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Efforts Toward the Total Synthesis of 7-Deoxyzaragozic Acid A and Galtamycinone

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Efforts Toward the Total Synthesis of 7-Deoxyzaragozic Acid A and Galtamycinone

by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

May, 2002

Dedication

I would like to thank all of the friends and family that have been there to support and encourage me throughout my life. Their patience, love, and guidance has helped more than I could ever say. I owe them all my deepest gratitude.

Acknowledgements

I would like to thank Dr. William Bailey, the organic chemistry professor who sparked my interest in organic chemistry, Dr. Dominic McGrath who introduced me to research, and finally to Dr. Stephen F. Martin for his guidance during my time at the University of Texas. Additional thanks to the Martin group members, past and present that were always there to give advice and support.

Efforts Toward the Total Synthesis of 7-Deoxyzaragozic Acid A and Galtamycinone

Publication No._____

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The University of Texas at Austin, 2002

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Studies toward the total synthesis of 7-deoxyzaragozic acid A (**2.56**) were intended to build upon the completion of the synthesis of 6,7-dideoxysqualestatin H5 (**2.47**) that featured the stereoselective intramolecular vinylogous aldol reaction of the furoic ester **2.23a** to give **2.26** or its trimethylsilyl ether derivative **2.30**, which possess the requisite absolute stereochemistry at C(3)-C(5) of the zaragozic acids. The improvement of the synthesis of α-ketoester **2.25a** from an 18% overall yield to 28% while also reducing the amount of chromatography needed for the intermediates was accomplished. Efforts toward the elaboration of butenolide **2.30** revealed that oxygen nucleophiles were incompatible with the system, however this issue was effectively addressed by the use of a silane nucleophile, which was added in a Michael fashion to the butenolide **2.30** with the correct stereochemistry. While this was proof of concept for elaboration of the

core system, it was unfortunate that the silane **2.71** could not be converted to the desired oxygen functionality. Additionally, efforts were made to incorporate functionality at C-6 from the beginning of the synthesis in the form of a brominated furoic acid derivative **2.90**, however the Lewis acid mediated cyclization of this species was low yielding with unknown stereochemical outcome.

In addition to the studies toward the total synthesis of 7-deoxyzaragozic acid A, the total synthesis of galtamycinone (**3.2**) was also investigated. Although the total synthesis could not be completed, methodologies have been developed that were used to synthesize *C*-aryl glycosides **3.80** and **3.85** which established these methods as a viable alternative to the *O*→*C* glycoside rearrangement.

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CHAPTER 1. APPROACHES TOWARD THE SYNTHESIS OF THE ZARAGOZIC ACIDS (SQUALESTATINS).

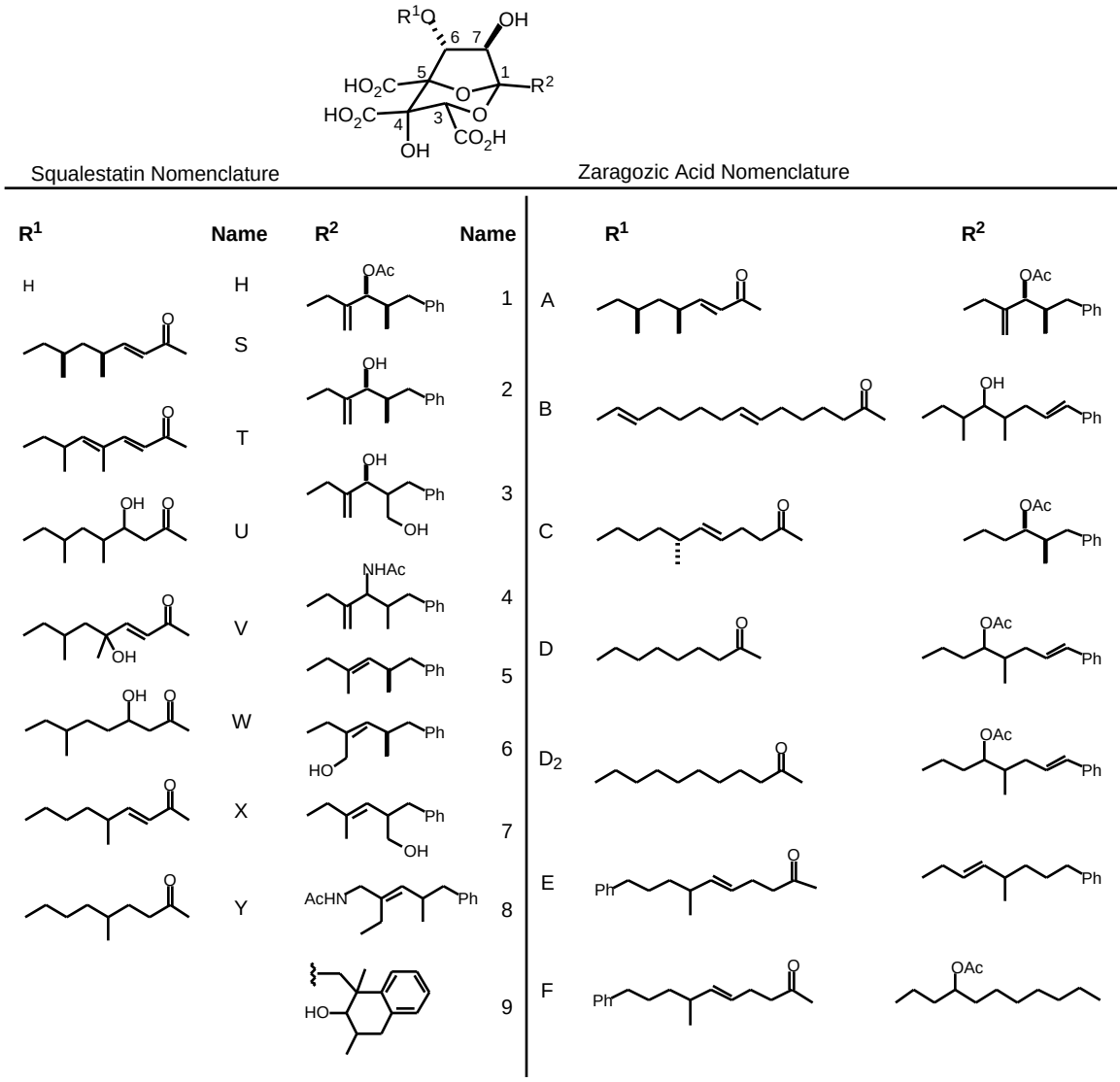
1.1 BIOLOGICAL ACTIVITY AND MECHANISM OF ACTION OF THE ZARAGOZIC ACIDS

The zaragozic acids and squalestatins were discovered independently by scientists at Merck and Glaxo respectively and were found to exhibit biological activity in the inhibition of squalene synthase.[1-8] After the structures of the zaragozic acids and the squalestatins had been elucidated, it was determined that they had the same core structure, and in fact that squalestatin S1 and zaragozic acid A were the same compound, in light of the commonality of these structures, they will be referred to only as the zaragozic acids from this point forward.

Squalene synthase is the enzyme that catalyzes the first committed step in cholesterol biosynthesis, and the fact that the zaragozic acids were potent inhibitors of this enzyme provided an opportunity to develop a new drug to combat high cholesterol. This could be done either by use of one of the naturally

occurring zaragozic acids or the development of a biologically active synthetic analog. Additionally, the structure of the squalestatins and zaragozic acids represents a synthetic challenge. All of the zaragozic acids contain a highly oxygenated bicyclic core flanked by a C-1 alkyl side chain and a C-6 acyl side chain, both of which vary among the different zaragozic acids (Figure 1.1).

Figure 1.1



Naturally occurring: S1, H1, S2, H2, H5, H6, H7, H9, S3, S4,S5,S8, T1, U1, U2, V2, W1, W2, X1, Y1, 6-deoxy H1, 6-deoxy H5, 7-deoxy S1, 6,7-dideoxy H5

High cholesterol levels have been a known risk factor for atherosclerosis, and therefore the discovery of drugs that lower blood cholesterol levels is an

important area of pharmaceutical research. Squalene synthase is the enzyme that acts in the first committed step in the cholesterol biosynthetic pathway. Since the zaragozic acids have been found to be the most potent inhibitors of squalene synthase to date, this represents a promising site for the selective inhibition of cholesterol biosynthesis. The biological assay methods for the Glaxo and Merck groups differ, resulting in different IC_{50} values for the same compound (zaragozic acid A *vs*. squalestatin S1). Despite the fact that the assay methods were not consistent between the two groups, general trends were observed in the biological activities of the various zaragozic acids. From the available data, it seems that the presence of the C-6 side chain as well as both the C-6 and C-7 hydroxyl groups are crucial to the biological activity. In fact, the IC_{50} becomes greater than 500 nM if both the C-6 side chain and hydroxyl group are absent (6-deoxysqualestatin H5).[9]

Table 1.1

Compound	**IC_{50} (nM) Rat SQS**
Zaragozic acid A (Merck)	0.5
Zaragozic acid B	0.2
Zaragozic acid C	0.4
Zaragozic acid D	6
Squalestatin S1 (Glaxo)	12
Squalestatin S2	5
Squalestatin H1	26
7-Deoxysqualestatin S1	35
7-Deoxysqualestatin H5	>200
6-Deoxysqualestatin H5	>500

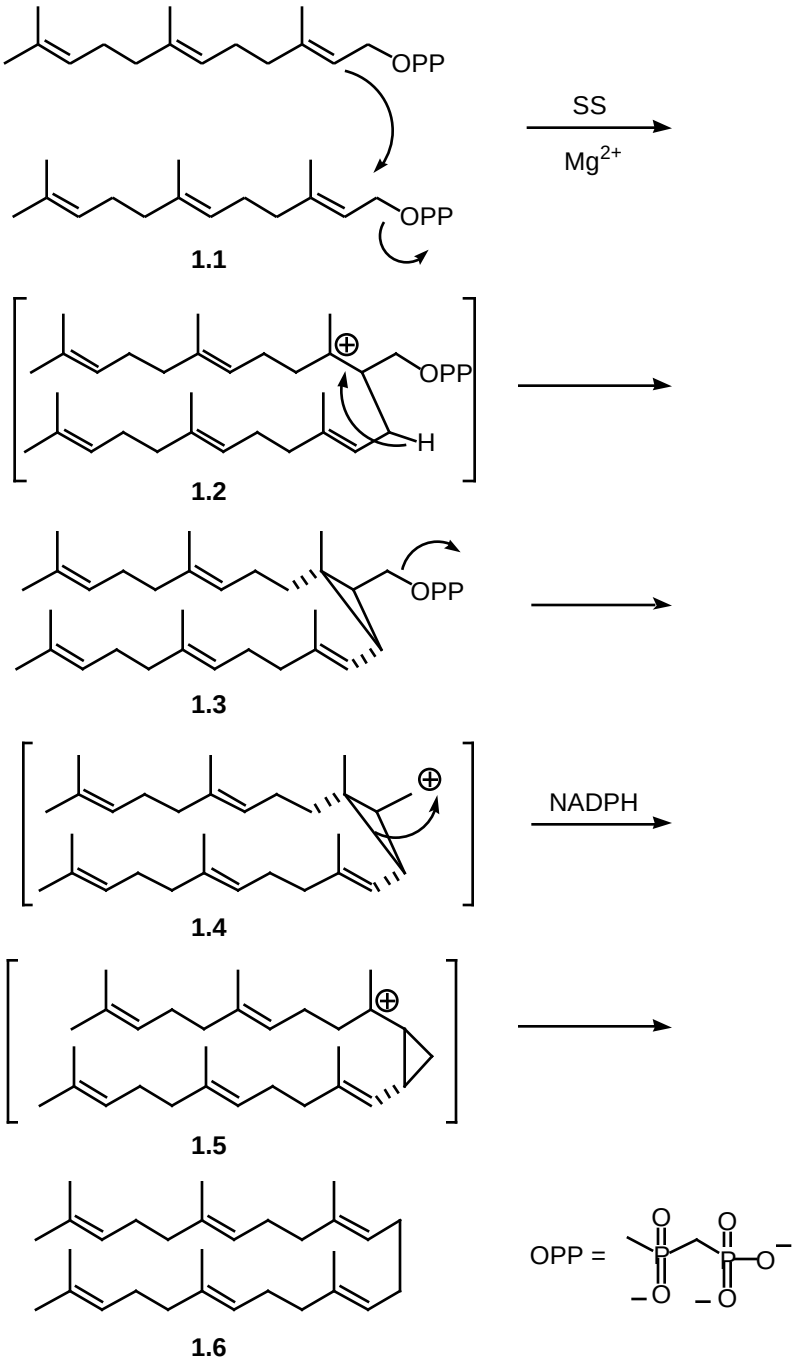
Unfortunately, the toxicity associated with the zaragozic acids would prevent their use as pharmaceutical drugs. More specifically, one possible consequence of blocking squalene synthase is that farnesylpyrophosphate (FPP) (**1.1**) can accumulate since it cannot be processed through the cholesterol

pathway. It has been shown that in rats that have been treated with zaragozic acid A (**1.54**), FPP levels increase and HMG-CoA reductase is upregulated. The excessive levels of FPP appear to be rapidly catabolized in the liver to a variety of farnesyl-derived dicarboxylic acids (FDDCAs) that are excreted in urine. It has been suggested that the toxic effects that have been associated with zaragozic acid A (**1.54**) are a result of the acidosis caused by massive overproduction of FDDCAs from an increased pool of FPP. When dogs were given zaragozic acid A (**1.54**) or zaragozic acid C (**1.7**), extreme toxicity was observed after one to two weeks. Additionally, little or no lowering of cholesterol was observed. In contrast, rhesus monkeys that had been dosed with zaragozic acid A showed lowered cholesterol and much lower levels of FDDCAs. The reasons for these differences are not clear.[10]

The mechanism of squalene synthase in the synthesis of cholesterol begins with the conversion of two molecules of FPP (**1.1**) to presqualene pyrophosphate (**1.3**) *via* carbocation **1.2** accompanied by loss of inorganic phosphate. Presqualene pyrophosphate (PSPP) (**1.3**) can then be converted to squalene (**1.6**) by loss of the remaining inorganic phosphate to form cyclopropyl cation **1.4**.

Rearrangement to tertiary carbocation **1.5** and reduction with NADPH then produces squalene (**1.6**). It is thought that the ability of the zaragozic acids to inhibit squalene synthase is derived from the resemblance of the zaragozic acids to presqualene pyrophosphate (**1.3**). Both contain a trianionic core and two long alkyl side chains.[10]

Scheme 1.1



Subsequent to the original publications containing structure elucidation and biological activity, studies were done on the mechanism of biological action of the zaragozic acids.[11] Research done by Harwood has shown that inhibition of mammalian squalene synthase is a result of mechanism-based irreversible inactivation, where the zaragozic acids function as a mimic of PSPP (**1.3**). Zaragozic acid A has been shown to bind competitively (with respect to FPP) to squalene synthase and then react covalently with the enzyme, rendering the enzyme inactive (suicide inhibition).

1.2. TOTAL SYNTHESES OF THE ZARAGOZIC ACIDS

The first total syntheses of the zaragozic acids were published in 1994 by Carreira (zaragozic acid C), Evans (zaragozic acid C), and Nicolaou (zaragozic acid A), just two years after the first publications on structure elucidation appeared.[10,12-20] These syntheses were followed by the syntheses of Heathcock (zaragozic acid A) in 1996, Hashimoto (zaragozic acid C) in 1998, Armstrong (zaragozic acid C) in 1998, and finally by Tomooka, Halcomb (zaragozic acid A), and Martin (6,7-dideoxysqualestatin H5) in 2000.[21-28] The discussion of the total

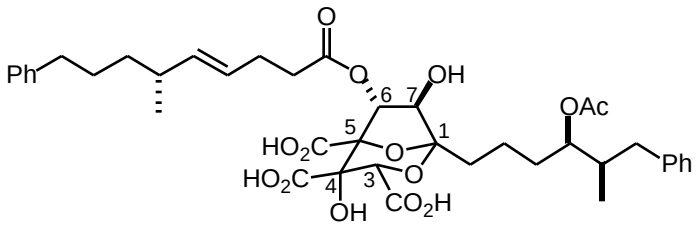
syntheses as well as the synthetic approaches will focus on the construction of the core structure.

1.2.1 Carreira's Synthesis of Zaragozic Acid C

The first synthesis of zaragozic acid C (**1.7**) was accomplished in 1994 by Carreira, who assembled the bicyclo[3.2.1]octane core **1.19** from an acyclic intermediate **1.18** that was derived from erythronolactone. Additional stereochemical centers were set using asymmetric dihydroxylation, although the selectivity in the dihydroxylation was only modest, even under Sharpless conditions. A unique aspect of Carreira's synthesis was the fact that the C-4 stereocenter was not set prior to the assembly of the zaragozic acid core system. The installation of the required alcohol and ester functionality at C-4 proved to be a challenge in the synthesis, but after some experimentation conditions were found that led to the formation of the correct stereochemistry at the C-4 center. Once the correct stereochemistry was established, the C-4 center could be further elaborated to the required ester and alcohol functionality. In the final stages of the Carreira synthesis, installation of the C-6 acyl side chain was problematic due

to a lack of regioselectivity in the acylation of the hydroxyl groups at C-6 and C-7. Fortunately, it was found that the C-7 hydroxyl could be selectively protected with greater than 20:1 regioselectivity, and therefore the C-6 side chain was installed regioselectivity. This strategy was later used in several subsequent syntheses of the zaragozic acids.

Figure 1.2

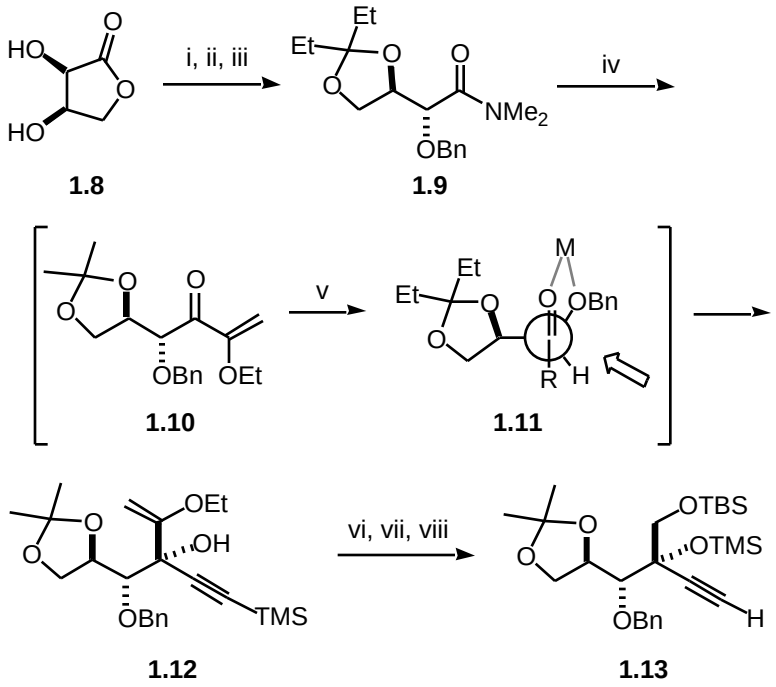


1.7

Carreira's synthesis began with the condensation of D-erythronolactone (**1.8**) with Me_2NH to give the amide **1.9** that was alkylated with ethyl vinyl ether to give **1.10** (Scheme 1.2).[14,15] Addition of a Grignard acetylide to ketone **1.10** gave alcohol **1.12** as a mixture (20:1) of diastereomers in an 84% yield over two steps. The high diastereoselectivity in the addition was due to chelation between the metal and the benzyloxy and carbonyl as shown in **1.11**. The synthesis of acetylene **1.13** was then accomplished in three steps from **1.12**. At this point, the

C-1 side chain could be introduced into the system. Unlike most of the other syntheses of the zaragozic acids, Carreira introduced the C-1 side chain relatively early in the synthesis. In doing so, the opportunity to prepare any of the other members of the zaragozic acid family from a common, late stage intermediate was sacrificed.

Scheme 1.2

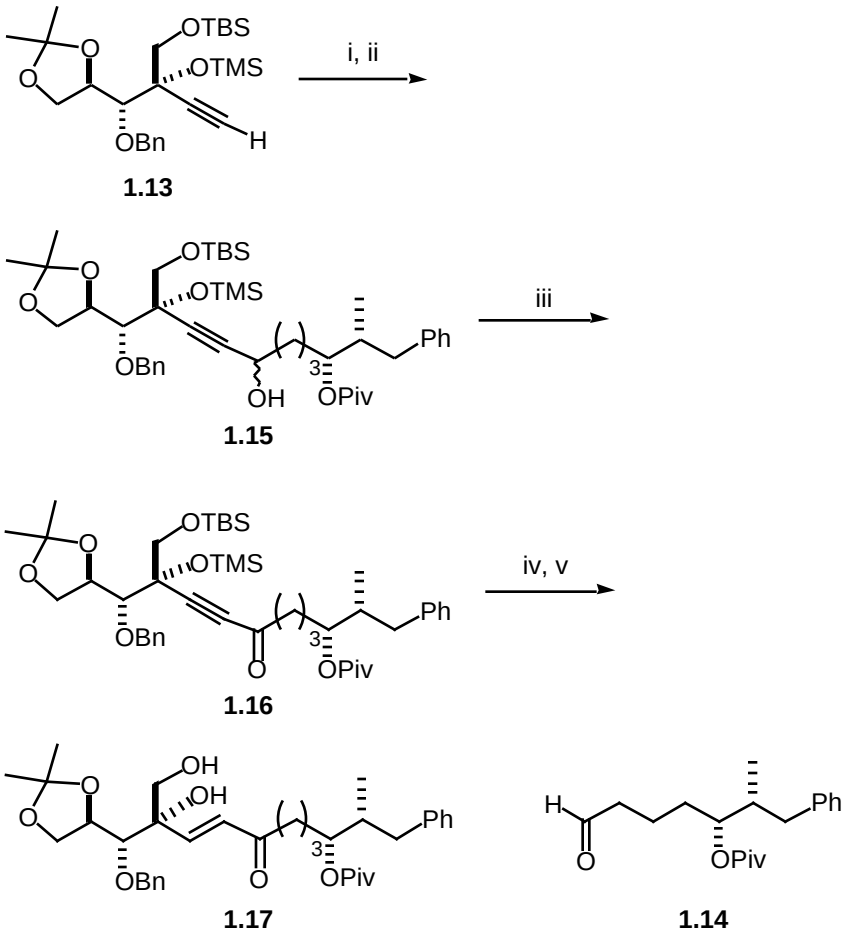


i) Me_2NH, MeOH, 97%; ii) $(MeO)_2CEt_2$, cat. TsOH, 90%;
iii) NaH, BnBr, THF, 96%; iv) (ethoxyvinyl)lithium, THF;
v) TMSC≡CMgBr, THF, 84%; vi) O_3, CH_2Cl_2/EtOH, 84%;
vi) $NaBH_4$, MeOH; vii) K_2CO_3, MeOH, 78%;
viii) TBSCl, Et_3N, DMAP, then TMSCl, Et_3N, CH_2Cl_2, 88%.

Incorporation of the C-1 side chain **1.14** into ynone **1.13** proceeded in excellent yield after extensive experimentation to identify suitable conditions (Scheme 1.3). Lithiation of acetylene **1.13** gave a mixture of desired product **1.15** and starting material. Recovery of starting material rather than formation of desired product **1.15** was thought to be due to proton transfer between acetylide **1.13** and aldehyde **1.14**. Transmetalation of the lithium acetylide **1.13** with

$MgBr_2$ or $CeCl_3$ was done in an attempt to improve the reaction, but this had little effect on the outcome. Effective coupling of the acetylide **1.13** and aldehyde **1.14** was finally accomplished using the lithium acetylide in the presence of LiBr, according to the method of Brandsma,[29] to give **1.15** in excellent yield. Although Brandsma has found the addition of LiBr to be beneficial in the addition of lithium acetylides to enolizable ketones, there was no explanation offered as to the reason that this improved the results of the addition. Dess-Martin oxidation of the resulting mixture of epimeric alcohols gave ynone **1.16**. Reduction of the ynone to the required *trans* enone was not as straightforward as anticipated. Use of metal hydrides, dissolving metal reductions, or partial reduction with H_2 in the presence of Pd/C gave only poor yields of *trans* product and extensive decomposition of the starting material. The desired reduction to the *trans* enone was eventually accomplished using chromium (II) acetate monohydrate dimer to give **1.17** in a 60% yield.

Scheme 1.3

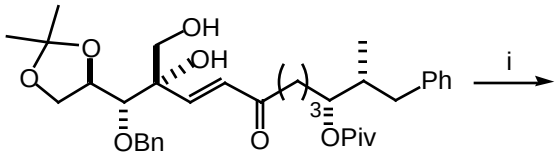


i) BuLi, THF; ii) **1.14**, LiBr, THF, 93%; iii) Dess-Martin, CH_2Cl_2, 93%;
iv) $[Cr(OAc)_2 \bullet H_2O]_2$, THF/$H_2O$, 60%; v) TBAF, THF, 93%.

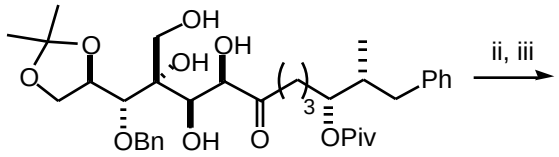
Once *trans* enone **1.17** had been made, the next step in the synthesis was the diastereoselective dihydroxylation of the enone double bond. Unfortunately, initial experiments using OsO_4 under catalytic conditions gave only a small amount of desired tetraol **1.18** as a mixture (1.1:1) of diastereomers (Scheme 1.4).

The Sharpless asymmetric dihydroxylation of **1.17** gave tetraol **1.18** with an improved diastereomeric ratio (1.7:1). Treatment of this tetraol with HCl/MeOH gave the [3.2.1]bicyclic core **1.19**. Silyl protection of the primary alcohols, benzyl deprotection, and Swern oxidation gave ketone **1.20**.

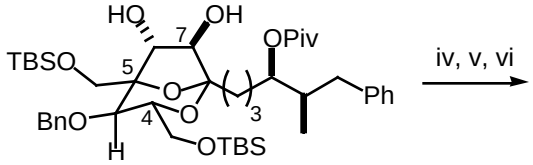
Scheme 1.4



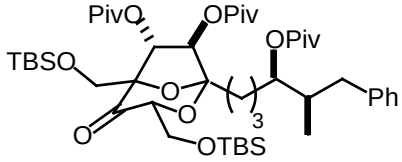
1.17



1.18



1.19



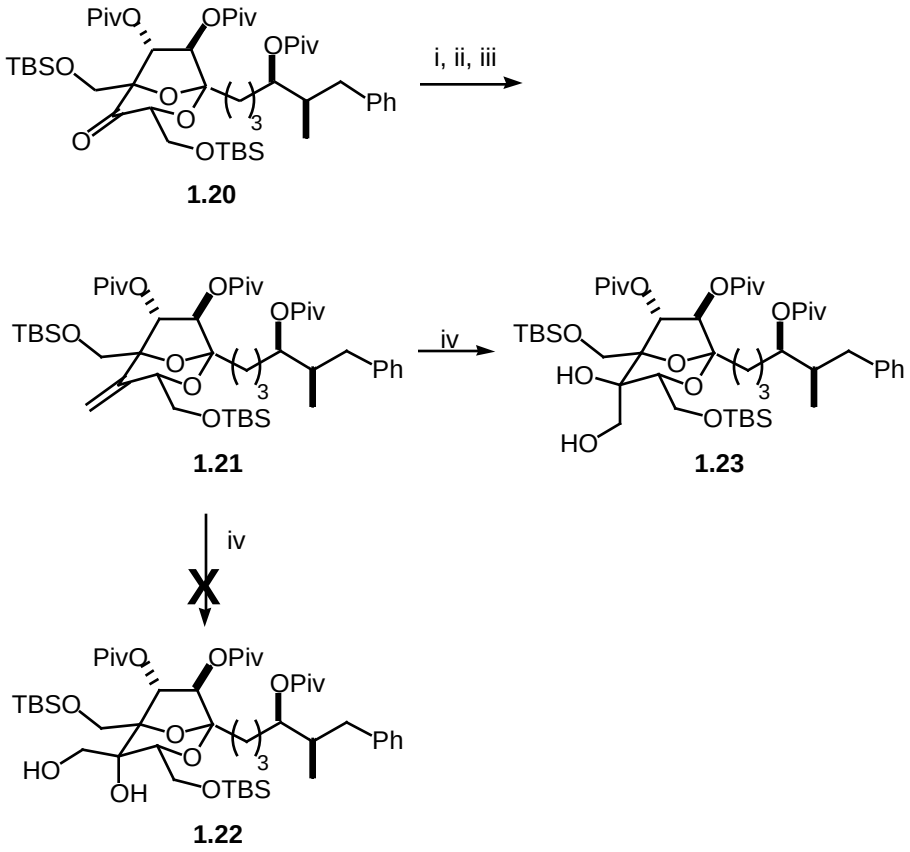
1.20

i) $(DHQD)_2PHAL$, NMO, $MeSO_2NH_2$, acetone;
ii) HCl/MeOH, 86%; iii) TBSCl, DMAP, Et_3N, CH_2Cl_2, 74%;
iv) PivCl, DMAP, $ClCH_2CH_2Cl$, 97%;
v) H_2, $Pd(OH)_2/C$, $Pd/CaCO_3$, EtOH, 99%;
vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 96%.

Ketone **1.20** was then subjected to a Peterson olefination to provide **1.21** followed by dihydroxylation of the olefin in an effort to set the stereochemistry at C-4 (Scheme 1.5). Unfortunately, attempts at implementing this strategy gave

exclusively **1.23** with the incorrect stereochemistry at C-4 rather than desired diol **1.22** with the correct stereochemistry at the C-4 center. This result was surprising in light of the fact that molecular models had suggested that the preferred attack would be from the convex face due to the distortion of the six membered ring to a half-chair conformation. This distortion would block the concave face of the exocyclic methylene. Additionally, dihydroxylation of exocyclic olefins in related ring systems had been shown to favor attack of OsO_4 from the convex face.

Scheme 1.5

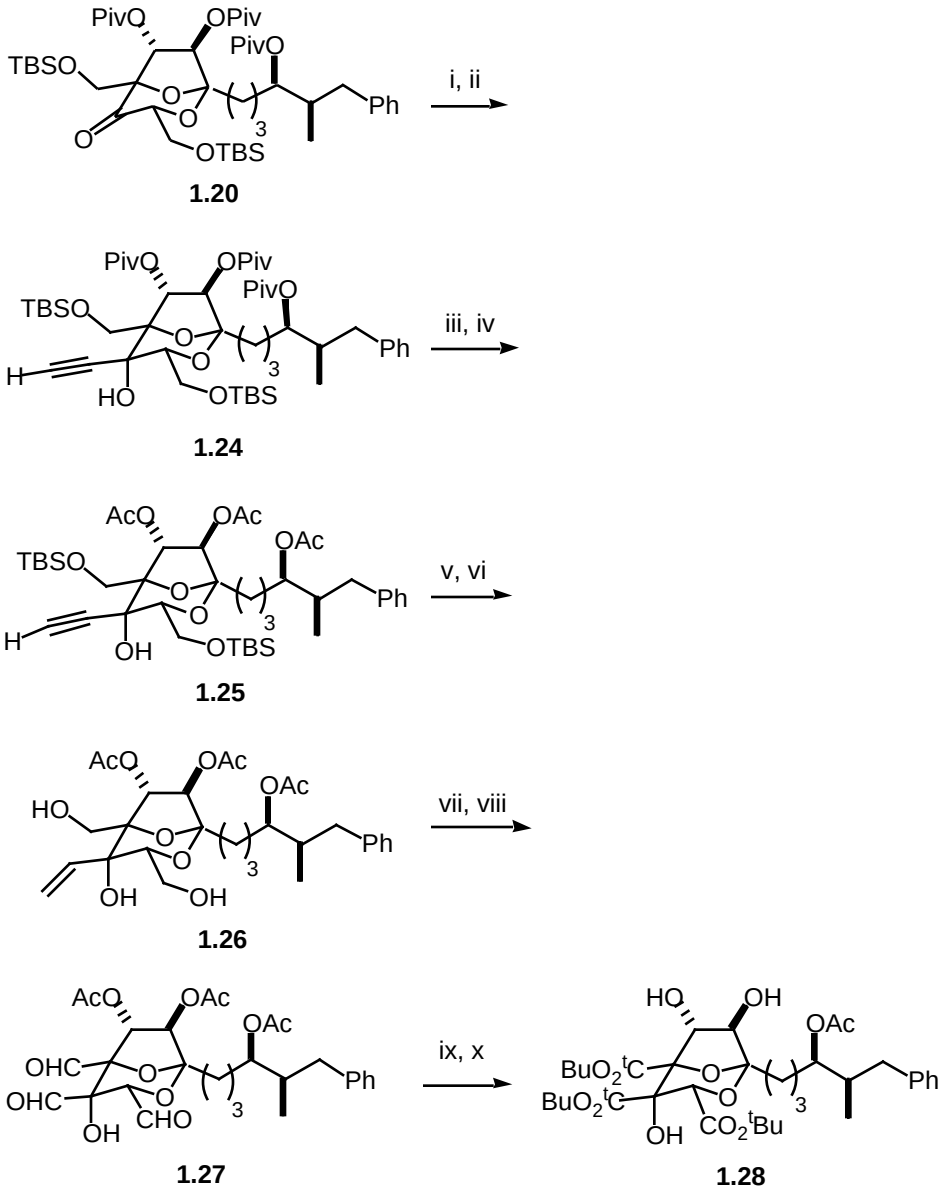


i) TMSLi, LiBr, THF/HMPA; ii) 18-cr-6, KHMDS, THF;
iii) TBSOTf, 2,6-lutidine, <35%; iv) OsO_4, NMO, *t*-BuOH/acetone

Since the dihydroxylation strategy to set the stereochemistry at C-4 was not successful, another approach involving acetylenic addition to the ketone **1.20** was investigated (Scheme 1.6). After some optimization of the conditions, it was found that addition of lithium acetylide to **1.20** in the presence of Me_3N gave a mixture (6.1:1) of diastereomers epimeric at C-4 of acetylide **1.24**. After several

steps, trialdehyde **1.27** was obtained, and subsequent oxidation and esterification afforded the completed zaragozic acid core **1.28**.

Scheme 1.6

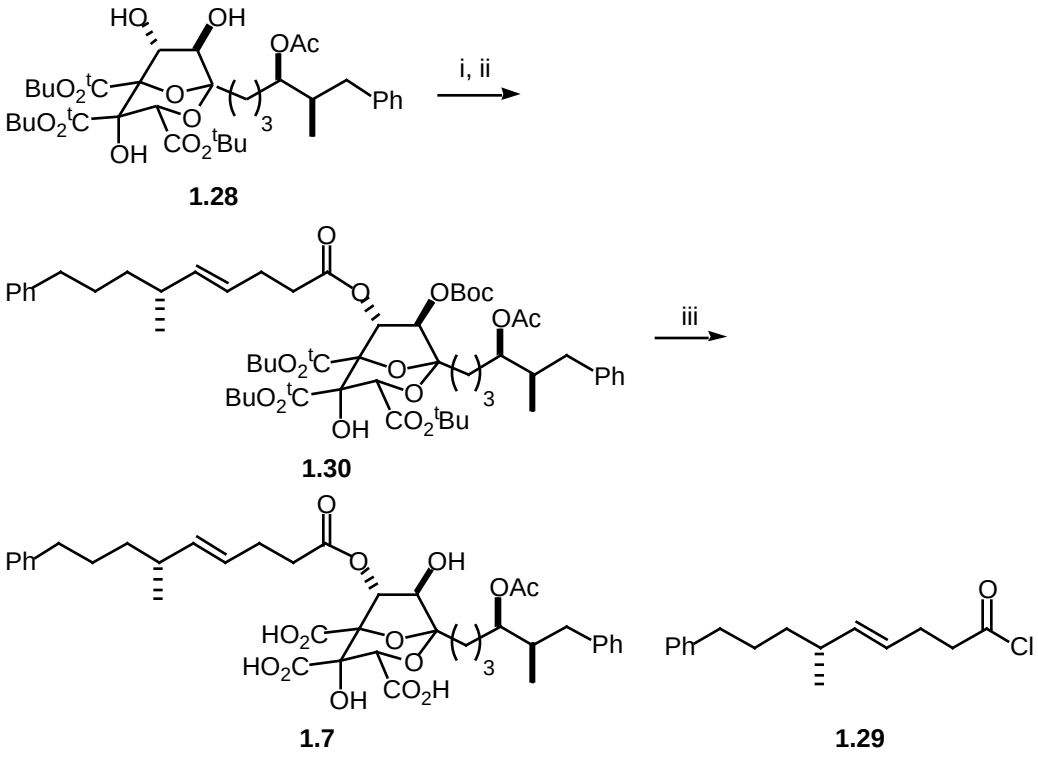


i) TMSC≡CH, *t*BuLi, Et_2O, Me_3N; ii) $AgNO_3$, 2,6-lutidine, 90%;
iii) Dibal-H, CH_2Cl_2/toluene, 84%; iv) Ac_2O, DMAP, CH_2Cl_2, 94%;
v) H_2, Pd/C, pyr.; vi) HF•pyr, THF/pyr., 64%;
vii) Dess-Martin, CH_2Cl_2/pyr, 93%; viii) O_3, CH_2Cl_2/MeOH;
ix) $NaClO_2$, NaH_2PO_4, β-isoamylene, THF/H_2O;
x) *N, N′*-diisopropyl-*O*-*tert*-butylisourea, CH_2Cl_2, 72%; K_2CO_3, MeOH, 90%.

All that remained to complete the synthesis of zaragozic acid C (**1.7**) was the installation of the C-6 side chain and saponification of the esters at C-3, C-4, and C-5. Initially it was anticipated that the regioselective acylation of **1.28** at C-6 could be accomplished to provide **1.30** with the completed C-6 side chain intact. However, deprotection of both the C-6 and C-7 hydroxyl groups and coupling of **1.28** to **1.29** resulted in an unfavorable (1:3) ratio of C-6 to C-7 acylated regioisomers. In order to circumvent this problem, another coupling strategy was developed that involved selective protection of the C-7 hydroxyl group. Thus, when **1.28** was allowed to react with Boc_2O in the presence of 4-pyrrolidinopyridine rather than the more commonly used DMAP, the C-7 hydroxyl was converted to the Boc ester with greater than 20:1 regioselectivity (Scheme 1.7). It was speculated that the high regioselectivity of the coupling of **1.28** to **1.29** was due to the bulkier character of the acylating agent that was generated using 4-pyrrolidinopyridine. This bulky acylating agent would be more selective for the less sterically hindered secondary alcohol at C-7. Coupling of the C-6 side chain then proceeded smoothly to give **1.30**. Completion of the synthesis of zaragozic acid C (**1.7**) was then accomplished by saponification of

the three esters. In summary, the Carreira synthesis of zaragozic acid C (**1.7**) was completed in 33 steps (longest linear sequence) and an overall yield of 1.4%.

Scheme 1.7



i) Boc_2O, 4-pyrrolidinopyridine, CH_2Cl_2, 82%; ii) **1.29**, DCC, DMAP, CH_2Cl_2, 78%; iii) TFA, CH_2Cl_2, 100 %

1.2.2 Nicolaou's Synthesis of Zaragozic Acid A

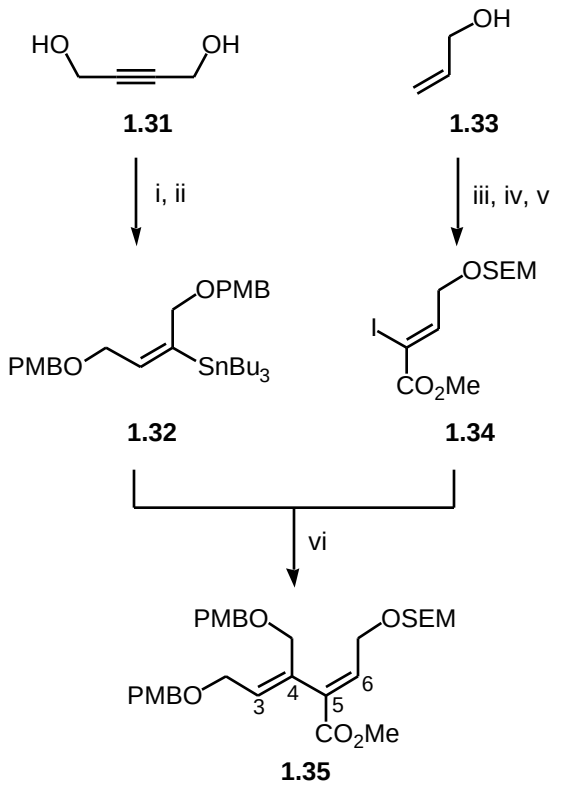
Later in 1994, Nicolaou published the first total synthesis of zaragozic acid A (**1.54**) as a relay synthesis through **1.51**. At the outset of the studies

toward the total synthesis, a sample of zaragozic acid A (**1.54**) was degraded to **1.51**, this compound was in turn, used to reassemble **1.54**. This study was followed by the total synthesis of **1.51** in order to complete the total synthesis of zaragozic acid A (**1.54**). Installation of the stereochemical centers of the zaragozic acid core system in this synthesis relied on a double dihydroxylation sequence involving a Sharpless enantioselective dihydroxylation followed by a diastereoselective dihydroxylation. The initial enantioselective dihydroxylation required a considerable amount of experimentation before the enantioselectivity was optimized to above 80% ee. Fortunately, the diastereoselective dihydroxylation that followed provided the desired tetraol as a single diastereomer. Analogous to the synthesis of zaragozic acid C (**1.7**) by Carreira, the C-6 and C-7 hydroxyl groups were not differentially protected. Unfortunately, Nicolaou was not able to overcome the regioselectivity issue leaving a disappointing 3:2 ratio of regioisomers in the final synthesis of zaragozic acid A (**1.54**).

The Nicolaou synthesis began with protection of 2-butyne-1,4-diol (**1.31**), followed by conversion to vinyl stannane **1.32** for use in a Stille coupling

(Scheme 1.8). Vinyl iodide **1.34** was prepared in three steps from allyl alcohol **1.33**. Stille coupling of vinyl iodide **1.34** and vinyl stannane **1.32** produced the desired diene **1.35** in a 70% yield.

Scheme 1.8



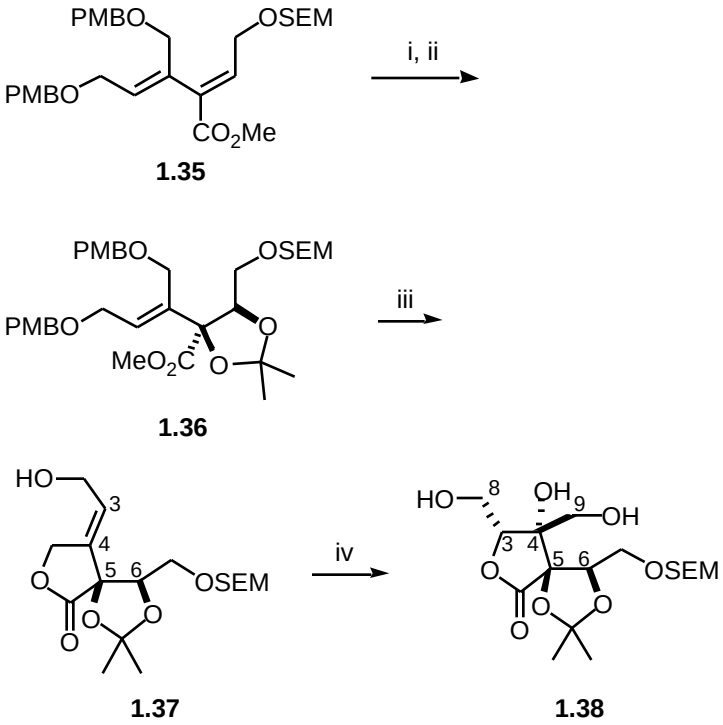
i) NaH, PMBCl, *n*-Bu_4NI, DMF, 94%; ii) Bu_3SnH, $Pd(PPh_3)_2Cl_2$, THF, 94%; iii) SEMCl, *i*Pr_2NEt, CH_2Cl_2, 98%; iv) O_3, CH_2Cl_2/MeOH; v) methyl iodo(triphenylphosphoranylidene) acetate, PhH, 78%; vi) $Pd(CH_3CN)_2Cl_2$, DMF, 70%.

The enantioselective dihydroxylation of **1.35** under Sharpless conditions gave exclusive dihydroxylation at the C-5 – C-6 olefin to give **1.36** with 83% ee

in a 30% yield (Scheme 1.9). While the yield was rather low, it was reported to be reproducible even on large scale. A considerable amount of experimentation was done in order to improve the yield and enantioselectivity of the dihydroxylation before it was established that the best results utilized either 2-methoxyethoxymethyl (MEM) or 2-(trimethylsilyl)ethoxymethyl (SEM) ethers at C-7, PMB protecting groups on the other alcohols, and a methyl ester at C-5. The dramatic effects of the protecting groups were attributed to the steric requirements in the binding pocket of the AD catalyst. It appeared that this binding pocket was unable to accommodate larger protecting groups such as the TBS group that was originally utilized. However, the binding pocket was able to accommodate smaller, linear protecting groups such as SEM or MEM. The rationale for the exclusive regioselectivity in the dihydroxylation was not as clear, but it was speculated that the methyl ester was twisted out of conjugation with the diene system. Additionally, the two allylic hydroxymethyl substituents were approximately orthogonal to the plane of the C-3 – C-4 olefin, which maximizes the hyperconjugative stabilization. In contrast, the C-5 – C-6 olefin only has one electron withdrawing hydroxymethyl group. These two features suggest that,

contrary to superficial inspection of the dienyl system, the C-5 – C-6 olefin is more electron rich, making it more reactive than the C-3 – C-4 olefin.

Scheme 1.9



i) *t*-BuOH/H_2O, $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, $MeSO_2NH_2$, 30%;
ii) 2-methoxypropene, PPTS, CH_2Cl_2, 88%;
iii) DDQ, $CHCl_3/H_2O$, 86%; iv) OsO_4, NMO, *t*-BuOH/THF/ H_2O, 83%.

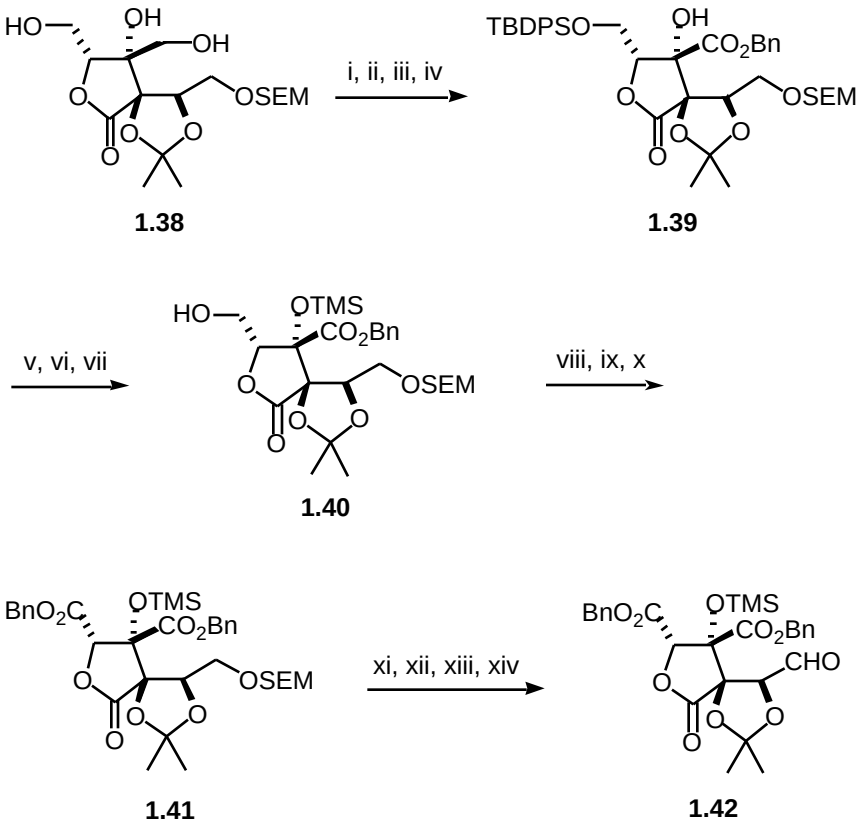
After satisfactory conditions for the enantioselective dihydroxylation had been found, attention was turned to the diastereoselective dihydroxylation of the C-3 – C-4 olefin. Initially, the diastereoselective dihydroxylation was attempted on **1.36** rather than on **1.37**, but **1.36** was found resistant to dihydroxylation using

either standard conditions or Sharpless asymmetric dihydroxylation conditions. Removal of the PMB protecting groups was anticipated to increase the reactivity by generating a less sterically hindered allylic alcohol. Additionally, it was anticipated that PMB deprotection would give lactone **1.37**, after spontaneous lactonization. Formation of lactol **1.37** had the advantage of providing steric hindrance to attack at the *re* face of the olefin in the dihydroxylation. Dihydroxylation of the C-3-C-4 olefin in **1.37** followed by base-catalyzed translactonization in one-pot formed **1.38** as a mixture (10:1) of diastereomers. Recrystallization of the mixture provided **1.38** as a single diastereomer in an 83% yield.

Originally, it was anticipated that both C-8 and C-9 could be oxidized simultaneously, unfortunately all attempts at doing so resulted in complex reaction mixtures. Consequently, a stepwise approach was necessary (Scheme 1.10). To this end, the C-8 hydroxyl of **1.38** was protected while the stepwise oxidation at C-9 was accomplished to provide **1.39**. The selective protection at C-4 was then accomplished while obtaining the free alcohol at C-8 to give **1.40**. Stepwise oxidation and esterification at C-8 then yielded **1.41**. If the second

oxidation sequence was performed without C-4 being protected, it was sometimes found that the reaction gave a very low yield of desired product, particularly with large scale reactions. These low yields were attributed to retro-aldol cleavage of the C-3 – C-4 bond. Aldehyde **1.42** was then obtained from **1.41** in four steps. Though this sequence of stepwise oxidations grew to be somewhat cumbersome with protection/deprotection sequences, the yields were generally high and reproducible on a large scale.

Scheme 1.10



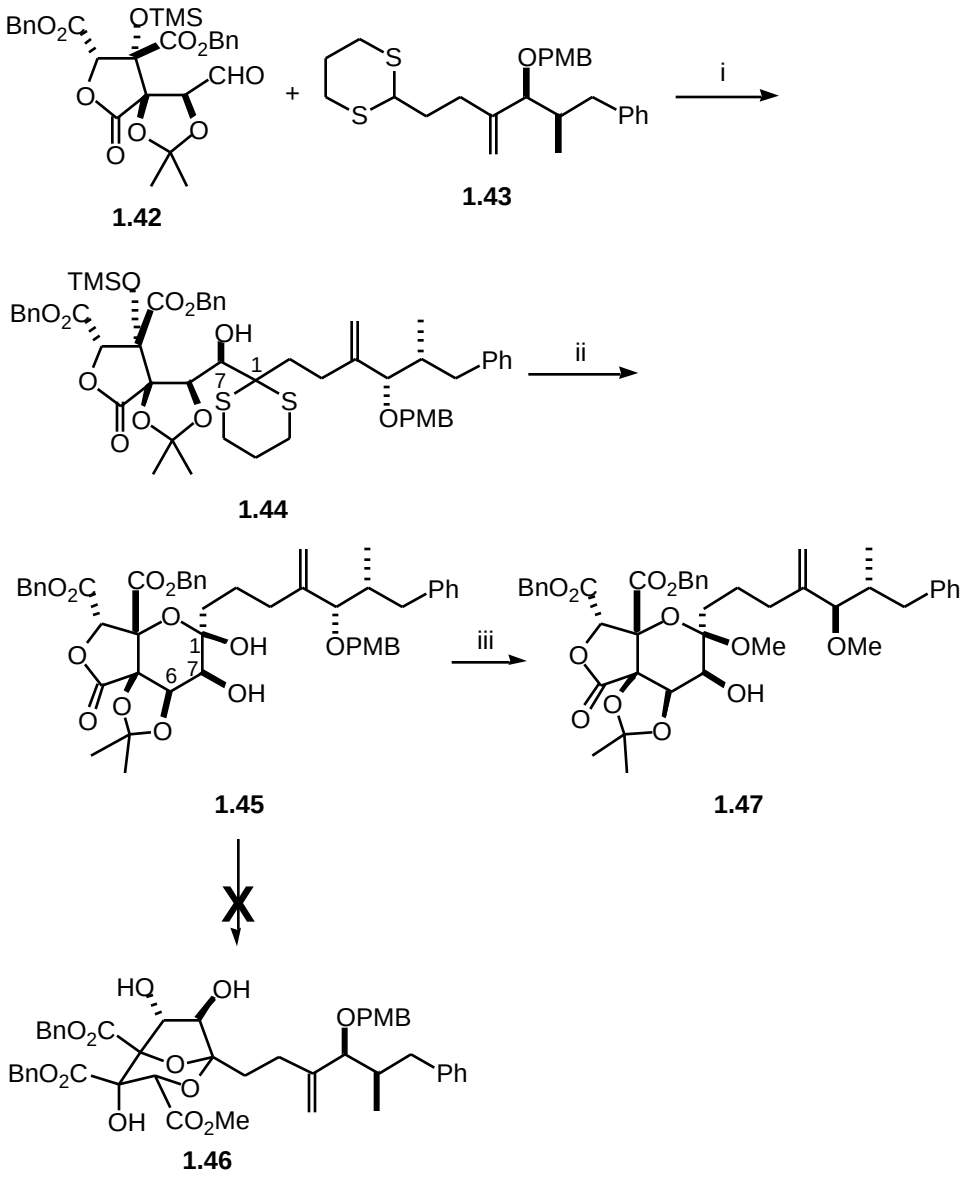
1.38 **1.39** **1.40** **1.41** **1.42**

i) TBDPSCl, imid., DMAP, DMF, 89%; ii) Dess-Martin, CH_2Cl_2, 89%; iii) $NaClO_2$, NaH_2PO_4, $Me_2C{=}CHMe$, *t*-BuOH/H_2O; iv) DCBI, $PhCH_3$, 96%; v) TBAF, AcOH, THF, 97%; vi) $CH_3N(TMS)COCF_3$; vii) PPTS, CH_2Cl_2/MeOH; viii) Dess-Martin, CH_2Cl_2, 97%; ix) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O; x) DCBI, $PhCH_3$, 60%; xi) TFA, CH_2Cl_2, 88%; xii) $CH_3N(TMS)COCF_3$; xiii) PPTS, CH_2Cl_2/ MeOH; xiv) Dess-Martin, CH_2Cl_2, 93%

Coupling of the C-1 side chain with the core structure was accomplished by lithiation of dithiane **1.43** and addition to aldehyde **1.42** to give the desired alcohol as a mixture (1:1) of diastereomers of **1.44** (Scheme 1.11). Unfortunately,

the undesired isomer could not be converted to the desired isomer **1.44**, but the two isomers were readily separable since the desired isomer could be selectively desilylated under the reaction conditions. After removal of the dithiane protecting group from **1.44**, treatment of **1.45** with HCl/MeOH did not produce the expected zaragozic acid [3.2.1] core **1.47**. Instead, it was found that the PMB group had undergone S_N2 displacement with methanol, as well as methanolysis at C-1 to provide **1.46**.

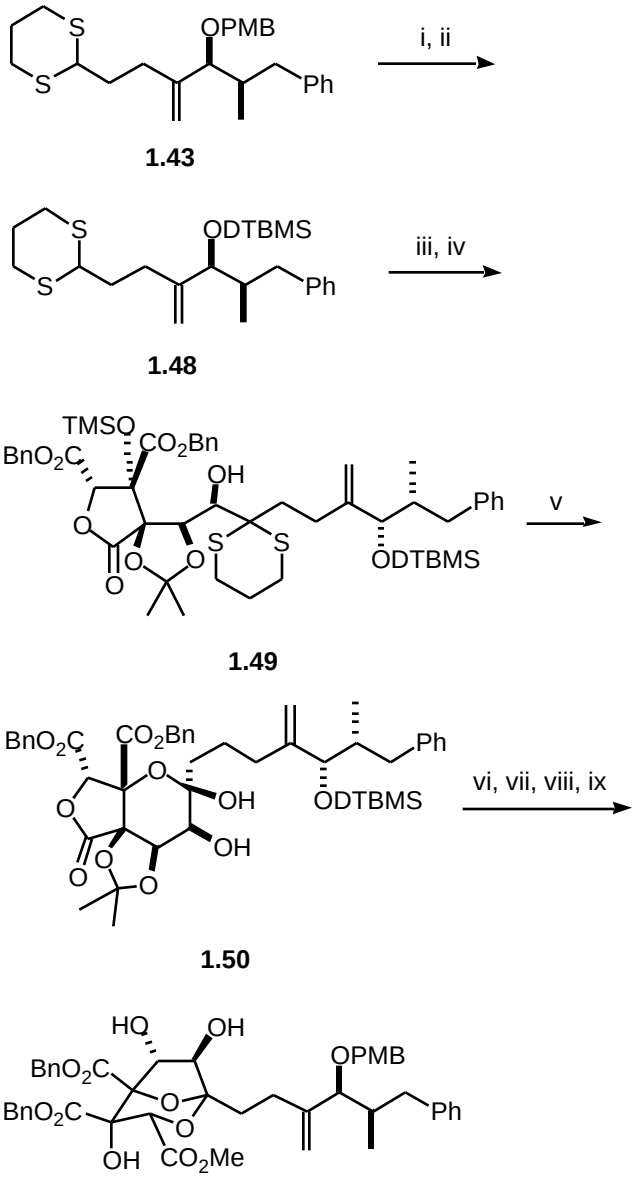
Scheme 1.11



i) BuLi, THF, 29% ; ii) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O, 67%;
iii) 2% HCl/ MeOH, 40%.

In order to circumvent this problem, the PMB group was removed from **1.43** using DDQ, and the resulting secondary alcohol was protected with the more acid stable di-*tert*-butylmethylsilyl (DTBMS) to give C-1 side chain **1.48** (Scheme 1.12). Coupling of **1.48** with aldehyde **1.42** gave a separable mixture of diastereomers, and the desired isomer **1.49** was carried on through the desilylation and dithiane removal as before to give **1.50**. Treatment of **1.50** with HCl/MeOH provided the zaragozic acid bicyclic core in 45% yield. Finally, the C-4' hydroxyl of the C-1 side chain was reprotected as the PMB ether, thereby completing the synthesis of relay compound **1.51** that had been shown by Nicolaou to be a viable intermediate for zaragozic acid A.

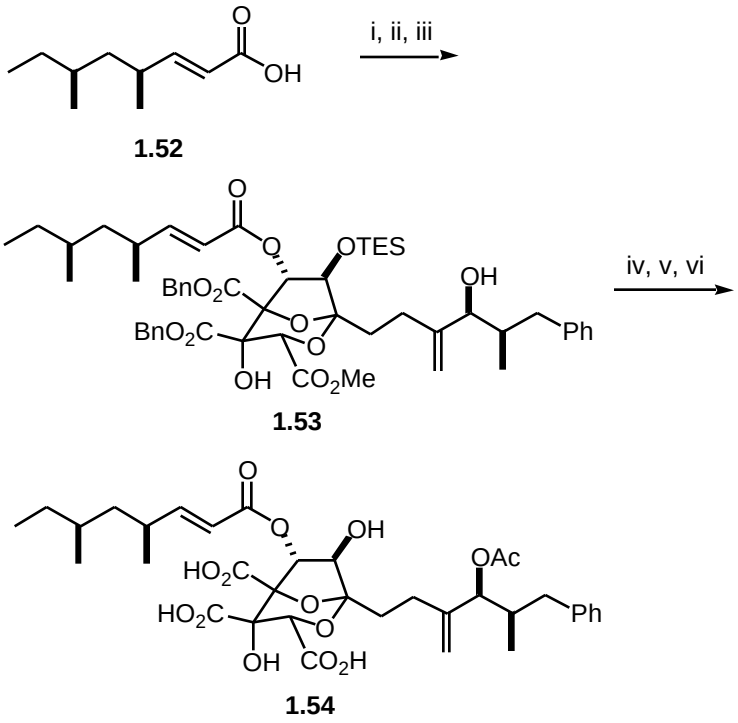
Scheme 1.12



i) DDQ, CH_2Cl_2/H_2O, 70%; ii) DTBMSOTf, 2,6-lutidine, DMAP, 87%;
iii) **1.42**, BuLi, THF, 40%; iv) 2% HCl/MeOH/CH_2Cl_2, 99%;
v)$Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O, 83%; vi) 1.8% HCl/MeOH, 45%;
vii) 49% aq, HF/$MeNO_2$, 30%; viii) LiOH•H_2O, THF/H_2O then DCBI, THF, 68%;
ix) CSA, $Cl_3C(OPMB)=NH$, CH_2Cl_2, 21%.

Final elaborations in the synthesis of zaragozic acid A began with the coupling of the C-6 side chain **1.52** with core structure **1.51** to give a disappointing mixture (3:2) of C-6 and C-7 acylated product (Scheme 1.13). Although both the yield and selectivity of the reaction were poor, it was possible to separate the two isomers by chromatography, hydrolyze the C-7 acylation product and recycle it. Silyl protection of the C-7 hydroxyl followed by PMB deprotection at C-4' gave **1.53**. Installation of the C-4' acetate, silyl deprotection, and saponification of the esters gave zaragozic acid A (**1.54**) in 34 steps and an overall yield of <1%.

Scheme 1.13

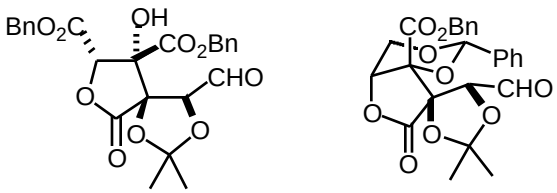


i) **1.51**, EDC, DMAP, CH_2Cl_2, 47%;
ii) TESOTf, pyr., CH_2Cl_2, 79%; iii) DDQ, CH_2Cl_2/H_2O, 98%;
iv) Ac_2O, pyr., DMAP, CH_2Cl_2, 99%; v) TBAF, THF, 85%;
vi) 10% Pd/C, 1,4-cyclohexadiene, 1,4-dioxane, 50%.

After the completion of the synthesis of zaragozic acid A (**1.54**), Nicolaou redesigned the preparation of aldehyde **1.42** to address some of the major problems in the synthesis (Figure 1.3). First, the lack of control in the diastereoselectivity in the coupling of aldehyde **1.42** to C-1 side chain **1.48** rendered half of the material unusable. This was unfortunate in light of the fact that it was such advanced intermediate in the synthesis. Secondly, the aldehyde

1.42 was not stable to chromatography. Thirdly, the C-3 benzyl ester was prone to attack by dithiane **1.48**. The rationale behind the design of aldehyde **1.55** to replace aldehyde **1.42** was the anticipation that the benzylidene acetal would have an influence on the approach of the C-1 side chain **1.48** to the aldehyde. Additionally, it was also thought that the benzylidene acetal of **1.55** would prove to be more stable to chromatography than the tertiary TMS ether of **1.42**. Lastly, the absence of the benzyl ester at C-3 would prevent attack of the dithiane anion **1.48** on the benzyl ester at C-3 as was observed in the case of **1.42**.

Figure 1.3

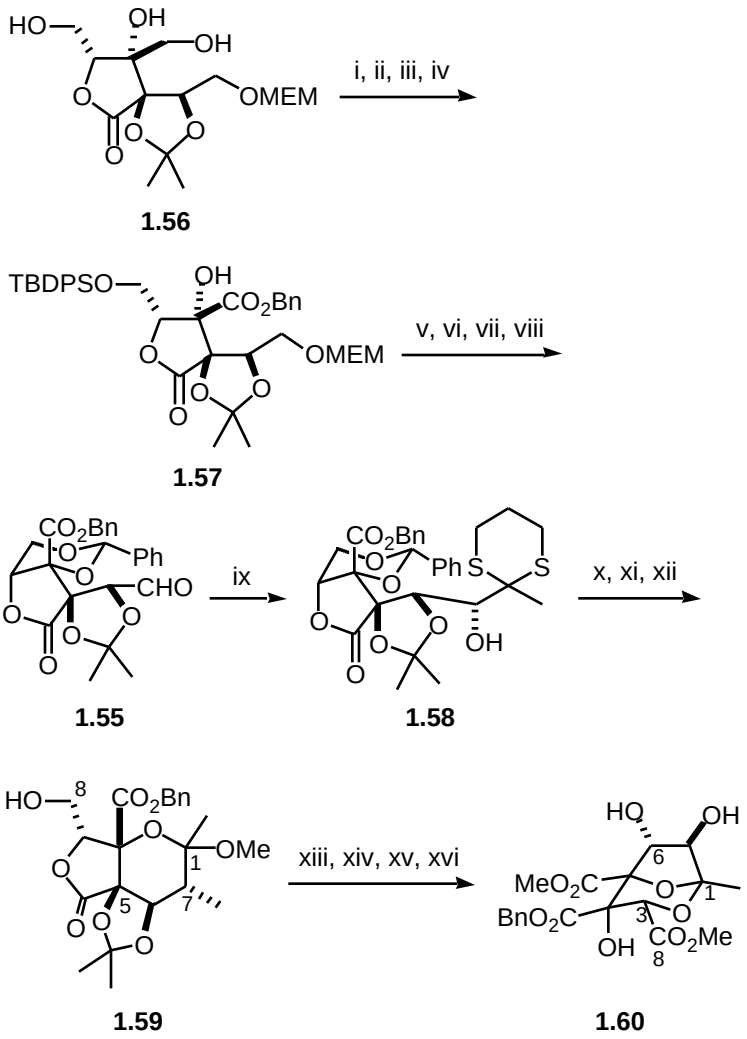


1.42 **1.55**

The preparation of aldehyde **1.55** began with selective protection of triol **1.56**, which was prepared analogously to **1.38**, at C-8 followed by oxidation of the remaining alcohol to benzyl ester **1.57** (Scheme 1.14). The preparation of aldehyde **1.55** was then accomplished in four steps from **1.57**. A model C-1 side chain was then used to examine the effect of aldehyde **1.55** on the

diastereoselectivity of the addition. The diastereoselectivity of the addition of methyl dithane to **1.55** was 3:1 favoring the desired alcohol, which was a significant improvement over previous results. Through a series of manipulations, dithiane **1.58** was converted to the zaragozic acid [3.2.1] core system **1.60** with the model C-1 side chain. This route is not as convergent as the previous route, because it necessitates the oxidation at C8 after the addition of the side chain. However, the benefit of the higher diastereoselectivity in the addition of the C-1 side chain makes the use of aldehyde **1.55** an improvement in the synthesis.

Scheme 1.14



i) TBDPSCl, imid., DMAP, DMF, 89%; ii) Dess-Martin, CH_2Cl_2;
iii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O;
iv) DCBI, $PhCH_3$, 93%; v) TMSCl, NaI, 66%;
vi) TBAF, AcOH, THF, 97%; vii) $PhCH(OMe)_2$, CSA, CH_2Cl_2, 85%;
viii) Dess-Martin, CH_2Cl_2, 90%; ix) 2-methyl-1,3-dithiane, BuLi, THF, 47%;
x) $Zn(OTf)_2$, EtSH, CH_2Cl_2, 89%; xi) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O, 81%;
xii) 2% HCl/MeOH, 82%; xiii) PCC, Celite, 3Å mol. sieves, CH_2Cl_2, 65%;
xiv) $NaClO_2$, NaH_2PO_4, $Me_2C{=}CHMe$, *t*-BuOH/H_2O;
xv) DCBI, $PhCH_3$, 92%; xvi) 2% HCl/MeOH, 64%.

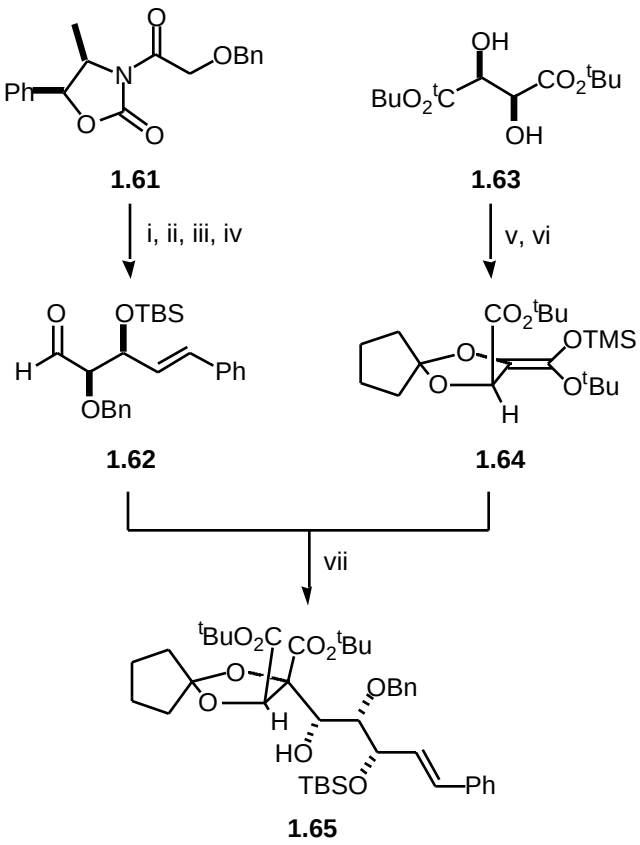
1.2.3 Evans' Synthesis of Zaragozic Acid C

The second synthesis of zaragozic acid C (**1.7**) by Evans was also published in 1994 subsequent to the Carreira synthesis. The synthesis featured both an Evans aldol as well as a Mukaiyama aldol reaction to set all of the stereocenters in **1.7** with the exception of the one at C-5. The required C-5 stereochemistry was established through a chelation controlled Grignard reaction. Interestingly, Evans chose to assemble the five-membered ring portion of the zaragozic acid core before the ketalization to close the six-membered ring. The syntheses by both Nicolaou and Carreira on the other hand assembled the entire core structure in one step. Evans, like Carreira, chose to introduce the C-1 side chain at an early stage, a decision that prevented the synthesis of a variety of zaragozic acids from a common, late stage intermediate. One of the most attractive features of this synthesis was the fact that Evans had the foresight to differentiate the C-6 and C-7 hydroxyl groups at an early stage. Differentiating these hydroxyl groups enabled Evans to incorporate the C-6 side chain with complete regioselectivity in contrast to the strategies of Carreira and Nicolaou. This synthesis of zaragozic acid C (**1.7**) was efficient in terms of both the number

of steps (22) and the overall yield (9.7%). Unfortunately, since there has been no full paper published, there is little insight as to the reasoning behind various steps in the synthesis.

The synthesis began with the diastereoselective aldol reaction of the boron enolate of **1.61** to give the desired adduct in excellent yield (Scheme 1.15). Subsequent modifications of the adduct provided aldehyde **1.62** in three steps, which was to be used in a Mukaiyama aldol reaction later in the synthesis. The synthesis of the coupling partner **1.64** commenced with protection of di-*t*-butyl tartrate (**1.63**) and formation of the silyl enol ether. Mukaiyama aldol coupling of the two fragments **1.62** and **1.64** under Lewis acidic conditions gave the adduct **1.65** as a single isomer in 94% yield.

Scheme 1.15

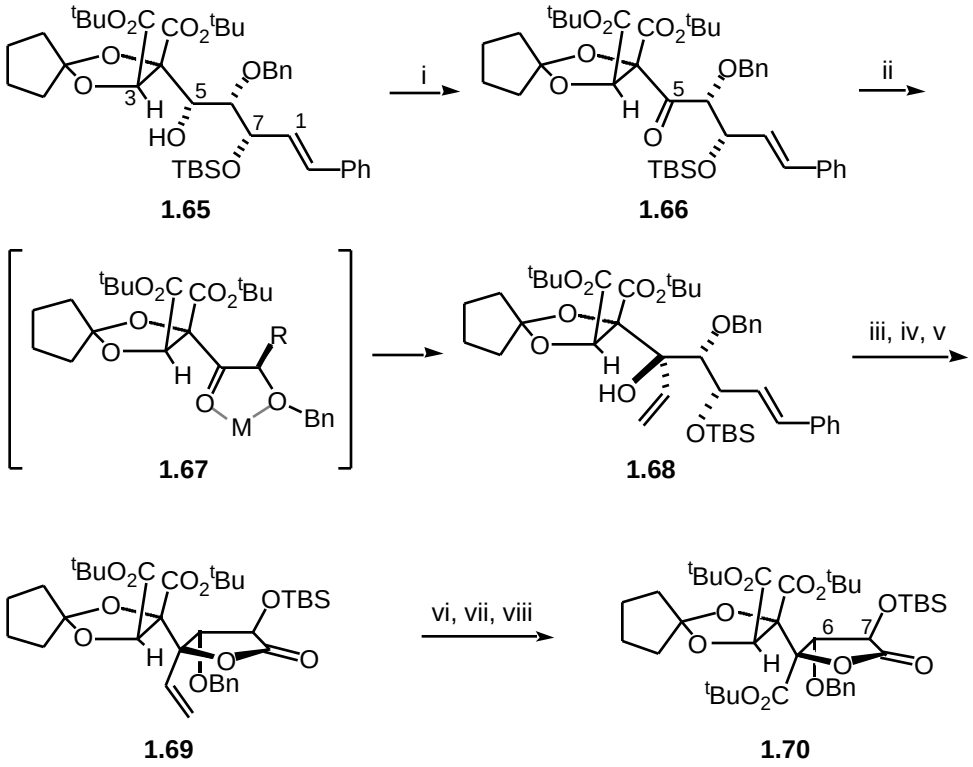


i) Bu_2BOTf, Et_3N, PhCH=CHCHO, CH_2Cl_2, 96%;
ii) TBSOTf, 2,6-lutidine, CH_2Cl_2; iii)$LiBH_4$, MeOH, THF;
iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; 92%;
v) cyclopentanone dimethyl ketal, TsOH, PhH, 85%;
vi) LiHMDS, TMSCl, THF, 97%; vii) (*i*-PrO)$TiCl_3$, CH_2Cl_2, 76%.

Once **1.62** and **1.64** had been coupled, oxidation at C-5 of **1.65** yielded ketone **1.66** (Scheme 1.16). Treatment of **1.66** with vinyl magnesium bromide formed the desired olefin **1.68** with high diastereoselectivity (10:1) due to chelation control between the ketone and benzyloxy functionality as shown in

1.67. Dihydroxylation of the C-1 olefin of **1.68** followed by oxidative cleavage of the diol and oxidation produced lactone **1.69** in an 84% yield. Triester **1.70** was then obtained in three steps and 91% overall yield from **1.69**.

Scheme 1.16

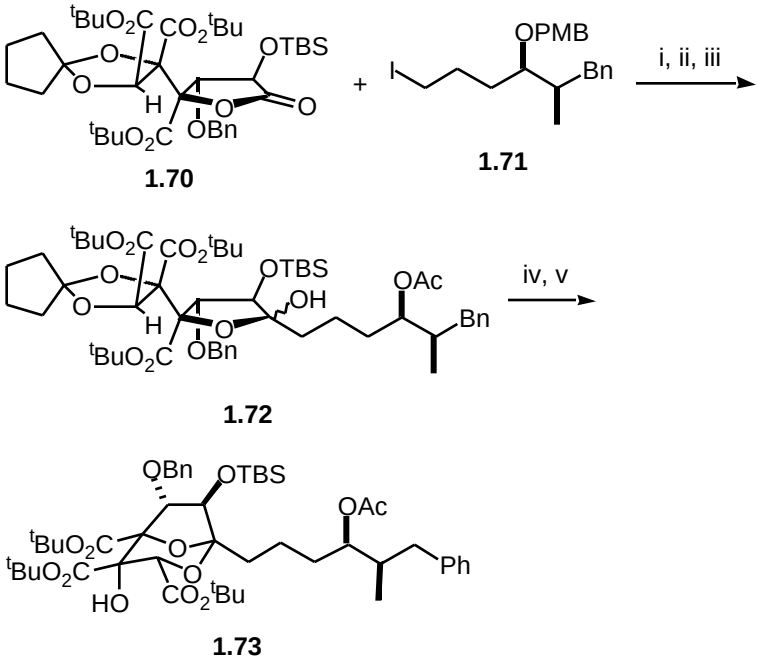


i) Dess-Martin, CH_2Cl_2, 94%; ii) CH_2=CHMgBr, CH_2Cl_2/THF, 76%;
iii) OsO_4, NMO, *t*-BuOH/THF, H_2O; iv) $Pb(OAc)_4$, PhH, ;
v) TPAP, NMO, 4Å mol. sieves, CH_2Cl_2, 84%; vi) O_3, NMO, CH_2Cl_2;
vii) $NaClO_2$, NaH_2PO_4, Me_2C=CHMe, *t*-BuOH;
viii) *N, N'*-diisopropyl-*O*-*t*-butylisourea, CH_2Cl_2, 91%.

Coupling of lactone **1.70** with **1.71** gave a mixture of lactols, and deprotection at C-4' and acetylation provided lactol **1.72** (Scheme 1.17).

Treatment of **1.72** with TFA and esterification yielded triester **1.73**. It is worth noting that the hydroxyl groups at C-6 and C-7 were differentiatially protected zaragozic acid core system, thereby avoiding the regioselectivity issues that both Carreira and Nicolaou had to overcome.

Scheme 1.17

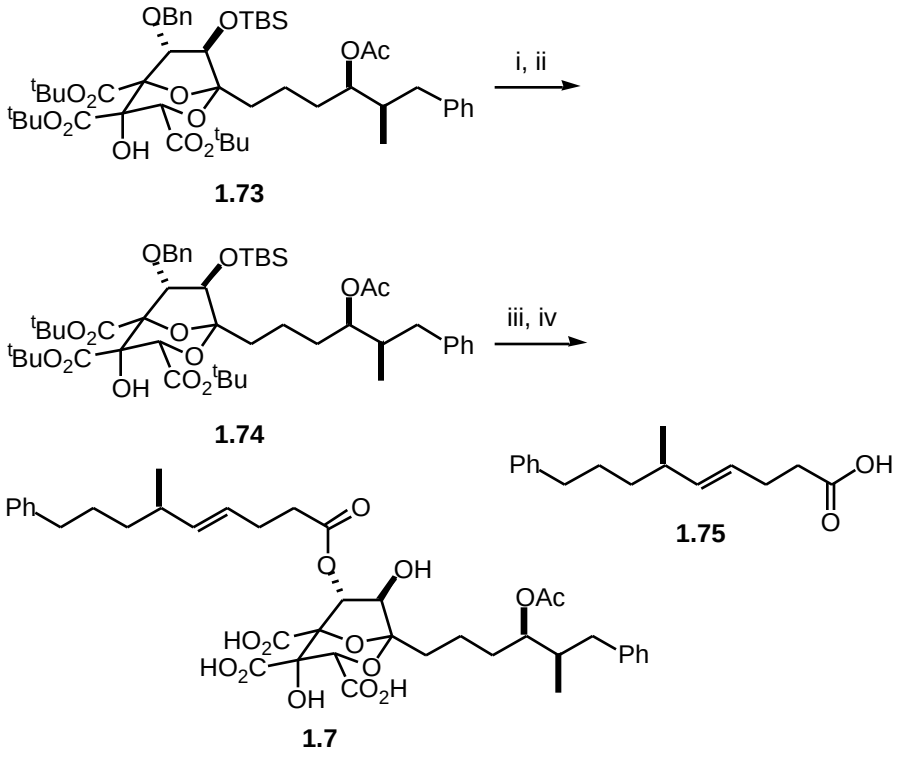


i) *t*-BuLi, 73%; ii) DDQ, CH_2Cl_2/H_2O; iii) Ac_2O, DMAP, pyr/PhH, 90%;
iv) CH_2Cl_2/TFA/H_2O; v) *N, N'*-diisopropyl-*O*-*t*-butylisourea, CH_2Cl_2, 52%

Completion of the synthesis of zaragozic acid C (**1.7**) was accomplished by deprotection of **1.73** to yield **1.74** and installation of the C-6 side chain **1.75** (Scheme 1.18). Finally, silyl deprotection and saponification of the three esters

provided zaragozic acid C (**1.7**) in a concise, high yielding, and highly stereocontrolled manner.

Scheme 1.18



i) H_2, 10% Pd/C, AcOH, MeOH; 96%; ii) **1.75**, DCC, DMAP, CH_2Cl_2, 82%; iii) TBAF, THF, 99%; iv) TFA, CH_2Cl_2, 99%

1.2.4 Heathcock's Synthesis of Zaragozic Acid A

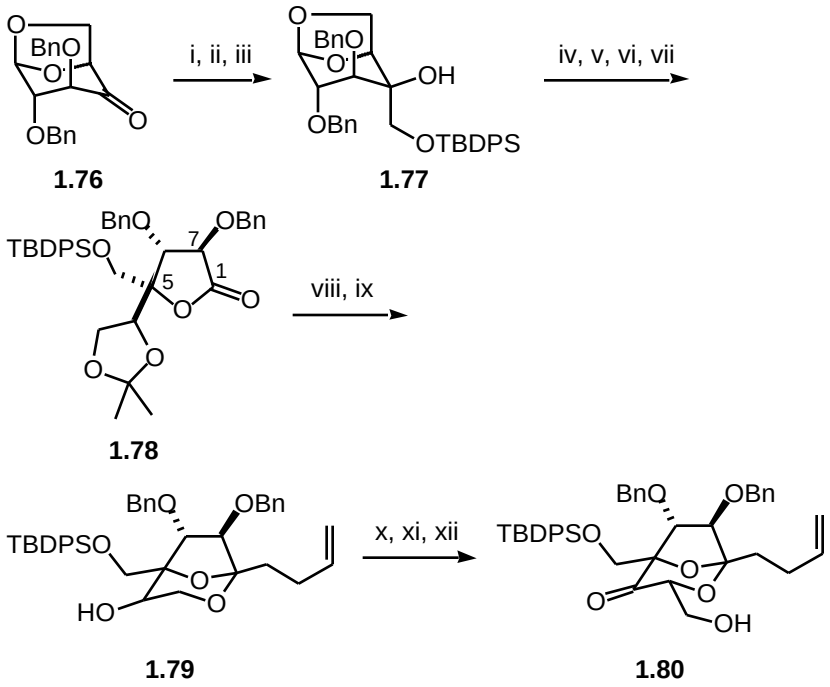
The second total synthesis of zaragozic acid A was completed by Heathcock in 1996 and was published as a relay synthesis from compound **1.86**. In the first of two papers, the synthesis of **1.86** from zaragozic acid A (**1.54)** and

the reconstitution of zaragozic acid A from relay compound **1.86** were detailed. The second publication presented the synthesis of **1.86** from methyl-D-pyranoside. Heathcock's synthesis of zaragozic acid was significantly longer than any of the other syntheses with forty-two steps (longest linear sequence) and an overall yield of less than 1%. The zaragozic acid core **1.79** was assembled prior to the functionalization of either C-3 or C-4. Elaboration of the C-5 center was facile, however, installing the requisite alcohol and ester at C-4 proved to be challenging. Although Heathcock had not differentiated the C-6 and C-7 hydroxyl groups early in the synthesis he was able to address this issue by selectively protecting C-7 using the incomplete C-1 side chain to give **1.87**. The use of the incomplete C-1 side chain as a protecting group for C-7 was a creative way to regioselectively incorporate the C-6 side chain. This was a creative way to approach the issue of regioselectively installing the C-6 side chain in the absence of differential protection early in the synthesis.

Compound **1.76**, which was made in five steps from methyl-α-D-pyranoside was converted to **1.77** with the requisite diol at C-5 in three steps (Scheme 1.19). Lactone **1.78**, which contained the completed five-membered ring

encompassing C-1 through C-5 of the zaragozic acid core, was then obtained from **1.77** in four steps. Allyl magnesium bromide was added after transmetalation to the cerium reagent to form the bicyclic[3.2.1]core **1.79** in a 74% yield after treatment with acid. If the Grignard reagent was used in the addition rather than the cerium reagent, elimination of the benzyloxy group β to the carbonyl was observed.

Scheme 1.19

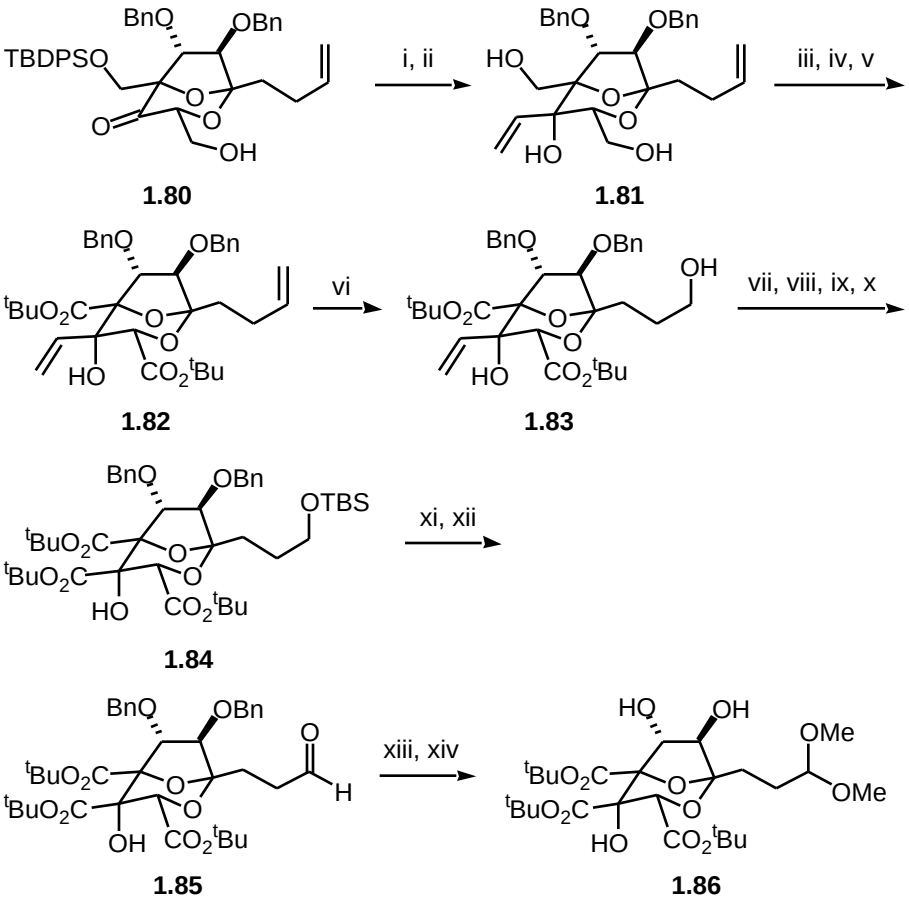


i) $Me_2(i\text{-}PrO)SiCH_2MgCl$, THF; ii) H_2O_2, MeOH, THF, $NaHCO_3$;
iii) TBDPSCl, imid., DMF, 92%; iv) TFA, Ac_2O; v) NaOMe, MeOH;
vi) acetone, H^+; vii) PDC, sieves, CH_2Cl_2, 77%; viii)$CH_2{=}CHCH_2CH_2CeCl_2$,
THF; ix) HCl, H_2O, THF, 74%; x) DMSO, TFAA, Et_3N, CH_2Cl_2, 94%;
xi) *t*-BuLi, CH_2O/THF, 96%; xii) TBSCl, imid., DMF, 98%.

One of the more difficult challenges in this synthesis was the elaboration of C-4. After considerable experimentation, it was found that after transmetalation of vinyl magnesium bromide to the cerium reagent and addition to **1.80** provided the requisite functionality at C-4. Treatment with TBAF provided triol **1.81** as a 15:1 diastereomeric mixture (Scheme 1.20). Diester **1.82** was then obtained from triol **1.81** in 76% overall yield using a three step oxidation

sequence. Selective ozonolysis of the C-1 side chain was then performed in the presence of the C-4 olefin to give **1.83**. Presumably, the selectivity in the reaction of **1.82** was due to the steric congestion about the C-4 olefin, though there was no comment on the this issue. The C-4 olefin was then subjected to ozonolysis and oxidation to the ester to give triester **1.84**. Aldehyde **1.85** was obtained in two steps from **1.84** and then protected as the dimethyl acetal to provide **1.86**, which constituted the synthesis of the relay compound in the Heathcock synthesis of zaragozic acid A (**1.54**).

Scheme 1.20

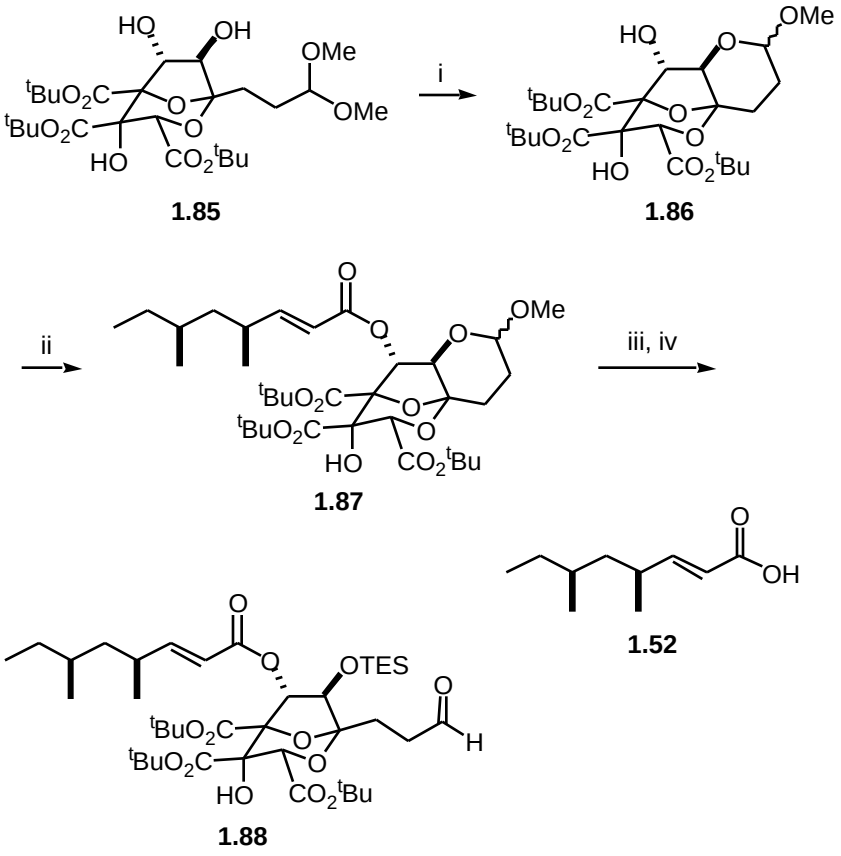


i) CH_2=CHMgBr, $CeCl_3$, THF; ii) TBAF, THF, 88%; iii) Dess-Martin, CH_2Cl_2;
iv) $NaClO_2$, NaH_2PO_4, Me_2C=CHMe, *t*-BuOH/H_2O;
v) *N, N'*-diisopropylisourea, CH_2Cl_2, 76%; vi) O_3, CH_2Cl_2/MeOH, then $NaBH_4$, 61%;
vii) O_3, CH_2Cl_2/MeOH; viii) TBSCl, imid., DMF; ix) $NaClO_2$, NaH_2PO_4, Me_2C=CHMe,
t-BuOH/H_2O; x) *N, N'*-diisopropylisourea, CH_2Cl_2, 41%; xi) TBAF, THF, 61%;
xii) Dess-Martin, CH_2Cl_2; xiii) $(MeO)_3CH$, MeOH, PPTS; xiv) H_2, $Pd(OH)_2$, MeOH.

The synthesis of zaragozic acid A (**1.54**) from the relay compound began with installing the C-6 side chain (Scheme 1.21). Initially, attempts to couple either the acid **1.52** or the corresponding acid chloride to diol **1.85** resulting

primarily in the acylation at C-7 rather than at C-6. In order to circumvent this problem, a novel approach was taken whereby the cyclic acetal **1.86** was made from **1.85**, thereby internally protecting the C-7 hydroxyl. Side chain **1.52** was then incorporated exclusively at C-6 to provide **1.87**. Aldehyde **1.88** was then obtained in two steps from acetal **1.87**.

Scheme 1.21



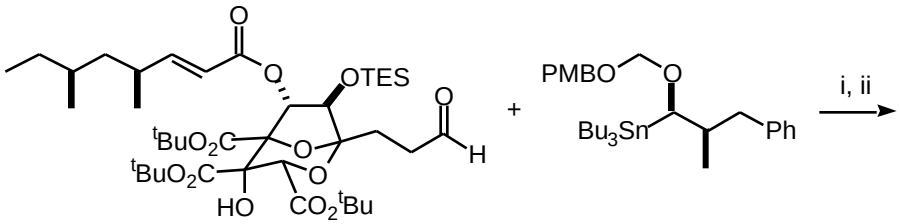
1.85 **1.86** **1.87** **1.52** **1.88**

i) PPTS, PhH, 4Å, 99%; ii) **1.52** DCC, DMAP, CH_2Cl_2, 95%;
iii) H_2O, acetone, PPTS; iv) TESCl, pyr., 80%.

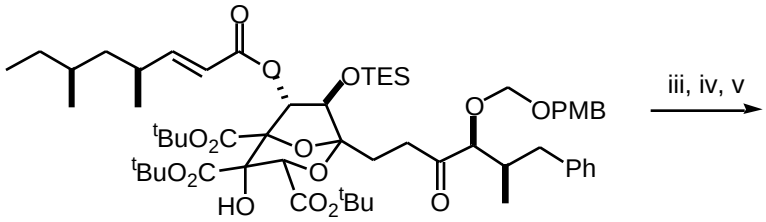
The conclusion of the total synthesis began with the incorporation of the remainder of the C-1 side chain (Scheme 1.22). This was accomplished by first transmetallating stannane **1.89** to the cerium anion and addition to aldehyde **1.88** to form **1.90** after Dess-Martin oxidation of the C-3' alcohol. Use of the organocerium rather than the organolithium was found critical in the addition of

1.89 to aldehyde **1.88** due to extensive enolization when the addition was attempted with the organolithium species. Additionally when the lithium anion was used, the diastereomeric ratio was a disappointing 1:1. Compound **1.91** was then obtained with a fully functionalized C-1 side chain. Removal of the protecting group at C-7 and saponification of the three *t*-butyl esters gave zaragozic acid A (**1.54**).

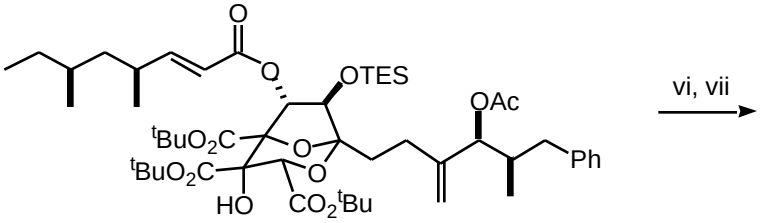
Scheme 1.22



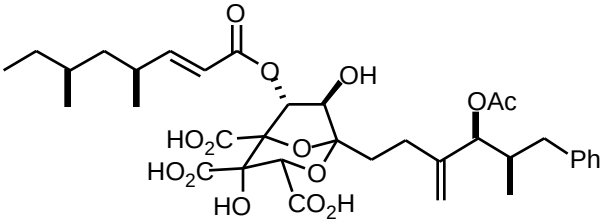
1.88 **1.89**



1.90



1.91



1.54

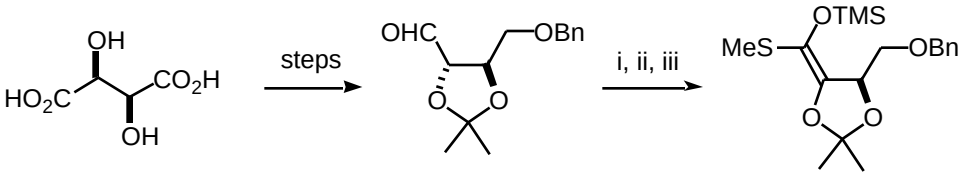
i) BuLi, THF, then $CeCl_3$, 87%; ii) Dess-Martin, pyr., CH_2Cl_2, 92%;
iii) Tebbe reagent, THF, 77%; iv) DDQ, CH_2Cl_2, H_2O, 91%;
v) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 100%; vi) HF•pyr, THF, 87%;
vii) TFA, CH_2Cl_2, 74%.

1.2.5 Hashimoto's Synthesis of Zaragozic Acid C

The third synthesis of zaragozic acid C was completed by Hashimoto in 1997. This synthesis utilized a tin triflate-mediated Mukaiyama aldol reaction between **1.94** and **1.97** to set the chiral centers at C-4 and C-5. Unfortunately, after extensive optimization of this key reaction, the best conditions gave only a 1.6:1 diastereomeric ratio of desired to undesired C5 epimer. After ketalization to assemble the zaragozic acid core, Hashimoto's synthesis intersected the synthesis of zaragozic acid C (**1.7**) published by Carreira

The two coupling partners **1.94** and **1.97** were prepared from D- and L-tartaric acid to form aldehydes **1.93** and **1.96** respectively (Schemes 1.23 and 1.24).[Mukaiyama, 1982 #441] Initial studies on the aldol addition of the silyl ketene thioacetal **1.94** to α-ketoester **1.97** provided rather disappointing results as the undesired C-5 epimer was formed preferentially from both the *E*- and *Z*-ketene thioacetals. Alternative protecting groups were explored to see if the diastereoselectivity of the reaction could be improved.

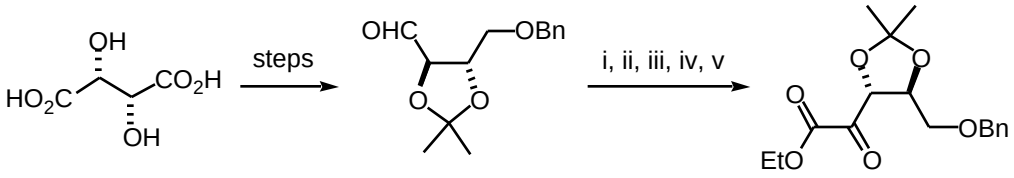
Scheme 1.23



1.92 **1.93** **1.94**

i) $NaClO_2$, NaH_2PO_4, $Me_2C{=}CHMe$, *t*-BuOH/H_2O; ii) $(COCl)_2$, DMF, CH_2Cl_2;
iii) NaSMe, Bu_4NI, CH_2Cl_2, THF, KHMDS or LiHMDS

Scheme 1.24

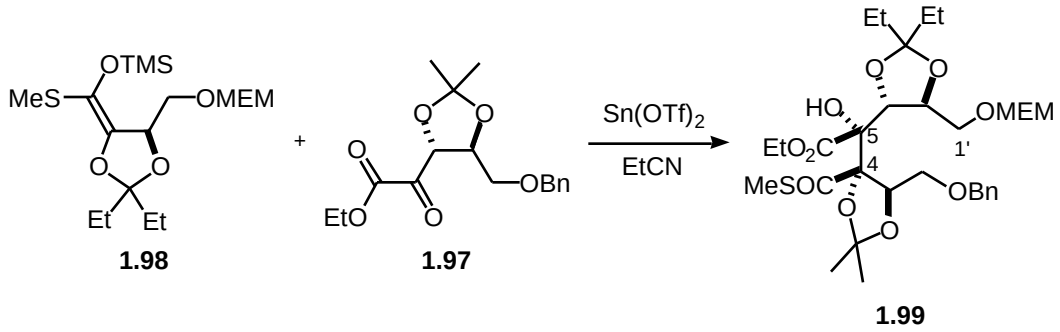


1.95 **1.96** **1.97**

i $NaClO_2$, $NaHPO_4$, $Me_2C{=}CHMe$, *t*-BuOH/H_2O; ii) $(COCl)_2$, DMF, CH_2Cl_2;
iii) MeONHMe•HCl, pyr., CH_2Cl_2; iv) ethyl vinyl ether, *t*-BuLi, THF; v) O_3, CH_2Cl_2

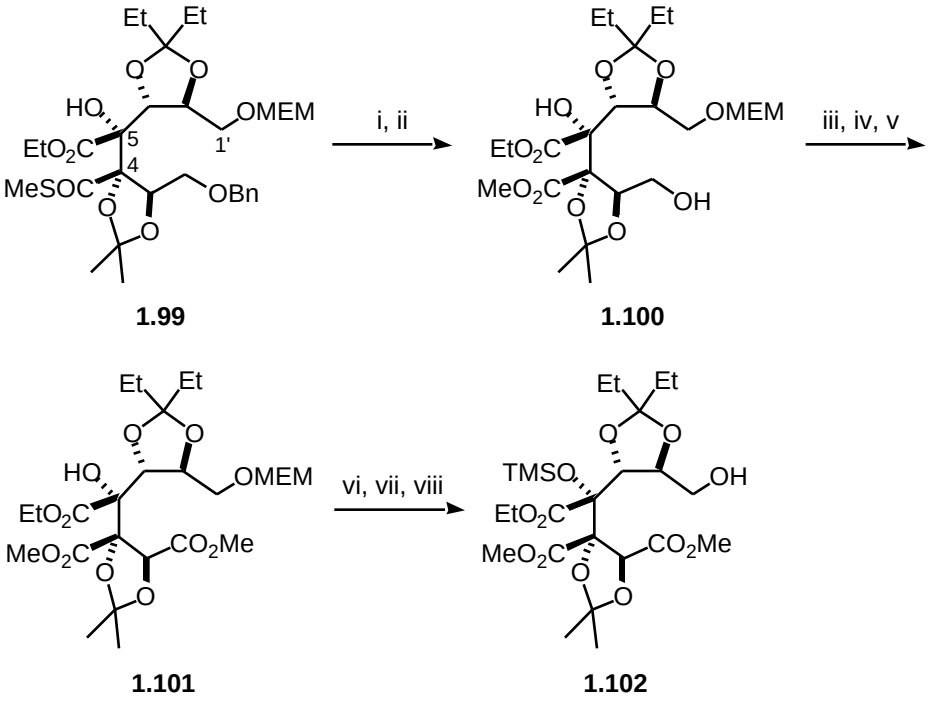
It was eventually found that protection of the C-1' hydroxyl with a strong chelating group was optimal, therefore MEM was selected to provide silyl ketene acetal **1.98** (Scheme 1.25). The Mukaiyama aldol of **1.98** and **1.97** provided a 1.6:1 ratio of desired C-5 epimer **1.99** to undesired (5-epi) aldol adduct. Although this ratio was certainly not ideal, it was the only experiment where the desired C-5 epimer **1.99** was the major product, and fortunately, the two diastereomers were separable.

Scheme 1.25



The correct diastereomer **1.99** was converted in eight steps to alcohol **1.100** (Scheme 1.26). Alcohol **1.101** was then made in several steps from **1.100**. Selective deprotection of the MEM group was followed by the selective silyl protection of the C-5 alcohol using a bissilylation/desilylation sequence to provide **1.102**.

Scheme 1.26

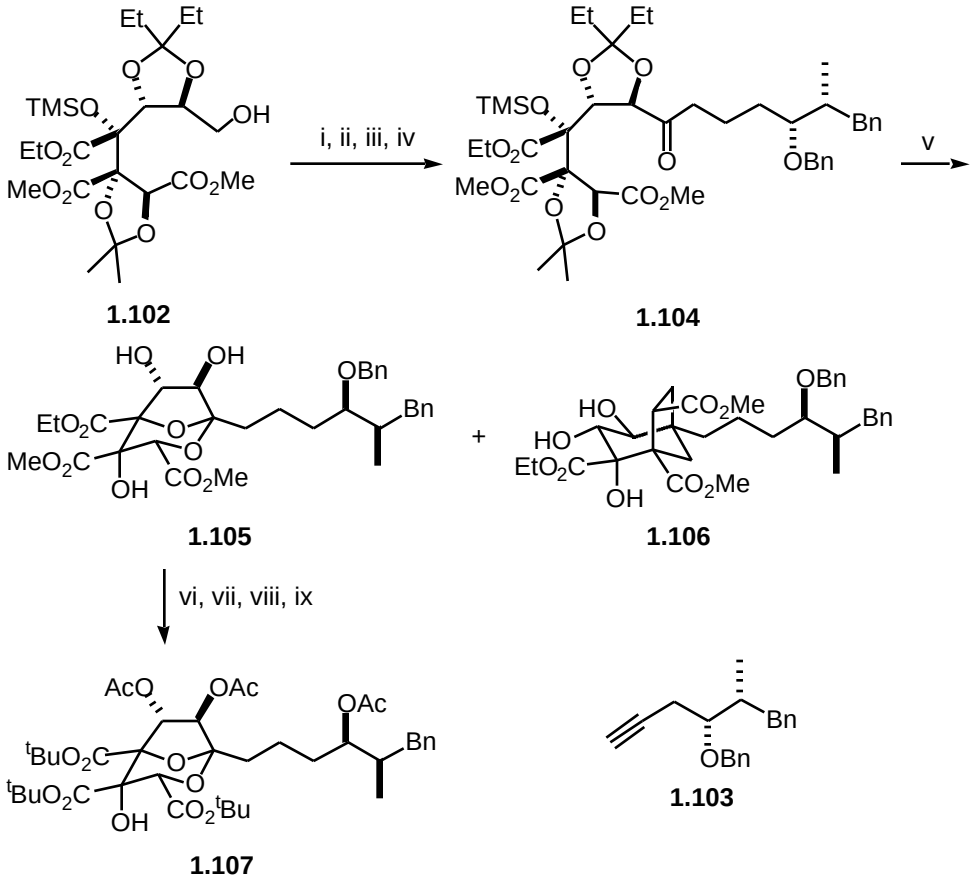


i) $Hg(OCOCF_3)$, MeOH, 82%; ii) H_2, Pd/C, MeOH; iii) Dess-Martin, CH_2Cl_2;
iv) $NaClO_2$, NaH_2PO_4, $Me_2C{=}CHMe$, *t*-BuOH/H_2O; v) CH_2N_2, Et_2O, 88%;
vi) TMSCl, NaI, MeCN, 88%; vii) $MeN(TMS)COCF_3$; viii)10% aq. HCl, Et_2O, 79%.

Dess-Martin oxidation of alcohol **1.102** was followed by installation of the C-1 side **1.103** chain *via* lithioacetylide addition to yield **1.104** (Scheme 1.27). Cyclization of **1.104** to give the zaragozic acid [3.2.1] core **1.105** then proceeded to give both the desired ketal as well as a small amount (7%) of an isomeric ketal **1.106**. The equilibration of **1.105** to **1.106** was attempted without success indicating that the ketalization was under kinetic control. The preferential

formation of **1.105** over **1.106** was ascribed to the fact that the C-6 – C-7 pentylidene acetal was hydrolyzed much more easily than the C-3 – C-4 isopropylidene acetal as monitored by TLC analysis. Triacetate **1.107**, which intersected Carreira's synthesis, was obtained in four steps from **1.105**. The remainder of the synthesis was carried out in an identical fashion to Carreira to give zaragozic acid C (**1.7**).

Scheme 1.27



i) Dess-Martin, CH_2Cl_2, 98%; ii) **1.103**, BuLi, THF;
iii) Dess-Martin, CH_2Cl_2, 79%; iv) H_2, Pd/C, EtOAc;
v) 90% aq. TFA, 68%; vi) 1N KOH, dioxane;
vii) *N, N'*-diisopropyl-*O*-*t*-butylisourea, CH_2Cl_2, 40%;
viii) H_2, Pd/C, MeOH, 86%; ix) Ac_2O, DMAP, CH_2Cl_2, 85%.

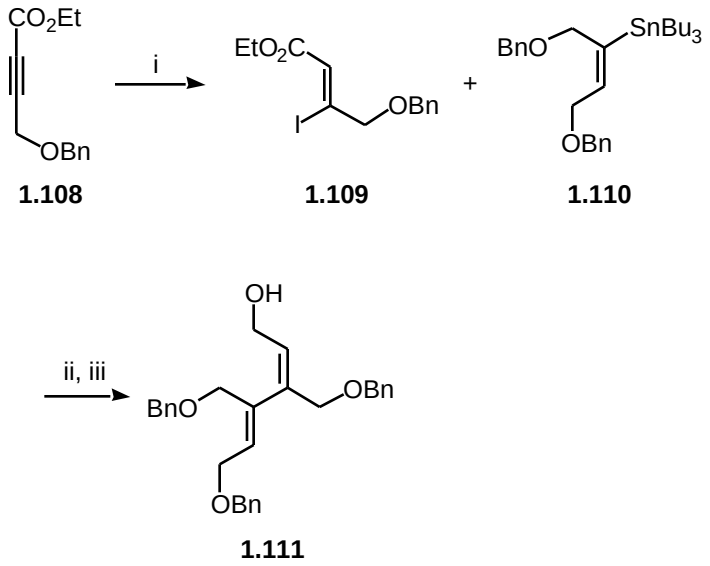
1.2.6 Armstrong's synthesis of Zaragozic Acid C

Armstrong's synthesis of zaragozic acid C (**1.7**) was strikingly similar to the Nicolaou approach to zaragozic acid A (**1.54**). The key steps for both

syntheses involved a Sharpless enantioselective dihydroxylation followed by a diastereoselective dihydroxylation to set the stereocenters in the [3.2.1] core system. Armstrong's synthesis of the zaragozic acid was shorter than Nicolaou's but the overall yields of the two syntheses were comparable at less than 1%.

The diene **1.111** was made in a similar manner to that in Nicolaou's synthesis (Scheme 1.28). Sharpless asymmetric double dihydroxylation was then examined on diene **1.111** as well as other dienes with various protecting group schemes. After some experimentation Armstrong found, as Nicolaou found, the best results were obatined with a stepwise, double dihydroxylation.

Scheme 1.28

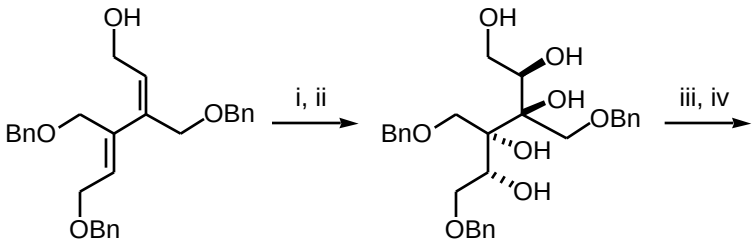


i) LiI, AcOH, 95%; ii) Cu(2-thiophenecarboxylate), NMP, 87%;
iii) Dibal-H, CH_2Cl_2, 94%

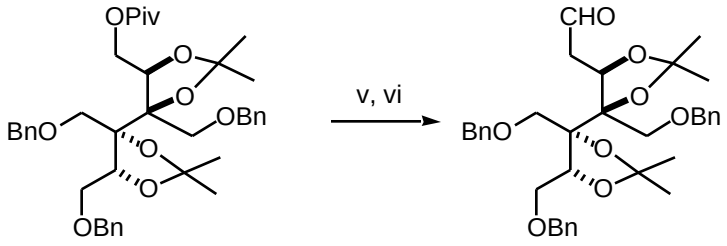
To this end, treatment of diene **1.111** with Super AD-mix followed by treatment of the resulting triol with OsO_4 in the presence of NMO produced tetraol **1.112** with 76% ee and >9:1 d.r., in about 47% overall yield (Scheme 1.29). Unfortunately, the dihydroxylation procedure required several days, but it was shortened by replacing the $K_2S_2O_8$ with the more soluble sodium salt in conjunction with higher loadings of osmium and ligand. This modification did succeed in shortening the reaction time, however, it was accompanied by a slight decrease in the enantioselectivity to give a 68% ee. Although it was unnecessary

to use the chiral ligand in the second dihydroxylation since the first dihydroxylation introduced the asymmetry to the system, the reaction rates were higher using the $(DHQD)_2$–PHAL ligand compared to the use of achiral quinuclidine. This process compares favorably to Nicolaou's results of 83% ee, 100% de with only a 30% yield for the first, and 83% yield for the second dihydroxylation. Diacetonide **1.113** was then obtained through a sequence of protecting group manipulations. Successive recrystallizations provided **1.113** in 96% ee. Swern oxidation to the aldehyde yielded **1.114**.

Scheme 1.29



1.111 **1.112**



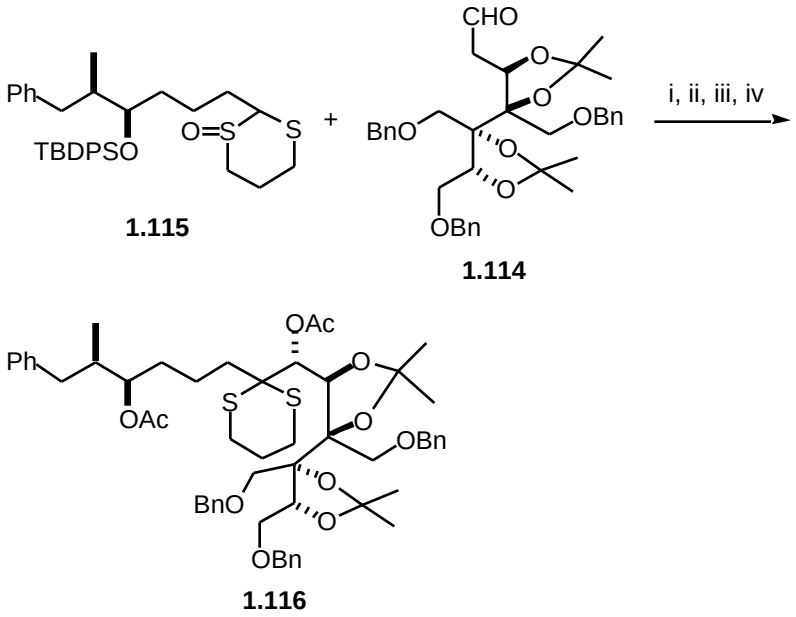
1.113 **1.114**

i) AD-mix β, OsO_4, $K_2S_2O_8$, $CH_3SO_2NH_2$, $(DHQD)_2PHAL$, NMO, *t*-BuOH/H_2O, 78%; ii) acetone, H_2O, $(DHQD)_2PHAL$, OsO_4, NMO, 58%; iii) PivCl, pyr., DMAP, CH_2Cl_2, 77%; iv) CH_2=CH(OMe)CH_3, cat. *p*-TsOH, DMF, 77%; v) Dibal-H, CH_2Cl_2, 91%; vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 75%

The C-1 side chain **1.115** was attached *via* dithiane monosulfoxide anion addition to the aldehyde **1.114** to give the desired adduct, albeit the diastereomeric ratio at C-7 was disappointingly only 1:1 (Scheme 1.30). It was necessary to use **1.115** rather than the corresponding dithiane because the latter could not be cleanly metallated. Difficulties in the metalation of 1,3 dithianes that have oxygen functionality in the δ-position have been noted previously, but in these

cases, the difficulty has been circumvented by use of a sodium base. This difficulty was interesting in light of the fact that Nicolaou was able to use a dithiane anion in the installation of C-1 side chain **1.43** or **1.48** to **1.42** without difficulty. The adduct was then subjected to deoxygenation to return the dithiane and silyl deprotection which provided **1.116** as a single diastereomer after column chromatography.

Scheme 1.30

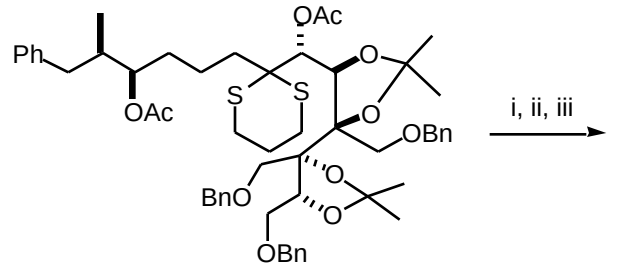


i) BuLi, THF; ii) P_2I_4, NEt_3, CH_2Cl_2, 59%;
iii) TBAF, THF, 32%; iv) Ac_2O, DMAP, pyr., 85%

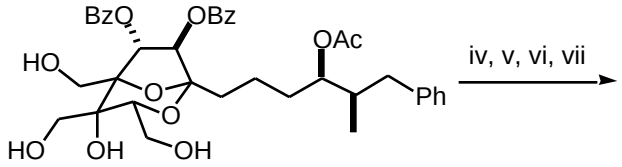
Ketalization of **1.116** then proceeded smoothly to provide the [3.2.1] zaragozic acid core (Scheme 1.31). Once the ketalization was accomplished,

protecting group manipulations followed to give tetraol **1.117**. All that remained to complete a formal synthesis of zaragozic acid C (**1.7**) was the oxidation of the core to the acid oxidation state at C-3, C-4, and C-5. To this end, all three hydroxyls were simultaneously oxidized followed by esterification to provide **1.28**, which intersected with the synthesis of zaragozic acid C by Carreira, and therefore constituted a formal total synthesis. Armstrong completed the remaining steps in the same manner as Carreira to complete a total synthesis of zaragozic acid C (**1.7**) in 23 steps and <1% overall yield.

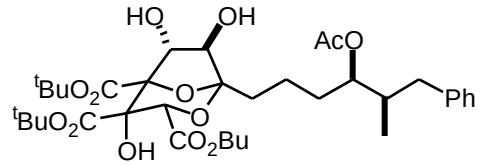
Scheme 1.31



1.116



1.117



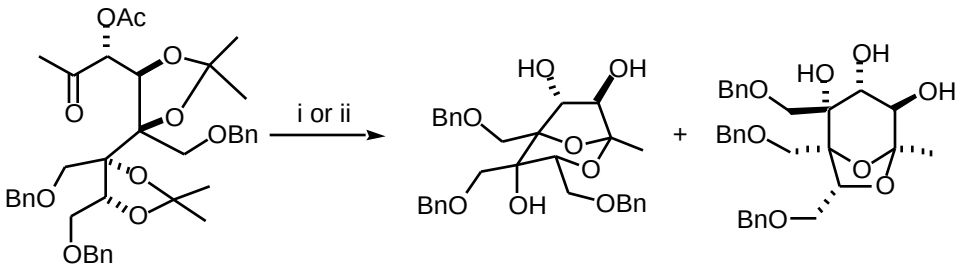
1.28

i) CH_2Cl_2/TFA/H_2O, 90%; ii) BzCl, DMAP, pyr., 97%; iii) H_2, Pd/C, 89%;
iv) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; v) $NaClO_2$, NaH_2PO_4, *t*-BuOH/β-isoamylene;
vi) *N, N'*-diisopropyl-*O*-*t*-butylisourea, CH_2Cl_2, 33%; vii) K_2CO_3, MeOH, 75%

An important side note to the ketalization was that when **1.118** was treated with either 2% HCl/MeOH or TFA, the desired ketal **1.119** was formed along with isomeric ketal **1.120** in nearly a 1:1 ratio (Scheme 1.32). If the ketalization was performed prior to the removal of the dithiane, the desired ketal **1.119** was the only product of the reaction. It was believed that depending on the substrate,

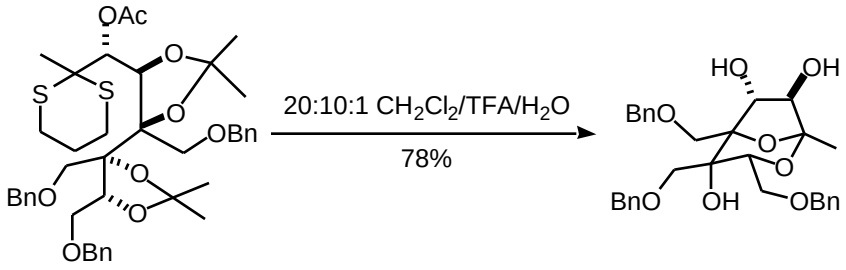
the ketalization could proceed under either kinetic or thermodynamic control. In the case of **1.118**, it was speculated that the reaction had proceeded under kinetic control since resubmitting the ketal isomers **1.119** and **1.120** to the reaction conditions did not result in their interconversion. It was hypothesized that the relative rate of hydrolysis of the two acetonides in **1.118** was responsible for the ratio of **1.119** to **1.120**. More specifically, if the C-3 – C4 acetonide was removed first, then formation of a six membered ring through closure of the C-4 hydroxyl onto the C-1 carbonyl might lead to **1.120**. Conversely, initial hydrolysis of the C-5 – C-6 acetonide might be followed by rapid cyclization of the C-5 hydroxyl group onto the C-1 carbonyl, leading to a five membered ring that may remain closed until hydrolysis of the other acetonide and subsequent closure of the second ring. In order to test this hypothesis, **1.121** was treated with TFA to remove both acetonide protecting groups before the removal of the dithiane protecting group. Unexpectedly, treatment of **1.121** with TFA not only effected the acetonide deprotection, but also the removal of the dithiane protecting group to give exclusively the desired ketal **1.119** in 78% yield.

Scheme 1.32



1.118 **1.119** **1.120**

i) 2% HCl, MeOH, 45% **1.119**, 47% **1.120**;
ii) 20:10:1 CH_2Cl_2/TFA/H_2O, 38% **1.119**, 38% **1.120**



1.121 **1.119**

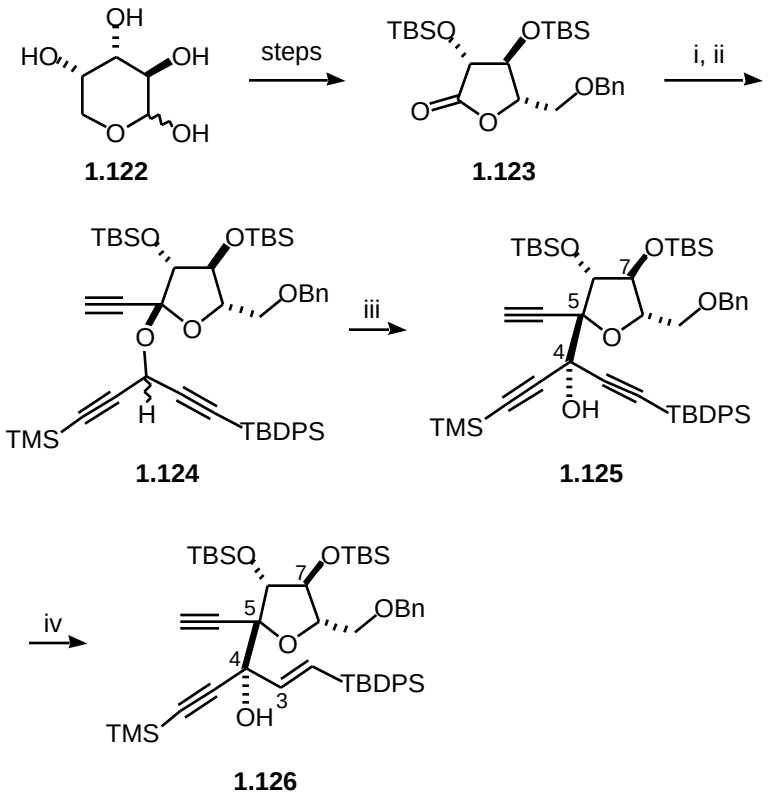
1.2.7 Tomooka's Synthesis of Zaragozic Acid A

In 2000 Tomooka published a synthesis of zaragozic acid A (**1.54**) that utilized the acetal 1,2-Wittig rearrangement as the key step. Tomooka's approach was not only novel, but also competitive in terms of overall length with the other syntheses of the zaragozic acids at 32 steps from L-arabinose. In Tomooka's

synthesis of zaragozic acid A (**1.54**) the assembly of the five membered ring in the core was completed before the six membered ring was assembled. Additionally, Tomooka, like many others, did not differentially protect C-6 and C-7, so the endgame of the synthesis utilized Carreira's selective protection strategy to install the C-6 side chain.

The synthesis began with L-arabinose (**1.122**) that was converted to **1.124** in seven steps (Scheme 1.33). Deprotonation of dialkyne **1.124** and 1,2-Wittig rearrangement provided **1.125** with high diastereoselectivity (84% d.r.). Fortunately, the two diastereomers were separable by chromatography, and the major diastereomer was then subjected to a reduction to *trans* olefin **1.126**.

Scheme 1.33



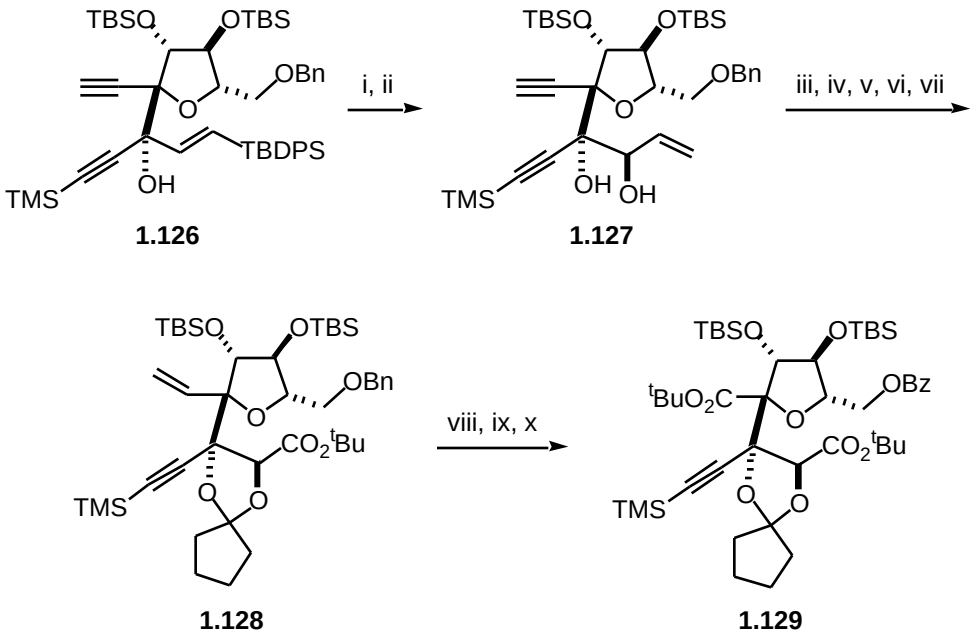
1.122 **1.123** **1.124** **1.125** **1.126**

i) LiC≡CH, Et_2O, 75%; ii) TBDPSC≡CCH(OH)C≡CTMS, montmorillonite K10, 4Å mol. sieves, CH_2Cl_2, 80%; iii) BuLi, THF, 54%; iv) Red-Al, Et_2O, 83%

Ozonolysis of the olefin provided the aldehyde that was then treated with vinylmagnesium bromide to form allyl alcohol **1.127** with high diastereoselectivity (>95%) that was due to chelation control through the C-4 hydroxyl. The resulting diol was protected as an acetal and the vinyl group at C-3 was converted to a *t*-butyl ester by a sequential oxidation/esterification (Scheme

1.34). Subsequent semihydrogenation of the C-5 alkyne then provided **1.128**, which was transformed into di-*t*-butyl ester **1.129**.

Scheme 1.34

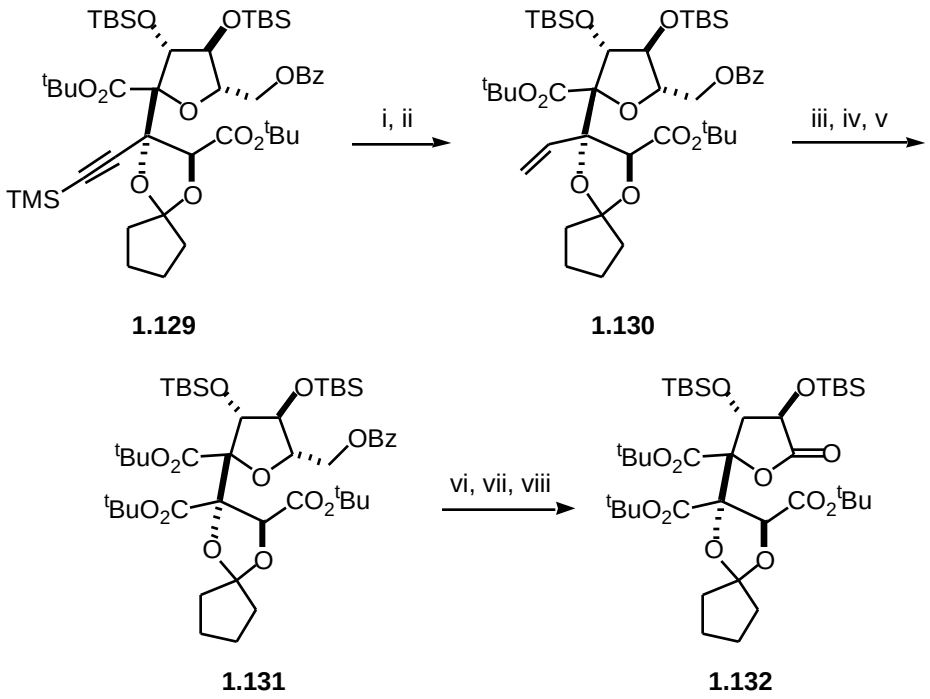


i) O_3, MeOH; ii) CH_2=CHMgBr, $PhCH_3$, 49%; iii) cyclopentanone dimethyl acetal, *p*TsOH, PhH, 87%; iv) O_3, MeOH; v) $NaClO_2$, NaH_2PO_4, Me_2C=CHMe, *t*-BuOH/H_2O; vi) *N, N′*-diisopropyl-*O*-*t*-butylisourea, CH_2Cl_2, 73-84%; vii) H_2, Pd/C, MeOH, 88%; viii) O_3, MeOH; ix) $NaClO_2$, NaH_2PO_4, Me_2C=CHMe, *t*-BuOH/H_2O; x) *N, N′*-diisopropyl-*O*-*t*-butylisourea, CH_2Cl_2, 73-84%

The TMS acetylene **1.129** was then deprotected and the alkyne subjected to semihydrogenation to give **1.130** and the same oxidation sequence that had been used to install the other two esters was performed again to provide triester **1.131** (Scheme 1.35). The fact that the three esters at C-3, C-4, and C-5 were

oxidized separately made the sequence rather cumbersome, although there was no comment made on whether simultaneous oxidations were attempted in this synthesis. Benzoyl deprotection was then followed by a two-step oxidation procedure to yield lactone **1.132** that was set for incorporation of the C-1 side chain.

Scheme 1.35

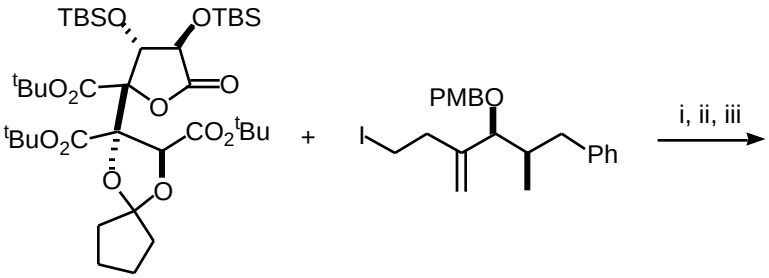


1.129 **1.130** **1.131** **1.132**

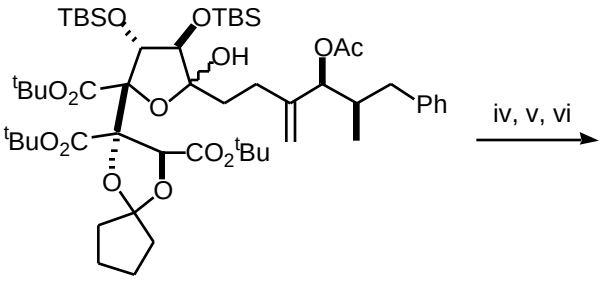
i) TBAF, THF, 94%; ii) H_2, Lindlar cat., MeOH, 93%; iii) O_3, MeOH;
iv) $NaClO_2$, $NaHPO_4$, *t*-BuOH/H_2O;
v) *N, N'*-diisopropyl-*O*-*t*-butylisourea, CH_2Cl_2; 73-84%;
vi) aq. KOH, MeOH, 78%; vii) cat. TPAP, NMO, 4Å mol. sieves, CH_2Cl_2, 98%;
viii) O_2, $Cu(OAc)_2$, 2, 2'-bipyridyl, DABCO, DMF, 72%.

The C-1 side chain was installed *via* addition of the organolithium reagent derived from **1.135**. Oxidative cleavage of the PMB group and acetylation gave **1.134** (Scheme 1.36). The [3.2.1] zaragozic acid core was assembled by treatment of **1.134** with acid, esterification, and silyl deprotection to form diol **1.135**. The C-6 side chain **1.52** was then attached using Carreira's strategy to provide zaragozic acid A **1.54**) in 32 steps.

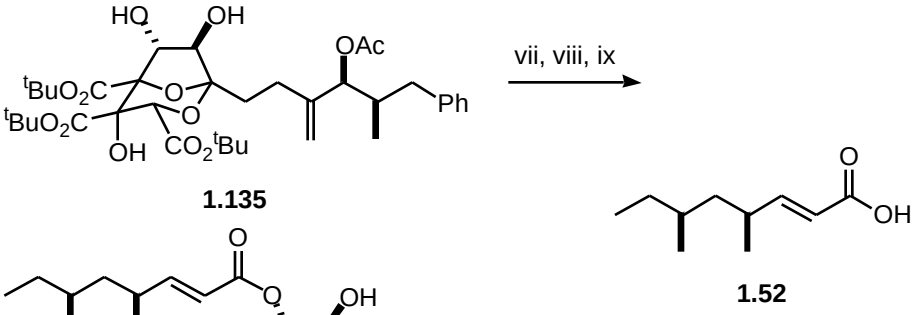
Scheme 1.36



1.132 **1.133**



1.134



1.135 **1.52**

1.54

i) *t*-BuLi, hexane/Et_2O, 96%; ii) DDQ, CH_2Cl_2, 96%; iii) Ac_2O, DMAP, CH_2Cl_2, 95%;
iv) TFA, CH_2Cl_2/H_2O; v) *N, N'*-diisopropy-*O*-*t*-butylisourea, CH_2Cl_2;
vi) TBAF, THF, 51%; vii) Boc_2O, 4-pyrrolidinopyridine, CH_2Cl_2, 81%;
viii) **1.52**, DCC, DMAP, CH_2Cl_2, 82%; ix) TFA, CH_2Cl_2, 73%

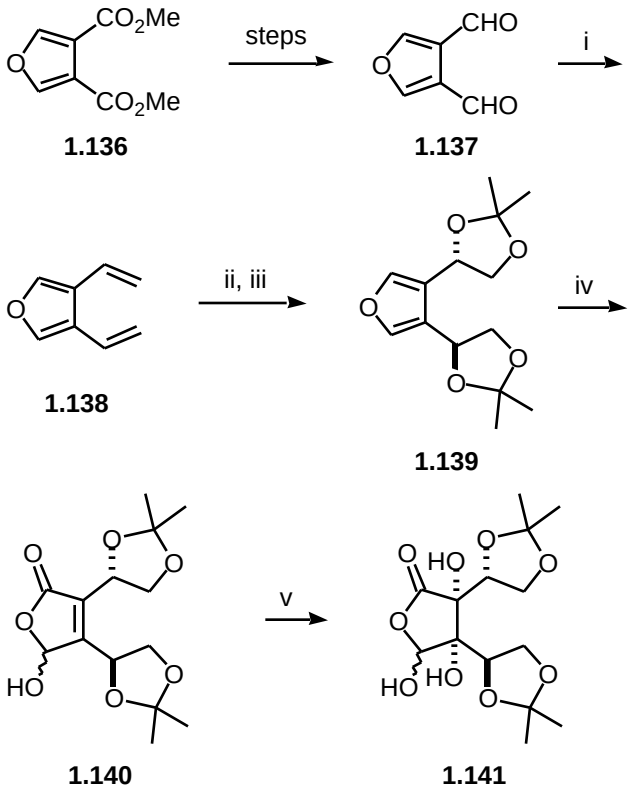
1.2.8 Halcomb's Formal Synthesis of Zaragozic Acid A

The next synthesis of zaragozic acid A (**1.54**) was actually presented as a formal synthesis that intersects an early intermediate in the Nicolaou synthesis. This approach is symmetry-based, beginning with furan diester **1.136** where the critical desymmetrization step is a singlet oxygen furan oxidation of **1.139** to produce a 5:1 mixture of epimers at the hemiacetal **1.140**. Halcomb, like many others, utilized the Sharpless asymmetric dihydroxylation as a tool for the introduction of the appropriate stereochemistry. While the novel symmetry-based approach that Halcomb had was a clever idea, the fact that Halcomb's synthesis is 19 steps and it intersects Nicolaou's total synthesis with 21 steps left to reach zaragozic acid A (**1.54**) makes it less appealing.

The approach begins with furan dimethyl ester **1.136** that was converted to dialdehyde **1.137** (Scheme 1.37). Dialdehyde **1.137** was subjected to a Peterson olefination to provide diene **1.138**. Sharpless asymmetric dihydroxylation of **1.138** gave the corresponding tetraol (>98% ee). Treatment of furan **1.139** with singlet oxygen provided olefin **1.140** as a mixture (5:1) of epimers at the acetal. Dihydroxylation of **1.140** with stoichiometric osmium tetraoxide installed the two

tertiary alcohol stereocenters to provide **1.141**. It was stated that **1.141** appeared to be a mixture (5:1) of inseparable hemiacetal in solution; however, a single isomer appeared to crystallize from solution. Although the dihydroxylation of **1.140** did not utilize a Sharpless asymmetric dihydroxylation, this reaction showed remarkable facial selectivity. The origin of the facial selectivity was not clear, however it was speculated that the chirality of the acetonide-protected secondary alcohols were responsible for controlling the facial selectivity in the dihydroxylation of **1.140** to provide **1.141**.

Scheme 1.37

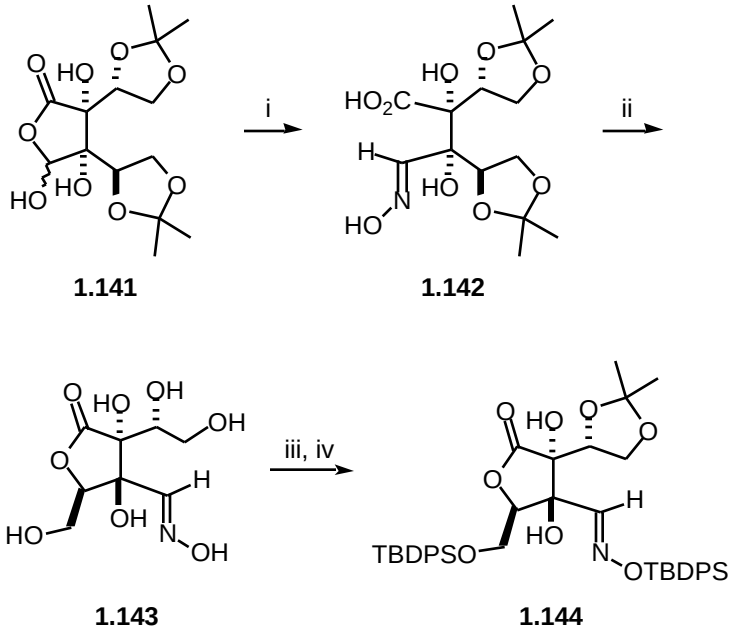


i) $TMSCH_2MgCl$, Et_2O; ii) AD-mix α, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O, 59%; iii) $CH_3C(OMe)_2CH_3$, *p*-TsOH, DMF, 69%; iv) Hünigs base, rose bengal, O_2, hν, CH_2Cl_2, 74%; v) OsO_4, pyr., *t*-BuOH, 66%.

Opening of lactone **1.141** was accomplished to give the oxime **1.142** (Scheme 1.38). This oxime was used as a protecting group for the aldehyde because of the fact that it could be installed under mildly basic conditions and was expected to be resistant to acetal formation. The carboxylic acid functionality of **1.142** was used in the discrimination of the two secondary alcohols in a selective

lactonization to produce **1.143** upon treatment with acid. Acetonide protection of the diol and silyl protection of the primary alcohol and oxime gave **1.144**.

Scheme 1.38

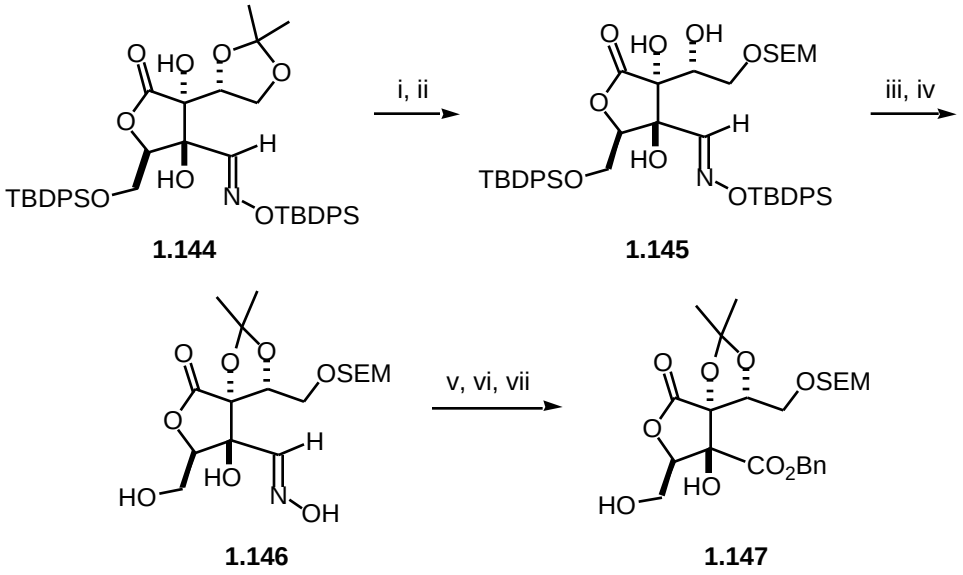


i) $HONH_2$•HCl, pyr., THF/MeOH, 94%; ii) PPTS, MeOH;
iii) PPTS, $CH_3(OCH_3)CH_3$, DMF, 68%;
iv) TBDPSCl, imid., DMF, 57%

Cleavage of the acetonide of **1.144** and subsequent protecting group manipulations resulted in the isolation of oxime **1.146** in four steps (Scheme 1.39). The final steps in the formal synthesis included ozonolysis to remove the oxime, oxidation of the aldehyde and esterification to the benzyl ester to give

1.147. Compound **1.147** was an intermediate in the Nicolaou synthesis, and therefore completed a formal synthesis of zaragozic acid A (**1.54**).

Scheme 1.39



i) PPTS, MeOH, 81%; ii) SEMCl, 2,6-di-*t*-butylpyridine, CH_2Cl_2/PhH, 56%; iii) PPTS, CH_2=C(OCH_3)CH_3, CH_2Cl_2, 52%; iv) TBAF, AcOH, THF, 80%; v) O_3, $NaHCO_3$, CH_2Cl_2/MeOH, 69%; vi) $NaClO_2$, NaH_2PO_4, Me_2C=CHMe, *t*-BuOH/H_2O; vii) DCBI, THF/$PhCH_3$, 70%.

Although the total synthesis of any member of the zaragozic acid family is an achievement, comparisons between the various synthetic approaches show a select few to be outstanding among the group. In particular, the most impressive total synthesis of them all was that of Evans, which constituted an outstanding use of stereocontrol. Additionally, the overall yield of the synthesis was nearly 10%

in only 22 steps. Carreira's total synthesis was also worth mention not only because it was the first total synthesis of any of the zaragozic acids, but because of the problem solving abilities that were apparent in the installation of the C-4 center. Furthermore, installation of the C-6 side chain proved to be challenging with respect to regioselectivity. Carreira also provided a strategy to regioselectively install the C-6 side chain that was used by several other zaragozic acid syntheses. While Nicolaou's total synthesis was rather cumbersome, it did provide a valuable springboard for the formal total synthesis by Halcomb as well as the total synthesis of zaragozic acid C by Armstrong. Armstrong's total synthesis was quite similar to Nicolaou's approach, however, Armstrong was able to produce a much shorter synthesis using the same strategy of using an enantioselective dihydroxylation followed by a diastereoselective dihydroxylation (23 steps compared to 34). Halcomb's formal synthesis of zaragozic acid A was a novel approach to the zaragozic acid core, however, in practice it was disappointing that this synthesis intersected Nicolaou's synthesis at such an early stage. Also, in all there were 40 steps in this synthesis which made Halcomb's synthesis one of the longest that has been published, second only to Heathcock's

synthesis. Tomooka's synthesis used a novel approach that was quite different from any of the other total syntheses, and furthermore was accomplished with high stereoselectivity. The use of the acetal Wittig rearrangement with such high stereocontrol was impressive. Heathcock's synthesis was the longest total synthesis at 42 steps overall and grew to be rather cumbersome, although his approach to the regioselective installation of the C-6 side chain was novel, and certainly managed to make the best of a challenging situation.

1.3 SYNTHETIC APPROACHES TO THE ZARAGOZIC ACID CORE

In addition to the total and formal syntheses of the zaragozic acids, there have also been a number of synthetic approaches to the unique [3.2.1] bicyclic core. An exhaustive survey of all of these will not be attempted here due to the fact that there are so many approaches that have been published; however, a few of the most novel examples to the core have been selected for discussion. Some of the total syntheses of the zaragozic acids did not have any particular "key" step, but rather approached the synthesis as a stepwise application of known chemistry.

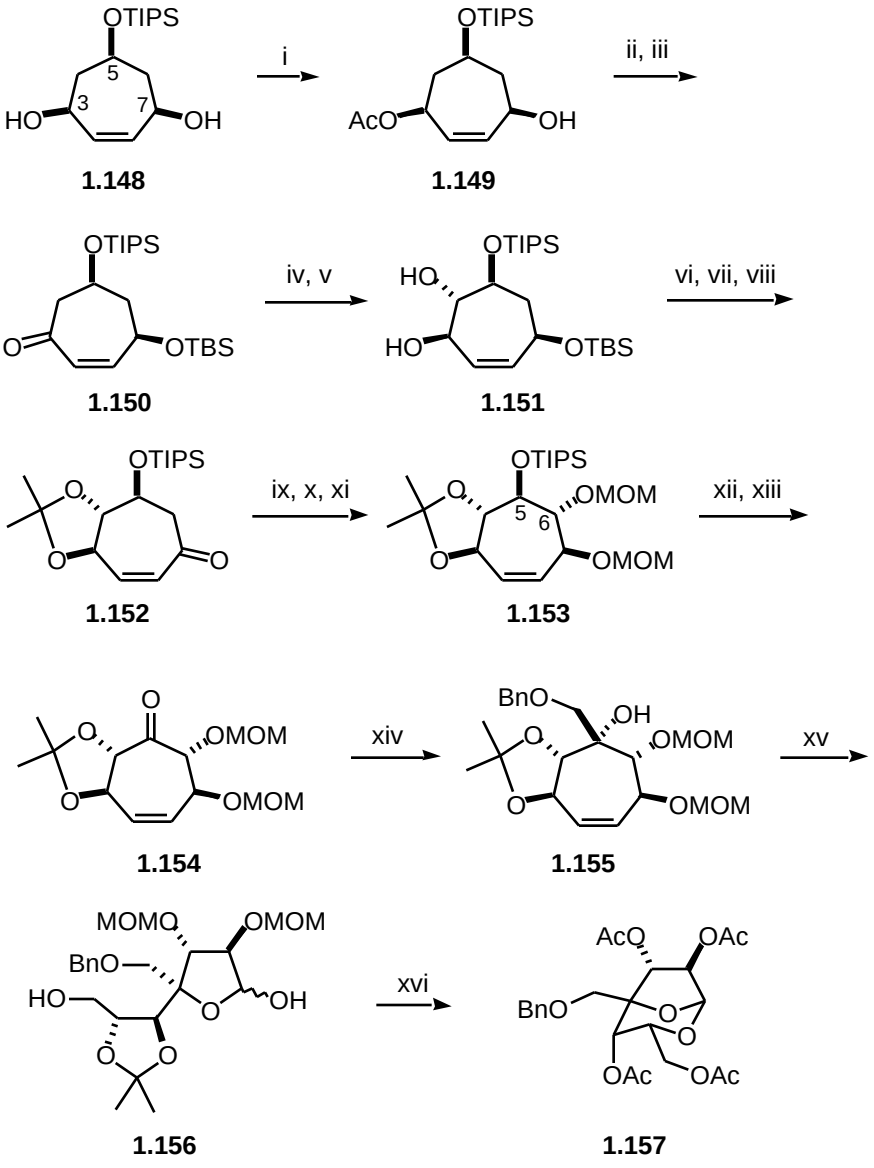
In this section, the strategies that appear were chosen based on the creativity of a key step in the assembly of the zaragozic acid core.

1.3.1 Johnson's Approach

In an effort to prepare a semi-functionalized core that did not include the C-1 side chain, Johnson made use of an enzyme in the key step to introduce asymmetry to the system.[30] Cycloheptene diol **1.148** (prepared from cycloheptatriene) was converted to acetate **1.149** with complete selectivity using *Candida antartica* lipase B (Scheme 1.40). Acetate **1.149** was then converted to ketone **1.150** in two steps. Rubottom oxidation of the ketone gave the diol that was reduced under Luche conditions to yield **1.151**. Ketone **1.154** was then obtained from **1.151** in eight steps. It was anticipated that nucleophilic attack of **1.154** would result in the correct stereochemistry, opposite to the two α-substituents of the ketone. Thus, the alkylation of **1.154** proceeded as expected to give **1.155** with the correct configuration at C-5. Ozonolysis of the olefin provided **1.156**, which was then cyclized to the zaragozic acid core **1.157** bearing functionality at C-3, C-4, and C-5. It is anticipated that **1.157** could be further

functionalized at C-4 using a strategy similar to that of Carreira or Heathcock; however, these operations were not conducted. Additionally, further oxidations at C-3 and C-5 would be necessary to complete the zaragozic acid [3.2.1] core. Unfortunately, this approach made no mention of a strategy for the introduction of the C-1 side chain to the system, however, if lactol **1.156** were oxidized to the lactone, a suitable handle would be present for the installation of the required alkyl side chain.

Scheme 1.40

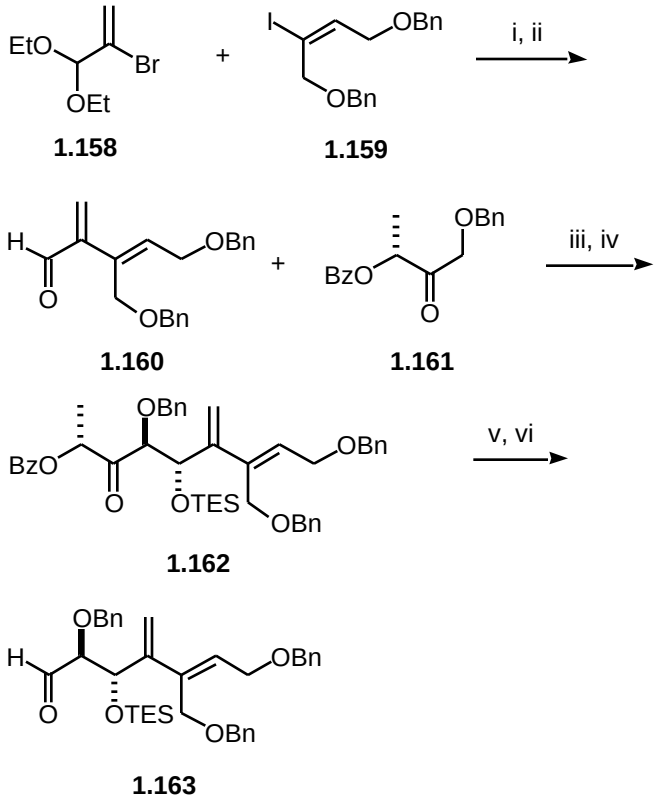


i) *Candida antartica* lipase B, isopropenyl acetate; ii) TBSCl, imid., DMF, 100%; iii) KCN, MeOH, then PDC, 98%; iv) TMSOTf, Et_3N, CH_2Cl_2; v) mCPBA, pentane, then $NaBH_4$, $CeCl_3$, MeOH, 59%; vi) $CH_3C(OCH_3)_2CH_3$, CSA, 100%; vii) H_2SiF_6, Et_3N, CH_3CN; viii) PDC, CH_2Cl_2, 78%; ix) TMSOTf, Et_3N, CH_2Cl_2; x) mCPBA, pentane, then $NaBH_4$, $CeCl_3$, MeOH, 54%; xi) MOMCl, Hünig's base, CH_2Cl_2, 100%; xii) TBAF, THF; xiii) PCC, CH_2Cl_2; xiv) Bu_3SnCH_2OBn, BuLi, THF, 88%; xv) O_3, $MeOH/CH_2Cl_2$, then $NaBH_4$; xvi) TFA, then Ac_2O, DMAP, 31%.

1.3.2 Paterson's Approach

Another approach to the zaragozic acid core was reported by Paterson, who utilized an epoxidation cyclization sequence to form the final desired ketal.[31,32] Unlike most of the other approaches to the zaragozic acids, Paterson chose to install the C-1 side chain very early in the synthesis, which limits the flexibility of the approach. Moreover, the advanced intermediate **1.169** had the incorrect stereochemistry at C-7, and there was no mention of correcting the C-7 stereochemistry. Additionally, the core was not fully oxidized at C-3, C-4, and C-5; however, these operations should be relatively straightforward. Nevertheless, the synthesis begins with the assembly of aldehyde **1.160** through a Negishi-type coupling of vinyl iodide **1.159** and vinyl bromide **1.158** (Scheme 1.41). Coupling of the aldehyde with ketone **1.161** was accomplished *via* a boron mediated aldol addition to give alcohol **1.162** with very high diastereoselectivity (>97%) after protection of the alcohol. Cleavage of the diol gave aldehyde **1.163**.

Scheme 1.41

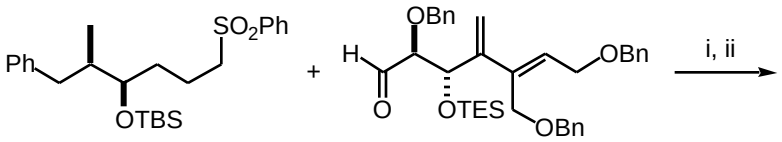


i) BuLi, THF, $ZnBr_2$, $Pd(MeCN)_2Cl_2$, DMF, 99%;
ii) 1 M HCl/THF; iii) (c-$C_6H_{11})_2BCl$, Me_2NEt, Et_2O, then H_2O_2, MeOH, pH 7 buffer , 68%; iv) TESOTf, 2,6-lutidine, CH_2Cl_2, 76%; v) $LiBH_4$, THF, 73%;
vi) $NaIO_4$, MeOH/pH 6.5 buffer, 82%

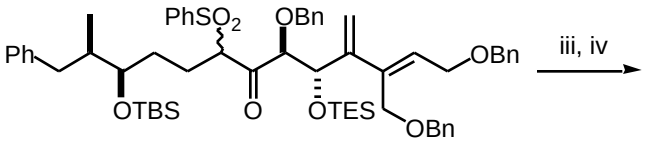
Although two routes to the bicyclic [3.2.1] ketal from **1.163** were examined, the route shown below proved far superior with respect to diastereoselectivity. Accordingly, aldehyde **1.163** and sulfone **1.164** were coupled, and the resulting alcohol was subjected to a Swern oxidation to provide

ketone **1.165** (Scheme 1.42). Removal of the sulfone was followed by silyl deprotection to give **1.166**. At this point, a Sharpless dihydroxylation was performed exclusively at the C-3 – C-4 olefin to yield **1.167** with high diastereoselectivity (>95%). Presumably the regioselectivity for the C-3 – C-4 olefin is based on the fact that the dihydroxylation of trisubstituted olefins was known to at a much higher rate than *cis*-disubstituted olefins.[33] Initially, attempts at dihydroxylation of **1.166** with enriched AD-mix-β led only to decomposition, but eventually the dihydroxylation was accomplished using substantially more ligand (25 mol%) to provide **1.167** in modest yield. Epoxidation of the remaining olefin was then accomplished producing **1.168** as a single isomer. Treatment of **1.168** with acid then produced the desired [3.2.1] bicyclic ketal in an impressive 95% yield. The C-5 alcohol was protected as the silyl ether to provide **1.169**, which was an advanced zaragozic acid intermediate. It should be noted, however, that the core structure **1.169** has the incorrect stereochemistry at C-7.

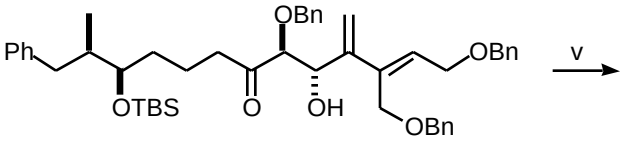
Scheme 1.42



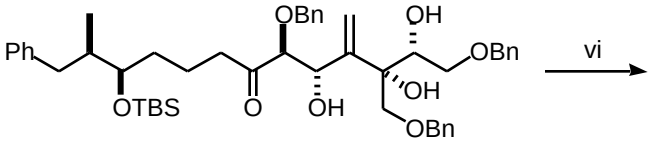
1.164 **1.163**



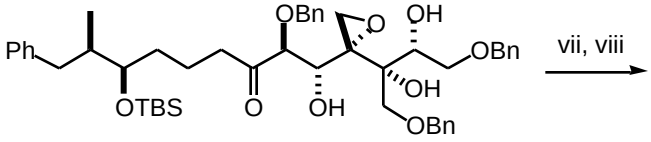
1.165



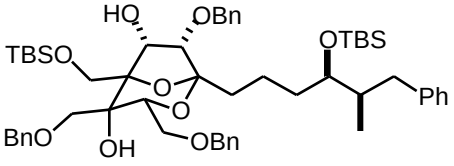
1.166



1.167



1.168

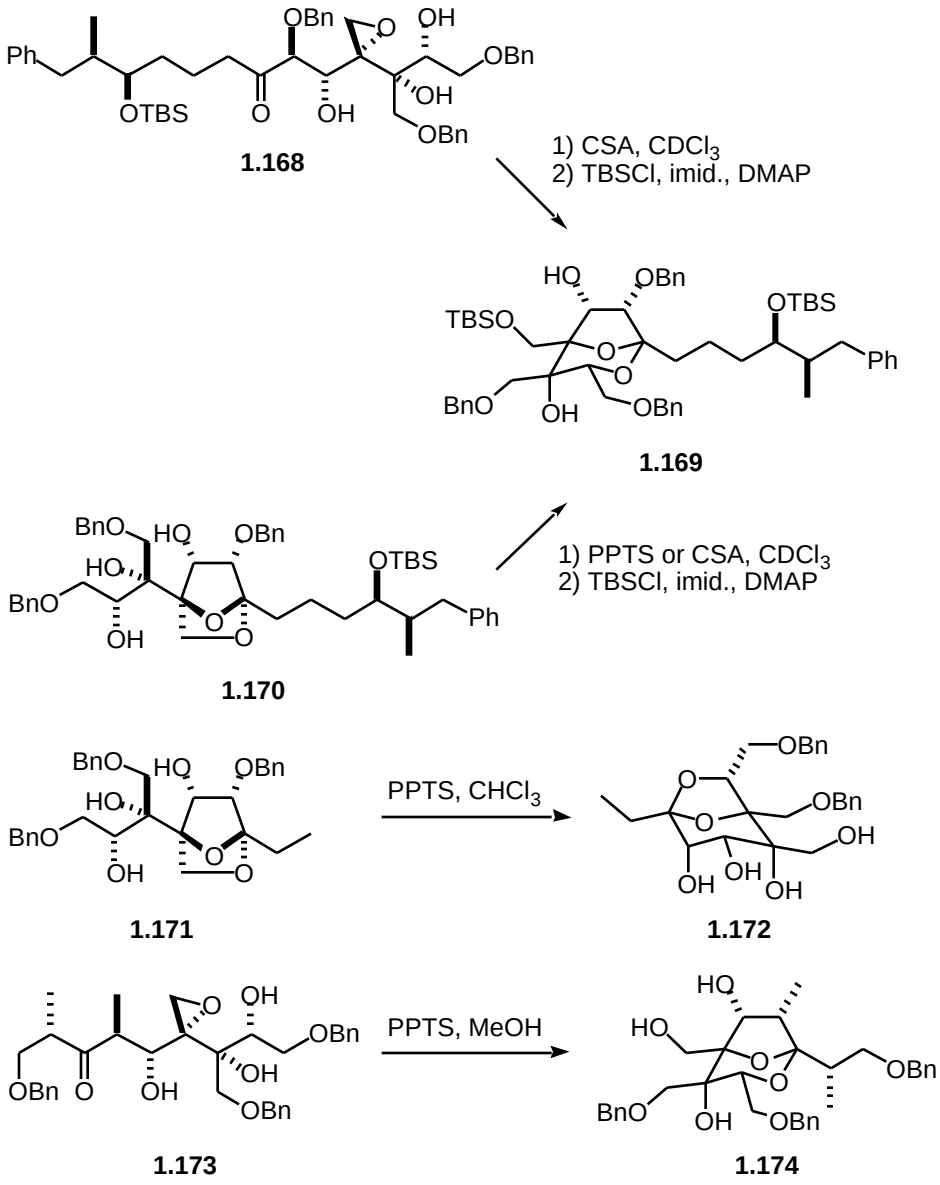


1.169

i) BuLi, THF/Et_2O; ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 95%;
iii) Na(Hg), Na_2HPO_4, MeOH/THF, iv) HF•pyr., pyr./THF, 64%;
v) AD-mix β, $[(DHQD)_2PHAL, K_2OsO_4•2H_2O]$, $MeSO_2NH_2$,
t-BuOH/H_2O, 54%; vi) $VO(acac)_2$, *t*-BuOOH, 78%,
vii) CSA, $CDCl_3$, 95%; viii) TBSCl, DMAP, CH_2Cl_2, 85%

One thing worth mention in Paterson's study was the pronounced effect of the nature of the C-1 side chain on the outcome of the ketalization. Specifically, if ketal **1.170** or epoxide **1.168** with the actual zaragozic acid C-1 side chain were subjected to treatment with CSA in $CDCl_3$, the desired [3.2.1] bicyclic core **1.169** was isolated from the reaction (Scheme 1.43). Alternatively, if ketal **1.171**, with a model C-1 side chain was treated with PPTS, the isomeric ketal **1.172** was produced. Additionally, treatment of epoxide **1.173** that includes a different model side chain with PPTS gave desired ketal **1.174**. The specific interactions that contribute to the differences in the products that were observed were not speculated upon; however, it is clear that the nature of the specific C-1 side chain is important to the outcome of the cyclization. This was also observed in Nicolaou's synthesis where a change in the C-4' protecting group made a significant difference in the outcome of the ketalization.

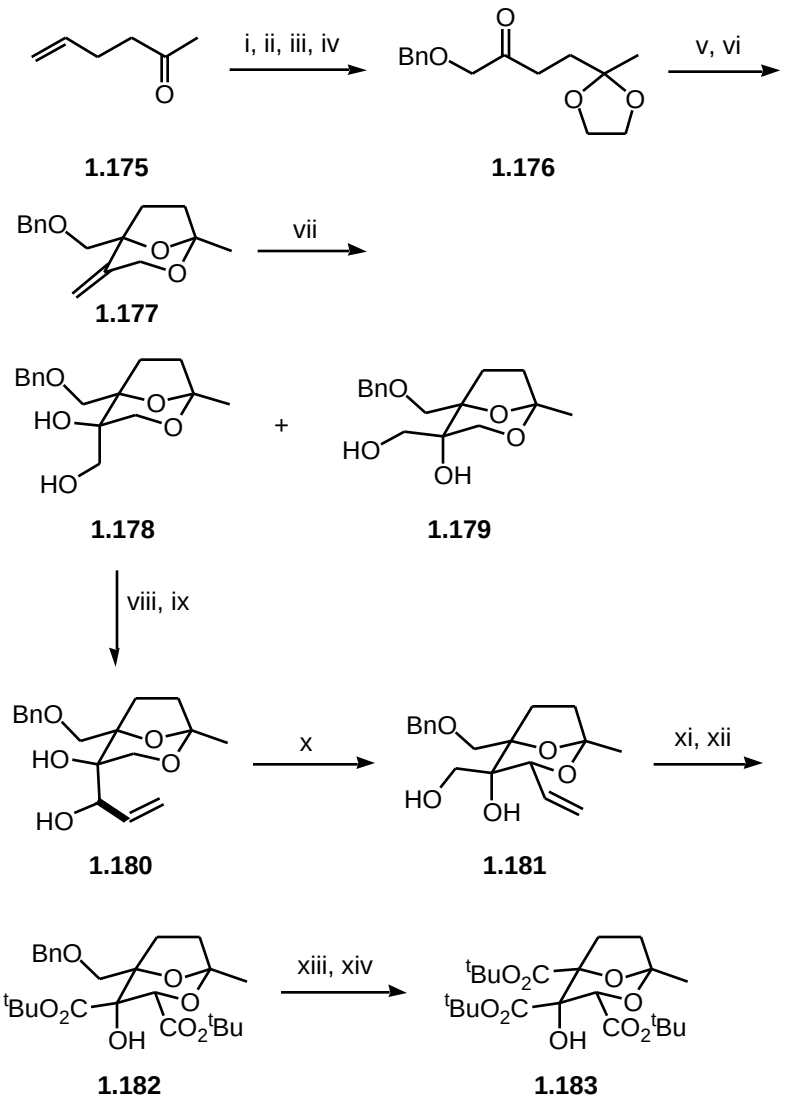
Scheme 1.43


OBn
O
OH
Ph
OBn
OTBS
O
OH
OH
OBn
1.168
1) CSA, CDCl3
2) TBSCl, imid., DMAP
HO
OBn
OTBS
TBSO
O
Ph
O
BnO
OH
OBn
1.169
BnO
HO
OBn
HO
OTBS
BnO
O
Ph
OH
O
1.170
1) PPTS or CSA, CDCl3
2) TBSCl, imid., DMAP
BnO
HO
OBn
HO
BnO
O
OH
O
1.171
PPTS, CHCl3
OBn
O
OBn
O
OH
OH
OH
OH
1.172
O
OH
OBn
OBn
O
OH
OH
OBn
1.173
PPTS, MeOH
HO
HO
O
OBn
O
BnO
OH
OBn
1.174

1.3.3 Myles' Approach

A third approach to the zaragozic acid core, was accompanied by an extensive study of the ketalization step that involved both computational as well as experimental data.[34,35] The ketalization was studied experimentally using substrates without functionalization at C-6 or C-7. To this end, ketone **1.175** homologated to provide acetal **1.176** (Scheme 1.44). Alkylation of ketone **1.176** and treatment with acid gave **1.177**. Dihydroxylation of the C-4 olefin gave a separable 1:2 mixture of isomers **1.178** and **1.179**, although through recycling, the mixture could be manipulated to provide predominantly either **1.178** or **1.179**. Swern oxidation of the alcohol and treatment with vinylmagnesium bromide gave **1.180** as a single diastereomer through chelation control between the ketone and the adjacent C-4 alcohol. Treatment of **1.180** with acid provided the desired zaragozic acid ketal **1.181**. Conversion of the C-5, C-4, and C-3 substituents to the necessary oxidation state was then accomplished stepwise to give the zaragozic acid [3.2.1] core **1.183**.

Scheme 1.44

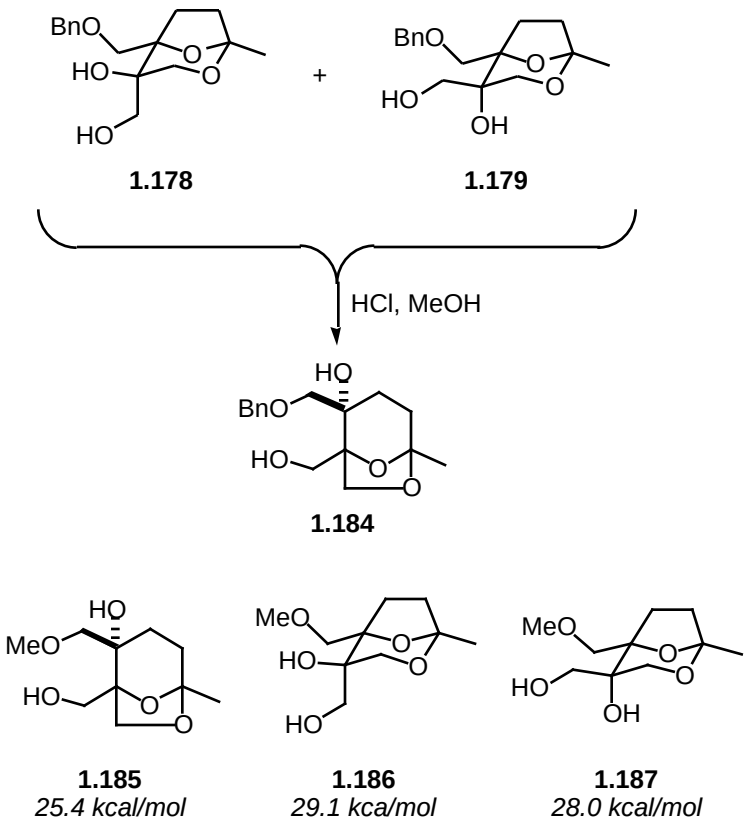


1.175 **1.176** **1.177** **1.178** **1.179** **1.180** **1.181** **1.182** **1.183**

i) $HO(CH_2)_2OH$, TsOH, PhH; ii) PhCN, H_2O_2; iii) BnOK, THF, 35%;
iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; v) $(CH_2{=}CCH_2O)^{2-}MgBrLi$, 45%;
vi) TFA, CH_2Cl_2, 93%; vii) OsO_4, K_3FeCN_6, *t*-BuOH/H_2O, 100%;
viii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; ix) $CH_2{=}CHMgBr$; x) TFA;
xi) IBX; $NaClO_2$; *t*-butylisourea, 70%; xii) O_3, PPh_3; $NaClO_2$;
t-butylisourea, 83%; xiii) H_2, Pd/C; xiv) IBX; $NaClO_2$; *t*-butylisourea, 50%.

An interesting side note to Myles' study of the ketal system was that when ketal isomers **1.178** or **1.179** were treated with more forcing conditions (2% HCl in methanol) for several days, equilibration takes place to form a third isomer **1.184** (Scheme 1.45). This isomer was formed when the tertiary alcohol at C-4 rather than the tertiary alcohol at C-5 was incorporated into the ketal moiety. The composition of the equilibrium mixture under HCl catalysis suggests that **1.184** is the lowest energy isomer of the three; however there appears to be a kinetic barrier to the formation of this isomer. These experimental findings correlate nicely with the computational study by Myles on a similar system **1.185** that showed ketal isomer **1.85** to be lowest in energy of all possible ketal isomers including both **1.186** and **1.187**.

Scheme 1.45



1.3.4 Nagaoka's Approach

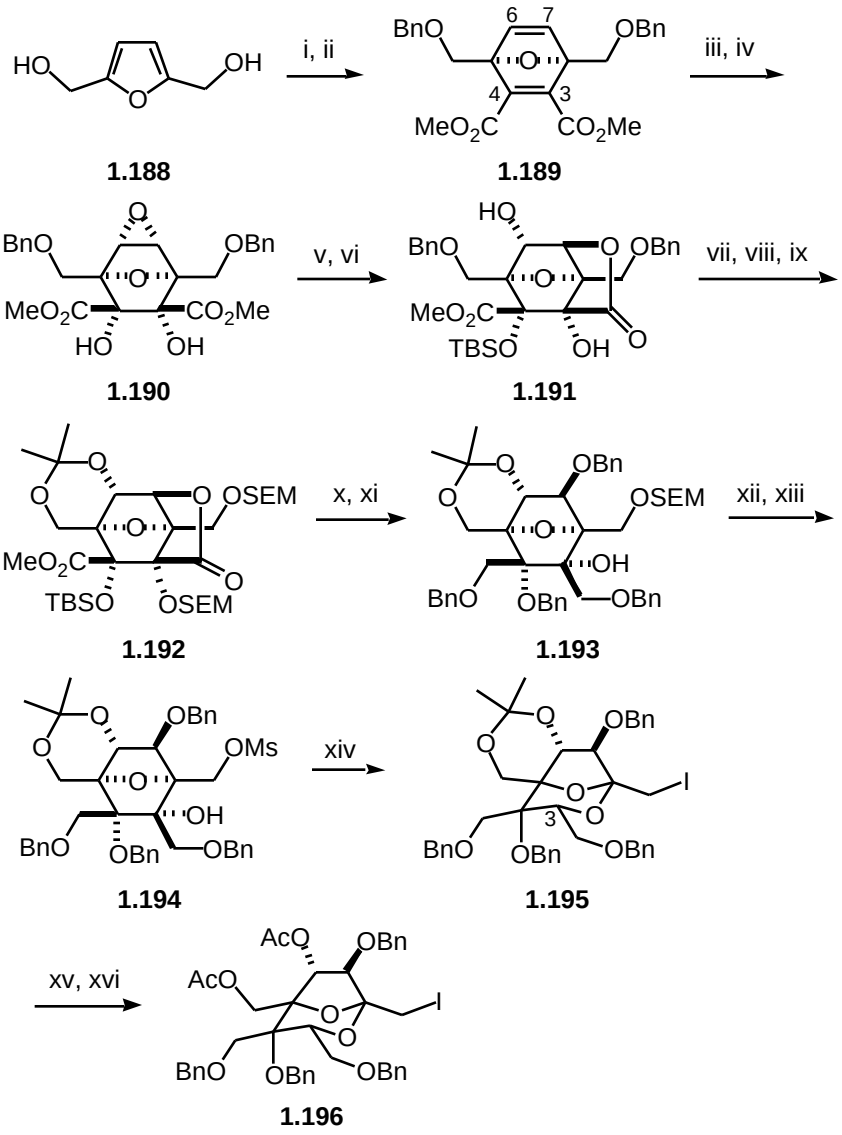
Another approach to the desired core system was developed by Nagaoka who utilized a Grob fragmentation in the ketalization to form **1.194**.[36]. An attractive feature of the synthesis included the differential protection of C-6 and C-7 at an early stage, therefore allowing for acylation at C-6 without issues of regioselectivity in the incorporation of the C-6 side chain. Although the zaragozic

acid core did not include a C-1 side chain or specific mention of a plan to incorporate a C-1 side chain, **1.195** does have a handle that could potentially be utilized to build the side chain. Additionally, if the C-1 side chain were incorporated at a late stage, it would allow for the synthesis of a wide variety of zaragozic acids from a common, late stage intermediate.

Adduct **1.189** was obtained after Diels-Alder cyclization of **1.188** (Scheme 1.46). Selective epoxidation of the C-6 – C-7 olefin in the presence of a radical inhibitor and dihydroxylation of the remaining olefin provided **1.190** as a single isomer. The regio- and stereoselectivity in the epoxidation and dihydroxylation sequence was explained on the basis of electronic effects and the convex attack of oxidants on the stereochemically rigid 7-oxabicyclo[2.2.1]heptadiene ring system **1.189**. Acid catalyzed lactonization of **1.190** gave the lactone triol that was selectively silylated at C-4 to provide **1.191**. Protecting group manipulations were then performed to give **1.192** in three steps. The lactone and methyl esters were then reduced and the newly formed hydroxyl groups were protected to provide **1.193**, which was elaborated in two additional steps to give **1.194**. Grob fragmentation of **1.194** was then accomplished to yield zaragozic acid core **1.195**.

Cleavage of the acetonide and acetate protection of the hydroxyls gave **1.196** as the final product.

Scheme 1.46



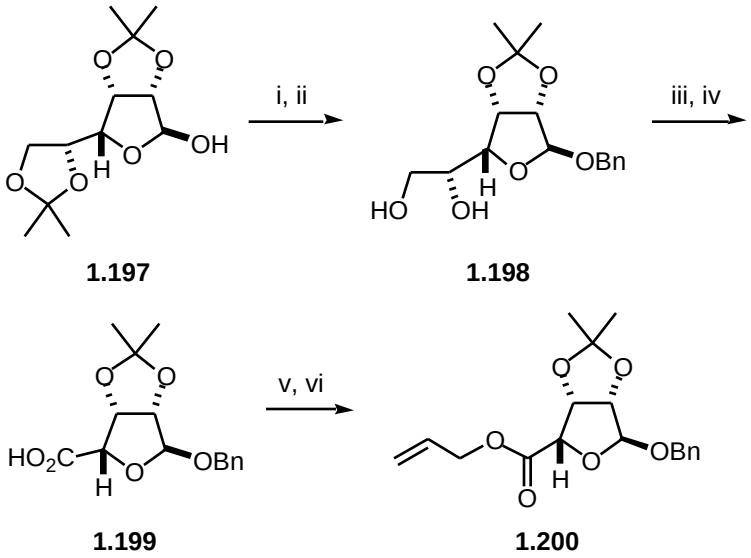
i) BnBr, NaH, Bu_4NI, THF, 92%; ii) $MeO_2C{\equiv}CO_2Me$, PhMe, 83%;
iii) mCPBA, 4, 4'-thiobis(2-*t*-butyl-5-methylphenol), DCE, 76%;
iv) OsO_4, NMO, $MeCN/H_2O$, 98%; v) *p*-TsOH, $MeOH/H_2O$, 95%;
vi) TBSCl, Et_3N, CH_2Cl_2, 94%; vii) H_2, Pd/C, MeOH;
viii) acetone, $Me_2C(OMe)_2$, CSA, 96%; ix) SEMCl, *i*-Pr_2NEt,
CH_2Cl_2, 84%; x) $LiAlH_4$, THF, 63%; xi) BnBr, NaH, Bu_4NI, THF, 90%;
xii) TBAF, DMPU, 94%; xiii) MsCl, Et_3N, I_2, 5% $NaHCO_3$, 43%;
xiv) KHMDS, dioxane, then$NaBH_4$, MeOH, then I_2, 5% $NaHCO_3$ 43%;
xv) $AcOH/H_2O$; xvii) Ac_2O, pyr., 91%.

1.3.5 Rizzacasa's Approach

Rizzacasa has published a synthesis of the zaragozic acid core using the Ireland ester enolate Claisen reaction to elaborate the C-5 center.[37-40] The synthesis began with D-mannose, which unfortunately had the wrong stereochemistry at C-7. This issue was addressed and the stereochemistry at C-7 corrected through a six-step sequence, however it made this synthetic approach somewhat cumbersome. Additionally, through this sequence, Rizzacasa had the opportunity to differentially protect C-6 and C-7, but chose not to do so. It is true that several syntheses and synthetic approaches were forced to deal with the problems associated with not differentially protecting the C-6 and C-7 hydroxyl groups. However, it was not clear why the two hydroxyl groups were protected identically. The fact that there was no functionality at C-4 reduced the appeal of the approach.

The allyl ester **1.200** necessary for the Ireland ester enolate Claisen was synthesized from diacetonide mannose **1.197** (Scheme 1.47). Acid **1.199** was obtained from **1.197** in four steps. Conversion to the acid chloride and treatment with allyl alcohol formed the desired Claisen precursor **1.200**.

Scheme 1.47



1.197 **1.198**

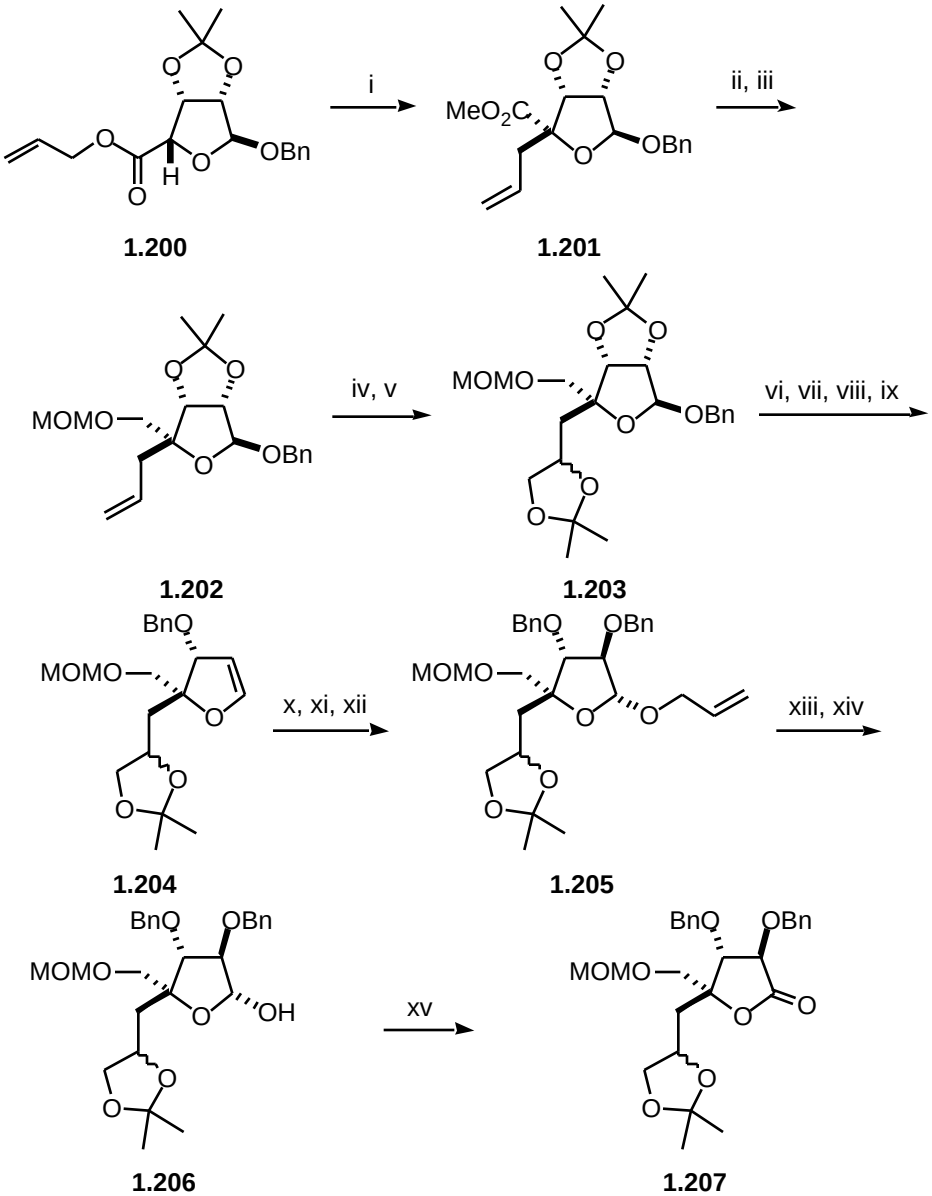
1.199 **1.200**

i) NaH, BnBr, DMF, 85%; ii) conc. HCl, aq. MeOH; iii) $NaIO_4$;
iv) $AgNO_3$, KOH, 82%; v) $(COCl)_2$, DMF, PhH;
vi) CH_2=$CHCH_2OH$, DMAP, CH_2Cl_2

Allyl ester **1.200** underwent an Ireland-Claisen rearrangement to form methyl ester **1.201** as the major product (5.7:1 d.r.) though there was no comment on the selectivity (Scheme 1.48). Fortunately, the mixture can be recrystallized to provide pure **1.201**. Reduction of the ester and MOM protection of the resulting alcohol provided **1.202**, which was dihydroxylated to give a mixture (1:1) of diastereomers that could later be epimerized to favor the desired configuration. Attempts at stereoselective dihydroxylation using the Sharpless dihydroxylation gave only low selectivity. Inversion at C-7 was than accomplished in six steps

beginning with **1.203**. Debenzylation and chlorination of the resulting lactol followed by reductive elimination to yield glycal **1.204**. Subsequent stereoselective epoxidation and opening of the epoxide with allyl alcohol provided **1.205** after benzyl protection of the C-7 hydroxyl. It seems as if it may have been wise to differentiate the C-6 and C-7 hydroxyl groups when the opportunity presented itself, however, they were protected identically after opening of the epoxide. Removal of the allyl group from **1.205** gave lactol **1.206** that was oxidized to lactone **1.207**.

Scheme 1.48

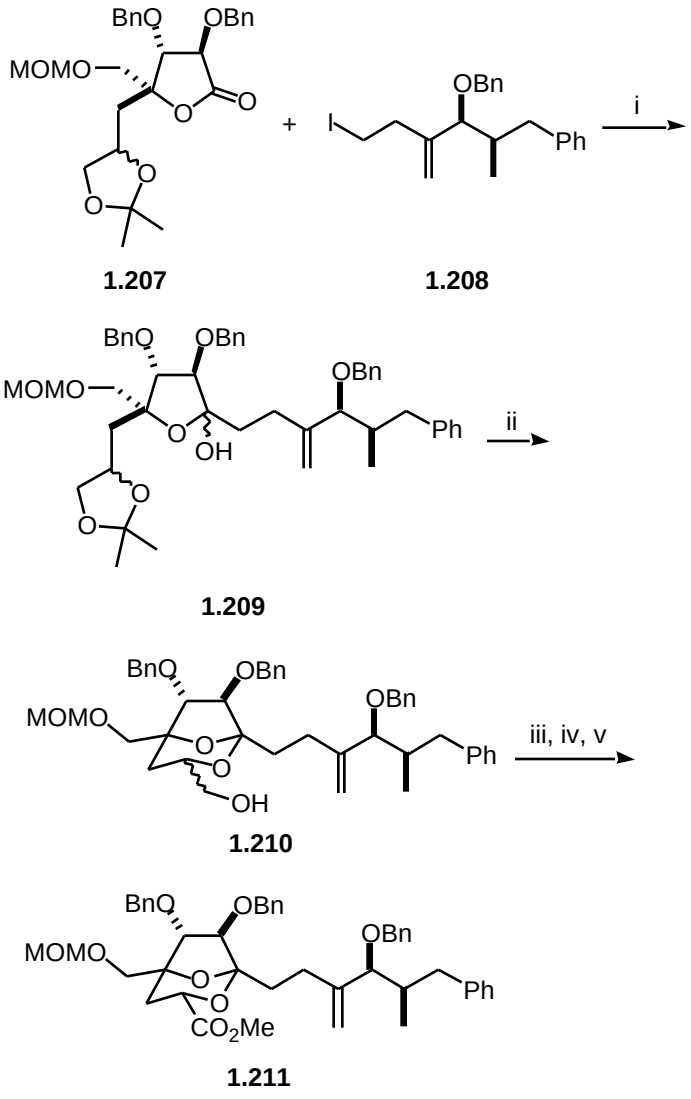


1.200 **1.201** **1.202** **1.203** **1.204** **1.205** **1.206** **1.207**

i) LDA, TMSCl, THF/HMPA, 74%; ii) $LiAlH_4$; iii) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 99%; iv) OsO_4, K_3FeCN_6, K_2CO_3, *t*-BuOH; v) $(MeO)_2CMe_2$, PPTS, acetone, 96%; vi) Li/NH_3, THF; vii) HMPT, CCl_4/THF; viii) Li/NH_3, THF, 68%; ix) NaH, BnBr, THF/DMF, 92%; x) DMDO, CH_2Cl_2; xi) CH_2=CHOH, 95%; xii) BnBr, THF, DMF, 90%; xiii) $(PPh_3)_3RhCl$, DABCO, EtOH; xiv) $Hg(OAc)_2$, THF, H_2O; xv) NaOAc, PCC, 4Å mol. sieves, CH_2Cl_2

Incorporation of the C-1 side chain was then accomplished by by alkylating lactone **1.207** with the anion of **1.208**. Lactone **1.207** was then converted to lactol **1.209** (Scheme 1.49). Treatment of **1.209** with acid gave the zaragozic acid [3.2.1] core **1.210** with a 3:1 epimeric ratio at C-3. Rizzacasa commented on this ratio being a result of the reluctance of the undesired acetonide epimer to cyclize. Oxidation of the C-3 hydroxyl to the methyl ester gave **1.211** as a single isomer, apparently resulting from epimerization at C-3 during the oxidation sequence. Similar oxidation at C-5 and elaboration at C-4 would then provide a fully functionalized zaragozic acid core.

Scheme 1.49



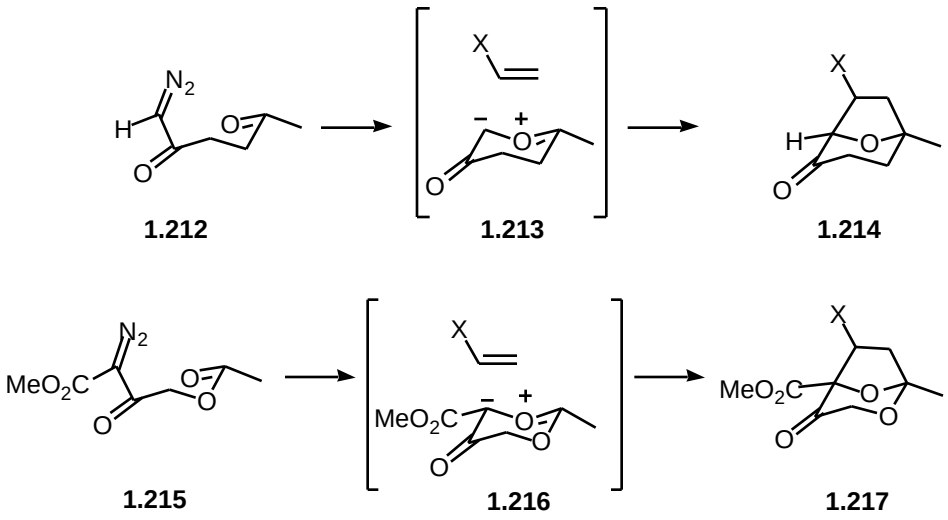
i) *t*-BuLi, Et_2O/hexane, 48%; ii) 10% HCl, MeOH, 67%; iii) Dess-Martin, pyr./CH_2Cl_2; iv) $NaClO_2$, NaH_2PO_4, *t*-BuOH/H_2O; v) CH_2N_2, Et_2O, 61%.

1.3.6 1,3-Dipolar Cycloaddition Approaches

Four different research groups approached the synthesis of the zaragozic acid core using the 1,3-dipolar cycloaddition of an oxonium ylide to assemble the dioxabicyclo[3.2.1] core system.[41-47] They have all been assembled into one section in order to provide a clear picture of the progress in the development of this approach toward the synthesis of the zaragozic acid core.

Koyama published the first approach that utilized a 1,3-dipolar in 1994. A general survey of diazoketones and dipolarophiles revealed that the most promising results for the synthesis of the zaragozic acid core came from the coupling of diazoketoesters such as **1.212** and **1.215** with various dipolarophiles to provide products such as **1.214** or **1.217** (Scheme 1.50). Although Koyama did show that this general strategy was certainly viable for the zaragozic acid core system, yields were low and there was much room for improvement.

Scheme 1.50

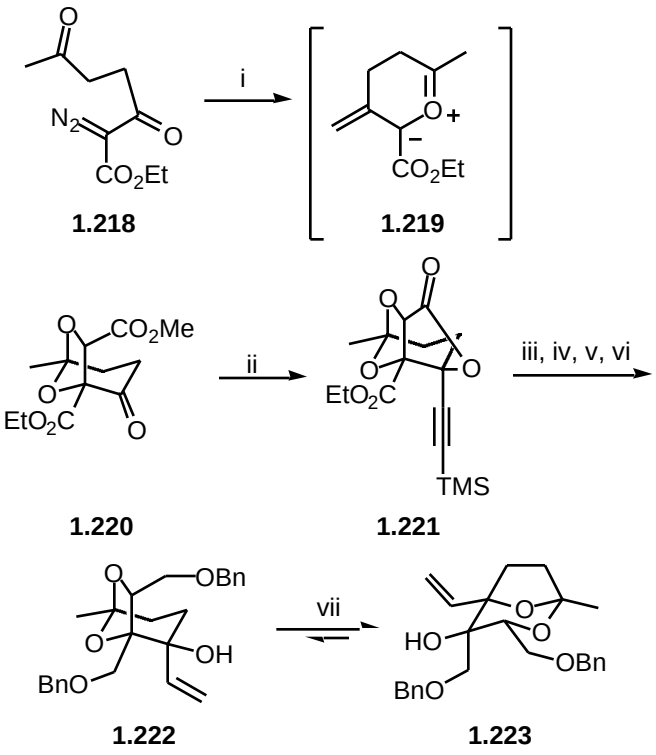


X	% yield **1.214**	% yield **1.217**
TMSO	16	16
BzO	15	9
AcO	40	

Hodgson also adopted a 1,3-dipolar cycloaddition strategy whereby diazoketoester **1.218** was treated with methyl glyoxylate to give a single cycloadduct **1.220** in modest yield (Scheme 1.51). Treatment of the ketone with TMS lithium acetylide gave **1.221**, which after several steps provided olefin **1.222**. Finally, treatment with acid to effect the desired rearrangement formed **1.223** as the dioxabicyclo[3.2.1] ring system. Unfortunately, the C-4 center of **1.223** had the wrong stereochemistry because of the propensity for *endo*

selectivity in the cycloaddition, which was due to the secondary overlap between the ester carbonyl of the glyoxylate and the ketone in ylide **1.219**.

Scheme 1.51



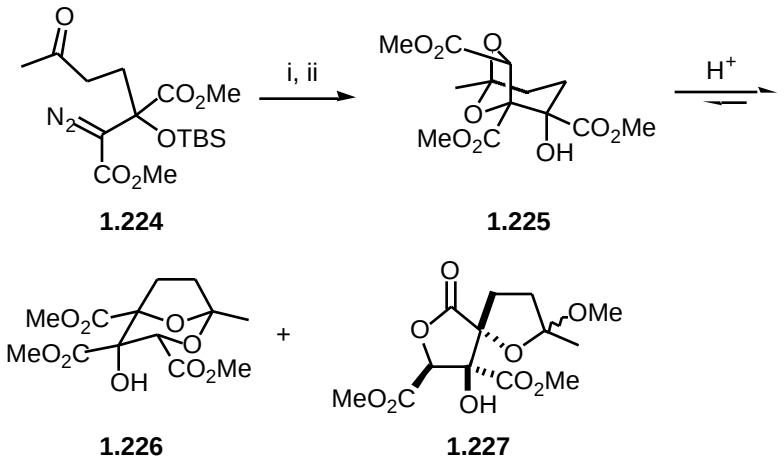
1.218 **1.219** **1.220** **1.221** **1.222** **1.223**

i) methyl glyoxylate, $Rh_2(OAc)_4$, PhMe, 60%; ii) TMSC≡CLi, THF, 80%; iii) K_2CO_3, DMF/H_2O, 98%; iv) H_2, Pd/C, 100%; v) $LiAlH_4$, Et_2O, 67%; vi) NaH, BnCl, NaI, DME, 52%; vii) 2% HCl, MeOH.

Further studies of the dipolar cycloaddition by Hodgson sought to disrupt the secondary overlap in **1.219** by altering substitution, therefore decreasing the propensity for *endo* selectivity (Scheme 1.52). To this end, diazoketoester **1.224** which was prepared in seven steps from γ-valerolactone, was treated with methyl

glyoxylate to give, after removal of the silyl protecting group, cycloadduct **1.225**. Treatment of **1.225** with TFA produced **1.226** with correct stereochemistry at C-4 in a 33:64 ratio of **1.225** to **1.226**. It should be noted that if HCl/MeOH or CSA/MeOH were used as the acid, **1.227** was also formed as a minor product with a 69:21:10 or 83:13:4 ratio of **1.225** to **1.226** to **1.227** respectively.

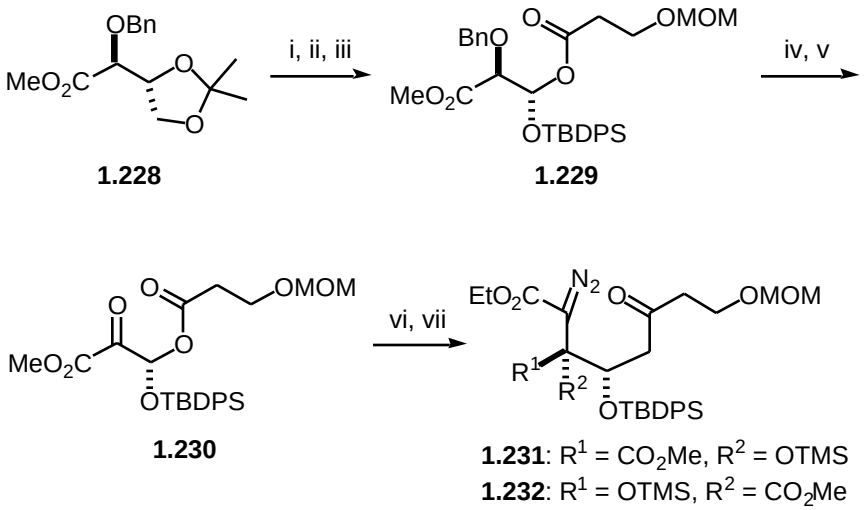
Scheme 1.53



i)methyl glyoxylate, $Rh_2(OAc)_4$, PhMe, 65%; ii) TBAF, THF, 74%.

Hashimoto also utilized the intermolecular 1,3-dipolar cycloaddition in a synthesis of the zaragozic acid core. The diazoesters **1.231** and **1.232** were prepared from ester **1.228** as a mixture (1.5:1) of epimers that were readily separable once the alcohols had been silyl protected (Scheme 1.54).

Scheme 1.54

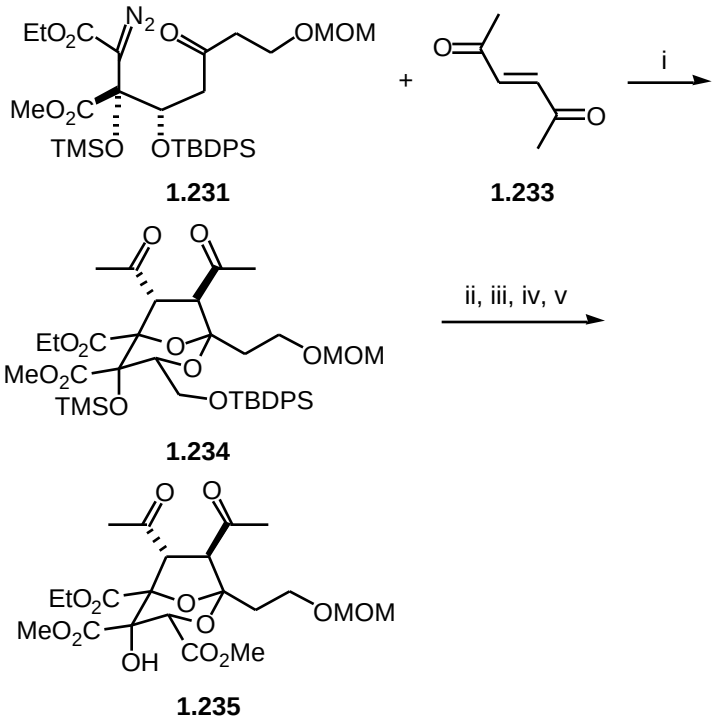


i) 10% aq. HCl/THF, 78%; ii) TBDPSCl, pyr., DMAP, CH_2Cl_2, 96%; iii) $MOMO(CH_2)_2CO_2H$, EDCI, DMAP, CH_2Cl_2, 89%; iv) H_2, $Pd(OH)_2/C$, MeOH, 85%; v) Dess-Martin, CH_2Cl_2, 94%; vi) N_2CHCO_2Et, LiHMDS, THF; vii) HMDS, imid., THF, 40% (**1.231**), 26% (**1.232**)

Diazoketoester **1.231** was then used in the 1,3-dipolar cycloaddition with dione **1.233** to form adduct **1.234** as a single diastereomer (Scheme 1.55). The stereochemical outcome of the cycloaddition was explained as a consequence of the dipolarophile **1.233**, which was presumed to proceed exclusively from the β-face of the carbonyl ylide in order to avoid non-bonding interaction with the C-4 pseudoaxial TMS group. Further elaboration of the core included deprotection of the C-4 alcohol and stepwise oxidation and esterification at C-3 to give the desired functionalized [3.2.1] core **1.235**. Hashimoto commented on the intention

to complete the synthesis of the fully functionalized zaragozic acid core through the Baeyer-Villiger oxidation at C-6 and C-7.

Scheme 1.55

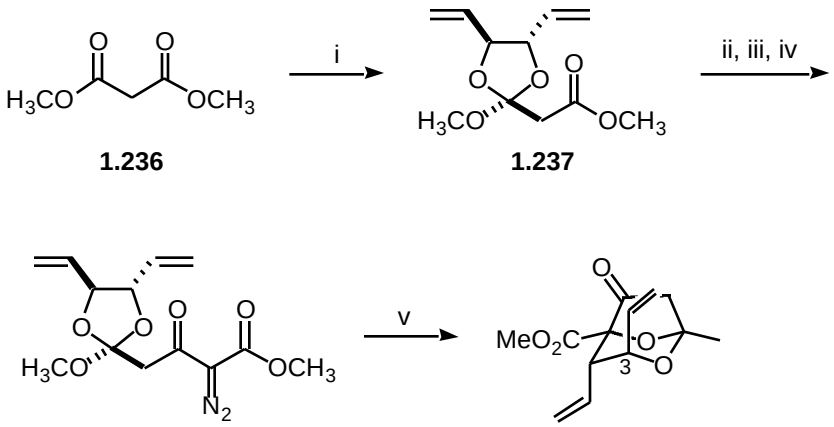


i) $Rh(OAc)_4$, PhH, 47%; ii) TBAF, AcOH, THF; iii) Dess-Martin, CH_2Cl_2; iv) $NaClO_2$, $NaHPO_4$, $(Me)_2C{=}CHMe$, *t*-BuOH/H_2O; v) CH_2N_2, 69%.

Zercher also contributed to the evolution of the 1,3-dipolar cycloaddition strategy, although his approach utilized an intramolecular rather than the previously examined intermolecular approach. Reaction of methyl acetoacetate (**1.236**), with mixture of *meso*- and *dl*- 1,5-hexadiene-3,4-diol produced **1.237** (Scheme 1.56). Subsequent conversion of **1.237** to the β-ketoester and

diazotization was performed to give **1.238**. Conversion to the zaragozic acid core was then accomplished *via* 1,3-dipolar cycloaddition to provide **1.239** as the major product with the incorrect stereochemistry at both C-3 and C-4. The fact that **1.239** was produced with the incorrect stereochemistry at both the C-3 and C-4 centers made this approach much less appealing, but since the 1,3-dipolar cycloaddition was used as the key step, it seemed appropriate to include Zercher's work.

Scheme 1.56



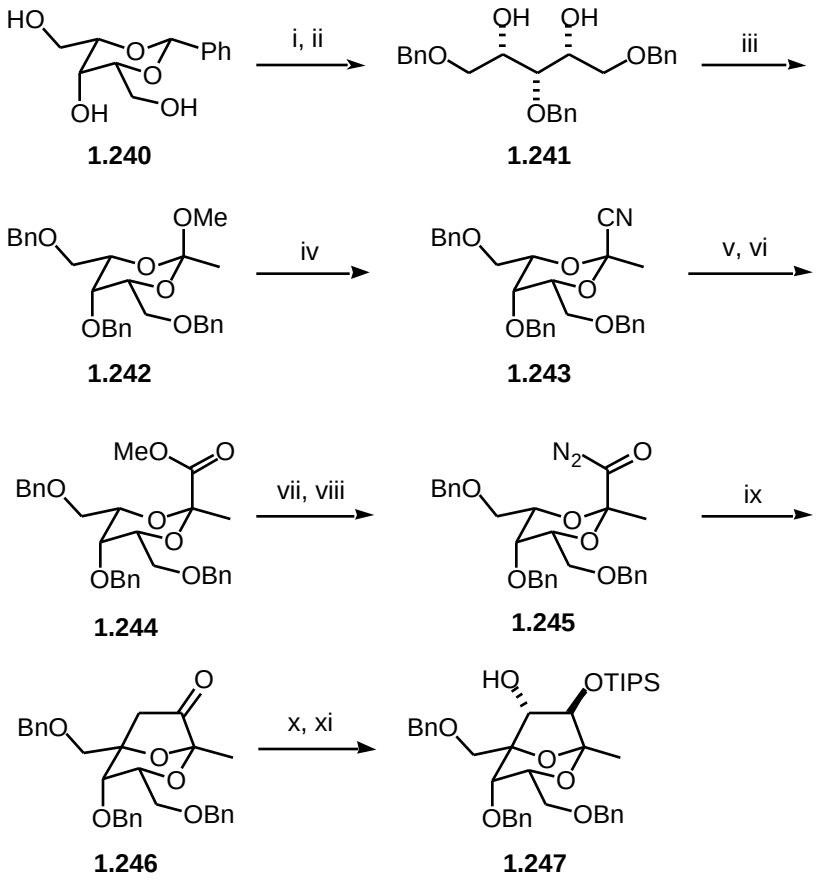
i) *meso* and *dl*-1,5-hexadien-3,4-diol, *p*-TsOH; ii) KOH, MeOH;
iii) carbonyldiimidazole, then $Mg(O_2CCH_2CO_2CH_3)_2$;
iv) *p*-carboxybenzenesulfonylazide, Et_3N; v) $Rh_2(OAc)_4$, PhH; 64%.

1.3.7 Wardrop's Approach

The last approach to the zaragozic acid core system that will be discussed by Wardrop utilized a directed C-H insertion as the key step in the assembly of the zaragozic acid core system.[44] The required diaoketone **1.245** was synthesized in eight steps from 3,5-*O*-benzylidene xylitol (**1.240**) (Scheme 1.57). Diazoketone **1.245** was then prepared and subjected to the cyclization conditions to provide the desired [3.2.1] system **1.246**. Formation of the C-6/C-7 *trans* diol **1.247** was then accomplished in two steps from **1.246** where the C-6 and C-7 hydroxyl groups had been differentiated. Although there was no mention of a

specific plan to fully functionalize C-4 to produce the zaragozic acid core, there was a comment indicating that work is ongoing toward the synthesis of zaragozic acid A (**1.54**)

Scheme 1.57



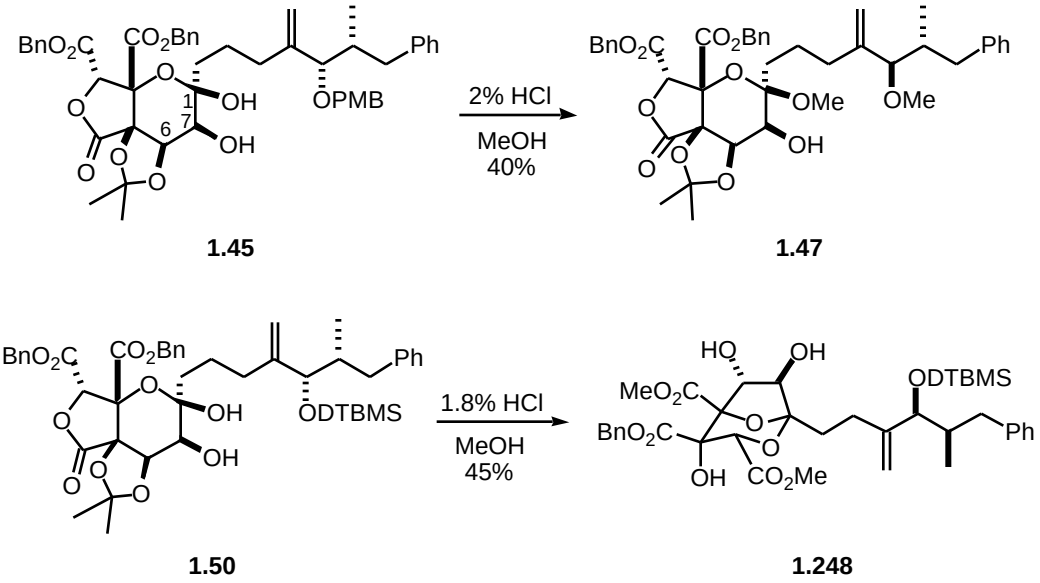
i) NaH, BnBr, TBAI, DMF; ii) EtSH, *p*-TsOH, $CHCl_3$, 40%; iii) $MeC(OMe)_3$, *p*-TsOH, 4Å mol. sieves, CH_2Cl_2 then Na_2CO_3; iv) TMSCN, $SnCl_2$, 4Å mol. sieves, CH_2Cl_2 then K_2CO_3; v) NaOH, H_2O_2, EtOH, 73%; vi) DMF, DMA,MeOH, 73%; vii) LiOH, THF, H_2O; viii) Et_3N, then *t*-BuOCOCl, CH_2Cl_2, then CH_2N_2, 88%; ix) $Rh_2(OAc)_4$, CH_2Cl_2, 48%; x) KHMDS, THF, then TIPSCl, 80%; xi) BH_3•Me_2S, THF, then H_2O_2, NaOH, 81%.

1.4 THE KETALIZATION

Since the ketalization to form the zaragozic acid [3.2.1] core is a key step in the synthesis of all members of the zaragozic acid family, it seemed worthwhile

to carefully examine this particular step. More specifically, examples of the ketalization that provide some insight as to how substituents might influence the outcome of the ketalization were selected in an effort to draw some general conclusions about the reaction. In order to gain insight about the important factors in the ketalization, examples were selected where different results were obtained depending on the substitution and/or reaction conditions that were used. For example, in Nicolaou's synthesis of zaragozic acid A (**1.54**), **1.45** was subjected to treatment with 2% HCl in methanol to give only undesired ketal **1.47** (Scheme 1.58). The formation of analogous methyl ketals was also observed in the work of Hodgson (Scheme 1.53) and Martin (Schemes 2.9 and 2.11). Surprisingly, when **1.50** was subjected to acidic conditions, the exclusive product of the reaction was the desired [3.2.1] bicyclic core **1.248**. Since the only difference between the two cyclization substrates **1.45** and **1.50** was the C-4' protecting group, this suggested that the specific nature of the C-1 substituent was crucial to the outcome of the ketalization.

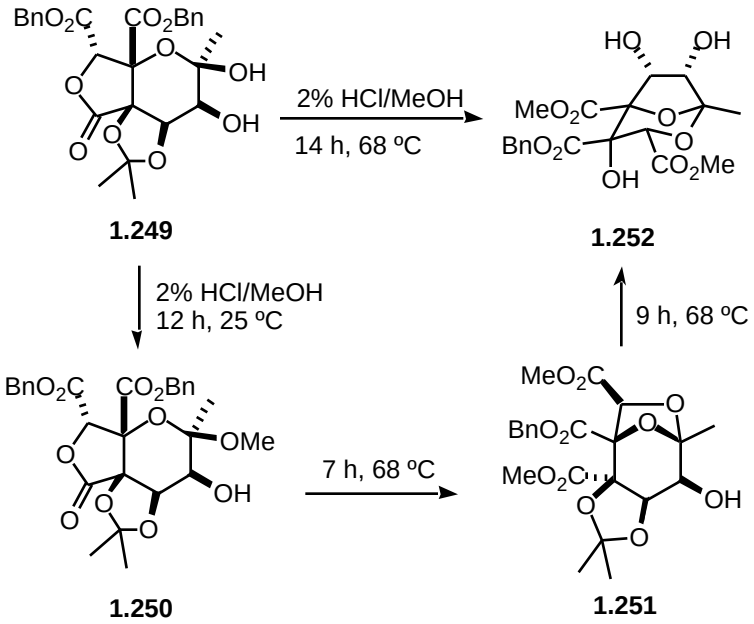
Scheme 1.58



In addition to the observations by Nicolaou presented above, there was also a short study by Nicolaou with **1.249** to determine the sequence of events in the cascade reaction to form desired ketal **1.250**. To this end, **1.249** was treated with 2% HCl/MeOH at room temperature for 12 h to yield the methyl glycoside **1.250** (Scheme 1.59). After seven additional hours at 68 ºC, the reaction mixture contained two major components, acetonide **1.251** and desired [3.2.1] bicyclic ketal **1.252**. When acetonide **1.251** was resubjected to the reaction conditions, desired ketal **1.252** was obtained. This experiment suggested that ketal **1.252** was the thermodynamically most stable ketal for this system. Unfortunately these

results cannot be applied as a general rule since when methyl ketal **1.47** was resubjected to the reaction conditions as **1.250** had been, only ketal **1.47** was recovered.

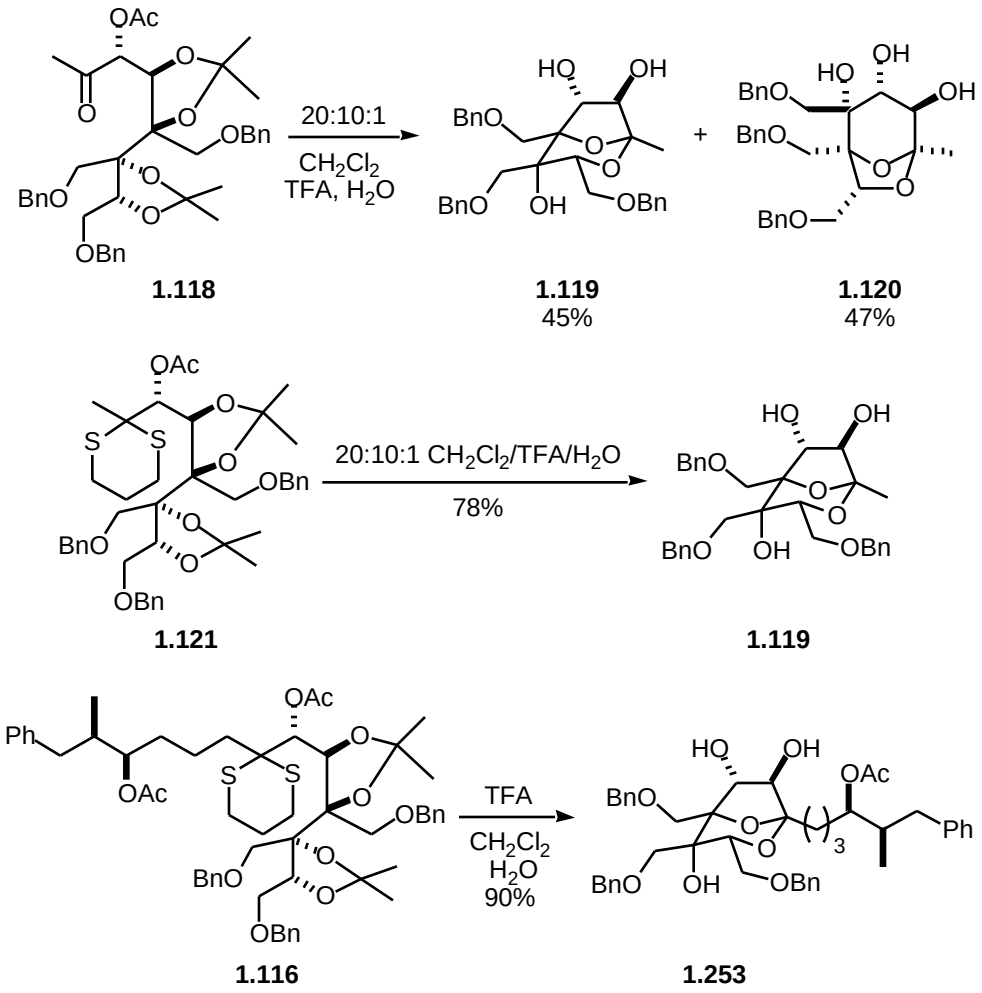
Scheme 1.59



Similarly, Armstrong's work demonstrated that the nature of the product depended on the C-1 side chain that was used in the precursor (Scheme 1.60). When the cyclization was performed in the presence of a methyl group **1.118** rather than the zaragozic acid C-1 side chain, a mixture of the desired ketal **1.119** and undesired ketal **1.120** was obtained in approximately equal amounts. In contrast, if the ketone in **1.118** were protected as the dithiane **1.121**, the

cyclization provided **1.19** as the exclusive product of the reaction. In agreement with this finding, when the actual zaragozic acid C-1 side chain was used with dithiane **1.116**, the cyclization resulted in the isolation of desired [3.2.1] bicyclic ketal **1.253** in excellent yield. These findings also support the theory that the nature of the C-1 side chain substituent is crucial to the outcome of the cyclization to the zaragozic acid core.

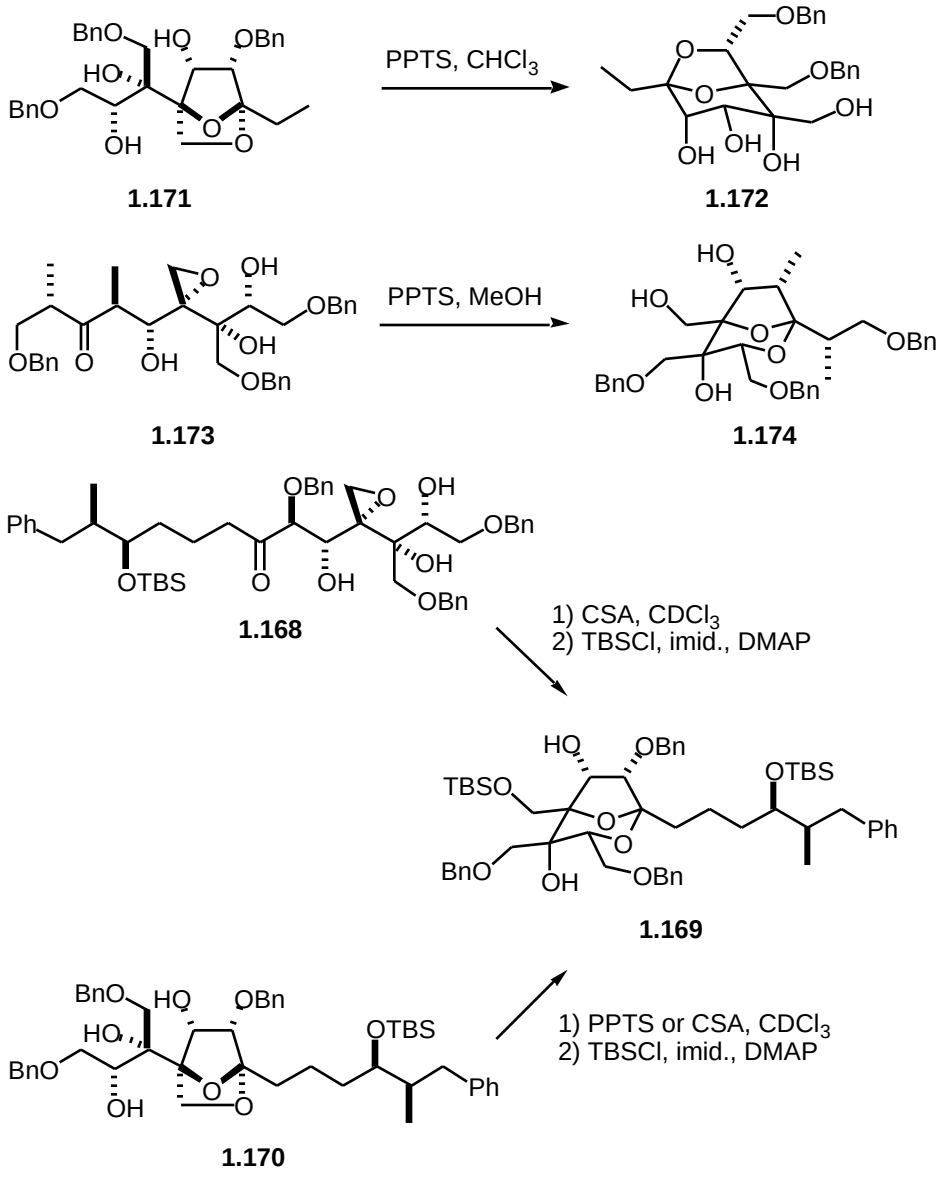
Scheme 1.60



Paterson also found that the ketalization of a series of substrates varied depending upon the nature of the substituent at C-1. If **1.171** was used with a simple alkyl group at C-1, treatment with acid provided only undesired ketal **1.172** (Scheme 1.61). Alternatively, when **1.173** was subjected to treatment with

acid, desired ketal **1.174** was the only product isolated from the reaction. Making a direct comparison between the cyclizations of **1.171** and **1.173** may be difficult in light of the fact that the nature of the substrate is different. However, the acid-catalyzed cyclizations of **1.168** and **1.170** using the actual zaragozic acid C-1 side chain confirms the theory that the nature of the C-1 substituent determined the outcome of the cyclization, since only the zaragozic acid [3.2.1] bicyclic core **1.169** was isolated from both of these reactions.

Scheme 1.61

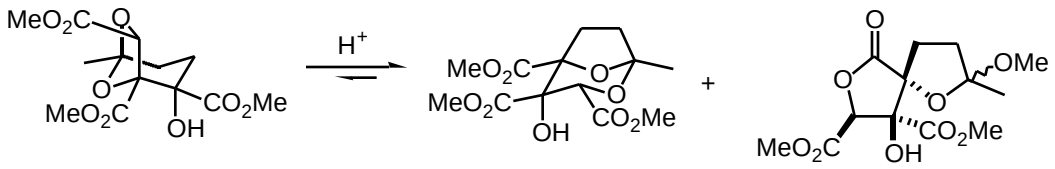


1.171 **1.172** **1.173** **1.174** **1.168** **1.169** **1.170**

Hodgson conducted a model study that gave provided some insight as to the importance of the nature of the acid (Scheme 1.62). To this end, treatment of

1.225 with camphorsulfonic acid or HCl in methanol provided starting material **1.225** along with desired ketal **1.226** and ketal **1.227** as a minor product. Nicolaou (Scheme 1.57) and Martin (Schemes 2.9 and 2.11) have observed the formation of analogous methyl ketals in the acid-catalyzed ketalization reaction to form the zaragozic acid [3.2.1] bicyclic core. Treatment of **1.225** with triflic acid produced the desired ketal **1.226**, but only in small amounts. Conversely, desired ketal **1.226** could be obtained as the major product by treatment of **1.225** with Evans' conditions using trifluoroacetic acid. When ketal **1.225** was subjected to the same conditions, the same ratio (33:64) of **1.225** to **1.226** was obtained, which indicated that thermodynamic equilibrium had been reached.

Scheme 1.62



1.225 **1.226** **1.227**

Conditions	**1.225:1.226:1.227**
CSA/MeOH	83:13:4
2% HCl/MeOH	69:21:10
TfOH/$CDCl_3$	75:25:-
CH_2Cl_2/TFA/H_2O	33:64:-

While it was anticipated that there would be some generalizations that could be made about the acid-catalyzed ketalization, it was found that the reaction is highly dependent upon the specific substrate. Evidence thus far indicates that there are at least two factors that are important to the outcome of the ketalization: first, the nature of the C-1 substituent is crucial, though there does not seem to be any pattern that could serve as a predictive indicator. Second, the nature of the acid catalyst and solvent are important to the outcome of the reaction, although there are no predictive patterns with this component with the possible exception that the formation of an undesired methyl acetal is a possible side product with the use of HCl in methanol.

CHAPTER 2. EFFORTS TOWARD THE TOTAL SYNTHESIS OF 7-DEOXYZARAGOZIC ACID A

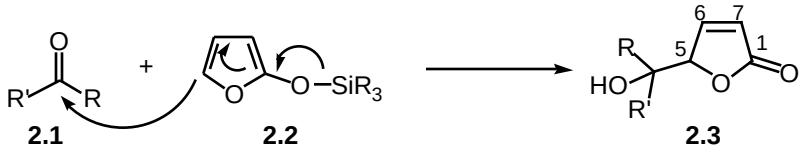
2.1 PREVIOUS WORK IN THE MARTIN GROUP

In addition to the approaches to the zaragozic acids that have already been discussed in Chapter 1, the Martin group also embarked on studies toward the synthesis of this group of natural products. The strategy in the Martin group has utilized a vinylogous aldol reaction as the key step in the synthesis. The aldol reaction has been used in other syntheses of the zaragozic acids. More specifically, Evans employed both an Evans aldol reaction using a chiral oxazolidinone and a Mukaiyama aldol reaction. Additionally, Hashimoto used a Lewis acid mediated Mukaiyama aldol reaction as a key step.

The vinylogous aldol reaction has not been employed in the synthesis of any of the members of the zaragozic acid family, although this reaction has been employed extensively in the context of both methodological studies, as well as total syntheses.[48,49] In a generic sense, the vinylogous Mukaiyama aldol consists

of the reaction of silyloxyfuran **2.2** and carbonyl **2.1** to provide butenolide **2.3** (Scheme 2.1). Butenolide **2.3** could then be further elaborated to the five-membered ring (C-5 – C-1) of the zaragozic acids.

Scheme 2.1



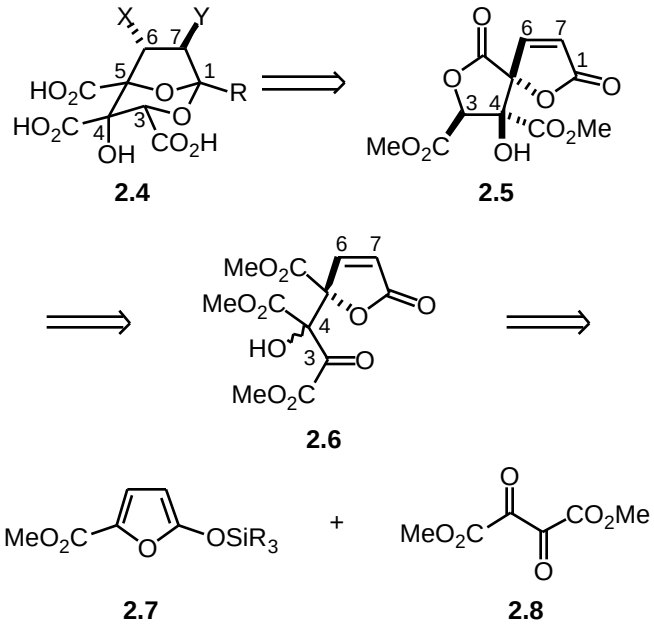
2.1 **2.2** **2.3**

2.1.1 First Generation Approach

In the first approach to the zaragozic acids **2.4**, Dr. Phil Kym targeted the bicyclic lactone **2.5** as a potentially versatile gateway since it contains the requisite absolute chirality at C-3 – C-5 of the zaragozic acid core **2.4** (Scheme 2.2). Bicyclic lactone **2.5** also has appropriate functional handles for introducing the remaining substituents and side chains of all the zaragozic acids. This compact intermediate might be rapidly assembled via reduction and cyclization of **2.6**, which would in turn be assembled using an intermolecular vinylogous Mukaiyama aldol reaction of furan **2.7** with dioxosuccinate **2.8**. Although this retrosynthetic analysis constitutes a racemic approach, it was envisaged that the

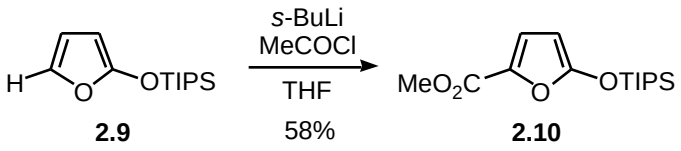
methods utlized here could later be applied to an enantioselective synthesis of any of the members of the zaragozic acid family.

Scheme 2.2



In accordance with the above retrosynthetic analysis, the requisite furan **2.10** was prepared by metallation and carbomethoxylation of the known furan **2.9** (Scheme 2.3).[50] The second building block, dimethyl dioxosuccinate (**2.8**) was prepared in one step by the acid catalyzed dehydration of dihydroxytartrate according to the method of Beak.[51]

Scheme 2.3



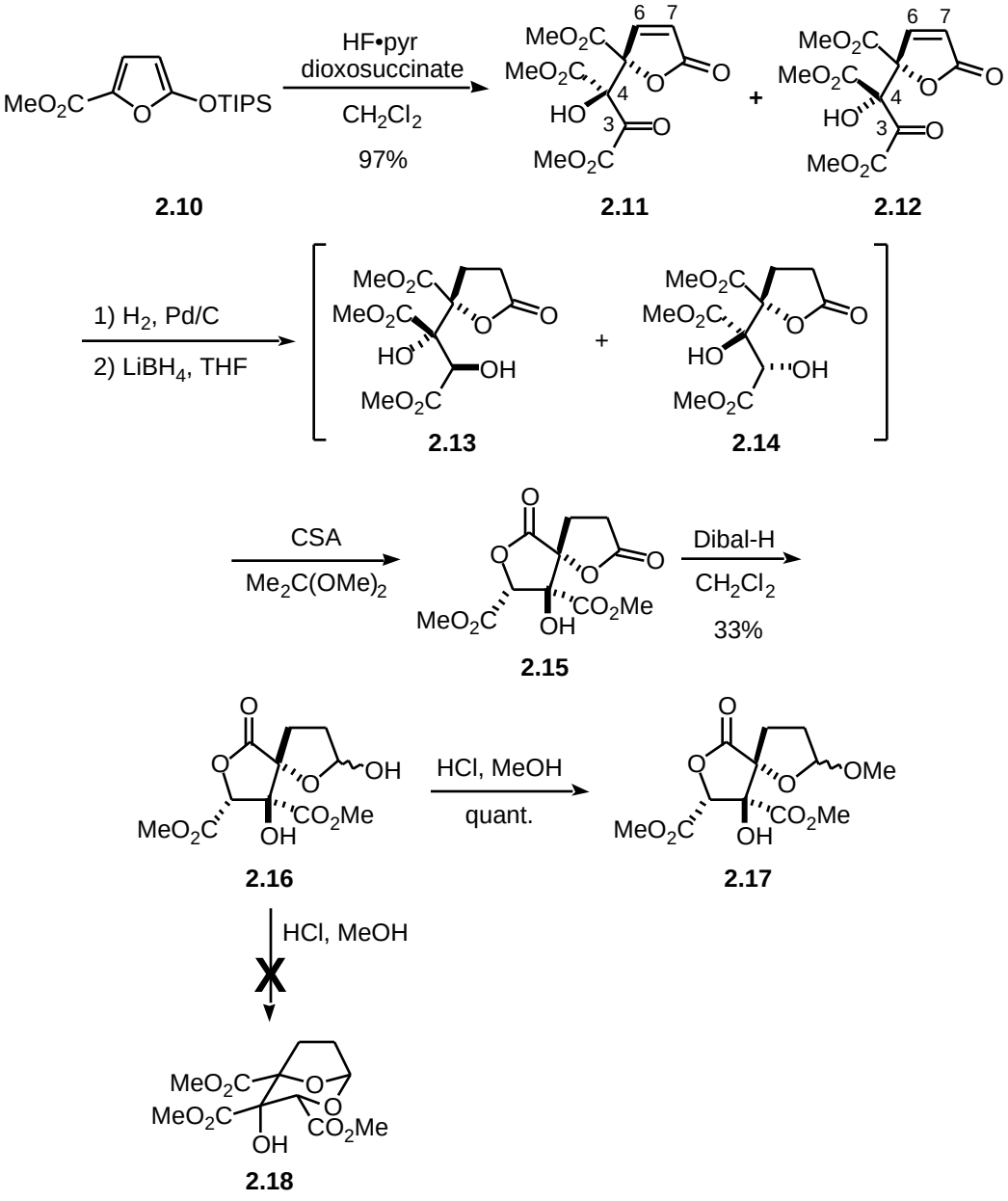
2.9 **2.10**

The stage was then set to examine the feasibility and the stereoselectivity of the key vinylogous Mukaiyama aldol reaction between **2.10** and **2.8**. A series of initial attempts to catalyze this reaction with a variety of Lewis acids, including $SnCl_4$, BF_3•OEt_2, Me_2AlCl, $TiCl_4$, and $AlCl_3$ were unsuccessful. However, the desired vinylogous aldol addition could be induced using excess HF•pyridine to provide an inseparable mixture (ca 2.3:1) of the diastereomeric adducts **2.11** and **2.12** in 91% yield (Scheme 2.4). At this stage it was not possible to assign the relative stereochemistry of the two adducts, but subsequent experiments revealed that the major isomer was the desired **2.11** (*vide infra*). Unfortunately, adducts **2.11** and **2.12** were extremely labile toward retro-aldolization under both acidic and basic conditions. The hydroxyl group at C-4 presumably serves as the trigger where the suceptibility of butenolide **2.11**/**2.12** toward the retro-aldolization was attributed to the stablization of the resulting anion at C-5. This stabilization of the C-5 anion was derived from the conjugation with the α,β-unsaturated lactone and from the electron withdrawing methyl ester at C-5. It was anticipated that

reduction of the double bond of the butenolide moiety in **2.11/2.12** would hinder the retro-aldolization process by removing the conjugation of the α,β-unsaturated lactone. It was found to be the case that the mixture of saturated lactones, which were prepared by catalytic hydrogenation of **2.11/2.12**, were stable and amenable to further manipulation.

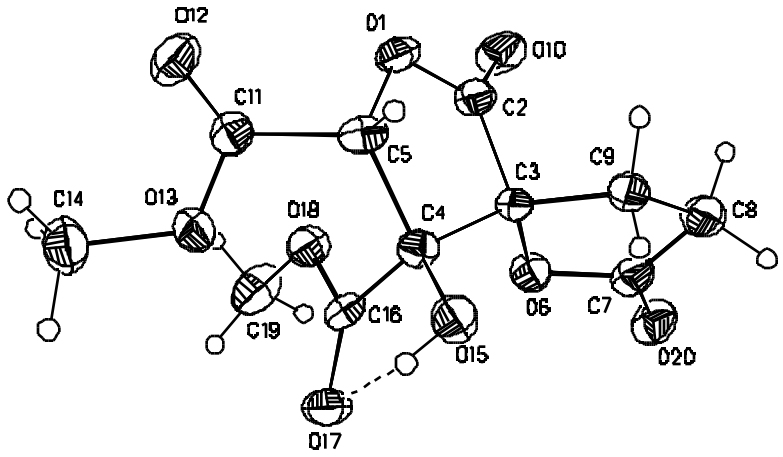
The stereoselectivity of the reduction of the carbonyl group at C-3 of **2.11/2.12** was then examined using a variety of hydride reducing agents, but reduction with $LiBH_4$ was the most selective, giving an inseparable mixture of **2.13** and **2.14** as the only identifiable products (Scheme 2.4). Fortunately, crystals of lactone **2.15** separated from the mixture of **2.13** and **2.14**, and the structure of this substance was unequivocally established by X-ray analysis (Figure 2.1). It was then found that treating the mixture of **2.13** and **2.14** with camphorsulfonic acid in 2,2-dimethoxypropane in an attempt to form the acetonide, unexpectedly gave a mixture (ca. 2.2:1) of **2.15** together with the corresponding lactone derived from **2.13**. Pure **2.15** was isolated in 26% overall yield from **2.10** after crystallization from chloroform.

Scheme 2.4


HF•pyr
dioxosuccinate
CH2Cl2
97%
2.10
2.11
2.12
1) H2, Pd/C
2) LiBH4, THF
2.13
2.14
CSA
Me2C(OMe)2
2.15
Dibal-H
CH2Cl2
33%
HCl, MeOH
quant.
2.16
2.17
HCl, MeOH
2.18

The X-ray structure of **2.15** revealed that the vinylogous aldol reaction had indeed proceeded predominantly in the desired stereochemical sense, but the hydride reduction of the carbonyl group at C-3 proceeded with apparent chelation control to give the incorrect relative stereochemistry (Figure 2.1). Because it seemed likely that it would be possible to correct this stereochemical error later in the synthesis, the feasibility of converting **2.15** into the 2,8-dioxabicyclo[3.2.1]octane system **2.18** characteristic of the zaragozic acids was explored (Scheme 2.4). Thus, selective reduction at C-1 of the less substituted lactone ring of **2.15** using Dibal-H proceeded smoothly to give a mixture of hemiacetals **2.16**. Subjecting this mixture to refluxing methanolic HCl gave a mixture of methyl acetals **2.17** rather than the desired oxabicyclic core **2.18**, presumably because the ester group at C-3 would be axial in such a product. It was thus apparent that an alternate strategy that provided an intermediate with the correct configuration at all centers was needed.

Figure 2.1

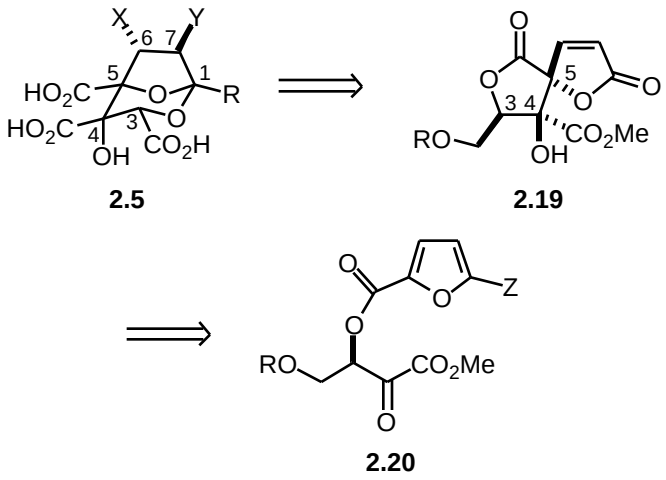


2.1.2 Second Generation Approach

Inasmuch as the bimolecular vinylogous aldol reaction of **2.10** and **2.8** proceeded with only modest selectivity, it was anticipated that an intramolecular variant of this process might be more stereoselective since the stereochemistry at C-3 could be set early in the synthesis. Hence, a different entry to the zaragozic acids was developed by Dr. Satoru Naito in which an intermediate such as **2.19**, which has the requisite stereochemistry at C(3)-C(5), might be formed by the cyclization of a furoic ester related to **2.20** (Scheme 3). Preparation of **2.20** by esterification of substituted furoic acids with the appropriate alcohols was

envisioned as being straightforward. The activating group Z on the furan ring would be varied as a tactical device to optimize the cyclization.

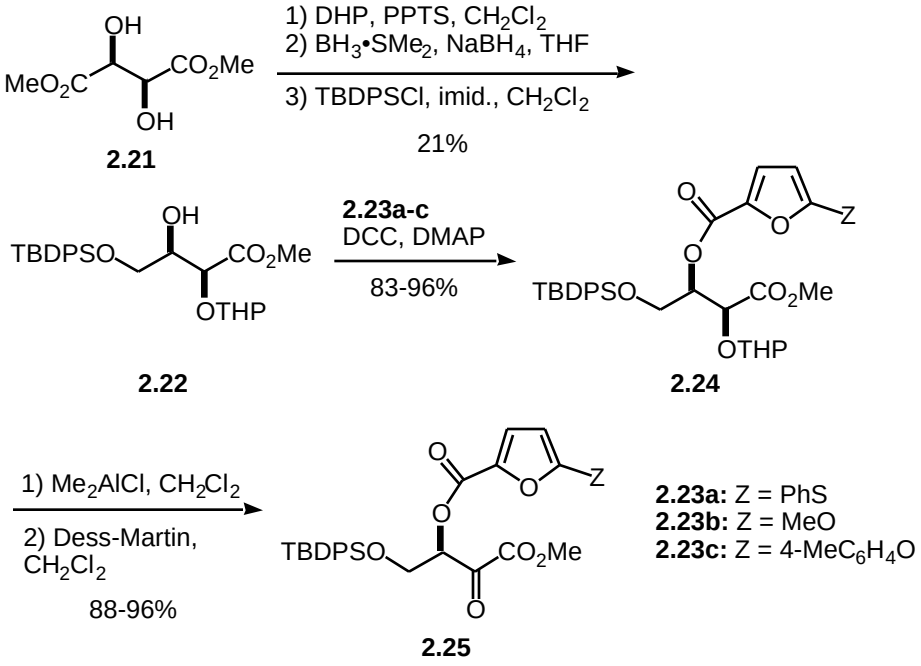
Scheme 2.5



At the outset of these studies, it was not clear what the optimal nature of the activating group Z on the furan ring would be, so the series of furoic acids **2.23a-c** was prepared from 5-bromofuroic acid according to literature procedures.[52,53] Several routes to the α-ketoester generally represented by **2.25a-c** were developed. In the first, dimethyl tartrate (**2.21**) was protected as the monotetrahydropyranyl (THP) derivative (Scheme 2.6). In practice, it was best to use excess dimethyl tartrate in this reaction (relative to dihydropyran) to minimize

formation of the bis-THP ether and to facilitate chromatographic purification. Selective reduction of the protected tartrate was achieved with the highest selectivity using BH_3•SMe_2 in the presence of catalytic $NaBH_4$ to give an inseparable mixture (4:1) of the 1,2- and 1,3 diols.[54-56] Saito has explained this selectivity in terms of the favored formation of a five-membered borane over the corresponding six-membered ring. Once this coordination complex had formed, the polarization of the ester C-O bond was enhanced, therefore facilitating the hydride delivery to the carbonyl. After silyl protection of the primary alcohol, the desired regioisomer **2.22** could be isolated in 50% yield. Esterification of **2.22** with the furoic acids **2.23a-c** gave the desired esters **2.24a-c** in high yields. Deprotection of the secondary alcohol using Me_2AlCl followed by Dess-Martin oxidation delivered the requisite α-ketoesters **2.25a-c**.[57-61]

Scheme 2.6



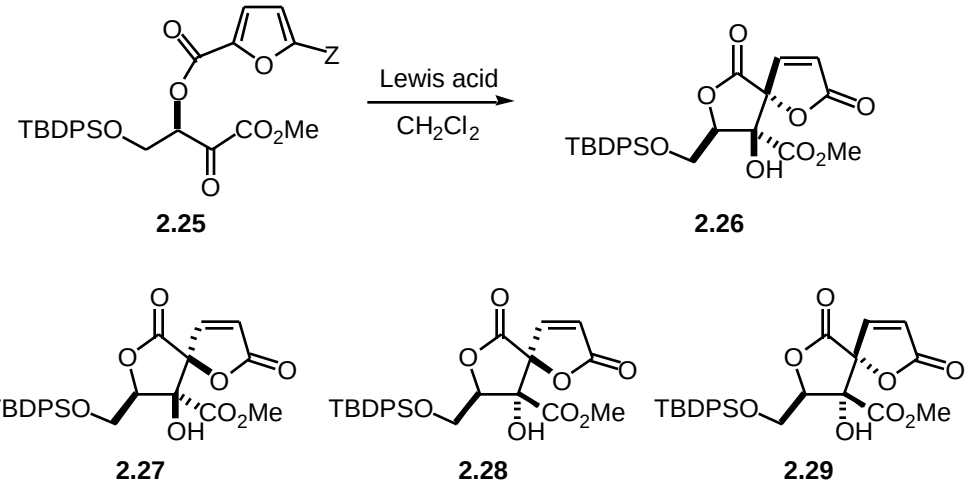
The intramolecular vinylogous aldol reactions of **2.25a-c** were then examined using various Lewis acids to induce the reaction (Scheme 2.7, Table 2.1). When **2.25a** was employed as the starting material, Lewis acids such as BF_3•OEt_2, $ZnCl_2$, $Sc(OTf)_3$, and TMSI did not induce the desired cyclization, but rather resulted in recovery of **2.25a** or isolation of unidentified products. On the other hand, $TiCl_4$ and $SnCl_4$ effected the cyclization, although all four possible diastereomers **2.26 – 2.29** in approximately equal amounts were obtained using $SnCl_4$. Fortunately, $TiCl_4$ induced the cyclization of **2.25a** to give **2.26** with the

highest selectivity, though the ratio of products was found to be highly dependent on the number of equivalents of $TiCl_4$ that were used. Poorer selectivities and lower yields were observed with fewer than three equivalents of $TiCl_4$, and use of more than three equivalents had little effect upon the results of the reaction.

That the number of equivalents and the nature of the Lewis acid had an effect upon the course of the reaction was expected. It was also expected that the nature of leaving group Z might have an effect upon the yield and/or rate of the reaction, but it was somewhat surprising that the nature of Z also had such a pronounced influence on the stereochemical outcome of the reaction (Table 2.1). For example, a methoxy group on the furan (i.e. **2.25b**) led to preferential formation of **2.28** and **2.29** in roughly equal amounts using $TiCl_4$, but significant amounts of **2.27** were isolated when TMSI was employed to catalyze the reaction. The presence of a phenoxy group (i.e. **2.25c**) on the furan led to the formation of **2.28** as the major product when $TiCl_4$ was used as the catalyst, whereas other acid catalysts gave mixtures of products. It was clear that Z must be an electron donating group as evidenced by the fact that when Z = H or Br there was no cyclization. Additionally, since both **2.25b** and **2.25c** contained oxygen

functionality, perhaps it is necessary that the Z contain a softer center, namely **2.25a** that utilized a sulfur rather than oxygen. That the Lewis acids employed in this study tend to be rather oxophilic may contribute to the stereoselectivity of **2.25a-c**. A rationale that would account for the effect of the various Lewis acids on the stereochemical outcome of the cyclization could not be developed to any substantial degree.

Scheme 2.7



2.25 **2.26** **2.27** **2.28** **2.29**

Table 2.1

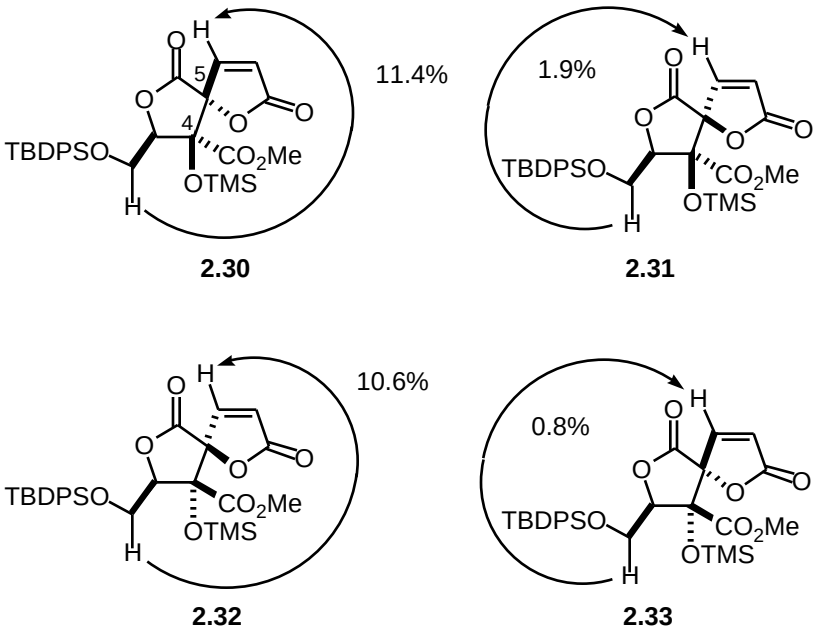
Compound	Lewis acid (equiv)	Conditions[a]	Isomer ratio[b] (**2.26:2.27: 2.28:2.29**)	Isolated isomer(s) (%yield)
2.23a	$TiCl_4$ (1.0)	rt, 3 h	6:2:1:0	**2.26** (11)
	$TiCl_4$ (2.5)	0 °C → rt, 1.5 h	14:1:1:0	**2.26** (33)
	$TiCl_4$ (3.0)	0 °C → rt, 1.5 h	>20:1:2:0	**2.26** (42)
	$TiCl_4$ (5.0)	0 °C → rt, 2 h	>20: 2:1:0	**2.26** (43)
	$SnCl_4$ (2.0)	rt, 4 h	1:2:1:1	
2.23b	$TiCl_4$ (3.0)	-78 → 0 °C, 2 h	0:0:2:1	**2.28** (56), **2.29** (30)

	$SnCl_4$ (1.0)	-78 °C → rt, 3 h	trace:1:4:5	
	BF_3•OEt_2 (1.0)	rt, 3 h	0:1:0:3.4	**2.27** (19), **2.29** (40)
	TMS–I (1.2)	0 °C → rt, 1 h	0:3:0:1	**2.27** (39), **2.29** (12)
2.23c	$TiCl_4$ (3.0)	-78 → 0 °C, 2 h	1:1:>20:1	**2.28** (65)
	$SnCl_4$ (2.0)	-78 °C → rt, 2 h	2:1:5:6	
	BF_3·OEt_2 (1.0)	rt, 12 h	0:1:trace:3	**2.27** (12), **2.29** (32)

[a]The reactants were combined in dichloromethane at the lower temperature and then stirred at the final temperature for the time indicated. [b]Ratio determined by ^1H NMR of crude reaction mixture.

In order to facilitate structure determination of adducts **2.26** – **2.29** as well as to increase their stability, they were all converted to their corresponding TMS ethers **2.30** – **2.34** (Figure 2.2). The structures of **2.30** – **2.34** were first tentatively assigned based upon the observed nOes, however it was not possible to assign the stereochemistry at C-4 based upon NMR alone. Consequently, the structures of **2.26**, **2.28**, and **2.29** were established by X-ray crystallographic analysis.

Figure 2.2



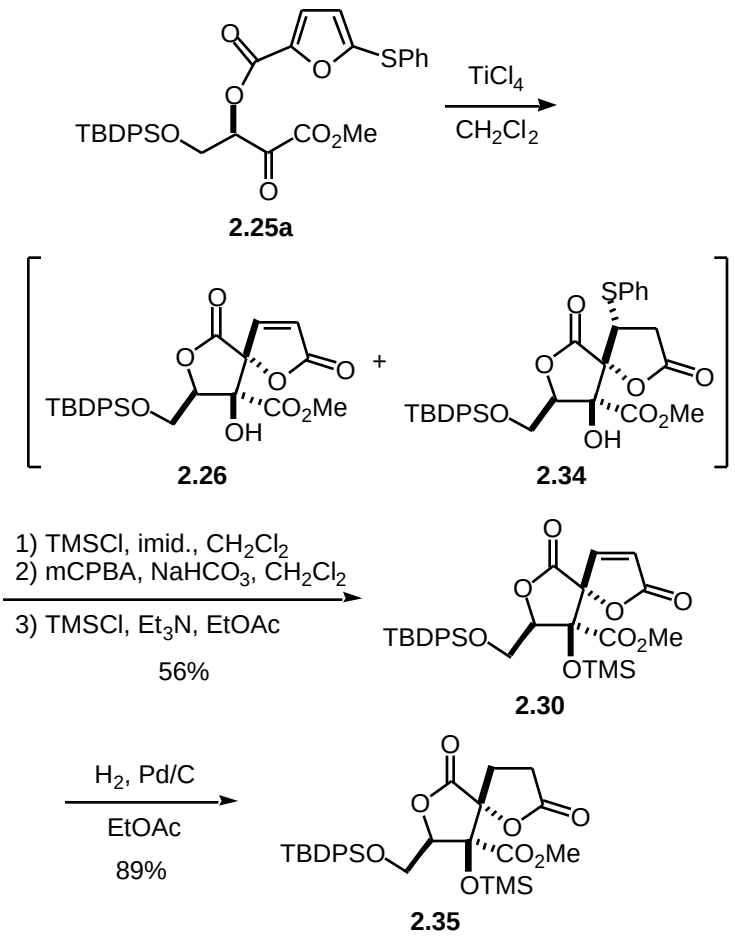
As noted previously, the spirocyclic adducts **2.26** – **2.29** could be isolated in pure form, but they were somewhat unstable and prone to retroaldolization,

especially in the presence of base. For example, if either pure **2.26** or **2.28** were heated in pyridine at 50 ºC, a mixture containing all four diastereomers **2.26** – **2.29** was obtained in a ratio of 5:10:5:1 that reflects their corresponding relative stabilities. When either **2.26** or **2.28** were resubjected to the cyclization conditions, no isomerization was observed, and hence it was assumed that the reactions were conducted under kinetically controlled conditions.

Careful analysis of the reaction mixtures obtained from the cyclization of **2.25a** revealed that sulfide **2.34** was formed in nearly 20% yield. Presumably **2.34** resulted from 1,4-addition of thiophenoxide anion that was released during the course of the reaction of **2.25a** to give **2.26** (Scheme 2.8). In order to circumvent this problem and therefore increase the yield of **2.26**, various thiophiles [Hg(II) and Cu(II) salts] were added in hopes of trapping the thiophenoxide prior to reaction with **2.26**. Ultimately, all efforts to reduce the amount of **2.34** formed during the reaction or workup were unsuccessful, and so a modified protocol was adopted that accomplished the conversion of **2.34** to **2.30**. Upon the completion of the cyclization of **2.25a** in the presence of $TiCl_4$, the crude product mixture was treated sequentially with TMSCl and imidazole then

mCPBA and finally Et_3N in the presence of TMSCl to give **2.30** in 54% overall yield. Catalytic hydrogenation of butenolide **2.34** then gave **2.35**, which was ready for installation of the C-1 side chain. The structure of **2.35** was confirmed by X-ray crystallography.

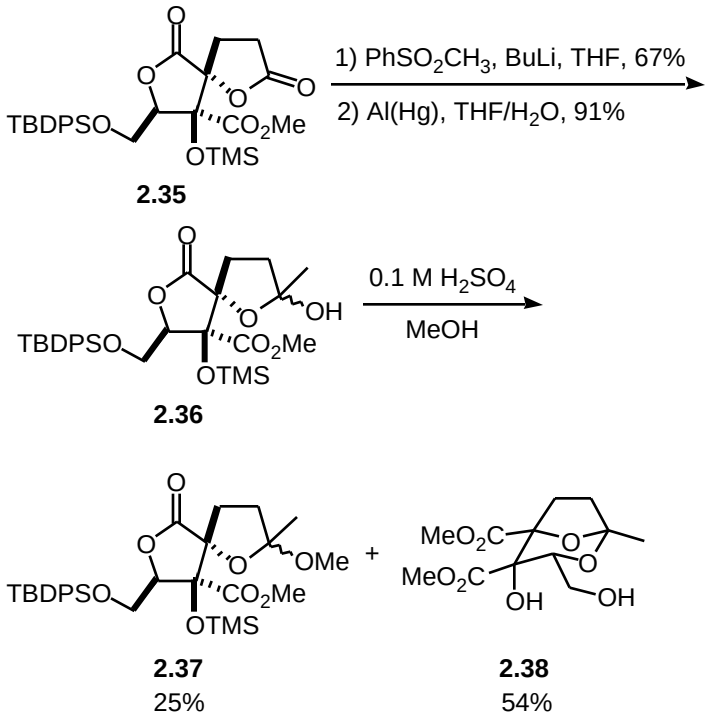
Scheme 2.8



In preliminary work directed toward the introduction of the C-1 aliphatic side chain, additions of various aliphatic Grignard, organolithium, and cerium reagents were examined. However, starting material was recovered as the major identifiable material from these reactions. On some occasions low yields of the cyclic hemiacetals arising from addition to the desired lactone carbonyl group

were obtained, where the regioselectivity of the addition was expected to arise from the higher steric accessibility of the desired carbonyl. Dianions of phenylsulfones are known to react cleanly with lactones,[62-66] and it was found that addition of methyl phenylsulfone to **2.35** resulted in formation of the desired adduct (Scheme 2.9). Reductive sulfonylation then furnished lactol **2.36** in good yield that was treated with with methanolic sulfuric acid to give a mixture (2:1) of **2.37** and **2.38**.[67,68]

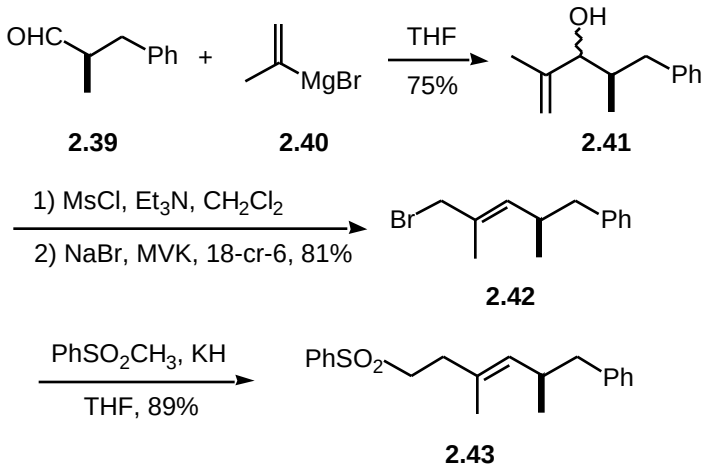
Scheme 2.9



In light of the positive results, efforts were directed toward the preparation of the sulfone of the requisite C-1 side chain as shown in Scheme 2.10. Accordingly, addition of 2-propenylmagnesium bromide **2.40** to aldehyde **2.39** gave alcohol **2.41**.[69] The optical purity of **2.41** (>95% ee) was established by degradation ($NaIO_4$, $RuO_2 \cdot xH_2O$) to the corresponding carboxylic acid derivative of **2.39** and NMR analysis of its methyl (*S*)-(+)-mandelate derivative. Mesylation of **2.41** followed by reaction of the intermediate mesylate with NaBr gave the

allyl bromide **2.42**. Initial attempts to convert **2.42** into **2.43** by alkylation of the lithiated monoanion of methyl phenyl sulfone gave significant quantities of dialkylated material. The potassium salts of sulfones were known to undergo selective monoalkylation,[70] and reaction of **2.42** with the potassium salt of methyl phenyl sulfone proceeded cleanly to give **2.43** in 89% yield.

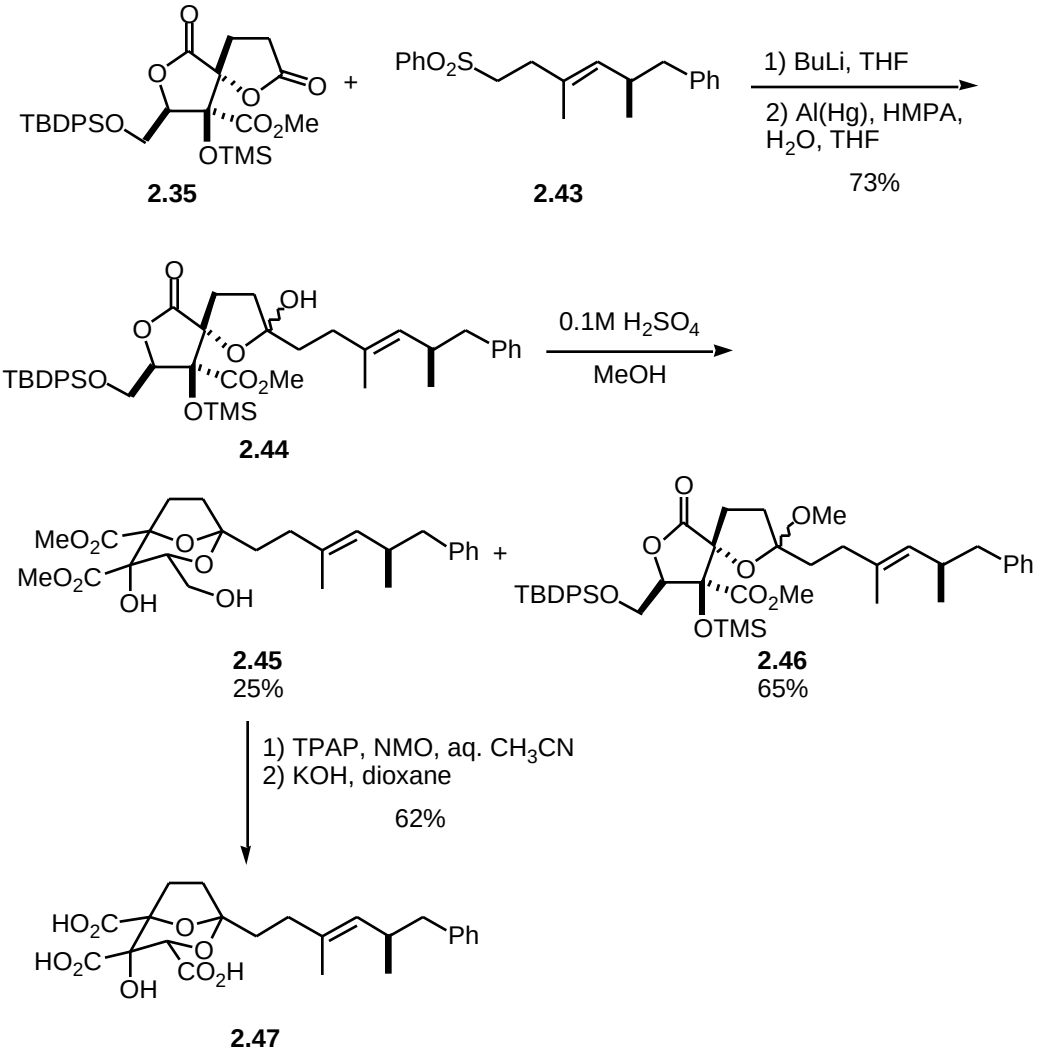
Scheme 2.10



The spirocycle **2.35** was then coupled with the C-1 side chain sulfone **2.43** to give **2.44** as a mixture of hemiacetals and the corresponding ring opened ketone after reductive desulfonylation with aluminum amalgam. This mixture was treated with methanolic sulfuric acid to give a separable mixture of the desired [3.2.1] bicycle **2.45** and acetals **2.46**. Oxidation of the C-3 primary alcohol of

2.45 with TPAP in the presence of water afforded the acid.[71] Subsequent saponification of the two methyl esters gave 6,7-dideoxysqualestatin H5 (**2.47**), which gave ^{1}H and ^{13}C spectra that were identical to those of an authentic sample.[72]

Scheme 2.11



In the ketalization reactions of both **2.44** and **2.36** not only was the desired bicyclooctane[3.2.1] zaragozic acid core obtained, but the methyl acetal was also recovered from the reactions as the major product. Hodgson had also observed similar results in the ketalization of **1.225** as discussed in Section 1.4.[41-43] As

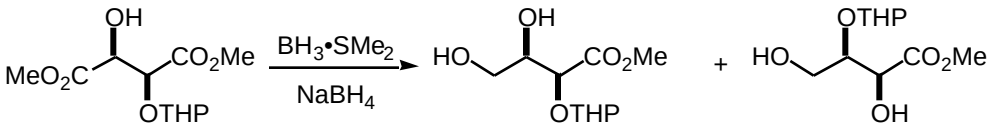
mentioned previously, there do not seem to be any predictive trends in the ketalization reaction, however, both Hodgson and Martin performed the ketalization on substrates where the core was not fully oxidized at C-3. The fact that Hodsgon later performed the ketalization with an alternative acid catalyst ($TFA/CH_2Cl_2/H_2O$) to obtain the zaragozic acid core system as the only product indicates that using these alternative reaction conditions, may have proven to be more effective. That being said, the total synthesis of 6,7-dideoxysqualestatin H5 was completed nevertheless.

2.2 IMPROVEMENTS TO THE SYNTHESIS OF THE α-KETOESTER

Although the desired α-ketoester **2.25a** could be made from dimethyl-D-tartrate (**2.21**), there were drawbacks that made further investigations into improving the route worthwhile. Namely, the initial THP protection of dimethyl tartrate (**2.21**) resulted in an equilibrium mixture of starting material, mono-, and diprotected tartrate, thereby requiring careful chromatography to isolate the desired product. Additionally, the borane reduction of **2.48** was only modestly selective and the two regioisomers **2.49** and **2.50** were not separable until after the

protection of the primary alcohol had been accomplished to provide **2.22**. There were various attemps to improve the selectivity of the borane reduction were as shown in Table 2.2, but this short study established THF was the best solvent for this reaction. With this in mind, alternative routes were investigated that would also address the concerns associated with the dimethyl tartrate route that have already been discussed.

Scheme 2.12



2.48 **2.49** **2.50**

Table 2.2

Solvent	Ratio 1,2 : 1,3 Diol[a]
THF	2-3 : 1
CH_2Cl_2	- : -
Ether	1 : 1.1
$MeOBu^t$	- : -[b]
THF/dioxane (1:1)	1.5 : 1
THF/$MeOBu^t$ (1:1)	- : -
Toluene	1.1 : 1

a) Ratio determined from the TBDPS protected ether

b)THP cleavage was found to be the predominant reaction

A new route to the α-ketoester that avoided these selectivity issues was thus developed that started with D-erythronolactone (**2.51**). Previous work from

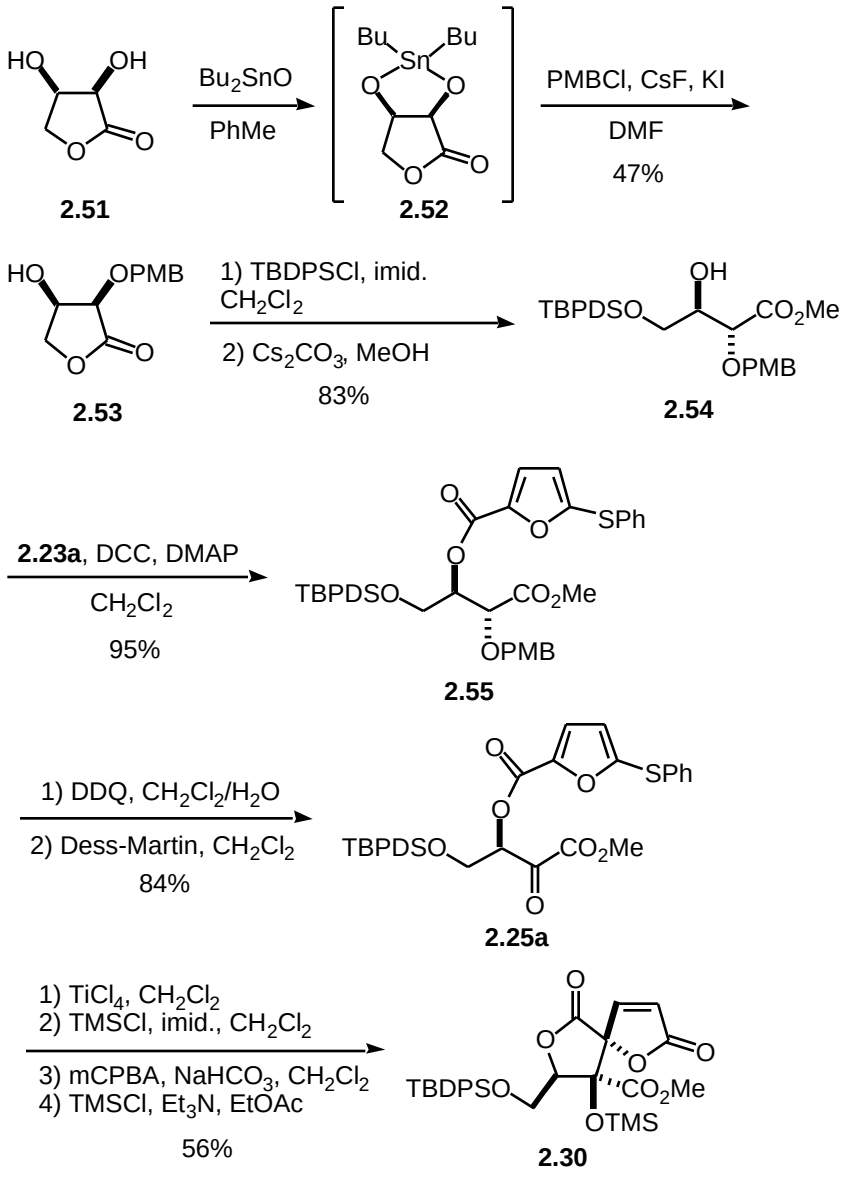
Scharf had shown that the position α to the carbonyl of **2.51** can be selectively benzylated by formation of the stannylidene acetal and subsequent treatment with BnBr.[73] The observed regioselectivity in this reaction was suggested to be due to the fact the higher basicity of the α-hydroxyl group causes the oxygen to be two-fold coordinated to the tin moiety while the more nucleophilic β-hydroxyl group is three-fold coordinated to the tin, and therefore masked from electrophilic attack. While Scharf's method was appealing for the regioselective protection of erythronolactone (**2.51**), the use of a benzyl protecting group raised some concerns about the deprotection later in the synthesis. The presence of a thiophenyl group would likely result in catalyst poisoning when attempting to remove a benzyl protecting group by hydrogenation. However, the *p*-methoxybenzyl (PMB) protecting group could be used because it could be removed using dichlorodicyanobenzoquinone (DDQ), which would not be affected by the presence of the thiophenyl moiety.

To this end, D-erythronolactone (**2.51**) was prepared from D-isoascorbic acid according to literature procedure (Scheme 2.13).[74] Selective protection of **2.51** was then accomplished according to the method of Scharf using dibutyltin

oxide in refluxing toluene to form the stannylidene acetal **2.52**. The crude stannylidene acetal was then treated with *p*-methoxybenzyl chloride in the presence of CsF and KI. The role of the CsF, according to Ohno, was primarily used to activate the alkyl halide through interaction of the cesium cation with the halogen.[75] It was also speculated that the activation of Sn-O bonds might be caused by the formation of a pentacoordinate complex as demonstrated by the need for nearly two equivalents of CsF. The crude reaction mixture contained a mixture (6:1) of regioisomers, but recrystallization of the mixture provided **2.53** as a single isomer. Alternatively, if erythronolactone (**2.51**) was simply treated with NaH and *p*-methoxybenzyl chloride, a mixture (1:1) of regioisomers was obtained. The remaining hydroxyl was protected a TBDPS ether, and methanolysis of the lactone occurred with concomitant silyl migration of the TBDPS to the primary alcohol to give **2.54**. Although silyl migrations are more commonly observed with the TBS protecting group, there are examples of the 1,2-silyl migration of the TBDPS group in polyols. The driving force was said to be the preference of the bulky TBDPS group for the primary position, which is favored by 8 – 9 kJ/mol compared to the secondary positions.[76]

Coupling of **2.54** with furoic acid **2.25a** using DCC gave ester **2.55** in high yield. Deprotection of ester **2.55** was accomplished using DDQ in a mixture of CH_2Cl_2 and water. Earlier work in the Martin group demonstrated that chromatography of **2.55** resulted in small amounts of acyl migration. The the *p*-methoxybenzaldehyde that was produced in the reaction thus had to be removed using an alternative purification method. Hence, the reaction mixture was concentrated and stirred vigorously with aqueous sodium bisulfite until TLC showed complete removal of the aldehyde. The intermediate alcohol was oxidized with Dess-Martin periodinane to give the desired α-ketoester **2.25a**.[58-61]

Scheme 2.13



Although the erythronolactone route to α-ketoester **2.25a** was one step longer than the tartrate route, the overall yield was improved from 18 to 28%.

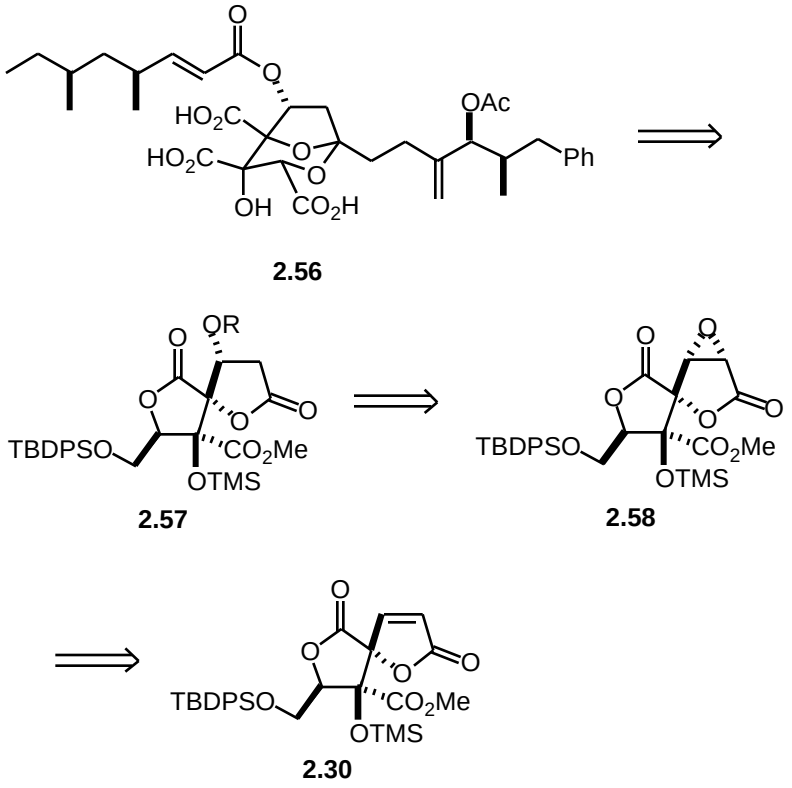
Moreover, ease of purification of the intermediates made this route a more favorable option. Additionally, the cost effectiveness of the route highly favored the erythronolactone route that used D-isoascorbic acid ($0.05/g) as the starting material, while the tartrate route utilized dimethyl-D-tartrate ($4.06/g). Cyclization of α-ketoester **2.25a** to give **2.30** was then carried out in the four step procedure described in Section 2.12 to give spirobislatone **2.30** (Scheme 2.13).

2.3 EFFORTS TOWARD THE SYNTHESIS OF THE 7-DEOXYZARAGOZIC ACID A CORE

At this point, it was anticipated that the C-6 – C-7 olefin of butenolide **2.30** could be elaborated to allow access to the more highly functionalized zaragozic acids, including 7-deoxyzaragozic acid A (**2.56**) (Scheme 2.14). It was anticipated that **2.56** could be made from bislactone **2.57**, which in turn would be accessible from the reductive opening of epoxide **2.58** using samarium diiodide as described by Molander.[77] Epoxide **2.58** could be synthesized from butenolide **2.30** *via* epoxidation of the C-6 –C-7 olefin. It was expected that the oxygen nucleophile would approach from the back face of **2.30** to give the desired

stereochemistry due to the steric congestion that hinders approach from the front face. The relative stereochemistry of sulfide **2.34** was shown by nOe studies to be a result of approach of thiophenoxide from the back face. This supports the hypothesis that the oxygen nucleophile would approach butenolide **2.30** from the back face to give the correct stereochemistry in epoxide **2.58**.

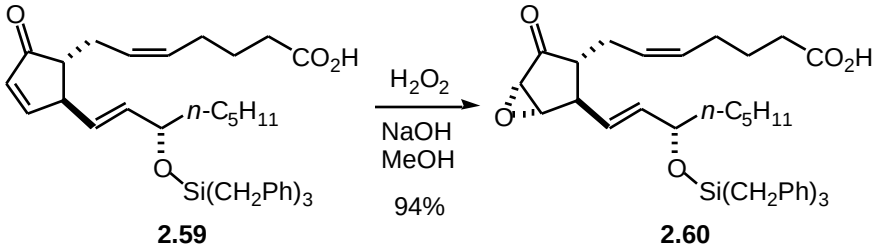
Scheme 2.14



Accordingly, efforts to effect the epoxidation of **2.30** commenced; however this transformation proved to be significantly more troublesome than

anticipated. When **2.30** was allowed to react with basic hydrogen peroxide, only starting material was recovered at low temperatures. Only unidentified material was isolated when the reaction was performed at higher temperatures. This was surprising in light of the fact that basic hydrogen peroxide has been used to epoxidize α,β-unsaturated carbonyl groups such as **2.59** to yield **2.60** (Scheme 2.15). This epoxidation strategy proved to be effective in the presence of other isolated olefins in **2.59** due to the high nucleophilicity of the peroxide anion matched with a relatively electron poor olefin.[78]

Scheme 2.15

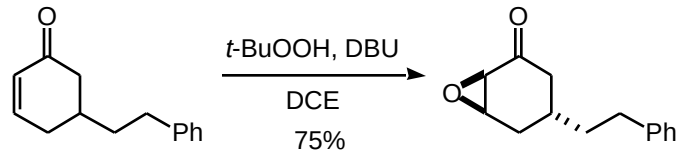


2.59 **2.60**

Alternatively, *t*-BuOOH in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was said to be highly effective in the epoxidation of electron poor olefins, and α,β-unsaturated-δ-lactones in particular in the epoxidation of lactone **2.61** to provide epoxide **2.62** (Scheme 2.16).[79]. However, when **2.30** was treated with *t*-BuOOH in the presence of DBU, ^{1}H NMR spectra indicated the enone was

still intact while the TMS and TBDPS groups had been cleaved, additionally, a change in the shift of the proton at C-3 may indicate that retroaldolization processes had occurred. Attempts to perform the epoxidation using *t*-BuOOH/DBU at lower temperatures to avoid the cleavage of the silyl protecting groups resulted in recovery of starting material. Numerous attempts to improve the reaction by altering the solvent and the reaction temperature, but these attempts did not provide the desired epoxide **2.58**.

Scheme 2.16

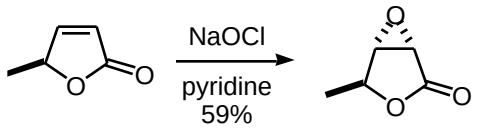


2.61 **2.62**

Hypochlorite in the presence of pyridine has also been used to oxidize α,β-unsaturated-δ-lactones (Scheme 2.17).[80,81] Unfortunately, treatment of butenolide **2.30** with hypochlorite in the presence of pyridine resulted in recovery of unidentified materials, although ^{1}H NMR spectra showed that the tertiary TMS group as well as the TBDPS group had been cleaved. Given the fact that harsher

conditions led to the decomposition of butenolide **2.30**, milder reaction conditions for the epoxidation of the C-6 – C-7 olefin were investigated.

Scheme 2.17



2.63 **2.64**

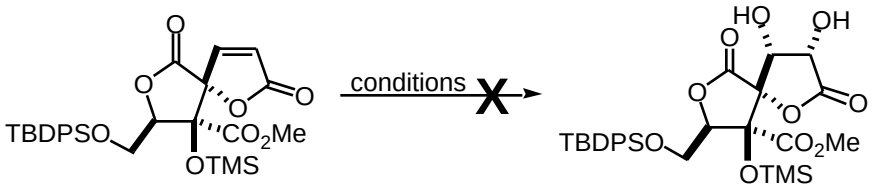
Both dimethyldioxirane and trifluoromethylmethyldioxirane are mild reagents that effect the epoxidation of olefins under neutral conditions.[82-85] Trifluoromethylmethyldioxirane is a more reactive reagent and because it can be generated *in situ*, it is more attractive option for the epoxidation of **2.30**. Yang had shown that trifluoromethylmethyldioxirane was capable of epoxidizing enones, though there were no examples of the epoxidation of butenolides. When butenolide **2.30** was exposed to trifluoromethylmethyldioxirane, starting material and a small amount of another compound were recovered from the reaction. The ^{1}H NMR spectra of this material revealed that the enone was still intact. Additionally, changes in the shifts of the C-3 protons were observed, and although the exact nature of the product was not determined, this may indicate that retroaldolization had taken place once the tertiary TMS group had been cleaved.

Since trifluoromethylmethyldioxirane was not a suitable reagent to effect the desired epoxidation, the lower reactivity of dimethyldioxirane (DMDO) might avoid the formation of unwanted side-products. Accordingly, DMDO was prepared according to literature procedure and used immediately after preparation. Unfortunately, reaction of DMDO with butenolide **2.30** gave only recovered starting material.

In addition to the aforementioned attempts at epoxidation, there was also work toward the dihydroxylation of **2.30** to provide **2.65** (Scheme 2.18). Since most methods of dihydroxylation would produce the *cis* diol, a selective deoxygenation would have been necessary to produce the required substitution for 7-deoxyzaragozic acid A (**2.56**). Furthermore, a deoxygenation/reoxygenation sequence would have been necessary to obtain the *trans* relationship present in zaragozic acid A (**1.54**). Attempted dihydroxylation of **2.30** with potassium permanganate resulted in the recovery of unidentified material. This was not terribly surprising since the butenolide **2.30** had thus far been rather sensitive to mild reaction conditions and permanganate is not a particularly mild reagent for

the dihydroxylation of olefins. The use of stoichiometric osmium tetraoxide in the presence of pyridine and *t*-butanol was equally unsuccessful.

Scheme 2.18

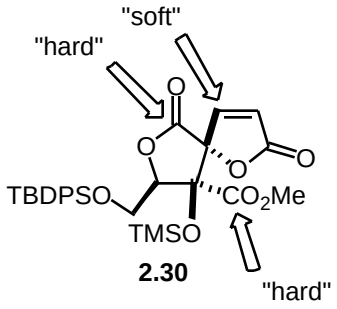


2.30 **2.65**

In light of the results thus far in the studies toward the functionalization of **2.30** by epoxidation or dihydroxylation, it seemed prudent to consider likely reasons lack of success. One of the more likely problems was the fact that the TMS protecting group on the tertiary alcohol was prone to cleavage, and the unprotected alcohol could serve as a trigger for retroaldolization. Previous work in the Martin group had already shown that in the case of butenolides **2.11**/**2.12**, the hydroxyl group δ to the butenolide carbonyl served as a trigger for retroaldolization (Scheme 2.4). Once the butenolide had been hydrogenated to provide bislactones **2.12**/**2.13**, the system was significantly more amenable to handling and manipulation. Unfortunately, the hydrogenation of butenolide **2.30** was not possible when attempting to epoxidize at C-6 – C-7.

Another likely issue with butenolide **2.30** was the fact that in addition to the butnolide, there were also two addiitonal elecrophilic sites that could react with oxygen nucleophiles (Figure 2.2). One way to address this point would be to utilize a softer nucleophile that could later be converted to the desired oxygen functionality. It was anticipated that a softer nucleophile would be more likely to add in a 1,4-fashion to the butenolide moiety, while the harder oxygen nucleophiles could easily react at either of the alternative electrophilic sites.

Figure 2.2

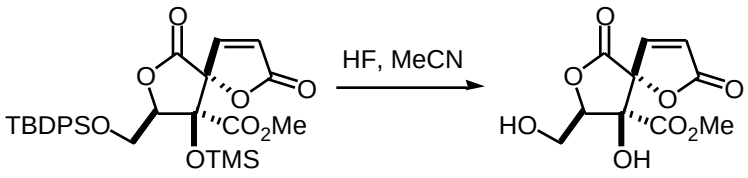


2.30

In an effort to address the issue of TMS cleavage, it was anticipated that both of the silyl protecting groups could be removed and replaced with a *p*-methoxyphenyl (PMP) acetal. This protecting group could later be removed under relatively mild conditions using DDQ in a CH_2Cl_2/H_2O mixture. In order to effect the deprotection of both silyl groups, **2.30** was first treated with TBAF.

Unfortunately, extensive decomposition of starting material was observed, even when acetic acid was added to buffer the system. With this in mind, alternative deprotection strategies were explored using HF. Treatment of **2.30** with aqueous HF effected the desired deprotection to yield **2.66** as shown by TLC analysis. Attempts to purify and characterize diol **2.66** resulted in decomposition of the material, so diol **2.66** was routinely carried on without purification. Thus, **2.30** was treated with HF and removal of the reaction solvent and treatment with dimethoxypropane in the presence of catalytic acid resulted in the recovery of small amounts of the diol while the remainder of the material had decomposed.

Scheme 2.19

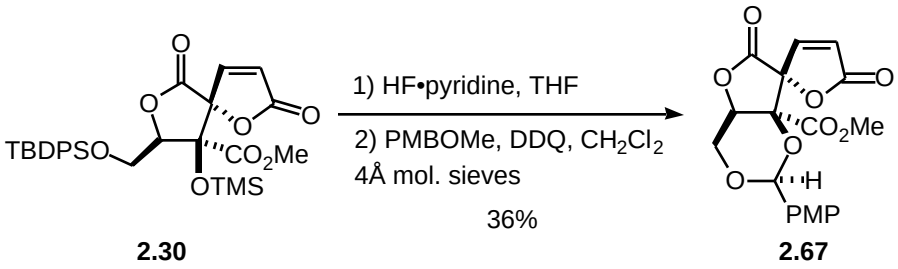


2.30 **2.66**

It was thought that the decomposition of **2.66** under the conditions for acetal formation (*p*-anisaldehyde/*p*-TsOH, *p*-methoxybenzaldehyde dimethyl acetal/*p*-TsOH, acetone/*p*-TsOH, or benzaldehyde/*p*-TsOH) may have been the result the presence of catalytic acid. Therefore neutral conditions for the

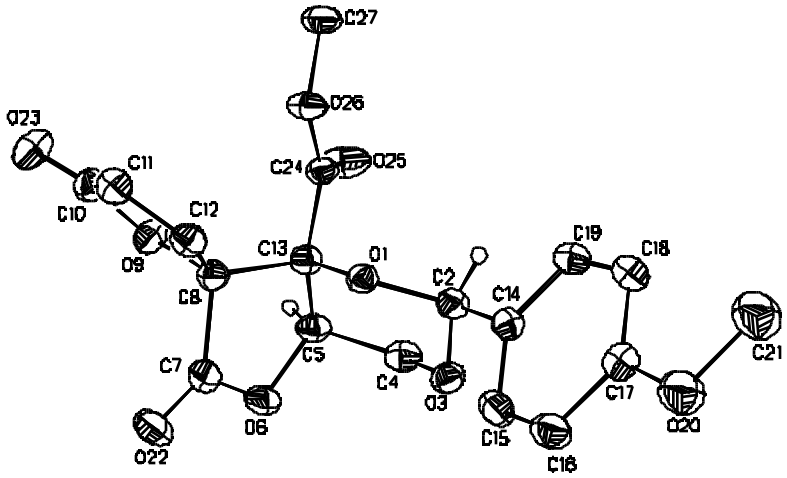
reprotection of the diol were investigated. Fortunately, Oikawa had shown that treatment of diols with PMBOMe in the presence of DDQ and molecular sieves produces the *p*-methoxyphenyl (PMP) acetal.[86] To this end, butenolide **2.30** was treated with HF to provide diol **2.66**, which was treated with *p*-methoxybenzyl methyl ether (PMBOMe) in the presence of DDQ to yield desired acetal **2.67**, albeit in low yield (<10%). Although the desired deprotection/reprotection scheme had been somewhat successful, it was anticipated that the yield could be improved. The deprotection protocol was altered slightly to enable the use of conditions that were nearly neutral using HF•pyridine instead of HF to give diol **2.66** (Scheme 2.20). Once the reaction was complete, it was found that an aqueous workup was not possible since the deprotected diol was rather soluble in the water layer. Hence, solid sodium bicarbonate was added to the reaction until all of the acid had been quenched as shown by the lack of CO_2 evolution. The resulting suspension was filtered to remove any solid, and crude **2.66** was reprotected using PMBOMe in the presence of DDQ to yield the desired acetal **2.67** in 44% yield as a single diastereomer. The structure of **2.67** was verified by X-ray crystallography (Figure 2.3).

Scheme 2.20



2.30 **2.67**

Figure 2.3

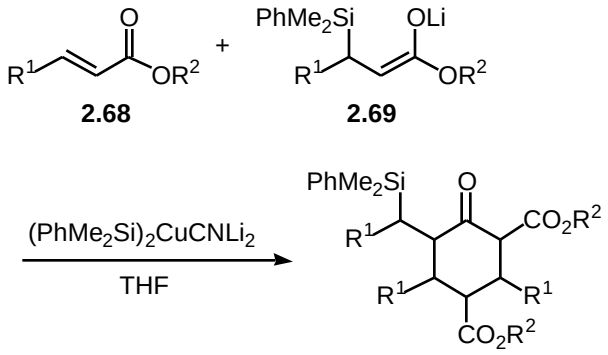


With acetal **2.67** in hand, it was possible to reinvestigate the epoxidation of the C-6 – C-7 olefin. However, reaction of **2.67** with *t*-BuOOH in the presence of DBU as described previously again led to extensive decomposition of **2.67**. Likewise, treatment of **2.67** with basic hydrogen peroxide gave many unidentified

products from the reaction. Acetal **2.67** was then treated with freshly prepared DMDO, which gave diol **2.66** as the major product resulting from cleavage of the acetal.

At this point it seemed as if the hard/soft interaction that had caused some concern earlier might be worth investigation. Fleming has done extensive work in developing dimethylphenylsilane as a hydroxyl group surrogate that can be unmasked to reveal the desired oxygen functionality.[87-93] The 1,4-addition of silyl groups to α,β-unsaturated ketones was accomplished using a cuprate that can be made from the corresponding silyllithium species. However, exposure of butenolide **2.67** to these conditions resulted in recovery of starting material. Fleming has also reported that the use of silyl zincates was superior to the cuprate because side products such as **2.70** have been isolated when the cuprate was used (Scheme 2.21). These products are a result of the reaction of intermediate enolate **2.69** with one or more equivalents of the α,β-unsaturated ester **2.68**.

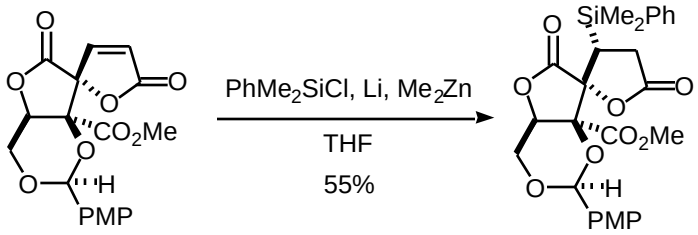
Scheme 2.21



2.68 **2.69** **2.70**

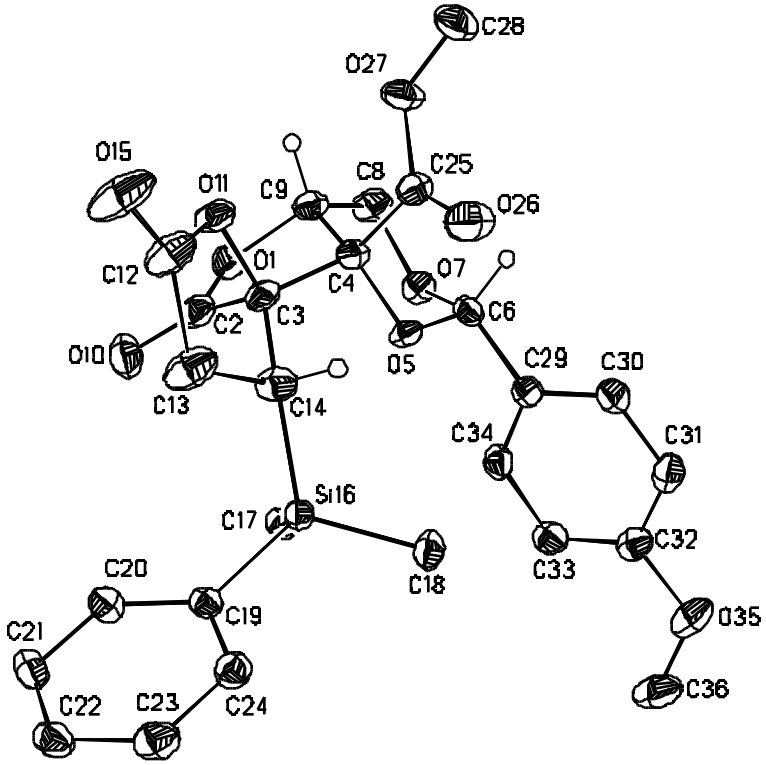
Although an oligomerization product analogous to **2.70** was never isolated from the reaction of the silyl cuprate with **2.67**, it seemed worthwhile to investigate use silyl zincate. Treatment of acetal **2.67** with $Me_2PhSiZnMe_2Li$, gave the desired silane **2.71** as a single diastereomer (Scheme 2.22). The stereochemistry of **2.71** was verified by X-ray crystallography (Figure 2.4). The stereoselectivity in the reaction of **2.67** was thought to be due to the steric congestion provided by the PMP acetal.

Scheme 2.22



2.67 **2.71**

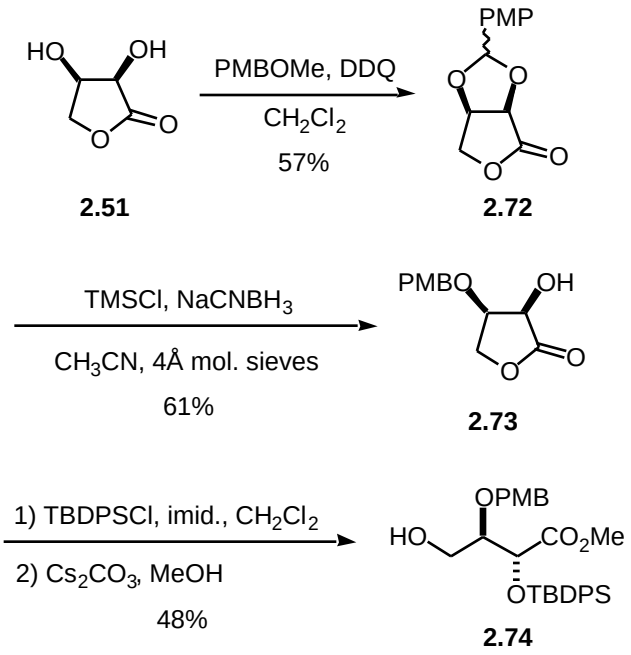
Figure 2.4



With silane **2.71** in hand, a more direct route to the PMP acetal was developed that avoided the cumbersome deprotection/reprotection sequence used previously (Scheme 2.20). Accordingly, the PMP acetal **2.72** was prepared from erythronolactone **2.51** in modest yield according to a procedure developed Dr. Phil Kym (Scheme 2.23). Formation of acetal **2.72** followed by regioselective opening with $TiCl_4$ in the presence of $NaCNBH_3$ provided **2.73** in good yield. Opening of the acetal with the desired regioselectivity was accomplished more consistently with TMSCl in the presence of $NaCNBH_3$ to yield **2.73**.[94] Methodological studies by Samuelsson of the opening of the PMP acetal on carbohydrates with $NaBH_3CN$ in the presence of TMSCl yielded one regioisomer while opening of the PMP acetal in the presence of TFA produced the other isomer. It was suggested that the regioselectivity in their system was derived from the fact that the silane is a more sterically demanding electrophile than the proton derived from TFA. While this steric argument may be the basis of selectivity in Samuelsson's work, application of this hypothesis to the opening of **2.72** does not seem reasonable. There were no experiments performed using $NaBH_3CN$ in the presence of TFA or with $NaBH_3CN$ alone gain further insight

into the source of regioselectivity in the opening of acetal **2.72**. Protection of the remaining alcohol and methanolysis of the lactone under basic conditions provided methyl ester **2.74**.

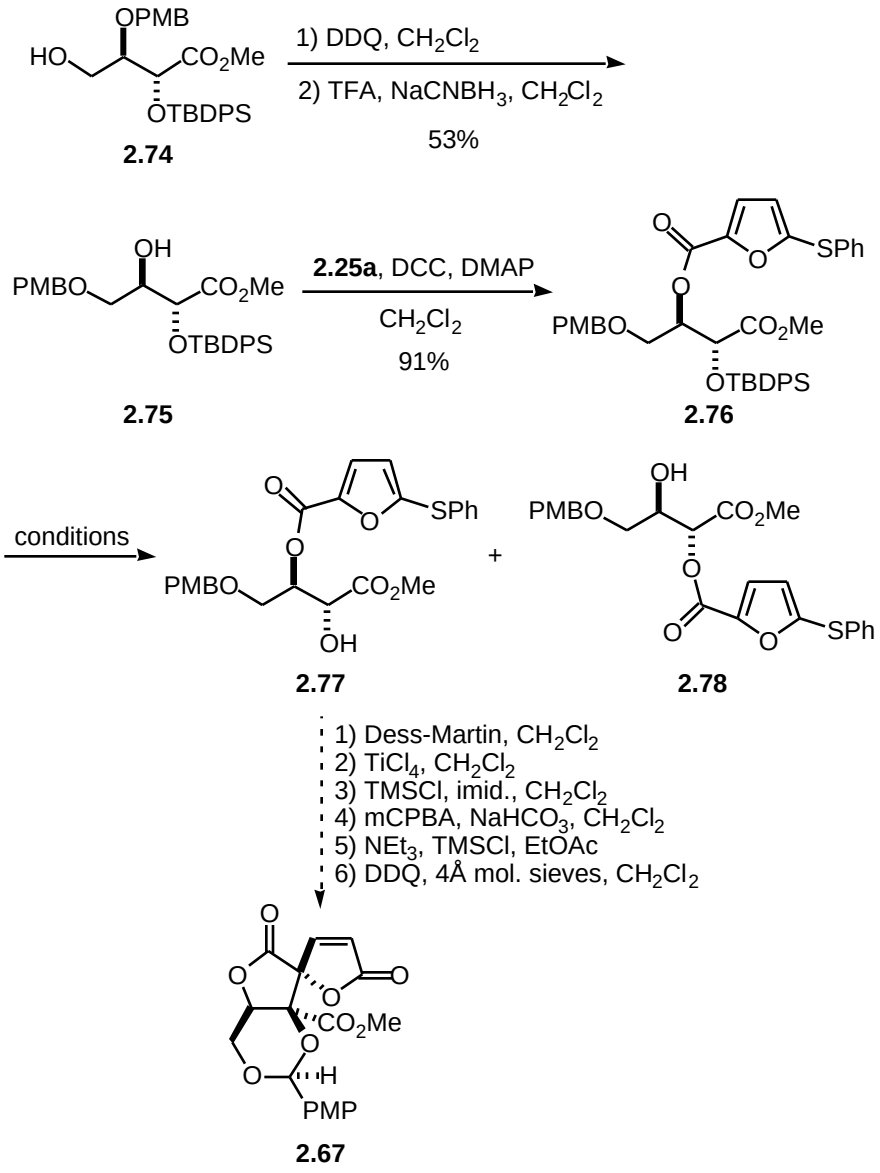
Scheme 2.23



Since spontaneous migration of the PMB in **2.74** from the secondary to the primary position was not possible under the conditions of the methanolysis, a two step method to move the PMB protecting group was developed (Scheme 2.24). Thus, reaction of **2.74** with DDQ formed an acetal that was opened regioselectively with trifluoroacetic acid and sodium cyanoborohydride to yield

2.75. Coupling of the alcohol **2.75** with furoic acid **2.25a** provided **2.76** in high yield. Unfortunately, it was not possible to effect complete removal of the TBDPS group under various conditions (TBAF, HF/MeCN, and HF•pyr) complete deprotection to give **2.77**. Additionally, attempts to purify **2.77** by flash chromatography led to a significant amount of acyl migration to provide **2.78**. Since suitable conditions for the deprotection of **2.76** could not be found, efforts toward the development of the alternate route to **2.67** were concluded.

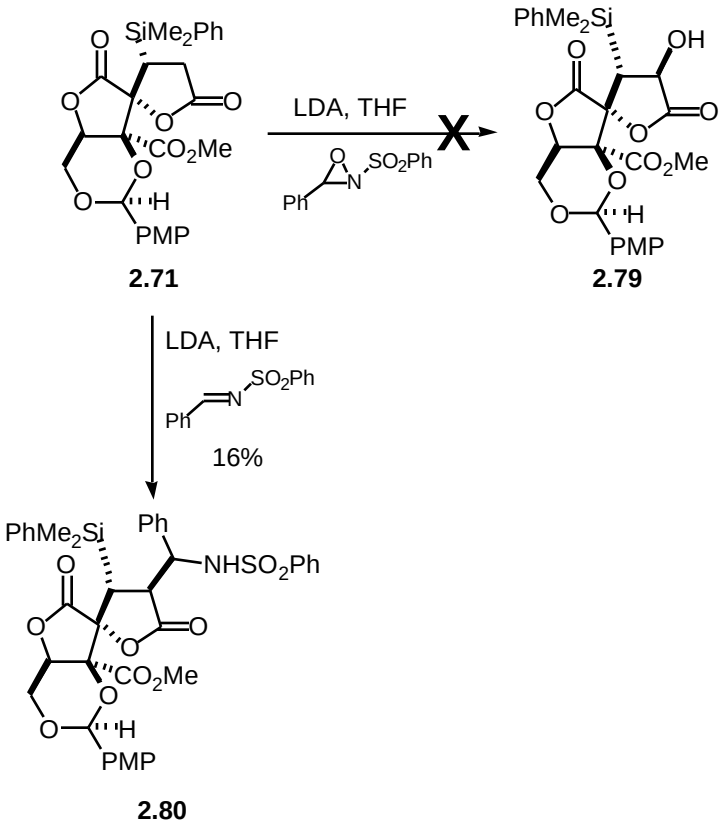
Scheme 2.24



Despite the fact that the alternative route to acetal **2.67** was not successful, efforts to oxidize the C-6 – C-7 olefin were continued. With the hydroxy

surrogate in place in **2.71**, it was anticipated that zaragozic acid A (**1.54**) could be a possible target if α-hydroxylation of the lactone **2.71** was accomplished. The first candidate that was explored for the installation of the additional oxygen was Davis reagent.[95] Since this reagent is not commercially available, it was prepared according to literature procedure. Formation of the enolate of lactone **2.67** and addition of Davis reagent gave recovered starting material along with small amounts of **2.80** derived from the imine impurities in the Davis reagent. In the absence of imine addition, only starting material was isolated (Scheme 2.25). Since no desired product **2.79** was formed, enolate formation was verified by treating **2.67** with LDA in THF followed by quenching with D_2O. The ^1H NMR showed 68% deuteration of **2.67**, which verified that the enolate was being formed, but not forming desired product **2.79** when exposed to the Davis oxaziridine. Purification of the Davis oxaziridine and treatment of **2.67** with purified reagent yielded only recovered starting material.

Scheme 2.25

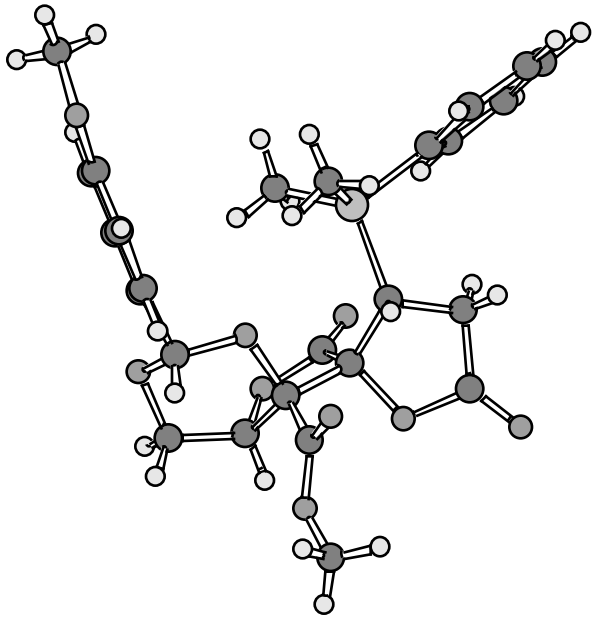


Another option to effect α-oxidation of a carbonyl group is MoOPH, a reagent that was developed by Vedejs and utilizes a molybdenum peroxide as the active oxidation species.[96,97] Reaction of MoOPH with the enolate of lactone **2.67** afforded only recovered starting material. A third tactic to effect oxidation of lactone **2.67** was the utilization of LDA/molecular oxygen as reported by Wasserman.[98] Unfortunately, use of this method resulted in complex reaction

mixtures. A two step oxidation procedure was explored in which the silyl enol ether is formed and treated with mCPBA and acid to give the desired α-hydroxy carbonyl compound.[99] Various attempts to form the silyl enol ether using TMSCl/LDA, TBSCl/LDA, TMSOTf/NEt_3, TIPSOTf/NEt_3, or TBSOTf/NEt_3 were unsuccessful and therefore the Rubottom oxidation could not be used. Experiments using the crude silyl enol ether in the second step of the Rubottom oxidation were also unsuccessful.

After close inspection of the X-ray crystallographic depiction of **2.67**, it was thought that the difficulties in the oxidizing C-7 might have been due to steric hindrance provided by the dimethylphenylsilyl group (Figure 2.5). This insight led to attempts to unmask the C-6 hydroxy surrogate to give bislactone **2.81**. It was anticipated that the α-hydroxylation could be accomplished after unmasking the hydroxyl group.

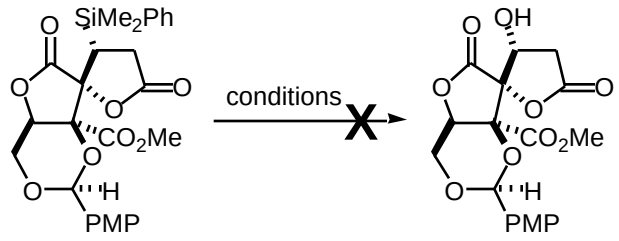
Figure 2.5



Conversion of the dimethylphenylsilyl group is most commonly accomplished in a two-step operation involving protodesilylation of the phenyldimethylsilane and rearrangement sequence with peracid. Fleming has demonstrated that both steps can be completed in a one-pot procedure using any of four methods.[100] The first one-pot procedure involves use of mercury which is electrophile to effect the aromatic desilylation, in the presence of the peracid. Treatment of **2.71** under these conditions resulted in the recovery of starting material even after prolonged reaction times or higher temperatures (Scheme 2.26). Another option to effect the oxidation was the using catalytic mercury in

the presence of catalytic palladium acetate to avoid use of stoichiometric quantities of mercury. Unfortunately, use of palladium acetate caused the removal of the *p*-methoxybenzylidene acetal from **2.71** to provide the diol.

Figure 2.26

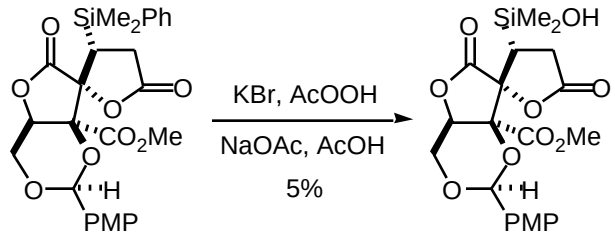


2.71 **2.72**

The remaining two options for the oxidation of the silane involve either the use of bromine or bromine generated *in situ* to effect the aromatic desilylation. The best results were found with the *in situ* generation of bromine from KBr. The reaction of **2.72** with bromine (generated from the reaction of KBr and peracid) accomplished the required aromatic desilylation, however the subsequent rearrangement in the presence of peracid would not proceed, therefore resulting in low yields of silanol **2.73**. Attempts to push the reaction using higher temperatures or longer reaction times did not result in either higher yields of the

silanol or any indication of the desired hydroxyl. The majority of the material from the reaction was recovered starting material **2.71**.

Scheme 2.27



2.71 **2.73**

Since the one-pot procedures were not successful, two-pot operations that utilize fluoride as the electrophile to accomplish the protodesilylation were examined.[91] Unfortunately, this method for protodesilylation generally requires the use of rather harsh reagents such as tetrafluoroboric acid-diethyl etherate or boron triflouoride-acetic acid, both of which gave complete decomposition of the starting material to a black tar. At the time that this research was being conducted, Fleming had reported failure in attempts to prepare aryl-silyl reagents by the Gilman cleavage of disilanes with lithium. Included in this report were several examples including *o*-methoxyphenyl, *p*-methoxyphenyl, tolyl, and 5-methylfuryl silanes. Given these results, the preparation of the *o*- or *p*-methoxyphenyl derivatives was not attempted, despite the fact that it was

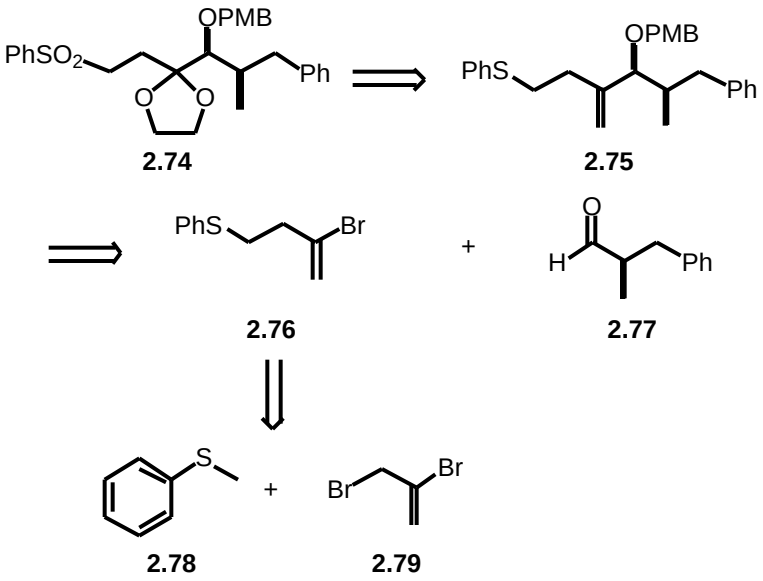
anticipated that these derivatives might be more ammenable to oxidation than the phenyldimethylsilane. Recently, Corey has reported the preparation of the *o*-methoxyphenyldimethylsilane group as a hydroxy surrogate.[Lee, 2001 #446] Corey was able to prepare this derivative from lithiation of *o*-methoxyphenyldimethylsilyl chloride rather than the Gilman cleavage of the disilane. The advantage of Corey's hydroxy surrogate, is that it can be cleaved under more mild conditions than its dimethylphenylsilyl counterpart. The use of the *o*-methoxyphenyldimethylsilyl group to give a compound analogous to **2.71** may have allowed the cleavage of the surrogate under mild conditions to yield **2.72**.

Since oxidation of silane **2.71** was unsuccessful, it was thought that perhaps addition of the C-1 side chain and conversion to the zaragozic acid core might allow the oxidation at C-6 and/or C-7. In such compounds, the C-6 and C-7 centers should be more sterically accessible once the rearrangement to the zaragozic acid core was accomplished. Synthesis of the C-1 side chain was then examined with the idea that the completed side chain would be incorporated into

2.71 analogously to the incorporation of C-1 side chain **2.43** into **2.35** using a sulfone anion addition to the C-1 center (Scheme 2.11).

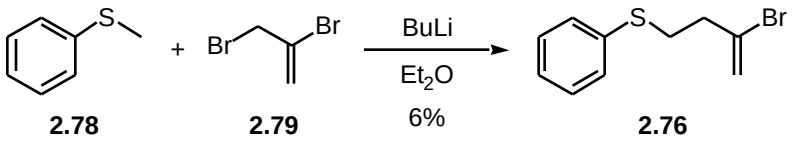
The completed sulfone side chain **2.74** may be synthesized from **2.75** after both the olefin and sulfide had been subjected to treatment with ozone (Scheme 2.28). Olefin **2.75** may be made from the addition of vinyl bromide **2.76** to known aldehyde **2.77** as the key step.[69] Since the desired diastereomer of the addition of **2.76** and **2.77** was the Cram product, it was anticipated that this might be the major product of the reaction. In the event that the Cram product was not produced selectively, there have been several tactics that have been developed in which chiral ligands of various types are used to promote selectivity in the alkylations of aldehydes (*vide infra*). While there are examples of the enantioselective addition of simple vinyl anions to aldehydes in the presence of chiral ligands, most notably by Oppolzer,[101,102] the addition of more elaborate vinyl anions to aldehydes is not well known.[103] Finally, the desired bromide was envisioned to come from the reaction of thioanisole (**2.78**) with 2,3-dibromopropene (**2.79**). This synthesis would constitute a very short and efficient synthesis of the zaragozic A C-1 side chain.

Scheme 2.28



The preparation of the C-1 side chain began with the alkylation of thioanisole (**2.78**) with 2,3-dibromopropene (**2.79**) to give bromide **2.76** (Scheme 2.29). This alkylation provided, only 6% yield of the desired product **2.76** as a mixture of the desired bromide and recovered thioanisole. Extensive experimentation with different solvents and temperatures led to no improvement in the outcome of the reaction. Additonally, transmetallation of the lithium anion to the zincate or cuprate led to no improvement in the results.

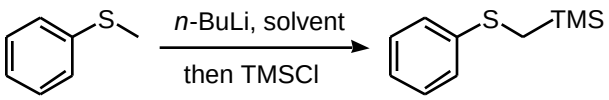
Scheme 2.29



2.78 **2.79** **2.76**

In light of these results, experiments were performed to ascertain the extent to which the anion of thioanisole was being produced. This was accomplished by quenching the anion with TMSCl to give sulfide **2.80** (Scheme 2.30).[104] When **2.78** was treated with *n*-BuLi in Et_2O, **2.80** was obtained in only 64% (as determined by ^1H NMR). If either DABCO or TMEDA were added to the reaction, the yield of **2.80** improved dramatically to 92% (Table 2.3).[105] When either DABCO or TMEDA were added to the reaction of the anion of thioanisole (**2.78**) with 2,3-dibromopropene (**2.79**), no product isolated from the reaction (Scheme 2.29). In fact, upon addition of dibromopropene (**2.79**) to a solution of thioanisole (**2.78**), *n*-BuLi, and DABCO or TMEDA, the reaction mixture immediately turned to a dark brown tar presumably as a result of the polymerization of **2.79**.

Scheme 2.30



2.78 **2.80**

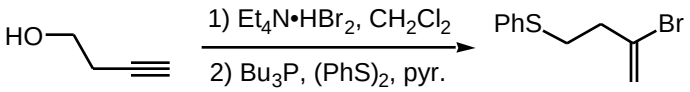
Table 2.3

Solvent	Additive	Yield (%)
Et_2O	none	64
THF	DABCO	92
Et_2O	TMEDA	88

In light of these negative results, another route to the side chain was explored that began with 3-buyne-1-ol rather than dibromobutene. Sulfide **2.76** was generated from butyn-1-ol by treating the alkyne with tetra-*n*-butylammonium bromide to yield the vinyl bromide as described by Ley (Scheme 2.31).[106] The vinyl bromide was then treated with diphenyl disulfide in the presence of tributylphosphine and pyridine to give the desired bromide **2.76**. Although the process was not high yielding, it was facile to perform these

reactions on a large scale since both the intermediate vinyl bromide and sulfide **2.76** could be purified by distillation.

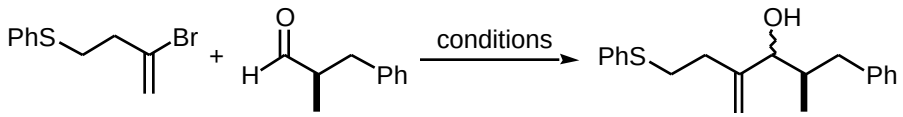
Scheme 2.31



2.81 29% **2.76**

Treatment of the known aldehyde **2.77** with the lithium anion of **2.76** gave a mixture (1:1) of both diastereomers of **2.82** in poor to modest yields, even after transmetallation of **2.76** to the zinc anion (Scheme 2.32).[69] Molander has reported the diastereoselective addition of organoytterbium reagents to carbonyl substrates. This tactic was reported to favor formation of the Cram product due to the imposing steric bulk of lanthanide complexes.[107] Therefore, transmetallation of the lithium anion of **2.76** was accomplished using ytterbium triflate. Addition of the required aldehyde **2.77** to a solution of the anion produced the desired alcohol **2.82**, albeit in low yield with no diastereoselectivity as determined by the integration of the methyl group in the ^{1}H NMR spectra of **2.82**.

Scheme 2.32



2.76 **2.77** **2.82**

Oppolzer has developed a strategy for the enantioselective addition of substituted vinylzinc species to aldehydes in the presence of *N*-methylephedrine with good overall selectivity (73 - 98% ee). Thus, the lithium anion of **2.76** was transmetallated to the zinc anion followed by addition of lithiated *N*-methylephedrine and aldehyde **2.77**.[101,102] Unfortunately, under these conditions, only **2.77** and reduced **2.76** were recovered from the reaction (Scheme 2.32).

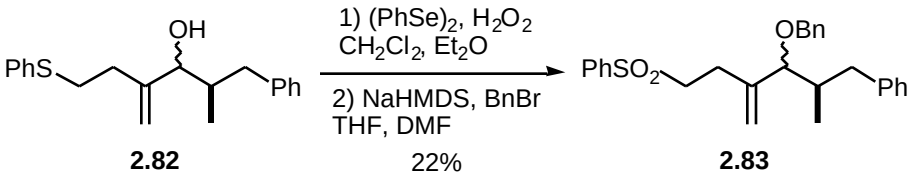
Seebach has also developed methods for the enantio- and diastereoselective additions of dialkylzinc compounds to aldehydes in the presence of titanium-TADDOLate complexes.[108-114] Thus, tetraphenyl-TADDOL was first treated with $(i\text{PrO})_4\text{Ti}$ to form the titanate complex. The lithium anion of **2.76** was then treated with dimethyl zinc to effect the desired transmetallation and the addition of the TADDOL titanate complex and aldehyde **2.77** gave a 19% yield of alcohol **2.82** as a mixture (1:1) of diastereomers. Use of the tetra(2-naphthyl)-TADDOL which was reported to be more effective than the tetraphenyl

TADDOL with aliphatic aldehydes in the addition of **2.76** to **2.77** gave **2.82** in 27% yield with no diastereoselectivity.

Kobayashi has developed a strategy that allows the enantio- and/or diastereoselective addition of dialkylzinc compounds to aldehydes using a C_2-symmetric disulfonamide titanates as a chiral Lewis acid.[115] Treatment of cyclohexyldisulfonamide with $(i\text{PrO})_4\text{Ti}$ to give the titanate, and addition to the zinc anion of **2.76** was followed by addition of the aldehyde resulting in a low yield of desired product **2.82** with no diastereoselectivity.

Although the diastereoselectivity of the addition of **2.76** to aldehyde **2.77** did not look very promising, work toward the completion of the side chain was conducted with the hope that the diastereomers could eventually be separated. To this end, sulfide **2.82** was oxidized to the sulfone in the presence of the olefin using phenylselenic acid, which was made from diphenyl diselenide and hydrogen peroxide (Scheme 2.33).[116] Subsequent protection of the alcohol gave **2.83** as a mixture (1:1) of diastereomers. Separation of the diastereomers by either column chromatography or HPLC was not possible.

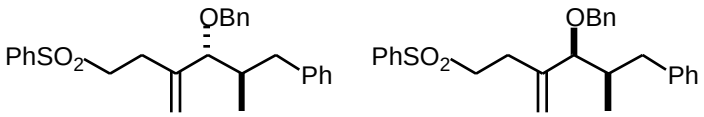
Scheme 2.33



2.82 **2.83**

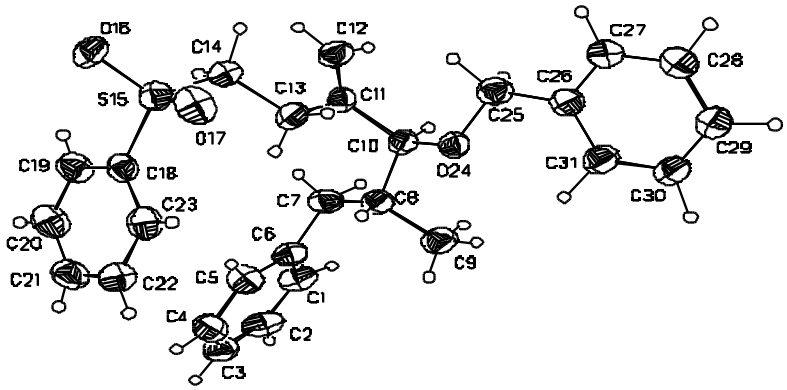
Benzyl ether **2.83** was a crystalline solid, and selective recrystallization could be used to separate the two diastereomers. After two recrystallizations, a mixture (14:1) of diastereomers was obtained, and the mother liquor composed of a 1:2 ratio of diastereomers by ^{1}H NMR. Further recrystallizations of either the 1:2 mixture or the 14:1 mixture of diastereomers of **2.83** did not result in any improvement of the diastereomeric ratio. In an effort to establish the relative stereochemistry of each diastereomer, a crystal isolated from the 14:1 mixture was submitted for X-ray crystallographic analysis. The crystal structure revealed that the relative stereochemistry was the undesired *anti* diastereomer **2.84** (Figure 2.5, Figure 2.6). While the aforementioned routed to the C-1 side chain was indeed short, it was unfortunately not diastereoselective. Furthermore, the two diastereomers were not easily separable, which made the synthesis of **2.84** unusable in the synthesis of 7-deoxyzaragozic acid A (**2.56**).

Figure 2.6



2.84 **2.85**

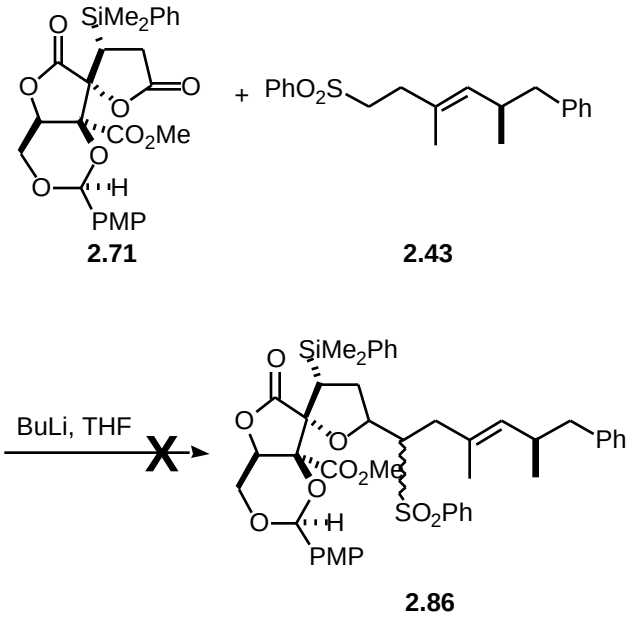
Figure 2.7



Although the approach to the zaragozic acid A C-1 side chain was not diastereoselective, the C-1 side chain described for the synthesis of 6,7-dideoxysqualestatin H5 (**2.47**) was used to explore further manipulations of silane **2.71**. Addition of the side chain **2.43** to **2.71** was then attempted by addition of **2.71** to a solution of the dianion of **2.43** (Scheme 2.34). Unfortunately, the addition of the side chain **2.43** to lactone **2.71** was not successful, resulting in recovery of starting material. Although it is only speculation, the fact that side

chain **2.43** did not add to lactone **2.71** was thought to be due to the steric bulk of the silyl group. In light of these results, it was concluded a route that necessitated the functionalization of C-6 at a late stage in the synthesis was no longer a feasible possibility for this project, therefore a number of alternatives were investigated.

Scheme 2.34



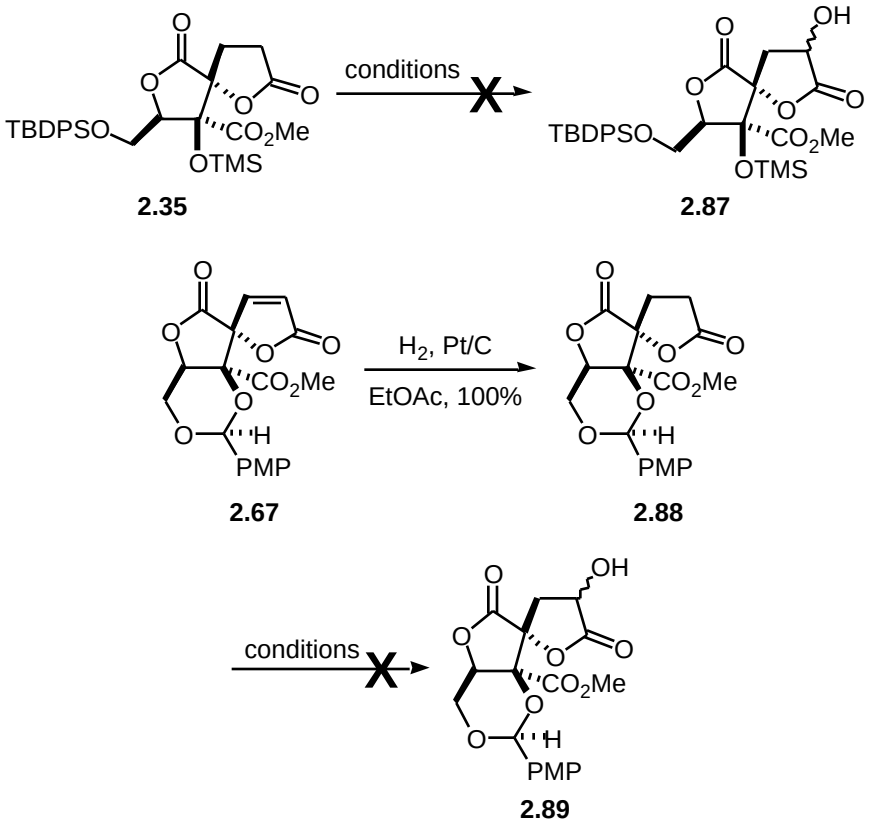
2.71 **2.43**

2.86

Although the oxidation of **2.71** at C-7 in the presence of the silyl group was unsuccessful, it was thought that installation of a hydroxyl group at C-7 might be more facile in the absence of a bulky group at C-6. Initial attempts at oxidation focused on anionic additions to bislactones **2.35** and **2.88** (Scheme

2.35). Treatment of the enolate of either **2.35** or **2.88** with Davis reagent resulted in recovered starting material. Attempts were also made with either the enolate of **2.35** or **2.88** using Davis reagent in the presence of either HMPA or crown ethers. These reactions provided recovered starting material under mild reaction conditions, while multiple unidentified products were recovered when the reactions were performed under more forcing conditions. Similarly, attempts at making the silyl enol ether of **2.35** or **2.88** with TMSOTf/NEt_3, TBSOTf/NEt_3, or TIPSOTf/NEt_3 in an effort to use the Rubottom oxidation resulted in recovered starting material. Finally, attempts were made to oxygenate both bislactones **2.35** and **2.88** with LDA/molecular oxygen, but only complex reaction mixtures were obtained.

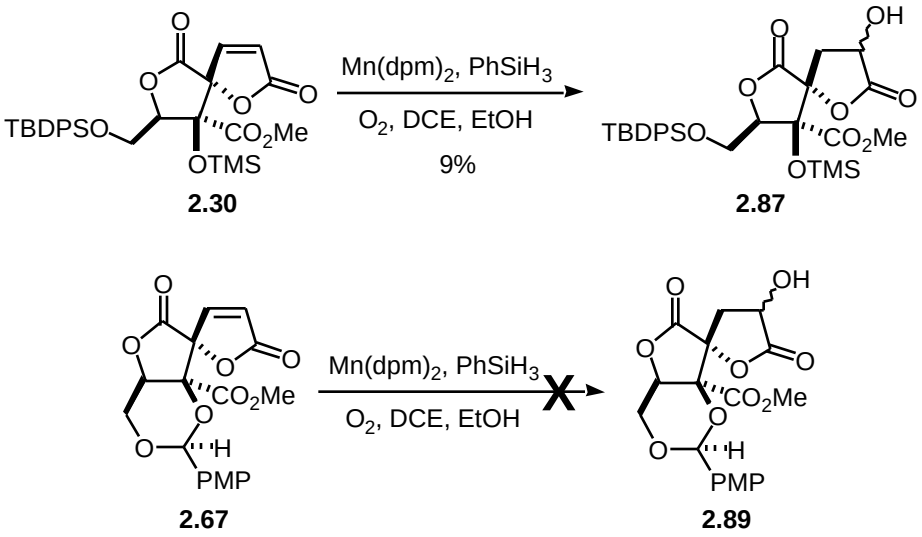
Scheme 2.35



Alternatively, an approach employing radical chemistry was considered as shown in Scheme 2.36. To this end, both **2.30** and **2.67** were treated with $Mn(dpm)_2$ in the presence of phenylsilane and oxygen,[117-119] to give a 10% yield of the desired product **2.90**. Unfortunately, alcohol **2.90** was contaminated with an unidentified impurity. The PMP acetal butenolide **2.67** gave only deprotected

diol and starting material upon treatment with $Mn(dpm)_2$ in the presence of phenylsilane and oxygen.

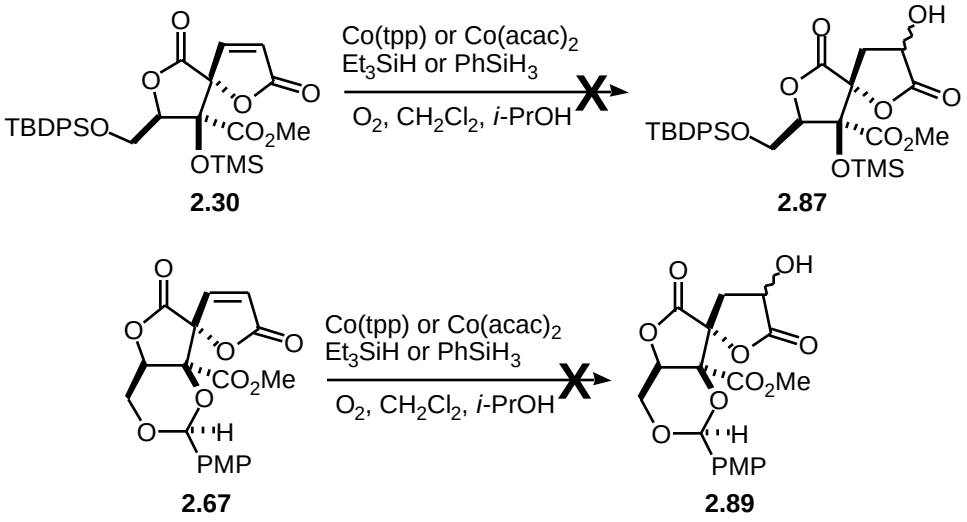
Scheme 2.36



In addition to the aforementioned manganese catalyst, a cobalt-based catalyst has been reported by Matsushita to convert α,β-unsaturated esters into α-hydroxyesters.[120] Accordingly, both silyl butenolide **2.30** and *p*-methoxybenzylidene acetal **2.67** were exposed to $Co(acac)_2$ or Co(tpp) in the presence of either Et_3SiH or $PhSiH_3$ and oxygen (Scheme 2.37). Unfortunately, only starting material was recovered from the reaction. Since all attempts to elaborate install oxygen functionality failed on **2.30** and **2.67**, it was hoped that

some functionality could be brought in with the furoic acid portion from the beginning of the synthesis and further manipulated at a later time. More specifically, it was anticipated that the furoic acid portion could be incorporated already functionalized as the bromide at the C-6 position.

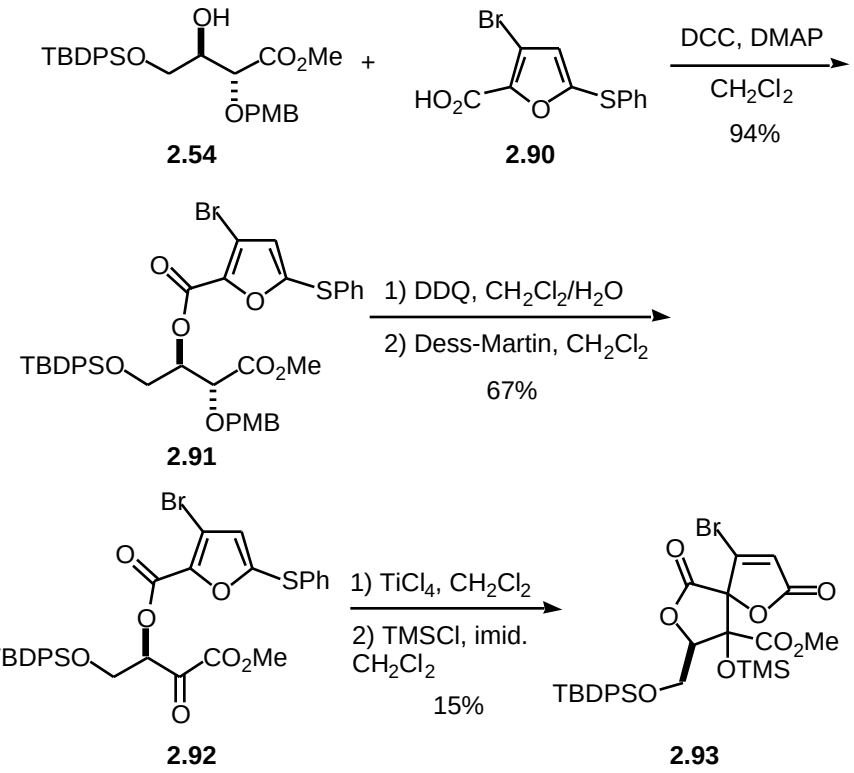
Scheme 2.37



Incorporation of the bromide into the furoic acid moiety began with the synthesis of known bromofuroic acid **2.90**,[121-123]. Coupling of **2.90** with alcohol **2.54** gave ester **2.91** in 94% yield (Scheme 2.38). Subsequent DDQ deprotection of **2.91** and Dess-Martin oxidation gave the α-ketoester **2.92**, which was then treated with $TiCl_4$ and TMSCl to give the cyclized product **2.93** with unknown stereochemistry in 15% yield. Unfortunately, butenolide **2.93** was an oil, so

purification using column chromatography was necessary. However, chromatography was accompanied by decomposition of **2.93** on silica gel, resulting in very low yields. It was not possible to isolate clean material even after repeated chromatography resulted in significant loss of material, rendering this route unfavorable. In light of all of the results thus far, it was concluded that studies toward the synthesis of 7-deoxyzaragozic acid A were terminated.

Scheme 2.38



In conclusion, studies toward the synthesis of 7-deoxyzaragozic acid A (**2.56**) included the improvement of the synthesis of α-ketoester **2.25** from an 18% overall yield to 28% while also reducing the amount of chromatography needed for the intermediates. Efforts toward the elaboration of butenolide **2.30** revealed that oxygen nucleophiles were incompatible with the system, most often resulting in the recovery of starting material or complex mixtures. This issue was effectively addressed by the use of a silane nucleophile, which was added in a

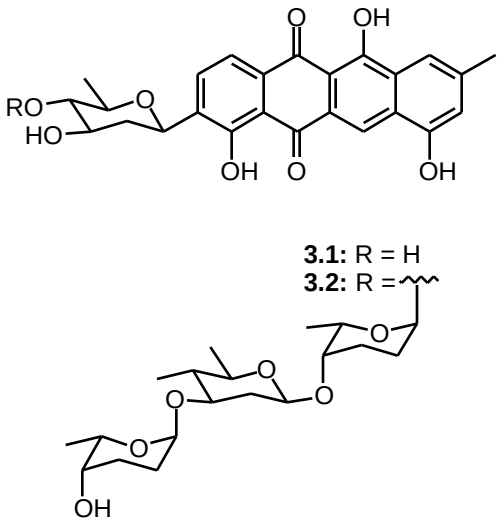
Michael fashion to the butenolide **2.30** with the correct stereochemistry. While this was proof of concept for elaboration of the core system, it was unfortunate that the silane **2.71** could not be converted to the desired oxygen functionality. Additionally, efforts were made to incorporate functionality at C-6 from the beginning of the synthesis in the form of a brominated furoic acid derivative **2.90**, however the Lewis acid mediated cyclization of this species was low yielding with unknown stereochemical outcome. Work toward the synthesis of the zaragozic acid A C-1 side chain gave the desired alcohol **2.82**; however, there was no diastereoselectivity in the addition of **2.76** to **2.77**. The two diastereomers were not separable which made this approach to the C-1 side chain impractical for the synthesis of 7-deoxyzaragozic acid A.

CHAPTER 3. TOWARD THE TOTAL SYNTHESIS OF GALTAMYCINONE

3.1 BIOLOGICAL ACTIVITY OF THE ANGUCYCLINS

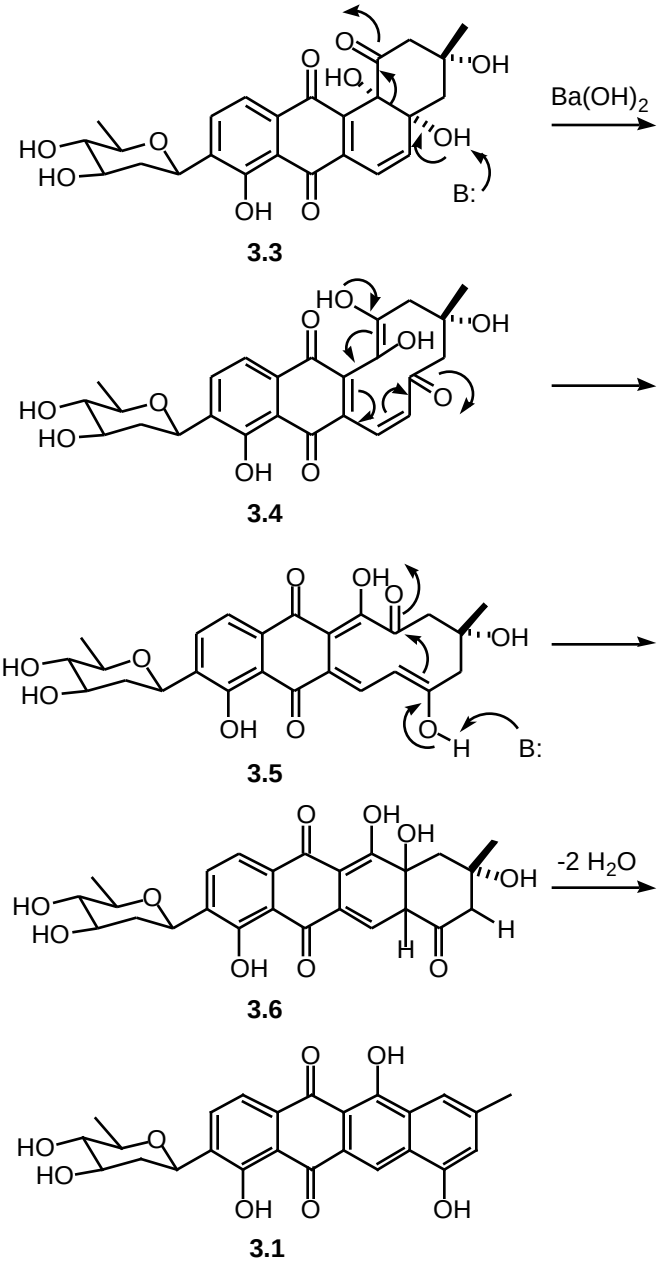
The angucycline group of natural products constitutes the largest family of *C*-aryl glycoside antibiotics including examples such as galtamycinone (**3.1**) and galtamycin (**3.2**) that are derived from a decaketide chain and formed *via* the polyketide biosynthetic pathway (Figure 3.1). These compounds are attractive synthetic targets not only because of the antibiotic and antitumor activities but also because of the synthetic challenge involved in the assembly of the linear tetracyclic framework and the formidable challenge involved in attaching the sugar moiety to the tetracyclic core.

Figure 3.1



The name angucycline is derived from the characteristic four-ring aglycone carbon framework, which is assembled in an angular manner to give compounds with the core structure **3.3**. Although both galtamycin and galtamycinone do not posses the angular framework, they are still classified as members of the angucyclin family since they are biosynthetically derived from an angucycline framework such as that in aquayamycin (**3.3**)(Scheme 3.1). Treatment of aquayamycinone with $Ba(OH)_2$ resulted in the isolation of galtamycinone through ring-expanded intermediates **3.4** and **3.5** to provide **3.6** that was converted to **3.1** through a double dehydration sequence.[124]

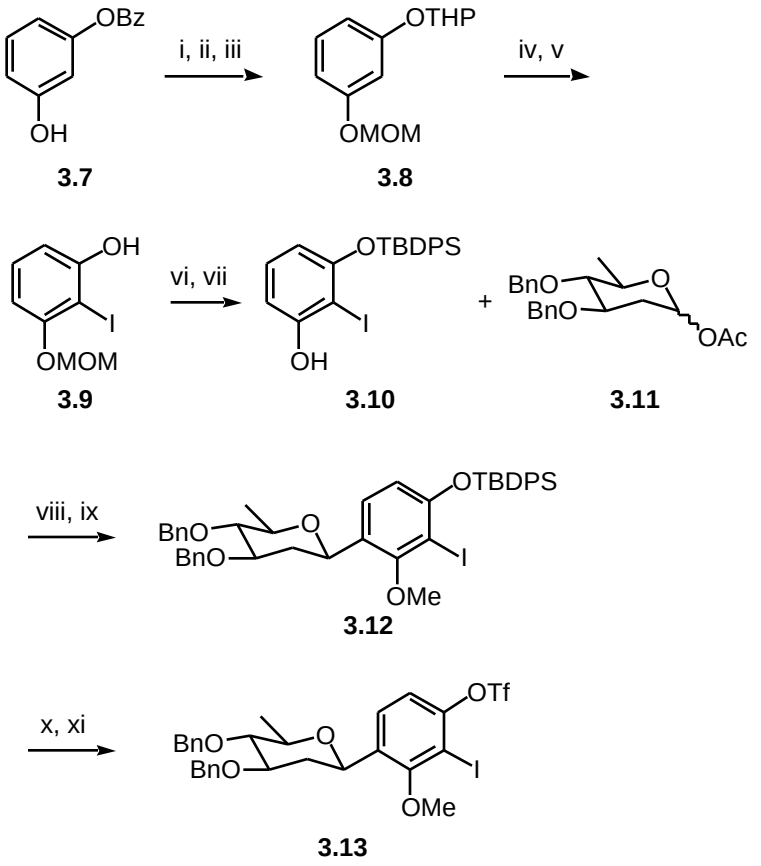
Scheme 3.1



3.2 SUZUKI'S TOTAL SYNTHESIS OF GALTAMYCINONE

Thus far, only one total synthesis of galtamycinone has been reported.[125,126] The general synthetic strategy of Suzuki's approach involved an $O \rightarrow C$-glycoside rearrangement and a regioselective benzyne cycloaddition to assemble the tetracyclic core. The total synthesis commenced with the preparation of the required benzyne precursor **3.13** from phenol **3.9** which was prepared in five steps from resorcinol monobenzoate (**3.7**) (Scheme 3.2).[127] A protection/deprotection sequence then gave **3.10**. Glycoside **3.11** was attached *via* an $O \rightarrow C$-glycoside rearrangement to give **3.12** after methylation. Suzuki has developed this $O \rightarrow C$-glycoside rearrangement method for the *O*-glycosidation of phenols, where the reaction proceeds through the initial formation of an *O*-glycoside that rearranges, in the presence of Lewis acids, to a *C*-glycoside.[128-135] Finally, removal of the protecting group and conversion to the triflate gave the benzyne precursor **3.13**.

Scheme 3.2

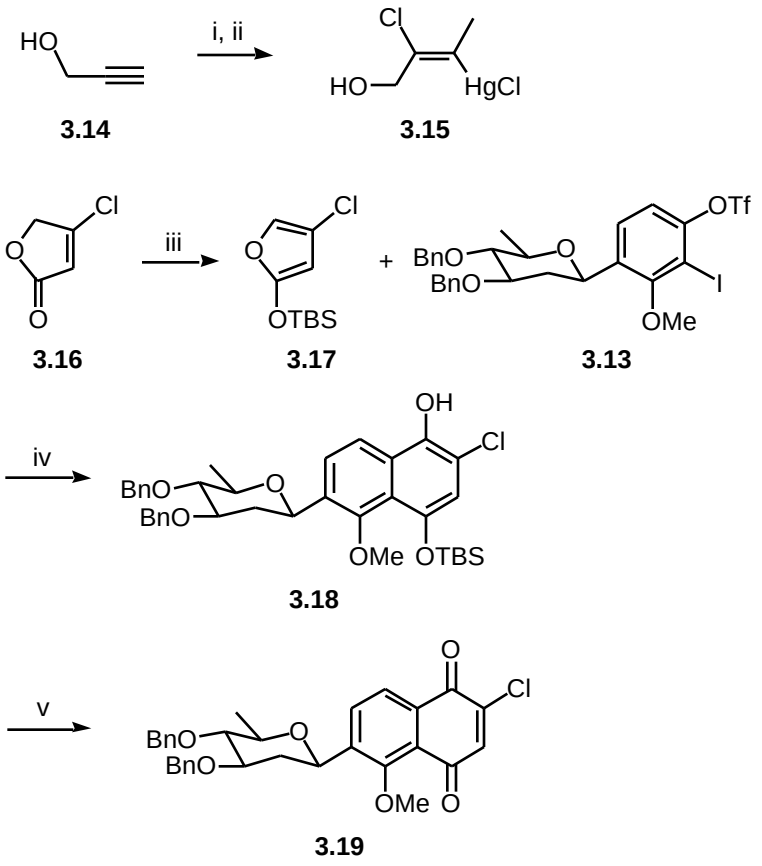


i) MOMCl, *i*-Pr_2NEt/CH_2Cl_2, quant.; ii) 3 M aq. NaOH/MeOH, quant.;iii) DHP, PPTS, CH_2Cl_2, 95%; iv) BuLi, hexane, then I_2, Et_2O; v) PPTS, EtOH, 81%; vi) TBDPSCl, imid., DMF, 92%; vii) 3 M H_2SO_4, aq. dioxane, 98%; viii) Cp_2HfCl_2, $AgClO_4$, CH_2Cl_2, 95%; ix) NaH, $(MeO)_2SO_2$, THF, DMF, 96%; x) TBAF, THF, 100%; xi) *i*-Pr_2NEt, Tf_2O, CH_2Cl_2, 99%

The synthesis of the diene required for the cycloaddition began with butenolide **3.16** that was made from acetylene **3.14** in two steps (Scheme 3.3). Butenolide **3.16** was converted to silyl enol ether **3.17**. The benzyne

cycloaddition was then performed with **3.17** and **3.13** to give **3.18** regioselectively. The inductive polarization induced in the benzyne by the methoxy group on **3.13** along with the electron donating silyl group on **3.17** were suggested to be responsible for the high regioselectivity.[136] Oxidation of the hydroquinone provided chlorojuglone **3.19**, which set the stage for the second regioselective cycloaddition in the synthesis.

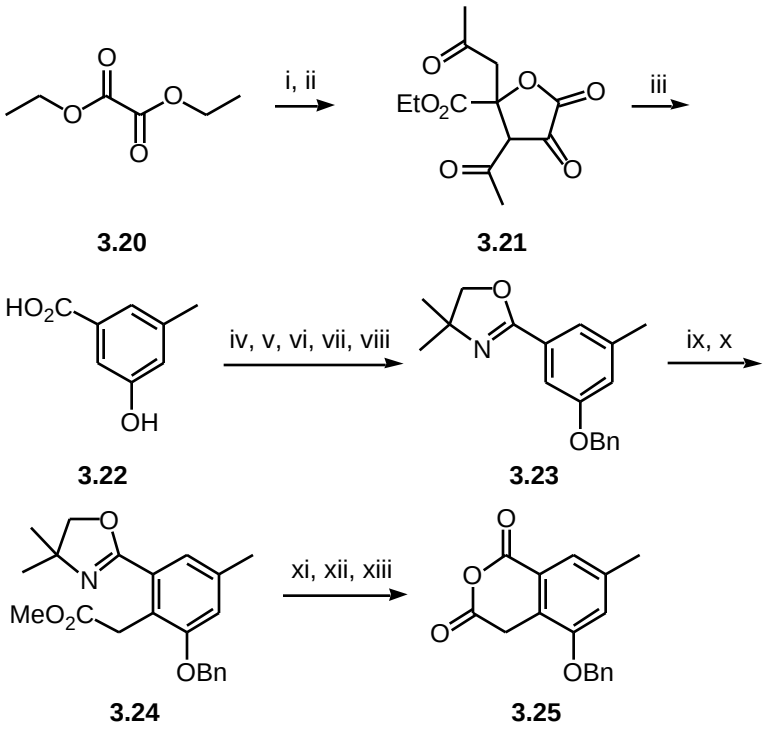
Scheme 3.3



i) $HgCl_2$, H_2O; ii) CO, Li_2PdCl_4, 96%; iii) TBSOTf, Et_3N, CH_2Cl_2, 74%; iv) *n*-BuLi, THF; v) CAN, aq. MeCN, 91%

The requisite diene precursor **3.25** was prepared in thirteen steps beginning with diethyl oxalate (**3.20**). Conversion of **3.20** to benzoic acid **3.22** was then accomplished in three steps (Scheme 3.3). Benzyl protection of **3.22** was followed by formation of the oxazoline gave **3.23**. Desired anhydride **3.25** was then made in five steps from **3.23**.

Scheme 3.4

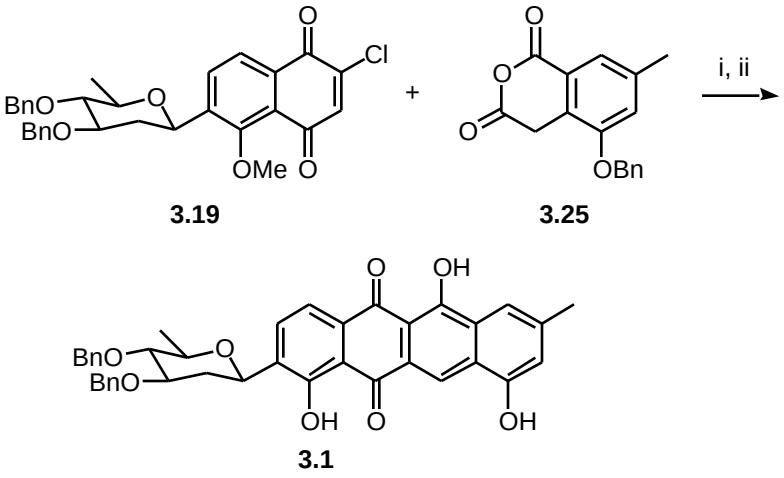


i) EtOH, Na, acetone; ii) HOAc, H_2O, 80%; iii) MgO, H_2O, 42%;
iv) BnBr, K_2CO_3, acetone; v) aq. NaOH, MeOH, 91%; vi) $SOCl_2$;
vii) $H_2NC(Me)_2CH_2OH$, CH_2Cl_2; viii) $SOCl_2$, 87%;
ix) BuLi, THF, then MeI, 55%; x) BuLi, THF, $ClCO_2Me$, 61%;
xi) $ClCO_2Bn$, aq. $NaHCO_3$, CH_2Cl_2; xii) NaOH, MeOH;
xiii) MeCOCl, acetone, 89%.

Regioselective cycloaddition of chlorojuglone **3.19** with anhydride **3.25** was accompanied by spontaneous decarboxylation to provide the desired cycloadduct as a single regioisomer (Scheme 3.5). Global deprotection then gave galtamycinone (**3.1**). The total synthesis of (**3.1**) was accomplished in 15 steps (longest linear sequence) and 31 total steps with an overall yield of 6%. The

synthesis showcased the $O \rightarrow C$-glycoside rearrangement that provided **3.12** in high yield with excellent selectivity for the β-anomer. Additionally, Suzuki obtained excellent regioselectivity in the benzyne cycloaddition to assemble the sugar-juglone moiety. The second cycloaddition to assemble the tetracyclic core was strikingly similar to the cycloaddition previously used by Tamura in the synthesis of SS-228R (**3.33**) (*vide infra*) which makes this reaction unoriginal, though well executed.

Scheme 3.5



i) NaH, THF, 90%; ii) BBr_3, CH_2Cl_2, 82%

3.3 SYNTHESES OF SS-228R

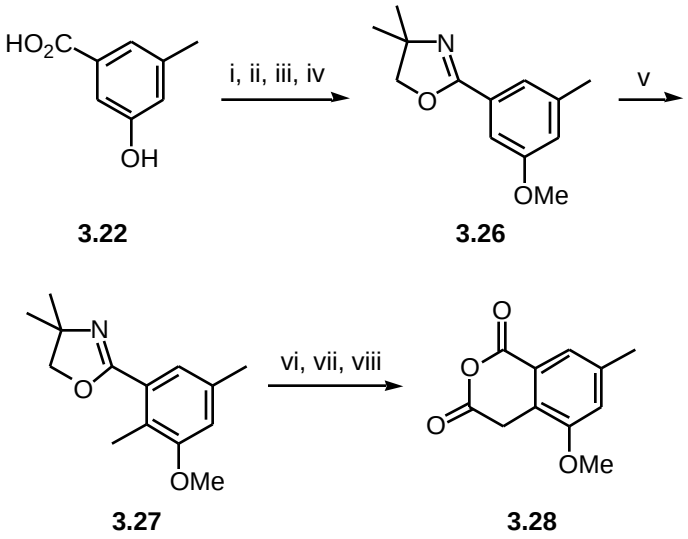
In addition to galtamycin (**3.2**) and galtamycinone (**3.1**) , SS-228R (**3.33**) is another natural product that contains the same tetracyclic framework. The structure of **3.33** differs from both **3.1** and **3.2** inasmuch as there is no *C*-glycoside present. To date, there have been three total syntheses of SS-228R.

3.3.1 Tamura's Synthesis of SS-228R

The first total synthesis of **3.33** was reported by Tamura in 1985 and utilized a base-catalyzed, regioselective cycloaddition of a homophthalic

anhydride as the key step.[137] The required anhydride **3.28** was synthesized analogously to **3.25** with the only difference between the two syntheses being the nature of the phenolic protecting group (Scheme 3.6).

Scheme 3.6

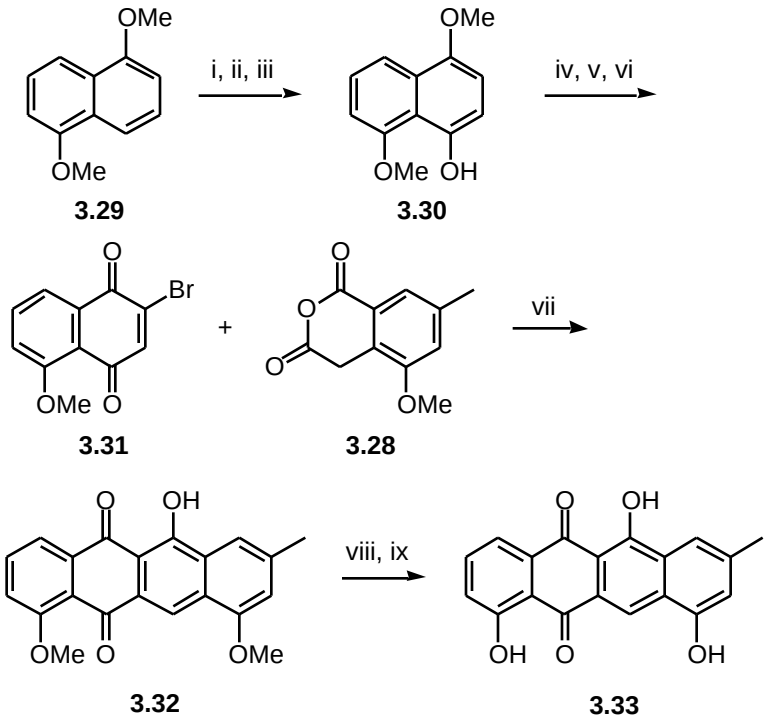


i) $(MeO)_2SO_2$, 30% NaOH, 78%; ii) $SOCl_2$;
iii) $HOCH_2C(CH_3)NH_2CH_3$, CH_2Cl_2; iv) $SOCl_2$, 86%;
v) BuLi, THF, MeI, 57%; vi) BuLi, THF, $MeOC(O)OMe$, 45%;
vii) 4.5 N HCl, 71%; viii) CH_3COCl, acetone, 81%.

Bromojuglone **3.31** was made in six steps from dimethoxynaphthalene (**3.29**)(Scheme 3.7). Treatment of anhydride **3.28** with NaH followed by addition of bromojuglone **3.31** gave the desired cycloadduct **3.32** in good yield as a single regioisomer. Treatment of **3.32** with boron tribromide provided the monomethyl SS-228R where the methyl group adjacent to the juglone had been cleaved, while

the other remained intact. Treatment once more with boron tribromide in a separate reaction under identical conditions provided SS-228R (**3.33**) in good yield. Tamura was also able to produce the other regioisomer in the cycloaddition, using an alternative diene precursor, which made it possible to verify the structure of SS-228R by comparison with authentic spectral date of **3.33**.

Scheme 3.7



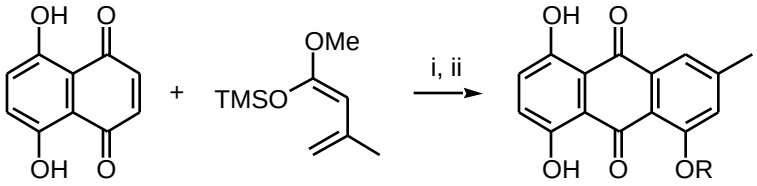
i) DMF, $PhCH_3$, $POCl_3$, 93%; ii) mCPBA, CH_2Cl_2;
iii) KOH, MeOH/THF, 77%; iv) CAN, MeCN/H_2O, 85%;
v) Br_2, $CHCl_3$ vi) AcOH, EtOH, 80%; vii) NaH, THF, 87%;
viii) BBr_3, CH_2Cl_2, 95%; ix) BBr_3, CH_2Cl_2, 51%

3.3.2 Cameron's Syntheses of SS-228R

The second total synthesis of SS-228R (**3.33**) by Cameron was also published in 1985 and commenced with the addition of diene **3.35** to commercially available, albeit expensive ($57.40/g), naphthoquinone **3.34**. After aromatization of the intermediate with DDQ, a mixture (7.3:1) of **3.36** and **3.37**

was obtained (Scheme 3.8).[138] Isomer **3.37** was deprotected and used to synthesize regioisomeric SS-228R to assist in proving the correct structure for the natural product, while **3.36** was carried on toward the synthesis of SS-228R.

Scheme 3.8

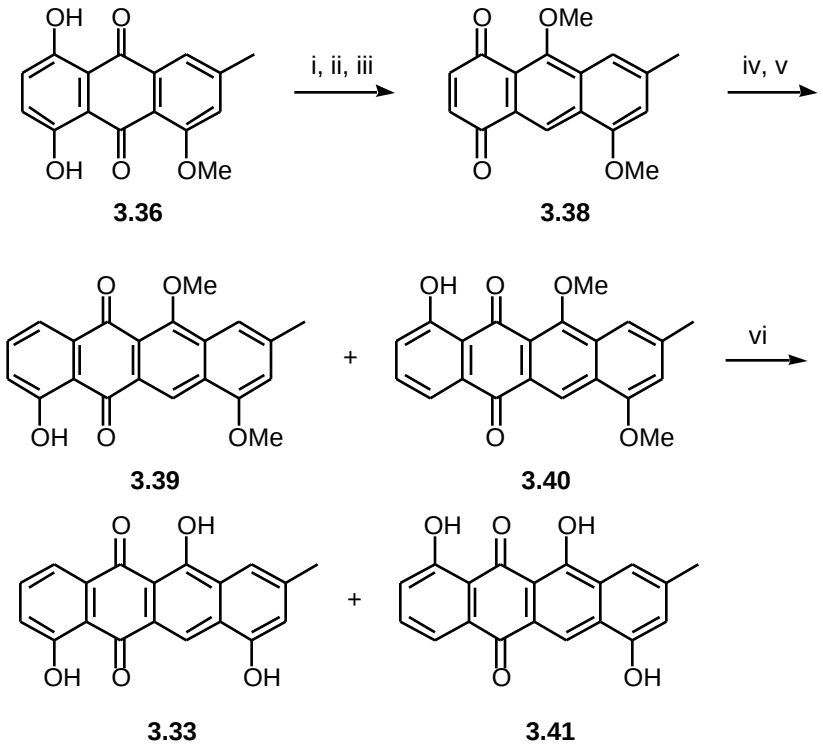


3.34 **3.35** **3.36:** R = Me
3.37: R = H

i) cycloaddition; ii) DDQ, 80% **3.36** 11% **3.37**

Isomer **3.36** was reduced with zinc borohydride and the intermediate anthracene was oxidized with Jones reagent and the phenol methylated to provide quinone **3.38** (Scheme 3.9). A second cycloaddition gave the desired cycloadduct as a mixture (1.7:1) of inseparable regioisomers **3.39** and **3.40**. Both of the regioisomers were then carried on through the global deprotection to give SS-228R (**3.33**) and regioisomer **3.41**, which were separable by column chromatography.

Scheme 3.9

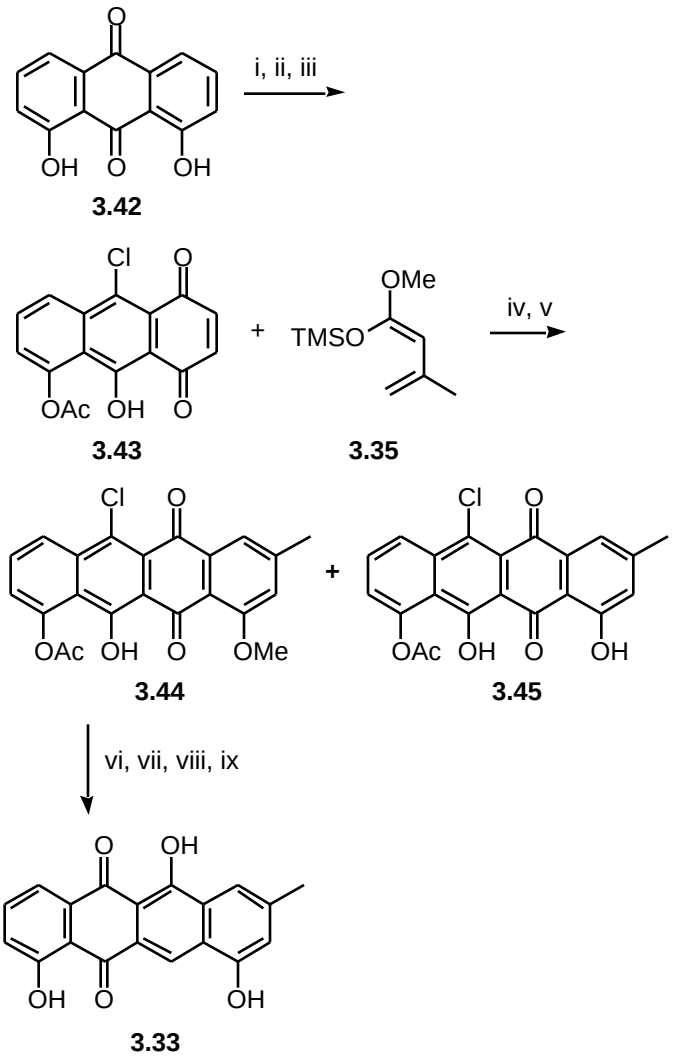


i) $ZnBH_4$, DME; ii) chloranil, 65%; iii) MeI, Ag_2O, $CHCl_3$, 95%;
iv) $TMSOCH{=}CHCH{=}CH_2$, CH_2Cl_2; v) Jones reagent, 29% **3.39**, 17% **3.40**
vi) BBr_3, CH_2Cl_2, 52% **3.33**, 38% **3.41**

Cameron later published a second synthesis of SS-228R that also employed a cycloaddition to assemble the tetracyclic core.[139] This synthesis began with chloroanthraquinone **3.43**, which can be made from commercially available 1,8-dihydroxy-9,10-anthraquinone (**3.42**) (Scheme 3.10).[140] Cycloaddition of anthraquinone **3.43** with diene **3.35** followed by aromatization with DDQ gave **3.44** as the only regioisomer along with a small amount of

deprotected **3.45**. Conversion of the chloro substituent to the required oxygen functionality was then accomplished by treatment with TFA. A reduction/oxidation sequence was then performed to give the desired dihydroxynaphthacenequinone. The synthesis of SS-228R (**3.33**) was then concluded by a global deprotection.

Scheme 3.10



i) oleum, H_3BO_3, then H_2O; ii) $SOCl_2$, 86%; iii) Ac_2O, pyr
iv) cycloaddition; v) DDQ, 71% **3.44**, 26% **3.45**; vi) TFA, 78%;
vii) H_2, PtO_2, EtOAc; viii) chloranil, 20%; ix) BBr_3, CH_2Cl_2, 75%

Although there have been three total syntheses of SS-228R (**3.33**), the primary goal of Cameron's was the proof of the structure of SS-228R. The first of

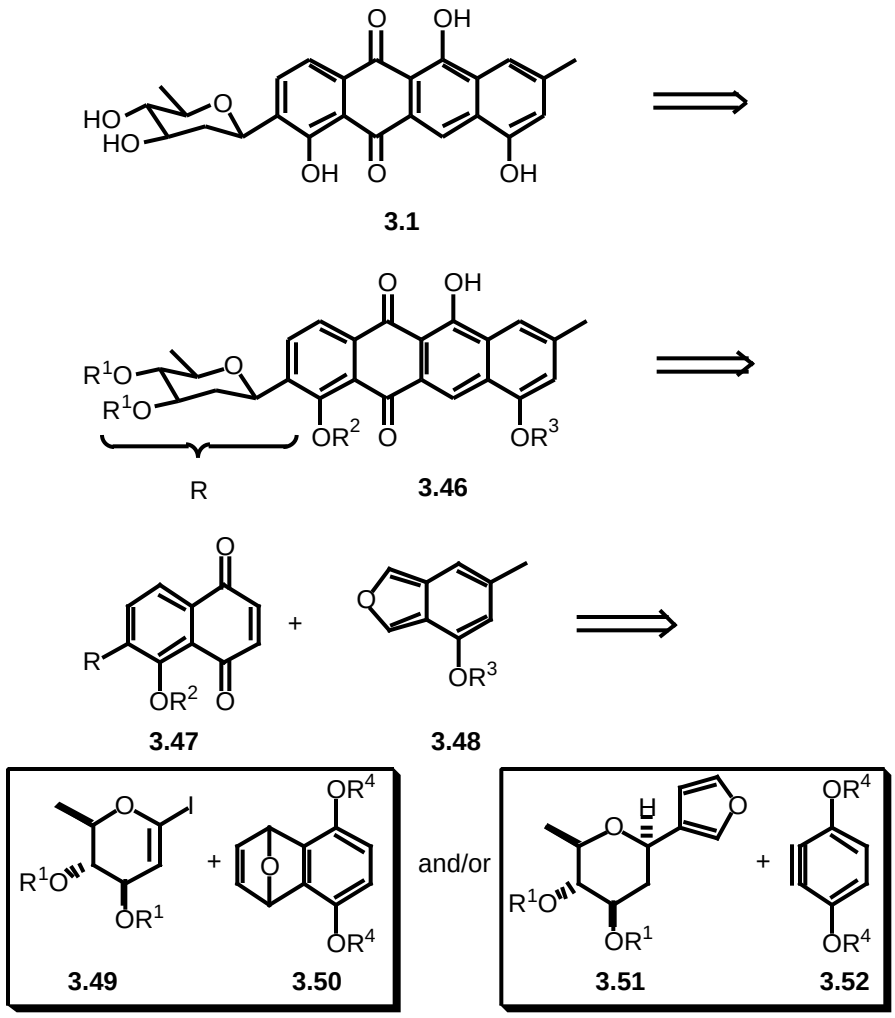
Cameron's syntheses of **3.33** began with an expensive starting material while the second synthesis began with an advanced intermediate, which made both of these syntheses rather synthetically uninteresting. Tamura's synthesis of **3.33**, however, was a true exercise in synthetic chemistry, and he developed a synthetic strategy, involving the regioselective cycloaddition of a phthalic anhydride that was later used in Suzuki's total synthesis of galtamycinone.

3.4 PREVIOUS WORK IN THE MARTIN GROUP

Previous work in the Martin group directed toward the total synthesis of **3.1** featured a benzyne cycloaddition as the key step to assemble the tetracyclic carbon frame (Scheme 3.11). It was envisioned that galtamycinone could be made from the cycloaddition of juglone **3.47** with an isobenzofuran **3.48**, which would be generated *in situ* by dehydration of a lactol. Juglone **3.47** could be made in either of two ways; the first involved a S_N2' palladium-catalyzed addition of vinyl iodide **3.49** to the bridged ether **3.50** followed by aromatization. The second method features a benzyne cycloaddition of sugar-furan **3.51** to dimethoxybenzyne **3.52** followed by opening of the bridging ether and

aromatization. Both of these strategies have been developed in the Martin group and provide a unified strategy for the synthesis of the four major subgroups of *C*-aryl glycosides.[141]

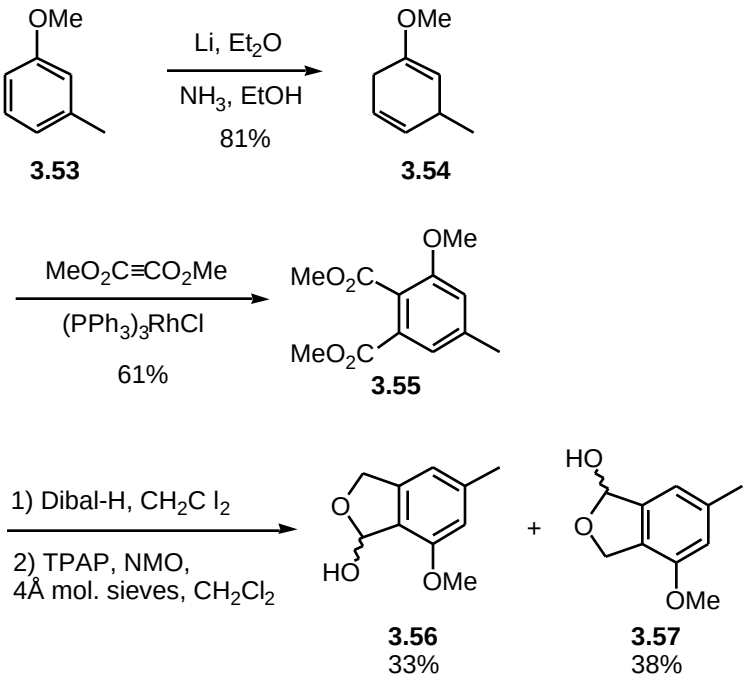
Scheme 3.11



Initial studies actually focused on the natural product SS-228R (**3.33**) as a model system. It was anticipated that similar, if not identical conditions could be used in the synthesis of the tetracyclic core of galtamycinone (**3.1**). Accordingly, methylanisole (**3.53**) was subjected to a Birch reduction to provide diene **3.54**.[142]

A cycloaddition was then performed whereby the diene was generated *in situ* from **3.54** and subsequently reacted with dimethyl acetylenedicarboxylate (Scheme 3.12).[143] Reduction of both esters was then accomplished with Dibal-H to form a diol that was oxidized with TPAP to provided a separable mixture (1:1.2) of lactols **3.56** and **3.57**.

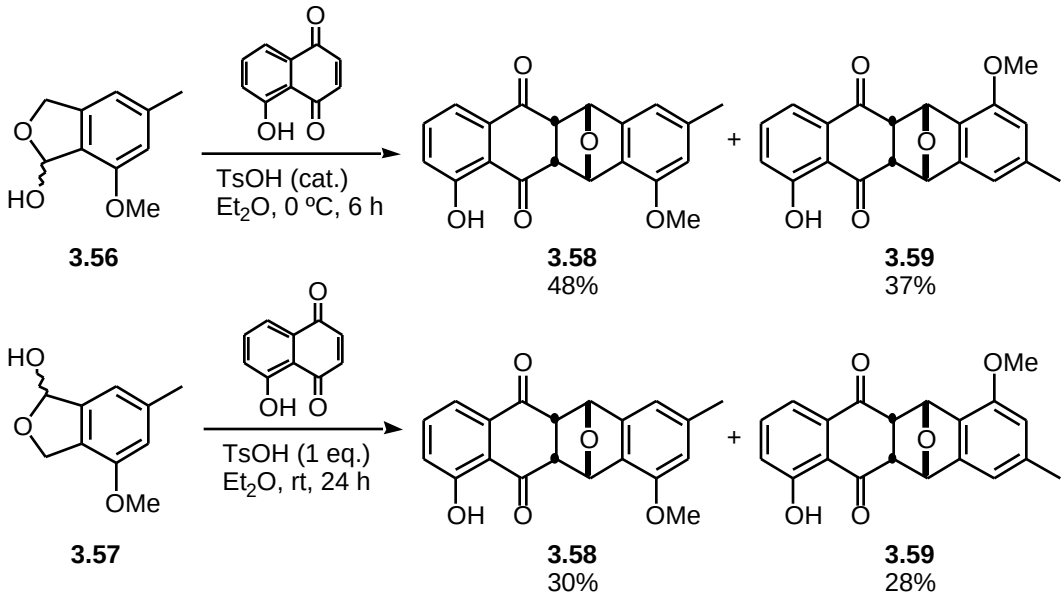
Scheme 3.12



Studies toward SS-228R then continued with the [4+2] cycloaddition of isobenzofuran generated from either lactol **3.56** or **3.57** with commercially available juglone under acidic conditions to give a separable mixture of

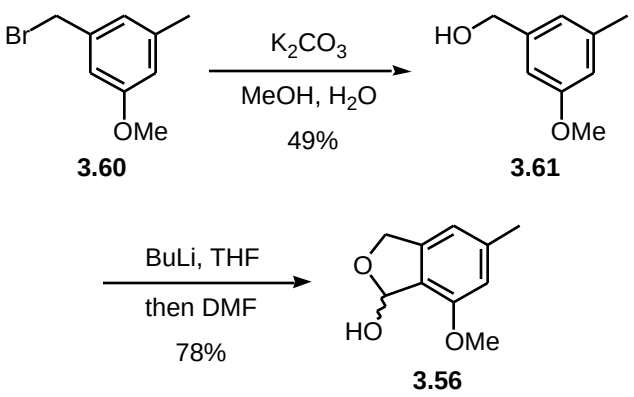
regioisomers **3.58** and **3.59** (Scheme 3.13). One feature of the cycloaddition that is notable is that lactol **3.56** reacted more rapidly and at lower temperatures than lactol **3.57** to form cycloadducts **3.58** and **3.59** in higher yields and with greater regioselectivity (1.3:1 compared to 1.1:1). This difference in reactivity is likely to be due to the ability of the electron rich methoxy group of lactol **3.56** to assist in the loss of water through resonance stabilization. Additionally, reactions of lactol **3.57** resulted in the isolation of small amounts of an inseparable mixture of exo-regioisomers (5%). Although speculative, it was thought that this difference in product distribution may have been due to the fact that at higher temperatures the reaction is readily reversible, and therefore subject to thermodynamic equilibrium. In light of these results, it became apparent that lactol **3.56** was better suited for the synthesis of both **3.33** and **3.1**, and therefore a strategy for the selective synthesis of **3.56** was developed.

Scheme 3.13



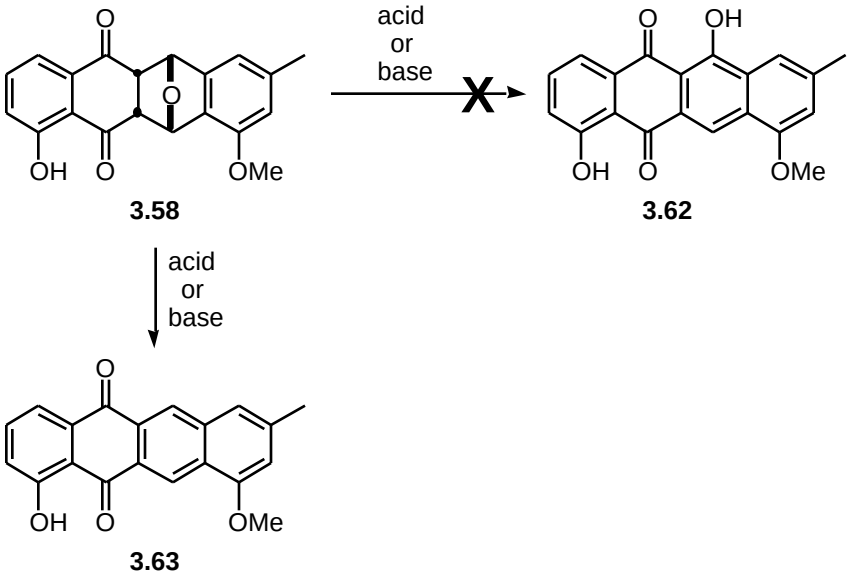
The synthesis of lactol **3.56** commenced with monobromination of dimethylanisole to give **3.60** (Scheme 3.14).[144] Hydrolysis of the bromide gave known benzyl alcohol **3.61**.[145] Formylation of the intermdiate benzyl alcohol was achieved by directed lithiation followed by reaction with DMF, according to the method of Dibble, to provide lactol **3.56**.[146].

Scheme 3.14



With a reliable route to lactol **3.56** in hand, studies toward the oxidation of the cycloadduct **3.58** were performed. It was initially anticipated that both the oxidation and opening of the bridging ether could be accomplished simultaneously under basic or acidic conditions to provide **3.62** (Scheme 3.15). Unfortunately, under these conditions, dehydration occurred to give **3.63** as the only product. These results indicated that the oxidation/opening sequence would have to be performed stepwise on **3.58** rather than as a single operation.

Scheme 3.15

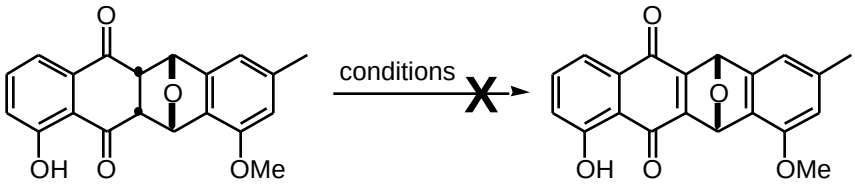


3.58 **3.62** **3.63**

Investigations then turned to a two-step protocol that began with the oxidation of the B-ring of **3.58** to quinone **3.64**. Treatment of **3.58** with manganese dioxide or $BaMnO_4$ gave no reaction. When **3.58** was treated with ceric ammonium nitrate (CAN) only a complex mixture was isolated from the reaction (Scheme 3.16). The attempted oxidation of **3.58** with Fremy's salt gave only dehydration product **3.63**. Reaction of **3.58** with dichlorodicycanohydroquinone (DDQ) or chloranil gave no reaction at room temperature, whereas at temperatures higher than 40 ºC, regioisomers **3.58** and **3.59** as well as exo isomers of **3.58** and **3.59** were recovered from the reaction.

These results indicated that at elevated temperatures, the starting material **3.58** undergoes a retro [4+2] cycloaddition followed by recombining *via* [4+2] cycloaddition. This difficulty in the oxidation of cycloadduct **3.58** was thought to be due to the increase in ring strain resulting from placing two additional sp^2 centers into the tetracyclic system. This hypothesis could be supported by the fact that the B-ring prefers to exist in the dicarbonyl form rather than the hydroquinone form as evidenced by the ^{13}C spectra that contained peaks that indicated the presence of carbonyl groups.

Scheme 3.16

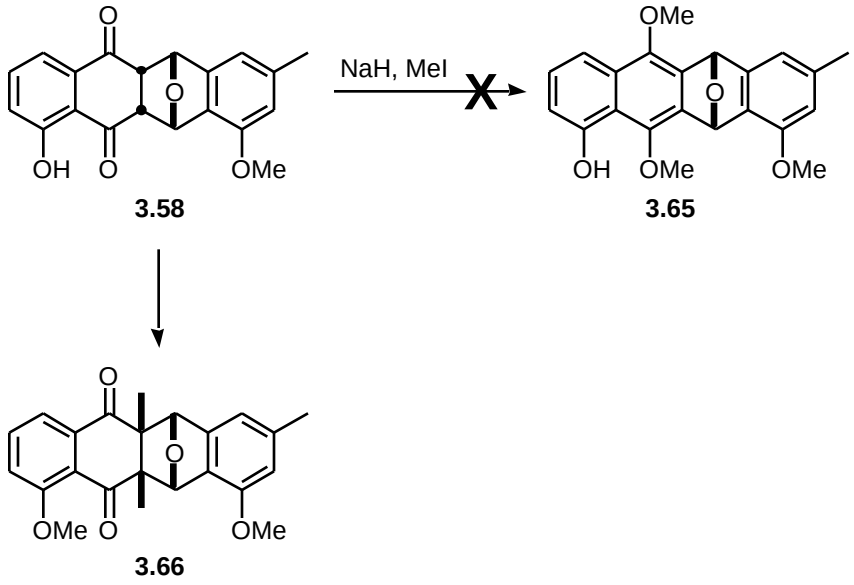


3.58 **3.64**

Since the oxidation of the B-ring of **3.58** prior to the opening of the bridging ether in the C-ring was not successful, it was anticipated that reversal of these steps would make the transformation of **3.58** to **3.62** possible. To this end, reaction of **3.58** with MeI resulted in *C*-alkylation to provide **3.66** rather than the desired *O*-alkylation to give **3.65** (Scheme 3.17). While the result of the reaction

was not the desired product, it did reveal that electrophiles could be placed adjacent to the carbonyl groups in **3.58**. Therefore, if an electrophile was installed adjacent to the carbonyl that could also act as a good leaving group, it could undergo β-elimination to accomplish the desired oxidation to **3.64**.

Scheme 3.17

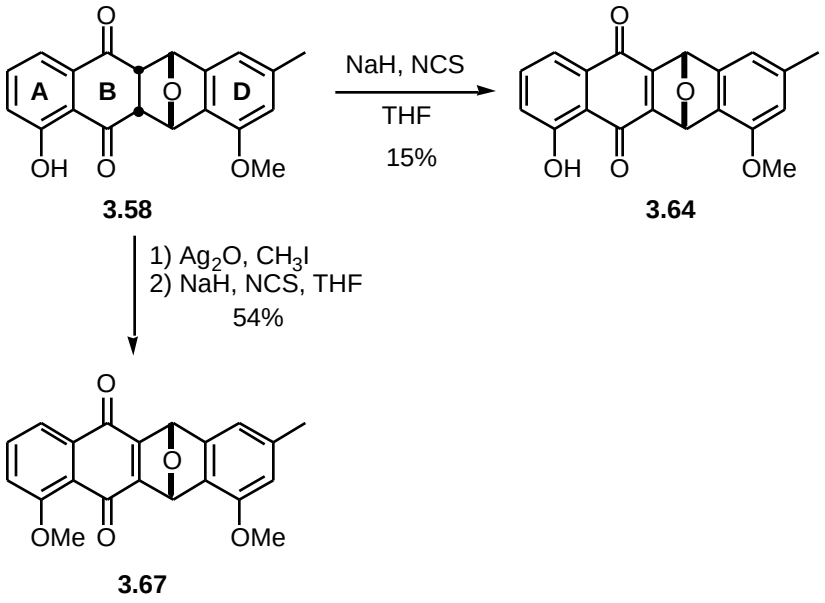


3.58 **3.65** **3.66**

It was anticipated that NCS would be an ideal candidate for the oxidation of **3.58** since it is a source of electrophilic chloride, and this chloride could later β-eliminate to provide quinone **3.64**. Thus, **3.58** was treated with NaH and NCS to give small amounts of **3.64** but the major product of the reaction was ortho or para chlorination of the A-ring as evidenced by ^{1}H NMR and LRMS(Scheme

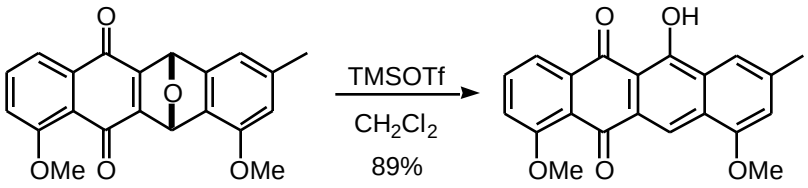
3.18). In an effort to limit the formation of the undesired product, the free phenol was protected as the methyl ether. Oxidation of this material under the same conditions gave the desired quinone **3.67** in modest yield.

Scheme 3.18



Once the oxidation of **3.58** had been completed to provide **3.67**, the bridging ether in the B-ring was opened regioselectively with TMSOTf to provide **3.32** (Scheme 3.19). Because the data for **3.32** matched all of the spectral data that was provided by Tamura in his synthesis of SS-228R (**3.33**), preparation of **3.32** constituted a formal synthesis of **3.33**.

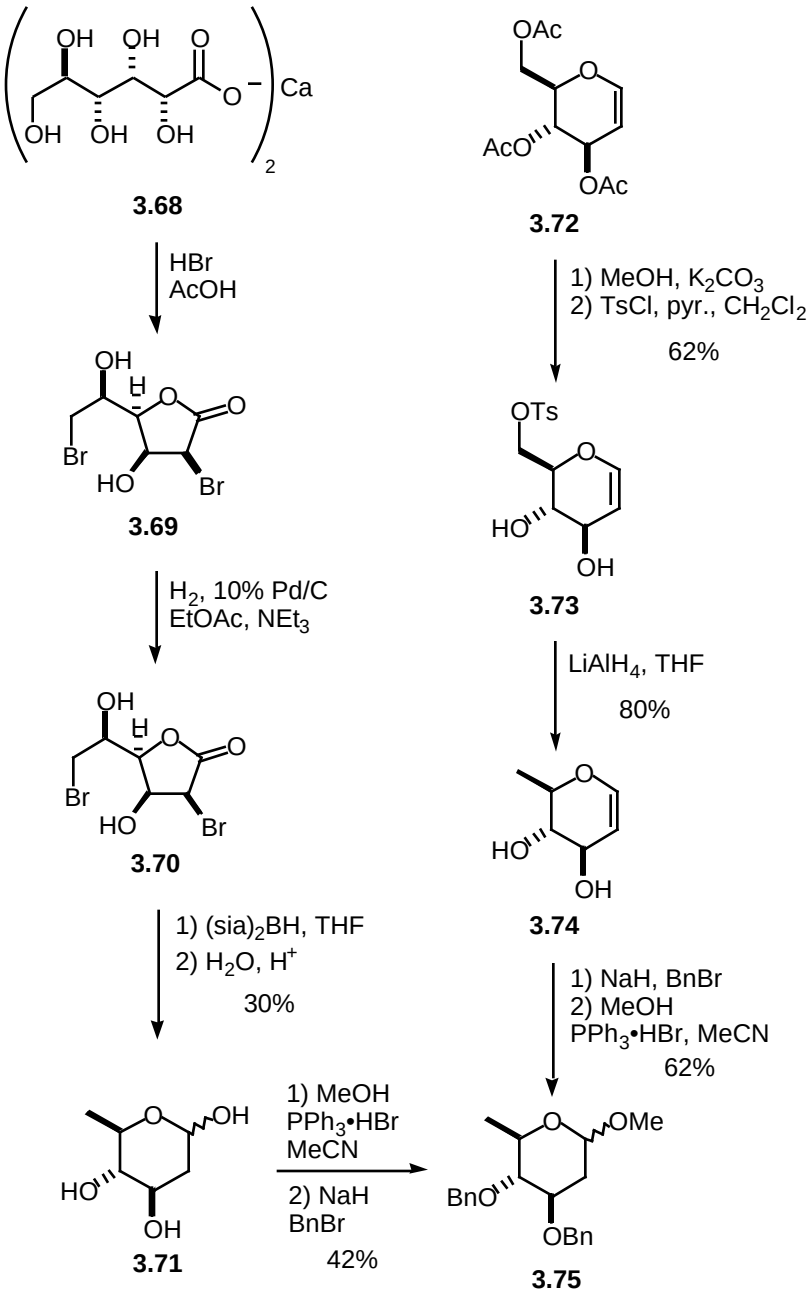
Scheme 3.19



3.67 **3.32**

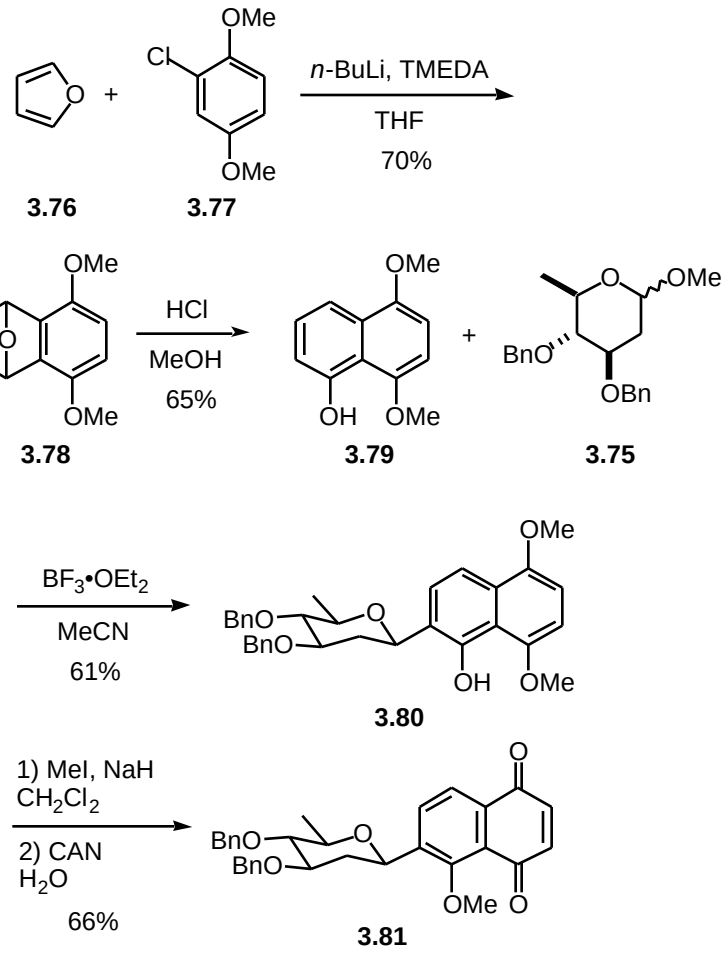
Efforts were then directed toward the total synthesis of galtamycinone. The synthesis of the required sugar-juglone was accomplished using each of three strategies. Dr. John Bender completed the first of the three methods by applying the $O \rightarrow C$-glycoside rearrangement to **3.79** and the mixed methyl acetal of D-olivose **3.75** (Scheme 3.20). The requisite D-olivose was prepared according to literature procedures beginning with either calcium-D-gluconate (**3.68**),[147,148] or from triacetyl-D-glucal (**3.72**) (Scheme 3.20).[149-151]

Scheme 3.20


OH
OH
O
O
Ca
OH
OH
OH
2
3.68
HBr
AcOH
OH
H
O
O
Br
HO
Br
3.69
H2, 10% Pd/C
EtOAc, NEt3
OH
H
O
O
Br
HO
Br
3.70
1) (sia)2BH, THF
2) H2O, H+
30%
O
OH
HO
OH
3.71
1) MeOH
PPh3•HBr
MeCN
2) NaH
BnBr
42%
OAc
O
AcO
OAc
3.72
1) MeOH, K2CO3
2) TsCl, pyr., CH2Cl2
62%
OTs
O
HO
OH
3.73
LiAlH4, THF
80%
O
HO
OH
3.74
1) NaH, BnBr
2) MeOH
PPh3•HBr, MeCN
62%
O
OMe
BnO
OBn
3.75

Naphthol **3.79** was prepared in two steps from chlorodimethoxybenzene. Cycloaddition of furan and chlorodimethoxybenzene provided **3.78** treatment with acid then provided **3.79** (Scheme 3.21). The *O*→*C*-glycoside rearrangement of **3.79** and **3.75** was then accomplished in modest, though inconsistent yield to provide **3.80**. Methylation of **3.80** was then followed by selective oxidation to the desired sugar-juglone **3.81**.

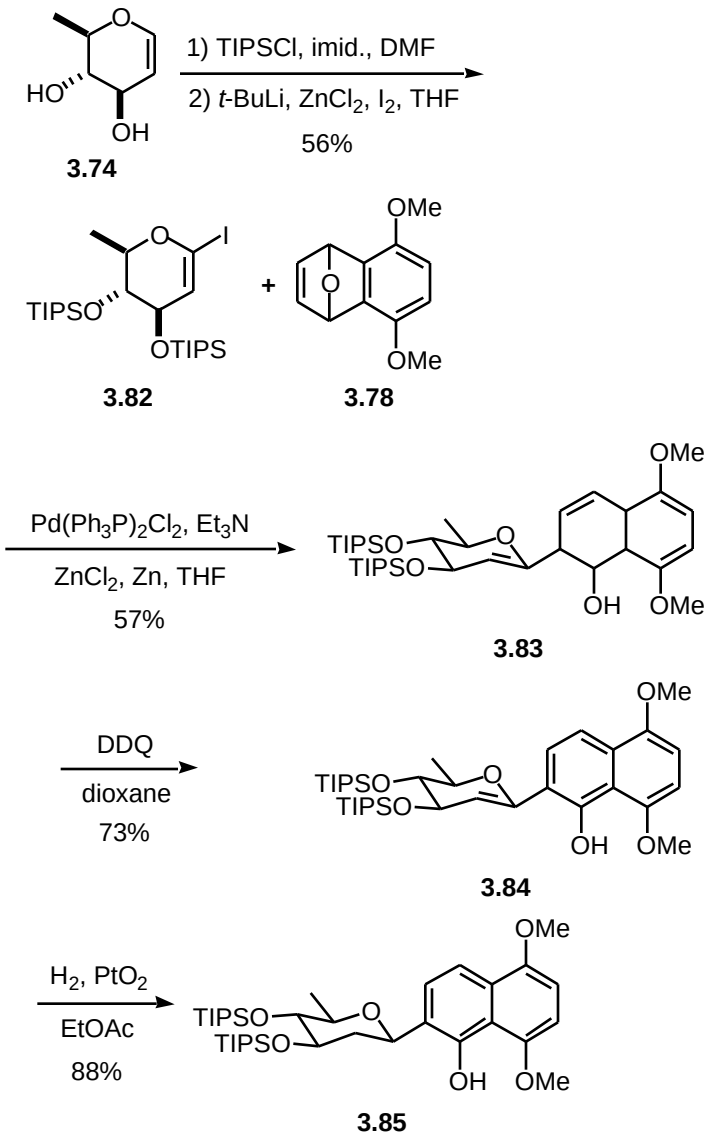
Scheme 3.21



Dr. Omar Lopez completed the second approach to the synthesis of the required sugar-juglone utlilizing the S_N2' opening of **3.78**, that was prepared from the cycloaddition of furan and chlorodimethoxybenzene, to incorporate the sugar moiety. Vinyl iodide **3.82** was prepared from D-olivose glucal **3.74** in two steps followed by the palladium-catalyzed reaction of **3.82** with **3.78** gave adduct **3.83**

as a mixture (1:1) of the diastereomeric *cis*-dihydronaphthol.[152] Oxidation of **3.83** was then accomplished using DDQ to give naphthol **3.84**. Reduction of the glucal using PtO_2 under an atmosphere of hydrogen yielded the desired sugar-juglone intermediate **3.85**.

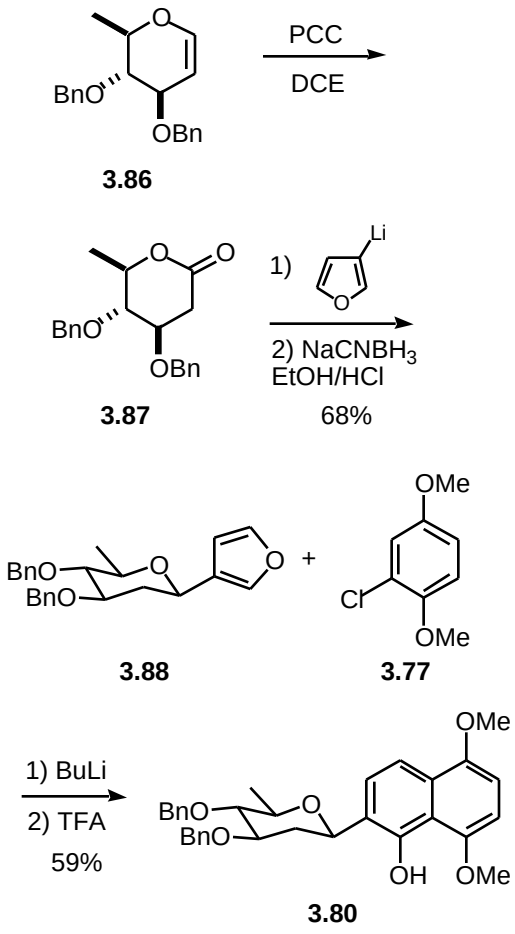
Scheme 3.22



David Kaelin completed the third and final route to the required sugar-juglone using the cycloaddition of furan **3.88** with chlorodimethoxybenzene **3.77** (Scheme 3.23). The required furan **3.88** was prepared in two steps from **3.86**

(Scheme 3.20). The cycloaddition of **3.88** with chlorodimethoxybenzene **3.77** proceeded smoothly to provide an adduct that was treated with trifluoroacetic acid to provide the desired naphthol **3.80**.

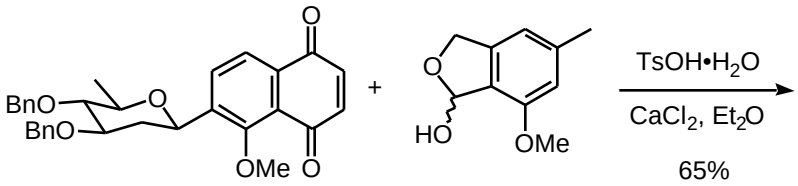
Scheme 3.23



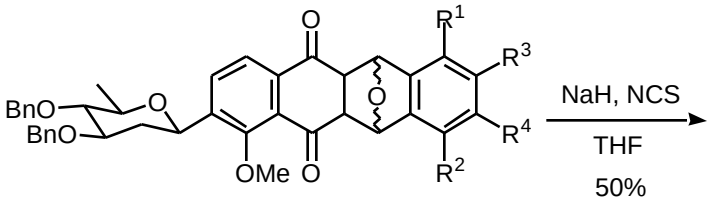
The key cycloaddition was then performed with sugar-juglone **3.81** that had been prepared using the *O→C* glycoside rearrangement route (Scheme 3.21),

and isobenzofuran derived from lactol **3.56** to give a mixture of stereo- and regioisomers **3.89** and **3.90** (Scheme 3.24). This mixture of **3.89** and **3.90** was then oxidized using NCS to give **3.91** and **3.92** as an inseparable mixture of isomers. Fortunately, it was found that after treatment of **3.91**/**3.92** with TMOTf, the two regioisomers **3.93** and **3.94** were separable by column chromatography to give **3.93** as a single isomer.

Scheme 3.24

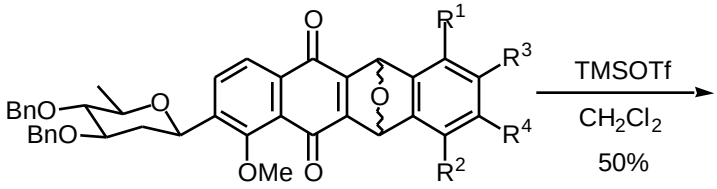


3.81 **3.56**



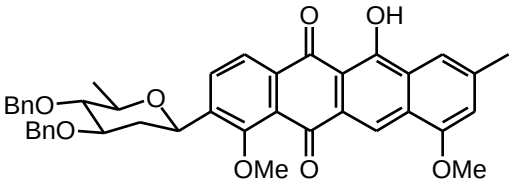
3.89: R^1 = H, R^2 = OMe, R^3 = Me, R^4 = H

3.90: R^1 = OMe, R^2 = H, R^3 = H, R^4 = Me

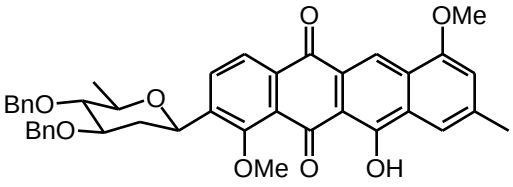


3.91: R^1 = H, R^2 = OMe, R^3 = Me, R^4 = H

3.92: R^1 = OMe, R^2 = H, R^3 = H, R^4 = Me



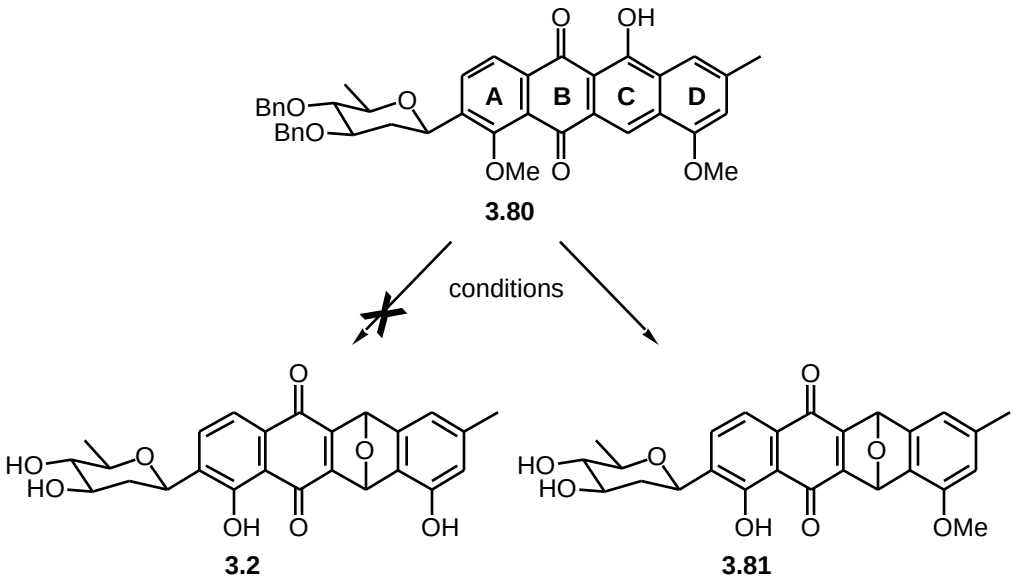
3.93



3.94

Completion of the total synthesis of galtamycinone (**3.1**) required the global deprotection of **3.93**, but this task proved much more difficult than anticipated. A variety of conditions were explored for the deprotection of **3.93** including BBr_3, NaI and TMSCl, and BI_3, but only **3.94** was recovered from the reaction (Scheme 3.25). The deprotection of the D-ring methyl ether could not be effected under any of these conditions.

Scheme 3.25



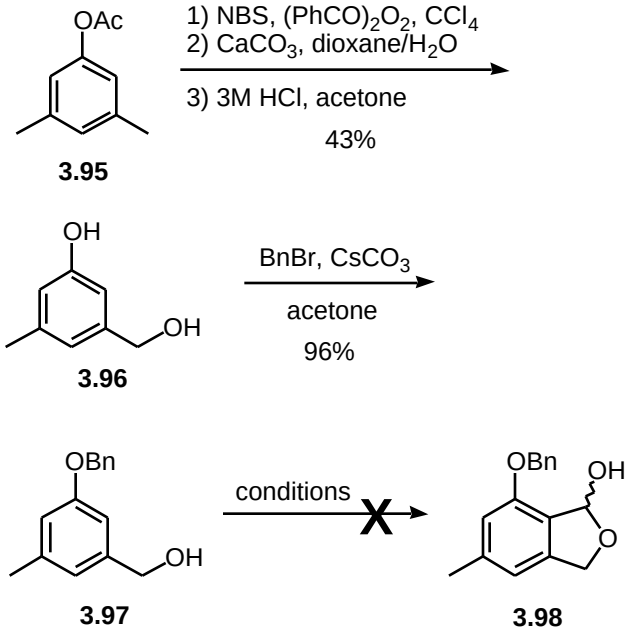
In light of these results, the choice of the protecting group on the D-ring phenol was reconsidered. It was thought that benzyl would be a better choice than the methyl ether since it was already known that a benzyl group at this

position could be deprotected because it coincided with an intermediate in the Suzuki synthesis of galtamycinone (**3.2**) (Scheme 3.5).[125]

3.5 STUDIES TOWARD THE SYNTHESIS OF GALTAMYCINONE

It was anticipated that the required benzyl lactol **3.98** could be prepared analogously to the approach used to make methoxylactol **3.56** (Scheme 3.15). Accordingly, Dr. Omar Lopez brominated acetoxydimethylphenol **3.95** (Scheme 3.26). Hydrolysis of the bromide and the acetyl protecting group gave **3.96**. Selective benzyl protection yielded the desired benzyl protected phenol **3.97**. Unfortunately, attempts to formylate **3.97** under the conditions that were used for the synthesis of lactol **3.56** were unsuccessful. Use of *n*-BuLi in refluxing hexane resulted in the isolation of a complex reaction mixture. Reaction of **3.97** with *n*-BuLi in THF at –78 ºC resulted in recovery of starting material. At this point, Dr. Omar Lopez concluded his studies toward the synthesis of galtamycinone (**3.1**).

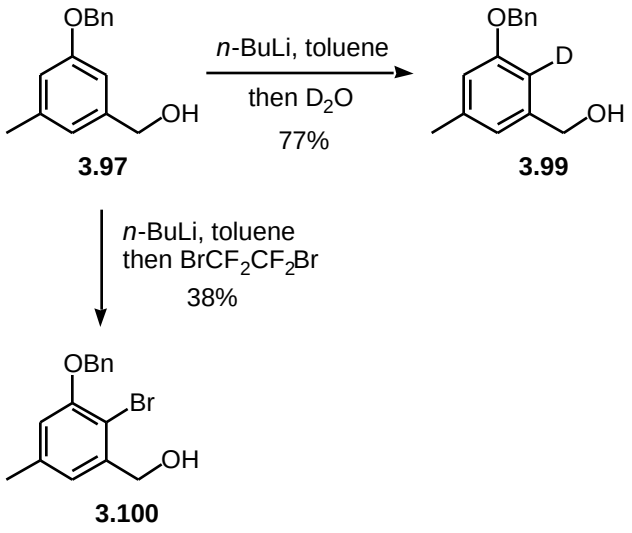
Scheme 3.26



Although these preliminary attempts to synthesize lactol **3.98** were unsuccessful, there were still options that could be explored for its synthesis. Other protecting group options were also possible. After considerable experimentation, it was discovered that treatment of the alcohol **3.97** with *n*-BuLi in toluene at –10 ºC and subsequent addition of DMF gave a mixture of starting material and an unidentified product that rapidly decomposed upon exposure to acidic conditions (such as dissolution in $CDCl_3$ or CD_2Cl_2). In light of these results, it was important to verify that **3.97** was being deprotonated effectively

(Scheme 3.27). Deuterium incorporation studies were performed by treating **3.97** with *n*-BuLi in toluene at –10 ºC. This experiment showed that there was 77% deuterium incorporation on the aryl ring at a single position. Furthermore, it was shown that the aryl ring could be brominated at the desired position to provide **3.100** by metallation with *n*-BuLi in toluene at –10 ºC followed by addition of dibromotetrafluoroethane. Since it was established that alcohol **3.97** was deprotonated effectively, and furthermore it was shown that electrophiles could be added to provide **3.100**, it was anticipated that lactol **3.98** could be synthesized from **3.97**.

Scheme 3.26



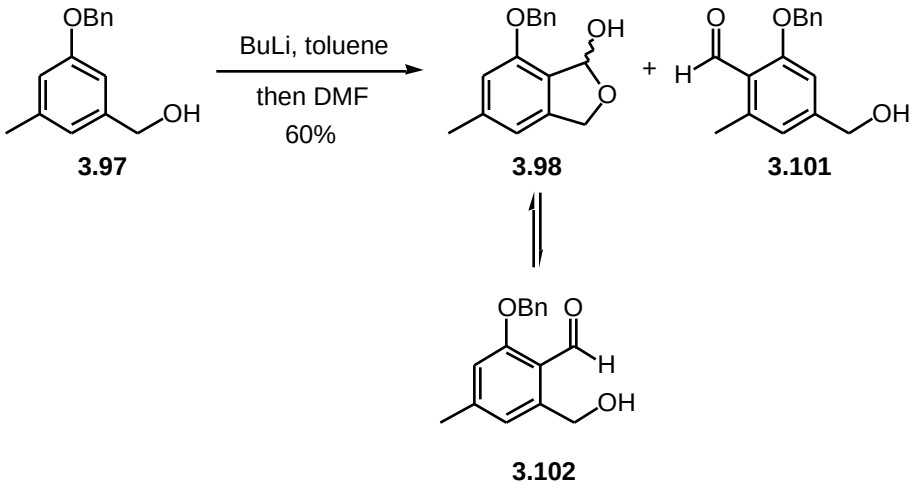
A solution of alcohol **3.97** in toluene was metallated with *n*-BuLi at –10 ºC followed by addition of DMF to produce the same results (by TLC) as those that were obtained previously (Scheme 3.27). Since it was known that the product of the reaction was sensitive to acidic conditions, the product was dissolved in benzene (C_6D_6) or methanol (CD_3OD) instead of chloroform ($CDCl_3$) or dichloromethane (CD_2Cl_2). The ^1H NMR of the reaction of **3.97** showed a mixture (4:1) of the desired lactol **3.98** as well as an unidentified aldehyde that was believed to be either **3.101** or **3.102**. Recrystallization of the mixture provided an improved ratio of desired product **3.98** to aldehyde (12:1).

At this point it was unknown whether the observed aldehyde corresponded to **3.101**, which would arise from lithiation in the wrong position or **3.102**, which would result from of the equilibration between the lactol **3.98** and aldehyde **3.102**.

In an effort to determine the nature of the unidentified aldehyde, several experiments were performed. An ^{1}H NMR spectrum was taken of the recrystallized mixture (12:1) in both benzene (C_6D_6) and methanol (CD_3OD) to see if the ratio of desired lactol **3.97** to aldehyde change over time as monitored by the signal of the aryl methyl group. It was anticipated that if the mixture was a combination of **3.97** and **3.102** rather than the two alkylation regioisomers **3.98** and **3.101**, the two isomers would equilibrate in solution and therefore, the ratio of lactol **3.98** to aldehyde **3.102** would change. Initially, the ratio of **3.97** to aldehyde in the two solvents was identical (12:1). After standing overnight in solution the ratio of **3.97** to aldehyde had changed. The solution in benzene (C_6D_6) had gone from a 12:1 mixture to a 3:1 mixture of lactol **3.98** to aldehyde **3.102**, whereas the solution in methanol (CD_3OD) had equilibrated to a 10:1 mixture of lactol **3.98** to aldehyde **3.102**. This experiment indicated that equilibration of **3.98** had occurred, and so the aldehyde contaminant must be

3.102.[153] Concurrent with the studies of benzyl protecting group **3.97** were studies using a *t*-buyl phenolic protecting group.

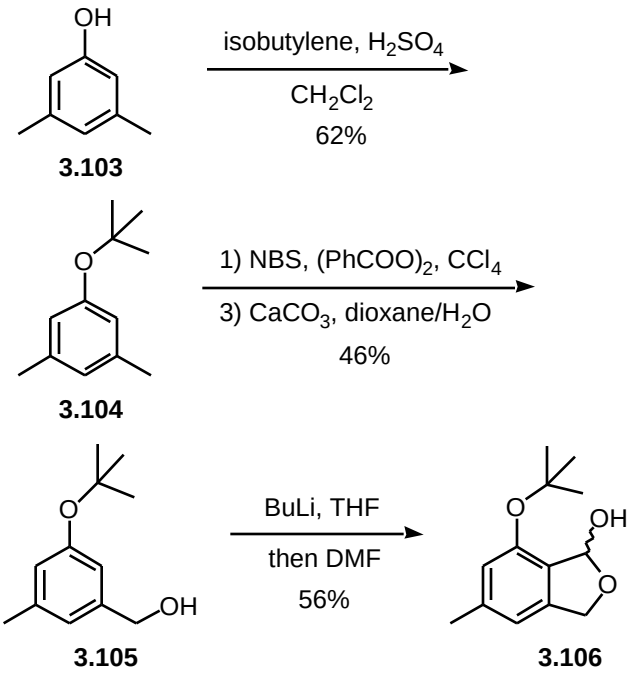
Scheme 3.27



The synthesis of *t*-butyl lactol **3.106** commenced with the synthesis of the *t*-butyl ether **3.104** from dimethylphenol **3.103**. Radical bromination of **3.104** and hydrolysis of bromide provided the desired alcohol **3.105**. Treatment of the alcohol **3.105** with *n*-BuLi and subsequent addition of DMF yielded the desired lactol **3.106**. Unfortunately, this reaction could not be reproduced, and only starting material **3.105** was recovered from the reaction, although the reason for this was not clear. Because formation of the lactol **3.106** was not reproducible, the use of a *t*-butyl protecting group was impractical, and efforts toward the

synthesis of galtamycinone (**3.1**) were therefore continued using benzyl protected lactol **3.98**.

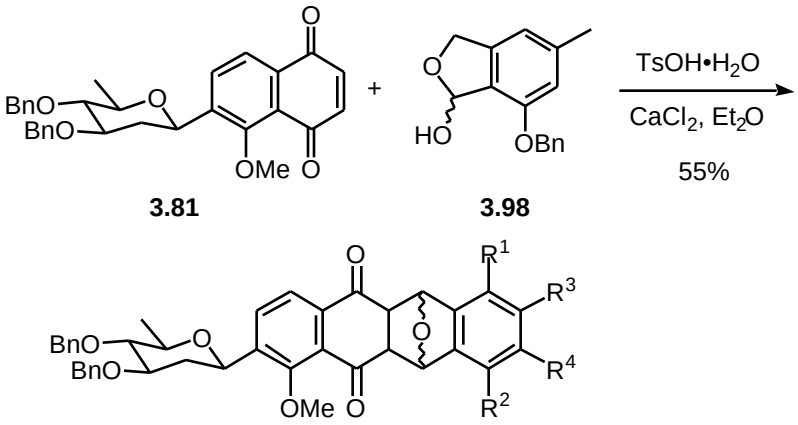
Scheme 3.28



The cycloaddition of the isobenzofuran derived from lactol **3.98** with juglone **3.81** gave an inseparable mixture of stereo- and regioisomers **3.107** and **3.108** (Scheme 3.29). Optimal results with this cycloaddition were obtained if the calcium chloride was flame-dried immediately before the reaction; otherwise significantly lower yields (40%) were observed. Additionally, all of the

compounds including and subsequent to the preparation **3.107**/**3.108** should be stored as solutions in ether under argon in the freezer to avoid decomposition.

Scheme 3.29

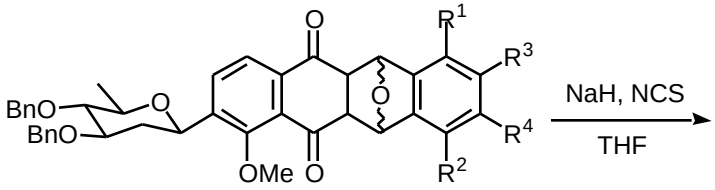


3.107: R^1 = H, R^2 = OBn, R^3 = Me, R^4 = H
3.108: R^1 = OBn, R^2 = H, R^3 = H, R^4 = Me

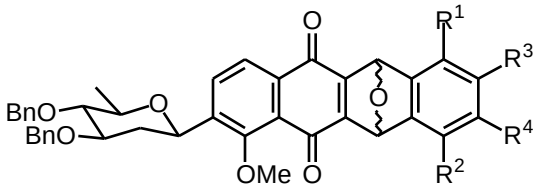
Oxidation of the mixture of compounds **3.107** and **3.108** with NCS to **3.109** and **3.110** then proved to be rather problematic. Initial attempts to effect the oxidation using unpurified NCS resulted the isolation of an inseparable mixture of quinones **3.109** and **3.110** as well as an inseparable mixture of another undesired side product that were tentatively assigned as being **3.111** and **3.112** (Scheme 3.30). The nature of the undesired side products **3.111/3.112** was determined by ^{1}H NMR where there were four singlets that correspond to the four

phenolic peaks. Additionally LRMS and HRMS gave a base peak at *m/z* 751 a value that corresponds to the mass of **3.111** and **3.112**.

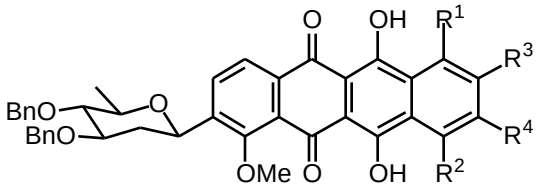
Scheme 3.30



3.107: R^1 = H, R^2 = OBn, R^3 = Me, R^4 = H
3.108: R^1 = OBn, R^2 = H, R^3 = H, R^4 = Me



3.109: R^1 = H, R^2 = OBn, R^3 = Me, R^4 = H
3.110: R^1 = OBn, R^2 = H, R^3 = H, R^4 = Me

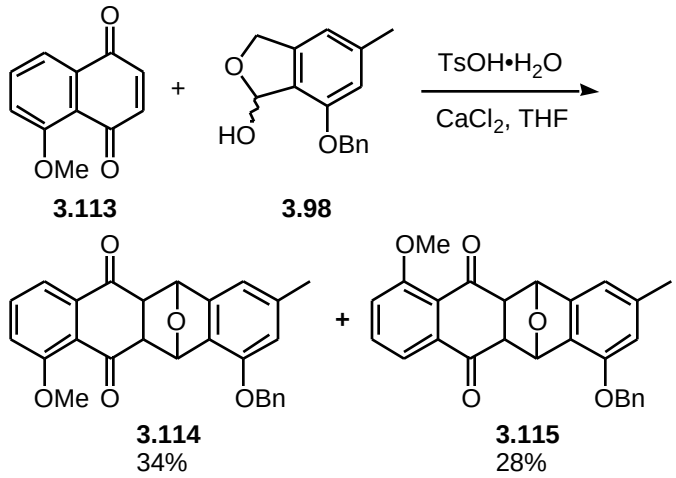


3.111: R^1 = H, R^2 = OBn, R^3 = Me, R^4 = H
3.112: R^1 = OBn, R^2 = H, R^3 = H, R^4 = Me

At this point other options were examined to effect the requisite oxidation of **3.107** and **3.108**. In an effort to conserve material, however, the cycloaddition was performed on the isobenzofuran generated from lactol **3.98** and juglone **3.113** (Scheme 3.31). An additional benefit to using **3.113** rather than **3.81** was the fact

that without the sugar, the two regioisomers **3.114** and **3.115** were separable by flash chromatography, thereby making characterization more facile.

Scheme 3.31



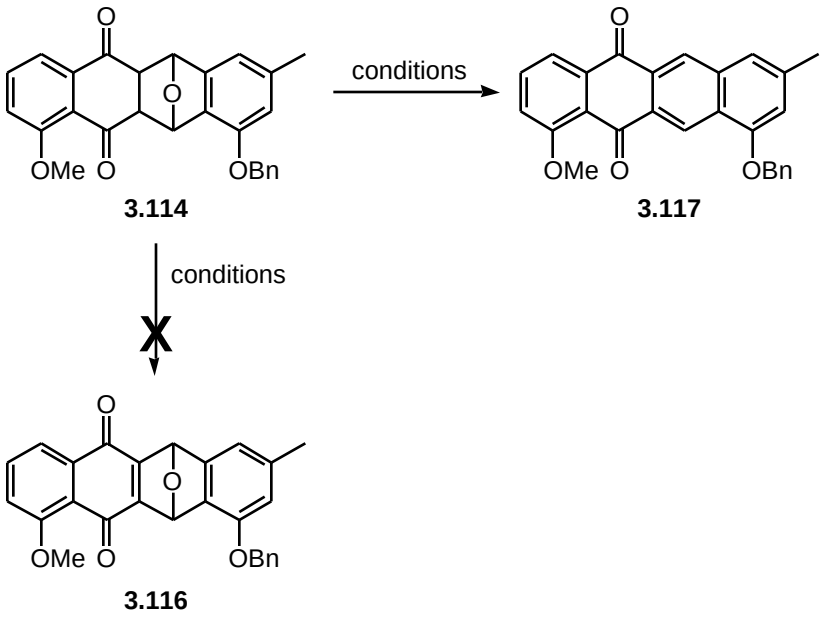
It was hoped that the oxidation of **3.114** and opening of the oxabicycle could be done in a one-pot procedure by subjecting the cycloadduct **3.114** to Lewis acidic conditions under an atmosphere of oxygen. Unfortunately, this tactic resulted in the dehydration of **3.114** to give **3.118**, the structure of which was supported by LRMS when either TMSOTf or $Sc(OTf)_3$ was used as the catalyst (Scheme 3.32).

The tendency of **3.114** to dehydrate to **3.118** under Lewis acidic conditions led to the return to a two-pot approach, and a number of conditions to

effect the requisite oxidation of **3.114** to **3.116** were investigated (Scheme 3.32). The use of NCS gave primarily **3.118**, analogous to the oxidation of **3.107** and **3.108** with NCS. Reaction of **3.114** with DDQ at room temperature gave only starting material. Higher temperatures could not be used because it was known that the retro[4+2] could take place as shown by Dr. John Bender. Cycloadduct **3.114** was also treated with chloranil, but again only starting material was recovered. The use of CAN at room temperature to oxidize **3.114** resulted in decomposition of the starting material. Dehydrogenation of cyclohexene and cyclohexadiene systems using transition metal catalysts is known, but only starting material was isolated when **3.114** heated with Pd/C in refluxing diglyme.[154] Silver-based oxidations are also known to convert hydroquinones to quinones, but when Fetizon's reagent (Ag_2CO_3 on celite) was used,[155] only **3.114** was recovered. Attempted oxidation of **3.114** with Fremy's salt (potassium nitrosodisulfonate) also resulted in the recovery of starting material.[156] In light of Nicolaou's recent successes in using IBX (2-iodoxybenzoic acid) as a mild oxidant to effect the stepwise, controlled oxidation of carbonyl compounds to α,β-unsaturated ketones,[157] this reagent was examined. However, reaction of

3.114 with IBX gave an unidentified mixture of compounds with no recovered starting material or desired product. After the investigation of many oxidative conditions for the desired transformation, it was decided that the NCS oxidation should be revisited in light of the fact that these conditions were previously successful.

Scheme 3.32



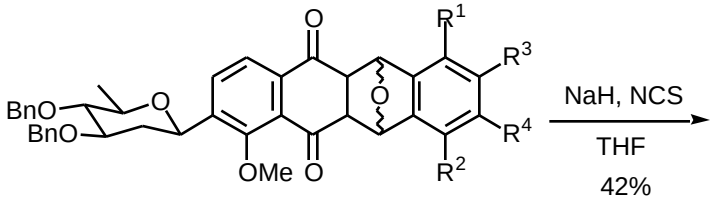
Successful oxidation of **3.89** and **3.90** to **3.91** and **3.92** and **3.58** to **3.67** had been previously performed in the Martin group with commercially available NCS that had not been purified. Because the oxidation of **3.107** and **3.108** could not be accomplished using the same NCS, it seemed reasonable to purify the

NCS. The NCS was first purified using published methods involving recrystallization from either benzene or acetic acid.[158] Treatment of **3.107** and **3.108** with NCS that had been recrystallized from benzene and stored in a dessicator over Drierite resulted in the isolation of primarily **3.111** and **3.112** rather than quinones **3.109** and **3.110** (Scheme 3.33). When the recrystallized NCS (from benzene) was stored over P_2O_5 under vacuum, the oxidation of **3.107** and **3.108** was still problematic. Use of NCS that had been recrystallized from acetic acid followed by storage over P_2O_5 did not effect the oxidation of **3.107** and **3.108**.

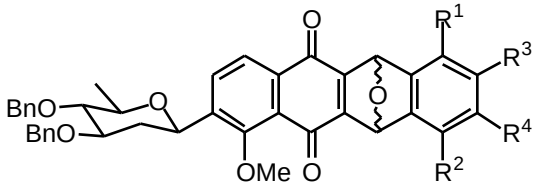
Recrystallization of the NCS from acetic acid could leave residual acid that could interfere with the desired reaction, even after the recrystallized NCS was dried under vacuum overnight. Because of this, the following process was developed for the purification of the NCS: (1) The NCS was recrystallized from acetic acid; (2) The crystals were then dissolved in methylene chloride containing solid potassium carbonate; (3) The solution was stirred vigorously to quench any residual acid; (4) The solvent was removed to give acid free NCS that was stored in a dessicator over Drierite and potassium carbonate. Use of NCS thusly purified

for the oxidation of **3.107** and **3.108** resulted in the isolation a mixture of quinones **3.109** and **3.110**, although there were still small amounts of **3.111** and **3.112** present as evidenced by LRMS and ^{1}H NMR. The exact ratio of **3.109** and **3.110** to **3.111** and **3.112** was difficult to determine since there was a rather complex mixture of stereo- and regio- isomers of **3.109** and **3.110** and **3.111** and **3.112**. Furthermore, the oxidation of **3.107** and **3.108** was rather capricious so an alternative synthesis of quinones **3.109** and **3.110** was investigated.

Scheme 3.33



3.107: R^1 = H, R^2 = OBn, R^3 = Me, R^4 = H
3.108: R^1 = OBn, R^2 = H, R^3 = H, R^4 = Me



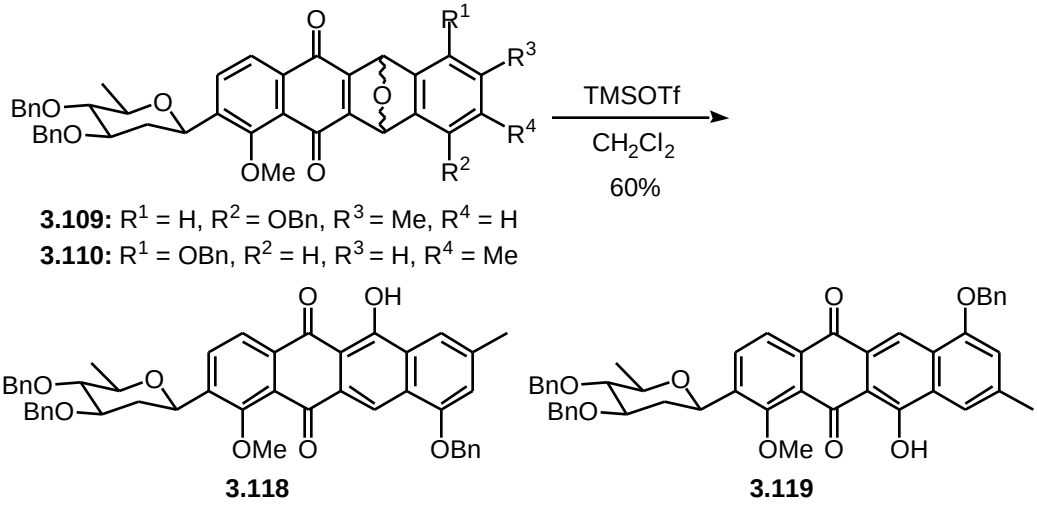
3.109: R^1 = H, R^2 = OBn, R^3 = Me, R^4 = H
3.110: R^1 = OBn, R^2 = H, R^3 = H, R^4 = Me

With quinones **3.109** and **3.110** in hand, attention was turned to the opening of the bridged oxabicycle. Treatment of **3.107** and **3.108** with TMSOTf

gave a mixture of regioisomers **3.118** and **3.119** that was inseparable by column chromatography (Scheme 3.34). Additionally, small amounts of unidentified isomeric compounds were observed, however regioisomers **3.118** and **3.119** were the major products as determined by the integration of the phenolic protons and comparison to the spectral data provided by Suzuki.[125] Although the regioisomeric methyl ethers **3.93** and **3.94** were separable by column chromatography, separation of benzyl ethers **3.118** and **3.119** was not possible using only column chromatography. HPLC separation of the four isomers using two silica columns in series gave partial separation a mixture of **3.118** and **3.119** from the other two isomers. Isolation of only **3.118** was not possible using either flash chromatography or HPLC with silica columns. Unfortunately, during the process of HPLC there was a significant amount of decomposition of the four isomers, although it is not clear at this time whether decomposition was due to the silica columns used on the HPLC, exposure to light, or exposure to air. The suspected decomposition of compounds **3.118** and **3.119** was supported by the fact that after collection of the desired compounds from HPLC, reinjection of the

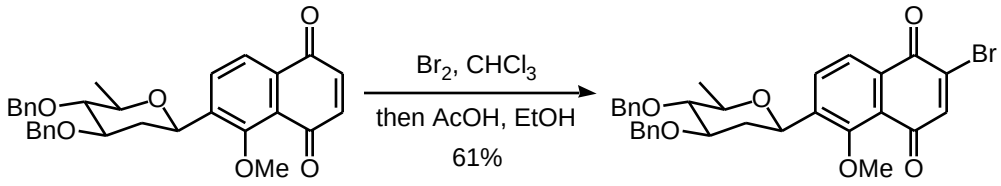
combined fractions showed a second peak that was not present when the fractions were collected.

Scheme 3.34



In light of Suzuki's results in his studies toward galtamycinone, it was anticipated that use of a halogenated juglone in the cycloaddition rather than juglone **3.81** could result in the isolation of quinones **3.118** and **3.119** after spontaneous dehydrohalogenation of the cycloadduct. The requisite halogenated juglone could be made in only one step from juglone **3.81** where juglone **3.81** was regioselectively brominated to give bromojuglone **3.120** (Scheme 3.35).[159]

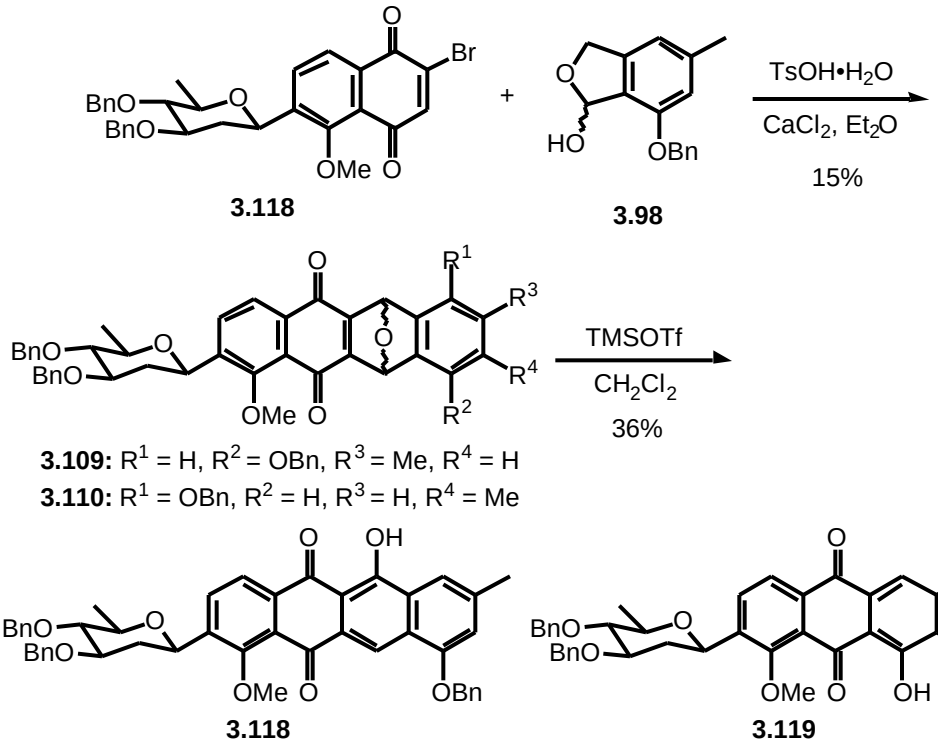
Scheme 3.35



3.81 **3.120**

The cycloaddition of bromojuglone with the isobenzofuran derived from lactol **3.98** was then accomplished, albeit in low yield, to give quinones **3.109** and **3.110** (Scheme 3.36). The bridging ether was then treated with TMSOTf to give a mixture of **3.118** and **3.119** that was inseparable by column chromatography. The two regioisomers **3.118** and **3.119** were separable with chiral HPLC using a Chiralpak AD column. The spectral data was identical to that reported by Suzuki, and therefore constituted a formal synthesis of galtamycinone (**3.1**).[125] The global deprotection to provide galtamycinone (**3.1**) was attempted, however because of lack of material, treatment of **3.118** with BBr_3 to effect the global deprotection following Suzuki's procedure resulted in the isolation of too little material to confirm its identity.

Scheme 3.36

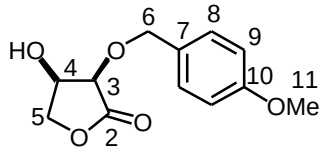


In conclusion, the formal synthesis of galtamycinone (**3.1**) was completed using both the S_N2' and the sugar-furan methodologies that have been developed in the Marting group as alternatives to the *O→C* glycoside rearrangement. Additionally, the viability of the isobenzofuran cycloaddition to assemble the tetracyclic core was established, although the regioselectivity of this reaction was rather disappointing. Current efforts in the Martin group are focusing on the development of methodologies to address the regioselectivity issue cycloaddition

to assemble the tetracyclic core. Additionally, efforts continue toward the synthesis of other *C*-aryl glycoside natural products such as pluramycin and vineomycinone to further demonstrate the utility of the methods developed thus far.

CHAPTER 4. EXPERIMENTAL PROCEDURES.

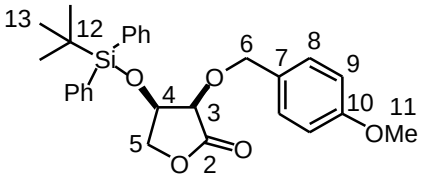
General Procedures. Unless otherwise noted, all starting materials were obtained from commercial sources and used without further purification. Melting points are uncorrected. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl immediately prior to use. Methanol (MeOH) was distilled from magnesium methoxide immediately prior to use. Triethylamine (TEA), and methylene chloride were distilled from calcium hydride immediately prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that had been flame dried. IR spectra were recorded as noted on an FTIR instrument. The ^{1}H (250 MHz) and ^{13}C (62.5 MHz) NMR spectra were determined as solutions as indicated; chemical shifts are expressed in parts per million (δ units) downfield from tetramethylsilane and referenced to the solvent. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; br, broad.



(3*R*,4*R*)-4-Hydroxy-3-(4-methoxybenzyloxy)dihydro-2(3*H*)-furanone (2.53). A suspension of erythronolactone (**2.51**) (5.90 g, 50.0 mmol) and dibutyltin oxide (12.45 g, 50.0 mmol) in toluene (250 mL) was heated at reflux for 6 h in an apparatus equipped with a Dean-Stark trap. After cooling, the solvent was removed under reduced pressure to give a tan solid that was combined with CsF (14.43 g, 95.0 mmol) and dried under reduced pressure. The solids were suspended in DMF (150 mL), and KI (11.05 g, 66.5 mmol) and *p*-$MeOC_6H_4CH_2Cl$ (10.17 mL, 75.0 mmol) were added. The mixture was stirred for 5 h at room temperature, EtOAc (350 mL) was added, and the mixture was poured into H_2O (300 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide a yellow solid that was purified by column chromatography eluting with hexanes/EtOAc (1:1-1:4) to afford 8.49 g of a mixture (6:1) of regioisomers. Recrystallization from hot EtOAc provided 5.65 g (47%) of **2.53** as white needles: mp 100-103 °C; ^{1}H NMR

δ 7.35 (dd, *J* = 2.0, 6.6 Hz, 2 H), 7.32 (dd, *J* = 2.0, 6.6 Hz, 2 H), 4.96 (d, *J* = 11.6 Hz, 1 H), 4.76 (d, *J* = 11.6 Hz, 1 H), 4.33 - 4.19 (comp, 3 H), 4.14 (d, *J* = 4.8 Hz, 1 H), 3.81 (s, 3 H); ^{13}C NMR δ 173.5, 159.9, 130.1, 128.1, 114.1, 73.7, 72.6, 71.3, 67.7, 55.3; IR (neat) 3462, 2958, 1781, 1612, 1514, 1465 cm^{-1}; mass spectrum (CI) *m/z* 238.0846 [$C_{12}H_{15}O_5$ (M+1) requires 238.0841] (base), 161, 154, 149, 137..

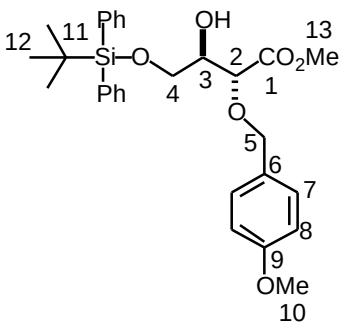
NMR Assignments. ^{1}H NMR δ 7.35 (dd, *J* = 2.0, 6.6 Hz, 2 H, C8-H), 7.32 (dd, *J* = 2.0, 6.6 Hz, 2 H, C9-H), 4.96 (d, *J* = 11.6 Hz, 1 H, C6-H), 4.76 (d, *J* = 11.6 Hz, 1 H, C6-H), 4.33 - 4.19 (comp, 3 H, C4-H and C5-H), 4.14 (d, *J* = 4.8 Hz, 1 H, C3-H), 3.81 (s, 3 H, C11-H); ^{13}C NMR δ 173.5 (C2), 159.9 (C10), 130.1 (C7), 128.1 (C8), 114.1 (C9), 73.7 (C6), 72.6 (C4), 71.3 (C5), 67.7 (C3), 55.3 (C11).



(3*R*,4*R*)-4-*tert*-Butyldiphenylsiloxy-3-(4-methoxybenzyloxy)dihydro-2(3*H*)-furanone. A solution of **2.53** (5.65 g, 23.7 mmol) in CH_2Cl_2 (85.0 mL) containing imidazole (2.02 g, 29.6 mmol) and TBDPSCl (7.40 mL, 28.5 mmol) was stirred for 5 h at room temperature. The mixture was poured into a mixture of EtOAc (200 mL) and H_2O (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography eluting with hexanes/EtOAc (9:1) to afford 9.88 g (87%) of diprotected lactone as a colorless oil; ^{1}H NMR δ 7.73-7.62 (comp, 4 H), 7.47-7.23 (comp, 6 H), 7.17 (d *J* = 8.7 Hz, 2 H), 6.82 (d, *J* = 8.7 Hz, 2 H), 4.67 (s, 2 H), 4.40 (ddd, *J* = 1.1, 3.0, 4.4 Hz, 1 H), 4.13 (dd, *J* = 1.1, 10.2 Hz, 1 H), 3.98 (dd, *J* = 3.0, 10.2 Hz, 1 H), 3.90 (d, *J* = 4.4 Hz, 1 H), 3.77 (s, 3 H), 1.07 (s, 9 H); ^{13}C NMR δ 173.8, 159.4, 135.9, 135.6, 133.1, 132.5, 130.0, 129.9, 129.7, 128.6, 127.8, 127.6, 113.7, 74.0, 71.9, 71.5, 69.1, 55.1, 26.7,

19.2; IR (neat) 2333, 2858, 1790, 1613, 1514, 1464, 1428 cm^{-1}; mass spectrum (CI) *m/z* 475.1932 [$C_{28}H_{32}O_5Si$ (M+1) requires 475.1941] (base), 257, 241.

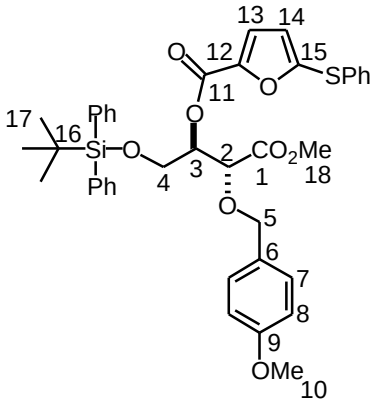
NMR Assignments. ^1H NMR δ .73-7.62 (comp, 4 H, Haro), 7.47 - 7.23 (comp, Haro, 6 H), 7.17 (d, *J* = 8.7 Hz, 2 H, C8-H), 6.82 (d, *J* = 8.7 Hz, 2 H, C9-H), 4.67 (s, 2 H, C6-H), 4.40 (ddd, *J* = 1.1, 3.0, 4.4 Hz, 1 H, C4-H), 4.13 (dd, *J* = 1.1, 10.2 Hz, 1 H, C5-H), 3.98 (dd, *J* = 3.0, 10.2 Hz, 1 H, C5-H), 3.90 (d, *J* = 4.4 Hz, 1 H, C3-H), 3.77 (s, 3 H, C11-H), 1.07 (s, 9 H, C13-H); ^{13}C NMR δ 173.8 (C2), 159.4 (C10), 135.9 (Caro), 135.6 (Caro), 133.1 (Caro), 132.5 (Caro), 130.0 (Caro), 129.9 (Caro), 129.7 (C8), 128.6 (C10), 127.8 (Caro), 127.6 (Caro), 113.7 (C9), 74.0 (C6), 71.9 (C4), 71.5 (C5), 69.1 (C3), 55.1 (C11), 26.7 (C13), 19.2 (C12).



Methyl (2*R*,3*R*)-4-*tert*-butyldiphenylsiloxy-3-hydroxy-2-(4'-methoxybenzyoxy)butanoate (2.54). A solution of Cs_2CO_3 (0.4 g, 1.0 mmol) and the diprotected lactone from the preceeding experiment (9.88 g, 20.7 mmol) in MeOH (70 mL) was stirred for 1 h at 0 °C. Brine (200 mL) and CH_2Cl_2 (100 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 10.84 g of a light yellow oil that was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to afford 10.01 g (95%) of **2.54** as a colorless oil; ^{1}H NMR δ 7.65-7.62 (comp, 4 H), 7.44-7.35 (comp, 6 H), 7.19 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 4.57 (d, *J* = 11.1 Hz, 1 H), 4.34 (d, *J* = 11.1 Hz, 1 H), 4.09 (d, *J* = 6.9 Hz, 1 H), 3.98-3.94 (m, 1 H), 3.80-3.77 (m, 2 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 2.56 (d, *J* = 6.9 Hz, 1 H),

1.05 (s, 9 H); ^{13}C NMR δ 171.6, 159.4, 135.5, 133.0, 129.8, 129.8, 129.0, 127.8, 113.8, 78.3, 72.5, 72.3, 63.7, 55.2, 52.0, 26.8, 19.2; IR (neat) 3490, 2952, 2932, 2856, 1750, 1611, 1513, 1427 cm^{-1}; mass spectrum (CI) *m/z* 507.2203 [$C_{29}H_{36}O_6Si$ (M+1) requires 507.2203] (base), 311, 251, 233.

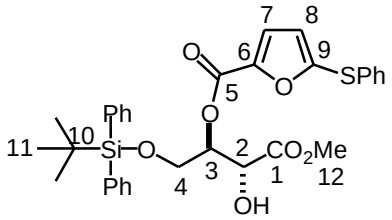
NMR Assignments. ^{1}H NMR δ 7.65 - 7.62 (comp, Haro, 4 H), 7.44 - 7.35 (comp, Haro, 6 H), 7.19 (d, *J* = 8.6 Hz, 2 H, C7-H), 6.83 (d, *J* = 8.6 Hz, 2 H, C8-H), 4.57 (d, *J* = 11.1 Hz, 1 H, C5-H), 4.34 (d, *J* = 11.1 Hz, 1 H, C5-H), 4.09 (d, *J* = 6.9 Hz, 1 H, C2-H), 3.98 - 3.94 (m, 1 H, C3-H), 3.80 - 3.77 (m, 2 H, C4-H), 3.79 (s, 3 H, C10-H), 3.74 (s, 3 H, C13-H), 2.56 (d, *J* = 6.9 Hz, 1 H, OH), 1.05 (s, 9 H, C12-H); ^{13}C NMR δ 171.6 (C1), 159.4 (C6), 135.5 (Caro), 133.0 (Caro), 129.8 (Caro), 129.8 (Caro), 129.0 (Caro), 127.8 (Caro), 113.8 (C8), 78.30 (C2), 72.5 (C3 or C5), 72.3 (C3 or C6), 63.7 (C4), 55.2 (C10), 52.0 (C13), 26.8 (C12), 19.2 (C11).



Methyl (2*R*,3*R*)-4-*tert*-butyldiphenylsiloxy-3-(5-phenylthio-2-furoyloxy)-2-(4'-methoxybenzyloxy)butanoate (2.55). A solution of **2.54** (10.01 g, 19.7 mmol), **2.23a** (4.77 g, 21.6 mmol), DMAP (1.20 g, 9.8 mmol), and DCC (4.87 g, 23.6 mmol) in CH_2Cl_2 (200 mL) was stirred at room temperature for 12 h. The mixture was filtered, and the filtrate was concentrated to give 16.4 g of a light tan oil that was purified by flash chromatography eluting with hexanes/EtOAc (85:15) to afford 11.95 g (95%) of **2.55** as a colorless oil; ^{1}H NMR δ 7.64-7.60 (comp, 4 H), 7.42-7.21 (comp, 11 H), 7.11 (d, *J* = 3.4 Hz, 1 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 6.65 (d, *J* = 3.4 Hz, 1 H), 5.45 (dt, *J* = 4.5, 9.9 Hz, 1 H), 4.71 (d, *J* = 11.5 Hz, 1 H), 4.46 (d, *J* = 11.5 Hz, 1 H), 4.38 (d, *J* = 5.4 Hz, 1 H), 3.99 (dd, *J* = 5.4, 11.1 Hz, 2 H), 3.93 (dd, *J* = 4.5, 11.1 Hz), 3.76 (s, 3 H), 3.66 (s, 3 H), 1.00 (s, 9 H); ^{13}C NMR δ 170.2, 159.3, 156.6, 150.2, 146.4, 135.6, 135.5,

135.4, 133.4, 132.9, 132.8, 129.7, 129.6, 129.6, 129.2, 128.8, 127.6, 127.5, 127.5, 119.6, 118.5, 113.7, 75.7, 74.4, 72.5, 61.3, 55.1, 52.0, 26.6, 19.0; IR (neat) 3070, 3012, 2931, 2856, 1731, 1612, 1577, 1513 cm^{-1}; mass spectrum (CI) *m/z* 711.2459 [$C_{40}H_{43}O_8SSi$ (M+1) requires 711.2448] (base), 653, 302, 207.

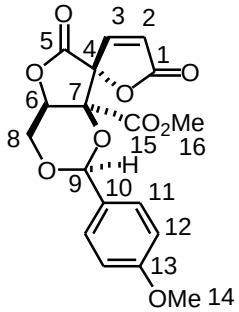
NMR Assignments. ^1H NMR δ 7.64 - 7.60 (comp, 4 H, Haro), 7.42 - 7.21 (comp, 13 H, Haro), 7.11 (d, *J* = 3.4 Hz, 1 H, C13-H), 6.79 (d, *J* = 8.7 Hz, 2 H, C8-H), 6.65 (d, *J* = 3.4 Hz, 1 H, C14-H), 5.45 (dt, *J* = 4.5, 9.9 Hz, 1 H, C3-H), 4.71 (d, *J* = 11.5 Hz, 1 H, C5-H), 4.46 (d, *J* = 11.5 Hz, 1 H, C5-H), 4.38 (d, *J* = 5.4 Hz, 1 H, C2-H), 3.99 (dd, *J* = 5.4, 11.1 Hz, 2 H), 3.93 (dd, *J* = 4.5, 11.1 Hz), 3.76 (s, 3 H, C18-H), 3.66 (s, 3 H, C10-H), 1.00 (s, 9 H, C17-H); ^{13}C NMR δ 170.2 (C1), 159.3 (C9), 156.6 (C11), 150.2 (C12), 146.4 (C15), 135.6 (Caro), 135.5 (Caro), 135.4 (Caro), 133.4 (Caro), 132.9 (Caro), 132.8 (Caro), 129.7 (Caro), 129.6 (Caro), 129.6 (Caro), 129.2 (Caro), 128.8 (Caro), 127.6 (Caro), 127.5 (Caro), 127.5 (Caro), 119.6 (C13 or C14), 118.5 (C13 or C14), 113.7 (C8), 75.7 (C5), 74.4 (C3 or C4), 72.5 (C3 or C4), 61.3 (C2), 55.1 (C10), 52.0 (C18), 26.6 (C17), 19.0 (C16).



Methyl (2*R*,3*R*)-4-*tert*-butyldiphenylsiloxy-3-(5-phenylthio-2-furoyloxy)-2-hydroxybutanoate. A solution of **2.55** (13.31 g, 18.7 mmol) and DDQ (8.50 g, 37.4 mmol) in CH_2Cl_2/H_2O (270 mL, 10:1) was stirred at 35 °C for 12 h. The solvent was removed under reduced pressure, and the residue was dissolved in Et_2O (300 mL) and poured into saturated $NaHCO_3$ (200 mL). The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ (5 x 100 mL). The organic layer was then stirred vigorously with saturated $NaHSO_3$ solution (500 mL) until no *p*-methoxybenzaldehyde could be detected by TLC. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give 9.86 g (89%) of alcohol as a yellow oil that was used in the next reaction without further purification; ^{1}H NMR δ 7.69-7.63 (comp, 4 H), 7.44-7.22 (comp, 11 H), 7.17 (d, *J* = 3.5 Hz, 1 H), 6.63 (d, *J* = 3.5 Hz, 1 H), 5.43 (dt, *J* = 3.7, 9.4 Hz, 1 H), 4.58 (dd, *J* = 3.7, 6.5 Hz, 1 H), 3.93 (dd, *J* = 1.4, 5.8 Hz, 2 H), 3.72 (s, 3 H), 3.37 (d, *J* = 6.5 Hz, 1 H), 1.03 (s, 9 H); ^{13}C NMR δ 172.3, 157.0,

150.5, 146.2, 135.4, 135.4, 133.3, 132.5, 129.7, 129.2, 127.7, 127.5, 119.9, 118.4, 74.8, 70.2, 61.5, 52.7, 26.7, 26.5, 19.0; IR (neat) 3489, 3070, 2953, 2856, 1736, 1566, 1463 cm^{-1}; mass spectrum (CI) *m/z* 591.1883 [$C_{32}H_{35}O_7SSi$ (M+1) requires 591.1873] (base), 513, 435, 302, 279.

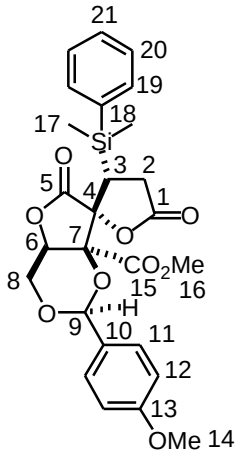
NMR Assignments. ^1H NMR δ 7.69 - 7.63 (comp, 4 H, Haro), 7.44 - 7.22 (comp, 11 H, Haro), 7.17 (d, *J* = 3.5 Hz, 1 H, C7-H), 6.63 (d, *J* = 3.5 Hz, 1 H, C8-H), 5.43 (dt, *J* = 3.7, 9.4 Hz, 1 H, C3-H), 4.58 (dd, *J* = 3.7, 6.5 Hz, 1 H, C2-H), 3.93 (dd, *J* = 1.4, 5.8 Hz, 2 H, C4-H), 3.72 (s, 3 H, C12-H), 3.37 (d, *J* = 6.5 Hz, 1 H, OH), 1.03 (s, 9 H, C11-H); ^{13}C NMR δ 172.3 (C1), 157.0 (C5), 150.5 (C6), 146.2 (C9), 135.4 (Caro), 135.4 (Caro), 133.3 (Caro), 132.5 (Caro), 129.7 (Caro), 129.2 (Caro), 127.7 (Caro), 127.5 (Caro), 119.9 (C7 or C8), 118.4 (C8 or C9), 74.8 (C3), 70.19 (C2), 61.52 (C4), 52.72 (C12), 26.65 (C12), 18.99 (C11).



(5*R*,8*R*,9*S*,1′*S*)-8,9-*O*-(*4′*-Methoxybenzylidene)-9-methoxycarbonyl-1,7-dioxaspiro[4.4]non-3-ene-2,6-dione (2.67). HF•pyridine (1.25 mL) was added to a solution of **2.30** (0.569 g, 1.00 mmol) in THF (10 mL) at 0 °C, the cooling bath was removed, and the solution was stirred for 1 h at room temperature. Solid $NaHCO_3$ was added until CO_2 evolution ceased. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a light brown oil. The crude diol was dissolved in CH_2Cl_2 (10 mL) containing 3 Å molecular sieves, *p*-$MeOC_6H_4CH_2OMe$ (0.300 g, 2.00 mmol), and DDQ (.028 g, 1.25 mmol), and the resulting mixture was stirred for 16 h t room temperature. The reaction mixture was filtered through a Celite pad, and the filtrate was washed with saturated $NaHCO_3$ (10 mL). The layers were separated, and the aqueous wash was back extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residual dark red oil was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (7:3) to give 0.164 g (44%) of **2.67** as a white crystalline solid; mp 150–151 °C; ^{1}H NMR δ 7.55 (d, *J* = 5.8 Hz, 1 H), 7.36 (d, *J* = 8.7 Hz, 2 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 6.43 (d, *J* = 5.8 Hz, 1 H), 5.51 (s, 1 H), 5.02 (t, *J* = 1.5

Hz, 1 H), 4.61 (dd, *J* = 1.5, 13.9 Hz, 1 H), 4.38 (dd, *J* = 1.5, 13.9 Hz, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H); ^{13}C NMR δ 168.9, 166.8, 165.1, 160.8, 149.3, 128.1, 127.5, 125.4, 113.9, 98.4, 88.5, 82.8, 72.4, 65.0, 55.4, 53.7; IR (neat) 3113, 2960, 2842, 1794, 1747 cm^{-1}; mass spectrum (CI) *m/z* 377.0867 [$C_{18}H_{17}O_9$ (M+1) requires 377.0873], 377, 269, 234.

NMR Assignments. ^{1}H NMR δ 7.55 (d, *J* = 5.8 Hz, 1 H, C2-H), 7.36 (d, *J* = 8.7 Hz, 2 H, C11-H), 6.91 (d, *J* = 8.7 Hz, 2 H, C12-H), 6.43 (d, *J* = 5.8 Hz, 1 H, C3-H), 5.51 (s, 1 H, C10-H), 5.02 (t, J = 1.5 Hz, 1 H, C6-H), 4.61 (dd, *J* = 1.5, 13.9 Hz, 1 H, C8-Ha), 4.38 (dd, *J* = 1.5, 13.9 Hz, 1 H, C8-Hb), 3.85 (s, 3 H, C14-H), 3.82 (s, 3 H, C16-H); ^{13}C NMR δ 168.9 (C1, C5, or C15) 166.8 (C1, C5, or C15), 165.1 (C1, C5, or C15), 160.8 (C3), 149.3 (C2) , 128.1 (Caro), 127.5 (Caro), 125.4 (Caro), 113.9 (Caro), 98.4 (C9), 88.5 (C4), 82.8 (C7) , 72.4 (C6), 65.0 (C8), 55.4 (C14), 53.7 (C16).

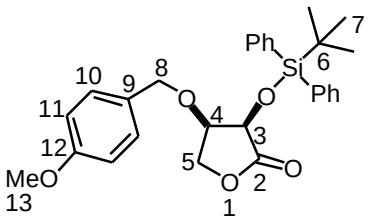


(4*R*,5*R*,8*R*,9*S*,1′*S*)-8,9-*O*-(*4′*-Methoxybenzylidene)-9-methoxycarbonyl-4-(dimethylphenylsilyl)-1,7-dioxaspiro[4.4]non-3-ene-2,6-dione (2.71). $Me_2PhSiCl$ (0.125 g, 0.123 mL, 0.733 mmol) was added to a suspension of Li (0.022 g, 3.29 mmol) in THF (0.8 mL) at room temperature, and the mixture was stirred for 3 h. This solution of silyllithium reagent was then added to a stirred solution of Me_2Zn (2.0 M in toluene, 0.367 mL, 0.733 mmol) in THF (2.2 mL) at 0 °C. After stirring the mixture for 15 min, it was cooled to –78 °C, and a solution of **2.67** (0.092 g, 0.244 mmol) in THF (1.8 mL) was added slowly. The reaction was stirred for 5 min, warmed to –60 °C, and stirred for 10 min. Saturated NH_4Cl (5 mL) and 1 M HCl (2 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), and

the combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The resulting in a yellow oil was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (4:1) to afford 0.076 g (61%) of **2.71** as a white crystalline solid; mp 154-155 ˚C; ^{1}H NMR δ 7.41–7.26 (comp, 7 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 5.51 (s, 1 H), 4.97 (dd, *J* = 1.2, 2.1 Hz, 1 H), 4.64 (dd, *J* = 1.2 Hz, 14.3 Hz, 1 H), 4.30 (dd, *J* = 2.1, 14.3 Hz, 1 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 2.74–2.40 (comp, 3 H), 0.38 (s, 3 H), 0.24 (s, 3 H); ^{13}C NMR δ 174.0, 171.0, 166.4, 160.5, 137.9, 133.7, 129.2, 127.8, 127.7, 113.6, 98.4, 89.2, 81.6, 77.1, 72.5, 65.4, 55.3, 53.6, 31.0, 22.7, -2.3, -3.7; IR (neat) 2959, 1799, 1744 cm^{-1}; mass spectrum (CI) *m/z* 513.1589 [$C_{26}H_{29}O_9Si$ (M+1) requires 513.1581] 513 (base), 435, 377, 269.

NMR Assignments. ^{1}H NMR δ 7.41 – 7.26 (comp, 7 H, Haro), 6.95 (d, *J* = 8.8 Hz, 2 H, C12-H), 5.51 (s, 1 H, C9-H), 4.97 (dd, *J* = 1.2, 2.1 Hz, 1 H, C6-H), 4.64 (dd, *J* = 1.2 Hz, 14.3 Hz, 1 H, C8-Ha), 4.30 (dd, *J* = 2.1, 14.3 Hz, 1 H, C8-Hb), 3.90 (s, 3 H, C14-H), 3.80 (s, 3 H, C16-H), 2.74 – 2.40 (comp, 3 H, C2 and C3-H), 0.38 (s, 3 H, C17-H), 0.24 (s, 3 H, C17-H); ^{13}C NMR δ 174.0 (C1, C5, or C11), 171.0 (C1, C5, or C11), 166.4 (C1, C5, or C11), 160.5 (Caro), 137.9 (Caro),

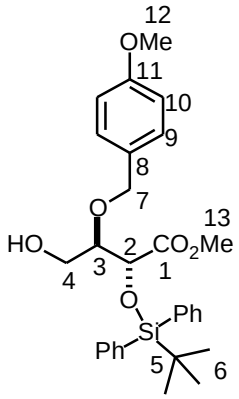
133.7 (Caro), 129.2 (Caro), 127.8 (Caro), 127.7 (Caro), 113.6 (Caro), 98.4 (C9), 89.2 (C4), 81.6 (C7), 77.1 (C3), 72.5 (C6), 65.4 (C9), 55.3 (C14), 53.6 (C16), 31.0 (C2 or C3), 22.7 (C2 or C3), -2.3 (C17a), -3.7 (C17b).



(3*R*,4*R*)-Dihydro-3-*tert*-butyldiphenylsiloxy-4-(4'-methoxybenzyoxy)-2(3*H*)-furanone. Imidazole (0.316 mmol, 0.022 g) and TBDPSCl (0.316 mmol, 0.082 mL) were added to a solution of **2.73** (0.244 mmol, 0.058 g) in CH_2Cl_2 (2.0 mL) at 0 ºC. The reaction was then warmed to rt by removing the cooling bath. After stirring for 12 h, H_2O (5 mL) and EtOAc (5 mL) were added. The organic layer was then washed with brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a clear colorless oil. Purification by flash chromatography (1.5 g silica) eluting with hexanes/EtOAc (70:30) afforded 89 mg (77%) of lactone as a clear colorless oil; ^{1}H NMR δ 7.78 - 7.70 (comp, 4 H), 7.45 - 7.33 (comp, 6 H), 7.19 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.42 (d, *J* = 11.5 Hz, 1 H), 4.36 (d, *J* = 4.9 Hz, 1 H), 4.21 (d, *J* = 10.6 Hz, 1 H), 3.97 (dd, *J* = 3.1, 10.6 Hz, 1 H), 3.80 - 3.78 (m, 1 H), 3.80 (s, 3 H), 1.15 (s, 9 H); ^{13}C NMR δ 173.8, 159.4, 136.0, 135.7, 133.5, 131.2, 130.1, 129.3, 127.8, 113.8, 75.1, 71.4, 71.0, 68.9, 55.3, 26.7, 19.3; IR (neat) 3499,

3070, 3048, 2956, 2931, 2857, 1794, 1613 cm^{-1}; mass spectrum (CI) *m/z* 475.1941[(M-1) requires 475.1941] 477 (base), 399, 279, 211.

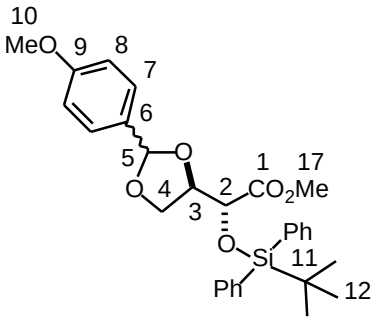
NMR Assignments. ^{1}H NMR δ 7.78 - 7.70 (comp, 4 H, Haro), 7.45 - 7.33 (comp, 6 H, Haro), 7.19 (d, *J* = 8.6 Hz, 2 H, C10-H), 6.83 (d, *J* = 8.6 Hz, 2 H, C11-H), 4.54 (d, *J* = 11.5 Hz, 1 H, C8-Ha), 4.42 (d, *J* = 11.5 Hz, 1 H, C8-Hb), 4.36 (d, *J* = 4.9 Hz, 1 H, C3-H), 4.21 (d, *J* = 10.6 Hz, 1 H, C5-Ha), 3.97 (dd, *J* = 3.1, 10.6 Hz, 1 H, C5-Hb), 3.80 - 3.78 (m, 1 H, C4-H), 3.80 (s, 3 H, C13-H), 1.15 (s, 9 H, C7-H); ^{13}C NMR δ 173.8 (C2), 159.4 (C9), 136.0 (Caro), 135.7 (Caro), 133.5 (Caro), 131.2 (Caro), 130.1 (Caro), 129.3 (Caro), 127.8 (Caro), 113.8 (C11), 75.1 (C4), 71.4 (C8), 71.0 (C3), 68.9 (C5), 55.3 (C13), 26.7 (C7), 19.3 (C6).



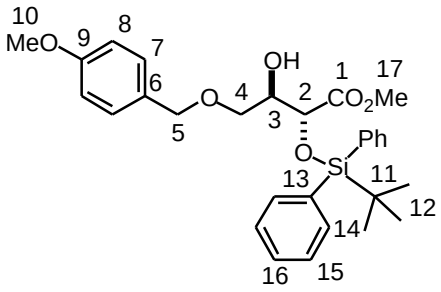
Methyl (2R,3R)-2-*tert*-butyldiphenylsiloxy-4-hydroxy-3-(4'-methoxybenzyoxy)butanoate (2.74). Cs_2CO_3 (0.001 g, 0.003 mmol) was added to a solution of lactone (0.032 g, 0.067 mmol) in MeOH (1.0 mL) at 0˚ C. After stirring for 1.5 h, brine (3.0 mL) and CH_2Cl_2 (3.0 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (2 x 3.0 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 0.084 g of a light yellow oil that was purified by flash chromatography (1.0 g silica) eluting with hexanes/EtOAc (1:9) to afford 0.021 g (62%) of **2.74** as a clear colorless oil; ^{1}H NMR δ 7.68 - 7.64 (comp, 4 H), 7.44 - 7.40 (comp, 2 H), 7.37 - 7.33 (comp, 4 H), 7.19 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 4.59 (d, *J* = 11.2 Hz, 1 H), 4.44 (d, *J* = 11.2 Hz, 1 H), 4.40 (d, *J* = 3.4 Hz, 1 H), 3.81 - 3.73 (m, 3 H), 3.79 (s, 3 H), 3.39

(s, 3 H), 1.11 (s, 9 H); ^{13}C NMR δ 171.7, 159.3, 136.1, 136.0, 133.5, 133.2, 129.9, 129.5, 127.7, 127.5, 113.8, 81.1, 73.0, 72.2, 61.2, 55.3, 51.6, 26.9, 19.3; IR (neat) 3568, 2951, 2857, 1751, 1611, 1513 cm^{-1}; mass spectrum (CI) *m/z* 507.2201 [(M-1) requires 507.2203] 509 (base), 507, 431.

NMR Assignments. ^{1}H NMR δ 7.68 - 7.64 (comp, 4 H, Haro), 7.44 - 7.40 (comp, 2 H, Haro), 7.37 - 7.33 (comp, 4 H, Haro), 7.19 (d, *J* = 8.6 Hz, 2 H, C9-H), 6.85 (d, *J* = 8.6 Hz, 2 H, C10-H), 4.59 (d, *J* = 11.2 Hz, 1 H, C7-Ha), 4.44 (d, *J* = 11.2 Hz, 1 H, C7 -Hb), 4.40 (d, *J* = 3.4 Hz, 1 H, C2-H), 3.81 - 3.73 (m, 3 H, C3-H, C4-H), 3.79 (s, 3 H, C12-H), 3.39 (s, 3 H, C13-H), 1.11 (s, 9 H, C6-H); ^{13}C NMR δ 171.7 (C1), 159.3 (C8), 136.1 (Caro), 136.0 (Caro), 133.5 (Caro), 133.2 (Caro), 129.9 (Caro), 129.5 (Caro), 127.7 (Caro), 127.5 (Caro), 113.8 (C10), 81.1 (C2), 73.0 (C3), 72.2 (C7), 61.2 (C4), 55.3 (12), 51.6 (13), 26.9 (6), 19.3 (C5).



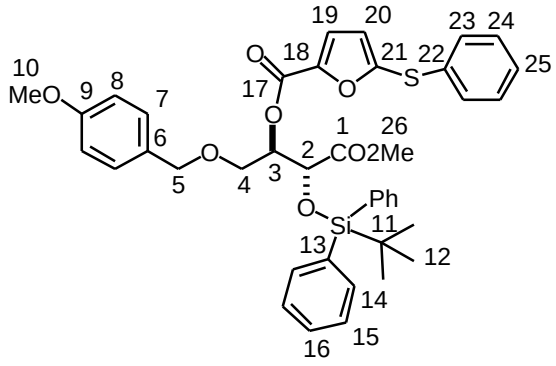
(*2R, 4R*)-(2-(4'methoxyphenyl)-[1,3]dioxolan-4-yl)-*tert*-butyldiphenylsiloxy-acetic acid methyl ester. A solution of **2.74** (2.94 g, 5.78 mmol) and DDQ (1.57 g, 6.94 mol) in CH_2Cl_2 (60 mL) containing 4Å molecular sieves was stirred at rt for 1 h. The reaction mixture was then filtered through celite and the filtrate washed with saturated $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a brown oil that was purified by flash chromatography (60 g silica) eluting with EtOAc/Hex (10:90) to provide 1.63 g (56%) of the acetal as a clear, colorless oil; IR (neat) 2859, 2360, 1743 cm^{-1}; mass spectrum (CI) *m/z* 507.2198 [(M+1) requires 507.2203] 507 (base), 429, 371, 279.



(*2R*, *3R*)-2-*tert*-butyldiphenylsiloxy-3-hydroxy-4-(4'-methoxybenzyloxy)butanoate (2.75). A solution of TFA (1.23 g, 0.832 mL, 10.80 mmol) in CH_3CN (6 mL) at –30 ºC was added *via* cannula to a solution of the acetal (0.547 g, 1.08 mmol) and $NaCNBH_3$ (0.339 g, 5.40 mmol) in MeCN (9.0 mL) at –30 ºC. After stirring for 30 min, saturated $NaHCO_3$ (5 mL) was added and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated to give a clear colorless oil that was purified by flash chromatography (7 g silica) eluting with EtOAc/Hex (30:70) to provide 0.523 g (95%) of **2.75** as a clear, colorless oil; ^{1}H NMR δ 7.65-7.62 (comp, 4 H), 7.44-7.25 (comp, 6 H), 7.20 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 4.43 (d, *J* = 11.3 Hz, 1 H), 4.37 (d, *J* = 11.3 Hz, 1 H), 4.31 (d, *J* = 5.7 Hz, 1 H), 4.07-3.86 (m, 1 H), 3.80 (s, 3 H), 3.59 (d, *J* = 4.9 Hz, 2 H), 3.37 (s, 3 H), 1.08 (s, 9 H); ^{13}C

NMR δ 171.3, 159.1, 135.8, 135.7, 129.8, 139.3, 127.5, 127.4, 113.6, 73.5, 72.9, 72.3, 69.4, 55.1, 51.3, 26.8, 19.3; IR (neat) 3537, 2949, 2858, 1749 cm^{-1}; mass spectrum (FAB) *m/z* 507.2210 [(M+) requires 507.2202] 507 (base), 431, 403, 323, 311, 279.

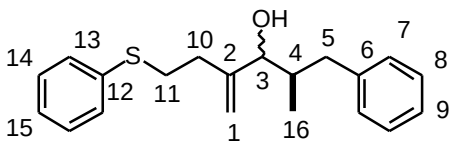
NMR Assignment: ^{1}H NMR δ 7.65-7.62 (comp, 4 H, Haro), 7.44-7.25 (comp, 6 H, Haro), 7.20 (d, *J* = 8.6 Hz, 2 H, Haro), 6.86 (d, *J* = 8.6 Hz, 2 H, Haro), 4.43 (d, *J* = 11.3 Hz, 1 H, C5-Ha), 4.37 (d, *J* = 11.3 Hz, 1 H, C5-Hb), 4.31 (d, *J* = 5.7 Hz, 1 H, C2-H), 4.07-3.86 (m, 1 H, C3-H), 3.80 (s, 3 H, C10-H), 3.59 (d, *J* = 4.9 Hz, 2 H, C4-H), 3.37 (s, 3 H, C117-H), 1.08 (s, 9 H, C12-H); ^{13}C NMR δ 171.3 (C1), 159.1 (Caro), 135.8 (Caro), 135.7 (Caro), 129.8 (Caro), 139.3 (Caro), 127.5 (Caro), 127.4 (Caro), 113.6 (Caro), 73.5 (C4), 72.9 (C3), 72.3 (C5), 69.4 (C2), 55.1 (C10), 51.3 (C17), 26.8 (C12), 19.3 (C11).



Methyl (2*R*,3*R*)- 2-*tert*-butyldiphenylsiloxy-4-(4'-methoxy-benzyloxy)-3-(5-phenylthio-2-furoyloxy)butanoate (2.76). Furoic acid **2.23a** (1.13 mmol, 0.249 g), DMAP (0.515 mmol, 0.063 g), and DCC (1.23 mmol, 0.254) were added sequentially to a solution of **2.75** (1.03 mmol, 0.523 g) in CH_2Cl_2 (10 mL) at 0 ºC. The reaction was then stirred at rt for 4.5 h and then filtered and concentrated to give a light brown oil that was purified by flash chromatography (10 g silica) eluting with EtOAc/Hex (30:70) to provide 0.664 g (91%) of **2.76** as a clear, colorless oil; ^{1}H NMR δ 7.64-7.57 (comp, 4 H), 7.38-7.15 (comp, 8 H), 6.99 (d, *J* = 3.4 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.63 (d, *J* = 3.4 Hz, 1 H), 5.55-5.47 (m, 1 H), 4.54 (d, *J* = 3.3 Hz, 1 H), 4.44 (d, *J* = 4.7, 2 H), 3.85-3.76 (m, 1 H), 3.78 (s, 3 H), 3.36 (s, 3 H), 1.07 (s, 9 H); ^{13}C NMR δ 170.1, 159.1, 156.8, 150.1, 146.4, 135.9, 135.8, 132.5, 132.4, 129.7, 129.2, 127.4, 127.3, 119.7, 118.5,

113.6, 74.1, 72.7, 72.2, 66.8, 55.1, 54.5, 26.7, 19.4; IR(neat) 2951, 2858, 2361, 1732 cm^{-1}; mass spectrum (FAB) *m/z* 711.2440 [(M+1) requires 711.2448] 711 (base) 513, 427, 366.

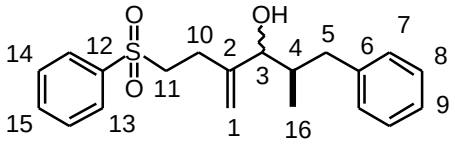
NMR Assigments: ^{1}H NMR δ 7.64-7.57 (comp, 4 H, Haro), 7.38-7.15 (comp, 8 H, Haro), 6.99 (d, *J* = 3.4 Hz, 1 H, C20-H), 6.84 (d, *J* = 8.7 Hz, 2 H, Haro), 6.63 (d, *J* = 3.4 Hz, 1 H, C19-H), 5.55-5.47 (m, 1 H, C3-H), 4.54 (d, *J* = 3.3 Hz, 1 H, C4-H), 4.44 (d, *J* = 4.7, 2 H, C5-H), 3.85-3.76 (m, 1 H, C2-H), 3.78 (s, 3 H, C10-H), 3.36 (s, 3 H, C26-H), 1.07 (s, 9 H, C12-H); ^{13}C NMR δ 170.1 (C1), 159.1 (C6), 156.8 (C17, C18, or C21), 150.1 (C17, C18, or C21), 146.4 (C17, C18, or C21), 135.9 (Caro), 135.8 (Caro), 132.5 (Caro), 132.4 (Caro), 129.7 (Caro), 129.2 (Caro), 127.4 (Caro), 127.3 (Caro), 119.7 (C19 or C20), 118.5 (C19 or C20), 113.6 (Caro), 74.1 (C4), 72.7 (C3), 72.2 (C5), 66.8 (C2), 55.1 (C10), 54.5 (C26), 26.7 (C12), 19.4 (C11).



(*3S, 4R*)-4-methyl-5-phenyl-2-(2-phenylsulfanyl-ethyl)-pent-1-en-3-ol (2.82). A *t*-BuLi solution (1.55M in hexanes, 2.58 mL, 4.00 mmol) was added to a solution of **2.76** (0.365 g, 2.00 mmol) in Et_2O (10 mL) at –78 ºC. After warming to 0 ºC and stirring for 1 h, the solution was warmed to rt for 10 min and then recooled to –78 ºC. A solution of **2.77** in Et_2O was added slowly and then the reaction was stirred at 0 ºC for 2.5 h. Saturated NH_4Cl (5mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 5 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated to give a bright yellow oil that was purified by flash chromatography (10 g silica) eluting with EtOAc/Hex (5:95 – 10:90) to provide 0.102 g (33%) of **2.82** as a yellow oil; ^{1}H NMR (500 MHz) δ 7.36-7.33 (comp, 1 H), 7.31-7.24 (comp, 5 H), 7.20-7.12 (comp, 4 H), 5.16 (s, 0.5 H), 5.13 (s, 0.5 H), 5.01 (s, 0.5 H), 5.01 (s, 0.5 H), 3.93 (d, *J* = 4.6 Hz, 0.5 H), 3.90 (d, *J* = 7.2 Hz, 0.5 H), 3.16-2.98 (comp, 3 H), 2.72 (dd, *J* = 6.6, 13.4 Hz, 1 H), 2.53-2.23 (comp, 2 H), 1.92-1.85 (comp, 1 H), 0.83

(d, *J* = 6.8 Hz, 1.5 H), 0.74 (d, *J* = 6.6 Hz, 1.5 H); IR (neat) 3448, 3061, 3025, 2925 cm^{-1}; mass spectrum (FAB) *m/z* 312.1547 [(M+) requires 312.1548] 313 (base), 295.

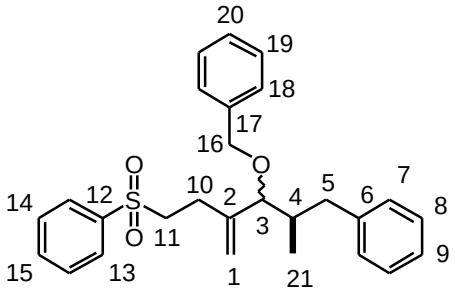
NMR Assignments. ^{1}H NMR (500 MHz) δ 7.36-7.33 (comp, 1 H, Haro), 7.31-7.24 (comp, 5 H, Haro), 7.20-7.12 (comp, 4 H, Haro), 5.16 (s, 0.5 H, C16-Ha (anti)), 5.13 (s, 0.5 H, C16-Ha (syn)), 5.01 (s, 0.5 H, C1-Hb (anti)), 5.01 (s, 0.5 H, C1-Hb(syn)), 3.93 (d, *J* = 4.6 Hz, 0.5 H, C3-H (anti)), 3.90 (d, *J* = 7.2 Hz, 0.5 H, C3-H (syn)), 3.16-2.98 (comp, 3 H, C11-H, C5-Hb), 2.72 (dd, *J* = 6.6, 13.4 Hz, 1 H, C5-Ha), 2.53-2.23 (comp, 2 H, C10-H), 1.92-1.85 (comp, 1 H, C4-H), 0.83 (d, *J* = 6.8 Hz, 1.5 H, C16-H (anti), 0.74 (d, *J* = 6.6 Hz, 1.5 H, C16-H (syn)). *Note: The NMR assignments of syn and anti are based on the assignments of compound* ***2.83****. These assignments were based on the crystal structure obtained from a 14:1 mixture as discussed in the appropriate experimental.*



(*3S, 4R*)- 4-methyl-5-phenyl-2-(2-phenylsulfonyl-ethyl)- pent-1-en-3-ol. A solution of **2.82** (0.049 g, 0.157 mmol), $(PhSe)_2$ (0.052 g, 0.165 mmol) and 30% H_2O_2 (0.106 mL) in 15% CH_2Cl_2/Et_2O (0.820 mL) was stirred for 2 h. Saturated $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were added and the organic layer and the layers were separated. The organic layer was then washed with 5% $NaHSO_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated to give a light yellow oil that was purified by flash chromatography (1 g silica) eluting with EtOAc/Hex (30:70) to provide 0.035 g (65%) of the sulfone as a clear, colorless oil; ^{1}H NMR (500 MHz) δ 7.95-7.88 (comp, 2 H), 7.69-7.65 (comp, 1 H), 7.60-7.56 (comp, 2 H), 7.28-7.25 (comp, 1 H), 7.21-7.17 (comp, 1 H), 7.14-7.09 (comp, 3 H), 5.12 (s, 0.5 H), 5.08 (s, 0.5 H), 4.90 (d, *J* = 0.6 Hz, 0.5 H), 4.89 (d, *J* = 0.8 Hz, 0.5 H), 3.87-3.86 (comp, 1 H), 3.39-3.12 (comp, 2 H), 3.01 (dd, *J* = 3.6, 13.5 Hz, 0.5 H), 2.66 (dd, *J* = 6.6, 13.5 Hz, 0.5 H), 2.61-2.26 (comp, 3 H), 1.88-1.80 (comp, 1 H), 0.82 (d, *J* = 6.6 Hz, 1.5 H), 0.69 (d, *J* = 6.6 Hz, 1.5 H); IR(neat)

3511, 3063, 3025, 2926 cm^{-1}; mass spectrum (FAB) *m/z* 345.1522 [(M+1) requires 345.1524] 345 (base), 327.

NMR Assignments. ^{1}H NMR (500 MHz) δ 7.95-7.88 (comp, 2 H, Haro), 7.69-7.65 (comp, 1 H, Haro), 7.60-7.56 (comp, 2 H, Haro), 7.28-7.25 (comp, 1 H, Haro), 7.21-7.17 (comp, 1 H, Haro), 7.14-7.09 (comp, 3 H, Haro), 5.12 (s, 0.5 H, C1-Ha (anti)), 5.08 (s, 0.5 H, C1-Ha (syn)), 4.90 (d, *J* = 0.6 Hz, 0.5 H, C1-Hb (anti)), 4.89 (d, *J* = 0.8 Hz, 0.5 H, C1-Hb (syn)), 3.87-3.86 (comp, 1 H, C3-H), 3.39-3.12 (comp, 2 H, C11-H), 3.01 (dd, *J* = 3.6, 13.5 Hz, 0.5 H, C5-H), 2.66 (dd, *J* = 6.6, 13.5 Hz, 0.5 H, C5-H), 2.61-2.26 (comp, 3 H, C10-H, C5-H), 1.88-1.80 (comp, 1 H, C4-H), 0.82 (d, *J* = 6.6 Hz, 1.5 H, C16-H (anti)), 0.69 (d, *J* = 6.6 Hz, 1.5 H, C16-H (syn)). *Note: The NMR assignments of syn and anti are based on the assignments of compound* ***2.83****. These assignments were based on the crystal structure obtained from a 14:1 mixture as discussed in the appropriate experimental.*



(*3S, 4R*)-3-benzyloxy-4-methyl-5-phenyl-2-(2-phenylsulfonyl-ethyl)-pent-1-ene (2.83). A solution of NaHMDS (1.0 M in THF, 0.026 mL, 0.026 mmol) and BnBr (0.007 mL, 0.061 mmol) were added to a solution of the alcohol (0.020 mmol, 0.007 g) in THF (0.1 mL) and DMF (0.05 mL). After stirring for 6 h, H_2O (2 mL) and CH_2Cl_2 (5 mL) were added and the layers were separated. The organic layer was washed with 2 mL each of saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give a yellow oil that was purified by flash chromatography (1 g silica) eluting with EtOAc/Hex (20:80) to provide 0.005 g (55%) of **2.83** as a white solid. Recrystallization (EtOAc/Hex) provided a 4.5:1 ratio of diastereomers. After recrystallizing once more (EtOAc/Hex) a 14:1 mixture of diastereomers was obtained. The mother liquor was found to contain a 2:1 mixture of diastereomers enriched in the other isomer; IR(neat) 2924, 1449

cm^{-1}; mass spectrum (FAB) *m/z* 435.1992 [(M+1) requires 435.1993] 435 (base), 417, 327.

The 14:1 mixture was submitted for X-ray crystallography and the results showed the anti diastereomer. Since this sample was not pure, it cannot be concluded that the X-ray structure represents the major diastereomer, however, tentatively all assignments were based on that assumption.

anti diastereomer (2.84): ^{1}H NMR (500 MHz) δ 7.91-7.89 (comp, 2 H), 7.69-7.65 (m, 1 H), 7.59-7.55 (comp, 2 H), 7.34-7.15 (comp, 8 H), 6.99-6.97 (comp, 2 H), 5.10 (s, 1 H), 5.01 (d, *J* = 1.0 Hz, 1 H), 4.43 (d, *J* = 11.8 Hz, 1 H), 4.17 (d, *J* = 11.8 Hz, 1 H), 3.44 (d, *J* = 6.4 Hz, 1 H), 3.28 (ddd, *J* = 4.7, 12.0, 16.8 Hz, 1 H), 3.16 (ddd, *J* = 4.7, 12.1, 16.8 Hz, 1 H), 2.58 (dd, *J* = 5.6, 13.5 Hz, 1 H), 2.47 (ddd, *J* = 4.7, 12.1, 15.8 Hz, 1 H), 2.35 (ddd, *J* = 4.7, 12.0, 15.8 Hz, 1 H), 2.23 (dd, *J* = 9.0, 13.5 Hz, 1 H), 1.88-1.79 (m, 1 H), 0.85 (d, *J* = 6.6 Hz, 3 H).

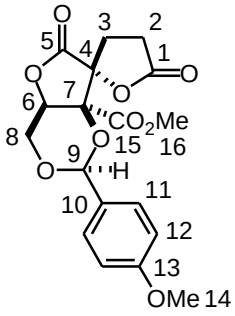
NMR Assignments. ^{1}H NMR (500 MHz) δ 7.91-7.89 (comp, 2 H, Haro), 7.69-7.65 (m, 1 H, Haro), 7.59-7.55 (comp, 2 H, Haro), 7.34-7.15 (comp, 8 H, Haro), 6.99-6.97 (comp, 2 H, Haro), 5.10 (s, 1 H, C1-Ha), 5.01 (d, *J* = 1.0 Hz, 1 H, C1-Hb), 4.43 (d, *J* = 11.8 Hz, 1 H, C16-Ha), 4.17 (d, *J* = 11.8 Hz, 1 H, C16-

Hb), 3.44 (d, *J* = 6.4 Hz, 1 H, C3-H), 3.28 (ddd, *J* = 4.7, 12.0, 16.8 Hz, 1 H, C11-Ha), 3.16 (ddd, *J* = 4.7, 12.1, 16.8 Hz, 1 H, C11-Hb), 2.58 (dd, *J* = 5.6, 13.5 Hz, 1 H, C5-Ha), 2.47 (ddd, *J* = 4.7, 12.1, 15.8 Hz, 1 H, C10-Ha), 2.35 (ddd, *J* = 4.7, 12.0, 15.8 Hz, 1 H, C10-Hb), 2.23 (dd, *J* = 9.0, 13.5 Hz, 1 H, C5-Hb), 1.88-1.79 (m, 1 H, C4-H), 0.85 (d, *J* = 6.6 Hz, 3 H, C21-H).

syn diastereomer (2.85): *Note: the peaks for the syn diastereomer were obtained by subtracting the protons known to belong to the trans isomer whenever possible.* ^{1}H NMR (500 MHz) δ 7.91-7.88 (comp, 4 H), 7.68-7.63 (comp, 2 H), 7.59-7.53 (comp, 4 H), 7.34-7.14 (comp, 16 H), 7.10-7.08 (comp, 2 H), 6.99-6.97 (comp, 2 H), 5.03 (s, 1 H), 5.00 (d, *J* = 1.0 Hz, 1 H), 4.42 (d, *J* = 11.8 Hz, 1 H), 4.22 (d, *J* = 11.8 Hz, 1 H), 3.41 (d, *J* = 8.8 Hz, 1 H), 3.34 (ddd, *J* = 4.8, 11.9, 16.9 Hz, 1 H), 3.23 (ddd, *J* = 5.0, 12.0, 16.9, 1 H), 2.61-2.31 (comp, 6 H), 2.18 (dd, *J* = 7.6, 11.3 Hz, 1 H), 2.04-1.81 (comp, 2 H), 0.60 (d, *J* = 6.8 Hz, 3 H).

NMR Assignments. ^{1}H NMR (500 MHz) δ 7.91-7.88 (comp, 4 H, Haro), 7.68-7.63 (comp, 2 H, Haro), 7.59-7.53 (comp, 4 H, Haro), 7.34-7.14 (comp, 16 H, Haro), 7.10-7.08 (comp, 2 H, Haro), 6.99-6.97 (comp, 2 H, Haro), 5.03 (s, 1 H, C21-Ha), 5.00 (d, *J* = 1.0 Hz, 1 H, C21-Hb), 4.42 (d, *J* = 11.8 Hz, 1 H, C16-Ha),

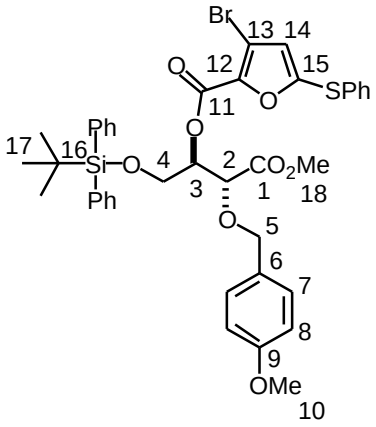
4.22 (d, *J* = 11.8 Hz, 1 H, C16-Hb), 3.41 (d, *J* = 8.8 Hz, 1 H, C3-H), 3.34 (ddd, *J* = 4.8, 11.9, 16.9 Hz, 1 H, C11-Ha), 3.23 (ddd, *J* = 5.0, 12.0, 16.9, 1 H, C11-Hb), 2.61-2.31 (comp, 6 H, C10-H, C5-Ha), 2.18 (dd, *J* = 7.6, 11.3 Hz, 1 H, C5-Hb), 2.04-1.81 (comp, 2 H, C4-H), 0.60 (d, *J* = 6.8 Hz, 3 H, C21-H).



(5*R*,8*R*,9*S*,1′*S*)-8,9-*O*-(*4′*-Methoxybenzylidene)-9-methoxycarbonyl-1,7-dioxaspiro[4.4]non-2,6-dione (**2.88**). 10% Pt/C (0.013 g, 5 mol%) was added to a solution of **2.67** (0.100 g, 0.27 mmol) in EtOAc (5.0 mL) under an atmosphere of H_2. After stirring for 14 h, the suspension was filtered through celite and concentrated under reduced pressure to give 0.101 g (100%) of **2.88** as a clear, colorless oil; ^{1}H NMR δ 7.30 (d, *J* = 8.7 Hz, 1 H), 6.86 (d, 8.7 Hz, 1 H), 5.48 (s, 1H), 4.88 (t, *J* = 1.5 Hz, 1 H), 4.53 (dd, *J* = 1.5, 13.7 Hz, 1 H), 4.32 (dd, *J* = 1.5, 13.7 Hz, 1 H), 3.88 (s, 3 H), 3.77 (s, 3 H), 2.87 - 2.45 (comp, 4 H); ^{13}C NMR δ 173.8, 170.7, 165.9, 160.5, 128.2, 127.3, 113.6, 97.9, 85.7, 80.2, 72.2, 64.9, 55.2, 53.5, 26.6, 21.1; IR (neat) 2959, 1802, 1745, 1615, 1517 cm^{-1}; mass spectrum (CI) *m/z* 379.1030 [(M+1) requires 379.1029] 379 (base).

NMR Assignments. ^{1}H NMR δ 7.30 (d, *J* = 8.7 Hz, 1 H, C11-H), 6.86 (d, 8.7 Hz, 1 H, C12-H), 5.48 (s, 1H, C9-H), 4.88 (t, *J* = 1.5 Hz, 1 H, C6-H), 4.53

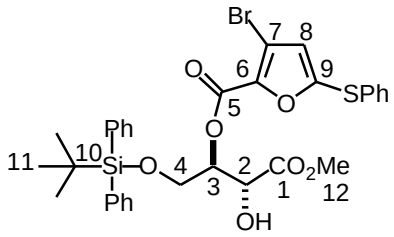
(dd, *J* = 1.5, 13.7 Hz, 1 H, C8-Ha), 4.32 (dd, *J* = 1.5, 13.7 Hz, 1 H, C8-Hb), 3.88 (s, 3 H, C14-H), 3.77 (s, 3 H, C16-H), 2.87 - 2.45 (comp, 4 H, C1-H and C2-H); ^{13}C NMR δ 173.8 (C1, C5, or C15), 170.7 (C1, C5, or C15), 165.9 (C1, C5, or C15), 160.5 (Caro), 128.2 (Caro), 127.3 (Caro), 113.6 (Caro), 97.9 (C9), 85.7 (C4), 80.2 (C7), 72.2 (C3), 64.9 (C9), 55.2 (C14), 53.5 (C16), 26.6 (C2 or C3), 21.1 (C2 or C3).



Methyl (2*R*, 3*R*)-4-*tert*-butyldiphenylsiloxy-3-(3-bromo-5-phenylthio-2-furoyloxy)-2-(4'-methoxybenzyloxy)butanoate (2.91). Furoic acid **2.23a** (0.680 g, 2.27 mmol), DMAP (0.126 g, 1.03 mmol), and DCC (0.512 g, 2.48 mmol) were added sequentially to a solution of alcohol **2.90** (1.05 g, 2.06 mmol) in CH_2Cl_2 (21 mL). After stirring for 1 d, the reaction was filtered and the filtrate was then concentrated under reduced pressure to give 2.05 g of a light tan oil that was purified by flash chromatography (20 g silica) eluting with hexanes/EtOAc (80:20) to afford 1.53 (94%) of **2.91** as a clear, colorless oil; ^{1}H NMR δ 7.64 - 7.60 (comp, 4 H), 7.42 - 7.21 (comp, 13 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 6.60 (s, 1 H), 5.46 (dt, *J* = 5.2, 10.1 Hz, 1 H), 4.72 (d, *J* = 11.5 Hz, 1 H), 4.46 (d, *J* = 11.5 Hz, 1 H), 4.41 (d, *J* = 5.2 Hz, 1 H), 3.99 - 3.92 (m, 2 H), 3.76 (s, 3 H), 3.67 (s, 3

H), 1.00 (s, 9 H); ^{13}C NMR δ 170.1, 159.3, 156.0, 151.2, 142.6, 135.5, 135.4, 132.9, 132.7, 131.7, 129.6, 129.5, 129.4, 128.8, 128.2, 127.5, 127.5, 121.1, 113.6, 109.6, 75.5, 74.8, 72.6, 61.2, 55.1, 52.0, 26.6, 19.0; IR (neat) 2935, 2858, 1727, 1612, 1560, 1513 cm^{-1}; mass spectrum (CI) *m/z* 789.1556 [(M+1) requires 789.1553] 791, 790, 789 (base), 657, 655, 329, 327.

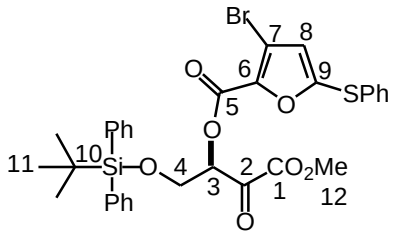
NMR Assignments. ^{1}H NMR δ 7.64 - 7.60 (comp, 4 H, Haro), 7.42 - 7.21 (comp, 13 H, Haro), 6.79 (d, *J* = 8.6 Hz, 2 H, C8-H), 6.60 (s, 1 H, C14-H), 5.46 (dt, *J* = 5.2, 10.1 Hz, 1 H, C3-H), 4.72 (d, *J* = 11.5 Hz, 1 H, C5-Ha), 4.46 (d, *J* = 11.5 Hz, 1 H, C5-Hb), 4.41 (d, *J* = 5.2 Hz, 1 H, C2-H), 3.99 - 3.92 (m, 2 H, C4-H), 3.76 (s, 3 H, C18-H), 3.67 (s, 3 H, C10-H), 1.00 (s, 9 H, C17-H); ^{13}C NMR δ 170.1 (C1), 159.3 (C6), 156.0 (C11), 151.2 (C12), 142.6 (C15), 135.5 (Caro), 135.4 (Caro), 132.9 (Caro), 132.7 (Caro), 131.7 (Caro), 129.6 (Caro), 129.5 (Caro), 129.4 (Caro), 128.8 (Caro), 128.2 (Caro), 127.5 (Caro), 127.5 (Caro), 121.1 (C13 or C14), 113.6 (C13 or C14), 109.6 (C8), 75.5 (C5), 74.8 (C3 or C4), 72.6 (C3 or C4), 61.2 (C2), 55.1 (C10), 52.0 (C18), 26.6 (C17), 19.0 (C16).



Methyl (2*R*, 3*R*)-4-*tert*-butyldiphenylsiloxy-3-(3-bromo-5-phenylthio-2-furoyloxy)-2-hydroxybutanoate. A solution of **2.91** (1.53 g, 1.94 mmol) and DDQ (0.880 g, 3.87 mmol) in CH_2Cl_2/H_2O (10:1, 28.6 mL was stirred for 1 d. The solution was then concentrated under reduced pressure, redissolved in Et_2O (25 mL) and poured into saturated $NaHCO_3$ (30 mL). The organic layer was then washed with saturated $NaHCO_3$ (5 x 25 mL) and subsequently stirred vigorously with a saturated $NaHSO_3$ solution (50 mL) until there was no remaining PMB aldehyde as monitored by TLC. The organic layer was then dried (Na_2SO_4) and concentrated under reduced pressure to give 1.22 g (94%) of the alcohol as a light yellow oil which was used in the next reaction without further purification; ^{1}H NMR δ 7.65 - 7.61 (comp, 5 H), 7.37 - 7.26 (comp, 10 H), 6.55 (s, 1 H), 5.45 (dt, *J* = 3.7, 5.8 Hz, 1 H), 4.58 (d, *J* = 3.7 Hz, 1 H), 3.93 (d, *J* = 5.8 Hz, 2 H), 3.69 (s, 3 H), 1.00 (s, 9 H); ^{13}C NMR δ 172.1, 156.5, 151.6, 142.4, 135.5, 135.4, 132.5,

130.9, 129.7, 129.4, 128.2, 127.6, 121.0, 109.9, 75.3, 70.0, 61.5, 52.7, 26.5, 19.0; IR (neat) 3503, 3133, 3069, 2935, 2858, 1730, 1560, 1468 cm^{-1}; mass spectrum (CI) *m/z* 669.0960 [(M+1) requires 669.0978] 671, 669 (base), 593, 591, 507, 505, 329, 327.

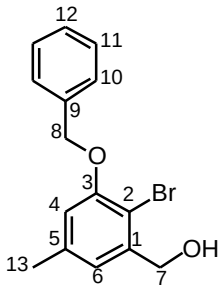
NMR Assignments. ^{1}H NMR δ 7.65 - 7.61 (comp, 5 H, Haro), 7.37 - 7.26 (comp, 10 H, Haro), 6.55 (s, 1 H, C8-H), 5.45 (dt, *J* = 3.7, 5.8 Hz, 1 H, C3-H), 4.58 (d, *J* = 3.7 Hz, 1 H, C2-H), 3.93 (d, *J* = 5.8 Hz, 2 H, C4-H), 3.69 (s, 3 H, C12-H), 1.00 (s, 9 H, C11-H); ^{13}C NMR δ 172.1 (C1), 156.5 (C5), 151.6 (C6), 142.4 (C9), 135.5 (Caro), 135.4 (Caro), 132.5 (Caro), 130.9 (Caro), 129.7 (Caro), 129.4 (Caro), 128.2 (Caro), 127.6 (Caro), 121.0 (Caro), 109.9 (C8), 75.3 (C3), 70.0 (C2), 61.5 (C4), 52.7 (C12), 26.5 (C11), 19.0 (C10).



Methyl (3*R*)-4-*tert*-butyldiphenylsiloxy-3-(3-bromo-5-phenylthio-2-furoyloxy)-2-oxobutanoate (2.92). Dess-Martin periodinane (1.16 g, 2.73 mmol) was added to a solution of the alcohol (1.22 g, 1.82 mmol) in CH_2Cl_2 (18.5 mL) at 0 ºC. After stirring for 5 min, H_2O saturated CH_2Cl_2 (46 mL) was added dropwise. After 1.5 h, the reaction mixture was concentrated under reduced pressure, redissolved in Et_2O and poured into saturated $NaHCO_3$/10% $NaHSO_3$ (1:1; 50 mL). The organic layer was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure to give 0.868 g (71%) of **2.92** as a light yellow oil which was used in the next reaction without further purificaton; ^{1}H NMR δ 7.67 - 7.58 (comp, 5 H), 7.41 - 7.27 (comp, 10 H), 6.59 (s, 1 H), 5.98 (dd, *J* = 3.4, 4.6 Hz, 1 H), 4.40 (dd, *J* = 4.6, 11.3 Hz, 1 H), 4.09 (dd, *J* = 3.4, 11.3 Hz, 1 H), 3.85 (s, 3 H), 0.97 (s, 9 H); ^{13}C NMR δ 186.8, 159.9, 156.1, 152.1, 141.9, 135.5, 135.3, 132.4, 132.0, 131.0, 129.8, 129.5, 128.4, 127.7, 121.1,

110.9, 77.2, 62.9, 53.0, 26.4, 19.1; IR (neat) 3134, 3068, 2935, 2858, 1731, 1561 cm^{-1}; mass spectrum (CI) *m/z* 667.0816 [(M+1) requires 667.0821] 669, 667 (base), 507, 505, 382, 380, 329, 327.

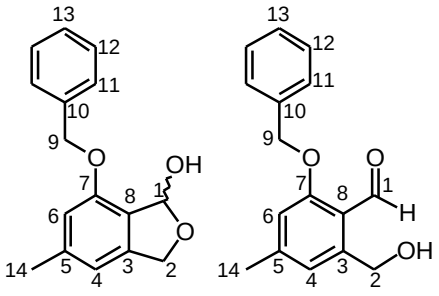
NMR Assignments. ^{1}H NMR δ 7.67 - 7.58 (comp, 5 H, Haro), 7.41 - 7.27 (comp, 10 H, Haro), 6.59 (s, 1 H, C8-H), 5.98 (dd, *J* = 3.4, 4.6 Hz, 1 H, C3-H), 4.40 (dd, *J* = 4.6, 11.3 Hz, 1 H, C4-Ha), 4.09 (dd, *J* = 3.4, 11.3 Hz, 1 H, C4-Hb), 3.85 (s, 3 H, C12-H), 0.97 (s, 9 H, C11-H); ^{13}C NMR δ 186.8 (C2), 159.9 (C5), 156.1 (C6), 152.1 (C9), 141.9 (Caro), 135.5 (Caro), 135.3 (Caro), 132.4 (Caro), 132.0 (Caro), 131.0 (Caro), 129.8 (Caro), 129.5 (Caro), 128.4 (Caro), 127.7 (Caro), 121.1 (Caro), 110.9 (Caro), 77.2 (C3), 62.9 (C4), 53.0 (C12), 26.4 (C11), 19.1 (C10).



(3-Benzyloxy-2-bromo-5-methylphenyl)methanol (3.100). A solution of *n*-BuLi in hexanes (1.61 M, 0.758 mL, 1.22 mmol) was added to a solution of **3.97** (0.114 g, 0.500 mmol) in toluene (1.6 mL) at –10 ºC, and the reaction was then warmed to –5 ºC. After 6 h, dibromotetrafluoroethane (0.122 mL, 1.02 mmol) was added, and the reaction was allowed to warm to rt. After stirring for 10 h, saturated NH_4Cl was added, and the aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was purified by flash chromatography (4 g silica) eluting with EtOAc/hexanes (15:85) to afford **3.100** as a white crystalline solid: m.p; 96 – 98 ºC; ^{1}H NMR δ 7.48 – 7.22 (comp, 5 H), 6.90 (s, 1 H), 6.70 (s, 1 H), 5.10 (s, 2 H), 4.70 (s, 2 H), 2.28 (s, 3 H), 2.00 (s, 1 H); ^{13}C NMR δ 154.8, 140.9, 138.3, 136.6, 128.5, 127.9, 126.9, 122.0, 113.8, 109.3,

70.9, 65.3, 21.4; IR (neat) 2914, 2867, 1588, 1454 cm^{-1}; mass spectrum (CI) *m/z* 306.0262 [(M+) requires 306.0255] 309 307, 291 (base), 289, 279, 277, 211, 209.

NMR Assignments: ^{1}H NMR δ 7.48 – 7.22 (comp, 5 H, Haro), 6.90 (s, 1 H, C6-H), 6.70 (s, 1 H, C4-H), 5.10 (s, 2 H, C9-H), 4.70 (s, 2 H, C7-H), 2.28 (s, 3 H, C13-H), 2.00 (s, 1 H, OH); ^{13}C NMR δ 154.8 (Caro), 140.9 (Caro), 138.3 (Caro), 136.6 (Caro), 128.5 (Caro), 127.9 (Caro), 126.9 (Caro), 122.0 (Caro), 113.8 (Caro), 109.3 (Caro), 70.9 (C9), 65.3 (C7), 21.4 (C13).



7-Benzyloxy-5-methyl-1,3-dihydro-isobenzofuran-1-ol (3.98) and 2-benxyloxy-6-hydroxymethyl-4-methylbenzaldehyde (3.102). A solution of *n*-BuLi in hexanes (1.07M, 4.33 mL, 4.63 mmol) was added slowly to a solution of **3.97** (0.423 g, 1.85 mmol) at –10 ºC to give a viscous yellow solution. The reaction was warmed to –5 ºC and stirred for 4 h. The reaction was then cooled to –78 ºC and DMF (0.716 g, 9.25 mmol). After 15 min, the cold bath was removed and brine (10 mL) was added. After warming to rt, the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL) and dried ($MgSO_4$) and the combined organic layers were concentrated under reduced pressure to give a yellow oil that was filtered through a plug of silica eluting with EtOAc/Hex (20:80) to give 0.456 g (96%) of a white solid as a mixture (4:1) of **3.98** and **3.102**. Recrystallization from EtOAc/Hex gave 0.287 g (60%) of a mixture (12:1) of **3.98** and **3.102** as a white crystalline solid: m.p. 100 – 102 ºC.

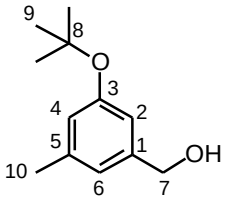
3.98: ^{1}H NMR δ 7.32 – 7.31 (comp, 2 H), 7.18 – 7.06 (comp, 3 H), 6.65 (dd, *J* = 2.1, 7.0 Hz, 1 H), 6.39 (s, 1 H), 6.24 (s, 1 H), 5.05 (dd, *J* = 2.1, 12.7 Hz, 1 H), 4.76 (s, 2 H), 4.72 (d, *J* = 12.7 Hz, 1 H), 2.67 (d, *J* = 7.0 Hz), 2.08 (s, 3 H); ^{13}C NMR δ 154.7, 142.9, 141.0, 137.6, 126.0, 114.1, 112.3, 100.7, 71.9, 69.9, 21.6; IR (neat) 3386, 2921, 2866, 1602, 1497, 1453 cm^{-1}; mass spectrum (CI) *m/z* 257.1185 [(M+1) requires 257.1178] 257, 239 (base), 229, 211, 149, 125, 113.

NMR Assignments for 3.98: ^{1}H NMR δ 7.32 – 7.31 (comp, 2 H, Haro), 7.18 – 7.06 (comp, 3 H, Haro), 6.65 (dd, *J* = 2.1, 7.0 Hz, 1 H, C1-H), 6.39 (s, 1 H, C4-H), 6.24 (s, 1 H, C6-H), 5.05 (dd, *J* = 2.1, 12.7 Hz, 1 H, C2-Ha), 4.76 (s, 2 H, C9-H), 4.72 (d, *J* = 12.7 Hz, 1 H, C2-Hb), 2.67 (d, *J* = 7.0 Hz, OH), 2.08 (s, 3 H, C14-H); ^{13}C NMR δ 154.7 (Caro), 142.9 (Caro), 141.0 (Caro), 137.6 (Caro), 126.0 (Caro), 114.1 (C6), 112.3 (C4), 100.7 (C1), 71.9 (C2), 69.9 (C9), 21.6 (C14).

3.102: ^{1}H NMR δ 10.68 (d, *J* = 0.6 Hz, 1 H), 7.32 – 7.31 (comp, 2 H), 7.18 – 7.06 (comp, 3 H), 6.62 (d, *J* = 0.6 Hz, 1 H), 6.3 (s, 1 H), 4.78, (d, *J* = 7.4

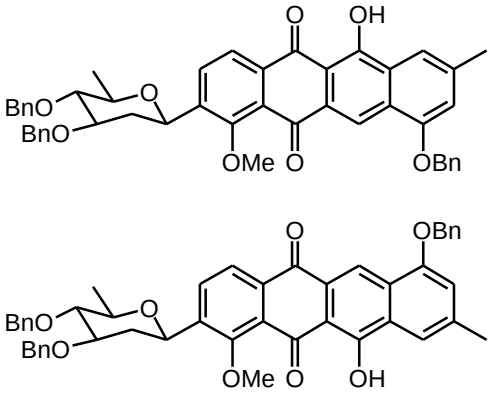
Hz, 2 H), 4.50 (s, 2 H), 3.88 (t, *J* = 7.4 Hz, 1 H), 1.91 (s, 3 H); ^{13}C NMR δ 192.0, 163.1, 146.7, 145.4, 136.5, 123.3, 112.8, 70.6, 64.8, 21.9.

NMR Assignments for 3.102: ^{1}H NMR δ 10.68 (d, *J* = 0.6 Hz, 1 H, C1-H), 7.32 – 7.31 (comp, 2 H, Haro), 7.18 – 7.06 (comp, 3 H, Haro), 6.62 (d, *J* = 0.6 Hz, 1 H, C4-H), 6.3 (s, 1 H, C6-H), 4.78, (d, *J* = 7.4 Hz, 2 H, C2-H), 4.50 (s, 2 H, C9-H), 3.88 (t, *J* = 7.4 Hz, 1 H, OH), 1.91 (s, 3 H, C14-H); ^{13}C NMR δ 192.0 (C1), 163.1 (Caro), 146.7 (Caro), 145.4 (Caro), 136.5 (Caro), 123.3 (C4), 112.8 (C6), 70.6 (C9), 64.8 (C2), 21.9 (C14).



(3-*t*-Butoxy-5-methylphenyl) methanol (3.105). $CaCO_3$ (4.00 g, 40.0 mmol) was added to a solution of the bromide (2.05 g, 8.00 mmol) in dioxane (16 mL) and H_2O (16 mL). After heating at reflux for 24 h, the reaction mixture was concentrated under reduced pressure and acidified with 3 M HCl (1 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and dried ($MgSO_4$) and the combined organic layers were concentrated under reduced pressure. The residual yellow oil was purified by flash chromatography (10 g silica) eluting with EtOAc/hexanes (10:90) to afford 0.724 (48%) of **3.105** as a yellow oil; ^{1}H NMR δ 6.86 (s, 1 H), 6.74 (s, 1 H), 6.70 (s, 1 H), 4.56 (d, *J* = 3.5 Hz, 2 H), 2.27 (s, 3 H), 1.92 (br s, 1 H), 1.30, (s, 9 H); ^{13}C NMR δ 155.4, 141.4, 138.8, 123.8, 122.5, 119,4, 78.2, 65.1, 28.8, 21.2; IR (neat) 3390, 2978, 2932, 2872, 1596 cm^{-1}; mass spectrum (CI) *m/z* 194.1300 [(M+) requires 194.1307] 195, 194, 193, 179, 178, 177 (base), 140, 139, 138, 137, 121.

NMR Assignments: ^{1}H NMR δ 6.86 (s, 1 H, C2-H), 6.74 (s, 1 H, C6-H), 6.70 (s, 1 H, C4-H), 4.56 (d, *J* = 3.5 Hz, 2 H, C7-H), 2.27 (s, 3 H, C10-H), 1.92 (br s, 1 H, OH), 1.30, (s, 9 H, C9-H); ^{13}C NMR δ 155.4 (C3), 141.4 (C5), 138.8 (C1), 123.8 (C2), 122.5 (C2), 119,4 (C6), 78.2 (C4), 65.1 (C7), 28.8 (C9), 21.2 (C8).



2-(3,4-Di-*O*-benzyl-2,6-dideoxy-β-D-*arabino*-hexopyranosyl)-10-benzyloxy-6-hydroxy-1-methoxy-8-methylnaphthacene-5,12-dione (3.118) and 2-(3,4-Di-*O*-benzyl-2,6-dideoxy-β-D-*arabino*-hexopyranosyl)-7-benzyloxy-11-hydroxy-1-methoxy-9-methylnaphthacene-5,12-dione (3.119)

Method A. $CaCl_2$ (0.05 g, 0.45 mmol) and *p*-TsOH (0.006 g, 0.03 mmol) were added to a solution of lactol **3.98** (0.046 g, 0.180 mmol) and juglone **3.81** (0.075 g, 0.150 mmol) in Et_2O (8.4 mL) at 0 ºC and the mixture was allowed to stand in the refrigerator at 4 ºC for 12 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residual dark oil was purified by flash chromatography (5 g silica) eluting with Et_2O/CH_2Cl_2 (0:100 →5:95) to afford

0.062 g of **3.107** and **3.108** as a yellow oil that was used without further purification.

NaH (0.009 g, 0.217 mmol) was added to a solution of **3.107** and **3.108** (0.032 g, 0.043 mmol) in THF (2.40 mL) at 0 ºC. After stirring for 10 min, NCS (0.011 g, 0.086 mmol) was added to the reaction. After 20 min the cold bath was removed, and the reaction was allowed to warm to rt. The mixture was stirred at rt for 4 h, whereupon saturated $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residual dark yellow oil was purified by flash chromatography to afford 0.015 g (47%) of **3.109** and **3.110** as a yellow oil that was used directly in the next step.

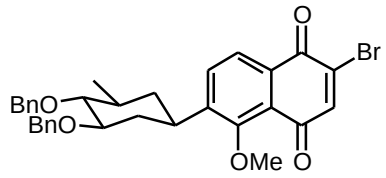
A solution of TMSOTf (0.020 mL, 0.110 mmol) in CH_2Cl_2 (0.5 mL) was added *via* cannula to a solution of **3.109** and **3.110** (0.016 g, 0.022 mmol) in CH_2Cl_2 (1.5 mL) at –78 ºC. After 20 min, the cold bath was removed and the reaction was allowed to warm to rt. The mixtue was stirred at rt for 1 h, and brine (2 mL) was added and stirring was continued for 10 min. The aqueous layer was

extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residual red oil was purified by flash chromatography (1 g silica) eluting with EtOAc/hexanes (30:70) to afford 0.009 g (56%) of a mixture of **3.118**, **3.119**, **3.120** and **3.121** as a red amorphous solid. HPLC separation using two silica gel columns in sequence was performed eluting with EtOAc/Hex (5:95) to afford a mixture of **3.118** and **3.119**.

Method B. $CaCl_2$ (0.021 g, 0.19 mmol) and *p*-TsOH (0.001 g, 0.006 mmol) were added to a solution of lactol **3.98** (0.020 g, 0.077 mmol) and bromojuglone **3.120** (0.037 g, 0.064 mmol) in THF (1.7 mL) at 0 ºC, and the mixture was allowed to stand in the refrigerator at 4 ºC for 12 h. Saturated $NaHCO_3$ (5 mL) was then added to the reaction and the aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residual yellow oil was purified by flash chromatography (5 g silica) eluting with EtOAc/Hex (15/85) to afford 0.011 g of **3.109** and **3.110** as a yellow oil that was used without further purification.

A solution of TMSOTf (0.014 mL, 0.075 mmol) in CH_2Cl_2 (0.4 mL) was added *via* cannula to a solution of **3.109** and **3.110** (0.011 g, 0.015 mmol) in CH_2Cl_2 (1.3 mL) at –78 ºC. After 10 min, the cold bath was removed and the reaction was allowed to warm to rt. The mixture was stirred at rt for 1h, whereupon brine (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residual dark red oil was purified by flash chromatography (2 g silica) eluting with EtOAc/Hex (15:85) to afford 0.004 g (36%) of a mixture of **3.118** and **3.119** as a red, amorphous solid. Further purification was accomplished using HPLC with a Chiralpak AD column eluting with *i*-PrOH/Hex (1:9) to afford 0.001 g of **3.118** as a red amorphous solid where the spectral data was identical to that reported by Suzuki, with the exception of the t at 3.24 ppm that was identified as a dd by Suzuki; ^{1}H NMR (500 MHz) δ 14.35 (s, 1 H), 8.73 (s, 1 H), 8.24 (d, *J* = 8.2 Hz), 7.96 (d, *J* = 8.2 Hz), 7.88 (s, 1 H), 7.52 – 7.55 (m, 2 H), 7.25 – 7.47 (m, 13 H), 6.97 (s, 1 H), 5.29 (s, 2 H), 5.02 (d, *J* = 11.0 Hz, 1 H), 4.85 (dd, *J* = 1.8, 11.7 Hz, 1 H), 4.73 (d, *J* = 11.0 Hz, 1 H), 4.72 (d, *J* = 11.7 Hz, 1 H), 4.64 (d, *J* = 11.7 Hz, 1 H), 3.93 (s, 3 H), 3.86 (ddd, *J* =

5.1, 9.0, 11.3 Hz, 1 H), 3.59 (dq, *J* = 6.1, 9.4 Hz, 1 H), 3.24 (t, 9.0 Hz, 1 H), 2.57 (ddd, *J* = 1.8, 5.0, 12.8 Hz, 1 H), 2.54 (s, 3 H), 1.55 (m, 1 H), 1.41 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (125 MHz) δ 187.5, 181.8, 162.4, 157.7, 156.2, 143.9, 140.1, 138.7, 138.5, 136.3, 135.3, 132.2, 128.8, 128.6, 128.4, 128.4, 128.2, 128.0, 127.7, 127.7, 127.6, 126.8, 126.6, 123.5, 116.3, 116.1, 113.0, 109.7, 83.9, 80.9, 75.9, 75.3, 71.8, 71.3, 70.6, 62.5, 38.3, 22.6, 18.7.



2-Bromo-6-(3.4-dideoxy-β-D-*arabino*-hexopyranosyl)-5-methoxy-1,4-naphthoquinone (3.120). A solution of Br_2 (0.009 mL, 0.179 mmol) in $CHCl_3$ (3.4 mL) was added slowly to a solution of juglone **3.81** (0.081 g, 0.162 mmol) in $CHCl_3$ (1.7 mL) at 0 ºC. After stirring for 20 min, the reaction mixture was concentrated, and 10% aqueous AcOH (0.1 mL) was added. The resulting solution was concentrated, and EtOH (5 mL) added, and the solution was then heated at reflux for 30 min. The reaction was cooled to rt, and H_2O (5 mL) and CH_2Cl_2 (5 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residual yellow oil was purified by flash chromatography (6 g silica) eluting with EtOAc/Hex (15:85) to afford 0.057 g (61%) of **3.120** as a yellow oil; ^{1}H NMR (500 MHz) δ 8.01 (d, *J* = 7.9 Hz, 1 H), 7.91 (dd, *J* = 0.6, 7.9 Hz, 1 H), 7.40 (s, 1 H), 7.27 – 7.35 (m, 9 H), 5.0 (d, *J* = 11.4 Hz, 1 H), 4.79 (dd, *J* = 1.8, 11.2 Hz, 1 H), 4.71 (d, *J* = 9.8 Hz, 1 H), 4.70 (d, *J* =

9.8 Hz), 4.62 (d, *J* = 11.4 Hz, 1 H), 3.86 (s, 3 H), 3.82 (ddd, *J* = 5.1, 9.0, 11.4 Hz, 1 H), 3.56 (dq, *J* = 6.0, 9.4 Hz, 1 H), 3.21 (t, *J* = 8.8 Hz, 1 H), 2.50 (ddd, *J* = 1.8, 4.8, 12.6 Hz, 1 H), 1.50 (m, 1 H), 1.39 (d, *J* = 6.0 Hz, 3 H); ^{13}C (125 MHz) δ 181.5, 177.7, 157.0, 144.4, 141.8, 138.5, 138, 3, 138.0, 132.5, 132.0, 128.4, 128.4, 128.0, 127.7, 127.7, 127.6, 124.7, 123.2, 83.7, 80.7, 75.9, 75.3, 71.5, 71.4, 62.4, 41.1, 41.0, 38.1, 18.6, 15.2; mass spectrum (CI) *m/z* 578.1296 [(M+1) requires 578.1304] 579, 578, 577 (base), 487, 485, 399, 397, 379.

APPENDIX. X-RAY CRYSTALLOGRAPHY DATA

Table A1. Crystal data and structure refinement for **2.67**.

Empirical formula	C18 H16 O9
Formula weight	376.31
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space groupP1 (No. 1)	
Unit cell dimensions	a = 9.759(2) Å alpha = 108.39(2)°.
	b = 10.026(3) Å beta = 97.06(2)°.
	c = 10.776(2) Å gamma = 113.17(2)°.
Volume, Z	882.2(4) A^3, 2
Density (calculated)	1.417 Mg/m^3
Absorption coefficient	0.116 mm^-1
F(000)	392
Crystal size	0.80 x 0.60 x 0.34 mm
Theta range for data collection	2.08 to 26.21 deg.
Limiting indices	-1<=h<=11, -11<=k<=10, -13<=l<=13
Reflections collected	3967
Independent reflections	3967 [R(int) = 0.0000]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3966 / 3 / 488
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0379, wR2 = 0.0953
R indices (all data)	R1 = 0.0428, wR2 = 0.0994
Absolute structure parameter	0.5(9)
Extinction coefficient	6.8(4)x10-5
Largest diff. peak and hole	0.295 and -0.272 e.A^-3

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **2.67**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O1	1904(2)	4886(2)	6144(2)	36(1)
C2	2884(4)	4524(3)	6960(3)	41(1)
O3	3842(3)	4081(2)	6230(2)	44(1)
C4	4886(4)	5363(4)	5986(3)	46(1)
C5	4023(4)	5919(4)	5184(3)	41(1)
O6	3195(3)	4688(3)	3812(2)	49(1)
C7	1770(5)	4552(4)	3380(3)	49(1)
C8	1544(4)	5791(3)	4479(3)	38(1)
O9	1968(3)	7143(3)	4136(2)	44(1)
C10	702(4)	7428(4)	3958(3)	44(1)
C11	-563(4)	6255(4)	4207(3)	43(1)
C12	-90(4)	5316(3)	4520(3)	40(1)
C13	2730(4)	6132(3)	5747(3)	37(1)
C14	1824(4)	3202(3)	7257(3)	40(1)
C15	1045(5)	1672(4)	6276(3)	50(1)
C16	26(5)	467(4)	6543(3)	53(1)
C17	-248(4)	769(4)	7811(3)	45(1)
C18	508(4)	2282(4)	8799(3)	48(1)
C19	1534(4)	3480(4)	8509(3)	45(1)
O20	-1263(4)	-526(3)	7975(2)	60(1)
C21	-1663(6)	-257(5)	9219(4)	65(1)
O22	881(4)	3603(4)	2303(2)	75(1)
O23	777(3)	8482(3)	3634(3)	58(1)
C24	3345(4)	7764(3)	6892(3)	39(1)
O25	4683(3)	8676(3)	7357(3)	70(1)
O26	2214(3)	8016(2)	7284(2)	48(1)
C27	2679(5)	9535(4)	8382(3)	55(1)
O1'	5911(2)	1731(2)	2249(2)	36(1)
C2'	5231(4)	2728(3)	2139(3)	38(1)

O3'	3627(3)	1843(3)	1524(2)	46(1)
C4'	2884(4)	1068(4)	2331(4)	51(1)
C5'	3519(4)	-15(4)	2532(3)	45(1)
O6'	3133(3)	-1281(2)	1205(2)	54(1)
C7'	4335(5)	-1566(4)	1055(3)	54(1)
C8'	5658(4)	-581(4)	2384(3)	41(1)
O9'	5404(2)	-1559(2)	3144(2)	42(1)
C10'	6677(4)	-1816(4)	3379(3)	45(1)
C11'	7823(4)	-906(5)	2830(4)	55(1)
C12'	7254(4)	-190(4)	2264(3)	48(1)
C13'	5297(3)	802(3)	2993(3)	36(1)
C14'	5968(4)	3557(3)	1278(3)	38(1)
C15'	5271(4)	4302(4)	748(3)	52(1)
C16'	5934(5)	5113(5)	-21(4)	58(1)
C17'	7304(4)	5181(4)	-281(3)	48(1)
C18'	8012(4)	4447(4)	237(3)	49(1)
C19'	7333(4)	3646(4)	1013(3)	44(1)
O20'	7839(4)	5985(3)	-1071(3)	66(1)
C21'	9240(6)	6106(6)	-1384(5)	79(1)
O22'	4328(5)	-2487(3)	32(3)	85(1)
O23'	6706(3)	-2648(3)	3959(2)	54(1)
C24'	6008(4)	1759(4)	4532(3)	42(1)
O25'	7067(4)	3019(4)	5015(3)	102(1)
O26'	5225(4)	1089(3)	5224(3)	81(1)
C27'	5831(8)	1904(5)	6691(4)	96(2)

Table A3. Bond lengths [A] and angles [°] for **2.67**

O1-C13	1.423(3)	C17-C18	1.373(4)
O1-C2	1.444(4)	C18-C19	1.383(5)
C2-O3	1.405(4)	C18-H18	0.96
C2-C14	1.483(4)	C19-H19	0.96
C2-H2	0.96	O20-C21	1.416(4)
O3-C4	1.417(4)	C21-H21A	0.96
C4-C5	1.504(5)	C21-H21B	0.96
C4-H4A	0.96	C21-H21C	0.96
C4-H4B	0.96	C24-O25	1.185(4)
C5-O6	1.460(4)	C24-O26	1.314(4)
C5-C13	1.524(4)	O26-C27	1.454(4)
C5-H5	0.96	C27-H27A	0.96
O6-C7	1.350(5)	C27-H27B	0.96
C7-O22	1.188(4)	C27-H27C	0.96
C7-C8	1.531(4)	O1'-C13'	1.421(3)
C8-O9	1.434(4)	O1'-C2'	1.426(4)
C8-C12	1.484(5)	C2'-O3'	1.399(4)
C8-C13	1.527(4)	C2'-C14'	1.500(4)
O9-C10	1.377(4)	C2'-H2'	0.96
C10-O23	1.193(4)	O3'-C4'	1.423(4)
C10-C11	1.455(4)	C4'-C5'	1.501(5)
C11-C12	1.311(5)	C4'-H4'A	0.96
C11-H11	0.96	C4'-H4'B	0.96
C12-H12	0.96	C5'-O6'	1.464(4)
C13-C24	1.527(4)	C5'-C13'	1.530(4)
C14-C19	1.377(4)	C5'-H5'	0.96
C14-C15	1.382(4)	O6'-C7'	1.328(5)
C15-C16	1.370(5)	C7'-O22'	1.192(4)
C15-H15	0.96	C7'-C8'	1.530(5)
C16-C17	1.386(5)	C8'-O9'	1.435(4)
C16-H16	0.96	C8'-C12'	1.482(5)
C17-O20	1.369(4)	C8'-C13'	1.531(5)

O9'-C10'	1.375(4)	C14-C2-H2	109.8(2)
C10'-O23'	1.196(4)	C2-O3-C4	110.7(2)
C10'-C11'	1.460(5)	O3-C4-C5	111.0(3)
C11'-C12'	1.305(5)	O3-C4-H4A	109.5(2)
C11'-H11'	0.96	C5-C4-H4A	109.3(2)
C12'-H12'	0.96	O3-C4-H4B	109.4(2)
C13'-C24'	1.530(4)	C5-C4-H4B	109.5(2)
C14'-C19'	1.372(5)	H4A-C4-H4B	108
C14'-C15'	1.386(5)	O6-C5-C4	109.3(2)
C15'-C16'	1.382(5)	O6-C5-C13	103.5(3)
C15'-H15'	0.96	C4-C5-C13	112.7(3)
C16'-C17'	1.380(6)	O6-C5-H5	110.2(2)
C16'-H16'	0.96	C4-C5-H5	110.5(2)
C17'-O20'	1.363(4)	C13-C5-H5	110.5(2)
C17'-C18'	1.377(5)	C7-O6-C5	111.3(2)
C18'-C19'	1.386(4)	O22-C7-O6	122.9(3)
C18'-H18'	0.96	O22-C7-C8	127.9(3)
C19'-H19'	0.96	O6-C7-C8	109.2(3)
O20'-C21'	1.416(6)	O9-C8-C12	104.8(3)
C21'-H21D	0.96	O9-C8-C13	111.4(2)
C21'-H21E	0.96	C12-C8-C13	117.7(2)
C21'-H21F	0.96	O9-C8-C7	106.9(2)
C24'-O25'	1.166(4)	C12-C8-C7	114.5(3)
C24'-O26'	1.282(4)	C13-C8-C7	101.2(3)
O26'-C27'	1.446(5)	C10-O9-C8	108.5(2)
C27'-H27D	0.96	O23-C10-O9	120.3(3)
C27'-H27E	0.96	O23-C10-C11	131.7(3)
C27'-H27F	0.96	O9-C10-C11	108.1(3)
C13-O1-C2	114.3(2)	C12-C11-C10	109.1(3)
O3-C2-O1	109.8(2)	C12-C11-H11	125.1(2)
O3-C2-C14	110.9(3)	C10-C11-H11	125.8(2)
O1-C2-C14	106.4(3)	C11-C12-C8	109.5(3)
O3-C2-H2	109.84(14)	C11-C12-H12	125.2(2)
O1-C2-H2	110.04(13)	C8-C12-H12	125.3(2)

O1-C13-C5	111.5(2)	C24-O26-C27	116.1(3)
O1-C13-C8	102.5(2)	O26-C27-H27A	109.7(2)
C5-C13-C8	102.9(2)	O26-C27-H27B	109.5(2)
O1-C13-C24	112.5(2)	H27A-C27-H27B	109.5
C5-C13-C24	111.5(3)	O26-C27-H27C	109.2(2)
C8-C13-C24	115.3(3)	H27A-C27-H27C	109.5
C19-C14-C15	117.9(3)	H27B-C27-H27C	109.5
C19-C14-C2	120.6(3)	C13'-O1'-C2'	115.4(2)
C15-C14-C2	121.4(3)	O3'-C2'-O1'	110.9(2)
C16-C15-C14	121.1(3)	O3'-C2'-C14'	109.3(2)
C16-C15-H15	119.2(2)	O1'-C2'-C14'	107.9(2)
C14-C15-H15	119.7(2)	O3'-C2'-H2'	109.6(2)
C15-C16-C17	120.1(3)	O1'-C2'-H2'	109.54(13)
C15-C16-H16	120.1(2)	C14'-C2'-H2'	109.60(14)
C17-C16-H16	119.7(2)	C2'-O3'-C4'	110.8(2)
O20-C17-C18	125.0(3)	O3'-C4'-C5'	111.0(3)
O20-C17-C16	115.2(3)	O3'-C4'-H4'A	109.3(2)
C18-C17-C16	119.8(3)	C5'-C4'-H4'A	109.5(2)
C17-C18-C19	119.1(3)	O3'-C4'-H4'B	109.3(2)
C17-C18-H18	120.7(2)	C5'-C4'-H4'B	109.7(2)
C19-C18-H18	120.2(2)	H4'A-C4'-H4'B	108
C14-C19-C18	121.9(3)	O6'-C5'-C4'	108.6(3)
C14-C19-H19	119.2(2)	O6'-C5'-C13'	103.4(3)
C18-C19-H19	118.8(2)	C4'-C5'-C13'	112.1(3)
C17-O20-C21	117.2(3)	O6'-C5'-H5'	110.8(2)
O20-C21-H21A	109.9(2)	C4'-C5'-H5'	110.7(2)
O20-C21-H21B	109.1(2)	C13'-C5'-H5'	110.9(2)
H21A-C21-H21B	109.5	C7'-O6'-C5'	111.1(3)
O20-C21-H21C	109.4(2)	O22'-C7'-O6'	123.4(4)
H21A-C21-H21C	109.5	O22'-C7'-C8'	126.7(4)
H21B-C21-H21C	109.5	O6'-C7'-C8'	109.8(3)
O25-C24-O26	125.0(3)	O9'-C8'-C12'	104.7(3)
O25-C24-C13	123.2(3)	O9'-C8'-C7'	105.3(2)
O26-C24-C13	111.7(3)	C12'-C8'-C7'	116.7(3)

O9'-C8'-C13'	112.3(2)	C14'-C19'-C18'	121.9(3)
C12'-C8'-C13'	117.3(3)	C14'-C19'-H19'	119.1(2)
C7'-C8'-C13'	100.2(3)	C18'-C19'-H19'	119.1(2)
C10'-O9'-C8'	108.7(2)	C17'-O20'-C21'	118.5(3)
O23'-C10'-O9'	120.7(3)	O20'-C21'-H21D	109.5(2)
O23'-C10'-C11'	131.7(3)	O20'-C21'-H21E	109.4(2)
O9'-C10'-C11'	107.6(3)	H21D-C21'-H21E	109.5
C12'-C11'-C10'	109.4(3)	O20'-C21'-H21F	109.6(3)
C12'-C11'-H11'	125.7(2)	H21D-C21'-H21F	109.5
C10'-C11'-H11'	124.9(2)	H21E-C21'-H21F	109.5
C11'-C12'-C8'	109.5(3)	O25'-C24'-O26'	123.7(3)
C11'-C12'-H12'	124.8(2)	O25'-C24'-C13'	123.5(3)
C8'-C12'-H12'	125.7(2)	O26'-C24'-C13'	112.5(3)
O1'-C13'-C5'	110.7(2)	C24'-O26'-C27'	116.2(3)
O1'-C13'-C24'	111.5(2)	O26'-C27'-H27D	109.8(2)
C5'-C13'-C24'	114.2(3)	O26'-C27'-H27E	109.5(3)
O1'-C13'-C8'	101.4(2)	H27D-C27'-H27E	109.5
C5'-C13'-C8'	102.0(2)	O26'-C27'-H27F	109.1(3)
C24'-C13'-C8'	115.9(3)	H27D-C27'-H27F	109.5
C19'-C14'-C15'	118.0(3)	H27E-C27'-H27F	109.5
C19'-C14'-C2'	122.8(3)		
C15'-C14'-C2'	119.2(3)		
C16'-C15'-C14'	121.0(3)		
C16'-C15'-H15'	119.5(2)		
C14'-C15'-H15'	119.5(2)		
C17'-C16'-C15'	120.1(3)		
C17'-C16'-H16'	120.1(2)		
C15'-C16'-H16'	119.9(2)		
O20'-C17'-C18'	125.1(4)		
O20'-C17'-C16'	115.2(3)		
C18'-C17'-C16'	119.7(3)		
C17'-C18'-C19'	119.4(3)		
C17'-C18'-H18'	120.2(2)		
C19'-C18'-H18'	120.4(2)		

Table A4. Anisotropic displacement parameters (A^2 x 10^3) for **2.67**. The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O1	39(1)	34(1)	37(1)	16(1)	14(1)	18(1)
C2	44(2)	40(2)	34(1)	10(1)	6(1)	21(1)
O3	46(1)	43(1)	48(1)	16(1)	14(1)	26(1)
C4	37(2)	44(2)	52(2)	12(1)	14(1)	18(2)
C5	43(2)	38(1)	45(2)	14(1)	20(1)	20(1)
O6	57(1)	58(1)	39(1)	13(1)	20(1)	36(1)
C7	62(2)	56(2)	39(2)	18(1)	16(2)	36(2)
C8	43(2)	37(1)	37(1)	15(1)	14(1)	20(1)
O9	45(1)	51(1)	54(1)	32(1)	25(1)	28(1)
C10	47(2)	48(2)	46(2)	22(1)	19(1)	27(2)
C11	36(2)	45(2)	44(2)	17(1)	12(1)	16(1)
C12	38(2)	35(1)	39(1)	12(1)	10(1)	12(1)
C13	39(2)	33(1)	39(1)	14(1)	15(1)	16(1)
C14	47(2)	38(1)	34(1)	12(1)	6(1)	22(1)
C15	69(2)	43(2)	32(1)	14(1)	14(2)	22(2)
C16	71(2)	38(2)	40(2)	10(1)	15(2)	19(2)
C17	57(2)	42(2)	42(2)	19(1)	14(1)	26(2)
C18	61(2)	50(2)	35(1)	15(1)	17(1)	29(2)
C19	54(2)	37(1)	37(1)	8(1)	10(1)	21(2)
O20	78(2)	49(1)	54(1)	24(1)	31(1)	24(1)
C21	78(3)	59(2)	58(2)	27(2)	31(2)	26(2)
O22	90(2)	92(2)	36(1)	0(1)	1(1)	60(2)
O23	54(2)	61(1)	85(2)	45(1)	32(1)	35(1)
C24	48(2)	32(1)	40(1)	13(1)	16(1)	21(1)
O25	44(2)	41(1)	91(2)	-1(1)	17(1)	10(1)
O26	47(1)	44(1)	45(1)	4(1)	14(1)	24(1)
C27	66(2)	45(2)	49(2)	6(1)	19(2)	31(2)
O1'	38(1)	41(1)	35(1)	16(1)	13(1)	21(1)

C2'	40(2)	37(1)	35(1)	6(1)	8(1)	22(1)
O3'	37(1)	47(1)	50(1)	13(1)	8(1)	22(1)
C4'	36(2)	48(2)	64(2)	17(2)	13(2)	20(2)
C5'	34(2)	42(2)	48(2)	13(1)	9(1)	13(1)
O6'	47(1)	36(1)	56(1)	3(1)	-7(1)	15(1)
C7'	66(2)	42(2)	48(2)	11(1)	0(2)	30(2)
C8'	42(2)	44(2)	40(2)	18(1)	12(1)	22(2)
O9'	38(1)	44(1)	50(1)	24(1)	15(1)	20(1)
C10'	43(2)	53(2)	44(2)	21(1)	14(1)	24(2)
C11'	48(2)	75(2)	64(2)	41(2)	27(2)	35(2)
C12'	55(2)	61(2)	50(2)	33(2)	30(2)	35(2)
C13'	31(2)	38(1)	36(1)	13(1)	8(1)	13(1)
C14'	44(2)	35(1)	30(1)	6(1)	6(1)	21(1)
C15'	56(2)	59(2)	56(2)	24(2)	16(2)	39(2)
C16'	71(2)	61(2)	60(2)	32(2)	17(2)	43(2)
C17'	63(2)	39(2)	38(2)	16(1)	7(2)	22(2)
C18'	48(2)	54(2)	50(2)	24(2)	15(2)	26(2)
C19'	50(2)	45(2)	42(2)	22(1)	10(1)	27(2)
O20'	76(2)	62(2)	67(2)	41(1)	19(1)	28(2)
C21'	64(3)	82(3)	87(3)	54(3)	19(2)	14(2)
O22'	121(3)	71(2)	49(1)	-9(1)	-10(2)	67(2)
O23'	55(2)	69(2)	61(1)	43(1)	24(1)	36(1)
C24'	41(2)	40(2)	38(1)	16(1)	13(1)	12(2)
O25'	77(2)	98(2)	40(1)	17(1)	4(1)	-33(2)
O26'	100(2)	54(1)	44(1)	13(1)	27(2)	-3(2)
C27'	151(5)	68(2)	41(2)	20(2)	37(3)	22(3)

Table A5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **2.67**.

	x	y	z	U(eq)
H2	3512(4)	5428(3)	7796(3)	49
H4A	5531(4)	5039(4)	5490(3)	56
H4B	5548(4)	6220(4)	6841(3)	56
H5	4730(4)	6880(4)	5140(3)	50
H11	-1587(4)	6168(4)	4141(3)	51
H12	-706(4)	4452(3)	4739(3)	48
H15	1226(5)	1444(4)	5395(3)	60
H16	-508(5)	-590(4)	5851(3)	64
H18	332(4)	2508(4)	9683(3)	57
H19	2059(4)	4536(4)	9202(3)	54
H21A	-2379(6)	-1242(5)	9219(4)	97
H21B	-738(6)	225(5)	9960(4)	97
H21C	-2134(6)	436(5)	9325(4)	97
H27A	1775(5)	9605(4)	8591(3)	82
H27B	3345(5)	9638(4)	9177(3)	82
H27C	3228(5)	10368(4)	8102(3)	82
H2'	5429(4)	3495(3)	3030(3)	46
H4'A	1787(4)	467(4)	1889(4)	61
H4'B	3038(4)	1846(4)	3201(4)	61
H5'	3102(4)	-442(4)	3160(3)	54
H11'	8835(4)	-849(5)	2882(4)	66
H12'	7787(4)	472(4)	1825(3)	58
H15'	4310(4)	4249(4)	913(3)	62
H16'	5435(5)	5624(5)	-379(4)	69
H18'	8970(4)	4495(4)	68(3)	58
H19'	7830(4)	3133(4)	1369(3)	52
H21D	9474(6)	6698(6)	-1943(5)	119
H21E	10069(6)	6636(6)	-553(5)	119
H21F	9127(6)	5066(6)	-1864(5)	119
H27D	5175(8)	1304(5)	7115(4)	144

H27E	6863(8)	2030(5)	6970(4)	144
H27F	5860(8)	2926(5)	6961(4)	144

Figure A1. View of molecule 1 of **2.67** showing the atom labeling scheme. Thermal ellipsoids are scaled to the 50% probability level. Most hydrogen atoms have been omitted for clarity.

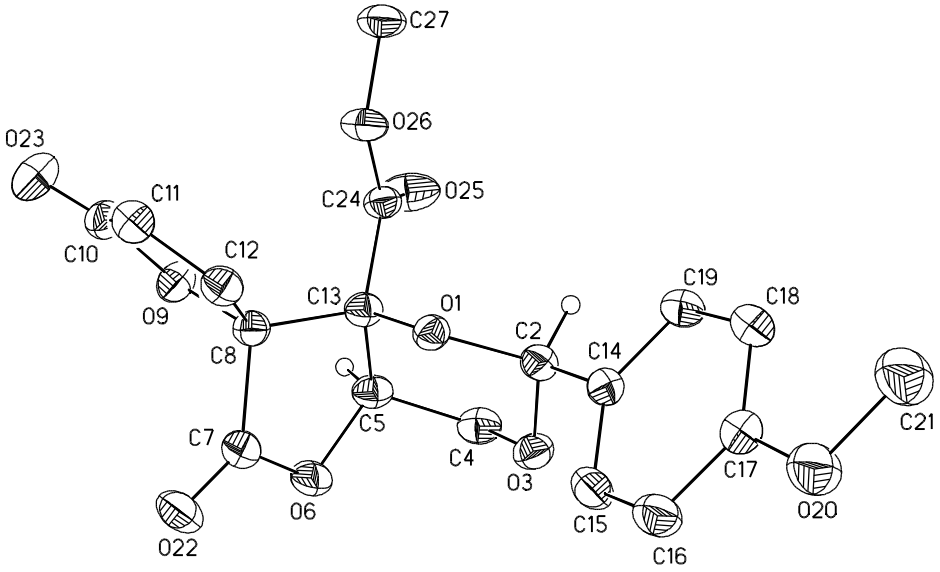


Figure A2. View of molecule 2 of **2.67** showing the atom labeling scheme. Thermal ellipsoids are scaled to the 50% probability level. Most hydrogen atoms have been omitted for clarity.

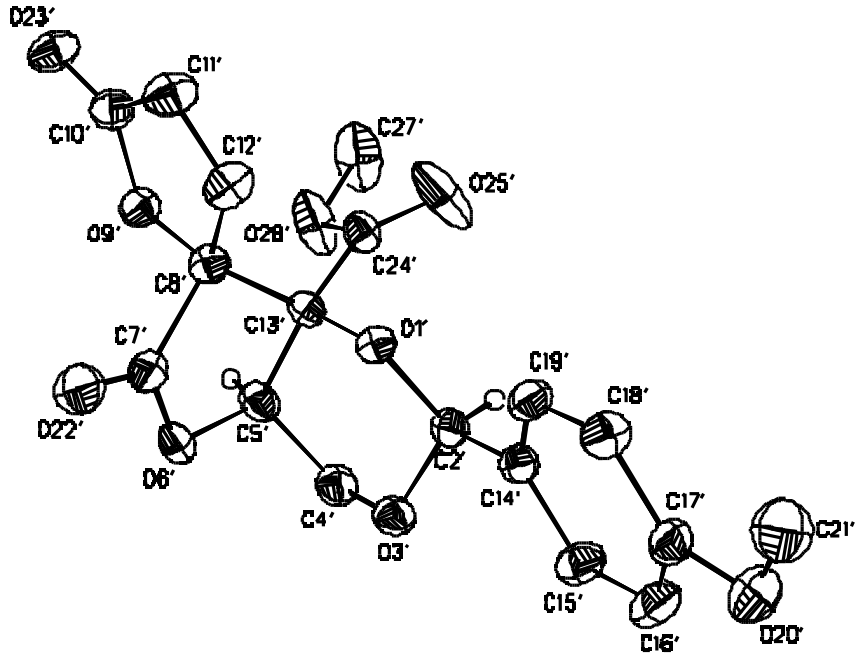


Figure A3. Fit by least squares of selected atoms from molecule 1 (dashed lines) to the equivalent atoms of molecule 2 (solid lines) of **2.67** illustrating the conformational differences between the two crystallographically independent molecules. The atoms of molecule 2 used in the fit are labeled.

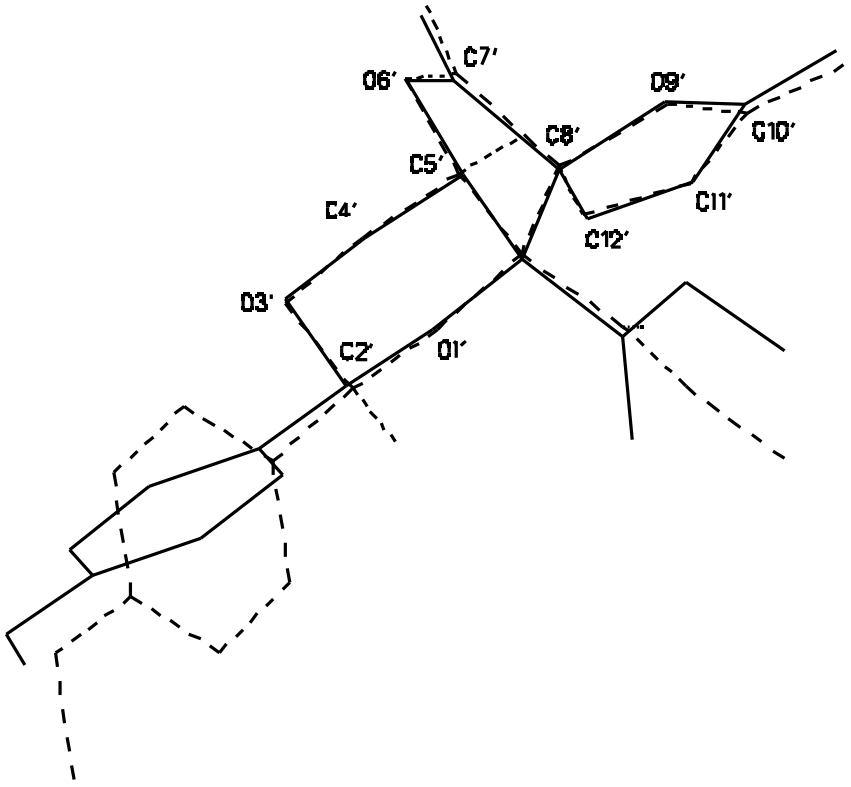


Figure A4. Unit cell packing diagram for **2.67**. The view direction is approximately down the **a** axis. Molecules 2 are shown in wireframe form. There are many close C-H···O contacts. A complete listing of these contacts is found in Table 6.

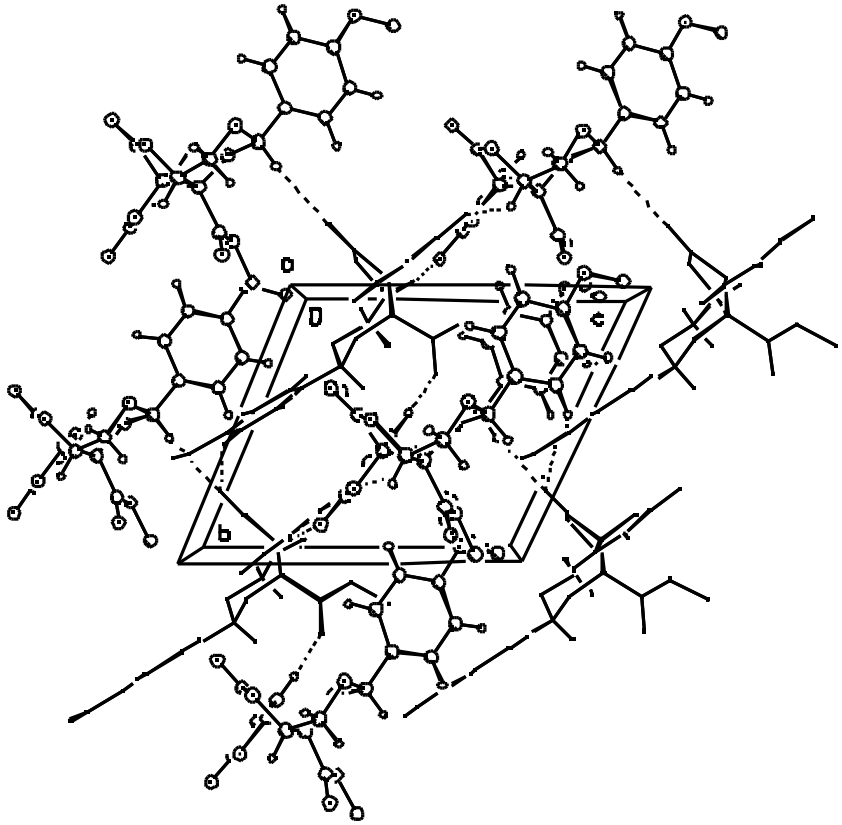


Table A6. Crystal data and structure refinement for **2.71**.

Empirical formula	C26 H28 O9 Si
Formula	512.57
Temperature	198(2) K
Wavelength	0.71073Å
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 8.744(3) alpha = 90_. b = 16.503(4) beta = 90_. c = 17.372(4) gamma = 90_.
Volume, Z	2506.8(12) A^3, 4
Density (calculated)	1.36 Mg/m^3
Absorption coefficient	0.15 mm^-1
F(000	1080
Crystal size	.17 x .28 x .64 mm
Theta range for data collection	2.3 to 27.5 deg.
Limiting indices	-11<=h<=11, 0<=k<=21, 0<=l<=22
Reflections collected	6125
Independent reflections	5755 [R(int) = 0.040]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5754 / 0 / 326
Goodness-of-fit on F^2	1.074
Final R indices [I>2sigma(I)]	R1 = 0.070, wR2 = 0.110
R indices (all data)	R1 = 0.138, wR2 = 0.132
Absolute structure parameter	-0.2(2)
Extinction coefficient	4.5(6)x10-6
Largest diff. peak and hole	0.27 and -0.22 e.A^-3

Table A7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **2.71**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O1	7837(3)	1899(2)	9350(2)	43(1)
C2	7210(6)	1185(3)	9136(2)	42(1)
C3	8455(5)	545(3)	9053(2)	34(1)
C4	9904(5)	1055(3)	9002(2)	33(1)
O5	10069(3)	1252(2)	8214(2)	32(1)
C6	11048(5)	1932(3)	8091(2)	35(1)
O7	10366(4)	2627(2)	8392(2)	41(1)
C8	10282(6)	2565(3)	9211(3)	47(1)
C9	9489(5)	1819(3)	9473(3)	40(1)
O10	5859(4)	1105(2)	9068(2)	61(1)
O11	8459(3)	134(2)	9785(2)	43(1)
C12	7831(7)	-623(3)	9702(3)	55(2)
C13	7360(7)	-745(3)	8881(2)	58(2)
C14	8207(5)	-109(3)	8439(2)	42(1)
O15	7715(6)	-1049(2)	10245(2)	83(1)
Si16	7530(1)	120(1)	7418(1)	29(1)
C17	6854(5)	1166(2)	7256(2)	36(1)
C18	9155(5)	-116(3)	6768(3)	45(1)
C19	5896(5)	-599(2)	7228(2)	30(1)
C20	4449(4)	-449(2)	7521(3)	36(1)
C21	3241(5)	-966(3)	7401(3)	44(1)
C22	3454(6)	-1655(3)	6976(3)	44(1)
C23	4875(6)	-1833(3)	6684(3)	47(1)
C24	6096(5)	-1310(3)	6808(2)	39(1)
C25	11321(6)	579(3)	9274(3)	40(1)
O26	11905(4)	73(2)	8896(2)	67(1)
O27	11765(3)	809(2)	9964(2)	48(1)
C28	13028(5)	343(3)	10284(3)	60(2)
C29	11327(5)	1995(3)	7247(2)	34(1)

C30	12603(6)	1636(3)	6951(3)	48(1)
C31	12863(5)	1601(3)	6172(3)	49(1)
C32	11819(6)	1931(3)	5677(3)	44(1)
C33	10530(6)	2322(3)	5957(3)	45(1)
C34	10299(5)	2349(3)	6747(3)	42(1)
O35	12146(4)	1841(2)	4912(2)	62(1)
C36	11032(7)	2104(4)	4374(3)	73(2)

Table A8. Bond lengths [Å] and angles [°] for **2.71**.

O1-C2	1.351(5)	C17-H17C	0.96
O1-C9	1.466(5)	C18-H18A	0.96
C2-O10	1.195(5)	C18-H18B	0.96
C2-C3	1.524(6)	C18-H18C	0.96
C3-O11	1.441(4)	C19-C20	1.386(6)
C3-C4	1.523(6)	C19-C24	1.392(5)
C3-C14	1.533(6)	C20-C21	1.375(5)
C4-O5	1.413(5)	C20-H20	0.96
C4-C25	1.541(6)	C21-C22	1.368(6)
C4-C9	1.546(6)	C21-H21	0.96
O5-C6	1.429(5)	C22-C23	1.373(6)
C6-O7	1.395(5)	C22-H22	0.96
C6-C29	1.489(6)	C23-C24	1.390(6)
C6-H6	0.96	C23-H23	0.96
O7-C8	1.429(5)	C24-H24	0.96
C8-C9	1.485(6)	C25-O26	1.180(5)
C8-H8A	0.96	C25-O27	1.316(5)
C8-H8B	0.96	O27-C28	1.455(5)
C9-H9	0.96	C28-H28A	0.96
O11-C12	1.373(6)	C28-H28B	0.96
C12-O15	1.180(5)	C28-H28C	0.96
C12-C13	1.499(6)	C29-C30	1.364(6)
C13-C14	1.497(6)	C29-C34	1.381(6)
C13-H13A	0.96	C30-C31	1.373(6)
C13-H13B	0.96	C30-H30	0.96
C14-Si16	1.907(4)	C31-C32	1.368(6)
C14-H14	0.96	C31-H31	0.96
Si16-C17	1.845(4)	C32-O35	1.367(5)
Si16-C18	1.857(4)	C32-C33	1.386(6)
Si16-C19	1.886(4)	C33-C34	1.386(6)
C17-H17A	0.96	C33-H33	0.96
C17-H17B	0.96	C34-H34	0.96

O35-C36	1.420(6)	O1-C9-C8	109.9(4)
C36-H36A	0.96	O1-C9-C4	103.2(3)
C36-H36B	0.96	C8-C9-C4	113.8(4)
C36-H36C	0.96	O1-C9-H9	109.6(2)
C2-O1-C9	111.2(4)	C8-C9-H9	110.2(3)
O10-C2-O1	121.7(5)	C4-C9-H9	109.9(2)
O10-C2-C3	128.4(5)	C12-O11-C3	109.6(3)
O1-C2-C3	109.9(4)	O15-C12-O11	119.5(4)
O11-C3-C4	108.1(3)	O15-C12-C13	131.1(5)
O11-C3-C14	106.4(3)	O11-C12-C13	109.4(4)
C4-C3-C14	117.7(4)	C12-C13-C14	104.9(4)
O11-C3-C2	104.2(3)	C12-C13-H13A	109.4(3)
C4-C3-C2	102.5(4)	C14-C13-H13A	108.3(3)
C14-C3-C2	116.9(4)	C12-C13-H13B	111.6(3)
O5-C4-C3	105.6(3)	C14-C13-H13B	113.1(3)
O5-C4-C25	109.4(3)	H13A-C13-H13B	109.3
C3-C4-C25	111.7(4)	C13-C14-C3	102.0(3)
O5-C4-C9	110.4(3)	C13-C14-Si16	117.5(3)
C3-C4-C9	102.9(3)	C3-C14-Si16	123.5(3)
C25-C4-C9	116.2(4)	C13-C14-H14	102.8(3)
C4-O5-C6	112.8(3)	C3-C14-H14	104.4(2)
O7-C6-O5	109.5(3)	Si16-C14-H14	104.2(2)
O7-C6-C29	112.4(4)	C17-Si16-C18	110.4(2)
O5-C6-C29	107.5(3)	C17-Si16-C19	108.6(2)
O7-C6-H6	109.2(2)	C18-Si16-C19	110.0(2)
O5-C6-H6	108.9(2)	C17-Si16-C14	115.2(2)
C29-C6-H6	109.3(2)	C18-Si16-C14	106.6(2)
C6-O7-C8	109.7(3)	C19-Si16-C14	105.8(2)
O7-C8-C9	112.9(4)	Si16-C17-H17A	110.34(13)
O7-C8-H8A	108.4(2)	Si16-C17-H17B	108.44(13)
C9-C8-H8A	109.0(3)	H17A-C17-H17B	109.4
O7-C8-H8B	108.6(2)	Si16-C17-H17C	109.63(13)
C9-C8-H8B	110.0(3)	H17A-C17-H17C	109.5
H8A-C8-H8B	108	H17B-C17-H17C	109.5

Si16-C18-H18A	110.2(2)	C30-C29-C34	118.6(4)
Si16-C18-H18B	109.5(2)	C30-C29-C6	118.3(4)
H18A-C18-H18B	109.5	C34-C29-C6	122.9(4)
Si16-C18-H18C	108.7(2)	C29-C30-C31	121.7(5)
H18A-C18-H18C	109.5	C29-C30-H30	119.2(3)
H18B-C18-H18C	109.5	C31-C30-H30	119.1(3)
C20-C19-C24	117.2(4)	C32-C31-C30	119.5(5)
C20-C19-Si16	121.0(3)	C32-C31-H31	118.9(3)
C24-C19-Si16	121.8(3)	C30-C31-H31	121.6(3)
C21-C20-C19	122.4(4)	C31-C32-O35	115.3(4)
C21-C20-H20	119.3(3)	C31-C32-C33	120.5(4)
C19-C20-H20	118.3(2)	O35-C32-C33	124.2(5)
C22-C21-C20	119.6(4)	C32-C33-C34	118.7(4)
C22-C21-H21	119.7(3)	C32-C33-H33	120.1(3)
C20-C21-H21	120.7(3)	C34-C33-H33	121.1(3)
C21-C22-C23	120.0(4)	C29-C34-C33	120.9(4)
C21-C22-H22	120.7(3)	C29-C34-H34	118.4(3)
C23-C22-H22	119.4(3)	C33-C34-H34	120.6(3)
C22-C23-C24	120.4(4)	C32-O35-C36	117.6(4)
C22-C23-H23	119.8(3)	O35-C36-H36A	109.4(3)
C24-C23-H23	119.8(3)	O35-C36-H36B	109.2(3)
C23-C24-C19	120.5(4)	H36A-C36-H36B	109.5
C23-C24-H24	120.2(3)	O35-C36-H36C	109.8(3)
C19-C24-H24	119.3(3)	H36A-C36-H36C	109.5
O26-C25-O27	125.7(5)	H36B-C36-H36C	109.5
O26-C25-C4	122.5(4)		
O27-C25-C4	111.8(4)		
C25-O27-C28	114.8(4)		
O27-C28-H28A	109.1(3)		
O27-C28-H28B	109.9(2)		
H28A-C28-H28B	109.5		
O27-C28-H28C	109.4(2)		
H28A-C28-H28C	109.4		
H28B-C28-H28C	109.5		

Table A9. Anisotropic displacement parameters (A^2 x 10^3) for **2.71**. The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O1	43(2)	43(2)	42(2)	-1(2)	3(2)	10(2)
C2	49(3)	48(3)	30(2)	10(2)	1(2)	1(3)
C3	43(3)	37(2)	24(2)	9(2)	1(2)	2(2)
C4	36(3)	35(2)	28(2)	-1(2)	-2(2)	1(2)
O5	43(2)	31(2)	22(2)	0(1)	1(1)	-7(2)
C6	27(2)	38(3)	39(3)	0(2)	-5(2)	-6(2)
O7	48(2)	32(2)	42(2)	-5(2)	0(2)	-5(2)
C8	63(4)	40(3)	39(3)	-9(2)	0(3)	-3(3)
C9	45(3)	44(3)	30(3)	-5(2)	-4(2)	3(2)
O10	35(2)	82(3)	65(2)	19(2)	6(2)	2(2)
O11	56(2)	46(2)	26(2)	9(2)	-1(1)	-3(2)
C12	91(4)	36(3)	37(3)	7(2)	8(3)	9(3)
C13	98(4)	39(3)	38(3)	4(2)	4(3)	-3(3)
C14	54(3)	35(2)	37(2)	4(2)	-5(2)	-3(2)
O15	159(4)	55(2)	36(2)	19(2)	9(3)	-4(3)
Si16	27(1)	31(1)	29(1)	0(1)	1(1)	1(1)
C17	34(2)	36(2)	37(3)	5(2)	-4(2)	-2(2)
C18	35(3)	54(3)	47(3)	-6(3)	12(2)	2(2)
C19	32(2)	30(2)	28(2)	5(2)	-5(2)	-3(2)
C20	33(2)	32(2)	43(3)	-4(2)	-2(2)	3(2)
C21	29(2)	50(3)	53(3)	3(3)	-1(2)	-6(2)
C22	45(3)	43(3)	43(3)	5(2)	-8(2)	-16(2)
C23	63(4)	35(3)	42(3)	-5(2)	-1(3)	-6(3)
C24	39(3)	40(3)	37(3)	-2(2)	2(2)	3(2)
C25	43(3)	45(3)	31(3)	-2(2)	1(2)	-2(2)
O26	70(3)	75(3)	55(2)	-17(2)	-12(2)	33(2)
O27	48(2)	58(2)	39(2)	-4(2)	-17(2)	9(2)
C28	46(3)	79(4)	54(3)	19(3)	-17(3)	1(3)
C29	36(3)	32(2)	34(3)	-1(2)	1(2)	-5(2)

C30	37(3)	62(3)	46(3)	4(2)	-3(3)	3(3)
C31	41(3)	59(3)	48(3)	-1(3)	10(2)	3(2)
C32	53(3)	41(3)	37(3)	3(2)	4(2)	-12(3)
C33	47(3)	49(3)	40(3)	11(2)	-4(2)	-6(3)
C34	33(3)	49(3)	44(3)	7(2)	5(2)	-3(2)
O35	84(3)	64(2)	38(2)	-1(2)	15(2)	-4(2)
C36	101(5)	80(4)	37(3)	1(3)	-6(3)	-21(4)

Table A10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **2.71**.

	x	y	z	U(eq)
H6	12003(5)	1838(3)	8350(2)	41
H8A	9741(6)	3029(3)	9404(3)	57
H8B	11303(6)	2580(3)	9416(3)	57
H9	9688(5)	1725(3)	10009(3)	47
H13A	6283(7)	-642(3)	8830(2)	70
H13B	7578(7)	-1286(3)	8708(2)	70
H14	9199(5)	-348(3)	8370(2)	50
H17A	6517(5)	1231(2)	6734(2)	53
H17B	6015(5)	1269(2)	7600(2)	53
H17C	7668(5)	1541(2)	7361(2)	53
H18A	8879(5)	-6(3)	6243(3)	68
H18B	10023(5)	210(3)	6908(3)	68
H18C	9410(5)	-679(3)	6822(3)	68
H20	4306(4)	23(2)	7836(3)	43
H21	2237(5)	-835(3)	7589(3)	53
H22	2618(6)	-2020(3)	6880(3)	53
H23	5032(6)	-2328(3)	6405(3)	56
H24	7092(5)	-1438(3)	6607(2)	46
H28A	13265(5)	547(3)	10788(3)	89
H28B	12747(5)	-218(3)	10321(3)	89
H28C	13908(5)	397(3)	9957(3)	89
H30	13346(6)	1407(3)	7296(3)	58
H31	13741(5)	1328(3)	5964(3)	59
H33	9814(6)	2565(3)	5607(3)	54
H34	9411(5)	2610(3)	6957(3)	50
H36A	11393(7)	2002(4)	3861(3)	109
H36B	10096(7)	1812(4)	4458(3)	109
H36C	10849(7)	2675(4)	4437(3)	109

Figure A5. View of **2.71** showing the atom labeling scheme. The thermal ellipsoids are scaled to the 30% probability level. The hydrogen atoms have been scaled to an arbitrary size. Most hydrogen atoms have been omitted for clarity.

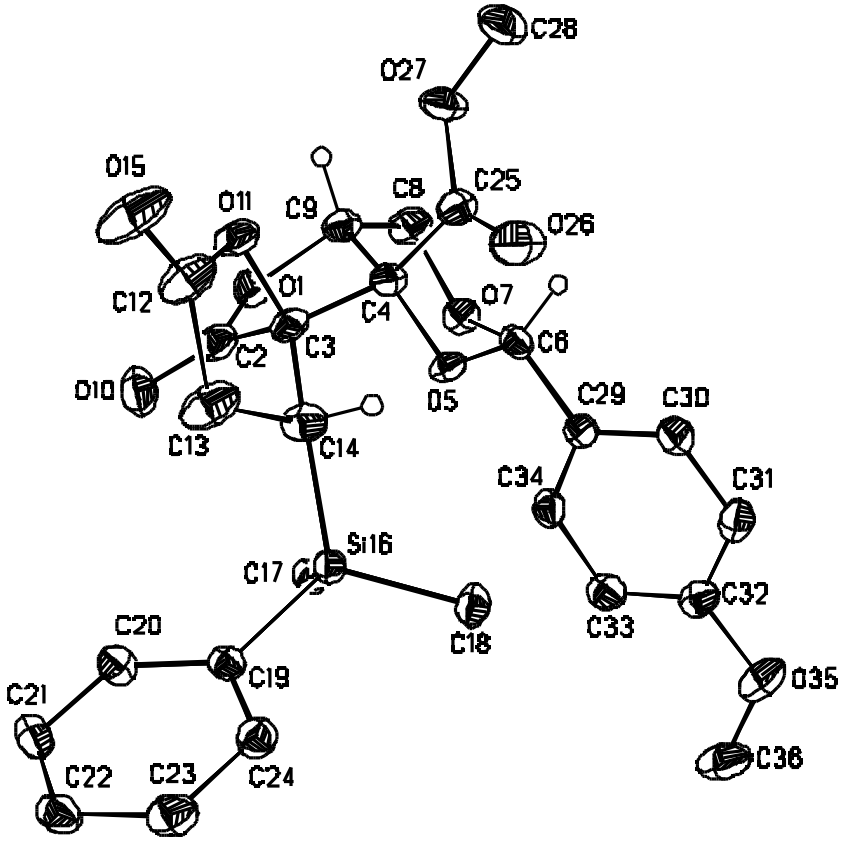


Figure A6. Unit cell packing diagram for **2.71**. The view direction is approximately down the **c** axis.

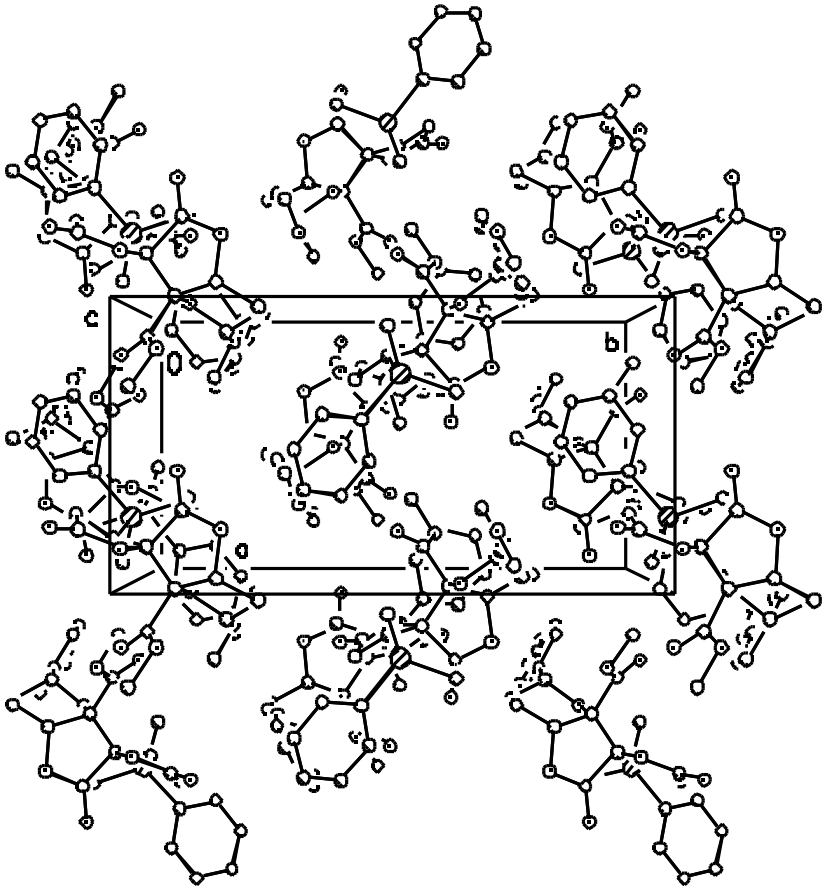


Table A11. Crystal data and structure refinement for **2.84**.

Empirical formula	C27 H30 O3 S
Formula weight	434.57
Temperature	153(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 5.6380(7) Å alpha = 90°.
	b = 15.1560(10) Å beta = 96.908(5)°.
	c = 13.8310(11) Å gamma = 90°.
Volume, Z	1173.3(2) A^3, 2
Density (calculated)	1.230 Mg/m^3
Absorption coefficient	0.163 mm^-1
F(000)	464
Crystal size	0.25 x 0.06 x 0.04 mm
Theta range for data collection	2.97 to 27.53 deg.
Limiting indices	-7<=h<=7, -19<=k<=16, -17<=l<=17
Reflections collected	4793
Independent reflections	4793 [R(int) = 0.0000]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4793 / 1 / 401
Goodness-of-fit on F^2	1.11
Final R indices [I>2sigma(I)]	R1 = 0.0608, wR2 = 0.1263
R indices (all data)	R1 = 0.1029, wR2 = 0.1546
Absolute structure parameter	0.13(11)
Largest diff. peak and hole	0.231 and -0.264 e.A^-3

Table A12. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **2.84**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C1	-1681(8)	440(3)	2303(3)	46(1)
C2	-1888(10)	-140(3)	3077(4)	53(1)
C3	-133(9)	-173(3)	3853(4)	47(1)
C4	1811(10)	380(3)	3882(3)	48(1)
C5	1993(9)	971(3)	3124(3)	43(1)
C6	232(8)	1003(3)	2321(3)	39(1)
C7	427(9)	1671(3)	1517(3)	43(1)
C8	2621(8)	1566(3)	983(3)	36(1)
C9	2553(11)	702(3)	418(4)	46(1)
C10	2899(8)	2356(2)	314(3)	33(1)
C11	3019(8)	3239(2)	844(3)	32(1)
C12	1516(10)	3875(3)	550(3)	46(1)
C13	5041(9)	3318(3)	1669(3)	37(1)
C14	5041(8)	4180(3)	2224(3)	35(1)
S15	7264(2)	4230(1)	3246(1)	36(1)
O16	7003(7)	5060(2)	3732(2)	50(1)
O17	9539(6)	4024(2)	2926(2)	48(1)
C18	6525(8)	3381(2)	4032(3)	33(1)
C19	4632(9)	3498(3)	4568(3)	44(1)
C20	4096(10)	2828(3)	5195(3)	51(1)
C21	5450(10)	2073(3)	5281(3)	48(1)
C22	7295(11)	1954(3)	4747(3)	50(1)
C23	7849(10)	2612(3)	4113(3)	43(1)
O24	5005(6)	2212(2)	-140(2)	36(1)
C25	5242(10)	2808(3)	-916(3)	42(1)
C26	6969(8)	2445(3)	-1556(3)	37(1)
C27	8138(10)	3006(3)	-2125(3)	46(1)
C28	9732(11)	2681(3)	-2726(4)	55(1)

C29	10187(10)	1783(3)	-2774(3)	47(1)
C30	9022(10)	1220(3)	-2206(3)	47(1)
C31	7394(9)	1543(3)	-1606(3)	45(1)

Table A13. Bond lengths [A] and angles [deg] for **2.84**.

C1-C6	1.374(6)	C14-S15	1.774(4)
C1-C2	1.400(7)	C14-H14A	0.91(5)
C1-H1	1.00(4)	C14-H14B	1.06(5)
C2-C3	1.371(7)	S15-O17	1.441(3)
C2-H2	1.03(7)	S15-O16	1.442(3)
C3-C4	1.376(7)	S15-C18	1.767(4)
C3-H3	0.96(6)	C18-C19	1.382(7)
C4-C5	1.392(6)	C18-C23	1.381(6)
C4-H4	1.02(4)	C19-C20	1.392(7)
C5-C6	1.399(6)	C19-H19	0.93(6)
C5-H5	1.00(5)	C20-C21	1.373(7)
C6-C7	1.517(6)	C20-H20	0.94(5)
C7-C8	1.523(7)	C21-C22	1.358(8)
C7-H7A	1.16(6)	C21-H21	0.86(6)
C7-H7B	0.84(5)	C22-C23	1.388(7)
C8-C9	1.524(6)	C22-H22	0.92(7)
C8-C10	1.533(5)	C23-H23	0.81(5)
C8-H8	0.89(5)	O24-C25	1.421(5)
C9-H9A	1.03(5)	C25-C26	1.497(6)
C9-H9B	1.01(7)	C25-H25A	0.82(5)
C9-H9C	0.90(5)	C25-H25B	1.15(6)
C10-O24	1.425(5)	C26-C27	1.379(6)
C10-C11	1.522(5)	C26-C31	1.391(6)
C10-H10	1.06(3)	C27-C28	1.386(7)
C11-C12	1.315(6)	C27-H27	0.98(5)
C11-C13	1.518(5)	C28-C29	1.388(7)
C12-H12A	1.00(5)	C28-H28	1.05(7)
C12-H12B	0.94(5)	C29-C30	1.380(7)
C13-C14	1.516(5)	C29-H29	1.04(6)
C13-H13A	1.08(6)	C30-C31	1.397(7)
C13-H13B	0.89(5)	C30-H30	1.06(5)

C31-H31	1.14(7)	C8-C9-H9C	117(3)
C6-C1-C2	120.9(4)	H9A-C9-H9C	107(4)
C6-C1-H1	120(2)	H9B-C9-H9C	105(4)
C2-C1-H1	118(2)	O24-C10-C11	110.8(3)
C3-C2-C1	120.2(5)	O24-C10-C8	107.3(3)
C3-C2-H2	119(3)	C11-C10-C8	113.5(3)
C1-C2-H2	121(3)	O24-C10-H10	110(2)
C2-C3-C4	119.9(5)	C11-C10-H10	108(2)
C2-C3-H3	120(4)	C8-C10-H10	107(2)
C4-C3-H3	120(4)	C12-C11-C13	124.9(4)
C3-C4-C5	120.0(5)	C12-C11-C10	120.4(4)
C3-C4-H4	119(3)	C13-C11-C10	114.6(3)
C5-C4-H4	121(3)	C11-C12-H12A	121(3)
C4-C5-C6	120.7(4)	C11-C12-H12B	123(3)
C4-C5-H5	114(3)	H12A-C12-H12B	116(4)
C6-C5-H5	126(3)		
C1-C6-C5	118.2(4)	C14-C13-C11	113.8(3)
C1-C6-C7	121.8(4)	C14-C13-H13A	110(3)
C5-C6-C7	119.9(4)	C11-C13-H13A	105(3)
C6-C7-C8	114.9(4)	C14-C13-H13B	109(3)
C6-C7-H7A	118(3)	C11-C13-H13B	103(4)
C8-C7-H7A	100(3)	H13A-C13-H13B	117(4)
C6-C7-H7B	113(3)		
C8-C7-H7B	111(4)	C13-C14-S15	113.4(3)
H7A-C7-H7B	98(4)	C13-C14-H14A	111(3)
C9-C8-C7	111.5(4)	S15-C14-H14A	104(2)
C9-C8-C10	111.1(3)	C13-C14-H14B	113(2)
C7-C8-C10	111.0(3)	S15-C14-H14B	103(2)
C9-C8-H8	103(3)	H14A-C14-H14B	112(4)
C7-C8-H8	117(3)		
C10-C8-H8	103(3)	O17-S15-O16	118.5(2)
C8-C9-H9A	109(3)	O17-S15-C18	108.4(2)
C8-C9-H9B	112(3)	O16-S15-C18	107.7(2)
H9A-C9-H9B	108(4)	O17-S15-C14	108.4(2)

O16-S15-C14	107.9(2)	C29-C28-C27	121.0(5)
C18-S15-C14	105.3(2)	C29-C28-H28	118(4)
C19-C18-C23	120.7(4)	C27-C28-H28	121(4)
C19-C18-S15	119.4(3)	C30-C29-C28	118.4(5)
C23-C18-S15	119.9(4)	C30-C29-H29	125(3)
C18-C19-C20	118.7(5)	C28-C29-H29	116(3)
C18-C19-H19	126(3)	C29-C30-C31	120.9(4)
C20-C19-H19	115(4)	C29-C30-H30	125(3)
C21-C20-C19	120.1(5)	C31-C30-H30	114(3)
C21-C20-H20	118(3)	C26-C31-C30	120.3(4)
C19-C20-H20	122(3)	C26-C31-H31	117(3)
C22-C21-C20	121.1(5)	C30-C31-H31	122(3)
C22-C21-H21	117(4)		
C20-C21-H21	121(4)		
C21-C22-C23	119.6(5)		
C21-C22-H22	125(4)		
C23-C22-H22	115(5)		
C18-C23-C22	119.8(5)		
C18-C23-H23	119(3)		
C22-C23-H23	121(3)		
C25-O24-C10	113.2(3)		
O24-C25-C26	109.9(3)		
O24-C25-H25A	109(3)		
C26-C25-H25A	112(3)		
O24-C25-H25B	104(3)		
C26-C25-H25B	115(3)		
H25A-C25-H25B	106(4)		
C27-C26-C31	118.7(4)		
C27-C26-C25	120.0(4)		
C31-C26-C25	121.3(4)		
C26-C27-C28	120.8(4)		
C26-C27-H27	120(3)		
C28-C27-H27	119(3)		

Table A14. Anisotropic displacement parameters (A^2 x 10^3) for **2.84**. The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C1	33(3)	41(3)	62(3)	-2(2)	-1(2)	2(2)
C2	41(3)	36(3)	84(4)	5(2)	14(3)	1(2)
C3	53(3)	37(3)	54(3)	3(2)	14(2)	0(2)
C4	50(3)	50(3)	44(2)	5(2)	5(2)	3(2)
C5	36(3)	46(3)	47(2)	2(2)	4(2)	-9(2)
C6	33(3)	33(2)	51(2)	1(2)	5(2)	5(2)
C7	42(3)	37(3)	47(2)	6(2)	1(2)	10(2)
C8	35(3)	35(2)	36(2)	-1(2)	-6(2)	5(2)
C9	55(4)	36(2)	45(3)	-4(2)	-5(2)	1(2)
C10	35(3)	33(2)	31(2)	-3(2)	-1(2)	6(2)
C11	29(2)	35(2)	30(2)	-2(2)	2(2)	5(2)
C12	52(3)	37(2)	46(3)	-2(2)	-4(2)	11(2)
C13	38(3)	32(2)	39(2)	-5(2)	0(2)	4(2)
C14	37(2)	30(2)	38(2)	-1(2)	5(2)	1(2)
S15	36(1)	38(1)	35(1)	-3(1)	6(1)	-8(1)
O16	69(3)	35(2)	47(2)	-12(1)	8(2)	-14(1)
O17	34(2)	66(2)	43(2)	2(1)	6(1)	-10(2)
C18	32(3)	38(2)	29(2)	-2(2)	0(2)	-6(2)
C19	43(3)	51(3)	39(2)	5(2)	14(2)	2(2)
C20	49(3)	62(3)	44(3)	7(2)	15(2)	-8(3)
C21	58(4)	43(3)	42(2)	8(2)	2(2)	-11(2)
C22	62(4)	40(3)	46(2)	0(2)	0(2)	5(2)
C23	40(3)	50(3)	39(2)	-2(2)	9(2)	-1(2)
O24	39(2)	37(2)	31(1)	-1(1)	3(1)	7(1)
C25	42(3)	39(2)	46(3)	3(2)	5(2)	6(2)
C26	37(3)	38(2)	32(2)	-1(2)	-3(2)	1(2)
C27	61(3)	36(3)	41(2)	1(2)	10(2)	2(2)
C28	73(4)	44(3)	51(3)	6(2)	24(3)	-1(3)

C29	54(3)	43(3)	47(3)	-2(2)	14(2)	4(2)
C30	60(3)	32(2)	50(3)	-4(2)	17(2)	1(2)
C31	51(3)	35(2)	51(3)	-4(2)	12(2)	-2(2)

Table A15. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **2.84**.

	x	y	z	U(eq)
H1	-2841(79)	382(26)	1704(28)	33(10)
H2	-3303(118)	-572(40)	3060(38)	82(18)
H3	-304(114)	-551(40)	4395(41)	89(20)
H4	3125(89)	335(28)	4456(30)	42(11)
H5	3416(99)	1368(32)	3237(33)	56(13)
H7A	-1069(115)	1672(35)	863(40)	80(17)
H7B	266(95)	2197(36)	1698(34)	55(15)
H8	4030(85)	1542(27)	1344(30)	33(10)
H9A	1072(98)	706(30)	-99(33)	51(13)
H9B	4008(120)	631(36)	65(39)	66(17)
H9C	2485(92)	198(33)	765(33)	48(13)
H10	1371(67)	2361(21)	-213(23)	21(9)
H12A	235(94)	3782(28)	-3(33)	46(12)
H12B	1514(82)	4424(30)	860(30)	39(12)
H13A	6651(108)	3272(32)	1321(34)	60(15)
H13B	4757(100)	2877(35)	2063(36)	59(15)
H14A	3638(85)	4251(31)	2482(28)	38(11)
H14B	5440(83)	4737(30)	1807(30)	43(12)
H19	3549(110)	3962(35)	4500(35)	67(17)
H20	2830(105)	2878(32)	5580(35)	59(16)
H21	5064(107)	1636(40)	5624(39)	74(18)
H22	8372(131)	1499(46)	4834(44)	93(21)
H23	9007(89)	2575(28)	3826(29)	31(12)
H25A	3920(88)	2900(26)	-1217(29)	29(11)
H25B	5809(121)	3461(41)	-531(41)	86(19)
H27	7888(87)	3645(33)	-2091(31)	42(12)
H28	10684(123)	3105(44)	-3134(45)	90(20)
H29	11144(115)	1582(38)	-3330(43)	82(18)
H30	9339(95)	534(35)	-2143(31)	58(14)

H31	6665(129)	1112(43)	-1033(45)	97(19)

Figure A7. View of **2.84** showing the atom labeling scheme. Thermal ellipsoids are scaled to the 50% probability level. Hydrogen atoms shown are drawn to an arbitrary scale.

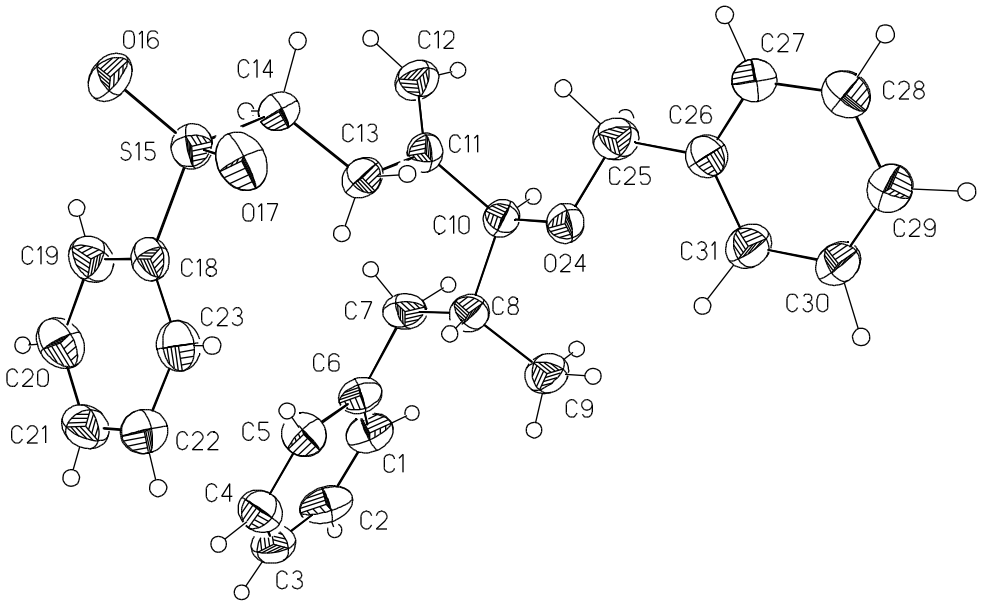
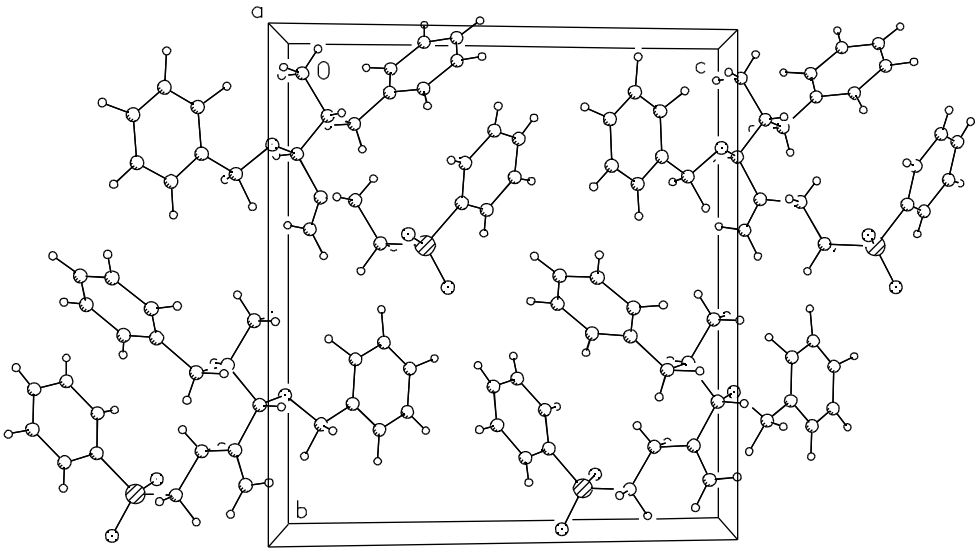


Figure A8. Unit cell packing diagram for **2.84**. The view is approximately down the **a** axis.



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Vita

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