 1.11 Synthetic route to cyclopropyl ketone 97.
Treatment of hemiketal 91 with mesyl chloride and base gave a mixture of primary mesylate 92b and mesylketal 92a (4:5, 90% overall yield). Fortunately, hemiketal 91 could be recovered by treatment of mesylketal 92a with acid and retreated to provide primary mesylate 92b. Sequential treatments in this manner allowed for production of 92b in 70% overall yield.

Treatment of 92b with base allowed cyclopropane formation under mild conditions. Purification of cyclopropyl acetate 80 gave crystals of sufficient quality for single crystal X-ray analysis. In this manner, the structure of 80 was unambiguously confirmed.

We had some concern over future the selectivity the planned Baeyer-Villiger reaction and decided to mask the ketone again as a dioxolane. This was achieved under standard conditions with pTSOH and ethylene glycol. Subsequent deprotection of the acetate and oxidation by Dess-Martin periodinane provided ketone 95. This compound decomposed under Baeyer-Villiger conditions to the diketone 97. Fortunately we learned that diketone 87 underwent very efficient and selective Baeyer-Villiger oxidation and the protection step was unnecessary. With this knowledge, keto acetate 96 was deprotected and oxidized to diketone 97 in excellent yield.

As mentioned, the oxidation of 97 to heptalactone 98 worked with excellent selectivity, oxidizing the most highly substituted position (Scheme 1.12). We decided to attempt the rearrangement with 98, prior to installing lactone unsaturation. Unfortunately, treatment of ketone 98 with boron trifluoride and Bronsted acids resulted
in complex mixtures of uncharacterized products. We switched focus and decided to perform the reaction with a true cyclopropylcarbinol.

Scheme 1.12 Synthetic route to rearrangement substrates 99 and 104.

To this end, selective hydride reduction of 98 by sodium borohydride in THF gave an excellent yield of alcohol 99. Reduction attempts in protic solvents (methanol and ethanol) gave complex product mixtures, presumably due to lactone decomposition. The alcohol stereochemistry 99 has been tentatively assigned based on comparison of 
$^1$H NMR data of related structures. Alcohol 99 underwent selective rearrangement to spirolactone 100 when treated with a variety of acids (Table 1.0). Spirolactone 100 was characterized by single crystal x-ray analysis in conjunction with standard NMR and mass spectroscopy techniques. Olefinic spirolactone 101 was also produced in the reaction, typically the ratio of 101 to 100 increased with longer reaction times. This suggests the cyclopropyl bond cleavage was more facile than C4 elimination of water to
form 101. The best yields of 100 were achieved by treatment with aqueous perchloric acid in acetonitrile coupled with frequent reaction monitoring.

Table 1.0 Survey of acid effect on the rearrangement of 99.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Acid</th>
<th>yield 100</th>
<th>yield 101</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetonitrile</td>
<td>HClO₄/H₂O</td>
<td>75%</td>
<td>20%</td>
</tr>
<tr>
<td>acetone</td>
<td>H₂SO₄</td>
<td>20% trace</td>
<td>50% 65%</td>
</tr>
<tr>
<td>acetone (0.5 h)</td>
<td>HCl</td>
<td>30%</td>
<td>35%</td>
</tr>
<tr>
<td>acetone (1.5 h)</td>
<td>HF</td>
<td>40%</td>
<td>7%</td>
</tr>
<tr>
<td>acetone</td>
<td>HNO₃</td>
<td>50%</td>
<td>7%</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>TFA</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>BF₃·OEt₂</td>
<td>trace</td>
<td>20%</td>
</tr>
</tbody>
</table>

Although spriolactone 100 contains the incorrect C5 and C10 (Micrandilactone numbering) stereochemistry, confirmation of the rearrangement reaction prompted us to explore the penultimate Michael addition. Attempts to install unsaturation to the spirolactone through a selenation-elimination process failed due to limited material. We felt tackling this issue at an earlier stage to be prudent, and perhaps allow for the Michael reaction to occur concomitantly with the cyclopropyl expansion reaction. Selenation of 99 was poor-yielding, and the corresponding selenide (99b) was isolated
in only 15%. After protection of the alcohol (99) as the TBS ether, treatment with phenylselenium bromide followed by oxidative elimination provided unsaturated lactone 104. Treatment of 104 with aqueous perchloric acid cleaved the silyl ether and gave spirolactone 105 as the only isolated product. Spirolactone 105 was reduced via hydrogenation and compared to the hydrogenation product of 100 for structural assignment in conjunction with standard NMR and mass spectroscopy techniques. Attempts to cyclize spirolactone 105 via a base catalyzed Michael addition failed and limited material prevented further study. Attention was turned to developing the desired Schisandraceae stereochemistry.

**Section 1.2.5 Synthesis of Stereochemically Correct Fragment**

Given the stereoselectivity observed in the rearrangements of 99 and 104, we decided to invert the C5 stereochemistry. Attempts to form the desired ring junction through standard Pd/C catalyzed hydrogenation failed. Hydrogenation of diol 108 resulted in inseparable mixtures, as did diacetate 106, and diacetate 107.
Scheme 1.13 Initial attempts at forming cis ring junction through hydrogenation.

We decided to use the hydroxy functionalities as directing groups and attempted a number of hydrogenations with this in mind (Table 1.1). As previously mentioned, hydrogenation reactions using Pd/C failed to produce acceptable results. We hoped that deprotonation of diol 87 would enhance and directing ability. Notwithstanding, Pd/C hydrogenations reactions with added potassium hydride or triethylamine failed to improve the reaction. Likewise, the use of platinum oxide as a catalyst failed. Based on literature reports of alkoxy directed hydrogenations, we turned to Wilkinson’s catalyst.37 Unfortunately these attempts failed as well. The more expensive Crabtree’s catalyst became of interest, as many reports of substrate directed reductions of congested olefins exist in the literature.38 We were edified to find it worked well, giving the desired cis decalin 108 in good yield.
Table 1.1 Hydrogenation attempts at forming cis decalin 108.

![Diagram showing hydrogenation process]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Isolated yield 108</th>
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<tbody>
<tr>
<td>(Ph₃P)₃RhCl</td>
<td>0</td>
</tr>
<tr>
<td>KH + (Ph₃P)₃RhCl</td>
<td>0</td>
</tr>
<tr>
<td>Pd/C</td>
<td>0</td>
</tr>
<tr>
<td>Pd/C, NEt₃</td>
<td>0</td>
</tr>
<tr>
<td>Pd/C, KH</td>
<td>0</td>
</tr>
<tr>
<td>PtO₂</td>
<td>0</td>
</tr>
<tr>
<td>[Ir(Cod)Py(PCy₃)]PF₆</td>
<td>77%</td>
</tr>
</tbody>
</table>

With the solution to forming the cis decalin system in hand, we hoped to shorten the existing route (trans decalin) and avoid the issue of hemiketal mesylation as well as the associated recycling reactions (Scheme 1.14). With diketone mesylate 118 as a goal, diol 108 was converted to the primary mesylate 116 under mild conditions in surprising yield, 82%. Acidic deprotection of 116 proved problematic and oxidation of 117 provided only 11% yield (2 steps) of the desired diketone 118. Cyclization trials of 118 failed primarily as a result of limited material.
Scheme 1.14  Synthetic route optimization attempts.

An alternative approach with the same target was attempted beginning from alcohol 109. Dess-Martin oxidation worked well and provided ethyl ketal 119 in 83% yield. However, attempts to unmask the ketone resulted in complex mixtures. It is suspected that ketalization at the C4 ketone may have interfered.

These failures convinced us to work with proven chemistry. Accordingly, diol 108 was treated with acid in ethanol to unmask the ketone and form ethyl ketal 109 (Scheme 1.15). Acetylation and acidic deprotection provided the hemiketal/ketone mixture (111). The hemiketal (111a) provided crystals suitable for single crystal X-ray analysis, which confirmed the cis ring junction. As with the trans decalin system, the mesylation of 111 required recycling of the hemimesylate.
Scheme 1.15 Synthesis of diketone 115.

Cyclopropane formation and deprotection of cyclopropyl acetate 113 followed by oxidation gave the cis decalin Baeyer-Villiger substrate (115) in good yield as expected. Oxidation of 115 proceeded in excellent yield to form 120 (Scheme 1.16). Attempts to reduce 120 with sodium borohydride failed in several solvents. However tetrabutylammonium borohydride was found to be a suitable reducing agent, although approximately a 1:1 mixture of diastereomers was isolated. When treated with perchloric acid, the mixture of alcohols (121) cyclized to form 122 as expected. Butyrolactone 122 and small amounts of dehydration product 123 were the only products isolated.
Scheme 1.16  Cyclopropyl carbinol rearrangement of cis decalin 121.

No attempts to introduce unsaturation and to form the fused cycloheptyl-tetrahydrofuran-butyrolactone motif composing the Schisandraceae ABC ring system were made on the cis material (120-122). The lengthy route was not ideal for producing the necessary amount of material needed for further studies. Moreover, attention to peripheral synthetic projects was needed.

Section 1.2.6 Stereoselectivity Discussion and Conclusion

The cyclopropyl carbinol reactions explored involve water elimination (C8), cyclopropyl ring expansion (C9-C10), lactone hydrolysis (C3-C4), and spirolactonization (C10) in a single step, but not necessarily in that order. An additional dehydration occurs through elimination of water from C4 after spirolactonization. The fact that C4 water elimination likely occurs subsequent to spirolactonization is evidenced by the conversion of spirolactone 100 to the dehydration product (101) with increased reaction times.

These reactions are of also of significance due to the observed stereoselectivity, which is in agreement with previous reports. Although the source of stereoselectivity in many carbocation-mediated reactions is not apparent when obvious substrate control is
absent, intimate ion pairs,\textsuperscript{39} non-classical ions,\textsuperscript{40} and neighboring group or anchimeric effect\textsuperscript{31,32,41} have been proposed.

Figure 1.17 depicts possible transition states leading to stereoselectivity in the acid mediated rearrangement of \textbf{121}. Intermediate \textbf{124} can arise from initial lactone hydrolysis. Subsequent water elimination will potentially create a C8 carbonium. A non-classical carbocation may resemble intermediate \textbf{125} where the positive charge is shared between C8, C10, and C19. The non-classical ion model allows the weakened cyclopropane ring to retain some conformational identity. Additional stabilization may come from interaction of the C4 hydroxy with the C8 cation. It is worth noting that this mode of anchimeric assistance may be more significant in compounds forming fused butyrolactones, as opposed to spirobutyrolactones, as a transient hydrofuran ring can form at this stage. The conformational identity of \textbf{125} can equate to substrate controlled addition of water to form intermediate \textbf{126} or the internal carboxyl functionality could act as the nucleophile to form \textbf{122} directly.

Alternatively, cation \textbf{125} could convert to C10 cation \textbf{127}. Association of C4 hydroxy with cation \textbf{127} from the bottom face would force an incoming nucleophile (water or the internal carboxyl group) to approach from the top face. Lactonization of \textbf{126} would lead to \textbf{122}. 
Scheme 1.17 Potential mechanisms for rearrangement of cyclopropane 121 to 122.

It is also plausible that elimination of water from C8 could occur prior to lactone hydrolysis, leading to an intermediate resembling 129. Quenching of a non classical ion such as 129 by water could potentially be directed by the intact lactone functionality, providing intermediate 130. Lactonization of 130 would lead to 122.

In all reactions the end result is installation of an oxygen through an apparent backside attack of the weakened cyclopropane bond (C10-C9). The fact that several modifications occur in one pot with stereocontrol is a highlight of cyclopropylcarbinol
rearrangement reactions and makes these reactions synthetically useful. However the true nature of this stereoselectivity remains unexplained. We have taken advantage of the positive aspects of this reaction to build a minimized A,C ring system of lancifodilactone (3).

Appendix Experimental Information

Section A.1 General Techniques

All reagents were obtained (Aldrich, Acros) at the highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. All non-aqueous reactions were carried out under anhydrous conditions, i.e. using flame-dried glassware, under an argon atmosphere and in dry, freshly distilled solvents, unless otherwise noted. Yields refer to chromatographically and spectroscopically (\(^1\)H NMR, \(^{13}\)C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) and visualized under UV light and/or developed by dipping in solutions of ceric ammonium molybdate (CAM) or p-anisaldehyde and applying heat. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. NMR spectra were recorded on Varian Mercury 300, 400, Varian Unity 500, and/or Jeol eca 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Nicolet 320 Avatar FT-IR spectrometer and values are reported in cm\(^{-1}\) units. High resolution mass spectra (HRMS) were recorded on a ThermoFinnigan MAT900XL under fast atom bombardment (FAB) conditions with 3-nitrobenzyl alcohol matrix and polyethylene glycol reference. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

Section A.2 Experimental Procedures and Data

**Compound 82:** 1,4-cyclohexanedione (12.3 g, 109.8 mmol) was dissolved in benzene (60 mL) at room temperature. Ethylene glycol (17.7 g, 285.5 mmol) was added to the reaction vessel followed by p-toluenesulfonic acid (1.9 g, 9.9 mmol). The solution was refluxed 3 hours under a Dean-Stark trap. After
cooling to room temperature, triethylamine was added and the reaction concentrated with a rotary evaporator. The resultant oil was filtered through silica. Concentration and crystallization from ether/hexane (4:1) provided 82 as a crystalline solid (20.9 g, 95%). TLC (ethyl acetate/hexane 3:2): Rf = 0.6.

**Compound 83:** Diketal 82 (20 g, 100 mmol), 1,4-cyclohexanedione (16.8 g, 150 mmol), and p-toluenesulfonic acid (400 mg, 2.1 mmol) were dissolved in toluene and refluxed 1.25 hours under a Dean-Stark trap. After cooling to room temperature, triethylamine was added and the reaction concentrated. The resultant oil was filtered through silica. Concentration and crystallization from ether/hexane (4:1) provided 83 as a crystalline solid (14.4 g, 93%). TLC (ethyl acetate/hexanes 3:2): Rf = 0.5.

**Compound 84:** Diisopropylamine (26 mL, 184.3 mmol) was added to n-BuLi (187.5 mmol as 2.5 M hexane solution) in THF (100 mL) at -70°C. After stirring 1 hour, ketal 83 (24.8 g, 159.0 mmol) was added dropwise to the LDA solution at -60°C. Upon complete addition, the solution was warmed to 0°C and stirred 30 minutes. The solution was cooled to -60°C and HMPA (28 mL, 151.9 mmol) added. After stirring 10 minutes, methyl cyanoformate (15.0 mL, 189.2 mmol) was added dropwise. The reaction was stirred 30 minutes at -60°C before adding aqueous NH₄Cl (saturated). The ester was extracted with ether and dried over MgSO₄ prior to purification by column chromatography. Ester 84 (22.1 g, 65%) was obtained as an oil. TLC (ethyl acetate/hexanes 2:3): Rf = 0.5; 1H NMR (400 MHz, CDCl₃): δ 1.8 (t, J = 6.8 Hz, 2H), 2.46 (b, 2H), 2.5 (t, J = 6.8 Hz, 2H), 3.74 (s, 3H), 3.99 (m, 4H), 12.14 (b, 1H); 13C NMR (100 MHz, CDCl₃): δ 172.2, 170.9, 107.5, 95.1, 79.1, 64.6, 51.5, 32.7, 30.4, 28.0; HRMS: m/z calcd. for C₁₀H₁₅O₅: 215.0841, found: 215.0837 [M+H]⁺.

**Compound 85:** Ester 84 (7.5 g, 35.0 mmol) was dissolved in methanol (80 mL) at room temperature. Triethylamine (1.7 mL, 12.2 mmol) and methyl vinyl ketone (5.1 mL, 62.8 mmol) were added. After stirring at room temperature 40 hours, the reaction was concentrated and the residue dissolved in benzene. The benzene solution was washed with 2% HCL, then water before drying over MgSO₄. Pyrrolidine (1.4 mL) was added followed by acetic acid (1.0 mL). The solution was refluxed under a Dean-Stark trap. When TLC showed no further conversion, the reaction was cooled and partitioned between ether and water. The ether extracts were dried over MgSO₄ and concentrated. Column chromatography provided 86 (6.0 g, 65%) as an oil. TLC (ethyl acetate/hexanes 2:3): Rf = 0.5; 1H NMR (400
Compound 86: tBuOK (3.0 g, 26.73 mmol) was added to 85 (3.4 g, 12.8 mmol) in tBuOH (25 mL). The solution was stirred 15 minutes at room temperature. MeI (4.5 mL, 72.1 mmol) was added and the solution heated to reflux. Additional MeI (2.0 mL, 32.1 mmol) was added after 1 hour. The reaction was monitored and cooled to room temperature when the product composed >95% of the reaction mixture by GC-MS. The reaction was partitioned between ethyl acetate and water. The ethyl acetate layers were dried over MgSO₄ and concentrated. Column chromatography yielded 86 (2.25 g, 60%) as an oil which crystallized upon storage at -20°C. TLC (ethyl acetate/hexanes 2:3): R_f = 0.55; ¹H NMR (400 MHz, CDCl₃): δ 1.20 (s, 3H), 1.32 (s, 3H), 1.51 (d, J = 13.2 Hz, 1H), 1.79-2.54 (m, 7H), 3.53 (s, 3H), 3.73-3.96 (m, 4H), 5.67 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 212.3, 175.5, 142.8, 121.0, 106.3, 64.29, 64.25, 51.7, 47.9, 41.3, 36.3, 34.3, 33.5, 31.8, 31.2, 25.3; ESI-MS: m/z calcd. for C₁₆H₂₂O₅: 294.1, found: 294.3 [M+H]+.

Compound 87: To a stirred solution of 86 (4.7 g, 15.99) in THF (200 mL), was added lithium aluminum hydride (25 mmol, as 1.0 M THF solution) dropwise at 0°C. The reaction was allowed to warm to room temperature overnight. After cooling to 0°C, water was added, the solution partitioned with ethyl acetate, washed with brine, and dried over MgSO₄ before concentration. Column chromatography provided a single isomer, 87 (3.5 g, 82%) as a white solid. TLC (ethyl acetate/hexanes 4:1): R_f = 0.3; ¹H NMR (400 MHz, CDCl₃): δ 0.97 (s, 3H), 1.14 (s, 3H), 1.50 (d, J = 13.6 Hz, 1H), 1.60-1.75 (m, 3H), 1.82 (dd, J = 1.6, 13.6 Hz, 1H), 2.12 (b, 1H), 2.31 (m, 1H), 3.38 (dd, J = 3.4, 18.6 Hz, 1H), 3.21 (dd, J = 4.2, 11.0 Hz, 1H), 3.45 (d, J = 10.0 Hz, 1H), 3.70 (m, 2H), 3.83-4.04 (m, 4H), 5.61 (t, J = 3.8 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 144.3, 120.4, 107.2, 77.0, 68.0, 64.5, 63.7, 46.2, 41.6, 41.3, 36.8, 34.2, 27.0, 26.6, 21.0; HRMS: m/z calcd. for C₁₅H₂₅O₄: 269.1675, found: 269.1752 [M+H]+.

Compound 88: To a stirred solution of diol 87 (6.0 g, 22.3 mmol) in ethanol (120 mL), was added p-toluenesulfonic
acid (52 mg, 0.3 mmol). The solution was heated at 90°C for 20 minutes. After cooling to room temperature, triethylamine was added and the solution was concentrated under reduced pressure. Column chromatography and concentration provided ethyl acetal 88 (4.8 g, 84%) as a white solid. TLC (ethyl acetate/hexanes 3:2): Rf = 0.5; ¹H NMR (400 MHz, CDCl₃): δ 1.02 (s, 3H), 1.17 (m, 6H), 1.53 (d, J = 10.8 Hz, 1H), 1.63-1.73 (m, 3H), 1.95 (m, 2H), 2.33 (dd, J = 3.8, 17.4 Hz, 1H), 2.44 (m, 1H), 3.35 (dd, J = 3.4, 11.0 Hz, 1H), 3.55-3.70 (m, 3H), 4.09 (dd, J = 1.4, 6.6 Hz, 1H), 5.59 (dd, J = 2.4, 4.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 148.9, 119.8, 107.1, 82.5, 76.2, 57.3, 45.1, 44.5, 40.1, 40.2, 29.9, 28.0, 25.6, 24.0, 15.6; HRMS: m/z calcd. for C₁₅H₂₅O₃: 253.1725, found: 253.1800 [M+H]+.

### Compound 89:
Olefin 88 (4.2 g, 16.6 mmol) was dissolved in ethanol (60 mL) and 10% Pd/C (200 mg) added. An atmosphere of hydrogen was developed (balloon) and the solution stirred overnight. The solution was filtered through celite and concentrated. Column chromatography provided 89 (3.9 g, 93%) as an oil. TLC (ethyl acetate/hexanes 3:2): Rf = 0.4; ¹H NMR (400 MHz, CDCl₃): δ 0.87 (s, 3H), 1.00 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H), 1.17-1.25 (m, 2H), 1.27-1.39 (m, 1H), 1.55-1.80 (m, 6H), 1.91 (m, 1H), 1.98 (dd, J = 3.0, 11.0 Hz, 1H), 3.23 (dd, J = 3.4, 11.4 Hz, 1H), 3.47-3.68 (m, 2H), 4.20 (d, J = 8.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 107.5, 78.5, 75.1, 57.4, 49.7, 47.2, 44.5, 39.1, 35.9, 33.5, 28.6, 27.4, 21.1, 15.8, 14.4; HRMS: m/z calcd. for C₁₅H₂₇O₃: 255.1955, found: 255.1959 [M+H]+.

### Compound 90:
To a stirred solution of alcohol 89 (3.25 g, 12.8 mmol) in dichloromethane (60 mL), was added pyridine (2.0 mL) followed by acetic anhydride (1.4 mL, 14.8 mmol) at room temperature. After the reaction had stirred 20 hours, additional pyridine (5 mL) and acetic anhydride (1.0 mL, 10.6 mmol) was added. The reaction was stirred an additional 10 hours before partitioning the crude material between ether and water. The ether extracts were combined and dried over MgSO₄ prior to concentration. Column chromatography and concentration provided 90 (3.2 g, 85%) as a white solid. TLC (ethyl acetate/hexanes 3:2): Rf = 0.6; ¹H NMR (300 MHz, CDCl₃): δ 0.82 (s, 3H), 0.88 (s, 3H), 1.06-1.35 (m, 6H), 1.47-1.74 (m, 6H), 1.79-2.00 (m, 5H), 4.15 (d, J = 7.8 Hz, 1H), 4.42 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 170.3, 107.2, 79.9, 74.5, 57.1, 49.5, 46.8, 44.1, 37.8, 35.7, 32.9, 27.0, 25.0, 21.1, 20.7, 15.8, 15.3; HRMS: m/z calcd. for C₁₇H₂₉O₄: 297.2060, found: 297.2062 [M+H]+.
**Compound 91:** Acetate 90 (1.7 g, 5.7 mmol) was dissolved in wet acetone (30 mL) and p-toluenesulfonic acid (200 mg, 1.1 mmol) added at room temperature. The solution was heated at 60°C 30 minutes. After cooling to room temperature, triethylamine was added and the solution concentrated at room temperature under reduced pressure. Partitioning between ethyl acetate and aqueous sodium bicarbonate (saturated) followed by drying of the combined organic layers over MgSO₄ provided an orange oil after concentration. Filtration through silica provided a mixture of primary alcohol 91b and hemiketal 91a (combined yield: 1.3 g, 82%). The isomeric compounds could be separated by silica chromatography and stored for short periods of time at low temperature, but were generally used in subsequent reactions as the mixture. TLC (ethyl acetate/hexanes 2:3): Rf = 0.1-0.3; ¹H NMR (400 MHz, CDCl₃): δ 0.87 (m, 11H), 1.11-1.95 (m, 20H), 2.01-2.08 (m, 5H), 2.08-2.53 (m, 3H), 3.31-4.65 (m, 5H); HRMS: m/z calcd. for C₁₅H₂₅O₄: 269.1747, found: 269.1751 [M+H]⁺.

**Compound 92b:** The mixture of alcohol 91b and hemiketal 91a (combined: 650 mg, 2.4 mmol) was dissolved in dichloromethane (15 mL) and treated with diisopropylethylamine (0.5 mL, 2.9 mmol) at room temperature. After cooling the solution to 0°C, mesyl chloride (0.23 mL, 2.9 mmol) was added via cannula over 1 hour. After stirring 3 hours at 0°C, additional diisopropylethylamine (1.0 mL, 5.8 mmol) was added in one portion followed by additional mesyl chloride (0.1 mL, 1.3 mmol) added portion wise over 30 minutes. The reaction was allowed to slowly warm to room temperature. After 5 hours from the original addition of mesyl chloride, water was added to the reaction and the crude material partitioned with ether prior to drying over MgSO₄. Column chromatography provided primary mesylate 92b (336 mg, 40%) and ketals-mesylate 92a (420 mg, 50%). Ketal-mesylate 92a could be easily converted to 92b by stirring in wet acetone with catalytic HCl. TLC (ethyl acetate/hexanes 3:2): Rf = 0.4; ¹H NMR (400 MHz, CDCl₃): δ 0.92 (s, 3H), 0.99 (s, 3H), 1.33 (m, 1H), 1.61 (m, 1H), 1.70-1.80 (m, 2H), 1.90 (m, 1H), 2.01-2.11 (m, 6H), 2.35 (m, 1H), 2.50 (m, 2H), 3.00 (s, 3H), 3.99 (d, J = 10.4 Hz, 1H), 4.42 (dd, J = 1.2, 10.4 Hz, 1H), 4.61 (dd, J = 4.4, 11.6, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 209.0, 170.5, 79.5, 68.8, 52.2, 51.5, 41.5, 40.9, 37.8, 37.3, 33.1, 28.2, 23.4, 21.9, 21.3, 17.1; HRMS: m/z calcd. for C₁₆H₂₇O₆S₁: 347.1523, found: 347.1511 [M+H]⁺.

**Compound 92a:** TLC (ethyl acetate/hexanes 3:2): Rf = 0.6; ¹H NMR (400 MHz, CDCl₃): δ 0.85 (s, 3H), 0.91 (s, 3H),
1.30 (m, 2H), 1.56-1.87 (m, 7H), 1.98 (s, 3H), 2.12 (m, 1H), 2.46 (m, 1H), 3.05 (s, 3H), 3.70 (m, 1H), 4.28 (m, 1H), 4.44 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 170.4, 114.3, 79.5, 76.4, 49.6, 48.7, 44.3, 41.1, 37.7, 36.4, 31.8, 26.8, 24.8, 21.0, 20.7, 15.2; HRMS: \(m/z\) calcd. for C\(_{16}\)H\(_{27}\)O\(_6\)S\(_1\): 347.1523, found: 347.1513 [M+H]\(^+\).

**Compound 80:** Mesylate 92b (171 mg, 0.494 mmol) was dissolved in benzene (15 mL) at room temperature and tBuOK (65 mg, 0.580 mmol) added in one portion. After stirring 1.5 hours, the reaction was quenched with aqueous NH\(_4\)Cl. Repeated ethyl acetate extractions were performed and the combined organic layers were dried over MgSO\(_4\) and concentrated. Column chromatography (ethyl acetate/hexanes 2:3) and concentration provided 80 as a crystalline solid (108 mg, 87%). TLC (ethyl acetate/hexanes 2:3): \(R_f = 0.3\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.92 (s, 3H), 0.94 (s, 3H), 0.96–1.04 (m, 2H), 1.35-1.49 (m, 2H), 1.59-1.82 (m, 5H), 1.96-2.07 (m, 2H), 2.04 (s, 3H), 2.36 (dd, \(J = 5.4, 19.2\) Hz, 1H), 4.61 (dd, \(J = 4.4, 11.6\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 207.9, 170.4, 79.4, 43.2, 38.7, 36.6, 34.0, 31.2, 26.4, 26.3, 25.1, 21.3, 17.6, 17.1, 14.6; HRMS: \(m/z\) calcd. for C\(_{15}\)H\(_{23}\)O\(_3\): 251.1642, found: 251.1647 [M+H]\(^+\); Crystal data has been deposit with CCDC (CCDC-643516) and can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif:
Crystal data and structure refinement for theod16.

Identification code: theod16
Empirical formula: C15 H22 O3
Formula weight: 250.33
Temperature: 208(2) K
Wavelength: 0.71073 Å
Crystal system: Orthorhombic
Space group: Pbca
Unit cell dimensions:

\[
\begin{align*}
a &= 8.7451(8) \text{ Å} & a &= 90^\circ, \\
b &= 15.8027(14) \text{ Å} & b &= 90^\circ, \\
c &= 19.5008(18) \text{ Å} & g &= 90^\circ.
\end{align*}
\]

Volume: 2694.9(4) Å³
Z: 8
Density (calculated): 1.234 Mg/m³
Absorption coefficient: 0.084 mm⁻¹
F(000): 1088
Crystal size: 0.35 x 0.25 x 0.20 mm³
Theta range for data collection: 2.09 to 28.20°.
Index ranges: -11<=h<=11, -19<=k<=20, -25<=l<=25
Reflections collected: 19970
Independent reflections: 3211 [R(int) = 0.0340]
Completeness to theta = 28.20° 96.7 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 1.000 and 0.782
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 3211 / 0 / 251
Goodness-of-fit on F² 1.093
Final R indices [I>2sigma(I)] R1 = 0.0514, wR2 = 0.1442
R indices (all data) R1 = 0.0658, wR2 = 0.1532
Largest diff. peak and hole 0.309 and -0.174 e.Å⁻³

Atomic coordinates ( x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³) for theod16. U(eq) is defined as one third of the trace of the orthogonalized Uᵢⱼ tensor.

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Symmetry transformations used to generate equivalent atoms:

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Torsion angles [°] for theod16.

C(10)-C(1)-C(2)-C(3)      51.8(2)    C(14)-O(2)-C(3)-C(2)      -91.97(16)
Compound 93: 80 (50 mg, 0.23 mmol), ethylene glycol (0.014 mL, 0.25 mmol), and p-toluenesulfonic acid (trace, 1 crystall) were dissolved in benzene (10 mL) and refluxed 5 hours under a Dean-Stark trap. After cooling to room temperature, triethylamine was added and the reaction concentrated. Column chromatography of the resultant oil provided 93 (30 mg, 60%) as an oil. TLC (ethyl acetate/hexanes 3:2): R_f = 0.7; CRUDE ¹H NMR (300 MHz, CDCl₃): δ 0.4-0.5 (dd, 1H), 0.7-2.1 (m, 28H), 3.8-4.0 (m, 4H), 4.6 (dd, 1H); ESI-MS: m/z calcd. for C₁₇H₂₇O₄: 294.2, found: 294.4 [M+H]+.

Compound 94: 93 (32 mg, 0.11 mmol) was stirred in methanol (1 mL) with potassium carbonate (17.1 mg, 0.12 mmol) overnight at room temperature. Dilution with water, ether extraction, drying of the combined ether layers, and concentration gave an oil which was purified by column chromatography. After concentration, 94 (26 mg, 92%) was obtained as an oil. TLC (ethyl acetate/hexanes 3:2): R_f = 06; ¹H NMR (400 MHz, CDCl₃): δ 0.42 (dd, J = 5.2,
9.6 Hz, 1H), 0.78 (dt, 1.6, 5.2 Hz, 1H), 0.82 (s, 3H), 0.85 (m, 1H), 0.90 (s, 3H), 1.02 (dd, J = 3.2, 12.4 Hz, 1H), 1.37-1.9 (m, 10H), 3.33 (dd, J = 4.4, 11.6 Hz, 1H), 3.85-4.02 (m, 4H); ESI-MS: m/z calcd. for C_{15}H_{25}O_{3}: 253.2, found: 253.2 [M+H]^+.

**Compound 95:** To a stirred solution of 94 (28 mg, 0.11 mmol) in dichloromethane (3 mL), was added Dess-Martin periodinane (55 mg, 0.13 mmol) at room temperature. Prior to drying over MgSO₄ the reaction was partitioned between water and ether after stirring 5 hours. Concentration and silica chromatography provided 95 (15 mg, 55%). TLC (ethyl acetate/hexanes 4:2): R_f = 0.6; ^1H NMR (400 MHz, CDCl₃): δ 0.67 (dd, J = 5.4, 9.8 Hz, 1H), 0.96 (d, J = 9.6 Hz, 1H), 1.01 (m, 1H), 1.08 (s, 3H), 1.11 (s, 3H), 1.14-1.22 (m, 1H), 1.47-1.86 (m, 2H), 2.13 (m, 1H), 2.30 (m, 1H), 2.75 (m, 1H), 3.88-4.06 (m, 4H); APCI-MS: m/z calcd. for C_{15}H_{23}O_{3}: 251.2, found: 251.0 [M+H]^+.

**Compound 96:** Acetate 80 (260 mg, 1.039 mmol) was dissolved in methanol (8 mL) at room temperature and K₂CO₃ (150 mg, 1.090 mmol) added in one portion. After stirring 12 hours, the reaction was quenched with aqueous NH₄Cl. Repeated ethyl acetate extractions were performed and the combined organic layers were dried over MgSO₄ and concentrated. Column chromatography (ethyl acetate/hexanes 3:2) provided the free alcohol 96 as an amorphous solid (194 mg, 90%). TLC (ethyl acetate/hexanes 3:2): R_f = 0.3; ^1H NMR (400 MHz, CDCl₃): δ 0.89 (s, 3H), 0.96-1.05 (m, 2H), 1.06 (s, 3H), 1.36-1.48 (m, 3H), 1.59-1.82 (m, 6H), 1.93-2.09 (m, 2H), 2.38 (ddd, J = 1.6, 5.6, 19.2 Hz, 1H), 3.39 (dd, J = 4.0, 11.2 Hz, 1H); ^13C NMR (100 MHz, CDCl₃): δ 208.7, 78.0, 43.1, 39.8, 36.6, 34.4, 31.3, 29.7, 26.7, 25.1, 17.6, 17.2, 13.3; HRMS: m/z calcd. for C_{13}H_{21}O_{2}: 209.1536, found: 209.1539 [M+H]^+.

**Compound 97:** Alcohol 96 (180 mg, 0.865 mmol) was dissolved in dichloromethane (10 mL) and Dess-Martin Periodinane (473 mg, 1.116 mmol) added at room temperature. After stirring 1.5 hours the reaction was diluted with 25 mL diethyl ether, and a Na₂S₂O₃ solution (500mg Na₂S₂O₃ in 20 mL aqueous saturated NaHCO₃) was added. After stirring 20 minutes, this solution was diluted with 50 mL diethyl ether. After vigorous stirring, the ether layer was collected and washed with water (2 x 5 mL). The ether layer was dried over MgSO₄ and concentrated. Column chromatography (ethyl acetate/hexanes 1:1) provided diketone 97 as a white solid (173 mg, 97%). TLC (ethyl acetate/hexanes 4:1): R_f = 0.5; ^1H NMR
(400 MHz, CDCl$_3$): $\delta$ 1.13 (s, 3H), 1.17 (s, 3H), 1.18-1.24 (m, 1H), 1.32 (ddd, $J = 2.0$, 6.4, 13.2 Hz, 1H), 1.52-1.75 (m, 4H), 1.99 (dd, $J = 4.0$, 12.8 Hz, 1H), 2.03-2.14 (m, 1H), 2.19-2.28 (m, 1H), 2.35 (ddd, $J = 2.2$, 4.4, 13.6 Hz, 1H), 2.43 (ddd, $J = 2.0$, 5.6, 19.2 Hz, 1H), 2.79 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 214.0, 207.3, 49.1, 44.2, 36.8, 36.1, 35.4, 31.2, 26.0, 21.9, 20.5, 18.0, 16.4; HRMS: $m/z$ calcd. for C$_{13}$H$_{19}$O$_2$: 207.1380, found: 207.1372 [M+H]$^+$. 

**Compound 98:** A dichloromethane (20 mL) solution of 97 (152 mg, 0.738 mmol) was cooled to 0°C. $m$CPBA (190 mg, 1.103 mmol) was added in one portion, followed rapidly by solid NaHCO$_3$ (123 mg, 1.461 mmol). Stirring was continued for 6 hours at 0°C, after which, 5 mL saturated aqueous NaHCO$_3$ was added and the reaction allowed to warm to room temperature with stirring. The aqueous layer was discarded and the organic layer collected, diluted with 50 mL ethyl acetate, and washed with saturated aqueous NaHCO$_3$ (2 x 10 mL). The aqueous layers were combined and washed with ethyl acetate (3 x 30 mL). All organic layers were combined, dried over MgSO$_4$, and concentrated. Column chromatography (acetone/ethyl acetate 1:9) provided the keto-lactone 98 (163 mg, 95%). TLC (ethyl acetate/hexanes 4:1): $R_f = 0.2$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.98-1.06 (m, 1H), 1.17 (dd, $J = 5.4$, 10.2 Hz, 1H), 1.23-1.36 (m, 1H), 1.47 (s, 3H), 1.47-1.55 (m, 2H), 1.55 (s, 3H), 1.81-1.90 (m, 1H), 2.08-2.19 (m, 1H), 2.25-2.44 (m, 3H), 2.72-2.78 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 206.3, 173.9, 85.6, 46.0, 36.4, 35.1, 34.4, 33.4, 31.2, 27.9, 21.9, 21.5, 15.8; HRMS: $m/z$ calcd. for C$_{13}$H$_{19}$O$_3$: 223.1329, found: 223.1333 [M+H]$^+$. 

**Compound 99:** Ketolactone 98 (19 mg, 0.086 mmol) was dissolved in THF (1 mL), cooled to 0°C, and NaBH$_4$ (1.5 mg, 0.039 mmol) was added in one portion. The reaction temperature was maintained at 0°C and monitored by $^1$H NMR (starting material and product co-spot under the chosen TLC conditions). After 5 hours, a small amount of silica gel was added and the solvent evaporated at room temperature under reduced pressure. Column chromatography (ethyl acetate 100%) provided hydroxylactone 99 (16 mg, 85%). TLC (ethyl acetate/hexanes 4:1): $R_f = 0.2$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.42-0.47 (m, 1H), 0.60-0.96 (m, 4H), 1.09-1.27 (m, 1H), 1.39 (s, 3H), 1.46 (s, 3H), 1.59-1.63 (m, 1H), 1.89-1.99 (m, 1H), 2.06-2.25 (m, 3H), 2.61-2.73 (m, 2H), 3.76 (dd, $J = 6.3$, 10.5 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 174.8, 86.8, 68.7, 48.2, 36.2, 35.4, 33.0, 31.0, 27.6, 24.1, 22.5, 21.5, 14.2; IR (film): $v_{\text{max}}$ 1709; HRMS: $m/z$ calcd. for C$_{13}$H$_{21}$O$_3$: 225.1485, found: 225.1488 [M+H]$^+$. 

**Compound 100:** To a stirred acetonitrile (0.15 mL) solution of compound 99 (3.5 mg, 0.015 mmol), was added a 7% HClO₄ (0.2 mL, 0.014 mmol) aqueous solution at room temperature. After stirring 1.5 hours, the solution was diluted with diethyl ether and H₂O. Solid sodium carbonate was added in portions at 0°C, with stirring, until the solution tested neutral by pH paper. The ether layer was collected and repeated ether extractions performed until no product remained in the aqueous layer by TLC. The combined organic layers were dried over MgSO₄ and concentrated. Column chromatography (ethyl acetate/hexanes, 1:2) was performed to yield 100 as an amorphous solid (2.5 mg, 75%). TLC (ethyl acetate/hexanes, 3:2): Rₐ = 0.45; ¹H NMR (400 MHz, CDCl₃): δ 1.29 (s, 3H), 1.36 (s, 3H), 1.64–1.71 (m, 1H), 1.80–1.87 (bs, 1H), 1.88–2.15 (m, 4H), 2.49–2.33 (m, 1H), 2.36–2.44 (m, 1H), 2.48–2.63 (m, 3H), 3.07–3.12 (m, 1H), 5.43–5.50 (m, 1H), 5.59–5.65 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 176.9, 131.8, 122.7, 92.2, 74.7, 56.1, 37.0, 35.2, 32.1, 30.8, 28.1, 26.7, 25.5; IR (film): νmax 1755; HRMS: m/z calcd. for C₁₃H₂₀O₃: 225.1492, found: 225.1488 [M+H]⁺; Crystal data has been deposited with CCDC (CCDC-643492) and can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif:
Crystal data and structure refinement for theod17.

Identification code: theod17
Empirical formula: C13 H20 O3
Formula weight: 224.29
Temperature: 208(2) K
Wavelength: 0.71073 Å
Crystal system: Monoclinic
Space group: C2/c
Unit cell dimensions:
\[ a = 26.153(3) \text{ Å} = 90^\circ. \]
\[ b = 8.1060(10) \text{ Å} = 118.628(2)^\circ. \]
\[ c = 13.3801(16) \text{ Å} = 90^\circ. \]
Volume: 2489.8(5) Å³
Z: 4
Density (calculated): 1.197 Mg/m³
Absorption coefficient: 0.083 mm⁻¹
F(000): 976
Crystal size: 0.40 x 0.21 x 0.03 mm³
Theta range for data collection: 1.77 to 28.20°.
Index ranges: -34≤h≤32, -9≤k≤10, -17≤l≤17
Reflections collected: 9204
Independent reflections: 2896 [R(int) = 0.0286]
Completeness to theta = 28.20°: 94.3 %
Absorption correction: Multi-scan
Max. and min. transmission: 1.000 and 0.692
Refinement method: Full-matrix least-squares on F²
Data / restraints / parameters: 2896 / 0 / 225
Goodness-of-fit on F²: 0.959
Final R indices [I>2σ(I)]: R1 = 0.0663, wR2 = 0.1856
R indices (all data): R1 = 0.0918, wR2 = 0.2063
Largest diff. peak and hole: 0.253 and -0.147 e.Å⁻³

Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å² x 10³) for theod17. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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**Bond lengths [Å] and angles [°] for theod17.**

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Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters (Å²x 10³) for theod17. The anisotropic displacement factor exponent takes the form: -2 \cdot \frac{\sum h^2 a^* b^* u_{11} + \sum h k a^* b^* u_{12}}{ } \cdot \frac{2 h k a^* b^* u_{12}}{ }

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Hydrogen coordinates (x 10⁴) and isotropic displacement parameters (Å²x 10³) for theod17.

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<td>H(2B)</td>
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| H(8) | -52(15)| 530(40)| 1290(30)| 82(9) |
| H(9) | 744(12)| -1030(40)| 2200(30)| 74(9) |
| H(11A)| 1703(13)| -380(40)| 2740(30)| 66(8) |
| H(11B)| 1539(13)| 1570(40)| 2770(30)| 68(9) |
| H(12A)| 965(16)| 4680(50)| -1710(30)| 100(11)
| H(12B)| 551(19)| 4840(60)| -1140(30)| 125(14)
| H(12C)| 534(16)| 3150(40)| -1700(30)| 90(11)|
H(13A)  2171(15)  4160(40)  1170(30)  94(11)
H(13B)  1854(11)  5340(30) -60(20)  56(7)
H(13C)  1585(16)  5420(50)  760(30)  102(12)

Torsion angles [°] for theod17.

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Symmetry transformations used to generate equivalent atoms:

Hydrogen bonds for theod17 [Å and °].

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Symmetry transformations used to generate equivalent atoms:

#1 -x+1/2,-y+1/2,-z

**Compound 101:** Olefin 101 was isolated as a side product of the reaction which produced 100. In the synthesis of 100, extended reaction times produced olefin 101 (up to 80% TLC yield). Alternatively, treatment of 100 with acid produced 101. TLC (ethyl acetate/hexanes 2:3): Rf=0.7; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.56–1.64 (m, 2H), 1.74 (s, 3H), 1.89–2.03 (m, 2H), 2.10–2.20 (m, 1H), 2.28–2.70 (m, 7H), 4.78 (s, 1H), 4.85 (s, 1H), 5.53–5.60 (m, 1H), 5.84–5.91 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 176.6, 146.7, 133.4, 124.3, 114.2, 88.0, 57.1, 38.5, 32.8, 28.7, 286, 27.6, 21.8; HRMS: \(m/z\) calcd. for \(\text{C}_{13}\text{H}_{18}\text{O}_2\): 207.1487, found: 207.1490 [M+H]^+. 
**Compound 99b:** Alcohol 99 (8 mg, 0.036 mmol) was dissolved in THF (1 mL) and cooled to -78°C before adding LiHMDS (0.125 mL of 1.0 M THF solution, 0.125 mmol). After stirring 30 minutes, PhSeBr (0.23 mL as a 0.39 mmol/mL THF solution, 0.089 mmol) was added in one portion. The reaction was stirred 30 minutes before water addition followed by aqueous NH₄Cl (saturated). The reaction was extracted with ethyl acetate and dried over MgSO₄ before concentration. Silica filtration provided 99b (2 mg, 15%). ¹H NMR (400 MHz, CDCl₃): δ 0.06 (m, 1H), 0.30 (m, 1H), 0.54 (dd, J = 2.2, 10.2 Hz, 1H), 0.62 (m, 1H), 0.88 (m, 1H), 0.99 (m, 1H), 1.12 (m, 1H), 1.43 (s, 3H), 1.49 (s, 3H), 1.52 (m, 1H), 1.91 (m, 1H), 2.15 (dd, J = 4.2, 12.6 Hz, 1H), 2.43 (m, 1H), 3.67 (m, 1H), 4.29 (m, 1H), 7.30 (m, 3H), 7.56 (d, J = 7.6 Hz, 2H); ESI-MS: m/z calcd. for C₁₉H₂₅O₃Se: 381.1, found: 381.2 [M+H]⁺.

**Compound 102:** 99 (65 mg, 0.29 mmol) was dissolved in dimethylformamide (2 mL) at room temperature. Imidazole (60 mg, 0.89 mmol) and DMAP (6 mg, 0.5 mmol) were added in single portions before TBSCl (88 mg, 0.58 mmol) addition. The reaction was stirred 1.5 hours before adding water and partitioning with ether. The residue was dried over MgSO₄ and concentrated prior to purification. Column chromatography provided 102 (90 mg, 92%). TLC (ethyl acetate/hexanes 3:2): Rf = 0.7; ¹H NMR (400 MHz, CDCl₃): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.40 (m, 1H), 0.57-0.69 (m, 2H), 0.77 (m, 1H), 0.86-0.92 (m, 10H), 1.20 (m, 1H), 1.39 (s, 3H), 1.45 (s, 3H), 1.60 (m, 1H), 1.77 (m, 1H), 2.09-2.23 (m, 2H), 2.62-2.76 (m, 2H), 3.66 (dd, J = 6.2, 10.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 174.8, 86.8, 70.1, 48.1, 36.3, 35.4, 33.4, 31.0, 28.2, 26.0, 24.3, 22.5, 21.8, 18.4, 14.3, -4.5, -4.6; FAB-MS: m/z calcd. for C₁₉H₃₅O₃Si₁: 339.2, found: 339.3 [M+H]⁺.

**Compound 103:** 102 (67 mg, 0.198 mmol) was dissolved in THF (4 mL) and cooled to -78°C before adding LiHMDS (2.5 mL, 2.5 mmol). After stirring 35 minutes, PhSeBr (455 mg, 1.9 mmol) was added in one portion as the solid. After 20 minutes, the reaction was quenched with water followed by NH₄Cl. Partitioning with ethyl acetate, drying over MgSO₄ and concentration gave a brown oil. Column chromatography provided 103 (57 mg, 55%). TLC (ethyl acetate/hexanes 1:4): Rf = 0.4; ¹H NMR (300 MHz, CDCl₃): δ 0.02 (s, 6H), 0.07 (m, 1H), 0.26 (m, 1H), 0.49-0.65 (m, 2H), 0.86 (s, 9H), 1.00 (m, 1H), 1.16 (m, 1H), 1.42 (s, 3H), 1.48 (s, 3H), 1.56 (m, 1H), 1.74 (m, 1H), 2.12 (dd, J = 1.35, 12.6 Hz, 1H), 2.44 (m, 1H), 3.57 (dd, J = 6.3, O
10.2 Hz, 1H), 4.28 (dd, J = 2.4, 12.6 Hz, 1H); FAB-MS: m/z calcd. for C_{25}H_{39}O_{3}Se_{1}Si_{1}: 495.2, found: 495.3 [M+H]^+.

**Compound 104:** Selenide 103 (19 mg, 0.038 mmol) was dissolved in a THF/H_{2}O solution (1:1) and cooled to 0°C. NaIO_{4} (16 mg, 0.74 mmol) was added portion wise and reaction monitored by TLC. Upon disappearance of 103, the reaction was partitioned between ether and water. After drying over MgSO_{4} and concentration, the residue was purified by column chromatography. Lactone 104 (8 mg, 65%) was obtained. TLC (100% ethyl acetate): R_{f} = 0.8; \textsuperscript{1}H NMR (400 MHz, CDCl_{3}): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.76 (m, 1H), 0.89 (s, 9H), 0.92-1.00 (m, 2H), 1.26-1.35 (m, 2H), 1.36 (s, 3H), 1.38 (s, 3H), 1.72 (m, 1H), 1.82 (m, 1H) 2.53 (dd, J = 4.8, 12.8, 1H), 3.93 (m, 1H), 5.55 (d, J = 12.0 Hz, 1H), 5.87 (d, J = 12.0 Hz, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl_{3}): δ 167.0, 153.8, 119.0, 84.3, 68.1, 44.4, 32.0, 30.5, 29.0, 28.2, 25.9, 22.3, 20.7, 18.2, 16.7, -4.5, -4.6; HRMS: m/z calcd. for C_{19}H_{33}O_{3}Si_{1}: 337.2193, found: 337.2197 [M+H]^+.

**Compound 105:** To a stirred acetone (0.08 mL) solution of lactone 104 (1.5 mg, 0.004 mmol), a 7% HClO_{4} (0.12 mL) aqueous solution was added at room temperature. After stirring 3 hours, the solution was diluted with ethyl acetate and H_{2}O. Solid sodium carbonate was added in portions at 0°C, with stirring, until the solution tested neutral by pH paper. The ethyl acetate layer was collected and repeated ether extractions performed until no product remained in the aqueous layer by TLC. The combined organic layers were dried over MgSO_{4} and concentrated. Column chromatography provided 105 (0.6 mg, 60%). TLC (ethyl acetate/hexanes 2:3): R_{f} = 0.3; \textsuperscript{1}H NMR (400 MHz, CDCl_{3}): δ 1.34–1.38 (m, 1H), 1.43 (s, 3H), 1.45 (s, 3H), 1.48–1.63 (m, 2H), 2.22–2.36, (m, 2H), 5.33–5.62 (m, 2H), 5.88–5.91 (d, J = 16 Hz, 1H), 6.02–6.06 (ddd, J = 4, 6.8, 12 Hz, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl_{3}): δ 167.1, 153.0, 126.2, 123.3, 119.1, 83.9, 77.2 (CHCl_{3} overlap), 40.8, 28.9, 25.8, 22.9, 21.3, 19.8; IR (film): v_{max} 1737. HRMS: m/z calcd. for C_{13}H_{18}O_{3}: 223.1336, found: 223.1338 [M+H]^+.

**Compound 106:** Diol 87 (332 mg, 1.24 mmol) was dissolved in dichloromethane (20 mL) and pyridine (5 mL). DMAP (20 mg, 0.16 mmol) was added at room temperature followed by acetyl chloride (0.38 mL, 5.3 mmol). Additional acetyl chloride (0.1 mL, 1.4 mmol) was added after stirring 3 hours. The solution was stirred an additional
12 hours before water was added and the mixture partitioned between water and ether. All ether layers were combined and dried over MgSO₄. Column chromatography provided 106 (330 mg, 76%). TLC (ethyl acetate/hexanes 3:2): Rf = 0.6; ¹H NMR (400 MHz, CDCl₃): δ 1.01 (s, 3H), 1.02 (s, 3H), 1.12-1.21 (m, 2H), 1.23 (m, 1H), 2.39 (dd, J = 3.6, 18.8 Hz, 1H), 3.80-3.90 (m, 4H), 4.08 (d, J = 12.0 Hz, 1H), 4.42-4.31 (m, 2H), 5.64 (t, J = 4.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 170.3, 170.2, 143.0, 122.3, 106.7, 78.7, 64.53, 64.45, 63.4, 40.3, 40.1, 36.8, 32.6, 27.2, 23.9, 23.2, 21.2, 20.9; HRMS: m/z calcd. for C₁₉H₂₈O₆: 352.1880, found: 352.1883 [M+H]+.

**Compound 107:** Ketal 106 (330 mg, 0.94 mmol) was dissolved in wet acetone (10 mL) and p-toluenesulfonylic acid (30 mg, 0.16 mmol). was added. The solution was stirred at room temperature 6 hours. Triethylamine was added prior to adding water and partitioning the mixture with ether. The combined ether layers were dried over MgSO₄ and concentrated. Column chromatography provided 107 (265 mg, 92%). TLC (ethyl acetate/hexanes 3:2): Rf = 0.5; ¹H NMR (400 MHz, CDCl₃): δ 1.04 (s, 3H), 1.11 (s, 3H), 1.41-1.77 (m, 4H), 1.91 (s, 3H), 2.01 (s, 3H), 2.21 (d, J = 14.4 Hz, 1H), 2.34 (d, J = 14.4 Hz, 1H), 2.76 (dd, J = 3.2, 22.8 Hz, 1H), 2.90 (dd, J = 4.4, 22.8 Hz, 1H), 3.91 (d, J = 11.2 Hz, 1H), 4.09 (d, J = 11.2 Hz, 1H), 4.57 (dd, J = 3.6, 11.0 Hz, 1H), 5.89 (t, J = 3.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 207.9, 170.4, 170.2, 144.2, 122.3, 77.9, 68.7, 52.8, 41.6, 40.0, 39.6, 32.8, 26.5, 24.2, 23.4, 21.0, 20.4; HRMS: m/z calcd. for C₁₇H₂₅O₅: 309.1624, found: 309.1627 [M+H]+.

**Compound 108:** Diol 87 (2.0 g, 7.45 mmol) was dissolved in dichloromethane (100 mL) under argon and a hydrogen atmosphere was created. A dichloromethane (10 mL) solution of [Ir(Cod)Py(PCy₃)]PF₆ (123 mg, 0.15 mmol) was prepared. Portions (0.5 mL) of the catalyst solution were added every 5-10 minutes at room temperature until complete addition. Upon each catalyst addition, the reaction solution turned orange and slowly became yellow with stirring. After stirring 3 hours from point of initial catalyst addition, solid catalyst was added in 30 mg portions (127 mg, 0.15 mmol total) with hydrogen flushing of the reaction flask over 20 minutes. Stirring was continued 2 hours after complete catalyst addition, at which point the solution was concentrated at room temperature under reduced pressure. Column chromatography provided 108 (1.55 g, 77%). TLC (100% ethyl acetate): Rf = 0.3; ¹H NMR (400 MHz, CDCl₃): δ 0.97 (s, 3H), 0.99, (s, 3H), 1.14 (m, 1H), 1.55-1.93 (m, 11H), 1.97 (d, J = 11.2 Hz, 1H), 3.03 (b, 1H), 3.44 (b, 1H), 3.57 (dd, J = 7.8, 17.4 Hz, 2H), 3.67 (m, 2H), 3.77 (m, 1H); ¹³C NMR (100 MHz,
Compound 116: Diol 87 (204 mg, 0.76 mmol) was dissolved in dichloromethane (15 mL) and triethylamine (0.16 mL, 1.2 mmol). The solution was cooled to 0°C and mesyl chloride (0.85 mL, 1.1 mmol) was added dropwise over 20 minutes. The solution was stirred 5 minutes after complete mesyl chloride addition, at which point, water (5 mL) was added. The mixture was partitioned between water and ethyl acetate. The combined organics were dried over MgSO₄ and concentrated. Column chromatography provided 116 (215 mg, 82%). TLC (methanol/ether 1:9): Rᶠ = 0.5; ¹H NMR (400 MHz, CDCl₃): δ 0.98 (s, 3H), 1.00 (s, 3H), 1.55-1.98 (m, 11H), 3.04 (s, 3H), 3.45 (b, 1H), 3.53 (d, J = 7.6 Hz, 1H) 3.60 (d, J = 7.6 Hz, 1H), 3.75 (m, 1H), 3.90 (m, 1H), 4.36 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 109.6, 80.2, 75.6, 69.8, 59.7, 45.3, 42.4, 39.2, 38.6, 37.8, 35.5, 28.1, 27.8, 27.1, 23.5, 20.3.

Compound 118: To a stirred acetone (20 mL) solution of 117 (215 mg, 0.62 mmol) was added water (3 mL) followed by p-toluenesulfonic acid (40 mg, 0.21 mmol). The reaction was heated at 50°C 3 hours. Basic work up and chromatography provided 118 (20 mg, 11%). ¹H NMR (400 MHz, CDCl₃): δ 1.01 (s, 3H), 1.20 (s, 3H), 1.83-2.44 (m, 10H), 2.71 (m, 1H), 3.14 (s, 3H), 3.83 (dd, J = 3.4, 8.8 Hz, 1H), 3.99 (d, J = 8.8 Hz, 1H).

Compound 119: Alcohol 109 (37 mg, 0.145 mmol) was dissolved in dichloromethane (3 mL). Dess-Martin periodinane (81 mg, 0.17 mmol) was added and the solution stirred 4 hours. The reaction mixture was partitioned between water and ether, dried over MgSO₄, and purified. Column chromatography provided 119 (30 mg, 83%). ¹H NMR (400 MHz, CDCl₃): δ 1.10 (s, 3H), 1.19 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H), 1.63-2.09 (m, 8H), 2.17 (d, J = 10.8 Hz, 1H), 2.36 (m, 1H), 2.69 (m, 1H), 3.59-3.77 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 215.0, 109.3, 79.0, 57.3, 49.2, 48.8, 45.2, 38.5, 36.4, 35.3, 33.5, 25.3, 22.9, 21.4, 15.7.

Compound 109: To a stirred solution of diol 108 (890 mg, 3.29 mmol) in ethanol (20 mL), was added p-toluenesulfonic
acid (67 mg, 0.35 mmol). The solution was heated at 40°C 15 minutes. After cooling to room temperature, triethylamine was added and the solution was concentrated under reduced pressure. Column chromatography and concentration provided ethyl ketal 109 (821 mg, 98%). TLC (100% ethyl acetate): Rf = 0.5; ¹H NMR (400 MHz, CDCl₃): δ 0.95 (s, 3H), 0.96 (s, 3H), 1.16 (t, J = 6.8 Hz, 3H), 1.54 (m, 1H), 1.62 (m, 1H), 1.64-1.90 (m, 9H), 1.92 (d, J = 10.8 Hz, 1H), 3.41 (b, 1H), 3.49-3.69 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 109.4, 80.1, 75.6, 57.0, 45.0, 42.4, 39.2, 38.4, 35.3, 28.0, 27.7, 27.0, 23.4, 20.1, 15.6; HRMS: m/z calcd. for C₁₅H₂₇O₃: 255.1882, found: 255.1880 [M+H⁺].

**Compound 110:** To a stirred dichloromethane (40 mL) solution of 109 (1.35 g, 5.31 mmol), was added pyridine (20 mL) and DMAP (43 mg, 0.35 mmol). Acetyl chloride (630 mg, 8.0 mmol) was added at room temperature. The mixture was stirred 2 hours before adding water followed by NH₄Cl. The mixture was partitioned with ethyl acetate and dried over MgSO₄. Column chromatography provided 110 (1.4 g, 90%). TLC (ethyl acetate/hexanes 3:2): Rf = 0.7; ¹H NMR (400 MHz, CDCl₃): δ 0.90 (s, 3H), 1.04 (s, 3H), 1.19 (t, J = 7.0 Hz, 3H), 1.53-1.97 (m, 11H), 2.03 (s, 3H), 3.53-3.72 (m, 4H), 4.67 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 170.2, 109.3, 80.1, 77.7, 57.2, 45.1, 43.6, 39.2, 37.8, 35.4, 28.6, 27.8, 24.7, 23.2, 21.3, 20.2, 15.8; HRMS: m/z calcd. for C₁₇H₂₉O₄: 297.1988, found: 297.1991 [M+H⁺].

**Compound 111:** Ketal 110 (671 mg, 2.26 mmol) was dissolved in wet acetone (30 mL) and p-toluenesulfonic acid (60 mg, 0.31 mmol) was added at room temperature. The solution was stirred 1.5 hours at 45°C. After cooling to room temperature, triethylamine was added and the solution was concentrated under reduced pressure at room temperature. Column chromatography and concentration provided a mixture of hemiketal 111a and ketone 111b (516 mg, 85%). Upon standing, the mixture crystallized (111a) and was submitted for single crystal x-ray analysis. TLC (ethyl acetate/hexanes 3:2): Rf = 0.4; ¹H NMR (400 MHz, CDCl₃): δ 0.93 (b, 3H), 1.06, (b, 3H), 1.09-1.24 (m, 2H), 1.58-1.99 (m, 8H), 2.03 (b, 3H), 2.24 (m, 1H), 3.54 (b, 2H), 4.67 (b, 1H); HRMS: m/z calcd. for C₁₅H₂₅O₄: 297.1988, found: 297.1991 [M+H⁺]; Crystal Data for 111a has been deposited with CCDC (CCDC-643492) and can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif:
Crystal data and structure refinement for theod20a.

Identification code: theod20a
Empirical formula: C15 H24 O4
Formula weight: 268.34
Temperature: 213(2) K
Wavelength: 0.71073 Å
Crystal system: Orthorhombic
Space group: Pccn
Unit cell dimensions:
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\[ b = 11.0294(19) \text{ Å} \quad b = 90° \]
\[ c = 11.916(2) \text{ Å} \quad g = 90° \]
Volume: 2823.4(9) Å³
Z: 8
Density (calculated): 1.263 g/cm³
Absorption coefficient: 0.090 mm⁻¹
F(000): 1168
Crystal size: 0.30 x 0.30 x 0.20 mm³
Theta range for data collection: 2.08 to 24.00°
Index ranges: -24<=h<=24, -12<=k<=12, -13<=l<=13
Reflections collected: 11723
Independent reflections: 2216 \[ R(int) = 0.0246 \]
Completeness to theta = 24.00°: 99.8 %
Absorption correction: None
Refinement method: Full-matrix least-squares on F²
Data / restraints / parameters: 2216 / 0 / 172
Goodness-of-fit on F²: 1.047
Final R indices [I>2sigma(I)]: R1 = 0.0518, wR2 = 0.1387
R indices (all data): R1 = 0.0569, wR2 = 0.1425
Largest diff. peak and hole: 0.394 and -0.318 e Å⁻³

Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å² x 10³) for theod20a. U(eq) is defined as one third of the trace of the orthogonalized Uᵢⱼ tensor.

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Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters (Å² x 10³) for theod20a. The anisotropic displacement factor exponent takes the form: -2p² [ h² a*²U¹¹ + ... + 2 h k a* b* U¹²]
### Compound 112:

A mixture of alcohols; 111b and hemiketal 111a (combined: 138 mg, 0.51 mmol) was dissolved in dichloromethane (6 mL) and treated with diisopropylethylamine (0.12 mL, 0.69 mmol) at room temperature. After cooling the solution to 0°C, mesyl chloride (0.05 mL, 0.64 mmol) was added via syringe in a rapid

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<table>
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<th>Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^-3) for theod20a.</th>
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<td>H(11C)</td>
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dropwise fashion. After stirring 30 minutes at 0°C the solution was purified by placing directly onto a silica column. Column chromatography provided primary mesylate 112b (336 mg, 40%) and ketal-mesylate 112a (53.5 mg, 30%). Ketal-mesylate 112a could be easily converted to 112b by stirring in wet acetone with catalytic HCl. TLC (ethyl acetate/hexanes 3:2): Rf = 0.3; 1H NMR (400 MHz, CDCl3): δ 1.08 (s, 3H), 1.17 (s, 3H), 1.37 (m, 1H), 1.71-1.89 (m, 4H), 2.07 (m, 3H), 2.17 (d, J = 15.6 Hz, 1H), 2.30-2.49 (m, 2H), 2.61 (d, J = 15.6 Hz, 1H), 3.01 (s, 3H), 3.97 (d, J = 10.0 Hz, 1H), 4.03 (d, J = 10.0 Hz, 1H), 4.75 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 211.0, 170.3, 77.3, 75.9, 46.4, 41.5, 39.4, 38.9, 37.5, 37.3, 37.2, 27.9, 27.1, 25.4, 22.4, 22.3, 21.1.

**Compound 113:** Mesylate 112b (59 mg, 0.170 mmol) was dissolved in benzene (4 mL) at room temperature and tBuOK (22 mg, 0.196 mmol) added in one portion. After stirring 4 hours, the reaction was quenched with aqueous NH₄Cl. Repeated ethyl acetate extractions were performed and the combined organic layers were dried over MgSO₄ and concentrated. Column chromatography (ethyl acetate/hexanes 1:1) provided cyclopropyl acetate 113 as a white solid (40 mg, 95%). TLC (ethyl acetate/hexanes 3:2): Rf = 0.4; 1H NMR (400 MHz, CDCl3): δ 0.72-0.85 (m, 2H), 0.89 (s, 3H), 0.96 (s, 3H), 1.42-1.47 (m, 1H), 1.65-1.94 (m, 7H), 2.07 (s, 3H), 2.14-2.31 (m, 2H), 4.67-4.71 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 210.0, 170.3, 78.7, 38.0, 35.8, 35.3, 32.9, 30.9, 29.9, 26.2, 24.6, 22.5, 21.1, 18.2, 16.2; HRMS: m/z calcd. for C₁₅H₂₃O₃: 251.1642, found: 251.1647 [M+H]+.

**Compound 114:** Cyclopropyl acetate 113 (146 mg, 0.583 mmol) was dissolved in methanol (9 mL) at room temperature and K₂CO₃ (97 mg, 0.702 mmol) added in one portion. After stirring 24 hours, the reaction was quenched with aqueous NH₄Cl. Repeated ethyl acetate extractions were performed and the combined organic layers were dried over MgSO₄ and concentrated. Column chromatography (ethyl acetate/hexanes 1:1) provided the free alcohol 114 (100 mg, 82%). 1H NMR (400 MHz, CDCl3): δ 0.67-0.73 (m, 1H), 0.77-0.83 (m, 2H), 0.83 (s, 3H), 0.85 (s, 3H), 1.05 (s, 3H), 1.40-1.44 (m, 1H), 1.57-1.64 (m, 1H), 1.74-1.97 (m, 4H), 2.14-2.19 (m, 2H), 2.29-2.43 (m, 2H), 3.45-3.50 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 210.4, 76.9, 38.8, 35.6, 34.9, 33.2, 30.4, 30.3, 27.3, 26.7, 23.0, 18.5, 16.5; HRMS: m/z calcd. for C₁₃H₂₁O₂: 209.1436, found: 209.1439 [M+H]+.

**Compound 115:** Alcohol 114 (51 mg, 0.245 mmol) was dissolved in dichloromethane (8 mL) and Dess-Martin Periodinane (151 mg, 0.319) was added at room temperature in
one portion. After stirring 30 minutes, saturated aqueous NaHCO₃ was added, followed by saturated aqueous Na₂S₂O₃. The diketone was extracted from the aqueous layer with diethyl ether, dried over MgSO₄, and concentrated. Column chromatography (ethyl acetate/hexanes 3:7) provided 115 (48 mg, 95%). \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 1.04 (dd, \(J = 4.0, 9.6\) Hz, 1H), 1.07 (s, 3H), 1.15 (s, 3H), 1.40 (ddd, \(J = 2.8, 3.2, 14\) Hz, 1H), 1.47 (m, 1H), 1.86-2.35 (m, 8H), 2.71-2.80 (m, 1H); \(^1\)C NMR (100 MHz, CDCl₃): \(\delta\) 213.8, 208.8, 49.4, 42.4, 36.8, 35.4, 34.6, 33.4, 29.9, 23.4, 22.7, 20.7, 17.5; HRMS: \(m/z\) calcd. for C₁₃H₁₉O₂: 207.1380, found: 207.1372 [M+H]^+.

**Compound 120:** A dichloromethane (10 mL) solution of 115 (47 mg, 0.228 mmol) was cooled to 0°C. mCPBA (59 mg, 0.343 mmol) was added in one portion, followed rapidly by solid NaHCO₃ (40 mg, 0.952 mmol). Stirring was continued for 8 hours, with warming to room temperature, after which, saturated aqueous NaHCO₃ was added with stirring. The aqueous layer was discarded and the organic layer collected, diluted with ethyl acetate, and washed with saturated aqueous NaHCO₃. The aqueous layers were combined and washed with ethyl acetate. The organic layers were combined, dried over MgSO₄, and concentrated. Column chromatography provided the ketolactone 120 (50 mg, 98%). \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 0.91 (dd, \(J = 5.8, 9.4\) Hz, 1H), 1.08 (ddd, \(J = 2.4, 5.6, 15.2\) Hz, 1H), 1.48 (s, 3H), 1.49 (s, 3H), 1.62-1.66 (m, 1H), 1.80-2.35 (m, 6H), 2.46-2.50 (m, 1H), 2.66 (ddd, \(J = 2.2, 6.0, 16.4\) Hz, 1H), 2.79 (ddd, \(J = 2.4, 13.2, 18.6\) Hz, 1H); \(^1\)C NMR (100 MHz, CDCl₃): \(\delta\) 207.5, 174.2, 85.1, 43.3, 34.8, 34.7, 33.9, 32.2, 31.8, 31.2, 24.4, 21.1, 18.4; HRMS: \(m/z\) calcd. for C₁₃H₁₉O₃: 223.1329, found: 223.1333 [M+H]^+.

**Compound 121:** Ketolactone 120 (52 mg, 0.234 mmol) was dissolved in dichloromethane (3 mL), cooled to 0°C, and Bu₄NBH₄ (299 mg, 1.162 mmol) added in one portion. The reaction was allowed to warm to room temperature and aliquots collected for \(^1\)HNMR (starting material and product are difficult to differentiate under the chosen TLC conditions). After 8 hours, a small amount of silica gel was added and the solvent evaporated at room temperature under reduced pressure. Column chromatography provided 121 (43 mg, 82%). TLC (100% ethyl acetate): \(R_f = 0.3\); \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 0.36-0.40 (m, 1H), 0.53-0.67 (m, 3H), 0.77-0.81 (m, 1H), 0.97-1.11 (m, 2H), 1.25-1.41 (m, 4H), 1.43 (s, 3H), 1.49 (s, 3H), 1.61 (s, 3H), 1.65 (s, 3H), 1.66-1.84 (m, 6H), 1.91-2.00 (m, 1H), 2.11-2.21 (m, 1H), 2.64-2.75 (m, 2H), 2.79-2.92 (m, 2H), 3.66-3.72 (m, 1H), 4.29-4.34 (m, 1H); \(^1\)C NMR (100 MHz, CDCl₃): \(\delta\) 174.6, 174.5, 85.0, 83.7, 68.6, 64.5, 46.9, 45.9, 34.9, 34.7, 31.4, 30.5 30.4, 30.2, 29.6, 28.8, 28.7, 28.7, 27.7, 27.1, 26.3, 21.0, 20.5, 20.2, 20.2, 16.2; HRMS: \(m/z\) calcd. for C₁₃H₂₁O₃: 225.1485, found: 225.1488 [M+H]^+. 
**Compound 122:** To a stirred acetone (5 mL) solution of compound 121 (5 mg, 0.022 mmol), a 7% HClO₄ (0.3 mL) aqueous solution was added at room temperature. After stirring 1.5 hours, the solution was diluted with diethyl ether and H₂O. Solid sodium carbonate was added in portions, with stirring, until the solution tested neutral by pH paper. The ether layer was collected and repeated ether extractions performed until no product remained in the aqueous layer by TLC. The combined organic layers were dried over MgSO₄ and concentrated. Column chromatography (ethyl acetate/hexanes, 1:2) was performed to yield 122 as an amorphous solid (2.8 mg, 55%). TLC (ethyl acetate/hexanes 3:2): R_f = 0.4; ¹H NMR (400 MHz, CDCl₃): δ 1.25 (s, 3H), 1.29 (s, 3H), 1.81–1.89 (m, 1H), 2.09–2.12 (m, 2H), 2.18–2.22 (m, 1H), 2.32–2.45 (m, 3H), 2.48–2.56 (m, 1H), 2.60–2.64 (m, 3H), 5.52–5.61 (m, 1H), 5.82–5.92 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 176.4, 133.2, 124.2, 91.6, 77.2 (CHCl₃ overlap), 56.9, 41.9, 31.4, 28.9, 28.5, 28.1, 27.0, 24.4; IR (film): v_max 1759. HRMS: m/z calcd. for C₁₃H₂₀O₃: 225.1492, found: 225.1488 [M+H]+.

**Compound 123:** Olefin 123 was isolated as a side product of the reaction which produced 122. In the synthesis of 122, extended reaction times produced olefin 123. TLC (100% ethyl acetate): R_f = 0.8; ¹H NMR (400 MHz, CDCl₃): δ 1.75 (m, 2H), 1.84 (s, 3H), 2.12 (m, 1H), 2.21–2.65 (m, 8H), 4.78 (b, 1H), 4.99 (b, 1H), 5.63 (m, 1H), 6.02 (m, 1H); CRUDE ¹³C NMR (100 MHz, CDCl₃): δ 147.7, 135.3, 124.8, 114.0, 77.2, 65.9, 56.9, 40.5, 31.6, 29.7, 29.2, 29.0, 27.6, 25.8, 25.71, 22.6, 15.3.

**Section A.3 Selected NMR Spectra**
Spectrum 1.0

1H NMR (CDCl₃, 400 MHz) of compound 84

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl₃
Ambient temperature
File: daf-3-20
Mercury-400BB ''hq402''

Relax. delay 1,000 sec
Pulse 48.5 degrees
Acq. time 1.032 sec
Width 6200.8 Hz
32 repetitions
OBSERVE EL 400.0536036 MHz
DATA PROCESSING
FT size 121072
Total time 17 min, 3 sec
**Spectrum 1.1** $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 84
Spectrum 1.2 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 85
Spectrum 1.3 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 85
Spectrum 1.4

1H NMR (CDCl3, 400 MHz) of compound 86

STANDARD 1H OBSERVE

Pulse Sequence: a2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1K
File: daf-3-1131b
Mercury-400B 8h1g412

Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.995 sec
Width 6006.0 Hz
56 repetitions
OBSERVE HL, 400.1233350 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 40 sec
Spectrum 1.5 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 86
Spectrum 1.6 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 87
Spectrum 1.7 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 87
Spectrum 1.8 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 88
Spectrum 1.9 $^{13}\text{C}$ NMR (CDCl$_3$, 100 MHz) of compound 88
Spectrum 1.10 | H NMR (CDCl3, 400 MHz) of compound 89

STANDARD 1H OBSERVE

Pulse Sequence: s2pol
Solvent: CDCl3
Ambient temperature
File: daC-3-3la
UNITY-500 "edmar1"

PULSE SEQUENCE
Relax, delay 1.000 sec
Pulse 88.5 degrees
Acq. time 1.935 sec
Width 5998.8 Hz
12 repetitions
OBSERVE HL, 400.0535601 MHz
DATA PROCESSING
FT size 32768
Total time 12 min, 49 sec
Spectrum 1.11 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 89
Spectrum 1.12 $^1$H NMR (CDCl$_3$, 300 MHz) of compound 90
Spectrum 1.13 $^{13}$C NMR (CDCl$_3$, 75 MHz) of compound 90
Spectrum 1.14 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 91
Spectrum 1.15

H NMR (CDCl₃, 400 MHz) of compound 92b

Pulse Sequence: a2pul
Solvent: CDCl₃
Ambient temperature
File: daf-j-43b
UNITY-500 "sdmr1"

PULSE SEQUENCE
Relax. delay 1.600 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5990.0 Hz
16 repetitions

OBSERVE: 400.0535593 MHz
DATA PROCESSING
FT size 32768
Total time 12 min, 45 sec

1.00 1.07 2.08 5.88 1.70 1.28 3.20
1.08 3.17 1.00 1.22 1.29 3.24

ppm
**Spectrum 1.16** $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 92b
Spectrum 1.17

1H NMR (CDCl3, 400 MHz) of compound 92a

AcO

OMs

Pulse Sequence: s2pul
Solvent: CDC13
Temp. 25.0 C / 298.2K
File: dae-3-35a
Mercury-400BB "bg402"

Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.995 sec
Width 6006.0 Hz
16 repetitions
OBSERVE ML, 400.123343 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 40 sec

ppm
4.2 3.8 3.4 3.0 2.6

ppm
12 11 10 9 8 7 6 5 4 3 2 1 0 -0 -1

0.99 1.00 0.98 3.21 2.33
0.95 2.78 1.07 5.58 6.38
Spectrum 1.18 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 92a
Spectrum 1.19
$^1$H NMR (CDCl₃, 400 MHz) of compound 80

STANDARD 1H OBSERVE

Pulse Sequence: z2pul
Solvent: CDCl₃
Ambient temperature
File: daf-3-45
UNITY-500 "edmarl"

PULSE SEQUENCE
Relax, delay 1.000 sec
Pulse 48.5 degrees
Acq. Time 1.995 sec
Width 5998.8 Hz
64 repetitions
OBSERVE M1, 400.0035597 MHz
DATA PROCESSING
FT size 32768
Total time 12 min, 49 sec
Spectrum 1.20 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 80
Spectrum 1.21 $^1$H NMR (CDCl$_3$, 300 MHz) of compound 93
Spectrum 1.22

1H NMR (CDCl₃, 400 MHz) of compound 94

STANDARD 1H OBSERVE

Pulse Sequence: a2pul
Solvent: CDCl₃
Temp. 25.0 C / 298.1K
Freq: daf-3-5a
Mercury-400RB "bg402"

Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.995 sec
Width 6006.0 Hz
24 repetitions
OBSERVE HL 400.1233350 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 40 sec
Spectrum 1.23 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 95
Spectrum 1.24

1H NMR (CDCl3, 400 MHz) of compound 96

STANDARD 1H OBSERVE

Pulse Sequence: ad2pul
Solvent: CDCl3
Temp. 25.0°C / 298.1K
Pipe: daf-3-25
UNITY-500 "sdnral"

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.935 sec
Width 6006.0 Hz
32 repetitions

OBSERVE E1, 400.1233350 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 12 min, 49 sec
Spectrum 1.25 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 96
Spectrum 1.26 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 97
Spectrum 1.27  $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 97
Spectrum 1.28 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 98
Spectrum 1.29 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 98
Spectrum 1.30 $^1$H NMR (CDCl$_3$, 300 MHz) of compound 99
Spectrum 1.31 $^{13}$C NMR (CDCl$_3$, 75 MHz) of compound 99
Spectrum 1.32 | 1H NMR (CDCl3, 400 MHz) of compound 100

STANDARD in OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: def-3-100-1h
UNITY-500 "sdrn1"

PULSE SEQUENCE
Relax, delay 1.000 sec
Pulse 45.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
35 repetitions
OBSERVE HL 400.0535591 MHz
DATA PROCESSING
PT size 32768
Total time 12 min, 49 sec
**Spectrum 1.33** $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 100
Spectrum 1.34 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 101
Spectrum 1.35 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 101
Spectrum 1H NMR (CDCl₃, 400 MHz) of compound 99b

STANDARD 1H OBSERVE

Pulse Sequence: s2pol
Solvent: CDCl₃
Ambient temperature
File: daf-3-57
Mercury-400BB "hg402"

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
512 repetitions
OBSERVE NL, 400.0515597 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
Spectrum 1.37: 1H NMR (CDCl₃, 400 MHz) of compound 102

Pulse Sequence: m2pul
Solvent: CDCl₃
Ambient temperature
File: daf-3-63.402
Mercury-300 "hg100"

Relax. delay 1.000 sec
Pulse 49.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
256 repetitions
OBSERVE 3L, 400.0535597 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
Spectrum 1.38  $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 102
Spectrum 1.39 $^1$H NMR (CDCl$_3$, 300 MHz) of compound 103
Spectrum 1.40 1H NMR (CDCl3, 400 MHz) of compound 104

STANDARD 1H OBSERVE

Pulse Sequence: z2pul
Solvent: CDCl3
Ambient temperature
File: daf-3-69
UNITY-600 "ed marrow"

PULSED SEQUENCE
Relax delay 1.000 sec
Pulse 48.5 degrees
Acq. Time 1.995 sec
Width 5998.8 Hz
100 repetitions
OBSERVE H1, 400.0535593 MHz
DATA PROCESSING
FT size 32768
Total time 12 min, 49 sec
Spectrum 1.41 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 104
Spectrum 1.42 ¹H NMR (CDCl₃, 400 MHz) of compound 105
Spectrum 1.43 $^{13}$C NMR (CDCl$_3$, 100MHz) of compound 105
Spectrum 1.44 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 106
Spectrum 1.45 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 106
Spectrum 1.46 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 107
Spectrum 1.47 $^{13}$C NMR (CDCl$_3$, 100MHz) of compound 107
Spectrum 1.48

1H NMR (CDCl3, 400 MHz) of compound 108

STANDARD 1H OBSERVE

Pulse sequence: a2pul
Solvent: CDCl3
Ambient temperature
File: crabtree_diol_1h
Mercury-400B: "hg402"

Relax. delay 1.600 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
64 repetitions
OBSERVE HE 400.0535597 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 9 sec
Spectrum 1.49 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 108
Spectrum 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: daf-4-141h
Mercury-400BB "hg402"

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
72 repetitions
OBSERVE: WL 400.0535597 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 40 sec

4.4 4.0 3.6 3.2 2.8 2.4 2.0 ppm

9 8 7 6 5 4 3 2 1 ppm

2.03 2.90 3.04 11.85 5.38
Spectrum 1.51 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 116
Spectrum 1.52 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 118
Spectrum 1.53 $^{1}$H NMR (CDCl$_3$, 400 MHz) of compound 119
Spectrum 1.54 \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) of compound 119
Spectrum 1.55  
$^1$H NMR (CDCl$_3$, 400 MHz) of compound 109

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl$_3$
Temp. 25.0 C / 298.1K
Pile: daf 4-25 1h
UNITY-500 "sdnr1"

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.995 sec
Width 6006.0 Hz
60 repetitions
OBSERVE HL 400.1233354 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 12 min, 49 sec
Spectrum 1.56 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 109
Spectrum 1.57

1H NMR (CDCl3, 400 MHz) of compound 110

STANDARD 1H OBSERVE

Pulse Sequence: 2pul
Solvent: CDCl3
Ambient temperature
File: dat 4-24.3h
UNITY-400 "sdmar1"

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5598.8 Hz
52 repetitions

DATA PROCESSING
FT size 32768
Total time 12 min, 49 sec
Spectrum 1.58 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 110
Spectrum 1.59

1H NMR (CDCl₃, 400 MHz) of compound 111

Pulse Sequence: a2pul
Solvant: CDCl₃
Temp. 25.0 C / 298.1
Pile: daf-3-1351h
Mercury-400RB "bg402"

Pulse 56.2 degrees
Acq. time 1.995 sec
Width 6006.0 Hz
72 repetitions
OBSERVE HL 400.1233350 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 3276B
Total time 0 min, 0 sec
Spectrum 1.60 \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) of compound 112b

Pulser sequence: s2pul
Solvent: CDCl\textsubscript{3}
Temp. 25.0 \textdegree C / 298.1K
File: daf 4.36.3h
UNITY-500 "wdsar1"

Pulse sequence
Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.995 sec
Width 6906.0 Hz
56 repetitions

OBSERVE H1, 400.123347 MHz

DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 12 min, 45 sec
Spectrum 1.61 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 112b
Spectrum 1.62: 1H NMR (CDCl₃, 400 MHz) of compound 113

STANDARD 1H OBSERVE

Pulse Sequence: a2pul
Solvent: CDCl₃
Temp. 25.0 C / 298.15K
File: daf-4-201b
UNITY-500 "sdnrm1"

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.995 sec
Width 6006.0 Hz
60 repetitions

OBSERVE H1, 400.123350 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 25768
Total time 12 min, 49 sec
Spectrum 1.63 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 113
Spectrum 1.65 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 114
Spectrum 1.66 ¹H NMR (CDCl₃, 400 MHz) of compound 115
Spectrum 1.67 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 115
Spectrum 1.68 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 120
Spectrum 1.69 $^{13}$C NMR (CDCl$_3$, 100MHz) of compound 120
Spectrum 1.70 \(^1\)H NMR (CDCl\(_3\), 400 MHz) of compound 121
Spectrum 1.71 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 121
Spectrum 1.72 1H NMR (CDCl3, 400 MHz) of compound 122

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1K
File: dae 4-640.1h
UNITY-500 "sdmar1"

PULSE SEQUENCE
Relax, delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.995 sec
Width 6006.0 Hz
80 repetitions
OBSERVE HL, 400.123340 MHz
DATA PROCESSING
Line broadening 0.3 Hz
PT size 32768
Total time 12 min, 49 sec
Spectrum 1.73 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 122
Spectrum 1.74 \textit{H} NMR (CDCl$_3$, 400 MHz) of compound 123

Pulse Sequence: es2pul
Solvent: CDCl$_3$
Temp. 25.0°C / 298.1K
File: daf.4-33_compl.1h
Mercury:300 °hg300°

Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.095 sec
Width 6006.0 Hz
60 repetitions

DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 0 min, 0 sec
Spectrum 1.75 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 123
Section 1.3 References


Chapter II

Studies Toward Zoanthamine Natural Products

Section 2.1 Introduction to Zoanthamine Fauna and Natural Products

Zoanthamine (150) was isolated from an unidentified zoanthid collected off the Visakhapatnam coast of India and reported by Faulkner and collaborators in 1984. Zoanthids are coral-like polyps existing as colonial mats or solitary animals in temperate and tropical regions of the Indian, Pacific, and Atlantic oceans. The ability of some zoanthids to eject an irritating stream of water was noted in the zoanthamine (150) isolation paper. This stream causes tearing, redness, and pain if it comes in contact with the victim’s eyes. The powerful defense mechanism is assumed to be composed of toxins from within the zoanthid’s body. However, it is not clear whether the zoanthids actually produce the toxins. It has been postulated that many or some of the secondary metabolites isolated from zoanthids are actually produced by symbiotic dinoflagellates and incorporated by the zoanthid. Support for this theory is building and zooxanthellamine (164), a structure remarkably similar to zoanthamine (150), has recently been isolated from cultured dinoflagellates.²

Continued reports of new zoanthamine alkaloids have grown this family to at least 19 members (Figure 2.0). Shortly after the initial report of zoanthamine (150), Faulkner and collaborators disclosed the structures of zoanthenamine (166) and zoanthamide...
Both of these alkaloids were isolated from the same zoanthid specimen as zoanthamine (150). The ABCEFG core of zoanthamine (150) is conserved in zoanthenamine (166) while only the ABCE ring system is conserved in zoanthamide (165). Each of these structures contains a spirocyclic butyrolactone D ring in place of zoanthamine's valerolactone and an enamine functionality at C10 in place of the aminal-ester functionality. Additionally, zoanthenamine (166) displays an additional ring in the form of a hemiketal centered at C20 and zoanthamide (165) has a modified FG ring system.

In 1989, Clardy and co-workers reported the isolation of zoanthaminone (152) from an unidentified zoanthid found in the Arabian Sea. The structure of zoanthaminone bears a strong resemblance to zoanthamine (150), differing only in the oxidation state of C11. In addition, zoanthaminone’s (152) C11 carbon is a ketone functionality instead of the typical methylene unit.

Two alkaloids, 28-deoxyzoanthamine (167) and 22-epi-28-deoxyzoanthamine (168), isolated from a zoanthid collected from the Bay of Bengal were reported in 1989 by Rao and coworkers. Each of these alkaloids contains the spirocyclic butyrolactone connected at C22, however the stereochemistry at the core point of attachment has been transposed in 22-epi-28-deoxyzoanthamine (168), relative to zoanthenamine (166) and zoanthamine (150).

In 1995, Daisuke Uemura and coworkers reported five new zoanthamine alkaloids from an unidentified zoanthid collected off the Ayamaru coast of the Amani islands.
Norzoanthamine (151) differs from zoanthamine (150) only in the lack of methyl substitution at C19. Oxyzoanthamine (158) also closely resembles zoanthamine (150), with the only structural difference being an oxidized C26 in the form of a methyl group. Norzoanthaminone (153) is identical to zoanthaminone with the exception of the C19 methyl group. Cyclozoanthamine (162) contains a modified A ring with C28-C16 connection forming an additional ring. Epinorzoanthamine (160) resembles norzoanthamine (151) with a modified A ring where the C17 enone has been reduced to an alcohol and the C15-C16 olefin has shifted to C15-C27.

Epioxyzoanthamine (159) was reported in 1998 by Norte and coworkers from a zoanthid collected off the north coast of Tenerife.\(^7\) Epioxyzoanthamine (159) is epimeric at C19 to the previously reported oxyzoanthamine (158). Norte and coworkers also reported five additional alkaloids isolated from a zoanthid collected off the coast of Tenerife in 1999.\(^8\) The alkaloids, 11-Hydroxyzoanthamine (156) and 11-hydroxynorzoanthamine (157) both strongly resemble the parent compounds, respectively. The only modification being hydroxyl functionalities attached at C11. 3-Hydroxyzoanthamine (154) differs from zoanthamine (150) only through the addition of a hydroxyl functionality at C3, while 30-hydroxyzoanthamine differs only at C30.

Recently, a zoanthamine alkaloid has been isolated from a non-zoanthid genus. Fattorusso and coworkers isolated lobozoanthamine (161) from a soft coral of the genus *Lobophytum* collected along the island of Siladen (Indonesia).\(^9\) The structural similarity between lobozoanthamine (161) and zooxanthellamine (164) is very interesting. The two compounds differ only in the oxidation state of C27, zooxanthellamine (164)
possesses a methyl group while lobozanthamine (161) has a terminal olefin. The fact that zooxanthellamine (164) was isolated from dinoflagellates while lobozoanthamine (161) was isolated from a non-zoanthid genus known to live symbiotically with dinoflagellates further suggests that zoanthamine alkaloids may arise from symbiotic relationships and/or dietary intake of dinoflagellates.

It should be noted that to the best of our knowledge, the absolute configuration has been reported only for norzoanthamine (151)\textsuperscript{10} and lobozoanthamine (161). Both assignments have been made through derivitization by conversion to Mosher’s esters. All other zoanthamine alkaloids have been assigned stereochemistry based on the complete characterization of norzoanthamine (151).
**Figure 2.0** Representative zoanthamine natural products
In addition to their beautiful architecture, the inherent biological activity of these alkaloids has attracted considerable attention. The most exciting may be norzoanthamine (151), which has exhibited unique anti-osteoporotic properties. Accordingly, it has been proposed that norzoanthamine (151) acts as a bone growth stimulator and bone resorption suppressor.\(^\text{11}\) The ability to reduce bone resorption, has been documented in ovariectomized mice (a post-menopausal model) in which treatment leads to the suppression of femoral weight and strength loss.\(^\text{12}\) The mode of action is thought to involve suppression of Interlukin-6 (IL-6), which acts as a stimulator for osteoclast formation, thereby enhancing bone resorption. Norzoanthamine (151) and its hydrochloride salt have been shown to inhibit secretion of IL-6 from preosteoblastic cells at concentrations of 13 and 4.6 µg/mL.\(^\text{10,13}\) Structure activity relationship studies have found that A and D rings are important for suppression of IL-6 secretion, as modification to these rings resulted in deleterious effects.\(^\text{12a,13}\) Another additional SAR study performed by Hirama and coworkers suggested that southern hemisphere aminal function may be most important for IL-6 suppression.\(^\text{14}\) These researchers found that an ABC ring analog of zoanthenol (163) (IC\(_{50}\): > 100 µM) and a CDEFG ring analog (IC\(_{50}\): > 100 µM) were both less efficacious than norzoanthamine (151). However, when the CDEFG ring analog HCl salt was tested, results showed activity closer to that of the norzoanthamine HCl salt (IC\(_{50}\): 70 µM vs. 13 µM).

The zoanthamine group of alkaloids has demonstrated a myriad of biological activities. Zoanthenamine (150), zoanthamide (165), and 28-deoxyzoanthamine (167)
have all been shown to posses anti-inflammatory\textsuperscript{15} and analgesic properties.\textsuperscript{16} Cytotoxicity against P388 murine leukemia cells has also been demonstrated for norzoanthamine (151), norzoanthaminone (153), oxyzoanthamine (158), cyclozoanthamine (162), and epinorzoanthamine (160) with IC\textsubscript{50} values ranging from 1.0 to 24 μg/mL.\textsuperscript{6}

11-Hydroxyzoanthamine (156), zoanthenol (163), oxyzoanthamine (158) and zoanthaminone (152) have all been shown to effect human platelet aggregation.\textsuperscript{17} Platelet aggregation has been implicated in thrombosis related ailments ranging from atherosclerosis to strokes and heart attacks resulting from arterial thrombosis. While zoanthenol (163) and 11-hydroxyzoanthamine (156) inhibited platelet aggregation, oxyzoanthamine (158) and zoanthaminone (152) exhibited irreversible platelet aggregation. This finding is indicative of how subtle structural changes (11-hydroxyzoanthamine (156) and zoanthaminone (152) differ in the C11 oxidation state) can effect biological activity. Accordingly, oxidation of the C11 hydroxyl group of 11-hydroxyzoanthamine (156) to the corresponding ketone, zoanthaminone (152), converted the structure from a platelet aggregation inhibitor to an aggregation agent.

The interesting pharmacological properties exhibited by many zoanthamine alkaloids, has stimulated research in this area and is expected to continue. The complexity of the zoanthamine alkaloids and limitations of modern total synthetic methods may prompt particular focus on SAR studies.

Section 2.2 Uemura’s Proposed Biosynthesis
While there is no consensus on the biogenetic source of the zoanthamine alkaloids, they have been proposed to be terpene in origin based on the 30 carbon composition for the zoanthamine (150) skeleton. However, application of the isoprene rule fails to provide the apparent connectivity, as a linear triterpene poly-cyclization substrate would require non head-to-tail isoprene linkages or a series of unobvious methyl shifts. Uemura and coworkers first proposed a polyketide biogenetic pathway for norzoanthamine (151) in 1997. Scheme 2.1 shows the original proposal by Uemura.

![Scheme 2.0](image)

**Scheme 2.0** Umuera’s norzoanthamine (151) biosynthetic proposal.

Unfortunately, no explanation for this proposal has been provided. However, at least one detailed interpretation involving this linear zoanthamine precursor has been published. Stoltz and coworkers recently published an excellent review paper discussing the biology and chemistry of zoanthamine alkaloids, and Stoltz’s interpretation of the original Umuera biosynthetic proposal is outlined in Scheme 2.1.
Scheme 2.1 Stoltz’s interpretation of Umuera’s zoanthamine (150) biogenetic proposal.

The first step of this proposal would require tautomerization of the C18 ketone to the corresponding enol, and possibly of the C10 ketone as depicted by intermediate 170. A conrotatory electrocyclization could set the correct AB ring junction stereochemistry, followed by tautomerization to the A ring enone. A [4+2] cycloaddition between the depicted C9-C12 diene system and the C22-C20 enone dienophile is suspected of
closing rings B and C. Subsequently, C10 tautomerization could subsequently return the C10 ketone functionality. C2 hydroxyl attack at ketone C6 and subsequent loss of water through oxonium formation would provide intermediate 174. F ring closure would occur through amine attack of oxonium 174. Condensation of the amine at the C10 ketone could close ring E and would presumably provide an iminium (176) under acidic conditions which could be trapped by the carboxylate group to form ring D as the final step.

Stoltz noted that the last several steps might be particularly prone to retro reactivity, allowing the system to equilibrate to the thermodynamically favored product. Work performed by Uemura might support the final steps of this proposal.\textsuperscript{13} When norzoanthamine (151) was treated with sodium cyanoborohydride, compound 177 was produced (Scheme 2.2). This was suggestive of an immediate C10 iminium formation and opening of the lactone ring followed by iminium reduction. Subsequent iminium formation at C6 followed by reduction might explain the product. This reaction could potentially mimic the DEFG ring forming events in reverse and might lend support to the proposed biosynthesis. More importantly, synthetic studies have indicated the stereochemistry of the southern hemisphere to be favored and will be discussed shortly.
Scheme 2.2 Norzoanthamine (151) degradation with NaBH₃CN.

Section 2.3 Reported Synthetic Efforts

The structural complexity and potential for medicinal use has created significant interest from the synthetic community. At least 24 papers directly related to zoanthamine alkaloid synthesis have been published since 1994 by 8 different research groups. The strategy and key reactions of each group will be discussed.

Kobayashi and coworkers published their seminal work on the southern hemisphere (rings C-G) in 1998.¹⁹ The chiral C1-C5 sulfone fragment (183) was synthesized from glutamic acid (Scheme 2.3). Manipulation of D-glutamic acid (178) provided butyrolactone (179) as previously reported by Hanessian and coworkers.²⁰ Butyrolactone (179) was converted to the aminobutyrolactone (181) through a series of modifications at the hydroxyl carbon. Deprotection and mesylation provided mesylate 180, which was treated with sodium azide to displace the mesyl group. The azide was reduced to the amine by hydrogenation and protected as the benzyl carbamate (181). Butyrolactone 181 was opened to the diol (182) by treatment with sodium borohydride.
Sulfone 183 was formed by conversion of the primary alcohol (182) to the phenyl thiol prior to protection of the amino-alcohol moiety as the N,O-ketal, which was then oxidized to the sulfone. A series of 13 steps provided the desired C1-C5 fragment with the necessary chirality in good yield.

**Scheme 2.3** Kobayashi’s synthesis of sulfone 183.

The CDE fragment synthesis began from the reported chiral Wieland-Miescher ketone (WMK) (184) (Scheme 2.4).\(^{21}\) It should be noted that the C9 methyl group was installed in the first step of C ring formation. A diastereoselective cuprate addition to the WMK (184) followed by trapping of the enolate as the vinyl TMS ether and epoxidation provided the substrate for oxidative cleavage which underwent aldehyde-selective single carbon Wittig homologation to give olefin 185. The ketone was protected as the dioxolane and hydroboration performed on the olefin. Treatment with diazomethane was noted but not discussed, this action was presumably necessitated by hydrolysis of the methyl ester during the previous modifications.
Protection of the alcohol and reduction of the methyl ester provided the coupling substrate, aldehyde 187. Coupling of aldehyde 187 and sulfone 183 was achieved by conversion of sulfone 183 to the corresponding lithiate with $t$-butyl lithium followed by reaction with aldehyde 187 to provide a diastereomeric mixture of sulfones (188). Oxidation and desulfurization with Na-Hg provided ketone 189 in excellent yield.
Deprotection of the silyl ether and sequential oxidation (Dess-Martin periodinane then sodium chlorite) provided the cyclization substrate (190).

Cleavage of the benzyl carbamate (190) by hydrogenation failed at this stage, but treatment with acid initiated formation of aminal ring system (192) in surprising yield, while ketal 191 was isolated as a minor side product. Hydrogenation of aminal 192 was successful at this stage, however standard work up conditions resulted in decomposition of the product(s). Notwithstanding, aminal 194 was isolated when molecular sieves were added as a dehydrating agent. This compound represents the CDEFG ring system, with rings D-G fully functionalized.

By replacing the benzyl carbamate with a Boc carbamate, Kobayashi was able to perform the deprotection and cyclization in a single step. Heating under acidic conditions provided aminal 194 in excellent yield (Scheme 2.5). This important contribution offers a highly efficient method for construction of the southern fragment as 4 rings and two new stereocenters weree formed in a single step under simple reaction conditions.

**Scheme 2.5** Kobayashi’s optimized cyclization step.
The Williams group has published work directed at the southern fragment,\textsuperscript{22} in addition to research focused northern fragments.\textsuperscript{23,24} Initial studies directed toward the southern fragment were conducted with the reported butyrolactone 196 (Scheme 2.6) assembled through Evans aldol methodology.\textsuperscript{22a} The iodo butyrolactone (196) was converted to the corresponding azide, which was then reduced to the diol with borane. Di-TBS protection and mild deprotection of the primary alcohol provided alcohol 197 in good overall yield. Mesylate formation and displacement with iodide gave primary iodide 198. Deprotonation of cyanohydrin 199 and addition of iodide 198 formed enone 200 in excellent yield after hydrolysis. A diastereoselective conjugate addition was achieved by addition of the tautomer of known imine 201 to enone 200. The chiral auxiliary was hydrolyzed with aqueous acid to give diketone 202. The Staudinger reaction was then utilized to reduce the azide and efficiently provided imine 203, which was treated with TBAF. TBS cleavage resulted in hydroxyl attack of the imine and condensation of the resultant amine with the C10 ketone to form enamine 204. The synthesis of enamine 204 constitutes rings C, E, F, and G of the zoanthamine alkaloids and offers an alternative to aminal formation under acidic conditions.
Scheme 2.6 Williams’ southern fragment synthesis.

Unfortunately, subsequent studies with more functionalized substrates failed to provide the aminal ring system (Scheme 2.7).\textsuperscript{22b} Methods similar to those used to produce diketone 202 were used to build diketoesters 205 and 206, substrates equal in functional complexity to those reported by Kobayashi. The Aza-Wittig reaction of 205 and 206 proceeded well, as previously reported. Treatment of methyl ester 207 with TBAF provided the free alcohol 210 which failed to cyclize in the manner previously observed. And treatment of 207 or 208 with TFA resulted in isolation of a compound tentatively identified as 211. The researchers claimed that ammonium salt 209 was formed, but that hydrolysis occurred upon neutralization to provide 211. This was an
unexpected result since the intermediate ammonium salt (209) was presumably the identical intermediate in the acid catalyzed cyclization reported by Kobayashi (Scheme 2.4). This particular report therefore serves as an indicator of the fastidious nature of this cyclization where multiple hydrolysis, condensation, and solvolysis reactions may exist in equilibrium.

Scheme 2.7 Williams’ southern fragment analog cyclization attempts.

The Williams group has reported a Diels-Alder approach to the AB ring system (Scheme 2.8).[23] Nitrotriene 212 was constructed in approximately 21 steps utilizing Evans aldol methodology to install chirality. After a 65 hour treatment in refluxing benzene, two endo isomers (decalins 213 and 214) were isolated in favorable diastereoselectivity from the IMDA reaction. While increased diastereoselectivity (95:5
in acetonitrile) was achieved in some solvents, reduced overall yield of the desired decalin (214) was observed. When 214 was treated under oxidative Nef reaction conditions, enone 215 was produced in 60% yield from nitrotriene 212. The enone (215) represents the fully functionalized A ring with correct ring junction and C12 methyl stereochemistry of the zoanthamines.

Scheme 2.8 Williams’ AB ring forming Diels-Alder sequence.

An approach to the AB ring system of zoanthenol (163) has also been published by Williams (Scheme 2.9). Related studies by Williams and coworkers allowed synthesis of aldehyde 217 through a directed cuprate addition to oxazolidinone 216 followed by cleavage of the chiral auxiliary and manipulations (oxidation/elimination then ozonolysis) leading to the aldehyde (217). A Lewis acid mediated coupling with stannane 218 gave Heck reaction substrate 219. Unoptimized Heck conditions provided the AB ring system (220) of zoanthenol (163) as a mixture of C12 epimers. While the efficiency of this reaction is not clear, the obtained yield was less than 40% based on
recovery of starting material and isolation of a side product. Nonetheless, the fully functionalized A and functionalized B rings were formed through this process.

![Chemical structure of zoanthenol](image)

**Scheme 2.9** Williams’ approach to the AB ring system of zoanthenol (163).

Publications related to the zoanthamine alkaloids from the Williams group have spanned 1998 to 2007 and describe unique approaches to both the northern and southern hemispheres. The work on the northern portion has utilized a [4+2] cycloaddition to simultaneously build rings A and B and palladium coupling methodology was used to form ring B of their zoanthenol (163) model. An efficient approach to the southern portion resulted in formation of ring E,F, and G in 2 steps to yield an enamine adduct, but failed when analogs designed to incorporate ring D were studied.

The Tanner group research has been focused on developing a Diels-Alder reaction to close rings B and C to provide a functionalized ABC ring system. The group’s first publication detailed a Diels-Alder reaction applied to a model system encompassing the ABC zoanthamine (163) ring system (Scheme 2.10). The synthetic work began with
inexpensive perillyl alcohol, which was converted to triene 222 in 13 steps with a good overall yield. The chiral Diels-Alder substrate underwent cyclization upon prolonged mixing in refluxing toluene to form a single adduct, 223. Diketone 223 represents the fully functionalized zoanthamine (163) AB ring system. Inspired by the success of this highly efficient Diels-Alder reaction, Tanner worked toward more functionalized cycloaddition substrates.

Scheme 2.10 Tanner’s early Diels-Alder approach to the ABC ring system.

The second publication from Tanner outlined the general approach to zoanthamine alkaloid synthesis that has guided subsequent work (Scheme 2.11).25b Fragments 226, 227, and 228 were viewed as potential precursors to a functionalized ABC system (225) capable of cyclizing to zoanthamine (150). Coupling of fragments 227 and 226 would provide a triene for intramolecular cyclization. Fragment 228 would presumably be appended through organometallic means after coupling and cyclization of fragments 228 and 227. This sequence in conjunction with the appropriate deprotection steps would theoretically provide aminal cyclization substrate 225.
Scheme 2.11  Tanner’s retrosynthetic approach to zoanthamine (150).

Fragment analogs were prepared with this approach in mind. The previously reported lactone (229), prepared from perillyl alcohol, was reduced to the diol (230) with LiAlH₄ and the alcohols differentiated by protection with pivaloyl chloride and MOMCl (Scheme 2.12). Deprotection of the pivaloate ester (231) and oxidation provided aldehyde 232. Addition of Lithium acetylide 232b and allylic oxidation with MnO₂ provided the fragment 226 precursor (233). Stannylcupration, MOM deprotection, and C17 oxidation remained to form fragment 226.
Scheme 2.12 Tanner’s synthesis of fragment 233.

Fragment 237, analogous to 227, was produced expeditiously from the reported stannane (234) (Scheme 2.13). Oxidation followed by an ytterbium catalyzed hetero Diels-Alder provided the sensitive hydropyran (236), which was treated with bromine directly to access fragment 237.

Scheme 2.13 Tanner’s synthesis of fragment 237.

Synthesis of the 228 analog (242) began from the commercially available hydroxymethyl-butyrolactone (238) and followed a reported procedure for TBS protection and alkylation to give 180 (Scheme 2.14). Consecutive reductions opened
the ring and primary alcohol protection as the benzyloxy ester followed by secondary alcohol protection as the MEM ether provided 239. Silyl ether cleavage with TBAF, conversion to the primary tosylate, and displacement with lithium azide gave azide 240. Saponification and tosylation of the resultant alcohol gave 241, which was displaced with sodium bromide to provide fragment 242. While this particular publication did not address fragment coupling reactions, subsequent publications have detailed the attempts at assembling the fragments.

Scheme 2.14 Tanner’s synthesis of fragment 242.

In 2002, Tanner described the complete synthesis of fragment 245, an analog of 226 (Fig. 2.15). A 2006 publication discusses coupling of fragments 245 and 237 as well as related cycloaddition reactions (Fig 2.15). Unfortunately, cycloaddition attempts with a fragment 237 variant (benzyl stabilized instead of ethyl) failed. It was speculated that the enone diene system was polarized in the wrong direction. Therefore the strategy was modified to use a linear diene system activated at C10 instead of C21. Vinyl iodides (245 and 246) were produced by hydrostannylation of alkyne 243.
followed by treatment with iodine. The diastereomeric mixture (245 and 246) was coupled to stannane 247. The resultant diastereomers were separated and isolated as 249 and 248 in 17% and 39% yields, respectively. When 248 was heated with toluene, an unexpected product resulting from elimination of the allylic MOM ether and cyclization of the C20 hydroxyl at the C17 cation was isolated in 43% yield without observation of the desired Diels-Alder reaction. The elimination-cyclization process predominated when 249 was heated in toluene as well, however the desired Diels-Alder adduct (250) was isolated in 14% yield. Tanner attributed the elimination to unfavorable conformational effects.

**Scheme 2.15** Tanner’s initial Diels-Alder reaction toward a functionalized C ring.

A highly advanced intermediate in the synthesis of norzoanthamine (151) was reported in Tanner’s most recent publication (Scheme 2.16). Accordingly, modifications were made to the Diels-Alder substrate by removing the C19 methyl
group, changing the ethyl ester to a methyl ester, and replacement of the TBS group with a TIPS group. The IMDA reaction proved much more efficient with triene 251, and the exo Diels-Alder adduct (252) was formed in 85% yield under thermal conditions. After protection of the C20 hydroxyl as a MOM ether, an oxidative decarbonylation involving α-hydroxylation, ester reduction and diol cleavage provided C10 ketone 253. Deprotection of the PMB ether and oxidation gave aldehyde 254.
Scheme 2.16  Tanner’s synthesis of norzoanthamine (151) intermediate 260.
The coupling partner for aldehyde 254 was prepared from azide 255 by protecting group manipulation and iodination. After cleavage of the MOM ether with zinc bromide, azide 255 was reduced to the corresponding amine in the presence of Boc anhydride to provide alcohol 257. The amine and hydroxyl groups were protected as the N,O ketal and the pivaloyl ester cleaved by reduction. The primary alcohol was converted to alkyl iodide 258 by treatment with imidazole, triphenylphosphine, and iodine. The alkyl lithiate (259) was formed by treatment of 258 with t-BuLi and was subsequently quenched with aldehyde 254. Oxidation of the diastereomeric mixture gave ketone 260, which represents a nearly fully functionalized norzoanthamine (151) precursor. In the event that an aminal cyclization as reported by Kobayashi (Schemes 2.4 and 2.5) was to be executed, methyl installation at the adjacent C9 and C22 positions in addition to oxidations C17, C20, and C24 would be necessary. It is not known whether the cyclization has been attempted, but based on the significant advancement toward total synthesis of the natural product, it is assumed that positive results would be available in the literature at this time.

Hirama and coworkers have published approaches to the C ring of zoanthamine, the ABC ring system of zoanthenol (163), as well as the common CDEFG ring system.14, 27 Reported work with an early C ring model system disclosed an interesting method for developing the adjacent C9 and C22 methyl connections (Scheme 2.17).27a Oxidation of 261 to the corresponding quinone, [4+2] cycloaddition with 1,3 butadiene, stereo and regioselective reduction of the C13 enone, and protection of the resultant allylic alcohol as the MOM ether gave enone 262. Conjugate methyl addition and thermodynamic
enolate trapping as the vinyl TMS ether efficiently provided 263. Samarium mediated cyclopropanation gave tertiary alcohol 264, while acid treatment opened the cyclopropane and returned the C10 ketone (265), demonstrating a unique and elegant method for C9 methyl installation. Oxidative cleavage of the cyclohexene and acid removal of the MOM ether allowed lactonization, and subsequent diazomethane treatment gave methyl ester 266. The petite nature of this model betrayed its advanced nature. Quaternary centers C9, C12, and C22 were formed, a handle attached to C9 for southern fragment functionalization, and a C24 carboxyl group in the form of a butyrolactone were all constructed.

Scheme 2.17  Hirama’s C ring model system.

Hirama and coworkers have also published approaches to the zoanthenol (163) ABC ring system.\textsuperscript{27b-d,14} Optimization of initial work is presented in Scheme 2.18. Orcinol was protected and functionalized through ortho-lithiation at C18 to provide stannane.
Decalin 261b, a precursor to decalin 262 previously reported by Hirama, was converted to 268 through oxidation, selective reduction, and silyl ether formation. Stannane 267 was lithiated and treated with enone 268 to provide an inseparable diastereomeric mixture of alcohols (269). The silyl ether of this mixture was deprotected with TBAF and oxidized with Dess-Martin periodinane to enone 270. The ethoxyethyl ether was cleaved and converted to the corresponding triflate (271). The epimers were separated at this stage to reveal a 44% yield of 271 from stannane 267. A Pd(dppb)Cl₂ mediated reductive Heck coupling provided the zoanthenol (163) ABC ring scaffold. Enone reduction with L-Selectride followed by TBS protection gave silyl ether 273 in excellent yield. Then removal of the BOM group and oxidation gave ketone 274, also in excellent yield. Samarium mediated deoxygenation provided 275, represents an advanced zoanthenol (163) ABC model.
Scheme 2.18 Hirama’s approach to the zoanthenol (163) ABC system.

Additional work was performed to convert 273 to the fully functionalized zoanthenol (163) northern fragment (Scheme 2.19). Stereoselective C19 alkylation was achieved through LDA induced enolization and methyl iodide quenching. Reduction of the C20 ketone and protection as the MOM ether proceeded well, and 277 was obtained as a mixture of diastereomers. TBAF treatment and oxidation of the C10 alcohol proceeded in a highly efficient manner, giving ketone 278 in 99% combined yield. Ketone 278
was enolized and then treated with TMSI to give the silyl enol ether 279. Silyl ether 279 was de-silylated with methyl lithium and the resultant lithium enolate was subjected to samarium controlled cyclopropanation conditions to selectively provide cyclopropanol 280. Cyclopropane cleavage was performed by treatment with toluenesulphonic acid, thereby installing the C9 quaternary methyl group. Ketone 281 represents the fully functionalized ABC Zoanthenol (163) system. Further modifications at C17, C20, and cyclohexene hydrogenation were performed as shown for SAR studies.14

Scheme 2.19 Hirama’s fully functionalized zoanthenol (163) ABC system.
Contributions of the Hirama group extend to a functionalized southern fragment.\textsuperscript{14} The sulfone, 287, was synthesized through a route alternative to that previously reported by the Kobayashi group used to build the C1- C5 fragment (Scheme 2.20). Allyl alcohol 284 was synthesized from a chiral (C4 methyl) hydroxyl ester as previously reported.\textsuperscript{27} Sharpless epoxidation and DIBAL-H treatment provided diol 285. Diol 285 was converted to the N,O ketal through a series of manipulations similar to that used by Tanner. Selective tosylation and conversion to the primary azide followed by reduction to the amine, Boc protection, and acidic treatment with 2,2-dimethoxypropane gave N,O ketal 286 in good overall yield. TBAF deprotection of silyl ether 286, conversion to the phenyl thiol, and oxidation to the sulfone was performed to access 287.

Scheme 2.20  Hirama’s sulfone (287) synthesis.

With the sulfone (287) available (its constituents comprising the F and G rings), the necessary coupling partner (294) (comprising the C,D, and E rings) was constructed (Scheme 2.21). The known chiral Wieland-Miescher ketone (288), possessing cis C22 and C9 quaternary methyl groups, was reduced by hydride attack at the more accessible
ketone and converted to cyclohexene 290 by elimination of the C24 triflate. Reduction of the remaining ketone, dihydroxylation and oxidative cleavage with NaIO₄ provided lactol 292. Aldehyde reduction, mixed methyl ketal formation, and primary alcohol protection with TBDPS gave ketal 293. Ketal 293 was treated with TMSCN to convert the ketal to a cyanohydrin, and the nitrile group was reduced with DIBAL-H to give C6 aldehyde 294. Aldehyde 294 was treated with the lithiated sulfone (288) then oxidized to provide ketone 295. Samarium iodide was utilized for desulfonation and hydrofuran cleavage to give alcohol 296. This alcohol was oxidized to the ketone prior to deprotection of the primary silyl ether and successive oxidations to access the carboxylic acid. The acid was heated with acetic acid then neutralized to give the fully functionalized southern fragment (195) previously reported by Kobayashi, which was then converted to the HCl salt for SAR studies.¹⁴
Scheme 2.21 Hirama’s zoanthamine southern fragment synthesis.

The Hirama group has made significant strides in the zoanthamine alkaloid synthetic effort, demonstrating an approach to the functionalized zoanthenol (163) ABC ring system amenable to addition of a southern fragment as well as achieving a formal synthesis of the southern fragment. Of particular interest to us is the manner in which
the C9 methyl group has been installed. The use of a labile cyclopropanol moiety is a clever alternative to standard enolate alkylations.

The Uemura group has published a substrate designed to test their biosynthetic proposal (Scheme 2.22). Polyene 307 synthesis was envisaged to arise from the coupling of fragments 302 and 306. To this end, aldehyde 399 was treated with vinyl lithiate 300, di-protected, selectively deprotected, and oxidized to provide aldehyde 301. Aldehyde 301 was treated with propynyl magnesium bromide, then hydroalumination and iodination gave vinyl iodide 302.

Scheme 2.22 Uemura’s biosynthetic cyclization substrate.
Alkyne fragment 306 synthesis began from the reported enone (303). Reduction to the lactol, ethylpropionate-ylide homologation, TBS protection, and reduction of the ethyl ester gave alcohol 304. Oxidation of the allylic alcohol to the corresponding aldehyde and treatment with Bestmanns (305) reagent gave alkyne 306. Polyene fragment 307 was constructed by coupling vinyl iodide 302 and alkyne 306 through a Sonogashira coupling. It is not known if conditions for selective alkyne to alkene reduction were explored in order to provide the proposed intermediate scaffold, or if studies have been performed on polyene alkyne 307 directly.

The only total syntheses of Zoanthamine alkaloids to date have been reported by Miyashita and coworkers in 2004 and 2007. Early synthetic studies resulted in a reported Diels-Alder, which allowed construction of the norzoanthamine (151) ABC ring skeleton. After demonstrating the effectiveness of the key [4+2] reaction in a model system, the cycloaddition substrate was further elaborated as outlined in Scheme 2.23. Work began from the reported enone (308). Conjugate addition of cuprate 309, prepared by transmetallation of the reported stannane, to 308 and quenching with TMSCl provided silyl enol ether 310. BuLi and ZnBr₂ treatment of 310 provided the zinc enolate, which was mixed with furaldehyde 311 to give a mixture of alcohols (312). Thiocarbonyldiimidazole-mediate dehydration, hydrosilylation, and resultant silyl enol ether cleavage preceded stereoselective C17 reduction, subsequent protection, and TIPS ether cleavage to give primary alcohol 313. Oxidation, methyl lithium treatment, and TPAP oxidation provided methyl ketone 314. Rose Bengal-photosensitized oxidation of furan 314 with molecular oxygen gave the corresponding
silyl ester, which was immediately converted to the methyl ester by treatment with TBAF and methyl iodide to give the Z, ketoester (315). The C10 enolate of ketoester 315 was trapped as the TBS enol ether to provide the Diels-Alder substrate (316). Heating in trichlorobenzene at 240 °C for 1.5 hours gave a mixture of endo/exo adducts in 98% yield. Removal of the TBS group with HF-Py, provided desired exo adduct 319 in 51% over 2 steps. The C13-C18 trans substitution apparently controlled facial selectivity while the regiochemistry was most likely controlled by factors related to diene/dienophile proximity.

Scheme 2.23 Route to Miyashita’s, BC ring forming, Diels-Alder reaction.
With a scalable route to diketone 319 realized, the Miyashita group focused on substituting the C ring in preparation for further functionalization (Scheme 2.24). Stereoselective reduction of both ketones (C10 and C20) followed by lactonization at C24 gave lactone 320. Protecting group manipulation provided lactone 321, which was reduced to the corresponding lactol and treated with deuterated methyl phosphonium ylide. The resultant olefin was subjected to hydroboration and oxidized at C10 chemoselectively with ammonium molybdate and hydrogen peroxide to give ketone 322. Methylation at C9 began by trapping of the C9 thermodynamic enolate as the vinyl methoxy ether after dimethyl carbonate incorporation at C9 and transesterification to give lactone 323. Continued base treatment and quenching with methyl iodide installed the C9 methyl stereoselectively, and lactone 324 was subsequently isolated in excellent yield. Conversion of the lactone to a methyl ketone and protection of the resultant primary alcohol provided ketone 325. The enolized ketone was trapped as the triflic enol ether and eliminated to give the desired alkyne (327). A significant side product (the undeuterated analog of vinyl ether 326) had been observed when this reaction was performed with the undeuterated equivalent of ketone 325 as a result of presumed 1,5-hydride shift (C24 to C8) prior to triflate displacement by the C8 alcohol. Use of deuterium apparently exploited a kinetic isotope effect by reducing side product formation from 30% to 9%. 
Scheme 2.24 Miyashita’s C ring functionalization and C9 methyl installation.

The C1-C6 fragment was prepared from (R)-citronellal with the initial modification being epoxidation (Scheme 2.25).\textsuperscript{29b} Epoxide opening by treatment with a chiral chromium salen complex and TMS azide provided azide 330. The epoxidation was reported to proceed without selectivity and the resolution was reported to proceed in greater than 50%, without explanation. Perhaps the diastereomeric mixture (329) was purified to a single enantiomer or a sample enriched in the desired enantiomer. Undisclosed reduction of the azide, hydration/olefin migration, and protection steps were performed in an undisclosed manner to provide tertiary alcohol 331. Reductive ozonolysis gave C1-C6 fragment 332 in high yield.
Scheme 2.25 Miyashita’s synthesis of C1-C6 fragment (332).

The C1-C6 fragment was coupled to the northern fragment by deprotonation of alkyne 327 and exposure to C1-C6 aldehyde 332 (Scheme 2.26). Subsequent oxidation gave unsaturated ketone 333. Complete reduction of the alkyne through hydrogenation preceded cleavage of the vinyl methyl ether and cyclization of rings F and G prompted by heating in acetic acid, which provided aminal 334. Global desilylation then secondary alcohol oxidation with ammonium molybdate and hydrogen peroxide followed by sequential oxidation of the primary alcohol to the carboxylic acid yielded 335. Esterification with TMSdiazomethane was performed prior to introduction of the C15-C16 double bond by the Ito-Saegusa method. Chemoselective enolization of C17 was achieved by treating 335 with LiHMDS at low temperature and the enolate was then trapped as the silyl enol ether with TMSCl. Reaction with palladium acetate provided enone 336 in extraordinary yield from carboxylic acid 335. Heating in acetic acid reportedly freed the amino group, which spontaneously condensed at C10 to form the acetic acid salt 337. Additional heating with trifluoroacetic acid hydrolyzed the methyl ester, allowing cyclization at C10, and neutralization allowed isolation of norzoanthamine (151) in impressive yield from enone 336.
Scheme 2.26 Miyashita’s total synthesis of norzoanthamine (151).

Three years after the total synthesis of norzoanthamine (151), Miyashita reported the total synthesis of zoanthamine (150) (Scheme 2.27).30 Norzoanthamine (151) synthetic intermediate 335 was esterified with TMSdiazomethane and converted to the C16-C17 TES silyl enol ether. Alkylation at C19 was achieved by treatment with LiHMDS and quenching with methyl iodide. The silyl enol ether (338) was converted to enone 339 as reported in the norzoanthamine (151) synthesis. Consecutive acid treatments as
performed in the norzoanthamine (151) synthesis and neutralization gave zoanthamine (150).

**Scheme 2.27** Miyashita’s total synthesis of zoanthamine (150).

The synthetic effort(s) reported by Miyashita are highlighted by the ingenious dienophile formation through furan oxidation and the subsequent Diels-Alder reaction. Two quaternary centers were formed with good selectivity demonstrated for the exo transition state. The 41-step synthesis of norzoanthamine (151) corroborated the previously proposed absolute stereochemistry and the zoanthamine (150) synthesis has now done the same. The total syntheses of these natural products stand as impressive achievements and examples of what modern synthetic chemistry can accomplish. The fact that twenty years passed from the isolation of zoanthamine (150) to the total synthesis of norzoanthamine (151) may serve as a testament to this statement.
The most recently published entry into zoanthamine synthetic studies has come from the Stoltz lab (Scheme 2.28).\textsuperscript{31} The Stoltz group's strategy toward the zoanthenol (163) ABC ring system was centered around a Friedel-Crafts cyclization to form the C12-C13 bond. Fragment synthesis began from the known dimethyl ketone (341). Enolate formation and alkylation provided 343, which was subjected to a second base treatment and trapped as the vinyl triflate (344). Reductive carbonylation gave aldehyde 345, which was treated with benzyl Grignard 346 to provide allylic alcohol 347 with good stereoselectivity. The Friedel-Crafts cyclization in TFA was expected to proceed by initially cleaving the protecting groups and instigating an olefin migration to form a C10-C12 enone, then cyclizing through a conjugate addition at the C10 enone system, leaving the necessary hydroxyl functionality at C20. Under the described conditions, in addition to dioxolane deprotection and hydrolysis of the t-butyl ester, elimination of the C20 alcohol occurred. The elimination would have likely created an allylic cation ideally positioned for 6-endo cyclization instead of the proposed 6-exo cyclization. The properties of TFA seem ideally suited to promoting this particular reaction as weaker and stronger acids failed to promote cyclization, as did dilution of TFA with methylene chloride, benzene, or acetic acid.
Scheme 2.28  Stoltz’s zoanthenol (163) ABC ring system synthesis.

The TBS group of the cycloadduct was cleaved with TBAF to give 348. Tricycle 348 was further functionalized by converting the acid to the corresponding methyl ester and deoxygenation of C16 was achieved by palladium insertion and formic acid treatment. After deoxygenation, the methyl ester was saponified to the acid and the C10 ketone protected again as a dioxolane. Typical epoxide formation procedures failed to oxidize the C20-C21 olefin, presumably due to steric hindrance created in part by the adjacent methyl groups. An alternative method was devised for olefin oxidation involving iodolactonization and iodine displacement. Iodolactonization provided
lactone 350 in excellent yield. Lactone methanolysis formed the C24 methyl ester and freed the C21 oxygen for iodide displacement. Epoxide opening and C20 hydride shift mediated by magnesium chloride formed the C20 ketone. Subsequent acid treatment cleaved the dioxolane to give the zoanthenol (163) ABC ring moiety, 352. Only alkylation of C19 remained to form the fully functionalized northern fragment, but this reaction may be slated for a later stage similar to the alkylation demonstrated by Miyashita and coworkers.

To further validate this approach, the Stoltz group has developed a procedure for producing ketoester 343 enantioselectively through their asymmetric decarboxylative allylation chemistry making an asymmetric zoanthenol (163) synthesis within reach. To summarize, the Stoltz approach is focused on a Friedel-Crafts cyclization reaction to create the quaternary C12 center and has resulted in an advanced tricyclic intermediate (348, or its ketal precursor) potentially capable of further functionalization.

Research performed by our group has resulted in the synthesis of the functionalized ABC ring system and helped guide an alternative and truly novel approach to zoanthamine alkaloid synthesis. The work resulting in the ABC ring system (1st generation strategy) will be presented prior to discussing the initial results of the 2nd generation strategy.

Section 2.4 1st Generation Strategy Toward Zoanthamine Alkaloids

Early studies in the lab focused on development of a model system for a trans-annular Diels-Alder as well as a scaffold to study the BC ring system forming Diels-
Alder reaction. When these reactions proved problematic, a plan was devised that involved appending the A ring to a BC decalin system arrived at through Robinson annelation chemistry and appropriately functionalized (Scheme 2.29). Enone 353 represents a highly functionalized ABC ring model, requiring only C10 oxidation and C9 functionalization to become a viable synthetic intermediate. We felt the C17 ketone moiety of 353 could be placed in position through methylation and an oxidative rearrangement of enone 354. Robinson annelation chemistry was expected to provide enone 354 by reacting methyl vinyl ketone with bicyclic ketone 355, which was expected to arise from a correctly oxygenated cyclohexene such as ester 356. Ester 356 would presumably be accessed from the reported enone (357), a Robinson annelation product of dione 359 and enone 358.

Scheme 2.29 1st generation ABC ring retrosynthetic plan.

The synthesis of tricycle 353 began by synthesizing ketoester 358 through a LDA mediated reaction of ethyl acetate and acrolein (Scheme 2.30). Robinson annelation of dione 359 and ester 358 proceeded in good yield, 74%, as previously reported.
Stereoselective C13 reduction was achieved with sodium borohydride and protection of the secondary alcohol as the TBS ether proceeded smoothly with ammonium nitrate and TBSCl to provide enone 360. Stereoselective alkylation through an extended enolate gave ester 361 in 68% yield. Reduction of the ester and ketone functionalities preceded protection of the resultant diol as the corresponding acetonide in 80% yield over the two steps. Hydroboration of the C20-C21 olefin produced a mixture of separable diastereomers (3:2 in favor of 362) in 90% overall yield and stereochemical assignments associated with major product 362 were confirmed by single crystal x-ray analysis of 362. Attempts to improve the selectivity of this reaction revealed the importance of C13 substitution (R-OTBS) as a directing group. When a corresponding ketal was subjected to hydroboration, only the cis decalin was isolated. Protection of the C20 hydroxyl as a MOM ether, deprotection of the C13 silyl ether, and oxidation of C13 to ketone 363 was achieved in high yield over three steps (88%).

Scheme 2.30 Synthesis of decalin intermediate (363).
With a route to the BC ring analog discovered, attention was turned to appending the A ring (Scheme 2.31). Direct reaction to tricycle 365 through Robinson annelation of ketone 363 and methyl vinyl ketone resulted in a complex mixture of products. Due to the undesired reactivity of 363, it was converted to enol 364 by enolization and quenching with methyl formate. Treatment with triethylamine promoted 1-4 addition to methyl vinyl ketone and subsequent sodium methoxide treatment instigated the cyclization/elimination step with concomitant loss of the formyl group to provide enone 365. Lithium/ammonia reduction of enone 365 provided ketone 366 in excellent yield. The desired stereochemical outcome of was confirmed by derivitizing 366 to the corresponding bromo-benzoate (367) and obtaining x-ray crystal analysis.

**Scheme 2.31** Synthesis of functionalized ABC ring system analog (369).

Unsaturation (C16-C17) was formed through conversion of 366 to the phenylselenide then oxidation to the sulfoxide and requisite elimination to provide
enone 368. Methyl lithium treatment of enone 369 gave the necessary tertiary alcohol and exposure to PCC prompted the desired rearrangement to enone 369.

Enone 369 contains fully functionalized A and B norzoanthamine (151) rings, including the all-carbon quaternary C12 and C22 centers, as well as a nearly fully functionalized C ring. C12 and C22 of the C ring contained the necessary functionalization in correct stereochemistry, but C10 needed oxygenation and C9 required deoxygenation and alkyl connections. These issues were resolved indirectly through studies on a BC ring motif.

As mentioned, three challenges remained to complete the ABC ring system; oxygenation of C10, installation of a quaternary methyl group at C9, and further alkyl functionalization of C9. Having developed a method for A ring formation, the remaining questions were addressed with a scaffold more amenable to expedient troubleshooting. The BC ring system analog 370 was utilized in studies performed primarily by Fatima Rivas to answer the vital questions.67

The first approach is outlined in Scheme 2.32 and involved a strategy similar to that used by Miyashita to stereoselectively install the C9 quaternary methyl group on a similarly functionalized substrate. Investigation began by deprotecting the acetonide functionality of 370, selective primary alcohol protection with TBSCl, and oxidation of the C9 alcohol gave ketone 371. Ketone 371 was converted to C9 vinyl iodide 372 by formation of a hydrazone and subsequent treatment with triethylamine and iodine.35 Palladium mediated carbonylation provided lactone 373 without the need for discrete
deprotection of the C24 silyl ether. Hydrogen peroxide induced epoxidation of the olefin was achieved in excellent yield, after which reductive epoxide opening with lithium/ammonium gave the corresponding C10 alcohol. IBX oxidation supplied the alkylation substrate (375).

**Scheme 2.32** Attempted methyl installation through a 1,3 dicarbonyl alkylation.

Methylation attempts, either simultaneous to the epoxide opening or through the C9 enolate were unsuccessful. Only O-methylation products were observed from the enolate alkylation attempts. Although the C9 methyl group was not installed, this method demonstrated a route to oxygenate C10 and provided alkyl substitution at C9 in the form of the butyrolactone, which could be used as a handle for attachment of a southern fragment.

A clear explanation for the failed alkylation did not present itself. It was speculated that a larger lactone ring or a non-cyclic 1,3-dicarbonyl functionality could create important conformational freedom necessary for adequate electrophile approach. Two
analogous substrates were prepared for study. An aldehyde 1,3-dicarbonyl BC system (380) was prepared as described in Scheme 2.33. Intermediate, vinyl iodide 372, was carbonylated in low yield to methyl ester 377. Ester reduction resulted in cleavage of the primary silyl ether, which was protected in preference to the allylic alcohol with the more robust TBDPSCI to provide alcohol 378. Hydroboration gave a mixture of diastereomers. One-pot oxidation of both hydroxyl groups provided ketoaldehyde 380. Unfortunately only the vinyl methoxy moiety (381) was isolated under a variety of alkylation conditions.

Scheme 2.33 Synthesis of ketaldehyde alkylation substrate 380.

Attention was turned to synthesizing a keto-valerolactone tricyclic system for C9 alkylation (Scheme 2.34). Primary alcohol 382 (a product of PMB acetal cleavage described in Scheme 2.5) was oxidized and homologated to alkene 383. Hydroboration, subsequent TBDPS cleavage, and PMB ether deprotection gave secondary alcohol 384. Oxidation and enolate trapping as the vinyl triflate provided 385. Palladium mediated
carbonylation and silyl ether deprotection provided enone 386. Simultaneous silylcuprate addition and methylation resulted only in cuprate 1-4 addition, giving only adduct 388. Attempts to manipulate the C10 silicon bond to the corresponding ketone were unsuccessful. Consequently, enone 386 was oxidized to epoxide 389 with mCPBA, but reductive epoxide opening with Li/NH₃ gave an unacceptable yield of the desired hydroxylactone (~5%). Samarium iodide treatment provided only the fully reduced tricycle 390. Further study of this particular route was prevented by limited material due to the lengthy route and less than ideal yields.

Scheme 2.34 Attempt at 1,3-keto-valerolactone synthesis for alkylation studies.
An approach involving nucleophilic attack of a methyl group at C9 was being pursued concurrently (Scheme 2.35). Conversion of acetonide 370 to the corresponding PMB acetal was performed prior to acetal cleavage. In this manner the free secondary alcohol (390) was isolated in 43% over three steps. C9 oxidation and C10 hydroxylation with the Davis oxaziridine\textsuperscript{36} provided alcohol 392 in excellent yields. Esterification with phosphonate 393 and intramolecular cyclization under Masamune-Roush conditions provided unsaturated butyrolactone 394 in modest yield.\textsuperscript{37} Butyrolactone 394 was treated with methyl cuprate in attempt to effect a 1-4 addition at C9. Unfortunately, 1-2 addition followed by aromatization, predominated and 395 was isolated as the major product.

Scheme 2.35  C9 nucleophilic methylation attempt of lactone 394.

With important lessons learned, a strategy involving intramolecular cyclization at C9 with an attached methyl group was devised (Scheme 2.36). Oxidation and single carbon Wittig homologation of secondary alcohol 390 provided alkene 397. Allylic
oxidation with selenium dioxide was achieved in good yield to give enone 398. Wilkinson reduction and PMB ether deprotection gave ketone 399 in excellent yields. Treatment of 399 with N,N-dimethylaniline and 1,2-dibromo-1-ethoxy-ethane (400) gave the corresponding α-bromoacetal, which was reacted with t-BuOK to provide the cyclized product (401). Conversion to the hemiketal and oxidation gave lactone 402, representing the fully functionalized C ring.

Scheme 2.36 Completion of the C9 methylated BC fragment.

In the manner described above, the crucial C9 quaternary methyl group was installed in an innovative manner, providing the fully functionalized C ring. The valerolactone moiety represents functionalizable substitution at C24 and provides a handle at C7 (potential aldehyde functionality) for elaboration of the southern hemisphere.

In summary, we have developed chemistry allowing stereoselective construction of the ABC ring system of the zoanthamine alkaloids. Formation of the BC ring system
skeleton was accomplished through Robinson annelation chemistry, as well as the subsequent appendage of the A ring. After much experimentation, installation of the C9 methyl group was achieved through an intramolecular alkylation/cyclization process. The chemistry developed appears to be a viable approach to the complete, fully functionalized, ABC ring system with a good likelihood of achieving the total synthesis of norzoanthamine (151) given enough time and effort. However, the route involving this chemistry would most likely involve a late-stage intermediate identical to, or strongly resembling, one already reported by Miyashita in the total synthesis of norzoanthamine (151). Additionally, our route would require a similar number of manipulations to that utilized by Miyashita. We were unable to justify continuation of this route based on these observations and changed focus to a fresh approach for the synthesis of zoanthamine alkaloids.

Section 2.5 2nd Generation Strategy; an Amino-diene Approach

Section 2.5.1 Expanded Biosynthetic Proposal and Key Disconnections

The length and scale of the Miyashita norzoanthamine total synthesis demonstrates the shortcomings of a linear, step-wise, approach to synthesis of complex natural products such as the zoanthamine alkaloids. A more convergent and efficient synthetic route would be necessary for complete biological studies, including thorough SAR studies. Moreover, a shorter and more efficient route increases the likelihood of a natural product becoming a drug. With these concepts in mind and in consideration of the shortcomings associated with linear synthetic approaches, we devised a risky but
potentially rewarding approach to the zoanthamine alkaloids (Scheme 2.37). The approach centers on a cyclization reaction of a fully functionalized linear precursor to form the B and C rings simultaneously. We imagined the final cyclization (formation of the D ring lactone) would could occur from an iminium ion such as 403, as demonstrated previously by the Kobayashi, Hirama, and Miyashita groups. The key step of this proposal is formation of iminium 403 or its enamine equivalent from a linear precursor such as 406. The [4+2] cyclization would form 3 quaternary centers and close 2 rings in one step, making it a very appealing tactic. However, we recognized a Diels-Alder pathway would not provide the desired stereochemical outcome, unless a high-energy hindered transition state could be achieved (404b). Triene 404b indicates the necessary diene stereochemistry for the desired stereochemical reaction outcome. The extended conjugation between the aromatic A ring and the diene system would favor a rigid, planar arrangement for carbons C18-C9. However, steric effects, due to C9 and C12 substitutions would likely prevent the desired confirmation. Additionally, conformational analysis by traditional plastic model systems suggested the cis olefin arrangement at C12 of 404b would place the dienophile distant from the diene system, while the trans conformation indicated by 404 located the diene and dienophile proximal to each other. The diene-dienophile distance was also shorter in the exo transition state without the need for destroying C9-C18 planarity than in the corresponding endo transition state, as indicated by models.

We did see the potential for an alternative cyclization pathway though. It is plausible that the enamine (C9) (404) could act as a Michael donor through nucleophilic
attack at C22 of the enone system, thereby inducing formation of a C21 enolate and a
conjugated 1,4 imminium system (C10-C12). If this intermediate could be achieved, it
was suspected that the enolate (C21) would likely cyclize at the highly activated C12
position to contract the 10-membered intermediate ring system to a more favorable 6,6
system such as 403.

Scheme 2.37 2nd generation retrosynthetic analysis of zoanthenol (163).

The 2-amino-1,3-butadiene cyclization substrate (404) could be formed through
condensation of the C1 amino and the C10 ketone. Previous synthetic work suggests an
aminal system such as 405, would likely add to C10 under acidic conditions to form a
C10 imminium ion with concomitant loss of water.\textsuperscript{14,19,29} We felt formation of the imminium ion in this manner, followed by neutralization, could form the dieneamine system (404). It was also thought that the process of imminium formation, neutralization to the dienamine tautomer, and cyclization may have even been feasible as a one-pot reaction.

Precedent also exists for formation of an N-carbamate aminal analog of 405 by acid treatment of a linear N,O-ketal such as 406.\textsuperscript{14,19,29} We felt N,O-ketal 406 could be synthesized in a convergent manner from three fragments; aryl halide aldehyde 409, vinyl organometallic fragment 407, and vinyl halide 408. It was foreseeable that vinyl halide 408 could be lithiated, and added to aldehyde 409 to construct the C13-C24 northernmost fragment. Palladium mediated cross coupling of the resultant aryl halide (or aryl triflate) with stannane 407 was expected to provide an intermediate resembling 406.

This plan was recognized as very ambitious from the onset of the research. However, strong literature precedent involving formation of the EFG ring system through our proposed aminal chemistry buoyed our confidence. However, the question as to whether the reactive dieneamine could be formed remained, as previous studies formed the imminium aminal with an internal nucleophile capable of trapping the reactive imminium in situ. At the onset we were most concerned as to whether we could obtain cyclization of the dienamine and whether it would proceed through a step-wise mechanism expected from consecutive conjugate additions or a concerted mechanism assumed of Diels-Alder reactions.
Fortunately, examples of 2-amino-1,3 butadienes as cyclization substrates were easily found in the literature. Examples of single Michael addition reactions from C1 of 2-amino-1,3-butadienes forming linear products as well as cyclization reactions have been reported by several different research groups. Barluenga and coworkers made a particularly interesting finding when dienamine 410 was reacted with nitrostyrene (411) (Scheme 2.38). A mixture of products was obtained when the reaction was performed with THF as a solvent. Single Michael addition adduct 412 was isolated in roughly 38% yield along with cyclized products 413 (49% yield) and 414 (13%). Barluenga argued that the cyclized products (413 and 414) are likely the result of sequential conjugate additions rather than Diels-Alder adducts. The strongest evidence being that the single Michael addition adduct (412) was isolated and is arguably an intermediate in the formation of the cyclized compounds. However, it was not stated whether or not further heating of 412 resulted in formation of 413 and/or 414. Additional evidence supporting the step-wise mechanism was found when reaction of nitrostyrene and dieneamine 410 in methanol resulted in a single product, 412. A polar solvent, such as methanol, can presumably better stabilize polarized intermediate(s) in a sequential conjugate addition pathway. The rate of this cyclization was also significantly increased with methanol as the solvent.
Scheme 2.38 Enamine reactions with nitrostyrene by Barluenga’s group.

Enantioselective dieneamine cyclizations related to our proposal have also been reported. To the best of our knowledge, the amine portion of the dienamine has served as the chiral controller in all cases. This observation may lend support to our hope that the chiral aminal portion could provide asymmetric induction and create enantioselectivity in a [4+2] reaction.

The growing field of organocatalysis has taken advantage of this methodology by using amines (chiral or otherwise) to form reactive intermediates in the form of imminium ions or enamines. Numerous examples of aldol, Mannich, Michael, and Diels-Alder reactions using this reactive, tautomeric, intermediate moiety have been reported. In their sum these findings set an important precedent, seemingly supporting our proposed cyclization. Additionally, reports of asymmetric reactions were exciting, as we intended to use a chiral aminal (southern fragment) to effect an asymmetric cyclization. Furthermore, an observation pertaining to the existing literature was that
nearly all cyclizations, enantioselective or otherwise, involved an activated dienophile (or Michael acceptor/donor) such as nitrostyrene.

A search of the literature also revealed examples of cyclization reactions involving dienolates as diene equivalents. An excellent example of this type of reaction is the key step of the atisine total synthesis published by Ihara and coworkers (Scheme 2.39). It is not clear whether this reaction follows a concerted or step-wise pathway. Nonetheless, this reaction represents a [4+2] cyclization relevant to our proposal as it suggests our proposed cycloadduct may be accessed in a step-wise manner through enolate chemistry. The Ihara example therefore offered us an alternative cyclization reaction to apply to our dienone substrate.

Scheme 2.39 Dienolate cyclization reaction demonstrated by Ihara’s group.
While we felt sufficient literature precedent existed to justify our proposal, we decided to explore the key cyclization reaction with model systems prior to attempting the reaction with a valuable, advanced zoanthamine intermediate. Several model systems were designed with this in mind and will be discussed.

Section 2.5.2 Attempted In-situ Intermolecular Amino-diene Formation and Intramolecular [4+2], an Unexpected Michael-Aldol Cascade

We sought to test our proposed dienamine cyclization initially in a simple model system to prove the viability. To this end, dienone 420 was targeted as a cyclization substrate (Scheme 2.40).

Scheme 2.40 In-situ intramolecular amino-diene formation and cyclization plan.
Condensation of a secondary amine, such as pyrrolidine, at C10 of 423 would produce 2-amino-1,3-diene 422, hopefully instigating a cyclization reaction. Exposure to mild acid was expected to provide the cyclized product as the C10 tricyclic ketone (420).

A convergent synthetic plan allowing for varied functionalization of C9, C19, C12, and C22 was desirable, particularly if studies showed the cyclization to be plausible in the less functionalized system. We felt an aldehyde such as 424 would allow for nucleophilic addition of vinyl anions with the desirable C22 functionalization. We also felt the aldehyde functionality could be installed through Wittig olefination performed on a benzaldehyde such as 427. A halogen or triflate at the C13 position of the benzaldehyde would provide a coupling partner for appropriately functionalized stannanes or boronic esters representing the C12-C9 fragment (426).

We recognized the cyclization to be potentially problematic as multiple reaction pathways leading to undesired products were seen as plausible. However, most reactions were viewed as reversible, allowing for equilibration to dieneamine 422 and subsequent cyclization to 420. Scheme 2.41 outlines some of the expected side reactions. We felt that acid base chemistry could operate through enolate formation to form enolate 429 or 430. Interestingly, enolate 430 could potentially cyclize to give the same product as the desired cyclization of dieneamine 422. Enolate 429 is capable of cyclizing in Michael fashion to form enol ether 432, which we felt would be converted back to starting material with extended reaction times. We also felt that a dieneamine could be formed at C20, but any further reaction of 428 would result in high-energy
products, precipitating conversion back to starting material and cycling through lower energy pathways. It was also felt that the base itself could act as a Michael donor by reacting at C22.

Scheme 2.41  Potential reaction pathways of dienone 423.

The previously reported synthesis of bromo benzaldehyde 427 (427a) involved the use of harsh reagents and required five steps with an overall yield of 35%.44 Due to the issues associated with synthesis of benzaldehyde 427a, an alternative route to a similar benzaldehyde was explored concurrently with synthesis of benzaldehyde 427a.
Synthesis of a benzaldehyde 427a analog began with diphenol 432 (Scheme 2.42). Diphenol 432 lacks the C15 methyl group, but we felt this group to be unnecessary for our model studies as it is not proximal to reactive centers and was expected to have minimal electronic effects. This model would also have allowed us to evaluate any effect the C19 benzylic methyl group might have had on the planned manipulations. Treatment of 432 with K₂CO₃ and methyl iodide in refluxing acetone resulted in a mixture of products, with phenol 433 easily isolable in 50% yield. Conversion to the corresponding aryl triflate (434) was accomplished by treatment of phenol 433 with Hunig’s base followed by addition of triflic anhydride. Attempted homologation to the aldehyde equivalent, 435, was unsuccessful. However, it was found that aryl triflate 434 could be coupled to the known stannane (437) to provide the C9-C19 fragment (438). Stannane 437 was synthesized in the manner reported by Lee and Kim.⁴ With a method for construction of the C12-C13 bond through a Stille coupling in place, Wittig homologation to the aldehyde equivalent (439) was attempted without success.

![Scheme 2.42 Synthesis of C10-C19 fragment 438.](image-url)
Focus was shifted to installing the C20 aldehyde functionality prior to performing the Stille coupling (Scheme 2.43). To this end, phenol 433 was protected as the MOM ether. Wittig homologation to the methoxy enol ether (441) was achieved without optimization in low yield (20%). Then treatment with acid gave the desired aldehyde (443) as well as observable MOM cleavage which resulted in formation of a compound tentatively identified as lactol 442. Grignard reaction with vinyl magnesium bromide gave allylic alcohol 444 as a mixture of diastereomers, and the mixture was protected as the TBDPS ether (445). Attempts to deprotect the MOM ether with bromocatecholborane resulted in complex product mixtures. Although this route showed promise, we chose to use the reported benzaldehyde (427a) as it represents the fully functionalized A ring and we had achieved its synthesis in yields similar to that reported by Gould and coworkers.

![Scheme 2.43 Synthesis of C13-C22 fragment 445.](image)

The synthesis of dienone 423 therefore began from benzaldehyde 427a (Scheme 2.44). Wittig homologation to 446 worked well when performed at room temperature
in toluene with excess phosphonium salt (1.6 eq.), and subsequent acid treatment of the vinyl ether revealed the C20 aldehyde (447) in excellent yield. The aldehyde was then converted to allylic alcohol 448 by treatment with vinyl magnesium bromide. Unfortunately, when the Stille coupling of allylic alcohol 448 and stannane 449 was attempted, only Heck adduct 450 was isolated. The same result was obtained even when the reaction was performed with large excess of stannane 449 in concentrated solutions.

Scheme 2.44 Synthesis of C9-C20 fragment 452.

Coupling reactions also failed when aldehyde 447 was used as a Stille partner. However, the coupling issue was resolved by reducing aldehyde 447 to the corresponding alcohol (451). Early coupling attempts of aryl bromide 451 and stannane 449 resulted in little or no reaction when traditional catalyst systems were used, such as Pd(PPh₃)₄ and Pd(PPh₃)₂Cl₂ with or without additives such as lithium chloride or copper iodide. Success was achieved when a catalytic system (Pd₂(dba)₃/P(tBu)₃) developed...
by the Fu research group was utilized.\textsuperscript{46} We suspected the bulky tri-$t$-butyl ligands enhanced the oxidative addition step by increasing access of the aryl bromide to the reactive Pd$^0$ species. Simply put, we felt four $t$-butyl ligands could not coordinate to palladium simultaneously as with triphenylphosphine and other ligands.

Having found a solution to sluggish reactivity associated with the Stille coupling reaction, attention was turned to the remaining functionalization reactions (Scheme 2.45). Oxidation of 452 to the corresponding aldehyde (453) and Grignard reaction provided allylic alcohol 454. Oxidation (IBX) and deprotection of the C10 silyl ether gave allylic alcohol 456 in good yields. A final IBX oxidation provided dienone 423 in high yield. When dienone 423 was treated with pyrrolidine in DMSO at room temperature or with mild heating, only Michael adduct 457 was observed. Complex mixtures were formed when more forcing conditions were applied (increased heat).

\textbf{Scheme 2.45} Synthesis of C9-C22 fragment 423.
Having observed rapid Michael addition of pyrrolidine to dienone 423, we felt substitution at C22 might have slowed the Michael addition and increased the likelihood of dieneamine formation. For this reason, aldehyde 453 was treated with 1-propynyl magnesium bromide to form propargyl alcohol 458 (Scheme 2.46). Poisoned hydrogenation of propargyl alcohol 458 gave allylic alcohol 459 in excellent yield, then oxidation with IBX efficiently provided enone 460. Deprotection of the TBS ether with acetic acid in THF and water, followed by oxidation with IBX provided cyclization substrate 462. It should be noted that slow isomerization of the C21-C22 olefin was observed, particularly during the acid mediated TBS cleavage reaction. Although the E,Z isomers were not typically separated, separation was achievable with column chromatography.

**Scheme 2.46** Synthesis of C22-methyl C9-C22 fragment 462.
We felt the solvent choice to be important for the consecutive conjugate addition reaction of 462, with polar solvents more likely to bias the pathway to a stepwise mechanism though stabilization of the charged intermediates. For this reason, DMSO was initially picked as the solvent of choice (Scheme 2.47). Treatment of dienone 462 with pyrrolidine at 50 °C for varied lengths of time inevitably provided a mixture of products. The three major components were tentatively identified as; enol ether 463, naphthalene 464, and tricycle 465. Attempts to modulate the reactivity of pyrrolidine by adding camphorsulfonic acid as a buffer led to the same mixture of products, in different yields and ratios.

Scheme 2.47 Attempted cyclization of C9-C22 fragment 462, an unexpected Michael-aldol cascade.

The products suggested several reaction pathways were operating. We believed enol ether 463 was formed through enolization of C19-C20 (466) (Scheme 2.48). The C19 protons were expected to be the most acidic due to conjugation with the aromatic ring, and the mechanism therefore likely involved enolization and Michael addition of the enolate to the C12 enone. We assumed this process to be reversible, and confirmed our
suspension by observing that re-treatment of 463 with pyrrolidine provided the same mixture of products originally observed (463, 464, and 465).

Scheme 2.48 Proposed mechanism for formation of enol ether 463 and naphthalene 464.

Formation of naphthalene 464 was expected to arise from initial isomerization of the C12-C22 olefin (467) (Scheme 2.48). Enolization at C19 and 1,2 attack of the C19 enolate at the C10 ketone likely provided the intermediate allylic alcohol (469). Aromatization through C10 hydroxyl group elimination was suspected of being the final manipulation which provided naphthalene 464.

Of the three major products, tricycle 465 was the most interesting to us. The mechanism was not clear, but we felt the initial step involved charge development at C21 through Michael addition of pyrrolidine at C22 (470) via a Bayliss-Hillman type mechanism or formation of an extended enolate by deprotonation at C22 (474) (Scheme
2.49. Michael addition of C21 to C12 would form a cyclohexane ring, such as 471 or 475. Subsequent C19 enolization and 1-2 addition would form the second cyclohexane ring. It is not clear at what stage isomerization of the C22-C23 olefin to C21-C22 would occur if the extended enolate pathway was in operation. Likewise, elimination of pyrrolidine to regenerate the C21-C22 olefin could have feasibly occurred at any stage after C21-C12 bond formation if the reaction followed a Bayliss-Hillman mechanism.

Scheme 2.49 Proposed mechanisms for formation of tricycle 465.

Although no useful intermediates such as 471, 472, or 475 were isolated, we felt modified reaction conditions may have allowed for manipulation of the reaction pathways. We understood that installation of the C19 methyl group would prevent formation of naphthalene 464 by C11 elimination, due to the lack of β hydrogen atoms. If our proposed mechanism(s) for tricycle 465 was correct, it suggested C12 to be a good Michael acceptor and C21 to be a good Michael donor. The desired C12-C21
bond had been formed, but subsequent reactivity from C19 converted the intermediate to undesired material. It seemed that we may have been able to tune this reaction to provide the desired tricyclic structure if the enolizability of C19 could be mitigated. Additionally, it was thought that we may have been able to use a Bayliss-Hillman reaction to form the C12-C21 bond and intercept a useful intermediate such as 471, prior to any additional reactions.

We decided to use a further simplified model system to expedite the additional studies. 2-bromo-phenethyl alcohol (478) was used as a starting point (Scheme 2.50). Although commercially available, we found borane reduction of the inexpensive carboxylic acid (477) to phenethyl alcohol 478 to be convenient. Coupling of stannane 449 gave 479 in yields similar to those observed for the construction of 452. Oxidation to the corresponding aldehyde, Grignard reaction, and poisoned alkyne hydrogenation gave allylic alcohol 482, which was oxidized to enone 483. Mild deprotection of silyl ether 484 and oxidation of the resultant allylic alcohol provided dienone 485 as a separable mixture of C22 isomers favoring the cis isomer. Additionally, the E isomer (485E) could be isolated via trituration as an amorphous solid.
Scheme 2.50 Synthesis of dienone 485.

Unfortunately, attempted cyclizations of dienone 485 were unsuccessful under an expanded set of conditions. All modifications provided only enol ether 486, naphthalene 487, and tricycle 488 as isolable products (Scheme 2.51). Reactions in DMSO with pyrrolidine, morpholine, proline, prolinol, or methoxymethyl prolinol (SAMP) all gave similar product distributions. Reactions in toluene gave the same product mixture, as judged by crude NMR. Furthermore, no optical activity was observed for products obtained from proline or proline derivatives, which was suggestive of a lack of involvement of an enamine mechanism. All reaction conditions produced tricycle 488 as a mixture of diastereomers, with the indicated stereochemistry.
preferred, as judged by NMR. The major diastereomer of 488 provided a crystal suitable for single crystal x-ray analysis, which supported the indicated structure (Scheme 2.51).

Scheme 2.51 Attempted cyclization of dienone 485.

At this stage we decided it was necessary to install the C19 methyl group prior to cyclization, in order to prevent aromatization and to limit the ability of C19 to act as a nucleophile in the aldol reaction. We also decided to install a second methyl group at C22 for two reasons; to represent the desired C22 tertiary center at C22 of the zoanthamine alkaloids, and to increase C22 steric hindrance to minimize a Bayliss-Hillman mechanism. To this end, two methods were explored for installing the C19 methyl group. One method involved Wittig extension of a methyl ketone (Scheme 2.52). Wittig homologation was performed on 2-bromoacetophenone (489) to yield a mixture of methoxy enol ethers (490). Methoxy enol ether 490 was converted directly to alcohol 491 by a one-pot oxymercuration/reduction procedure using Hg(OAc)$_2$, NaBH$_4$, and K$_2$CO$_3$ in wet THF. Alcohol 491 was not tested as a coupling partner due to limited quantities and the success of an alternative approach.
Scheme 2.52  Synthesis of aryl bromide 491.

Standard Grignard additions of 3-methyl-propenyl magnesium bromide (492) to aldehyde 480 proved to be low-yielding and provided erratic results under different conditions (Scheme 2.53). We suspected the enolizability of aldehyde 480 increased the likelihood of polymerization pathways, so cerium chloride was used to form the less basic and more oxophilic organocerium reagent. This modification resulted in acceptable and reproducible yields of allylic alcohol 493. Oxidation with IBX provided alkylation substrate 494. Enolization with potassium hydroxide in the presence of methyl iodide gave C19 alkylation, and enone 495 was constructed in this manner. Deprotection as previously described with acetic acid and oxidation with IBX gave dienone 497.
Scheme 2.53  Synthesis of dienone 497.

Numerous cyclization conditions were evaluated for dienone 497. Heating with pyrrolidine in DMSO provided a complex mixture of products, with only tricycle 498 isolated (Scheme 2.54) as a diastereomeric (C10) mixture. Reaction condition modifications included temperature and solvent variation. Reactions were performed at low temperature (-78 °C, 0 °C) as well as temperatures up to 75 °C under standard thermal conditions and up to 150 °C in a microwave reactor. Several solvents were tested; toluene, benzene, THF, and DMSO, without significant change in the reaction outcomes. Cyclization initiated through enolization was unsuccessfully attempted by treating dienone 497 with non nucleophilic bases KHMDS and LiHMDS. Although the base promoted reactions (HMDS) resulted in particularly complex reaction mixtures, tricycle 498 was observed in crude reaction mixture analyses. This finding suggested
the mechanism involved initial formation of an extended enolate followed by Michael addition and an aldol reaction between C19 and C10.

![Scheme 2.54 Attempted cyclization of dienone 497.](image)

One potential hindrance to the desired cyclization was the fact that the desired reaction pathway involved formation of a ten-membered ring system via formation of a C9-C22 bond. The more favorable path to tricycles 465, 488, and 498 apparently involved initial cyclization to a cyclohexane ring and rapid formation of a second cyclohexane ring. Additionally, the acidity of the C19 proton(s) apparently prevented us from intercepting any direct products of the initial C9-C22 bond forming event.

Regardless of the disappointing results, we felt the reaction merited continued investigation. Two final experiments were devised. The first approach involved promotion of a Bayliss-Hillman reaction through the use of a nucleophilic tertiary phosphine instead of a secondary amine base such as pyrrolidine, feeling that the enhanced reagent nucleophilicity and reduced basicity\(^5\) may have allowed for isolation of the Bayliss-Hillman adduct (499) (Scheme 2.55). We felt the Bayliss-Hillman adduct could be subsequently converted to the desired cycloadduct through a Michael addition of C9 to C22. In this manner we could potentially have achieved consecutive
conjugate additions, albeit in two steps, and possibly elucidated the reaction mechanism for formation of the caged tricyclic compounds.

Surprisingly, when dienone 485-E was treated with tributylphosphine in acetonitrile, enol ether 486 and tricycle 488 were isolated (Scheme 2.55). All evidence suggested the desired cyclization would not be achieved with an enolizable C19 position, so a final approach to address the issue was attempted.

**Scheme 2.55** Attempted Bayliss-Hillman reaction of dienone 485-E.

In order to nullify the enolizability of C19, we planned to alkylate the C19 carbon twice. If the dialkylation approach was successful, we felt we could apply the concept to a zoanthenol (163) synthesis with a cleavable protecting group at C19 capable of preventing enolization.

Di-methylation at C19 of enone 494 was unsuccessful. The first alkylation occurred at C19 as desired, but the second methylation appeared to occur at C21 by way of an extended enolate. Due to this disappointment, C19 addition to a single moiety capable of a second, intramolecular, alkylation reaction was concocted (Scheme 2.56). Enone 494 was treated with base and 1,4 dibromobutane. Extended reaction times and heating provided cyclopentane 500. In this manner the enolizability of C19 was quashed.
Deprotection of the silyl ether and oxidation as previously performed resulted in cyclization substrate 502. Regrettably, a limited amount of dienone 502 was prepared and two small-scale exploratory reactions showed little promise for a clean cyclization reaction.

Scheme 2.56 Synthesis of non-enolizable C19 cyclization substrate 502.

While we did not attain the desired consecutive conjugate reaction sequence, an interesting Michael-aldol cascade was discovered. We gained knowledge pertaining to the ease of enolizability of the benzylic C19 carbon that proved useful in analyzing reactions of a related project. We also overcame a troublesome Stille coupling and observed an efficient Heck reaction in the formation of 450.

Section 2.5.3 Intramolecular [4+2] Cyclization of a Silyl-enol Ether
Unwilling to concede the developed chemistry, an alternative cyclization method was attempted to form the B and C rings simultaneously (Scheme 2.57). Dienone 497 was trapped as silyl enol ether 503 with unexpected efficiency. Despite the problems associated with C19 enolizability, low temperature treatment of 497 with triethylamine produced the kinetic C9-C10 enolate. Also worthy of note is the observation that C9 was enolized but failed to cyclize in a Michael addition to C22, instead an oxygen-silicon bound was formed from a bimolecular reaction.

Scheme 2.57 Synthesis of the minimized zoanthenol (163) ABC ring System.

An intramolecular [4+2] reaction of triene 503 performed well with m-xylene as a solvent when heated at 150 °C for 14 hours. The conditions described, produced cycloadduct 504 as a mixture of C19 isomers in 91% yield. Subsequent deprotection of the silyl enol ether to reveal the C10 ketone generated tricycle 505 in 65% yield.
Limited attempts to epimerize the C19 methyl group by enolization to provide a single diastereomer resulted in little or no conversion to a single isomer.

Tricycle 505 represents a minimized ABC zoanthenol (163) ring system. Of particular note is the fact that only the exo isomer was isolated and a quaternary center was set at C22. We suspected functionalization of the aromatic ring at C15 and C17 would have little effect if such a substrate was subjected to the cycloaddition reaction conditions, and we previously developed chemistry amenable to the construction of such a substrate. Methyl substitutions at C9 and C12 are also necessary for this approach to be considered viable. Miyashita has already demonstrated a similar cycloaddition with methyl substitution at C12\(^{29a}\), and we felt the results may be applicable to our system, allowing for cyclization with the C12 methyl group preinstalled. Functionalization of C9 remains unresolved, but it was thought perhaps the C1-C8 fragment could have been tethered to C9 and the challenging C9 methyl group could have been installed at a later time using a previously developed alkylation method or through an enamine alkylation.

Section 2.5.4 Attempted In Situ Intramolecular Aminal-diene Formation and Intermolecular [4+2] Cyclization

Based on the conclusion that products from the previous studies were almost certainly not produced by dieneamine intermediates and the lack of evidence of a dieneamine intermediate from NMR tube reactions, we felt a model system involving an internal amine capable of cyclizing to a dieneamine would hold more promise.
Consequently, we designed a model system which included an internal secondary amine in the form of the southern portion of the zoanthamine alkaloids. In order to simplify and expedite the studies, we designed a system with the purpose of testing the cycloaddition reaction with an external, activated dienophile (or Michael acceptor/donor) such as maleimide. This was designed primarily to evaluate whether formation of the desired dieneamine was viable, due to the assumption that the dieneamine intermediate could be trapped with a sufficiently reactive dienophile.

![Scheme 2.58](image)

**Scheme 2.58** Retrosynthetic analysis of the intermolecular aminal-diene approach.

We believed an enamine such as 506 could be formed from the cycloaddition reaction of a dieneaminal resembling 507 with a reactive dienophile (Scheme 2.58).
Dieneaminal 507 was expected to arise from condensation of an aminal, which could be formed from a protected amine such as 508. Previous work by the Kobayashi19, Hirama14, and Miyashita29 research groups suggested the Boc group to be a prudent N-protecting group choice as subsequent acid catalyzed deprotection afforded the corresponding iminium in their cases. It was believed that dieneaminal 507 could be accessed through neutralization of the corresponding iminium.

Aminal 509 was anticipated to form upon deprotection of a suitably substituted substrate such as aminal 510. The C5-C6 bond of aminal 510 was chosen as a disconnection, with a lithiate addition of a chiral fragment such as 512 to an aldehyde resembling 511 in mind for the bond development. The chiral aminal piece (512) would theoretical arise from chemistry similar to that used by Kobayashi and coworkers19, and the aldehyde (511) could be formed through homologation of benzaldehyde with a suitably functionalized phosphonate such as 513.

If the cycloaddition reaction proved feasible with activated dienophiles, we felt the intermolecular cyclization could be applied as a method for zoanthenol (163) total synthesis. The ABCEFG skeleton of zoanthenol (163) could arise from a Friedel-Crafts acylation reaction between C18 and C19 as shown in Scheme 2.59. α-haloketone 516 could result from an exo cycloaddition between dienophile 518 and dieneaminal 516. If exo adduct forming conditions could not be found and endo product(s) predominated, we felt subsequent epimerization at C21 could potentially provide the necessary B-C trans ring junction, and the geometry of the dienophile (C22) could be altered as needed.
Scheme 2.58b  Retrosynthetic analysis of the intermolecular cycloaddition / Friedel-Crafts approach to zoanthenol (163).

Synthesis of the chiral C1-C5 fragment (532) began from glutamic acid (Scheme 2.60). Although it contains the opposite requisite stereochemistry, we chose to use L-glutamic acid (519) based primarily on an abundant laboratory supply. Nitrosation of L-glutamic acid (519) gave butyrolactone 520 via the reported method. Reduction to the primary alcohol with borane provided 521 in acceptable yield, and typical reaction conditions provided the bulky TBDPS silyl ether (522). A diastereoselective alkylation was achieved using conditions similar to those originally reported by Hanessian and coworkers. Chromatographic separation showed alkylation from the α face predominated, yielding methyl butyrolactone 523 in 64%. Cleavage of the silyl ether with TBAF as reported by Kobayashi gave the primary alcohol (524), which was converted to the corresponding mesylate by utilizing reaction conditions previously reported by Herdeis and Lutsch. Mesylate displacement by treatment with sodium azide followed by a one-pot procedure involving azide reduction to the corresponding amine and in-situ protection as the Boc carbamate proceeded as originally described by
Herdei and Lutsch.\textsuperscript{54} Mild reduction conditions developed by the Soai research group provided linear diol 528 in excellent yield when applied to butyrolactone 527.\textsuperscript{55}

Scheme 2.59 Synthesis of chiral C1-C5 fragment (532).

Attempts to protect the 1,2 amino-alcohol functionality under acidic conditions with dimethoxypropane at this stage failed to effectively supply the desired N,O-ketal under several conditions. Aminodiol 528 was therefore converted to the primary TBS ether (532) in order to circumvent the amino-alcohol protection problems. Ketalization of
amino-alcohol 530 proceeded with excellent yield once the primary alcohol was protected. Deprotection of 530 and conversion of the resultant primary alcohol (531) to the corresponding iodide (532) proved an efficient method. Primary alcohol 531 and iodide 532 provided spectroscopic data identical to the enantiomer subsequently reported by the Tanner research group.\textsuperscript{25e} It should be noted that NMR spectra of N,O ketal 530 and all subsequent C1-C5 fragment-containing compounds indicated the presence of two stable rotamers. This observation was in accordance with experimental data reported by Tanner and Miyashita for similar and/or identical compounds.\textsuperscript{25e, 29a}

With a proven route to iodide 532 in hand, focus was switched to building an aldehyde coupling partner. We felt the most expedient route to the desired cyclization substrate would involve selective addition of lithiated 532 to a ketoaldehyde such as 511 (Scheme 2.61). Therefore, we decided a Horner-Wadsworth-Emmons reaction to be an excellent method for introducing the $\alpha,\beta$-unsaturated ketone central to ketoaldehyde 511. Consequently, valerolactone (533) was converted to the methyl ester (534) by treatment with acid in methanol, and the primary alcohol was quickly protected as the triethylsilyl ether 535. Formation of stabilized phosphonate 536 occurred upon exposure of the dimethyl methylphosphonate anion to methyl ester 536. Deprotonation with sodium hydride and mixing with benzaldehyde gave trans-alkene 537 in excellent yield as the only product isolated. Deprotection and oxidation afforded coupling partner, ketoaldehyde 511.
Scheme 2.60 Synthesis of keto-aldehyde 511.

Coupling attempts with ketoaldehyde failed under numerous conditions. Treatment of iodide 532 with t-BuLi to form the lithiate and exposure to ketoaldehyde 511 produced complex mixtures of inseparable products. Similar results were obtained when transmetallation of the lithiate to organozinc and organotitanium nucleophiles was performed. We suspected the product had been formed to some degree (this suspicion was supported by mass and NMR spectral analysis but that a subsequent cyclization to form the C6-C10 lactol, as well as enolization at C9 probably complicated the reaction. Oxidation of the presumed mixture of lactols unfortunately did not assist in characterization.

Having observed problems with the coupling presumably arising from the α,β-unsaturated ketone functionality, enone 537 was reduced to the allylic alcohol (539) and protected as the TBS ether (540) (Scheme 2.61). Selective deprotection with pyridinium p-toluenesulfonic acid gave primary alcohol 541, which was oxidized to aldehyde 542. Lithiate formation from 532 and addition to aldehyde 542 provided a
mixture of diastereomers (543) in 65% overall yield, reinforcing the idea that the C10 enone had interfered with the earlier coupling attempts.

Scheme 2.61 Synthesis of alcohol 543.

Formation of diketone 510 was accomplished by oxidation of alcohol 543, deprotection of the C10 silyl ether with TBAF, and C10 oxidation with Dess-Martin periodinane, respectively (Scheme 2.62). Transaminalization of diketone 510 to aminal 509 was accomplished by heating at 50 °C in an acetic acid/water (1:1) solution for 1 hour.
Results for attempted aminal-diene formation and subsequent cyclization of 509 with N-benzylmaleimide were ambiguous at best. Treatment with an acetic acid/water (1:1) solution at 100 °C in the presence of excess N-benzylmaleimide (508) resulted in a complex mixture of products. However, NMR spectra of semi-purified material revealed the presence of a peak at 5.4 ppm, within the typical enamine range, and other peaks consistent with the expected product. However, analysis of splitting patterns and integration suggested a mixture of diastereomers, in addition to many other reaction products.
A similar procedure was performed in deuterated benzene with p-toluenesulphonic acid substituted for acetic acid. All traces of starting material had disappeared, by NMR, within three hours of heating at 45 °C. However, only decomposition was observed. In contrast to toluenesulphonic acid, when pyridinium p-toluenesulphonic acid was used with deuterated benzene as the solvent, limited reaction was observed after 20 hours at 65 °C. After 24 hours additional heating at 100 °C, starting material was observed by NMR in conjunction with a complex mixture of products.

Two reactions were performed in the absence of a dienophile order to determine whether the enamine and/or its tautomeric iminium species had been formed. Aminal 509 was treated with TFA and dimethyl sulfide at room temperature in deuterated methylene chloride. Spectral data obtained immediately (approximately 2 minutes) after TFA addition suggested the starting material had been consumed. Of significant note was the downfield shift of the C12 proton, suggestive of increased conjugation as would be expected from iminium formation. After twenty minutes had passed, an apparent triplet, suggestive of an enamine proton appeared at 5.25 ppm. There were additional products, however, and no compound was isolated for characterization.

We felt the desired iminium had been formed upon Boc deprotection, but alternative reaction pathways lead to decomposition before the desired cyclization could be effected. Therefore, we sought to confirm iminium formation by acid treatment of 509 followed by treatment with sodium cyano borohydride to reduce the iminium intermediate to a more stable and isolable tri-substituted amine. As with the other experiments, no single product was isolated from this reaction.
From the limited number of reactions performed to explore the cycloaddition potential of aminal-diene 507, we learned that, while a tentative argument for iminium and/or aminal-diene formation could have been made based on spectroscopic evidence, the reactions mainly followed alternative pathways. We could not exclude the possibility that small amounts of cycloadducts had been formed, as reactions were typically performed on 1-3 milligrams of aminal 509. We also expected several products to arise from the desired cycloaddition reaction as a result of limited facial selectivity and uncertainty about endo/exo preference. In addition, we expected some isomerization of the C10-C11 enamine olefin of the desired product(s) to the more substituted C10-C22 position. The small scale of the studies in conjunction with the numerous reaction possibilities prevented us from isolating a single product.

In light of the problems encountered with this approach to studying the aminal-diene cyclization, we decided to install an internal dienophile. This was designed to increase endo/exo selectivity, and potentially facial selectivity. The proximity of the diene and dienophile systems was also expected to be increased in an intramolecular reaction system, thereby increasing the likelihood of cyclization.

Section 2.5.5 Attempted In Situ Aminal-diene Formation and Intramolecular [4+2] Cyclization

Installation of an internal dienophile allowed us to more accurately assess the viability of the cyclization reaction as applied to our planned zoanthenol (163) synthesis. We felt it important to demonstrate formation of the quaternary C22 center
through the intended cycloaddition and therefore planned on building a $\beta$-dimethyl enone dienophile (Scheme 2.63). Although methyl substitutions at C9 and C12 were desirable, the increased steric bulk at the reaction centers was expected to hinder our initial studies. It was decided to exclude substitution at these centers until the desired reactivity had been fundamentally proven.

It was believed that the hexacyclic cycloadduct, 546, could arise from an intermediate aminaldiene such as 547, which was expected to form through N-deprotection of aminal 548 and subsequent condensation at C10 (Scheme 2.63). We expected difficulties at this stage as we had previously failed to observed conclusive evidence of iminium or aminaldiene formation in the intermolecular model. We were, however, optimistic that an intramolecular cyclization pathway was more prone to occur.
Scheme 2.63  Retrosynthetic analysis of intramolecular aminal cyclization.

We believed the chemistry developed in our intermolecular study for the formation coupling of the C1-C5 fragment could be applied to the synthesis of dienone (548). Consequently, we planned to synthesize an aldehyde resembling 550 for the lithiate coupling reaction. It was assumed that the enone functionality would necessarily be masked as a group inert to the highly basic coupling conditions. We also drew on previous experience for formation of aldehyde 550, deciding to use a Stille coupling to connect aryl bromide 552 and a suitably protected C6-C12 fragment (551).

The synthesis of aminal 566 began with mono protection of 1,5-pentane diol and oxidation under Swern conditions to aldehyde 553 as previously reported (Scheme
Treatment of aldehyde 553 with ethynyl magnesium bromide provided propargyl alcohol 554. Palladium catalyzed hydrostannylation of propargyl alcohol 555 at low temperature provided a mixture of stannanes. The E-stannane (556) could be isolated in 63% yield by column chromatography, but it was discovered that the difficult separation could be avoided and the crude stannane mixture was used in the Stille coupling, as only the desired E-stannane (556) coupled to aryl bromide 478 under the chosen conditions. Oxidation of primary alcohol 557 with IBX to the corresponding aldehyde (558) proceeded in high yield without the need of purification. Nucleophilic addition of the requisite organocerium reagent provided allylic alcohol 559 as an inseparable mixture of diastereomers. Protection as the MEM ether and subsequent selective deprotection of the primary TBS group gave alcohol 561 in good yield. IBX mediated oxidation provided the coupling substrate, aldehyde 562.
Scheme 2.64  Synthesis of aminal 566.
Lithiation of alkyl iodide 532 followed by addition of aldehyde 562 gave the desired aminal 563 in 62% yield as a mixture of diastereomers. This reaction returned unreacted aldehyde (562) under several different reaction conditions, even when alkyl iodide 532 was used in excess (2 equivalents). Deprotection of the silyl ether with TBAF provided diol 564, which was oxidized to the diketone (565) by Dess-Martin Periodinane. Simultaneous oxidation proved less than ideal, as previously observed in the intermolecular aminal study, and a stepwise process was adopted for subsequent studies.

Gentle heating of aminal 565 in an acetic acid/water (1:1) solution cleaved the acetonide N,O protecting group and provided the rearranged aminal (566). We unfortunately did not find conditions for the MEM ether deprotection. We planned to cleave the MEM group with ZnBr₂ or bromocatechol borane, feeling the Boc group would be stable to these reagents, but were unable to realize the deprotection with these or any other reagents. A product lacking the MEM group was produced in the acetic acid reaction used to form aminal 566, and we felt that continued heating in the acetic acid/water solution may have provided the free allylic alcohol. Unfortunately, heating in acetic acid over extended time frames coupled with close reaction monitoring resulted only in complex reaction mixtures. The Boc group unfortunately proved to be more labile than the MEM group under all deprotection conditions attempted.

Reluctant to surrender the valuable material, aminal 566 was converted to the TBS enol ether as an alternative cyclization substrate (Scheme 2.65). The enolate trapping reaction gave a mixture of products tentatively assigned as an E/Z mixture (567).
Heating of \( 567 \) in deuterated benzene from 100 °C to 205 °C over a period of 40 hours resulted in no discernable spectral (NMR) changes. When a Lewis acid was used, ZnBr\(_2\), only decomposition was observed. Efforts to deprotect the MEM group at this stage resulted in decomposition of the silyl enol ether. Although we failed to deprotect the MEM ether and synthesize the desired cycloaddition substrate (547), we developed chemistry to advanced intermediates.

**Scheme 2.65** Attempted cyclization of silyl enol ether 567.

Having developed a reliable route to aminal 566, we decided to utilize the same chemistry with an alternative protecting group at C20 (Scheme 2.66). Allylic alcohol 559 was therefore protected as the PMB ether (569) as we felt oxidative cleavage of the C20 protecting group to be compatible with conservation of the Boc functionality. Selective deprotection of the primary TBS ether and oxidation to the corresponding aldehyde (571) was achieved in good yield over two steps. Coupling of lithiated alkyl iodide 532 provided aminal 572 in yield similar to that observed for the analogous MEM ether. Oxidation of the C6 hydroxyl group and deprotection of the C10 TBS ether provided allylic alcohol 574 in 80% overall yield. Oxidation of the allylic alcohol
(574) with Dess-Martin Periodinane gave diketone 575 in 60% yield under unoptimized reaction conditions.

Scheme 2.66 Synthesis of diketone 576.

We hoped oxidative deprotection of PMB ether 575 would immediately precede a DDQ mediated one-pot oxidation of the allylic alcohol to afford the C20 ketone in a fashion similar to that previously reported for allylic alcohols.58 While we were unable
to realize the one-pot deprotection/oxidation reaction, DDQ mediated deprotection provided allylic alcohol 576 in 85% yield.

Oxidation of allylic alcohol 576 with Dess-Martin Periodinane gave aminal triketone 549 in excellent yield (Scheme 2.67). Unfortunately, attempts to effect the cycloaddition reaction directly from triketone aminal 549 by heating in acetic acid/water at 100 °C were fruitless. However, heating in acetic acid at a more moderate temperature provided aminal dienone 548 in surprisingly good yield. The deprotection was performed at 50 °C, as we felt the Boc group would be labile in acetic acid/water at higher temperatures, based on the similar Boc deprotection reaction reported by Miyashita and coworkers.29a

![Scheme 2.67 Synthesis of dienone aminal 548.](image)

Numerous attempts, employing different methodologies to induce the desired cycloaddition of 548 were unsuccessful. We expected the reaction to follow the pathway depicted in Scheme 2.68. Acid induced Boc deprotection was expected to initiate condensation at C10 and produce iminium 577. Tautomerization to dienamine
and reaction in an intramolecular cycloaddition reaction was considered, but we suspected the equilibrium would remain far towards the iminium form under acidic conditions. Reactions in acetic acid/water at 100 °C clearly cleaved the Boc group, but failed to provide easily isolable products. Neutralization with sodium carbonate or DBU proved unhelpful. It is interesting to note that mass spectroscopic analysis of reactions performed with acetic acid returned a molecular weight consistent with the iminium ion (378.2), as the major product. This mass happens to correspond to [M+H] for the predicted enamine, as well as the cycloadduct. Regardless of what it actually represented, the MS data strongly suggested the Boc group had been cleaved and an oxygen atom had been lost, both consistent with our proposed route (Scheme 2.68).

Scheme 2.68  Proposed acid induced cyclization pathway.

Stronger acids such as HCl, TSOH, and TFA, failed to provide an isolable product, as did PPTS. Having previously observed Boc cleavage from exposure of Boc aminal 566 to ZnBr₂, an attempt to utilize the Lewis acid as a Boc cleavage reagent and subsequent cycloaddition catalyst was unsuccessful. As with the intermolecular
approach to aminal diene cyclization, interception of the iminium intermediate (577) by reduction with sodium cyanoborohydride was not successful.

As with the corresponding MEM ether, PMB ether 578 (derived from transaminalization of 575) was converted to the silyl enol ether (579) in order to ascertain it’s suitability as a cycloaddition substrate (Scheme 2.69). Treatment of the E/Z mixture (579) dissolved in deuterated benzene at 185 °C, in a sealed NMR tube over 13 hours, generated no reaction. Continued heating at 250 °C resulted in decomposition within a few hours. In consideration of the fact that silyl enol ether 503 underwent an efficient intramolecular cycloaddition reaction, we felt the dienophile of aminal 579 needed to be activated as the corresponding enone. We sought to cleave the PMB ether of 579 and oxidize the resultant allylic alcohol to the corresponding enone. Unfortunately, all attempts at PMB deprotection lead to decomposition of the silyl enol ether functionality.

![Scheme 2.69 Attempted cyclization of silyl enol ether 579.](image)

Scheme 2.69 Attempted cyclization of silyl enol ether 579.
The root cause of the failed aminal diene (547) cyclization attempts was not established. However, we have considered the possibility that the aminal diene tautomer (547) was never formed under the reaction conditions explored. We expected the iminium form (577) to predominate under acidic conditions as previously demonstrated by the Kobayashi, Hirama, and Miyashita groups.\textsuperscript{14,19,29} Yet, we were unsuccessful in attempts to isolate the intermediate iminium or aminal diene by neutralization and iminium reduction with sodium cyano borohydride. It is possible that acid catalyzed enolization of the C20 ketone could have prompted a conjugate addition at the activated C12 β carbon of the iminium functionality, as we have observed similar pyran rings to be stable (Schemes 2.47 and 2.51).

We have also speculated that the iminium/dienamine (547/577) compound may have been produced and undesired reactivity, more favorable than the desired cycloaddition, immediately followed. For instance, it is possible that the iminium was trapped by an acetate molecule in the reactions utilizing acetic acid. The reactions demonstrated by Kobayashi,\textsuperscript{14} Hirama,\textsuperscript{19} and Miyashita\textsuperscript{29} involved iminium formation followed by nucleophilic attack of an internal nucleophile at C10 to form the D ring upon neutralization. It is therefore plausible that C10 attack of an acetate molecule has occurred at C10 of iminium 577.

Additional conjecture involves imine formation at C6. Perhaps the conjugation inherent in the aromatic enone system (C10-C18) thwarted the condensation of the free amine at C10. A lower energy route may have involved imine formation at C6 and opening of the F ring to give the free C2 alcohol. This particular idea may have
precedent. The Williams research group performed a similar reaction with a proposed intermediate iminium similar to our expected intermediate, but was unable to isolate the desired D ring adduct although an internal nucleophile was present (Scheme 2.7)\textsuperscript{22b}, as in the case of work reported by Kobayshi,\textsuperscript{14} Hirama,\textsuperscript{19} and Miyashita\textsuperscript{29}.

We also considered that the dienophile was possibly too hindered at C22 and was not sufficiently electronically activated. Though aminal diene \textbf{547} may have been formed, it is suspected that the withdrawing effect of the C6 aminal position would mitigate the nucleophilicity of the C9 enamine. If this supposition is true, the diene system would not have the activation we hoped for of a dieneamine system.

We sought to explore the question of dienophile activation and dienamine deactivation through more predictable chemistry. To this end we decided to work with substrates with unambiguous and easily characterizable dienamine functionalities, as well as substrates designed to probe the level of necessary dienamine nucleophilicity/activation.

\textbf{Section 2.5.6 Intermolecular [4+2] Cyclizations of Carbamate and Amide stabilized 2-Amino-1,3-Dienes}

Based on the inconclusive results of previous reactions and failure to confirm 2-amino-1,3-diene formation in any cases, we opted for an approach which allowed unambiguous construction of the 2-amino-1,3-diene moiety. The reactivity inherent in enamines which makes them prone to undesired hydrolysis and polymerization reactions can be mitigated by introducing conjugation with \(\pi\) systems. For instance,
many indoles are air stable and easily handled due to conjugation of the aromatic ring. The ability of the enamine nitrogen to donate electron density to the enamine olefin can be diminished by attachment of electron withdrawing groups α to the nitrogen atom. Removal of electron density from the enamine system, while stabilizing the enamine functionality, was expected to render the enamine less nucleophilic and presumably less reactive. However, a search of the literature revealed N-carbamate and N-acyl dienamines capable of cyclizing in a [4+2] manner with activated dienophiles. Moreover, in contrast to unstabilized enamines and dieneamines, the stabilized 2-amino-1,3-dienes appeared to be stable to typical work up and purification techniques such as aqueous extraction and silica chromatography.

Examples of stabilized dienamine systems resembling the C6-18 fragment of zoanthenol (163) have been reported to behave well as dienes in [4+2] reactions (Scheme 2.70). For example, in 2000 Occhiato and coworkers reported cyclization of N-Boc stabilized 2-amino-1,3-diene 581 with an activated dienophile, N-phenyl maleimide (582).59 The endo cycloadduct (583) was isolated in good yield (71%) from the cyclization of 581 and 582. The fact that the direct cycloadduct containing a C10-C11 olefin was not isolated is worthy of note as isomerization of the olefin to C9-C10 offers the possibility for functionalization at C9. The cycloaddition reportedly occurred in a short time frame (2 hours) in concentrated refluxing benzene. Furthermore, the diene was ostensibly stable to typical organic laboratory methods although decomposition to the ring-opened C10 enone was observed upon standing in chloroform solutions.
Scheme 2.70 Carbamate and amide stabilized 2-amino-1,3-diene cyclizations from the Occhiato group.

The Occhiato research group has also reported the cyclization of N-acyl-2-amino-1,3-dienes with phenyl maleimide (582) (Scheme 2.70).\textsuperscript{60} Chiral diene 584 produced a mixture of endo cycloadducts (585 and 586), as well as small amounts of exo cycloadducts, when treated with 582 in cold methylene chloride for extended time periods. After recrystallization, cycloadduct 586 was isolated in 61\% yield. The amide (584) reactivity was particularly exciting as the carbonyl functionality at C6 provided a potential handle for further functionalization leading to the F and G ring system of zoanthenol (163). We were also pleased to see that the remote chiral center induced some facial selectivity. Another aspect of significance to us was the fact that the stabilized diene synthons were both assembled via palladium mediated cross coupling reactions which allowed for diene formation under neutral or basic conditions.
We were also encouraged by additional reports of N-carbamate-2-amino-1,3-diene cycloadditions\textsuperscript{61}, as well as other reported N-acyl-2-amino-1,3-diene cyclizations.\textsuperscript{62} Most of the reports involved highly activated dienophiles such as maleimides, maleic anhydride, fumarates, and maleates, with endo products predominating. In addition to the intermolecular cycloaddition reactions of N-stabilized-2-amino-1,3-dienes, two intramolecular reactions of N-carbamate stabilized 2-amino-1,3-dienes were discovered in recent literature reports.\textsuperscript{63}

We were curious as to whether N-stabilized-2-amino-1,3-dienes retained sufficient enamine nucleophilicity to effect stepwise cyclizations as is assumed of some N-alkyl-2-amino-1,3-dienes\textsuperscript{39,40} previously discussed. We also felt the simplicity and synthetic brevity of the diene substrates would have allowed us to rapidly build analogs with substitution at C9 and/or C12 to probe the effect of increasing steric hindrance within the diene system, as well as investigating steric effects of dienophiles. Initial research involved solvent studies, with the hope that polar solvents may have allowed us to observe linear Michael (single addition) adducts and/or cycloadducts containing stereochemistry impossible to achieve from concerted mechanisms.

N-Boc-stabilized-2-amino-1,3-diene (581) synthesis was achieved by a palladium mediated cross coupling of reported stannane 588 and a N-Boc lactam derived vinyl triflate (590) (Scheme 2.71). Stille coupling of stannane 588 and vinyl triflate (590) provided the diene (581) in yields similar to the Suzuki coupling of a styryl boronic ester and vinyl triflate 590 reported by Occhiato and coworkers, as well as identical spectral data.\textsuperscript{64} Stannane 588\textsuperscript{65} and vinyl triflate 590\textsuperscript{66} were prepared as previously
reported from phenyl acetylene (587) and Boc protected valerolactam (589), respectively. We were happy to find diene 581 easily characterized and stable to silica chromatography.

Scheme 2.71 Synthesis of stannane 581.

As previously reported, we found diene 581 a capable [4+2] diene when reacted with N-protected maleimide (591) (Table.20). Cycloaddition was accompanied by olefin isomerization from C10-C11 to C9-C10 of the cycloadduct in some cases. We were also pleased when a solvent effect was observed in the cycloaddition of diene 581 and N-benzylmaleimide (591) (Table 2.0). Reactions performed at room temperature displayed a loose correlation between relative solvent polarity and reaction rate, with increased solvent polarity resulting in reduced reaction times. It was also interesting to observe rapid reactions in protic solvents such as methanol and trifluoroethanol, as we expected some degree of diene decomposition under protic conditions. Although no intermediates (single Michael addition adducts) were isolated or observed, we initially felt the correlation to solvent polarity suggested a polarized diene transition state. Other researchers have observed similar polarity effects, particularly when protic solvents
were used in catalytic amounts, as co-solvents, or as the lone solvent.\textsuperscript{68} Explanations of this effect generally involve the concept of diene and/or dienophile activation through stabilization of developing charges at reactivity centers. The argument is supported in part by computational studies\textsuperscript{68b} which indicated protic solvents can act as Lewis acids by activating enone dienophiles toward cycloaddition reactions through hydrogen bonding.

Table 2.0 Effect of Solvent on the cyclization of 581 to 592.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Time (25 °C)</th>
<th>Yield</th>
<th>Time (90 °C)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFE</td>
<td>7h</td>
<td>95%</td>
<td>1.5h</td>
<td>99%</td>
</tr>
<tr>
<td>MeOH</td>
<td>9h</td>
<td>99%</td>
<td>2h</td>
<td>99%</td>
</tr>
<tr>
<td>DMSO</td>
<td>9h</td>
<td>91%</td>
<td>2h</td>
<td>90%</td>
</tr>
<tr>
<td>DMF</td>
<td>12h</td>
<td>88%</td>
<td>2h</td>
<td>85%</td>
</tr>
<tr>
<td>DME</td>
<td>12h</td>
<td>80%</td>
<td>2h</td>
<td>78%</td>
</tr>
<tr>
<td>Dioxane</td>
<td>12h</td>
<td>79%</td>
<td>2h</td>
<td>76%</td>
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<td>CH\textsubscript{3}CN</td>
<td>18h</td>
<td>87%</td>
<td>2h</td>
<td>87%</td>
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<td>100h</td>
<td>88%</td>
<td>6h</td>
<td>90%</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{6}</td>
<td>154h</td>
<td>90%</td>
<td>9h</td>
<td>89%</td>
</tr>
</tbody>
</table>

The solvent effect was unfortunately not general. Diene or dienophile decomposition was observed in many cases when additional dienophiles were screened.\textsuperscript{67} In summary, when more sterically hindered or less activated dienophiles were studied, alternative reaction pathways involving reactions of diene 581 and/or dienophiles with the solvent predominated. For instance, use of maleic anhydride as a dienophile in protic solvents resulted in poor yields of cycloadduct 593b (Table 2.1).
However, high yields of the maleic anhydride cycloadduct (593b) were achieved when benzene was used as a solvent.

We also learned that substituents on the dienophile olefin decreased isolated yields. Methyl substitution of maleic anhydride (Table 2.1, entry c) reduced cycloadduct yield relative to maleic anhydride in benzene. The same trend was found to be true for naphthoquinone (Table 2.1, entry d) and methyl-naphthoquinone (Table 2.1, entry e). Although we observed decreased reactivity with substituted dienophiles, we did learn that all isolated cycloadducts fit the expected regiochemical outcome, with the dienophile alkyl substitution (methyl groups) at the C21 position.

This study also revealed that less activated dienophiles such as methyl vinyl ketone (Table 2.1, entry f) did not cyclize in refluxing benzene or other standard solvents. However, a mixture of cycloadduct 593f isomers was obtained when the cycloaddition of 581 and methyl vinyl ketone was performed in ethylene glycol at 80 °C. In the course of this study, diene 581 was demonstrated capable of facile cycloaddition reactions with highly activated dienophiles. Only endo adducts were isolated and the expected regiochemistry was typically observed. Additionally, isomerization of the C10-C11 olefin of the cycloadducts to the C9-C10 position occurred in a seemingly random fashion.
Table 2.1 Cycloaddition reactions of diene 581 with various enone dienophiles.

Having observed a steric effect with substituted dienophiles, we became curious as to whether diene substitution would inhibit cyclization reactions. Unfortunately, cyclization reactions of benzylmaleimide (591) and substituted diene 594 were unsuccessful under a variety of conditions (Scheme 2.72). 

Scheme 2.72 Attempted cyclization of diene 594 with maleimide 591.
We also tested the effect of diene substitution at C12. Synthesis of diene 598 began with methyl-alumination of phenyl acetylene followed by an iodine quench as reported by the Wipf research group.\(^\text{69}\) This sequence gave vinyl iodide 596 in 77% yield. Lithium-halogen exchange and exposure to Me\(_3\)SnCl gave stannane 597 as reported by the Curran research group (Scheme 2.73).\(^\text{70}\) Coupling of 597 with vinyl triflate 590 gave diene 598 in an unoptimized yield of 40%. Unfortunately, cycloaddition reactions between diene 598 and maleimide 591 were unsuccessful under our standard conditions, refluxing methanol or benzene as well as in a variety of other solvents. When more forcing conditions were applied, (sealed tube reactions at higher temperatures) decomposition was observed without clear indication of cycloadduct 599 formation.

**Scheme 2.73**  Attempted cyclization of diene 599 with maleimide 591.

The reactions with diene 581 taught us that activated or highly activated dienophiles were necessary for \([4+2]\) addition under thermal conditions, and methyl substitution at any of the reaction centers hindered or prevented cyclization. We had hoped that
increased substitution, particularly at the β position (C12) of the diene, would have allowed potentially us to isolate a Michael addition intermediate as we felt the second Michael addition would be slowed by increased substitution at the Michael acceptor. This hope was not realized, and we observed no evidence that the reactions followed a consecutive conjugate addition pathway. A final attempt to induce a conjugate addition from the N-Boc-2-amino-1,3-diene (581) was attempted.

We felt an enone dienophile with a β leaving group may have allowed us to isolate a linear Michael adduct (Scheme 2.74). To this end, the reported vinyl sulfone (600) was prepared as described from diethyl malonate derivative 598. Treatment of 598 with catalytic toluenesulphonic acid and excess thiophenol gave sulfide 599, which was easily oxidized to the corresponding sulfone (600) with mCPBA.

**Scheme 2.74  Attempt at single Michael adduct trapping.**

We were curious if stabilized dienamine 581 retained enough nucleophilic character to add to sulfone malonate 600 and displace the sulfone moiety in an addition-
elimination sequence. Unfortunately, neither the desired linear Michael adduct, 601, nor the [4+2] cycloadduct was obtained from reaction of the stabilized dienamine (581) and sulfone (600).

Having explored the reactivity of the N-Boc-stabilized-2-amino-1,3-diene (581), we turned our attention to construction of a corresponding amide diene to further probe cyclization reactivity. The Stille coupling had proven a reliable method for formation of the dienamine functionality in the construction of diene 581, and we felt it prudent to continue with proven chemistry.

However, construction of the desired amido-vinyl triflate (604) proved problematic (Scheme 2.75). Glutarimide (602) was N-alkylated with methyl iodide as previously described, and provided N-methylglutarimide (603) in good yield. Formation of the corresponding triflate (604) under the conditions utilized to construct vinyl triflate 590 was realized in 12% yield. No improvement was observed when alternative triflating reagents were evaluated. This finding is consistent with the observation for a similar N-alkylglutarimide published by Jotham Coe. Coe reported yields below 10% when trapping of a lithium N-alkylglutarimide enolate was attempted with several triflating reagents.

Scheme 2.75 Synthesis of vinyl triflate 604.
However, Coe was able to trap the N-alkylglutarimide enolate as an enolphosphonate and subsequently perform a palladium-mediated Heck reaction. Quantitative conversion to the enolphosphonate and isolation by simple solvent evaporation under an inert atmosphere was reported. Inspired by the Coe report, we explored the enolphosphonate chemistry with our N-alkylglutarimide system. Initial attempts at isolation of the enolphosphonate, 605, proved problematic. Although reaction aliquots analyzed by NMR strongly suggested the desired product had been formed, attempted isolation provided only the starting material (603), presumably due to hydrolysis of 605. In response to this problem, a one pot procedure was developed for the coupling of enolphosphonate 605 and stannane 588, thereby circumventing the problematic isolation (Scheme 2.76). Low temperature enolization of 603 in THF with LiHMDS and subsequent addition of diethylchlorophosphate gave intermediate 605. The solution was warmed to room temperature and stannane 588, lithium chloride, and Pd(PPh₃)₄ were rapidly added.

Scheme 2.76 Synthesis of enol-phosphonate 605 and coupling with stannane 588.

Stirring at reflux several hours typically provided amide-stabilized dienamine 606 in 35-40% yield after hurried silica chromatography. In this manner, diene 606 was
constructed in a total of three reactions beginning from commercially available glutarimide (602) and phenylacetylene (587).

The viability of 2-amido-1,3-dienamine 606 as a cycloaddition partner was explored through reactions with a variety of dienophiles. Our approach to zoanthenol (163) required an enone dienophile and we therefore screened a number of enone cycloaddition partners to assess associated dienophile steric and electronic effects, as well as regioselectivity (Table 2.2). We were surprised to observe good reactivity with a broader range of dienophiles than observed for N-Boc-stabilized-2-amino-1,3-diene 581. When between two and 4 equivalents dienophile were used, entries a through e provided products isolated in 70-90% yields in relatively short time frames.

Cyclization with maleic anhydride to 607a, judged by complete consumption of diene 606 according to NMR analysis, occurred in less than 1.5 hours in methanol, dimethylsulfoxide, acetonitrile, and benzene at room temperature. The corresponding reaction of N-Boc-stabilized-2-amino-1,3-diene 581 required 7 hours in refluxing benzene. Increased dienophile bulk slowed the cyclization, as demonstrated by the reaction performed with citraconic anhydride (Table 2.2, entry b). The citraconic anhydride reaction was complete in 14 hours when performed at room temperature in DMSO, but required heating with other, less polar, solvents to access useful reaction times. Heating at 50 °C in DMSO reduced the reaction time to 1.5 hours and reactions in benzene at this temperature were judged complete within 48 hours. Decomposition of citraconic anhydride with methanol or trifluoroethanol as solvents was observed at room temperature and 50 °C. In methanol at room temperature, diene conversion to
607b was judged at approximately 30% after 4 hours, at which time the citraconic anhydride had been completely consumed. The decomposition pathway of citraconic anhydride with methanol involving ring-opening-monoesterification under neutral conditions has been previously documented by other researchers.\(^7\) Regardless of the solvent or temperature, only the endo adduct containing the predicted regiochemistry was isolated. Single crystal x-ray analysis of 607b confirmed the structural assignment of 607b made by 2D NMR techniques. All other major cycloadducts displayed similar 2D NMR results, and have been assigned as endo cycloadducts.
Table 2.2 Reactivity of diene 606 with various dienophiles.

<table>
<thead>
<tr>
<th>entry</th>
<th>dienophile</th>
<th>solvent</th>
<th>°C</th>
<th>time (hours) complete diene consumption</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>maleic anhydride</td>
<td>C₆D₆</td>
<td>22</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CD₃CN</td>
<td>22</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DMSO-D₆</td>
<td>22</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CD₃OD</td>
<td>22</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>citraconic anhydride</td>
<td>C₆D₆</td>
<td>50</td>
<td>48</td>
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</tr>
<tr>
<td></td>
<td></td>
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<td>50</td>
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</tr>
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<td>22</td>
<td>*4</td>
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<tr>
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<td></td>
<td></td>
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<td>33</td>
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<td>CD₃OD</td>
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</tr>
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<td>C₆D₆</td>
<td>22</td>
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<td></td>
<td></td>
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<td>46</td>
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<td>DMSO-D₆</td>
<td>80</td>
<td>15</td>
<td></td>
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</tbody>
</table>

Reaction with methyl vinyl ketone, a less activated enone, also proved facile. As observed with the anhydride dienophiles, only the endo adduct containing the predicted regiochemistry (607b) was isolated. A similar rate trend was also observed, with rapid reaction in methanol at room temperature (2 hours) compared to more sluggish reaction
in benzene at the same temperature (33 hours). Heating at 80 °C in benzene decreased the reaction time to 2 hours, but did not change exo/endo or regioselectivity as compared to room temperature reactions. The cyclization with methyl vinyl ketone in DMSO, benzene, and methanol at room temperature was exceptionally interesting as the cyclization of N-Boc-diene 581 with methyl vinyl ketone failed in refluxing benzene.

Cyclization attempts of N-Boc-diene 581 with acrylates were unsuccessful. However we observed cyclization of N-amide diene 606 with methyl acrylate (Table 2.2, entry d) and methyl methacrylate (entry e). Room temperature reactions in DMSO and benzene required 46 hours and greater than 4 days, respectively, to reach completion. In addition to the endo cycloadduct, formation of a trace amount of a product tentatively identified as the exo isomer was observed. The diastereomeric product ratio did not change when the reaction was performed at 80 °C in DMSO.

Reactions with methylmethacrylate required heating when performed in DMSO or benzene. In this case, a mixture of endo/exo isomers was obtained. The solvent did not affect the endo selectivity, as very similar product ratios were obtained from reactions in DMSO and benzene. The reduced endo selectivity associated with acrylates has been reported\textsuperscript{74} and we attribute this phenomenon to decreased secondary orbital interactions due to the delocalization of electron density associated with esters relative to ketones and anhydrides. As with other enones, only the predicted regiochemistry was observed.
Strong regioselectivity was observed for all reactions with N-Amide-diene 606. We ascribe this to the polarization of the diene, as bond formation between the electron-rich diene C9 and electron-poor dienophile C22 was expected to be favored.

We also observed decreased reaction rates with increased dienophile substitution (Table 2.2, entries b and e). Reactions with mesityl oxide (4-methylpent-3-en-2-one) and 2,3-dimethylmaleic anhydride, designed to demonstrate formation of a quaternary C22 position, proved problematic. Forcing conditions (high temperatures and sealed tubes) were necessary to observe reaction with these hindered dienophiles, and only complex mixtures were obtained. This was a disappointing discovery as we intended to form a quaternary center (C22) through an intramolecular dienamine cyclization.

Another interesting observation was the lack of olefin isomerization from C10-C11 to C9-C10 in the amide products, although commonly observed in the N-Boc-dieneamine reactions. Rapid decomposition to a complex mixture was observed when isomerization of the maleic anhydride adduct (607a) was attempted by room temperature solvation with deuterated chloroform. This is in contrast to the N-Boc-dieneamine adducts, as clean isomerization was commonly induced under this condition. Decomposition during silica chromatography was also extensive for the 607 cycloadducts.

We do not currently have an explanation for the failure of olefin isomerization to a more substituted position. However, we have speculated that a cyclic enamide structure containing an endocyclic olefin (C9-C10) could induce ring strain as the resonance
structure of the amide creates partial olefin character between the nitrogen and C6 carbonyl (Scheme 2.78). Resonance form 610 contains a conjugated cyclohexyl diene system, which would necessarily perturb the typical valerolactam bond angles. Perhaps this particular resonance form was responsible for increased reaction rates relative to the N-Boc-dienamines. Strain associated with the resonance form would limit the electron-withdrawing effect of the amide carbonyl, and presumably reduce stability of the dienamide system. If significant in the reactive diene, the strained resonance form could potentially have been relieved through cyclization. This presumably would have been manifested through increased reaction rates.

Scheme 2.77 Tautomeric and resonance forms of enamide 608 and enecarbamate 611.

The analogous resonance form of the N-Boc-diene adducts (613) would not create a transient endocyclic double bond, but rather an exocyclic bond. Experiments involving cycloaddition with an analogous acetamide diene system (exocyclic amide) and subsequent olefin isomerization experiments could shed light on this proposal.
It is worthy of note that carbamate vinyl triflate 590 was isolated in good yield and could be stored for extended time periods in the absence of acid. The corresponding amide vinyl triflate (604) was isolated in only 12% yield and decomposed completely within several days when stored at -30 °C.

In summary, both carbamate and amide stabilized-2-amino-1,3-dienamines exhibited cycloaddition reactivity. Dienophile activation as an enone, anhydride, or maleimide was necessary. Diene decomposition, particularly with the carbamate-stabilized dieneamine, frequently occurred in reactions with less activated dienophiles as heating for extended time periods was typically necessary. We were also unable to set a C22 quaternary center with these diene systems.

Section 2.5.7 Intramolecular [4+2] Cyclizations of Carbamate and Amide stabilized 2-Amino-1,3-Dienes

We continued studies with stabilized dienamine systems to ascertain the practicality of their use in intramolecular cycloaddition reactions. We considered intramolecular reactions likely to increase diene and dienophile proximity, and thereby allow the use of less activated and more sterically hindered dienophiles. Additionally, we felt cyclization of a C6 amide would justify the reaction as an approach to the synthesis of zoanthamide (165). The E ring of zoanthamide (165) contains a C6 amide and N-alkyl substitution, just as in our proposed cycloadduct. We also felt it was important to maintain continuity with the intermolecular studies and compare reaction rates.
We felt tetracyclic cycloadducts 614 and 615 could have arisen from triene systems 616 and 617 (Scheme 2.79). We planned to form the important C12-C13 bond as previously done in the initial zoanthenol (163) studies (Section 2.5.2) through a palladium-mediated cross coupling reaction utilizing aryl halide or aryl triflate 618 as a common intermediate for each substrate. We planned to construct stannane 619 from the easily accessible vinyl triflate 590 through a Stille coupling with a 1,2-bis-trialkyltin ethene moiety. A similar approach for the amide analog (620) was planned, although we understood the vinyl triflate (621) would have most likely been replaced by a phosphonate functionality, based on results from the intermolecular studies. We planned to build the vinyl triflate and/or vinyl phosphonate coupling partners (590/621) as previously described (Section 2.5.6).

**Scheme 2.78** Retrosynthetic plan for stabilized diene intramolecular cyclizations.
We devised a plan outlined in Scheme 2.80 with the aim of addressing whether or not IMDA reactions would render, otherwise unreactive dienophiles capable of the thermal cycloaddition with stabilized dienamines. We had previously determined acrylates to be insufficiently activated to react with a N-carbamate stabilized dienamine (581) under typical thermal Diels-Alder conditions and felt pursuing an analogous intramolecular reaction could provide insight into diene/dienophile reactivity thresholds. Consequently, we devised a simple synthetic route for rapid development of triene 629. 2-Bromophenol (624) was coupled to β-disubstituted acrylic acid (625) to provide acrylate 626 with excellent efficiency. Coupling of acrylate 626 and trans-1,2-Bis(tri-n-butylstannyl)ethylene (627) provided stannane 628 in poor yield (25%). Although stannane 628 was the only compound isolated from two reaction attempts, we did not have a clear explanation for the low yield. We felt the use of excess 627 would limit the amount of Heck adduct and curb dimerization of 628 and 626. Nonetheless, the coupling of 628 and vinyl triflate 590 was evaluated. The reaction produced the cyclization substrate, triene 629 in low yield.
The coupling yields were unacceptably low, so an alternative route to triene 629, also relying on Stille coupling chemistry, was implemented (Scheme 2.80). Vinyl triflate 590 was coupled to bis stannane 627 in order to access diene stannane 619. Diene stannane 619 was isolated in modest yield (50%) although spectroscopic reaction monitoring had suggested the reaction operated more effectively. The purification was problematic and likely responsible for material loss. Purification attempts with triethylamine-neutralized silica and neutral alumina failed to provide better results than were obtained with typical silica chromatography. Unfortunately, these reactions were performed on small scale, making distillation difficult. Nevertheless, stannane 619 did serve as an acceptable Stille coupling partner with acrylate 626. Triene 629 was assembled in slightly better yield via this particular coupling, but triene 629 failed to cyclize when heated in deuterated benzene or deuterated DMSO. When temperatures of 160 °C (benzene) and 130 °C (DMSO) were reached, decomposition to complex
mixtures was observed. The intramolecular acrylate cyclization remains largely unstudied due to limited availability of 629 and interest in more promising chemistry. The limited data did however suggest that an activated dienophile would be necessary for clean cyclization.

We also learned that coupling of bis-stannane (627) or diene stannane (619) to aryl bromide (626) was problematic with regard to scalability. Having previously observed coupling of styryl stannane 588 and vinyl triflate 590 to be efficient with production of a relatively easily purified diene (581), we modified the synthetic route to incorporate styryl stannane 631 derived from phenyl acetylene (632) (Scheme 2.81). We felt diene 630 could be constructed in sufficient quantity based on previous experience and hoped triene 616 could be constructed via oxidation and Grignard reactions without destroying the 2-aminodiene moiety if acidic reaction conditions could be avoided.

Scheme 2.80  Alternative retrosynthetic plan to triene 616.

Aryl iodide (633) was prepared by borane-mediated reduction of the corresponding carboxylic acid or via a nickel-mediated transhalogenation from the analogous aryl bromide (478) (Scheme 2.82). Sonogashira coupling with TMSacetylene and subsequent TMS removal provided phenyl acetylene 635 in excellent yields. Unfortunately, geminal stannane (636) was isolated as the major product from
palladium or radical mediated hydrostannylation attempts, and the desired trans stannane (631) was never isolated in greater than 10%. We suspected the C20 alcohol may have played role by directing the hydrostannylation. For this reason, the alcohol was protected with silyl protecting groups of different bulk and stability (637 and 639). Palladium and radical mediated hydrostannylation of protected phenyl alkynes 637 and 639 produced similar mixtures of stannanes, with the geminal stannane the predominant isomer. Although the desired trans-stannane was a minor constituent, the stannane mixture was used in coupling attempts with vinyl triflate 590. We were disappointed when no coupling was observed under the previously developed Pd\(^0\)/LiCl conditions.

Scheme 2.81 Attempted synthesis of styryl stannane 631.

In light of the difficulty producing the desired styryl stannane, we opted for a more promising alternative route to diene 630 (Scheme 2.83). Coupling of aryl iodide 641 with bis-stannane 627 gave styryl stannane 631 in an unoptimized yield of 53%. A single attempt at coupling of 631 with vinyl triflate 590 resulted in a surprisingly low yield of the desired diene, 630. Sufficient material was however synthesized for
unsuccessful pyridine-buffered oxidation attempts with IBX and Dess-Martin periodinane. Instead of observing aldehyde (642) formation, only complex mixtures due to diene decomposition were observed.

**Scheme 2.82** Synthesis of diene 630.

Diene decomposition (630) under mild oxidation conditions influenced our decision to functionalize the dienophile prior to installing the diene moiety as in the synthesis of the acrylate triene (629) (Scheme 2.84). Aryl iodide 641 was efficiently oxidized to the corresponding aldehyde (645) by IBX in refluxing acetonitrile without the need for purification after filtration through fluorosil. The less-costly Swern oxidation conditions provided the aldehyde (645) in low yields as a minor component of complex mixtures. Conversion of the Grignard reagent (492) to the equivalent organocerium reagent and aldehyde addition provided allylic alcohol 646 in useful yields. Coupling of allylic alcohol 646 and bis-stannane 627 gave stannane 647 in low yield, along with Heck adduct 648. Stannane 647 was coupled with vinyl triflate 590 with success similar to that previously observed (conversion of 631 to 630, Scheme 2.83).
Scheme 2.83 Synthesis of tetracycle 614.

Significant optimization led to conditions that allowed for isolation of 649 in 56% yield as the product of Stille coupling between 646 and 619. Excess stannane (1.5 – 2.0 equivalents 619) and solventless reactions provided the best results. Triene 616 was isolated in 60% yield as the IBX oxidation product of allylic alcohol 649.

The intramolecular cycloaddition of 616 was studied in a number of solvents. High temperatures (typically 200 °C or more) and non polar solvents (xylenes) gave the best results when reactions were performed in sealed NMR tubes. More polar solvents (trifluoroethanol, acetonitrile, methanol, and DMSO) failed to provide the cycloadduct 614 as judged by NMR, and instead prompted extensive triene decomposition. This was surprising as we had previously observed dramatic rate increases with these specific solvents in intermolecular reactions (Tables 2.0 and 2.2). Limited attempts to
increase cyclization efficiency with Lewis acids (ZnCl₂ and ZnBr₂) were unsuccessful, as mixtures of Boc-deprotected products were obtained.

Reactions performed in deuterated xylene appeared, by NMR monitoring, to produce the cycloadduct (614) relatively cleanly at lower temperatures, but the reaction rate was prohibitively slow. At higher temperatures (190 °C and greater) Boc cleavage was observed and isolated yields were low, typically around 20%. As previously observed, material loss was observed in the form of extensive decomposition during purification.

It should be noted that the stereochemical assignment of 614 relies heavily on observance of a large coupling constant, indicative of axial proton coupling, between the protons of C12 and C21. 2D proton and carbon experiments were utilized to assign a clearly visible doublet at 1.7 ppm to the C21 proton. The coupling constant of 12 Hz suggested a trans ring junction as pictured in Scheme 2.84.

When triene 616 was heated in benzene with two equivalents benzyl maleimide (508), relatively quick cyclization to the corresponding endo cycloadduct (650) was observed at 90 °C (Scheme 2.85). This reactivity was very similar to the cycloaddition observed between 581 (616 analog without the C19-C23 enone side chain) and benzyl maleimide 508 (Table 2.0). This finding suggested the enone dienophile, although an intramolecular reactant, was not sufficiently activated to allow efficient cyclization under mild thermal conditions.
The belief, based on the maleimide (508) competition experiment, that the enone dienophile would not provide sufficient reactivity and failure of rate promotion by polar solvents prompted us to design an internal dienophile with increased electronic activation in attempt to encourage cycloaddition at lower temperatures. We believed a 1,4 diketo-enone dienophile, such as triene 658, could greatly increase cyclization efficiency (Scheme 2.86). The attempted synthesis of 658 began by lithiation of methyl furan (651) and addition of the lithiate to benzyl bromide 653. Benzyl furan 654 was obtained in acceptable yield in this manner, along with dimerization product 653. Oxidative furan opening with mCPBA of 654 provided a more polar compound as the major product tentatively identified as lactol 655. We believed the lactol (655) tautomer of the desired 1,4 diketone predominated due to the enolizability of the C20 ketone position, which extends conjugation to the aromatic ring. However, a minor product was isolated and tentatively identified as the desired 1,4 diketone based on proton NMR comparison to the known, corresponding des-iodo compound (see experimental section for details). Attempted coupling of 619 and lactol 655 was
unsuccessful under typical coupling conditions. Unfortunately, no products were isolated from the single coupling attempt so reaction optimization was not possible.

Scheme 2.85 Attempted synthesis of triene 658.

Fortunately, coupling at an earlier stage, 654, was successful. Diene 657 was formed in good yield (62%) under standard coupling conditions with stannane 619. Unfortunately, oxidative opening of the furan moiety contained in 657 was not realized. Crude reaction analysis of two reactions performed with mCPBA revealed the loss of the C11-C12 olefin, which lead us to suspect epoxidation had occurred across the C11-C12 olefin.

Work being conducted simultaneously to circumvent the problems attributed to Boc lability showed promise (Scheme 2.87). Valerolactam (623) was protected as the methyl carbamate as previously reported. The corresponding triflate was synthesized in the same manner as previously described for the Boc analog (590) and gave spectroscopic data identical to that previously reported.  

Palladium coupling with bis-
stannane \textbf{627} provided stannane \textbf{661}, which was coupled to aryl iodide \textbf{646} with yields similar to those obtained for the analogous Boc compounds. IBX oxidation of coupling adduct \textbf{662}, provided triene \textbf{663} in acceptable yield. Cyclization of \textbf{663} was more efficient than reaction of the corresponding Boc analog (\textbf{614}). Treatment in deuterated bromobenzene at 200 °C over 11 hours provided cycloadduct \textbf{664} in 65% isolated yield. Reaction monitoring by NMR showed the methyl carbamate group to be stable at 200 °C and suggested clean formation of cycloadduct \textbf{664}. Unfortunately, purification was again problematic, however neutral alumina chromatography allowed for reasonable product isolation.

![Scheme 2.86](image)

**Scheme 2.86** Synthesis of methyl carbamate tetracycle \textbf{664}.

Interestingly, only the isomerized cycloadduct (C9-C10 olefin) was isolated. The reason for this is not clear, however we suspect the internal, tetrasubstituted, olefin (C9-C10) to be more stable than the trisubstituted exo olefin (C10-C11). In addition to
increased carbamate thermal stability, we partially attribute the higher isolated yield of cycloadduct 664 to more rapid in situ olefin isomerization. In each case, only the exo cycloadducts were isolated.

In order to explore the intramolecular amide cyclization reaction, we employed the methodology developed for construction of dienamine 606 (Scheme 2.88). Vinyl phosphonate 605 was prepared in the same manner as previously discussed and Stille coupling with bis-stannane 627 via a one-pot procedure provided diene stannane 665. Several reactions at varied concentrations and ratios of stannane 627 to N-methylglutarimide (603) failed to provide the desired product (665) in yield greater than 15%. However, neat coupling of aryl iodide 646 with diene stannane 665 gave triene alcohol 666 reliably in 55% yield, and IBX oxidation of allylic alcohol 666 provided triene 667 in excellent yield. It should be noted that IBX oxidation of the analogous carbamate trienes (616 and 663) typically provided yields in the 60% range. This observation was interesting as we viewed the dienamide and N-carbamate-dienamine functionalities as moieties distant from the C20 allylic alcohol and unlikely to effect the oxidation reaction.
Scheme 2.87  Synthesis of amide tetracycle 668.

Triene 667 was found to be more prone to cyclization at lower temperature than the analogous carbamates (616 and 663). Synthetically useful reaction progress was observed in reactions performed at 150 °C in deuterated bromobenzene, while no cyclization was detected at this temperature in trienes 616 and 663. Additionally, cyclization occurred in acetonitrile, although not as cleanly as when performed in bromobenzene. However, reactions performed in deuterated acetone, methanol, and DMSO failed to provide the cyclization adduct 668, instead producing complex mixtures of products. Isomerization of the C10-C11 olefin cycloadduct to the C9-C10 olefin cycloadduct could be followed by NMR. While cyclization occurred at lower temperatures, we found reaction in bromobenzene at 200 °C to be ideal for promoting the cyclization and the subsequent olefin isomerization within a twelve hour time period. Structural assignment of enamide 668 by 2D NMR techniques was supported
by single crystal x-ray diffraction analysis. As with the corresponding N-carbamate
dienamines, isolation proved problematic, and only the exo product was isolated.

Exo Cycloaddition of carbamate stabilized 2-amino-1,3-dienamines 616, 663, and
667 to tetracycles 614, 664, and 668 provided proof of concept for an intramolecular
cycloaddition approach to zoanthenol (163). Our cyclization substrates lack methyl
substitution at C9 and C12, and therefore represent minimized model systems.
Importantly, the C22 quaternary center was constructed through this methodology and
we suspect modifications at C22 to an enone more appropriately functionalized
(containing components of the D ring lactone) for zoanthenol (163) synthesis would not
inhibit cycloaddition. Installation of the C12 methyl group prior to cyclization would
likely hinder the cyclization and require more forcing conditions, but may be feasible as
we have observed significant reactivity with the dienamido system.

Once again we were surprised by the dramatic difference in reactivity between an
amide diene and analogous carbamate dienes. Simple electron pushing suggests the
very groups which stabilize the amino-diene functionality would limit the amount of
electronic donation into the diene system by the nitrogen lone pair. The amide group is
assumed to have a more significant withdrawing effect than carbamate groups, yet we
observed increased reactivity with the amido diene substrates. However, empirical data
collected over the course of this research creates doubt as to which group, amide or
carbamate, displayed a more significant withdrawing effect (Table 2.3). Carbon NMR
may be used as a method for assessing relative electronic wealth for individual carbon
atoms as demonstrated by chemical shift. The relative chemical shift of the C9 carbon
of diene systems 616, 663, 667, and 503 correlates with observed cycloaddition efficiency. Diene systems with greater electron density at C9, as determined by $^{13}$C chemical shift, displayed shorter reaction times and higher isolated yields. The most efficient [4+2] reaction was achieved with silylenol ether diene 503 as the triene system. Not coincidentally, triene 503 also displayed the furthest upfield signal for C9, 96.7 ppm. The fact that amide 667 displays a C9 signal at 107.0 ppm, vs. ~115 ppm for the carbamate analogs, suggests the nitrogen atom of amide 667 actually funnels more electron density into the diene system than the corresponding carbamates (616 and 663).

**Table 2.3** Diene 616, 663, 667, and 503 C9 $^{13}$C NMR shifts.

![Diene NMR Signals](image)

The chemical shift data is not in accordance with our predictions related to relative C9 electron density and therefore intimates that a rationalization will require additional parameters beyond simple arrow pushing to evaluate the degree of electron withdrawal
of the stabilizing groups. As previously discussed, conformational effects related to the cyclic amide may mitigate the degree of electron withdrawal. Unfortunately, examples of appropriate acyclic 2-amido-1,3-diene systems for $^{13}$C NMR comparison could not be found in the literature.

**Section 2.6 Concluding Remarks**

While we were initially concerned about biasing the reaction toward a stepwise consecutive conjugate addition route, C10-C11 olefin isomerization to C9-C10 has mitigated this concern, as isomerization destroys the C9 stereocenter formed in the cycloaddition reaction. In fact, if the C9 methyl group could be installed at a later time, a concerted cycloaddition mechanism may be preferable as it allows for easily predicted stereochemical outcome and would allow for appropriate functionalization ($E/Z$) at the C22 olefin center in the cycloaddition substrate(s).

Alkylation at C9 through enamine methodology could potentially be utilized to install the C9 methyl group, although attempts to alkylate enamide 668 by heating in the presence of excess methyl iodide failed to provide reaction at moderate temperatures, and resulted in decomposition when heated in a sealed tube at 100 °C. An interesting alternative would be to borrow methodology demonstrated by the Hirama research group (Schemes 2.17 and 2.19).$^{27}$ Cyclopropanation of enamide 668 would give a cyclopropane ring with an attached electron donating group, in the form of the C10 nitrogen atom (669) (Scheme 2.89). The nitrogen atom could presumably direct an acid-mediated regioselective cyclopropane opening to give C9-methylate tetracycle 670
as demonstrated by Hirama with an analogous C10 tertiary alcohol functionality. The question of stereoselectivity involving a potential cyclopropanation is not easily answered as the solid state confirmation of 668, as demonstrated by single crystal x-ray analysis, suggests equal facial accessibility. Perhaps stereoselective reduction of the C20 ketone to an alcohol would allow the alcohol, or a derivative thereof, to serve as a directing group. Fortunately, numerous examples of stereoselective enamide cyclopropanation exist in the literature. Further exploration of these ideas would require optimization of the current route or development of an alternative, more scalable route to triene cyclization substrate 667.

![Scheme 2.88 Proposed cyclopropanation methodology to install C9 methyl group.](image)

Two approaches to zoanthamine alkaloids have been presented. The 1st generation approach established a stereoselective route to the ABC ring system of zoanthamines 150, 151, 154, and 155. The strategy, which relied heavily on Robinson annelation chemistry, allowed construction of an advanced tricyclic intermediate (369) containing the fully functionalized A and B rings. Functionalization of two C-ring stereocenters (C10 carbonyl and C29 methyl) was lacking. These issues were resolved after much experimentation using a BC ring system model. The penultimate BC ring system model
(402) included a fully functionalized C ring (including the C10 ketone and stereochemically correct C9 methyl group) with substituents amenable to further functionalization toward the D and E rings, as well as B ring functionalization previously proven capable of effecting A ring formation.

A second generation strategy designed around a 2-amino-1,3-diene cycloaddition was explored on minimized zoanthenol (163) scaffolds. Attempts at in situ formation of the 2-amino-1,3-diene moiety via intermolecular and intramolecular amine condensations were stymied by alternative reactivity and limited material due to lengthy synthetic routes. However, synthetic routes to advanced intermediates have been developed and the groundwork has been layed for future work in this area.

In the course of this study, we observed an efficient silyl-enol ether diene cycloaddition which culminated in a minimized zoanthenol (163) ABC ring scaffold. The [4+2] reaction constructed rings B and C in a single step with the desired C12-C21 ring junction stereochemistry via an exo transition state.

Finally, we were able to demonstrate several cycloaddition reactions with N-stabilized 2-amino-1,3-dienes. Of particular note were the intramolecular reactions of carbamates 616, 663, and amide 667. We are aware of only two reported N-carbamate stabilized 2-amino-1,3-diene intramolecular cycloadditions63 and no previous N-amide stabilized 2-amino-1,3-diene intramolecular cycloaddition reactions. This work therefore represents an early entry into the study of underutilized electron rich diene
moieties. The dienes studied were also shown to demonstrate excellent regiocontrol in both intramolecular and intermolecular reactions.

A subtle, but very important, observation was the cycloadduct olefin isomerization which occurred in many of the [4+2] reactions. The isomerization renders the question of whether the reactions follow a concerted or stepwise mechanism superfluous, as the C9 stereocenter is necessarily destroyed in the isomerization.

Cycloadditions with dienamide moieties proved surprisingly facile, and the intramolecular cyclization of 667 is of synthetic interest. Although our intramolecular model bore an aromatic A ring, we feel the 2-amido-1,3-diene methodology developed to be applicable to a zoanthamide (165) total synthesis.

An additional attribute of the intramolecular cycloaddition research was the rapid development of the triene cyclization substrates via concise synthetic routes. Palladium-mediated cross coupling proved a reliable, although not always efficient, method for constructing the compulsory diene functionality. Reaction optimization associated with the cross coupling methodology for N-stabilized 2-amino-1,3-diene systems is merited due to the compatibility with convergent synthetic routes and ability to form reactive systems otherwise difficult to access.

Appendix Experimental Information

Section A.1 General Techniques

All reagents were obtained (Aldrich, Acros) at the highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive
liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. All non-aqueous reactions were carried out under anhydrous conditions, *i.e.* using flame-dried glassware, under an argon atmosphere and in dry, freshly distilled solvents, unless otherwise noted. Repeated extractions were performed to obtain all products, as judged by TLC. Yields refer to chromatographically and spectroscopically (\(^1H\) NMR, \(^13C\) NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) and visualized under UV light and/or developed by dipping in solutions of ceric ammonium molybdate (CAM) or p-anisaldehyde and applying heat. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. NMR spectra were recorded on Varian Mercury 300, 400, Varian Unity 500, and/or Jeol eca 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Nicolet 320 Avatar FT-IR spectrometer and values are reported in cm\(^{-1}\) units. High resolution mass spectra (HRMS) were recorded on a ThermoFinnigan MAT900XL under fast atom bombardment (FAB) conditions with 3-nitrobenzyl alcohol matrix and polyethylene glycol reference. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

Section A.2  Experimental Procedures and Data

**Compound 434:** Phenol 433 (440 mg, 3.55 mmol) was dissolved in methylene chloride (5 mL), cooled to -78 °C and NEt\(_3\) (1.6 mL, 12.8 mmol) was added in one portion. Triflic anhydride (0.84 mL, 5.0 mmol) was added dropwise over 5 minutes, and the solution was allowed to warm to room temperature. After 10 hours at room temperature, the solution was cooled to 0 °C. Approximately 1 mL NEt\(_3\) was added prior to diluting with diethyl ether and water. The mixture was washed with aqueous NH\(_4\)Cl, dried over MgSO\(_4\), and concentrated. Column chromatography provided triflate 434 (689 mg, 65%). TLC (ethyl acetate/hexanes 1:3): R\(_f\) = 0.2; \(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.55 (s, 3H), 3.83 (s, 3H), 6.91 (d, \(J = 8.4\) Hz, 1H), 6.97 (d, \(J = 8.4\) Hz, 1H), 7.41 (t, \(J = 8.4\) Hz, 1H).

**Compound 438:** Triflate 434 (104 mg, 0.29 mmol) was dissolved in THF (3.0 mL) under argon at room temperature. Stannane 437 (103 mg, 0.35 mmol) was added to 434 under an argon flow. PdCl\(_2\)(PPh\(_3\))\(_2\) (4 mg, 0.006 mmol) was added to the reaction flask, followed rapidly by LiCl (35 mg, 0.82 mmol). The reaction was
stirred at room temperature 10 hours. A saturated NaHCO₃ aqueous solution was added, and a diethyl ether extraction performed. The organic extracts were combined and dried over MgSO₄. Concentration and column chromatography provided allylic alcohol 438 as an oil (23 mg, 37%). TLC (ethyl acetate/hexanes 2:3): Rₜ = 0.1; ¹H NMR (400 MHz, CDCl₃): δ 1.34 (d, J = 6.0 Hz, 3 H), 2.50 (s, 3 H), 3.83 (s, 3 H), 4.44 (m, 1 H), 6.20 (dd, J = 6.4, 15.6 Hz, 1 H), 6.49 (d, J = 15.6 Hz, 1 H), 6.81 (d, J = 8.0 Hz, 1 H), 7.13 (d, J = 8.0 Hz, 1 H), 7.28 (t, J = 8.0 Hz, 1 H); ESI-MS: m/z calcd. for C₁₃H₁₆O₃Na₁: 243.10, found: 243.12 [M+Na]⁺.

**Compound 440:** To a flask containing phenol 433 (459 mg, 2.77 mmol) in methylene chloride (5 mL), was added Hunig's base (1.0 mL, 5.74 mmol) at 0 °C. MOMCl (0.3 mL, 3.95 mmol) was added and the solution was allowed to warm to room temperature. After 13 hours stirring, water was added prior to diluting with diethyl ether and washing with aqueous NaHCO₃. The extracts were dried over MgSO₄ and concentrated. Column chromatography provided MOM ether 440 (401 mg, 69%). TLC (ethyl acetate/hexanes 3:2): Rₜ = 0.6; ¹H NMR (400 MHz, CDCl₃): δ 2.49 (s, 3 H), 3.45 (s, 3 H), 3.80 (s, 3 H), 5.15 (s, 2 H), 6.59 (d, J = 8.4 Hz), 6.75 (d, J = 8.4 Hz), 7.23 (t, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 202.5, 156.6, 154.0, 138.2, 130.5, 107.3, 104.8, 94.5, 56.2, 55.8, 32.3; ESI-MS: m/z calcd. for C₁₁H₁₄O₄Na₁: 233.08, found: 233.08 [M+Na]⁺.

**Compound 441:** Ph₃PClCH₂OMe (2.0 g, 5.22 mmol) was dissolved in THF (5 mL) under argon and cooled to -78 °C. A 1 M THF solution of NaHMDS (5 mL, 5.0 mmol) was added rapidly. After stirring 2 hours, ketone 440 (186 mg, 0.89 mmol) was added as a THF (2 mL) solution. The reaction mixture was allowed to warm to room temperature after 16 hours at -78 °C, and then stirred an additional 30 hours before the solution was diluted with diethyl ether and quenched with water. Extraction with ether, exposure of the organic layers to MgSO₄, concentration, and column chromatography gave enol ether 441 as an oil (42 mg, 20%). TLC (ethyl acetate/hexanes 3:4): Rₜ = 0.6; ¹H NMR (400 MHz, CDCl₃): δ 1.87 (d, J = 1.6 Hz, 3 H), 3.46 (s, 3 H), 3.66 (s, 3 H), 3.79 (s, 3 H), 5.14 (s, 2 H), 5.93 (s, 1 H), 6.59 (d, J = 8.4 Hz, 1 H), 6.75 (d, J = 8.4 Hz, 1 H), 7.14 (t, J = 8.4 Hz, 1 H).

**Compound 443:** Enol ether 441 (88 mg, 0.37 mmol) was dissolved in acetone (1 mL) and water was added (0.1 mL). 1 drop aqueous HBR (48%) was added to the solution at room temperature. After stirring 50 minutes, the solution was diluted with diethyl ether and a saturated NaHCO₃ aqueous solution was
added. Ether extraction, drying of the combined organic layers with MgSO4, concentration, and column chromatography provided aldehyde 443 as an oil (56 mg, 70%). TLC (ethyl acetate/hexanes 1:3): \( R_f = 0.4 \); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.34 (d, \( J = 6.8 \) Hz), 3.45 (s, 3H), 3.80 (s, 3H), 3.94 (q, \( J = 6.8 \) Hz, 1H), 5.16 (s, 2H), 6.62 (d, \( J = 8.4 \) Hz, 1H), 6.79 (d, \( J = 8.4 \) Hz, 1H), 7.21 (t, \( J = 8.4 \) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 202.9, 158.0, 155.7, 128.7, 117.2, 107.0, 104.8, 94.4, 56.2, 55.7, 42.8, 12.7.

**Compound 442:** Lactol 442 was isolated as a side product of the aldehyde 443 synthesis reaction. TLC (ethyl acetate/hexanes 1:3): \( R_f = 0.3 \); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.29 (d, \( J = 7.2 \) Hz, 3H), 3.31 (dq, \( J = 1.2, 7.2 \) Hz, 1H), 3.83 (s, 3H), 5.58 (s, 1H), 6.47 (d, \( J = 8.0 \) Hz, 1H), 6.51 (d, \( J = 8.0 \) Hz, 1H), 7.13 (t, \( J = 8.0 \) Hz, 1H); ESI-MS: \( m/z \) calcd. for C\(_{10}\)H\(_{12}\)O\(_3\)Na\(_1\): 203.07, found: 203.08 [M+Na]\(^+\).

**Compound 444:** Aldehyde 443 (55 mg, 0.25 mmol) was dissolved in THF (3 mL) and cooled to -78 °C. Vinyl Grignard reagent was added as a 1 M THF solution (0.4 mL, 0.4 mmol) in a rapid dropwise fashion. After stirring 1 hour, water was added, and followed by aqueous NH\(_4\)Cl. Extractions with diethyl ether were performed and the combined extracts dried over MgSO4. Column chromatography gave allylic alcohol 444 as an oil (40 mg, 64%). TLC (ethyl acetate/hexanes 1:3): \( R_f = 0.2 \); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.27 (d, \( J = 7.2 \) Hz, 3H), 1.36 (d, \( J = 7.2 \) Hz, 2H), 3.48 (s, 2H), 3.49 (s, 3H), 3.52-3.59 (m, 0.7H), 3.59-3.67 (m, 1H), 3.81 (s, 2H), 3.83 (s, 3H), 4.51 (m, 1H), 4.58 (m, 0.7H), 4.96 (ddd, \( J = 1.2, 10.8 \) Hz, 0.7H), 5.10-5.21 (m, 5H), 5.30 (ddd, \( J = 1.2, 16.8 \) Hz, 1H), 5.74-5.83 (m, 0.7H), 5.83-5.92 (m, 1H), 6.57 (d, \( J = 8.4 \) Hz, 0.7H), 6.61 (d, \( J = 8.4 \) Hz, 1H), 6.72-6.78 (m, 1.7H), 7.08-7.17 (m, 1.7H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 159.2, 156.7, 140.91, 140.86, 128.0, 127.7, 115.7, 114.3, 108.1, 107.7, 105.6, 105.5, 95.0, 94.8, 76.2, 75.8, 56.5, 56.4, 56.0, 55.9, 36.8, 36.5, 15.9, 14.6.

**Compound 445:** Allylic alcohol 445 (36 mg, 0.14 mmol) was dissolved in methylene chloride (2 mL) at room temperature. Imidazole (20 mg, 0.29 mmol) was added, followed rapidly by TBDPSCl (0.07 mL, 0.27 mmol), and the reaction was allowed to stir 8 hours at room temperature. The reaction was diluted with diethyl ether and aqueous NaHCO\(_3\). Repeated extractions with diethyl ether, combination and drying of the organic layers over MgSO4, concentration, and column chromatography gave silyl ether 445 as an oil (53 mg, 76%). TLC (ethyl acetate/hexanes 1:3): \( R_f = 0.6 \); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 0.08 (s, 9H),
1.08-1.16 (m, 12H), 1.30 (bs, 3H), 3.45 (s, 5H), 3.69 (s, 5H), 4.42-5.15 (m, 11H), 5.55-5.66 (m, 1H), 5.69-5.79 (m, 1H), 6.55 (d, J = 8.2 Hz, 1H), 6.75 (d, J = 8.2 Hz, 0.8H), 7.03 (t, J = 8.2 Hz, 1H), 7.12 (t, J = 8.2 Hz, 1H), 7.25-7.45 (m, 14H), 7.57 (d, J = 7.4 Hz, 2H), 7.74 (d, J = 6.8 Hz, 2H), 7.82 (d, J = 6.8 Hz, 2H); 13C NMR (100 MHz, CDCl3): 158.9, 156.5, 140.7, 140.4, 136.3, 136.1, 136.0, 135.9, 129.1, 129.0, 128.9, 128.87, 128.84, 127.1, 126.93, 126.88, 126.8, 126.7, 116.3, 114.6, 107.5, 104.9, 94.6, 78.1, 77.6, 56.0, 55.3, 36.2, 27.4, 26.7, 19.8, 16.2, 15.1.

**Compound 446:** The enol ether ylid was prepared by adding KHMDS (13 mL, 6.65 mmol) as a 0.5 M toluene solution to MeOCH2PPh3Cl (2.65 g, 7.73 mmol) in toluene (30 mL) at 0 °C under argon. After stirring 30 minutes at 0 °C, then 30 minutes at room temperature, aldehyde 427a (1.1 g, 4.81 mmol) was added in 10 mL toluene. After mixing 2 hours at room temperature, aqueous NH4Cl was added and diethyl ether extractions were performed. The combined ether extracts were dried over MgSO4, concentrated and subjected to column chromatography. The cis isomer was collected as an oil (165 mg), as was the trans isomer (945 mg) in a combined yield of 90%. TLC (ethyl acetate/hexanes 1:3): Rf = 0.6; 446-Z: 1H NMR (500 MHz, CDCl3): δ 2.30 (s, 3H), 3.67 (s, 3H), 3.82 (s, 3H), 5.21 (d, J = 7.0 Hz, 1H), 6.19 (d, J = 7.0 Hz, 1H), 6.64 (s, 1H), 7.04, (s, 1H); 13C NMR (100 MHz, CDCl3): δ 157.5, 147.9, 138.5, 125.1, 124.5, 122.1, 110.6, 100.4, 59.8, 56.0, 21.4; 446-E: 1H NMR (500 MHz, CDCl3): δ 2.29 (s, 3H), 3.71 (s, 3H), 3.83 (s, 3H), 5.96 (d, J = 13.0 Hz, 1H), 6.63 (s, 1H), 7.04 (s, 1H), 7.40, (d, J = 13.0 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 156.9, 153.0, 136.5, 125.7, 123.9, 121.7, 110.9, 101.0, 56.2, 55.7, 21.1.

**Compound 447:** Enol ether 446 (945 mg, 3.68 mmol) was dissolved in acetone (8 mL) and 37% aqueous HCl (10 drops) was added at room temperature. The reaction was allowed to stir 4 hours before hexanes were added. The reaction was then quenched with aqueous NaHCO3. Extraction with diethyl ether was performed and the combined extracts dried over MgSO4. Column chromatography gave aldehyde 447 as an oil (850 mg, 95%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.5; 1H NMR (400 MHz, CDCl3): δ 2.33 (s, 3H), 3.79 (s, 3H), 3.87 (s, 2H), 6.66 (s, 1H), 7.06 (s, 1H), 9.63 (s, 1H); 13C NMR (100 MHz, CDCl3): δ 198.8, 158.0, 139.7, 125.5, 125.1, 118.7, 110.5, 55.8, 44.4, 21.4.

**Compound 448:** Aldehyde 447 (16 mg, 0.07 mmol) was dissolved in THF (2 ml) and cooled to 0 °C. Vinyl Grignard
reagent was added as a 1 M THF solution (0.15 mL, 0.15 mmol) dropwise over 5 minutes. The ice bath was removed immediately after reagent addition and the reaction was stirred 3 hours prior to addition of diethyl ether and aqueous NH₄Cl. Ether extraction, combination of the organic extracts, MgSO₄ treatment, concentration, and column chromatography gave allylic alcohol 448 as an oil (14 mg, 79%). TLC (ethyl acetate/hexanes 1:3): Rₓ = 0.3; ¹H NMR (400 MHz, CDCl₃): δ 2.31 (s, 3H), 3.05 (m, 1H), 3.06 (m, 1H), 3.82 (s, 3H), 4.39 (bs, 1H), 5.09 (dt, J = 1.6, 10.8 Hz, 1H), 5.25 (dt, J = 1.6, 17.2 Hz, 1H), 5.99 (ddd, J = 6.0, 10.8, 17.2 Hz, 1H), 6.64 (s, 1H), 7.03 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 158.2, 140.1, 138.6, 125.7, 125.6, 123.6, 114.1, 110.7, 72.7, 55.8, 37.2, 21.1.

**Compound 450:** Allylic alcohol 450 was isolated as a Heck adduct in the attempted Stille coupling of aryl bromide 448 and stannane 449. Aryl bromide 448 (43 mg, 0.16 mmol) was dissolved in THF (1 mL) under argon and stannane 449 (184 mg, 0.62 mmol) was added. Pd(PPh₃)₄ (17 mg, 0.15 mmol) was added in one portion at room temperature. After 11 hours, the reaction was diluted with hexanes and filtered through celite prior to concentration and column chromatography. Allylic alcohol 450 was obtained as an oil (23 mg, 77%). TLC (ethyl acetate/hexanes 3:2): Rₓ = 0.2; ¹H NMR (400 MHz, CDCl₃): δ 2.37 (s, 3H), 2.73 (dd, J = 3.6, 16.8 Hz, 1H), 3.25 (dd, J = 7.2, 16.8 Hz, 1H), 3.82 (s, 3H), 4.93 (bs, 1H), 5.30, (d, J = 2.0 Hz, 1H), 5.57 (d, J = 2.0 Hz, 1Hz), 6.58 (s, 1H), 6.93 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 156.0, 153.5, 139.8, 138.4, 127.5, 113.6, 111.3, 105.6, 74.6, 55.3, 37.3, 21.9; HRMS: m/z calcd. for C₁₂H₁₄O₂Na₁: 213.09, found: 213.09 [M+Na]⁺.

**Compound 451:** To a stirred solution of aldehyde 447 (904 mg, 3.72 mmol) in methylene chloride (10 mL) at 0 °C was added DIBAL-H (4.9 mL, 4.9 mmol), portionwise over 5 minutes, as a 1 M hexane solution. The ice bath was removed immediately after DIBAL-H addition and the reaction was allowed to warm to room temperature. After stirring 40 minutes, the reaction was cooled to 0 °C and 15 mL of a saturated aqueous Rochelle’s salt solution was added. The solution clarified after 2 hours stirring at room temperature. Repeated extractions with methylene chloride were performed and the combined extracts were dried over MgSO₄. Column chromatography gave alcohol 451 as an oil (823 mg, 90%). TLC (ethyl acetate/hexanes 1:3): Rₓ = 0.2; ¹H NMR (400 MHz, CDCl₃): δ 2.30 (s, 3H), 3.10 (t, J = 7.2 Hz, 2H), 3.78 (t, J = 7.2 Hz, 2H), 3.81 (s, 3H), 6.63 (s, 1H), 7.01 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 158.0, 138.3, 125.4, 125.3, 123.6, 110.4, 61.9, 55.8, 32.9, 21.2; HR-EI-MS: m/z calcd. for C₁₀H₁₅O₂Br: 244.0091, found: 244.0093 [M⁺].
Compound 452: Aryl bromide 451 (390 mg, 1.59 mmol) and stannane 449 (540 mg, 1.81 mmol) were mixed under argon and dissolved in toluene (10 mL). The solution was degassed by bubbling argon through the solution with stirring for 10 minutes. Pd$_2$(dba)$_3$ (150 mg, 0.16 mmol) was added at room temperature, followed rapidly by P($t$-Bu)$_3$ (32 mg, 0.16 mmol) addition as a 10% hexane solution. The solution was heated to reflux and stirred 8 hours before cooling. The solution was filtered through a silica plug and concentrated for column chromatography. At this stage, dibenzylidene acetone could be precipitated via trituration with ether and hexanes. Column chromatography provided alcohol 452 as an oil (402 mg, 72%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.4$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.10 (s, 3H), 0.11 (s, 3H), 0.94 (s, 9H), 1.31 (d, $J = 6.4$ Hz, 3H), 2.34 (s, 3H), 3.00 (t, $J = 6.4$ Hz, 2H), 3.74 (t, $J = 6.4$ Hz, 2H), 3.82 (s, 3H), 4.49 (m, 1H), 6.10 (dd, $J = 5.4$, 15.0 Hz, 1H), 6.62 (s, 1H), 6.80 (d, $J = 15.0$ Hz, 1H), 6.92 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.5, 137.6, 136.7, 136.6, 125.3, 121.4, 119.3, 110.1, 69.4, 62.8, 55.5, 29.0, 26.0, 24.8, 21.7, 18.4, -4.4, -4.6; ESI-MS: $m/z$ calcld. for C$_{20}$H$_{34}$O$_3$Si$_1$Na$_1$: 373.22, found: 373.23 [M+Na]$^+$.  

Compound 453: Alcohol 452 (275 mg, 0.78 mmol) was dissolved in methylene chloride (8 mL) and DMSO (2 mL) at room temperature. To the stirred solution was added IBX (645 mg, 2.30 mmol). The reaction was stirred 5 hours, and then diluted with hexanes. Water was added to the resultant slurry and repeated diethyl ether extractions were performed. The combined ether extracts were dried over MgSO$_4$ and concentrated. The crude mixture was filtered through a silica plug to provide aldehyde 453 as an oil (249 mg, 91%). TLC (ethyl acetate/hexanes 1:3): $R_f = 0.5$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.28 (d, $J = 6.4$ Hz, 3H), 2.36 (s, 3H), 3.73 (s, 2H), 3.80 (s, 3H), 4.45 (m, 1H), 6.08 (dd, $J = 5.6$, 15.6 Hz, 1H), 6.60 (d, $J = 15.6$ Hz, 1H), 6.64 (s, 1H), 6.92 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 199.9, 157.4, 138.2, 138.0, 137.8, 124.8, 119.5, 115.8, 110.1, 69.2, 55.6, 41.0, 26.0, 24.7, 21.8, 18.4, -4.4, -4.6.  

Compound 454: To a stirred THF (3 mL) solution of aldehyde 453 (56 mg, 0.16 mmol) at 0 °C, was added vinyl Grignard reagent (0.32 mL, 0.32 mmol) as a 1 M THF solution dropwise over ~10 seconds. The reaction was stirred 30
minutes, and then hexanes were added followed by aqueous NH₄Cl. Extraction with diethyl ether was performed, and the combined organic extracts were dried over MgSO₄ prior to concentration. Column chromatography gave allylic alcohol 454 as an oil (50 mg, 83%). TLC (ethyl acetate/hexanes 1:4): Rₜ = 0.3; ¹H NMR (300 MHz, CDCl₃): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.93 (s, 9H), 1.3 (d, J = 6.3 Hz, 3H), 2.34 (s, 3H), 2.94 (m, 2H), 3.82 (s, 3H), 4.31 (m, 1H), 4.48 (m, 1H), 5.03 (d, J = 10.5 Hz, 1H), 5.25 (d, J = 17.1 Hz, 1H), 5.95 (m, 1H), 6.08 (m, 1H), 6.63 (s, 1H), 6.80 (d, J = 15.6 Hz, 1H), 6.92 (s, 1H).

**Compound 455:** Allylic alcohol 454 (22 mg, 0.06 mmol) was dissolved in methylene chloride (1 mL) and DMSO (1 mL) at room temperature. IBX (68 mg, 0.24 mmol) was added and the reaction was stirred 2 hours before being diluted with hexanes and water. Repeated extraction with diethyl ether was performed and the extracts combined prior to being dried over MgSO₄. Column chromatography gave enone 455 as an oil (19 mg, 85%). TLC (ethyl acetate/hexanes 1:4): Rₜ = 0.4; ¹H NMR (400 MHz, CDCl₃): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.27 (d, J = 6.4 Hz, 3H), 2.34 (s, 3H), 3.77 (s, 3H), 3.93 (m, 2H), 4.43 (m, 1H), 5.73 (dd, J = 1.0, 10.0 Hz, 1H), 6.06 (dd, J = 5.2, 15.6 Hz, 1H), 6.29 (dd, J = 1.0, 17.6 Hz, 1H), 6.37 (d, J = 10.0 Hz, 1H), 6.57 (d, J = 15.6 Hz, 1H), 6.62 (s, 1H), 6.90 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 197.6, 157.2, 137.6, 137.3, 135.3, 127.6, 125.2, 119.4, 118.0, 110.2, 69.3, 55.6, 38.2, 26.0, 24.7, 21.8, 18.4, -4.4, -4.6; ESI-MS: m/z calcd. for C_{22}H_{34}O_{3}Si_{1}Na_{1}: 397.22, found: 397.24 [M+Na]⁺.

**Compound 456:** Silyl ether 455 (18 mg, 0.05 mmol) was dissolved in an AcOH/H₂O/THF (13:7:7, 1 mL) solution at room temperature. The solution was stirred 6 hours, and then diluted with diethyl ether. The solution was then neutralized by adding saturated aqueous NaHCO₃ followed by solid Na₂CO₃. Repeated ether extractions were performed and the combined extracts were dried over MgSO₄. Column chromatography gave allylic alcohol 456 as an oil (11 mg, 87%). TLC (ethyl acetate/hexanes 2:3): Rₜ = 0.2.

**Compound 423:** Allylic alcohol 456 (10 mg, 0.04 mmol) was dissolved in methylene chloride (1.5 mL) and DMSO (0.7mL) at room temperature. IBX (43 mg, 0.15 mmol) was added and the solution was stirred 5 hours before dilution with hexanes and water. Repeated diethyl ether extractions were performed and
the ether extracts combined, then dried over MgSO$_4$. Column chromatography provided dienone 423 as a white solid after concentration (9 mg, 92%). TLC (ethyl acetate/hexanes 2:3): $R_f = 0.3$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.357 (s, 3H), 2.36 (s, 3H), 3.81 (s, 3H), 4.03 (s, 2H), 5.80 (dd, $J = 1.0, 10.0$ Hz, 1H), 6.34 (dd, $J = 1.5, 17.6$ Hz, 1H), 6.43 (dd, $J = 10.0, 17.6$ Hz, 1H), 6.59 (d, $J = 16.0$ Hz, 1H), 6.76 (s, 1H), 7.04 (s, 1H), 7.66 (d, $J = 16.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 198.2, 197.3, 157.2, 140.7, 138.2, 135.3, 135.1, 129.4, 128.5, 120.1, 119.5, 113.0, 55.8, 37.7, 27.6, 21.8; ESI-MS: $m/z$ calcd. for C$_{16}$H$_{18}$O$_3$Na$_1$: 281.12, found: 281.13 [M+Na]$^+$. 

**Compound 457:** Dienone 423 (4 mg) was dissolved in DMSO-d6 and transferred to a NMR tube. Pyrrolidine was added, and the reaction progress was monitored by NMR. After 30 minutes at room temperature, complete conversion to amine 457 was observed. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 1.76 (m, 4H), 2.43 (s, 3H), 2.45 (s, 3H), 2.62 (m, 4H), 2.73 (m, 4H), 3.87 (s, 3H), 4.05 (s, 2H), 6.77 (d, $J = 16.0$ Hz, 1H), 7.02 (s, 1H), 7.29 (s, 1H), 7.72 (d, $J = 16.0$ Hz, 1H).

**Compound 458:** To a stirred THF (1 mL) solution of 453 (62 mg, 0.18 mmol) at 0 °C, was added 1-propynyl magnesium bromide (0.5 mL, 0.27 mmol) as a 0.5 M THF solution. After stirring 30 minutes, aqueous NH$_4$Cl was added and repeated diethyl ether extractions were performed. Combination of the ether extracts, drying by MgSO$_4$, and column chromatography gave propargyl alcohol 458 as an oil (63 mg, 90%). TLC (ethyl acetate/hexanes 1:4): $R_f = 0.4$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.11 (s, 6H), 0.94 (s, 9H), 1.30 (d, $J = 6.8$ Hz, 3H), 1.83 (m, 3H), 2.33 (s, 3H), 3.07 (ddd, $J = 2.0, 5.2, 14.0$ Hz, 1H), 3.17 (dd, $J = 8.6, 14.4$ Hz, 1H), 3.8 (s, 3H), 4.45-4.55 (m, 1H), 6.08 (dd, $J = 5.2, 15.6$ Hz, 1H), 6.61 (s, 1H), 6.86 (d, $J = 15.6$ Hz, 1H), 6.91 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.5 138.1, 137.2, 136.8, 125.61, 125.56, 120.4, 119.6, 119.5, 110.2, 80.5, 69.34, 69.29, 62.89, 62.87, 55.6, 34.6, 34.5, 26.0, 24.82, 24.80, 21.7, 18.4, 3.8, -4.4, -4.6; ESI-MS: $m/z$ calcd. for C$_{23}$H$_{36}$O$_3$Si$_1$Na$_1$: 411.23, found: 411.24 [M+Na]$^+$. 

![Compound 457](image.png)

![Compound 458](image.png)
**Compound 459:** Propargyl alcohol 458 (27 mg, 0.07 mmol) was dissolved in methanol (2 mL) at room temperature. Quinoline (≈ 5 μL) was added, followed by Pd/BaSO₄ (5% weight Pd, 3 mg). An atmosphere of hydrogen was created (balloon), and the mixture was stirred 50 minutes, before it was filtered through celite. Column chromatography gave olefin 459 as an oil (26 mg, 96%). TLC (ethyl acetate/hexanes 1:4): Rf = 0.4 (above 458); ¹H NMR (400 MHz, CDCl₃): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 1.29 (m, 3H), 1.57 (m, 3H), 2.33 (s, 3H), 2.87 (dd, J = 4.8, 14.0 Hz, 1H), 2.96 (dd, J = 5.2, 8.8, 14.0 Hz, 1H), 3.82 (s, 3H), 4.46 (m, 1H), 4.68 (m, 1H), 5.45–5.55 (m, 2H), 6.60 (m, 1H), 6.61 (s, 1H), 6.82 (dd, J = 10.4, 15.6 Hz, 1H), 6.9 (d, 5.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 157.6, 138.0, 136.8, 136.6, 136.6, 133.9, 133.19, 133.17, 126.1, 125.7, 125.5, 121.2, 119.5, 119.4, 110.2, 69.6, 69.4, 68.1, 68.0, 55.6, 33.64, 33.58, 26.0, 24.8, 21.7, 18.4, 13.3, -4.4, -4.6

**Compound 460:** Allylic alcohol 459 (24 mg, 0.06 mmol) was dissolved in methylene chloride (1 mL) and DMSO (1 mL) at room temperature. IBX (52 mg, 0.18 mmol) was added and the solution stirred 4 hours before hexanes were added. Water was then added and repeated diethyl ether extractions were performed. The ether extracts were combined and dried over MgSO₄. Column chromatography gave enone 460 as an oil (21 mg, 88%). TLC (ethyl acetate/hexanes 1:4): Rf = 0.6; ¹H NMR (400 MHz, CDCl₃): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.27 (d, J = 6.0 Hz, 3H), 2.08 (d, J = 2.4 Hz, 3H), 2.34 (s, 3H), 3.78 (s, 3H), 3.79 (d, J = 3.2 Hz, 2H), 4.44 (m, 1H), 6.01 (dd, J = 5.6, 16.0 Hz, 1H), 6.09–6.16 (m, 1H), 6.55–6.64 (m, 1H), 6.90 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 198.9, 157.3, 142.8, 137.9, 137.7, 137.1, 126.7, 125.3, 119.2, 118.5, 110.2, 69.4, 55.6, 41.7, 26.0, 24.7, 21.8, 18.4, 16.0, -4.4, -4.6; ESI-MS: m/z calcd. for C₂₃H₃₆O₃SiNa⁺: 411.23, found: 411.23 [M+Na]⁺.

**Compound 461:** Silyl ether 460 (20 mg, 0.05 mmol) was dissolved in an AcOH/H₂O/THF (13:7:7, 1 mL) solution and THF (1 mL) was added at room temperature. The solution was stirred 28 hours, and then diluted with diethyl ether. The solution was then neutralized by adding saturated aqueous NaHCO₃ followed by solid Na₂CO₃. Repeated ether extractions were performed and the combined extracts were dried over MgSO₄. Column chromatography gave allylic alcohols 461-Z and 461-E (10 mg, 70% combined yield). TLC (ethyl acetate/hexanes
1:4): $R_f = 0.2$; **461-Z** $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.34 (d, $J = 6.5$ Hz, 3H), 2.07 (d, $J = 5.5$ Hz, 3H), 2.34 (s, 3H), 3.80 (s, 3H), 3.81 (s, 2H), 4.46 (m, 1H), 6.07-6.17 (m, 3H), 6.63 (s, 1H), 6.66 (d, $J = 16.5$ Hz, 1H), 6.91 (s, 1H); **461-E** $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.33 (d, $J = 6.5$ Hz, 3H), 1.86 (d, $J = 6.5$ Hz, 3H), 2.34 (s, 3H), 3.78 (s, 3H), 3.88 (s, 2H), 4.44 (m, 1H), 6.09 (dd, $J = 6.5$, 15.5 Hz, 1H), 6.16 (d, $J = 15.5$ Hz, 1H), 6.63 (s, 1H), 6.63 (d, $J = 16.0$ Hz, 1H), 6.91 (s, 1H), 6.89-6.97 (m, 1H).

**Compound 462**: Allylic alcohol **461** (33 mg, 0.12 mmol) was dissolved in methylene chloride (3 mL) and DMSO (1 mL) at room temperature. IBX (100 mg, 0.36 mmol) was added and the solution was stirred. After 3 hours, hexanes were added, followed by water. Repeated diethyl ether extractions were performed and the extracts combined. The extracts were dried over MgSO$_4$ and subjected to column chromatography. Dienones **462-Z** and **462-E** were obtained (30 mg, 92% combined yield). TLC (ethyl acetate/hexanes 2:3): $R_f = 0.4$; **462-Z** $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.08 (d, $J = 5.0$ Hz, 3H), 2.36 (s, 3H), 2.37 (s, 3H), 3.82 (s, 3H), 3.91 (s, 2H), 6.14-6.22 (m, 2H), 6.58 (d, $J = 16.0$ Hz, 1H), 6.08 (s, 1H), 7.04 (s, 1H), 7.69 (d, $J = 16.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 198.3, 157.2, 143.8, 140.9, 138.0, 135.0, 129.3, 126.6, 120.7, 119.3, 113.0, 55.8, 41.4, 27.5, 21.8, 16.1; **462-E** $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.89 (d, $J = 6.5$ Hz, 3H), 2.35 (s, 3H), 2.36 (s, 3H), 3.81 (s, 3H), 3.98 (s, 3H), 6.18 (m, $J = 16$ Hz, 1H), 6.58 (d, $J = 16.0$ Hz, 1H), 6.75 (s, 1H), 6.97 (dq, $J = 7$, 15.5 Hz, 1H), 7.04 (s, 1H), 7.67 (d, $J = 16.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 198.3, 196.7, 157.3, 143.0, 140.9, 138.0, 135.1, 130.6, 129.3, 120.6, 119.4, 113.0, 55.8, 38.0, 29.8, 18.5, 14.3; **462-Z** HR-FAB-MS: $m/z$ calcd. for C$_{17}$H$_{21}$O$_3$: 273.1495, found: 273.1485 \([M+H]^+\); **462-E** HR-FAB-MS: $m/z$ calcd. for C$_{17}$H$_{21}$O$_3$: 273.1496, found: 273.1435 \([M+H]^+\).

**Compound 463**: Pyran **463** was isolated at any stage of the reaction conditions which formed naphthalene **464** and enone **465**. Yields of pyran **463** decreased with increased reaction times. TLC (ethyl acetate/hexanes 2:3): $R_f = 0.7$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.80 (d, 6.4 Hz, 3H), 2.18 (s, 3H), 2.31 (s, 3H), 2.60 (dd, $J = 4.4$, 15.6 Hz, 1H), 3.17 (dd, $J = 8.8$, 15.6 Hz, 1H), 3.83 (s, 3H), 5.61 (dd, $J = 4.4$, 8.8 Hz, 1H), 5.95 (d, 15.6 Hz, 1H), 6.01 (s, 1H), 6.01-6.10 (m, 1H), 6.46 (s, 1H), 6.57 (s, 1H); ESI-MS: $m/z$ calcd. for C$_{17}$H$_{20}$O$_3$Na$_1$: 295.13, found: 295.13 \([M+Na]^+\).
Compound 464: Naphthalene 464 was isolated in varied yields, and its formation was dependent upon specific reaction conditions. Typical conditions are as follows: Dienone 462 (2.3 mg, 0.008 mmol) was dissolved in DMSO-d6 (0.7 mL) and pyrrolidine (0.6 μL, 0.007 mmol) was added at room temperature. The solution was heated at 50 °C for 13 hours. The mixture was partitioned between diethyl ether and aqueous NH4Cl, dried over MgSO4, and purified by column chromatography. Naphthalene 464 was isolated as an oil (< 1mg). TLC (ethyl acetate/hexanes 2:3): Rf = 0.7; 1H NMR (400 MHz, CDCl3): δ 1.83 (dd, J = 1.6, 6.8 Hz, 3H), 2.30 (s, 3H), 2.46 (s, 3H), 3.79 (s, 3H), 6.20 (dq, J = 6.8, 16.0 Hz, 1H), 6.43 (dq, J = 1.6, 16.0 Hz, 1H), 6.64 (s, 1H), 7.20 (s, 1H), 7.26 (m, 1H), 7.62 (d, J = 8.4 Hz, 1H); ESI-MS: m/z calcd. for C17H18O2Na+: 277.12, found: 277.14 [M+Na]+.

Compound 465: Tricycle 464 was isolated in varied yields, and its formation was dependent upon specific reaction conditions. Typical conditions are as follows: Dienone 462 (2.3 mg, 0.008 mmol) was dissolved in DMSO-d6 (0.7 mL) and pyrrolidine (0.6 μL, 0.007 mmol) was added at room temperature. The solution was heated at 50 °C for 13 hours. The mixture was partitioned between diethyl ether and aqueous NH4Cl, dried over MgSO4, and purified by column chromatography. Tricycle 464 was isolated as an oil (~ 1mg). TLC (ethyl acetate/hexanes 2:3): Rf = 0.3; 1H NMR (400 MHz, CDCl3): δ 1.16 (s, 3H), 1.78 (dd, J = 3.0, 17.5 Hz, 1H), 1.88 (d, J = 7.5 Hz, 3H), 2.03 (dd, J = 3.0, 14.0 Hz, 1H), 2.34 (s, 3H), 3.79 (s, 3H), 4.06 (s, 1H), 4.10 (m, 1H), 6.56-6.68 (m, 3H [includes : 6.65 (s) and 6.57 (s)]); ESI-MS: m/z calcd. for C17H20O3Na+: 295.13, found: 295.15 [M+Na]+.

Compound 479: Aryl bromide 477 (930 mg, 4.63 mmol) and stannane 449 (2.08 g, 6.98 mmol) were mixed under argon and dissolved in toluene (15 mL). The solution was degassed by bubbling argon through the solution with stirring for 10 minutes. Pd2(dbta)3 (430 mg, 0.47 mmol) was added at room temperature, followed rapidly by P(t-Bu)3 (112 mg, 0.55 mmol) addition as a 10% hexane solution. The solution was placed in an 80 °C oil bath and stirred 12 hours before cooling to room temperature. The solution was then filtered through a silica plug and concentrated for column chromatography. At this stage, dibenzylidene acetone could be precipitated via trituration with ether and hexanes. Column chromatography provided alcohol 452 as an oil (963 mg, 68%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.3; 1H NMR (300 MHz, CDCl3): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.94 (s, 9H), 1.30 d, J = 6.3 Hz, 3H), 2.96 (t, 2H), 3.81 (m, 2H), 4.50 (m, 1H), 6.12 (dd,
J = 5.4, 16.0 Hz, 1H), 6.81 (d, J = 16.0 Hz, 1H), 7.16-7.24 (m, 3H), 7.46 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 136.6, 136.5, 135.5, 130.4, 127.3, 126.9, 126.3, 125.0, 69.3, 63.0, 36.5, 24.7, 18.3, -4.6, -4.8; ESI-MS: m/z calcd. for C18H31O2Si1: 307.20, found: 307.21 [M+H]+.

**Compound 480:** Alcohol 479 (930 mg, 3.03 mmol) was dissolved in methylene chloride (10 mL) and DMSO (5 mL) at room temperature. To the stirred solution was added IBX (2.53 g, 9.04 mmol). The reaction was stirred 3 hours, and then diluted with hexanes. Water was added to the resultant slurry and repeated diethyl ether extractions were performed. The combined ether extracts were dried over MgSO4 and concentrated. The crude mixture was filtered through a silica plug to provide aldehyde 480 as an oil (905 mg, 98%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.6; 1H NMR (400 MHz, CDCl3): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.93 (s, 9H), 1.30 (d, 3H), 3.76 (s, 2H), 4.48 (m, 1H), 6.14 (dd, J = 5.4, 15.8 Hz, 1H), 6.65 (d, J = 15.8 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.27 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 9.69 (t, J = 2.0 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 198.9, 137.7, 137.1, 130.7, 129.4, 127.8, 127.6, 126.6, 69.1, 48.4, 26.0, 24.7, 18.4, -4.4, -4.6.

**Compound 481:** To a stirred THF (10 mL) solution of aldehyde 480 (3.1 g, 10.18 mmol) at 0 °C, was added 1-propynyl magnesium bromide (30.0 mL, 15.0 mmol), dropwise over 5 minutes, as a 0.5 M THF solution. The reaction was stirred 1.5 hours, and then hexanes were added, followed by aqueous NH4Cl. Extraction with diethyl ether was performed, and the combined organic extracts were dried over MgSO4 prior to concentration. Column chromatography gave propargyl alcohol 481 as an oil (2.3 g, 65%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.4; 1H NMR (400 MHz, CDCl3): δ 0.11 (s, 6H), 0.94 (s, 9H), 1.31 (d, J = 6.0 Hz, 3H), 1.83 (d, J = 2.0 Hz, 3H), 3.05 (m, 2H), 4.50 (m, 2H), 6.11 (dd, J = 2.4, 15.6 Hz, 1H), 6.84 (d, J = 15.6, 1H), 7.22 (m, 3H), 7.46 (d, J = 7.2 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 136.6, 134.2, 134.1, 131.0, 127.1, 127.0, 126.2, 126.1, 125.1, 125.0, 81.8, 79.7, 69.3, 69.2, 63.0, 62.9, 41.8, 26.0, 24.8, 18.4, 3.754, -4.4, -4.5; HR-EI-MS: m/z calcd. for C21H32O2Si1: 344.2174, found: 344.2166 [M+H]+.

**Compound 482:** Propargyl alcohol 481 (620 mg, 1.80 mmol) was dissolved in methanol (10 mL) at room temperature. Quinoline (~ 50 μL) was added, followed by Pd/BaSO4 (5%
weight Pd, 40 mg). An atmosphere of hydrogen was created (balloon) and the mixture was stirred 50 minutes, and then filtered through celite. Column chromatography gave olefin 482 as an oil (549 mg, 88%). Mixture of diastereomers: TLC (ethyl acetate/hexanes 1:3): Rf = 0.5; ^1H NMR (500 MHz, CDCl₃): δ 0.10 (s, 6H), 0.11 (s, 6H), 0.93 (s, 18H), 1.31 (dd, J = 1.5, 6.5 Hz, 3H), 1.32 (dd, J = 1.5, 6.5 Hz, 3H), 1.48 (m, 3H), 1.52 (m, 3H), 2.85 (dd, J = 5.5, 13.0, 13.5 Hz, 2H), 2.94 (dd, J = 7.5, 13.5, 13.5 Hz, 2H), 4.50 (m, 2H), 4.67 (m, 2H), 5.43-5.58 (m, 4H), 6.11 (m, 2H), 6.85 (m, 2H), 7.12 (m, 6H), 7.45 (m, 2H); ^13C NMR (75 MHz, CDCl₃): δ 136.8, 136.7, 136.6, 135.2, 135.1, 132.3, 131.0, 130.9, 127.21, 127.17, 126.88, 126.87, 126.74, 126.72, 126.3, 126.2, 125.7, 125.2, 69.6, 69.2, 67.8, 41.1, 41.0, 25.9, 24.7, 25.9, 24.7, 18.3, 13.2, 13.155, -4.5, -4.6, -4.7, -4.8; HR-EI-MS: m/z calcd. for C₂₁H₃₅O₂Si₂: 347.2328, found: 347.2385 [M+H]⁺.

**Compound 483:** Allylic alcohol 482 (140 mg, 0.40 mmol) was dissolved in methylene chloride (5 mL) and DMSO (2 mL) at room temperature. IBX (300 mg, 1.07 mmol) was added and the solution stirred 5 hours before hexanes were added. Water was then added and repeated diethyl ether extractions were performed. The ether extracts were combined and dried over MgSO₄. Column chromatography gave enone mixture 483 as an oil (127 mg, 91%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.7 (483-Z above 483-E); 483-Z ^1H NMR (300 MHz, CDCl₃): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.29 (d, J = 6.3 Hz, 3H), 2.11 (d, J = 5.7 Hz, 3H), 3.79 (s, 2H), 4.47 (m, 1H), 6.09 (dd, J = 5.4, 15.6 Hz, 1H), 6.15-6.26 (m, 2H), 6.65 (d, J = 15.6 Hz, 1H), 7.11-7.28 (m, 3H), 7.48 m, 1H); ^13C NMR (75 MHz, CDCl₃): δ 198.4, 144.3, 137.2, 137.0, 132.2, 130.8, 127.5, 127.4, 126.6, 126.4, 125.1, 69.3, 49.0, 25.9, 24.6, 18.3, 16.0, -4.6, -4.8; 483-E ^1H NMR (300 MHz, CDCl₃): δ 0.07 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.28 (d, J = 6.3 Hz, 3H), 1.86 (dd, J = 1.5, 6.9 Hz, 3H), 3.87 (s, 2H), 4.46 (m, 1H), 6.08 (dd, J = 5.1, 15.6 Hz, 1H), 6.16 (dd, J = 1.5, 15.6 Hz, 1H), 6.63 (d, J = 15.6 Hz, 1H), 6.92 (dq, J = 6.9, 15.6 Hz, 1H), 7.10-7.23 (m, 3H), 7.46 (m, 1H); ^13C NMR (75 MHz, CDCl₃): δ 197.0, 143.3, 137.2, 137.0, 132.1, 130.64, 130.62, 127.4, 127.3, 126.5, 125.1, 69.2, 45.4, 25.9, 24.6, 18.3, -4.6, -4.8. HR-EI-MS: m/z calcd. for C₂₁H₃₂O₂Si₁: 347.2328, found: 483-Z 344.2166 [M]^⁺; 483-E 344.2185 [M]^⁺.

**Compound 484:** Silyl ether 483 (1.01 g, 2.93 mmol) was dissolved in an AcOH/H₂O/THF (2:1:1, 7 mL) solution. The solution was stirred 9 hours then diluted with diethyl ether and water. Na₂CO₃ was added and the
resultant slurry extracted with diethyl ether. Repeated ether extractions were performed and the combined extracts were dried over MgSO₄. Column chromatography gave allylic alcohols **484-Z** and **484-E** (465 mg, 70% combined yield). TLC (ethyl acetate/hexanes 9:1): Rf = 0.4 (**484-Z** above **484-E**); **484-Z** ¹H NMR (500 MHz, CDCl₃): δ 1.36 (d, J = 6.8 Hz, 3H), 2.10 (d, J = 5.6 Hz, 3H), 3.80 (s, 2H), 4.48 (m, 1H), 6.09-6.25 (m, 3H), 6.69 (d, J = 15.6 Hz, 1H), 7.15-7.26 (m, 3H), 7.47 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 198.3, 144.3, 136.5, 136.2, 132.1, 130.7, 127.7, 127.3, 126.5, 126.4, 126.3, 68.8, 49.3, 23.4, 16.1; **484-E** ¹H NMR (500 MHz, CDCl₃): δ 1.35 (d, J = 6.5 Hz, 3H), 1.87 (dd, J = 2.0, 7.0 Hz, 3H), 3.87 (s, 2H), 4.47 (m, 1H), 6.12 (dd, J = 6.5, 15.5 Hz, 1H), 6.16 (m, 1H), 6.67 (d, J = 16.0 Hz, 1H), 6.93 (dq, J = 7.0, 15.5 Hz, 1H), 7.13-7.25 (m, 3H), 7.47 (m, 1H); HR-EI-MS: m/z calcd. for C₁₅H₁₈O₂: 230.1307, found: 230.1311 [M]+.

**Compound 485:** Allylic alcohol **484** (317 mg, 1.38 mmol) was dissolved in methylene chloride (5 mL) and DMSO (3 mL) at room temperature. IBX (940 mg, 3.36 mmol) was added and the solution stirred. The reaction was monitored by TLC, and when the starting material had been consumed, hexanes were added, followed by water. Repeated diethyl ether extractions were performed and the extracts combined. The extracts were dried over MgSO₄ and subjected to column chromatography. Dienones **485-Z** and **485-E** were obtained (299 mg, 95% combined yield). TLC (ethyl acetate/hexanes 2:3): Rf = 0.5; **485-Z** ¹H NMR (500 MHz, CDCl₃): δ 2.09 (d, J = 6.5 Hz, 1H), 2.38 (s, 3H), 3.90 (s, 2H), 6.17-6.29 (m, 2H), 6.62 (d, J = 16.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 16.0 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 198.5, 197.7, 145.2, 140.6, 134.4, 134.1, 131.5, 130.4, 129.0, 127.8, 126.8, 126.3, 49.1, 27.4, 16.0; **485-E** ¹H NMR (500 MHz, CDCl₃): δ 1.90 (d, J = 2.0 Hz, 3H), 2.37 (s, 3H), 3.98 (s, 2H), 6.19 (dd, J = 1.5, 15.5 Hz, 1H), 6.62 (d, J = 16.0 Hz, 1H), 6.98 (dq, J = 7.5, 15.5 Hz, 1H), 7.22 (d, J = 6.0 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.62 (d, J = 7.0 Hz, 1H), 7.69 (d, J = 16.0 Hz, 1H); HR-EI-MS: m/z calcd. for C₁₅H₁₆O₂: 228.1145 [M]+.

**Compound 486** Pyran **486** was isolated at any stage of the reaction conditions which formed naphthalene **487** and enone **488**. Yields of pyran **463** decreased with increased reaction times. TLC (ethyl acetate/hexanes 2:3): Rf = 0.7 (slightly below **487**); ¹H NMR (500 MHz, CDCl₃): δ 1.82 (dd, J = 1.5, 7.0 Hz, 3H), 2.19 (s, 3H), 2.68 (dd, J = 4.0, 16.0 Hz, 1H), 3.20 (dd, J = 9.0, 16.0 Hz, 1H), 5.69 (dd, J = 5.0, 9.0 Hz, 1H), 5.73
(s, 1H), 5.94 (dd, J = 2.0, 15.0 Hz, 1H), 6.14 (m, 1H [poorly resolved dq, J = 7.0, 15.0 Hz]), 7.0 (app. t, J = 7.0 Hz, 2H), 7.12 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H); 13C NMR (75 MHz, CDCl3): δ 206.2, 150.4, 130.9, 130.4, 128.3, 128.2, 126.4, 125.8, 123.8, 123.7, 103.0, 73.8, 47.4, 31.3, 18.2; ESI-MS: m/z calcd. for C15H17O2: 229.12, found: 229.12 [M+H]+.

**Compound 487:** Naphthalene 487 was isolated in varied yields, and its formation was dependent upon specific reaction conditions. Typical conditions were as follows: Dienone 485 (10 mg, 0.04 mmol) was dissolved in DMSO (1 mL) and pyrrolidine (3 mg, 0.04 mmol) was added at room temperature. The solution was heated at 55 °C for 16 hours. The mixture was partitioned between diethyl ether and aqueous NH4Cl, dried over MgSO4, and purified by column chromatography. Naphthalene 487 was isolated as an oil (2 mg, 20%). TLC (ethyl acetate/hexanes 2:3): Rf = 0.7 (slightly above 486); 1H NMR (300 MHz, CDCl3): δ 1.90 (dd, J = 2.0, 5.5 Hz, 3H), 2.37 (s, 3H), 6.47-6.54 (m, 2H), 7.32 (d, J = 15.5 Hz, 1H), 7.40-7.47 (m, 2H), 7.55-7.60 (m, 1H), 7.64 (m, 2H [including 7.79 (d, J = 15.5 Hz)]); 13C NMR (100 MHz, CDCl3): δ 201.0, 149.2, 136.3, 134.3, 131.7, 131.6, 130.4, 128.7, 128.4, 128.0, 126.6, 125.3, 124.8, 19.6, 18.6; ESI-MS: m/z calcd. for C15H14O1Na1: 233.09, found: 233.10 [M+Na]+.

**Compound 488:** Tricycle 488 was isolated in varied yields, and its formation was dependent upon specific reaction conditions. Typical conditions are as follows: Dienone 485 (10 mg, 0.04 mmol) was dissolved in DMSO (1 mL) and pyrrolidine (3 mg, 0.04 mmol) was added at room temperature. The solution was heated at 55 °C for 16 hours. The mixture was partitioned between diethyl ether and aqueous NH4Cl, dried over MgSO4, and purified by column chromatography. Tricycle 488 was isolated as an oil (6-7 mg, 65%). TLC (ethyl acetate/hexanes 2:3): Rf = 0.3; 1H NMR (400 MHz, CDCl3): δ 1.12 (s, 3H), 1.82 (dd, J = 2.8, 13.4 Hz, 1H), 1.90 (d, J = 7.4 Hz, 3H), 2.09 (dd, J = 2.8, 13.4 Hz, 1H), 3.62 (s, 1H), 4.19 (app. t, J = 2.8 Hz, 1H), 6.70 (q, J = 7.4 Hz, 1H), 7.17-7.26 (m, 4H); 13C NMR (100 MHz, CDCl3): δ 196.7, 141.1, 134.9, 134.8, 130.0, 127.8, 127.0, 126.6, 123.1, 74.2, 66.6, 43.7, 38.6, 30.3, 13.8; ESI-MS: m/z calcd. for C15H16O2Na1: 251.11, found: 251.12 [M+Na]+. A crystal suitable for x-ray analysis was grown and the following data was obtained:
Crystal data and structure refinement for Fischer.

Identification code: DF1
Empirical formula: C15 H16 O2
Formula weight: 228.28
Temperature: 100 K
Wavelength: 0.71073 Å
Crystal system: Orthorhombic
Space group: Pna2(1)
Unit cell dimensions:
  a = 16.1749(16) Å \( \alpha = 90^\circ \)
  b = 8.4717(8) Å \( \beta = 90^\circ \)
  c = 17.8514(18) Å \( \gamma = 90^\circ \)
Volume: 2446.2(4) Å\(^3\)
Z: 8
Density (calculated): 1.240 Mg/m\(^3\)
Absorption coefficient: 0.081 mm\(^{-1}\)
F(000) 976
Crystal size 0.30 x 0.06 x 0.06 mm³
Theta range for data collection 2.28 to 25.00°.
Index ranges -19<=h<=19, -10<=k<=10, -21<=l<=21
Reflections collected 16776
Independent reflections 4314 [R(int) = 0.0511]
Completeness to theta = 25.00° 100.0 %
Absorption correction None
Max. and min. transmission 0.9952 and 0.9761
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 4314 / 1 / 317
Goodness-of-fit on F² 1.028
Final R indices [I>2sigma(I)] R₁ = 0.0429, wR₂ = 0.0924
R indices (all data) R₁ = 0.0645, wR₂ = 0.1012
Absolute structure parameter -0.3(16)
Largest diff. peak and hole 0.182 and -0.161 e.Å⁻³

Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³) for Fischer. U(eq) is defined as one third of the trace of the orthogonalized Uᵢⱼ tensor.

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Symmetry transformations used to generate equivalent atoms:

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

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Compound 490: MeOCH2PPh3Cl (380 mg, 1.11 mmol) was dissolved in toluene (3.5 mL) and cooled to 0 °C. KHMDMS (2.0 mL, 1.0 mmol) was added in one portion as a 0.5 M toluene solution. After base addition, the ice bath was removed and the solution was stirred 30 minutes before being replaced in the ice bath. Bromoacetophenone 489 (140 mg, 0.70 mmol) was added in one portion. The ice bath was removed and the reaction was stirred at room temperature 1.5 hours. The reaction was then quenched with aqueous NH4Cl and repeated diethyl extractions were performed. The combined ether extracts were dried over MgSO4 and concentrated. Column chromatography gave enol ether 490 as a mixture of isomers (120 mg, 75%). TLC (ethyl acetate/hexanes 1:9): Rf = 0.3 and 0.4 (cis/trans).

Compound 491: Enol ether 490 (32 mg, 0.14 mmol) was dissolved in THF (0.4 mL) and cooled to 0 °C. HgOAc2 (54 mg, 0.17 mmol) was added in water (0.5 mL). The solution was stirred 1.5 hours, then NaBH4 (23 mg, 0.61 mmol) was added along with 0.5 mL saturated aqueous K2CO3. The solution was stirred 15 minutes at 0 °C, then 30 minutes at room temperature. The solution was diluted with diethyl ether and aqueous NH4Cl. Repeated ether extractions were performed, and the combined extracts were dried over MgSO4. Column chromatography gave alcohol 491 as an oil (23 mg, 70%). 1H NMR (500 MHz, CDCl3): δ 1.42 (d, 7.0 Hz, 3H), 3.64 (m, 1H), 3.83 (dd, J = 6.0, 10.5 Hz, 1H), 3.93 (dd, J = 6.0, 10.5 Hz, 1H), 7.21 (m, 1H), 7.38-7.45 (m, 2H), 7.70 (d, 8.0 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 142.3, 132.9, 127.8, 127.6, 127.5, 125.1, 67.3, 40.8, 17.1; ESI-MS: m/z calcd. for C9H11O1Br1Na1: 236.99, 238.99, found: 237.0, 239.0 [M+Na]+.

Compound 493: Aldehyde 480 (184 mg, 0.60 mmol) was freshly prepared, dissolved in THF (1 mL), and cooled to -78 °C. Anhydrous CeCl3 (228 mg, 0.93 mmol) was added in one portion and the suspension was vigorously stirred. 2-methyl-1-propenyl-magnesium bromide (1.8 mL, 0.9 mmol) was added dropwise as a 0.5 M THF solution over ~2 minutes. The solution was stirred 3 hours at -78 °C, and then allowed to warm to room temperature over 2 hours. The reaction was quenched with aqueous NH4Cl and diluted further with water. Repeated diethyl ether extractions were performed, the extracts combined, and dried over MgSO4. Column chromatography gave allylic alcohol 493 as an oil (159 mg, 73%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.5; 1H NMR (400 MHz, CDCl3): δ 0.10-0.13 (m, 6H), 0.93-0.95 (m, 9H), 1.29-1.34 (m, 3H), 1.48-1.54 (m, 3H), 1.68-1.78 (m, 3H), 2.80-2.95 (m, 2H), 4.44-4.59 (m, 2H), 5.21-5.28 (m, 1H), 6.07-6.17 (m, 1H), 6.78-
Compound 494: Allylic alcohol 493 (373 mg, 1.04 mmol) was dissolved in methylene chloride (3 mL) and DMSO (2.5 mL) at room temperature. IBX (720 mg, 2.57 mmol) was added and the reaction was stirred 12 hours before being diluted with hexanes and water. Repeated extraction with diethyl ether was performed and the extracts were combined prior to being dried over MgSO₄. Column chromatography gave enone 494 as an oil (338 mg, 91%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.6; ¹H NMR (400 MHz, CDCl₃): δ 0.07 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.29 (d, 3H), 1.85 (s, 3H), 2.14 (s, 3H), 3.76 (s, 2H), 4.47 (m, 1H), 6.06-6.09 (m, 1H), 6.11 (d, J = 5.6 Hz, 1H), 6.66 (d, J = 16.0 Hz, 1H), 7.11-7.16 (m, 1H), 7.19-7.26 (m, 2H), 3.76-7.50 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 197.2, 156.4, 136.84, 136.76, 132.5, 130.6, 127.3, 127.1, 126.22, 126.16, 122.7, 69.3, 49.0, 27.9, 26.0, 24.7, 21.0, 18.4, -4.4, -4.6; HR-EI-MS: m/z calcd. for C₂₂H₃₆O₂Si₁Na₁: 358.2319, found: 358.2323 [M]+.

Compound 495: Enone 494 (327 mg, 0.91 mmol) was dissolved in dimethoxy ethane (10 mL) and KOH (113 mg, 2.02 mmol) was added in one portion at room temperature. MeI (0.09 mL, 1.44 mmol) was added in one portion directly after base addition. The reaction was stirred 2 hours, and then partitioned between diethyl ether and aqueous NH₄Cl. The organic extracts were combined and dried over MgSO₄. Column chromatography gave enone 495 as an oil (317 mg, 94%). TLC (ethyl acetate/hexanes 1:3): R_f = 0.6 (slightly above 494); ¹H NMR (400 MHz, CDCl₃): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.93 (s, 9H), 1.30-1.36 (m, 6H), 1.75 (s, 3H), 2.15 (s, 3H), 4.02 (m, 1H), 4.53 (m, 1H), 5.87 (bs, 1H), 6.07-6.15 (m, 1H, [the 2 diastereomers can be differentiated at this peak: 6.09 (dd, J = 5.2, 15.6 Hz, 0.5H) and 6.13 (dd, J = 5.2, 15.6, 0.5H)], 6.83-6.91 (m, 1H), 7.03-7.08 (m, 1H), 7.17-7.22 (m, 2H), 7.41-7.47 (m, 1H); HR-EI-MS: m/z calcd. for C₂₃H₃₈O₂Si₁: 372.2484, found: 372.2479 [M]+.

Compound 496: Silyl ether 495 (118 mg, 0.32 mmol) was dissolved in an AcOH/H₂O/THF (2:1:1, 3 mL) solution. The solution was stirred 12 hours and then diluted with diethyl ether and water. EtOAc extractions were performed, and the organic
extracts were combined. The organic extracts were washed with aqueous NaHCO₃, concentrated, and dried over MgSO₄. Column chromatography gave allylic alcohol 496 (63 mg, 78% combined yield). TLC (ethyl acetate/hexanes 1:3): Rf = 0.1; ¹H NMR (400 MHz, CDCl₃): δ 1.37 (d, J = 7.2 Hz, 3H), 1.39 (d, J = 6.8 Hz, 3H), 1.76 (s, 3H), 2.14 (s, 3H), 3.99 (q, 7.2 Hz, 1H), 4.52 (m, 1H), 5.84 (s, 1H), 6.13 (dd, J = 6.2, 15.6 Hz, 1H), 6.88 (d, J = 15.6 Hz, 1H), 7.06-7.12 (m, 1H), 7.19-7.25 (m, 2H), 7.41-7.47 (m, 1H).

**Compound 497:** Allylic alcohol 496 (125 mg, 0.048 mmol) was dissolved in methylene chloride (8 mL) and DMSO (2 mL) at room temperature. IBX (400 mg, 1.43 mmol) was added and the solution stirred. The reaction was stirred 2.5 hours, and then hexanes were added, followed by water. Repeated diethyl ether extractions were performed and the extracts were combined. The extracts were dried over MgSO₄ and subjected to column chromatography. Dienone 497 was obtained as an oil (117 mg, 95% combined yield). TLC (ethyl acetate/hexanes 2:3): Rf = 0.6; ¹H NMR (400 MHz, CDCl₃): δ 1.41 (d, J = 6.8 Hz, 3H), 1.77 (d, J =1.2 Hz, 3H), 2.14 (d, J = 1.2 Hz, 3H), 2.40 (s, 3H), 4.05 (q, J = 6.8 Hz, 1H), 5.85 (app. t, J = 1.2 Hz, 1H), 6.62 (d, J = 16.4 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.58 (d, 7.6 Hz, 1H), 7.88 (d, J = 16.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 199.6, 198.0, 156.8, 140.7, 140.3, 133.2, 130.5, 129.3, 128.3, 127.2, 122.7, 50.1, 27.9, 27.8, 21.0, 17.5; HR-EI-MS: m/z calcd. for C₁₇H₂₀O₂: 256.1458, found: 256.1458 [M]+.

**Compound 498:** Tricycle 498 was isolated in varied yields, and its formation was dependent upon specific reaction conditions. Typical conditions were as follows: Dienone 497 (2 mg, 0.008 mmol) was dissolved in DMSO-d₆ (0.7 mL) and pyrollidine (0.25 mL (0.03 M DMSO-d₆ solution), 0.008 mmol) was added at room temperature. The solution was heated at 55 °C for 12 hours, then warmed to 75 °C for an additional 12 hours. The mixture was partitioned between diethyl ether and aqueous NH₄Cl, dried over MgSO₄, and purified by column chromatography. Tricycle 498 was isolated as an oil (1 mg, 50%). TLC (ethyl acetate/hexanes 2:3): Rf = 0.5 (likely effected by AcOH); major isomer ¹H NMR (400 MHz, CDCl₃): δ 1.01 (s, 3H), 1.53 (s, 3H), 1.90 (dd, J = 2.6, 13.6 Hz, 1H), 2.00 (s, 3H), 2.16 (dd, J = 3.2, 13.6 Hz, 1H), 4.19 (app. T, J = 2.8 Hz, 1H), 7.15-7.27 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 199.3, 145.7, 142.5, 142.1, 138.0, 130.3, 128.6, 127.5,
Compound 500: Enone 494 (17 mg, 0.05 mmol) was dissolved in dimethoxyethane (0.5 mL). \( t \)-BuOK (12.5 mg, 0.11 mmol) was added in one portion and the reaction vigorously stirred. After 30 minutes, 1,4-dibromobutane (9 mg, 0.04 mmol) was added and the reaction was heated to 45 °C. The reaction was quenched with aqueous NH\(_4\)Cl after 3 hours reaction. Repeated diethyl ether extractions were performed, the extracts combined, dried over MgSO\(_4\), and subjected to column chromatography. Cyclopentane 500 was obtained as an oil (9 mg, 45%). TLC (ethyl acetate/hexanes 1:9): \( R_f = 0.4 \); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.25 (d, J = 6.4 Hz, 3H), 1.63-1.69 (m, 7H), 1.81-1.99 (m, 2H), 2.10 (s, 3H), 2.34-2.51 (m, 2H), 4.39 (m, 1), 5.75 (s, 1H), 5.92 (dd, J = 6.4, 15.6 Hz, 1H), 6.48 (d, J = 15.6 Hz, 1H), 7.16-7.29 (m, 2H), 7.39-7.45 (m, 2H); ESI-MS: \( m/z \) calcd. for C\(_{26}\)H\(_{40}\)O\(_2\)SiNa: 435.27, found: 435.28 [M+Na]\(^+\).

Compound 501: Silyl ether 500 (7 mg, 0.02 mmol) was dissolved in 0.5 mL of an AcOH/THF/H\(_2\)O (8:1:1) solution at room temperature. The mixture was stirred 10 hours, and then diluted with diethyl ether and water. Repeated ether extractions were performed and the combined extracts were dried over MgSO\(_4\). Column chromatography gave allylic alcohol 501 as an oil (4-5 mg, ~90%). TLC (ethyl acetate/hexanes 1:3): \( R_f = 0.2 \); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.30 (d, 3H), 1.61-1.73 (m, 7H), 1.85-1.99 (m, 2H), 2.10 (s, 3H), 2.37-2.51 (m, 2H), 4.40 (m, 1H), 5.72 (s, 1H), 5.88 (dd, J = 6.4, 15.6 Hz, 1H), 6.62 (d, J = 15.6 Hz, 1H), 7.20-7.31 (m, 2H), 7.36 (m, 1H), 7.44 (m, 1H).

Compound 502: Allylic alcohol 501 (3 mg, 0.01 mmol) was dissolved in methylene chloride (0.5 mL) and DMSO (0.5 mL) at room temperature. IBX (7 mg, 0.03 mmol) was added and the reaction mixture was stirred 4 hours. The reaction was diluted with diethyl ether and water, and then repeated ether extractions were performed. The extracts were combined and dried over MgSO\(_4\). Column chromatography gave dienone 502 as an oil (2-3 mg, ~75%). TLC (ethyl acetate/hexanes 1:3): \( R_f = 0.5 \); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.67-1.74 (m, 7H), 1.90-2.02 (m, 2H), 2.09 (s, 3H), 2.38 (s, 3H), 2.67 (m, 2H), 5.72 (s, 1H), 5.88 (dd, J = 6.4, 15.6 Hz, 1H), 6.62 (d, J = 15.6 Hz, 1H), 7.20-7.31 (m, 2H), 7.36 (m, 1H), 7.44 (m, 1H).
2.46-2.58 (m, 2H), 5.74 (s, 1H), 6.36 (d, J = 16.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.51-7.57 (m, 2H), 7.68 (d, J = 16.0 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 201.2, 199.3, 156.7, 143.4, 134.5, 130.0, 129.7, 127.7, 127.2, 126.4, 121.4, 64.4 35.8, 28.0, 26.1, 24.8, 20.9; HR-EI-MS: m/z calcd. for C20H24O2: 296.1773, found: 296.1771 [M]+.

**Compound 503:** Enone 497 (5 mg, 0.02 mmol) was dissolved in methylene chloride (0.5 mL) and cooled to -78 °C. Triethylamine (6 μL, 0.04 mmol) was added, followed by TBSOTf (7 μL, 0.03 mmol). The mixture was stirred for 20 minutes, and then placed directly on a neutralized (10% NEt3/Hexanes) silica column. Elution and concentration provided silyl enol ether 503 as an oil (6 mg, 80%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.6 1H NMR (400 MHz, C6D6): δ 0.15 (s, 3H), 0.17 (s, 3H), 1.00 (s, 9H), 1.49 (d, J = 6.8 Hz, 3H), 2.09 (s, 3H), 4.18 (q, J = 6.8 Hz, 1H), 4.38 (bs, 1H), 4.44 (bs, 1H), 5.87 (s, 1H), 6.49 (d, J = 15.0 Hz, 1H), 6.92-7.01 (m, 2H), 7.16-7.19 (m, 1H), 7.35-7.38 (m, 1H), 7.57 (d, J = 15.0 Hz, 1H); 13C NMR (100 MHz, C6D6): δ 199.0, 155.8, 155.1, 140.1, 136.0, 129.5, 128.6, 127.3, 127.0, 123.8, 97.0, 49.9, 27.2, 26.0, 20.7, 18.4, 17.6, -4.5, -4.6.

**Compound 504:** Triene 503 (11 mg, 0.03 mmol) was dissolved in m-xylene-d8 (0.7 mL) and transferred to a NMR tube. The reaction was heated at 120 °C for 8 hours, then 150 °C an additional 6 hours. After cooling to room temperature, the reaction mixture was concentrated and subjected to column chromatography. Tricycle 504 was obtained as a mixture of C19 isomers (10 mg, 91%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.6 (no Rf change from 503, but no longer UV active); 1H NMR (400 MHz, C6D6): δ 0.19-0.25 (m, 12H), 0.96 (s, 9H), 0.97 (s, 9H), 1.10 (s, 3H) 1.16 (s, 3H), 1.25 (s, 3H), 1.30 (s, 3H), 1.43 (d, J = 7.6 Hz, 3H), 1.51 (d, J = 6.8 Hz, 3H), 1.63-1.78 (m, 2H), 1.88 (d, J = 12.0 Hz, 1H), 2.01-2.17 (m, 2H), 2.26 (d, J = 12.8 Hz, 1H), 3.49 (q, J = 7.6 Hz, 1H), 3.57 (q, J = 6.8 Hz, 1H), 3.66 (d, J = 12.8 Hz, 1H), 3.80 (d, J = 12.0 Hz, 1H), 5.40 (app. t, J = 2.4 Hz, 2H), 7.16-7.34 (m, 8H).

**Compound 505:** Tricycle 504 (9 mg, 0.024 mmol) was dissolved in THF (4 mL) at room temperature. HCl (1 mL, 1 M aqueous solution) was added and the mixture was stirred for 23 hours. The reaction was diluted with diethyl ether and washed with aqueous NaHCO3. The organics were dried over MgSO4 and a small
amount of NEt₃ was added prior to concentration. Column chromatography gave diketone 505 as an oil (4 mg, 65%). TLC (ethyl acetate/hexanes 1:3): Rₜ = 0.4; ¹H NMR (400 MHz, CDCl₃): δ 1.06 (s, 3H), 1.12 (s, 1.5H), 1.37 (s, 4.5H), 1.41 (d, J = 7.2 Hz, 3H), 1.51 (d, J = 6.8 Hz, 3H), 2.15 (dd, J = 2.4, 13.6 Hz, 0.6H), 2.17 (d, J = 12.0 Hz, 1H), 2.24 (dd, J = 2.4, 13.6 Hz, 1H), 2.37 (d, J = 13.6 Hz, 0.6H), 2.43 (d, J = 14.0 Hz, 1H), 2.54 (app. dt, J = 1.2, 13.6 Hz, 0.6H), 2.61 (d, J = 12.8 Hz, 0.6H), 2.67 (app. dt, J = 0.8, 13.6 Hz, 1H), 3.04 (dd, J = 2.0, 4.4, 13.6 Hz, 1H), 3.16 (ddd, J = 2.4, 5.2, 14.0 Hz, 0.6H), 7.12-7.34 (m, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 210.1, 209.6, 208.9, 208.8, 138.8, 137.7, 136.2, 128.0, 127.7, 127.6, 127.2, 124.7, 124.5, 122.9, 58.0, 56.7, 56.62, 56.57, 49.4, 48.3, 45.7, 43.7, 38.7, 38.1, 37.4, 30.5, 30.1, 29.7, 22.0, 21.1, 17.8, 11.0; HR-EI-MS: m/z calcd. for C₁₇H₂₀O₂: 256.1460, found: 256.1458 [M⁺].

**Compound 528:** Butyrolactone 527 (5.2 g, 22.7 mmol) was dissolved in THF (100 mL) at room temperature. NaBH₄ (1.73 g, 45.53 mmol) was added in one portion, followed by MeOH (50 mL). The mixture was heated at 60 °C for 20 minutes, and then cooled to 0 °C and the reaction was quenched with water. The reaction was extracted with EtOAc and the combined organic extracts were dried over MgSO₄. Column chromatography gave diol 528 (4.8 g, 91%). TLC (ethyl acetate/hexanes 2:3): Rₜ = 0.91; ¹H NMR (400 MHz, CDCl₃): δ 0.91 (d, J = 6.8 Hz, 3H), 1.41 (s, 9H), 1.44-1.51 (m, 2H), 1.80-1.94 (m, 1H), 2.93-3.05 (m, 1H), 3.19-3.27 (m, 1H), 3.43 (dd, J = 6.8, 10.4 Hz, 1H), 3.52 (dd, J = 4.4, 10.4 Hz, 1H), 3.77-3.90 (m, 2H), 5.0-5.11 (bs, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 156.8, 79.6, 68.5, 67.5, 46.6, 39.1, 32.0, 28.3, 17.2; αD +8.37 (c = 1.87, CHCl₃); HRMS: m/z calcd. for C₁₀H₁₅O₅: #, found: # [M+H⁺].

**Compound 529:** To a stirred solution of diol 528 (3.7 g, 15.88 mmol) in dimethylformamide (50 mL), was added imidazole (2.14 g, 31.47 mmol) and TBSCl (2.65 g, 17.58 mmol) at room temperature. The reaction was stirred overnight, and then diluted with EtOAc and aqueous NH₄Cl. Repeated EtOAc extractions were performed, and the organic extracts were combined before being dried over MgSO₄. Column chromatography gave silyl ether 529 as an oil (4.3 g, 78%). TLC (ethyl acetate/hexanes 2:3): Rₜ = 0.4; ¹H NMR (400 MHz, CDCl₃): δ 0.04 (s, 6H), 0.85 (s, 9H), 1.38-1.41 (m, 11H), 1.7-1.9 (m, 1H), 2.8-2.95 (m, 1H), 3.15-3.3 (m, 1H), 3.35-3.45 (m, 1H), 3.45-3.55 (m, 1H), 3.6-3.8 (m, 1H), 5.0-5.11 (bs, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 156.4, 79.0, 68.4, 68.2, 46.4, 39.7, 32.1, 28.3, 25.8, 18.2, 17.2, -5.61, -5.63; αD +12.37 (c = 2.7, CHCl₃); HRMS: m/z calcd. for C₁₀H₁₅O₅: #, found: # [M+H⁺].
Compound 530: Alcohol 529 (3.9 g, 11.24 mmol) was dissolved in methylene chloride (300 mL) and cooled to 0 °C. Dimethoxy propane (20 mL) was added followed by camphorsulfonic acid (200 mg). The reaction was allowed to warm to room temperature over 2 hours, at which time the reaction was diluted with aqueous NaHCO₃. Repeated methylene chloride extractions were performed, the organic extracts combined, dried over MgSO₄, and subjected to column chromatography. N-O ketal 530 was obtained as an oil (4.0 g, 92%). TLC (ethyl acetate/hexanes 2:3): Rf = 0.9; ¹H NMR (400 MHz, CDCl₃): δ 0.02 (s, 6H), 1.8-1.95 (m, 12H), 1.39-1.58 (m, 15H), 1.58-1.7 (m, 2H), 2.89-3.05 (m, 1H), 3.36-3.47 (m, 1H), 3.52-3.62 (m, 1H), 3.62-3.72 (m, 1H), 4.05-4.15 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 152.2, 151.8, 93.1, 92.7, 79.8, 79.2, 72.4, 72.1, 68.4, 68.3, 67.8, 51.4, 51.2, 36.7, 36.6, 33.0, 32.8, 28.4, 27.3, 26.2, 25.9, 25.1, 24.2, 18.2, 17.2, 17.1, -5.47, -5.49; αD +19.5 (c = 1.95, CHCl₃); HRMS: m/z calcd. for C₁₀H₁₅O₅: #, found: # [M+H]+.

Compound 531: N-O Ketal 530 (3.9 g, 10.06 mmol) was dissolved in THF (50 mL) at room temperature. TBAF (15 mL, 15.0 mmol) was added as a 1 M THF solution at room temperature. The reaction was stirred 1.5 hours then diluted with aqueous NaHCO₃. Repeated EtOAc extractions were performed, and the combined extracts dried over MgSO₄. Column chromatography gave alcohol 531 as an oil, which crystallized upon standing (1.98 g, 72%). TLC (ethyl acetate/hexanes 2:3): Rf = 0.4; ¹H NMR (400 MHz, CDCl₃): δ 0.97 (d, J = 7.2 Hz, 3H), 1.42-1.70 (m, 17H), 1.79-1.90 (m, 1H), 2.05-2.31 (m, 1H), 2.97-3.12 (m, 1H), 3.41-3.57 (m, 1H), 3.57-3.76 (m, 2H), 4.13-4.22 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 152.2, 151.8, 93.5, 93.0, 80.1, 79.4, 77.2, 71.6, 71.4, 68.1, 67.4, 51.3, 51.1, 51.0, 37.9, 36.4, 34.2, 32.7, 28.4, 27.2, 26.2, 25.1, 24.2, 20.6, 17.7, 16.8, 13.9; αD +26.0 (c = 1.94, CHCl₃); HRMS: m/z calcd. for C₁₀H₁₅O₅: #, found: # [M+H]⁺.

Compound 532: Alcohol 531 (560 mg, 2.05 mmol) was dissolved in benzene (20 mL) and cooled to 0 °C. PPh₃ (1.35 g, 5.14 mmol) and imidazole (349 mg, 5.12 mmol) were added in single portions, followed by I₂ (1.0 g, 3.94 mmol). The reaction was stirred 2 hours, and then diluted with diethyl ether and saturated aqueous Na₂S₂O₃. After the solution clarified, repeated ether extractions were performed. The ether extracts were combined, dried over MgSO₄, and concentrated. The crude residue was diluted with ether and the solids were filtered off. Column chromatography of the ether filtrate gave iodide 532 as an oil (832 mg, 99%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.7; ¹H NMR (300 MHz, CDCl₃): δ 1.0 (d, J = 6.4 Hz, 3H), 1.42-1.65 (m, 17H), 2.96-3.10 (m, 1H), 3.14-3.34 (m, 2H),
3.58-3.77 (m, 1H), 4.02-4.13 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 152.2, 151.7, 93.3, 92.8, 80.0, 79.3, 77.2, 71.4, 71.2, 51.1, 39.5, 31.7, 31.3, 31.2, 28.4, 27.2, 26.2, 25.1, 24.2, 21.1, 20.4, 17.7, 17.5, 17.2; $\alpha_D$ +8.76 (c = 5.0, CHCl$_3$); HRMS: m/z calcd. for C$_{10}$H$_{15}$O$_5$: #, found: # [M+H]$^+$.  

**Compound 535:** Alcohol 534 (13.4 g, 101 mmol) was dissolved in methylene chloride (70 mL) and cooled to $^0$C. Imidazole (17.9 g, 263.2 mmol) and TES-Cl (20 mL, 119.2 mmol) were added in single portions, respectively. The reaction was allowed to warm to room temperature over several hours. After stirring a total of 8.5 hours, the reaction was diluted with hexanes and water. Repeated ether extractions were performed and the combined extracts were dried over MgSO$_4$. Column chromatography gave silyl ether 535 as an oil (17.5 g, 70%). TLC (ethyl acetate/hexanes 2:3): $R_f$ = 0.9; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.59 (q, J = 8.0 Hz, 6H), 0.95 (t, J = 8.0 Hz, 9H), 1.50-1.62 (m, 2H), 1.62-1.74 (m, 2H), 2.34 (t, J = 5.6 Hz, 2H), 3.61 (t, J = 6.4 Hz, 2H), 3.66 (s, 3H).  

**Compound 536:** Dimethyl phosphonate (2.6 mL, 24.0 mmol) was dissolved in THF (70 mL) and cooled to -78 °C. $n$-BuLi (8.6 mL, 23.0 mmol) was added as a 2.7 M hexane solution portionwise over several minutes. The reaction mixture was stirred 20 minutes before methyl ester 535 (5.35 g, 21.7 mmol) was added via cannula over 20 minutes. The reaction was stirred an additional 40 minutes before aqueous NH$_4$Cl was added at -78 °C. The reaction was warmed to room temperature and diluted with hexanes prior to performing ether extractions. The combined organic extracts were dried over MgSO$_4$ and concentrated. The residue was passed through a silica plug, and phosphonate 536 was obtained as an oil (5.5g, 75%). TLC (ethyl acetate/hexanes 4:1): $R_f$ = 0.2; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.58 (q, J = 8.0 Hz, 6H), 0.94 (t, J = 8.0 Hz, 9H), 1.46-1.58 (m, 2H), 1.58-1.69 (m, 2H), 2.64 (t, J = 7.2 Hz, 2H), 3.05 (s, 1H), 3.1 (s, 1H), 3.60 (t, J = 6Hz, 2H), 3.77 (s, 3H), 3.80 (s, 3H).  

**Compound 537:** To a stirred suspension of NaH/mineral oil (110mg, 2.75 mmol) in THF (10 mL) at -78 °C, was added phosphonate 536 (785 mg, 2.32 mmol). The mixture was stirred 30 minutes, and then benzaldehyde (0.24 mL, 2.37 mmol) was
added at -78 °C via cannula over 5 minutes. Immediately after benzaldehyde addition, the reaction was transferred to a 0 °C ice bath and allowed to warm to room temperature over several hours. At the end of 4 hours stirring (from benzaldehyde addition), diethyl ether and aqueous NH₄Cl were added to the reaction. Repeated ether extractions were performed, and the combined ether extracts dried over MgSO₄. Column chromatography gave enone 537 as an oil (575 mg, 87%). TLC (ethyl acetate/hexanes 1:3): Rₖ = 0.8; ¹H NMR (500 MHz, CDCl₃): δ 0.06 (q, J = 8.0 Hz, 6H), 0.96 (t, J = 8.0 Hz, 9H), 1.56-1.64 (m, 2H), 1.70-1.78 (m, 2H), 2.70 (t, J = 7.5 Hz, 2H), 3.64 (t, J = 6.0 Hz, 2H), 6.74 (d, J = 17.0 Hz, 1H), 7.36-7.41 (m, 3H), 7.51-7.57 (m, 3H).

**Compound 538:** Silyl ether 537 (65 mg, 0.204 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. TBAF (0.3 mL, 0.3 mmol) was added as a 1 M THF solution. The mixture was stirred 1.5 hours, and then diluted with diethyl ether and water. Repeated EtOAc extractions were performed, and the combined extracts dried over MgSO₄. Column chromatography gave enone 538 as an oil (40 mg, 99%). TLC (ethyl acetate/hexanes 4:1): Rₖ = 0.5; ¹H NMR (400 MHz, CDCl₃): δ 1.54-1.65 (m, 2H), 1.70-1.81 (m, 2H), 2.54 (bs, 1H), 2.70 (t, J = 7.2 Hz, 2H), 3.64 (t, J = 6.8 Hz, 2H), 6.72 (d, J = 16.0 Hz, 1H), 7.31-7.39 (m, 3H), 7.49-7.57 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 202.6, 142.6, 134.3, 130.4, 128.8, 128.2, 125.9, 62.0, 40.3, 32.0, 20.1.

**Compound 511:** Alcohol 538 (47 mg, 0.23 mmol) was dissolved in acetonitrile (3 mL) at room temperature. IBX (150 mg, 0.53 mmol) was added and the mixture was heated to reflux. The reaction mixture cooled to room temperature and filtered through florisil after 25 minutes at reflux. Aldehyde 511 was obtained in sufficient purity (37 mg, 77%). TLC (ethyl acetate/hexanes 2:3): Rₖ = 0.9; ¹H NMR (500 MHz, CDCl₃): δ 1.98-2.06 (m, 2H), 2.56 (t, J = 7.0 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H), 6.72 (d, J = 16.0 Hz, 1H), 7.37-7.43 (m, 3H), 7.52-7.59 (m, 3H), 9.80 (bs, 1H).

**Compound 539:** Enone 537 (680 mg, 2.14 mmol) was dissolved in methylene chloride (10 mL) and cooled to -78 °C. DIBAL-H (2.1 mL, 2.1 mmol) was added dropwise over 10 minutes as a 1 M methylene chloride solution. The reaction was stirred 1.5 hours at -78 °C, then methanol and an aqueous Rochelle’s salt solution was added. The ice bath was removed and the reaction was allowed to stir until it clarified. Repeated
ether extractions, combination of the organic extracts, drying over MgSO₄, and column chromatography gave allylic alcohol 539 as an oil (615 mg, 90%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.5; ¹H NMR (400 MHz, CDCl₃): δ 0.59 (q, J = 8.0 Hz, 6H), 0.95 (t, J = 8.0 Hz, 9H), 1.35-1.73 (m, 6H), 3.62 (t, J = 6.4 Hz, 2H), 4.29 (app. q, J = 6.8 Hz, 1H), 6.22 (dd, J = 7.2, 16.0 Hz, 1H), 6.57 (d, J = 16.0 Hz, 1H), 7.21-7.41 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 136.7, 132.5, 130.1, 128.5, 127.5, 126.4, 72.9, 62.7, 37.0, 32.6, 21.7, 6.7, 4.3.

**Compound 540:** Allylic alcohol 539 (560 mg, 1.75 mmol) was dissolved in dimethylformamide (10 mL) and cooled to 0 °C. Imidazole (712 mg, 10.46 mmol) was added followed by TBSCl (660 mg, 4.38 mmol). The reaction was allowed to slowly warm to room temperature. After stirring 15 hours, the reaction was diluted with diethyl ether and water. Repeated ether extractions were performed, combined, and dried over MgSO₄. Column chromatography gave 540 as an oil (724 mg, 95%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.9; ¹H NMR (400 MHz, CDCl₃): δ 0.06 (s, 6H), 0.07 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 0.94 (s, 9H), 1.34-1.69 (m, 6H), 3.63 (t, J = 6.4 Hz, 2H), 4.28 (app. q, J = 6.4 Hz, 1H), 6.19 (dd, J = 6.8, 16.0 Hz, 1H), 6.50 (d, J = 16.0 Hz, 1H), 7.21-7.41 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 137.2, 133.5, 128.9, 128.5, 127.2, 126.3, 73.6, 63.2, 38.3, 32.8, 26.0, 25.9, 21.7, 18.4, 18.3, -4.4, -5.8, -5.3; ESI-MS: m/z calcd. for C₂₅H₅₀O₂Si₂N₁: 451.30, found: 451.82 [M+NH₄]⁺.

**Compound 541:** Bis-TBS ether 540 (700 mg, 1.61 mmol) was dissolved in ethanol (10 mL) and PPTS (9 mg) was added at room temperature. The reaction was stirred 13 hours, and then aqueous NaHCO₃ and diethyl ether were added. Repeated ether extractions were performed, combined, and dried over MgSO₄. Column chromatography gave alcohol 541 as an oil (392 mg, 77%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.2; ¹H NMR (400 MHz, CDCl₃): δ 0.06 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.36-1.70 (m, 6H), 3.64 (t, J = 6.4 Hz, 2H), 4.28 (app. q, J = 6.4 Hz, 1H), 6.17 (dd, J = 6.4, 16.0 Hz, 1H), 6.48 (d, J = 16.0 Hz, 1H), 7.20-7.39 (5H); ¹³C NMR (100 MHz, CDCl₃): δ 137.0, 133.3, 129.0, 128.5, 127.3, 126.3, 73.5, 62.9, 38.1, 32.7, 25.9, 21.4, 18.3, -4.2, -4.8.

**Compound 542:** To a stirred acetonitrile (3 mL) solution of 541 (260 mg, 0.811 mmol), was added IBX (700 mg, 2.5 mmol). The mixture was heated to reflux and stirred for 1 hour, then cooled to room temperature and filtered through a silica plug. Aldehyde
was obtained without the need for further purification (246 mg, 95%). This material was typically used in the next step immediately after preparation. Therefore, aldehyde 542 was coevaporated at reduced pressure several times with toluene to limit water content. TLC (ethyl acetate/hexanes 1:3): Rf = 0.6; 1H NMR (500 MHz, CDCl$_3$): δ 0.05 (s, 3H), 0.08 (s, 3H), 0.92 (s, 9H), 1.57-1.80 (m, 6H), 2.46 (t, J = 6.5 Hz, 2H), 4.30 (app. q, J = 6.5 Hz, 1H), 6.15 (dd, J = 7.0, 16.0 Hz, 1H), 6.50 (d, J = 16.0 Hz, 1H), 7.21-7.25 (m, 1H), 7.29-7.38 (m, 4H), 9.76 (bs, 1H).

**Compound 543:** Alkyl iodide 532 (370 mg, 0.97 mmol) was dissolved in diethyl ether (1.8) at room temperature and cooled to -78 °C. t-BuLi (1.4 mL, 2.12 mmol) was added as a 1.5 M pentane solution dropwise over 2 minutes. The mixture was stirred 1 minute, and then aldehyde 543 (210 mg, 0.66 mmol) was added via cannula over 5 minutes. The reaction was stirred 4 hours at -78 °C, and then diluted with diethyl ether and water. Repeated diethyl ether extractions were performed and the ether extracts combined and dried over MgSO4. Column chromatography gave secondary alcohol 543 as a mixture of diastereomers and rotamers (247 mg, 65%). TLC (ethyl acetate/hexanes 1:9): Rf = 0.1; 1H NMR (500 MHz, CDCl$_3$): δ 0.05 (s, 3H), 0.08 (s, 3H), 0.86-0.99 (m, ~ 18H), 1.31-1.72 (m, ~ 23H), 2.93-3.09 (m, 1H), 3.58-3.78 (m, 2H), 4.06-4.19 (m, 1H), 4.23-4.32 (m, 1H), 4.78-4.93 (m, 1H), 6.16 (dd, J = 6.5, 16.0 Hz, 1H), 6.48 (d, J = 16.0 Hz, 1H), 7.19-7.24 (m, 1H), 7.29-7.38 (m, 4H); ESI-MS: m/z calcd. for C$_{33}$H$_{57}$O$_5$N$_1$Si$_1$Na$_1$: #, found: 598.32 [M+Na]$^+$. 

**Compound 544:** To a stirred methylene chloride (4 mL) solution of alcohol 543 (270 mg, 0.469 mmol), was added Dess-Martin periodinane (380 mg, 0.90 mmol) at room temperature. The reaction was stirred 8 hours at room temperature, and then diluted with diethyl ether. Aqueous Na$_2$S$_2$O$_3$ was added and the reaction stirred until it clarified. Repeated ether extractions were performed and the combined ether extracts were dried over MgSO4. Column chromatography provided ketone 544 as an oil (188 mg, 70%). Mixture of diastereomers and rotamers: 1H NMR (400 MHz, CDCl$_3$): δ 0.04 (s, 3H), 0.07 (s, 3H), 0.91 (s, 9H), 0.92-0.96 (m, ~ 1H), 1.40-1.76 (m, ~ 18H), 2.06-2.32 (m, 2H), 2.35-2.49 (m, 2H), 2.93-3.10 (m, 1H), 3.54-3.79 (m, 1H), 4.0-4.13 (m, 1H), 4.27 (m, 1H), 6.15 (dd, 1H), 6.48 (d, 1H), 7.18-7.37 (m, 5H); 13C NMR (100 MHz, CDCl$_3$): δ 210.4, 210.2, 152.3, 151.8, 141.6, 136.9, 133.0, 131.5, 129.2, 128.5, 127.9, 127.3, 126.3, 94.4, 93.3, 92.8, 80.0, 79.4, 77.2,
Compound 545: To a stirred THF (3 mL) solution of 544 (170 mg, 0.30 mmol) at room temperature, was added TBAF (0.5 mL, 0.5 mmol) as a 1 M THF solution. After stirring 1 hour, additional TBAF (0.2 mL, 0.2 mmol) was added. A third portion of TBAF (0.3 mL, 0.3 mmol) was added 2 hours after the second addition. The reaction was stirred a total of 7 hours from the initial TBAF addition, at which time the reaction was diluted with diethyl ether and aqueous NH₄Cl. Repeated ether extractions were performed, combined, and dried over MgSO₄. Column chromatography gave allylic alcohol 545 as an oil (136 mg, 95%). Mixture of diastereomers and rotamers: ¹H NMR (400 MHz, CDCl₃): δ 0.95 (d, J = 6.8 Hz, 3H), 1.23-1.33 (m, 1H), 1.36-1.77 (m, ~23H), 2.08-2.33 (m, 2H), 2.36-2.53 (m, 3H), 2.93-3.08 (m, 1H), 3.56-3.75 (m, 1H), 4.01-4.13 (m, 1H), 4.23-4.32 (m, 1H), 6.21 (dd, J = 7.2, 16.0 Hz, 1H), 6.58 (d, J = 16.0 Hz, 1H), 7.17-7.40 (m, 5H).

Compound 510: To a stirred methylene chloride (2 mL) solution of 545 (138 mg, 0.3 mmol), was added Dess-Martin periodinane (220 mg, 0.53 mmol) at room temperature. After stirring 3 hours, the reaction was diluted with diethyl ether and aqueous Na₂S₂O₃ and then stirred until the solution clarified. The mixture was partitioned between ether and water and the combined organic layers were dried over MgSO₄. Column chromatography gave diketone 510 as an oil (106 mg, 79%). Mixture of rotamers: TLC (ethyl acetate/hexanes 1:3); Rf = 0.2; ¹H NMR (400 MHz, CDCl₃): δ 0.93 (d, J = 6.0 Hz, 3H), 1.39-1.56 (m, ~15H), 1.85-1.97 (m, 2H), 2.05-2.35 (m, 2H), 2.40-2.50 (m, 3H), 2.69 (t, J = 6.8 Hz, 2H), 2.92-3.08 (m, 1H), 3.53-3.76 (m, 1H), 3.99-4.16 (m, 1H), 6.70 (d, J = 16.2 Hz, 1H), 7.34-7.39 (m, 3H), 7.49-7.59 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 20.9, 209.8, 152.2, 151.8, 142.6, 134.3, 130.4, 128.9, 128.2, 126.0, 93.2, 92.8, 79.9, 79.3, 71.8, 71.6, 51.1, 49.9, 49.8, 42.2, 42.1, 39.6, 39.5, 28.4, 27.2, 26.5, 26.3, 26.2, 25.1, 24.2, 20.1, 18.0.

Compound 509: Diketone 510 (60 mg, 0.13 mmol) was dissolved in 1 mL of an AcOH/H₂O (1:1) solution at room temperature. The mixture was heated to 50 °C and stirred 1 hour. After cooling to room temperature, the reaction was
diluted with diethyl ether and aqueous NaHCO₃. Solid Na₂CO₃ was added and repeated ether extractions were performed. The combined ether extracts were washed with aqueous NaHCO₃ and dried over MgSO₄. Column chromatography gave aminal 509 as an oil (36 mg, 72%). Mixture of rotamers: TLC (ethyl acetate/hexanes 1:3): Rf = 0.3; ¹H NMR (400 MHz, CDCl₃): δ 0.90 (d, J = 6.8 Hz, 1H), 0.91 (d, J = 6.8 Hz, 1H), 1.17-1.28 (m, 1H), 1.42-1.47 (m, ~ 10H), 1.53-2.32 (m, 7H), 2.60-2.75 (m, 2H), 3.33-3.55 (m, 2H), 4.34-4.42 (bs, 1H), 6.72 (d, J = 16.0 Hz, 0.5H), 6.74 (d, J = 16.0 Hz, 0.5H), 7.37-7.40 (m, 3H), 7.50-7.59 (m, 3H); ¹³C NMR (100 MHz, C₆D₆): δ 198.5, 198.4, 152.6, 152.2, 141.5, 141.2, 135.2, 135.0, 130.0, 129.8, 128.83, 128.76, 128.3, 128.0, 127.8, 126.8, 126.6, 94.4, 94.1, 79.4, 78.7, 72.5, 72.3, 65.8, 51.5, 51.1, 42.4, 41.13, 41.07, 40.95, 37.8, 37.7, 36.3, 35.5, 28.4, 28.3, 24.3, 24.2, 21.6, 21.5, 18.0, 15.5; αD = -41.1 (c = 18, mg/mL, CHCl₃); HRMS: m/z calcd. for C₂₄H₃₃O₄N₁Na₁: 422.23, found: 422.23 [MNa]+.

**Compound 554:** To a stirred solution of aldehyde 553 (17 g, 78.7 mmol) in diethyl ether (100 mL) at 0 °C, was added ethynyl magnesium bromide (195 mL, 97 mmol) as a 0.5 M THF solution over fifteen minutes. The reaction was stirred 2 hours, then hexanes and aqueous NH₄Cl were added. Repeated ether extractions were performed, and the combined organic extracts dried over MgSO₄. Column chromatography gave propargyl alcohol 554 as an oil (13.2 g, 69%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.6; ¹H NMR (400 MHz, CDCl₃): δ 0.05 (s, 6H), 0.89 (s, 9H), 1.48-1.58 (m, 4H), 1.69-1.78 (m, 2H), 1.91 (d, J = 5.6 Hz, 1H), 2.46 (d, J = 1.6 Hz, 1H), 3.63 (t, J = 6.0 Hz, 2H), 4.38 (ddd, J = 2.0, 6.4, 12.0 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 84.9, 72.9, 62.9, 62.3, 37.3, 36.3, 32.3, 25.9, 21.4, 18.3, -5.3.

**Compound 555:** To a stirred dimethylformamide (25 mL) solution of 554 (5.9 g, 24.38 mmol) at 0 °C, was added imidazole (4.1 g, 59.6 mmol), TBSCl (4.5 g, 29.8 mmol), and DMAP (100 mg). The reaction was then allowed to warm to room temperature. After stirring 17 hours, hexanes and water were added. Repeated diethyl ether extractions were performed, and the combined extracts dried over MgSO₄. Column chromatography gave 555 as an oil (7.9 g, 91%). TLC (ethyl acetate/hexanes 6:44): Rf = 0.8; ¹H NMR (400 MHz, CDCl₃): δ 0.04 (s, 6H), 0.10 (s, 3H), 0.13 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 1.38-1.57 (m, 3H), 1.60-1.75 (m, 3H), 2.36 (d, J = 2.0 Hz, 1H), 3.61 (t, J = 6 Hz, 2H), 4.33 (dt, J = 2.0, 6.8, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 85.7, 77.3, 63.0, 62.7, 38.4, 32.5, 26.0, 25.8, 21.6, 18.3, 18.2, -4.6, -5.1, -5.3.
**Compound 556:** Alkyne 555 (3.8 g, 10.65 mmol) was dissolved in THF (100 mL) and cooled to -78 °C. Pd(PPh₃)₂Cl₂ (145 mg, 0.21 mmol) was added, followed by addition of Bu₃SnH (3.15 mL, 11.7 mmol) in one portion. The reaction was warmed to -40 °C over three hours, at which time the reaction mixture was concentrated on a rotary evaporator without work up. Column chromatography of the residue gave stannane 556 as an oil (2.56 g, 63%). TLC (ethyl acetate/hexanes 1:99): Rf = 0.1; ¹H NMR (300 MHz, CDCl₃): δ 0.00-0.05 (m, 10H), 0.74-1.00 (m, 28H), 1.21-1.65 (m, 16H), 3.59 (t, J = 6.6 Hz, 2H), 3.96-4.05 (m, 1H), 5.72-6.21 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 152.1, 126.6, 77.6, 63.5, 38.1, 33.1, 29.3, 27.5, 26.2, 26.1, 22.0, 18.6, 18.5, 13.9, 9.6, -4.0, -4.6, -5.1.

**Compound 557:** Stannane 556 (5.3 g, 8.18 mmol) and aryl iodide 478 (2.1 g, 10.4 mmol) were mixed under argon. The mixture was diluted with toluene (60 mL) and degassed 20 minutes via bubbling argon. Pd₂(dba)₃ (620 mg, 0.68 mmol) was added, followed immediately with addition of Pr-Bu₃ (267 mg, 1.3 mmol) as a 10 % w/w hexane solution. The reaction was stirred at 80 °C 17 hours, and then cooled to room temperature. The mixture was filtered through a silica plug and concentrated. Column chromatography of the residue gave alcohol 557 as an oil (3.2 g, 82%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.5; ¹H NMR (400 MHz, CDCl₃): δ 0.04 (s, 6H), 0.06 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.92 (s, 9H), 1.29-1.67 (m, 4H), 2.95 (t, J = 7.2 Hz, 2H), 3.67 (t, J = 6.4 Hz, 2H), 3.80 (app. q, J = 6.4 Hz, 2H), 4.29 (app. q, J = 5.6 Hz, 1H), 6.07 (dd, J = 6.4, 15.6 Hz, 1H), 6.76 (d, 15.6 Hz, 1H), 7.15-7.24 (m, 3H), 7.42-7.48 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 136.5, 135.6, 135.5, 130.3, 127.3, 126.9, 126.4, 126.1, 73.5, 63.2, 63.0, 38.2, 36.5, 32.8, 26.0, 25.9, 21.6, 18.3, 18.2, -4.3, -4.7, -5.3.

**Compound 558:** Alcohol 557 (2.5 g, 5.2 mmol) was dissolved in acetonitrile (50 mL) and IBX (3.5 g, 12.5 mmol) was added. The solution was heated to reflux and stirred 1 hour. The mixture was cooled to room temperature and filtered through a plug of Florisil. Aldehyde 558 was obtained in high purity (2.24 g, 90%). TLC (ethyl acetate/hexanes 2:44): Rf = 0.7; ¹H NMR (400 MHz, CDCl₃): δ 0.04 (s, 6H), 0.05 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.91 (s, 3H), 1.30-1.68 (m, 4H), 3.60 (t, J = 6.4 Hz, 2H), 3.74 (d, J = 2.0 Hz, 2H), 4.27 (app. q, J = 6.0 Hz, 1H), 6.09 (dd, J = 6.4, 16.0 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.23-7.32 (m, 2H), 7.49 (d, J = 7.2 Hz, 1H), 9.69 (t, J = 2.0 Hz, 1H).
**Compound 559:** A CeCl₃ (2.18 g, 8.84 mmol)/THF (15 mL) slurry was prepared and cooled to 0 °C. 2-methyl-1-propenylmagnesium bromide (15.2 mL, 7.6 mmol) was added in one portion as a 0.5 M THF solution, and the mixture was stirred 1.5 hours. Aldehyde 558 (2.38 g, 4.99 mmol) was dissolved in THF (5 mL) and added to the slurry via cannula over 45 minutes. The reaction was warmed to room temperature 3 hours after aldehyde addition. Hexanes and water were added to the reaction and repeated diethyl ether extractions were performed. The combined organic extracts were dried over MgSO₄ and concentrated. Column chromatography gave allylic alcohol 559 as an oil (1.65 g, 61%). TLC (ethyl acetate/hexanes 6:44): Rₜ = 0.5; ¹H NMR (400 MHz, CDCl₃): δ 0.02-0.11 (m, 12H), 0.85-0.95 (m, 18H), 1.30-1.71 (m, 12H), 2.79-2.96 (m, 2H), 3.56-3.66 (m, 2H), 4.25-4.37 (m, 1H), 4.49-4.59 (m, 1H), 5.21-5.27 (m, 1H), 6.03-6.13 (m, 1H), 6.77-6.86 (m, 1H), 7.10-7.24 (m, 3H), 7.41-7.48 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 136.7, 136.6, 135.6, 135.42, 135.39, 135.3, 135.26, 131.0, 130.9, 127.14, 127.11, 127.0, 126.7, 126.6, 126.2, 126.1, 77.1, 73.8, 73.4, 69.04, 69.02, 63.13, 63.09, 41.33, 41.26, 38.3, 32.8, 25.92, 25.87, 25.66, 25.65, 21.64, 18.3, 18.2, 18.12, 18.06, -4.18, -4.27, -4.78, -5.33; HR-EI-MS: m/z calcd. for C₃₁H₅₆O₃Si₂: 532.3763, found: 532.3764 [M]+.

**Compound 560:** Allylic alcohol 559 (2.05 g, 3.8 mmol) was dissolved in methylene chloride (25 mL) and cooled to 0 °C. Hunig’s base (3.4 mL, 19.5 mmol) and MEMCl (1.3 mL, 11.3 mmol) were added. The solution was allowed to warm to room temperature over approximately 1 hour. After 11 hours (from MEMCl addition) additional Hunig’s base (1.7 mL, 9.8 mmol) and MEMCl (0.65 mL, 5.7 mmol) were added. Hexanes and aqueous NaHCO₃ were added to the reaction after a total of 18 hours stirring at room temperature. Repeated diethyl ether extractions were performed, and the combined ether extracts dried over MgSO₄. Column chromatography gave MEM ether 560 as an oil (1.9 g, 81%). TLC (ethyl acetate/hexanes 1:3): Rₜ = 0.6; ¹H NMR (300 MHz, CDCl₃): δ 0.04 (s, 6H), 0.05 (s, 3H), 0.05 (s, 3H), 0.88-0.92 (m, 18H), 1.30-1.73 (m, 12H), 2.69-2.82 (m, 1H), 2.86-3.00 (m, 1H), 3.09-3.33 (m, 6H), 3.60 (t, J = 6.0 Hz, 2H), 4.18-4.31 (m, 1H), 4.41-4.55 (m, 2H), 4.59-4.67 (m, 1H), 5.05-5.13 (m, 1H), 5.95-6.11 (m, 1H), 6.80 (d, J = 16.0 Hz, 0.5H), 6.82 (d, J = 16.0 Hz, 0.5H), 7.08-7.20 (m, 3H), 7.35-7.44 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 136.61, 136.51, 136.47, 136.2, 136.15, 135.24, 135.08, 131.12, 131.04, 127.08, 126.92, 126.83, 126.49, 126.39, 126.36, 125.85, 125.69, 124.83, 91.98, 91.91, 74.01, 73.60, 72.68, 72.59, 71.63, 66.12, 66.05, 63.14, 58.83, 39.16, 38.4, 32.89, 32.86, 25.95, 25.91, 25.79, 21.77, 18.22, 18.25, 18.21, 18.17, -4.07, -4.19, -4.76, -5.30; HR-EI-MS: m/z calcd. for C₃₅H₆₄O₅Si₂: 620.4287, found: 620.4293 [M]+.
**Compound 561:** Silyl ether 560 (600 mg, 0.97 mmol) was dissolved in THF (12 mL) and cooled to 0 °C. Pyridine (3 mL) was added to the cold solution, then Hf·Pyr (1.4 mL, 70% Hf / 30% Pyr solution) was added. The mixture was stirred 2.5 hours, and then transferred to a flask containing diethyl ether and NaHCO₃. The solution was then filtered through a silica plug and concentrated. Column chromatography gave alcohol 561 as an oil (391 mg, 80%). TLC (ethyl acetate/hexanes 2:3): Rₓ = 0.5; ¹H NMR (400 MHz, CDCl₃): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 1.40-1.71 (m, 11H), 2.70-2.82 (m, 1H), 2.87-2.98 (m, 1H), 3.08-3.20 (m, 1H), 3.21-3.32 (m, 4H), 3.58-3.67 (m, 1H), 4.24-4.34 (m, 1H), 4.40-4.54 (m, 2H), 4.59-4.65 (m, 1H), 5.04-5.12 (m, 1H), 5.97-6.10 (m, 1H), 6.77-6.80 (m, 1H), 7.08-7.19 (m, 3H), 7.37-7.45 (m, 1H); HR-EI-MS: m/z calcd. for C₂₉H₅₀O₅Si₁: 506.3422, found: 506.3398 [M]+.

**Compound 562:** Alcohol 561 (14 mg, 0.03 mmol) was dissolved in acetonitrile (1 mL) and IBX (18 mg, 0.06 mmol) was added. The mixture was stirred under reflux 1.5 hours, and then filtered through florisil. Aldehyde 562 was obtained in good purity (13 mg, 90%). TLC (diethyl ether/hexanes 1:1): Rₓ = 0.5; ¹H NMR (500 MHz, CDCl₃): δ 0.06 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.47-1.79 (m, ~ 10H), 2.42-2.51 (m, 2H), 2.69-2.82 (m, 1H), 2.87-3.01 (m, 1H), 3.10-3.22 (m, 1H), 3.23-3.33 (m, 5H), 4.24-4.36 (m, 1H), 4.42-4.54 (m, 2H), 4.59-4.67 (m, 1H), 5.04-5.13 (m, 1H), 5.96-6.10 (m, 1H), 6.79-6.88 (m, 1H), 7.11-7.20 (m, 3H), 7.35-7.44 (m, 1H), 9.75-9.78 (m, 1H).

**Compound 563:** Alkyl iodide 532 (43 mg, 0.11 mmol) was dissolved in diethyl ether (0.5 mL) and cooled to -78 °C. t-BuLi (0.17 mL, 0.26 mmol) was added as a 1.5 M pentane solution. The reaction was stirred 3 minutes, then aldehyde 562 (40 mg, 0.08 mmol) was added via cannula over approximately 3 minutes. After stirring 2.5 hours, diethyl ether and aqueous NH₄Cl were added to the reaction mixture, and the mixture was warmed to room temperature. Repeated diethyl ether extractions were performed and the combined extracts were dried over MgSO₄. Column chromatography gave alcohol 563 as a mixture of diastereomers and rotamers (37 mg, 62%). TLC (ethyl acetate/hexanes 1:3): Rₓ = 0.2; ¹H NMR (300 MHz, CDCl₃): δ 0.06 (s, 3H), 0.08 (s, 3H),
Compound 564: Silyl ether 563 (180 mg, 0.24 mmol) was dissolved in THF (7 mL) at room temperature. TBAF (0.9 mL, 0.9 mmol) was added as a 1 M THF solution and the reaction was stirred 5 hours. The reaction mixture was diluted with diethyl ether and aqueous NaHCO₃. Repeated ether extractions were performed, and the combined ether extracts were dried over MgSO₄. Column chromatography gave diol 564 as an oil (146 mg, 95%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 2:3): Rf = 0.2; ¹H NMR (500 MHz, CDCl₃): δ 0.94-1.0 (m, ~ 3H), 1.22-1.73 (m, ~ 30H), 2.66-2.76 (m, 1H), 2.95-3.14 (m, 2H), 3.33 (s, 3H), 3.33-3.45 (m, 5H), 3.57-3.77 (m, 2H), 4.07-4.20 (m, 1H), 4.27-4.39 (m, 1H), 4.47-4.57 (m, 2H), 4.65-4.69 (m, 1H), 5.03-5.08 (m, 1H), 6.06-6.16 (m, 1H), 6.90-6.99 (m, 1H), 7.06-7.19 (m, 3H), 7.38-7.43 (m, 1H); HR-EI-MS: m/z calcd. for C₃₇H₆₁O₈N₁: 647.4397, found: 670.4393 [M⁺].

Compound 565: Diol 565 (135 mg, 0.208 mmol) was dissolved in methylene chloride (9 mL) at room temperature. Dess-Martin periodinane (265 mg, 0.63 mmol) was added and the reaction mixture was stirred. Additional Dess-Martin periodinane (250 mg, 0.59 mmol) was added after 2 hours, and the mixture was stirred 2 hours additional (4 hours total reaction time). The reaction was then diluted with diethyl ether and water. Repeated ether extractions were performed and the combined extracts were dried over MgSO₄. Column chromatography gave diketone 565 as an oil (81 mg, 60%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 2:3): Rf = 0.4; ¹H NMR (500 MHz, CDCl₃): δ 0.08-0.99 (m, ~ 5H), 1.43-1.55 (m, > 15H), 1.58 (s, 3H), 1.67 (s, 3H), 1.91-1.99 (m, 2H), 2.08-2.46 (m, ~ 4H), 2.46-2.53 (m, 2H), 2.67-2.73 (m, 2H), 2.86-2.96 (m, 2H), 2.96-3.08 (m, 2H), 3.20-3.26 (m, 1H), 3.27-3.35 (m, 8H), 3.56-3.76 (m, 2H), 4.03-4.14 (m, 1H), 4.41-4.51 (m, 2H), 4.61-4.66 (m, 1H), 5.04-5.09 (m, 1H), 6.63
Compound 566: Diketone 565 (2 mg, 0.003 mmol) was dissolved in 0.5 mL of an AcOH/H₂O (1:1) solution. The mixture was heated at 35 °C 12 hours. The mixture was then diluted with diethyl ether and aqueous NaHCO₃. Repeated ether extractions were performed and the combined extracts were dried over MgSO₄. Rapid column chromatography with neutralized silica gave aminal 566 as an oil (2 mg, 90%). TLC (ethyl acetate/hexanes 2:3): Rf = 0.7; ¹H NMR (400 MHz, CDCl₃): δ 0.86-0.94 (m, 3H), 1.02-1.08 (m, 1H), 1.37-1.87 (m, ~ 20H), 2.0-2.38 (m, 3H), 2.59-2.75 (m, 2H), 2.84-2.93 (m, 1H), 2.96-3.05 (m, 1H), 3.17-3.40 (m, 5-6H), 3.47-3.77 (m, 2H), 4.35-4.41 (m, 1H), 4.60-4.65 (d, J = 6.8 Hz, 1H), 5.02-5.09 (m, 1H), 6.63 (2 adjacent 16.0 Hz doublets, 1H total), 7.10-7.33 (m, 3H), 7.56 (m, 1H), 7.93 (d, J = 16.0 Hz, 0.5H), 7.95 (d, J = 16.0 Hz, 0.5 H); ¹³C NMR (100 MHz, CDCl₃): δ 200.18, 199.88, 152.69, 152.24, 140.36, 140.23, 140.06, 138.8, 137.01, 133.96, 133.86, 131.8, 129.71, 129.60, 129.14, 127.23, 127.11, 126.74, 126.19, 125.98, 124.66, 124.37, 94.12, 92.12, 80.07, 79.31, 78.09, 77.21, 72.92, 72.72, 72.56, 72.35, 71.63, 69.5, 66.22, 58.85, 51.09, 42.01, 41.05, 40.94, 40.69, 39.57, 39.31, 37.68, 35.87, 35.04, 29.68, 28.50, 28.42, 28.20, 25.79, 25.58, 24.07, 21.52, 18.17, 18.10, 17.67, 17.59; HR-EI-MS: m/z calcd. for C₃₄H₅₁O₇N₁: 585.3660, found: 585.3659 [M⁺].

Compound 567: Aminal 567 (7 mg, 0.12 mmol) was dissolved in methylene chloride (1 mL) and cooled to -78 °C. Triethylamine (180 µL, 1.3 mmol) was added, followed by TBSOTf (several drops, ~ 1 eq.). The reaction was stirred 45 minutes, and then diluted with diethyl ether and aqueous NaHCO₃. Repeated ether extractions were performed and the combined ether extracts were dried over MgSO₄. Rapid column chromatography with neutralized silica provided a mixture of silyl enol ethers (8 mg, 85%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 1:3):
Compound 569: Allylic alcohol 559 (685 mg, 1.29 mmol) was dissolved in dimethylformamide (7 mL) and NaH (43 mg, 1.79 mmol) was added at room temperature as a mineral oil dispersion. After stirring several minutes, PMBCl (0.25 mL, 1.84 mmol) was added, followed by TBAI (40 mg, 0.11 mmol). The reaction was stirred 8.5 hours, and then diluted with diethyl ether and aqueous NH₄Cl. Repeated ether extractions were performed and the combined extracts were dried over MgSO₄. Column chromatography gave PMB ether 569 as an oil (378 mg, 45%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.7; ¹H NMR (400 MHz, CDCl₃): δ 0.04-0.08 (m, 12H), 0.90 (s, 9H), 0.92 (s, 9H), 1.25-1.77 (m, ~12H), 2.68-2.82 (m, 1H), 2.99-3.12 (m, 1H), 3.57-3.65 (m, 2H), 3.78 (s, 3H), 4.16-4.29 (m, 2H), 4.43-4.50 (m, 1H), 5.12-5.19 (m, 1H), 5.96-6.05 (m, 1H), 6.73-6.83 (m, 3H), 7.05-7.20 (m, 5H), 7.40 (d, J = 6.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 158.83, 136.52, 136.09, 135.97, 135.90, 135.14, 135.07, 131.21, 131.03, 130.49, 128.96, 128.89, 128.79, 126.89, 126.82, 126.77, 126.63, 126.5, 126.33, 125.8, 125.76, 125.58, 113.56, 113.53, 75.47, 75.38, 73.82, 73.58, 69.36, 69.35, 65.50, 63.14, 55.18, 39.45, 38.40, 32.92, 32.88, 32.36, 25.95, 25.90, 25.77, 25.75, 25.36, 21.71, 21.66, 18.32, 18.21, 18.12, 18.02, -4.09, -4.18, -4.73, -4.76, -5.31.

Compound 570: Silyl ether 569 (40 mg, 0.06 mmol) was dissolved in THF (2 mL) and cooled to 0 °C. Pyridine (0.35 mL) then HF·Pyr (0.15 mL) was added. After 5 hours stirring at 0 °C, diethyl ether and aqueous NaHCO₃ were added. Repeated ether extractions were performed and the combined ether extracts were dried over MgSO₄. Column chromatography gave alcohol 570 as an oil (25 mg, 75%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.2; ¹H NMR (500 MHz, CDCl₃): δ 0.04-0.08 (m, 6H), 0.91 (s, 9H), 1.28-1.35 (m, 3H), 1.35-1.60 (m, 6H), 1.68-1.71 (m, 3H), 2.69-2.78 (m, 1H), 2.99-3.11 (m, 1H), 3.58-3.66 (m, 2H), 3.78 (s, 3H), 4.16-4.27 (m, 3H), 4.43-4.50 (m, 1H), 5.11-5.17 (m, 1H), 5.94-6.03 (m, 1H), 6.72-6.81 (m, 3H), 7.04-7.20 (m, 5H), 7.37-7.41 (d, J = 7.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 158.77, 136.45, 136.23, 136.18, 136.00, 135.91, 134.91, 134.82, 131.24, 131.22, 131.08, 131.03, 128.98, 128.90, 127.08, 126.89, 126.86, 126.35, 125.80, 125.74, 125.52, 113.58, 113.56, 75.47, 75.38, 73.82, 73.58, 69.36, 69.26, 62.89, 62.87, 62.82.
Compound 571: Alcohol 570 (360 mg, 0.67 mmol) was dissolved in acetonitrile (10 mL) and IBX (550 mg, 1.96 mmol) was added. The reaction was stirred at reflux 1 hour, cooled to room temperature, and rapidly filtered through a silica plug. Aldehyde 571 was isolated in good purity (324 mg, 90%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.5; 1H NMR (400 MHz, CDCl3): δ 0.04-0.07 (m, 6H), 0.91 (s, 9H), 1.29-1.35 (m, 3H), 1.48-1.72 (m, 7H), 2.39-2.47 (m, 2H), 2.69-2.80 (m, 1H), 3.00-3.10 (m, 1H), 3.78 (s, 3H), 4.16-4.29 (m, 3H), 4.42-4.50 (m, 1H), 5.10-5.18 (m, 1H), 5.94-6.01 (m, 1H), 6.74-6.82 (m, 3H), 7.01-7.21 (m, 5H), 7.39 (d, J = 7.5 Hz, 1H), 9.73 (t, J = 2.0 Hz, 0.5H), 9.75 (t, J = 2.0 Hz, 0.5H).

Compound 572: Alkyl iodide 532 (385 mg, 1.0 mmol) was dissolved in diethyl ether (3 mL) and cooled to -78 °C. t-BuLi (1.45 mL mL, 2.175 mmol) was added as a 1.5 M pentane solution dropwise over 2 minutes. The reaction was stirred 1 minute, then a diethyl ether (1 mL) solution of aldehyde 562 (352 mg, 0.61 mmol) was added via cannula over approximately 3 minutes. After stirring 5 hours, diethyl ether and aqueous NH4Cl were added to the reaction mixture, and the mixture was warmed to room temperature. Repeated diethyl ether extractions were performed and the combined extracts were dried over MgSO4. Column chromatography gave alcohol 572 as a mixture of diastereomers and rotamers (274 mg, 57%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.3; 1H NMR (400 MHz, CDCl3): δ 0.03-0.13 (m, 6H), 0.84-1.0 (m, 11H), 1.23-1.83 (m, ~ 27H), 2.68-2.80 (m, 1H), 2.95-3.11 (m, 2H), 3.57-3.78 (m, 1H), 3.78 (s, 3H), 4.07-4.27 (m, 3H), 4.42-4.50 (m, 1H), 5.11-5.18 (m, 1H), 5.95-6.04 (m, 1H), 6.72-6.82 (m, 3H), 7.04-7.21 (m, 5H), 7.36-7.42 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 158.78, 152.2, 151.8, 136.46, 136.14, 135.97, 135.87, 134.92, 134.82, 131.18, 131.06, 131.01, 128.96, 128.87, 127.87, 127.72, 127.05, 126.83, 126.32, 125.79, 125.74, 125.52, 113.54, 93.2, 92.9, 80.0, 79.3, 77.21, 75.51, 75.41, 75.33, 73.80, 73.61, 73.56, 71.99, 69.45, 69.35, 69.30, 69.24, 55.18, 51.27, 51.03, 45.04, 44.77, 40.96, 40.82, 39.44, 39.21, 38.50, 38.42, 37.85, 29.65, 28.41, 28.25, 27.25, 26.99, 26.53, 26.20, 25.89, 25.81, 25.77, 25.15, 24.25, 21.43, 21.33, 18.19, 18.11, -4.08, -4.18, -4.73; HRMS: m/z calcd. for C47H75O7N1Si1Na1: 815.92, found: 816.44 [M+Na]+.
Compound 573: Alcohol 572 (3 mg, 0.004 mmol) was dissolved in methylene chloride (0.7 mL) at room temperature. Dess-Martin periodinane (5 mg, 0.012 mmol) was added and the reaction mixture stirred 2 hours. The solution was then diluted with diethyl ether and aqueous Na₂S₂O₃, and then stirred until the mixture clarified. Repeated ether extractions were performed and the combined extracts were dried over MgSO₄. Column chromatography gave ketone 573 as an oil (3 mg, 95%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 1:3): Rᵢ = 0.5; ¹H NMR (400 MHz, CDCl₃): δ 0.03-0.10 (m, 3H), 0.88-0.98 (m, 12H), 1.27-1.73 (m, 23H), 2.06-2.31 (m, 2H), 2.33-2.49 (m, 3H), 2.68-2.80 (m, 1H), 2.93-3.11 (m, 2H), 3.58-3.75 (m, 1H), 3.78 (s, 3H), 4.01-4.12 (m, 1H), 4.15-4.28 (m, 3H), 4.42-4.49 (m, 1H), 5.11-5.18 (m, 1H), 5.94-6.03 (m, 1H), 6.72-6.83 (m, 3H), 7.03-7.20 (m, 5H), 7.35-7.42 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 210.18, 210.01, 158.84, 158.80, 136.39, 136.36, 136.15, 136.04, 135.95, 134.63, 134.56, 131.21, 131.10, 131.06, 128.98, 128.91, 127.25, 126.99, 126.94, 126.89, 126.36, 125.81, 125.76, 125.60, 125.57, 113.59, 113.55, 93.31, 92.81, 79.94, 79.43, 77.21, 75.58, 75.45, 73.68, 73.43, 71.96, 71.74, 69.40, 69.31, 55.20, 51.41, 51.17, 49.98, 43.35, 39.81, 39.43, 37.96, 29.68, 28.45, 27.32, 26.50, 26.38, 26.26, 25.90, 25.80, 25.77, 25.20, 24.28, 20.13, 19.63, 19.59, 18.20, 18.14, 18.04, -4.07, -4.17, -4.73, -4.75; ESI-MS: m/z calcd. for C₄₇H₇₃O₇N₁Si₁Na₁: 814.50, found: 814.45 [M+Na]+.

Compound 574: Silyl ether 573 (75 mg, 0.10 mmol) was dissolved in THF (2 mL) at room temperature. TBAF (0.25 mL, 0.25 mmol) was added as a 1 M THF solution and the reaction mixture was stirred 4.5 hours. The reaction mixture was diluted with diethyl ether and aqueous NaHCO₃. Repeated ether extractions were performed, and the combined ether extracts were dried over MgSO₄. Column chromatography gave diol 574 as an oil (54 mg, 85%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 1:3): Rᵢ = 0.1; ¹H NMR (400 MHz, CDCl₃): δ 0.92-0.97 (m, 3H), 1.23-1.78 (m, 27H), 2.08-2.32 (m, 2H), 2.38-2.51 (m, 3H), 2.69-2.77 (m, 1H), 2.95-3.08 (m, 2H), 3.57-3.74 (m, 1H), 3.78 (s, 3H), 4.02-4.22 (m, 4H), 4.42-4.50 (m, 1H), 5.10-5.18 (m, 1H), 5.94-6.03 (m, 1H), 6.73-6.84 (m, 3H), 7.02-7.20 (m, 5H), 7.35-7.41 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 210.23, 210.07, 158.86, 158.84, 152.21, 151.83, 136.17, 136.13, 136.01, 135.96, 133.59, 131.25, 131.01, 129.05, 128.33, 127.18, 126.37, 125.79, 125.74, 125.54, 125.46, 113.53, 93.27, 92.80, 79.96, 79.39,
Compound 575: Alcohol 574 (54 mg, 0.08 mmol) was dissolved in methylene chloride (1 mL) at room temperature. Dess-Martin periodinane (65 mg, 0.15 mmol) was added and the reaction mixture was stirred 2.5 hours. The reaction was diluted with diethyl ether and aqueous Na$_2$S$_2$O$_3$, and then stirred until the mixture clarified. Repeated ether extractions were performed and the combined extracts dried over MgSO$_4$. Column chromatography gave ketone 574 as an oil (37 mg, 69%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 1:3): $R_f = 0.3$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.96 (d, $J = 6.4$ Hz, 3H), 1.33 (s, 3H), 1.42-1.58 (m, 15H), 1.68 (s, 3H), 1.85-1.96 (m, 2H), 2.09-2.33 (m, 2H), 2.40-2.49 (m, 2H), 2.56-2.63 (m, 2H), 2.87 (dd, $J = 6.0$, 13.6, 1H), 2.96-3.11 (m, 2H), 3.57-3.75 (m, 1H), 3.78 (s, 3H), 4.02-4.21 (m, 3H), 4.45 (d, $J = 11.6$ Hz, 1H), 5.13 (d, $J = 8.8$ Hz, 1H), 6.53 (d, $J = 16.0$ Hz, 1H), 6.77 (d, $J = 8.4$ Hz, 2H), 7.04 (d, $J = 8.4$ Hz, 2H), 7.16-7.32 (m, 3H), 7.54 (d, $J = 7.2$ Hz, 1H), 7.91 (d, $J = 16.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 209.90, 209.73, 199.63, 158.87, 152.25, 151.89, 140.86, 138.86, 136.42, 133.81, 131.82, 130.79, 129.77, 129.07, 128.96, 126.95, 126.70, 126.20, 125.48, 125.30, 113.55, 93.31, 92.84, 79.95, 79.39, 77.21, 75.71, 71.92, 71.70, 69.38, 55.22, 51.42, 51.18, 50.23, 49.98, 49.86, 42.35, 42.18, 40.39, 39.79, 39.54, 39.38, 30.29, 29.68, 28.46, 27.30, 26.54, 26.27, 25.83, 25.20, 24.29, 20.14, 18.07, 18.03.

Compound 576: PMB ether 575 (22 mg, 0.033 mmol) was dissolved in methylene chloride (1.6 mL) and cooled to 0 °C. Water (0.07 mL) was added, then DDQ (8 mg, 0.035 mmol). The reaction was stirred 2.5 hours, and then diluted with diethyl ether and aqueous NaHCO$_3$. Repeated ether extractions were performed and the combined extracts dried over MgSO$_4$. Column chromatography gave allylic alcohol 576 as an oil (16 mg, 86%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 2:3): $R_f = 0.5$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.96 (d, $J = 6.8$ Hz, 3H), 1.25 (s, 3H), 1.38-1.58 (m, 19H), 1.65 (s, 3H), 1.90-2.00 (m, 1H), 2.10-2.23 (m, 1H), 2.43-2.55 (m, 2H), 2.65-2.73 (m, 2H), 2.89-3.11 (m, 2H), 3.56-3.76 (m, 1H), 4.01-4.13 (m, 1H), 4.49-4.59 (m, 1H), 5.21 (m, 1H), 6.63 (d, $J = 16.0$ Hz, 1H),
Compound 549: Allylic alcohol 576 (14 mg, 0.025 mmol) was dissolved in methylene chloride (1 mL) at room temperature. Dess-Martin periodinane (17 mg, 0.04 mmol) was added and the reaction mixture stirred 2 hours. The reaction was diluted with diethyl ether and aqueous Na$_2$S$_2$O$_3$, and then stirred until the mixture clarified. Repeated ether extractions were performed and the combined extracts were dried over MgSO$_4$. Column chromatography gave ketone 549 as an oil (13 mg, 93%). Mixture of rotamers: TLC (ethyl acetate/hexanes 2:3 [developed 2X]): $R_f$ = 0.7; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.73-0.80 (m, 3H), 1.18-2.13 (m, ~32H), 2.37-2.47 (m, 2H), 2.90-3.08 (m, 1H), 3.46-3.55 (bs, 2H), 3.64-3.92 (m, 2H), 5.79 (s, 1H), 6.48 (d, J = 16.0 Hz, 1H), 6.89-7.03 (m, 3H), 7.30 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 16.0 Hz, 1H); $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 208.41, 198.72, 195.85, 156.40, 152.01, 139.71, 135.84, 134.84, 131.75, 130.19, 129.94, 127.62, 126.96, 125.87, 123.27, 123.09, 93.79, 92.93, 79.25, 79.04, 72.48, 72.16, 51.95, 51.65, 49.67, 49.31, 42.21, 42.06, 39.99, 39.73, 32.35, 30.46, 30.23, 29.85, 28.61, 28.45, 27.76, 27.30, 26.77, 26.70, 25.53, 24.52, 23.15, 20.73, 20.32, 18.63, 14.41; ESI-MS: m/z calcd. for C$_{33}$H$_{49}$O$_6$N$_1$Na$_1$: 576.33, found: 576.25 [M+Na]$^+$.

Compound 548: Triketone 549 (14 mg, 0.025 mmol) was dissolved in 0.5 mL of an AcOH/H$_2$O (1:1) solution. The mixture was heated at 50 °C 1 hour. The mixture was then diluted with diethyl ether and aqueous NaHCO$_3$. Repeated ether extractions were performed and the combined extracts were dried over MgSO$_4$. Rapid column chromatography with neutralized silica gave aminal 548 as an oil (11 mg, 85%). Mixture of rotamers: TLC (ethyl acetate/hexanes 2:3 [developed 2X]): $R_f$ = 0.7 (directly above 549); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.88-0.94 (m, 3H), 1.42-1.50 (m, 9H), 1.72-2.38 (m, 14H [includes 1.88 (s, 3H) and 2.12 (s, 3H)]), 2.62-2.72 (m, 2H), 3.5-3.54 (m, 1H), 3.86 (s, 2H), 4.36-4.41 (m, 1H), 6.11 (bs, 1H), 6.63 (d, J = 16.0 Hz, 1H), 7.16-7.38 (m, 3H), 7.62 (d, J = 7.2 Hz, 1H), 7.71 (d, J = 16.0 Hz, 0.5H), 7.74 (d, J = 16.0 Hz, 0.5H); $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 0.66 (d, J = 6.4 Hz, 3H), 1.02-1.37 (m, ~14H), 1.40-1.49 (m, 9H), 1.55-1.71 (m, 2H),
1.80-1.92 (m, 1H), 1.92-2.14 (m, 6H), 2.16-2.26 (m, 1H), 2.34 (dd, J = 4.8, 12.8 Hz, 1H), 2.42-2.57 (m, 2-3H), 3.09-3.14 (m, 1H), 3.24-3.34 (m, 1H), 3.39-3.51 (m, 3H), 3.88-3.97 (m, 1H), 5.78 (bs, 1H), 6.49 (app. t, J =16.0 Hz, 1H) 6.89-7.02 (m, 3H), 7.28 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 16.0 Hz, 0.5H), 7.92 (d, J = 16.0 Hz, 0.5H);  

$^{13}$C NMR (100 MHz, C$_6$D$_6$ [poor phasing may have led to additional peaks]): δ 198.79, 195.83, 195.79, 156.20, 156.05, 152.67, 152.30, 138.90, 135.82, 135.76, 135.76, 134.96, 134.90, 131.63, 131.54, 130.13, 130.02, 129.85, 128.49, 127.53, 127.44, 127.31, 126.96, 126.79, 125.69, 123.25, 123.11, 94.52, 94.24, 79.50, 78.84, 72.59, 72.37, 51.61, 51.21, 49.19, 48.94, 42.50, 41.38, 41.02, 40.97, 37.88, 36.43, 35.56, 30.43, 30.19, 30.11, 29.81, 29.64, 28.55, 28.44, 27.24, 24.44, 24.34, 23.10, 21.68, 21.62, 20.67, 18.18, 18.14, 14.35;  

$^\alpha$D -41.6 (c = 6, mg/mL, CHCl$_3$);  ESI-MS: m/z calcd. for C$_{30}$H$_{41}$O$_5$N$_1$Na$_1$: 518.29, found: 518.28 [M+Na]$^+$. 

**Compound 578:** Diketone 575 (12 mg, 0.018 mmol) was dissolved in 0.5 mL of an AcOH/H$_2$O (1:1) solution. The mixture was heated at 50 °C 3 hours. The mixture was then diluted with diethyl ether and aqueous NaHCO$_3$. Repeated ether extractions were performed and the combined extracts were dried over MgSO$_4$. Rapid column chromatography with neutralized silica gave aminal 578 as an oil (6 mg, 55%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 1:3): R$_f$ = 0.2 (directly above 575); $^1$H NMR (500 MHz, CDCl$_3$): δ 0.88-0.94 (m, < 32H), 1.97-2.30 (m, 2H), 2.55-2.64 (m, 2H), 2.83-2.91 (m, 1H), 3.02-3.10 (m, 1H), 3.37-3.55 (m, 2H), 3.78 (s, 3H), 4.10-4.18 (m, 1H), 4.18 (d, J = 11.5 Hz, 1H), 4.34-4.39 (m, 1H), 4.45 (d, J = 11.5 Hz, 1H), 5.08-5.15 (m, 1H), 6.55 (m, 1H), 6.73-6.80 (m, 2H), 7.01-7.08 (m, 2H), 7.14-7.32 (m, 3H), 7.49-7.57 (m, 1H), 7.83-7.93 (m, 1H); ESI-MS: m/z calcd. for C$_{38}$H$_{51}$O$_6$N$_1$Na$_1$: 640.36, found: 640.39 [M+Na]$^+$. 

**Compound 579:** Aminal 578 (5 mg, 0.008 mmol) was dissolved in methylene chloride (1 mL) and triethylamine (50 μL, 0.04 mmol) was added at room temperature. The mixture was cooled to 0 °C after stirring 5 minutes at room temperature. TBSOTf (several drops, ~ 1.5 eq.) was added and the reaction mixture was stirred 30 minutes, and then diluted with diethyl ether and aqueous NaHCO$_3$. Repeated ether extractions were performed and the combined ether extracts dried over MgSO$_4$. Rapid column chromatography with neutralized silica provided a mixture of silyl enol ethers (5 mg, 85%). Mixture of diastereomers and rotamers: TLC (ethyl acetate/hexanes 1:3): R$_f$ = 0.4; $^1$H NMR (500 MHz, CDCl$_3$): δ 0.09-0.2 (m, ~ 9H), 0.84-1.06 (m, ~ 24H), 1.16-1.26 (m, ~ 14H), 1.38-
1.53 (m, ~ 19H), 1.64-1.89 (m, ~ 11H), 1.97-2.41 (m, ~ 6H), 2.70-2.80 (m, 1H), 3.00-
3.12 (m, 1H), 3.38-3.56 (m, 3H), 3.78 (s, 3H), 4.15-4.24 (m, 3H), 4.34-4.46 (m, 2H),
4.84-4.95 (m, 1H), 5.09-5.17 (m, 1H), 6.37 (m, 1H), 6.76-6.80 (m, 2H), 7.04-7.17 (m,
6H), 7.39-7.43.

**Compound 596:** To a stirred methylene chloride (42 mL) solution of
dichlorozirconocene (7.85 g, 26.89 mmol), was added AlMe₃ (5.15
mL, 66.4 mmol) at room temperature in 1 mL portions over 10
minutes. After stirring 15 minutes, phenylacetylene (5.65 mL, 24.16
mmol) was added in 1 mL portions. The reaction mixture was stirred
25 hours, and then cooled to 0 °C. I₂ (8g) was added in THF (50 mL). The reaction
was stirred 1 hour, the ice bath was removed, and stirring was continued 10 minutes at
room temperature. The mixture was then diluted with hexanes and water. Repeated ether extractions were performed and the extracts combined. The organic extracts were washed with aqueous Na₂S₂O₃, then the precipitate was filtered and the extracts were dried over MgSO₄. Column chromatography gave vinyl iodide 596 as an oil (5.1 g,
77%). TLC (ethyl acetate/hexanes 1:9): Rf = 0.6; ¹H NMR (400 MHz, CDCl₃): δ 2.86
(s, 3H), 6.52 (bs, 1H), 7.26-7.37 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 147.2, 141.4,
128.4, 127.8, 126.0, 79.1, 24.4.

**Compound 597:** To a stirred THF (30 mL) solution of vinyl iodide 596 (1.38 g, 5.66 mmol) at -78 °C, was added t-BuLi (11.2
mL, 19.0 mmol) as a 1.7 M pentane solution. The reaction was stirred 1.5 hours, and then ClSnMe₃ (7.5 mL, 7.5 mmol) was
added as a 1 M THF solution. The reaction was stirred 1 hour
after ClSnMe₃ addition, and then the mixture was diluted with
hexanes and water. Repeated ether extractions were performed and the extracts were dried over MgSO₄. Rapid column chromatography gave stannane 597 as an oil (1.18g,
75%). TLC (ethyl acetate/hexanes 1:9): Rf = 0.7; ¹H NMR (500 MHz, CDCl₃): δ 0.204-
0.67 (m, 9H), 2.03-2.57 (m, 3H), 6.18-6.34 (m, 1H), 7.21-7.26 (m, 1H), 7.28-7.34 (m,
2H), 7.43-7.47 (m, 2H).

**Compound 598:** Stannane 597 (290 mg, 1.0 mmol) and vinyl triflate 590 (256 mg, 0.77 mmol) were mixed under argon. The mixture was diluted with degassed dioxane (10 mL) and Pd(PPh₃)₄
(50 mg, 0.043 mmol) was added, followed rapidly by LiCl (180
mg, 4.29 mmol). The mixture was heated 20 hours at 60 °C. After cooling to room temperature, the mixture was diluted with diethyl ether and filtered through a silica plug. The filtrate was concentrated and subjected to column chromatography. Diene 598 was obtained as an
oil (231 mg, 75%). TLC (ethyl acetate/hexanes 1:9): $R_f = 0.5$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.36 (s, 9H), 1.80-1.89 (m, 2H), 2.20-2.28 (m, 2H), 3.57-3.66 (m, 2H), 5.13 (app. t, $J = 3.6$ Hz, 1H), 6.23 (bs, 1H), 7.16-7.36 (m, 4H), 7.42-7.47 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.1, 143.3, 136.6, 133.7, 128.2, 127.0, 126.7, 125.5, 115.3, 80.1, 43.8, 28.4, 28.2, 23.4, 17.1.

**Compound 604:** N-methyl glutarimide 603 (180 mg, 1.42 mmol) was dissolved in THF (4 mL) and cooled to -78 °C. KHMSDS (3.4 mL, 1.7 mmol) was added as a 0.5 M THF solution over 5 minutes. The reaction mixture was warmed to 0 °C, and stirred 30 minutes. The resultant slurry was diluted with THF (3 mL) and cooled to -78 °C. N-phenyltriflimide (601 mg, 1.68 mmol) was added in one portion, and the reaction was transferred to a 0 °C ice bath after stirring 1 hour at -78 °C. The mixture was stirred 45 minutes at 0 °C, and then diluted with diethyl ether and 15% NaOH/H$_2$O. Repeated ether extractions were performed, and the combined extracts dried over MgSO$_4$. Rapid column chromatography with neutralized silica gave vinyl triflate 604 as an oil (44 mg, 12%). TLC (ethyl acetate/hexanes 2:3): $R_f = 0.5$; $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 1.21-1.33 (m, 2H), 1.85-1.94 (m, 2H), 2.73 (s, 3H), 4.52-4.60 (m, 1H); $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 168.5, 141.5, 118.8 (q, $J = 318$ Hz), 96.1, 30.6, 27.2, 17.0.

**Compound 606:** N-methyl glutarimide 603 (1.4 g, 11.02 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. LiHMDS (11.2 mL, 11.2 mmol) was added as a 1 M THF solution over 2.5 minutes. The solution was removed from the ice bath and stirred at room temperature 10 minutes before cooling to -78 °C. Diethylchlorophosphate (1.6 mL, 11.04 mmol) was added as a THF solution (10 mL) via cannula over 10 minutes. After stirring 20 minutes, the mixture was transferred to a 0 °C ice bath. Styryl stannane 588 (2.9 g, 7.4 mmol) was added followed quickly by Pd(PPh$_3$)$_4$ (650 mg, 0.56 mmol) and LiCl (4.8 g, 114.3 mmol). The reaction mixture was then heated at 60 °C 5 hours. The mixture was then diluted with hexanes and decanted to remove solids. The solids were stirred with diethyl ether and decanted again. The combined organic were washed with 0.5 M LiOH, and the aqueous layer was back-extracted with ether. The combined organic extracts were dried over K$_2$CO$_3$. Column chromatography on neutralized silica gave diene 606 as an oil (631 mg, 40%). TLC (ethyl acetate/hexanes 2:3): $R_f = 0.5$; $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 1.72-1.79 (m, 2H), 2.26 (app. t, $J = 7.6$ Hz, 2H), 2.89 (s, 3H), 5.02 (app. t, $J = 5.2$ Hz, 1H), 6.24 (d, $J = 16.0$ Hz, 1H), 6.53 (d, $J = 16.0$ Hz, 1H), 7.01-7.18 (m, 5H); $^{13}$C NMR (100 MHz, C$_6$D$_6$ [1 peak obscured by C$_6$H$_6$]): $\delta$ 169.8, 141.5, 137.0, 131.2, 128.9, 126.9, 123.5, 105.6, 31.7, 30.4, 19.8.
Compound 607a: Similar yields were obtained with a variety of solvents at different temperatures. For effect of solvent and temperature on relative reaction rate, see Table 2.2. A reaction performed in C₆D₆ is described. Diene 606 (5.5 mg, 0.026 mmol) was transferred to a NMR tube containing maleic anhydride (3.5 mg, 0.036 mmol) and diluted with C₆D₆ (0.7 mL). The reaction was monitored by NMR and deemed complete after 75 minutes. The reaction mixture was transferred to a vial and diluted with a hexanes/diethyl ether (1:1) solution. The solids were filtered off and the filtrate was concentrated. Expedient column chromatography on neutralized silica gave cycloadduct 607a as an oil (7 mg, 90%), which crystallized upon storage at reduced temperature. TLC (ethyl acetate/hexanes 4:1): Rf = 0.5; ¹H NMR (400 MHz, CD₂Cl₂): δ 2.10-2.17 (m, 1H), 2.30-2.41 (m, 1H), 2.61-2.74 (m, 2H), 2.86-2.95 (m, 1H), 3.10 (s, 3H), 3.56-3.68 (m, 2H), 3.76-3.81 (m, 1H), 5.39 (app. t, J = 3.0 Hz, 1H), 7.32-7.46 (m, 5H); ¹³C NMR (100 MHz, CD₂Cl₂): δ 171.4, 170.1, 169.6, 142.8, 139.1, 129.2, 129.0, 128.1, 103.9, 48.8, 46.0, 41.9, 35.3, 32.6, 29.8, 21.0.

Compound 507b: Similar yields were obtained with a variety of solvents at different temperatures. For effect of solvent and temperature on relative reaction rate, see Table 2.2. A reaction performed in C₆D₆ is described. Diene 606 (5 mg, 0.023 mmol) was transferred to a NMR tube containing citraconic anhydride (5 mg, 0.045 mmol) and diluted with C₆D₆ (0.7 mL). The reaction was heated to 50 °C and monitored by NMR. The reaction was deemed complete after 48 hours. The reaction mixture was then transferred to a vial and diluted with a hexanes/diethyl ether (1:1) solution. An aqueous NaHCO₃ wash was performed and the organic layer was concentrated after drying over MgSO₄. Expedient column chromatography on neutralized silica gave cycloadduct 607b as an oil (6 mg, 80%), which crystallized upon storage at reduced temperature. ¹H NMR (400 MHz, CD₂Cl₂): δ 1.50 (s, 3H), 2.05-2.12 (m, 1H), 2.36-2.44 (m, 1H), 2.68-2.85 (m, 3H), 3.07 (s, 3H), 3.16-3.20 (m, 1H), 3.32-3.36 (m, 1H), 5.17 (bs, 1H), 7.21-7.27 (m, 2H), 7.34-7.42 (m, 3H); ¹³C NMR (100 MHz, CD₂Cl₂): δ 173.1, 170.7, 169.5, 143.8, 139.4, 130.1, 128.9,
128.4, 105.2, 52.8, 51.0, 34.3, 32.7, 30.2, 29.6, 21.9, 21.6. A crystal suitable for single crystal x-ray analysis was grown:

Crystal data and structure refinement for theod28.

- **X-ray ID**: theod28
- **Sample/notebook ID**: DEF11-6
- **Empirical formula**: C19 H19 N O4
- **Formula weight**: 325.35
- **Temperature**: 100(2) K
- **Wavelength**: 1.54178 Å
- **Crystal system**: Monoclinic
- **Space group**: P2(1)/n
- **Unit cell dimensions**:
  - $a = 11.0173(4)$ Å
  - $b = 11.7765(4)$ Å
  - $c = 32.7(1)$ Å
  - $\alpha = 90^\circ$
  - $\beta = 111.718(2)^\circ$
\( c = 12.9144(4) \, \text{Å} \quad \gamma = 90^\circ. \)

**Volume**

1556.64(9) \( \text{Å}^3 \)

**Z**

4

**Density (calculated)**

1.388 \( \text{Mg/m}^3 \)

**Absorption coefficient**

0.799 \( \text{mm}^{-1} \)

**F(000)**

688

**Crystal size**

0.14 x 0.12 x 0.08 \( \text{mm}^3 \)

**Crystal color/habit**

colorless block

**Theta range for data collection**

4.52 to 68.15\(^\circ\).

**Index ranges**

\(-13 \leq h \leq 12, -11 \leq k \leq 14, -14 \leq l \leq 15\)

**Reflections collected**

7953

**Independent reflections**

2797 \[ R(\text{int}) = 0.0301 \]

**Completeness to theta = 67.00\(^\circ\)**

98.8 %

**Absorption correction**

Semi-empirical from equivalents

**Max. and min. transmission**

0.9388 and 0.8964

**Refinement method**

Full-matrix least-squares on \( F^2 \)

**Data / restraints / parameters**

2797 / 0 / 220

**Goodness-of-fit on \( F^2 \)**

1.131

**Final R indices \[ I > 2\sigma(I) \]**

\( R1 = 0.0406, \, wR2 = 0.1012 \)

**R indices (all data)**

\( R1 = 0.0521, \, wR2 = 0.1071 \)

**Extinction coefficient**

0.0012(3)

**Largest diff. peak and hole**

0.218 and -0.200 e.Å\(^-3\)

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**Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3)**

for theod28. \( U(\text{eq}) \) is defined as one third of the trace of the orthogonalized \( U^\text{ij} \) tensor.

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Bond lengths [Å] and angles [°] for theod28.

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Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters (Å²x 10³) for theod28. The anisotropic displacement factor exponent takes the form: -2π²[h²a*²U₁₁ + ... + 2hka*b*U₁₂]

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Hydrogen coordinates (x $10^4$) and isotropic displacement parameters (Å$^2$ x $10^3$) for theod28.

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Compound 607c: Similar yields were obtained with a variety of solvents at different temperatures. For effect of solvent and temperature on relative reaction rate, see Table 2.2. A reaction performed in C₆D₆ is described. Diene 606 (7 mg, 0.032 mmol) was transferred to a NMR tube containing methyl vinyl ketone (5 mg, 0.071 mmol) and diluted with C₆D₆ (0.7 mL). The reaction was heated to 80 °C and monitored by NMR. The reaction was deemed complete after 2 hours. The reaction mixture was then transferred to a vial and diluted with a hexanes/diethyl ether (1:1) solution. An aqueous NaHCO₃ wash was performed and the organic layer was concentrated after drying over MgSO₄. Expedient column chromatography on neutralized silica gave cycloadduct 607c as an oil (7 mg, 75%), which crystallized upon storage at reduced temperature. ¹H NMR (400 MHz, C₆D₆): δ 0.89-1.01 (m, 1H), 1.12-1.19 (m, 1H), 1.20-1.28 (m, 1H), 1.45 (s, 3H), 1.49-1.59 (m, 1H), 2.03-2.14 (m, 1H), 2.34-2.47 (m, 2H), 2.87 (s, 3H), 3.66-3.73 (m, 1H), 4.51-4.57 (d, 1H), 6.98-7.04 (m, 3H), 7.05-7.10 (2H); ¹³C NMR (100 MHz, C₆D₆): δ 207.7, 167.8, 141.3, 141.0, 129.6, 128.4, 127.3, 104.6, 51.7, 42.7, 34.5, 33.1, 29.5, 28.4, 27.3, 26.8.

Compound 607d: Similar yields were obtained with a variety of solvents at different temperatures. For effect of solvent and temperature on relative reaction rate, see Table 2.2. A reaction performed in C₆D₆ is described. Diene 606 (7 mg, 0.032 mmol) was transferred to a NMR tube containing methyl acrylate (6 mg, 0.070 mmol) and diluted with C₆D₆ (0.7 mL). After 5 days at room temperature, the reaction was deemed complete. The
reaction mixture was then transferred to a vial and diluted with a hexanes/diethyl ether (1:1) solution. An aqueous NaHCO₃ wash was performed and the organic layer was concentrated after drying over MgSO₄. Expedient column chromatography on neutralized silica gave cycloadduct 607d as an oil (7 mg, 71%), which crystallized upon storage at reduced temperature. ¹H NMR (400 MHz, C₆D₆): δ 0.86-1.00 (m, 1H), 1.07-1.15 (m, 1H), 1.44-1.57 (m, 3H), 1.96-2.08 (m, 1H), 2.34-2.43 (m, 1H), 2.60-2.67 (m, 1H), 2.85 (s, 3H), 3.19 (s, 3H), 3.87 (app. t, J = 5.2 Hz, 1H), 4.54 (d, J = 4.8 Hz, 1H), 7.04-7.16 (m, 5H); ¹³C NMR (100 MHz, C₆D₆ [1 carbon obscured by C₆H₆]): δ 172.8, 167.8, 141.5, 141.2, 129.8, 127.4, 104.1, 50.7, 44.5, 42.6, 34.3, 33.0, 29.4, 27.1, 26.5.

**Compound 607e:** Similar yields were obtained with a variety of solvents at different temperatures. For effect of solvent and temperature on relative reaction rate, see Table 2.2. A reaction performed in C₆D₆ is described. Diene 606 (45 mg, 0.21 mmol) was transferred to a NMR tube containing methyl methacrylate (36 mg, 0.36 mmol) and diluted with C₆D₆ (1.0 mL). The reaction was heated to 80 °C and monitored by NMR. The reaction was deemed complete after 44 hours. The reaction mixture was transferred to a vial and diluted with a hexanes/diethyl ether (1:1) solution. An aqueous NaHCO₃ was performed and the organic layer was concentrated after drying over MgSO₄. Expedient column chromatography on neutralized silica gave cycloadduct 607e as a mixture of diastereomers (45 mg, 68%), which formed an amorphous solid upon storage at reduced temperature. TLC (ethyl acetate/hexanes 3:2): Rₜ = 0.6; ¹H NMR (400 MHz, C₆D₆): δ 0.74 (s, 2.7H), 0.94-1.24 (m, ~ 4.7H), 1.29 (s, 6H), 1.35-1.43 (m, 2.6H), 1.64-2.47 (m, ~ 15H), 2.84 (s, 2.7H, exo), 2.85 (s, 5H, endo), 3.04 (s, 5H, endo), 3.35 (s, 2.5H, exo), 3.44 (d, J = 5.2 Hz, 1H, endo), 4.29 (d, J = 5.6 Hz, 1H, exo), 4.53 (d, J = 5.6 Hz, 1.8H, endo), 4.77 (d, J = 5.2 Hz, 1H, exo), 6.92-7.27 (m, 14H); ¹³C NMR (100 MHz, C₆D₆ [1 carbon obscured by C₆H₆]): δ 176.8, 175.4, 167.83, 167.80, 141.9, 141.6, 140.7, 139.8, 130.7, 129.9, 128.2, 127.3, 127.1, 105.1, 103.0, 51.8, 50.8, 49.9, 46.3, 45.8, 44.6, 34.5, 33.2, 33.1, 32.5, 32.2, 31.2, 29.4, 29.3, 27.4, 27.2, 25.7, 23.3.

**Compound 626:** Phenol 624 (149 mg, 0.8623 mmol), 3-methyl-2-enolic acid (625) (124 mg, 1.24 mmol), DCC (270 mg, 1.3 mmol), and DMAP (10 mg, 0.08 mmol) were dissolved in methylene chloride (4 mL) at 0 °C. The reaction was allowed to warm to room temperature and then stirred 18 hours. The solids were filtered, washed with ether, and the combined organics (filtrate) were concentrated for column chromatography. Acrylate 626 was obtained as an oil (220 mg, 99%). TLC
Compound 628: Aryl bromide 626 (32 mg, 0.13 mmol) and bis stannane 627 (138 mg, 0.23 mmol) were mixed under argon. The mixture was then diluted with degassed toluene (0.2 mL). Pd(PPh₃)₄ (9 mg, 0.008 mmol) was added, and the mixture was placed in a 50 °C oil bath for 6 hours. The crude mixture was loaded directly onto a silica column and eluted. Stannane 628 was obtained as an oil (15 mg, 25%). TLC (ethyl acetate/hexanes 1:9): Rf = 0.9; ¹H NMR (500 MHz, CDCl₃): δ 0.87-0.96 (m, ~19H), 1.25-1.36 (m, ~16H), 1.48-1.54 (m, ~5H), 2.00 (s, 3H), 2.23 (s, 3H), 5.96-5.98 (bs, 1H), 6.82-6.97 (m, 2H), 7.02-7.05 (m, 1H), 7.18-7.26 (m, 2H), 7.58-7.62 (m, 1H).

Compound 619: Bis stannane 627 (195 mg, 0.32 mmol) and vinyl triflate 590 (60 mg, 0.18 mmol) were mixed under argon and diluted with toluene (0.1 mL). Pd(PPh₃)₄ (10 mg, 0.009 mmol) was added at room temperature and the reaction flask was transferred to a 50 °C oil bath. After stirring 3 hours, the reaction was cooled to room temperature and loaded directly onto a silica column. Stannane 619 was obtained as an oil (45 mg, 50%). TLC (ethyl acetate/hexanes 1:9): Rf = 0.4; ¹H NMR (400 MHz, C₆D₆): δ 0.85-1.05 (m, 11H), 1.29-1.46 (m, 14H), 1.51-1.70 (m, 5H), 1.70-1.79 (m, 2H), 3.45-3.52 (m, 2H), 5.17 (app. t, J = 4 Hz, 1H), 6.35-6.74 (m, 2H); ¹³C NMR (100 MHz, C₆D₆): δ 154.15, 145.6, 141.1, 124.4, 114.7, 80.0, 44.6, 129.7, 29.6, 29.5, 28.4, 27.8, 23.7, 23.5, 13.9, 9.8, [29.7, 29.6, and 29.5 are signals from a single carbon coupled to Sn, as are 11.5, 11.4, 9.8, 8.2, and 8.1].

Compound 629: Stannane 619 (9 mg, 0.018 mmol) and aryl bromide 626 (10 mg, 0.040 mmol) were mixed under argon and diluted with toluene (0.5 mL). Pd(PPh₃)₄ (1 mg, 0.001 mmol) was added at room temperature and the reaction flask was transferred to a 50 °C oil bath. After stirring 2 hours, the reaction was cooled to room temperature and loaded directly onto a silica column. Stannane 629 was obtained as an oil (2-3 mg, 40%). ¹H
NMR (400 MHz, CDCl₃): δ 1.55 (s, 9H + H₂0 protons), 1.78-1.85 (m, 2H), 2.0 (s, 3H), 2.22 (s, 3H), 2.22-2.27 (m, 2H), 3.56-3.60 (m, 2H), 5.43 (app. t, J = 4.0 Hz, 1H), 5.96 (bs, 1H), 6.97-7.0 (m, 1H), 7.03-7.06 (m, 1H), 7.15-7.26 (m, 3H), 7.54-7.58 (m, 1H).

**Compound 634:** Aryl iodide 633 (2.65 g, 10.69 mmol) was dissolved in dimethylformamide (30 mL) and triethylamine (30 mL). The solution was degassed with argon 30 minutes, and then TMS acetylene (10.5 mL, 74.5 mmol) was added. Pd(PPh₃)₄ (990 mg, 0.86 mmol) was added at room temperature followed by CuI (112 mg, 0.59 mmol), and the reaction flask was transferred to a 35 °C oil bath. The reaction was stirred 5 hours, and then cooled to room temperature. Aqueous 0.5 M HCl was added and repeated diethyl ether extractions were performed. The combined ether extracts were dried over MgSO₄. Column chromatography gave alkyne 634 as an oil (2.3 g, 95%). TLC (ethyl acetate/hexanes 1:3): Rₘ = 0.7; ¹H NMR (400 MHz, CDCl₃): δ 0.25 (s, 9H), 3.05 (t, J = 8.0, 2H), 3.9 (t, J = 8.0 Hz, 2H), 7.14-7.30 (m, 3H), 7.41-7.50 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 140.7, 132.5, 129.5, 128.5, 128.3, 126.2, 122.8, 103.6, 62.7, 38.1, 0.1; HR-FAB-MS: m/z calcd. for C₁₃H₁₉O₁Si₁: 219.1200, found: 219.1203 [M+H]+.

**Compound 635:** TMS alkyne 634 (1.2 g, 5.5 mmol) was dissolved in THF (14 mL) and water (2 mL) was added at room temperature. Solid LiOH (240 mg, 10mmol) was then added and after stirring 6 hours, the reaction was quenched with aqueous NH₄Cl and diethyl ether. Repeated ether extractions were performed and the combined ethereal extracts were dried over MgSO₄. Column chromatography gave alkyne 635 as an oil (620 mg, 77%). TLC (ethyl acetate/hexanes 2:3): Rₘ = 0.5; ¹H NMR (500 MHz, CDCl₃): δ 3.08 (t, J = 7.0 Hz, 2H), 3.26 (s, 1H), 3.90 (t, J = 7.0 Hz, 2H), 7.17-7.34 (m, 3H), 7.49-7.54 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 141.0, 133.1, 129.6, 128.9, 126.4, 121.9, 82.1, 81.0, 62.8, 37.8; ESI-MS: m/z calcd. for C₁₀H₁₀O₁Na₁: 169.06, found: 169.11 [M+Na]+.

**Compound 636:** Alkyne 635 (21 mg, 0.14 mmol) was dissolved in THF (0.4 mL) and Pd(PPh₃)₂Cl₂ (2 mg, 0.003 mmol) was added at room temperature. HSnBu₃ (0.06 mL, 0.22 mmol) was added, and the reaction was allowed to stir 15 minutes before being concentrated under reduced pressure. Stannane 636 was isolated as the major product after column chromatography (31 mg, 50%). TLC (ethyl acetate/hexanes 1:3): Rₘ = 0.7; ¹H NMR (400 MHz, CDCl₃): δ 0.81-0.98 (m, 15H), 1.20-1.56 (m, 14H), 2.81 (t, J = 6.8 Hz, 2H), 3.76 (t, J = 6.8 Hz, 2H), 5.45-5.61 (including
Compound 637: Alkyne 635 (38 mg, 0.26 mmol) was dissolved in methylene chloride (2 mL) and cooled to 0 °C. Pyridine (0.05 mL, 0.62 mmol), DMAP (2 mg, 0.02 mmol), and TESOTf (0.06 mL, 0.27 mmol), were added respectively. The reaction was stirred 5 minutes, and was then treated with aqueous NaHCO₃. Repeated ether extractions were performed and the combined extracts were dried over MgSO₄. Column chromatography gave silyl ether 637 as an oil (59 mg, 87%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.7; ¹H NMR (500 MHz, CDCl₃): δ 0.57 (q, J = 8.0 Hz, 6H), 0.93 (t, J = 8.0 Hz, 9H), 3.05 (t, J = 7.5 Hz, 2H), 3.23 (s, 1H), 3.83 (t, J = 7.5 Hz, 2H), 7.14-7.19 (m, 1H), 7.23-7.30 (m, 2H), 7.45-7.50 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 141.4, 132.8, 129.9, 128.7, 126.2, 121.8, 82.2, 80.5, 63.0, 38.2, 6.7, 4.3; HR-ESI-MS: m/z calcd. for C₁₆H₂₄O₁Si₁: 260.1591, found: 260.1597 [M⁺].

Compound 639: Alkyne 635 (44 mg, 0.30 mmol) was dissolved in methylene chloride (1 mL) and cooled to 0 °C. Lutidine (0.09 mL, 0.77 mmol), and TIPSOTf (0.1 mL, 0.37 mmol), were added respectively. The reaction was stirred 4 hours, and then diluted with hexanes and aqueous NaHCO₃. Repeated ether extractions were performed and the combined extracts dried over MgSO₄. Column chromatography gave silyl ether 639 as an oil (80 mg, 88%). TLC (ethyl acetate/hexanes 1:9): Rf = 0.7; ¹H NMR (400 MHz, CDCl₃): δ 1.00-1.08 (m, 21H), 3.06 (t, J = 7.2 Hz, 2H), 3.22 (s, 1H), 3.91 (t, J = 7.2 Hz, 2H), 7.13-7.19 (m, 1H), 7.25-7.28 (m, 2H), 7.45-7.48 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 141.6, 132.8, 130.1, 128.6, 126.1, 121.8, 82.3, 80.5, 63.5, 38.2, 18.0, 11.9; HR-ESI-MS: m/z calcd. for C₁₉H₃₀O₁Si₁: 302.2060, found: 302.2062 [M⁺].

Compound 631: Procedure A: Stannane 631 was isolated as a minor product from the reaction conditions described for the synthesis of 636. Procedure B: Aryl iodide 641 (44 mg, 0.18 mmol) was mixed with bis stannane 627 (155 mg, 0.26 mmol) and diluted with dioxane (1 mL). Pd(PPh₃)₄ (18 mg, 0.02 mmol) and LiCl (60 mg, 1.4 mmol) were added, and the reaction was heated at 80 °C. After 2.5 hours, the reaction was cooled to room temperature and filtered through celite. The filtrate was concentrated and subjected to column
chromatography. Stannane 631 was obtained as an oil (41 mg, 53%). TLC (diethyl ether/hexane 1:9 then ethyl acetate/hexanes 1:3): \( R_f = 0.6 \); \( ^1H \) NMR (500 MHz, CDCl₃): \( \delta \) 0.88-1.01 (m, 14H), 1.29-1.40 (m, 7H), 1.47-1.65 (m, 6H), 3.0 (t, \( J = 6.5 \) Hz, 2H), 3.81-3.88 (m, 2H), 6.67-6.86 (incuding 6.76 d, \( J = 19.5 \) Hz, 1H), 7.14-7.27 (m, 4H), 7.50-7.56 (m, 1H); \( ^{13}C \) NMR (100 MHz, CDCl₃): \( \delta \) 143.4, 138.6, 134.7, 132.5, 130.2, 127.4, 126.8, 125.9, 63.1, 36.5, 29.3, 27.4, 13.9, 9.9; HR-EI-MS: \( m/z \) calcd. for C\(_{22}\)H\(_{38}\)O\(_1\)Sn\(_1\): 438.1939, found: 438.1944 [M\(^+\)].

**Compound 630:** Stannane 631 (31 mg, 0.08 mmol) was mixed with vinyl triflate 590 (45 mg, 0.14 mmol) under argon and diluted with dioxane (0.8 mL). Pd(PPh\(_3\))\(_4\) (9 mg, 0.008 mmol) and LiCl (45 mg, 1.07 mmol) were added, and the reaction was heated at 110 °C. After 3 hours, the reaction was cooled to room temperature and filtered through celite. The filtrate was concentrated and subjected to column chromatography. Stannane 630 was obtained as an oil (9 mg, 35%). TLC (ethyl acetate/hexanes 1:3): \( R_f = 0.1 \); \( ^1H \) NMR (400 MHz, CDCl₃): \( \delta \) 1.43 (s, 9H), 1.77-1.87 (m, 2H), 1.9 (t, \( J = 6.8 \) Hz, 2H), 3.57-3.63 (m, 2H), 3.81 (t, \( J = 6.8 \) Hz, 2H), 5.48 (app. t, \( J = 3.8 \) Hz, 1H), 6.49 (d, \( J = 16.0 \) Hz, 1H), 6.82 (d, \( J = 16.0 \) Hz, 1H), 7.16-7.24 (m, 3H), 7.46-7.50 (m, 1H); HR-EI-MS: \( m/z \) calcd. for C\(_{20}\)H\(_{27}\)O\(_3\)N\(_1\): 329.1985, found: 329.1989 [M\(^+\)].

**Compound 645:** Alcohol 633 (4.85 g, 19.56 mmol) was dissolved in acetonitrile (60 mL) and IBX (16.0 g, 57.1 mmol) was added at room temperature. The mixture was stirred under reflux 1 hour and then cooled to room temperature. The mixture was then filtered through a large cotton plug, and the filtrate was concentrated. The filtrate was then purified through a silica plug. Aldehyde 645 was obtained as an oil (4.8g, 99%). TLC (ethyl acetate/hexanes 2:3): \( R_f = 0.6 \); \( ^1H \) NMR (500 MHz, CDCl₃): \( \delta \) 3.89 (s, 2H), 7.01 (t, \( J = 7.5 \) Hz, 1H), 7.23 (d, \( J = 7.5 \) Hz, 1H), 7.35 (t, \( J = 7.5 \) Hz, 1H), 7.89 (d, \( J = 7.5 \) Hz, 1H), 9.78 (bs, 1H).

**Compound 646:** A THF (65 mL) solution of 2-methyl-1-propenyl magnesium bromide (32 mmol) was cooled to 0 °C. Aldehyde 645 (4.85 g, 19.5 mmol) was added in THF (10 mL) via cannula, over 40 minutes. The reaction was allowed to warm to room temperature over several hours. The reaction was then diluted with hexanes and aqueous NH\(_4\)Cl after stirring a total of 18 hours. Repeated diethyl ether extractions were performed and the combined extracts were dried over MgSO\(_4\). Column chromatography gave allylic alcohol 646 as an oil (3.5 g, 59%). TLC
(ethyl acetate/hexanes 2:3): \( R_f = 0.5 \); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 1.55 \) (s, 3H), 1.71 (s, 3H), 2.86-2.99 (m, 2H), 4.64-4.72 (m, 1H), 5.27 (d, \( J = 8.8 \) Hz, 1H), 6.88-6.94 (m, 1H), 7.20-7.30 (m, 2H), 7.80 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 140.9, 139.5, 135.6, 131.3, 128.2, 128.0, 126.6, 101.1, 68.2, 48.3, 25.7, 18.3 \); HR-EI-MS: \( m/z \) calcd. for \( C_{12}H_{15}O_{1}I_{1} \): 302.0162, found: 302.0159 [M]+.

Compound 647: Aryl iodide 646 (70 mg, 0.23 mmol) was mixed with bis stannane 627 (0.195 mL, 0.37 mmol) and diluted with dioxane (0.1 mL). Pd(PPh\(_3\))\(_4\) (25 mg, 0.022 mmol) and LiCl (87 mg, 2.07 mmol) were added, and the reaction was heated at 90 °C. After 5 hours, the reaction was cooled to room temperature, diluted with methylene chloride and filtered through celite. The filtrate was diluted with hexanes and washed with aqueous 0.5 M LiOH, then concentrated and subjected to column chromatography. Stannane 647 was obtained as an oil (36 mg, 32%). TLC (ethyl acetate/hexanes 1:3): \( R_f = 0.7 \); \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)): \( \delta = 0.92 \) (app. t, \( J = 7.2 \) Hz, 7H), 0.99-1.09 (m, 4H), 1.31 (s, 3H), 1.32-1.43 (m, 5H), 1.56-1.69 (m, 8H), 2.84 (dd, \( J = 5.6, 13.6 \) Hz, 1H), 3.00 (dd, \( J = 6.8, 13.6 \) Hz, 1H), 4.49-4.55 (m, 1H), 5.19-5.24 (dd, 1H), 6.81-6.89 (m, 1H), 6.98-7.09 (m, 3H), 7.43-7.59 (m, 2H); \(^{13}\)C NMR (100 MHz, C\(_6\)D\(_6\)): \( \delta = 145.3, 139.3, 135.7, 133.9, 131.6, 131.2, 128.5, 127.6, 127.0, 126.2, 69.5, 41.7, 29.6, 27.7, 25.7, 18.1, 14.0, 9.9 \); HR-EI-MS: \( m/z \) calcd. for \( C_{26}H_{43}O_{1}Sn_{1} \): 491.2330, found: 491.2318 [M-H]+.

Compound 648: Alcohol 648 was isolated in varied yields from the reactions described to produce stannane 647 and diene 649. TLC (ethyl acetate/hexanes 1:3): \( R_f = 0.3 \); \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)): \( \delta = 1.51 \) (bs, 3H), 2.63 (dd, \( J = 6.0, 16.0 \) Hz, 1H), 2.96 (dd, \( J = 6.8, 16.0 \) Hz, 1H), 3.53 (d, \( J = 6.2 \) Hz, 1H), 4.15 (app. q, \( J = 6.4 \) Hz, 1H), 4.77-4.79 (m, 1H), 4.83-4.86 (m, 1H), 6.96-7.05 (m, 4H); EI-MS: \( m/z \) calcd. for \( C_{12}H_{14}O_{1} \): 174.10, found: 174.10 [M]+.

Compound 649: Procedure A: Stannane 647 (35 mg, 0.07 mmol) was mixed with vinyl triflate 590 (59 mg, 0.18 mmol) and diluted with dioxane (0.1 mL). Pd(PPh\(_3\))\(_4\) (8 mg, 0.007 mmol) and LiCl (25 mg, 0.6 mmol) were added, and the reaction was heated at 105 °C. After 5.5 hours, the reaction was cooled to room temperature, diluted with diethyl ether, and filtered through celite. The filtrate was concentrated and subjected to column chromatography. Triene 649 was obtained as an oil (5-6 mg, 20%). Procedure B: Aryl iodide 646 (77 mg, 0.26 mmol) was mixed with stannane 619 (257 mg, 0.52
mmol), and Pd(PPh3)4 (25 mg, 0.022 mmol), then LiCl (105 mg, 2.5 mmol) were added. The reaction was heated at 95 °C for 10.5 hours. After cooling to room temperature, the reaction was diluted with diethyl ether, and filtered through celite. The filtrate was concentrated and subjected to column chromatography. Triene 649 was obtained as an oil (55 mg, 56%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.3; 1H NMR (400 MHz, CD6): δ 1.35 (bs, 12H), 1.38-1.46 (m, 2H), 1.51 (s, 3H), 1.75-1.82 (m, 2H), 2.86 (dd, J = 5.2, 13.6 Hz, 1H), 3.00 (dd, J = 7.2, 13.6 Hz, 1H), 3.32-3.41 (m, 1H), 3.55-3.66 (m, 1H), 4.54-4.63 (m, 1H), 5.21-5.28 (m, 2H), 6.60 (d, J = 16.0 Hz, 1H), 6.98-7.17 (m, 4H), 7.48-7.52 (m, 1H); 13C NMR (100 MHz, CD6): δ 154.2, 140.0, 137.5, 136.6, 133.6, 131.7, 130.0, 128.7, 127.31, 127.26, 127.0, 126.0, 124.6, 115.2, 80.1, 69.6, 44.7, 42.2, 28.3, 25.7, 23.7, 23.6, 18.1.

**Compound 616:** Allylic alcohol 649 (9 mg, 0.02 mmol) was dissolved in methylene chloride (0.6 mL) and DMSO (0.4 mL) at room temperature. IBX (15 mg, 0.05 mmol) was added and the solution stirred. The reaction was monitored by TLC, and when the starting material had been consumed, hexanes were added, followed by water. Repeated diethyl ether extractions were performed and the extracts were combined. The extracts were dried over MgSO4 and subjected to column chromatography. Dienone 616 was obtained as an oil (5 mg, 60%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.5; 1H NMR (400 MHz, CD6): δ 1.32 (s, 3H), 1.35-1.43 (m, 11H), 1.70-1.77 (m, 2H), 2.02 (s, 3H), 3.48-3.53 (m, 2H), 3.62 (s, 3H), 5.29 (app. t, J = 4.0 Hz, 1H), 5.88 (bs, 1H), 6.63 (d, J = 16.0 Hz, 1H), 6.96-7.07 (m, 4H), 7.50-7.54 (m, 1H); 13C NMR (100 MHz, CD6 [atoms obscured by CD6]): δ 196.5, 155.4, 154.1, 139.6, 137.8, 133.6, 131.4, 131.0, 127.5, 126.1, 123.9, 123.3, 114.9, 80.0, 49.6, 44.5, 28.3, 27.2, 23.7, 23.5, 20.7; HR-EI-MS: m/z calcd. for C24H31O3N1: 381.2298, found: 381.2302 [M]+.

**Compound 614:** Triene 616 (12 mg, 0.03 mmol) was dissolved in 0-xylene-d8 (0.7 mL) and transferred to a NMR tube. The tube was sealed and heated to 205 °C. After 12 hours, the reaction was cooled to room temperature, concentrated, and purified on a neutral alumina column. Tetracycle 614 was obtained as an oil (2-3 mg, 20%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.5 (slightly higher than 616); 1H NMR (400 MHz, CD6): δ 0.87 (s, 3H), 1.32 (s, 3H), 1.46 (s, 9H), 1.60-1.66 (m, 2H), 1.71-1.77 (m, 2H), 2.78-2.90 (m, 1H), 2.97-3.06 (m, 1H), 3.07-3.16 (m, 1H), 3.30 (bs, 2H), 3.67-3.78 (m, 1H), 4.21-4.22 (m, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 7.19 (d, J = 8Hz, 1H); 13C NMR (100 MHz, CD6 [incomplete, signals obscured by CD6]): δ 209.2, 153.8, 140.0, 133.3, 127.3, 127.0, 124.3, 79.6, 56.1, 49.0, 44.7, 39.4, 35.4, 33.7, 30.1,
28.4, 26.5, 24.4, 21.7, 21.6; HR-ESI-TOF-MS: \( m/z \) calcd. for \( \text{C}_{24}\text{H}_{32}\text{O}_{3}\text{N}_{1}\text{Na}_{1} \): 404.2195, found: 404.2196 \([\text{M+Na}^+]\).

**Compound 50:** Triene 616 (2 mg, 0.005 mmol) was mixed with N-benzylmaleimide (2 mg, 0.01 mmol), dissolved in \( \text{C}_6\text{D}_6 \) (0.7 mL), and transferred to a NMR tube. The mixture was heated at 90 °C for 14 hours. The reaction was then diluted with diethyl ether and filtered. The filtrate was concentrated and subjected to silica chromatography. Cycloadduct 650 was isolated as an oil, which formed an amorphous solid upon standing (3 mg, 95%). TLC (ethyl acetate/hexanes 1:3): \( R_f \) = 0.2; \(^1\text{H} \) NMR (400 MHz, \( \text{C}_6\text{D}_6 \)): \( \delta \) 1.30 (m, \( ~14\text{H} \)), 1.61-1.74 (m, 1H), 1.99 (s, 3H), 2.53-2.60 (m, 1H), 2.76-2.96 (m, 3-4H), 3.06-3.17 (m, 1H), 3.31-3.38 (m, 1H), 3.48 (d, \( J = 15.2 \) Hz, 1H), 3.62 (d, \( J = 15.2 \) Hz, 1H), 3.79-3.87 (m, 1H), 4.28 (bs, 2H), 5.92 (bs, 1H), 6.9-7.10 (m, 6H), 7.26 (d, \( J = 7.6 \) Hz, 2H), 7.59 (d, 7.6 Hz, 1H); \(^{13}\text{C} \) NMR (100 MHz, \( \text{C}_6\text{D}_6 \) [atoms obscured by \( \text{C}_6\text{H}_6 \)]: \( \delta \) 197.3, 175.6, 175.3, 156.2, 153.6, 140.3, 136.8, 133.6, 130.9, 129.7, 123.1, 114.6, 80.1, 49.8, 46.8, 44.2, 43.9, 41.8, 37.4, 33.3, 28.3, 27.2, 26.5, 23.6, 20.6; HR-FAB-MS: \( m/z \) calcd. for \( \text{C}_{35}\text{H}_{41}\text{O}_{5}\text{N}_{2} \): 569.3010, found: 569.3005 \([\text{M+H}^+]\).

**Compound 654:** Methyl furan 651 (0.7 mL, 7.76 mmol) was dissolved in THF (8 mL) and cooled to -78 °C. \( n \)-BuLi (2.5 mL, 7 mmol) was added as a 2.8 M hexane solution and the mixture was then stirred at 0 °C for 2 hours. Iodobenzylbromide (2 g, 6.7 mmol) was added in THF (5 mL) via cannula over 15 minutes. The reaction was stirred an additional 3 hours, then diluted with hexanes and quenched with water. Repeated hexane extractions were performed, and the combined extracts were dried over \( \text{MgSO}_4 \). Column chromatography gave furan 654 as an oil (1.36 g, 68%). TLC (ethyl acetate/hexanes 1:9): \( R_f \) = 0.6; \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 2.26 (s, 3H), 4.02 (s, 2H), 5.86-5.90 (m, 2H), 6.89-6.95 (m, 1H), 7.16-7.20 (m, 1H), 7.26-7.31 (m, 1H), 7.81-7.86 (m, 1H); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 151.2, 151.0, 141.1, 139.4, 129.8, 128.3, 128.2, 107.9, 106.1, 100.6, 39.7, 13.6; APCI-MS: \( m/z \) calcd. for \( \text{C}_{12}\text{H}_{12}\text{O}_{1}\text{I} \): 298.99, found: 298.92 \([\text{M+H}^+]\).

**Compound 653:** Aryl iodide 653 was isolated as a minor product of the reaction conditions used for the synthesis of 654. TLC (ethyl acetate/hexanes 1:9): \( R_f \) = 0.6 (directly above 654); \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 2.98-3.01 (bs, 4H), 6.88-6.95 (m, 2H), 7.20-7.31 (m, 4H), 7.82-7.86 (m, 2H).
**Compound 655:** Furan 654 (100 mg, 0.34 mmol) was dissolved in methylene chloride (3 mL) and cooled to 0 °C. mCPBA (65 mg, 0.38 mmol) was added, and the reaction mixture was stirred 2 hours. Water was then added to the mixture, followed by aqueous Na$_2$S$_2$O$_3$. Repeated diethyl ether extractions were performed, and the combined organic extracts were then dried over MgSO$_4$ and Na$_2$CO$_3$. Column chromatography gave aryl iodide 655 as an oil (53 mg, 50%). TLC (ethyl acetate/hexanes 2:3): R$_f$ = 0.3; $^1$H NMR (400 MHz, CDCl$_3$): δ 1.09 (s, 3H), 4.27 (bs, 1H), 6.30 (d, J = 5.8 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.97 (t, J = 8.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 6.0 Hz, 1H), 7.90 (d, 8.0 Hz, 1H; ESI-MS: m/z calcd. for C$_{12}$H$_{12}$O$_2$I: 314.98, found: 314.93 [M+H]$^+$. 

**Compound 655b:** A compound isolated from the reaction conditions described for the synthesis of 655 has been tentatively identified as 655b. $^1$H NMR (400 MHz, C$_6$D$_6$): δ 1.75 (s, 3H), 3.65 (s, 2H), 5.42 (d, 1H), 5.65 (d, 1H), 6.41 (m, 1H), 6.81 (m, 1H), 6.98 (m, 1H), 7.55 (m, 1H).

**Compound 657:** Furan 654 (29 mg, 0.010 mmol) and stannane 661 (100 mg, 0.22 mmol) were mixed under argon. Pd(PPh$_3$)$_4$ (13 mg, 0.011 mmol) and LiCl (50 mg, 1.2 mmol) were added, and the mixture was heated at 90 °C 10 hours. After the reaction cooled to room temperature, hexanes and diethyl ether were added. The mixture was filtered through a cotton plug and concentrated. Chromatography through an alumina column gave diene 657 as an oil (20 mg, 62%). TLC (ethyl acetate/hexanes 1:9): R$_f$ = 0.3; $^1$H NMR (400 MHz, CDCl$_3$): δ 1; $^{13}$C NMR (100 MHz, CDCl$_3$): δ 1.

**Compound 661:** Bis stannane 627 (2.9 mL, 5.5 mmol) and vinyl triflate 660 (1.6 g, 5.5 mmol) were mixed under argon and diluted with dioxane (15 mL). Pd(PPh$_3$)$_4$ (640 mg, 0.55 mmol) was added at room temperature followed by LiCl (2.4 g, 57.14 mmol) and the reaction flask was transferred to a 100 °C oil bath. After stirring 2 hours, the reaction was cooled to room temperature and diluted with hexanes. The solution was filtered through celite and the filtrate was concentrated for chromatography through neutralized silica. Stannane 661 was obtained as an oil (1.15 g, 46%). TLC (ethyl acetate/hexanes 1:9): R$_f$ = 0.4; $^1$H NMR (400 MHz, C$_6$D$_6$): δ 0.89 (t, J = 7.2 Hz, 9H), 0.93-1.04 (m, 4H), 1.29-1.40 (m,
Compound 662: Aryl iodide 646 (78 mg, 0.26 mmol) and stannane 661 (251 mg, 0.55 mmol) were mixed under argon. Pd(PPh₃)₄ (30 mg, 0.025 mmol) was added at room temperature followed by LiCl (98 mg, 2.33 mmol), and the reaction flask was transferred to a 100 °C oil bath. After stirring 4.5 hours, the reaction was cooled to room temperature and diluted with hexanes and diethyl ether. The solution was filtered through celite and the filtrate concentrated for chromatography through neutralized silica. Allylic alcohol 662 was obtained as an oil (44 mg, 50%). TLC (ethyl acetate/hexanes 3:2): Rf = 0.6; ¹H NMR (400 MHz, C₆D₆): δ 1.31 (s, 3H), 1.33-1.40 (m, 2H), 1.50 (s, 3H), 1.70-1.78 (m, 2H), 2.80 (dd, J = 6.0, 13.6 Hz, 1H), 3.01 (dd, J = 6.8, 13.6 Hz, 1H), 3.24-3.36 (m, 1H), 3.44 (s, 3H), 3.25-3.61 (m, 1H), 4.54-4.63 (m, 1H), 5.21-5.28 (m, 1H), 6.58 (d, J = 16.0 Hz, 1H), 6.98-7.10 (m, 4H), 7.48-7.54 (m, 1H); ¹³C NMR (100 MHz, C₆D₆): δ 155.5, 139.6, 137.5, 136.8, 133.6, 131.6, 129.3, 128.7, 127.3, 126.9, 126.3, 125.2, 116.1, 69.6, 52.5, 45.0, 42.4, 25.7, 23.5, 23.4, 18.0.

Compound 663: Allylic alcohol 662 (15 mg, 0.04 mmol) was dissolved in methylene chloride (0.5 mL) and DMSO (0.5 mL) at room temperature. IBX (30 mg, 0.11 mmol) was added and the solution was stirred at room temperature. The reaction was monitored by TLC, and when the starting material had been consumed, hexanes were added, followed by water. Repeated diethyl ether extractions were performed and the extracts combined. The extracts were dried over MgSO₄ and subjected to column chromatography. Triene 663 was obtained as an oil (9 mg, 60%). TLC (ethyl acetate/hexanes 2:3): Rf = 0.9; ¹H NMR (400 MHz, C₆D₆): δ 1.27-1.38 (m, 5H), 1.67-1.76 (m, 2H), 2.02 (s, 3H), 3.39-3.46 (m, 2H), 3.46 (s, 3H), 3.60 (s, 2H), 5.26-5.34 (m, 1H), 5.88 (bs, 1H), 6.63 (d, J = 16.0 Hz, 1H), 6.98-7.10 (m, 4H), 7.48-7.54 (m, 1H); ¹³C NMR (100 MHz, C₆D₆): δ 196.5, 155.3, 139.3, 137.8, 133.6, 131.3, 129.9, 127.5, 127.4, 126.3, 124.4, 123.1, 52.3, 49.7, 44.8, 27.1, 23.5, 23.2, 20.6.

Compound 664: Triene 663 (8 mg, 0.02 mmol) was dissolved in bromobenzene-d₅ (0.7 mL) and transferred to a NMR tube. The tube was sealed and heated to 200 °C. After 11 hours, the reaction was cooled to room temperature, concentrated, and purified on a
neutral alumina column. Tetracycle 664 was obtained as an oil (5 mg, 65%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.5; ¹H NMR (400 MHz, C₆D₆): δ 0.86 (s, 3H), 1.22-1.31 (m, 2H), 1.33 (s, 3H), 1.37-1.50 (m, 2H), 1.57-1.63 (m, 2H), 1.69 (d, J = 12.0 Hz, 1H), 2.76-2.85 (m, 2H), 2.93-3.03 (m, 1H), 3.08-3.16 (m, 1H), 3.26-3.30 (m, 2H), 3.50 (s, 3H), 3.53-3.64 (m, 1H), 6.76 (d, J = 7.2 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 7.13-7.15 (m, 1H); ¹³C NMR (100 MHz, C₆D₆ [1 carbon obscured by C₆H₆]): δ 209.3, 155.1, 139.9, 133.3, 130.9, 127.6, 127.3, 127.1, 124.6, 56.0, 52.2, 49.0, 44.8, 39.4, 35.3, 33.1, 26.6, 24.3, 21.7, 21.6; HR-ESI-TOF-MS: m/z calcd. for C₂₁H₂₆O₃N₁: 340.1907, found: 340.1898# [M+H]+.

Compound 665: N-methyl glutarimide 603 (1.3 g, 10.24 mmol) was dissolved in THF (8 mL) and cooled to 0 °C. LiHMDS (10.2 mL, 10.2 mmol) was added as a 1 M THF solution over 4 minutes. The solution was removed from the ice bath and stirred at room temperature 30 minutes before cooling to -78 °C. Diethylchlorophosphate (1.77 g, 10.2 mmol) was added as a THF solution (5 mL) via cannula over 8 minutes. After stirring 15 minutes, the mixture was transferred to a 0 °C ice bath and stirred 50 minutes. The ice bath was removed and the reaction was stirred 30 minutes at room temperature. Bis stannane 627 (7.2 g, 11.9 mmol) was added followed quickly by Pd(PPh₃)₄ (400 mg, 0.35 mmol) and LiCl (4.1 g, 98 mmol). The reaction mixture was then heated at reflux 4 hours. The mixture was then diluted with hexanes and decanted to remove solids. The solids were stirred with diethyl ether and decanted again. The combined organics were subjected to column chromatography on neutralized silica. Stannane 665 was obtained as an oil (655 mg, 15%). TLC (ethyl acetate/hexanes 1:3): Rf = 0.5; ¹H NMR (400 MHz, C₆D₆): δ 0.82-1.01 (m, 15H), 1.23-1.62 (m, 13H), 1.71-1.78 (m, 2H), 2.23 (app. t, J = 7.2 Hz, 2H), 3.01 (s, 3H), 5.07 (app. t, J = 5.2 Hz, 1H), 6.20-6.60 (including: [6.30, d, J = 19.2 Hz, 1H] and [6.49, d, J = 19.2 Hz, 1H]); ¹³C NMR (100 MHz, C₆D₆): δ 169.8, 143.5, 141.5, 132.2, 105.4, 31.6, 30.3, 29.4, 27.5, 19.6, 13.8, 9.7.

Compound 666: Aryl iodide 646 (305 mg, 1.0 mmol) and stannane 665 (515 mg, 1.21 mmol) were mixed under argon. Pd(PPh₃)₄ (50 mg, 0.04 mmol) was added at room temperature followed by LiCl (500 mg, 11.9 mmol), and the reaction flask was transferred to a 95 °C oil bath. After stirring 2.5 hours, the reaction was diluted with methylene chloride while still warm, and then diluted with hexanes and filtered through neutralized silica. Fractions of interest were combined for chromatographic purification. Allylic alcohol 666 was obtained as an oil after column chromatography (176 mg, 55%). TLC (ethyl acetate/hexanes 2:3): Rf = 0.1; ¹H NMR (400 MHz, C₆D₆): δ 1.23 (s, 3H), 1.46 (s, 3H), 1.70-1.80 (m, 2H), 2.25 (app. t, J =
7.6 Hz, 2H), 2.73 (dd, J = 6.0, 13.6 Hz, 1H), 2.91 (dd, J = 7.6, 13.6 Hz, 1H), 2.96 (s, 3H), 4.38-4.47 (m, 1H), 5.11-5.17 (m, 2H), 6.18 (d, J = 16.0 Hz, 1H), 7.01-7.14 (m, 3H), 7.28-7.32 (m, 1H); 13C NMR (100 MHz, CD2Cl2): δ 171.1, 141.6, 136.9, 136.2, 134.8, 131.6, 129.5, 128.0, 127.7, 126.9, 126.0, 124.6, 106.6, 69.5, 41.6, 31.6, 30.8, 25.7, 19.9, 18.0.

**Compound 667:** Allylic alcohol 666 (105 mg, 0.34 mmol) was dissolved in EtOAc (10 mL) and IBX (420 mg, 1.5 mmol) was added at room temperature. The reaction mixture was heated to reflux and stirred 2.5 hours. After cooling to room temperature, the reaction mixture was rapidly filtered through Florisil. Triene 667 was obtained as an oil (93 mg, 89%). TLC (ethyl acetate/hexanes 3:2): Rf = 0.4; 1H NMR (400 MHz, CD2Cl2): δ 1.88 (s, 3H), 2.13 (s, 3H), 2.26-2.35 (m, 2H), 2.48 (app. t, J = 7.6 Hz, 2H), 3.12 (s, 3H), 3.82 (s, 2H), 5.54 (app. t, J = 4.8 Hz, 1H), 6.15 (bs, 1H), 6.51 (d, J = 15.6 Hz, 1H), 7.14-7.33 (m, 3H), 7.52-7.57 (m, 1H); 13C NMR (100 MHz, CD2Cl2): δ 197.3, 171.1, 157.0, 141.5, 136.6, 133.8, 131.4, 129.0, 128.3, 127.6, 126.2, 125.3, 123.0, 107.0, 49.4, 30.8, 30.3, 27.8, 20.8, 19.9.

**Compound 668:** Triene 667 (5.5 mg, 0.18 mmol) was dissolved in 1,2-dichlorobenzene (1 mL) and heated at 195 °C 10 hours. The reaction mixture was cooled to room temperature and diluted with EtOAc. The EtOAc solution was washed with water and dried over MgSO4. The extracts were concentrated and rapidly passed through a neutralized silica column. The fractions of interest were concentrated and cycloadduct 668 was obtained as a solid via trituration with a hexanes/diethyl ether solution (4 mg, 72%). TLC (ethyl acetate/hexanes 3:2): Rf = 0.3; 1H NMR (500 MHz, CD2Cl2): δ 1.14 (s, 3H), 1.29 (s, 3H), 1.89 (d, J = 11.5 Hz, 1H), 2.14-2.23 (m, 2H), 2.30 (ddd, J = 7.5, 13.7, 22 Hz, 1H), 2.46 (app. dt, J = 4.0, 15.5 Hz, 1H), 2.50-2.57 (m, 1H), 2.81-2.87 (m, 1H), 3.14 (s, 3H), 3.39 (ddd, J = 5.0, 11.5, 16.5 Hz, 1H), 3.47 (d, J = 14.3 Hz, 1H), 3.73 (d, J = 14.9 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 7.21-7.25 (m, 1H), 7.28-7.31 (m, 2H); 13C NMR (125 MHz, CD2Cl2 [1 alkene C signal missing, a C6D6 sample revealed a peak (100.4 ppm) absent in the CD2Cl2 sample]): δ 210.1, 170.1, 139.1, 133.2, 130.6, 127.6, 127.3, 123.0, 122.9, 55.6, 49.1, 39.1, 35.0, 32.0, 29.0, 29.8, 24.9, 22.0, 20.3; HR-ESI-TOF-MS: m/z calcd. for C20H24O2N1: 310.1801, found: 310.1800 [M+H]⁺. A crystal suitable for single crystal x-ray analysis was grown:
Crystal data and structure refinement for theod30.

Identification code: theod30

Empirical formula: C20 H23 N O2

Formula weight: 309.39

Temperature: 100(2) K

Wavelength: 0.71073 Å

Crystal system: Orthorhombic

Space group: Pbca

Unit cell dimensions:
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\[ b = 8.9538(8) \text{ Å} \]
\[ c = 28.545(3) \text{ Å} \]

\[ \alpha = 90^\circ \]
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Volume: 3110.7(5) Å³

Z: 8

Density (calculated): 1.321 g/cm³

Absorption coefficient: 0.085 mm⁻¹

F(000): 1328

Crystal size: 0.24 x 0.14 x 0.08 mm³
Theta range for data collection 1.43 to 25.35°

Index ranges -14<=h<=13, -10<=k<=8, -34<=l<=29

Reflections collected 15463

Independent reflections 2848 [R(int) = 0.0598]

Completeness to theta = 25.00° 100.0 %

Absorption correction Multi-scan

Max. and min. transmission 0.9933 and 0.9800

Refinement method Full-matrix least-squares on F²

Data / restraints / parameters 2848 / 0 / 208

Goodness-of-fit on F² 1.026

Final R indices [I>2sigma(I)] R1 = 0.0530, wR2 = 0.1240

R indices (all data) R1 = 0.0788, wR2 = 0.1395

Largest diff. peak and hole 0.479 and -0.413 e Å⁻³

Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³)for theo30. U(eq) is defined as one third of the trace of the orthogonalized U_ij tensor.

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<td>C(4)-C(17)-C(16)</td>
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<td>N(1)-C(17)-C(16)</td>
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Anisotropic displacement parameters \((\AA^2 \times 10^3)\) for theod30. The anisotropic displacement factor exponent takes the form: 

\[-2\pi^2 [ h^2 a^* a^* U^{11} + \ldots + 2h k a^* b^* U^{12} ]\]
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Hydrogen coordinates (x \(10^4\)) and isotropic displacement parameters (Å\(^2\) x \(10^{-3}\)) for theod30.
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Section A.3  Selected NMR Spectra
Spectrum 2.0 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 423
1H NMR (DMSO-d6, 400 MHz) of compound 423

Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
File: daf_5-26_1H_DMSO
Mercury-400NN "hg402"

Relax. delay 1.000 sec
Pulse 45.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
308 repetitions
OBSERVE 61, 400.0554509 MHz
DATA PROCESSING
FT size 32768
Total time 29 min, 20 sec

7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 ppm

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 ppm

1.02 1.01 0.99 1.03 1.05 2.03 2.83 3.01 3.16
STD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: benzaldehyde_1h
Mercury-400Bk *bg402*

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
256 repetitions
OBSERVE H1, 400.0535612 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 40 sec
Spectrum 2.3 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 427
Spectrum 2.4 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 433
Spectrum 2.5 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 433
Spectrum 2.6 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 434
Spectrum 2.7

1H NMR (CDCl₃, 400 MHz) of compound 437

STANDARD 1H OBSERVE

Pulse Sequence: a2pul
Solvent: CDCl₃
Temp. 25.0 °C / 298.1K
File: def_4-98_1h
Mercury-400BB *bg402*

Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.995 sec
Width 5906.0 Hz
122 repetitions
OBSERVE HL, 400.1233 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 40 sec

ppm
6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8
Spectrum 2.8 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 437
Spectrum 2.9 1H NMR (CDCl₃, 400 MHz) of compound 438

Pulse Sequence: a2pul
Solvent: CDCl₃
Temp. 25.0 C / 298.1K
File: saf.4-996.1h
Mercury-400Bb "bg402"

Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 3.995 sec
Width 6006.0 Hz
140 repetitions
OBSERVE H1, 400.1233143 MHz
DATA PROCESSING
Line broadening 0.3 Hz
PT size 32768
Total time 14 min, 40 sec

7.0 6.6 6.2 5.8 5.4 5.0 ppm

0.79 1.01 0.98
1.03 0.91 1.01
3.38 3.07
3.52

ppm
Spectrum 2.10 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 440
Spectrum 2.11 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 440
Spectrum 2.12 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 441
Spectrum 2.13 1H NMR (CDCl3, 400 MHz) of compound 442

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 °C / 298.1K
File: daf 4-84c_1b
Mercury-400BB *hs402*

Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.995 sec
Width 6006.0 Hz
64 repetitions

OBSERVE H1, 400.1233347 MHz
DATA PROCESSING
Lins broadening 0.3 Hz
PT size 32768
Total time 14 min, 40 sec
Spectrum 2.14

1H NMR (CDCl₃, 400 MHz) of compound 443

STANDARD IN OBSERVE

Pulse Sequence: z2pul
Solvent: CDCl₃
Temp. 25.0 °C / 298.1K
File: daf_4-84b_1b
Mercury-400BB "hg402"

Relax. Delay 1.000 sec
Pulse 90.2 degrees
Acq. time 1.995 sec
Width 6006.0 Hz
64 repetitions

DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 14 min, 40 sec

7.0 6.5 6.0 5.5 5.0 4.5 ppm

0.83 0.97 1.99 3.08 3.18
0.95 0.98 0.98 2.71
Spectrum 2.15 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 443
Spectrum 2.16 1H NMR (CDCl₃, 400 MHz) of compound 444
Spectrum 2.17 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 444
Spectrum 2.18 1H NMR (CDCl3, 400 MHz) of compound 445
Spectrum 2.19 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 445
Spectrum 2.20  $^1$H NMR (CDCl$_3$, 500 MHz) of compound 446E
Spectrum 2.21 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 446E
Spectrum 2.22 | H NMR (CDCl₃, 500 MHz) of compound 446Z

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl₃
Temp. 25.0 C / 298.1K
File: daf_5-50b_1b
Mercury-400BB  "bg402"

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
256 repetitions
Observe H1, 500.3087940 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 33768
Total time 10 min, 22 sec

0.94 1.09 3.14
1.23 3.25 3.43

ppm
Spectrum 2.23 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 446Z.
Spectrum 2.24  

1H NMR (CDCl₃, 400 MHz) of compound 447

STANDARD 1H OBSERVE

Pulse Sequence: z2pul
Solvent: CDCl₃
Ambient temperature
File: da5  62.1b
Mercury-400BB *hg402*

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
80 repetitions
OBSERVE H1, 400.0535586 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 40 sec
Spectrum 2.25 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 447
Spectrum 2.26  $^1$H NMR (CDCl$_3$, 400 MHz) of compound 448
Spectrum 2.27 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 448
Spectrum 2.28 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 449
Spectrum 2.29 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 449
Spectrum 2.30 1H NMR (CDCl3, 400 MHz) of compound 450

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: s4-c3h-b1h
Mercury-400BN "hg402"

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.599 sec
Width 5998.6 Hz
244 repetitions
OBSERVE H1, 400.05335097 MHz
DATA PROCESSING
FT size 32768
Total time 95514 hr, 35 min, 7 sec
Spectrum 2.31 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 450
Spectrum 2.32 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 451
Spectrum 2.33 1H NMR (CDCl₃, 400 MHz) of compound 452

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl₃
Ambient temperature
File: daf 5-30 1h
Mercury-400BB "hg402"

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
196 repetitions
OBSERVE R1, 400.0535590 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 40 sec
Spectrum 2.34 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 452
Spectrum 2.35 \( ^1H \) NMR (CDCl_3, 400 MHz) of compound 453

**STANDARD 1H OBSERVE**

Pulse Sequence: s2pul
Solvent: CDCl_3
Ambient temperature
File: dae_5-31_1h
Mercury-400BB *hb402*

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
4 repetitions
OBSERVE H1, 400.0535597 MHz
DATA PROCESSING
FT size 32768
Total time 6 min, 41 sec
Spectrum 2.36 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 453
Spectrum 2.37
1H NMR (CDCl3, 400 MHz) of compound 454
Spectrum 2.38 \( ^1 \)H NMR (CDCl\(_3\), 400 MHz) of compound 455
Spectrum 2.39 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 455
Spectrum 2.40 $^1$H NMR (DMSO-d$_6$, 400 MHz) of compound 457
Spectrum 2.41 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 458
Spectrum 2.42 \( ^{13}C \) NMR (CDCl\(_3\), 100 MHz) of compound 458
Spectrum 2.43 1H NMR (CDCl3, 400 MHz) of compound 459
Spectrum 2.44 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 459
Spectrum 2.45 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 460
Spectrum 2.46 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 460
Spectrum 2.47

1H NMR (CDCl3, 500 MHz) of compound 461E

STANDARD PROTON PARAMETERS

Pulse Sequence: e2pul
Solute: CDC13
Temp. 25.0 C / 298.1K
File: da5_45b_1b
Mercury-300 "hg300"

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
220 repetitions
Observe H1, 500.3087940 MHz
Data Processing
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec

7.0  6.8  6.6  6.4  6.2 ppm
Spectrum 2.49: \(^1\)H NMR (CDCl\(_3\), 500 MHz) of compound 462E

**STANDARD PROTON PARAMETERS**

Pulse Sequence: z2pul
Solvent: CDCl\(_3\)
Temp. 25.0 \(^\circ\)C / 298.1K
File: def_5-47_1h
Mercury-300 *hg300*

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
152 repetitions
OVERSAMP 81, 500.3087944 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 30 min, 22 sec

**Chemical Shifts**

- 7.6, 7.4, 7.2, 7.0 ppm
- 6.8, 6.6, 6.4 ppm
- Other peaks at 1.03, 0.99, 0.85, 3.46, 1.95, 0.97, 2.52, 3.08, 6.41 ppm
Spectrum 2.50 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 462E
Spectrum 2.51 | 1H NMR (CDCl3, 500 MHz) of compound 462Z

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1K
File: def_5-46_1h
Mercury-300 "Hz300"

Pulse 51.5 degrees
Acq. time 1.692 sec
Width 8000.0 Hz
112 repetitions
OBSERVE H1, 500.3087940 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 0 min. 0 sec

7.6 7.4 7.2 7.0 6.8 6.6 6.4 ppm

9 8 7 6 5 4 3 2 1 ppm

0.98 0.96 1.94 3.65
0.98 1.01 2.32 2.58
0.62
Spectrum 2.52 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 462Z
Spectrum 2.53 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 463
Spectrum 2.54 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 464
Spectrum 2.55 $^1$H NMR (CDCl$_3$, 500 MHz) of compound 465
Spectrum 2.56

1H NMR (CDCl3, 400 MHz) of compound 478

STANDARD 1H OBSERVE

Pulse Sequence: e2pul
Solvent: CDCl3
Ambient temperature
Pile: def 5-70 1h
Mercury-300 *hq300*

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.999 sec
Width 5998.8 Hz
96 repetitions
OBSERVE HI, 400.0535626 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32760
Total time 0 min, 0 sec
Spectrum 2.57 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 478
Spectrum 2.58 \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) of compound 479

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl\textsubscript{3}
Ambient temperature
File: daq_5-72_1h
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 52.2 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
256 repetitions
OBSERVE H1, 300.755597 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 0 min, 0 sec
Spectrum 2.59 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 479
Spectrum 2.60 \text{ H NMR (CDCl$_3$, 400 MHz) of compound 480}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{spectrum.png}
\end{figure}

\begin{itemize}
\item **Pulse Sequence:** s2pul
\item **Solvant:** CDCl$_3$
\item **Ambient temperature:**
\item **File:** daf_5-73_1h
\item **Mercury-300:** "hg300"
\item **Relax. delay:** 1.000 sec
\item **Pulse 46.5 degrees**
\item **Acq. time:** 1.995 sec
\item **Width:** 5999.0 Hz
\item **24 repetitions**
\item **OBSERVE:** H1, 400.0535597 MHz
\item **DATA PROCESSING**
\item **Line broadening:** 0.3 Hz
\item **FT size:** 32768
\item **Total time:** 34 min, 40 sec
\end{itemize}

\begin{table}[h]
\centering
\begin{tabular}{cccccccccc}
9.5 & 9.0 & 8.5 & 8.0 & 7.5 & 7.0 & 6.5 & 6.0 & 5.5 & 5.0 & ppm
\hline
3.28 & 9.88 & 5.68 & 3.28 & 9.88 & 5.68 & 3.28 & 9.88 & 5.68 & ppm
\end{tabular}
\end{table}
Spectrum 2.61 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 480
Spectrum 2.62: \(^1\)H NMR (CDCl\(_3\), 400 MHz) of compound 481

- Pulse Sequence: z2pul
- Solvent: CDCl\(_3\)
- Ambient temperature
- File: daf_5-75.1h
- Mercury-300 "hg300"

- Relax. delay: 1.000 sec
- Pulse 48.5 degrees
- Acq. time: 1.995 sec
- Width: 5998.8 Hz
- 16 repetitions
- OBSERVE E1, 400.0535597 MHz
- DATA PROCESSING
- Line broadening: 0.3 Hz
- FT size: 32768
- Total time: 0 min, 50 sec
Spectrum 2.63 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 481
Spectrum 2.64 $^1$H NMR (CDCl$_3$, 500 MHz) of compound 482
Spectrum 2.65 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 482
**Spectrum 2.66** $^1$H NMR (CDCl$_3$, 300 MHz) of compound 483E
Spectrum 2.67 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 483E
Spectrum 2.68 $^1$H NMR (CDCl$_3$, 300 MHz) of compound 483Z
Spectrum 2.69 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 483Z
Spectrum 2.70 $^1$H NMR (CDCl$_3$, 500 MHz) of compound 484E
Spectrum 2.71

1H NMR (CDCl₃, 400 MHz) of compound 484Z

STANDARD 1H OBSERVE

Pulse Sequence: s2pol
Solvent: CDCl₃
Ambient temperature
File: daf 5-85 1h
Mercury-300 "bg100"

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
80 repetitions
OBSERVE H1, 400.0535597 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 40 sec

6.8  6.7  6.6  6.5  6.4  6.3  6.2  ppm

9  8  7  6  5  4  3  2  1  ppm

0.98 0.94 2.91 1.01 1.00 1.96 2.77 3.11
Spectrum 2.72 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 484Z
Spectrum 2.73 $^1$H NMR (CDCl$_3$, 500 MHz) of compound 485E
Spectrum 2.74 1H NMR (CDCl3, 500 MHz) of compound 485Z

STANDARD PROTON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDC13
Temp. 25.0 C / 298.1K
File: def_5-67cis_lh
Mercury-300 *3hr300*

Pulse 51.5 degrees
Acq. time 1.692 sec
Width 8000.0 Hz
80 repetitions
RESOLVE N, 500.3087950 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec
**Spectrum 2.75** $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 485Z
Spectrum 2.76

1H NMR (CDCl3, 500 MHz) of compound 486

STANDARD PROTON PARAMETERS

Pulse Sequence: a2pul
Solvent: CDC13
Temp. 25.0 C / 298.1K
File: daf.6.19a
Mercury-300 "hg300"

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
140 repetitions
OBSEERVE NL, 500.3087950 MHz
DATA PROCESSING
Line broadening 0.3 Hz
PT size 32768
Total time 0 min, 0 sec
Spectrum 2.77 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 486
Spectrum 2.78  $^1$H NMR (CDCl$_3$, 300 MHz) of compound 487
Spectrum 2.79 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 487
Spectrum 2.80 $^1$H NMR (CDCl$_3$, 500 MHz) of compound 488
Spectrum 2.81 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 488
Spectrum 2.82

1H NMR (CDCl₃, 500 MHz) of compound 491

STANDARD PROTON PARAMETERS
Pulse Sequence: a2pul
Solvent: CDCl₃
Temp. 25.0 C / 298.1K
File: def 5-119
Mercury-300 "hg300"

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
184 repetitions
OBSERVE H1, 500.3087320 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec
Spectrum 2.83 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 491
Spectrum 2.84 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 493
Spectrum 2.85 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 493
Spectrum 2.86 \textit{H} NMR (CDCl$_3$, 400 MHz) of compound 494

Pulse Sequence: a2pul
Solvent: CDCl$_3$
Ambient temperature
File: def 5-125.1h
Mercury-300 *bg300*

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
60 repetitions
OBSERVE NL, 400.0535590 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 16 min, 40 sec
Spectrum 2.87 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 494
Spectrum 2.88 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 495
Spectrum 2.89 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 496
Spectrum 2.90

1H NMR (CDCl₃, 400 MHz) of compound 497

Pulse Sequence: s2pul
Solvent: CDCl₃
Ambient temperature
File: daf_5-129_1b
Mercury-300 "hp400"

Relax. delay 1.000 sec
Pulse 45.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
60 repetitions

OBSERVE H1, 400.0535597 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 40 sec
Spectrum 2.91 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 497
Spectrum 2.92 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 498
Spectrum 2.93 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 498
Spectrum 2.94 \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) of compound 500
Spectrum 2.95 1H NMR (CDCl₃, 400 MHz) of compound S01
Spectrum 2.96 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 502
Spectrum 2.97 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 502
Spectrum 2.98 \( {^1}H \) NMR (C\(_6\)D\(_6\), 400 MHz) of compound 503

Pulse Sequence: e2pul
Solvent: Benzene
Ambient temperature
File: daa-6-26 lh
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6066.0 Hz
16 repetitions
OBSERVE H1, 400.1233710 MHz
DATA PROCESSING
PT size 32768
Total time 24 min, 39 sec
Spectrum 2.99 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 503
Spectrum 2.100 1H NMR (CDCl3, 400 MHz) of compound 504

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0°C / 298.1K
File: df_6-50c
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 46.5 degrees
Acq. time 1.995 sec
Width 5598.8 Hz
40 repetitions

OBSERVE: H1, 400.0535697 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 16 min, 40 sec
Spectrum 2.101 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 505
Spectrum 2.102 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 505
Spectrum 2.103 
$^1$H NMR (CDCl$_3$, 400 MHz) of compound 509

Pulse Sequence: a2pul
Solvent: CDCl$_3$
Ambient temperature
Pipes: daf 30-98
Made chloroform
Mercury-300 *hg300*

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6066.0 Hz
112 repetitions
BEGIN
EI, 395.9089597 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 39 sec

3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 ppm

9 8 7 6 5 4 3 2 1 ppm

5.87 1.04
1.00 0.56
1.58 2.06
6.41 10.42 3.24
1.12 1.61
**Spectrum 2.104**

**1H NMR (C6D6, 400 MHz) of compound 509**

**STANDARD 1H OBSERVE**

Pulse Sequence: s2pul
Solvent: Bensene
Ambient temperature
File: def 10-98_bensene
Mercury-300 "by300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 1006.0 Hz
80 repetitions
OBSERVE HL, 399.9090357 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 39 sec
STANDARD PROTON PARAMETERS

Pulse Sequence: a2pul
Solvent: cd2cl2
Temp. 25.0 C / 298.1K
File: daf.30-98.dom
Mercury-100 *hg100*

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8800.0 Hz
92 repetitions
OBSERVE m2 500.3007556 MHz
DATA PROCESSING
line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec

Spectrum 2.105
$^1$H NMR (CD$_2$Cl$_2$, 500 MHz) of compound 309
Spectrum 2.106 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 509
Spectrum 2.107 1H NMR (CDCl₃, 400 MHz) of compound 510

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl₃
Ambient temperature
File: df10-97_1h
Mercury: 300 °Hg300°

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
40 repetitions
OBSERVE H1, 396.9085997 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 55760
Total time 14 min, 39 sec

ppm
4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2

5.33 0.89 0.99 1.07 1.02 2.75 2.29 2.88

ppm
9 8 7 6 5 4 3 2 1 2

Boc N

O
Spectrum 2.108 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 510
Spectrum 2.109 $^1$H NMR (CDCl$_3$, 500 MHz) of compound 511
Spectrum 2.110 1H NMR (CDCl3, 400 MHz) of compound 520

STANDARD 1H OBSERVE
Pulse Sequence: sp2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1K
File: Pho-16
Mercury-300 'hg300'

Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.995 sec
Width 6006.0 Hz
168 repetitions
OBSERVE HL, 400.1233350 MHz
DATA PROCESSING
Line broadening 0.3 Hz
PT size 32768
Total time 14 min, 40 sec

ppm

9 8 7 6 5 4 3 2 1 0

1.00 6.15
Spectrum 2.111 \( ^1 \)H NMR (CDCl\(_3\), 400 MHz) of compound 521
Spectrum 2.112 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 521
Spectrum 2.113

1H NMR (CDCl3, 400 MHz) of compound 522

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 °C / 298.1K
File: daf-Phol4
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.995 sec
Width 6006.0 Hz
44 repetitions
OBSERVE NL, 400.1233 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 29 min, 20 sec

4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 ppm

9 8 7 6 5 4 3 2 1 ppm

3.01 5.57
1.00 1.10
2.28 9.49
Spectrum 2.114 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 522
Spectrum 2.115 1H NMR (CDCl3, 400 MHz) of compound 523
Spectrum 2.116 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 523
Spectrum 2.117 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 524
Spectrum 2.118 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 524
Spectrum 2.119

$^1$H NMR (CDCl$_3$, 400 MHz) of compound 525

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl$_3$
Temp. 25.0 °C / 298.1 K
File: Pho-mesyrate
Mercury-300 *hg300*

Relax. delay 1.000 sec
Pulse 56.2 degrees
Aqg. time 1.995 sec
Width 5006.0 Hz
44 repetitions
Observe Hz, 400.123350 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 40 sec

4.8 4.7 4.6 4.5 4.4 4.3 4.2 ppm

9 8 7 6 5 4 3 2 1 ppm

0.91 1.10 2.84 1.05 3.17 1.00 1.06
Spectrum 2.120 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 525
Spectrum 2.121

1H NMR (CDCl₃, 400 MHz) of compound 526

Pulse Sequence: m2pul
Solvent: CDC13
Temp. 25.0 C / 298.1K
File: Pco-20
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 56.2 degrees
Acq. time 1.995 sec
Width 6006.0 Hz
96 repetitions
OBSERVE H1, 400.1233350 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 40 sec
Spectrum 2.122 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 526
Spectrum 2.123 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 527
Spectrum 2.124 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 527
Spectrum 2.125 \^1H NMR (CDCl\textsubscript{3}, 400 MHz) of compound 528
Spectrum 2.126 ¹³C NMR (CDCl₃, 100 MHz) of compound 528
Spectrum 2.127 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 529
Spectrum 2.128 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 529
Spectrum 2.129 ¹H NMR (CDCl₃, 400 MHz) of compound 530
Spectrum 2.130 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 530
Spectrum 2.131  \( ^1H \) NMR (CDCl\(_3\), 400 MHz) of compound 531

STANDARD 1H OBSERVE

Pulse Sequence: a2pul
Solvent: CDC\(_3\)
Ambient temperature
File: daf-2-102
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5998.0 Hz
16 repetitions
OBSERVE N1, 400.0535597 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 48 sec
Spectrum 2.132 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 531
Spectrum 2.133 1H NMR (CDCl3, 300 MHz) of compound 532

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Pile: def 9-10, hexane wash
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 43.2 degrees
Acq. time 1.995 sec
Width 6506.5 Hz
256 repetitions
OBSERVE H1, 300.0755102 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 19 sec
Spectrum 2.134 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 532
Spectrum 2.135

$^1$H NMR (CD$_6$, 500 MHz) of compound 534

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: Benzene
Temp. 25.0 C / 298.1K
File: dae_8_5_9hours
Mercury-300 "mg300"

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
120 repetitions

OBSERVE H1, 500.3088400 MHz
DATA PROCESSING
Line broadening 0.3 Hz
PT size 32768
Total time 10 min, 22 sec
Spectrum 2.136 1H NMR (CDCl₃, 400 MHz) of compound 535

STANDARD 1H OBSERVE

Pulse Sequence: s1pul
Solvent: CDCl₃
Ambient temperature
File: daf_8-7a
Mercury-300 *hg300*

Relax. delay 1.000 sec
Pulse 42.8 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
20 repetitions
OBSERVE XL, 400.0535597 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec

O

MeO

OTES

3.6 3.2 2.8 2.4 2.0 ppm

9 8 7 6 5 4 3 2 1 ppm

2.87 2.00 2.25 3.43
2.10 2.09 9.63
Spectrum 2.137

$^1$H NMR (CDCl$_3$, 400 MHz) of compound 536

Pulse Sequence: s2pul
Solvent: CDCl$_3$
Ambient temperature
File: daf_8-18_1h
Mercury-300 "hq300"

Relax, delay 1.000 sec
Pulse 42.9 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
40 repetitions
OBSERVE H1, 400.0535597 MHz
DATA PROCESSING
PT size 32768
Total time 14 min, 39 sec
Spectrum 2.138 $^1$H NMR (CDCl$_3$, 500 MHz) of compound 537
Spectrum 2.139 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 538
Spectrum 2.140 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 538
Spectrum 2.141

**1H NMR (CDCl₃, 400 MHz) of compound 539**

**STANDARD 1H OBSERVE**

- Pulse Sequence: z2pul
- Solvent: CDCl₃
- Ambient temperature
- File: daf_8-46.1h
- Mercury-300 *hg300*

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
136 repetitions

**OBSERVE** E1, 399.9089997 MHz

**DATA PROCESSING**
- Line broadening 0.3 Hz
- FT size 32768
- Total time 14 min, 39 sec

**NMR Spectra**

- Resonance labels and chemical shifts are present in the spectrum.

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504
Spectrum 2.142 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 539
Spectrum 2.143 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 540
Spectrum 2.144 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 540
Spectrum 2.145

1H NMR (CDCl₃, 400 MHz) of compound 541

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl₃
Ambient temperature
File: daf 6-60 lb
Mercury-300 °Hg300°

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 3.993 sec
Width 0.065.0 Hz
116 repetitions
OBSERVE H1, 399.9089997 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min. 39 sec

6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 ppm

9 8 7 6 5 4 3 2 1 ppm

4.27 1.01 1.00 1.04 6.54 9.12 5.67
Spectrum 2.146 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 541
Spectrum 2.147 $^1$H NMR (CDCl$_3$, 500 MHz) of compound 542
Spectrum 2.148 $^1$H NMR (CDCl$_3$, 500 MHz) of compound 543
Spectrum 2.149

\[ ^1H \text{NMR (CDCl}_3, 400 \text{ MHz) of compound 544} \]

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: daf_10-92.1b
Mercury-300 *hg300*

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
52 repetitions

DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 39 sec
Spectrum 2.150 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 544
Spectrum 2.151 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 545
Spectrum 2.152 \(^1\)H NMR (CDCl\(_3\), 400 MHz) of compound 548

STANDARD IN OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl\(_3\)
Ambient temperature
File: daf_30-58
Mercury-300 *hg300*

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
112 repetitions
OBSERVR H1, 399.9099997 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 29 min. 19 sec
Spectrum 2.153 $^1$H NMR (C$_6$D$_6$, 400 MHz) of compound 548
13C NMR (C₆D₆, 100 MHz) of compound 548
Spectrum 2.155 1H NMR (CDCl3, 400 MHz) of compound 549
Spectrum 2.156 1H NMR (CD6, 400 MHz) of compound 549

**STANDARD 1H OBSERVE**

- **Pulse Sequence:** sipul
- **Solvent:** Benzene
- **Ambient temperature:**
- **File:** daf 10-77 1h
- **Mercury-300 *bg300*”

- **Relax. delay:** 1.000 sec
- **Pulse:** 42.9 degrees
- **Acq. time:** 1.993 sec
- **Width:** 6056.0 Hz
- **56 repetitions**

**OBSERVE** kHz, 400.0535957 MHz
**DATA PROCESSING**
**FT size:** 32768
**Total time:** 14 min, 39 sec

**NMR Chart**

- **Chemical Shifts:**
  - 9.86 ppm
  - 8.95 ppm
  - 7.84 ppm
  - 6.76 ppm
  - 5.68 ppm
  - 4.59 ppm
  - 3.50 ppm
  - 2.41 ppm
  - 1.32 ppm

**Additional Notes**

- **Synthesis Details:**
  - Reaction conditions:...
  - Yields:...
  - Isolation method:...

- **References:**
  - (Insert relevant references here)

**Discussion:**

- Analysis of chemical shifts and integration of peaks...
- Implications for structure confirmation...

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519
Spectrum 2.157 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 549
Spectrum 2.158

1H NMR (CDCl₃, 400 MHz) of compound 553

O

TBSO

STANDARD 1H OBSERVE

Pulse Sequence: a2pul
Solvent: CDCl₃
Ambient temperature
File: daf_9-74_crude
Mercury-300 *hg300*

Relax. delay 1.000 sec
Pulse 42.9 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
76 repetitions
OBSERVE M1, 400.0535597 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec
Spectrum 2.159 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 554

Pulse Sequence: a2p1
Solvent: CDC13
Ambient temperature
File: daf_9-75.1h
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 95.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
52 repetitions
OBSEwire 11, 399.999997 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 39 sec
Spectrum 2.160 $^{13}$C NMR (CDCl$_3$, 75 MHz) of compound 554
1H NMR (CDCl₃, 400 MHz) of compound 555
Spectrum 2.162 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 555
Spectrum 2.163 $^1$H NMR (CDCl$_3$, 300 MHz) of compound 556
Spectrum 2.164 $^{13}$C NMR (CDCl$_3$, 75 MHz) of compound 556
Spectrum 2.165 ¹H NMR (CDCl₃, 400 MHz) of compound 557

STANDARD 1H OBSERVE

Pulse Sequence: azpul
Solvent: CDCl₃
Ambient temperature
File: daf 10-26
Mercury-300 *hg300*

Relax. delay 1.000 sec
Pulse 42.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
44 repetitions
OBSERVE RI, 400.0535557 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec
Spectrum 2.166 $^{13}$C NMR (CDCl$_3$, 75 MHz) of compound 557
Spectrum 2.167 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 558
Spectrum 2.168 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 559
Spectrum 2.169 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 559
Spectrum 2.170 1H NMR (CDCl3, 300 MHz) of compound 560

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDC13
Ambient temperature
File: def.9-111.1h
Mercury-300  "hg300"

Relax. delay 1.000 sec
Pulse 43.2 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
256 repetitions
OBSERVE Hi, 300.0755102 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 19 sec
Spectrum 2.171 $^{13}$C NMR (CDCl$_3$, 75 MHz) of compound 560
Spectrum 2.172  $^1$H NMR (CDCl$_3$, 400 MHz) of compound 561

Pulse Sequence: s2pul
Solvent: CDCl$_3$
Ambient temperature
File: daf 9-86
Mercury-300 **bg100**

Relax, delay 1.000 sec
Pulse 42.9 degrees
Acq. time 1.993 sec
Width 5096.0 Hz
168 repetitions
OBSERVE W, 400.0535597 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec
Spectrum 2.173

^H NMR (CDCl3, 500 MHz) of compound 562

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 °C / 298.1K
Pile: def_9-120最后一次
Mercury-300 °Hz

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
52 repetitions

OBSERVE H1, 500.3087950 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec

6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 ppm

9 8 7 6 5 4 3 2 1 ppm

0.43 0.89 1.00 0.99 4.56 7.07 1.49 6.15 11.03 5.15
Spectrum 2.174 $^1H$ NMR (CDCl$_3$, 300 MHz) of compound 563
Spectrum 2.175

1H NMR (CDCl₃, 500 MHz) of compound 564

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl₃
Temp. 25.0°C / 298.1K
File: daf_9-121
Mercury-300 °hg300°

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
120 repetitions
OBSEERVE H1, 500.3087950 MHz
DATA PROCESSING
Line broadening 0.3 Hz
YT size 32768
Total time 10 min, 22 sec
Spectrum 2.176 $^{13}$C NMR (CDCl$_3$, 75 MHz) of compound 564
Spectrum 2.177 $^1$H NMR (CDCl$_3$, 500 MHz) of compound 565
Spectrum 2.178 $^{13}$C NMR (CDCl$_3$, 75 MHz) of compound 565
Spectrum 2.179 1H NRM (CDCl3, 400 MHz) of compound 566
Spectrum 2.180 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 566
Spectrum 2.181 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 567
Spectrum 2.182  \(^1\)H NMR (CDCl\(_3\), 400 MHz) of compound 569

Pulse Sequence: s2pul
Solvent: CDCl\(_3\)
Ambient temperature
File: daf_30-34
Mercury-300 "hq300"

Relax. delay 1.000 sec
Pulse 42.5 degrees
Acq. time 1.993 sec
Width 4006.0 Hz
44 repetitions

DATA PROCESSING
Pt size 32768
Total time 14 min, 39 sec

![NMR Spectrum Diagram]
Spectrum 2.183 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 569
Spectrum 2.184

\(^1\)H NMR (CDCl\(_3\), 500 MHz) of compound 570

**STANDARD PROTON PARAMETERS**

Pulse Sequence: a2pul
Solvent: CDCl\(_3\)
Temp. 25.0°C / 298.1 K
Filer: def.10-36
Mercury-300 MHz

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
104 repetitions
OBSERVE H1, 500.3087950 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec
Spectrum 2.185 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 570
Spectrum 2.186

1H NMR (CDCl3, 400 MHz) of compound 571

STD 1H OBSERV
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: daf_10-42
Mercury: 300 "hg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 5006.0 Hz
256 repetitions
OBSERVE = 398.959997 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 2048
Total time 29 min. 19 sec

5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 ppm

9 8 7 6 5 4 3 2 1 ppm

0.02 5.48 1.10 2.07 1.07 2.99 1.17 6.76 3.29 9.24 5.33
Spectrum 2.187

1H NMR (CDCl₃, 400 MHz) of compound 572

STANDARD 1H OBSERVE

Pulse Sequence: a2pul
Solvent: CDCl₃
Ambient temperature
File: daf 10-31 1h
Mercury-300 *hg300*

Relax, delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
56 repetitions
OBSERVE H1, 399.9089957 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 39 sec
$^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 572

Spectrum 2.188
Spectrum 2.189  \(^1\)H NMR (CDCl\(_3\), 400 MHz) of compound 573

**STANDARD IN OBSERVE**

Pulse Sequence: z2pul
Solvent: CDCl\(_3\)
Ambient temperature
File: def 10-61.1h
Mercury-300  "hg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 606.0 Hz
40 repetitions
OBSERVE H1, 399.989998 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 39 sec

ppm
**Spectrum 2.190** $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 573
Spectrum 2.191  
$^1$H NMR (CDCl$_3$, 400 MHz) of compound 574

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl$_3$
Ambient temperature
File: daf 10-62 lh
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 5056.0 Hz
44 repetitions
OBSERVE M1, 399.9085997 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 39 sec

4.2  3.8  3.4  3.0  2.6 ppm

9  8  7  6  5  4  3  2  1 ppm
0.96  2.76  4.47  0.96  1.00  1.02  3.62  1.32  1.92  2.83  37.83  2.64
Spectrum 2.192 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 574
Spectrum 2.193

$^{1}H$ NMR (CDCl$_3$, 400 MHz) of compound 575

STANDARD 1H OBSERVE

Pulse Sequence: a2pul
Solvent: CDCl$_3$
Ambient temperature
File: daf 10-62 lh
Mercury-300 *hg300*

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 5056.0 Hz
20 repetitions
OBSERVE XL, 399.9685997 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 39 sec
Spectrum 2.194 $^{13}$C NMR (CDCl₃, 100 MHz) of compound 575
Spectrum 2.196

^1H NMR (CDCl3, 500 MHz) of compound 578

STANDARD PROTON PARAMETERS

Pulse Sequence: e2pul
Solvent: CDCl3
Temp. 25.0 °C / 298.1K
File: daf_10-64II
Mercury-300 "hg300"

Pulse 51.5 degrees
Acq. time 1.692 sec
Width 8000.0 Hz
88 repetitions
OBSERVE H, 500.308750 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec

5.0 4.6 4.2 3.8 3.4 ppm

9 8 7 6 5 4 3 2 1 ppm

1.02 1.00 1.93 2.02 2.18 2.41 3.18 3.03 1.93 2.02 2.61 32.30 4.76
Spectrum 2.197

$^1$H NMR (CDCl$_3$, 500 MHz) of compound

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl$_3$
Temp. 25.0 $^\circ$C / 298.1K
File: def_10-65
Mercury-300 "bg300"

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
116 repetitions
OBSERVE H1, 500.3887950 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec

5.2 4.8 4.4 4.0 3.6 3.2 ppm

9 8 7 6 5 4 3 2 1 ppm

0.68 2.25 1.02 1.33 2.28 3.11 3.16 1.48 6.68 75.46 8.75
Spectrum 2.198 $^1$H NMR (CDCl$_3$, 500 MHz) of compound 588
Spectrum 2.199

$^{1}H$ NMR (CDCl$_3$, 400 MHz) of compound 590

Pulse Sequence: a2pul
Solvent: CDCl$_3$
Ambient temperature
File: def.6-79.1h
Mercury-300 "Hg300"

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
68 repetitions
OBSERVE H1, 400.0535590 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 40 sec
Spectrum 2.200 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 590
Spectrum 2.201 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 596
Spectrum 2.202 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 596
Spectrum 2.203

\(^1H\) NMR (CDCl₃, 500 MHz) of compound 597

STANDARD PROTON PARAMETERS

Pulse Sequence: a2pul
Solvent: CDCl₃
Temp. 25.0 °C / 298.1K
File: daf_6-107_1b
Mercury-300 *bg300*

Pulse 61.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
124 repetitions
OBSERVE M1, 500.3087940 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec

6.6  6.5  6.4  6.3  6.2  6.1  6.0  5.9  ppm

9   8   7   6   5   4   3   2   1   0  ppm

1.90 90  1.92 0.87  3.50  9.07
Spectrum 2.204 1H NMR (CDCl3, 400 MHz) of compound 598

Pulse Sequence: z2pul
Solvent: CDC13
Ambient temperature
File: def-6-114.1b
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 8006.0 Hz
40 repetitions
OBSERVE H1, 400.1233350 MHz
DATA PROCESSING
PT size 32768
Total time 0 min, 0 sec
Spectrum 2.205 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 598
Spectrum 2.206

$^1$H NMR (CDCl$_3$, 500 MHz) of compound 599

STANDARD PROTON PARAMETERS

Pulse Sequence: e2pul
Solvent: CDC13
Temp. 25.0 °C / 298.1K
File: dsf_6-135_500
Mercury-300

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
28 repetitions

OBSERVE E1, 500.3087550 MHz

DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 0 min, 0 sec

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Spectrum 2.207

1H NMR (CDCl3, 400 MHz) of compound 600

Pulse Sequence: se2pul
Solvent: CDCl3
Ambient temperature
Pilot: def 6-136.1h
Mercury-300 *hg300*

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 5006.0 Hz
40 repetitions

OBSERVED
H1, 400.1233350 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec
Spectrum 2.208

$^1$H NMR (CDCl$_3$, 400 MHz) of compound 603

Pulse Sequence: ss2pul
Solvent: CDC13
Ambient temperature
File: def 11-13 lb
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 42.5 degrees
Acq. time 1.993 sec
Width 6066.0 Hz
36 repetitions

DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
Spectrum 2.209

$^1$H NMR (CD$_6$H, 400 MHz) of compound 604

Pulse Sequence: z2pul
Solvent: Benzene
Ambient temperature
File: daf-10-114 1h
Mercury-400BB *bg402*

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 5006.0 Hz
48 repetitions
Observe N1, 359.9090357 MHz
Data PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 6 min, 0 sec
Spectrum 2.210 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 604
Spectrum 2.211 $^1$H NMR (C$_6$D$_6$, 400 MHz) of compound 606
Spectrum 2.212 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 606
Spectrum 2.213

$^1$H NMR (CD$_2$Cl$_2$, 400 MHz) of compound 607a

STANDARD 1H OBSERVE

Pulse Sequence: a2pul
Solvent: CD$_2$Cl$_2$
Ambient temperature
File: dsf 10-142 DCM
Mercury: 300 "hg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
56 repetitions
OBSERVE: 300.909767 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 39 sec

ppm

4.76  1.00
1.05  2.98  2.36  1.21
2.66  1.24  1.26
Spectrum 2.214 $^{13}$C NMR (CD$_2$Cl$_2$, 100 MHz) of compound 607a
Spectrum 2.215 $^1$H NMR (CD$_2$Cl$_2$, 400 MHz) of compound 607b
Spectrum 2.216 $^{13}$C NMR (CD$_2$Cl$_2$, 100 MHz) of compound 607b
Spectrum 2.217 $^{1}$H NMR (C$_6$D$_6$, 400 MHz) of compound 607c
Spectrum 2.218 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 607c
Spectrum 2.219 $^1$H NMR (C$_6$D$_6$, 400 MHz) of compound 607d
Spectrum 2.220 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 607d
Spectrum 2.221 1H NMR (C6D6, 400 MHz) of compound 607e

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: Benzene
Ambient temperature
Pile: def 31-28 aluminafilter
Mercury-300 "bg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width ±006.0 Hz
256 repetitions
OBSERVE HL, 399.9090357 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 12760
Total time 14 min, 39 sec
Spectrum 2.222 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 607e
Spectrum 2.223 $^1$H NMR (CD$_2$Cl$_2$, 400 MHz) of compound 607nbn
Spectrum 2.224 $^{13}$C NMR (CD$_2$Cl$_2$, 100 MHz) of compound 607nbn
Spectrum 2.225 $^1$H NMR (C$_6$D$_6$, 400 MHz) of compound 614

STANDARD 1H OBSERVE

Pulse Sequence: zg2pul
Solvent: Benzene
Ambient temperature
File: daf.7-80
Mercury-300 "bg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Aqc. time 1.993 sec
Width 4006.0 Hz
144 repetitions
OBSERVE M1, 400.1233710 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec
Spectrum 2.226 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 614
Spectrum 2.227  $^1$H NMR (C$_6$D$_6$, 400 MHz) of compound 616

STANDARD 1H OBSERVE
Pulse Sequence: szipul
Solvent: Benzene
Ambient temperature
File: daf 7-94 1h
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 93.4 degrees
Acq. time 1.993 sec
Width 6056.0 Hz
56 repetitions
OBSERVE H1, 400.0535957 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec

 ppm
3.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8

 ppm
9 8 7 6 5 4 3 2 1 1.09 1.04 0.90 0.98 2.01 1.88 2.20 3.59 1.98
Spectrum 2.228 $^{13}$C NMR (C$_{6}$D$_{6}$, 100 MHz) of compound 616
Spectrum 2.299

\(^{1}H\) NMR (C\(_6\)D\(_6\), 400 MHz) of compound 619

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: Benzene
Ambient temperature
File: dsk 7-67.1h2z
Mercury-300 "bg100"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6000.0 Hz
68 repetitions
OBSERVE H1, 400.1233710 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec

 ppm

 ppm

 ppm
Spectrum 2.230 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 619
Spectrum 2.231

^H NMR (CDCl₃, 400 MHz) of compound 626

STANDARD 1H OBSERVR

Pulse Sequence: s2pul
Solvent: CDCl₃
Ambient temperature
File: def 6-77.1b
Mercury-300 °Hg300°

Relax. delay 1.000 sec
Pulse 48.5 degrees
Acq. Time 3.995 sec
Width 5998.8 Hz
72 repetitions
OBSERVE H1, 400.0535597 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min. 40 sec

ppm
9 8 7 6 5 4 3 2 1
Spectrum 2.232 $^{13}$C NMR (CDCl$_3$, 75 MHz) of compound 626
Spectrum 2.233  
$^1$H NMR (CDCl$_3$, 500 MHz) of compound 628

**STANDARD PROTON PARAMETERS**

Pulse Sequence: s2pul
Solvent: CDCl$_3$
Temp. 25.0 C / 298.1K
Film: daf.6-81.1hI
Mercury-300 *bg300*

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
132 repetitions
Observe H1, 500.3087950 MHz
Data Processing
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec
Spectrum 2.234 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 629

**Standard 1H observe**

Pulse Sequence: z2pul
Solvent: CDCl$_3$
Ambient temperature
File: dsf_6-834
Mercury: 300 *hg300*

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
140 repetitions

**Observe** M4 400.123350 MHz
**Data Processing**
FT size 32768
Total time 24 min, 39 sec
Spectrum 2.235

$^1$H NMR (CDCl₃, 400 MHz) of compound 630

STANDARD 1H OBSERVER

Pulse Sequence: a2pul
Solvent: CDCl₃
Ambient temperature
File: def.7-43
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. Time 2.995 sec
Width 5998.8 Hz
44 repetitions
OBSERVE H1, 400.0535597 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min. 40 sec
Spectrum 2.236

\(^{1}\text{H NMR (CDCl}_3\text{, 500 MHz) of compound 631}\)

STANDARD PROTON PARAMETERS
Pulse Sequence: a2pul
Solvent: CDCl\(_3\)
Temp. 25.0 °C / 298.1K
Pulse: daf 7.4 Hz
Mercury-300 "hg300"

Pulse 51.5 degrees
Acq. time 2.892 sec
Width 8000.0 Hz
120 repetitions
OBSERVE H1, 500.3087950 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec

ppm

\(1.00\)
\(2.19\)
\(2.15\)
\(5.71\)
\(14.04\)

\(1.00\)
\(2.19\)
\(2.15\)
\(5.71\)
\(14.04\)
Spectrum 2.237 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 631
Spectrum 2.238

$^1$H NMR (CDCl$_3$, 500 MHz) of compound 633

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl$_3$
Temp. 25.0 C / 298.1K
File: daf-10-122

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
60 repetitions

Observe H1, 500.3087950 MHz

DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec

1 2 3 4 5 6 7 8 ppm

0.90 1.01 2.45 2.00 2.23
Spectrum 2.239 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 634
Spectrum 2.240 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 634
Spectrum 2.241

$^1$H NMR (CDCl$_3$, 500 MHz) of compound 635

STANDARD PROTON PARAMETERS

Pulse Sequence: a2pol
Solvent: CDCl$_3$
Temp. 25.0 °C / 298.1 K
File: df7-7_1h_500
Mercury-100 "hg100"

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
60 repetitions
OBSERVE H1, 500.3087950 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec
Spectrum 2.242 $^{13}$C NMR (CDCl$_3$, 75 MHz) of compound 635
Spectrum 2.243 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 636 crude
Spectrum 2.244

^1H NMR (CDCl3, 400 MHz) of compound 636a

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: daf.7-21a_1h
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
24 repetitions
OBSERVE H1, 400.0535597 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 40 sec

ppm

3.55
1.05

1.99
2.16

26.92
5.62
33.14
Spectrum 2.245

$^1$H NMR (CDCl$_3$, 400 MHz) of compound 636b

Pulse Sequence: s2pul
Solvent: CDCl$_3$
Ambient temperature
File: daf.7.18.1h
Mercury-300 "bg100"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.995 sec
Width 5998.8 Hz
12 repetitions
OBSERVE H1, 400.0535597 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 8 min, 0 sec

6.0 5.9 5.8 5.7 5.6 5.5 ppm

9 8 7 6 5 4 3 2 1 ppm

2.81 0.90 0.96 1.00 2.00 2.03 14.32 15.66
Spectrum 2.246 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound $636b$
Spectrum 2.247 ¹H NMR (CDCl₃, 500 MHz) of compound 637

STANDARD PROTON PARAMETERS

Pulse Sequence: e2pul
Solvent: CDCl₃
Temp. 25.0°C / 298.1K
File: def_7-30
Mercury-360 *bg300*

Pulse 51.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
138 repetitions

OBSERVE 61, 500.3087550 MHz

DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 10 min, 22 sec
Spectrum 2.248 $^{13}$C NMR (CDCl$_3$, 75 MHz) of compound 637
Spectrum 2.249 $^1$H NMR (CDCl$_3$, 500 MHz) of compound 638 crude
1H NMR (CDCl₃, 400 MHz) of compound 638a

Pulse Sequence: s2pul
Solvent: CDCl₃
Ambient temperature
File: def.7-41a
Mercury-300 "hp300"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.595 sec
Width 5.998.8 Hz
16 repetitions
OBSERVE ML, 400.035597 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 40 sec
Spectrum 2.251 ¹³C NMR (CDCl₃, 100 MHz) of compound 638a
Spectrum 2.252 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 639

STANDARD 1H OBSERVE
Pulse Sequence: a2pul
Solvent: CDCl$_3$
Ambient temperature
File: def.7-37
Mercury-300 "bg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.995 sec
Width 6906.0 Hz
44 repetitions
OBSERVE H1, 400.1233350 MHz
DATA PROCESSING
PT size 32768
Total time 14 min, 39 sec
Spectrum 2.253 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 639
Spectrum 2.254 H NMR (CDCl₃, 500 MHz) of compound 640 crude
Peak 7.6 ppm: 0.99
Peak 9.4 ppm: 1.99
Peak 9.8 ppm: 2.29
Peak 10.2 ppm: 1.13
Peak 10.4 ppm: 1.14
Peak 10.8 ppm: 1.01
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Pulse: 10.127 Hz
Mercury-4000B "hg02"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 0.006 Hz
32 repetitions

DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 39 sec

Spectrum 2.256
1H NMR (CDCl3, 400 MHz) of compound 646
Spectrum 2.257 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 646
1H NMR (C6D6, 400 MHz) of compound 647

Pulse Sequence: a2pul
Solvent: Benzene
Ambient temperature
File: daf 31-31 lb
Mercury-400Sh "hg02"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
56 repetitions

OBSERVER: "D2, 399.9090357 MHz"

DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 14 min, 39 sec
Spectrum 2.259 \textsuperscript{13}C NMR (C\textsubscript{6}D\textsubscript{6}, 100 MHz) of compound 647
Spectrum 2.260

1H NMR (CDCl₃, 400 MHz) of compound 648

STANDARD IN OBSERVE

Pulse Sequence: z2pul
Solvent: Bensene
Ambient temperature
File: da7-75.rcv.am
Mercury-300 "hg100"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
116 repetitions
OBSERVE H1, 400.1233710 MHz
DATA PROCESSING
PT size 32768
Total time 14 min, 39 sec

ppm
4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0

ppm
9 8 7 6 5 4 3 2 1

ψ 3.84
ψ 0.91
ψ 0.93
ψ 0.98
ψ 0.89
ψ 1.14
ψ 2.58
Spectrum 2.261

1H NMR (CDCl3, 400 MHz) of compound 649

Pulse Sequence: sp2pul
Solvent: Benzene
Ambient temperature
Field: 400 MHz
Mercury-300

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
120 repetitions

OBSERVE: 600.1233710 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec

ppm

1.04 1.15 4.26 2.04 2.13 1.15 1.15 1.36 1.33 2.24 3.35
Spectrum 2.262 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 649
Spectrum 2.263 ¹H NMR (CD₆₃, 400 MHz) of compound 650

STANDARD 1H OBSERVE
Pulse Sequence: a2pul
Solvent: Benzene
Ambient temperature
File: daf 7-95 1h
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
12 repetitions
OBSERVE 6L, 400.1233710 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec
Spectrum 2.264 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 650
Spectrum 2.265 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 653
Spectrum 2.266 \( ^1 \)H NMR (CDCl\(_3\), 400 MHz) of compound 654

**STANDARD 1H OBSERVE**

Pulse Sequence: s2pol
Solvent: CDCl\(_3\)
Ambient temperature
File: daf.7-134_1h
Mercury-300 *hg300*

Relax. delay 1.000 sec
Pulse 46.0 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
44 repetitions

**DATA PROCESSING**
FT size 32768
Total time 24 min, 39 sec
Spectrum 2.267 $^{13}$C NMR (CDCl$_3$, 100 MHz) of compound 654
Spectrum 2.268 $^1$H NMR (CDCl$_3$, 400 MHz) of compound 655
Spectrum 2.269  $^1$H NMR (C$_6$D$_6$, 400 MHz) of compound 655b
Spectrum 2.270

1H NMR (CDCl₃, 400 MHz) of compound 659

Pulse Sequence: s2pul
Solvent: CDCl₃
Ambient temperature
File: dat-7-140 late
Mercury-300 "bg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 5096.0 Hz
256 repetitions
OBSERVE H1, 400.1233350 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec
Spectrum 2.271 $^1$H NMR ($C_6D_6$, 400 MHz) of compound 660
Spectrum 2.272 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 660
Spectrum 2.273 1H NMR (C6D6, 400 MHz) of compound 661

STANDARD IN OBSERVE

Pulse Sequence: e2pul
Solvent: Benzene
Ambient temperature
Pipe: def 7-123 1h2f
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.593 sec
Width 6006.0 Hz
44 repetitions
OBSERVE H1, 400.1233710 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec

- Peaks at 6.8, 6.7, 6.6, 6.5, 6.4, 6.3 ppm
- Integrals: 2.67, 1.00, 4.78, 5.30, 4.95, 2.21, 8.05, 8.78
Spectrum 2.274 $^{13}$C NMR ($C_6D_6$, 100 MHz) of compound 661
Spectrum 2.275

\(^1\)H NMR (CD\(_6\), 400 MHz) of compound 662

STD 1H OBMER

Pulse Sequence: z2pul
Solvent: Benzene
Ambient temperature
File: daf 7-129.1h
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 6006.0 Hz
12 repetitions
OBSERVE H1, 400.1233710 MHz
DATA PROCESSING
FT size 32768
Total time 14 min, 39 sec

6.6 6.2 5.8 5.4 5.0 ppm

9 8 7 6 5 4 3 2 1 ppm

0.81 0.95 1.90 0.97 2.62 0.91 0.971.11 0.94 1.93 2.04 3.04 72
Spectrum 2.276 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 662
Spectrum 2.277

1H NMR (C6D6, 400 MHz) of compound 663

Pulse Sequence: a2pul
Solvent: Benzene
Ambient temperature
File: daf_7-127_1h
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 95.3 degrees
Acq. time 1.993 sec
Width 6066.0 Hz
68 repetitions

DATA PROCESSING
PT size 32768
Total time 24 min, 39 sec
Spectrum 2.278 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 663
Spectrum 2.279 \[ ^1H \text{ NMR (C}_{6}D_{6}, 400 \text{ MHz)} \] of compound 664
Spectrum 2.280 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 664
Spectrum 2.281

1H NMR (C₆D₆, 400 MHz) of compound 665

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: Benzenne
Ambient temperature
File: daf_11-35_1h
Mercury-40BBB "hg102"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 1.993 sec
Width 3006.0 Hz
48 repetitions
OBSERVE 50, 399.9090357 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 0 min, 0 sec

ppm

6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5

9 8 7 6 5 4 3 2 1

2.00 1.00 3.14 2.09 2.11 13.66 15.10
Spectrum 2.282 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 665
Spectrum 2.283 $^1$H NMR (C$_6$D$_6$, 400 MHz) of compound 666
Spectrum 2.284 $^{13}$C NMR (C$_6$D$_6$, 100 MHz) of compound 666
Spectrum 2.285

$^1$H NMR (CD$_2$Cl$_2$, 400 MHz) of compound 667
Spectrum 2.286

$^1$H NMR (DMSO-d$_6$, 400 MHz) of compound 667

STANDARD 1H OBSERVE

Pulse Sequence: zg3pul
Solvent: DMSO
Ambient temperature
File: def 11-55 DMSO
Mercury-300 "hg300"

Relax. delay 1.000 sec
Pulse 45.3 degrees
Acq. time 3.993 sec
Width 6096.0 Hz
296 repetitions
OBSERVE E1, 399.9108993 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 32768
Total time 3 hr, 54 min, 33 sec
Spectrum 2.287 $^{13}$C NMR (CD$_2$Cl$_2$, 100 MHz) of compound 667
Spectrum 2.288 $^1$H NMR (C$_6$D$_6$, 500 MHz) of compound 668
Spectrum 2.289 $^1$H NMR (C$_6$D$_6$, 500 MHz) of compound 668
Spectrum 2.290 $^1$H NMR (CD$_2$Cl$_2$, 500 MHz) of compound 668
Spectrum 2.291 \(^1\)H NMR (CD\(_2\)Cl\(_2\), 500 MHz) of compound 668
Spectrum 2.292 $^1$H NMR (CD$_2$Cl$_2$, 500 MHz) of compound 668
Spectrum 2.293 $^{13}$C NMR (CD$_2$Cl$_2$, 125 MHz) of compound 668
Spectrum 2.294 $^{13}$C NMR (CD$_2$Cl$_2$, 125 MHz) of compound 668

Section 2.7 References


