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**Total Synthesis of Bisabosqual A**

A Dissertation Presented

by

**Christopher William am Ende**

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Abstract of the Dissertation

**Total Synthesis of Bisabosqual A**

by

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**Doctor of Philosophy**

in

**Chemistry**

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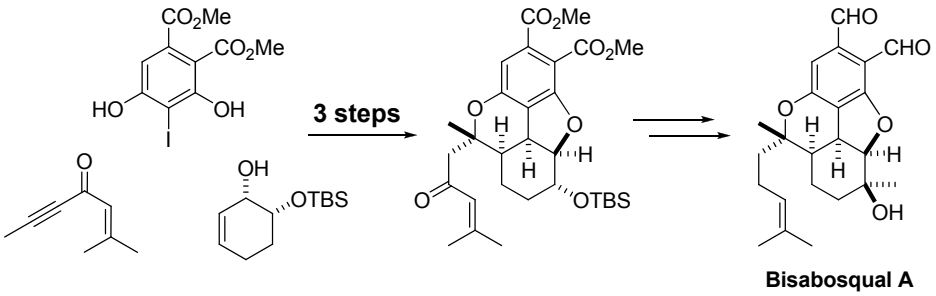
An efficient total synthesis of the novel squalene synthase inhibitor, bisabosqual A, is presented herein. The key step, a 5-*exo,* 6-*exo* tandem radical cyclization assembles the fully functionalized bisabosqual core, providing two rings and setting three stereogenic centers (two with complete specificity) in one step. Additional effective transformations include a regioselective deoxygentation reaction utilizing the Trost-Hutchins reducing system and a chemo- and diastereoselective addition of trimethylaluminum to an advanced ketone intermediate in the presence of esters. The doubly convergent synthesis requires 14 steps (longest linear sequence) from commercially available starting materials.

*To my family and friends*




**Bisabosqual A**

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## List of Abbreviations

| | |
|---|---|
| Ac | acetyl |
| AD mix-β | a commercially available mixture of $(DHQD)_2PHAL$, $K_2CO_3$, $K_3Fe(CN)_6$, $K_2OsO_4 \cdot 2H_2O$ |
| AIBN | 2,2'-azobisisobutyronitrile |
| APCI | atmospheric-pressure chemical ionization |
| aq | aqueous |
| Ar | aryl |
| br | broad |
| Bu | butyl |
| CDI | carbonyl diimidazole |
| COSY | correlation spectroscopy |
| d | doublet |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DABAL-$Me_3$ | a commercially available trimethylaluminum, DABCO adduct |
| DIAD | diisopropyl azodicarboxylate |
| DIBAL-H | diisobutyl aluminum hydride |
| DIPEA | *N,N*-diisopropylethylamine |
| DMAD | dimethyl acetylenedicarboxylate |
| DMF | dimethylformamide |
| DMAP | 4-dimethylaminopyridine |
| DMP | Dess-Martin periodinane |
| dr | diastereomeric ratio |
| *E* | entgegen |
| ee | enantiomeric excess |

| | |
|---|---|
| *epi* | epimer |
| Et | ethyl |
| equiv. | equivalent |
| ES+ | electrospray, positive ionization mode |
| ESI | electrospray ionization |
| *fac* | facial |
| FID | flame ionization detector |
| FTIR | Fourier transform infrared |
| g | gram |
| GC | gas chromatography |
| HMBC | heteronuclear multiple bond correlation |
| HPLC | high-performance liquid chromatography |
| hr | hour |
| HRMS | high-resolution mass spectrometry |
| Hz | hertz |
| $IC_{50}$ | 50% inhibitory concentration |
| *i* | *iso* |
| Im | imidazole |
| IR | infrared |
| *J* | NMR first order coupling constant |
| KHMDS | potassium hexamethyldisilazide |
| L | ligand |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |

| | |
|---|---|
| LDBBA | lithium diisobutyl-*t*-butoxyaluminum hydride |
| LDL-C | low-density lipoprotein cholesterol |
| LRMS | low resolution mass spectrometry |
| L-Selectride | lithium tri-*s*-butylborohydride |
| | |
| m | multiplet |
| M | molar |
| *m*CPBA | *meta*-chloroperoxybenzoic acid |
| Me | methyl |
| MeCN | acetonitrile |
| mg | milligram |
| MHz | megahertz |
| min | minute |
| mL | milliliter |
| mmol | millimol |
| mol | mole |
| MOM | methoxymethyl ether |
| mp | melting point |
| MS | mass spectrometry |
| | |
| *n* | normal |
| N | normal |
| ND | not determined |
| NFPA | National Fire Protection Association |
| NMR | nuclear magnetic resonance |
| NOE | nuclear Overhauser effect |
| NOESY | nuclear Overhauser effect spectroscopy |
| | |
| [O] | oxidant |
| OAc | acetate |

| | |
|---|---|
| OTf | triflate |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| ppm | part per million |
| pr | propyl |
| PTA | 1,3,5-Triaza-7-phosphaadamantane |
| py | pyridine |
| q | quartet |
| quant | quantitative |
| RREM | regiodivergent reaction of an enantioenriched mixture |
| RRRM | regiodivergent reaction of a racemic mixture |
| rt | room temperature |
| s | singlet |
| *s* | secondary |
| SFC | supercritical fluid chromatography |
| $S_H2$ | homolytic substitution |
| spt | septet |
| t | triplet |
| *t* | tertiary |
| TBAF | tetrabutylammonium fluoride |
| TBD | 1,5,7-triazabicyclo[4.4.0]dec-5-ene |
| TBS | *tert*-butyldimethylsilane |
| TEA | triethylamine |
| THC | tetrahydrocannabinol |
| THF | tetrahydrofuran |

| | |
|---|---|
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| UPLC | ultra performance liquid chromatography |
| UV | ultraviolet |
| X | halide (F, Cl, Br, I) |

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Lastly, I wanted to thank my family for their support throughout this process. Specifically, my wife Megan who has put up with my many nights and weekends spent working. Hopefully now that I am finished, we'll have plenty of time to play with our baby girl.

# Chapter 1

# Bisabosqual A Isolation and Previous Synthetic Strategies

## 1.1 Isolation and Structure Determination

Bisabosquals A - D (**1.1** - **1.4**, Figure 1) are *Stachybotrys* metabolites that were isolated by Minagawa and coworkers in 2001 from the culture broth of the fungal strains *Stachybotrys* sp. RF-7260 (bisabosqual A) and *Stachybotrys ruwenzoriensis* RF-6853 (bisabosquals B-D).[1, 2] The fungi were collected from unidentified decaying broad-leaved tree leaves from the Amami-oshima, Kagoshima Prefecture and Sanda, Hyogo Prefecture regions of Japan. Subsequently, the bisabosquals were identified to be inhibitors of the microsomal squalene synthases from *Saccharomyces cerevisiae*, *Candida albicans*, HepG2 and rat liver cells suggesting potential antifungal and antihypercholesteremic properties (*vide infra*).

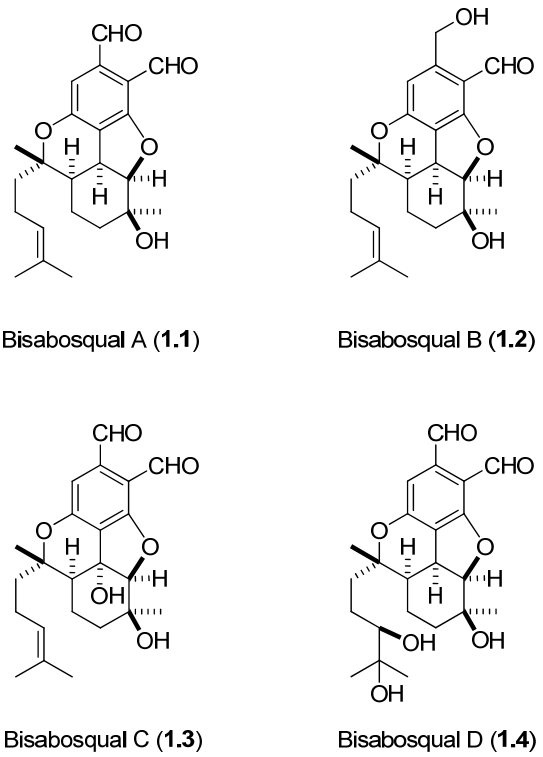



**Figure 1.1.** The bisabosquals A-D.

The structures of bisabosquals A - D were determined by 2D NMR experiments (COSY, NOESY and HMBC) and the relative stereochemistry confirmed by the X-ray crystal structure of bisabosqual B (**1.2,** Figure 1.2).[2] Absolute stereochemistry was determined by single crystal X-ray analysis of a brominated analogue (**1.5**) of bisabosqual D (Figure 1.2). The structures of the bisabosquals are unique among natural products in that they contain the hexahydrobenzofurobenzopyran ring system, which was only known previously in a synthetic cannabinoid derivative.[3] In addition, the phthalaldehyde moiety contained in bisabosquals A, C and D is a rare structural motif found in only a few natural products.[4-9] Many of these natural products, including the K-76 complement inhibitor[4] and stachybotrydial,[5] were also isolated as metabolites from *Stachybotrys* organisms (Figure 1.3). The bisabosquals are of further interest

as synthetic targets as a result of the novel *cis*, *cis*-fused tetracyclic ring system which contains five contiguous stereocenters, two of which are quaternary.

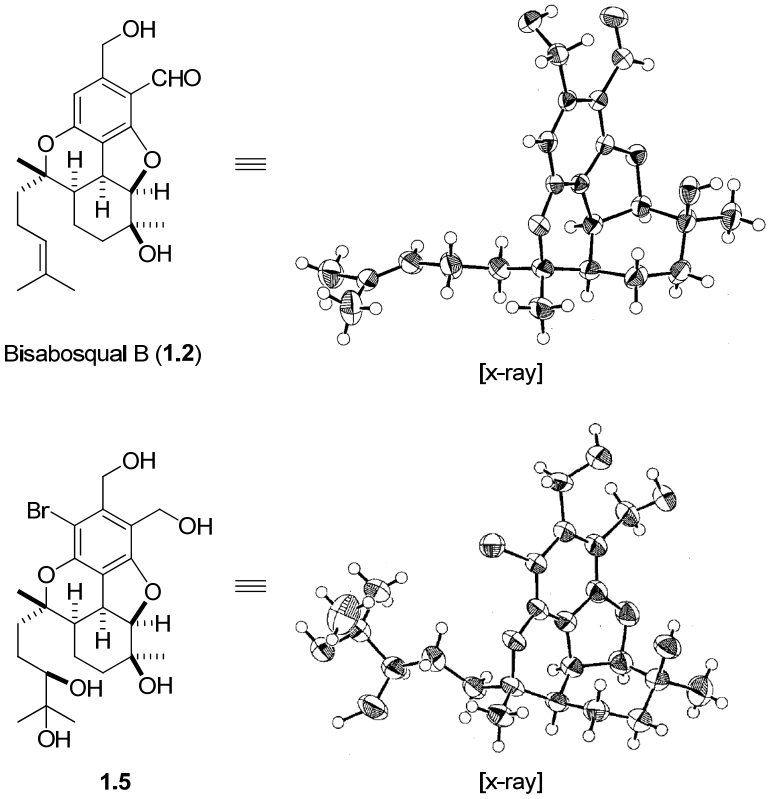



**Figure 1.2.** X-ray crystal structures of bisabosqual B and brominated analogue **1.5**.

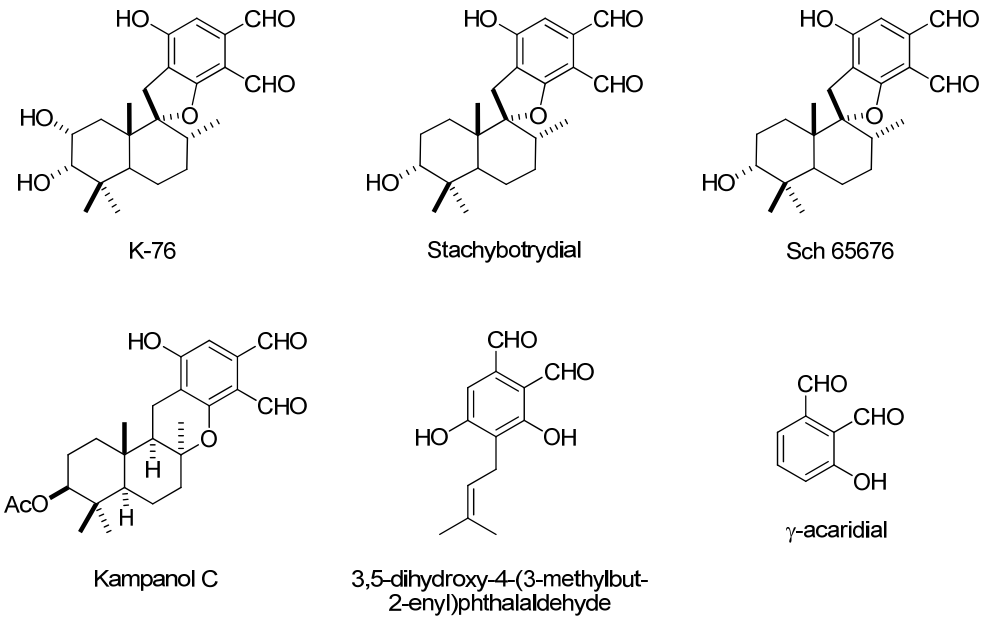



**Figure 1.3.** Natural products containing the phthalaldehyde moiety.

### 1.2 Antihypercholesteremic and Antifungal Activity

Elevated levels of plasma low-density lipoprotein cholesterol (LDL-C) are associated with an increased risk of cardiovascular disease.[10] Currently, inhibitors of HMG-CoA reductase (i.e. statins) are the primary treatment used to lower cholesterol levels. However, in some patients, statins have been shown to have adverse side effects such as myophathies, hepatotoxicity and rabdomyolysis.[11-13] The suppression of mevalonate production may be the cause of these undesired effects (see Figure 1.4 for the biosynthetic pathway of cholesterol).[14, 15] The decrease in mevalonate can affect production of many downstream products that are essential for cell energy, growth and viability. Statins have also been associated with lack of efficacy and as a result, do not produce the desired outcomes in some patients.[11] Therefore, squalene synthase, the enzyme responsible for the first committed step in the biosynthesis of

cholesterol, has emerged as an attractive target for the treatment of high LDL-C without affecting other critical processes. [16-21]

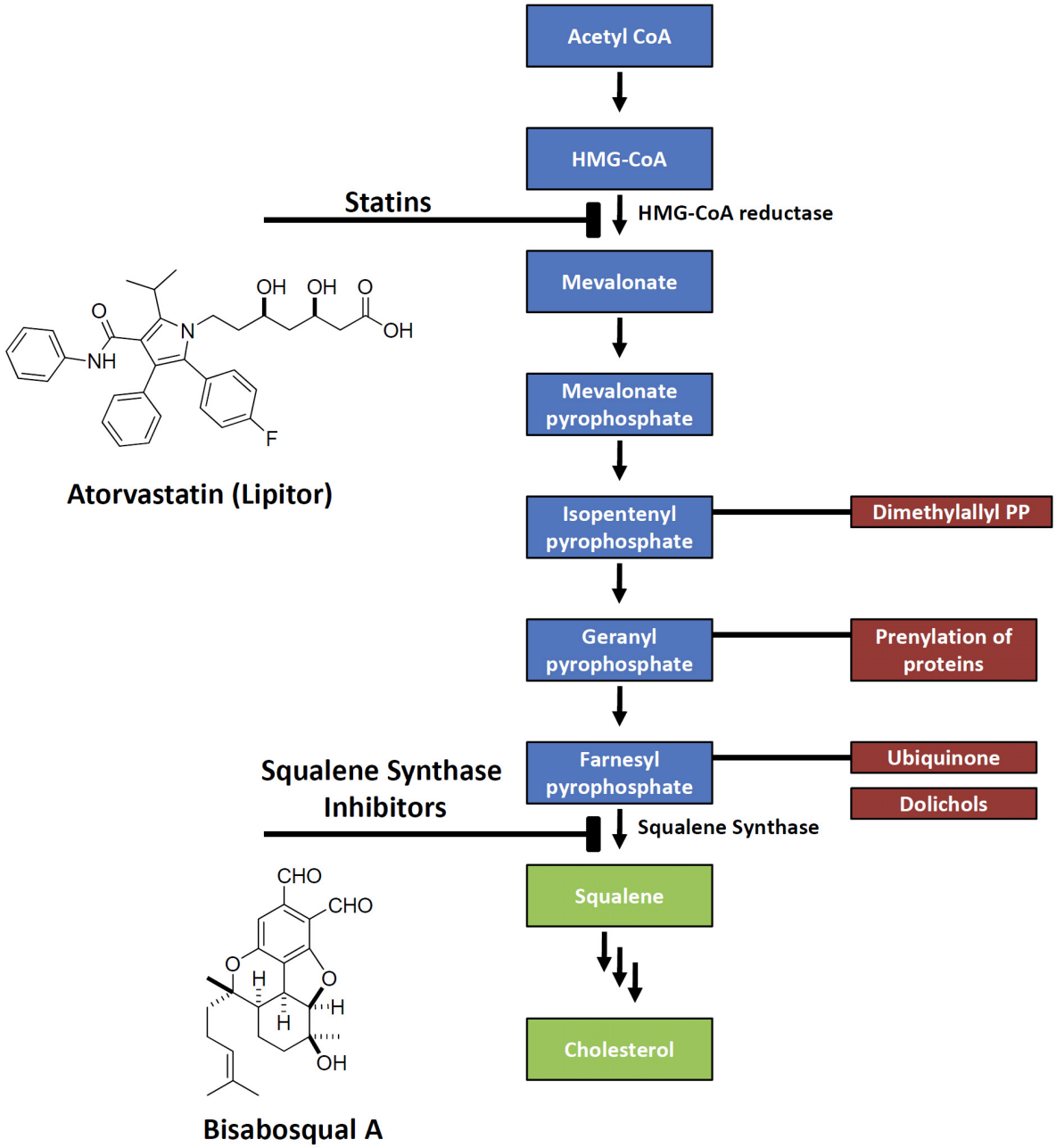



**Figure 1.4.** Biosynthesis of cholesterol.

The bisabosquals were found to inhibit fungal squalene synthases from *Saccharomyces cerevisiae* and *Candida albicans*. Additionally, they were shown to be active against mammalian squalene synthases from HepG2 and rat liver cells with low micromolar activity (Table 1.1). Therefore, the bisabosquals are a unique structural class that offers a potential lead for the development of antihypercholesteremic agents.[16-21] In addition, the inhibition of fungal squalene synthases suggests bisabosqual A may have potential utility as an antifungal agent. The antimicrobial activities were also examined across a variety of yeast and filamentous fungal species as shown in Table 1.2.

**Table 1.1.** Squalene synthase *in vitro* inhibitory activities of the bisabosquals.[1]

| | **$IC_{50}$ (μg/mL)** | | | |
|---|---|---|---|---|
| **Squalene Synthase** | **Bisabosqual A** | **Bisabosqual B** | **Bisabosqual C** | **Bisabosqual D** |
| *S. Cerevisiae* | 0.43 | 31.5 | 1.0 | 18.5 |
| *C. albicans* | 0.25 | 50 | 1.0 | 12 |
| HepG2 | 0.95 | 12 | 0.9 | 5.1 |
| Rat Liver | 2.5 | > 100 | 5.8 | 37 |

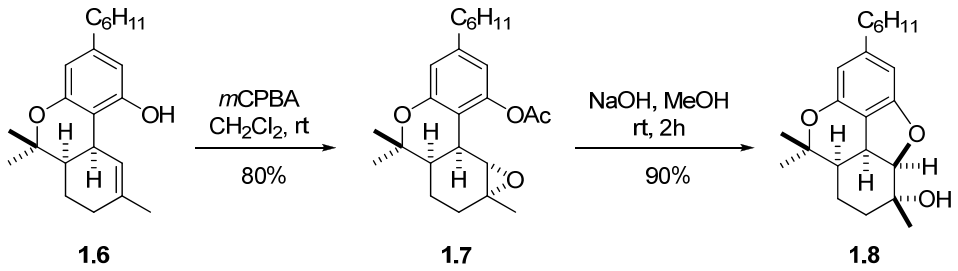
**Table 1.2.** Antimicrobial activities of the bisabosquals.[1]

| | $MIC_{50}$ (μg/mL) | | | |
|---|---|---|---|---|
| **Fungal Species** | **Bisabosqual A** | **Bisabosqual B** | **Bisabosqual C** | **Bisabosqual D** |
| *Candida albicans* | 25 | > 100 | > 100 | > 100 |
| *Candida kurusei* | 12.5 | > 100 | > 100 | > 100 |
| *Candida glabrata* | 25 | > 100 | > 100 | > 100 |
| *Saccharomyces cerevisiae* | 25 | > 100 | > 100 | > 100 |
| *Cryptococcus neoformans* | 3.13 | > 100 | > 100 | > 100 |
| *Aspergillus fumigatus* | 25 | 50 | > 100 | > 100 |
| *Trichophyton asteroides* | > 100 | > 100 | > 100 | > 100 |

## 1.3 Previous Approaches Toward the Bisabosqual Ring System

### 1.3.1 Razden's Synthesis of the Hexahydrobenzofurobenzopyran Ring System

The first synthesis of the bisabosqual hexahydrobenzofurobenzopyran ring system was reported by Razden and coworkers in 1977 in an effort to access *cis*-tetrahydrocannabinols (Scheme 1.1). Their approach relies on a stereoselective epoxidation of the *cis*-THC derivative **1.6** with *m*CPBA from the less-hindered α-face of the olefin to provide epoxide **1.7** as a single diastereomer. Subsequent basic hydrolysis of the acetate (**1.7**) affords a phenolate anion which undergoes intramolecular addition to the epoxide to give tetracycle **1.8** in excellent yield. This synthesis forms the bisabosqual ring system; however, it imparts the incorrect stereochemistry at the tertiary alcohol. Inspired by this approach, the Snider group utilized a similar strategy in their synthesis of the bisabosqual stereochemical array.

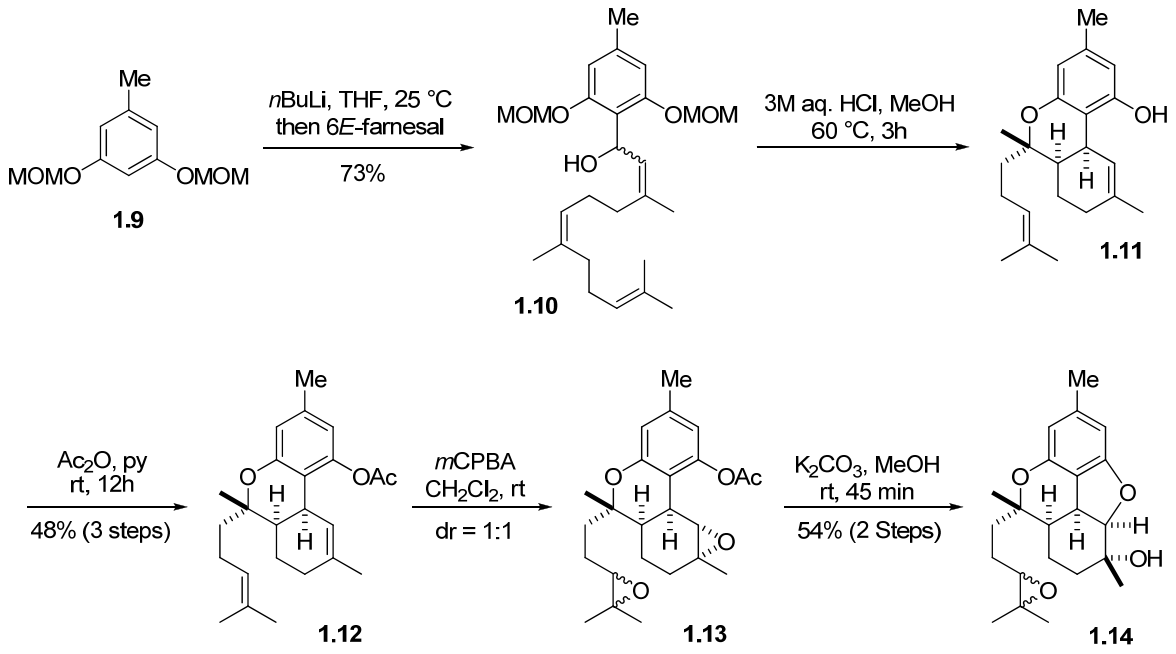



**1.6** **1.7** **1.8**

**Scheme 1.1.** Razden's synthesis of the hexahydrobenzofurobenzopyran ring system.

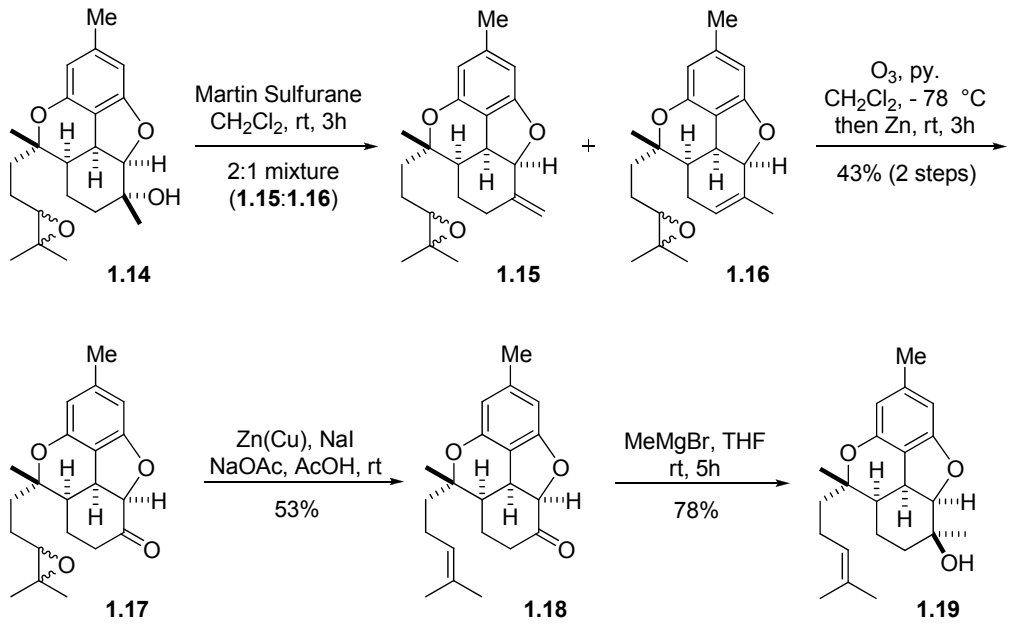
### 1.3.2 Snider's Synthesis of the Bisabosqual Tetracyclic Core and Stereochemical Array

The Snider group envisioned using an inverse electron demand Diels-Alder reaction of a quinine methide to form a *cis*-fused THF derivative analogous to compound **1.6**. [22, 23] This intermediate could then be subjected to chemistry similar to that described by Razden and coworkers to access the bisabosqual core (*vide supra*). Toward this end, their synthesis commenced with deprotonation of the MOM-protected orcinol **1.9** followed by addition of 6*E*-farnesal to yield alcohol **1.10** as a mixture of *E*/*Z* isomers (Scheme 1.2). Subjecting alcohol **1.10** to aqueous HCl in methanol afforded the desired *cis*-fused tricycle **1.11** in moderate yield after formation of acetate **1.12** (48% over three steps). A subsequent epoxidation of the less hindered α-face of the cyclohexene with *m*CPBA was stereoselective; however, concurrent epoxidation of the side chain also took place, resulting in a 1:1 mixture of diastereomers (**1.13**). This initially undesired epoxidation of the side chain turned out to be beneficial because it could be exploited as a method for protection of the olefin during a subsequent oxidative cleavage. As expected, hydrolysis of the acetate resulted in cyclization to the undesired diastereomer **1.14**. Preliminary attempts to circumvent this inversion route were unsuccessful and therefore, a four step sequence to invert the stereochemistry at this position was developed.[24]




**Scheme 1.2.** Snider and coworkers' approach to the bisabosqual tetracycle.

Dehydration of tertiary alcohol **1.14** with Martin's sulfurane reagent yielded an inseparable mixture (2:1) of the exo and endocyclic olefin isomers **1.15** and **1.16** (Scheme 1.3). Ozonolysis of the mixture followed by zinc reduction provided ketone **1.17** in 43% yield over two steps. Next, a reductive deoxygenation of the side chain epoxide of ketone **1.17** by Cornforth's procedure[25] afforded the requisite prenyl side chain (**1.18**). Capitalizing on the rigid bisabosqual core, a diastereoselective addition of methyl magnesium bromide occurred from the less hindered α-face to yield the desired tertiary alcohol **1.19** in good yield. This completed the synthesis of the bisabosqual core along with the five contiguous stereocenters; however, despite additional efforts, it did not provide access to the phthalaldehyde motif. [26, 27]




**Scheme 1.3.** Synthesis of the bisabosqual stereochemical array by Snider and coworkers.

The strength of this approach was the rapid assembly of the *cis*-tetracyclic core of bisabosqual in only five steps utilizing a presumably biomimetic intramolecular inverse electron Diels-Alder cyclization of a quinine methide.[28] Unfortunately, to access the necessary stereochemistry at C-3, this synthesis required a multi-step inversion strategy to afford the desired tertiary alcohol **1.19** in low overall yield for the sequence. More importantly, this approach did not incorporate the required substitution to provide the phthalaldehyde motif present in bisabosqual A. Efforts focused on incorporation of the aldehydes proved problematic and to date, no further progress towards the synthesis of bisabosqual A has been reported.[26, 27]

**1.4 Conclusions**

The squalene synthase activity along with the structural complexity of the bisabosquals makes these natural products interesting and challenging targets for total synthesis. However,

only Snider and coworkers have published an approach to the bisabosqual stereochemical array. Herein, we describe the first total synthesis of bisabosqual A via a tandem radical cyclization. Other effective transformations include a chemo- and diastereoselective addition of trimethylaluminum to a ketone in the presence of esters as well as a regioselective deoxygenation of an advanced enone intermediate.

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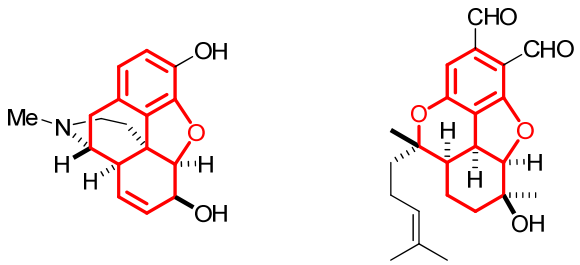
# Chapter 2

# Synthetic Strategy

## 2.1 Introduction

Our synthetic strategy began with the recognition of the utility of tandem radical cyclizations for the efficient construction of *cis*, *cis*-fused ring systems. This was exemplified in the formal synthesis of morphine by the Parker laboratory which shares a similar topology to the bisabosqual tetracyclic core (Figure 2.1).[1-5] Their synthesis incorporated a tandem 5-*exo*, 6-*endo* radical cyclization to establish the *cis*-fused octahydrophenanthrofuran core (*vide infra*). It was postulated that the bisabosqual tetracyclic core could result from a similar radical cascade approach and therefore, we sought to investigate this hypothesis.




Morphine (**2.1**) Bisabosqual A (**1.1**)

**Figure 2.1.** Structures of bisabosqual A and morphine.

## 2.2 Radical Cyclization to Form Five- and Six-Membered Rings

Radical reactions are commonly used in the synthesis of five and six-membered ring systems via 5-*exo*-*trig* and 6-*exo*-*trig* cyclizations, respectively.[6-9] For example, formation of the thermodynamically less stable *5-exo-trig* primary radical product is much faster than the *6-endo-trig* cyclization indicating a kinetically controlled process (Figure 2.2).[10-12] This bias

towards 5-*exo* cyclization can be attributed to the premise that the incoming singly occupied orbital of the radical approaches the preferential angle of attack and therefore possesses a more favorable overlap with the π*-orbital of the internal olefin carbon. The preference of a 5-hexenyl radical for 5-*exo* cyclization has been used extensively in radical chemistry to form five-membered rings. However, despite the almost 50-fold difference in rates for 5-*exo* vs. 6-*endo* cyclization, this corresponds to only a 1.7 kcal $mol^{-1}$ difference in the activation energy. Therefore, the rates of cyclization can be altered by factors such as geometric constraint, steric hindrance or incorporation of heteroatoms into the structure. Such contributions can occasionally lead to preference for the 6-*endo* mode of cyclization as observed by the Parker laboratory in the synthesis of morphine.[13, 14]

In a similar manner, six-membered rings can be synthesized through a 6-*exo*-*trig* cyclization of a 6-heptenyl radical, albeit at a slower rate than the corresponding 5-*exo* cyclization described above (Figure 2.2).[10, 15, 16] The observed reduction in rate can be attributed to entropic factors and therefore geometric constraints can be important in affecting the preference for *exo* vs. *endo* cyclizations. This process can be complicated by competing 1,5-hydrogen atom abstraction yielding stabilized allylic radicals.[17] Fortunately, our system possesses an oxygen at the 5-position with respect to the incoming radical and therefore this competing reaction is not expected to be a concern (*vide infra*).

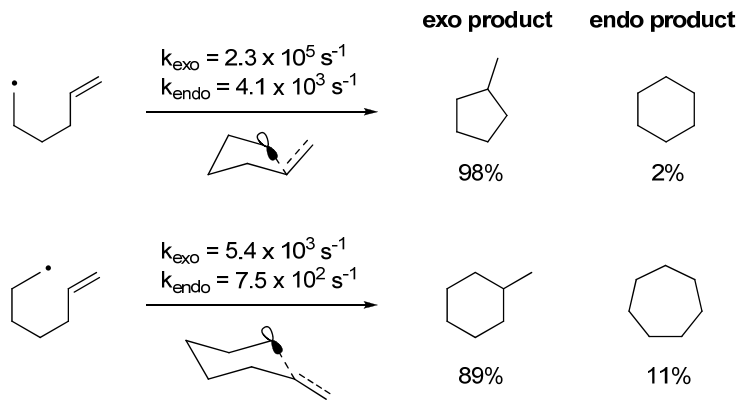
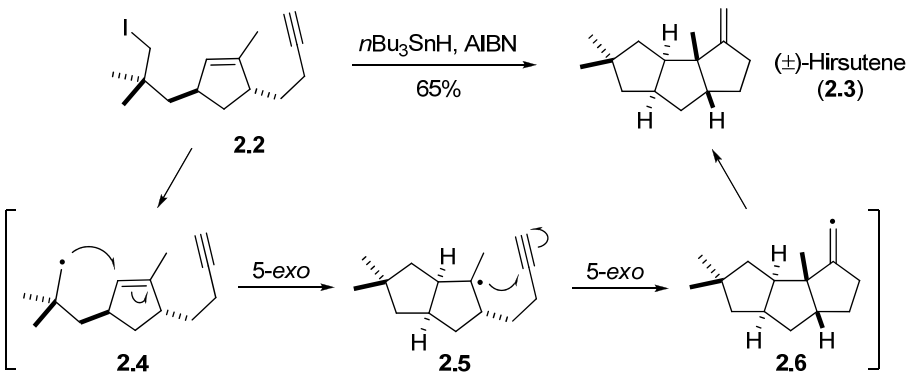



**Figure 2.2.** Preference for 5-*exo* and 6-*exo* radical cyclizations over the corresponding *endo* cyclization.[10]

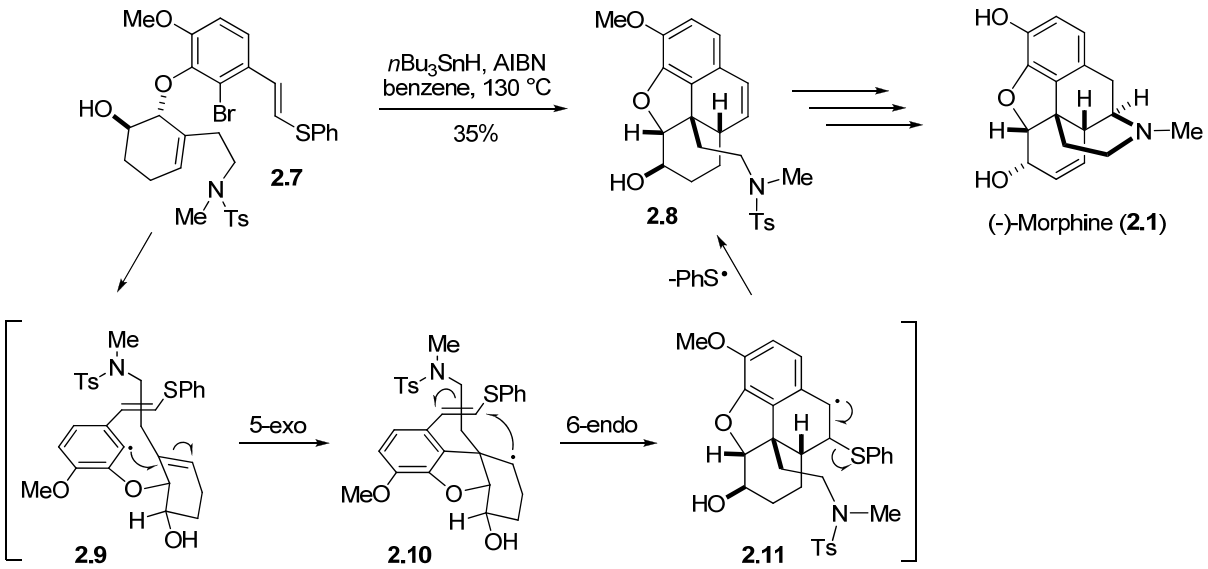
### 2.3 Stereoselectivity of Radical Cyclizations in Fused Systems

Radical cyclization has a propensity to form *cis*-fused ring systems as a result of geometric constraint. This penchant for high *cis*-selectivity has been exploited in the synthesis of 5,5-,[18] 6,5-[19] and 6,6-[20] ring systems; however, for larger ring systems, additional factors begin to dictate selectivity.[21, 22] In the seminal series of publications highlighting the total synthesis of hirsutene, Curran and coworkers describe a tandem radical cyclization approach to construct two 5,5-*cis*-fused ring systems in one step (Scheme 2.1).[7, 23, 24] The reaction begins by formation of the $sp^3$ radical **2.4** which cyclizes to the five-membered ring in a 5-*exo* fashion to afford tertiary radical **2.5**. An additional 5-*exo* cyclization to the tethered alkyne installs the required *cis*-fused ring system yielding hirsutene in a single step from precursor **2.2**. This synthesis illustrates that *cis*-selectivity predominates regardless of whether the radical or olefin is contained in the ring.




**Scheme 2.1.** Curran's tandem radical cyclization for the synthesis of hirsutene.

Another classic example of *cis*-selectivity in natural product synthesis was demonstrated by Parker and coworkers for the synthesis of morphine.[2-5] The key step in their synthesis relied on a tandem radical cyclization to construct the *cis, cis*-fused tetracycle and install an all-carbon quaternary center (Scheme 2.2). Subjecting substrate **2.7** to standard radical conditions ($n$Bu$_3$SnH, AIBN) generates aryl radical **2.9** which upon a 5-*exo*-*trig* cyclization affords a dihydrobenzofuran that contains the quaternary center. Radical **2.10** was then in position to undergo a 6-*endo*-*trig* addition to the β-carbon of the styrene to afford the resonance stabilized radical **2.11**. Subsequent elimination of the thiophenol radical completed the cascade, resulting in the desired tetracycle **2.8**. The six-membered ring formation was preferential over the kinetically favored 5-*exo* cyclization as a result of geometrical constraints. This synthesis showcased the power of a tandem radical cyclization approach for the synthesis of the *cis*-fused tetracyclic core similar to that found in the bisabosquals.

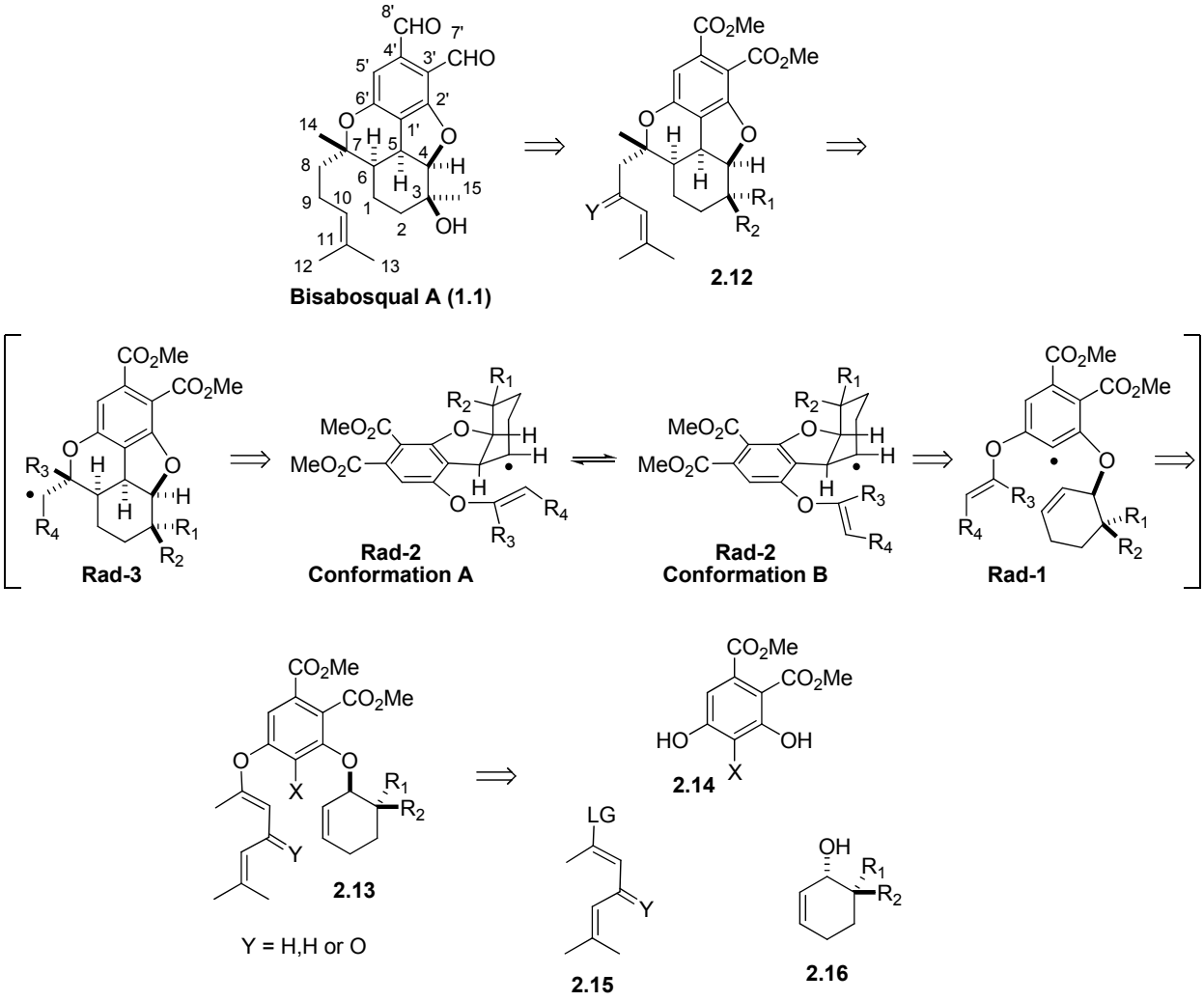



**Scheme 2.2.** The Parker synthesis of morphine via a 5-*exo*, 6-*endo* tandem radical cyclization.

### 2.4 Retrosynthesis of the Bisabosqual Tetracyclic Core

We became intrigued by the possibility of utilizing a regio- and stereoselective 5-*exo*, 6-*exo* tandem radical cyclization to generate the *cis*-fused core of bisabosqual A (Scheme 2.3). This cascade would construct two rings and introduce three stereogenic centers in one step from a relatively simple substrate. Toward this end, our synthetic planning began with diester synthon **2.12**, a likely precursor of bisabosqual A. In turn, tetracycle **2.12** could be accessed by a radical cascade of cyclization substrate **2.13**. The proposed cyclization would proceed through formation of the $sp^2$ carbon-based radical, **Rad-1**. A 5-*exo* closure of **Rad-1** would afford the tricyclic **Rad-2** with the required *cis* junction as a result of geometric constraint. **Rad-2** can participate in a 6-*exo* addition to the enol ether double bond from either of the two accessible reactive conformations (**A** and **B**). The radical center is available for this interaction only on the concave surface of the ring system. However, *a priori*, it was difficult to predict whether attack on one face of the enol ether double bond would be favored. Thus, closure to

the tetracyclic **Rad-3** and subsequent reductive trapping was expected to afford the tetracycle **2.12** with the *cis, cis* ring system but it would not necessarily control stereochemistry at C-7.




**Scheme 2.3.** Retrosynthetic analysis of bisabosqual A and conformational analysis of the radical intermediates in the key cyclization.

The assembly of structure **2.13** would be available through a doubly convergent scheme based on readily available pentasubstituted resorcinol **2.14** and a suitably substituted side chain precursor **2.15** and cyclohexenol **2.16**. The choice of side chains considered includes simple enol ethers as well as vinylogous esters. Although, the use of a vinylogous ester would require

the eventual removal of the oxygen functionality at C-9, this option is expected to offer greater stability of intermediates and a more efficient **Rad-2** to **Rad-3** step. In addition, the cyclohexenol appendage **2.16** required the tertiary center at C-3 in bisabosqual A to be present prior to cyclization or contain a functional group that would provide a handle to install the stereocenter following the radical cascade. Chapter 4 details the investigation into the choice of appropriate substitution of both side chain precursor **2.15** and cyclohexenol **2.16**. Furthermore, in order to gain a better understanding of the proposed radical cyclization, a series of model systems was explored (see Chapter 3 for details).

## 2.5 References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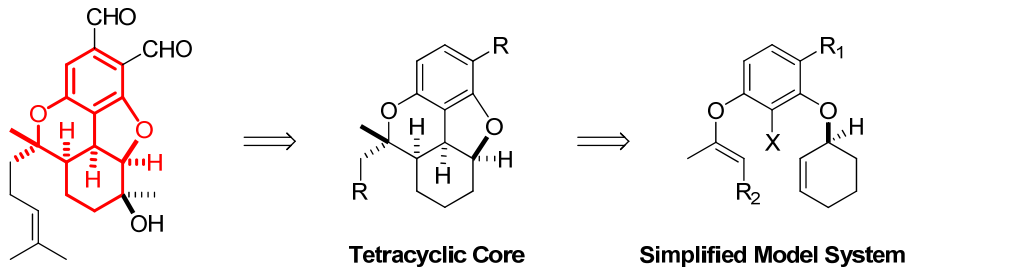
# Chapter 3

## Tandem Radical Cyclization Model Systems

### 3.1 Introduction

In an effort to understand the viability of the tandem 5-*exo*, 6-*exo* radical cyclization approach to access the *cis*-fused bisabosqual core, a series of model systems were explored (Scheme 3.1). Relative to the fully elaborated substrate **2.13**, these compounds are more easily accessed. They would also allow for a simplified analysis of the newly formed stereocenters as well as exploration of radical cyclization conditions. Furthermore, additional model system studies were previously performed in the Parker laboratory. For details of these systems, refer to the thesis of Zhou Zhou.[1]




**Bisabosqual A (1.1)**

**Tetracyclic Core**

**Simplified Model System**

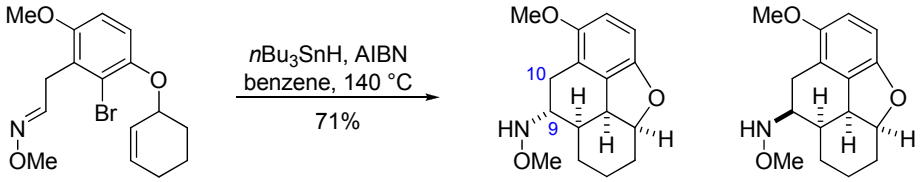
**3.1** - $R_1$ = H, $R_2$ = H, X = Br
**3.2** - $R_1$ = $CO_2Me$, $R_2$ = $CO_2Et$, X = I

**Scheme 3.1.** Bisabosqual model system design.

### 3.2 Parker's Morphine Model System

The Parker group had previously synthesized model system **3.3** for a 5-*exo*, 6-*exo* cyclization during their studies toward the synthesis of (-)-morphine (Scheme 3.2).[2-4] The cyclization, initiated by aryl radical formation, proceeded in 71% yield affording a mixture of C-9

diastereomers **3.4** and **3.5**. This reaction showcased the efficient construction of both the five and six-membered rings, forming the desired *cis, cis*-fused tetracycle. However, due to the lack of stereochemical control at the C-9 center, an alternative approach was integrated into the formal synthesis of morphine.[4, 5] While this model system provided confidence in our approach towards bisabosqual A, it lacked the required oxygen center in place of the C-10 carbon and the quaternary center at C-9 of bisabosqual A. Therefore, our initial efforts focused on generating a model system that more closely resembled the bisabosqual core.




**3.3** **3.4** - 40% **3.5** - 31%

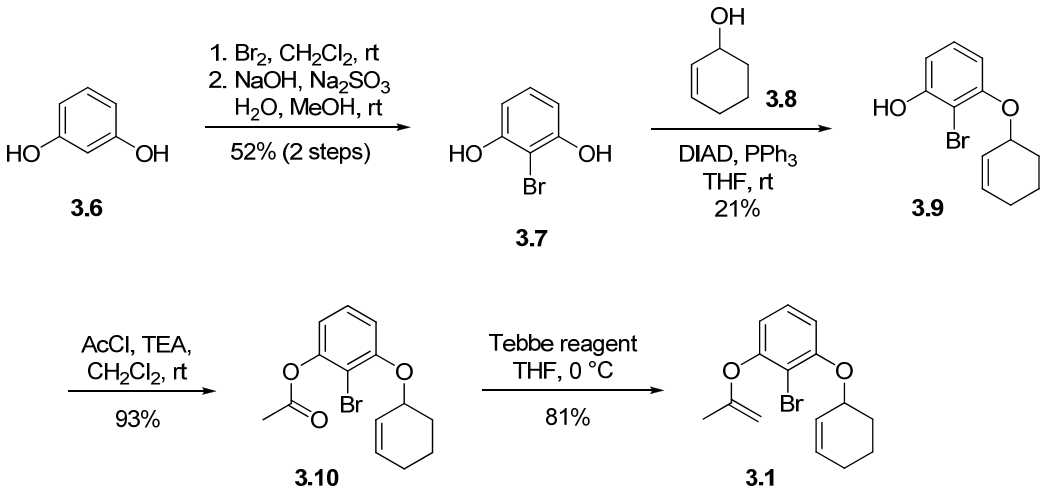
**Scheme 3.2.** Morphine model systems studies from Parker and coworkers.

### 3.3 Bisabosqual Model Systems

#### 3.3.1 Enol Ether Model System

We decided to pursue the relatively simple radical cyclization substrate **3.1** as shown in Scheme 3.3. This substrate is expected to result in a single diastereomer upon cyclization as a result of the lack of chirality at the C-7 position, thus imparting a potentially simplified analysis of the reaction mixture. The synthesis commenced by tribromination of resorcinol (**3.6**) followed by dehalogenation with a sodium sulfite and sodium hydroxide mixture to afford 2-bromoresorcinol **3.7** in 52% yield (two steps from resorcinol **3.6**).[6, 7] Mitsunobu reaction[8] installed the cyclohexene in low yield due, in part, to the expected mixture of starting material,

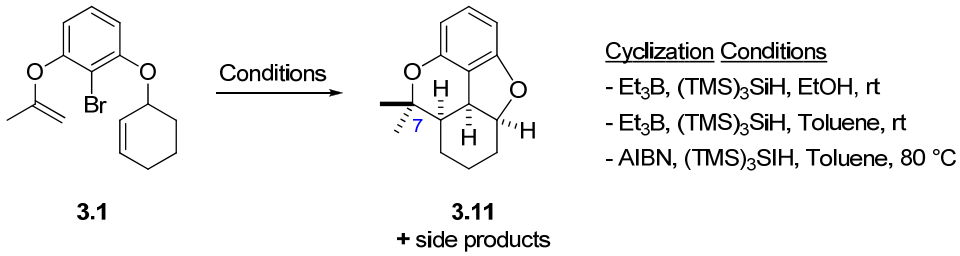
mono- and bis-cyclohexenyl products.[8] Acetylation of phenol **3.9** with acetyl chloride and triethylamine provided acetate **3.10** in 93% yield. The acetate was then converted to the corresponding enol ether by treatment with Tebbe reagent in THF to generate enol ether **3.1** in 81% yield after purification on a basic alumina.[9] This unoptimized short sequence provided the desired radical cyclization substrate **3.1** in five steps.




**Scheme 3.3.** Synthesis of enol ether model system **3.1.**

Preliminary analysis of the radical cyclization of enol ether **3.1** under several reaction conditions (temperature, solvent and radical initiator) indicated that the reaction was not selective for a single product (Scheme 3.4). Examination of the crude $^{1}$H NMR and mass spectra suggests the desired tetracycle was forming; however, the presence of a complex mixture of products made isolation of the desired product challenging. It is noteworthy that intermediate **3.9** (see Scheme 3.3) was observed in each of the conditions attempted, suggesting that the enol ether was not stable to the radical cyclization conditions. Moreover, additional challenges were encountered synthesizing a more elaborated enol ether system as shown in Chapter 4

(see Table 4.1 and Scheme 4.7). Therefore, an alternative model system that would integrate a stabilizing electron-withdrawing group on the side-chain was investigated.




**3.1** **3.11** + side products

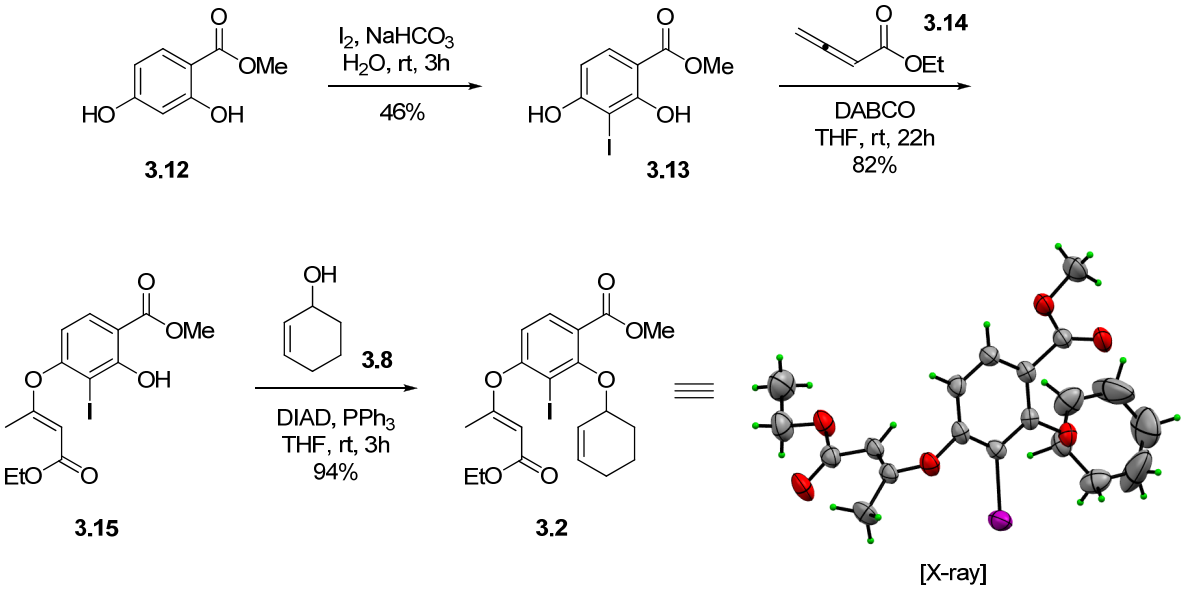
**Scheme 3.4.** Preliminary cyclization attempts on enol ether substrate **3.1.**

### 3.3.2 Vinylogous Carbonate Model System

We sought a model system that would have improved stability compared to enol ether **3.1** and would provide a stabilized terminal radical to prevent possible undesired side reactions. Therefore, vinylogous carbonate **3.2** was considered as a model system substrate. The ester substituent would not only provide a more robust side chain, but the 6-*exo* cyclization event would also result in a stabilized α-keto radical. Furthermore, incorporation of the aryl ester at C-3' would differentiate the resorcinol alcohols, providing a higher yielding and consequently, more scalable synthesis. This substrate is also electronically similar to the fully elaborated substrate as a result of the ester moiety.

Assembly of the model system commenced with iodination of resorcinol **3.12** utilizing iodine and $NaHCO_3$ in THF/$H_20$ to afford tetrasubstituted resorcinol **3.13** in an unoptimized 46% yield (Scheme 3.5).[10] A DABCO-catalyzed, regioselective 1,4 addition of resorcinol **3.13** to commercially available ethyl 2,3-butadienoate provided vinylogous carbonate **3.15** in 82% yield.[11, 12] The regioselectivity that was observed in this reaction is presumably due to an

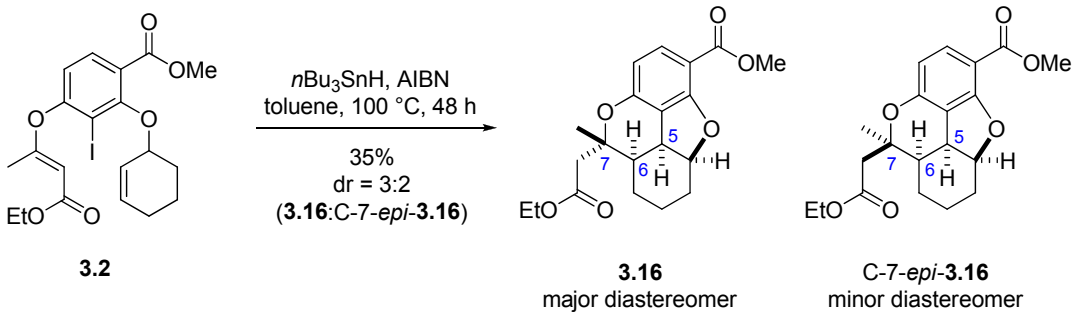
intramolecular hydrogen bond between the C-2' alcohol and the aryl ester.[13] A Mitsunobu reaction[8] of phenol **3.15** and 2-cyclohexenol was achieved under standard conditions (DIAD, $PPh_3$) to furnish the desired radical cyclization substrate in a rapid, scalable three-step sequence. A crystal structure of cyclization synbstrate **3.2** was obtained, revealing the side chain olefin configuration and confirming the structure (Scheme 3.5).




**Scheme 3.5.** Synthesis and X-ray crystal structure of model system **3.2**. Non-hydrogen atoms are displayed at a 50% probability level.

With access to cyclization substrate **3.2**, we were poised to examine the key tandem 5-*exo*, 6-*exo* radical cyclization. We were gratified to find that exposure of substrate **3.2** to tributyltin hydride and AIBN at elevated temperature provided the desired tetracycle in 35% yield (Scheme 3.6). The tandem radical cyclization formed the desired *cis,cis*-junction with complete specificity; however, the stereocenter at C-7 was obtained as a 3:2 mixture of

epimers, favoring the desired isomer **3.16**. Multiple side products were also produced, some of which are described in subsequent sections (*vide infra*).




**Scheme 3.6.** Tandem radical cyclization with $n$Bu$_3$SnH and AIBN.

The stereochemistry of the newly formed tetracyclic products was assigned by NOE analysis (Figure 3.1). Irradiation of the benzylic proton signal of both diastereomers revealed a distinct correlation to the protons on both C-5 and C-6, indicative of the convex nature of these tetracycles. The assignment of the two compounds was established on the observation that, for the major diastereomer **3.16**, the C-5 proton was correlated to the protons alpha to the ester. Whereas with the epimer C-7-*epi*-**3.16**, the benzylic proton was in proximity to the methyl group, thus consistent with the undesired stereochemistry. The NOE experiments were validated by the X-ray crystal structure of the minor diastereomer (Figure 3.1). During assignment of the $^1$H NMR, it was observed that in place of the expected doublet for the aromatic proton at C-4', a doublet of doublets ($J$ = 1, 8.8 Hz) was observed. Analysis of the COSY spectrum readily established the doublet of doublet to be a result of a long range coupling to the benzylic proton on C-5, as well as to the adjacent aromatic proton. This initial model system cyclization result confirmed our ability to construct the tetracyclic core of

bisabosqual A through a tandem radical cyclization; however, because the reaction suffered from a low yield and use of toxic tin reagents,[16, 17] we decided to pursue alternative radical reducing reagents.

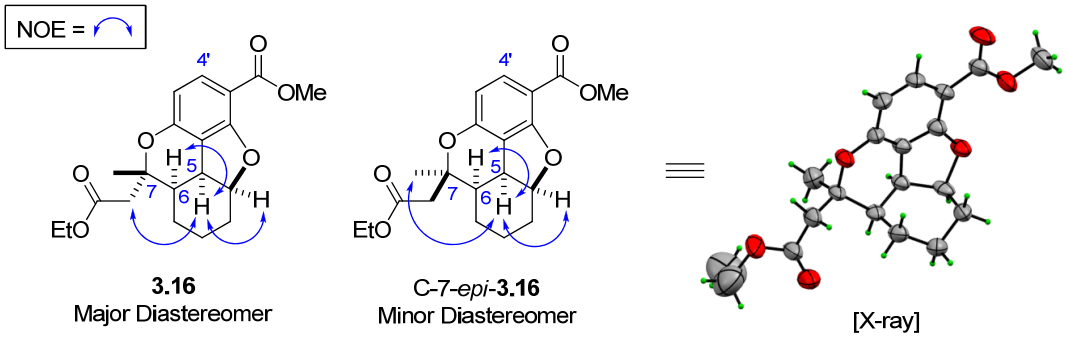



**Figure 3.1.** NOE analysis of diastereomers **3.16** and C-7-*epi*-**3.16** and X-ray crystal structure of C-7-*epi*-**3.16**. Non-hydrogen atoms are displayed at a 50% probability level.

### 3.3.2.1 Replacing Toxic Tin Reagents

The use of tributyltin hydride as a reducing agent has been prevalent in the field of free radical chemistry and thus has been utilized in a wide range of synthetic transformations.[14-17] Unfortunately, many obstacles plague the utility of tin reagents such as toxicity and tedious removal of organotin byproducts.[18, 19] Therefore, there has been extensive effort to develop catalytic tin hydride procedures, as well as, identify new radical reducing reagents as alternatives to the toxic tin species. For example, Chatgilialoglu and coworkers reported the use of tris(trimethylsilyl)silane as an effective radical reducing reagent.[20-22] This reagent has a relatively low toxicity (NFPA Health Hazard Rating: 1) and is not burdened by difficult purifications. The Si-H bond in $(TMS)_3SiH$ is 5 kcal $mol^{-1}$ stronger than the Sn-H bond ($nBu_3SnH$), and thus the rate of hydrogen-abstraction is slightly reduced (Figure 3.2).[20] It is of note that

when a single TMS group is replaced with a methyl group (i.e. $(TMS)_2MeSiH$) , there is a 10-fold reduction in rate. Whereas, the combination of $(TMS)_3SiH$ with alkyl and aryl thiols, greatly increases the hydrogen atom abstraction rate of this reducing system.

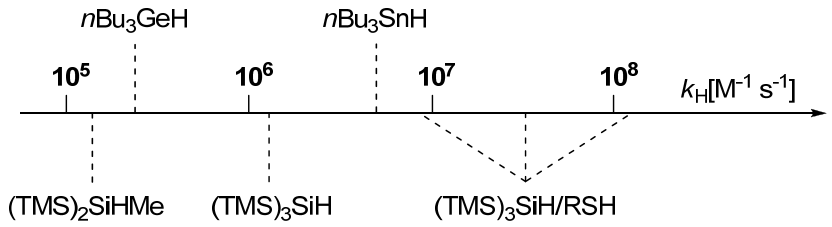
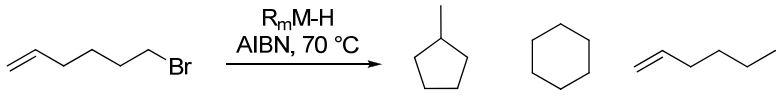



**Figure 3.2.** Hydrogen atom abstraction rates for a variety of radical reducing systems. Figure adapted from Chatgilialoglu and coworkers.[20]

The slightly stronger bond dissociation energy of $(TMS)_3SiH$ over $n Bu_3SnH$ can be exploited for cyclization reactions to prevent premature reduction side products. For example, relative to $n Bu_3SnH$, $(TMS)_3SiH$ provides an increased amount of the desired 5-*exo*-*trig* cyclization product **3.18** from alkyl halide **3.17**.[23] Therefore, incorporation of $(TMS)_3SiH$ into our cyclization procedure may help prevent premature reduction products.




**3.17** **3.18** **3.19** **3.20**

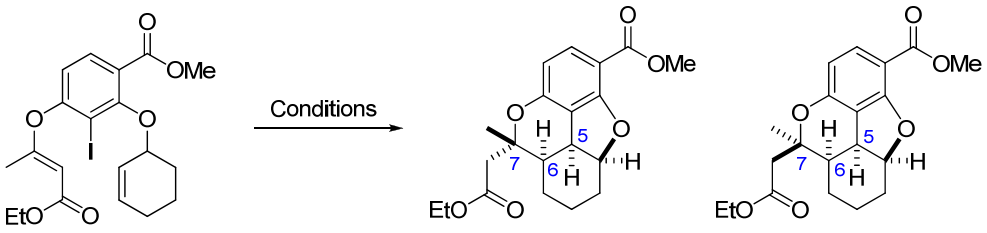
| | | | |
|---|---|---|---|
| $(TMS)_3SiH$ | 93% | 2.0% | 4.1% |
| $n Bu_3SiH$ | 83% | 1.2% | 15% |

**Figure 3.3.** Direct comparison of $(TMS)_3SiH$ and $n Bu_3SnH$ in the cyclization of aryl halide **3.17**.[23]

### 3.3.2.2 Tris(trimethylsilyl)silane Radical Cyclization (Chatgilialoglu's Reagent)

Application of tris(trimethylsilyl)silane in place of tin reagents for our model substrate cyclization is outlined in Table 3.1. Running the reaction at 80 °C resulted in an improved yield of the cyclized products as compared to the $n$Bu$_3$SnH conditions (Entry 3). However, no noticeable change in diastereoselectivity was observed with (TMS)$_3$SiH over the range of temperatures investigated, with all reactions affording the same 3:2 mixture of isomers. While a slight improvement in yield (10%) was realized by utilizing a different reducing agent and lower temperature, we sought to further optimize the reaction by turning our attention to a radical initiator.

**Table 3.1.** Tris(trimethylsilyl)silane radical cyclization results.




**3.2** | **3.16** major diastereomer | C-7-*epi*-**3.16** minor diastereomer

| Entry | Reducing Agent | Initiator | Solvent | Temperature | Time | Yield[a] |
|---|---|---|---|---|---|---|
| 1 | $n$Bu$_3$SnH | AIBN | Benzene | 100 °C | 48 h | 35% |
| 2 | (TMS)$_3$SiH | AIBN | Toluene | 60 °C | 20 h | 37% |
| 3 | (TMS)$_3$SiH | AIBN | Toluene | 80 °C | 20 h | 45% |
| 4 | (TMS)$_3$SiH | AIBN | Toluene | 120 °C | 4 h | 25% |

[a]dr = 3:2 (**3.16**:C-7-*epi*-**3.16**) across all conditions.

### 3.3.2.3 Trialkylboranes: Low Temperature Radical Initiators

One of the most common methods for initiation of free radical reactions is the decomposition of azo compounds. Specifically, 2,2′-azobis(2-methylpropionitrile) has been

used for a wide variety of transformations.[23, 24] Under thermal conditions, AIBN homolytically cleaves, liberating nitrogen, to produce two alkyl radicals which function as a radical initiator (Figure 3.4). As a result of the elevated temperatures required for initiation, alternative reagents have been developed that can operate at reduced temperatures.

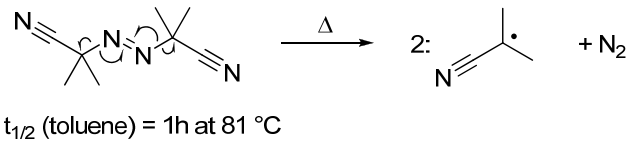
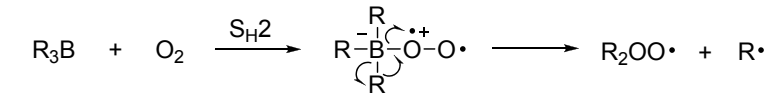


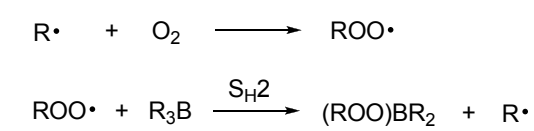

**Figure 3.4** Mechanism of thermally induced AIBN radical initiation.

In particular, trialkylboranes have emerged as tremendously effective low temperature radical initiators as a result of their ability to be autooxidized by molecular oxygen (Figure 3.5).[24-26] Consequently, reagents such as triethylborane are able to function at temperatures as low as -78 °C across a wide variety of solvents. This characteristic has attracted significant interest in trialkylboranes particularly for stereoselective radical processes.[27, 28] Therefore, we decided to integrate this radical initiator into the 5-*exo*, 6-*exo* tandem radical cyclization procedure.

**Initiation:**



**Propogation:**



**Additional Reactions:**

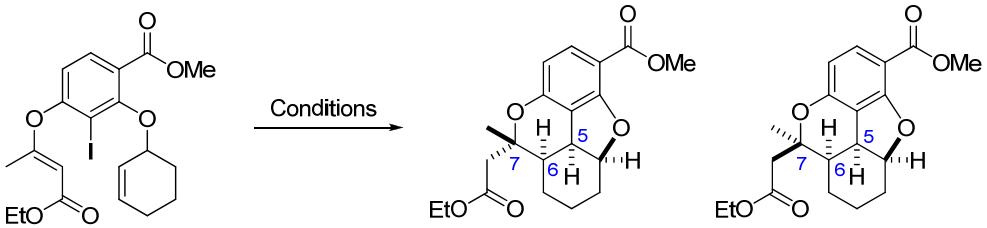
**Figure 3.5.** Trialkylborane initiation occurs through a homolytic substitution ($S_H2$) reaction with triplet oxygen to generate an alkyl radical. This radical can react with an additional oxygen molecule to form the peroxyl radical which can further propagate the chain through an additional $S_H2$ reaction. Additional processes that follow include reaction of the monoperoxyborane with oxygen to form the diperoxyborane which is inert towards further reactions with oxygen. The monoperoxyborane can also react with the trialkyborane to afford a dialkylboronate which upon addition of oxygen goes on to produce a trialkylborate. Figure adapted from Renaud and coworkers.[24, 26]

### 3.3.2.4 Tandem Cyclization Promoted by Trialkylboranes

Incorporation of trialkylboranes into the radical cyclization procedure is shown in Table 3.2. Entries 1 and 2 illustrate the ability of triethyborane to initiate the tandem cyclization at room temperature in both ethanol and methylene chloride with improved yields over the AIBN conditions. In addition, the reaction time was considerably reduced from several hours to just 30 minutes. It was also shown that *s*$Bu_3B$ can function as an effective initiator producing the desired tetracycle in 49% yield. To our knowledge, this is the first example of

$(TMS)_3SiH/sBu_3B/O_2$ system being used for radical initiation and reduction. Furthermore, entry 4 showcases the use of triphenylgermanium hydride as an alternative to $(TMS)_3SiH$ affording product in a comparable yield.[29] Despite the reduced temperature, all reactions investigated generated identical diastereomeric ratios to that previously observed (dr = 3:2, **3.16**:C-7-*epi*-**3.16**).

**Table 3.2.** Trialkylborane initiated radical cyclizations.




**3.2** | **3.16** major diastereomer | C-7-*epi*-**3.16** minor diastereomer

| Entry | Reducing Agent | Initiator | Solvent | Temperature | Time | Yield[a] |
|---|---|---|---|---|---|---|
| 1 | $(TMS)_3SiH$ | $Et_3B$/air | EtOH | rt | 30 m | 52%[b] |
| 2 | $(TMS)_3SiH$ | $Et_3B$/air | $CH_2Cl_2$ | rt | 30 m | 61% |
| 3 | $(TMS)_3SiH$ | $sBu_3B$/air | 2-MeTHF | rt | 30 m | 49% |
| 4 | $Ph_3GeH$ | $Et_3B$/air | $CH_2Cl_2$ | rt | 30 m | 50% |

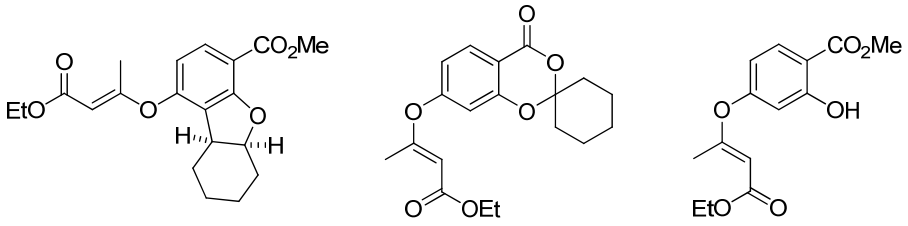
[a] dr = 3:2 (**3.16**:C-7-*epi*-**3.16**) across all conditions.

[b] Reaction performed on 1.5 gram scale.

### 3.3.2.5 Analysis of Side Products – Optimizing the Cyclization

Initial attempts to improve product formation focused on optimizing concentration, temperature and choice of solvent. It was observed that concentration had an effect on the side product profile. For example, at a high concentration of cyclization substrate **3.2,** the side product of premature reduction, tricycle **3.21**, was observed (Figure 3.6). This result suggested

reduction of the intermediate radical after 5-*exo* cyclization. This undesired pathway was readily avoided by application of dilute reactions conditions for the cyclization (≤ 0.025 M). It is noteworthy that performing the reaction at high temperature with AIBN and $(TMS)_3SiH$ resulted in the proposed ketal side product **3.22**. Formation of this product was easily suppressed by application of room temperature trialkylborane initiated conditions. Attempts at decreasing the temperature to -78 °C did not appear to influence the diastereoselectivity at C-7 and generally lower conversion to desired product was observed as a result of competing formation of phenol **3.23**. It is notable that phenol **3.23** was observed in all cyclizations regardless of temperature. The origin of this side product will be discussed in the subsequent section. After examining a wide range of solvents such as benzene, toluene, tetrahydrofuran, 2-methyltetrahydrofuran, ethanol, ethyl acetate, trifluoroethanol, acetonitrile and water, we observed that methylene chloride generally resulted in the cleanest conversion.




**3.21** **3.22** **3.23**

**Figure 3.6.** Side products observed in the radical cyclization of model system **3.2**.

### 3.3.2.6 Source of Phenol Side Product – Deuterium Labeling Experiments

Intramolecular hydrogen transfer is often observed in radical reactions and can be exploited for desirable processes; however, typically the resulting shift is a source of unexpected outcomes. We suspected side product **3.23** could be a product of 1,4-hydrogen

abstraction by the aryl radical. There is a strong preference for 1,5 hydrogen shifts which proceed through a 6-membered transition state and have the lowest activation energy based on ab initio calculations on a simple alkyl system (Figure 3.7).[14, 30] Nevertheless, 1,4 hydrogen shifts are possible if geometric and steric constraints permit proper orientation to be achieved.[31-34] Figure 3.7 shows the activation energies for various 1, *n* hydrogen migrations. In general, determination of the presence of a hydrogen atom transfer is facilitated by deuterium labeling experiments.

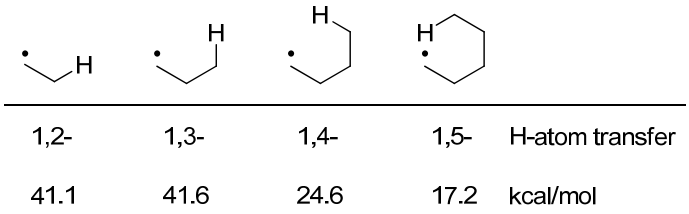
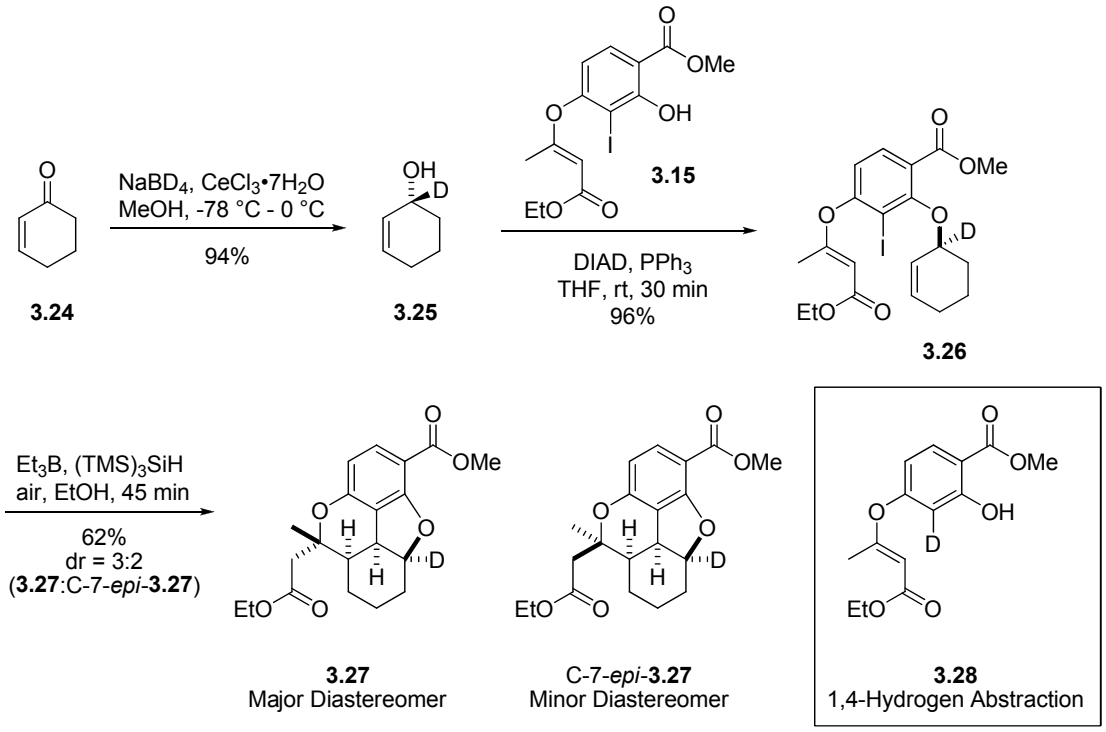



**Figure 3.7.** Activation energies for hydrogen atom transfer.[30]

To investigate the source of phenol **3.23**, we prepared the corresponding deuterium labeled radical cyclization substrate **3.26** (Scheme 3.7). This was accomplished by reduction of cyclohexenone **3.24** with sodium borodeuteride, thus providing access to the deuterium labeled alcohol **3.25** with greater than 90% deuterium incorporation (as determined by $^{1}$H NMR). A Mitsunobu reaction[8] with phenol **3.15** furnished the requisite labeled product **3.26** in excellent yield. This material was subjected to the $Et_3B$ and $(TMS)_3SiH$ radical cyclization conditions, affording the expected mixture of deuterium labeled diastereomers (**3.27** and C-7-*epi*-**3.27**). Notably, aryl labeled product **3.28** was also identified, confirming our speculation that 1,4-hydrogen abstraction is responsible for side product formation. However,

incorporation of deuterium into the aryl ring (C-1') was observed to be only ~65%, conceivably signifying the presence of multiple pathways to phenol **3.23**.

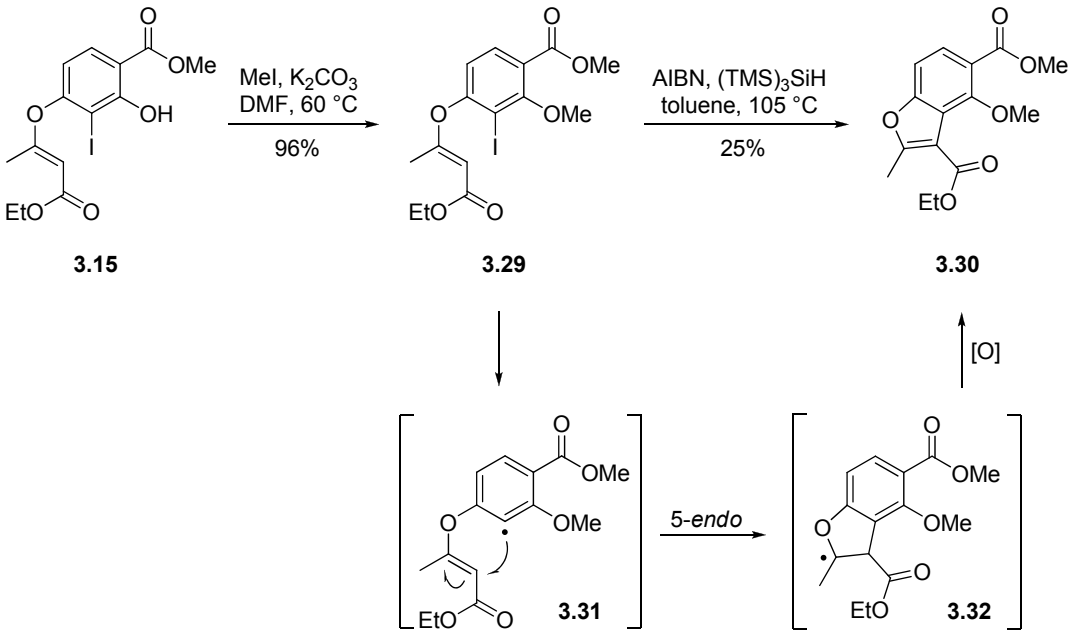



**Scheme 3.7.** Synthesis of a deuterium labeled cyclization substrate and identification of the source of side product formation.

### 3.4 5-*Endo*-*trig* Cyclization

In an attempt to gain a better understanding of potential side products that could be formed in the cyclization reaction, we synthesized substrate **3.29**. This would allow analysis of competing cyclizations onto the side chain since the ability for 5-*exo* cyclization would be eliminated. It is noteworthy that when substrate **3.29** was subjected to radical conditions, the benzofuran product **3.30** was obtained in 25% yield. A proposed mechanism for this transformation begins with the expected aryl radical **3.31** formation which can undergo a 5-*endo* cyclization to afford radical **3.32**. A subsequent oxidation of an intermediate

dihydrobenzofuran would yield the isolated benzofuran **3.30**. While 5-*endo*-*trig* cyclizations are disfavored according to Baldwin's rules,[35] Chatgilialoglu and coworkers have demonstrated 5-*endo*-*trig* radical cyclizations to be both thermodynamically and kinetically favored.[36] Nevertheless, benzofuran compounds of this type were not isolated in the fully elaborated model system, presumably this is a result of the increased rate of 5-*exo*-*trig* cyclization onto the cyclohexene as compared to 5-*endo*-*trig* cyclization onto the side chain.




**Scheme 3.8.** Possible 5-*endo*-*trig* cyclization to access benzofuran **3.30**.

### 3.5 Conclusion

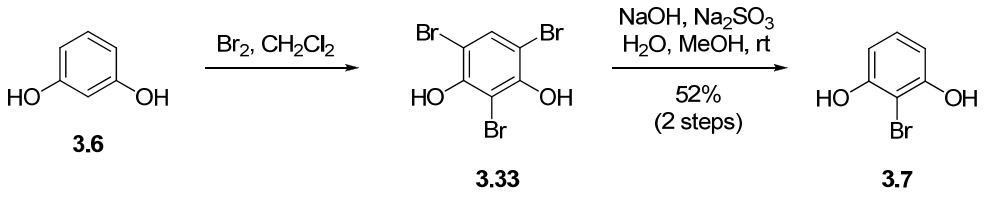
A model system was developed that could be rapidly accessed (3 steps) on a multi-gram scale, providing a method to evaluate the proposed tandem 5-*exo*, 6-*exo* radical cyclization. The cyclization proceeded with complete specificity at C-5 and C-6 to form the *cis*,*cis*-fused tetracycle while affording a 3:2 mixture of epimers at C-7 (**3.16**:C-7-*epi*-**3.16**). It was identified

that subjecting cyclization substrate **3.2** to the trialkylborane/tris(trimethylsilyl)silane/oxygen reducing system afforded the desired teteracycle in good yield. This provided a method to avoid the use of toxic tin reagents, as well as the elevated temperature required with AIBN. Furthermore, deuterium labeling experiments revealed a 1,4-hydrogen atom transfer as a culprit in the side product formation of phenol **3.23**. These results gave us confidence to extend this methodology to the fully elaborated substrate en route to the synthesis of bisabosqual A.

## 3.6 Experimental Section

### *General Methods*

Unless otherwise stated, all air and moisture-sensitive reactions were performed in oven-dried glassware under nitrogen. Unless otherwise stated, all commercially available chemicals, reagents and solvents were used as received. Reactions were monitored by thin layer chromatography (TLC) performed on Analtech, Inc. silica gel GF 250 µm plates and were visualized with ultraviolet (UV) light (254 nm) and/or $KMnO_4$ staining or by UPLC-MS (Waters Acquity, ESCI (ESI +/-, APCI +/-)). Gas chromatography – mass spectrometry (GC-MS) was performed with an Agilent 5890 GC Oven and an Agilent 5973 Mass Selective Detector. Silica gel flash chromatography was performed with RediSep®Rf normal phase silica flash columns on a CombiFlash Rf system from Teledyne Isco, Inc. $^{1}H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra were recorded on a Varian-Inova 400 (400 MHz and 101 MHz, respectively), a Bruker 400 (400 MHz and 101 MHz, respectively), or a Bruker 500 (500 MHz and 126 MHz, respectively) spectrometer. Chemical shifts are reported in ppm relative to $CHCl_3$ ($^{1}H$, $\delta$ = 7.26 and $^{13}C$ NMR $\delta$ = 77.0). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; spt, septet; m, multiplet; br s, broad singlet. Melting points are uncorrected. Infrared (IR) spectra were recorded with a Thermo-Nicolet Avatar 360 FT-IR. High-resolution mass spectra (HRMS) were acquired on an Agilent model 6220 MS(TOF).




**2-bromobenzene-1,3-diol (3.7):**

To a stirred solution of **3.6** (6.0 g, 54.5 mmol) in $CH_2Cl_2$ (100 mL) was added bromine (26.1 g, 164 mmol, 3 equiv.) over a period of 45 minutes and then the mixture was concentrated under reduced pressure to yield a crude orange solid **3.33**. To the crude residue was added MeOH (20 mL) followed by a solution of NaOH (4.36 g, 109 mmol, 2 equiv.) and $Na_2SO_3$ (13.7 g, 109 mmol, 2 equiv.) in water (100 mL) over a period of 30 minutes. An exotherm was observed and therefore, care should be taken on large scales. The mixture was acidified to pH 7 with HCl and extracted with $CH_2Cl_2$ (4x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography to afford **3.7** (5.35 g, 52% yield) as a light pink solid. The spectroscopic data are in full agreement with that reported previously.[6, 7]

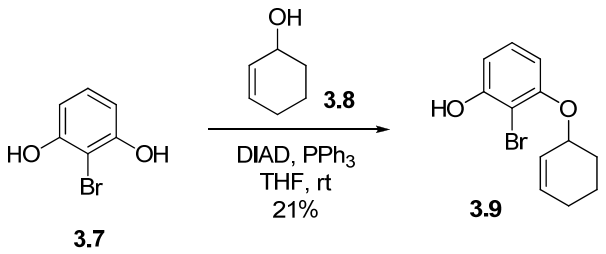
$^1$H NMR (400MHz, $CDCl_3$) δ 7.10 (t, *J*=8.1 Hz, 1H), 6.61 (d, *J*=8.2 Hz, 2H), 5.45 (s, 2H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 152.90, 129.02, 108.11, 99.30

**2,4,6-tribromobenzene-1,3-diol (3.33):**

$^1$H NMR (400MHz, $CDCl_3$) δ 7.59 (s, 1H), 5.91 (br. s., 2H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 149.74, 132.95, 100.35, 98.26

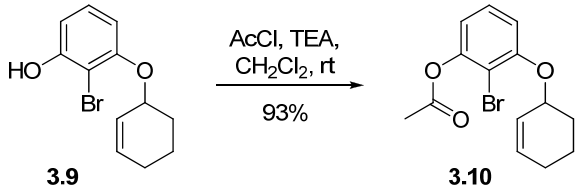



3.7 3.9

**2-bromo-3-(cyclohex-2-enyloxy)phenol (3.9):**

To a stirred solution of **3.7** (2.73 g, 14.4 mmol), **3.8** (1.28g, 13.0 mmol, 0.9 equiv.) and $PPh_3$ (5.67 g, 21.6 mmol, 1.5 equiv.) in THF (100 mL) at 0 °C was added DIAD (4.37 g, 21.6 mmol, 1.5 equiv.) dropwise over a period of 20 minutes. The mixture was warmed to room temperature and stirred for 12 hours. The mixture was poured over water and extracted with EtOAc (2x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **3.9** (820 mg, 21% yield) as a light yellow oil.

$^1$H NMR (400MHz, $CDCl_3$) δ 7.13 (t, *J*=8.2 Hz, 1H), 6.66 (dd, *J*=1.2, 8.2 Hz, 1H), 6.54 (dd, *J*=1.1, 8.5 Hz, 1H), 6.04 - 5.94 (m, 1H), 5.94 - 5.82 (m, 1H), 5.71 (br. s., 1H), 4.85 - 4.72 (m, 1H), 2.22 - 2.10 (m, 1H), 2.10 - 1.99 (m, 1H), 1.98 - 1.84 (m, 3H), 1.72 - 1.56 (m, 1H)




3.9 3.10

**2-bromo-3-(cyclohex-2-enyloxy)phenyl acetate (3.10):**

To a stirred solution of **3.9** (750 mg, 2.8 mmol) in $CH_2Cl_2$ (20 mL) was added TEA (847 mg, 8.4 mmol, 3 equiv.) followed by AcCl (437 mg, 5.6 mmol, 2 equiv.) dropwise over a period of 5 minutes. The mixture was stirred at room temperature for 1h and then poured over water.

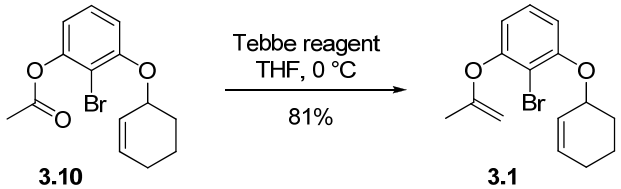
The mixture was extracted with EtOAc (2x) and the combined organic fractions were washed with brine (1x), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **3.10** (834 mg, 93% yield) as a colorless oil.

$^1$H NMR (400MHz, $CDCl_3$) δ 7.24 (t, *J*=8.0 Hz, 1H), 6.85 (dd, *J*=1.1, 8.7 Hz, 1H), 6.74 (dd, *J*=1.3, 8.1 Hz, 1H), 6.05 - 5.94 (m, 1H), 5.94 - 5.80 (m, 1H), 4.85 - 4.70 (m, 1H), 2.35 (s, 3H), 2.20 - 2.11 (m, 1H), 2.08 - 1.98 (m, 1H), 1.98 - 1.85 (m, 3H), 1.71 - 1.60 (m, 1H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 168.53, 156.03, 149.66, 132.80, 127.94, 125.57, 115.65, 112.45, 108.14, 73.05, 28.33, 25.07, 20.83, 18.85

FTIR ($cm^{-1}$) = 2937, 1768, 1589, 1461, 1270, 1190, 1033

HRMS (ESI) calculated for $C_{14}H_{15}BrNaO_3$ $[M+Na]^+$ 333.0097, found 333.0098.




**3.10** **3.1**

**2-bromo-1-(cyclohex-2-enyloxy)-3-(prop-1-en-2-yloxy)benzene (3.1):**

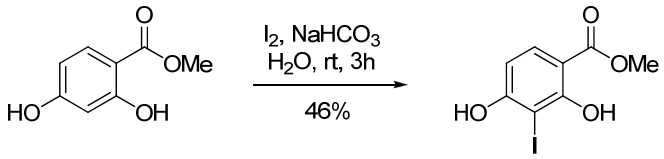
To a stirred solution of **3.10** (0.10 g, 0.32 mmol) in THF (2 mL) at 0 °C was added Tebbe reagent (1.28 mL, 0.5M in toluene, 0.64 mmol, 2 equiv.) dropwise over a period of 10 minutes. The mixture was stirred at 0 °C for 1 hour upon which TLC indicated consumption of starting material. The mixture was carefully quenched with 0.5 N NaOH (2mL) and extracted with $Et_2O$ (3x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under

reduced pressure. The crude residue was purified by basic alumina flash chromatography to afford **3.1** (80 mg, 81% yield) as a yellow oil.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 7.20 (t, *J*=8.2 Hz, 1H), 6.80 - 6.68 (m, 2H), 6.03 - 5.95 (m, 1H), 5.95 - 5.83 (m, 1H), 4.83 - 4.76 (m, 1H), 4.15 – 4.13 (m, 1H), 3.84 (s, 1H), 2.21 - 2.10 (m, 1H), 2.03 (s, 3H), 2.08 - 1.98 (m, 1H), 1.98 - 1.90 (m, 3H), 1.72 - 1.59 (m, 1H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 158.66, 156.22, 153.65, 132.68, 127.86, 125.76, 114.95, 111.18, 108.03, 88.91, 73.07, 28.41, 25.11, 19.85, 18.91

GCMS (FID) calculated for $C_{15}H_{17}BrO_2$ [M, Br isotopes] 308.0, 310.0, found 308, 310.




**3.12** **3.13**

**Methyl 2,4-dihydroxy-3-iodobenzoate (3.13):**

To a stirred solution of **3.12** (20.0 g, 0.119 mol) in THF (150 mL) and water (150 mL) at 0 °C was added $I_2$ (30.2 g, 0.119 mol, 1 equiv.) in one portion followed by $NaHCO_3$ (11.0g, 0.131 mol, 1.1 equiv.) portionwise over a period of 30 minutes. The mixture was allowed to warm to room temperature and stirred at this temperature for 3 hours. The mixture was extracted with $Et_2O$ (2x). The combined organic solution was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by recrystallization from EtOAc/Heptane to afford **3.13** (16.1g, 46% yield) as a light pink crystals.

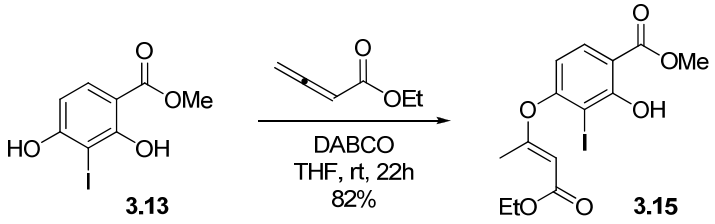
$^{1}$H NMR (400MHz, $CDCl_3$) δ 11.93 (s, 1H), 7.76 (d, *J*=8.8 Hz, 1H), 6.59 (d, *J*=8.8 Hz, 1H), 5.92 (br. s., 1H), 3.94 (s, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 169.87, 162.02, 161.03, 131.54, 106.85, 105.74, 76.64, 52.47

FTIR ($cm^{-1}$) = 3285, 1635, 1434, 1412, 1271, 1017

mp = 141 – 143 °C

HRMS (ESI) calculated for $C_8H_8IO_4$ $[M+H]^+$ 294.9462, found 294.9458.




**(*E*)-methyl 4-(4-ethoxy-4-oxobut-2-en-2-yloxy)-2-hydroxy-3-iodobenzoate (3.15):**

To a stirred solution of **3.13** (2.6 g, 8.8 mmol) in THF (90 mL) was added 4 Å molecular sieves (500 mg) and DABCO (200 mg, 1.8 mmol, 0.2 equiv.) followed by ethyl buta-2,3-dienoate (1.0 g, 8.8 mmol, 1 equiv.) in one portion. The mixture was stirred at room temperature for 22 hours. The mixture was poured over water and extracted with $Et_2O$ (2x). The combined organic fractions was washed with brine (1x), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **3.15** (2.95 g, 82% yield) as a white solid.

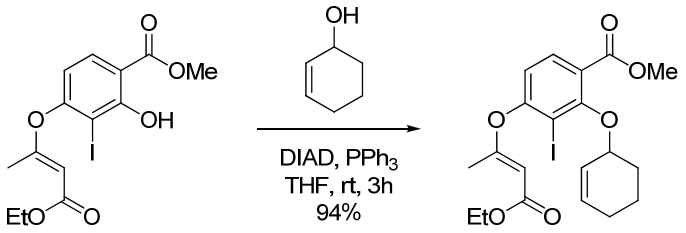
$^1$H NMR (400MHz, $CDCl_3$) δ 11.89 (br. s., 1H), 7.88 (d, *J*=8.6 Hz, 1H), 6.63 (d, *J*=8.6 Hz, 1H), 4.82 (s, 1H), 4.09 (q, *J*=7.2 Hz, 2H), 3.98 (s, 3H), 2.53 (s, 3H), 1.21 (t, *J*=7.1 Hz, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 169.96, 169.57, 166.94, 162.79, 159.42, 131.25, 113.39, 109.83, 97.66, 82.17, 59.77, 52.86, 18.13, 14.23

FTIR ($cm^{-1}$) = 2981, 1712, 1675, 1640, 1437, 1319, 1256, 1204, 1126, 1035

mp = 95 – 96 °C

HRMS (ESI) calculated for $C_{14}H_{16}IO_6$ $[M+H]^+$ 406.9986, found 406.9984.




**(*E*)-methyl 2-(cyclohex-2-enyloxy)-4-(4-ethoxy-4-oxobut-2-en-2-yloxy)-3-iodobenzoate (3.2):**

To a stirred solution of **3.15** (1.50 g, 3.69 mmol), cyclohexenol (0.435 g, 4.43 mmol, 1.2 equiv.) and $PPh_3$ (1.55 g, 5.90 mmol, 1.6 equiv.) in THF (40 mL) at room temperature was added DIAD (1.19 g, 5.90 mmol, 1.6 equiv.) dropwise over a period of five minutes. After stirring an additional 19 hours, the reaction mixture was concentrated under reduced pressure. $Et_2O$ was added and washed with 0.5 N HCl (1x), saturated $NaHCO_3$ (1x) and brine (1x). The organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **3.2** (1.67 g, 95% yield) of a white crystalline solid.

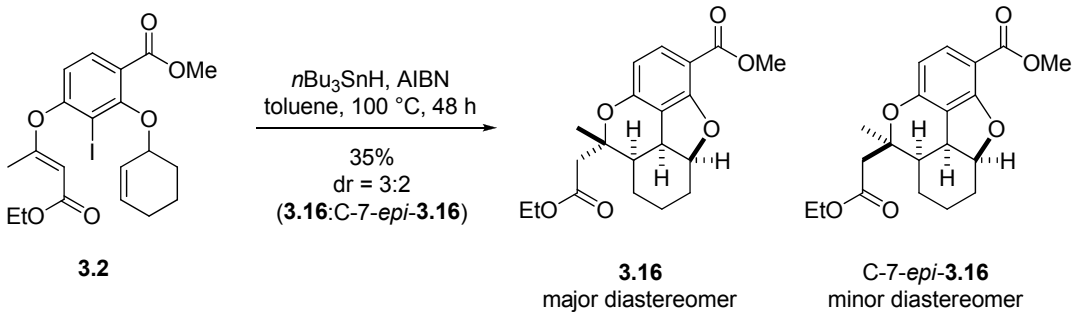
$^1$H NMR (400MHz, $CDCl_3$) δ 7.78 (d, *J*=8.4 Hz, 1H), 6.86 (d, *J*=8.4 Hz, 1H), 6.00 - 5.93 (m, 1H), 5.86 - 5.79 (m, 1H), 4.76 (s, 1H), 4.60 - 4.54 (m, 1H), 4.09 (q, *J*=7.2 Hz, 2H), 3.90 (s, 3H), 2.53 (s, 3H), 2.23 - 2.10 (m, 1H), 2.10 - 1.93 (m, 3H), 1.83 - 1.72 (m, 1H), 1.66 - 1.54 (m, 1H), 1.22 (t, *J*=7.1 Hz, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 170.17, 166.89, 165.86, 159.23, 157.31, 132.85, 132.40, 125.83, 123.46, 117.24, 97.17, 92.55, 79.35, 59.64, 52.37, 28.67, 25.06, 18.73, 18.09, 14.16

FTIR ($cm^{-1}$) = 2946, 1713, 1640, 1581, 1393, 1281, 1243, 1212, 1127, 1039

mp = 84.5 – 85 °C

HRMS (ESI) calculated for $C_{20}H_{23}INaO_6$ $[M+Na]^+$ 509.0432, found 509.0432.




**3.2**

**3.16**
major diastereomer

C-7-*epi*-**3.16**
minor diastereomer

**(±)-(2S,2aR,2a1S,5aS)-methyl 2-(2-ethoxy-2-oxoethyl)-2-methyl-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7-carboxylate (3.16):**

Nitrogen was bubbled through a stirred solution of **3.2** (102 mg, 0.210 mmol) in $CH_2Cl_2$ (8 mL) for 5 minutes, followed by addition of $Et_3B$ (0.42 mL, 1M in hexanes, 0.42 mmol, 2 equiv.) and $(TMS)_3SiH$ (78 mg, 0.315 mmol, 1.5 equiv.). Next, air was added via syringe (10 mL) over a period of 15 minutes. The mixture was stirred an additional 30 minutes at room temperature and then concentrated under reduced pressure. The crude $^1H$ NMR spectrum indicated a 3:2 mixture of diastereomers about C-7, favoring **3.16**. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **3.16** and C-7-*epi*-**3.16** (46 mg, 61% yield) as a 3:2 mixture of diastereomers. The isomers were separated by chiral HPLC (Phenomenex Luna (2) C18 150 x 21.2 mm 5µ, 5 to 95% 0.1% formic acid in water to 0.1% formic acid in methanol, flow = 28 mL/min)

$^1H$ NMR (400MHz, $CDCl_3$) δ 7.65 (dd, *J*=1.0, 8.8 Hz, 1H), 6.34 (d, *J*=8.6 Hz, 1H), 5.20 (td, *J*=7.6, 9.1 Hz, 1H), 4.17 - 4.08 (m, 2H), 3.84 (s, 3H), 3.60 (t, *J*=7.0 Hz, 1H), 2.69 - 2.52 (m, 2H), 2.32 - 2.22

(m, 1H), 2.07 - 1.98 (m, 1H), 1.75 - 1.66 (m, 1H), 1.64 - 1.56 (m, 1H), 1.54 (s, 3H), 1.23 (t, *J*=7.1 Hz, 3H), 1.09 - 0.91 (m, 2H), 0.84 - 0.71 (m, 1H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 169.77, 165.53, 160.76, 155.56, 131.97, 110.79, 107.99, 107.47, 87.75, 80.25, 60.62, 51.58, 42.99, 35.91, 33.75, 27.64, 23.43, 21.44, 20.64, 14.09

FTIR ($cm^{-1}$) = 2943, 1706, 1628, 1609, 1431, 1257, 1188

HRMS (ESI) calculated for $C_{20}H_{25}O_6$ $[M+H]^+$ 361.1645, found 361.1634

**(±)-(2R,2aR,2a1S,5aS)-methyl 2-(2-ethoxy-2-oxoethyl)-2-methyl-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7-carboxylate (C-7-*epi*-3.16):**

$^{1}$H NMR (400MHz, $CDCl_3$) δ 7.67 (dd, *J*=1.0, 8.8 Hz, 1H), 6.36 (d, *J*=8.8 Hz, 1H), 5.22 (td, *J*=7.6, 9.0 Hz, 1H), 4.18 (q, *J*=7.2 Hz, 2H), 3.87 (s, 3H), 3.56 (t, *J*=7.0 Hz, 1H), 2.87 - 2.74 (m, 2H), 2.38 - 2.31 (m, 1H), 2.09 - 2.01 (m, 1H), 1.77 - 1.71 (m, 1H), 1.64 - 1.57 (m, 1H), 1.45 (s, 3H), 1.29 (t, *J*=7.1 Hz, 3H), 1.10 - 0.95 (m, 2H), 0.83 - 0.70 (m, 1H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 169.85, 165.66, 160.73, 155.39, 131.93, 111.20, 108.17, 107.40, 87.81, 80.61, 60.65, 51.66, 42.90, 36.18, 33.51, 27.73, 23.91, 21.78, 20.66, 14.18

FTIR ($cm^{-1}$) = 2943, 1706, 1628, 1609, 1431, 1257, 1188

HRMS (ESI) calculated for $C_{20}H_{25}O_6$ $[M+H]^+$ 361.1645, found 361.1634

**(E)-methyl 4-(4-ethoxy-4-oxobut-2-en-2-yloxy)-2-hydroxybenzoate (3.23)**

$^{1}$H NMR (400MHz, $CDCl_3$) δ 10.93 (s, 1H), 7.85 (d, *J*=8.6 Hz, 1H), 6.63 (d, *J*=2.1 Hz, 1H), 6.55 (dd, *J*=2.2, 8.7 Hz, 1H), 5.04 (s, 1H), 4.10 (q, *J*=7.0 Hz, 2H), 3.95 (s, 3H), 2.45 (s, 3H), 1.22 (t, *J*=7.1 Hz, 3H)

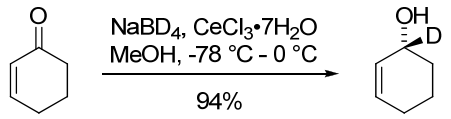
$^{13}$C NMR (101MHz, $CDCl_3$) δ 170.77, 169.97, 167.16, 163.31, 159.35, 131.73, 112.51, 109.76, 109.74, 98.61, 59.74, 52.36, 18.14, 14.26

**(*E*)-ethyl 3-(4-oxo-4H-spiro[benzo[d][1,3]dioxine-2,1'-cyclohexane]-7-yloxy)but-2-enoate (3.22)**

$^{1}$H NMR (400MHz, $CDCl_3$) δ 7.95 (d, *J*=8.6 Hz, 1H), 6.75 (dd, *J*=2.1, 8.6 Hz, 1H), 6.64 (d, *J*=2.1 Hz, 1H), 5.08 (s, 1H), 4.11 (q, *J*=7.1 Hz, 2H), 2.45 (s, 3H), 2.08 - 1.89 (m, 4H), 1.79 - 1.58 (m, 4H), 1.55 - 1.43 (m, 2H), 1.23 (t, *J*=7.1 Hz, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 170.24, 166.87, 160.26, 160.08, 157.25, 131.57, 115.50, 110.98, 109.33, 107.40, 99.52, 59.87, 34.48, 24.45, 22.12, 18.05, 14.24

LRMS (AP+) calculated for $C_{19}H_{23}O_6$ $[M+H]^+$ 347.4, found 347.0



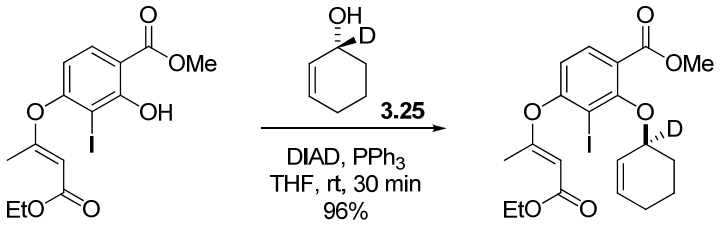

**3.24** **3.25**

**[$^2$H] - cyclohex-2-enol (3.25):**

To a stirred solution of **3.24** (1.0 g, 0.010 mol) and $CeCl_3 \cdot 7H_2O$ (4.6 g, 0.012 mol, 1.2 equiv.) in MeOH at -78 °C was added $NaBD_4$ (0.65 g, 0.016 mol, 1.5 equiv.) in portions over 5 minutes. The mixture warmed to 0 °C and stirred until TLC indicated consumption of SM (1 h). The mixture was poured over water and extracted with EtOAc (4x). The combined organic solution was washed with brine, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford **3.25** (0.94g, 94% yield) as a light beige oil and used directly in the next step without additional purification.

$^{1}$H NMR (400MHz , $CDCl_3$) δ 5.88 - 5.78 (m, 1 H), 5.76 - 5.70 (m, 1 H), 2.09 - 1.90 (m, 2 H), 1.90 - 1.79 (m, 1 H), 1.79 - 1.65 (m, 2 H), 1.65 - 1.50 (m, 2 H)

$^{13}$C NMR (100MHz, $CDCl_3$) δ 130.58, 129.74, 65.44, 31.81, 25.01, 18.85




**3.15** **3.26**

**[$^{2}$H] - (*E*)-methyl 2-(cyclohex-2-enyloxy)-4-(4-ethoxy-4-oxobut-2-en-2-yloxy)-3-iodobenzoate (3.26):**

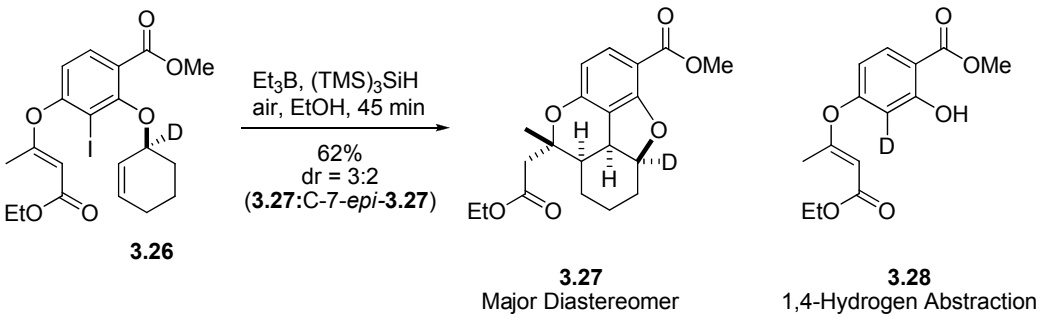
To a stirred solution of **3.15** (1.02 g, 2.51 mmol), cyclohexenol **3.25** (348 mg, 3.52 mmol, 1.4 equiv.) and $PPh_3$ (988 mg, 3.77 mmol, 1.5 equiv.) in THF (10 mL) at room temperature was added DIAD (761 mg, 3.77 mmol, 1.5 equiv.) dropwise over a period of two minutes. After stirring an additional 30 minutes, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **3.26** (1.17 g, 96% yield) of a white solid.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 7.78 (d, *J*=8.6 Hz, 1H), 6.86 (d, *J*=8.6 Hz, 1H), 5.97 (td, *J*=3.5, 10.1 Hz, 1H), 5.83 – 5.81 (m, 1H), 4.76 (s, 1H), 4.09 (q, *J*=7.3 Hz, 2H), 3.90 (s, 3H), 2.53 (s, 3H), 2.21 - 2.11 (m, 1H), 2.08 - 1.94 (m, 3H), 1.81 - 1.73 (m, 1H), 1.66 - 1.58 (m, 1H), 1.22 (t, *J*=7.2 Hz, 3H)

$^{13}$C NMR (100MHz, $CDCl_3$) δ 170.49, 167.25, 166.23, 159.54, 157.65, 133.27, 132.72, 126.04, 123.75, 117.53, 97.52, 92.85, 59.97, 52.68, 28.99, 28.86, 25.37, 19.02, 18.41, 14.46

FTIR ($cm^{-1}$) = 2945, 1712, 1639, 1580, 1432, 1389, 1281, 1242, 1212, 1126

HRMS (ESI) calculated for $C_{20}H_{23}DIO_6$ $[M+H]^+$ 488.0675, found 488.0678.




**[$^2$H] - Methyl-2-(2-ethoxy-2-oxoethyl)-2-methyl-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde] chromene-7-carboxylate (3.27):**

To a stirred solution of **3.26** (1.08 g, 2.22 mmol) and $(TMS)_3SiH$ (828 mg, 3.33 mmol, 1.5 equiv.) in EtOH (90 mL) at room temperature was simultaneously added $Et_3B$ (2.22 mL, 1M in hexanes, 2.22 mmol, 1 equiv.) and air via a syringe (10 mL). The addition procedure took place over a period of 30 minutes. The mixture was stirred an additional 30 minutes at room temperature and then concentrated under reduced pressure. The crude $^1$H NMR spectrum indicated a 3:2 mixture of diastereomers about C-7, favoring **3.27**. The crude residue was subjected to silica gel flash chromatography (EtOAc/Heptane) to afford a mixture (402 mg, 50% yield) of a 3:2 (**3.27**:C-7-*epi*-**3.27**) mixture of diastereomers as a colorless oil. Additionally, **3.28** (125 mg, 20% yield) was obtained.

Tetracycle HNMR (**3.27**): $^1$H NMR (400MHz, $CDCl_3$) δ 7.68 (dd, *J*=0.9, 8.7 Hz, 1H), 6.37 (d, *J*=8.6 Hz, 1H), 4.20 - 4.10 (m, 2H), 3.88 (s, 3H), 3.62 (d, *J*=6.2 Hz, 1H), 2.73 - 2.57 (m, 2H), 2.34 - 2.25 (m, 1H), 2.08 - 2.01 (m, 1H), 1.78 - 1.69 (m, 1H), 1.66 - 1.60 (m, 1H), 1.57 (s, 3H), 1.26 (t, *J*=7.1 Hz, 3H), 1.11 - 0.94 (m, 2H), 0.89 - 0.75 (m, 1H)

CNMR: $^{13}$C NMR (100MHz, $CDCl_3$) δ 169.90, 165.66, 160.85, 155.66, 132.08, 110.89, 108.09, 107.58, 99.78, 80.35, 60.73, 51.69, 43.09, 36.01, 33.74, 27.61, 23.52, 21.53, 20.75, 14.17

FTIR ($cm^{-1}$) = 2945, 1706, 1629, 1609, 1429, 1254, 1188

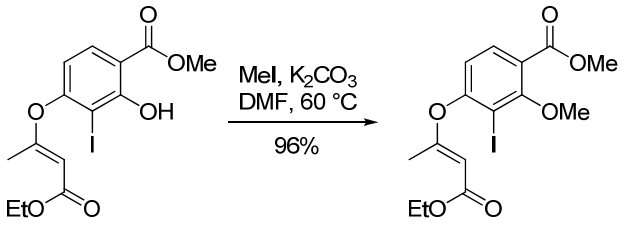
HRMS (ESI) calculated for $C_{20}H_{24}DO_6$ $[M+H]^+$ 362.1708, found 362.1716.

**3.28**: $^1$H NMR (400MHz, $CDCl_3$) δ 10.92 (s, 1H), 7.85 (d, *J*=8.8 Hz, 2H), 6.57 - 6.53 (m, 1H), 5.04 - 5.03 (m, 1H), 4.10 (q, *J*=7.0 Hz, 2H), 3.95 (s, 3H), 2.45 (s, 3H), 1.22 (t, *J*=7.0 Hz, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 170.76, 169.96, 167.14, 163.27, 159.34, 131.71, 112.50, 109.75, 109.73, 98.59, 59.73, 52.36, 18.13, 14.26

FTIR ($cm^{-1}$) = 2956, 1712, 1676, 1639, 1609, 1440, 1334, 1255, 1125

HRMS (ESI) calculated for $C_{14}H_{16}DO_6$ $[M+H]^+$ 282.1082, found 282.1079.




**3.15** **3.29**

**(*E*)-methyl 4-(4-ethoxy-4-oxobut-2-en-2-yloxy)-3-iodo-2-methoxybenzoate (3.29):**

To a stirred solution of **3.15** (0.30 g, 0.74 mmol), $K_2CO_3$ (0.20 g, 1.5 mmol, 2 equiv.) in DMF (5 mL) was added MeI (0.13 g, 0.89 mmol, 1.2 equiv.). The mixture was heated to 60 °C for 2 hours and then poured over water. The mixture was extracted with $CH_2Cl_2$ (2x). The combined organic fraction was washed with 0.5N KOH (1x) and brine (1x). The organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue

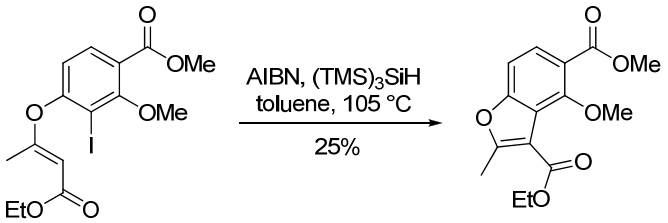
was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **3.29** (297 mg, 96% yield) as a colorless oil.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 7.86 (d, *J*=8.6 Hz, 1H), 6.88 (d, *J*=8.6 Hz, 1H), 4.78 (s, 1H), 4.09 (d, *J*=7.1 Hz, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 2.53 (s, 3H), 1.22 (d, *J*=7.1 Hz, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 170.22, 166.94, 164.85, 161.80, 157.72, 132.86, 122.55, 117.88, 97.42, 91.40, 62.52, 59.79, 52.52, 18.17, 14.23

FTIR ($cm^{-1}$) = 2950, 1710, 1638, 1580, 1464, 1432, 1382, 1123, 1044

HRMS (ESI) calculated for $C_{15}H_{18}IO_6$ $[M+H]^+$ 421.0143, found 421.0157.




**3.29** **3.30**

**3-ethyl 5-methyl 4-methoxy-2-methylbenzofuran-3,5-dicarboxylate (3.30):**

Nitrogen was bubbled through a stirred solution of **3.29** (130 mg, 0.31 mmol) in toluene (10 mL) for 30 minutes followed by addition of AIBN (5.1 mg, 0.031 mmol, 0.1 equiv.) and $(TMS)_3SiH$ (92mg, 0.37 mmol, 1.2 equiv.). The mixture was heated to 60 °C and stirred at this temperature for 18 hours. Water was added and the mixture was extracted with EtOAc (2x). The combined organic fraction was washed with water (1x) and brine (1x), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **3.30** (23 mg, 25% yield) as a white solid.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 7.76 (d, *J*=8.6 Hz, 1H), 7.22 (d, *J*=8.8 Hz, 1H), 4.42 (q, *J*=7.1 Hz, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 2.67 (s, 3H), 1.43 (t, *J*=7.1 Hz, 3H)

$^{13}$C NMR (101MHz $CDCl_3$) δ 166.77, 163.79, 162.25, 157.07, 154.83, 127.80, 120.31, 120.14, 110.10, 107.08, 63.25, 60.95, 52.17, 14.37, 14.35

LRMS (ES+) calculated for $C_{15}H_{17}O_7$ $[M+H]^+$ 293.3, found 293.1

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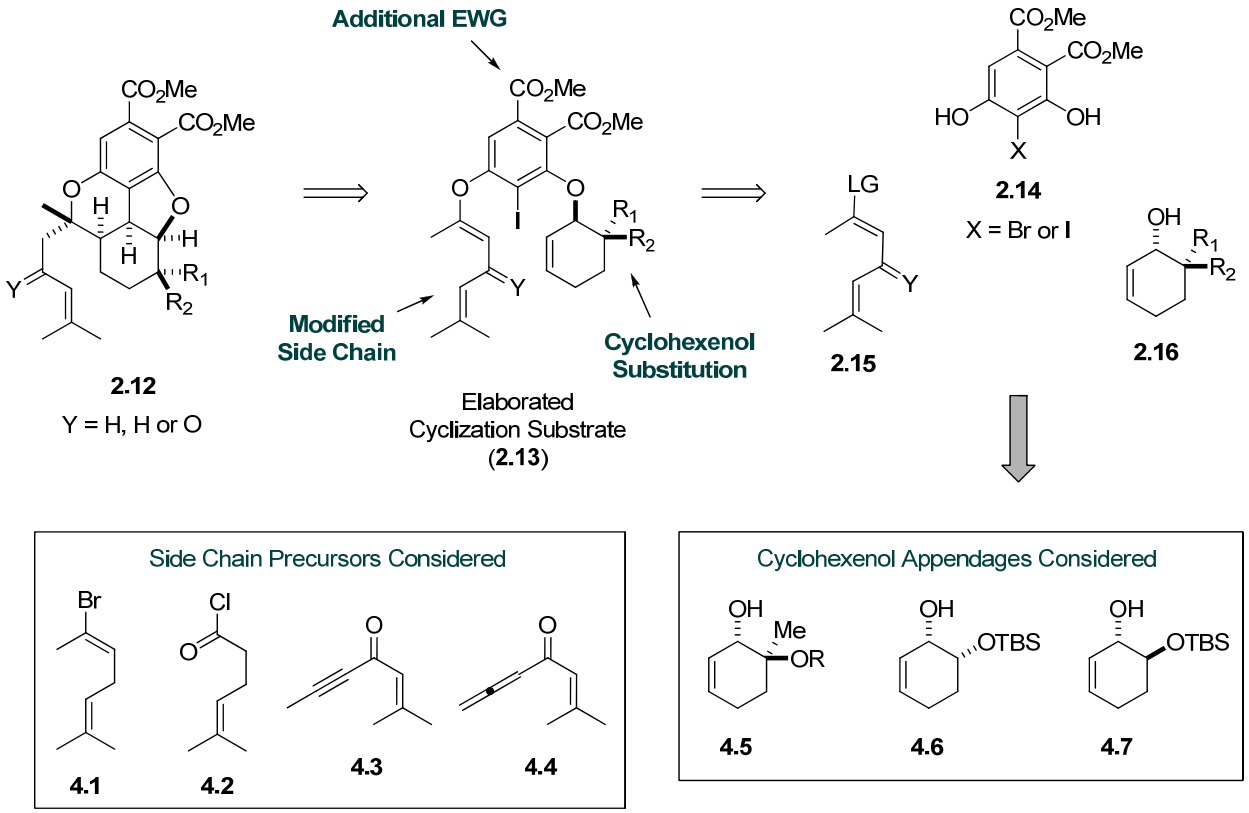
# Chapter 4

## Total Synthesis of Bisabosqual A

### 4.1 Introduction

As outlined in Chapter 3, the 5-*exo*, 6-*exo* radical cyclization on model system **3.2** indicated the validity of this approach to construct the bisabosqual tetracyclic core. However, the fully elaborated system differed in several key respects from the model system. The differences include an additional electron withdrawing group on the aromatic system, the presence of substitution on the cyclohexenol ring and a modified side chain (Scheme 4.1). Furthermore, *a priori*, it was difficult to predict whether the diastereoselectivity at the C-7 center would be different in the fully elaborated substrate as compared to the model system. However, the principles of the cyclization, as described in the retrosynthetic analysis, should be comparable (See Chapter 2 for a detailed description of the cyclization strategy). In order to access the desired cyclization substrate **2.13**, we required syntheses of the pentasubstituted resorcinol **2.14**, a suitably substituted side chain precursor **2.15** and cyclohexenol **2.16**. Considerations for the side chain precursor and cyclohexenol moieties are also shown.

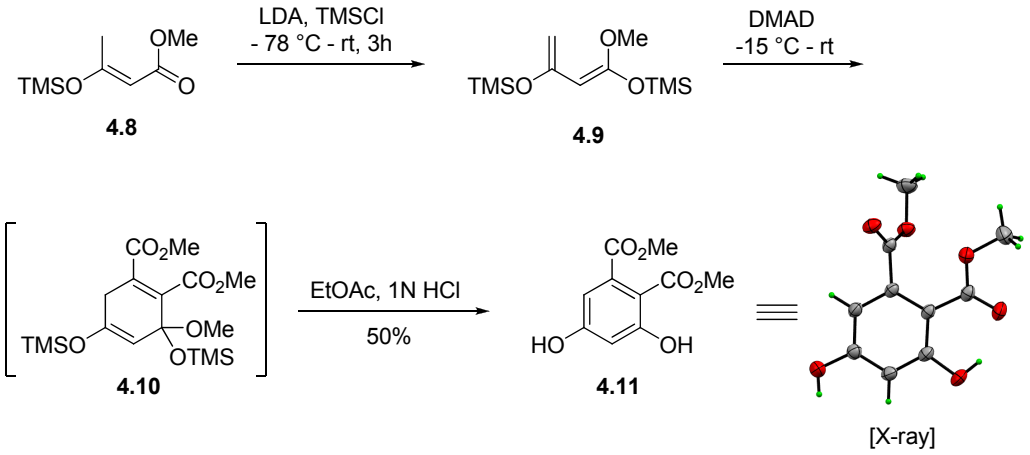



**Scheme 4.1.** Analysis of the cyclization substrate and considerations for side chain precursors and cyclohexenol appendages.

### 4.2 Synthesis of the Aromatic Core

We were intrigued by the rapid synthesis of the well-known diester **4.11**, as described by Tsuji and coworkers.[1] This would provide a tetrasubstituted resorcinol which could be further elaborated to provide the aromatic core required for the cyclization substrate. Toward this end, commercially available methyl 3-trimethylsiloxy-2-butenoate (**4.8**) was treated with LDA and TMSCl in tetrahydrofuran to afford diene **4.9** in quantitative yield (Scheme 4.2). Treatment of diene **4.9** with dimethyl acetylenedicarboxylate underwent a [4+2] cycloaddition to afford silylated intermediate **4.10**, which upon exposure to acid was converted to desired resorcinol **4.11** in 50% yield. In our hands, a cleaner conversion to resorcinol **4.11** was achieved

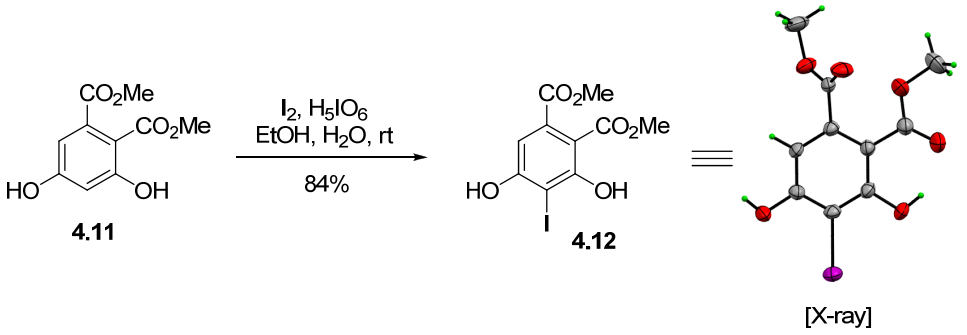
when the cycloaddition was run without solvent and then was subjected to an acidic workup. This mild procedure is an improvement to the originally described method which required elevated temperatures and challenging chromatography. While not necessary for structure determination, a crystal structure displaying the expected internal hydrogen bond between the phenol and ester groups was obtained.




**Scheme 4.2.** [4+2] cycloaddition for the synthesis of resorcinol **4.11** and X-ray crystal structure. Non-hydrogen atoms are displayed at a 50% probability level.

Iodination by modification of the iodine/periodic acid procedure of Hathaway provided the pentasubstituted resorcinol **4.12** in 84% yield similar to what was observed previously in the Parker laboratory (Scheme 4.3).[2, 3] A minor amount of the undesired regiosiomer as well as bis-iodinated products were also observed; however, these side products were easily removed by recrystallization from a methylene chloride/heptane mixture. As a result, the crystal structure of resorcinol **4.12** was also obtained, confirming iodination regiochemistry. Conversely, the use of Hathaway's iodine/silver nitrate conditions to iodinate **4.11** yielded a near statistical mixture of starting material to iodinated products. Despite a moderate

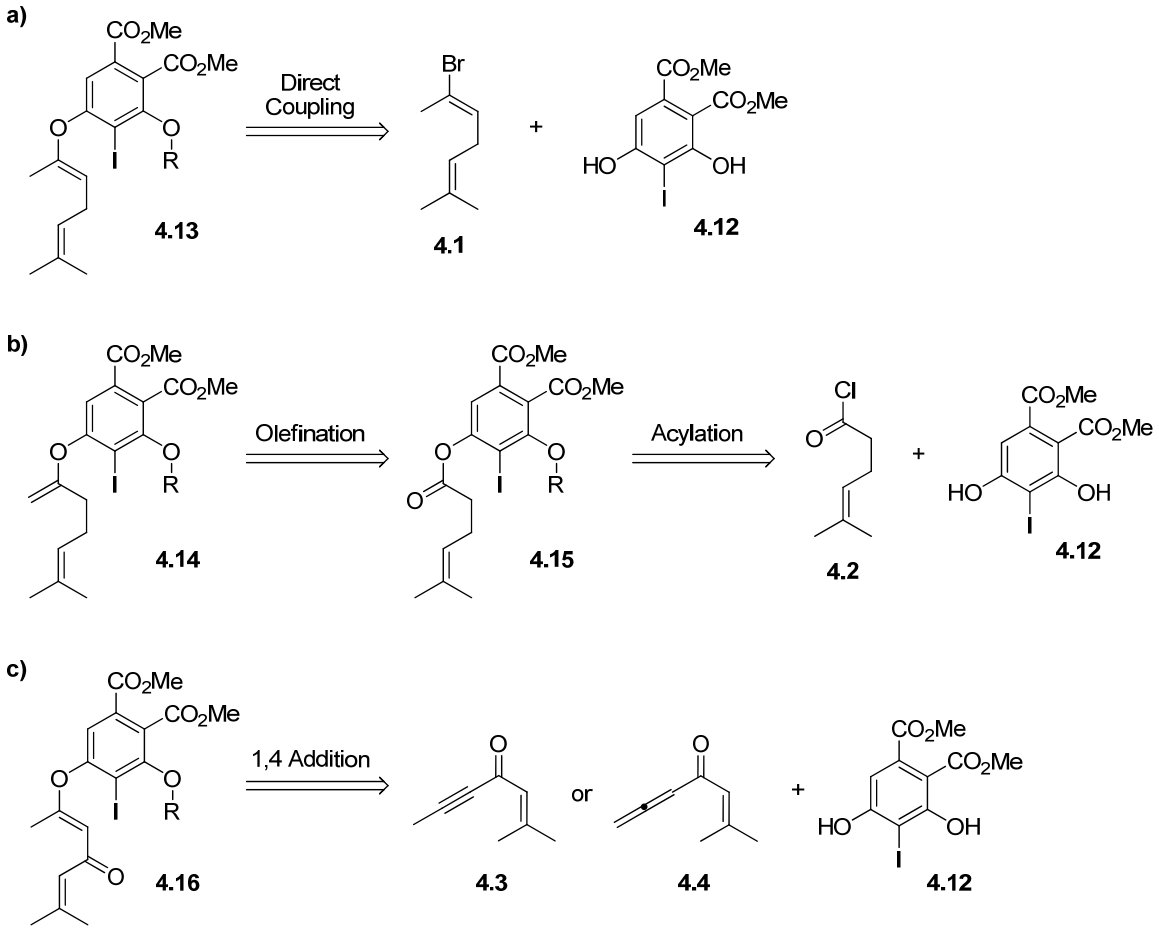
cycloaddition yield, this three-step procedure was run on a multigram scale to produce the pentasubstituted resorcinol product **4.12**.




**Scheme 4.3.** Synthesis of pentasubstituted resorcinol **4.12** and X-ray crystal structure. Non-hydrogen atoms are displayed at a 50% probability level.

### 4.3 Side Chain Determination

The side chain of bisabosqual A is not part of the tetracyclic core and therefore, in principle, could be introduced after formation of the tetracycle. While this was a valid strategy, we decided to pursue approaches that would include the carbon backbone (C-8 to C-14) of the side chain in the cyclization, in an attempt to reduce the number of linear steps. Several of the options considered for the side chain included: a) direct coupling of vinyl bromide **4.1**, b) an acylation/olefination approach with acyl chloride **4.2**, or c) a 1,4 addition with the enynone **4.3** or allene **4.4** (Scheme 4.4). Each of these strategies would utilize the same pentasubstituted resorcinol **4.12**; however, the side chain substitution, as well as, the chemistry required to introduce these substituents is different.

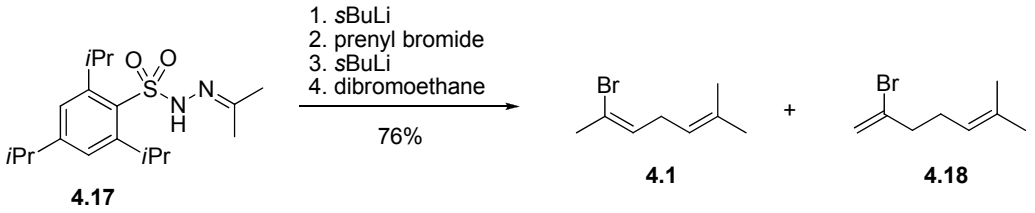



**Scheme 4.4.** Side chain synthetic strategies.

### 4.3.1 Direct Coupling Strategy

Initially we investigated the preparation of 1,4 diene substrate **4.13** which could be accessed by direct coupling of vinyl bromide **4.1** to resorcinol **4.12** (Scheme 4.4a). The bromide was previously synthesized in the Parker laboratory by application of the Shapiro reaction in a one-pot procedure from trisyl hydrazone **4.17** as described by Sorenson (Scheme 4.5).[3, 4] This procedure provided the desired vinyl bromide in good yield, albeit as a mixture of isomers. To avoid this mixture, Mulzer and coworkers developed an alternative route to access vinyl bromide **4.1** as a single isomer in a high yielding, six step sequence (not shown).[5] Although it

would add several steps to the overall sequence, the Mulzer route could be employed if a single isomer of vinyl bromide was required.

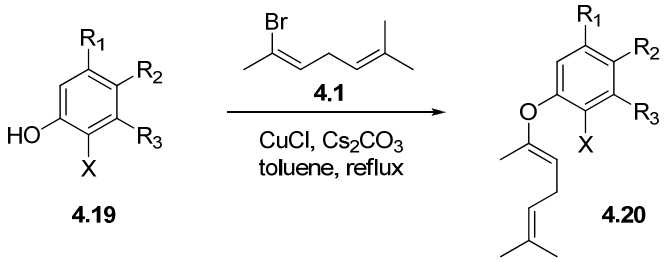



**4.17** **4.1** **4.18**

**Scheme 4.5.** Synthesis of vinyl bromide **4.1** by the Parker group.[3]

The Parker laboratory previously demonstrated that a copper mediated coupling of the vinyl bromide **4.1** with simple phenols and resorcinols (**4.19**) afforded desired product **4.20** in good yield (Table 4.1, Entries 1 and 2).[3] Unfortunately, when **4.19** contained electron withdrawing substituents and possibility for competing reactions from the aryl halide, no desired product **4.20** was observed (Entries 3 and 4). Therefore, this route did not appear to be a viable approach. Furthermore, unsatisfactory cyclization results and stability problems observed with the enol ether model system **3.1** (Refer to Chapter 3 for details), along with a lengthy synthesis of a single isomer of the vinyl bromide **4.1**, led us to pursue alternative strategies.

**Table 4.1.** Direct coupling of vinyl bromide **4.1** with phenols and resorcinols as previously described by the Parker laboratory.[3]

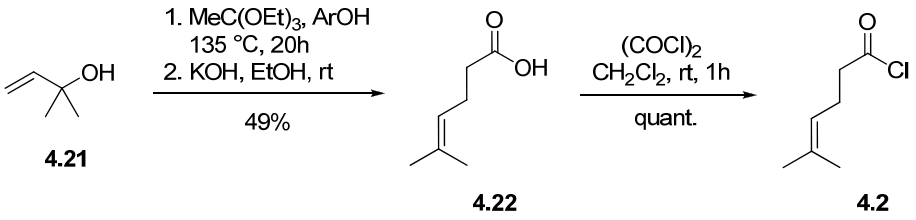



| Entry | $R_1$ | $R_2$ | $R_3$ | X | Yield |
|---|---|---|---|---|---|
| 1 | H | H | H | H | 78% |
| 2 | H | H | OH | H | 70% |
| 3 | $CO_2Me$ | H | OH | Br | 0% |
| 4 | Me | $CO_2Et$ | OH | Br | 0% |

[a] Table adapted from the thesis of Zhou Zhou.[3]

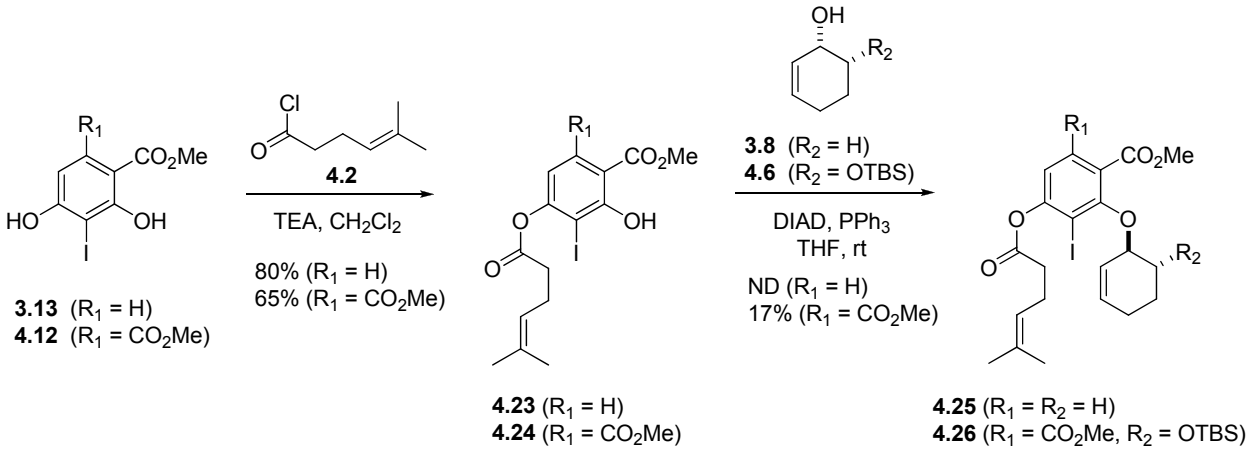
### 4.3.2 Acylation/Olefination Approach

As a result of the difficulty accessing 1,4-diene substrate **4.13**, our focus was placed on enol ether **4.14**. This intermediate could be assembled by olefination of the corresponding ester as described in the retrosynthetic analysis (Scheme 4.4b). The known acid chloride **4.2** was obtained in a three step approach shown in Scheme 4.6. A Johnson-Claisen rearrangement of 2-methyl-3-buten-2-ol (**4.21**) followed by hydrolysis produced carboxylic acid **4.22**.[6-8] Treatment with oxalyl chloride gave the corresponding acid chloride **4.2** which was used directly without additional purification.



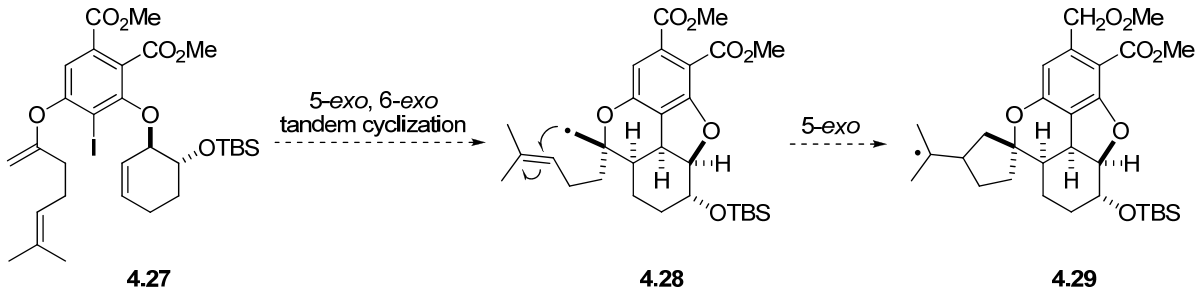

**Scheme 4.6.** Johnson-Claisen rearrangement to access acid chloride **4.2**.

Acylation was achieved on both ester **3.13** and diester **4.12** by treatment with acid chloride **4.2** and TEA to give both acyl products **4.23** and **4.24** in moderate yields (Scheme 4.7). Next, a Mitsunobu[9] reaction (DIAD, $PPh_3$) installed the cyclohexenyl group; however, the diester product **4.26** was only isolated in 17% yield along with the product of addition of two cyclohexene groups, suggesting cleavage of the acyl side chain under the reaction conditions. In addition, the ester product **4.25** was isolated in low yield as an inseparable mixture of desired product and the corresponding deacylated product. These results suggested the acyl group was not stable to the Mitsunobu reaction conditions.




**Scheme 4.7.** Resorcinol acylation followed by Mitsunobu reaction.

Alternative coupling strategies to introduce the cyclohexenol were not explored because of concern that the enol ether was not an suitable radical cyclization substrate as a result of previous model compound studies (See Chapter 3 for details). Moreover, we were concerned this system had the potential for an additional 5-*exo*-*trig* cyclization event to form a more stable tertiary radical as shown in Scheme 4.8.



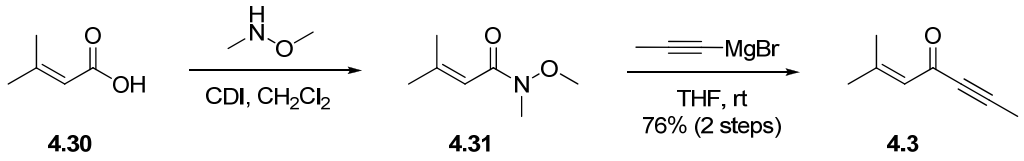

**4.27** **4.28** **4.29**

**Scheme 4.8.** Potential 5-*exo* cyclization of radical **4.28**.

### 4.3.3 Vinylogous Ester Approach

Considering the aforementioned challenges and concerns with enol ethers **4.13** and **4.14**, we sought an alternative strategy that would utilize a vinylogous ester side chain (Figure 4.4c). Although the use of a vinylogous ester would require the eventual removal of the C-9 oxygen, we decided to pursue this approach because of the expected convenience of substituent introduction, improved stability of intermediates and anticipated efficiency of the 6-*exo* radical cyclization step. Both enynone **4.3** and the corresponding allene **4.4** were synthesized previously in the Parker laboratory and were shown to afford the same vinylogous ester side chain.[3] We chose to pursue enynone **4.3** because it appeared operationally easier to synthesize, especially on scale. Toward this end, enynone **4.3** was synthesized by modification of the method of Jacobi and coworkers and similar to that previously described in the Parker

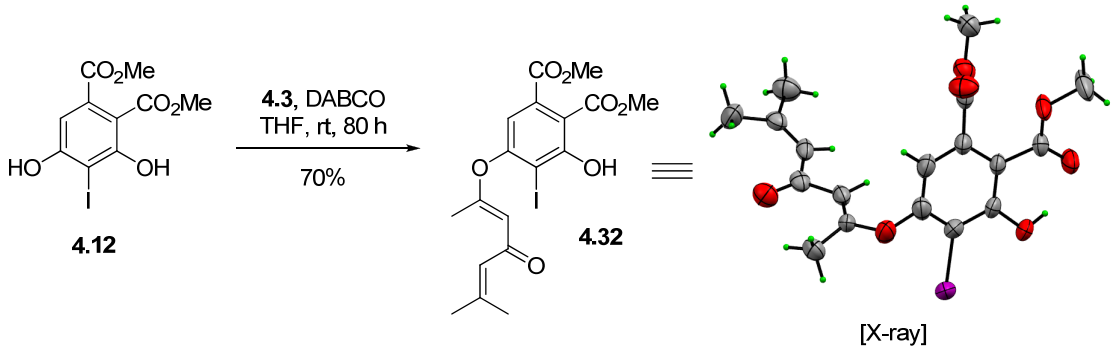
laboratory.[3, 10] Formation of Weinreb amide **4.31** was accomplished by a CDI coupling of 3,3-dimethylacrylic acid with *N,O*-dimethylhydroxylamine. Subsequent treatment with commercially available 1-propynylmagnesium bromide afforded desired enynone **4.3** in 76% yield (two steps from acid **4.30**).




**4.30** **4.31** **4.3**

**Scheme 4.9.** Synthesis of enynone **4.3** by modification of the method of Jacobi et al.[10]

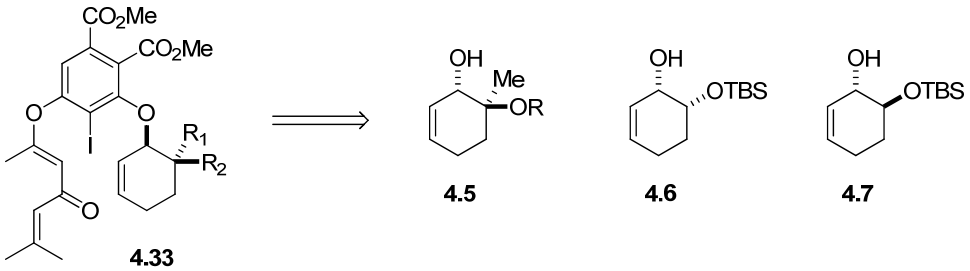
Installation of the vinylogous ester side chain was achieved by a DABCO-catalyzed 1,4 addition of acetylenic ketone **4.3** with resorcinol **4.12** to give the desired product **4.32** in 70% yield (Scheme 4.10).[11, 12] This reaction affords the *E*-isomer **4.32** exclusively as determined by X-ray crystallography. Differentiation of the two phenol groups is presumably a result of the intramolecular hydrogen bonding to the C-2' alcohol as observed in the crystal structure.[13] Attempts to circumvent the long reaction time by heating the mixture or utilizing stoichiometric DABCO typically resulted in lower yields as a result of formation of the des-iodo side product **4.11**. Exploration of reaction conditions using alternative bases ($K_2CO_3$, $PPh_3$, or PTA) and solvents (THF, toluene, $CH_2Cl_2$) proved unsuccessful, providing little or no yield of the desired product. Alternatively, vinylogous ester **4.32** was previously synthesized in the Parker group by reaction with the corresponding allene **4.4** affording product in 59% yield.[3]




**Scheme 4.10.** DABCO catalyzed 1,4-addition and X-ray crystal structure of vinylogous ester **4.32**. Non-hydrogen atoms are displayed at a 50% probability level.

### 4.4 Synthesis of the Cyclohexenol Moiety

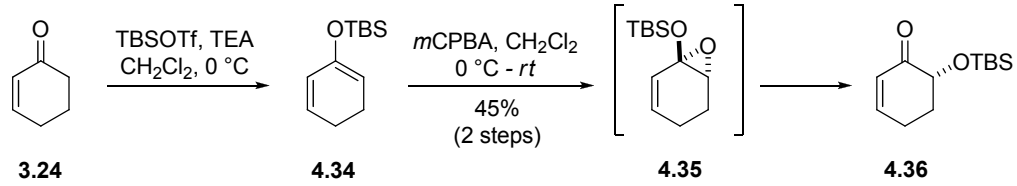
The stereochemistry at C-4 is responsible for establishing the stereochemistry of the tetracycle and thus the enantiomeric series. This is because our tandem radical cyclization strategy relies upon geometric constraints to impart the stereochemistry at the C-5 and C-6 centers. An asymmetric synthesis would therefore hinge on establishing the C-4 stereocenter (Scheme 4.11). We considered incorporation of the C-3 quaternary center prior to phenol coupling (see alcohol **4.5**); however, concerns over a competing $S_N2'$ reaction due to steric hindrance (*vide infra*) and proposed multistep reaction sequences led us to focus on alternative strategies. Therefore, we sought a synthesis of cyclohexenol substrates **4.6** or **4.7** which would provide the necessary handle for the eventual construction of the C-3 quaternary center.




**Scheme 4.11.** Considerations for cyclohexenol substrates.

### 4.4.1 Racemic Synthesis

Initially, we focused on a racemic synthesis of both the *cis* and *trans* monoprotected cyclohexenediols **4.6** and **4.7**. Toward this end, treatment of cyclohexenone with TEA and TBSOTf provided silyl enol ether **4.34** which was used directly without purification (Scheme 4.12).[14] A Rubottom oxidation with *m*CPBA installed the silyl protected α-hydoxy group in 45% yield over two steps.[15] An asymmetric Rubottom oxidation would provide a method to access enone **4.36** in an enantioselective fashion. However, attempts to employ a Jacobson epoxidation or Sharpless dihydroxylation did not appear to provide desired product. Investigation into alternative asymmetric oxidations has yet to be explored.[16, 17]

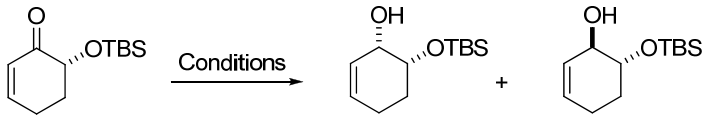



**Scheme 4.12** Silyl enol ether formation and Rubottom oxidation.

To obtain the protected diol, traditional Luche conditions[18] using $CeCl_3 \cdot 7H_2O$ and $NaBH_4$ in methanol were explored. This reaction provided the desired reduction product as a 2:1 mixture of diastereomers, favoring *cis* (**4.6**), regardless of temperature (Table 4.2, Entries 1 and 2). Lanthanum chloride in place of cerium had no effect on selectivity (Entry 3). However, when lanthanide salts were omitted from the reaction, a slight increase in diastereoselectivity was observed (Entry 4). Attempts to alter the hydride source proved detrimental with DIBAL-H yielding a ~1:1 mixture of diastereomers and L-selectride affording the product of 1,4 addition (Entries 5 and 6). Analysis of the literature led us to pursue calcium chloride/sodium

borohydride reducing conditions described by Utimoto and coworkers.[19] While Utimoto's system had been optimized for *trans* reduction of α, β-epoxy ketones, when **4.36** was subjected to $CaCl_2$ and $NaBH_4$ in methanol at 0 °C, a preference for the *cis*-reduction product was observed (Entry 7). Further cooling of the mixture to -78 °C was beneficial, providing the desired product **4.6** in excellent yield and adequate diastereoselectivity (3.5:1, Entry 8). The diastereomers were readily separated by silica gel flash chromatography, resulting in a 68% isolated yield of *cis*-diol **4.6**. The procedure was easily scaled (6.0 g, 26.5 mmol scale) to provide multi-gram quantities of *cis*-diol **4.6** and therefore, additional efforts focused on improving diastereoselectivity were not performed.

**Table 4.2.** Reduction of ketone **4.36.**




**4.36** **4.6** **4.7**

| Entry | Hydride | Additive | Temperature | Solvent | Yield | dr[a] |
|---|---|---|---|---|---|---|
| 1 | $NaBH_4$ | $CeCl_3$ | 0 °C | MeOH | 94% | 2:1 |
| 2 | $NaBH_4$ | $CeCl_3$ | -78 °C | MeOH | 92% | 2:1 |
| 3 | $NaBH_4$ | $LaCl_3$ | -78 °C | MeOH | N.D.[b] | 2:1 |
| 4 | $NaBH_4$ | --- | -78 °C | MeOH | N.D.[b] | 2.5:1 |
| 5 | L-Selectride | --- | -78 °C | THF | 0%[c] | --- |
| 6[d] | DIBAL-H | --- | 0 °C | $CH_2Cl_2$ | 76% | 1:1 |
| 7 | $NaBH_4$ | $CaCl_2$ | 0 °C | MeOH | N.D.[b] | 2.5:1 |
| 8 | $NaBH_4$ | $CaCl_2$ | -78 °C | MeOH | 90% | 3.5:1 |

[a]dr – *cis*:*trans* (**4.6**:**4.7**) diastereoselectivity.

[b]N.D. – Yield not determined.

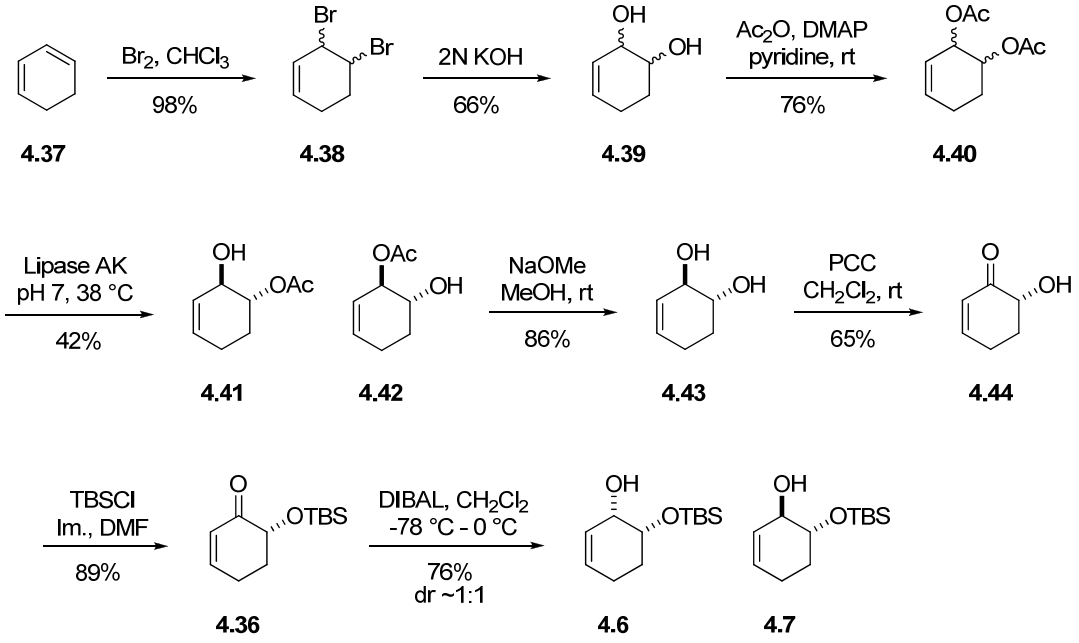
[c]Major product was 1,4 addition.

[d]Reaction from the thesis of Zhou Zhou.[3]

### 4.4.2 Enantioselective Synthesis

#### 4.4.2.1 Prior Art in the Parker Group

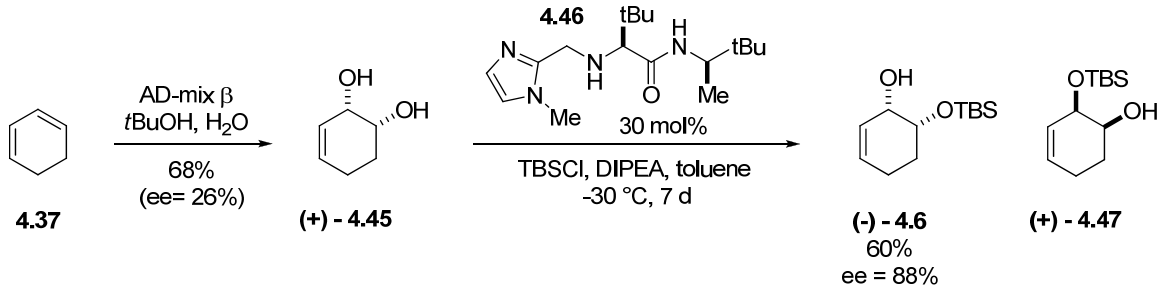
An enantioselective route to access a single isomer of cyclohexenol **4.6** was desired in order to develop an asymmetric synthesis of bisabosqual A. Previously in the Parker laboratory, an enantioselective synthesis of substrate **4.6** was performed in an eight step sequence as shown in Scheme 4.13.[3, 20] The key step in this route was an enzymatic lipase resolution of the diacetate **4.40**, which after hydrolysis provided an enantioenriched diol **4.43**. While this approach provided access to the requisite diol **4.6**, the lengthy synthesis provided only milligram quantities and therefore, alterative tactics were explored.




**Scheme 4.13.** Enantioselective synthesis of *cis* and *trans* diols **4.6** and **4.7**.

#### 4.4.2.2 Hoveyda-Snapper Enantioselective Silylation

During the course of our research, the Hoveyda and Snapper laboratories published a regiodivergent silyation of diols producing enantioenriched, regioisomeric monosilylated products.[21] The commercially available amino-acid-based organocatalyst **4.46** was used to distinguish between hydroxyl groups that have only subtle steric and electronic differences. The authors describe a regiodivergent reaction of a racemic mixture (RRRM) providing a method to access monosilyated products with high levels of enantioselectivity. In addition, a regiodivergent reaction of an enantioenriched mixture (RREM) was also reported. This RREM sequence provides a method to increase the yield of the desired enantioenriched substrate as compared to the RRRM process. Toward this end, a Sharpless asymmetric dihydroxylation with AD-mix β was performed, affording diol **4.45** in 26% ee from 1,3-cyclohexadiene as shown in Scheme 4.14.[22, 23] A selective silylation was achieved using the Hoveyda-Snapper organocatalyst **4.46** to give the desired monosilylated material (-)-**4.6** in 88% ee and 60% yield. The two isomers, **4.6** and **4.47**, were easily separable by silica gel flash chromatography. It is noteworthy that this two-step enantioselective sequence is shorter and higher yielding than the corresponding three-step synthesis of racemic material that was previously described (Scheme 4.12 and Table 4.2).




**Scheme 4.14.** Snapper-Hoveyda enantioselective silylation to access *cis*-diol **(-)-4.6**.

The source of enantioenrichment is a result of the differentiation of the two enantiomers by Hoveyda-Snapper catalyst **4.46** (Figure 4.1).[24] Hydrogen-bonding of the substrate to the chiral catalyst provides a mechanism to distinguish the two enantiomers, while the imidazole moiety functions to increase the electophilicity of the silyl group, as well as deliver the protecting group to the desired alcohol. The ability of this catalyst to discriminate between two sterically similar hydroxyl groups is a remarkable example of organocatalysis.

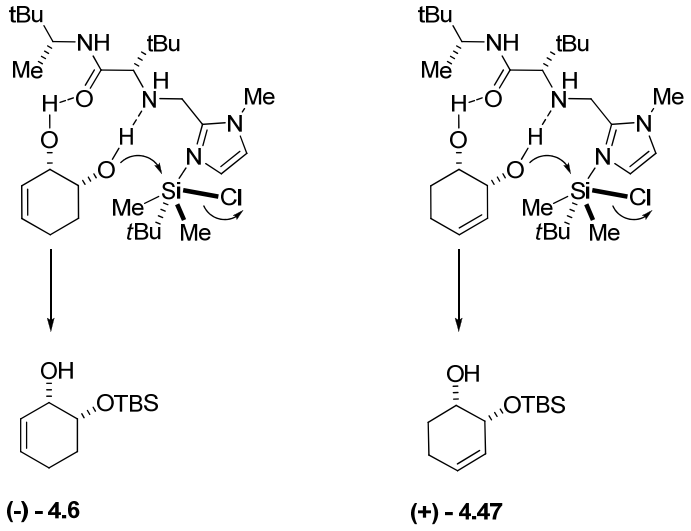
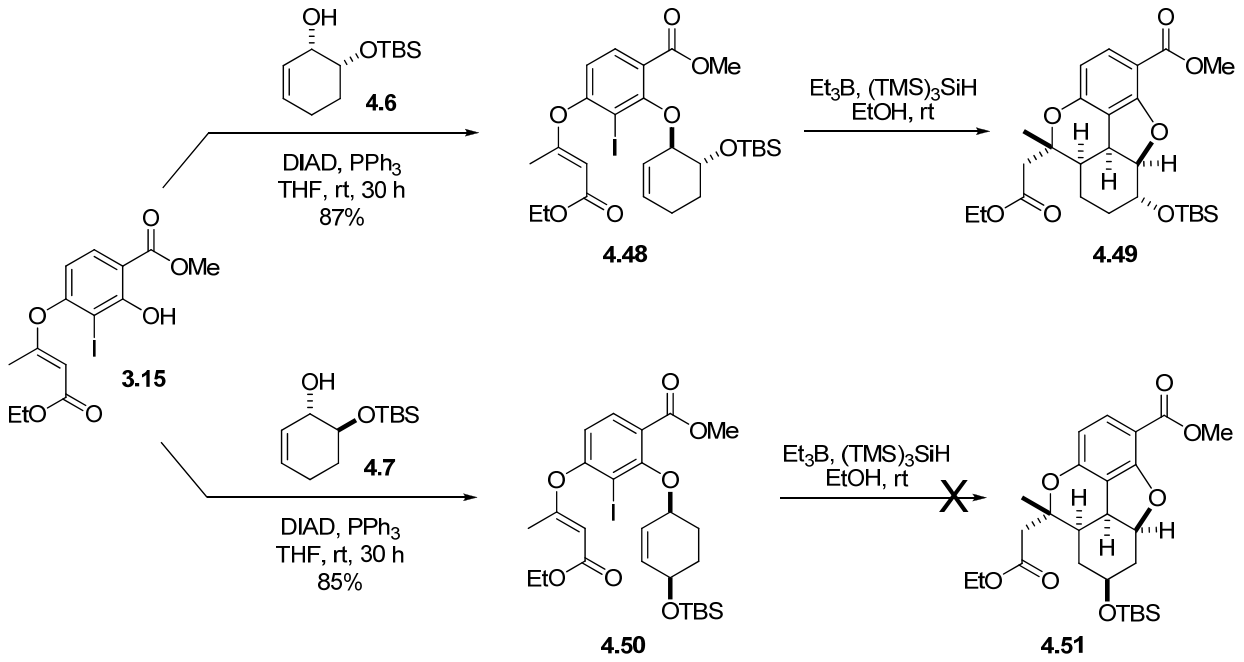



**Figure 4.1.** Subtle differences required for enantioselective silylation. Figure adapted from the thesis of Rodrigo.[24]

**4.5 Assembly of Cyclization Substrate**

Installation of the monosilylated cyclohexenol appendage was required to access the radical cyclization substrate. The stereocenter at C-4 of bisabosqual A would require the opposite configuration at the allylic alcohol of diol **4.6** and as a result, inversion of this center was necessary for the asymmetric synthesis.[25] However, we did not initially recognize whether there would be a preference for the *cis* **4.6** or *trans* **4.7** diols in the subsequent radical cyclization. Toward this end, a Mitsunobu[9] reaction on the monoester model system **3.15** and *cis*-diol **4.6** with DIAD and $PPh_3$ afforded **4.48** in 87% yield with the anticipated inversion of stereochemistry. It is noteworthy that when the *trans*-isomer **4.7** was subjected to identical Mitsunobu conditions on the monoester model system **3.15**, the major product was not the expected inversion product. Instead, reaction at the allylic center ($S_N2'$) took place, affording the substrate **4.50** in 85% yield.

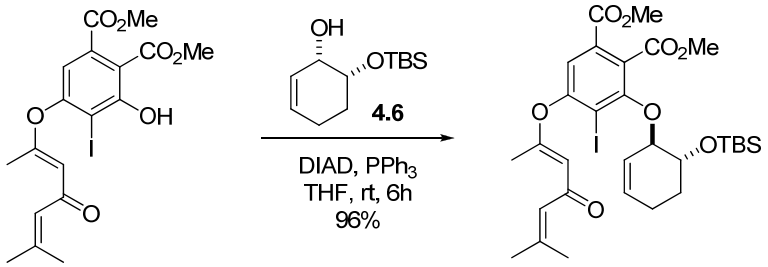



**Scheme 4.15.** Mitsunobu reactions of *cis* **4.6** and *trans* **4.7** diols and subsequent radical cyclization.

The regiochemistry of **4.50** was established by analysis of 2-D COSY and HMBC NMR spectra and the stereochemistry was tentatively assigned as drawn on account of the large *J*-coupling values of the two allylic hydrogens. Presumably the steric bulk of the *trans*-OTBS group prevents direct displacement of the alcohol, thus resulting in reaction at the allylic center. The observed $S_N2'$ displacement under Mitsunobu coupling conditions is similar to what was observed by Koreeda and coworkers on related cyclohexenol substrates.[26] It is noteworthy that substrate **4.50** did not undergo radical cyclization to afford the desired tetracycle. However, substrate **4.48** provided cyclization product as expected (yield not determined). The inability of substrate **4.50** to form the tetracycle is presumably a result of the steric bulk of the silyl ether group impeding the desired cyclization. Furthermore, the identification of the $S_N2'$

pathway with *trans*-diol **4.7** led us away from pursuing a cyclohexenol substrate that incorporated the bulky C-3 tertiary center prior to cyclization (see **4.5**, Scheme 4.11).

As a result of the observations described in Scheme 4.15, we decided to pursue the *cis*-cycohexenol substrate **4.6** for the synthesis of bisabosqual A. Coupling of *cis*-diol **4.6** with phenol **4.32** was accomplished via Mitsunobu[9] reaction (DIAD, $PPh_3$) to afford the radical cyclization substrate **4.52** in excellent yield (scheme 4.16). The doubly convergent, short synthesis of this key intermediate could be carried out on multigram scale. Therefore, we next turned our attention to the tandem 5-*exo*, 6-*exo* radical cyclization step to construct the bisabosqual tetracyclic core.



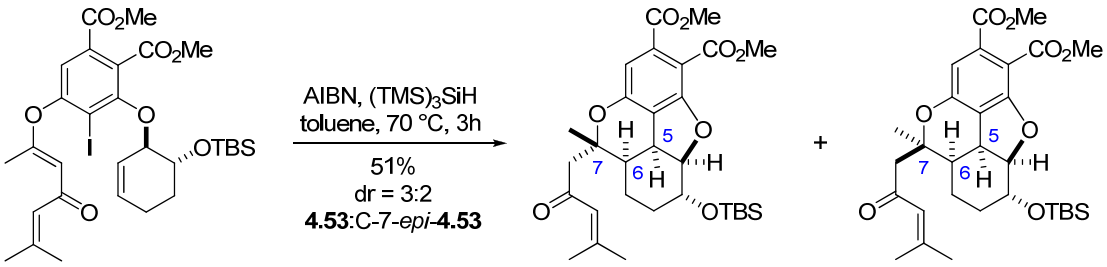

**4.32** **4.52**

**Scheme 4.16.** Synthesis of the cyclization substrate **4.52**.

**4.6 Tandem Radical Cyclization**

Having developed an efficient synthesis of the cyclization substrate, we sought conditions for the key radical cyclization step. We were pleased to find that heating substrate **4.52** with AIBN and $(TMS)_3SiH$ in toluene provided the desired *cis, cis*-fused tetracyclic core in 51% yield as a mixture of C-7 epimers, favoring the desired tetracycle **4.53**, over its diastereomer C-7-*epi*-**4.53** (Scheme 4.17). Analysis of the $^1H$ NMR of the crude product

indicated the cyclization afforded complete selectivity at C-5 and C-6 while imparting a 3:2 mixture of epimers at the C-7 quaternary center.




**Scheme 4.17.** Synthesis of the bisabosqual tetracyclic core via a tandem radical cyclization.

The stereochemistry of each isomer was confirmed by NOE analysis (Figure 4.2). Irradiation of the benzylic proton provided clear evidence for the formation of the *cis, cis*-fused tetracycle in both epimers (arrows A and B). The NOE between the benzylic proton and the α-keto hydrogens of the side chain in the major diastereomer indicated desired product **4.53** (arrow C). Conversely, an NOE to the methyl hydrogens in the minor isomer signified the diastereomer (C-7-*epi*-**4.53**) with the non-natural stereochemistry (arrow C). The observed diastereoselectivity along with results from the NOE analysis is consistent with that described for the model system (Refer to Chapter 3 for details).

The diastereomers **4.53** and C-7-*epi*-**4.53** could be separated by silica gel flash chromatography. However, despite surveying a wide variety of solvent combinations, the separation was challenging and the purification often required multiple columns to obtain desired product. It was identified that preparative HPLC using a chiral polysaccharide column

gave excellent resolution and therefore this method was used to separate the diastereomers on scale (see Chapter 4 Experimental for additional details).

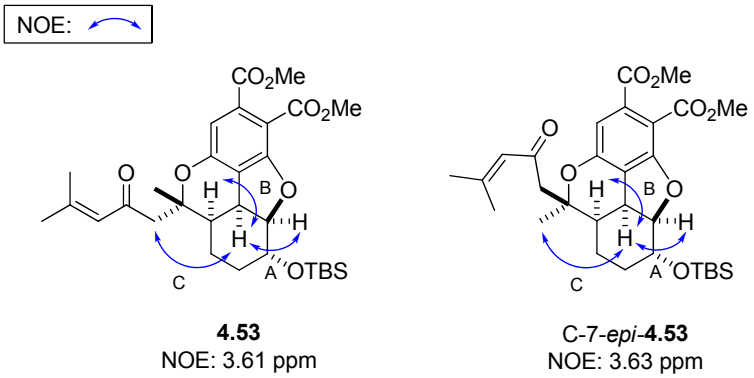



**Figure 4.2.** NOE analyses of the C-7 diastereomers.

The major side product isolated in the tandem radical cyclization is phenol **4.54** (Figure 4.3). This is analogous to the side product phenol **3.23** observed with the model system and therefore, can be attributed to a 1,4-hydrogen abstraction process (see Chapter 3, Figure 3.6). The proposed mechanism of side product formation was confirmed by deuterium labeling experiments on a model substrate (see Chapter 3, Scheme 3.7). Furthermore, a crystal structure of this side product was obtained, unambiguously confirming the structure. Without alteration of the structure of the cyclization substrate, it is not immediately clear how to prevent this common side product.

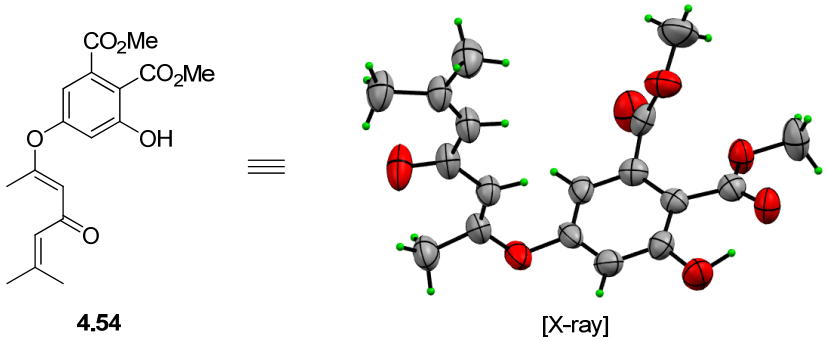
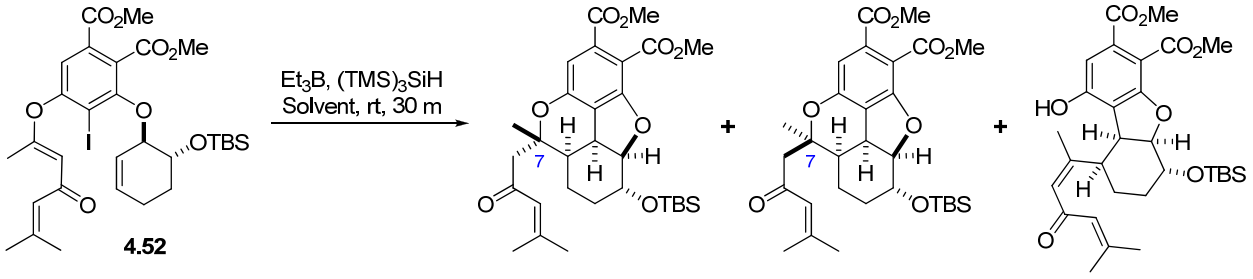



**Figure 4.3.** X-ray structure of the 1,4-hydrogen abstraction product **4.54**. Non-hydrogen atoms are displayed at a 50% probability level.

The key radical cyclization was studied in some detail as described in Table 4.3. On a model system, triethylborane initiation had been shown to afford desired product in higher yield than traditional AIBN initiation (see Chapter 3, Table 3.2).[27] Therefore, we attempted to utilize these reaction conditions on the fully elaborated substrate. However, when cyclization substrate **4.52** was subjected to identical triethylborane initiated radical cyclization conditions, the yield was only 31% and significant side product formation was observed (Scheme 4.18 and Table 4.3, Entry 2). This was a considerable reduction in yield compared to the 51% yield obtained from the AIBN conditions (Entry 1). Furthermore, a change in diastereoselectivity was also observed with the undesired diastereomer C-7-*epi*-**4.53** now favored under the triethylborane conditions. This result was notable since this was the first instance in which the diastereoselectivity at C-7 was altered to favor the undesired C-7-*epi*-**4.53** epimer over the desired tetracycle **4.53**. A similar result was also observed when tributylborane was used as a radical initiator (yield not determined). When, a coordinating solvent such as acetonitrile was employed with triethylborane, the diastereoselectivity was restored to the usual 3:2 (**4.53**:C-7-*epi*-**4.53**) mixture of isomers with only a slight improvement in yield (Scheme 4.18 and Table

4.3, Entry 3). It was observed that in addition to the expected 1,4-hydrogen abstraction product (**4.54**), we observe the formation of the retro-Michael product **4.55** regardless of solvent. This side product was only observed in triethylborane and tributylborane initiated reactions, suggesting a specific interaction between the radical initiator and the starting material, product and/or intermediate. It was also discovered that retro-Michael product **4.55** converts to a 3:1 mixture of **4.53**:C7-*epi*-**4.53** in a $CDCl_3$ solution (NMR tube), potentially revealing a useful method to epimerize the undesired diastereomer. Therefore, the observed difference in diastereoselectivity between solvents could be a result of this epimerization event being sensitive to changes in solvent or potentially other factors that are affected by the Lewis acidity of triethylborane.[28] Efforts towards understanding these observations are currently being pursued.




| Solvent | Yield | dr* |
|---|---|---|
| $CH_2Cl_2$ | 31% | 2:3 |
| $CH_3CN$ | 39% | 3:2 |

**Scheme 4.18.** Triethylborane initiated tandem radical cyclization.

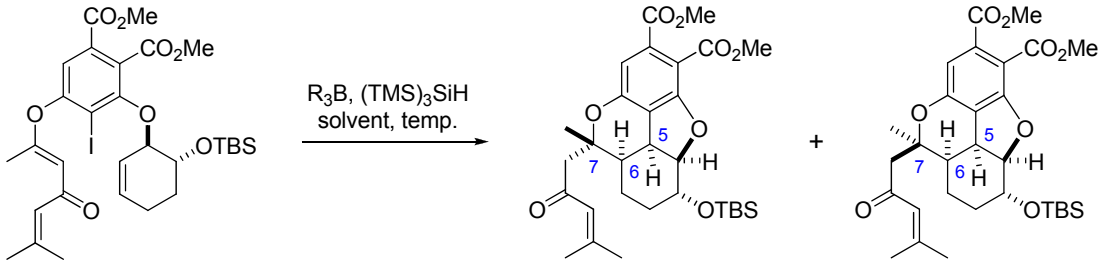
Our hypothesis of triethylborane functioning as a Lewis acid and making interactions with the cyclization substrate is supported by the results obtained using tri-*sec*-butylborane as a radical initiator (Table 4.3, Entries 4-8). We observed that the desired diastereomer is favored

in all instances, with improved yields and we did not detect retro-Michael product **4.55**. This suggested that the more sterically-encumbered Lewis acid does not participate in interactions similar to those that occur with triethylborane. However, an alternative explanation of this observation is the retro-Michael product is forming in the $s$Bu$_3$B reactions and converting to the desired tetracycle *in situ*.

We were pleased to find that treatment of **4.52** with $s$Bu$_3$B and (TMS)$_3$SiH in dichloromethane afforded the 5-*exo*, 6-*exo* cyclization in 72% yield on a multigram scale (Entry 4). This high yielding result further showcases the differences between tri-*sec*-butylborane and triethylborane initiated radical cyclizations. Experiments with additional solvents and increased temperatures resulted in slightly lower yields (Entries 5-7). Investigation of the cyclization at reduced temperature showed a modest improvement in diastereoselectivity, albeit with a reduced yield of 46% (Entry 8). Additional low temperature cyclizations have yet to be explored. Moreover, attempts to influence the diastereoselectivity at C-7 through addition of exogenous Lewis and Brønsted acids and bases did not result in significant differences. (e.g. $MgI_2$, $ZnCl_2$, DABAL-Me$_3$, $InCl_3$, CuCl, $BF_3{\cdot}OEt_2$, B(OMe)$_3$, HCl, pyrrolidine, etc.)

We are not aware of any previous examples in which the $s$Bu$_3$B/(TMS)$_3$SiH/$O_2$ conditions have been used for reductive radical cyclizations. Accordingly, this is the first instance in which a difference in reaction profiles between triethylborane and tri-*sec*-butylborane has been observed in radical cyclizations. Therefore, while not yet fully understood, these conditions have implications for a variety of radical reactions in which triethylborane may be affecting the reaction outcome.

**Table 4.3.** Key tandem radical cyclization.




**4.52** **4.53** C-7-*epi*-**4.53**

| Entry | Reducing Agent | Initiator | Solvent | Temperature | Time | Yield[a] | dr[b] |
|---|---|---|---|---|---|---|---|
| 1 | $(TMS)_3SiH$ | AIBN | Toluene | 70 °C | 3 h | 51% | 3:2 |
| 2 | $(TMS)_3SiH$ | $Et_3B$ | $CH_2Cl_2$ | rt | 30 m | 31% | 2:3 |
| 3 | $(TMS)_3SiH$ | $Et_3B$ | $CH_3CN$ | rt | 30 m | 39% | 3:2 |
| 4 | $(TMS)_3SiH$ | *s*$Bu_3B$ | $CH_2Cl_2$ | rt | 30 m | 72%[c] | 3:2 |
| 5 | $(TMS)_3SiH$ | *s*$Bu_3B$ | Toluene | rt | 30 m | 60% | 3:2 |
| 6 | $(TMS)_3SiH$ | *s*$Bu_3B$ | $CH_2Cl_2$ | 40 °C | 15 m | 58% | 3:2 |
| 7 | $(TMS)_3SiH$ | *s*$Bu_3B$ | 2-MeTHF | 50 °C | 15 m | 62% | 3:2 |
| 8 | $(TMS)_3SiH$ | *s*$Bu_3B$ | $CH_2Cl_2$ | -40 °C | 4 h | 46% | 5:2 |

[a]Yield is reported for the mixture of diastereomers.

[b]dr – **4.53**:C7-epi-**4.53**.

[c]Reaction run on gram scale.

### 4.6.1 Visible Light Photoredox Catalysis

Visible light photoredox catalysis has emerged as a valuable tool for initiating single electron, radical processes.[29, 30] Recently, several groups have showcased this methodology for a diverse assortment of chemical transformations.[31-33] The source of this reactivity is a result of the ability of metal complexes such as tris(2,2'-bipyridyl)dichlororuthenium (II) ($Ru(bpy)_3^{2+}$) or *fac*-tris[2-phenylpyridinato-$C^2$,N]iridium(III) (*fac*-$Ir(ppy)_3$) to undergo photoexcitation upon

exposure to visible light. Remarkably, the photoredox catalyst can function either as a reductant or oxidant through either oxidative or reductive quenching cycles, respectively (Figure 4.4). Upon excitation with visible-light from a household lightbulb, $Ru(bpy)_3^{2+}$ is converted to a high energy photoexcited species. In the oxidative quenching cycle, an electron acceptor (**A**) is reduced to afford a radical anion along with the oxidized metal center. $Ru(bpy)_3^{3+}$ can then oxidize a donor (**D**) to yield the radical cation along with the regenerated catalyst. In the reductive quenching cycle, the excited-state catalyst can oxidize **D**, thus reducing the catalyst, which can then function as a reductant and give an electron to **A**, to restore the ground state ruthenium species. The redox potentials of the various segments of the catalytic cycles can thus be exploited in single electron processes.

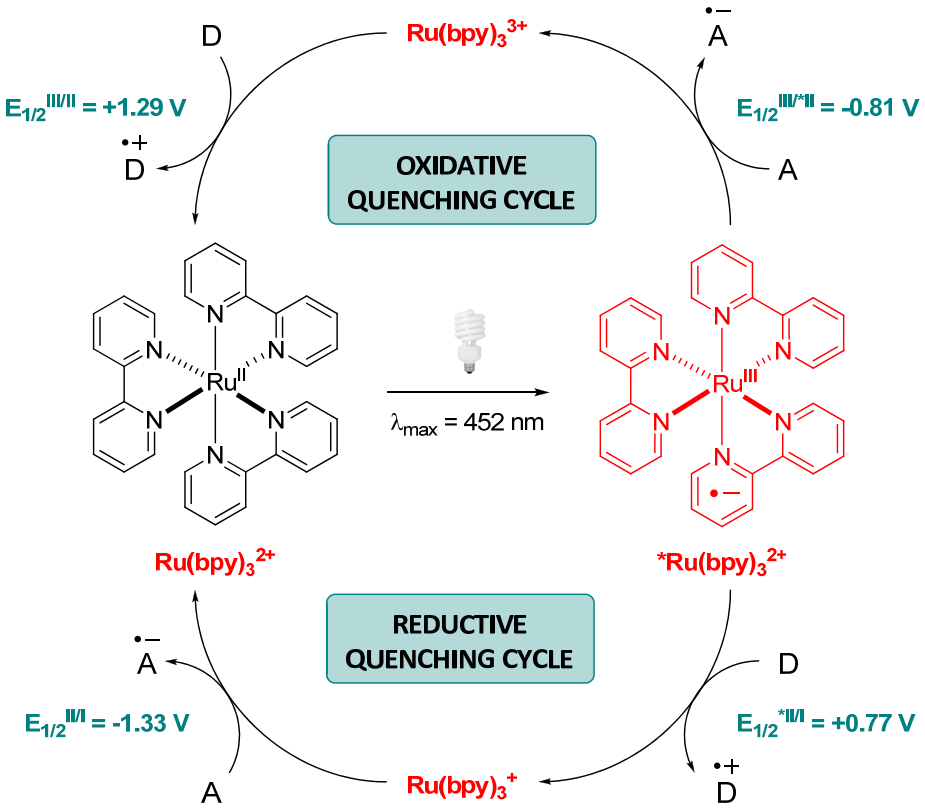
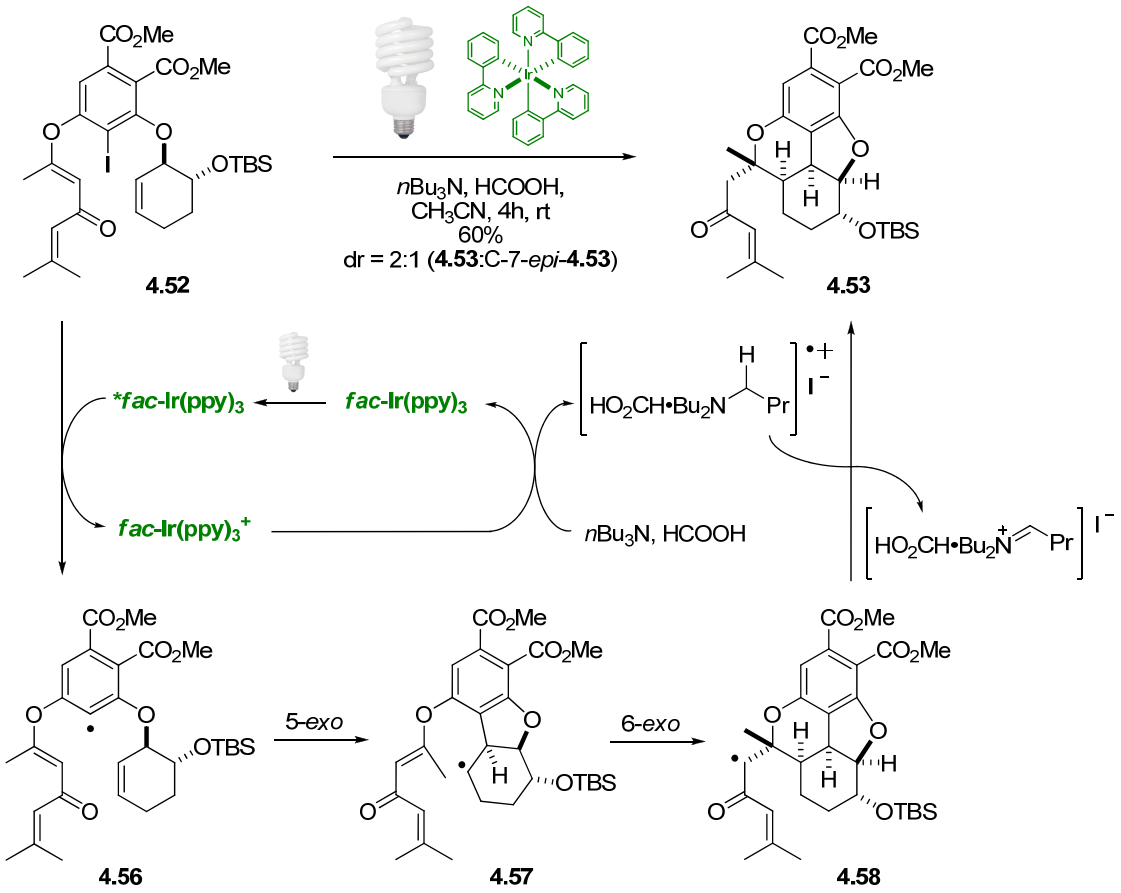



**Figure 4.4.** The oxidative and reductive quenching cycles of the $Ru(bpy)_3^{2+}$ catalyst. Figure adapted from MacMillan and coworkers.[30]

The Stephenson laboratory developed conditions to effectively reduce aryl iodides using the *fac*-Ir(ppy)$_3$ photocatalyst along with tributylamine and formic acid.[31] Encouraged by their intramolecular cyclization results, we set out to test this chemistry on the bisabosqual cyclization substrate **4.52**. Toward this end, we were pleased to find that subjecting a solution of **4.52**, *fac*-Ir(ppy)$_3$, *n*Bu$_3$N and $HCO_2H$ in acetonitrile to visible light resulted in formation of desired product in 60% yield (Scheme 4.19. see experimental for a picture of the reaction set up). The diastereoselectivity was similar to that was previously observed in the tri-*sec*-butylborane reactions, favoring the desired tetracycle **4.53** (dr = 2:1, **4.53**:C-7-*epi*-**4.53**).

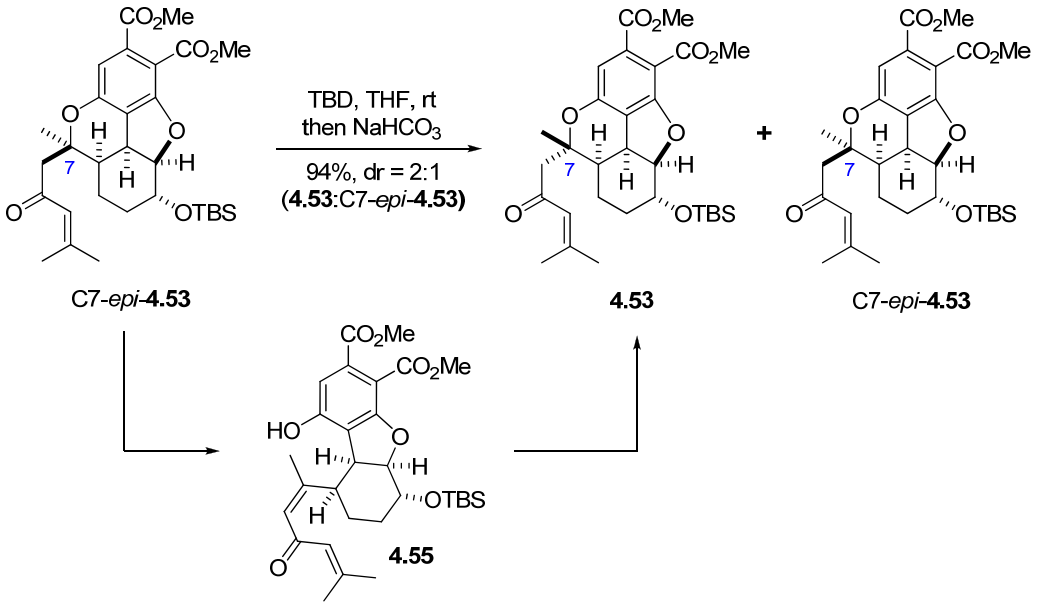



**Scheme 4.19.** Visible light photoredox radical cyclization.

The reaction is expected to proceed through the oxidative quenching cycle of the iridium catalyst because of studies performed by Stephenson and coworkers (scheme 4.19).[31] Irradiation with a household light bulb affords the excited state catalyst which upon reductive cleavage can generate the $sp^2$ radical **4.56**. This aryl radical can then undergo the expected 5-*exo*, 6-*exo* tandem cyclization. The oxidized catalyst is then regenerated by oxidation of a tributylamine/formic acid to form a radical cation, thus completing the catalytic cycle. A hydrogen atom abstraction by the α–keto radical species **4.58** from the aminium radical cation generates an iminium species along with the desired product.

### 4.7 Recycling the Minor Diastereomer

It was envisioned that the minor diastereomer could be epimerized via a retro-Michael reaction to form intermediate **4.55** (Scheme 4.20), which could then reform the tetracycle similar to what was observed in the triethylborane reactions shown previously (see Scheme 4.18). Initially, we were pleased to find on small scale that treatment of C7-*epi*-**4.53** with KHMDS in tetrahydrofuran produced a mixture of **4.53** and C7-*epi*-**4.53** albeit with side product formation. Upon further experimentation, it was found that treatment of C7-*epi*-**4.53** with the guanidine base, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) followed by stirring with $NaHCO_3$ cleanly afforded a 2:1 (**4.53**:C7-*epi*-**4.53**) mixture of diastereomers (Scheme 4.20). Incorporation of this procedure into the synthetic sequence helps contribute to the overall efficiency.



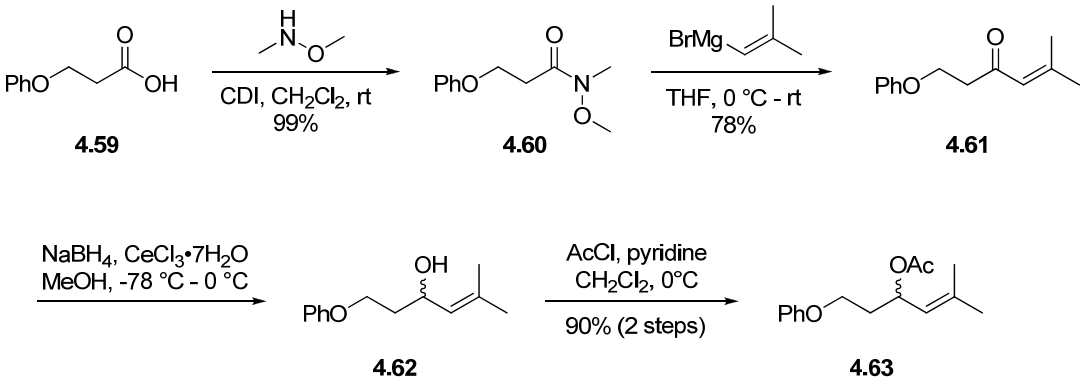

**Scheme 4.20.** Conversion of the minor epimer C-7-*epi*-**4.53** into a 2:1 mixture of diastereomers **4.53** and C-7-*epi*-**4.53**.

### 4.8 Reduction of the C-9 Ketone

Having developed an effective, doubly convergent synthesis of tetracyclic ketone **4.53**, we sought a method for removing the oxygen functionality at C-9 which would leave the prenyl group unaffected. Classical methods for reduction of a ketone to an alkane include the Wolff-Kishner[34, 35] and Clemmenson[36-39] reductions. Unfortunately, the harsh reaction conditions required for these reactions are typically incompatible with many functional groups. Furthermore, modifications of the Wolf-Kishner reduction which utilize tosylhydrazone are known to afford the olefin migration product through a 1,5 sigmatropic rearrangement.[40] Alternatively, the reduction of the corresponding thioketal (Mozingo reduction)[41, 42] was also considered; however, preliminary efforts on a model system resulted in significant olefin migration as well as hydrogenation of the olefin.[43]

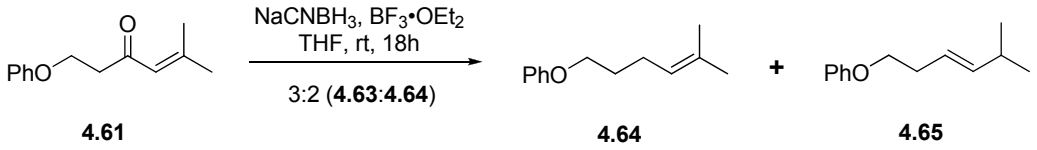
#### 4.8.1 Model System Studies

In order to investigate additional reduction conditions, a straightforward model system was synthesized that would allow analysis of reduction on the α,β-unsaturated ketone **4.61** as well as on the allylic acetate **4.63**. Consequently, a CDI coupling of **4.59** with *N,N*-dimethylhydroxylamine afforded the Weinreb amide **4.60**, which upon addition of 2-methyl-1-propenylmagnesium bromide yielded the requisite α,β-unsaturated ketone **4.61**. A Luche reduction[18] with $CeCl_3 \cdot 7H_2O$ gave alcohol **4.62**, which was treated with acetyl chloride and pyridine to supply the allylic acetate **4.63** in 90% yield over two steps.




**Scheme 4.21.** Synthesis of model systems for ketone and allylic acetate reduction studies.

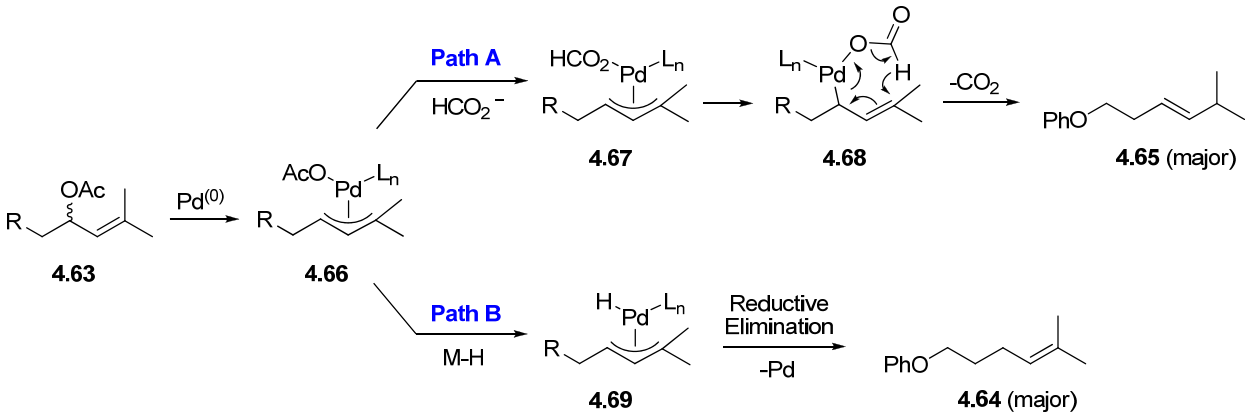
Initially, attempts to reduce the ketone **4.61** directly with a Lewis acid and hydride source were examined. For example, the use of $NaCNBH_3$ and $BF_3{\cdot}OEt_2$ in tetraydrofuran afforded a mixture of the desired reduction product **4.64** and the isomer **4.65** as a 3:2 mixture (Scheme 4.22, yield not determined).[44] Investigation of additional Lewis acid/hydride/solvent combinations proved futile, providing only reduced selectivity or multiple side products. Therefore, alternative methods for reduction of the C-9 ketone to methylene were explored.




**Scheme 4.22.** Direct reduction of enone **4.61** to prenyl substrate **4.64**.

We investigated the Tsuji-Trost palladium-catalyzed regioselective deoxygenation of allylic acetate **4.63**.[45-50] Analysis of the literature suggested two different pathways resulting in either the product of olefin migration **4.65** or the desired retention product **4.64** are possible.[49] Both pathways would begin by coordination of the allylic acetate to palladium followed by oxidative addition to form the $\eta^3$ π-allyl complex **4.66**. Treatment with a formate source

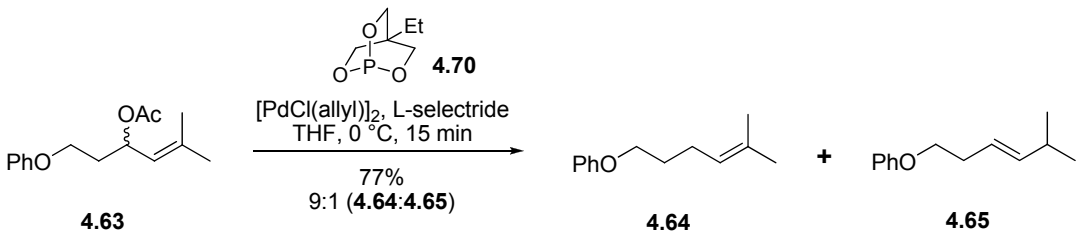
delivers the hydride at the more substituted carbon by a proposed concerted mechanism as shown in path A. Alternatively, various hydride sources, such as L-selectride, react as 'hard' nucleophiles and directly attack the metal center forming the palladium hydride **4.69**. Reductive elimination then delivers the hydride to the less hindered carbon forming **4.64** as the major product. The regioselectivity of each of these pathways has been shown to be sensitive to reaction conditions (e.g. choice of ligand).




**Scheme 4.23.** Regioselectivity in the Tsuji-Trost reaction.

We were drawn to the mild conditions described by Trost and coworkers for the regioselective deoxygenation of an allylic carbonate with a similar substitution pattern.[50] Toward this end, treatment of model system **4.63** with allylpalladium (II) chloride dimer, phosphite ligand **4.70** and L-selectride resulted in a clean conversion to a 9:1 mixture of desired product **4.64** and the isomerized product **4.65** in 77% yield. Several attempts to vary reaction parameters such as the hydride source, ligand, palladium species or solvent, typically resulted in reduced regioselectivity and/or side product formation. For example, phosphine ligands such as SPhos, XantPhos and $PCy_3$ proved detrimental, resulting in greater than 5-fold reduction in regioselectivity. When a large excess of phosphite ligand **4.70** (> 6 equivalents) was used,

formation of alcohol **4.62** was the only product observed, suggesting excess phosphite could be preventing the formation of the π-allyl complex. We observed that rapid addition of L-selectride appeared to be beneficial for regioselectivity. While this addition protocol was incorporated into the synthesis of bisabosqual A, a reverse addition of a mixture of **4.63**, allylpalladium (II) chloride dimer and ligand **4.70** to a solution of L-selectride appears to offer similar benefits and operationally may be more straightforward, especially on larger scales.

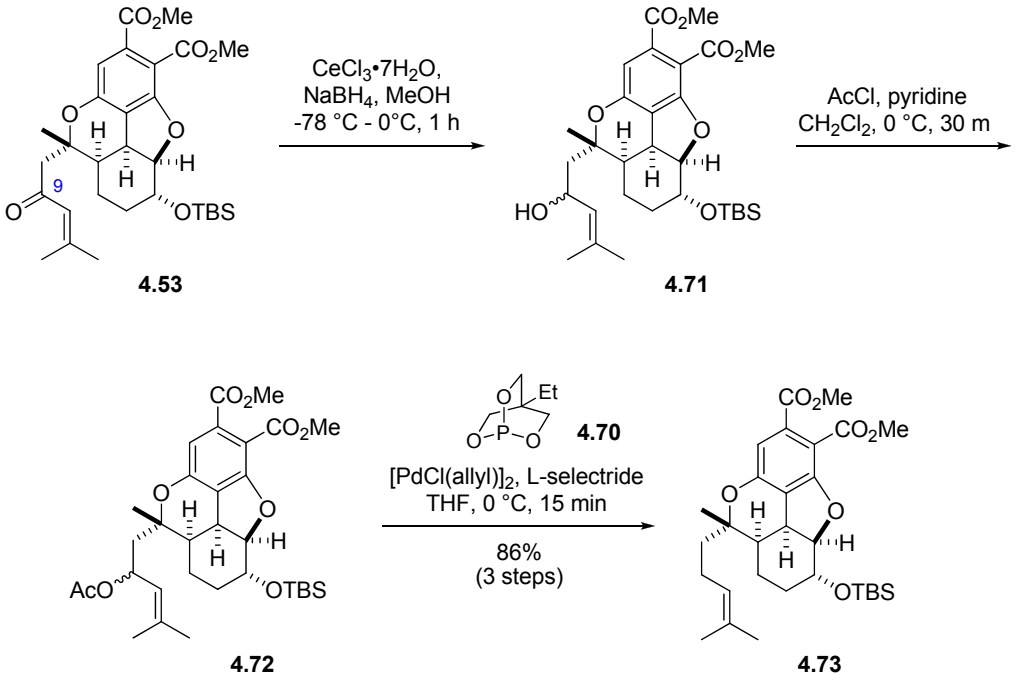



**Scheme 4.24.** Application of Trost-Hutchins conditions for allylic deoxygenation on a model system.

### 4.8.2 Application of the Trost-Hutchins Reducing Conditions

In order to access the allylic acetate required for our synthesis, we performed a Luche reduction[18] of ketone **4.53** with $CeCl_3 \cdot 7H_2O$ and $NaBH_4$ to obtain alcohol **4.71** as an 8:1 mixture of diastereomers (Scheme 4.25). Treatment of alcohol **4.71** with acetyl chloride and pyridine in methylene chloride cleanly provided allylic acetate **4.72** without the need for purification. Utilization of triethylamine rather than pyridine resulted in significant side product formation. A similar result was also observed in the synthesis of the model system substrate **4.63**. Next, we were gratified to find that addition of L-selectride in one portion to a mixture of allylic acetate **4.72**, $[PdCl(allyl)]_2$ and phosphite **4.70** at 0 °C afforded the desired product **4.73** in 86%

yield (three steps from ketone **4.53**) with only trace amounts of the olefin migration product observed.




**Scheme 4.25.** Application of Trost-Hutchins conditions for the allylic deoxygenation of acetate **4.72**.

When excess L-selectride and extended reaction times were employed, lactone **4.74** was isolated as a minor side product (Figure 4.5). A benefit of obtaining lactone **4.74** was that it was readily crystallized from EtOAc/heptane, thus allowing determination of the structure by single crystal X-ray analysis. Not surprisingly, the more electron-deficient ester was reduced, forming lactone **4.74** upon intramolecular cyclization. Identification of the structure was also advantageous since it was the first crystal structure obtained of the tetracycle. This validated our previous NOE analysis (Figure 4.2) and confirmed the stereochemistry of the cyclohexenol starting material **4.6**.

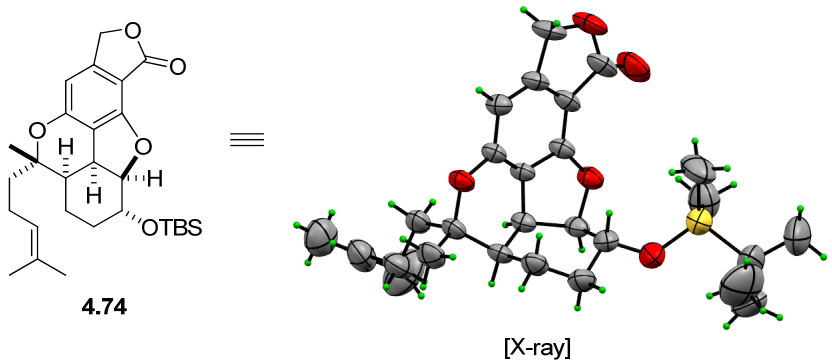
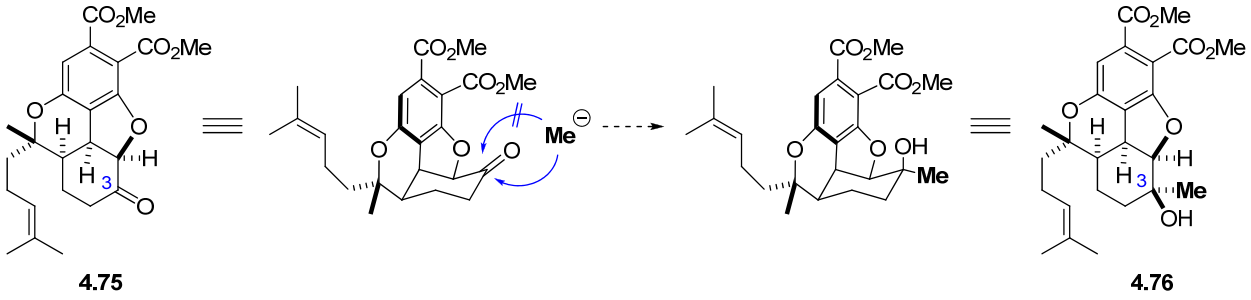



**Figure 4.5.** X-ray crystal structure of lactone side **4.74**. Non-hydrogen atoms are displayed at a 50% probability level.

### 4.9 Synthesis of the C-3 Quaternary Center

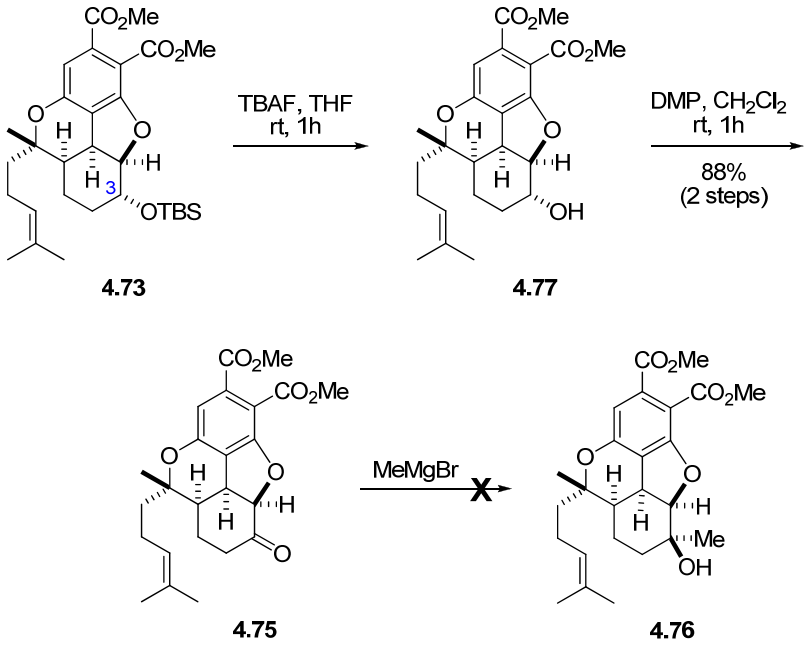
#### 4.9.1 Addition of Methylmagnesium Bromide – The Snider Approach

We were now poised to install the quaternary center at C-3. Our approach focused on addition of a methyl nucleophile to ketone **4.75** (Scheme 4.26). We envisioned exploiting the rigid tetracyclic core to direct a methyl nucleophile from the less hindered face, thus, installing the methyl group on the convex side of the ring system. This is a tactic similar to that described by Snider and coworkers in their synthesis of the bisabosqual stereochemical array (see Chapter 1).[51, 52]




**Scheme 4.26.** Strategy for addition of a methyl nucleophile.

The synthesis of ketone **4.75** commenced with liberation of the secondary alcohol at C-3 of substrate **4.73** through treatment with TBAF in tetrahydrofuran. Deprotection under acidic conditions generally resulted in degradation and desired product was not isolated. A Dess-Martin periodinane[53] oxidation in methylene chloride afforded the requisite ketone in 88% yield (two steps from substrate **4.73**). Exploratory attempts to add methylmagnesium bromide to the keto group gave multiple spots by TLC suggesting that this reagent would not be selective for a single product. This result was discouraging since the Snider substrate (**1.18**) proceeded in high yield and diastereoselectivity, however, their system lacked the diester moiety found in our system.[51] Therefore, alternative methods for methyl addition were examined.

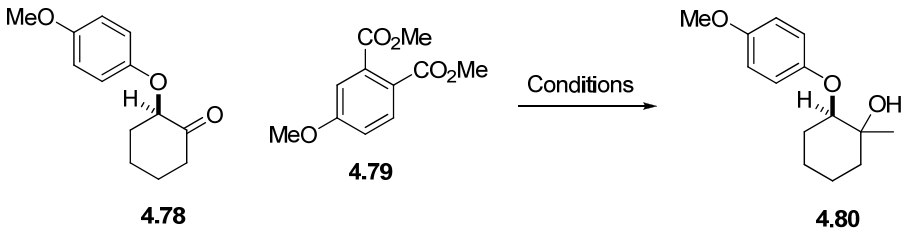



**Scheme 4.27.** Formation of ketone **4.75** and attempts at MeMgBr addition.

### 4.9.2 Model System Studies for Methyl Addition

We decided to use a dual substrate model system shown in Table 4.4 to investigate chemoselective methyl additions to a ketone (**4.78**) in the presence of esters (**4.79**). We determined that, in this system, methylmagnesium bromide effectively added to ketone **4.78** without significant reaction of the esters only at -78 °C. However, no reaction was observed with tetracyclic ketone **4.75** at -78 °C and attempts at warming resulted in side product formation. Next, we explored the addition of sulfur ylides to ketone **4.78**.[54] While we were pleased to find that both trimethylsulfoxonium iodide and trimethylsulfonium iodide affectively added to ketone without affecting the esters, the epoxide would require eventual opening to provide the desired product. Furthermore, there is evidence on related systems that suggests the stereochemical outcome of these reactions is not straightforward.[55] Efforts to add reagents such as $MeTi(iPrO)_3$,[56] DABAL-$Me_3$[57] and $AlMe_3$[58] in tetrahydrofuran all resulted in side product formation or recovery of starting material. However, when the dual model system (ketone **4.78** and diester **4.79**) was subjected to trimethylaluminum in a non-coordinating solvent such as toluene, the reaction proceeded cleanly, forming the desired tertiary alcohol **4.80** with no evidence of degradation of the esters even upon heating.

**Table 4.4.** Analysis of methyl addition chemistry on a model system. Reactions analyzed by GC-MS and/or NMR of the crude reaction mixture.




**4.78** **4.79** **4.80**

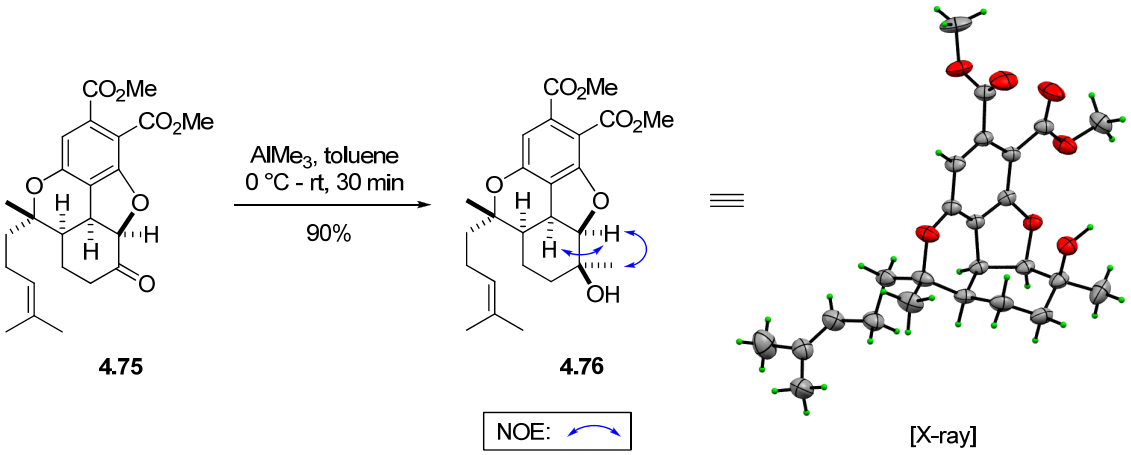
| Conditions | Selective for Ketone[a, (b)] |
|---|---|
| MeMgBr | * (-78 °C only) |
| $Me_3S(O)^+I^-$ | * (Requires epoxide opening) |
| $Me_3S^+I^-$ | * (Requires epoxide opening) |
| MeTi(*i*PrO)$_3$ | (Side Product Observed) |
| DABAL-Me$_3$ | (Recovered SM) |
| AlMe$_3$/THF | (Recovered SM) |
| AlMe$_3$/toluene | * (rt) |

[a] Asterisks indicates selectivity for ketone over esters

[b] (conditions and observations)

### 4.9.3 Chemo- and Diastereoselective Addition of Trimethylaluminum

Treatment of ketone **4.75** with trimethylaluminum in toluene cleanly provided the anticipated tertiary alcohol **4.76** as a single diastereomer in excellent yield.[58-61] The protons of the newly introduced methyl group had a chemical shift of δ 1.27 ppm, similar to the protons at δ 1.31 ppm observed in the $^1$H NMR of authentic bisabosqual A (Figure 4.6).[25] Snider and coworkers showed that the epimer on their model system (**1.14**) was shifted upfield to δ 0.87 ppm, thus, providing evidence that the desired diastereomer was prepared.




**Scheme 4.28.** Chemo- and diastereoselective methyl addition with trimethylaluminum and X-ray crystal structure of **4.76**. Non-hydrogen atoms are displayed at a 50% probability level.

A clear NOE signal was also observed between the methyl group and the C-4 hydrogen; this signifies that these protons are on the same face of the ring system (Scheme 4.28). Furthermore, unambiguous assignment of the five contiguous stereocenters was confirmed by X-ray crystallography of this diester (**4.76**). The C-3' ester is almost in plane with the aryl ring, presumably because of electron density in conjugation with the *ortho* and *para* oxygen substituents; on the other hand, the C-4' ester sits perpendicular to the ring.

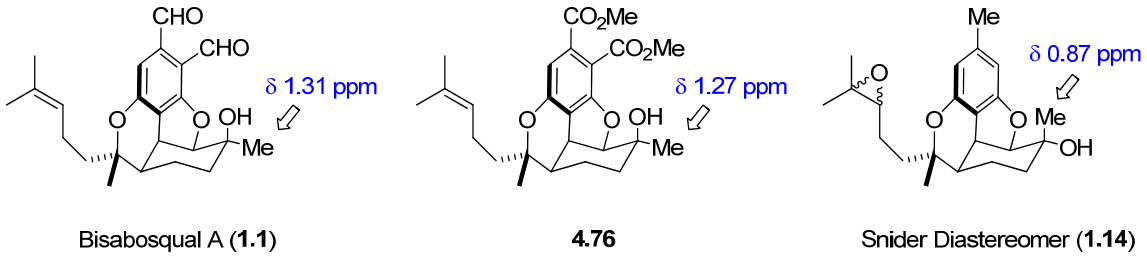
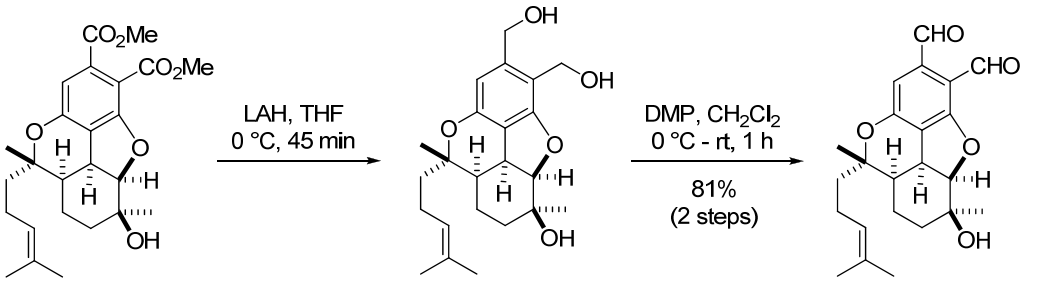



**Figure 4.6.** Comparison of the methyl group shifts.

**4.10 Synthesis of Bisabosqual A**

All that remained for the completion of bisabosqual A was elaboration of the phthalaldehyde functionality at C-7' and C-8'. Initial examination into the direct conversion from the diesters to the dialdehyde suggested a reduction to the diol and subsequent oxidation might be a superior approach. A survey of a small subset of reducing agents on a simple model system indicated lithium aluminum hydride to be a suitable reagent for this conversion (not shown, see experimental for details). Toward this end, reduction of diester **4.76** was achieved with LAH in tetrahydrofuran at 0 °C to give diol **4.81** (Scheme 4.29). However, attempts to chromatograph this material on silica gel resulted in degradation, thus indicating this compound was not stable to purification conditions. Consequently, after filtering through Celite, diol **4.81** was used directly in the next step.




**Scheme 4.29.** Synthesis of bisabosqual A.

Next, we were pleased to find that when diol **4.81** was subjected to Dess-Martin periodinane in methylene chloride, bisabosqual A was isolated in 81% yield (two steps from diester **4.76**). Dess-Martin reagent was found to be superior to both Swern and barium manganate oxidation conditions.[62] The $^{1}$H NMR and $^{13}$C NMR spectroscopic data of this product

was indistinguishable from that reported for the originally isolated (+)-bisabosqual A. Moreover, the structure of our synthetic (±)-bisabosqual A was further confirmed by X-ray crystallographic analysis (Figure 4.7).

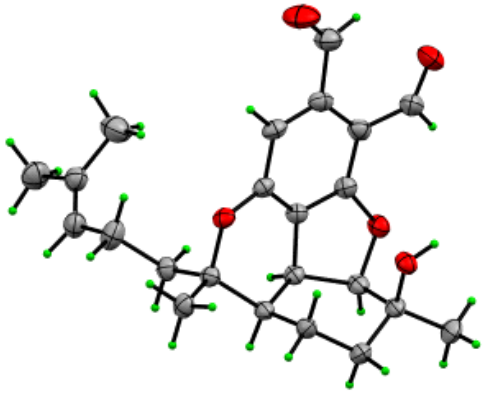
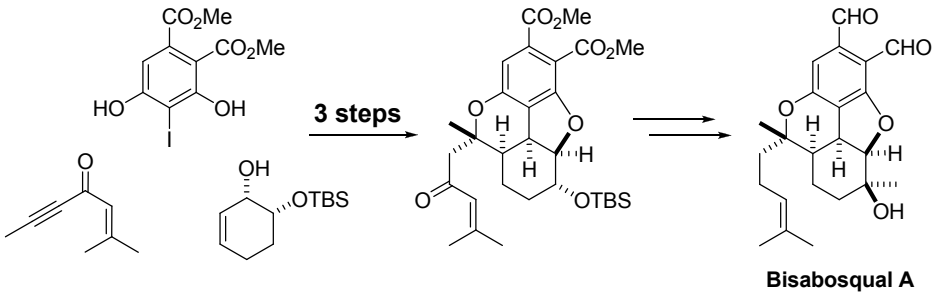



**Figure 4.7.** X-ray crystal structure of bisabosqual A. Non-hydrogen atoms are displayed at a 50% probability level.

**4.11 Conclusions:**

This total synthesis of (±)-bisabosqual A (**1.1**) is the first synthesis of a bisabosqual.[63] The key step, a 5-*exo*, 6-*exo* radical cyclization, establishes two rings and sets three of the five stereogenic centers (two of them with complete specificity) in the product. This strategy showcases the utility of radical cyclizations to access complex *cis*-fused polycyclic ring systems. It also highlights the functional group selectivity of the trimethylaluminum reagent and the high regioselectivity of the Trost–Hutchins reductive deoxygenation. The doubly convergent synthesis requires 14 steps (longest linear sequence) from commercially available materials (Scheme 4.30). Additionally, the enantioselective synthesis of cyclohexenol **4.6** (Scheme 4.14), offers entry to an asymmetric synthesis of bisabosqual A.

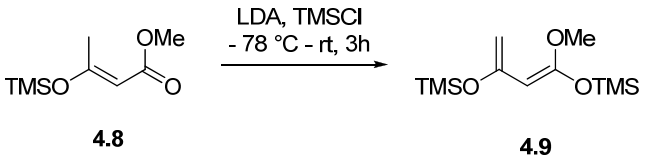



**Scheme 4.30.** The doubly convergent synthesis of bisabosqual A.

## 4.12 Experimental Section

### *General Methods*

Unless otherwise stated, all air and moisture-sensitive reactions were performed in oven-dried glassware under nitrogen. Unless otherwise stated, all commercially available chemicals, reagents and solvents were used as received. Triethylborane and tri-*sec*-butylborane were purchased from Sigma-Aldrich as solutions in THF or hexanes. Reactions were monitored by thin layer chromatography (TLC) performed on Analtech, Inc. silica gel GF 250 μm plates and were visualized with ultraviolet (UV) light (254 nm) and/or $KMnO_4$ staining or by UPLC-MS (Waters Acquity, ESCI (ESI +/-, APCI +/-)). Gas chromatography – mass spectrometry (GC-MS) was performed with an Agilent 5890 GC Oven and an Agilent 5973 Mass Selective Detector. Silica gel flash chromatography was performed with RediSep®Rf normal phase silica flash columns on a CombiFlash Rf system from Teledyne Isco, Inc. $^{1}H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra were recorded on a Varian-Inova 400 (400 MHz and 101 MHz, respectively), a Bruker 400 (400 MHz and 101 MHz, respectively), or a Bruker 500 (500 MHz and 126 MHz, respectively) spectrometer. Chemical shifts are reported in ppm relative to $CHCl_3$ ($^{1}H$, $\delta$ = 7.26 and $^{13}C$ NMR $\delta$ = 77.0). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; spt, septet; m, multiplet; br s, broad singlet. Melting points are uncorrected. Infrared (IR) spectra were recorded with a Thermo-Nicolet Avatar 360 FT-IR. High-resolution mass spectra (HRMS) were acquired on an Agilent model 6220 MS(TOF).



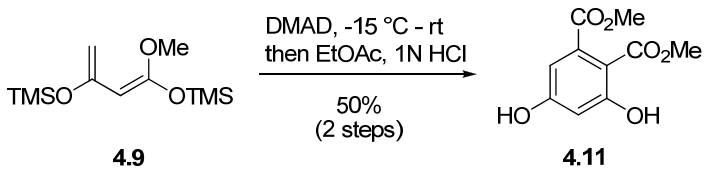

**4.8** **4.9**

**4-methoxy-2,2,8,8-tetramethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene (4.9):**

To a stirred solution of diisopropyl amine (10.4 g, 103 mmol, 1.3 equiv.) in THF (100 mL) at -78 °C was added *n*BuLi (38.0 mL, 2.5 M in hexanes, 94.8 mmol, 1.2 equiv.) over a period of 10 minutes. The mixture was warmed to 0 °C and stirred for 15 minutes then cooled back down to -78 °C and **4.8** (15.0 g, 79 mmol, 1 equiv.) was added over a period of 5 minutes. After stirring for 30 minutes, TMSCl (12.9 g, 119 mmol, 1.5 equiv.) was added over a period of 10 minutes and then the mixture was warmed to room temperature and stirred an additional 3 hours. The mixture was concentrated under reduced pressure and filtered through celite, washing with hexanes to rid of a white precipitate. The mixture was concentrated under reduced pressure again to afford **4.9** (20.5 g, 100%) as an amber oil which was used directly in the cycloaddition without additional purification. The spectroscopic data is consistent with that previously reported.[1]

$^{1}$H NMR (400MHz, $CDCl_3$) δ 4.47 (s, 1H), 4.14 (d, *J*=1.4 Hz, 1H), 3.94 (d, *J*=1.4 Hz, 1H), 3.55 (s, 3H), 0.24 (s, 9H), 0.21 (s, 9H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 158.7, 153.5, 89.4, 77.8, 55.1, 0.6, 0.4 ppm




**4.9** **4.11**

**Dimethyl 3,5-dihydroxyphthalate (4.11):**

To a round bottom flask containing DMAD (5.09 g, 35.8 mmol, 1.5 equiv.) at an internal temperature of -15 °C was added **4.9** (6.23 g, 23.9 mmol, 1 equiv.) over a period of 30 minutes, while maintaining the internal temperature between -15 °C and -20 °C. The mixture was warmed to room temperature and stirred for 1 hour until crude NMR indicated consumption of diene. The mixture was poured over EtOAc (150 mL) and washed with 0.1N HCl. The organic fraction was transferred to an Erlenmeyer flask and 1N HCl (150 mL) was added and the biphasic mixture was stirred vigorously at room temperature for 2 hours. The organic phase was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to yield a crude amber oil. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **4.11** (2.7 g, 50 % yield) as a pale yellow solid. Recrystallization was performed from $CH_2Cl_2$/Heptane to obtain the X-ray crystal structure. The spectroscopic data is consistent with that previously reported.[1]

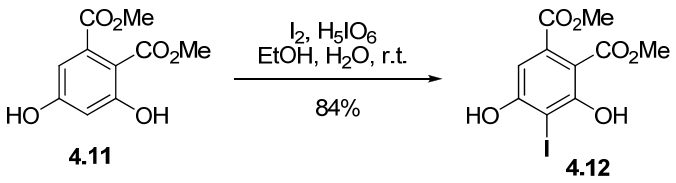
$^1$H NMR (500MHz, $CDCl_3$) δ 10.97 (s, 1H), 7.25 (s, 1H), 6.46 (d, *J*=2.4 Hz, 1H), 6.41 (d, *J*=2.4 Hz, 1H), 3.89 (s, 3H), 3.87 ppm (s, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 170.3, 169.0, 163.6, 161.4, 137.1, 108.1, 104.9, 102.7, 53.0, 52.7

FTIR ($cm^{-1}$) = 3349, 2955, 1709, 1668, 1618, 1590, 1463.

mp = 125 – 126.5 °C

HRMS (ESI) calculated for $C_{10}H_{11}O_6$ $[M+H]^+$ 227.0550, found 227.0555.




**Dimethyl 3,5-dihydroxy-4-iodophthalate (4.12):**

To a stirred solution of **4.11** (5.2 g, 0.023 mol) in EtOH (150 mL) was added $I_2$ (3.5 g, 0.0138 mol, 0.6 equiv.) in one portion followed by $H_5IO_6$ (1.05 g, 4.6 mmol, 0.2 equiv.) as a solution in water (4 mL). The reaction mixture was stirred at room temperature for 6 hours and then it was concentrated under reduced pressure. EtOAc was added and the resulting mixture was washed with 10% aqueous $Na_2S_2O_3$ and brine. The organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (EtOAc/Heptane) to afford **4.12** (6.8 g, 84% yield) as a white solid. A recrystallization from $CH_2Cl_2$/Heptane was performed to obtain an X-ray crystal structure. The spectroscopic data is consistent with that previously reported in the Parker laboratory.[3]

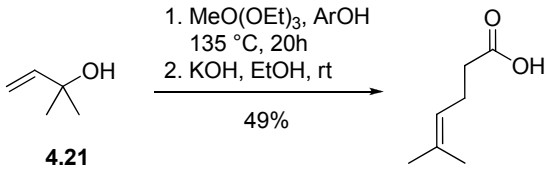
$^1$H NMR (400MHz, $CDCl_3$) δ 12.00 (s, 1H), 6.63 (s, 1H), 6.19 (s, 1H), 3.91 (s, 3H), 3.88 ppm (s, 3H).

$^{13}$C NMR (126 MHz, $CDCl_3$) δ 168.8, 168.8, 162.1, 160.4, 137.3, 106.7, 102.7, 78.3, 53.1, 52.9.

FTIR ($cm^{-1}$) = 3219, 1691, 1665, 1595, 1438, 1409, 1331, 1251 $cm^{-1}$.

mp = 153 – 155 °C

HRMS (ESI) calculated for $C_{10}H_{10}IO_6$ $[M+H]^+$ 352.9515, found 352.9517.




**4.21** **4.22**

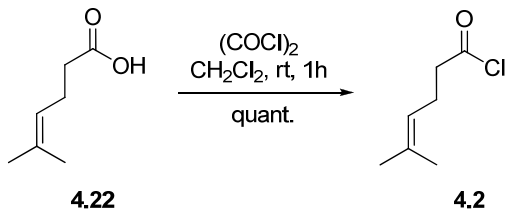
**5-methylhex-4-enoic acid (4.22):**

To a stirred solution of **4.21** (5.0 g, 0.058 mol) and 2,3-difluorophenol (0.45 g, 0.0035 mol, 0.06 equiv.) in triethyl orthoacetate (84.7 g, 0.52 mol, 9 equiv.) was heated to reflux (145 °C) for 20 hours. The mixture was allowed to cool to room temperature and $Et_2O$ was added and then washed with 0.5N HCl and brine. The organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was added to a stirred solution of KOH (10 mL, 5N solution) in ethanol (100 mL) and the mixture was heated to 70 °C for 6 hours. The mixture was allowed to cool to room temperature, poured over water and acidified to pH 3 with concentrated HCl. The mixture was extracted with $Et_2O$ (3x) and the combined organic fraction was washed with 0.5N HCl, then dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to yield a crude orange oil. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **4.22** (3.6 g, 49% yield) as a pale yellow oil. The spectroscopic data is consistent with that previously reported.[6, 7]

$^1$H NMR (400MHz, $CDCl_3$) δ 10.26 (br. s., 1H), 5.16 - 5.05 (m, 1H), 2.40 - 2.35 (m, 2H), 2.35 - 2.28 (m, 2H), 1.69 (d, *J*=1.2 Hz, 3H), 1.62 (d, *J*=0.8 Hz, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 180.02, 133.36, 122.03, 34.28, 25.63, 23.30, 17.62

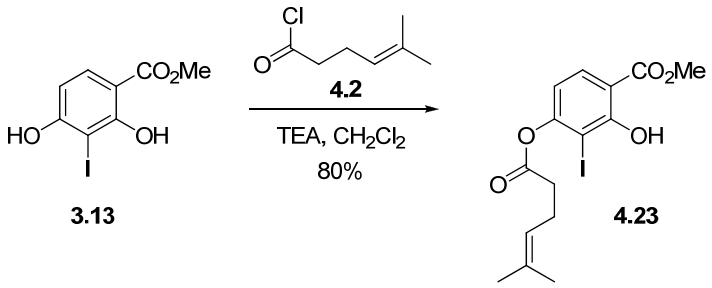
FTIR ($cm^{-1}$) = 2970, 2917, 1706, 1412, 1281




**4.22** **4.2**

**5-methylhex-4-enoyl chloride (4.2):**

To a stirred solution of **4.22** (256 mg, 2.0 mmol) in $CH_2Cl_2$ (4 mL) was added oxalyl chloride (305 mg, 2.4 mmol, 1.2 equiv.) over a period of 10 minutes. The mixture was stirred at room temperature for 1 hour and then the mixture was concentrated under reduced pressure to yield a crude yellow oil. The crude residue was used directly in following steps without additional purification.




**3.13** **4.23**

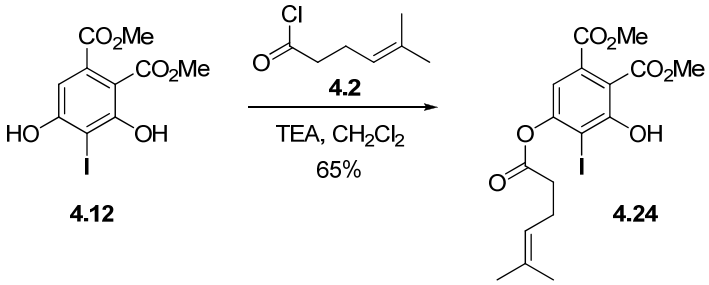
**Methyl 2-hydroxy-3-iodo-4-(5-methylhex-4-enoyloxy)benzoate (4.23):**

To a stirred solution of **3.13** (167 mg, 0.570 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C was added TEA (69 mg, 0.68 mmol, 1.2 equiv.) followed by **4.2** (83 mg, 0.57 mmol, 1 equiv.) over a period of 5 minutes. The mixture was allowed to warm to room temperature and stir for 1 hour. The mixture was poured over saturated $NH_4Cl$ and extracted with $CH_2Cl_2$ (3x). The combined organic fraction was washed with brine, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/Heptane) to afford **4.23** (183 mg, 80% yield) as a white solid.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 11.86 (s, 1H), 7.87 (d, *J*=8.6 Hz, 1H), 6.69 (d, *J*=8.8 Hz, 1H), 5.20 (tdt, *J*=1.4, 2.8, 7.1 Hz, 1H), 3.97 (s, 3H), 2.70 - 2.64 (m, 2H), 2.52 - 2.44 (m, 2H), 1.72 (d, *J*=1.0 Hz, 3H), 1.67 (d, *J*=0.6 Hz, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 170.32, 169.65, 162.28, 157.30, 133.69, 130.72, 121.89, 114.23, 110.12, 82.66, 52.83, 34.70, 25.72, 23.47, 17.78

LRMS (ES+) calculated for $C_{15}H_{18}IO_5$ $[M+H]^+$ 405.2, found 405.1



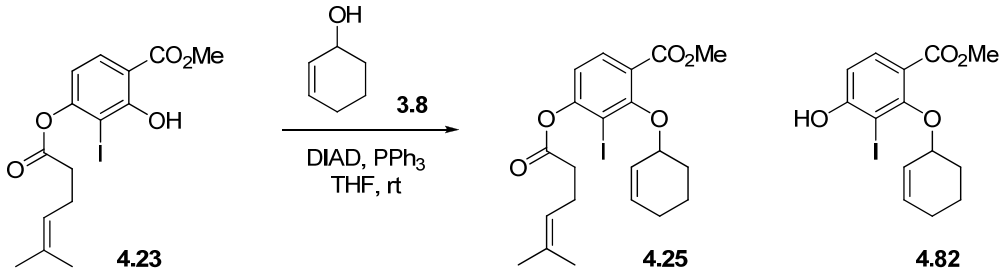

**Dimethyl 3-hydroxy-4-iodo-5-(5-methylhex-4-enoyloxy)phthalate (4.24):**

To a stirred solution of **4.12** (200 mg, 0.57 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C was added TEA (69 mg, 0.68 mmol, 1.2 equiv.) followed by **4.2** (83 mg, 0.57 mmol, 1 equiv.) over a period of 5 minutes. The mixture was allowed to warm to room temperature and stir for 1 hour. The mixture was poured over saturated $NH_4Cl$ and extracted with $CH_2Cl_2$ (3x). The combined organic fraction was washed with brine, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/Heptane) to afford **4.24** (172 mg, 65% yield) as a white solid.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 11.62 (br. s., 1H), 6.80 (s, 1H), 5.27 - 5.07 (m, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 2.69 - 2.63 (m, 2H), 2.47 (q, *J*=7.4 Hz, 2H), 1.72 (d, *J*=0.8 Hz, 3H), 1.66 (s, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 169.98, 168.72, 167.91, 161.85, 156.37, 136.32, 133.84, 121.76, 114.21, 107.77, 85.42, 53.40, 52.82, 34.64, 25.72, 23.42, 17.79

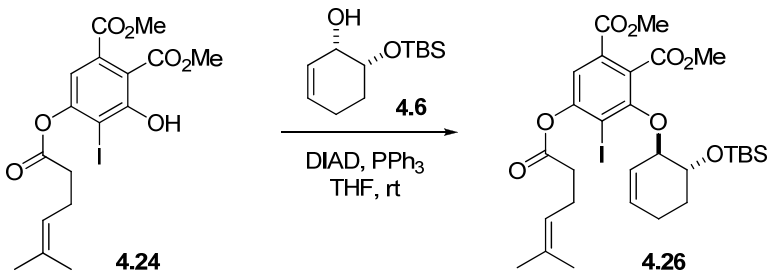
LRMS (ES+) calculated for $C_{34}H_{38}I_2NaO_{14}$ $[2M+Na]^+$ 947.4, found 947.2




**Methyl 2-(cyclohex-2-enyloxy)-3-iodo-4-(5-methylhex-4-enoyloxy)benzoate (4.25):**

To a stirred solution of **4.23** (180 mg, 0.45 mmol) in THF (5 mL) was added **3.8** (52 mg, 0.53 mmol, 1.2 equiv.) and $PPh_3$ (187 mg, 0.712 mmol, 1.6 equiv.) followed by DIAD (144 mg, 0.712 mmol, 1.6 equiv.) over a period of 15 minutes. The reaction mixture was stirred at room temperature for 17 hours then poured over water. The mixture was extracted with EtOAc (3x) and then dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/Heptane) to afford **4.25** and **4.82** (80 mg) as a 2:1 mixture (**4.25**:**4.82**). Attempts at separation by TLC were not successful. The $^1$H NMR was extracted from the major isomer.

$^1$H NMR (400MHz, $CDCl_3$) δ 7.73 (d, *J*=8.6 Hz, 1H), 6.86 (d, *J*=8.4 Hz, 1H), 6.01 - 5.65 (m, 2H), 5.22 - 5.09 (m, 1H), 4.57 - 4.46 (m, 1H), 3.84 (s, 3H), 2.64 - 2.59 (m, 2H), 2.43 (q, *J*=7.3 Hz, 2H), 2.16 - 2.04 (m, 1H), 2.03 - 1.87 (m, 3H), 1.77 - 1.69 (m, 1H), 1.67 (d, *J*=0.8 Hz, 3H), 1.62 (s, 3H), 1.59 - 1.49 (m, 1H)




**(±)-Dimethyl-3-((1S,6R)-6-(tert-butyldimethylsilyloxy)cyclohex-2-enyloxy)-4-iodo-5-(5-methylhex-4-enoyloxy)phthalate (4.26):**

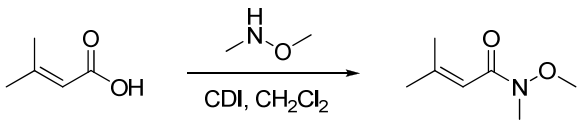
To a stirred solution of **4.24** (167 mg, 0.35 mmol) in THF (5 mL) was added **4.6** (120mg, 0.53 mmol, 1.5 equiv.) and $PPh_3$ (138 mg, 0.53 mmol, 1.5 equiv.) followed by DIAD (106 mg, 0.53 mmol, 1.5 equiv.) over a period of 5 minutes. The mixture was stirred at room temperature for 3 hours and then poured over water. The mixture was extracted with $CH_2Cl_2$ (3x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **4.26** (40 mg, 17% yield) as a colorless oil.

$^1$H NMR (400MHz, $CDCl_3$) δ 7.45 (s, 1H), 5.95 (td, *J*=3.4, 9.9 Hz, 1H), 5.61 - 5.55 (m, 1H), 5.24 - 5.15 (m, 1H), 4.73 - 4.66 (m, 1H), 4.22 (td, *J*=3.0, 6.6 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.69 - 2.63 (m, 2H), 2.48 (q, *J*=7.4 Hz, 2H), 2.28 - 2.14 (m, 1H), 2.11 - 2.01 (m, 1H), 2.01 - 1.91 (m, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 170.34, 166.17, 164.62, 156.28, 152.99, 133.74, 133.38, 129.78, 128.06, 122.43, 121.84, 119.38, 97.00, 81.48, 68.88, 52.79, 52.77, 34.59, 26.80, 25.75, 25.70, 23.45, 21.93, 18.08, 17.77, -4.76, -4.86

FTIR ($cm^{-1}$) = 2951, 2929, 2856, 1771, 1731, 1252, 1230, 1085

HRMS (ESI) calculated for $C_{29}H_{41}INaO_8Si$ $[M+Na]^+$ 696.1536, found 696.1535.




**4.30** **4.31**

**N-methoxy-N,3-dimethylbut-2-enamide (4.31):**

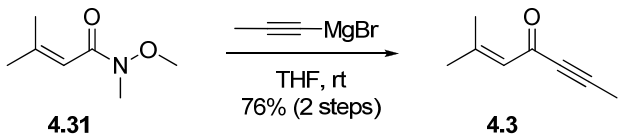
To a stirred solution of **4.30** (10.0 g, 99.9 mmol) in $CH_2Cl_2$ at 0 °C was added CDI (19.4 g, 120 mmol, 1.2 equiv.) over a period of 15 minutes. The mixture was allowed to warm to room temperature and stir for 1 hour. Then, *N*,*O*-Dimethylhydroxylamine hydrochloride (11.7 g, 120 mmol, 1.2 equiv.) was added in portions over a period of 15 minutes and stirred at room temperature for 6 hours. The mixture was washed with 1N HCl and brine, then dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to yield **4.31** (14.2g) as a light yellow oil. The crude residue was used directly in the next step without additional purification. The spectroscopic data is consistent with that previously reported.[3, 10]

$^1$H NMR (400MHz, $CDCl_3$) δ 6.02 (br. s., 1H), 3.58 (s, 3H), 3.10 (s, 3H), 2.04 (d, *J*=1.4 Hz, 2H), 1.81 (d, *J*=1.4 Hz, 2H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 167.8, 152.8, 114.1, 61.1, 35.9, 27.3, 19.9 ppm

FTIR ($cm^{-1}$) = 2972, 2937, 1652, 1445, 1366

HRMS (ESI) calculated for $C_7H_{14}NO_2$ $[M+H]^+$ 144.1019, found 144.1023.




**4.31** **4.3**

**2-methylhept-2-en-5-yn-4-one (4.3):**

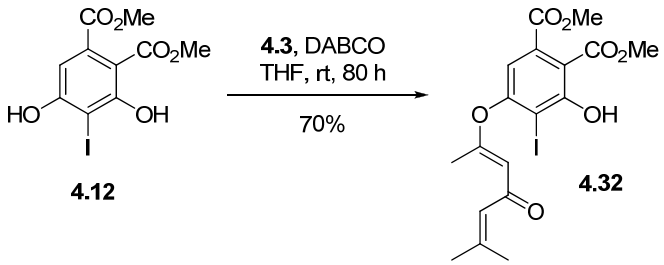
To a stirred solution of **4.31** (4.0 g, 28 mmol) in THF (50 mL) at -78 °C was added 1-propynylmagnesium bromide (55.8 mL, 0.5M in THF, 55.8 mmol, 2 equiv.) over a period of 30 minutes. The mixture was warmed to room temperature and stirred for 18 hours. The mixture was cooled to 0 °C and saturated $NH_4Cl$ was added and then was poured over water. The mixture was extracted with $Et_2O$ (4x) and the combined organic fraction was washed with 0.1N HCl (2x) and brine (1x). The $Et_2O$ layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The mixture was passed through a plug of silica gel ($Et_2O$/pentane) to afford **4.3** (2.59 g, 76% yield) as a pale yellow oil. The spectroscopic data is consistent with that previously reported.[3, 10]

$^1$H NMR (500MHz, $CDCl_3$) δ 6.13 (spt, *J*=1.3 Hz, 1H), 2.20 (d, *J*=1.5 Hz, 3H), 2.01 (s, 3H), 1.92 (d, *J*=1.2 Hz, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 176.8, 157.5, 126.0, 88.3, 82.5, 27.8, 21.0, 4.1 ppm

FTIR ($cm^{-1}$) = 2978, 2213, 1650, 1607, 1440, 1378

HRMS (ESI) calculated for $C_8H_{11}O$ $[M+H]^+$ 123.0804, found 123.0807




**(*E*)-dimethyl 3-hydroxy-4-iodo-5-(6-methyl-4-oxohepta-2,5-dien-2-yloxy)phthalate (4.32):**

To a stirred solution of **4.12** (8.00 g, 22.7 mmol) and **4.3** (4.2 g, 34 mmol, 1.5 equiv.) in THF (150 mL) was added DABCO (0.51g, 4.5 mmol, 0.2 equiv.) in one portion at room temperature. The mixture was stirred at room temperature for 80 hours and then $CH_2Cl_2$ was added followed by water. The aqueous layer was carefully adjusted to pH 3 with a 1N aqueous solution of $KHSO_4$ and extracted with $CH_2Cl_2$ (2x). The organic layer was dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The crude product was purified by silica gel chromatography (EtOAc/Heptane) to afford **4.32** (7.52 g, 70% yield, 84% yield based on recovered starting material) of a white solid. A portion was recrystallized from EtOAc/Heptane to obtain an X-ray crystal structure. The spectroscopic data is consistent with that previously reported in the Parker laboratory.[3]

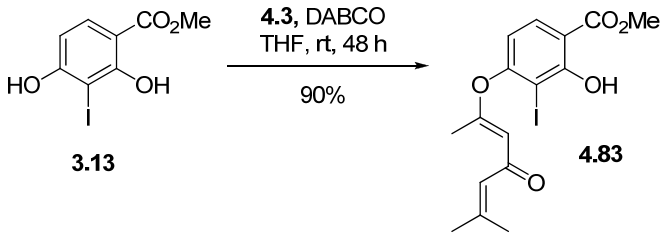
$^1$H NMR (400 MHz, $CDCl_3$) δ ppm 11.70 (s, 1 H), 6.70 (s, 1 H), 5.83-5.80 (m, 1 H), 5.30 (s, 1 H), 3.95 (s, 3 H), 3.89 (s, 3 H), 2.52 (s, 3 H), 2.14 (d, *J*=1.2 Hz, 3 H), 1.83 (d, , *J*=1.2 Hz, 3 H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 189.5, 168.6, 168.5, 167.9, 162.4, 158.8, 154.9, 136.9, 126.3, 112.8, 108.4, 107.1, 84.5, 53.4, 52.9, 27.7, 20.6, 18.4 ppm

FTIR ($cm^{-1}$) = 2953, 1737, 1675, 1621, 1584, 1438, 1390, 1323, 1252, 1191, 1161, 1100, 1056

mp = 116.5 – 119 °C

HRMS (ESI) calculated for $C_{18}H_{20}IO_7$ $[M+H]^+$ 475.0248, found 475.0238.




3.13 4.83

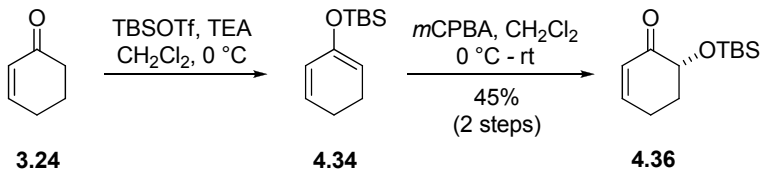
**(*E*)-methyl 2-hydroxy-3-iodo-4-(6-methyl-4-oxohepta-2,5-dien-2-yloxy)benzoate (4.83):**

A solution of **3.13** (150mg, 0.51 mmol), **4.3** (74 mg, 0.61 mmol, 1.2 equiv.) and DABCO (11 mg, 0.10 mmol, 0.2 equiv.) in THF (2.5 mL) was stirred at room temperature for 48 hours. The mixture was concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **4.83** (190 mg, 90% yield) as a white solid. A single crystal was obtained by recrystallization from $Et_2O$. The crystal structure confirmed the side chain olefin to be the *E* isomer.

$^1$H NMR (400MHz, $CDCl_3$) δ 11.91 (s, 1H), 7.89 (d, *J*=8.6 Hz, 1H), 6.63 (d, *J*=8.6 Hz, 1H), 5.83 - 5.79 (m, 1H), 5.25 (d, *J*=0.6 Hz, 1H), 3.99 (s, 3H), 2.54 (s, 3H), 2.13 (d, *J*=1.2 Hz, 3H), 1.81 (d, *J*=1.2 Hz, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 189.70, 169.62, 169.14, 162.79, 159.67, 154.42, 131.18, 126.37, 113.29, 109.68, 107.60, 82.09, 52.86, 27.64, 20.58, 18.53

LRMS (ES+) calculated for $C_{16}H_{17}IO_5$ $[M+H]^+$ 417.0, found 416.9.



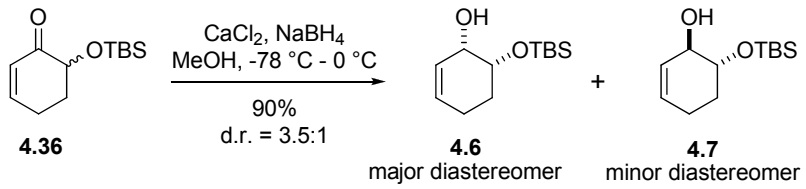

**3.24** **4.34** **4.36**

**(±)- 6-(tert-butyldimethylsilyloxy)cyclohex-2-enone (4.36):**

To a stirred solution of **3.24** (1.45 g, 15.1 mmol) in $CH_2Cl_2$ (80 mL) and TEA (2.44 g, 24.1 mmol, 1.6 equiv.) at 0 °C was added TBSOTf (5.0 g, 18.9 mmol, 1.25 equiv.) over a period of 20 minutes and the mixture was stirred at 0 °C for 1 hour. The mixture was poured over ice-cold saturated $NaHCO_3$ and extracted with hexanes (2x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford **4.34** as a light yellow oil which was used directly without additional purification. To a stirred solution of crude **4.34** in $CH_2Cl_2$ (100 mL) at 0 °C was added *m*CPBA (3.13 g, 18.1 mmol, 1.2 equiv.) over a period of 30 minutes. The mixture was warmed to room temperature and stirred for an additional 45 minutes (as determined by TLC). The mixture was washed with saturated $NaHCO_3$ and brine, then dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **4.36** (1.54 g, 45% yield) as a colorless oil. The reaction was also run on a 45 mmol scale to afford **4.36** (4.11 g, 40% yield). The spectroscopic data is consistent with that previously reported.[14]

$^1$H NMR (400MHz, $CDCl_3$) δ 6.91 - 6.85 (m, 1H), 6.01 - 5.94 (m, 1H), 4.16 (dd, *J*=4.9, 11.3 Hz, 1H), 2.57 - 2.35 (m, 2H), 2.20 - 2.11 (m, 1H), 2.11 - 1.97 (m, 1H), 0.90 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 198.6, 149.4, 128.4, 74.1, 32.4, 25.7, 25.2, 18.4, -4.5, -5.4 ppm.




**4.36** **4.6** major diastereomer **4.7** minor diastereomer

**(±)- (1S,6R)-6-(tert-butyldimethylsilyloxy)cyclohex-2-enol (4.6):**

To a stirred solution of **4.36** (6.00 g, 26.5 mmol) in MeOH (150 mL) was added $CaCl_2$ (4.40 g, 39.8 mmol, 1.5 equiv.). The mixture was cooled to -78 °C and $NaBH_4$ (1.20 g, 31.8 mmol, 1.2 equiv.) was added in portions over a period of 20 minutes. The mixture was stirred at -78 °C for 6 hours and then the mixture was allowed to slowly warm to 0 °C and stirred for 1 hour. Saturated aqueous $NaHCO_3$ was added and the resulting mixture was extracted with $CH_2Cl_2$ (4x). The combined organic solution was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The $^1$H NMR spectrum of the crude product indicated a 3.5:1 mixture of diastereomers favoring **4.6.** The mixture was purified via silica gel flash chromatography (EtOAc/Heptane) to afford **4.6** (4.11 g, 68% yield) as a colorless oil and **4.7** (1.34 g, 22% yield) as a colorless oil. The spectroscopic data is consistent with that previously reported.[3]

$^1$H NMR (400MHz, $CDCl_3$) δ 5.88 - 5.81 (m, 1H), 5.75 - 5.69 (m, 1H), 4.05 - 3.97 (m, 1H), 3.89 - 3.82 (m, 1H), 2.54 (br s, 1H), 2.25 - 2.13 (m, 1H), 2.06 - 1.94 (m, 1H), 1.89 - 1.77 (m, 1H), 1.64 - 1.53 (m, 1H), 0.91 (s, 9H), 0.11 (s, 6H).

$^{13}$C NMR (101MHz, $CDCl_3$): δ 130.8, 127.0, 70.3, 66.5, 26.1, 25.8, 23.8, 18.1, -4.5, -4.9 ppm.

FTIR ($cm^{-1}$) = 3559, 3029, 2952, 2929, 2886, 2857, 1463, 1252, 1094.

HRMS (ESI) calculated for $C_{12}H_{24}O_2SiNa$ $[M+Na]^+$ 251.1438, found 251.1444.

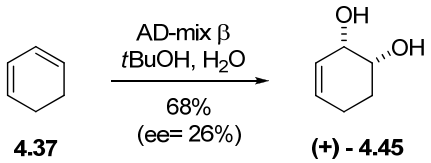
**(±)- (1R,6R)-6-(tert-butyldimethylsilyloxy)cyclohex-2-enol (4.7)**:

$^{1}$H NMR (400MHz, $CDCl_3$) δ 5.74 - 5.66 (m, 1H), 5.62 - 5.56 (m, 1H), 4.07 - 3.99 (m, 1H), 3.64 (ddd, *J*=3.5, 7.0, 10.8 Hz, 1H), 2.17 - 2.08 (m, 2H), 2.06 (d, *J*=3.7 Hz, 1H), 1.86 - 1.77 (m, 1H), 1.69 - 1.57 (m, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 128.8, 127.8, 74.2, 73.1, 29.1, 25.8, 24.6, 18.1, -4.3, -4.6 ppm

FTIR ($cm^{-1}$) = 3364, 3028, 2929, 2890, 2856, 1463

HRMS (ESI) calculated for $C_{12}H_{24}O_2SiNa$ $[M+Na]^+$ 251.1438, found 251.1443.

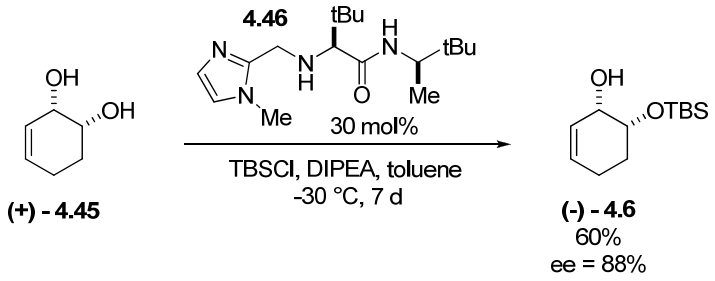



**(+)-(1R,2S)-cyclohex-3-ene-1,2-diol (4.45):**

To a stirred solution of and AD-mix β (20g) and $MeSO_2NH_2$ (2.38 g, 25 mmol) in a *t*-BuOH (30 mL) and water (30 mL) at 0 °C was added **4.37** (2.0 g, 25 mmol) over 5 minutes. The mixture was stirred at 0 °C for 8 hours followed addition of $Na_2SO_3$ (20g) and then the mixture was warmed to room temperature and stirred for 1 hour. The mixture was poured over water and extracted with $CH_2Cl_2$ (5x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/hexanes) to afford **4.45** (1.94 g, 68% yield, 26% ee) of a colorless oil. The enantiomeric purity was determined by supercritical fluid chromatography (Chiralpak IC, 4.6 mm x 25 cm, $CO_2$/Propanol (85/15), Flowrate = 2.5 mL/min). The spectroscopic data is consistent with that previously reported.[22]

$^{1}$H NMR (400MHz, $CDCl_3$) δ 5.84 - 5.78 (m, 1H), 5.67 (ddt, *J*=2.0, 4.1, 10.0 Hz, 1H), 4.11 - 4.06 (m, 1H), 3.77 (td, *J*=3.6, 9.6 Hz, 1H), 3.51 (br. s., 1H), 3.05 (s, 1H), 2.24 - 2.10 (m, 1H), 2.06 - 1.92 (m, 1H), 1.81 - 1.60 (m, 2H)

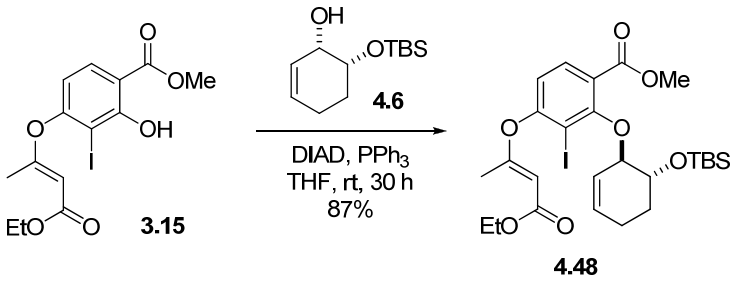
$^{13}$C NMR (101MHz, $CDCl_3$) δ 131.04, 126.83, 68.79, 66.37, 25.57, 23.48




**(-)-(1S,6R)-6-(tert-butyldimethylsilyloxy)cyclohex-2-enol (4.6):**

To a stirred solution of **4.45** (502 mg, 4.40 mmol) and (–)-(*S*)-*N*-((*R*)-3,3-Dimethylbutan-2-yl)-3,3-dimethyl-2-((1-methyl-1*H*-imidazol-2-yl)methylamino)butanamide **4.46** (407 mg, 1.32 mmol, 0.3 equiv.) in THF (3 mL) at -78 °C was added DIPEA (569 mg, 4.40 mmol, 1 equiv.) followed by TBSCl (829 mg, 5.50 mmol, 1.25 equiv.) over a period of 10 minutes. The mixture was warmed to -30 °C and stirred at this temperature for 7 days using a cryocool apparatus (reaction monitored by TLC). The mixture was cooled to -78 °C and quenched by addition of MeOH (1 mL) and DIPEA (1 mL) and allowed to warm to room temperature. Next, 0.1N $KHSO_4$ was added and the mixture was extracted with EtOAc (4x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Hexanes) to afford **4.6** (603 mg, 60% yield, 88% ee) as a colorless oil. The enantiomeric purity was determined by chiral GC analysis (Supelco Beta Dex 120, 30 m X 0.25 mm X 0.25 um. Temperature starts at 80 °C, ramp to 140 °C

at 10 °C/min, hold at 140 °C for 90 min, then ramp again to 180 °C at 5 °C/min and hold at 180 °C for 10 min.) The $^{1}$H NMR and $^{13}$CNMR are in full agreement with racemic **4.6** (*vide supra*) and to that previously reported.[21]




**(±)- methyl 2-((1R,6R)-6-(tert-butyldimethylsilyloxy)cyclohex-2-enyloxy)-4-((E)-4-ethoxy-4-oxobut-2-en-2-yloxy)-3-iodobenzoate (4.48):**

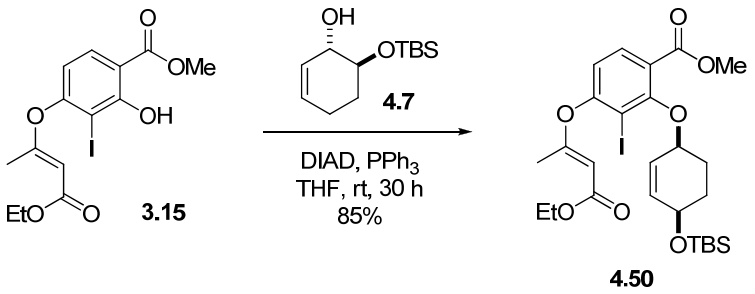
To a stirred solution of **3.15** (500 mg, 1.23 mmol) in THF (10 mL) was added **4.6** (421 mg, 1.84 mmol, 1.5 equiv.) and $PPh_3$ (482 mg, 1.84 mmol, 1.5 equiv.) followed by DIAD (373 mg, 1.84 mmol, 1.5 equiv.) over a period of 15 minutes. The mixture was stirred at room temperature for 30 hours. Next, $CH_2Cl_2$ was added and the mixture was washed with brine. The organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **4.48** (662 mg, 87% yield) as a colorless oil.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 7.74 (d, *J*=8.4 Hz, 1H), 6.83 (d, *J*=8.6 Hz, 1H), 6.04 - 5.96 (m, 1H), 5.64 - 5.55 (m, 1H), 4.73 (s, 1H), 4.32 - 4.26 (m, 1H), 4.20 - 4.14 (m, 1H), 4.06 (q, *J*=7.2 Hz, 2H), 3.86 (s, 3H), 2.50 (s, 3H), 2.30 - 2.17 (m, 1H), 2.17 - 2.08 (m, 1H), 2.08 - 1.97 (m, 1H), 1.74 - 1.65 (m, 1H), 1.53 (s, 3H), 1.18 (t, *J*=7.1 Hz, 4H), 0.78 (s, 9H), -0.03 (s, 3H), -0.07 (s, 3H)

$^{13}$C NMR (101MHz , $CDCl_3$) δ 170.3, 169.4, 167.0, 165.8, 157.4, 134.1, 132.4, 123.6, 122.4, 117.4, 97.2, 92.3, 81.8, 68.4, 59.7, 52.5, 26.2, 25.7, 21.3, 18.2, 18.1, 14.3, -4.8, -4.8

FTIR ($cm^{-1}$) = 2951, 1717, 1640, 1582, 1433, 1248, 1128

HRMS (ESI) calculated for $C_{26}H_{37}IO_7SiNa$ $[M+Na]^+$ 639.1245, found 639.1237.



4.50

**(±)- methyl 2-((1S,4R)-4-(tert-butyldimethylsilyloxy)cyclohex-2-enyloxy)-4-((E)-4-ethoxy-4-oxobut-2-en-2-yloxy)-3-iodobenzoate (4.50):**

To a stirred solution of **3.15** (500 mg, 1.23 mmol) in THF (10 mL) was added **4.7** (421 mg, 1.84 mmol, 1.5 equiv.) and $PPh_3$ (482 mg, 1.84 mmol, 1.5 equiv.) followed by DIAD (373 mg, 1.84 mmol, 1.5 equiv.) over a period of 15 minutes. The mixture was stirred at room temperature for 30 hours. Next, $CH_2Cl_2$ was added and the mixture was washed with brine. The organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **4.50** (646 mg, 85% yield) as a colorless oil.

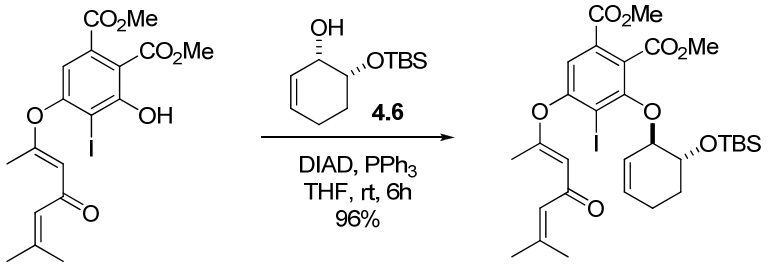
$^1$H NMR (400MHz, $CDCl_3$) δ 7.80 (d, *J*=8.6 Hz, 1H), 6.86 (d, *J*=8.6 Hz, 1H), 5.90 - 5.77 (m, 2H), 4.74 (s, 1H), 4.68 - 4.62 (m, 1H), 4.35 - 4.29 (m, 1H), 4.08 (q, *J*=7.2 Hz, 2H), 3.89 (s, 3H), 2.51 (s, 3H),

2.17 - 2.03 (m, 2H), 1.99 - 1.87 (m, 1H), 1.57 - 1.47 (m, 1H), 1.20 (t, *J*=7.1 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 170.21, 166.98, 165.60, 159.15, 157.49, 135.09, 132.69, 127.94, 123.10, 117.47, 97.35, 92.66, 80.46, 66.40, 59.77, 52.52, 30.51, 29.68, 27.17, 25.84, 18.17, 14.24, -4.59, -4.66

FTIR ($cm^{-1}$) = 2951, 2856, 1715, 1640, 1581, 1388, 1245, 1126

HRMS (ESI) calculated for $C_{26}H_{37}IO_7SiNa$ $[M+Na]^+$ 639.1245, found 639.1240.




**4.32** **4.52**

**(±)- dimethyl 3-((1R,6R)-6-(tert-butyldimethylsilyloxy)cyclohex-2-enyloxy)-4-iodo-5-((E)-6-methyl-4-oxohepta-2,5-dien-2-yloxy)phthalate (4.52):**

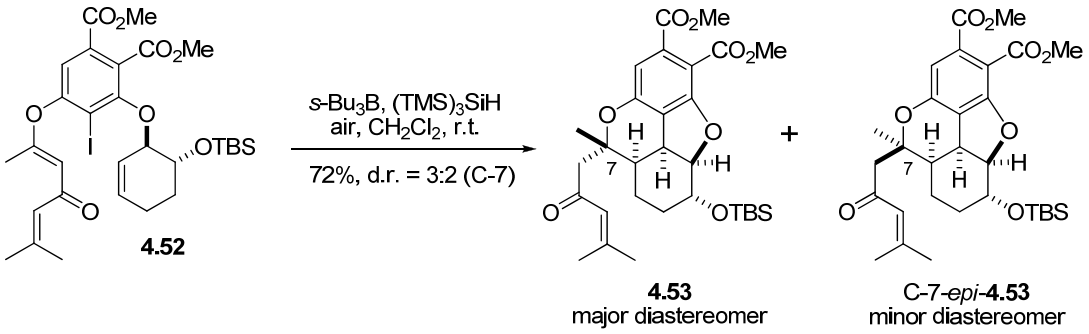
To a stirred solution of **4.32** (1.66 g, 3.50 mmol), **4.6** (0.96 g, 4.2 mmol, 1.2 equiv.) and $PPh_3$ (1.38 g, 5.25 mmol, 1.5 equiv.) in THF (35 mL) at room temperature was added DIAD (1.06 g, 5.25 mmol, 1.5 equiv.) dropwise over a period of 10 minutes. After stirring an additional 6 hours, the reaction mixture was quenched by the addition of water and the resulting mixture was extracted with EtOAc. The combined organic solution was dried with anhydrous $MgSO_4$ and then concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **4.52** (2.30 g, 96% yield) as a colorless gum.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 7.41 (s, 1H), 5.98 (dt, *J*=3.5, 10.0 Hz, 1H), 5.84 - 5.78 (m, 1H), 5.64 - 5.55 (m, 1H), 5.15 (s, 1H), 4.72 - 4.65 (m, 1H), 4.23 (dt, *J*=2.9, 6.2 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 2.55 (s, 3H), 2.30 - 2.16 (m, 1H), 2.13 (d, *J*=0.8 Hz, 3H), 2.11 - 2.02 (m, 1H), 2.01 - 1.92 (m, 1H), 1.82 (d, *J*=1.0 Hz, 3H), 1.77 - 1.67 (m, 1H), 0.84 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 189.6, 169.6, 166.2, 164.6, 157.0, 155.3, 154.6, 133.8, 130.3, 127.7, 126.4, 122.2, 118.7, 107.0, 96.7, 81.4, 68.7, 52.9, 52.9, 27.6, 26.6, 25.7, 21.7, 20.6, 18.5, 18.1, -4.7, -4.8 ppm

FTIR ($cm^{-1}$) = 2951, 2855, 1732, 1620, 1572, 1382, 1278, 1250, 1096

HRMS (ESI) calculated for $C_{30}H_{41}IO_8SiNa$ $[M+Na]^+$ 707.1507, found 707.1492.




**(±)- (2S,2aR,2a1S,5R,5aR)-dimethyl 5-(tert-butyldimethylsilyloxy)-2-methyl-2-(4-methyl-2-oxopent-3-enyl)-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7,8-dicarboxylate (4.53):**

To a stirred solution of **4.52** (2.30 g, 3.36 mmol) and $(TMS)_3SiH$ (1.25g, 3.36 mmol, 1.5 equiv.) in $CH_2Cl_2$ at room temperature was simultaneously added *s*-$Bu_3B$ (3.36 mL, 1M in THF, 3.36 mmol, 1 equiv.) and air via a syringe (10 mL). The addition procedure took place over a period of 30 min. The mixture was stirred an additional 15 minutes at room temperature and

then the mixture was concentrated under reduced pressure. The crude $^{1}$H NMR spectrum indicated a 3:2 mixture of diastereomers about C-7, favoring **4.53**. The crude residue was subjected to silica gel flash chromatography (EtOAc/Heptane) to afford 1.36 g (72% yield) of a 3:2 (**4.53**:C-7-*epi*-**4.53**) mixture of diastereomers as a pale yellow foam. Separation of diastereomers was performed by preparative HPLC (5-100% EtOH in Heptane, Phenomenex Cellulose-2, 250 x 21.2mm 5µ, Flow = 28 mL/min) to afford **4.53** (0.79 g, 42%) as a white solid and C-7-*epi*-**4.53** (0.41 g, 22%) as a pale yellow solid.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 6.69 (s, 1H), 6.01 (s, 1H), 4.90-4.84 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.61 (t, *J*=7.3 Hz, 1H), 3.25-3.17 (m, 1H), 2.77-2.62 (m, 2H), 2.47-2.39 (m, 1H), 2.15 (s, 3H), 1.88 (s, 3H), 1.80-1.71 (m, 1H), 1.70-1.62 (m, 1H), 1.52 (s, 3H), 1.32-1.19 (m, 1H), 0.85 (s, 9H), 0.92-0.79 (m, 1H), 0.04 (s, 3H), -0.07 ppm (s, 3H)

$^{13}$C NMR (100MHz, $CDCl_3$) δ 197.3, 168.4, 165.4, 159.6, 157.5, 153.0, 135.3, 124.5, 114.5, 109.7, 108.0, 95.9, 81.5, 72.5, 52.7, 52.2, 51.5, 35.6, 35.3, 30.8, 27.9, 25.7, 23.5, 20.9, 20.1, 17.9, -4.9, -5.2 ppm

FTIR ($cm^{-1}$) = 2950, 1727, 1683, 1622, 1432, 1377

mp = 54 – 58 °C

HRMS (ESI) calculated for $C_{30}H_{43}O_8Si$ $[M+H]^+$ 559.2722, found 559.2718.

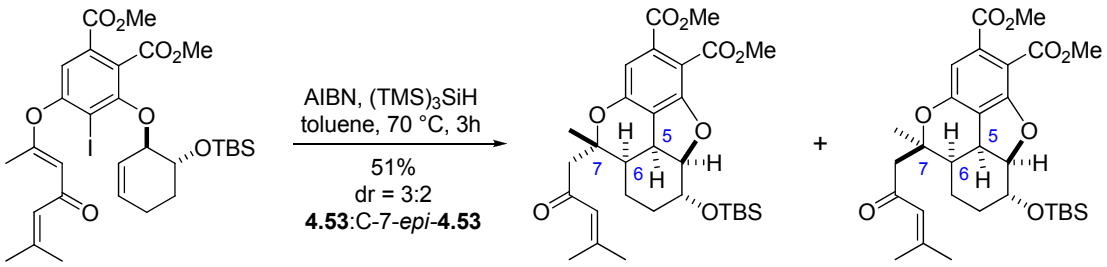
**(±)-(2R,2aR,2a1S,5R,5aR)-dimethyl 5-(tert-butyldimethylsilyloxy)-2-methyl-2-(4-methyl-2-oxopent-3-enyl)-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7,8-dicarboxylate (C-7-*epi*-4.53):**

$^{1}$H NMR (500MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.15 - 6.13 (m, 1H), 4.86 (dd, *J*=6.7, 8.2 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.63 (t, *J*=7.3 Hz, 1H), 3.20 (ddd, *J*=4.4, 6.8, 11.7 Hz, 1H), 2.98 - 2.81 (m, 2H), 2.52 - 2.43 (m, 1H), 2.15 (d, *J*=1.2 Hz, 3H), 1.91 (d, *J*=1.2 Hz, 3H), 1.65 - 1.54 (m, 2H), 1.41 (s, 3H), 1.30 - 1.17 (m, 1H), 0.84 (s, 9H), 0.87 - 0.75 (m, 1H), 0.03 (s, 3H), -0.08 (s, 3H)

$^{13}$C NMR (126 MHz, $CDCl_3$) δ 197.0, 168.5, 165.5, 159.5, 156.9, 152.7, 135.3, 124.3, 114.7, 109.9, 107.7, 95.8, 81.8, 72.5, 52.7, 52.1, 51.5, 35.6, 34.6, 30.8, 27.9, 25.7, 24.3, 20.9, 20.7, 17.9, -4.9, -5.2

FTIR ($cm^{-1}$) = 2950, 1725, 1686, 1620, 1433, 1377

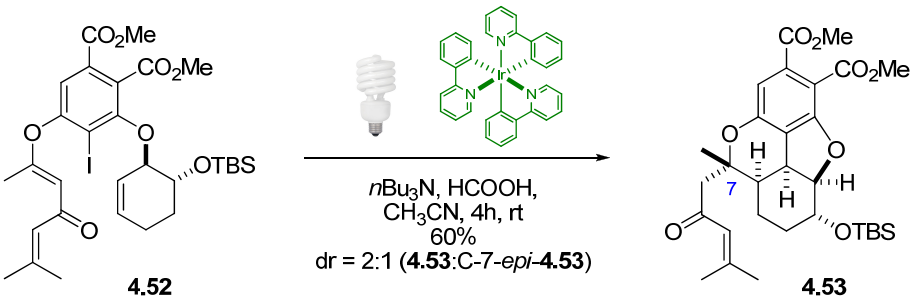
HRMS (ESI) calculated for $C_{30}H_{43}O_8Si$ $[M+H]^+$ 559.2722, found 559.2720.




**4.52** **4.53** C-7-*epi*-**4.53**

**(±)- (2S,2aR,2a1S,5R,5aR)-dimethyl 5-(tert-butyldimethylsilyloxy)-2-methyl-2-(4-methyl-2-oxopent-3-enyl)-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7,8-dicarboxylate (4.53):**

Nitrogen was bubbled through a stirred solution of **4.52** (304 mg, 0.444 mmol) in toluene (15 mL) for 15 minutes and then, AIBN (7 mg, 0.044 mmol, 0.1 equiv.) and $(TMS)_3SiH$ (221 mg, 0.888 mmol, 2 equiv.) were added. The mixture was heated to 70 °C until TLC indicated consumption of starting material (3 hours). The mixture was poured over water and extracted with EtOAc (3x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The $^1H$ NMR of the crude product indicated a 3:2 mixture of diastereomers about C-7, favoring **4.53**. The crude residue was purified by flash chromatography (EtOAc/Heptane) to afford a mixture of **4.53** and C-7-*epi*-**4.53** (126 mg, 51% yield as a 3:2 (**4.53**:C-7-*epi*-**4.53**) mixture of diastereomers) as a colorless gum. The spectroscopic data are in full agreement with that reported above.




**(±)- (2S,2aR,2a1S,5R,5aR)-dimethyl 5-(tert-butyldimethylsilyloxy)-2-methyl-2-(4-methyl-2-oxopent-3-enyl)-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7,8-dicarboxylate (4.53):**

To a stirred solution of **4.52** (99 mg, 0.14 mmol) in MeCN (10 mL) was added tributylamine (269 mg, 1.45 mmol, 10 equiv.), formic acid (66.7 mg, 1.45 mmol, 10 equiv.) and *fac*-Ir(ppy)$_3$ (4.8 mg, 0.0072 mmol, 0.05 equiv.) in a 30 mL vial. The bright yellow solution was degassed by passing nitrogen through the solution for a period of 45 minutes. A household lightbulb (GE Helical 26 W) was placed ~5 cm from the reaction vial (see Figure 4.8) and the mixture was stirred at room temperature until TLC indicated consumption of starting material (4 hours). The mixture was poured over water and extracted with $CH_2Cl_2$ (4x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The $^1$H NMR of the crude product indicated a 2:1 mixture of diastereomers about C-7, favoring **4.53**. The crude residue was purified by flash chromatography (EtOAc/Heptane) to afford a mixture of **4.53** and C-7-*epi*-**4.53** (49 mg, 60% yield as a 2:1 (**4.53**:C-7-*epi*-**4.53**) mixture of diastereomers) as a colorless gum. The spectroscopic data are in full agreement with that reported previously for **4.53**.

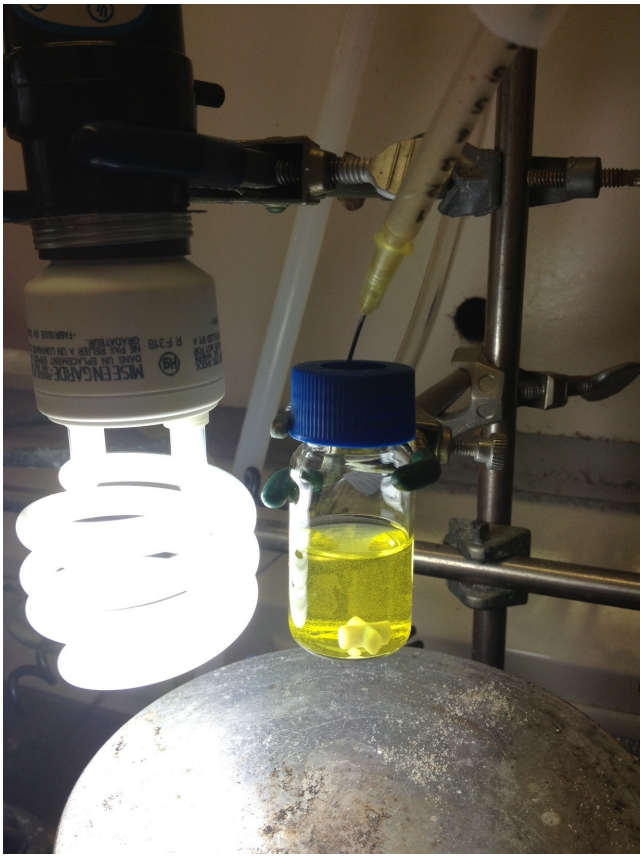
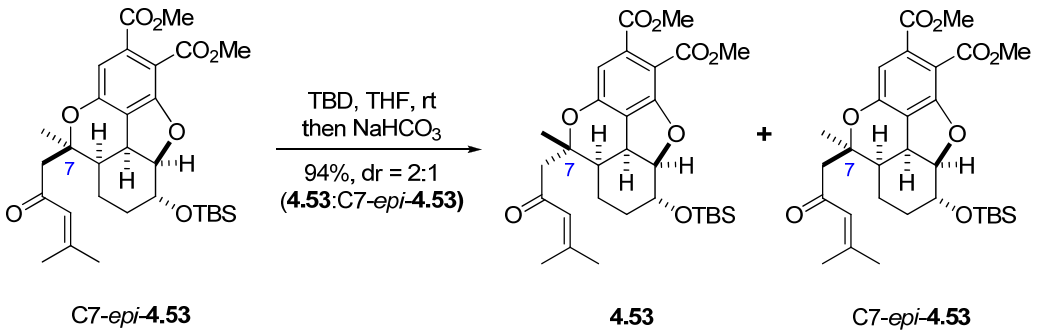


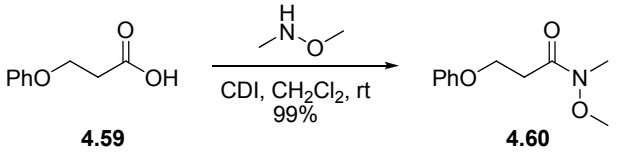
**Figure 4.8**. Visible light photocatalysis reaction set-up.




C7-*epi*-**4.53** **4.53** C7-*epi*-**4.53**

**(±)- (2S,2aR,2a1S,5R,5aR)-dimethyl 5-(tert-butyldimethylsilyloxy)-2-methyl-2-(4-methyl-2-oxopent-3-enyl)-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7,8-dicarboxylate (4.53):**

To a stirred solution of C-7-*epi*-**4.53** (50 mg, 0.089 mmol) in THF (1 mL) at room temperature was added 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (18.7 mg, 0.13 mmol, 1.5 equiv.) in one portion. The resulting mixture was stirred at room temperature for 20 minutes and then saturated aqueous $NaHCO_3$ (1 mL) was added followed by $CH_2Cl_2$ (1 mL). The mixture was allowed to stir at room temperature for 2 hours and then it was extracted with $CH_2Cl_2$ (3x). The combined organic solution was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The $^1H$ NMR of the crude product indicated a 2:1 mixture of diastereomers about C-7, favoring **4.53**. The crude residue was purified via flash chromatography (EtOAc/Heptane) to afford a mixture of **4.53** and C-7-*epi*-**4.53** (47 mg, 94% yield as a 2:1 (**4.53**:C-7-*epi*-**4.53**) mixture of diastereomers) as a colorless gum. The spectroscopic data are in full agreement with that reported above.



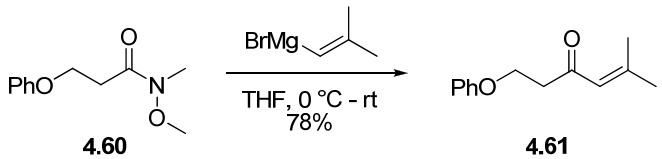

**4.59** **4.60**

**N-methoxy-N-methyl-3-phenoxypropanamide (4.60):**

To a stirred solution of **4.59** (5.0 g, 30 mmol) in $CH_2Cl_2$ (100 mL) at 0 °C was added CDI (5.8g, 36 mmol, 1.2 equiv.) over a period of 15 minutes. The mixture was allowed to warm to room temperature and stir for 1 hour. Next, *N*,*O*-Dimethylhydroxylamine hydrochloride (3.5 g, 36 mmol, 1.2 equiv.) was added over a period of 15 minutes and the mixture was stirred at room temperature for 4 hours. The mixture was washed with 0.1 N $KHSO_4$ (2x) and brine. The mixture was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford **4.60** (6.25 g, 99% yield) of a colorless oil. The crude residue was used directly without additional purification.

$^1$H NMR (400MHz, $CDCl_3$) δ 7.31 - 7.21 (m, 2H), 6.99 - 6.84 (m, 3H), 4.30 (t, *J*=6.6 Hz, 2H), 3.73 (s, 3H), 3.22 (s, 3H), 2.94 (t, *J*=6.6 Hz, 2H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 177.06, 158.55, 129.36, 120.77, 114.51, 63.43, 61.30, 32.04, 31.85




**4.60** **4.61**

**5-methyl-1-phenoxyhex-4-en-3-one (4.61):**

To a stirred solution of **4.60** (6.25 g, 29.9 mmol) in THF (100 mL) at -78 °C was added 2-methyl-1-propenylmagnesium bromide (100 mL, 0.5M in THF, 50 mmol, 1.67 equiv.) over a period of 15 minutes. The mixture was warmed to room temperature and stirred for 3 hours,

then cooled to 0 °C and quenched with saturated $NH_4Cl$. The mixture was poured over water and extracted with $CH_2Cl_2$ (4x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/Heptane) to afford **4.61** (4.8 g, 78% yield) as a white solid.

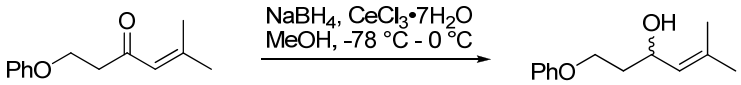
$^1$H NMR (400MHz, $CDCl_3$) δ 7.31 - 7.24 (m, 2H), 6.98 - 6.87 (m, 3H), 6.14 (spt, *J*=1.3 Hz, 1H), 4.27 (t, *J*=6.5 Hz, 2H), 2.90 (t, *J*=6.5 Hz, 2H), 2.18 (d, *J*=1.2 Hz, 3H), 1.91 (d, *J*=1.4 Hz, 3H)

$^{13}$C NMR (100MHz, $CDCl_3$) δ 197.94, 158.67, 156.48, 129.38, 123.67, 120.76, 114.57, 63.17, 43.42, 27.72, 20.88

FTIR ($cm^{-1}$) = 3041, 2908, 1681, 1619, 1598, 1497, 1386, 1245, 1013

mp: 53-57 °C

HRMS (ESI) calculated for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1223, found 205.1221




**4.61** **4.62**

**5-methyl-1-phenoxyhex-4-en-3-ol (4.62):**

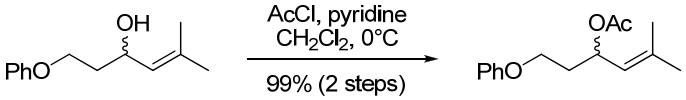
To a stirred solution of **4.61** (2.0 g, 9.8 mmol) and cerium chloride heptahydrate (5.47 g, 14.7 mmol, 1.5 equiv.) in MeOH (50 mL) at -78 °C was added $NaBH_4$ (444 mg, 11.7 mmol, 1.2 equiv.) in one portion. The mixture was warmed to room temperature and stirred for 1 hour. The mixture was partially concentrated under reduced pressure and poured over EtOAc. The mixture was washed with water and brine, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford **4.62** (2 g) as a colorless oil. The crude oil was used directly without additional purification.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 7.33 - 7.20 (m, 2H), 6.98 - 6.87 (m, 3H), 5.27 - 5.21 (m, 1H), 4.67 (dt, *J*=5.3, 8.1 Hz, 1H), 4.16 - 4.09 (m, 1H), 4.06 - 3.99 (m, 1H), 2.06 (dtd, *J*=5.4, 7.3, 14.3 Hz, 1H), 1.95 - 1.85 (m, 1H), 1.79 (br. s., 1H), 1.73 (d, *J*=1.2 Hz, 3H), 1.68 (d, *J*=1.4 Hz, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 158.78, 135.58, 129.42, 127.34, 120.74, 114.50, 66.49, 65.12, 36.88, 25.76, 18.18

FTIR ($cm^{-1}$) = 3337, 2927, 1597, 1496, 1242, 1078, 1045

HRMS (ESI) calculated for $C_{13}H_{18}NaO_2$ [M+Na]+ 229.1199, found 229.1195




**4.62** **4.63**

**5-methyl-1-phenoxyhex-4-en-3-yl acetate (4.63):**

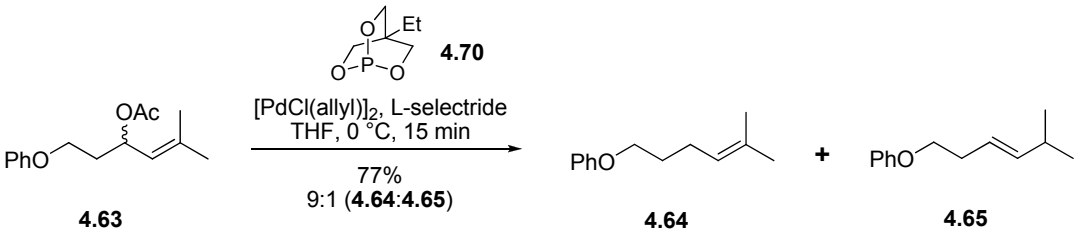
To a stirred solution of **4.62** (2.0 g, 9.7 mmol) in $CH_2Cl_2$ (50 mL) at 0 °C was added pyridine (999 mg, 12.6 mmol, 1.3 equiv.) followed by AcCl (914 mg, 11.6 mmol, 1.2 equiv.) over a period of 10 minutes. The mixture was stirred at 0 °C for 2 hours until TLC indicated consumption of starting material. The mixture was washed with 0.1N HCl (2x) and brine. The organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **4.63** (2.15 g, 90 % yield for 2 steps) as a colorless oil.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 7.30 - 7.19 (m, 2H), 6.93 - 6.89 (t, *J*=7.3 Hz, 1H), 6.88 - 6.83 (m, 2H), 5.71 (td, *J*=6.9, 9.2 Hz, 1H), 5.11 (td, *J*=1.3, 9.2 Hz, 1H), 4.00 - 3.87 (m, 2H), 2.20 - 2.08 (m, 1H), 2.00 (s, 3H), 1.98 - 1.88 (m, 1H), 1.72 - 1.68 (m, 6H)

$^{13}$C NMR (100MHz, $CDCl_3$) δ 170.24, 158.76, 137.84, 129.37, 122.94, 120.67, 114.49, 69.00, 63.98, 34.49, 25.73, 21.26, 18.34

FTIR ($cm^{-1}$) = 2927, 1731, 1599, 1496, 1471, 1371, 1043, 1017

HRMS (ESI) calculated for $C_{15}H_{20}O_3$ $[M+H]^+$ 271.1305, found 271.1311




**4.63** **4.64** **4.65**

**(5-methylhex-4-enyloxy)benzene (4.64):**

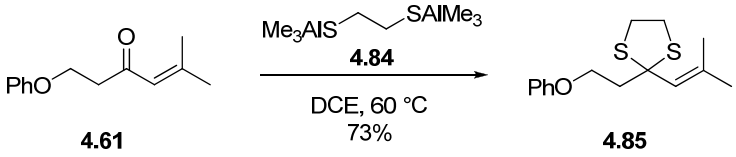
To a stirred solution of **4.63** (150 mg, 0.604 mmol) in THF (10 mL) was added $[PdCl(allyl)]_2$ (11 mg, 0.030 mmol, 0.05 equiv.) and phosphite **4.70** (20 mg, 0.12 mmol, 0.2 equiv.). The solution was cooled to 0 °C and L-selectride was added in one portion and stirred at 0 °C until TLC indicated consumption of starting material (5 minutes). The reaction mixture was quenched with saturated $NH_4Cl$. The resulting mixture was diluted with water and extracted with $CH_2Cl_2$ (4x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Analysis of the crude $^1$H NMR spectrum revealed a 9:1 mixture of isomers, favoring **4.64**. The crude residue was purified by silica gel flash chromatography ($Et_2O$/pentane) to afford **4.64** (89 mg, 77% yield) as a pale yellow oil. Analysis of the purified $^1$H NMR spectrum indicated a 13:1 mixture of isomers, favoring **4.64**.

$^1$H NMR (400MHz , $CDCl_3$) δ 7.32 - 7.24 (m, 2 H), 6.97 - 6.86 (m, 3 H), 5.20 - 5.12 (m, 1 H), 3.96 (t, *J* = 6.4 Hz, 2 H), 2.18 (q, *J* = 7.3 Hz, 2 H), 1.83 (quin, *J* = 6.9 Hz, 2 H), 1.71 (d, *J* = 0.7 Hz, 3 H), 1.62 (s, 3 H)

$^{13}$C NMR (100MHz , $CDCl_3$) δ 159.1, 132.4, 129.4, 123.5, 120.4, 114.5, 67.1, 29.4, 25.7, 24.4, 17.6

FTIR ($cm^{-1}$) = 2927, 1600, 1496, 1470, 1242, 1040

HRMS (ESI) calculated for $C_{13}H_{19}O$ $[M+H]^+$ 191.1430, found 191.1426.



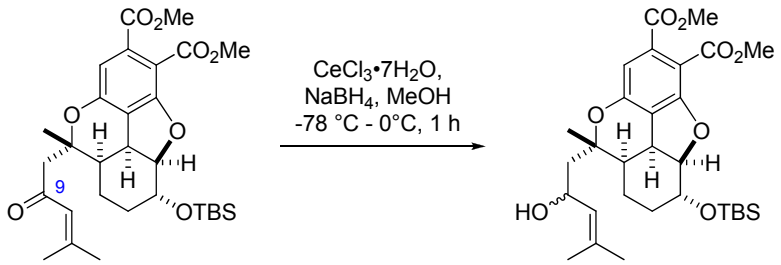

**4.61** **4.85**

**2-(2-methylprop-1-enyl)-2-(2-phenoxyethyl)-1,3-dithiolane (4.85):**

To a vial containing $CH_2Cl_2$ (2 mL) at -78 °C was added $AlMe_3$ (1.0 mL, 2M in hexanes, 2 mmol, 2 equiv.) followed by dithioethane (94 mg, 1.0 mmol, 1 equiv.) over a period of 5 minutes and then allowed to warm to 0 °C. The mixture was concentrated under reduced pressure to yield **4.84** as a free-flowing white solid which was used directly. To a stirred solution of **4.61** (50 mg, 0.25 mmol) in DCE (8 mL) was added **4.84** (177 mg, 0.75 mmol, 3 equiv.) and the mixture was heated to 60 °C for 30 minutes. The mixture was cooled to room temperature and the mixture was quenched with TEA (0.2 mL), poured over saturated $NaHCO_3$ and extracted with $CH_2Cl_2$ (2x). The combined organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography (EtOAc/Heptane) to afford **4.85** (50 mg, 73% yield) as a colorless oil.

$^1$H NMR (400MHz, $CDCl_3$) δ 7.32 - 7.17 (m, 2H), 6.97 - 6.77 (m, 3H), 5.68 - 5.63 (m, 1H), 4.18 - 4.07 (m, 2H), 3.42 - 3.24 (m, 4H), 2.60 - 2.50 (m, 2H), 1.86 (d, *J*=1.2 Hz, 3H), 1.71 (d, *J*=1.6 Hz, 3H)

GCMS (FID) calculated for $C_{15}H_{20}OS_2$ [M] 280.4, found 280.

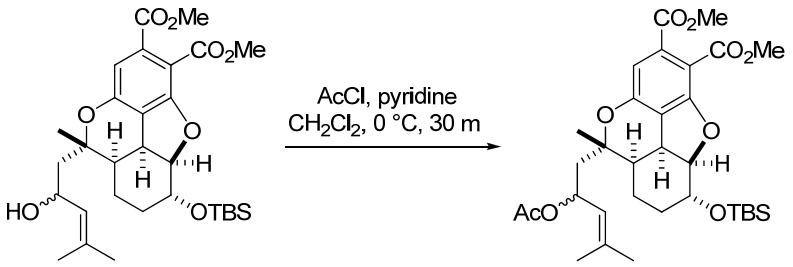



**(±)- (2S,2aR,2a1S,5R,5aR)-dimethyl 5-(tert-butyldimethylsilyloxy)-2-(2-hydroxy-4-methylpent-3-enyl)-2-methyl-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7,8-dicarboxylate (4.71):**

To a stirred solution of **4.53** (250 mg, 0.45 mmol) and cerium chloride heptahydrate (333 mg, 0.89 mmol, 2 equiv.) in MeOH (10 mL) at -78 °C was added $NaBH_4$ (25 mg, 0.67 mmol, 1.5 equiv.) in one portion. The mixture was allowed to warm to 0 °C. After stirring for 1h, the mixture was quenched with saturated aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$ (3x). The combined organic solution was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to provide **4.71** (250 mg) as a white foam as a mixture of diastereomers at C-9 (~8:1). The crude residue was used directly in the next step. Crude NMR data was extracted from the major diastereomer.

$^1$H NMR (400MHz, $CDCl_3$) δ 6.71 (s, 1H), 5.17-5.10 (m, 1H), 4.87 (dd, *J*=8.2, 6.7 Hz, 1H), 4.75-4.67 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.67-3.61 (m, 1H), 3.23 (ddd, *J*=11.8, 6.7, 4.7 Hz, 1H), 2.08-1.99 (m, 1H), 1.98-1.90 (m, 2H), 1.80-1.72 (m, 1H), 1.69 (s, 3H), 1.69 (s, 3H), 1.60 (s, 1H), 1.53 (s, 3H), 1.55-1.49 (m, 1H), 1.31-1.17 (m, 1H) 0.94-0.80 ppm (m, 1H), 0.85 (s, 9H), 0.84-0.86 (m, 1H), 0.04 (s, 3H), -0.06 ppm (s, 3H).

HRMS (ESI) calculated for $C_{30}H_{45}O_8Si$ $[M+H]^+$ 561.2878, found 561.2876.



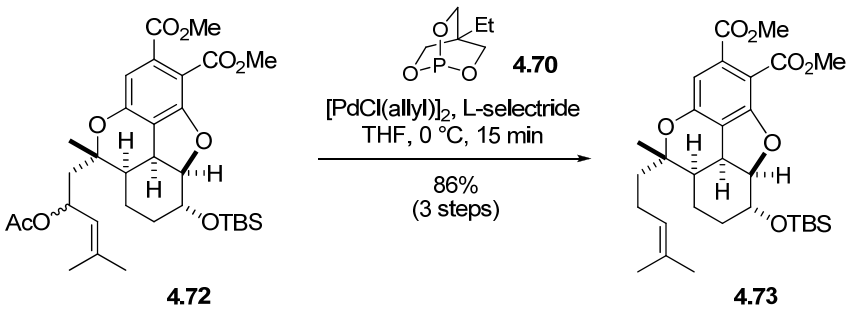

**4.71** **4.72**

**(±)- (2S,2aR,2a1S,5R,5aR)-dimethyl 2-(2-acetoxy-4-methylpent-3-enyl)-5-(tert-butyldimethylsilyloxy)-2-methyl-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7,8-dicarboxylate (4.72):**

To a stirred solution of **4.71** (250 mg) in $CH_2Cl_2$ (8 mL) at 0 °C was added pyridine (72 µL, 0.89 mmol, 2 equiv.) followed by acetyl chloride (38 µL, 0.54 mmol, 1.2 equiv.) dropwise over a period of 5 minutes. The mixture was stirred at 0 °C for 30 minutes after which TLC indicated the consumption of starting material. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ (5 mL) and extracted with $CH_2Cl_2$ (3x). The combined organic solution was washed with 0.1 N aqueous $KHSO_4$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to provide **4.72** (268 mg, 99% crude yield) of a white solid as a mixture of diastereomers at C-9. Crude NMR data was extracted from the major diastereomer.

$^1$H NMR (400MHz, $CDCl_3$) δ 6.65 (s, 1H), 5.77 (dt, *J*=3.5, 8.9 Hz, 1H), 5.10 - 5.03 (m, 1H), 4.87 (dd, *J*=6.6, 8.3 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.64 - 3.57 (m, 1H), 3.22 (ddd, *J*=4.6, 6.7, 11.8 Hz, 1H), 2.13 - 2.05 (m, 1H), 2.04 - 1.96 (m, 1H), 1.96 (s, 3H), 1.76 (d, *J*=1.2 Hz, 3H), 1.69 (d, *J*=1.2 Hz, 3H), 1.68 - 1.63 (m, 2H), 1.44 (s, 3H), 1.47 - 1.40 (m, 1H), 1.32 - 1.18 (m, 1H), 0.86 (s, 9H), 0.91 - 0.79 (m, 1H), 0.04 (s, 3H), -0.06 (s, 3H).

HRMS (ESI) calculated for $C_{32}H_{46}O_9Si$ Na $[M+Na]^+$ 625.2803, found 625.2797.




**(±)-(2S,2aR,2a1S,5R,5aR)-dimethyl 5-(tert-butyldimethylsilyloxy)-2-methyl-2-(4-methylpent-3-enyl)-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7,8-dicarboxylate (4.73):**

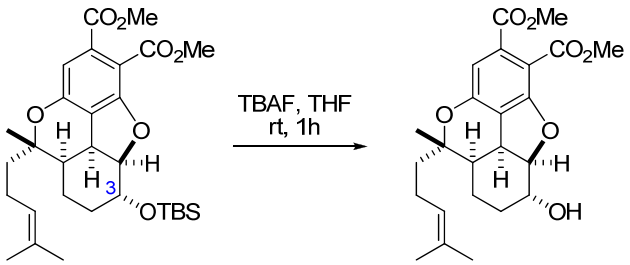
To a stirred solution of **4.72** (180 mg, 0.30 mmol) in THF (15mL) at room temperature was added allylpalladium (II) chloride dimer (5.5 mg, 0.015 mmol, 0.05 equiv.) and phosphite **4.70** (9.7 mg, 0.06 mmol, 0.2 equiv.). The solution was cooled to 0 °C and L-selectride (0.6 mL, 1.0 M in THF, 0.6 mmol, 2 equiv.) was added in one portion and stirred at 0 °C until TLC indicated consumption of starting material (15 min). The reaction mixture was quenched with saturated aqueous $NH_4Cl$ (5 mL) and the resulting mixture was diluted with water and then extracted with $CH_2Cl_2$ (3x). The combined organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was subjected to silica gel flash chromatography (EtOAc/Heptane) to afford **4.73** (140 mg, 86% yield for 3 steps) as a colorless gum.

$^1$H NMR (400MHz, $CDCl_3$) δ 6.66 (s, 1H), 5.05 - 4.96 (m, 1H), 4.85 (dd, *J*=6.8, 7.8 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.61 (t, *J*=7.3 Hz, 1H), 3.26 - 3.16 (m, 1H), 2.10 - 1.93 (m, 3H), 1.77 - 1.66 (m, 1H), 1.63 (s, 3H), 1.65 - 1.57 (m, 1H), 1.55 (s, 3H), 1.53 - 1.44 (m, 1H), 1.39 (s, 3H), 1.29 - 1.18 (m, 2H), 0.84 (s, 9H), 0.88 - 0.81 (m, 1H), 0.04 (s, 3H), -0.06 - -0.09 (m, 3H)

$^{13}$C NMR (101MHz, $CDCl_3$): δ 168.5, 165.5, 159.4, 153.5, 135.2, 132.3, 123.1, 114.3, 109.8, 107.4, 95.6, 82.6, 72.5, 52.6, 52.1, 38.4, 36.5, 35.1, 30.9, 25.7, 25.6, 22.3, 22.2, 20.4, 17.9, 17.6, -4.9, -5.3 ppm

FTIR ($cm^{-1}$) = 2951, 1723, 1624, 1432, 1377

HRMS (ESI) calculated for $C_{30}H_{45}O_7Si$ $[M+H]^+$ 545.2929, found 545.2940.




**4.73** **4.77**

**(±)- (2S,2aR,2a1S,5R,5aR)-dimethyl 5-hydroxy-2-methyl-2-(4-methylpent-3-enyl)-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7,8-dicarboxylate (4.77):**

To a stirred solution of **4.73** (80 mg, 0.15 mmol) in THF (3 mL) at 0 °C was added TBAF (0.49 mL, 1.0 M in THF, 0.49 mmol, 1.5 equiv.) dropwise over a period of 5 minutes. The reaction mixture was warmed to room temperature and stirred until TLC indicated consumption of starting material (1 h). The reaction mixture was diluted with $CH_2Cl_2$ and the resulting solution was washed with water (3x) and brine (2x) and then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield **4.77** as white solid (62mg). The crude residue was used directly in the next step without additional purification.

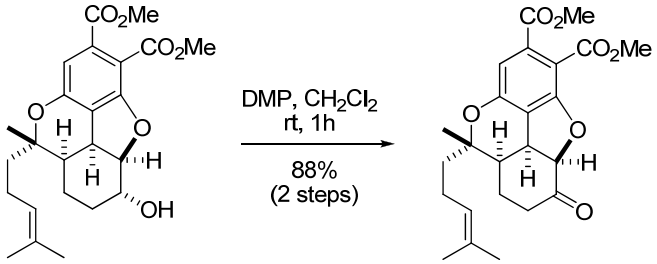
$^1$H NMR (400MHz, $CDCl_3$) δ 6.69 (s, 1H), 5.04 - 4.98 (m, 1H), 4.90 (dd, *J*=7.0, 8.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.65 (t, *J*=7.2 Hz, 1H), 3.33 (ddd, *J*=4.3, 7.1, 12.0 Hz, 1H), 2.12 - 2.00 (m, 3H),

1.86 - 1.75 (m, 2H), 1.65 (s, 3H), 1.68 - 1.59 (m, 1H), 1.57 (s, 3H), 1.55 - 1.47 (m, 1H), 1.41 (s, 3H), 1.32 - 1.18 (m, 1H), 0.98 (s, 1H), 0.95 - 0.84 (m, 1H)

$^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.2, 165.7, 159.3, 153.5, 134.9, 132.4, 123.1, 114.3, 110.0, 107.6, 95.4, 82.7, 71.7, 52.6, 52.4, 38.5, 36.4, 35.0, 29.1, 25.6, 22.3, 22.2, 20.6, 17.6

FTIR ($cm^{-1}$) = 3394, 2952, 1715, 1623, 1433, 1377

HRMS (ESI) calculated for $C_{24}H_{31}O_7$ $[M+H]^+$ 431.2070, found 431.2073.




**4.77** **4.75**

**(±)- (2S,2aR,2a1S,5aR)-dimethyl 2-methyl-2-(4-methylpent-3-enyl)-5-oxo-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7,8-dicarboxylateF (4.75):**

To a stirred solution of **4.77** (62 mg, 0.14 mmol) in $CH_2Cl_2$ (3 mL) at room temperature was added Dess-Martin periodinane (91 mg, 0.21 mmol, 1.5 equiv.) in one portion. The reaction mixture was stirred at room temperature until TLC indicated consumption of starting material (20 min). A 1:1 mixture of saturated aqueous $NaHCO_3$ and 10% aqueous $Na_2S_2O_3$ (3 mL) was added and the resulting mixture was stirred at room temperature for 15 minutes and then extracted with $CH_2Cl_2$, (3x). The combined organic solution was washed with a 1:1 mixture of saturated aqueous $NaHCO_3$ and 10% aqueous $Na_2S_2O_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to silica gel flash

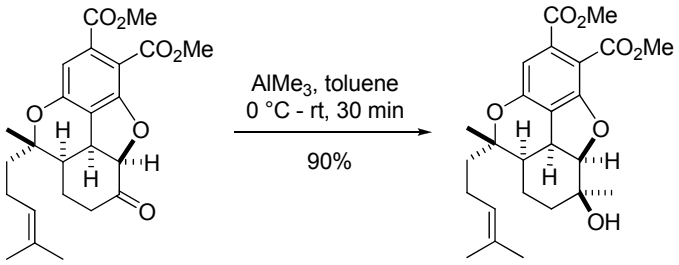
chromatography (EtOAc/Heptane) to afford **4.75** (54 mg, 88% yield over 2 steps) as a white solid.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 6.68 (s, 1H), 5.22 (d, *J*=8.6 Hz, 1H), 5.03 (t, *J*=7.0 Hz, 1H), 4.08 (t, *J*=6.8 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 2.47 - 2.25 (m, 3H), 2.16 - 2.02 (m, 3H), 1.65 (s, 3H), 1.73 - 1.62 (m, 1H), 1.59 (s, 3H), 1.44 (s, 3H), 1.30 - 1.16 (m, 2H)

$^{13}$C NMR (101MHz, $CDCl_3$): δ 205.4, 168.0, 165.0, 159.9, 153.4, 135.6, 132.6, 122.8, 111.1, 110.1, 107.4, 88.3, 82.4, 52.6, 52.5, 38.5, 38.5, 38.5, 36.3, 25.6, 22.6, 22.5, 22.2, 17.6 ppm

FTIR ($cm^{-1}$) = 2951, 1722, 1621, 1432, 1375

HRMS calculated for $C_{24}H_{29}O_7$ $[M+H]^+$ 429.1908, found 429.1914.




**4.75** **4.76**

**(±)- (2S,2aR,2a1S,5S,5aR)-dimethyl 5-hydroxy-2,5-dimethyl-2-(4-methylpent-3-enyl)-2a,2a1,3,4,5,5a-hexahydro-2H-benzofuro[4,3,2-cde]chromene-7,8-dicarboxylate (4.76):**

To a stirred solution of **4.75** (52 mg, 0.12 mmol) in toluene (3 mL) at 0 °C was added $AlMe_3$ (0.09 mL, 2.0 M in heptane, 0.18 mmol, 1.5 equiv.) dropwise over a period of 5 minutes. The reaction mixture was allowed to warm to room temperature and then stir until TLC indicated consumption of starting material (30 min). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with $CH_2Cl_2$ (4x). The

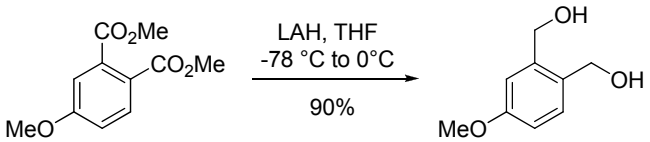
combined organic solution was filtered through Celite and concentrated under reduced pressure. The residue was subjected to silica gel flash chromatography (EtOAc/Heptane) to afford **4.76** (49 mg, 90% yield) as a white solid.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 1H), 4.99-5.06 (m, 1H), 4.86 (d, *J*=8.98 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.62-3.69 (m, 1H), 2.02-2.11 (m, 2H), 1.93-2.01 (m, 1H), 1.73-1.81 (m, 1H), 1.65 (s, 3H), 1.61-1.71 (m, 1H), 1.58 (s, 3H), 1.56 (br. s., 1H), 1.47-1.55 (m, 2H), 1.42 (s, 3H), 1.27 (s, 3H), 1.25-1.33 (m, 1H), 1.12-1.24 (m, 1H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 168.0, 166.1, 161.0, 153.3, 133.6, 132.3, 123.3, 114.7, 110.3, 106.1, 92.0, 82.5, 69.1, 52.5, 52.3, 38.5, 36.2, 34.8, 33.7, 29.8, 25.6, 22.2, 22.2, 17.6, 16.3 ppm

FTIR ($cm^{-1}$) = 2956, 1627, 1433, 1376, 1289, 1263

HRMS (ESI) calculated for $C_{25}H_{33}O_7$ $[M+H]^+$ 445.2221, found 445.2224.



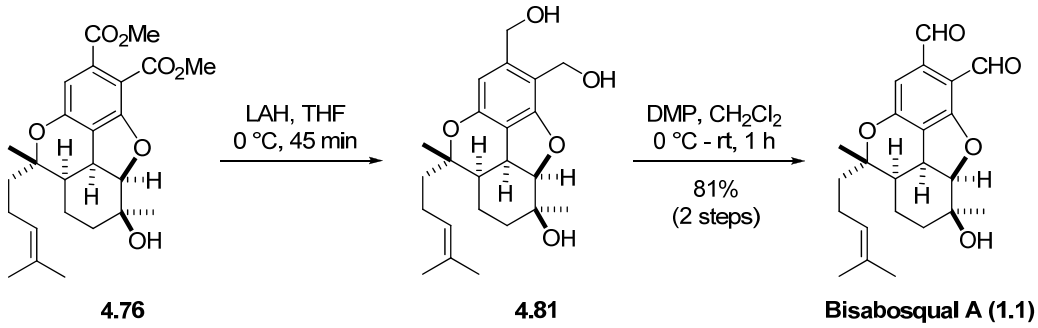

**4.79** **4.86**

**(4-methoxy-1,2-phenylene)dimethanol (4.86):**

To a stirred solution of **4.79** (150 mg, 0.67 mmol) in THF (3 mL) at -78 °C was added LAH (1.34 mL, 1 M in THF, 1.34 mmol, 2 equiv.) over a period of 5 minutes. The mixture was warmed to 0 °C and stirred at this temperature for 1 hour. The mixture was carefully quenched with saturated $NaHCO_3$ and filtered through Celite, washing with $CH_2Cl_2$. The mixture was concentrated under reduced pressure to afford **4.86** (135 mg, 90% yield) as a colorless oil.

$^{1}$H NMR (400MHz, $CDCl_3$) δ 7.27 - 7.23 (m, 1H), 6.92 (d, *J*=2.7 Hz, 1H), 6.81 (dd, *J*=2.7, 8.2 Hz, 1H), 4.68 (s, 2H), 4.66 (s, 2H), 3.81 (s, 3H), 2.80 (s, 2H)

$^{13}$C NMR (101MHz, $CDCl_3$) δ 159.63, 141.11, 131.43, 131.18, 115.56, 112.93, 64.25, 63.66, 55.32




**Bisabosqual A (1.1):**

To a stirred solution of **4.76** (25.1 mg, 0.0565 mmol) in THF (3 mL) at -78 °C was added LAH (0.14 mL, 1.0 M in THF, 0.14 mmol, 2.5 equiv.) dropwise over a period of 10 minutes. The reaction mixture was allowed to warm to 0 °C and stirred at this temperature until TLC analysis indicated the reaction to be complete (30 min). The reaction mixture was carefully quenched with $Na_2SO_4 \cdot 10H_2O$ and the resulting mixture was filtered through Celite and then concentrated under reduced pressure. The crude residue was used immediately in the subsequent step without purification. To a stirred solution of crude **4.81** (from above) in $CH_2Cl_2$ (3 mL) at 0 °C was added Dess-Martin periodinane (59 mg, 0.14 mmol, 2.5 equiv.) in one portion. The reaction mixture was warmed to room temperature and then stirred until TLC indicated consumption of starting material (45 min). Then a 1:1 mixture of saturated aqueous $NaHCO_3$ and 10% aqueous $Na_2S_2O_3$ (3 mL) was added and the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was extracted with $CH_2Cl_2$, (3x). The combined organic solution was washed with a 1:1 mixture of saturated aqueous $NaHCO_3$ and

10% aqueous $Na_2S_2O_3$, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel flash chromatography (EtOAc/Heptane) to afford **1.1** (17.5 mg, 81% yield over 2 steps) as a white solid.

$^1$H NMR (400MHz, $CDCl_3$) δ 10.47 (s, 1H), 10.37 (s, 1H), 6.93 (s, 1H), 5.03 (tdt, *J*=1.4, 2.9, 7.1 Hz, 1H), 4.97 (d, *J*=8.8 Hz, 1H), 3.69 - 3.63 (m, 1H), 2.13 - 2.05 (m, 2H), 2.09 - 2.00 (m, 1H), 1.83 - 1.76 (m, 1H), 1.72 - 1.64 (m, 1H), 1.65 (s, 3H), 1.59 (s, 3H), 1.59 - 1.56 (m, 1H), 1.57 (br. s, 1H), 1.56 - 1.53 (m, 1H), 1.46 (s, 3H), 1.32 (s, 3H), 1.32 - 1.26 (m, 1H), 1.25 - 1.17 (m, 1H)

$^{13}$C NMR (101MHz, $CDCl_3$): δ 192.2, 188.1, 165.5, 155.7, 139.3, 132.5, 123.1, 117.3, 113.8, 112.4, 92.7, 83.5, 69.2, 38.7, 36.0, 34.9, 33.3, 29.6, 25.6, 22.2, 22.1, 17.7, 16.4

FTIR ($cm^{-1}$) = 3469, 2967, 1685, 1618, 1382

HRMS (ESI) calculated for $C_{23}H_{29}O_5$ $[M+H]^+$ 385.2010, found 385.2007.

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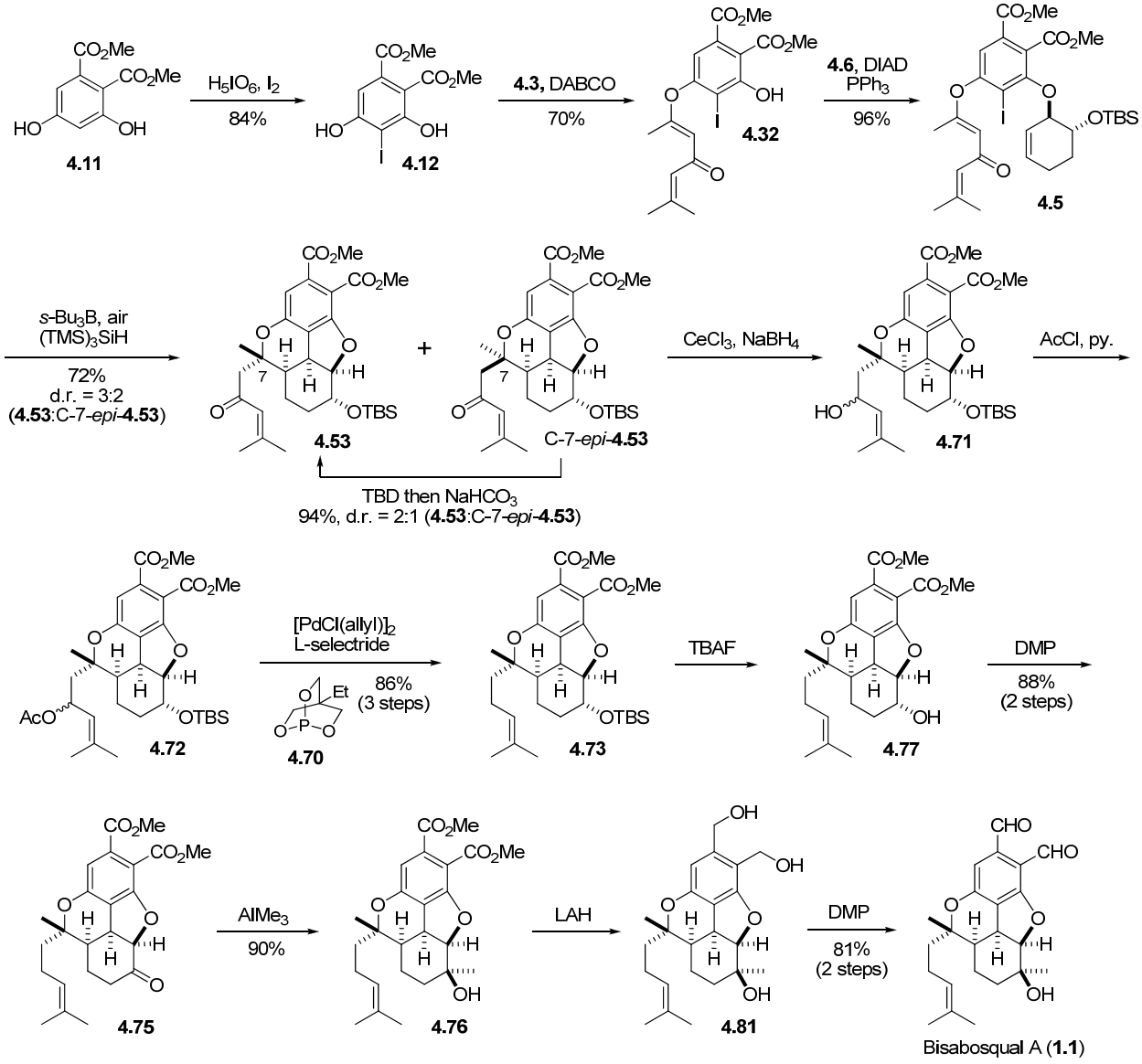
**Appendix 1.** Comparison of Natural and Synthetic Bisabosqual A.

**Table A1.1**. Comparison of $^{1}$HNMR and $^{13}$CNMR spectra.

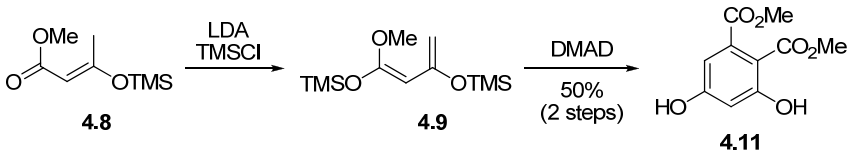
| Position | Authentic ($^{1}$H) | Synthetic ($^{1}$H) | Authentic ($^{13}$C) | Synthetic ($^{13}$C) |
|---|---|---|---|---|
| 1 | 1.55 (m, 1H), 1.28 (m, 1H) | 1.55 (m, 1H), 1.29 (m, 1H) | 16.33 | 16.4 |
| 2 | 1.79 (m, 1H), 1.21 (m, 1H) | 1.80 (m, 1H), 1.21 (m, 1H) | 34.93 | 34.9 |
| 3 | - | - | 69.14 | 69.2 |
| 4 | 4.97 (d, *J*=8.8 Hz, 1H) | 4.97 (d, *J*=8.8 Hz, 1H) | 92.77 | 92.7 |
| 5 | 3.66 (dd, *J*=8.8, 6.6 Hz, 1H) | 3.66 (m, 1H) | 33.27 | 33.3 |
| 6 | 2.05 (m, 1H) | 2.05 (m, 1H) | 35.94 | 36.0 |
| 7 | - | - | 83.52 | 83.5 |
| 8 | 1.67 (m, 1H), 1.57 (m, 1H) | 1.68 (m, 1H), 1.58 (m, 1H) | 38.71 | 38.7 |
| 9 | 2.08 (m, 2H) | 2.09 (m, 2H) | 22.21 | 22.2 |
| 10 | 5.03 (m, 1H) | 5.03 (tdt, *J*=7.1,2.9,1.4, 1H) | 123.08 | 123.1 |
| 11 | - | - | 132.47 | 132.5 |
| 12 | 1.65 (br. s, 3H) | 1.65 (s, 3H) | 25.57 | 25.6 |
| 13 | 1.59 (br. s, 3H) | 1.59 (s, 3H) | 17.63 | 17.7 |
| 14 | 1.46 (s, 3H) | 1.46 (s, 3H) | 22.11 | 22.1 |
| 15 | 1.31 (s, 3H) | 1.32 (s, 3H) | 29.53 | 29.6 |
| 1’ | - | - | 117.31 | 117.3 |
| 2’ | - | - | 165.69 | 165.5 |
| 3’ | - | - | 112.08 | 112.4 |
| 4’ | - | - | 139.26 | 139.3 |
| 5’ | 6.93 (s, 1H) | 6.93 (s, 1H) | 113.67 | 113.8 |
| 6’ | - | - | 155.71 | 155.7 |
| 7’ | 10.46 (s, 1H) | 10.47 (s, 1H) | 188.27 | 188.1 |
| 8’ | 10.36 (s, 1H) | 10.37 (s, 1H) | 192.24 | 192.2 |
| 3-OH | 1.55 (br. s, 1H) | 1.57 (br. s, 1H) | - | - |

**Appendix 2.** Bisabosqual Synthetic Schemes.

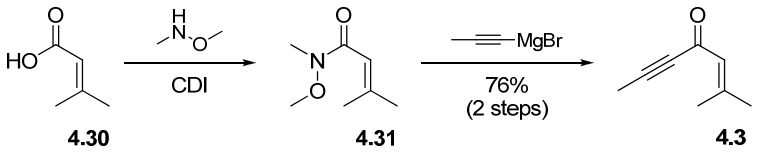
**Scheme A2.1.** Total synthesis of bisabosqual A.



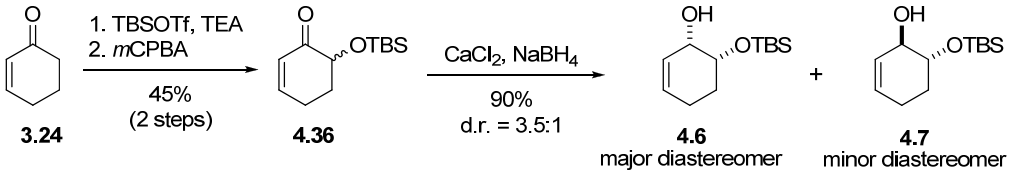
**Scheme A2.2**. Synthesis of the aromatic core.




**Scheme A2.3**. Synthesis of the side chain precursor.




**Scheme A2.4**. Synthesis of the cyclohexenol moiety.



**Appendix 3.** X-Ray Crystal Structure of Bisabosqual A.

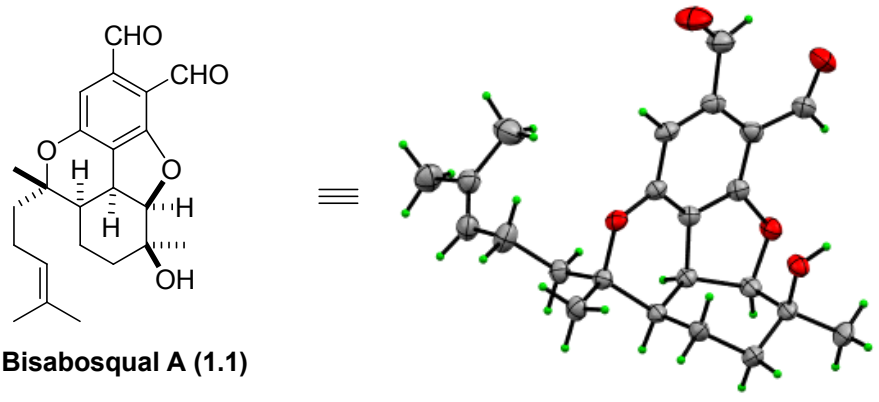



**Figure A3.1.** Bisabosqual A crystal structure. Non-hydrogen atoms are displayed at a 50% probability level.

**Table A3.1.** Crystal data and structure refinement for bisabosqual A.

| | | |
|---|---|---|
| Identification code | bisabosqual A | |
| Empirical formula | C23 H28 O5 | |
| Formula weight | 384.45 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 5.4428(3) Å | α = 87.538(2)°. |
| | b = 9.2903(5) Å | β = 85.332(2)°. |
| | c = 19.7811(10) Å | γ = 85.189(2)°. |
| Volume | 992.75(9) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.286 $Mg/m^3$ | |
| Absorption coefficient | 0.726 $mm^{-1}$ | |
| F(000) | 412 | |
| Crystal size | 0.35 x 0.03 x 0.01 $mm^3$ | |
| Theta range for data collection | 4.49 to 70.05° | |
| Index ranges | -5<=h<=6, -11<=k<=11, -24<=l<=24 | |
| Reflections collected | 23571 | |
| Independent reflections | 3725 [R(int) = 0.0375] | |
| Completeness to theta = 70.05° | 98.6 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9928 and 0.7851 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3725 / 1 / 260 | |
| Goodness-of-fit on $F^2$ | 1.062 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0526, wR2 = 0.1506 | |
| R indices (all data) | R1 = 0.0565, wR2 = 0.1550 | |
| Largest diff. peak and hole | 0.448 and -0.348 $e.Å^{-3}$ | |

**Table A3.2.** Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 x\ 10^3$) for bisabosqual A. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 10219(2) | 9754(1) | 6879(1) | 26(1) |
| O(2) | 5858(2) | 9170(1) | 8938(1) | 29(1) |
| O(3) | 9792(2) | 7166(1) | 8773(1) | 28(1) |
| O(4) | 9836(3) | 11986(2) | 9908(1) | 53(1) |
| O(5) | 13981(3) | 13213(2) | 8294(1) | 58(1) |
| C(1) | 8463(3) | 8821(2) | 6620(1) | 25(1) |
| C(2) | 7347(3) | 7764(2) | 7174(1) | 24(1) |
| C(3) | 9159(3) | 6564(2) | 7430(1) | 27(1) |
| C(4) | 7921(3) | 5741(2) | 8033(1) | 31(1) |
| C(5) | 7442(3) | 6680(2) | 8654(1) | 27(1) |
| C(6) | 5611(3) | 7970(2) | 8480(1) | 26(1) |
| C(7) | 6084(3) | 8656(2) | 7764(1) | 23(1) |
| C(8) | 7728(3) | 9780(2) | 7919(1) | 23(1) |
| C(9) | 7458(3) | 10058(2) | 8599(1) | 26(1) |
| C(10) | 8853(3) | 11049(2) | 8882(1) | 29(1) |
| C(11) | 10658(3) | 11687(2) | 8423(1) | 29(1) |
| C(12) | 11054(3) | 11310(2) | 7753(1) | 28(1) |
| C(13) | 9621(3) | 10289(2) | 7502(1) | 24(1) |
| C(14) | 6415(3) | 9828(2) | 6328(1) | 28(1) |
| C(15) | 7287(4) | 10940(2) | 5789(1) | 39(1) |
| C(16) | 5213(4) | 11973(2) | 5579(1) | 37(1) |
| C(17) | 4451(4) | 13249(2) | 5843(1) | 35(1) |
| C(18) | 5578(5) | 13885(3) | 6414(1) | 53(1) |
| C(19) | 2300(4) | 14160(2) | 5580(1) | 46(1) |
| C(20) | 10036(3) | 7983(2) | 6072(1) | 30(1) |
| C(21) | 6391(4) | 5841(2) | 9273(1) | 36(1) |
| C(22) | 8509(4) | 11287(2) | 9604(1) | 34(1) |
| C(23) | 12265(4) | 12791(2) | 8637(1) | 41(1) |

**Table A3.3.** Bond lengths [Å] and angles [°] for bisabosqual A.

| | |
|---|---|
| O(1)-C(13) | 1.353(2) |
| O(1)-C(1) | 1.4779(19) |
| O(2)-C(9) | 1.366(2) |
| O(2)-C(6) | 1.4879(19) |
| O(3)-C(5) | 1.4315(19) |
| O(3)-H(3) | 0.827(16) |
| O(4)-C(22) | 1.221(2) |
| O(5)-C(23) | 1.193(3) |
| C(1)-C(20) | 1.524(2) |
| C(1)-C(14) | 1.528(2) |
| C(1)-C(2) | 1.561(2) |
| C(2)-C(3) | 1.523(2) |
| C(2)-C(7) | 1.542(2) |
| C(2)-H(2) | 1.0000 |
| C(3)-C(4) | 1.529(2) |
| C(3)-H(3A) | 0.9900 |
| C(3)-H(3B) | 0.9900 |
| C(4)-C(5) | 1.531(2) |
| C(4)-H(4A) | 0.9900 |
| C(4)-H(4B) | 0.9900 |
| C(5)-C(21) | 1.520(2) |
| C(5)-C(6) | 1.539(2) |
| C(6)-C(7) | 1.539(2) |
| C(6)-H(6) | 1.0000 |
| C(7)-C(8) | 1.488(2) |
| C(7)-H(7) | 1.0000 |
| C(8)-C(13) | 1.369(2) |
| C(8)-C(9) | 1.375(2) |
| C(9)-C(10) | 1.403(2) |
| C(10)-C(11) | 1.431(3) |
| C(10)-C(22) | 1.448(2) |
| C(11)-C(12) | 1.382(2) |
| C(11)-C(23) | 1.498(2) |
| C(12)-C(13) | 1.408(2) |
| C(12)-H(12) | 0.9500 |

| | |
|---|---|
| C(14)-C(15) | 1.527(2) |
| C(14)-H(14A) | 0.9900 |
| C(14)-H(14B) | 0.9900 |
| C(15)-C(16) | 1.493(3) |
| C(15)-H(15A) | 0.9900 |
| C(15)-H(15B) | 0.9900 |
| C(16)-C(17) | 1.336(3) |
| C(16)-H(16) | 0.9500 |
| C(17)-C(18) | 1.494(3) |
| C(17)-C(19) | 1.501(3) |
| C(18)-H(18A) | 0.9800 |
| C(18)-H(18B) | 0.9800 |
| C(18)-H(18C) | 0.9800 |
| C(19)-H(19A) | 0.9800 |
| C(19)-H(19B) | 0.9800 |
| C(19)-H(19C) | 0.9800 |
| C(20)-H(20A) | 0.9800 |
| C(20)-H(20B) | 0.9800 |
| C(20)-H(20C) | 0.9800 |
| C(21)-H(21A) | 0.9800 |
| C(21)-H(21B) | 0.9800 |
| C(21)-H(21C) | 0.9800 |
| C(22)-H(22) | 0.9500 |
| C(23)-H(23) | 0.9500 |

| | |
|---|---|
| C(13)-O(1)-C(1) | 116.97(11) |
| C(9)-O(2)-C(6) | 106.46(11) |
| C(5)-O(3)-H(3) | 109.1(15) |
| O(1)-C(1)-C(20) | 103.29(12) |
| O(1)-C(1)-C(14) | 106.69(12) |
| C(20)-C(1)-C(14) | 112.31(14) |
| O(1)-C(1)-C(2) | 113.29(12) |
| C(20)-C(1)-C(2) | 110.59(13) |
| C(14)-C(1)-C(2) | 110.46(13) |
| C(3)-C(2)-C(7) | 111.29(13) |
| C(3)-C(2)-C(1) | 115.27(13) |
| C(7)-C(2)-C(1) | 108.64(12) |

| | |
|---|---|
| C(3)-C(2)-H(2) | 107.1 |
| C(7)-C(2)-H(2) | 107.1 |
| C(1)-C(2)-H(2) | 107.1 |
| C(2)-C(3)-C(4) | 109.67(14) |
| C(2)-C(3)-H(3A) | 109.7 |
| C(4)-C(3)-H(3A) | 109.7 |
| C(2)-C(3)-H(3B) | 109.7 |
| C(4)-C(3)-H(3B) | 109.7 |
| H(3A)-C(3)-H(3B) | 108.2 |
| C(3)-C(4)-C(5) | 111.43(13) |
| C(3)-C(4)-H(4A) | 109.3 |
| C(5)-C(4)-H(4A) | 109.3 |
| C(3)-C(4)-H(4B) | 109.3 |
| C(5)-C(4)-H(4B) | 109.3 |
| H(4A)-C(4)-H(4B) | 108.0 |
| O(3)-C(5)-C(21) | 110.75(14) |
| O(3)-C(5)-C(4) | 105.54(13) |
| C(21)-C(5)-C(4) | 111.97(14) |
| O(3)-C(5)-C(6) | 110.53(13) |
| C(21)-C(5)-C(6) | 109.65(14) |
| C(4)-C(5)-C(6) | 108.31(14) |
| O(2)-C(6)-C(5) | 109.48(13) |
| O(2)-C(6)-C(7) | 103.81(12) |
| C(5)-C(6)-C(7) | 114.78(13) |
| O(2)-C(6)-H(6) | 109.5 |
| C(5)-C(6)-H(6) | 109.5 |
| C(7)-C(6)-H(6) | 109.5 |
| C(8)-C(7)-C(6) | 99.59(12) |
| C(8)-C(7)-C(2) | 108.80(12) |
| C(6)-C(7)-C(2) | 121.37(13) |
| C(8)-C(7)-H(7) | 108.8 |
| C(6)-C(7)-H(7) | 108.8 |
| C(2)-C(7)-H(7) | 108.8 |
| C(13)-C(8)-C(9) | 121.43(15) |
| C(13)-C(8)-C(7) | 126.95(14) |
| C(9)-C(8)-C(7) | 110.42(14) |
| O(2)-C(9)-C(8) | 110.76(14) |

| | |
|---|---|
| O(2)-C(9)-C(10) | 127.06(15) |
| C(8)-C(9)-C(10) | 121.98(15) |
| C(9)-C(10)-C(11) | 115.46(15) |
| C(9)-C(10)-C(22) | 119.58(16) |
| C(11)-C(10)-C(22) | 124.83(16) |
| C(12)-C(11)-C(10) | 122.02(15) |
| C(12)-C(11)-C(23) | 115.48(16) |
| C(10)-C(11)-C(23) | 122.49(16) |
| C(11)-C(12)-C(13) | 119.74(15) |
| C(11)-C(12)-H(12) | 120.1 |
| C(13)-C(12)-H(12) | 120.1 |
| O(1)-C(13)-C(8) | 120.95(14) |
| O(1)-C(13)-C(12) | 120.33(14) |
| C(8)-C(13)-C(12) | 118.56(15) |
| C(15)-C(14)-C(1) | 115.34(14) |
| C(15)-C(14)-H(14A) | 108.4 |
| C(1)-C(14)-H(14A) | 108.4 |
| C(15)-C(14)-H(14B) | 108.4 |
| C(1)-C(14)-H(14B) | 108.4 |
| H(14A)-C(14)-H(14B) | 107.5 |
| C(16)-C(15)-C(14) | 112.13(16) |
| C(16)-C(15)-H(15A) | 109.2 |
| C(14)-C(15)-H(15A) | 109.2 |
| C(16)-C(15)-H(15B) | 109.2 |
| C(14)-C(15)-H(15B) | 109.2 |
| H(15A)-C(15)-H(15B) | 107.9 |
| C(17)-C(16)-C(15) | 127.28(19) |
| C(17)-C(16)-H(16) | 116.4 |
| C(15)-C(16)-H(16) | 116.4 |
| C(16)-C(17)-C(18) | 124.7(2) |
| C(16)-C(17)-C(19) | 120.94(18) |
| C(18)-C(17)-C(19) | 114.36(18) |
| C(17)-C(18)-H(18A) | 109.5 |
| C(17)-C(18)-H(18B) | 109.5 |
| H(18A)-C(18)-H(18B) | 109.5 |
| C(17)-C(18)-H(18C) | 109.5 |
| H(18A)-C(18)-H(18C) | 109.5 |

| | |
|---|---|
| H(18B)-C(18)-H(18C) | 109.5 |
| C(17)-C(19)-H(19A) | 109.5 |
| C(17)-C(19)-H(19B) | 109.5 |
| H(19A)-C(19)-H(19B) | 109.5 |
| C(17)-C(19)-H(19C) | 109.5 |
| H(19A)-C(19)-H(19C) | 109.5 |
| H(19B)-C(19)-H(19C) | 109.5 |
| C(1)-C(20)-H(20A) | 109.5 |
| C(1)-C(20)-H(20B) | 109.5 |
| H(20A)-C(20)-H(20B) | 109.5 |
| C(1)-C(20)-H(20C) | 109.5 |
| H(20A)-C(20)-H(20C) | 109.5 |
| H(20B)-C(20)-H(20C) | 109.5 |
| C(5)-C(21)-H(21A) | 109.5 |
| C(5)-C(21)-H(21B) | 109.5 |
| H(21A)-C(21)-H(21B) | 109.5 |
| C(5)-C(21)-H(21C) | 109.5 |
| H(21A)-C(21)-H(21C) | 109.5 |
| H(21B)-C(21)-H(21C) | 109.5 |
| O(4)-C(22)-C(10) | 124.14(18) |
| O(4)-C(22)-H(22) | 117.9 |
| C(10)-C(22)-H(22) | 117.9 |
| O(5)-C(23)-C(11) | 124.11(19) |
| O(5)-C(23)-H(23) | 117.9 |
| C(11)-C(23)-H(23) | 117.9 |

Symmetry transformations used to generate equivalent atoms:

**Table A3.4.** Anisotropic displacement parameters ($Å^2 x\ 10^3$) for bisabosqual A. The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$.

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 23(1) | 26(1) | 27(1) | -1(1) | 4(1) | -6(1) |
| O(2) | 27(1) | 35(1) | 24(1) | -5(1) | 4(1) | -6(1) |
| O(3) | 24(1) | 37(1) | 25(1) | -3(1) | -2(1) | -7(1) |
| O(4) | 74(1) | 56(1) | 35(1) | -9(1) | -13(1) | -24(1) |
| O(5) | 49(1) | 52(1) | 75(1) | -12(1) | 2(1) | -26(1) |
| C(1) | 25(1) | 26(1) | 23(1) | -1(1) | 2(1) | -5(1) |
| C(2) | 24(1) | 27(1) | 21(1) | -2(1) | 0(1) | -8(1) |
| C(3) | 33(1) | 25(1) | 24(1) | -3(1) | 1(1) | -3(1) |
| C(4) | 40(1) | 25(1) | 28(1) | 1(1) | -3(1) | -9(1) |
| C(5) | 27(1) | 30(1) | 24(1) | 1(1) | 0(1) | -11(1) |
| C(6) | 21(1) | 33(1) | 24(1) | -3(1) | 2(1) | -9(1) |
| C(7) | 18(1) | 26(1) | 24(1) | 0(1) | 1(1) | -4(1) |
| C(8) | 20(1) | 23(1) | 27(1) | -2(1) | -1(1) | -2(1) |
| C(9) | 23(1) | 26(1) | 28(1) | -3(1) | 2(1) | -1(1) |
| C(10) | 31(1) | 25(1) | 32(1) | -5(1) | -6(1) | 1(1) |
| C(11) | 27(1) | 23(1) | 38(1) | -3(1) | -6(1) | -1(1) |
| C(12) | 23(1) | 23(1) | 38(1) | 0(1) | 0(1) | -4(1) |
| C(13) | 21(1) | 21(1) | 28(1) | 0(1) | -1(1) | 0(1) |
| C(14) | 27(1) | 32(1) | 24(1) | 0(1) | 1(1) | -2(1) |
| C(15) | 40(1) | 38(1) | 37(1) | 9(1) | 5(1) | 4(1) |
| C(16) | 43(1) | 35(1) | 30(1) | 2(1) | -2(1) | 1(1) |
| C(17) | 40(1) | 33(1) | 31(1) | 0(1) | 1(1) | -5(1) |
| C(18) | 56(1) | 56(1) | 51(1) | -12(1) | -7(1) | -15(1) |
| C(19) | 52(1) | 36(1) | 48(1) | -1(1) | -4(1) | 6(1) |
| C(20) | 34(1) | 31(1) | 25(1) | -2(1) | 4(1) | -1(1) |
| C(21) | 41(1) | 39(1) | 29(1) | 6(1) | 2(1) | -13(1) |
| C(22) | 41(1) | 29(1) | 31(1) | -3(1) | -5(1) | -4(1) |
| C(23) | 42(1) | 36(1) | 46(1) | -5(1) | -4(1) | -12(1) |

**Table A3.5.** Hydrogen coordinates (x $10^4$) and isotropic displacement parameters (Å$^2$x $10^3$) for bisabosqual A.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(3) | 9770(40) | 7400(20) | 9172(8) | 34 |
| H(2) | 6021 | 7288 | 6968 | 29 |
| H(3A) | 10643 | 6984 | 7570 | 33 |
| H(3B) | 9691 | 5892 | 7061 | 33 |
| H(4A) | 8996 | 4867 | 8147 | 37 |
| H(4B) | 6333 | 5426 | 7905 | 37 |
| H(6) | 3884 | 7667 | 8540 | 31 |
| H(7) | 4495 | 9144 | 7619 | 28 |
| H(12) | 12289 | 11739 | 7462 | 33 |
| H(14A) | 5256 | 9232 | 6128 | 34 |
| H(14B) | 5481 | 10350 | 6706 | 34 |
| H(15A) | 8558 | 11487 | 5971 | 47 |
| H(15B) | 8062 | 10430 | 5387 | 47 |
| H(16) | 4337 | 11692 | 5216 | 44 |
| H(18A) | 6963 | 13231 | 6556 | 80 |
| H(18B) | 4331 | 14022 | 6797 | 80 |
| H(18C) | 6178 | 14821 | 6263 | 80 |
| H(19A) | 2860 | 15076 | 5387 | 69 |
| H(19B) | 1033 | 14352 | 5953 | 69 |
| H(19C) | 1602 | 13645 | 5228 | 69 |
| H(20A) | 10711 | 8663 | 5727 | 46 |
| H(20B) | 9012 | 7339 | 5860 | 46 |
| H(20C) | 11397 | 7410 | 6276 | 46 |
| H(21A) | 7594 | 5047 | 9395 | 54 |
| H(21B) | 4856 | 5447 | 9168 | 54 |
| H(21C) | 6047 | 6487 | 9653 | 54 |
| H(22) | 7167 | 10872 | 9856 | 40 |
| H(23) | 11894 | 13179 | 9074 | 49 |

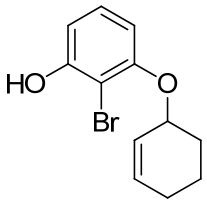
**Table A3.6.** Hydrogen bonds for bisabosqual A [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| O(3)-H(3)...O(4)#1 | 0.827(16) | 1.964(16) | 2.7852(18) | 172(2) |

Symmetry transformations used to generate equivalent atoms:
#1 -x+2,-y+2,-z+2

**Appendix 4.** Relevant Spectra

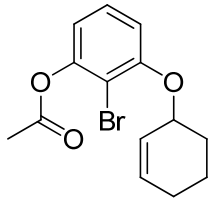
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Date*** | Aug 25 2010 | ***Date Stamp*** | Aug 25 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\100825\5101.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 38.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2411.4619 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.9**

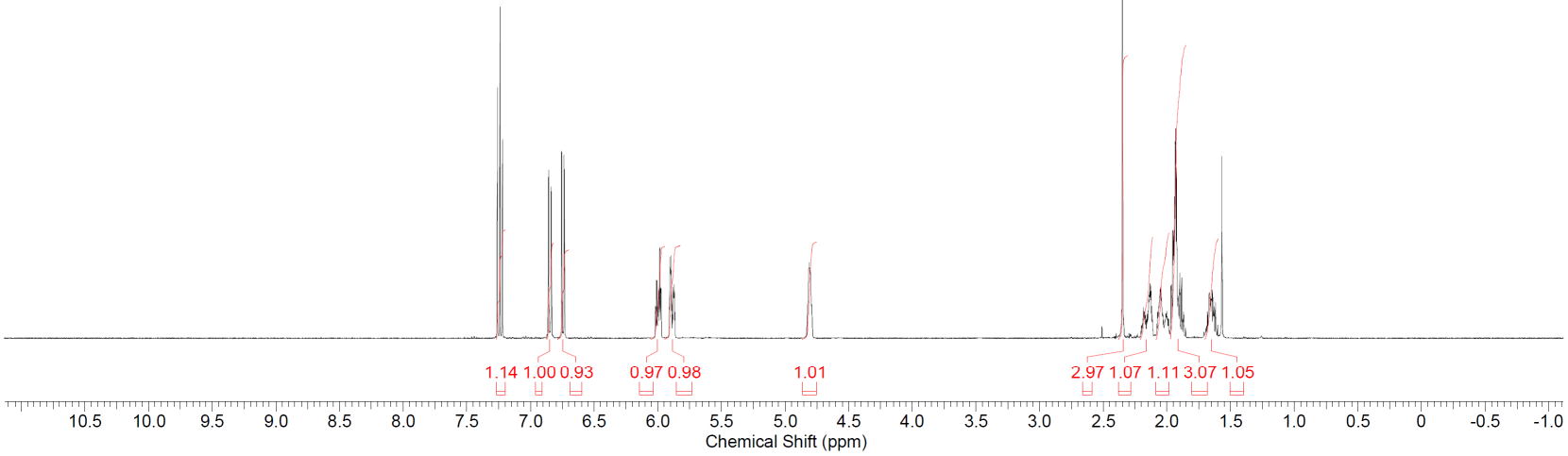
$^1$HNMR (400 MHz) in $CDCl_3$

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Date*** | Sep 5 2010 | ***Date Stamp*** | Sep 5 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\100905\0101.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 44.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2411.2666 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |

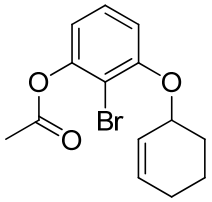



**3.10**

$^{1}$HNMR (400 MHz) in $CDCl_3$



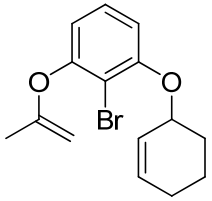
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Date*** | Sep 5 2010 | ***Date Stamp*** | Sep 5 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\100905\0102.FID\FID | | | ***Frequency (MHz)*** | 100.55 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 256 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10031.5898 |
| ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.10**

$^{13}$CNMR (100 MHz) in $CDCl_3$

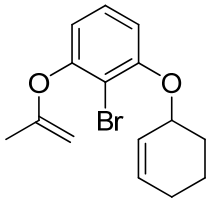
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Date*** | Oct 19 2010 | ***Date Stamp*** | Oct 19 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\101019\3001.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 48.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2411.2666 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.1**

$^{1}$HNMR (400 MHz) in $CDCl_3$

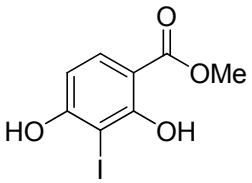
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Date*** | Oct 19 2010 | ***Date Stamp*** | Oct 19 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\101019\9002.FID\FID | | | ***Frequency (MHz)*** | 100.55 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 2048 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10033.0625 |
| ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.1**

$^{13}$CNMR (100 MHz) in $CDCl_3$

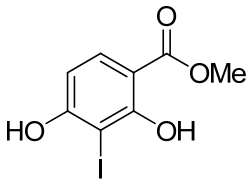
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 5.1118 | ***Comment*** | 00701217-C229-1234 | | | ***Date*** | Sep 15 2010 |
| ***Date Stamp*** | Sep 15 2010 | ***File Name*** | \\UNITYJ.PFIZER.COM\AUTO\2010\20100915\00701217-C229-1234_20100915_01\PROTON_01.FID\FID | | | | |
| ***Frequency (MHz)*** | 399.65 | ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 32768 |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 42.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 2404.6633 | ***Sweep Width (Hz)*** | 6410.26 | ***Temperature (degree C)*** | 25.000 | | |




**3.13**

$^{1}$HNMR (400 MHz) in $CDCl_3$

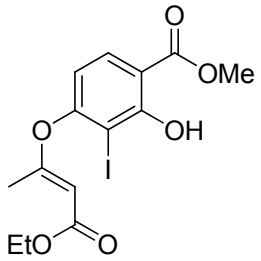
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.2788 | ***Comment*** | 00701217-C227-pure | | | ***Date*** | Sep 15 2010 |
| ***Date Stamp*** | Sep 15 2010 | ***File Name*** | \\UNITYJ.PFIZER.COM\AUTO\2010\20100915\00701217-C227-PURE_20100915_01\CARBON_01.FID\FID | | | | |
| ***Frequency (MHz)*** | 100.50 | ***Nucleus*** | 13C | ***Number of Transients*** | 13312 | ***Original Points Count*** | 33301 |
| ***Points Count*** | 65536 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 10805.0107 | ***Sweep Width (Hz)*** | 26041.67 | ***Temperature (degree C)*** | 25.000 | | |




**3.13**

$^{13}$CNMR (100 MHz) in $CDCl_3$

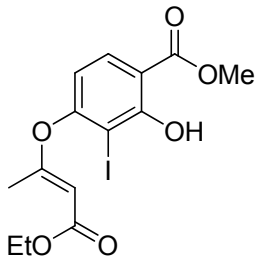
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Date*** | Nov 5 2009 | ***Date Stamp*** | Nov 5 2009 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\091105\1001.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 48.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2410.8760 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.15**

$^{1}$HNMR (400 MHz) in $CDCl_3$

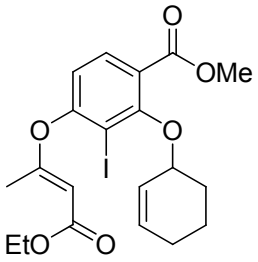
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Date*** | Nov 5 2009 | ***Date Stamp*** | Nov 5 2009 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\091105\1002.FID\FID | | | ***Frequency (MHz)*** | 100.55 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10031.5898 |
| ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.15**

$^{13}$CNMR (100 MHz) in $CDCl_3$

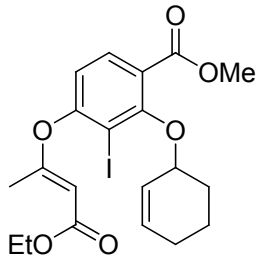
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 5.1220 | ***Date*** | Aug 25 2010 | ***Date Stamp*** | Aug 25 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\100825\1001.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 64 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 48.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2411.4619 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.2**

$^{1}$HNMR (400 MHz) in $CDCl_3$

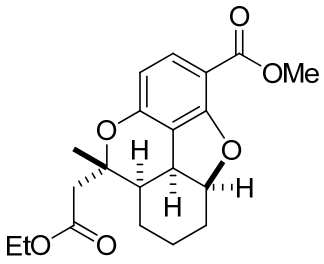
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Date*** | Nov 6 2009 | ***Date Stamp*** | Nov 6 2009 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\091106\2802.FID\FID | | | ***Frequency (MHz)*** | 100.55 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10025.6992 |
| ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.2**

$^{13}$CNMR (100 MHz)
in $CDCl_3$

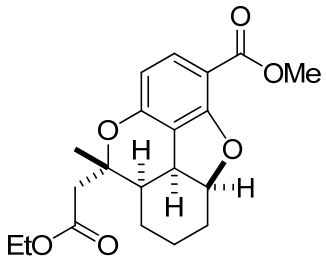
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 5.1118 | ***Comment*** | 00701217-C257-desired_long | | | ***Date*** | Oct 9 2010 |
| ***Date Stamp*** | Oct 9 2010 | ***File Name*** | \\UNITYJ.PFIZER.COM\AUTO\2010\20101009\00701217-C257-DESIRED_LONG_20101009_01\PROTON_01.FID\FID | | | | |
| ***Frequency (MHz)*** | 399.65 | ***Nucleus*** | 1H | ***Number of Transients*** | 192 | ***Original Points Count*** | 32768 |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 22.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 2405.0547 | ***Sweep Width (Hz)*** | 6410.26 | ***Temperature (degree C)*** | 25.000 | | |




**3.16**

$^{1}$HNMR (400 MHz) in $CDCl_3$

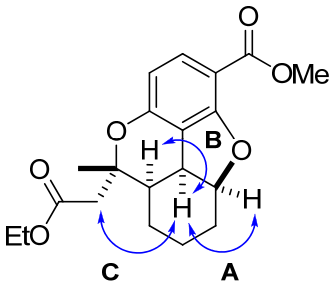
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.2788 | ***Comment*** | 00701217-C257-desired_long | | | ***Date*** | Oct 9 2010 |
| ***Date Stamp*** | Oct 9 2010 | ***File Name*** | \\UNITYJ.PFIZER.COM\AUTO\2010\20101009\00701217-C257-DESIRED_LONG_20101009_01\CARBON_01.FID\FID | | | | |
| ***Frequency (MHz)*** | 100.50 | ***Nucleus*** | 13C | ***Number of Transients*** | 13312 | ***Original Points Count*** | 33301 |
| ***Points Count*** | 65536 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 10798.6523 | ***Sweep Width (Hz)*** | 26041.67 | ***Temperature (degree C)*** | 25.000 | | |



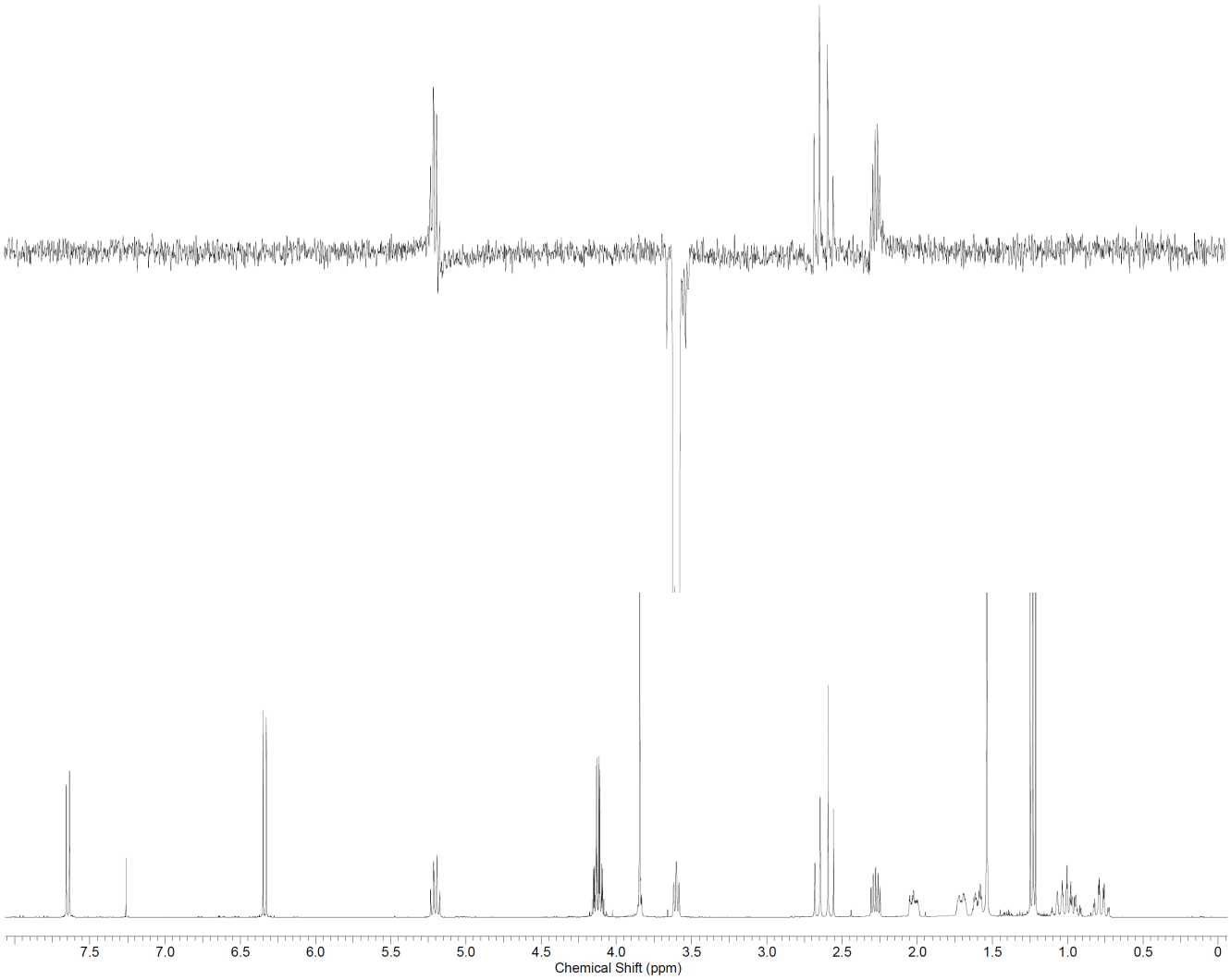

**3.16**

$^{13}$CNMR (100 MHz) in $CDCl_3$

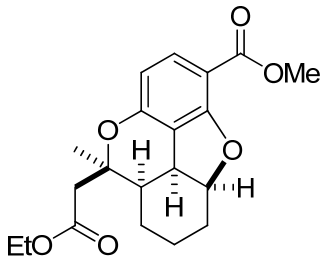
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5623 | ***Comment*** | 00701217-C35-NOE-3.6 | | | ***Date*** | Jun 25 2010 |
| ***Date Stamp*** | Jun 25 2010 | | | | | | |
| ***File Name*** | C:\DOCUME~1\AMENDC01\LOCALS~1\TEMP\GAINS4520.TMP\PRODUCTION\UNITYJ\AMENDC01\00701217-C35-NOE-3.6.2010176104641.FID\FID | | | | | | |
| ***Frequency (MHz)*** | 399.65 | ***Nucleus*** | 1H | ***Number of Transients*** | 64 | ***Original Points Count*** | 16384 |
| ***Points Count*** | 16384 | ***Pulse Sequence*** | NOESY1D | ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 2397.8594 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6394.37 | ***Temperature (degree C)*** | 25.000 |




**3.16**
NOE 3.60 ppm



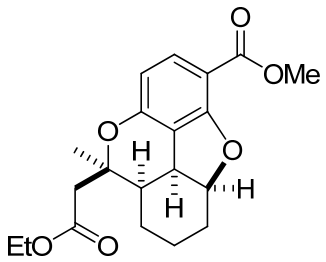
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 5.1118 | ***Comment*** | 00701217-C257-other-pure | | | ***Date*** | Nov 2 2010 |
| ***Date Stamp*** | Nov 2 2010 | ***File Name*** | \\UNITYJ.PFIZER.COM\AUTO\2010\20101102\00701217-C257-OTHER-PURE_20101102_01\PROTON_01.FID\FID | | | | |
| ***Frequency (MHz)*** | 399.65 | ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 32768 |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 30.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 2404.8589 | ***Sweep Width (Hz)*** | 6410.26 | ***Temperature (degree C)*** | 25.000 | | |




C-7-*epi*-**3.16**

$^1$HNMR (400 MHz) in $CDCl_3$

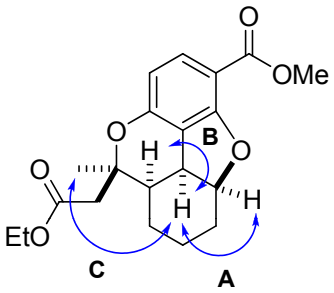
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.2780 | ***Comment*** | 00701217-C257-other-pure | | | ***Date*** | Nov 2 2010 |
| ***Date Stamp*** | Nov 2 2010 | ***File Name*** | \\UNITYJ.PFIZER.COM\AUTO\2010\20101102\00701217-C257-OTHER-PURE_20101102_01\CARBON_01.FID\FID | | | | |
| ***Frequency (MHz)*** | 100.50 | ***Nucleus*** | 13C | ***Number of Transients*** | 512 | ***Original Points Count*** | 33280 |
| ***Points Count*** | 65536 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 10803.8193 | ***Sweep Width (Hz)*** | 26041.67 | ***Temperature (degree C)*** | 25.000 | | |



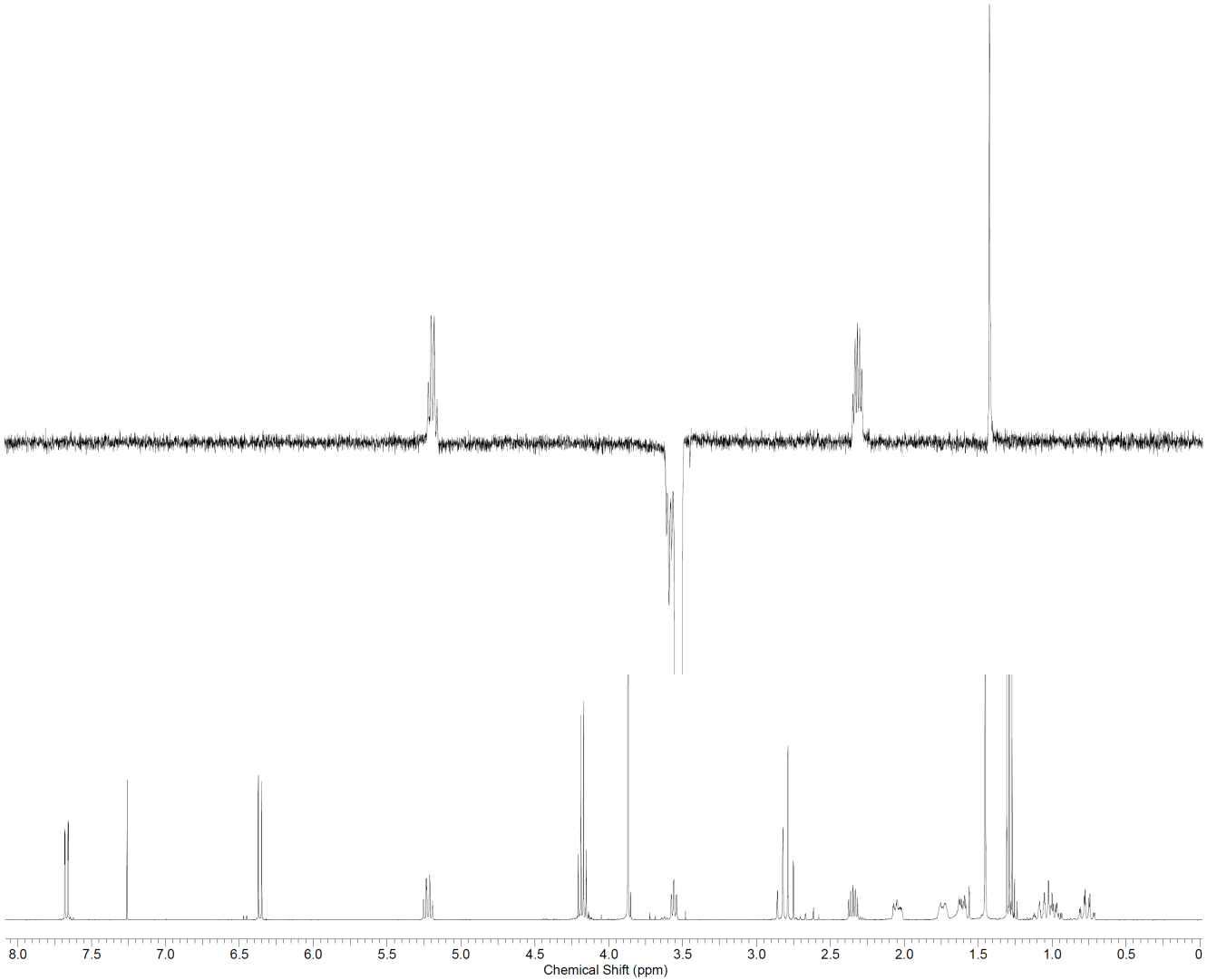

C-7-*epi*-**3.16**

$^{13}$CNMR (100 MHz) in $CDCl_3$

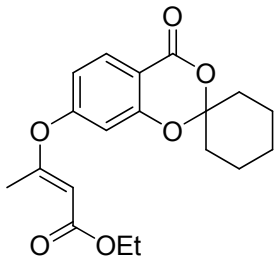
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5610 | ***Date*** | Nov 3 2010 | ***Date Stamp*** | Nov 3 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\101103\3402.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 64 | ***Original Points Count*** | 16384 | ***Points Count*** | 16384 | ***Pulse Sequence*** | NOESY1D |
| ***Receiver Gain*** | 52.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2398.9565 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




C-7-*epi*-**3.16**
NOE 3.52 ppm



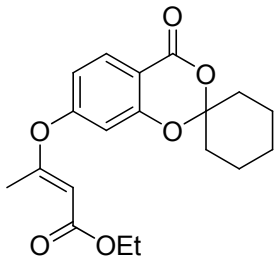
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Date*** | Nov 28 2009 | ***Date Stamp*** | Nov 28 2009 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\091128\0301.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 38.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2413.2190 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.22**

$^{1}$HNMR (400 MHz) in $CDCl_3$

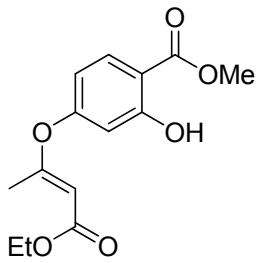
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Date*** | Nov 28 2009 | ***Date Stamp*** | Nov 28 2009 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\091128\0302.FID\FID | | | ***Frequency (MHz)*** | 100.55 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10031.5898 |
| ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.22**

$^{13}$CNMR (100 MHz) in $CDCl_3$

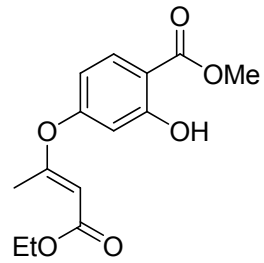
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 5.1220 | ***Date*** | Dec 4 2009 | ***Date Stamp*** | Dec 4 2009 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\091204\2101.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 64 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 54.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2412.4380 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.23**

$^{1}$HNMR (400 MHz) in $CDCl_3$

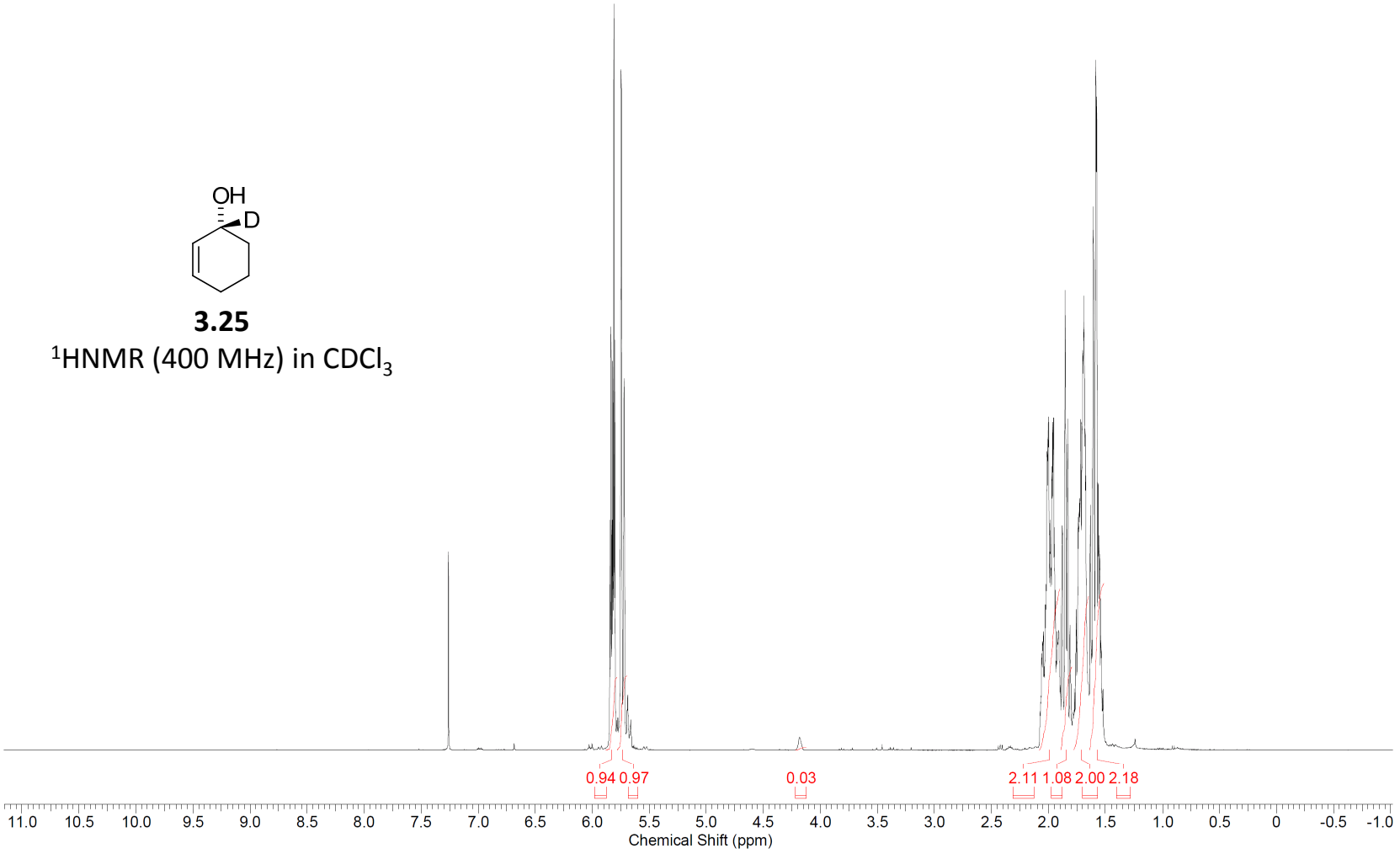
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3586 | ***Date*** | Nov 28 2009 | ***Date Stamp*** | Nov 28 2009 | | |
| ***File Name*** | \\UNITYJ.PFIZER.COM\SAMBA\091128\0302.FID\FID | | | ***Frequency (MHz)*** | 100.50 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 256 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10028.1289 |
| ***Sweep Width (Hz)*** | 24118.18 | ***Temperature (degree C)*** | 25.000 | | | | |



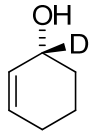

**3.23**

$^{13}$CNMR (100 MHz) in $CDCl_3$

| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5625 | ***Comment*** | NMR System BNMR_319-1 400 10025582 Pfizer Confidential proton CDCl3 {C:\Bruker\TopSpin3.0pl4} amendc01 58 | | |
| ***Date*** | 25 Jan 2013 17:06:56 | ***Date Stamp*** | 25 Jan 2013 17:06:56 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-C245\3\PDATA\1\1r | | | | |
| ***Frequency (MHz)*** | 399.54 | ***Nucleus*** | 1H | ***Number of Transients*** | 16 |
| ***Origin*** | spect | ***Original Points Count*** | 16384 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 65536 | ***Pulse Sequence*** | zg30 | ***Receiver Gain*** | 71.80 |
| ***SW(cyclical) (Hz)*** | 6393.86 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 2385.9692 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6393.76 | ***Temperature (degree C)*** | 25.150 |



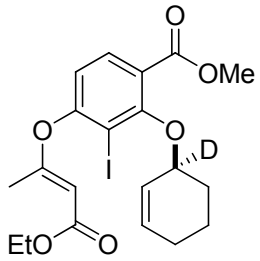
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3631 | ***Comment*** | NMR System BNMR_319-1 400 10025582 Pfizer Confidential carbon_320 CDCl3 {C:\Bruker\TopSpin3.0pl4} amendc01 42 | | |
| ***Date*** | 26 Jan 2013 05:48:32 | ***Date Stamp*** | 26 Jan 2013 05:48:32 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-C245-CARBON\1\PDATA\1\1r | | | | |
| ***Frequency (MHz)*** | 100.46 | ***Nucleus*** | 13C | ***Number of Transients*** | 8192 |
| ***Origin*** | spect | ***Original Points Count*** | 32768 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 65536 | ***Pulse Sequence*** | zgpg30 | ***Receiver Gain*** | 362.00 |
| ***SW(cyclical) (Hz)*** | 24038.46 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 10046.7695 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24038.09 | ***Temperature (degree C)*** | 25.147 |




**3.25**

$^{13}$CNMR (100 MHz) in $CDCl_3$

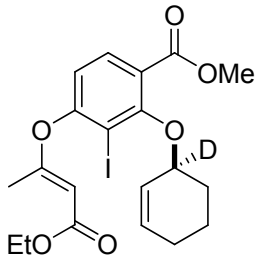
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Date*** | Sep 24 2010 | ***Date Stamp*** | Sep 24 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\100924\0401.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 48.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2411.4619 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.26**

$^1$HNMR (400 MHz) in $CDCl_3$

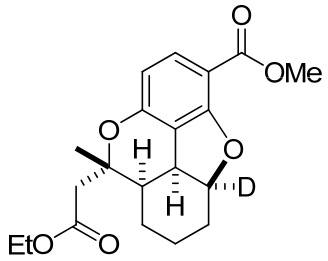
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3591 | ***Date*** | Sep 24 2010 | ***Date Stamp*** | Sep 24 2010 | | |
| ***File Name*** | \\UNITYG.PFIZER.COM\SAMBA\100924\9002.FID\FID | | | ***Frequency (MHz)*** | 100.47 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 8192 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10023.8232 |
| ***Sweep Width (Hz)*** | 24110.91 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.26**

$^{13}$CNMR (100 MHz) in $CDCl_3$

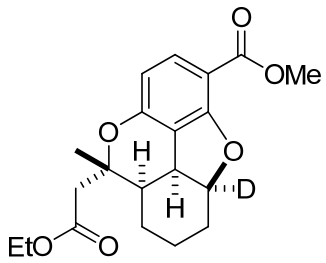
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 5.1257 | ***Date*** | Sep 28 2010 | ***Date Stamp*** | Sep 28 2010 | | |
| ***File Name*** | \\UNITYG.PFIZER.COM\SAMBA\100928\9001.FID\FID | | | ***Frequency (MHz)*** | 399.54 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 64 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 50.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2402.0876 |
| ***Sweep Width (Hz)*** | 6392.84 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.27**

$^{1}$HNMR (400 MHz) in $CDCl_3$

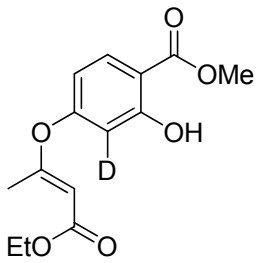
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3591 | ***Date*** | Sep 28 2010 | ***Date Stamp*** | Sep 28 2010 | | |
| ***File Name*** | \\UNITYG.PFIZER.COM\SAMBA\100928\9002.FID\FID | | | ***Frequency (MHz)*** | 100.47 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 2048 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10024.5586 |
| ***Sweep Width (Hz)*** | 24110.91 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.27**

$^{13}$CNMR (100 MHz) in $CDCl_3$

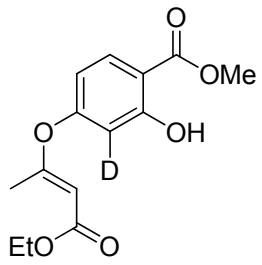
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 5.1118 | ***Comment*** | 00701217-F135-18N | | | ***Date*** | Jan 29 2013 |
| ***Date Stamp*** | Jan 29 2013 | ***File Name*** | \\UNITYH.PFIZER.COM\AUTO\2013\20130129\00701217-F135-18N_20130129_01\PROTON_01.FID\FID | | | | |
| ***Frequency (MHz)*** | 400.20 | ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 32768 |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 30.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 2401.8123 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6410.26 | ***Temperature (degree C)*** | 25.000 |




**3.28**

$^{1}$HNMR (400 MHz) in $CDCl_3$

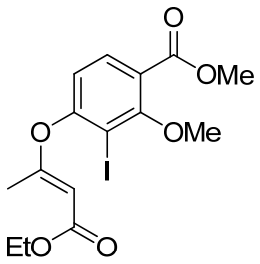
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.4680 | ***Comment*** | 00701217-F135-18N | | | ***Date*** | Jan 29 2013 |
| ***Date Stamp*** | Jan 29 2013 | ***File Name*** | \\UNITYH.PFIZER.COM\AUTO\2013\20130129\00701217-F135-18N_20130129_01\CARBON_01.FID\FID | | | | |
| ***Frequency (MHz)*** | 100.64 | ***Nucleus*** | 13C | ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 40.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 10063.0557 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 22321.43 | ***Temperature (degree C)*** | 25.000 |




**3.28**

$^{13}$CNMR (100 MHz) in $CDCl_3$

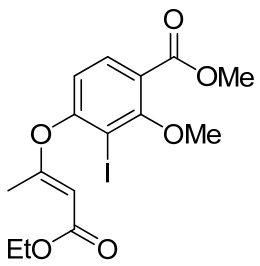
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Date*** | Nov 23 2009 | ***Date Stamp*** | Nov 23 2009 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\091123\0501.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 44.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2412.8286 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.29**

$^{1}$HNMR (400 MHz) in $CDCl_3$

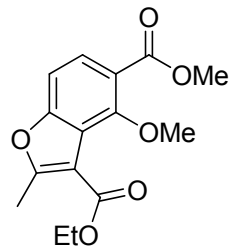
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Date*** | Nov 23 2009 | ***Date Stamp*** | Nov 23 2009 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\091123\0502.FID\FID | | | ***Frequency (MHz)*** | 100.55 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10032.3262 |
| ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.29**

$^{13}$CNMR (100 MHz) in $CDCl_3$

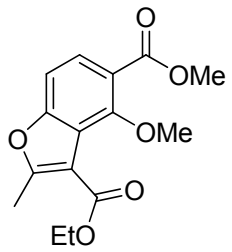
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Date*** | Dec 3 2009 | ***Date Stamp*** | Dec 3 2009 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\091203\2301.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 44.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2413.2190 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.30**

$^1$HNMR (400 MHz) in $CDCl_3$

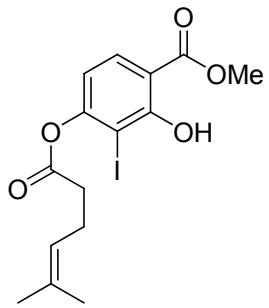
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Date*** | Dec 3 2009 | ***Date Stamp*** | Dec 3 2009 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\091203\2302.FID\FID | | | ***Frequency (MHz)*** | 100.55 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10032.3262 |
| ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 | | | | |




**3.30**

$^{13}$CNMR (100 MHz) in $CDCl_3$

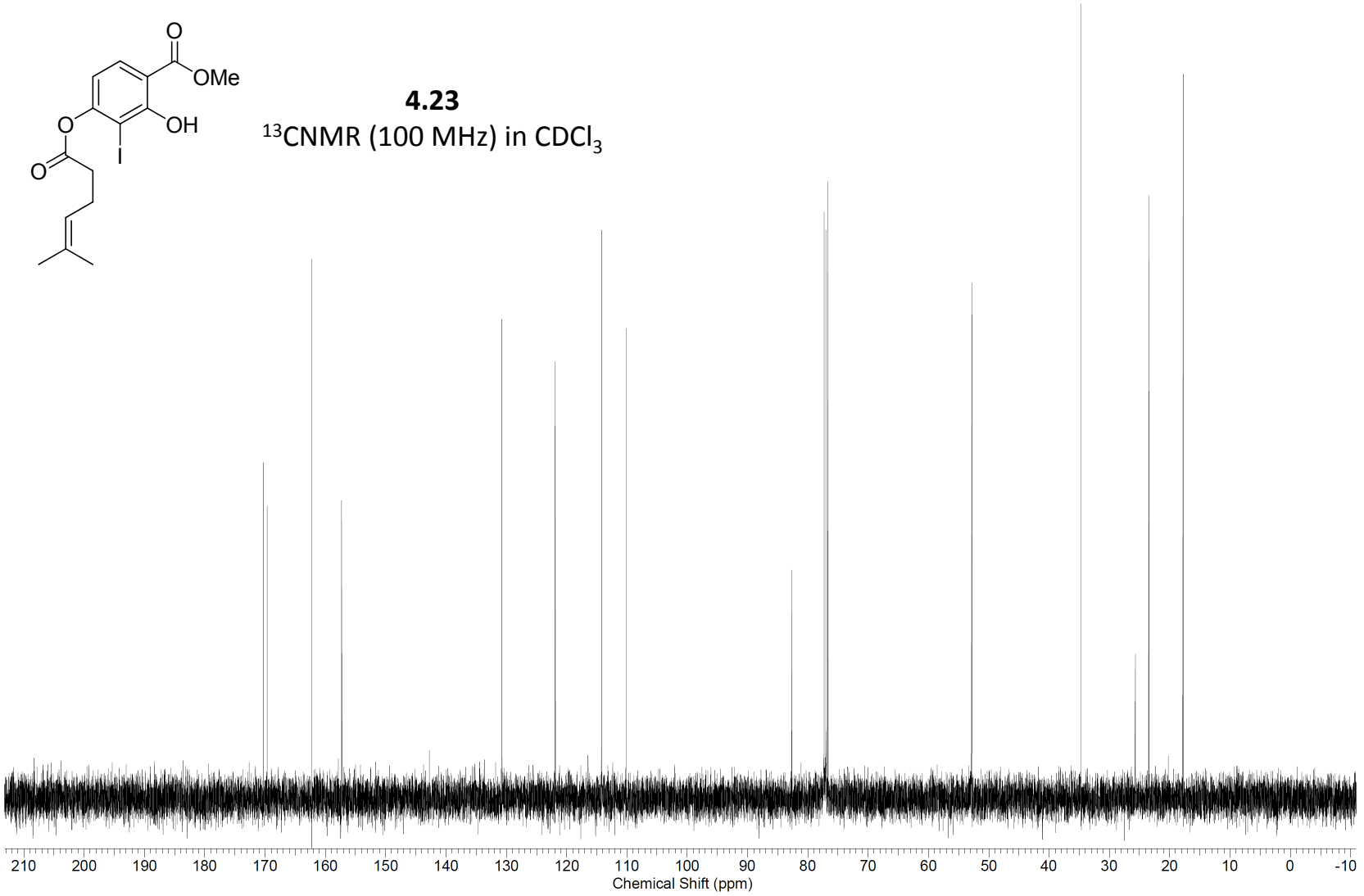
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6832 | ***Comment*** | 00701217-B103-pure | | | ***Date*** | Feb 20 2010 |
| ***Date Stamp*** | Feb 20 2010 | ***File Name*** | \\UNITYJ.PFIZER.COM\SAMBA\100220\0101.FID\FID | | | ***Frequency (MHz)*** | 399.65 |
| ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 44.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 2407.8457 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6394.37 | ***Temperature (degree C)*** | 25.000 |



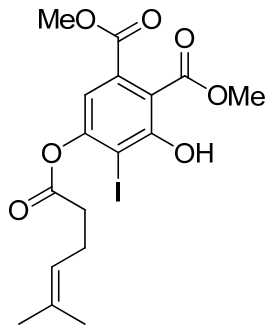

**4.23**

$^{1}$HNMR (400 MHz) in $CDCl_3$

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3586 | ***Comment*** | 00701217-B103-pure Quick C-13 for concentrated sample | | | ***Date*** | Feb 20 2010 |
| ***Date Stamp*** | Feb 20 2010 | ***File Name*** | \\UNITYJ.PFIZER.COM\SAMBA\100220\0102.FID\FID | | | ***Frequency (MHz)*** | 100.50 |
| ***Nucleus*** | 13C | ***Number of Transients*** | 256 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 10027.3936 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24118.18 | ***Temperature (degree C)*** | 25.000 |



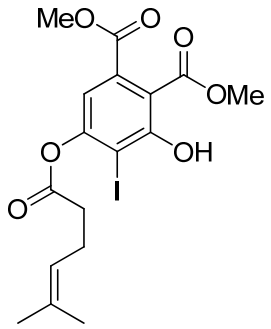
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Comment*** | 00701217-B101-pure | | | ***Date*** | Feb 20 2010 |
| ***Date Stamp*** | Feb 20 2010 | ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\100220\0101.FID\FID | | | ***Frequency (MHz)*** | 399.83 |
| ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 48.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 2411.2666 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 |




**4.24**

$^1$HNMR (400 MHz) in $CDCl_3$

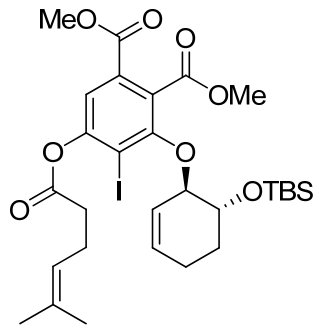
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Comment*** | 00701217-B101-pure ¦ ¦ ¦ Medium C-13 for moderate concentration | | | | |
| ***Date*** | Feb 20 2010 | ***Date Stamp*** | Feb 20 2010 | ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\100220\0102.FID\FID | | |
| ***Frequency (MHz)*** | 100.55 | ***Nucleus*** | 13C | ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 10033.7988 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 |




**4.24**

$^{13}$CNMR (100 MHz) in $CDCl_3$

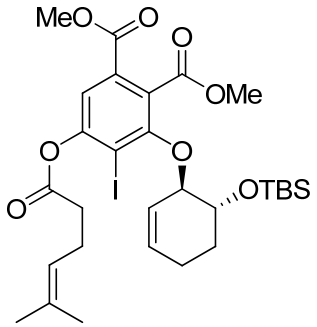
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 5.1118 | ***Comment*** | 00701217-C63-p | ***Date*** | Jan 31 2013 | ***Date Stamp*** | Jan 31 2013 |
| ***File Name*** | \\UNITYH.PFIZER.COM\AUTO\2013\20130131\00701217-C63-P_20130131_01\PROTON_01.FID\FID | | | | | ***Frequency (MHz)*** | 400.20 |
| ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 30.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 2401.8123 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6410.26 | ***Temperature (degree C)*** | 25.000 |




**4.26**

$^{1}$HNMR (400 MHz) in $CDCl_3$

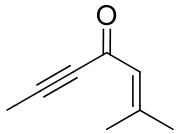
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.4680 | ***Comment*** | 00701217-C63-p | ***Date*** | Jan 31 2013 | ***Date Stamp*** | Jan 31 2013 |
| ***File Name*** | \\UNITYH.PFIZER.COM\AUTO\2013\20130131\00701217-C63-P_20130131_01\CARBON_01.FID\FID | | | | | ***Frequency (MHz)*** | 100.64 |
| ***Nucleus*** | 13C | ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 40.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 10062.3750 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 22321.43 | ***Temperature (degree C)*** | 25.000 |




**4.26**

$^{13}$CNMR (100 MHz) in $CDCl_3$

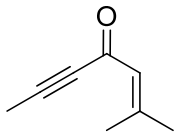
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.9464 | ***Comment*** | 00701217-E293-P | | | ***Date*** | Jun 17 2012 |
| ***Date Stamp*** | Jun 17 2012 | ***File Name*** | \\UNITYI.PFIZER.COM\SAMBA\120617\0201.FID\FID | | | ***Frequency (MHz)*** | 499.58 |
| ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 44.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 2992.8242 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 7993.60 | ***Temperature (degree C)*** | 25.000 |



**4.3**

$^{1}$HNMR (500 MHz) in $CDCl_3$

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.4680 | ***Comment*** | 00701217-E-293 | ***Date*** | Jun 17 2012 | ***Date Stamp*** | Jun 17 2012 |
| ***File Name*** | \\UNITYH.PFIZER.COM\AUTO\2012\20120617\00701217-E-293_20120617_03\CARBON_01.FID\FID | | | | | ***Frequency (MHz)*** | 100.64 |
| ***Nucleus*** | 13C | ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 40.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 10061.6934 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 22321.43 | ***Temperature (degree C)*** | 25.000 |

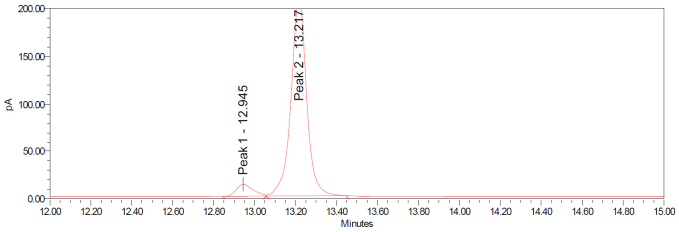



**4.3**

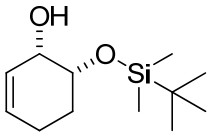
$^{13}$CNMR (100 MHz) in $CDCl_3$

| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5625 | ***Comment*** | | | |
| ***Date*** | 05 Aug 2012 14:20:48 | ***Date Stamp*** | 05 Aug 2012 14:20:48 | | |
| ***File Name*** | | | | | |
| ***Frequency (MHz)*** | 399.54 | ***Nucleus*** | 1H | ***Number of Transients*** | 16 |
| ***Origin*** | spect | ***Original Points Count*** | 16384 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 16384 | ***Pulse Sequence*** | zg30 | ***Receiver Gain*** | 57.00 |
| ***SW(cyclical) (Hz)*** | 6393.86 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 2384.9451 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6393.47 | ***Temperature (degree C)*** | 25.148 |

## Chiral GC – ee determination



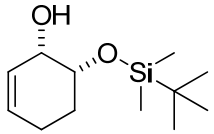

| | Peak Name | Result Id | Retention Time (min) | Area | Height | RRF | Impurity Level | Imp_Calc |
|---|---|---|---|---|---|---|---|---|
| 1 | Peak1 | 37404 | 12.945 | 69 | 13 | 1.000 | 5.90 | Area % Total |
| 2 | Peak2 | 37404 | 13.217 | 1109 | 209 | 1.000 | 94.10 | Area % Total |
| Sum | | | | | | | 100.00 | |




**4.6**

$^{1}$HNMR (400 MHz) in $CDCl_3$

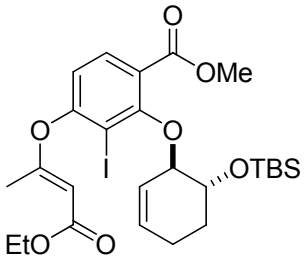
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.4680 | ***Comment*** | 00701217-D-161 | ***Date*** | Jun 17 2012 | ***Date Stamp*** | Jun 17 2012 |
| ***File Name*** | | | | | | ***Frequency (MHz)*** | 100.64 |
| ***Nucleus*** | 13C | ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 40.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 10063.0557 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 22321.43 | ***Temperature (degree C)*** | 25.000 |




**4.6**

$^{13}$CNMR (100 MHz) in $CDCl_3$

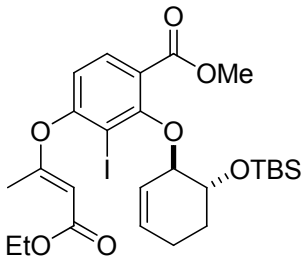
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 5.1220 | ***Date*** | Sep 22 2010 | ***Date Stamp*** | Sep 22 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\100922\9001.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 64 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 48.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2411.8523 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




**4.48**

$^{1}$HNMR (400 MHz) in $CDCl_3$

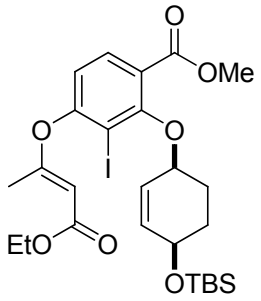
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Date*** | Sep 22 2010 | ***Date Stamp*** | Sep 22 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\100922\9002.FID\FID | | | ***Frequency (MHz)*** | 100.55 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 2048 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10033.7988 |
| ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 | | | | |




**4.48**

$^{13}$CNMR (100 MHz) in $CDCl_3$

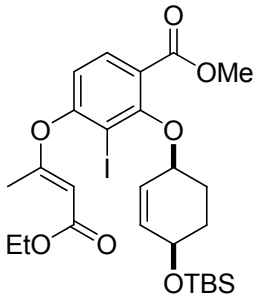
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.7039 | ***Comment*** | 00701217-c239-600 | ***Date*** | Feb 1 2013 | ***Date Stamp*** | Feb 1 2013 |
| ***File Name*** | C:\DOCUME~1\AMENDC01\LOCALS~1\TEMP\GAINS4570.TMP\DLDA-GLDA\OPENLAB\UNITYI\AMENDC01\00701217-C239-600_2013032091127.FID\FID | | | | | | |
| ***Frequency (MHz)*** | 599.82 | ***Nucleus*** | 1H | ***Number of Transients*** | 256 | ***Original Points Count*** | 16384 |
| ***Points Count*** | 16384 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 30.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 3598.9031 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 9615.38 | ***Temperature (degree C)*** | 25.000 |




**4.50**

$^{1}$HNMR (600 MHz) in $CDCl_3$

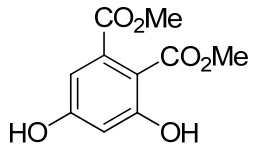
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.2788 | ***Comment*** | 00701217-C239-long | | | ***Date*** | Feb 2 2013 |
| ***Date Stamp*** | Feb 2 2013 | ***File Name*** | \\UNITYH.PFIZER.COM\AUTO\2013\20130202\00701217-C239-LONG_20130202_01\CARBON_01.FID\FID | | | | |
| ***Frequency (MHz)*** | 100.64 | ***Nucleus*** | 13C | ***Number of Transients*** | 16384 | ***Original Points Count*** | 28544 |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 40.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 10063.0557 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 22321.43 | ***Temperature (degree C)*** | 25.000 |




**4.50**

$^{13}$CNMR (100 MHz) in $CDCl_3$

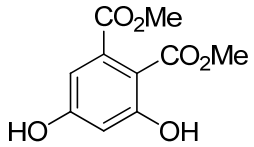
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.9464 | ***Comment*** | 00701217-E215-P | | | ***Date*** | Jun 17 2012 |
| ***Date Stamp*** | Jun 17 2012 | ***File Name*** | \\UNITYI.PFIZER.COM\SAMBA\120617\0101.FID\FID | | | ***Frequency (MHz)*** | 499.58 |
| ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 42.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 2993.0684 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 7993.60 | ***Temperature (degree C)*** | 25.000 |




**4.11**

$^1$HNMR (500 MHz) in $CDCl_3$

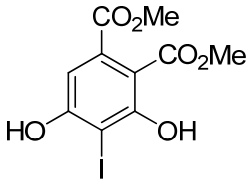
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.4680 | ***Comment*** | 00701217-E-215 | ***Date*** | Jun 17 2012 | ***Date Stamp*** | Jun 17 2012 |
| ***File Name*** | \\UNITYH.PFIZER.COM\AUTO\2012\20120617\00701217-E-215_20120617_02\CARBON_01.FID\FID | | | | | ***Frequency (MHz)*** | 100.64 |
| ***Nucleus*** | 13C | ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 40.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 10061.0127 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 22321.43 | ***Temperature (degree C)*** | 25.000 |




**4.11**

$^{13}$CNMR (100 MHz) in $CDCl_3$

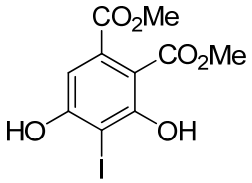
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Date*** | Aug 22 2010 | ***Date Stamp*** | Aug 22 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\100822\0401.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 48.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2411.4619 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




**4.12**

$^{1}$HNMR (400 MHz) in $CDCl_3$

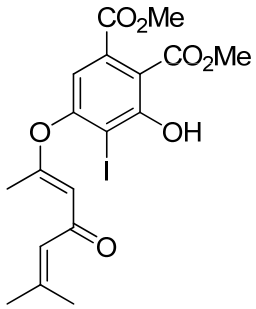
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.0871 | ***Comment*** | 00701217-C139 | Very long C-13 for dilute sample | | ***Date*** | Jul 5 2012 |
| ***Date Stamp*** | Jul 5 2012 | ***File Name*** | \\UNITYI.PFIZER.COM\SAMBA\120705\4002.FID\FID | | | ***Frequency (MHz)*** | 125.63 |
| ***Nucleus*** | 13C | ***Number of Transients*** | 8192 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 12529.5928 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 30143.18 | ***Temperature (degree C)*** | 25.000 |




**4.12**

$^{13}$CNMR (125 MHz) in $CDCl_3$

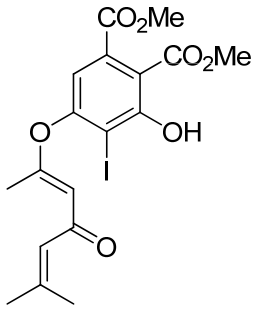
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Comment*** | 00701217-D159 | | | ***Date*** | Mar 18 2011 |
| ***Date Stamp*** | Mar 18 2011 | ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\110318\1601.FID\FID | | | ***Frequency (MHz)*** | 399.83 |
| ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 48.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 2411.8523 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 |




**4.32**

$^{1}$HNMR (400 MHz) in $CDCl_3$

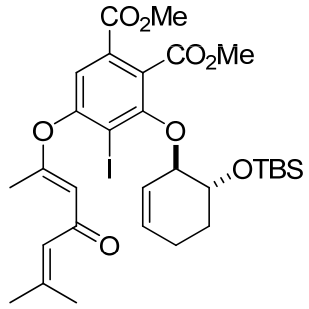
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Comment*** | 00701217-D159 | Longer C-13 for more dilute sample | | ***Date*** | Mar 18 2011 |
| ***Date Stamp*** | Mar 18 2011 | ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\110318\9002.FID\FID | | | ***Frequency (MHz)*** | 100.55 |
| ***Nucleus*** | 13C | ***Number of Transients*** | 2048 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 10033.0625 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 |




**4.32**

$^{13}$CNMR (100 MHz) in $CDCl_3$

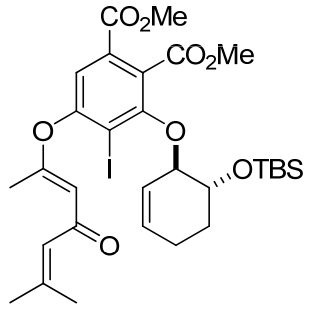
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Date*** | Nov 22 2010 | ***Date Stamp*** | Nov 22 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\101122\1601.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 42.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2411.6570 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |




**4.52**

$^1$HNMR (400 MHz) in $CDCl_3$

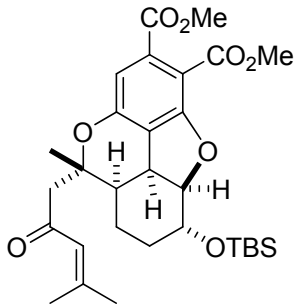
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Date*** | Nov 23 2010 | ***Date Stamp*** | Nov 23 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\101122\9102.FID\FID | | | ***Frequency (MHz)*** | 100.55 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 2048 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10517.7051 |
| ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 | | | | |




**4.52**

$^{13}$CNMR (100 MHz) in $CDCl_3$

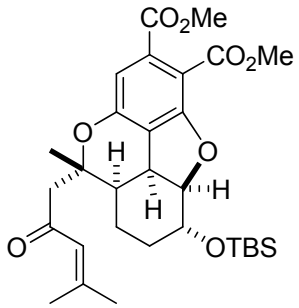
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5625 | ***Comment*** | | | |
| ***Date*** | 13 Apr 2012 09:52:00 | ***Date Stamp*** | 13 Apr 2012 09:52:00 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-E239\2\PDATA\1\1r | | | | |
| ***Frequency (MHz)*** | 399.54 | ***Nucleus*** | 1H | ***Number of Transients*** | 16 |
| ***Origin*** | spect | ***Original Points Count*** | 16384 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 65536 | ***Pulse Sequence*** | zg30 | ***Receiver Gain*** | 114.00 |
| ***SW(cyclical) (Hz)*** | 6393.86 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 2385.2864 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6393.76 | ***Temperature (degree C)*** | 25.152 |




**4.53**

$^{1}$HNMR (400 MHz) in $CDCl_3$

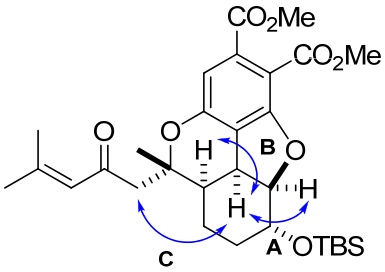
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.2788 | ***Comment*** | 00701217-E-239 | ***Date*** | Sep 20 2012 | ***Date Stamp*** | Sep 20 2012 |
| ***File Name*** | \\UNITYH.PFIZER.COM\AUTO\2012\20120920\00701217-E-239_20120920_01\CARBON_01.FID\FID | | | | | ***Frequency (MHz)*** | 100.64 |
| ***Nucleus*** | 13C | ***Number of Transients*** | 16384 | ***Original Points Count*** | 28544 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 40.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 10063.0029 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 22321.43 | ***Temperature (degree C)*** | 25.000 |




**4.53**

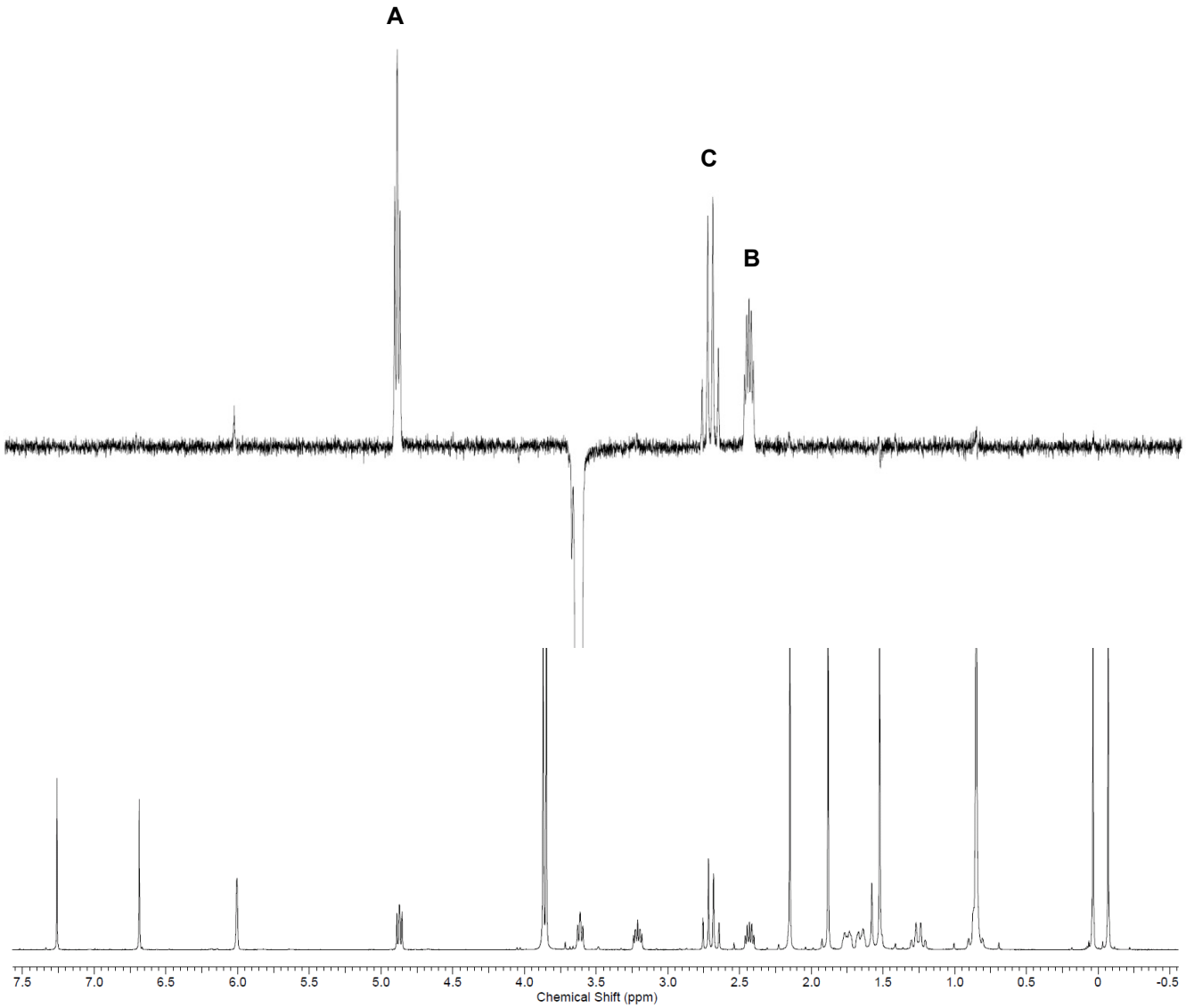
$^{13}$CNMR (100 MHz) in $CDCl_3$

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5559 | ***Comment*** | 00701217-E239-361 | ***Date*** | Jun 19 2012 | ***Date Stamp*** | Jun 19 2012 |
| ***File Name*** | C:\DOCUME~1\AMENDC01\LOCALS~1\TEMP\GAINS9192.TMP\PRODUCTION\UNITYH\AMENDC01\00701217-E239-361_2012171110916.FID\FID | | | | | | |
| ***Frequency (MHz)*** | 400.20 | ***Nucleus*** | 1H | ***Number of Transients*** | 64 | ***Original Points Count*** | 16384 |
| ***Points Count*** | 16384 | ***Pulse Sequence*** | NOESY1D | ***Receiver Gain*** | 30.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 2401.1633 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6410.26 | ***Temperature (degree C)*** | 25.000 |

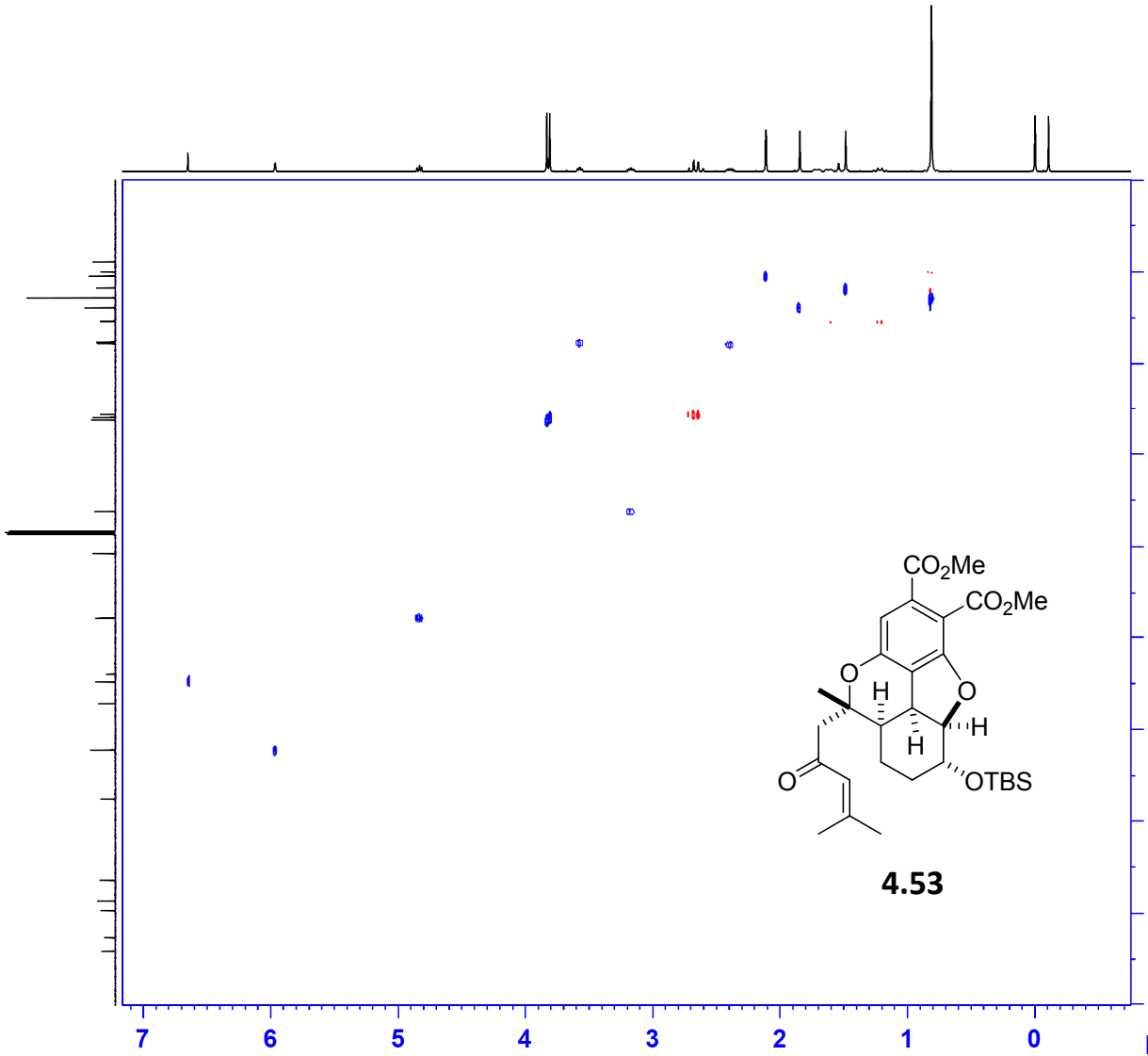



**4.53**

NOE 3.61 ppm



NMR System BNMR_319-1 400 10025582
Pfizer Confidential
hsqc CDCl3 {C:\Bruker\TopSpin3.0pl4} amendc01 53




**4.53**

```
Current Data Parameters
NAME      00701217-E239
EXPNO                5
PROCNO               1

F2 - Acquisition Parameters
Date_          20120710
Time               0.51
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG      hsqcedetgp
TD                 4096
SOLVENT           CDCl3
NS                    4
DS                   16
SWH           3164.557 Hz
FIDRES         0.772597 Hz
AQ            0.6471680 sec
RG                 2050
DW              158.000 usec
DE                6.50 usec
TE               298.3 K
CNST2        145.0000000
D0            0.00000300 sec
D1            0.97313923 sec
D4            0.00172414 sec
D11           0.03000000 sec
D13           0.00000400 sec
D16           0.00020000 sec
D21           0.00345000 sec
IN0           0.00002760 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         399.5413088 MHz
NUC1                   1H
P1                 15.00 usec
P2                 30.00 usec
P28              1000.00 usec
PLW1         13.50000000 W

======== CHANNEL f2 ========
SFO2         100.4734607 MHz
NUC2                  13C
CPDPRG[2             garp
P3                  9.75 usec
P4                 19.50 usec
PCPD2              80.00 usec
PLW2         65.00000000 W
PLW12         0.96548003 W

====== GRADIENT CHANNEL =====
```

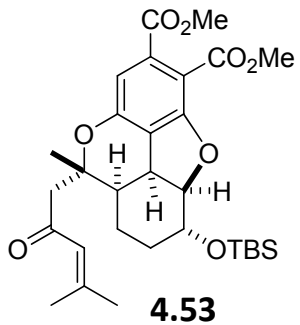
```
GAINS_SAMPLE_REFERENCE:  00701217-E47-peak2
         GAINS_USER_ID:  amendc01
      GAINS_INSTRUMENT:  unityf
 GAINS_EXPERIMENT_TIME:  08/18/2011 20:42:12
        GAINS_END_TIME:  08/18/2011 20:50:28


00701217-E47-peak2
H-H CORRELATION

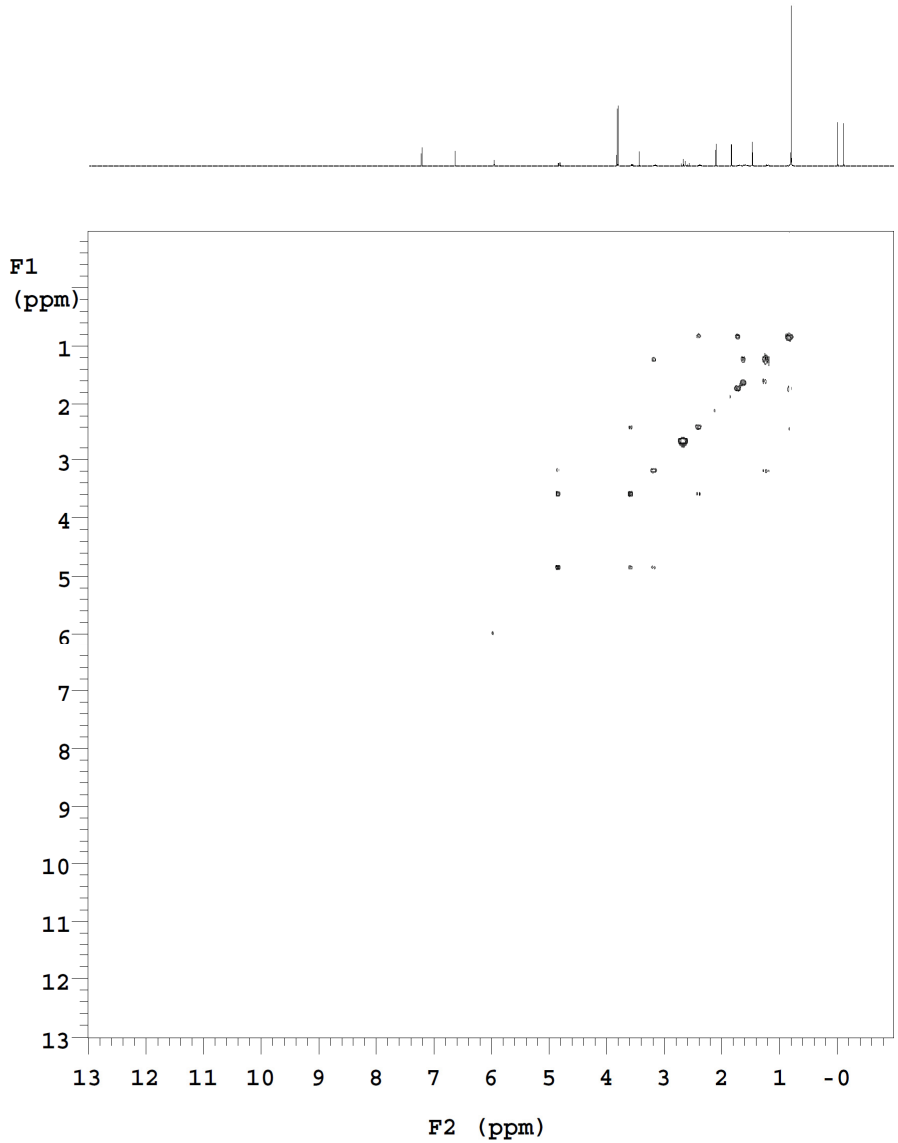
  Automation directory: /auto/Automation_data/110818

Experiment Type: 2D-COSY (H1)
Pulse Sequence: gDQCOSY
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Sample #90, user christopher.amende@pfizer.com
File: 9003
INOVA-400  "unityf"

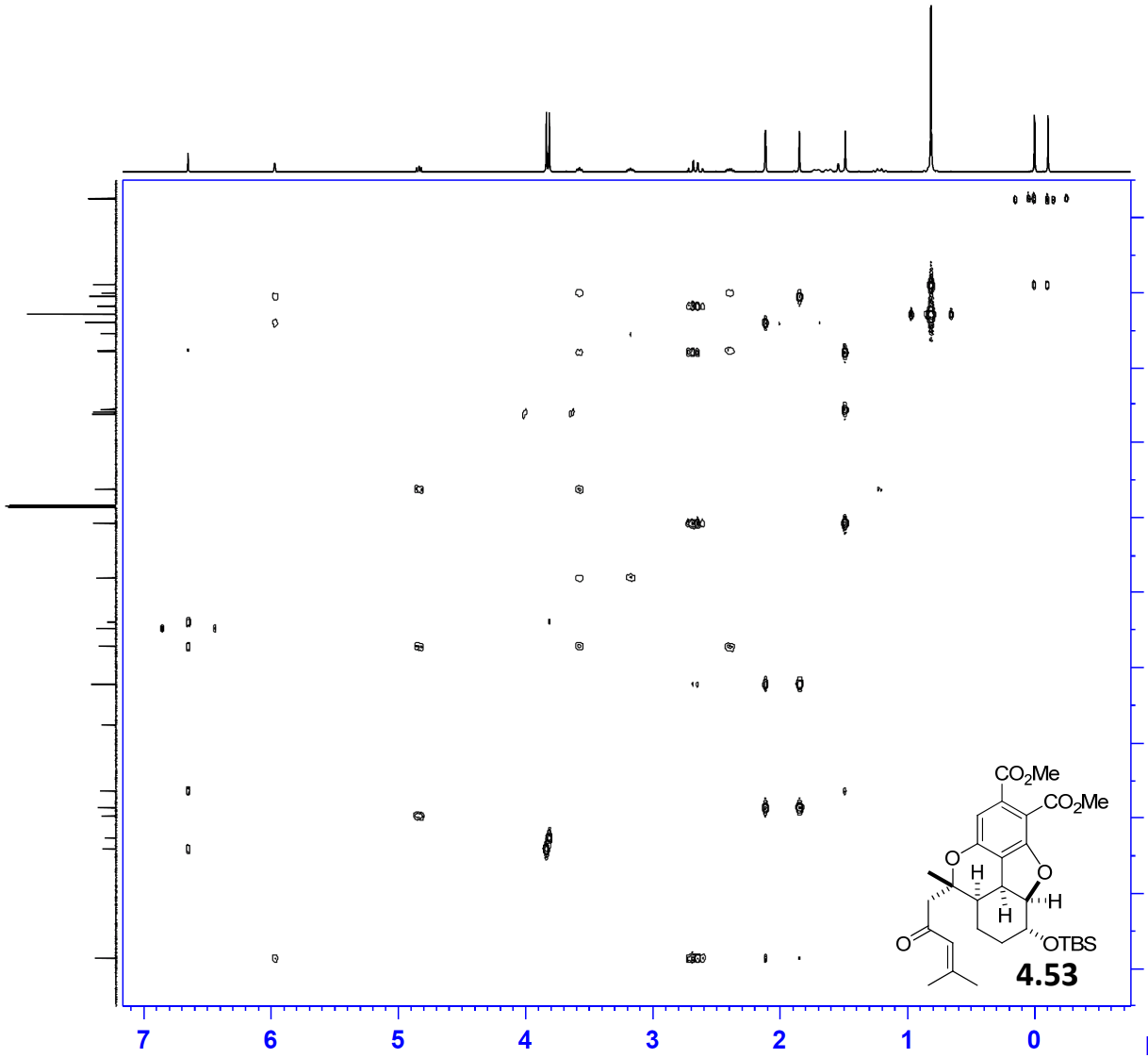

 Relax. delay 0.700 sec
 Acq. time 0.183 sec
 Width    5597.5 Hz
 2D Width 5597.5 Hz
 2 repetitions
 2 x 128 increments
OBSERVE   H1, 399.8301174 MHz
DATA PROCESSING
 Sq. sine bell 0.137 sec
  Shifted by -0.091 sec
F1 DATA PROCESSING
 Sq. sine bell 0.069 sec
  Shifted by -0.046 sec
FT size 2048 x 2048
Total time 8 min, 18 sec
```




**4.53**



NMR System BNMR_319-1 400 10025582
Pfizer Confidential
hmbc CDCl3 {C:\Bruker\TopSpin3.0pl4} amendc01 53

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Current Data Parameters
NAME       00701217-E239
EXPNO                 6
PROCNO                1

F2 - Acquisition Parameters
Date_          20120710
Time               1.08
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG    hmbcgplpndqf
TD                 4096
SOLVENT            CDCl3
NS                   16
DS                   16
SWH             3164.557 Hz
FIDRES          0.772597 Hz
AQ              0.6471680 sec
RG                 2050
DW               158.000 usec
DE                 6.50 usec
TE                298.2 K
CNST2        145.0000000
CNST13         8.0000000
D0            0.00000300 sec
D1            1.00203206 sec
D2            0.00344828 sec
D6            0.06250000 sec
D16           0.00020000 sec
IN0           0.00002260 sec

======== CHANNEL f1 ========
SFO1         399.5413088 MHz
NUC1                1H
P1                15.00 usec
P2                30.00 usec
PLW1         13.50000000 W

======== CHANNEL f2 ========
SFO2         100.4744660 MHz
NUC2                13C
P3                 9.75 usec
PLW2         65.00000000 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPNAM[3]      SMSQ10.100
GPZ1              50.00 %
GPZ2              30.00 %
GPZ3              40.10 %
P16             1000.00 usec
```

```
GAINS_SAMPLE_REFERENCE:  00701217-E47-peak2
         GAINS_USER_ID:  amendc01
      GAINS_INSTRUMENT:  unityf
 GAINS_EXPERIMENT_TIME:  08/18/2011 22:56:33
        GAINS_END_TIME:  08/18/2011 23:56:37

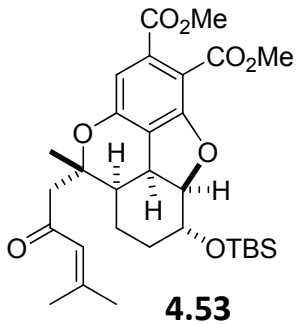

00701217-E47-peak2
H-H THROUGH-SPACE CORRELATION

  Automation directory: /auto/Automation_data/110818

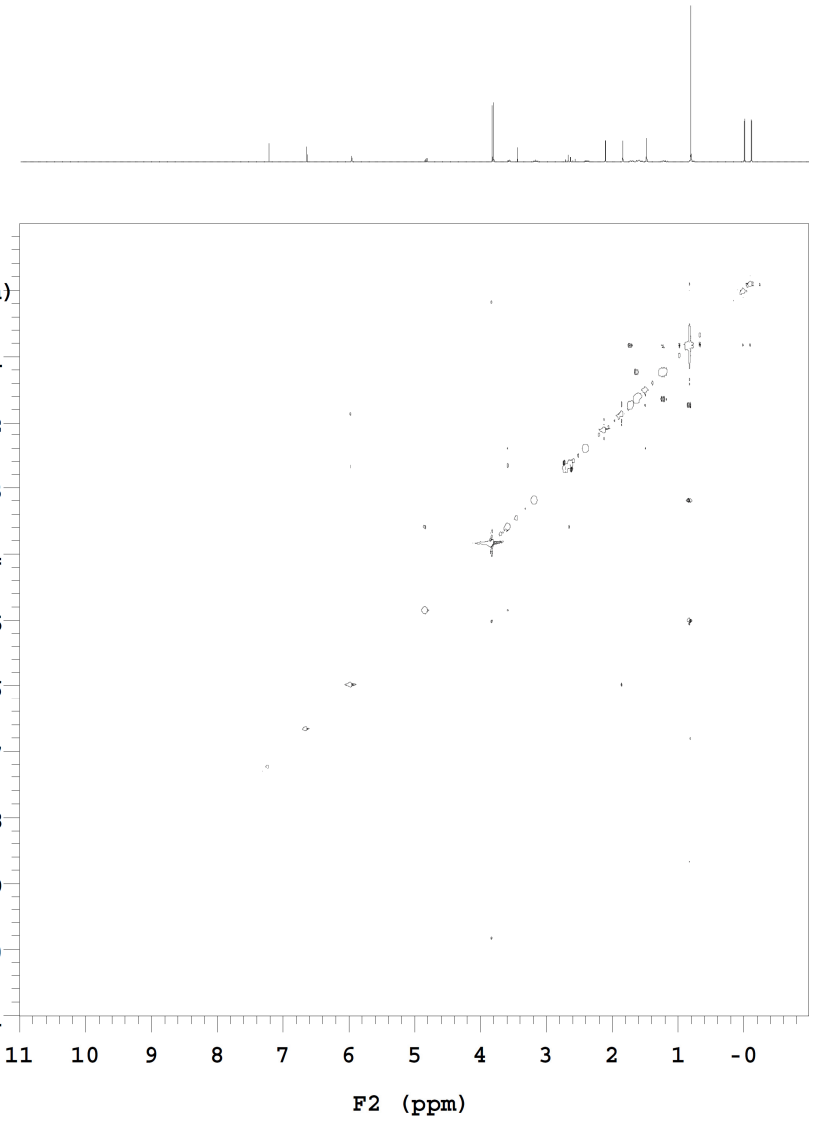
Experiment Type: 2D-NOESY (H1)
Pulse Sequence: NOESY

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
Sample #90, user christopher.amende@pfizer.com
File: 9006
INOVA-400  "unityf"

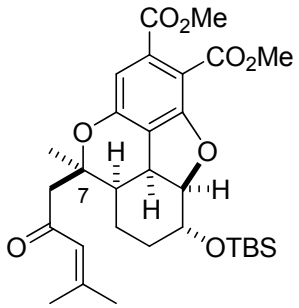

 Relax. delay 1.000 sec
 Mixing 0.500 sec
 Acq. time 0.213 sec
 Width    4797.9 Hz
 2D Width 4797.9 Hz
 8 repetitions
 2 x 128 increments
OBSERVE   H1, 399.8301174 MHz
DATA PROCESSING
 Gauss apodization 0.099 sec
F1 DATA PROCESSING
 Gauss apodization 0.049 sec
FT size 2048 x 2048
Total time 1 hr, 19 sec
```




**4.53**



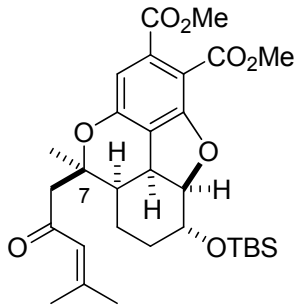
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.9464 | ***Comment*** | 00701217-E239-364 | | | ***Date*** | Jul 28 2012 |
| ***Date Stamp*** | Jul 28 2012 | ***File Name*** | \\UNITYI.PFIZER.COM\SAMBA\120728\0401.FID\FID | | | ***Frequency (MHz)*** | 499.58 |
| ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 42.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 2992.8242 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 7993.60 | ***Temperature (degree C)*** | 25.000 |




C-7-*epi*-**4.53**

$^{1}$HNMR (500 MHz) in $CDCl_3$

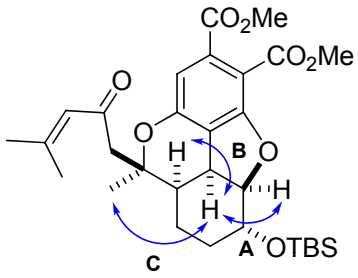
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3631 | ***Comment*** | | | 5 |
| ***Date*** | 01 Aug 2012 00:22:24 | ***Date Stamp*** | 01 Aug 2012 00:22:24 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-E239-CNMR\1\FID | | | | |
| ***Frequency (MHz)*** | 100.46 | ***Nucleus*** | 13C | ***Number of Transients*** | 8192 |
| ***Origin*** | spect | ***Original Points Count*** | 32768 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | zgpg30 | ***Receiver Gain*** | 228.00 |
| ***SW(cyclical) (Hz)*** | 24038.46 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 10046.9531 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24037.73 | ***Temperature (degree C)*** | 25.152 |



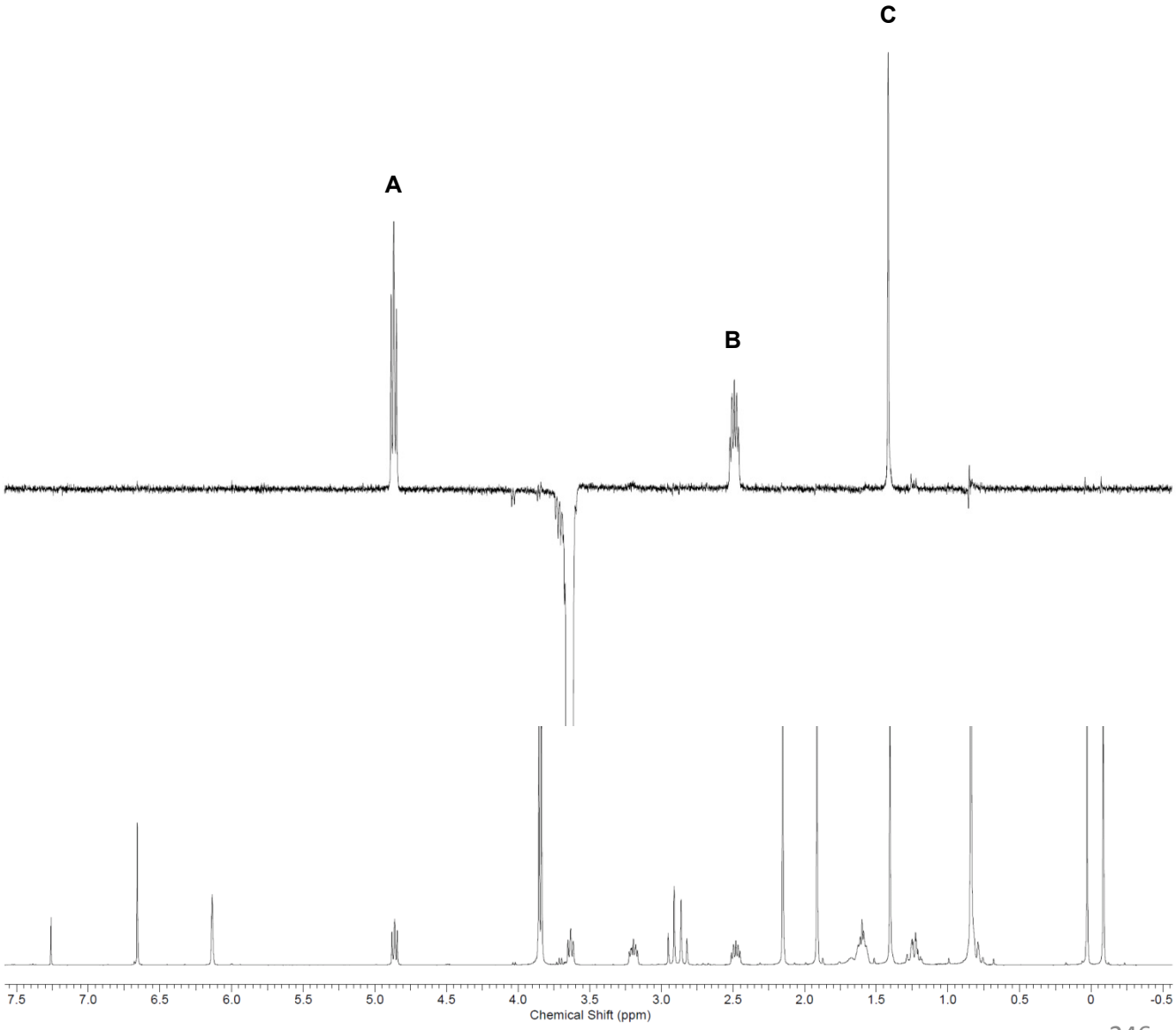

C-7-*epi*-**4.53**

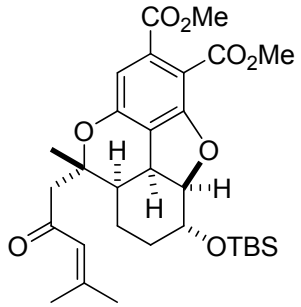
$^{13}$CNMR (100 MHz) in $CDCl_3$

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5559 | ***Comment*** | 00701217-E239-363 | ***Date*** | Jul 31 2012 | ***Date Stamp*** | Jul 31 2012 |
| ***File Name*** | C:\DOCUME~1\AMENDC01\LOCALS~1\TEMP\GAINS19712.TMP\PRODUCTION\UNITYH\AMENDC01\00701217-E239-363_2012213110542.FID\FID | | | | | | |
| ***Frequency (MHz)*** | 400.20 | ***Nucleus*** | 1H | ***Number of Transients*** | 64 | ***Original Points Count*** | 16384 |
| ***Points Count*** | 16384 | ***Pulse Sequence*** | NOESY1D | ***Receiver Gain*** | 30.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 2401.1633 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6410.26 | ***Temperature (degree C)*** | 25.000 |

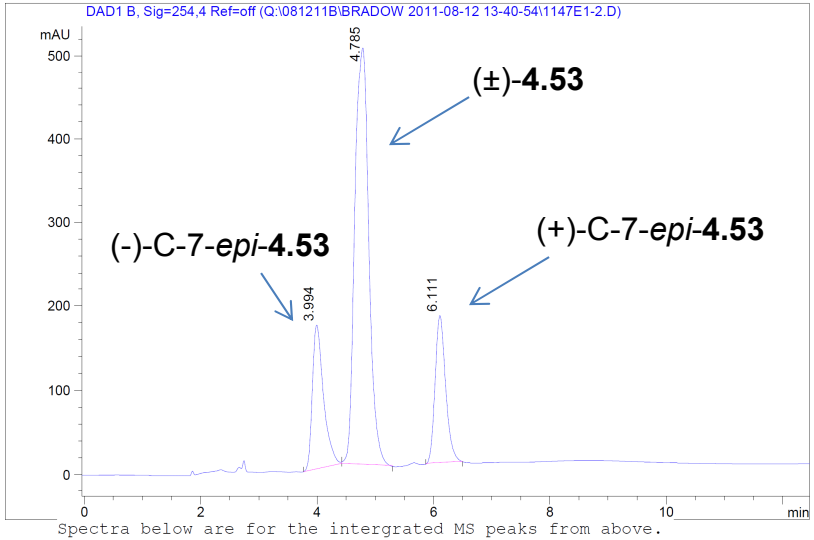



C-7-*epi*-**4.53**
NOE 3.63 ppm





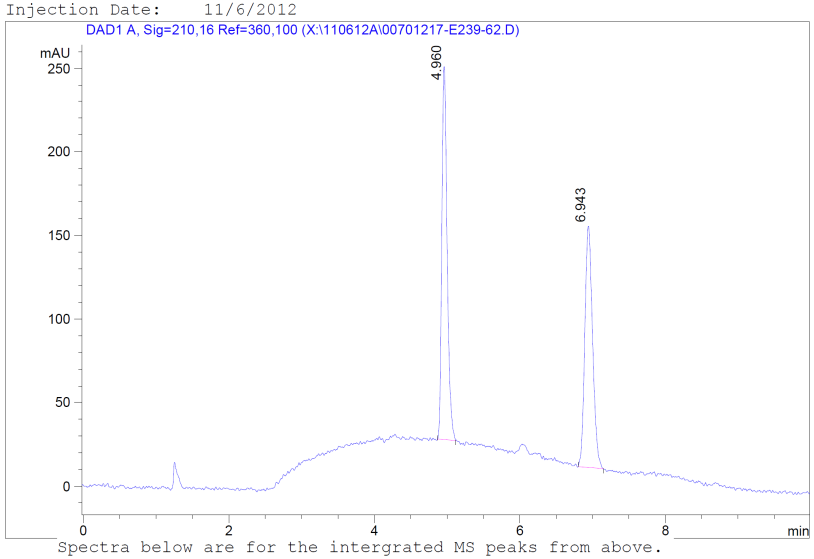

```
  Data:Q:\081211B\BRADOW 2011-08-12 13-40-54\1147E1-2.D
Method:C:\Chem32\1\DATA\081211B\BRADOW 2011-08-12 13-40-54\COLUMN2.M
data acquired by:
              on:  8/12/2011
        location:  Vial 1
   Injection Vol:  5.000
Injection Date:    8/12/2011
```




```
Spectra below are for the intergrated MS peaks from above.
See Spetra header for details.
 #  Meas. R  Area    Area %   Signal Desc.
-------------------------------------------
  1   3.994 2.269e3  17.809 DAD1 B, Sig=254
  2   4.785 8.293e3  65.099
  3   6.111 2.177e3  17.092
-------------------------------------------
```

Separation of Diastereomers **4.53** and C-7-*epi*-**4.53**

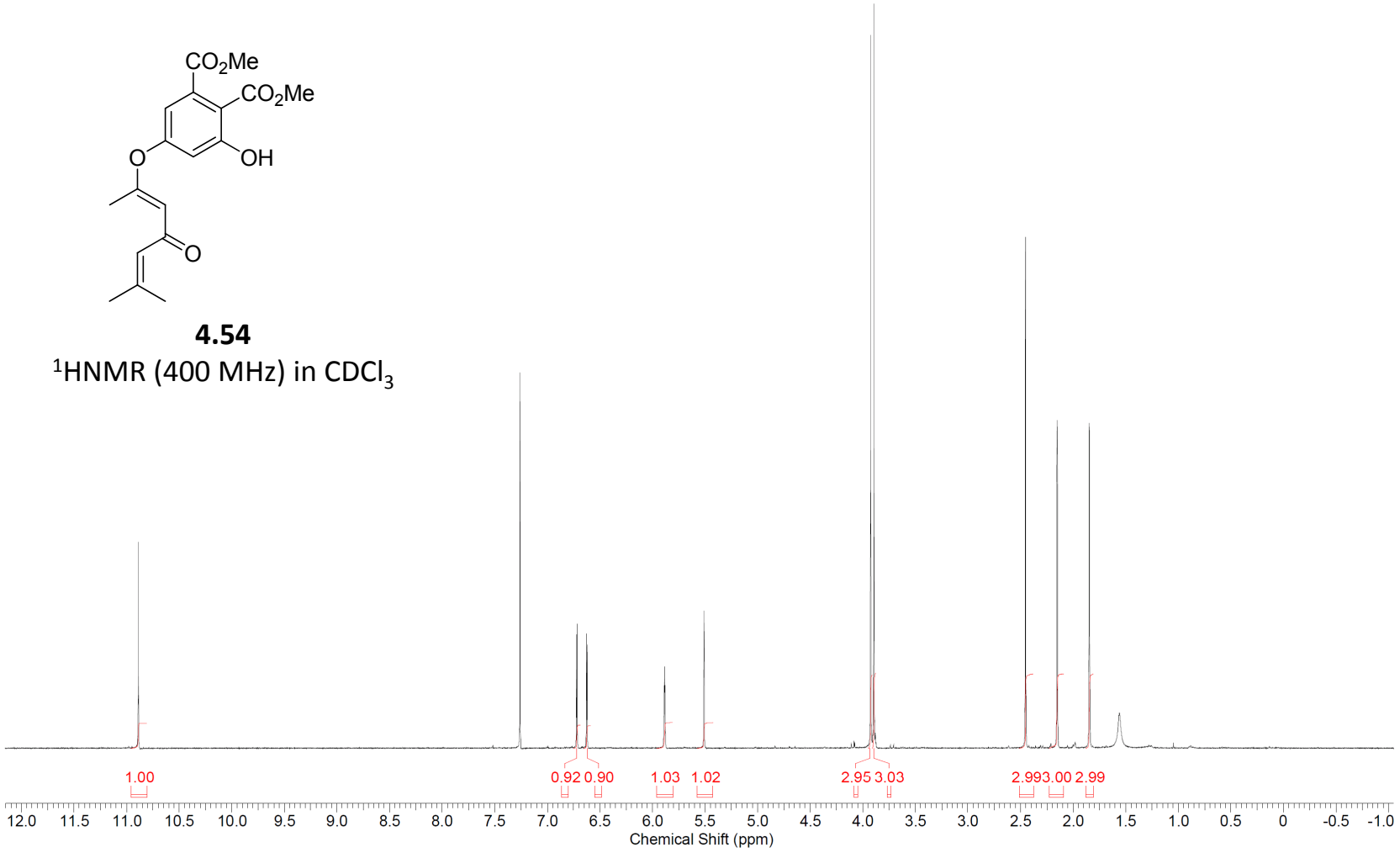
```
Sample:00701217-E239
  Data:X:\110612A\00701217-E239-62.D
Method:C:\CHEM32\1\METHODS\COLUMN_6_METHANOL.M
data acquired by:
              on:  11/6/2012
        location:  Vial 1
   Injection Vol:  Actual Injection Volume not  ->
Injection Date:    11/6/2012
```




```
Spectra below are for the intergrated MS peaks from above.
See Spetra header for details.
 #  Meas. R  Area    Area %   Signal Desc.
-------------------------------------------
  1   4.960 1.135e3  51.606 DAD1 A, Sig=210
  2   6.943 1.064e3  48.394
-------------------------------------------
```

Separation of Enantiomers (**4.53**)

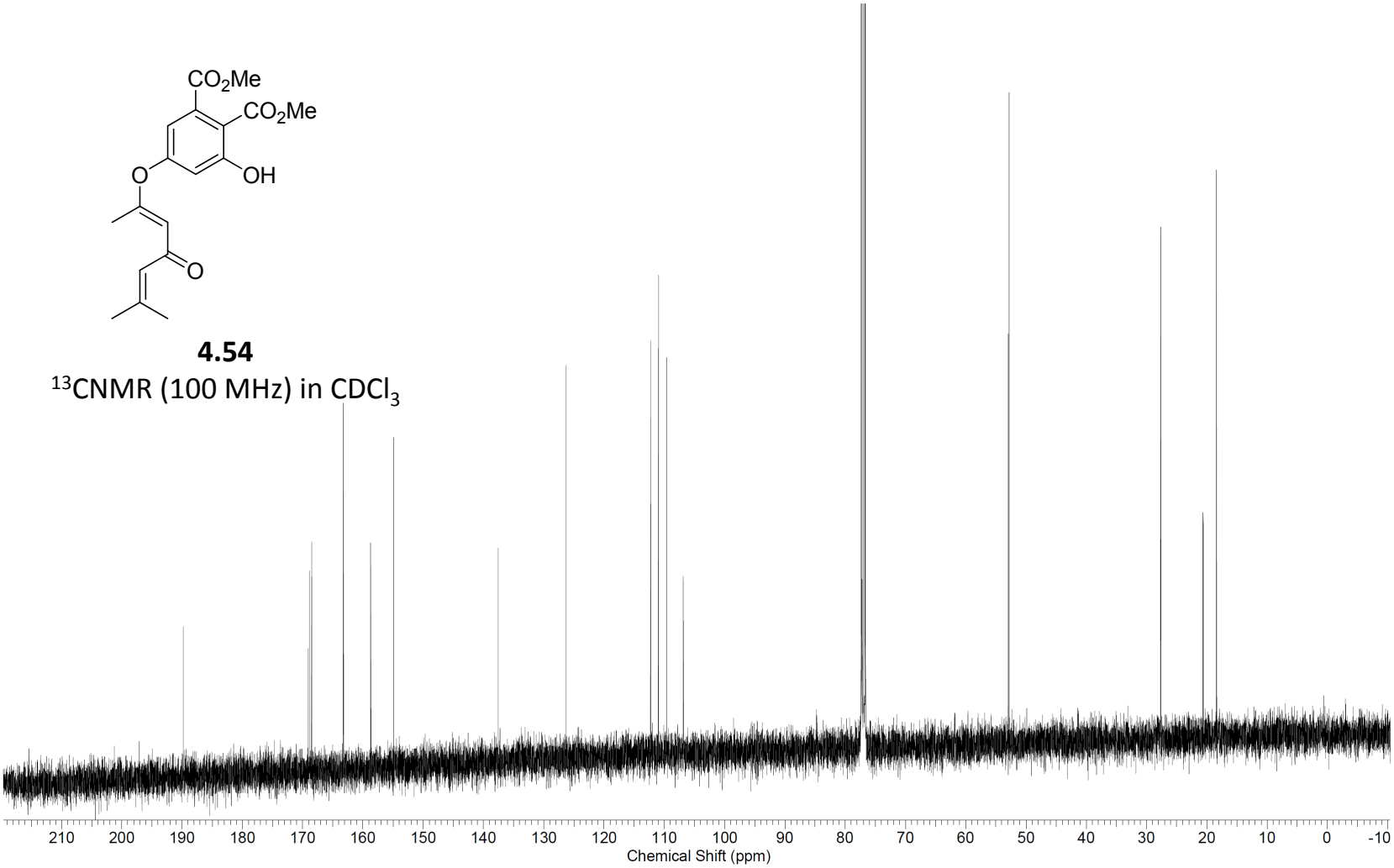
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5625 | ***Comment*** | NMR System BNMR_319-1 400 10025582 Pfizer Confidential proton CDCl3 {C:\Bruker\TopSpin3.0pl4} amendc01 43 | | |
| ***Date*** | 25 Jan 2013 17:00:32 | ***Date Stamp*** | 25 Jan 2013 17:00:32 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-D155\1\FID | | | | |
| ***Frequency (MHz)*** | 399.54 | ***Nucleus*** | 1H | ***Number of Transients*** | 16 |
| ***Origin*** | spect | ***Original Points Count*** | 16384 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 16384 | ***Pulse Sequence*** | zg30 | ***Receiver Gain*** | 362.00 |
| ***SW(cyclical) (Hz)*** | 6393.86 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 2385.7258 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6393.47 | ***Temperature (degree C)*** | 25.154 |




**4.54**

$^{1}$HNMR (400 MHz) in $CDCl_3$

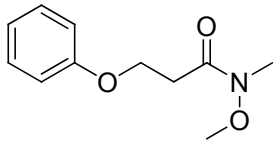
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3631 | ***Comment*** | NMR System BNMR_319-1 400 10025582 Pfizer Confidential carbon_320 CDCl3 {C:\Bruker\TopSpin3.0pl4} amendc01 41 | | |
| ***Date*** | 26 Jan 2013 00:26:24 | ***Date Stamp*** | 26 Jan 2013 00:26:24 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-D155-CARBON\1\FID | | | | |
| ***Frequency (MHz)*** | 100.46 | ***Nucleus*** | 13C | ***Number of Transients*** | 8192 |
| ***Origin*** | spect | ***Original Points Count*** | 32768 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | zgpg30 | ***Receiver Gain*** | 322.00 |
| ***SW(cyclical) (Hz)*** | 24038.46 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 10049.1533 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24037.73 | ***Temperature (degree C)*** | 25.159 |




**4.54**

$^{13}$CNMR (100 MHz) in $CDCl_3$

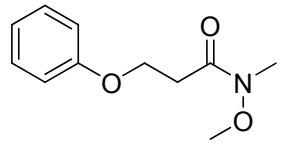
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Date*** | Jul 22 2010 | ***Date Stamp*** | Jul 22 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\100722\1801.FID\FID | | | ***Frequency (MHz)*** | 399.83 | ***Nucleus*** | 1H |
| ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 36.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 2398.9565 |
| ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 | | | | |



**4.60**

$^{1}$HNMR (400 MHz) in $CDCl_3$

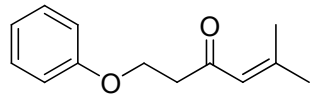
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Date*** | Jul 22 2010 | ***Date Stamp*** | Jul 22 2010 | | |
| ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\100722\1802.FID\FID | | | ***Frequency (MHz)*** | 100.55 | ***Nucleus*** | 13C |
| ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul |
| ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | | ***Spectrum Offset (Hz)*** | 10027.1719 |
| ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 | | | | |




**4.60**

$^{13}$CNMR (100 MHz) in $CDCl_3$

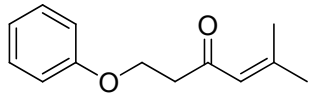
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Comment*** | 00701217-E15 | | | ***Date*** | Jul 1 2011 |
| ***Date Stamp*** | Jul 1 2011 | ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\110701\0901.FID\FID | | | ***Frequency (MHz)*** | 399.83 |
| ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 48.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 2411.4619 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 |




**4.61**

$^{1}$HNMR (400 MHz) in $CDCl_3$

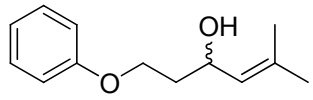
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3631 | ***Comment*** | NMR System BNMR_319-1 400 10025582 Pfizer Confidential carbon CDCl3 {C:\Bruker\TopSpin3.0pl4} amendc01 23 | | |
| ***Date*** | 11 Nov 2012 12:38:08 | ***Date Stamp*** | 11 Nov 2012 12:38:08 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-E15-CNMR\1\PDATA\1\1r | | | | |
| ***Frequency (MHz)*** | 100.46 | ***Nucleus*** | 13C | ***Number of Transients*** | 512 |
| ***Origin*** | spect | ***Original Points Count*** | 32768 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 65536 | ***Pulse Sequence*** | zgpg30 | ***Receiver Gain*** | 322.00 |
| ***SW(cyclical) (Hz)*** | 24038.46 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 10046.0361 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24038.09 | ***Temperature (degree C)*** | 25.153 |




**4.61**

$^{13}$CNMR (100 MHz) in $CDCl_3$

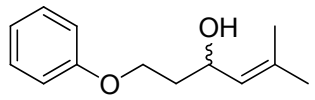
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6815 | ***Comment*** | 00701217-e29 | | | ***Date*** | Jul 11 2011 |
| ***Date Stamp*** | Jul 11 2011 | ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\110711\1601.FID\FID | | | ***Frequency (MHz)*** | 399.83 |
| ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 48.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 2411.0713 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6397.44 | ***Temperature (degree C)*** | 25.000 |




**4.62**

$^{1}$HNMR (400 MHz) in $CDCl_3$

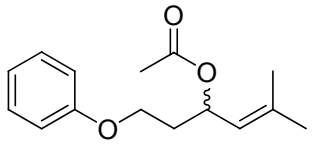
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3582 | ***Comment*** | 00701217-e29 | Quick C-13 for concentrated sample | | ***Date*** | Jul 11 2011 |
| ***Date Stamp*** | Jul 11 2011 | ***File Name*** | \\UNITYF.PFIZER.COM\SAMBA\110711\1602.FID\FID | | | ***Frequency (MHz)*** | 100.55 |
| ***Nucleus*** | 13C | ***Number of Transients*** | 256 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 10033.0625 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24125.45 | ***Temperature (degree C)*** | 25.000 |




**4.62**

$^{13}$CNMR (100 MHz) in $CDCl_3$

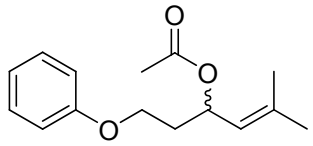
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5625 | ***Comment*** | NMR System BNMR_319-1 400 10025582 Pfizer Confidential proton CDCl3 {C:\Bruker\TopSpin3.0pl4} youngj35 36 | | |
| ***Date*** | 12 Nov 2012 16:56:16 | ***Date Stamp*** | 12 Nov 2012 16:56:16 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\YOUNGJ35\NMR\00702112-F79-P\1\PDATA\1\1r | | | | |
| ***Frequency (MHz)*** | 399.54 | ***Nucleus*** | 1H | ***Number of Transients*** | 16 |
| ***Origin*** | spect | ***Original Points Count*** | 16384 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 65536 | ***Pulse Sequence*** | zg30 | ***Receiver Gain*** | 57.00 |
| ***SW(cyclical) (Hz)*** | 6393.86 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 2373.3835 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6393.76 | ***Temperature (degree C)*** | 25.148 |




**4.63**

$^{1}$HNMR (400 MHz) in $CDCl_3$

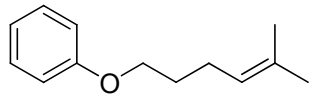
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3631 | ***Comment*** | NMR System BNMR_319-1 400 10025582 Pfizer Confidential carbon CDCl3 {C:\Bruker\TopSpin3.0pl4} amendc01 49 | | |
| ***Date*** | 12 Nov 2012 17:30:24 | ***Date Stamp*** | 12 Nov 2012 17:30:24 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-F79-P\1\PDATA\1\1r | | | | |
| ***Frequency (MHz)*** | 100.46 | ***Nucleus*** | 13C | ***Number of Transients*** | 512 |
| ***Origin*** | spect | ***Original Points Count*** | 32768 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 65536 | ***Pulse Sequence*** | zgpg30 | ***Receiver Gain*** | 322.00 |
| ***SW(cyclical) (Hz)*** | 24038.46 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 10046.0361 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24038.09 | ***Temperature (degree C)*** | 25.150 |




**4.63**

$^{13}$CNMR (100 MHz) in $CDCl_3$

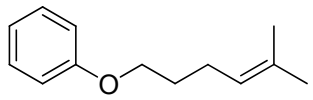
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5625 | ***Comment*** | NMR System BNMR_319-1 400 10025582 Pfizer Confidential proton CDCl3 {C:\Bruker\TopSpin3.0pl4} amendc01 40 | | |
| ***Date*** | 14 Nov 2012 18:00:16 | ***Date Stamp*** | 14 Nov 2012 18:00:16 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-F81-PURE\4\PDATA\1\1r | | | | |
| ***Frequency (MHz)*** | 399.54 | ***Nucleus*** | 1H | ***Number of Transients*** | 16 |
| ***Origin*** | spect | ***Original Points Count*** | 16384 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 65536 | ***Pulse Sequence*** | zg30 | ***Receiver Gain*** | 64.00 |
| ***SW(cyclical) (Hz)*** | 6393.86 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 2369.0908 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6393.76 | ***Temperature (degree C)*** | 25.153 |



**4.64**

$^{1}$HNMR (400 MHz) in $CDCl_3$

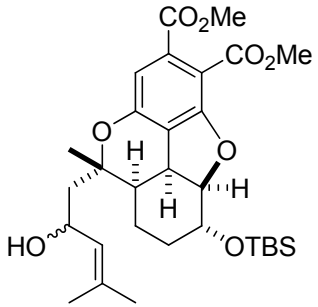
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3631 | ***Comment*** | NMR System BNMR_319-1 400 10025582 Pfizer Confidential carbon CDCl3 {C:\Bruker\TopSpin3.0pl4} amendc01 40 | | |
| ***Date*** | 14 Nov 2012 17:58:08 | ***Date Stamp*** | 14 Nov 2012 17:58:08 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-F81-PURE\5\PDATA\1\1r | | | | |
| ***Frequency (MHz)*** | 100.46 | ***Nucleus*** | 13C | ***Number of Transients*** | 512 |
| ***Origin*** | spect | ***Original Points Count*** | 32768 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 65536 | ***Pulse Sequence*** | zgpg30 | ***Receiver Gain*** | 287.00 |
| ***SW(cyclical) (Hz)*** | 24038.46 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 10047.5029 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24038.09 | ***Temperature (degree C)*** | 25.146 |



**4.64**

$^{13}$CNMR (100 MHz) in $CDCl_3$

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 5.1118 | ***Comment*** | 00701217-F53-long | | | ***Date*** | Sep 17 2012 |
| ***Date Stamp*** | Sep 17 2012 | ***File Name*** | \\UNITYH.PFIZER.COM\AUTO\2012\20120917\00701217-F53-LONG_20120917_01\PROTON_01.FID\FID | | | | |
| ***Frequency (MHz)*** | 400.20 | ***Nucleus*** | 1H | ***Number of Transients*** | 80 | ***Original Points Count*** | 32768 |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 30.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 2401.1633 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6410.26 | ***Temperature (degree C)*** | 25.000 |

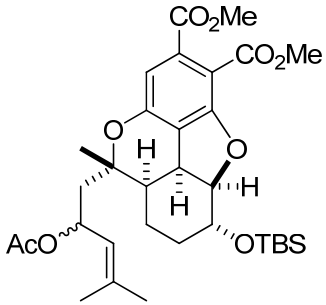



**4.71**

(crude NMR)

$^1$HNMR (400 MHz) in $CDCl_3$

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 5.1118 | ***Comment*** | 00701217-E-83 | ***Date*** | Sep 28 2011 | ***Date Stamp*** | Sep 28 2011 |
| ***File Name*** | \\UNITYH.PFIZER.COM\AUTO\2011\20110928\00701217-E-83_20110928_01\PROTON_01.FID\FID | | | | | ***Frequency (MHz)*** | 400.20 |
| ***Nucleus*** | 1H | ***Number of Transients*** | 192 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 30.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 2401.6167 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6410.26 | ***Temperature (degree C)*** | 25.000 |

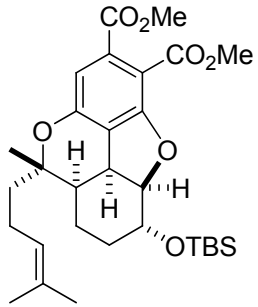



**4.72**

(crude NMR)

$^1$HNMR (400 MHz) in $CDCl_3$

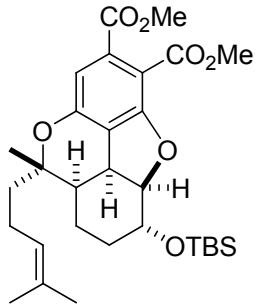
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6841 | ***Comment*** | 00701217-E91-pure | | | ***Date*** | Oct 1 2011 |
| ***Date Stamp*** | Oct 1 2011 | ***File Name*** | \\UNITYG.PFIZER.COM\SAMBA\111001\0201.FID\FID | | | ***Frequency (MHz)*** | 399.54 |
| ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 26.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 2401.5022 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6392.84 | ***Temperature (degree C)*** | 25.000 |




**4.73**

$^{1}$HNMR (400 MHz) in $CDCl_3$

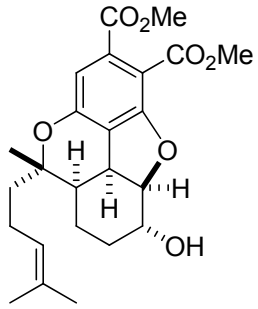
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.4680 | ***Comment*** | 00701217-E91-pure | | | ***Date*** | Oct 1 2011 |
| ***Date Stamp*** | Oct 1 2011 | ***File Name*** | \\UNITYH.PFIZER.COM\AUTO\2011\20111001\00701217-E91-PURE_20111001_01\CARBON_01.FID\FID | | | | |
| ***Frequency (MHz)*** | 100.64 | ***Nucleus*** | 13C | ***Number of Transients*** | 512 | ***Original Points Count*** | 32768 |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 40.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 10555.1309 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 22321.43 | ***Temperature (degree C)*** | 25.000 |




**4.73**

$^{13}$CNMR (100 MHz) in $CDCl_3$

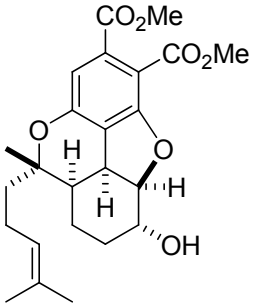
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5625 | ***Comment*** | | | |
| ***Date*** | 09 Jul 2012 19:04:32 | ***Date Stamp*** | 09 Jul 2012 19:04:32 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-E97-NOE\2\FID | | | | |
| ***Frequency (MHz)*** | 399.54 | ***Nucleus*** | 1H | ***Number of Transients*** | 16 |
| ***Origin*** | spect | ***Original Points Count*** | 16384 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 16384 | ***Pulse Sequence*** | zg30 | ***Receiver Gain*** | 203.00 |
| ***SW(cyclical) (Hz)*** | 6393.86 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 2384.5544 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6393.47 | ***Temperature (degree C)*** | 25.146 |




**4.77**

$^{1}$HNMR (400 MHz) in $CDCl_3$

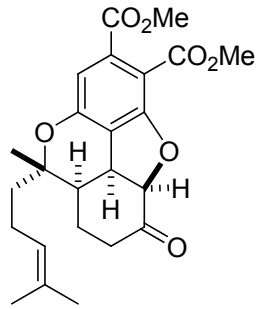
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3631 | ***Comment*** | | | |
| ***Date*** | 09 Jul 2012 20:27:44 | ***Date Stamp*** | 09 Jul 2012 20:27:44 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-E97-NOE\3\FID | | | | |
| ***Frequency (MHz)*** | 100.46 | ***Nucleus*** | 13C | ***Number of Transients*** | 2048 |
| ***Origin*** | spect | ***Original Points Count*** | 32768 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | zgpg30 | ***Receiver Gain*** | 362.00 |
| ***SW(cyclical) (Hz)*** | 24038.46 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 10048.4209 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24037.73 | ***Temperature (degree C)*** | 25.149 |




**4.77**

$^{13}$CNMR (100 MHz) in $CDCl_3$

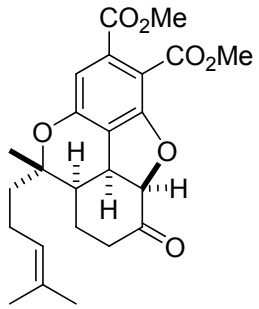
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 3.6841 | ***Comment*** | 00701217-E109-pure | | | ***Date*** | Oct 20 2011 |
| ***Date Stamp*** | Oct 20 2011 | ***File Name*** | \\UNITYG.PFIZER.COM\SAMBA\111020\0201.FID\FID | | | ***Frequency (MHz)*** | 399.54 |
| ***Nucleus*** | 1H | ***Number of Transients*** | 16 | ***Original Points Count*** | 23552 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 36.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 2397.1536 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6392.84 | ***Temperature (degree C)*** | 25.000 |




**4.75**

$^{1}$HNMR (400 MHz) in $CDCl_3$

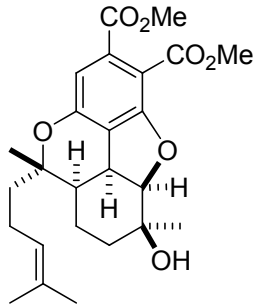
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3591 | ***Comment*** | 00701217-E109-pure Quick C-13 for concentrated sample | | | ***Date*** | Oct 20 2011 |
| ***Date Stamp*** | Oct 20 2011 | ***File Name*** | \\UNITYG.PFIZER.COM\SAMBA\111020\0202.FID\FID | | | ***Frequency (MHz)*** | 100.47 |
| ***Nucleus*** | 13C | ***Number of Transients*** | 256 | ***Original Points Count*** | 32768 | ***Points Count*** | 32768 |
| ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 60.00 | ***Solvent*** | CHLOROFORM-d | | |
| ***Spectrum Offset (Hz)*** | 10046.3643 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24110.91 | ***Temperature (degree C)*** | 25.000 |




**4.75**

$^{13}$CNMR (100 MHz) in $CDCl_3$

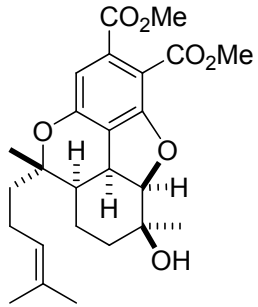
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5625 | ***Comment*** | | | |
| ***Date*** | 12 Jul 2012 13:44:32 | ***Date Stamp*** | 12 Jul 2012 13:44:32 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:DATA\AMENDC01\NMR\00701217-E281-3\2\FID | | | | |
| ***Frequency (MHz)*** | 399.54 | ***Nucleus*** | 1H | ***Number of Transients*** | 16 |
| ***Origin*** | spect | ***Original Points Count*** | 16384 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 16384 | ***Pulse Sequence*** | zg30 | ***Receiver Gain*** | 256.00 |
| ***SW(cyclical) (Hz)*** | 6393.86 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 2384.5544 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6393.47 | ***Temperature (degree C)*** | 25.152 |




**4.76**

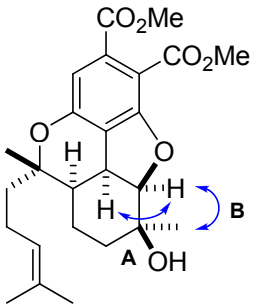
$^{1}$HNMR (400 MHz) in $CDCl_3$

| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.3631 | ***Comment*** | | | |
| ***Date*** | 07 Jul 2012 17:17:52 | ***Date Stamp*** | 07 Jul 2012 17:17:52 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-E281-NOE\3\FID | | | | |
| ***Frequency (MHz)*** | 100.46 | ***Nucleus*** | 13C | ***Number of Transients*** | 2048 |
| ***Origin*** | spect | ***Original Points Count*** | 32768 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | zgpg30 | ***Receiver Gain*** | 144.00 |
| ***SW(cyclical) (Hz)*** | 24038.46 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 10047.6865 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 24037.73 | ***Temperature (degree C)*** | 25.149 |




**4.76**

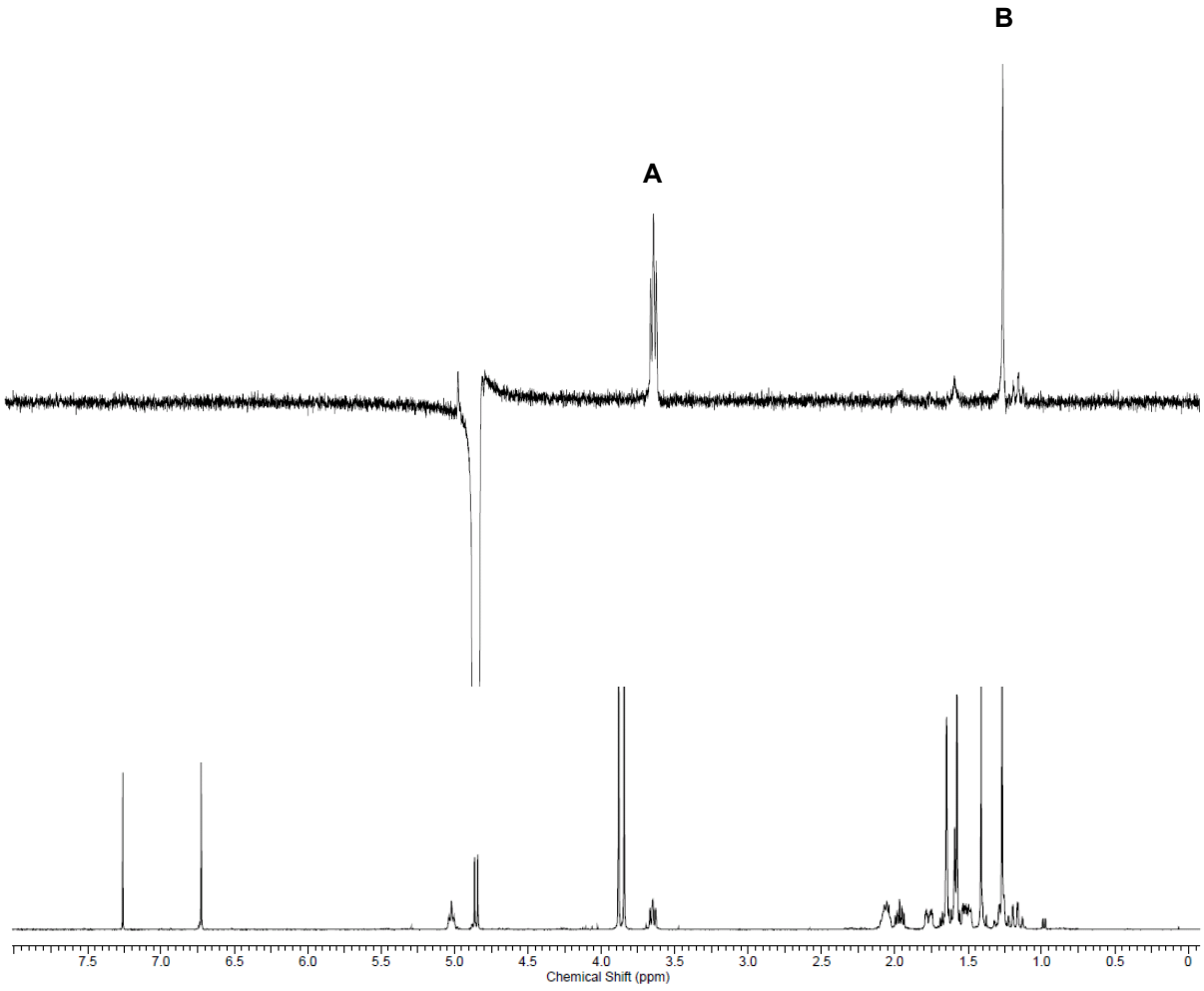
$^{13}$CNMR (100 MHz) in $CDCl_3$



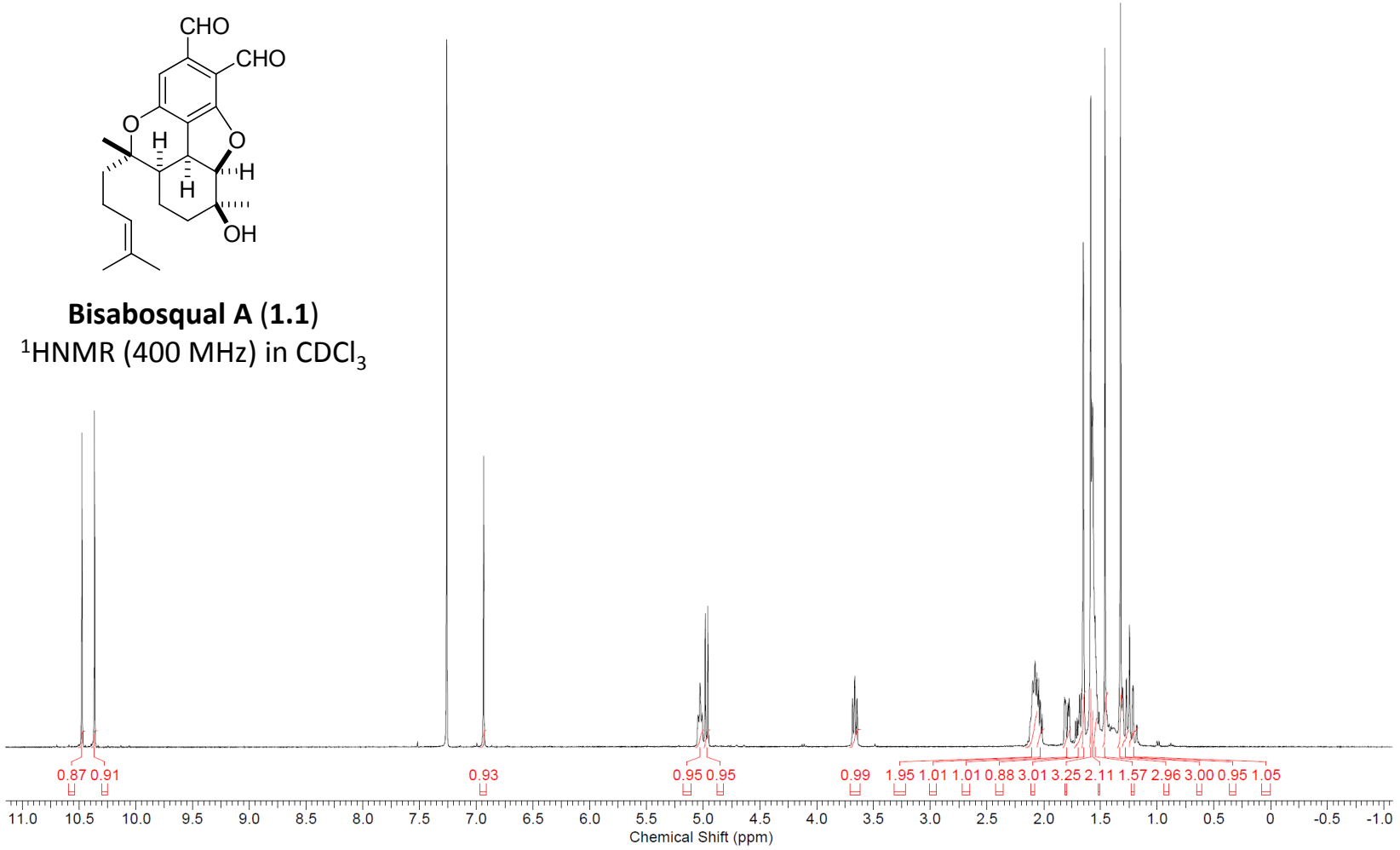

**4.76**

NOE 4.85 ppm

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Acquisition Time (sec)* | 2.5559 | *Comment* | 00701217-E281-485 | *Date* | Jul 8 2012 | *Date Stamp* | Jul 8 2012 |
| *File Name* | C:\DOCUME~1\AMENDC01\LOCALS~1\TEMP\GAINS9193.TMP\PRODUCTION\UNITYH\AMENDC01\00701217-E281-485_2012190115707.FID\FID | | | | | | |
| *Frequency (MHz)* | 400.20 | *Nucleus* | 1H | *Number of Transients* | 64 | *Original Points Count* | 16384 |
| *Points Count* | 16384 | *Pulse Sequence* | NOESY1D | *Receiver Gain* | 30.00 | *Solvent* | CHLOROFORM-d |
| *Spectrum Offset (Hz)* | 2401.1633 | *Spectrum Type* | STANDARD | *Sweep Width (Hz)* | 6410.26 | *Temperature (degree C)* | 25.000 |



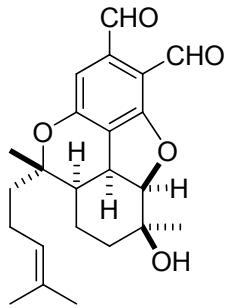
| | | | | | |
|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 2.5625 | ***Comment*** | | | |
| ***Date*** | 18 Sep 2012 14:12:16 | ***Date Stamp*** | 18 Sep 2012 14:12:16 | | |
| ***File Name*** | \\AMRGROB10025582.AMER.PFIZER.COM\BKDATA:.DATA\AMENDC01\NMR\00701217-BISABOSQUAL\1\FID | | | | |
| ***Frequency (MHz)*** | 399.54 | ***Nucleus*** | 1H | ***Number of Transients*** | 256 |
| ***Origin*** | spect | ***Original Points Count*** | 16384 | ***Owner*** | FCNGRO-BRKOA |
| ***Points Count*** | 16384 | ***Pulse Sequence*** | zg30 | ***Receiver Gain*** | 322.00 |
| ***SW(cyclical) (Hz)*** | 6393.86 | ***Solvent*** | CHLOROFORM-d | ***Spectrum Offset (Hz)*** | 2385.7253 |
| ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 6393.47 | ***Temperature (degree C)*** | 25.150 |




**Bisabosqual A (1.1)**

$^{1}$HNMR (400 MHz) in $CDCl_3$

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Acquisition Time (sec)*** | 1.2788 | ***Comment*** | 00701217-Bis-pure | | | ***Date*** | Sep 18 2012 |
| ***Date Stamp*** | Sep 18 2012 | ***File Name*** | \\UNITYH.PFIZER.COM\AUTO\2012\20120918\00701217-BIS-PURE_20120918_01\CARBON_01.FID\FID | | | | |
| ***Frequency (MHz)*** | 100.64 | ***Nucleus*** | 13C | ***Number of Transients*** | 16384 | ***Original Points Count*** | 28544 |
| ***Points Count*** | 32768 | ***Pulse Sequence*** | s2pul | ***Receiver Gain*** | 40.00 | ***Solvent*** | CHLOROFORM-d |
| ***Spectrum Offset (Hz)*** | 10063.7373 | ***Spectrum Type*** | STANDARD | ***Sweep Width (Hz)*** | 22321.43 | ***Temperature (degree C)*** | 25.000 |




**Bisabosqual A (1.1)**

$^{13}$CNMR (100 MHz) in $CDCl_3$