Studies in Natural Product Chemistry: Synthesis of Palmarumycin CP_1 Analogs and Total Synthesis and Structure Validation of (+)-Bistramide C

by

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ABSTRACT

Studies in Natural Product Chemistry: Synthesis of Palmarumycin CP_1 Analogs and Total Synthesis and Structure Validation of (+)-Bistramide C

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The first chapter describes our preparation of novel analogs of the natural product, palmarumycin CP_1. Several derivatives demonstrated potent and selective inhibition of thioredoxin or thioredoxin reductase as well as antiproliferative activity against MCF-7 and MDA-MB-231 human breast cancer cell lines. Furthermore, we also made progress towards the synthesis of the structurally related naphthalenediol spiroacetal natural product, spiroxin C. We developed efficient, facile syntheses for the preparation of the two building blocks required for the key Ullmann ether coupling reaction.

The second chapter details the asymmetric total synthesis of the *Lissoclinum bistratum* natural product, bistramide C. Our synthetic route featured a highly-convergent three-component coupling strategy for the final assembly of the target molecule. In addition, our total synthesis highlighted our MAO-mediated, chiral zirconocene-catalyzed methylalumination of terminal olefins, a tandem $BiBr_3$-initiated cyclization-allylation for the formation of a 2,6-*trans*-substituted pyran and a hypervalent iodine-promoted spiroketalization. The spectroscopic properties (*i.e.* ^1H and ^{13}C NMR, $[\alpha]_D$, CD) of the synthetic material were in very close agreement to the measurements of an authentic sample of the natural product. Thus, our synthetic efforts in conjunction with NMR methodology and chiroptical tools culminated in the first total synthesis of (+)-bistramide C.

ACKNOWLEDGEMENTS

First and foremost, I would like to sincerely thank my research advisor, Professor Peter Wipf, for his extreme patience, guidance and support throughout my tenure as a graduate student at the University of Pittsburgh. He provided me with the opportunity to tackle several challenging projects, not the least of which was the total synthesis of (+)-bistramide C. I greatly appreciate his advice and unwillingness (and perhaps inability) to fall victim to my natural sense of pessimism, especially during the difficult times. He has most definitely shaped my appreciation and understanding of chemistry. Furthermore, I would like to extend my appreciation to Professors Paul Floreancig, Craig Wilcox and Billy Day for serving on my thesis committee.

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Many thanks are extended to the University of Pittsburgh for financial support. I would also like to acknowledge the National Science Foundation, the Department of Defense, the National Institutes of Health, Merck Research Laboratories and Eli Lily & Co for additional funding for my research endeavors.

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LIST OF ABBREVIATIONS

18-C-6	18-Crown-6
Ac	Acetyl
Ac_2O	Acetic anhydride
AcOH	Acetic acid
AIBN	2,2'-Azobisisobutyronitrile
app.	Approximate
app	Apparent
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
brsm	Based on Recovered Starting Material
Bu	*n*-Butyl
CAN	Ceric Ammonium Nitrate
CD	Circular Dichroism
COLOC	Correlated Spectroscopy for Long Range Coupling
COSY	Correlation Spectroscopy
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dce	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DiBAL-H	Diisobutylaluminum hydride
DMAB	Dimethylaminobenzoate
DMAP	4-*N*,*N*-Dimethylaminopyridine
DMBU	1,4-Dimethoxy-1,3-butadiene
DMDO	Dimethyldioxirane
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dppp	1,3-Bis(diphenylphosphino)propane
dpppe	1,5-Bis(diphenylphosphino)pentane
dr	Diastereomeric ratio
DTT	Dithiothreitol
ECCD	Exciton Coupled Circular Dichroism
ee	Enantiomeric Excess
EG	Ethylene Glycol
EI	Electrospray Ionization
Et	Ethyl
Et_2O	Diethyl Ether
EtOAc	Ethyl Acetate
FAD	Flavin Adenine Dinucleotide
Fremy's salt	Dipotassium nitrosodisulfonate
FTPase	Ras Farnesyl-Protein Transferase
HETCOR	Heteronuclear Correlation Spectroscopy

HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Correlation
HRMS	High Resolution Mass Spectroscopy
HSQC	Heteronuclear Single Quantum Correlation
IC_{50}	Inhibitory Concentration 50%
Imid.	Imidazole
INADEQUATE	Incredible Natural Abundance Double Quantum Transfer Experiment
KHMDS	Potassium Hexamethyldisilazide
LAH	Lithium Aluminum Hydride
LiDMAE	Lithium Dimethylaminoethanol
LiHMDS	Lithium Hexamethyldisilazide
MAO	Methylaluminoxane
Me	Methyl
MOM	Methoxymethyl
Mont.	Montmorillonite
Ms	Mesyl or Methanesulfonyl
MS	Molecular Sieves
Ms_2O	Methanesulfonic Anhydride
NaHMDS	Sodium Hexamethyldisilazide
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NBS	*N*-Bromosuccinimide
NMP	*N*-Methylpyrrolidine
O.b.t.	Oil Bath Temperature
PCC	Pyridinium Chlorochromate
PDC	Pyridinium Dichromate
PhH	Benzene
PhMe	Toluene
$PhNO_2$	Nitrobenzene
PIDA	Phenyliodonium Diacetate
Piv	Pivaloyl or Trimethylacetyl
PLD	Phospholipase D
PPA	Polyphosphoric Acid
PPTS	Pyridinium *p*-Toluenesulfonate
PyBOP	Benzotriazole-1-yloxy-trispyrrolidinophosphonium
Pyr	Pyridine
quant.	Quantitative
Red-Al	Sodium Bis(2-methoxyethoxy)aluminum Dihydride
rt	Room Temperature
SAR	Structure Activity Relationship
TBAF	Tetrabutylammonium Fluoride
TBDMS, TBS	*tert*-Butyldimethylsilyl
TBDMS-OTf	*tert*-Butyldimethylsilyltriflate
TBHP	tert-Butyl Hydroperoxide
TDA-1	Tris[2-(2-methoxyethoxy)ethyl]amine
TEA	Triethylamine

TEG	Triethylene Glycol
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
Tf	Transcription Factor
Tf	Triflic or Trifluorosulfonyl
Tf_2O	Triflic acid or Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TMS-OTf	Trimethylsilyl Triflate
Tol	Toluene
TR	Thioredoxin Reductase
Trx	Thioredoxin
Ts	Tosyl or Toluenesulfonyl
TsOH	*p*-Toluenesulfonic acid

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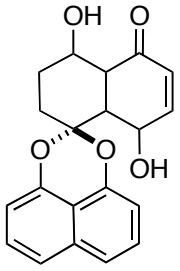
1.1. Introduction

1.1.1. Historical and Biological Background of Naphthalenediol Spiroacetal Natural Products

1.1.1.1. Palmarumycins

The isolation of MK 3018[1] in 1989 by Ogishi *et al.* from the fungus *Tetraploa aristata* marked the introduction of a new family of bioactive naphthalenediol spiroacetal natural products. They include the following classes: palmarumycins,[2,3,4] preussomerins,[5,6] diepoxins[7] and spiroxins.[8] The palmarumycins are further subdivided into two categories based upon their type and/or source (of isolation). Palmarumycins CP_1-CP_5[2,3] are fungal metabolites isolated from *Coniothyrium palmarum*. Palmarumycins C_1-C_{16}[4] are endophytic fungal metabolites isolated from an unidentified *Coniothyrium* species.



MK 3018 (**1**)

Figure 1. Structure of MK 3018.

Palmarumycins CP_1-CP_4 (Figure 2, **2**-**5**) were isolated in 1994 by Krohn and coworkers.[2] Three years later, Krohn reported palmarumycins CP_{4a} and CP_5 (Figure 2, **6** and **7**), close structural analogs of **4**.[3] The structure of pentacycle **4** was confirmed by X-ray analysis.[2] The absolute configurations of the two newest bridging ethers, **6** and **7** (Figure 2), were determined by circular dichroism (CD) studies.[3] For most palmarumycins, only the relative configuration had been elucidated.

In general, the palmarumycins show varying degrees of antibacterial and antifungal activity. Palmarumycin CP_3 (**4**) exhibited greater antibacterial activity as compared to palmarumycins CP_1 (**2**), CP_2 (**3**) and CP_4 (**5**). In addition, **4** proved to be particularly effective against fungi (as compared to **2**, **3** and **5**). Thus, it was postulated that an oxygen function at C(8) correlated to enhanced biological activity.[2]

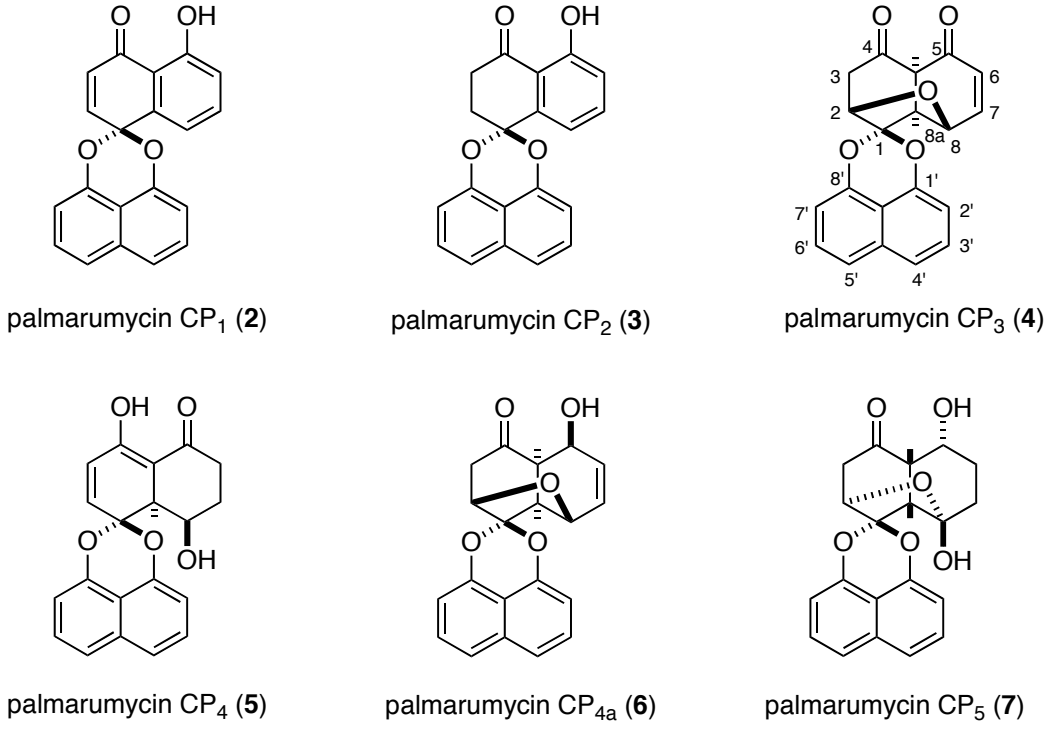


Figure 2. Palmarumycins from *Coniothyrium palmarum*.

In 1994, Krohn *et al.* isolated palmarumycins C_1-C_{16}, new fermentation products from forest soil on West Borneo (Figures 3-5, **8**-**24**). The structures of palmarumycins C_2 (**9**), C_3 (**10**) and C_5 (**12**) were confirmed by X-ray analysis. Palmarumycins C_{10}-C_{14} (**1 7**, **19**-**22**) are structurally related or identical to other, recently isolated fungal metabolites[4] bearing different nomenclature(s). For example, the structure of palmarumycin C_{10} (**17**, Figure 4) is identical to the oxidation product of cladospirone bisepoxide (**18**, Scheme 1). The latter compound was isolated in 1994 by a group from Ciba Geigy from cultures of a saprophytic fungus originally classified as a *Cladosporium chlorocephalum* strain.[9,10] This fungus was later reassigned as a member of the *Sphaeropsidales* group.[11] Thus, the treatment of **18** with MnO_2 represents a semisynthetic route to palmarumycin C_{10} (**17**).[4] The structural assignment of palmarumycin C_{11} (**19**) was confirmed by comparison of the natural product to the PCC oxidation product of bipendensin,[12] also known as palmarumycin C_2 (**9**). Bipendensin was isolated by Connolly from wood samples of the African tree, *Afzelia bipendensis*.[12] Chu has also reported the isolation of **19** from other natural sources.[13]

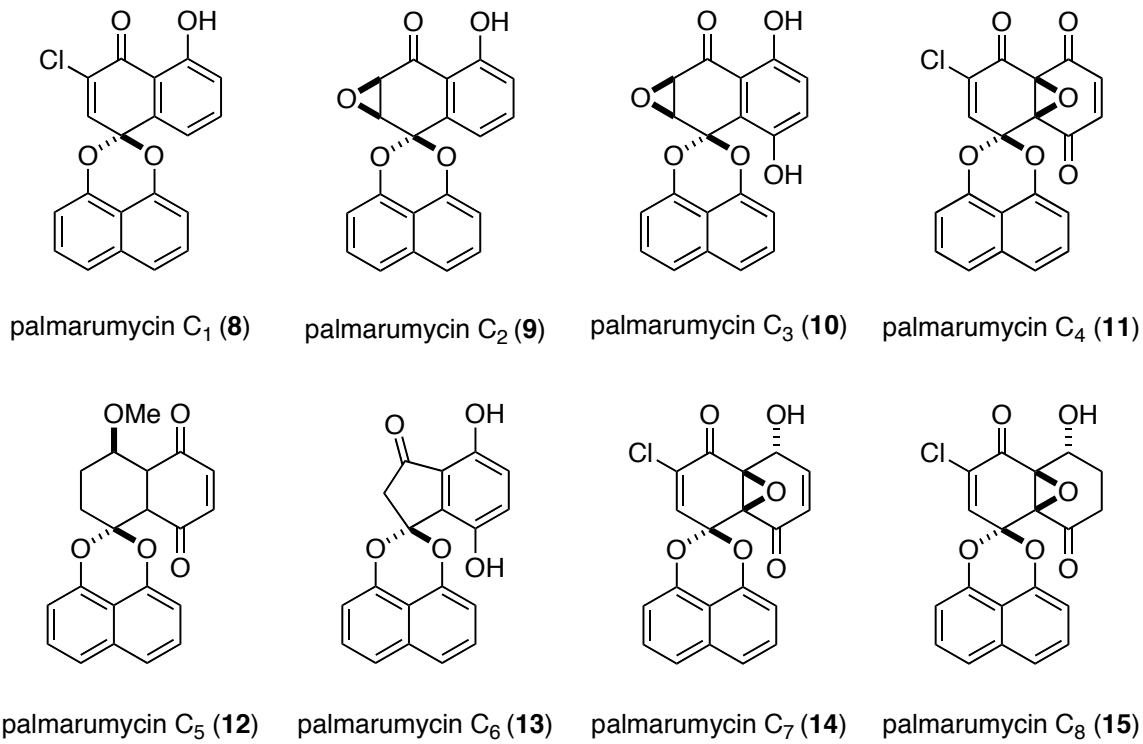
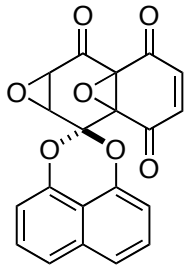
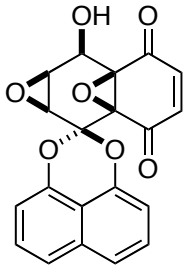


Figure 3. Palmarumycins from an Unidentified *Coniothyrium* Species.

The NMR data for palmarumycins C_{13} (**21**) and C_{14} (**22**)[4] correlated to those recorded for diepoxin η and diepoxin ζ, respectively, both of which were isolated by Schlingmann *et al.*[7] Once again, Chu independently assigned the aforementioned compounds as Sch 53516 (**22**) and 53514 (**21**). Both were extracts of a fermentation broth from the following culture, *N. mangiferae*.[14] In general, these spiroacetal metabolites show antibacterial, antifungal and herbicidal activities at concentrations of 10^{-6} to 10^{-4} mol/L.[4]

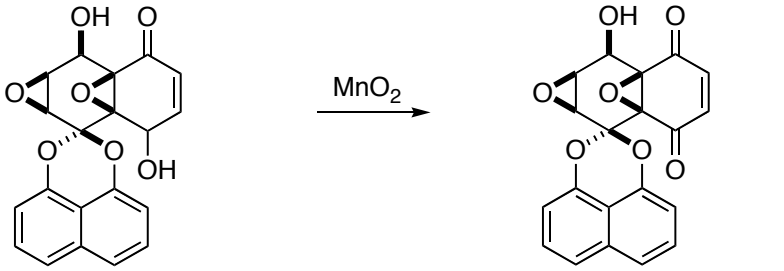


palmarumycin C_9 (**16**)



palmarumycin C_{10} (**17**)

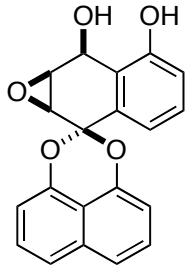
Figure 4. Palmarumycins from an Unidentified *Coniothyrium* Species, con.



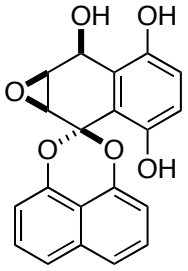
cladosporin bisepoxide (**18**)

palmarumycin C_{10} (**17**)

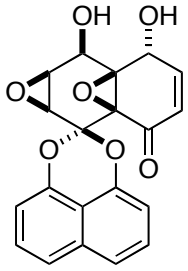
Scheme 1. Semisynthetic Preparation of Palmarumycin C_{10}.



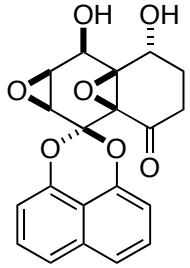
palmarumycin C_{11}, bipendensin, Sch 53-823 (**19**)



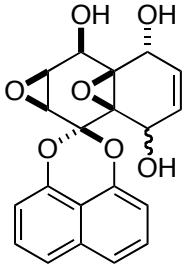
palmarumycin C_{12} (**20**)



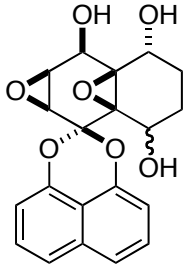
palmarumycin C_{13}, diepoxin η (**21**)



palmarumycin C_{14}, diepoxin ζ (**22**)



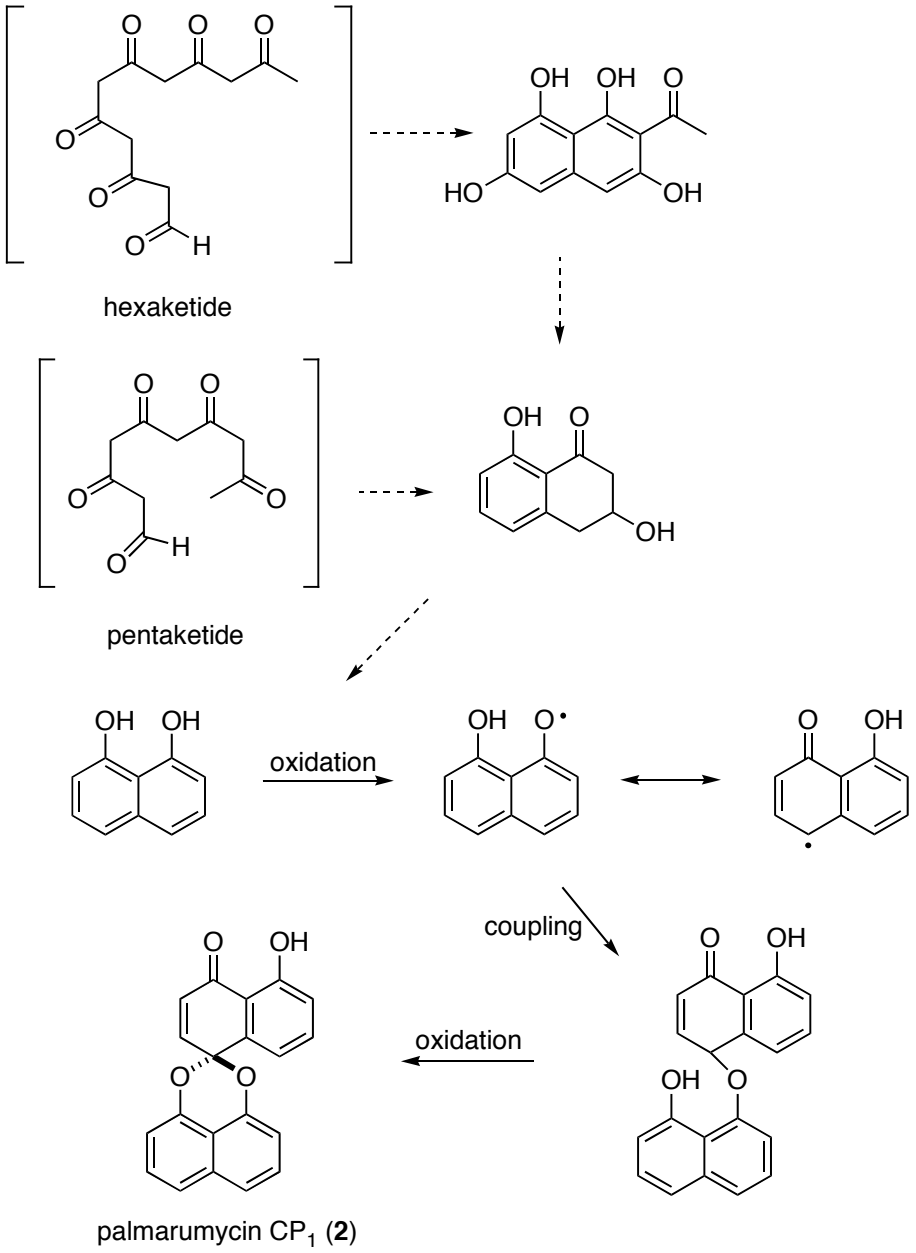
palmarumycin C_{15} (**23**)



palmarumycin C_{16} (**24**)

Figure 5. Additional Palmarumycins from an Unidentified *Coniothyrium* Species.

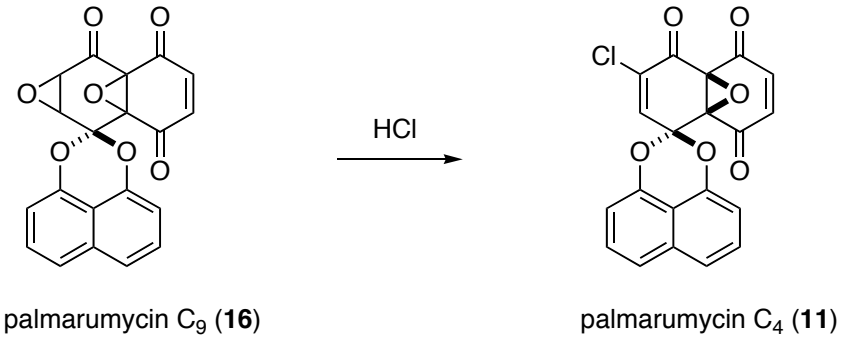
The biosynthesis of palmarumycins and related spirobisnaphthalenes, including the preussomerins, is quite intriguing. A hypothesis for the biosynthetic pathway of palmarumycin CP_1 is depicted in Scheme 2. The coupling of one hexaketide-, pentaketide-derived 1,8-naphthalenediol unit to another occurs by way of phenolic oxidation, a process highly reminiscent of polyketide biosynthesis.[15,16] Then, presumably, palmarumycin CP_1 is further elaborated into the remaining, structurally similar fungal metabolites via a variety of reactions, *e.g.* hydroxylation, oxygenation, dehydrogenation, chlorination, etc.[4]



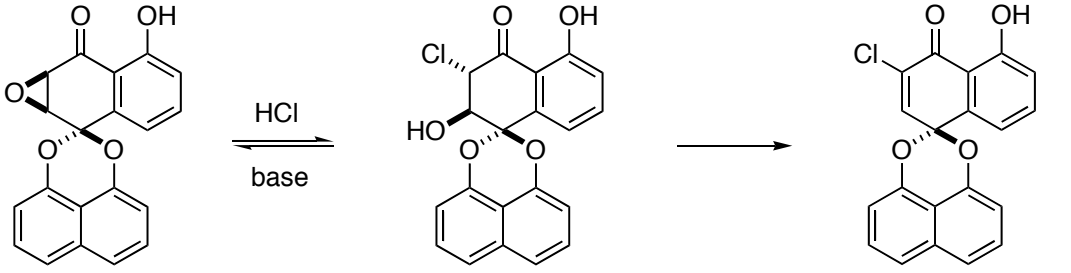
Scheme 2. Hypothetical Biosynthesis of Palmarumycin CP_1.

Krohn *et al.* demonstrated the feasibility of functionalizing the naphthalenediol spiroacetal core at a late-stage with the following experiments. The diepoxide **16** (Scheme 3), as a mixture of diastereomers, was converted to palmarumycin C_4 (**11**) upon treatment with methanolic HCl. Similar treatment of the phenolic epoxide, palmarumycin C_2 (**9**), delivered an intermediate

chlorohydrin (**25**). Compound **25** reverted back to palmarumycin C_2 (**9**) upon treatment with base and decomposed to palmarumycin C_1 (**8**) upon prolonged standing in chloroform. Krohn's experiments establish a possible pathway to the chlorinated palmarumycins, C_1 (**8**) and C_4 (**11**). The unusual stability of the acetal moiety, which consistently withstood harshly acidic reaction conditions, *i.e.* acetic acid at 100 °C, is particularly noteworthy.[4]



palmarumycin C_9 (**16**) palmarumycin C_4 (**11**)



palmarumycin C_2 (**9**) **25** palmarumycin C_1 (**8**)

Scheme 3. Pathway to the Chlorinated Palmarumycins.

1.1.1.2. Preussomerins

The preussomerin family of natural products is comprised of 10 fungal metabolites (**26-35**, Figures 6 and 7), all of which possess a unique and unusually stable bis-acetal ring system. Neither the novel polycyclic bis-acetal ring system nor the unusual α-hydroxy moiety of

preussomerins A-D (**26-29**) had been reported prior to 1990.[5,6] Preussomerin A (**26**) was first isolated from the coprophilous (dung-colonizing) fungus *Preussia isomera* by Gloer *et al.* in 1990 during studies of interspecies competition among dung-colonizing fungi.[5] Shortly thereafter, Gloer introduced five additional, structurally-related compounds (preussomerins B-F, **27-31**), also isolated from the same natural source.[6]

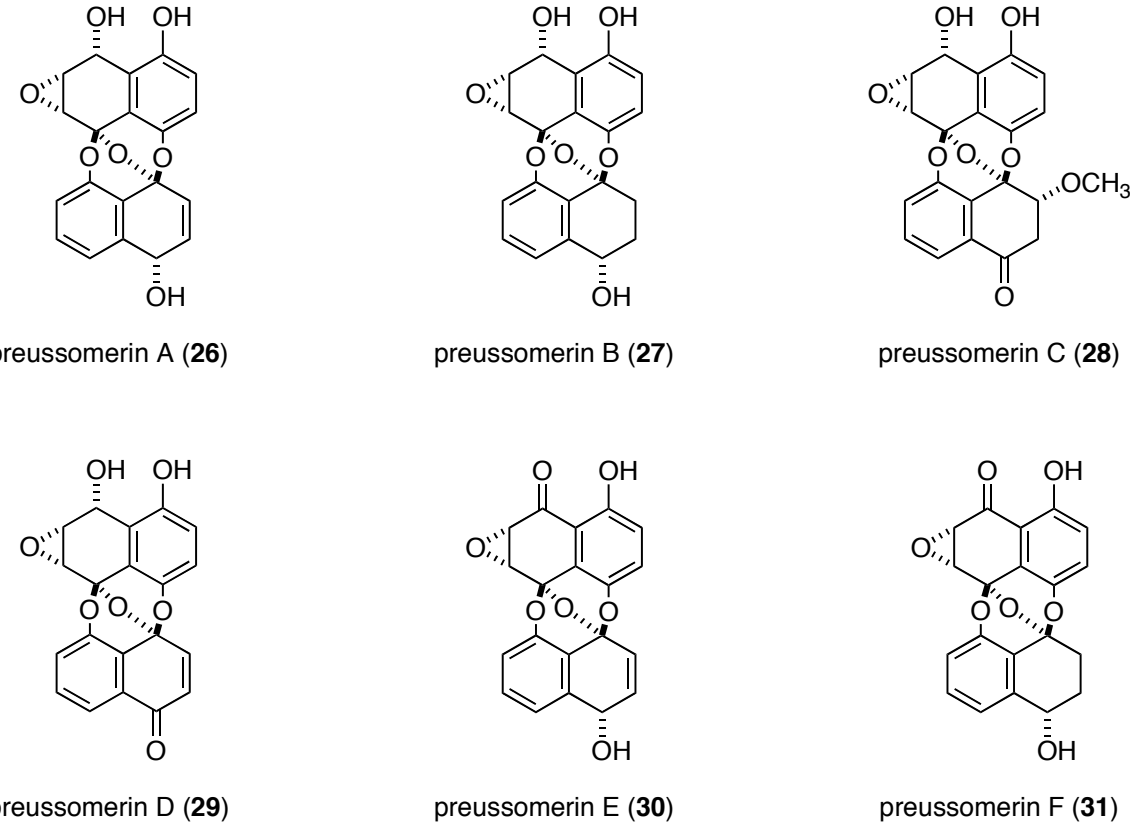


Figure 6. Pressomerins Isolated from *Preussia isomera*.

Preussomerin D (**29**) was also isolated from a second source, an endophytic fungus that was recovered from the living plant tissue of a coniferous tree, *Harmonema dematioides*.[17] Preussomerins D (**29**), G-I (**32-34**) and deoxypreussomerins A (**9**) and B (**3**) were isolated by Singh *et al.* in 1994 from the fermentation broth of an unidentified coelomycetes (MF 5916)

collected in Bajo Verde, Argentina.[18] Several years later, Gloer introduced an additional preussomerin analog, 3'-O-desmethyl-1-*epi*preussomerin C (**35**, Figure 8), isolated from cultures of the coprophilous fungus-*Sporormiella vexans*.[19] Most recently, Krohn *et al*. isolated three new representatives[20] of the bisspirobisnaphthalene natural products class from the endophytic fungus, *Mycelia sterila*.

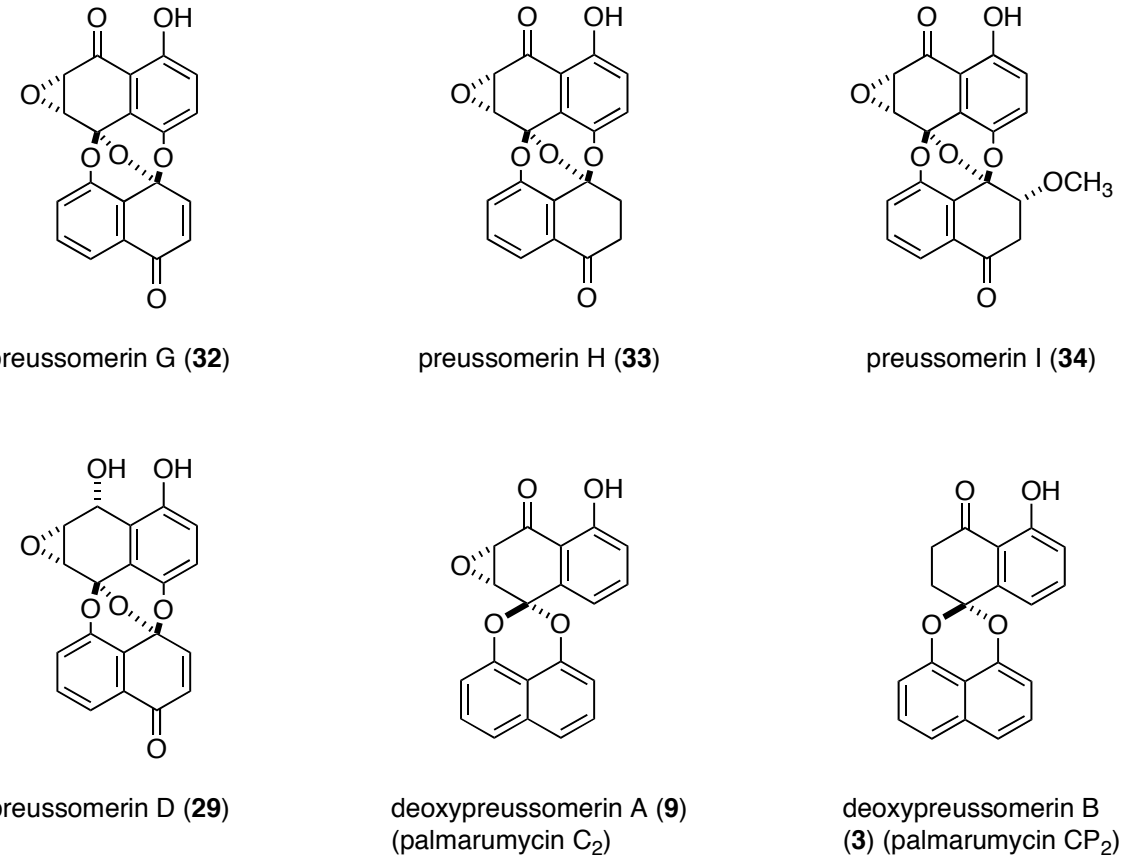
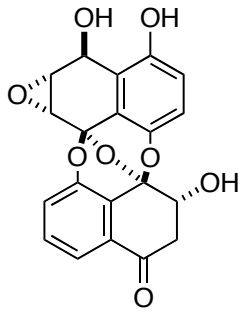


Figure 7. Preussomerins and Deoxypreussomerins Isolated from a Coelomycetes Fungus.

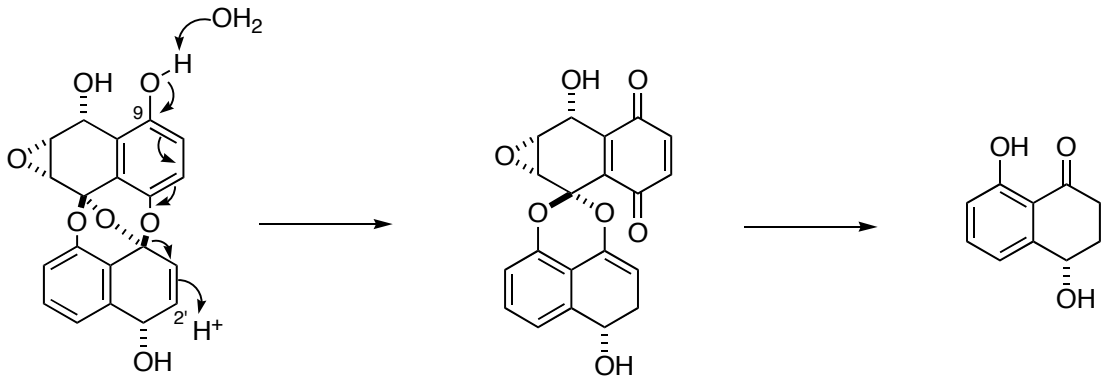


3'-O-desmethyl-1-*epi*preussomerin C

(**35**)

Figure 8. Additional Preussomerin Analog.

The absolute stereochemistry of preussomerin A (**26**) was determined by degradation studies. Upon treatment of preussomerin A with 6 M HCl-acetone (1:1) at 100 °C, **26** decomposed to a number of products. The major component of the product mixture possessed identical properties to those reported for (-)-regiolone. A possible mechanistic rationale is depicted in Scheme 4. Protonation at C(2') followed by loss of the phenolic proton at C(9) could lead to the formation of intermediate enol ether (***A***). Hydrolysis of the remaining acetal followed by tautomerization should deliver enantiomerically pure regiolone. The relative stereochemistry of preussomerin A was determined by X-ray diffraction studies.[6] Consequently, the absolute configuration of **26** could be assigned as shown in Scheme 4. Since all preussomerins, including preussomerins G-I (**32**-**34**) and deoxypreussomerin A (**9**), exhibit large negative optical rotations, they are likely to possess the same absolute stereochemistry.[18]



preussomerin A (**26**) ***A*** (-)-regiolone

Scheme 4. Acidic Degradation of Preussomerin A.

The preussomerins are especially noted for their ability to inhibit Ras farnesyl-protein transferase (FPTase), an enzyme associated with the regulation of tumor growth. Since inhibitors of FPTase exhibit antitumorgenic effects, preussomerins offer promise as potential cancer chemotherapeutics. The IC_{50}'s corresponding to the FTPase inhibitory activity of preussomerins, deoxypreussomerins and derivatives of preussomerin G (**32**) range between 1 and 20 μM.[18] Preussomerins G (**32**) and D (**29**) were found to be the most active. The deoxypreussomerins, possible biosynthetic precursors of preussomerins, demonstrated equal or better activity than preussomerins H (**33**) and I (**34**).[18] Preussomerin A also exhibited low-micromolar cytotoxicity towards a mammalian cell line.[6]

1.1.1.3. Diepoxins and Related Fungal Metabolites

The highly oxygenated diepoxins (Figure 9, **36-40**) were isolated by Schlingmann *et al.* from fermentation broths of a non-sporulating fungus, culture LL-07F275.[7] The spiroacetal-linked bisepoxides represent a new class of antibiotics with wide-ranging biological activity. The most oxygenated member of the class, diepoxin σ (**37**), displayed both antifungal and antibacterial activity with MIC's against selected bacteria ranging from 4-32 μg/mL. The less oxygenated diepoxin η (**22**) proved to be inactive. Diepoxins α (**36**) and ζ (**21**) possess the same level of oxidation and demonstrated similar antibacterial potencies at 2-4 times lower activity than that which was observed for **37**.[7]

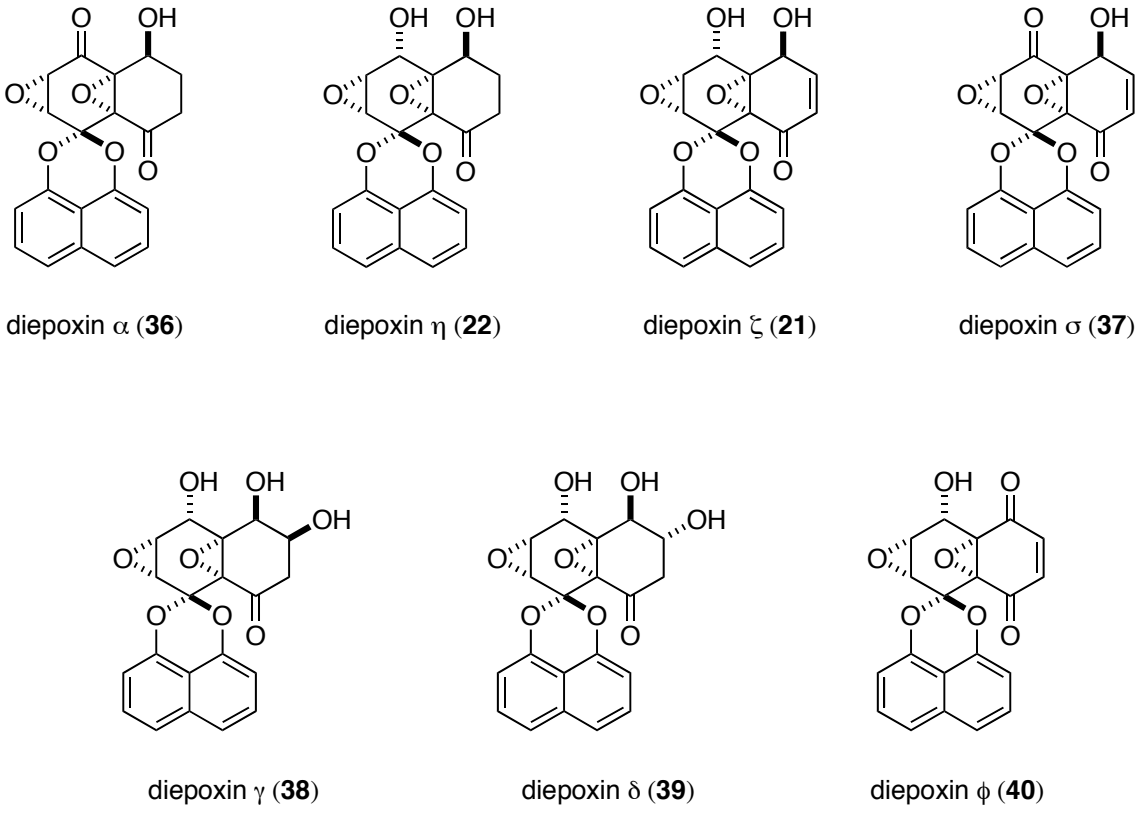
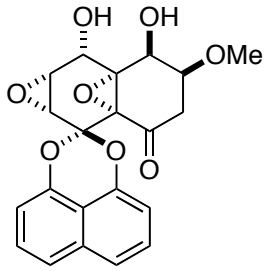
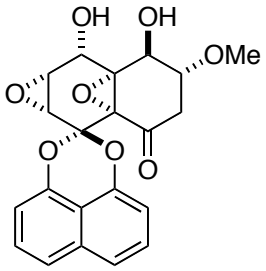


Figure 9. Diepoxins.

The absolute configuration of the diepoxins was elucidated in 1996 by exciton-coupled CD (ECCD) methodology.[21] Diepoxins η (**22**), ι (**41**), and κ (**42**) were converted to their respective bis-dimethylaminobenzoate (DMAB) derivatives. The CD spectra of the DMAB derivatives revealed a positive chiral twist between the two substituted hydroxyl groups. This determination implied that the (*S*)-configuration existed at both chiral centers. X-ray diffraction studies of diepoxin κ were relied upon to deduce the relative configurations of the remaining chiral centers of the diepoxins.[21]



diepoxin ι (**41**)

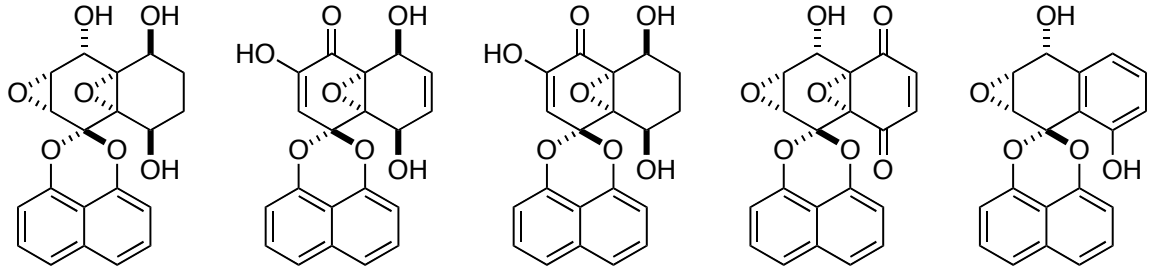


diepoxin κ (**42**)

Figure 10. Diepoxin Derivatives from Base-catalyzed Methylation of **21**.

Chu and coworkers revealed pertinent data with regard to the antitumor properties of Sch 49209 (diepoxin σ, **37**). This particular sample was isolated from the fermentation broth of a fungal culture, SCF-0642, *Nattrassia mangiferae*, collected in Guatemala.[22] Sch 49209 and its triepoxide derivative Sch 50674 demonstrated potent *in vitro* activity against HT 1080 human fibrosarcoma cells in an invasion chamber assay with IC_{50} values of 0.75 and 0.25 μM respectively. In addition, *in vivo* studies revealed that both compounds led to a significant reduction in the size of primary tumors and the number of metastases.[22]

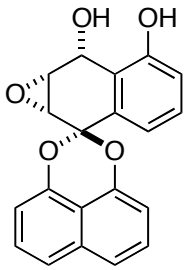
From Chu's biological evaluation, it was determined that diepoxin η (Sch 53516, **22**)[14] and diepoxin ζ (Sch 53514, **21**)[14] displayed potent phospholipase D (PLD) activity and anti-invasive activity against a variety of tumor cells. The more active Sch 53514 (**21**) was found to have an IC_{50} of 0.2 μM in the PLD assay and 0.37 μM in the antitumor invasion assay.[14] Figure 11 depicts other novel fungal metabolites isolated by Chu *et al.* from *N. mangiferae*.[14,23,24] Compounds **43**-**45** exhibited *in vitro* PLD activity with IC_{50} values of 1.6, 11 and 12 μM, respectively. In addition, the three metabolites demonstrated inhibitory activity in a tumor cell invasion assay with IC_{50} values of 0.26, 6.2 and 2.8 μM, respectively.[23,24]



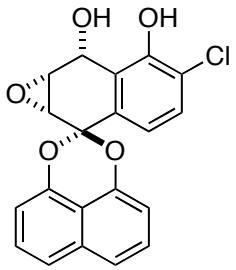
Sch 49210 (**43**) Sch 49211 (**44**) Sch 49212 (**45**) Sch 50673 (**46**) Sch 50676 (**47**)

Figure 11. Novel Fungal Metabolites from *N. mangiferae*.

In 1996, two additional fungal metabolites, Sch 53823 and Sch 53825 (Figure 12), were reported by Chu and coworkers.[13] They were isolated from the fermentation broth of an unidentified fungus collected from the dead leaves of *Ruerus virginiana* Miller growing in Tamalupas, Mexico. These compounds also demonstrated PLD inhibitory activity with IC_{50} values of 24 and 19 μM, respectively.[13]



Sch 53823 (**48**)

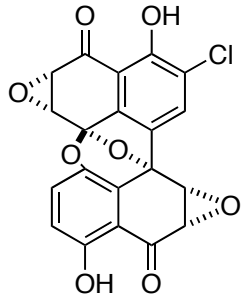


Sch 53825 (**49**)

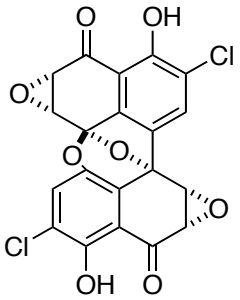
Figure 12. Fungal Metabolites with Phospholipase D Inhibitory Activity.

1.1.1.4. Spiroxins

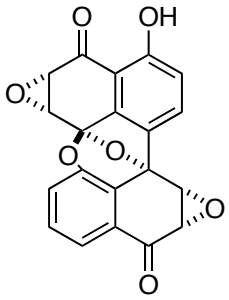
The spiroxins represent the newest members of the general class of naphthodecalin spiroacetals. Spiroxins A-E (Figure 13, **50**-**54**) were isolated in 1999 by a group from Wyeth-Ayerst.[8] The natural products were obtained from the extract of a marine-derived fungus, specifically from the fungal strain LL-37H248 isolated from a soft orange coral near Dixon Bay, Vancouver Island, Canada. The highly unusual octacyclic ring system is common to all spiroxins. Subtle variation in structure is characterized by varying degrees of halogenation and oxidation. Spiroxin A (**50**), the major component in the culture, demonstrated moderate activity against Gram-positive bacteria. In addition, **50** displayed antitumor activity in nude mice against ovarian carcinoma (59% inhibition after 21 days). In a screening against a panel of 25 different cell lines, spiroxin A exhibited a mean IC_{50} of 0.09 μg/mL. Further studies revealed that spiroxins hold promise as DNA cleaving agents. In the presence of the reducing agents dithiothreitol (DTT) or 2-mercaptoethanol, spiroxin A (**50**) caused concentration-dependent cytotoxic nicking of pBR322 DNA. Thus, it is possible that **50** acts by way of a single-stranded DNA cleavage mechanism.[8]



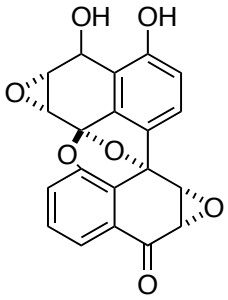
spiroxin A (**50**)



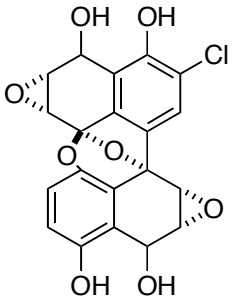
spiroxin B (**51**)



spiroxin C (**52**)



spiroxin D (**53**)



spiroxin E (**54**)

Figure 13. Spiroxins A-E.

1.2. The Thioredoxin Redox System

As part of some earlier exploratory studies of the biological activity of naphthoquinone acetals and a COMPARE analysis,[25] it became clear that inhibition of thioredoxin was another, yet undiscovered mode of action of these structurally intriguing fungal metabolites. The thioredoxin redox system is comprised of two essential elements-thioredoxin (trx) and thioredoxin reductase (TR). Trx is a low molecular weight redox protein characterized by a highly conserved active site (Trp-Cys-Gly-Pro-Cys-Lys).[26] The mammalian TR is a selenium-containing, NADPH-dependent flavoprotein that catalyzes the reduction of the active-site cysteine residues of oxidized trx.[27] The reduced trx shuttles electrons to a number of protein thiol acceptors in an effort to maintain and regulate the intracellular redox environment.[28] TR

reduction of trx is comprised of two half reactions, the first of which is the reduction of the tightly bound flavin adenine dinucleotide (FAD) prosthetic group of TR by NADPH followed by the subsequent transfer of electrons to the active-site cysteine residues of TR. The second reaction is the reduction of bound oxidized trx by TR.[28,29]

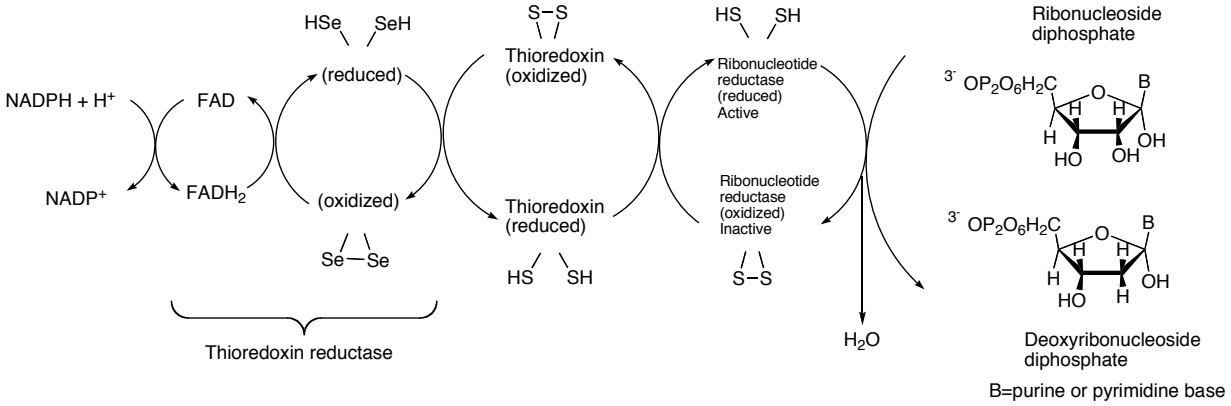


Figure 14. Thioredoxin Redox System.

Trx activity is evident in both eukaryotes and prokaryotes. However, the redox system of higher organisms is both structurally and functionally different from that of bacteria. Prokaryotic thioredoxins show roughly 50% sequence homology.[30] Human thioredoxin is a 11.5 kDa protein which bears 27% amino acid identity (overall sequence homology) to *Escherichia coli* trx.[27,30] It contains two redox active cysteine residues (Cys^{32} and Cys^{35}) in addition to three other residues (Cys^{62}, Cys^{69}, Cys^{73}) not found in bacterial trx.[26,27] TR is a 58 kDa dimeric enzyme in mammalian cells and a 35 kDa dimeric enzyme in *E. coli*.[30]

Such structural deviations result in distinct functional differences. Human thioredoxin possesses a wide range of unique biological properties. For example, the trx/TR system is a critical regulator of both intracellular and extracellular processes.[28] Thioredoxin is linked to DNA synthesis due to its ability to act as a reducing cofactor for ribonucleotide reductase.[27] In

addition, *in vitro* studies indicate thioredoxin's involvement in the reduction of methionine sulfoxide reductase and insulin.[29] Trx also regulates gene expression.[31] It exerts redox control over a variety of transcription factors (tf). The modified tf's exhibit different DNA binding capabilities; thus, ultimately resulting in altered gene expression.[27] Trx has also been implicated in posttranslational protein modification and protein folding processes.[31]

Trx possesses unique extracellular functions despite its nonclassical secretion mechanism by a leaderless pathway.[32] It acts exogenously as a redox active growth factor.[26] However, it lacks the appropriate signal sequence (usually a stretch of hydrophobic amino acids, either N-terminal or internal) to effect secretion by way of the endoplasmic reticulum-Golgi route.[32]

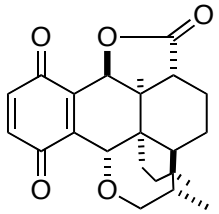
Human trx is identical to leukemic cell autocrine growth factor adult T-cell leukemic factor. Thus, it stimulates the growth of both normal fibroblasts and human hematologic and solid tumor cancer cells in culture.[26] Human recombinant trx exhibits the same trend. Powis' findings link increased cell proliferation with thioredoxin's unique ability to enhance the cell's sensitivities to growth factors secreted by the cells themselves.[27] Further studies indicate that mutant human trx's, where the Cys^{32} and Cys^{35} residues at the catalytic site are converted to serines, do not stimulate cell growth. Thus, the redox activity of the trx/TR redox system is essential for cell growth.[26,27] Ironically, the trx system regulates cell growth in addition to cell death through its inhibition of apoptosis in transfected cells. Apoptosis or programmed cell death is a critical feature of cell development. It serves to mediate normal cell turnover through its elimination of cancer-prone cells. Apoptosis is, by far, the most potent natural defense a higher organism possesses to combat malignancy![27,31]

It is clear that the thioredoxin redox system plays an integral role in the regulation of the growth of some human cancers. Thus, it serves as a rational target for the development of novel

chemotherapeutic agents.[27] Both thioredoxin and thioredoxin reductase are overexpressed in a number of human cancers as compared to normal tissue. For example, trx gene expression is increased many fold in a large percentage of human primary lung and colorectal tumors in addition to cervical tumors and hepatocellular carcinoma. Similarly, TR levels are elevated in many tumor cell lines and in human primary colorectal tumors.[31] In some cases, trx mRNA is increased up to 100-fold as compared to the corresponding normal tissue.[33,34] Powis reported studies of trx mRNA levels in a variety of human breast cancer cell lines, specifically those overexpressing mRNA.[34] Two cell lines, MCF-7 and MDA-MB-231, were closely evaluated. Both cell types were originally derived from an adenocarcinoma of the breast. The former represents the low end of mRNA overexpression. These highly differentiated cells retain several characteristics of mammary epithelium, the most significant of which is the ability to process estradiol. In addition, MCF-7 cells express p53, a tumor suppressor gene that is required for apoptosis.[35] The less differentiated MDA-MB-231 cells represent the high end of mRNA overexpression. They lack both functional estrogen receptors and p53, factors that contribute to their use as therapeutic targets. The loss of estrogen receptor expression correlates to poor patient prognosis.[36,37]

Further evidence of the importance of the trx system stems from additional studies from the Powis laboratories. The stable transfection of human MCF-7 breast cancer cells with a dominant negative mutant redox-inactive trx resulted in the almost complete reversal of the transformed phenotype both *in vitro* and *in vivo*. In contrast, the transfection of MCF-7 cells and WEHI 7.2 lymphoid cells with trx resulted in the enhancement of the transformed phenotype and tumor growth *in vivo*.[31]

Thioredoxin regulates both cell growth and death.[27] It enhances tumor growth and causes these tumors to be resistant to anticancer drugs.[31,38] Thus, the thioredoxin redox system is a valid target in cancer drug discovery. To date, there are no selective and potent inhibitors of thioredoxin-dependent cell proliferation, even though mixed disulfides, such as 1-methylpropyl 2-imidazolyl disulfide have been studied. The disulfide competitively inhibits trx and TR with IC_{50}'s of 31 and 37 μM, respectively. However, it is neither selective nor potent. Alkyl 2-imidazolyl disulfides also block MCF-7 human breast cancer cells in the G_2/M phase of the cell cycle. In addition, they have demonstrated the ability to suppress the growth of several human primary tumors in the NCI 60 cancer cell line panel.[25,38] Furthermore, a disulfide's ability to react with all accessible cysteine residues reduces its overall appeal as a viable drug candidate.[26,28,31] Cell line directed screening studies by Kunkel *et al.* revealed trx and TR inhibitors with possible pharmacological potential. These include several fungal-derived quinones, *i.e.* pleurotin (NSC401005) and NSC 208731. The *para*-quinone natural product, pleurotin (**55**, Figure 15), is the most potent trx/TR inhibitor known to date.[39] The IC_{50} of **55** against trx/TR was determined to be 0.17 μM. However, the average IC_{50} of pleurotin for growth inhibition in the NCI 60 tumor cell line panel was a mere 21.5 μM.[39] Despite the fact that auranofin and nitrosoureas are also able to effectively inhibit TR, the quest for novel, more specific and less toxic compounds is clearly justifiable.



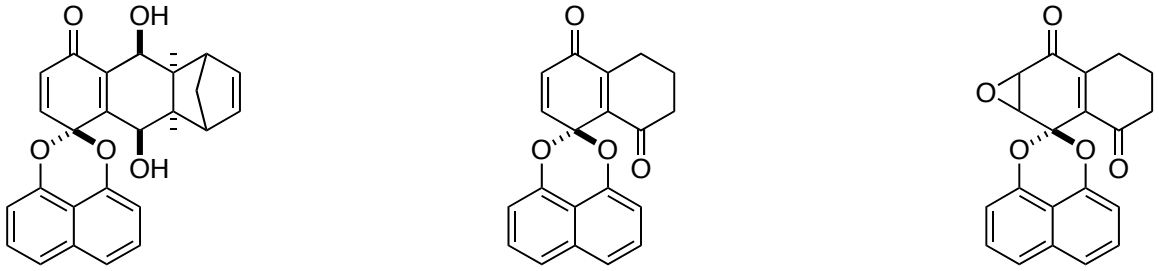
pleurotin (**55**)

Figure 15. Structure of Pleurotin.

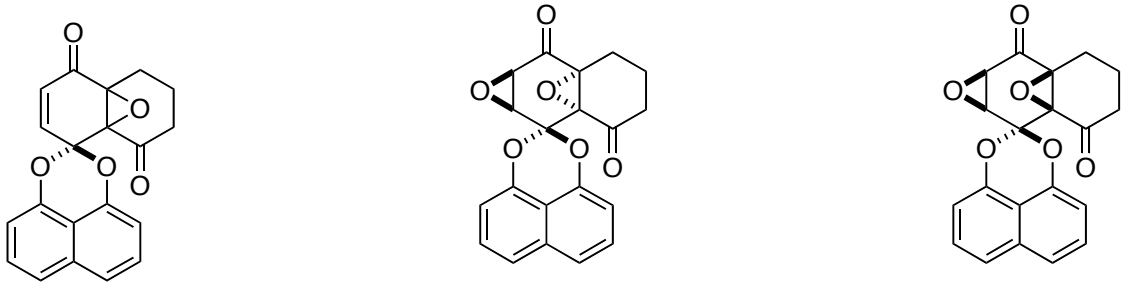
1.3. Potential Inhibitors of the Thioredoxin Redox System

1.3.1. JK-Series

An initial set of seven diepoxin σ/palmarumycin CP_1 analogs, prepared in the Wipf group (**56-61**, Figure 16) by Dr. Jae-Kyu Jung, demonstrated potent and selective activity in the trx/TR differential assay[40,41] with IC_{50}'s of up to 350 nmol.[42]



JK-2 (**56**) JK-3 (**57**) JK-4 (**58**)



JK-5 (**59**) JK-6 (**60**) JK-7 (**61**)

Figure 16. Diepoxin Analogs-JK-Series.

1.3.2. SAR Studies

Both the efficiency of the Wipf/Jung synthesis to access palmarumycin CP_1 (**2**)[43] and the positive preliminary biological data (inclusive of trx/TR differential assay data[42] and cytotoxicity data[44]) associated with **2** played important roles in the decision to prepare a series of analogs of

the natural product. Four sites of structural modifications were of immediate interest (Figure 17).

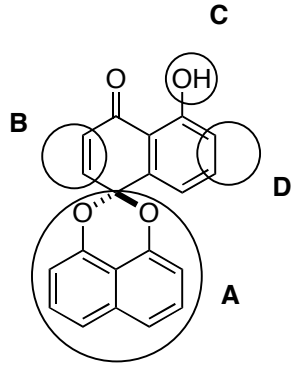
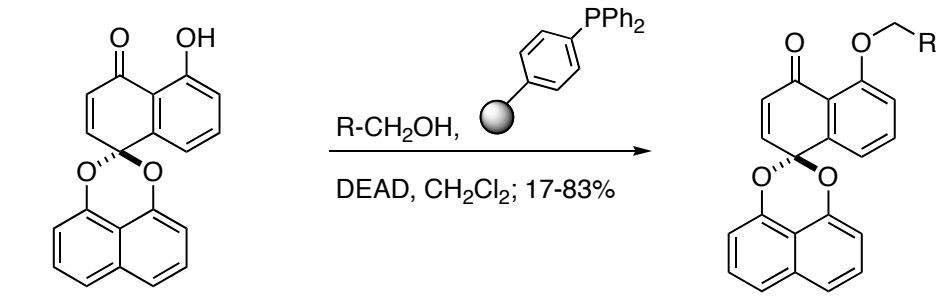


Figure 17. Planned SAR Studies of the Palmarumycin Core Structure.

Site A and site D modifications address the significance of hydrophobic interactions. Modifications of the enone function (site B) should greatly influence trx activity (as was evident from preliminary SAR studies of the initial JK-series). For example, the introduction of polar groups might provide additional points of binding. In fact, preussomerin G reacts with thiols via a conjugate addition reaction in a highly stereospecific manner to give the corresponding C(3') adduct.[18] Lastly, the conversion of the phenol at site C to ethers of varying types by the introduction of polar and apolar chains should influence both the binding and water solubility of the resulting derivatives. Hopefully, as a result, the selectivity of these compounds will be enhanced. Modifications at sites A, B and C have been investigated thus far. Very recent work by Dr. Stephen Lynch has resulted in the development of oxime derivatives.[45] In our laboratory, Dr. Sonia Rodriguez developed a small library of palmarumycin CP_1 (site C) analogs via Mitsunobu reactions with polymer-supported triphenylphosphine on the natural product itself (SR-series).[44] Thirteen allylic and benzylic alcohols were employed as coupling partners (Scheme 5).

1.3.3. SR-Series



palmarumycin CP_1 (**2**) **62-74**

62, R = (*E*)-HC=CHPh
63, R = (*E*)-HC=CHMe
64, R = *n*-C_5H_{11}
65, R = (*E*)-CH_2HC=CHEt
66, R = (*m*)-MeOPh
67, R = Bn
68, R = 2-furyl
69, R = (*E*,*E*)-HC=C(Me)CH_2CH_2CH=CMe_2
70, R = 3-furyl
71, R = 2-pyridyl
72, R = 3-pyridyl
73, R = 4-pyridyl
74, R = HC=CH_2

Scheme 5. Site C Analogs of Palmarumycin, SR-Series.

Most of the Mitsunobu reactions delivered a single isomer, with one notable exception. Both the desired ether product **68** and the C-alkylated phenol were observed in the coupling between 2-furyl methanol and palmarumycin CP_1 (**2**). All of the spiroketal products were screened against two very widely used human breast cancer cell lines, MCF-7 (estrogen receptor positive) and MDA-MB-231 (estrogen receptor negative), tumor cells characterized by high levels of trx and TR. Table 1 summarizes trx/TR assay data and growth inhibition values for the JK- and SR-series and other related compounds.[42,44] The results indicate that 45% of the compounds tested exhibit an IC_{50} of less than 3 μM in both cell types. This includes the

particularly potent furan derivative **68**, which possesses IC_{50}'s of 1.1 μM for MCF-7 cells and 2.5 μM for MDA-MB-231 cells. Half of the compounds demonstrate absolutely no selectivity for either tumor cell type. Roughly one-third of the analogs demonstrate more cytotoxicity towards MCF-7 cells as compared to MDA-MB-231 cells. For example, epoxy diketone **58** proved to be 5-fold more cytotoxic to estrogen receptor positive cells (as compared to MDA-MB-231 cells). Equally notable is the enhanced sensitivity of allyl ether **65** to estrogen receptor negative cells as compared to MCF-7 cells.[42,44] Both JK-2 (**56**) and palmarumycin CP_1 (**2**) exhibit 10-20 times greater cell growth inhibition against both cancer cell lines,[42,44] compared to the inhibitory activity of the most potent trx/TR inhibitor-pleurotin[39] (**55**, Figure 15).

The structure of pleurotin (**55**) is most closely related to JK-2 (**56**, Figure 16). However, the latter exhibits considerably lower activity. A comparison of the members of the JK-series reveals that the conjugated enone is not essential. The diepoxy-diketone, JK-7 (**61**), maintains a respectable level of trx/TR inhibition as compared to the parent dienone, JK-3 (**57**). In general, there is no obvious direct relationship between cell growth inhibitory activity and trx/TR inhibition in the JK-series.[42]

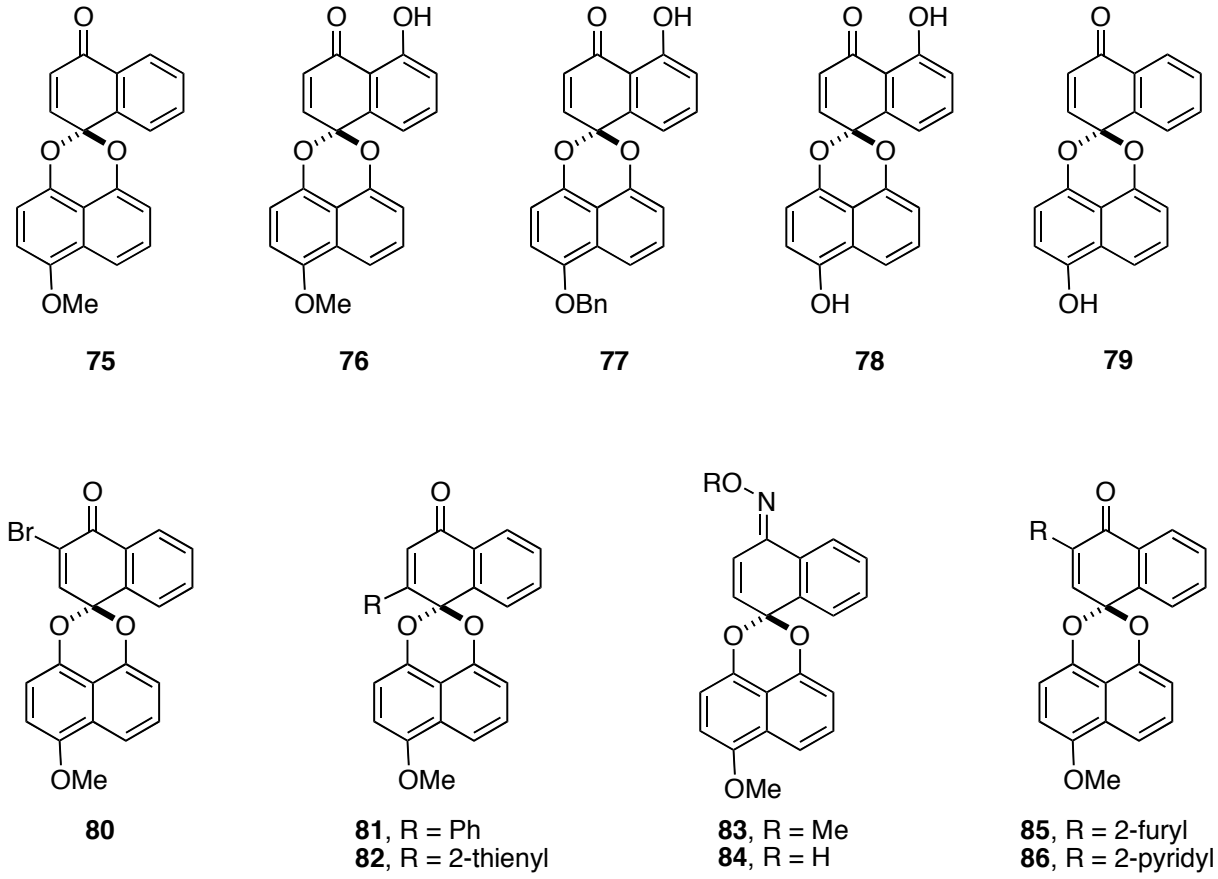
Table 1. IC_{50} Values [μM] for 2 Cancer Cell Lines and TR and TR/trx Inhibition.

Entry	Compound	MCF-7	MDA-MB-231	TR	TR/trx
1	**62**	7.9	7.5	nd[a]	>50
2	**63**	1.3	2.9	nd	>50
3	**64**	13.4	13.6	nd	>50
4	**65**	43.4	9.2	nd	>50
5	**66**	2.3	2.7	nd	>50
6	**67**	3.9	4.6	nd	>50
7	**68**	1.1	2.5	nd	>50
8	**69**	4.6	2.0	nd	>50
9	**70**	2.0	2.0	>50	23.2
10	**71**	2	2.8	>50	41.8
11	**72**	1.5	1.4	>50	>50
12	**73**	8.0	7.3	>50	>50
13	**74**	2.0	2.7	>50	23.2
14	**Diepoxin σ (37)**	1.5	2.0	13.5	4.5
15	**Palmarumycin CP_1 (2)**	0.9	2.4	12.0	0.35
16	**56**	1.3	2.1	nd	8.0
17	**57**	3.8	6.4	nd	2.1
18	**58**	4.6	23.0	nd	12.2
19	**59**	1.3	3.4	nd	44.0
20	**60**	4.6	8.2	nd	>50
21	**61**	2.8	2.9	nd	13.5

[a]nd, not determined.

1.3.4. SL-Series

The most recent set of palmarumycin analogs (Figure 18) was prepared by Dr. Stephen Lynch.[45] Table 2 depicts the biological data obtained for this series.



75 **76** **77** **78** **79**

80

81, R = Ph
82, R = 2-thienyl

83, R = Me
84, R = H

85, R = 2-furyl
86, R = 2-pyridyl

Figure 18. Additional Palmarumycin Analogs-SL-Series.

Table 2. IC_{50} Values [μM] for Trx Inhibition and MCF-7 Cytotoxicity.

Entry	Compound	Trx Inhibition	MCF-7 Cytotoxicity
1	Pleurotin (**55**)	0.17	4.1
2	Palmarumycin CP_1 (**2**)	0.35	1.0
3	Palmarumycin CP_2 (**3**)	>100	>50
4	MK 3018 (**1**)	8.4	10.0
5	**75**	3.2	9.2
6	**76**	1.0	14.0
7	**77**	5.2	14.2
8	**78**	0.20	2.6
9	**79**	0.34	2.8
10	**80**	3.1	2.6
11	**81**	>50	>100
12	**82**	4.7	60.0
13	**83**	>50	80.0
14	**84**	23.6	10.2
15	**85**	6.4	6.0
16	**86**	5.0	1.6

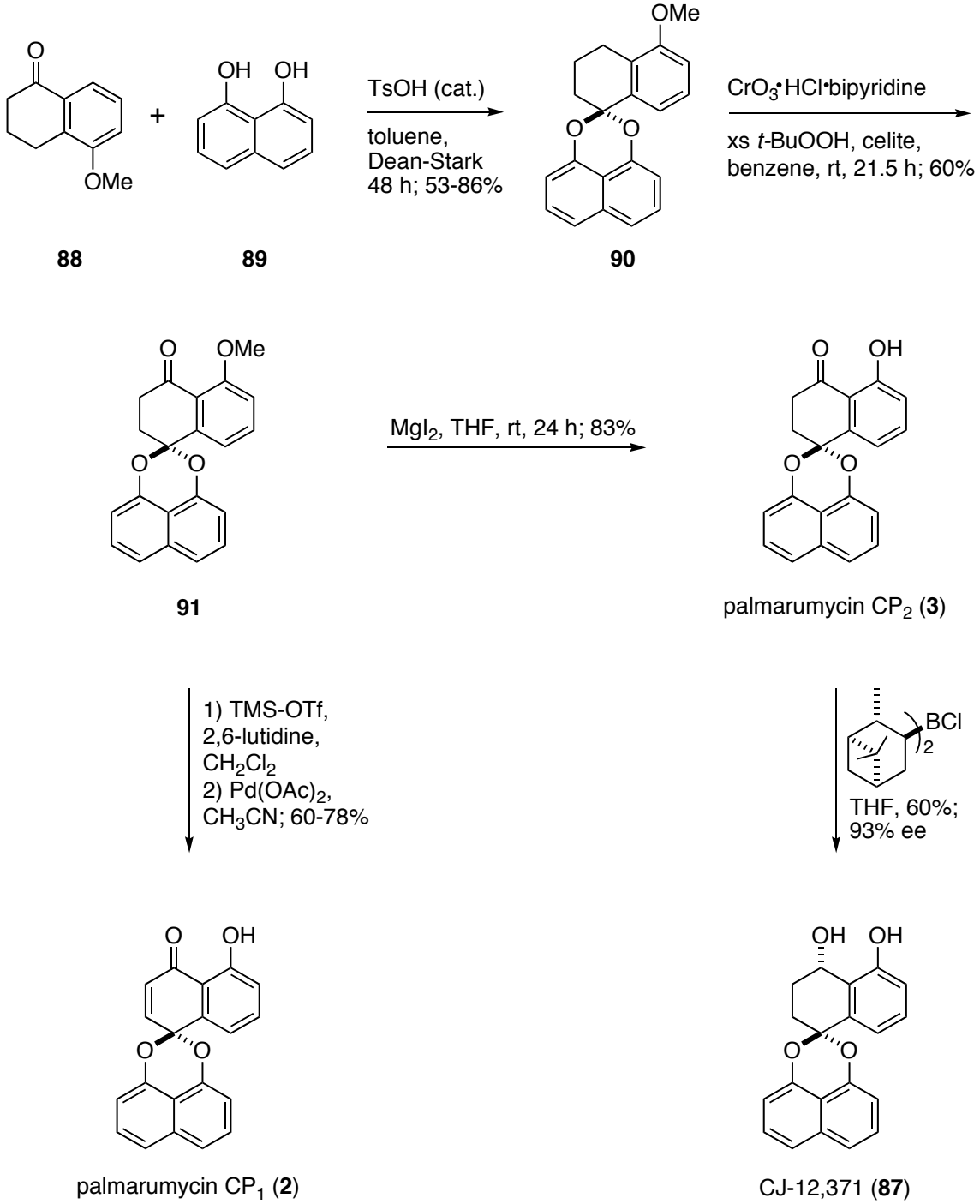
1.4. Synthetic Approaches Toward the Naphthalenediol Spiroacetals

1.4.1. Synthetic Approaches Toward the Palmarumycins

The unique structural features and attractive biological activity, common to the naphthalenediol spiroacetals, sparked considerable interest in the synthetic organic community. In 1998, both Barrett[46] and Taylor[47] reported independent total syntheses of three natural products-palmarumycin CP_1 (**2**),[2] palmarumycin CP_2 (**3**)[2] and the structurally related DNA-gyrase inhibitor-CJ-12,371 (**87**),[48] an isolate from an unidentified fungus (N983-46). A couple of years later, Coutts *et al*. published novel synthetic approaches to the palmarumycin skeleton.[49] In 2002, Barrett *et al*. presented a unified approach to the palmarumycin and preussomerin natural products.[50] Their synthetic efforts (*i.e*. Barrett research group) culminated in an improved synthesis of palmarumycin CP_1 (**2**) and palmarumycin CP_2 (**3**) (Scheme 6), in addition to the syntheses of the following palmarumycins: C_2 (also referred to as deoxypreussomerin B), C_3, C_{11} and C_{12}.

Barrett[46,50] introduced the spiroacetal moiety of palmarumycin via the acetalization of commercially available 5-methoxytetralone **88** with 1,8-naphthalenediol **89** under acid catalysis in 53-86% yield, depending upon the scale (Scheme 6). The resulting spiroacetal **90** was subjected to an unusual set of benzylic oxidation conditions to effect the conversion of cyclohexane to cyclohexanone in 60% yield. The ketone product (**91)** served as a common intermediate for both natural products, **2** and **3**. Deprotection of the methyl ether of **91** with freshly prepared magnesium iodide led directly to palmarumycin CP_2 (**3)** in a yield of 84%. Dehydrogenation with DDQ followed by methyl ether deprotection with *B*-bromocatecholborane gave palmarumycin CP_1 (**2)** in a two-step yield of 33%. Finally, palmarumycin CP_2 (**3**) was

converted to the DNA-gyrase inhibitor, CJ-12,371 (**87**), in 60% yield and 93% enantioselectivity by an asymmetric reduction with (+)-*B*-chlorodiisopinocampheylborane.

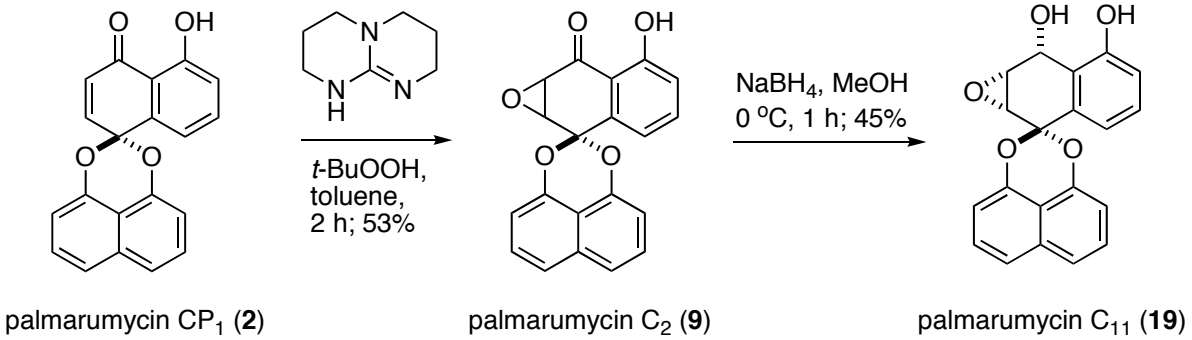


Scheme 6. Barrett's Approach to the Total Syntheses of Palmarumycins CP_1 and CP_2.

Taylor's approach[47] to the palmarumycins was very similar to Barrett's.[46,50] The same 5-methoxytetralone (**88)** was condensed with **89** in the presence of catalytic acid (*i.e.* 20 mol% H_2SO_4 or triflic acid) to provide spiroacetal **90** in 69% yield as illustrated in Scheme 6. Benzylic oxidation with PDC and *tert*-butyl hydroperoxide afforded the common intermediate, ketone **91**, in 64% yield. Demethylation transformed **91** into palmarumycin CP_2 **(3)** in 61% yield. Alternatively, **91** was subjected to a two-step dehydrogenation, demethylation sequence to give palmarumycin CP_1 (**2**) in a 37% overall yield. Finally, reduction of the ketone function of **3** with sodium borohydride delivered racemic CJ-12,371 (**87**) in a quantitative yield.

Palmarumycin CP_1 (**2**) served as the precursor for Taylor's syntheses (Scheme 7) of both palmarumycin C_2 (**9**) (deoxypreussomerin A) and palmarumycin C_{11} (**19**).[51] Treatment of the parent compound **2** with *tert*-butyl hydroperoxide and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (DBU) delivered the requisite epoxide. The conversion of **2** to palmarumycin C_2 (**9**) represented the first successful epoxidation of the palmarumycin nucleus, to date. Sodium borohydride reduction of the oxidized nucleus afforded a single diastereomer (**19)** in 45% yield. The *syn*-hydroxy epoxide is the expected product of a borohydride reduction and further corroborates Krohn's tentative structure assignment of palmarumycin C_{11} (**19**).[4] Both Connolly and Chu reported the isolation(s) of bipendensin[12] and Sch 53,823,[13] respectively, from natural sources. The structures of both natural products were purported to be identical to palmarumycin C_{11} (**19**).[4] However, Taylor's inspection of Connolly and Chu's reports revealed not only NMR differences between the two isolated structures, but discrepancies between bipendensin and the above *syn*-hydroxy epoxide (tentatively referred to as palmarumycin C_{11}, **19**) in addition to Sch 53,823 and **19**. Since additional spectroscopic studies revealed that both bipendensin and Sch 53,823 possessed the same relative stereochemistry, it could be deduced that all three compounds shared the same

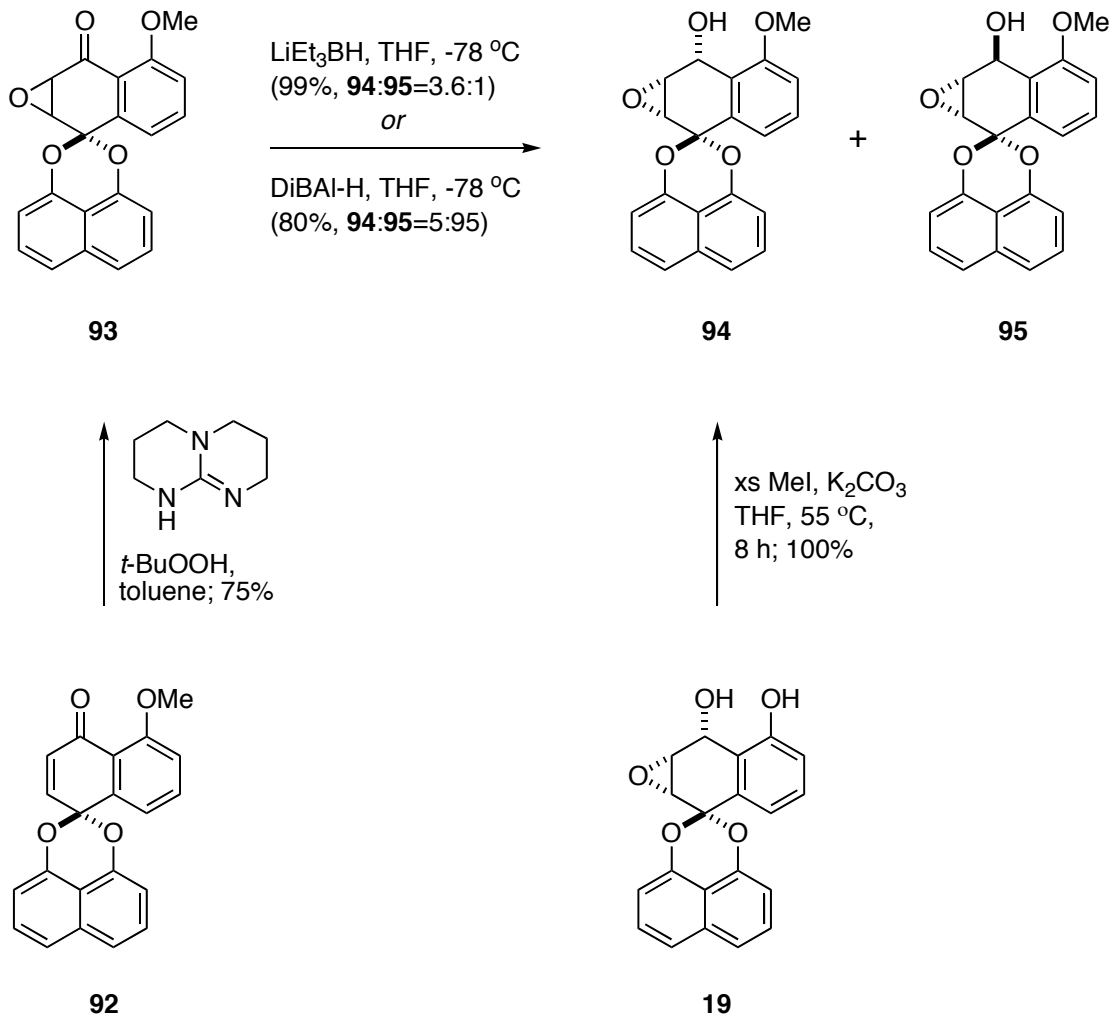
gross structure. The melting point and optical rotation data did not correlate among the three, however.[51]



palmarumycin CP_1 (**2**) palmarumycin C_2 (**9**) palmarumycin C_{11} (**19**)

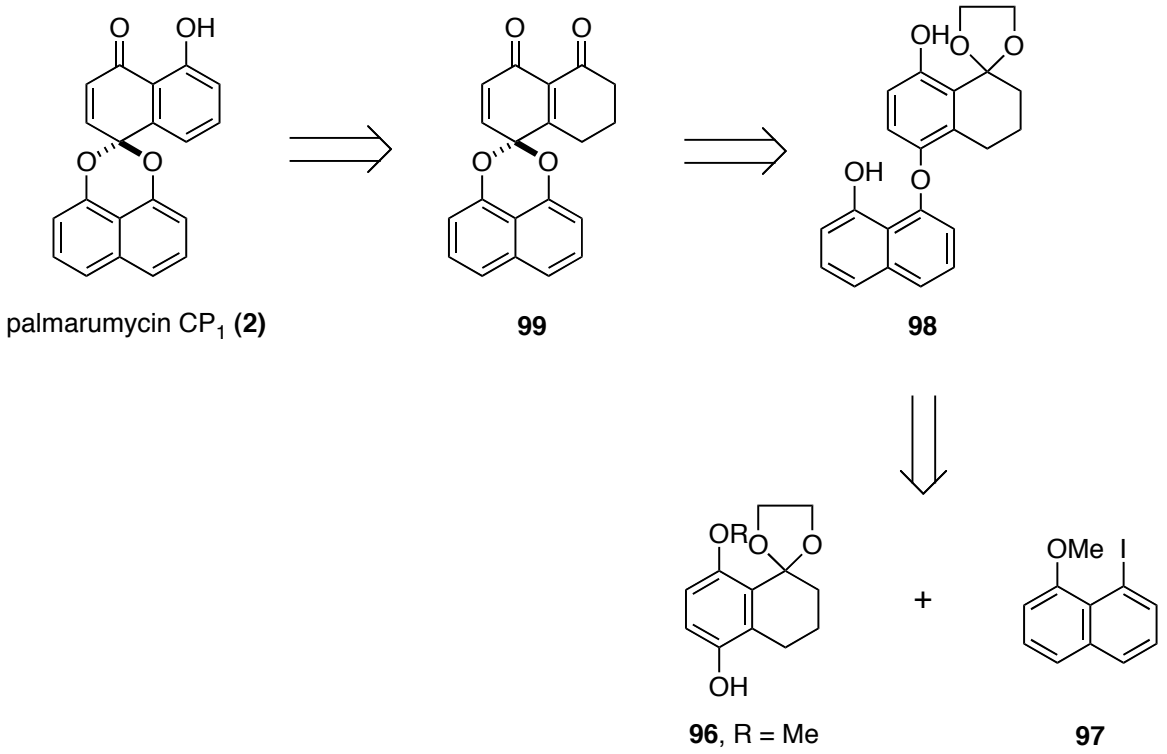
Scheme 7. Taylor's Approach to Palmarumycins C_2 and C_{11}.

Taylor probed the hydroxy epoxide stereochemical relationship issue by performing two critical reactions (Scheme 8).[51] First, epoxy ketone **93** was subjected to a Super-Hydride reduction. An inseparable mixture of products, **94**/**95**, in a ratio of 3.6:1 was obtained in a quantitative yield. Then, epoxy ketone **93** was subjected to a DiBAl-H reduction. This reaction gave a predominance of **95** (80%, 95:5), a structural match to the minor isomer obtained from the first reduction. Furthermore, Taylor's epoxy alcohol (tentatively referred to as **19**) was quantitatively methylated to also give **94** (*i.e.* major product from the above borohydride reduction). Such evidence lends sufficient support to a *syn* relationship between the hydroxy and epoxide functions of palmarumycin C_{11} (**19**). Thus, it can be deduced that Sch 53,823 and bipendensin share the opposite *anti*-hydroxy epoxide relationship, despite Chu's report[13] to the contrary.



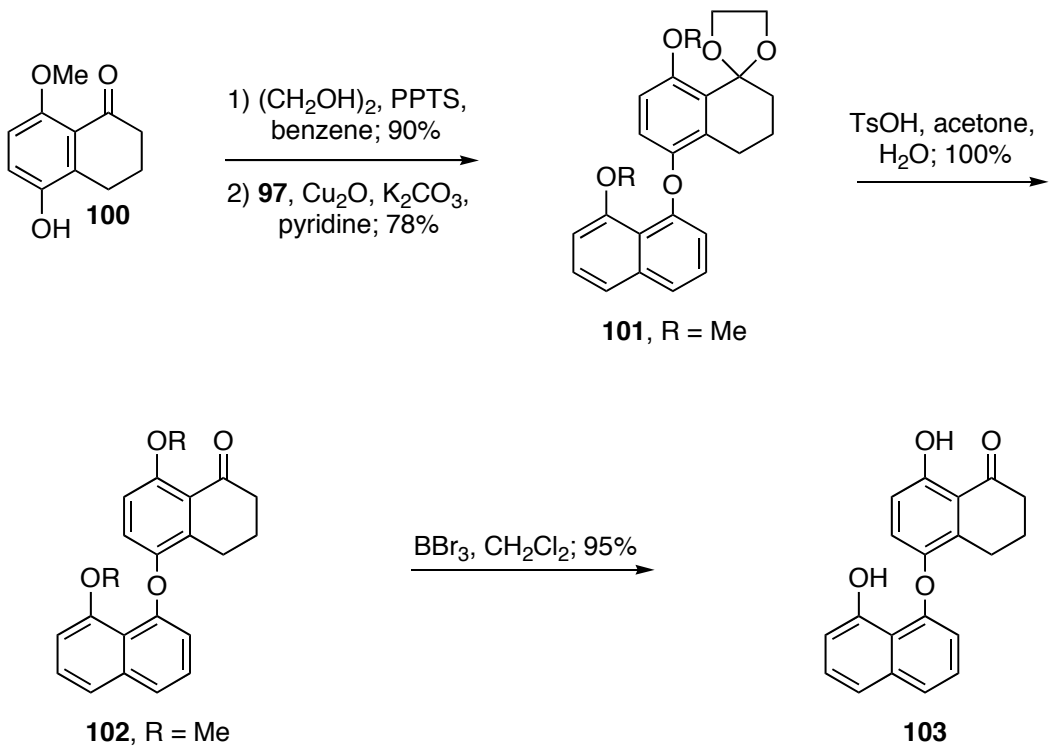
Scheme 8. Taylor's Determination of the Relative Stereochemistry of Palmarumycin C_{11}.

Our approach[43,44,52] to the syntheses of palmarumycin CP_1 (**2**) and palmarumycin C_2 (**9**) (deoxypreussomerin A) differed greatly from the efforts of both Taylor[47,51] and Barrett.[46,50] The retrosynthesis of palmarumycin CP_1 (**2**) is depicted below in Scheme 9. The key transformation features the late-stage introduction of the spiroacetal moiety via a hypervalent-iodine-mediated oxidative spirocyclization of **98**.



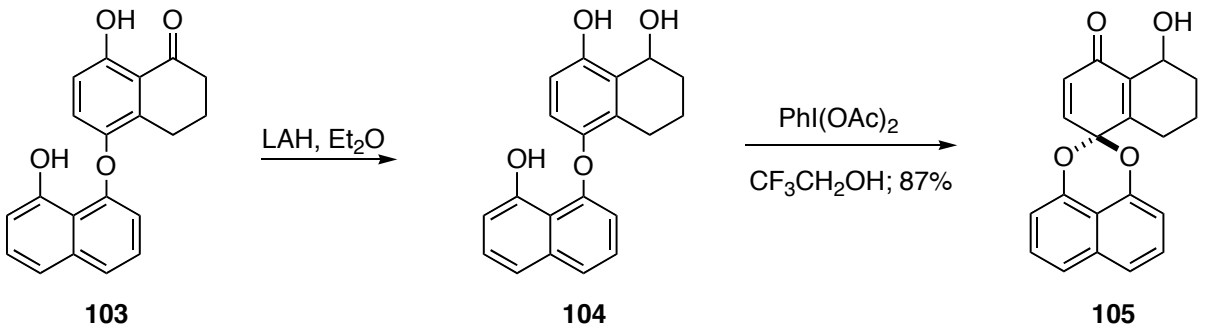
Scheme 9. Wipf's Retrosynthesis of Palmarumycin CP_1.

Binaphthyl ether **101** (Scheme 10) was derived from functionalized tetralone **96** and naphthalene derivative[53,54,52] **97** (Scheme 9). Acetalization of the known 5-hydroxy-8-methoxy-1-tetralone[55] (**100**, Scheme 10) provided the intermediate tetraline **96** in 90% yield. The other segment was accessed by the stereospecific iodination of 1-methoxynaphthalene[52,53,54] via *ortho*-lithiation at C(8) with *t*-BuLi in a solution of pentane and ether (4:1) followed by trapping with iodine. 1-Iodo-8-methoxynaphthalene (**97**) and its separable 2-iodo isomer were isolated in 72% and 9%, respectively.[52,54] Standard Ullmann[56] ether conditions were used to couple the two building blocks (*i.e.* **96** and **97**) in 78% yield. Quantitative removal of the acetal of naphthyl ether **101** followed by a high yielding deprotection of the methyl ethers with boron tribromide afforded bisphenol **103**.



Scheme 10. Synthesis of Biaryl Ether **103**.

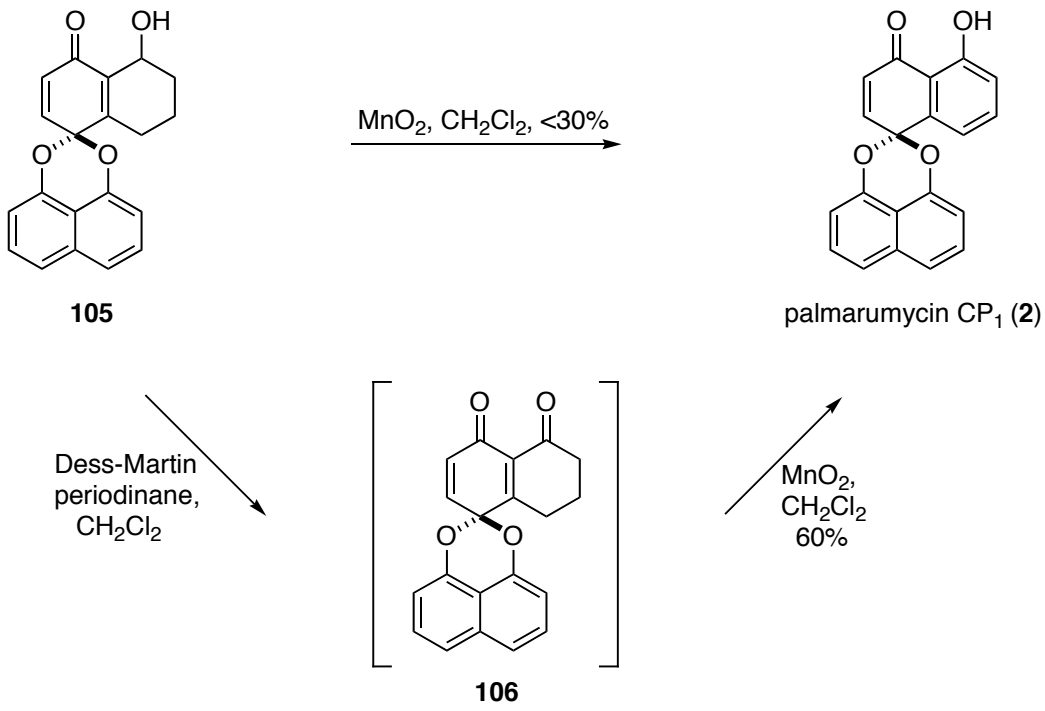
The key oxidative cyclization proceeds through an electron-deficient transition state. The transition state suffers from additional destabilization due to the presence of a ketone in close proximity. Attempted masking of the carbonyl moiety of **103** via standard acetalization conditions met with no success. After extensive experimentation, the following conditions were developed for the preparation of spiroacetal **105** in a high two-step yield of 87%: lithium aluminum hydride reduction of diol **103** followed by an oxidative cyclization of the resultant triol (**104**, Scheme 11).[57,58,59,60,61,62,54]



103 **104** **105**

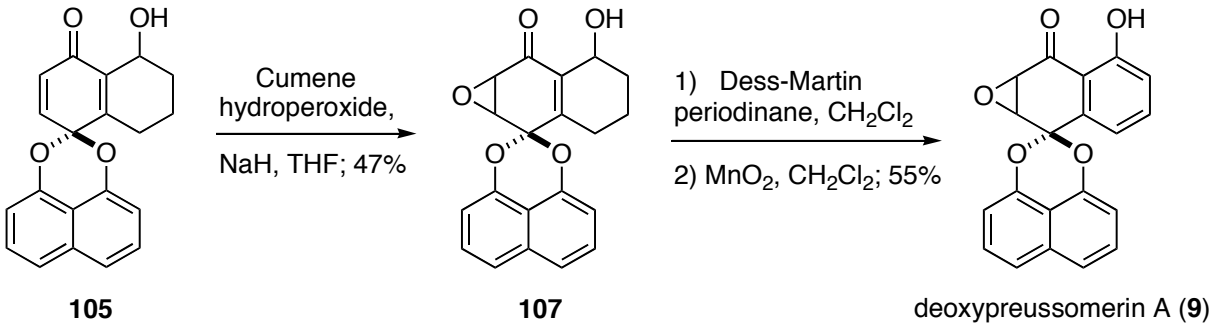
Scheme 11. Oxidative Spiroacetalization.

Treatment of **105** with activated MnO_2 at room temperature led to the aromatized product **2** in very low yield (<30%). When a large excess of oxidant was used to force the reaction to completion, product isolation became a problem. Fewer equivalents of oxidant and higher reaction temperatures led to **2**, contaminated with an inseparable by-product. Finally, a two-step oxidation protocol was employed to effect the clean conversion of **105** to palmarumycin CP_1 (**2**) in 60% yield (Scheme 12). Thus, the synthesis of palmarumycin CP_1 (**2**) was achieved in 8 steps from **100** in 35% overall yield.[43,44]



Scheme 12. Completion of the Total Synthesis of Palmarumycin CP_1.

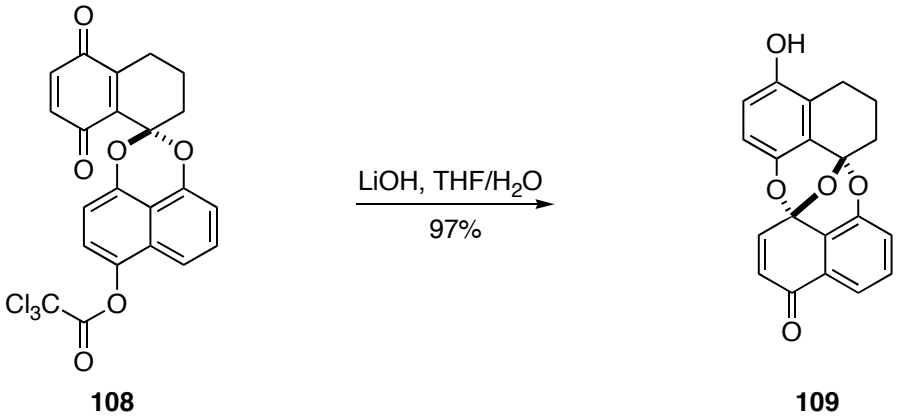
The direct conversion of palmarumycin CP_1 (**2**) to the ras-farnesyl-protein transferase inhibitor, deoxypreussomerin A (**9**), via the simple oxidation of the palmarumycin nucleus proved to be problematic. Treatment of the palmarumycin nucleus under a variety of epoxidation conditions, including nucleophilic H_2O_2/K_2CO_3 and electrophilic DMDO, led mostly to decomposition. Initial protection of the free phenol as a TBS ether followed by epoxidation attempts met with a similar lack of success.[44,54] Finally dienone **105** was evaluated as a potential candidate for epoxidation. The best yield (47%) of monoepoxide **107** was achieved with bulky cumene hydroperoxide as oxidant and sodium hydride as base at –20 °C.[43,44] Monoepoxide **107** was further elaborated into deoxypreussomerin A **(9)** in 55% yield via the previously described two-step oxidation protocol (Scheme 13). Thus, deoxypreussomerin A (**9**) was accessed in a mere 9 steps and a 15% overall yield from tetralone **100**.



Scheme 13. Synthesis of Deoxypreussomerin A from Advanced Intermediate **105**.

1.4.2. Synthetic Approaches Toward the Preussomerins

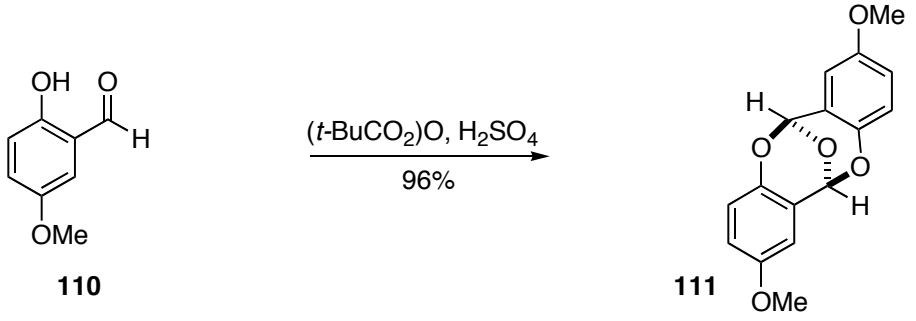
In 1999, Heathcock and Chi reported the first total syntheses of (+/-)-preussomerins G (**32**) and I (**34**).[63] The key transformation featured the construction of the bis-acetal moiety via a nucleophilic 1,6-addition of a phenoxide anion to the oxygen end of a quinone carbonyl (Scheme 14). The unusual "ring-chain tautomerization" is highly reminiscent of a biomimetic process. The syntheses of **32** and **34** were completed from intermediate **109** in nine and eight steps, respectively.



Scheme 14. Preparation of the Bis-acetal Moiety of the Preussomerins.

Taylor established a novel route to the hexacyclic nucleus of the preussomerins via the use of 2-arylacetal anions (Scheme 15).[64] Finally, the first enantioselective synthesis of (-)-

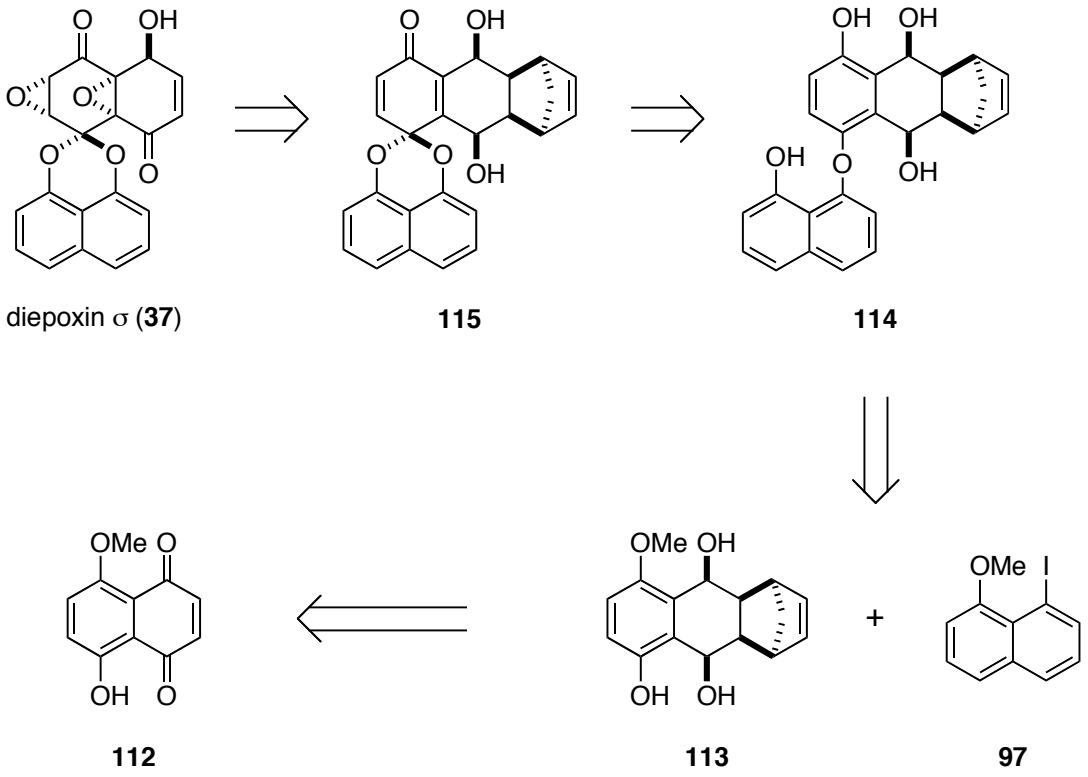
preussomerin G was reported by Barrett *et al.* in 2002.[50] Spiroketal **91** (Scheme 6) was used to access the palmarumycins and (-)-preussomerin G (**32**).



Scheme 15. Dimerization of β-Hydroxy Aldehydes.

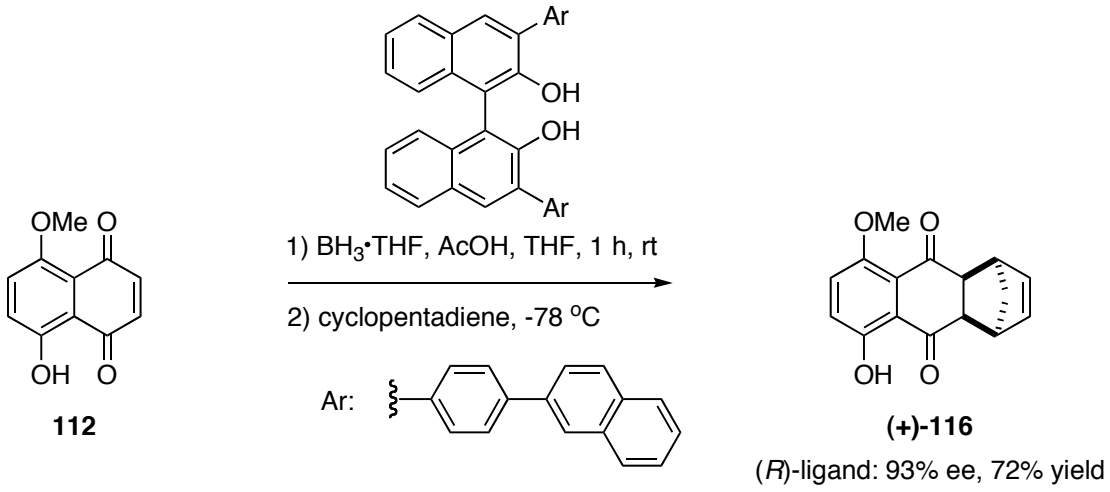
1.4.3. Synthetic Approach Towards Diepoxin σ

Wipf and Jung reported the first total synthesis of diepoxin σ (**37**, Figure 9) in 2000.[52] The retrosynthesis is outlined below in Scheme 16. Ullmann ether coupling[56] methodology was employed for the preparation of the oxidative spirocyclization precursor **114**. Fragment **97**[53,54] was prepared in the usual fashion. Triol **113** was accessed in a mere two steps[52] (quantitative Diels-Alder cycloaddition followed by a double reduction with sodium borohydride) from *O*-methylnaphthazarin (**112**) in 88% yield. The naphthoquinone derivative **112** was prepared[65] in 95% yield from the corresponding C_2-symmetric naphthalenediol.[54] The key conversion of tetraol **114** to spiroacetal **115** represents a possible biomimetic process. Furthermore, the transformation of **115** into that of the natural product, (+/-)-diepoxin σ (**37**), requires only five additional steps.



Scheme 16. Retrosynthetic Analysis of Diepoxin σ.

To achieve the asymmetric total synthesis of (+)-diepoxin σ, an enantioselective Diels-Alder reaction was investigated (Scheme 17).[66,67,54] To compensate for a small diene with no steric bias (cyclopentadiene), a chiral binaphthol auxiliary with bulky substituents at the *ortho* positions[68,69,70] was employed for the conversion of **112** to (+)-**116**. Chiral boron Lewis acids bearing *p*-(2-naphthyl)phenyl-substituted binaphthols[69,70] gave the highest asymmetric induction. (*R*)-Ligands[68] gave the (+)-adduct as the major enantiomer. Analogously, (*S*)-ligands[68] provided the (-)-adduct as the major enantiomer. The preparation of the appropriate Diels-Alder adduct, (+)-**116**, was achieved in 72% yield and 93% ee; thus, constituting the first formal asymmetric total synthesis of (+)-diepoxin σ.



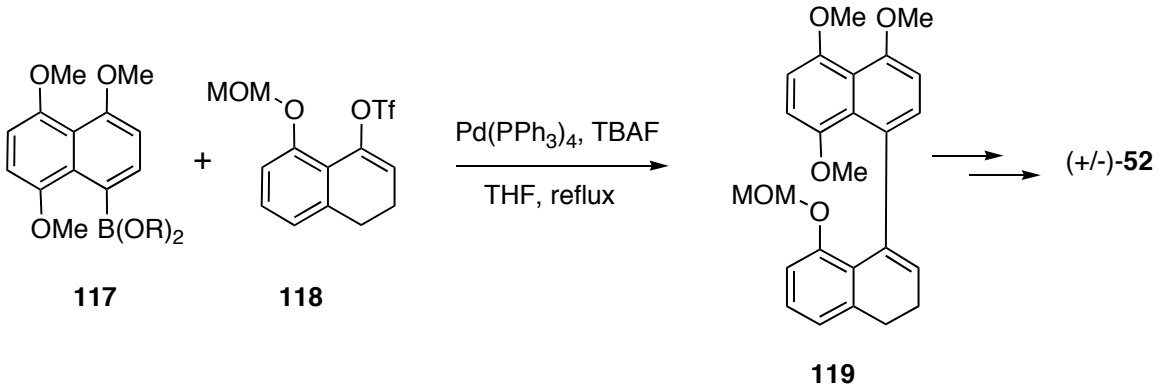
112 **(+)-116**

(*R*)-ligand: 93% ee, 72% yield

Scheme 17. Enantioselective Diels-Alder Reaction.

1.4.4. Synthetic Approach Towards Spiroxin C

The first (and only) total synthesis of the marine-derived, potent antitumor antibiotic (+/-)-spiroxin C (**52**) was reported in 2000 by Imanishi *et al.*[71] A TBAF-activated Suzuki[72]-Miyaura[73] cross-coupling reaction (Scheme 18) was used to link the two subunits together. The total synthesis of **52** was achieved in 15 steps and an overall yield of 1.3% from the commercially available 5-methoxytetralone. Our group had also initiated efforts toward the synthesis of the spiroxins prior to the publication of Imanishi's work. Some of our work will be detailed in the sections to follow.



117 **118** **119**

Scheme 18. TBAF-activated Suzuki-Miyaura Cross-coupling Reaction.

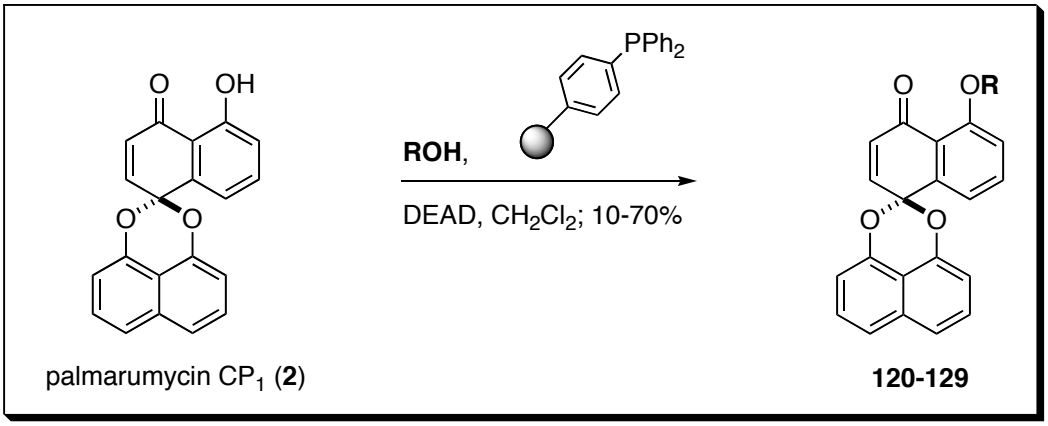
1.5. Results and Discussion

1.5.1. Synthesis of Palmarumycin CP_1 Analogs

1.5.1.1. Site C Analogs

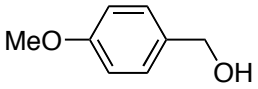
The potency of the palmarumycin analog bearing the furan moiety **(**Scheme 5, **68**) in an initial thioredoxin/thioredoxin reductase (trx/TR) assay precipitated interest in the generation of a library of furanyl analogs. Thus, we developed another small library (TH-series) of ten site C analogs. Half of the members of the library featured a substituted furan moiety **(**Scheme 19, **125-129)**. The other five consisted of additional allylic, benzylic, and propargylic ether variants **(**Scheme 19, **120-124)**.

The starting alcohols for products **120-122** were commercially available. The remaining benzylic and furanyl alcohol coupling partners were readily accessible in high yields from sodium borohydride reductions of the corresponding commercially available aldehydes. Mitsunobu reactions[42,44] were performed on very small scales due to the limited supply of palmarumycin CP_1 (**2**) which had been prepared previously by Dr. Sonia Rodriguez. Thus, extensive characterization of the resulting ether products was not an option. Diphenylphosphino-polystyrene served as the phosphine reagent of choice. Yields ranged from 10-70%.



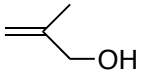
ROH

for **120**:



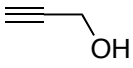
(***TH-39***)

for **121**:



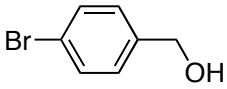
(***TH-40***)

for **122**:



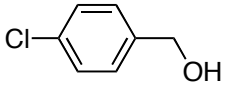
(***TH-44***)

for **123**:



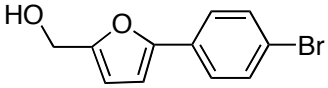
(***TH-48***)

for **124**:



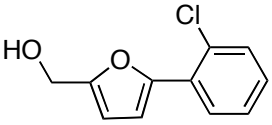
(***TH-49***)

for **125**:



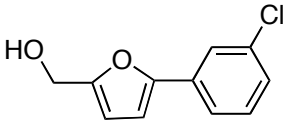
(***TH-62***)

for **126**:



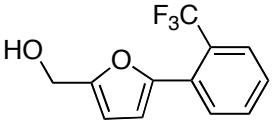
(***TH-63***)

for **127**:



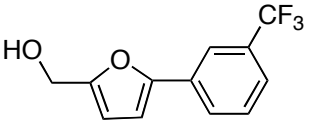
(***TH-64***)

for **128**:



(***TH-65***)

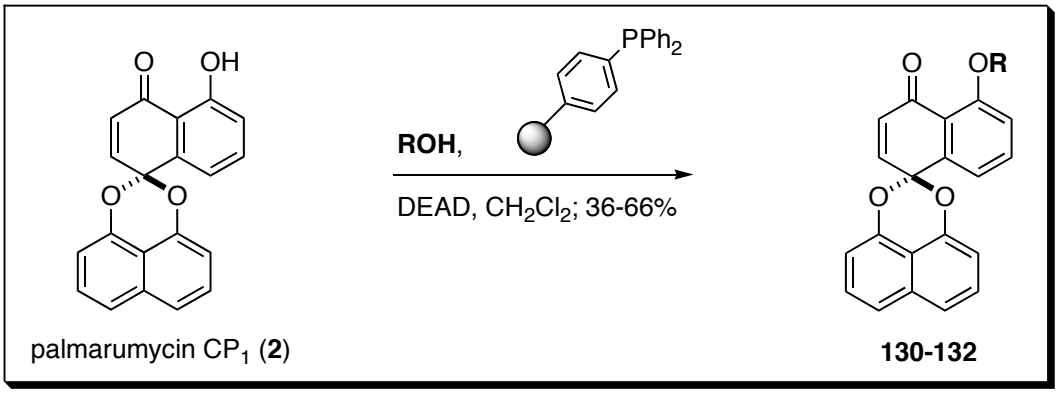
for **129**:



(***TH-66***)

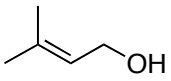
Scheme 19. Site C Analogs of Palmarumycin CP_1-TH-Series.

The observed potency of **120** and **122** in the trx/TR differential assay (Table 7) in combination with biological data obtained earlier (Table 1) prompted the synthesis of additional analogs (Scheme 20). Commercially available allylic alcohol (*i.e.* 3-methyl-2-buten-1-ol) was used for the preparation of **130** via the standard Mitsunobu conditions previously described. Lithium aluminum hydride reductions of both tiglic acid and angelic methyl ester provided the appropriate alcohol partners for two additional coupling reactions, leading to the preparation of **131** and **132**, respectively. The yields ranged from 36-66%. All analogs (**120**-**132**) were characterized by ^{1}H NMR and HR-MS prior to submission for biological testing. Furthermore, all of the aforementioned analogs were determined to be at least 90% pure by ^{1}H NMR.



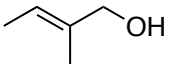
ROH

for **130**:



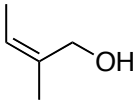
(***TH-126***)

for **131**:



(***TH-139***)

for **132**:



(***TH-140***)

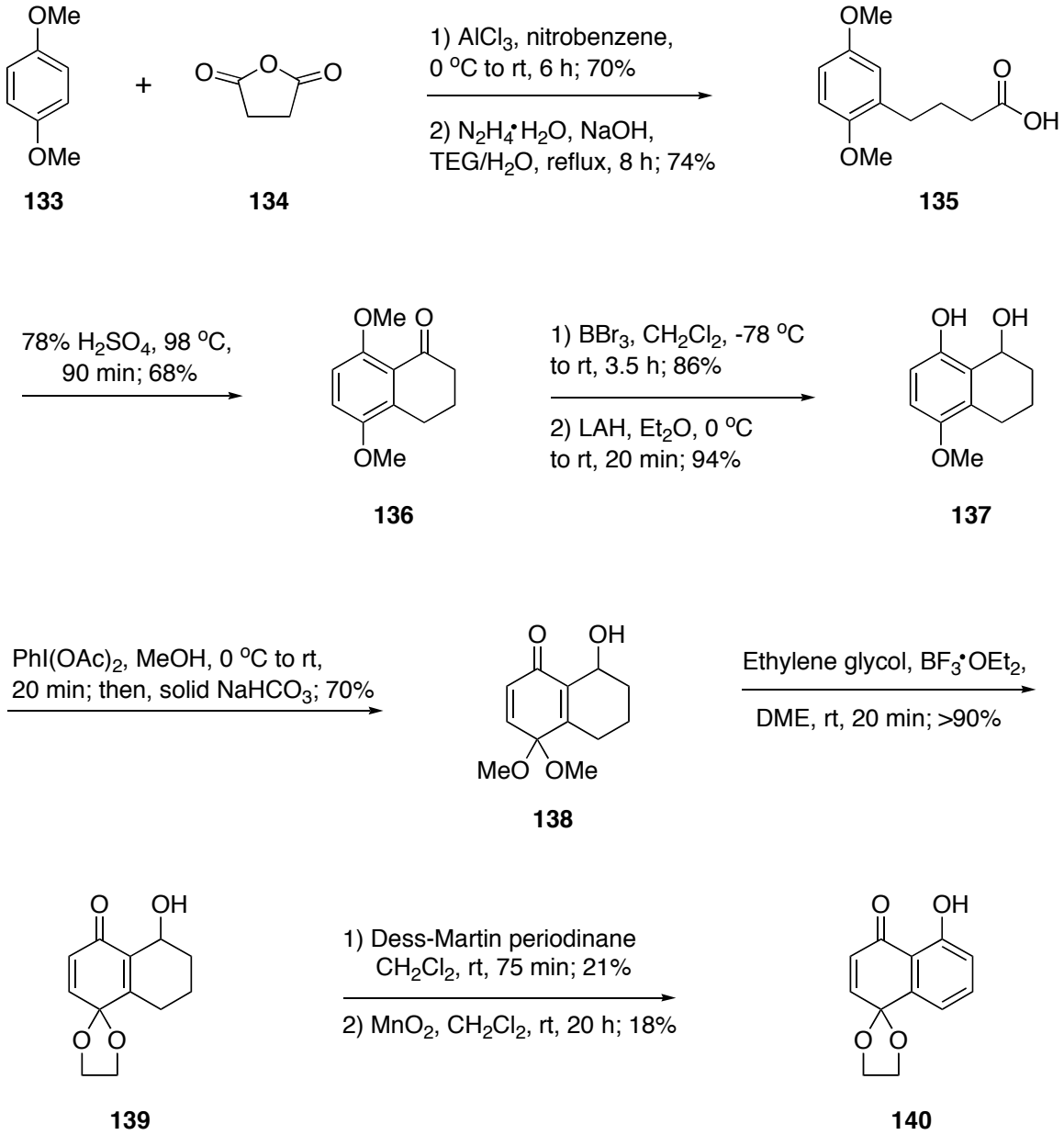
Scheme 20. Additional Site C Analogs of Palmarumycin CP_1-TH-Series.

1.5.1.2. Site A Analogs

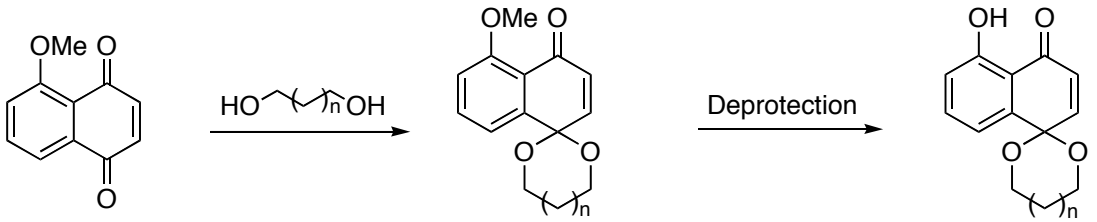
Two independent routes to Site A analogs were developed. The first synthetic sequence (Method A, Scheme 21) featured the Haworth Process[74] for the three-step conversion of the commercially available 1,4-dimethoxybenzene **133** to the known 5,8-dimethoxytetralone **136**[75,76] in an overall yield of 34%. The first intermolecular electrophilic aromatic substitution provided the intermediate acid[75,76] in a yield of 70%. A Wolff-Kishner reduction[76] followed by a second intramolecular Friedel-Crafts reaction delivered **136** in 68% yield. The (second) cyclization step was promoted by a variety of harshly acidic agents, *i.e.* 78% H_2SO_4,[77] commercially available polyphosphoric acid (PPA)[75,76] or *in situ*-generated PPA. However, yields were consistently better with H_2SO_4, albeit still only moderate at best.

Next, tetralone **136** was submitted to a low temperature, boron tribromide-mediated methyl ether deprotection.[78] Lewis acid coordination to the carbonyl moiety allowed for the highly regioselective demethylation at C(8) to provide the expected product in 86% yield. The resulting phenol was cleanly reduced to the diol **137** with lithium aluminum hydride, also in high yield. Upon treatment with iodobenzene diacetate in methanol,[79] diol **137** was transformed into the corresponding dimethyl acetal **138**. Subsequent to that, the key $BF_3 \bullet Et_2O$-mediated transketalization[80] reaction transformed **138** into the corresponding cyclic acetal **139**. Typically, reaction times were short and yields were high. For example, when ethylene glycol was used as the diol partner, **139** was isolated in over 90% yield in less than 20 minutes. Acetal **139** was then submitted to a two-step oxidation sequence. First, a solution of the quinone monoacetal **139** in CH_2Cl_2 was treated with Dess-Martin periodinane[42,44] at room temperature for 75 min. Then, the resultant diketone, isolated in only 21% yield, was further oxidized to the desired phenol **140**[42] with pretreated MnO_2 (previously dried over P_2O_5). In theory, the above sequence is clearly

amenable to analog synthesis. The diol exchange reaction[80] allows for the seemingly facile introduction of a variety of cyclic acetals. Unfortunately, the final oxidation is very low yielding in its current unoptimized state. Since an alternate strategy had already been initiated, further optimization of the nontrivial oxidation sequence was not actively pursued.



Scheme 21. Synthesis of Site A Analogs (Method A).

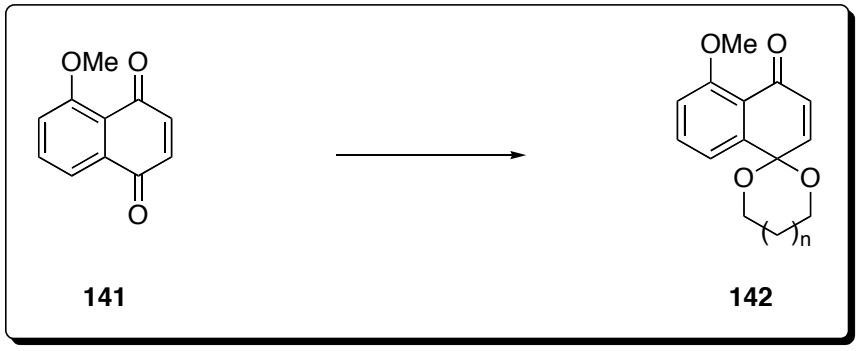


Juglone methyl ether, **141** **142** **143**

Scheme 22. Initial Strategy Towards the Synthesis of Site A Analogs (Method B).

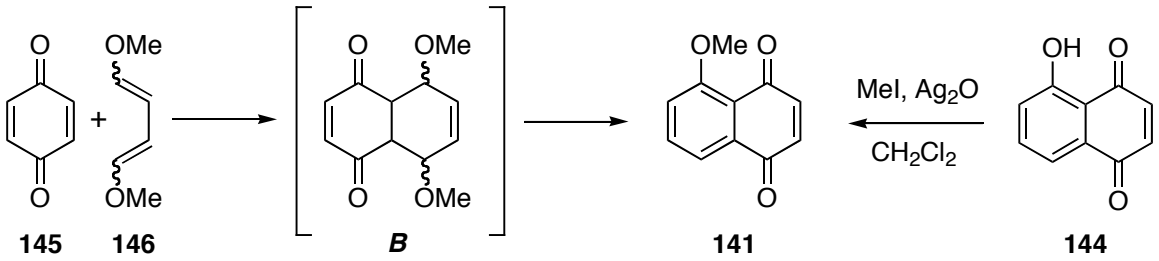
Scheme 22 depicts the alternate strategy, Method B, in its early stages of development. The original plan featured selective acetalization of the distal carbon of juglone methyl ether[81] **141** followed by demethylation. Unfortunately, all attempts at the selective incorporation of an acetal function in the naphthoquinone nucleus met with little to no success (Table 3). Standard protection conditions, *i.e.* ethylene glycol, catalytic PPTS, toluene reflux, resulted in either unreacted starting material with trace product formation (10-15% acetal incorporation) or highly complex mixtures (Entries 1-3). The replacement of PPTS with TsOH provided a complex mixture similar to that observed in Entry 3. Noyori conditions[82] (Entry 6) led to the recovery of starting material, unchanged even after a total reaction time of 36 hours. The solution was further warmed from -78° C to room temperature during this period. Finally, the transketalization pathway was revisited. First, the selective introduction of a small acetal function (*i.e.* dimethyl acetal) was attempted through the use of the following reaction conditions: trimethyl orthoformate, K-10 Montmorillonite and $BF_3 \bullet Et_2O$.[83] ^1H NMR analysis of the crude material revealed the presence of unreacted starting material in addition to a complex mixture of methylated products. Furthermore, purification via column chromatography on neutral alumina proved to be unsuccessful as well. Thus, the subsequent diol exchange reaction (transketalization) was never fully investigated. Based on the extremely poor initial results, method B in its current state was soon abandoned.

Table 3. Selective Acetalization Attempts.

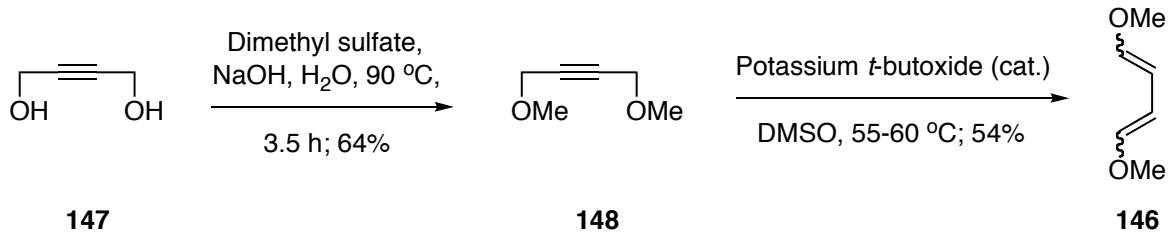


Entry	Conditions for 141 → 142	Results
1	Ethylene glycol (EG), PPTS, toluene, Dean-Stark, 30 h	Unreacted starting material (SM) + acetal incorporation (10%)
2	Excess EG, PPTS, toluene, Dean-Stark, 30 h	Unreacted SM + acetal incorporation (15%)
3	Excess EG, PPTS, toluene, Dean-Stark, 6 d	Complex mixture (SM consumption)
4	EG, TsOH, toluene, Dean-Stark, 30 h	Complex mixture (identical to that of previous reaction)
5	Trimethylorthoformate, K-10 Mont., $BF_3 \bullet Et_2O$, CCl_4/CH_2Cl_2, 20 h	SM + mixture of methylated compounds
6	1,2-Bis(trimethylsilyloxy)-ethane, cat. TMS-OTf, CH_2Cl_2, -78 °C to rt, 3 d	Recovered SM

Juglone methyl ether **141**[81] could be accessed from the commercially available juglone **144** via a facile methylation with methyl iodide and Ag_2O. Alternatively, it could be prepared by a Diels-Alder reaction between benzoquinone (**145**) and 1,4-dimethoxy-1,3-butadiene (DMBU, **146**), as illustrated in Scheme 23. Clearly, the Diels-Alder adduct is not the isolated product. The transformation of intermediate B into **141** still requires both an oxidation and an elimination reaction.



Scheme 23. Synthesis of Juglone Methyl Ether.

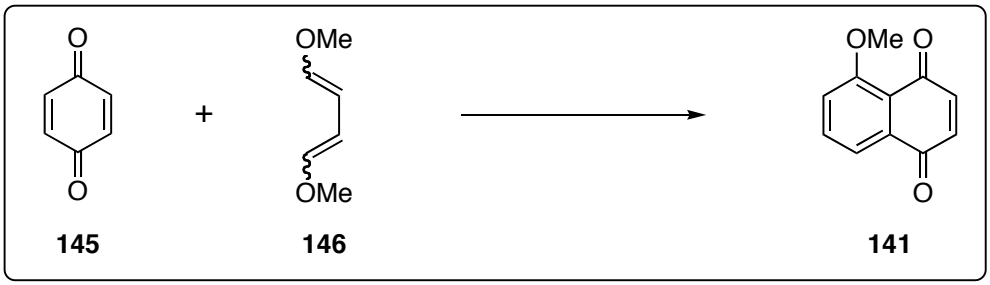


Scheme 24. Synthesis of DMBU.

DMBU (**146**)[81,84] was readily obtained in two steps from commercially available 1,4-dihydroxy-2-butyne (**147**)[84] (Scheme 24). The reported literature yield of **141** is 43%. My attempts at reproducing the reaction conditions led to much lower conversions (Table 4). The first entry represents Miller's published protocol[81] with the exception of the toluene replacement for benzene. Similarly low yields were obtained for standard 20 hour reactions and extended reaction times. Doubling the number of equivalents of both oxidants led to 14% of the desired

naphthoquinone derivative **141**. Since we were not convinced that silver (I) oxide was playing its "intended role" very effectively, it was left out of the reaction mixture for trials 4-9. Indeed, the isolated yield remained largely unaffected. The number of equivalents of the remaining oxidant was increased to compensate for the removal of silver (Entries 7-9). A six day reaction in toluene with 3.5 equivalents of benzoquinone (**145**) provided the highest conversion, a 33% yield of **141**. The replacement of toluene with water resulted in lower yields (*ca.* 10%). A solvent switch was invoked in an effort to probe the potential rate enhancement of the [4 + 2] cycloaddition in a highly polar medium. Microwave reactions with water or toluene as solvent led to low conversions as well (Entries 8 and 9).

Table 4. Diels-Alder Reaction Trials.



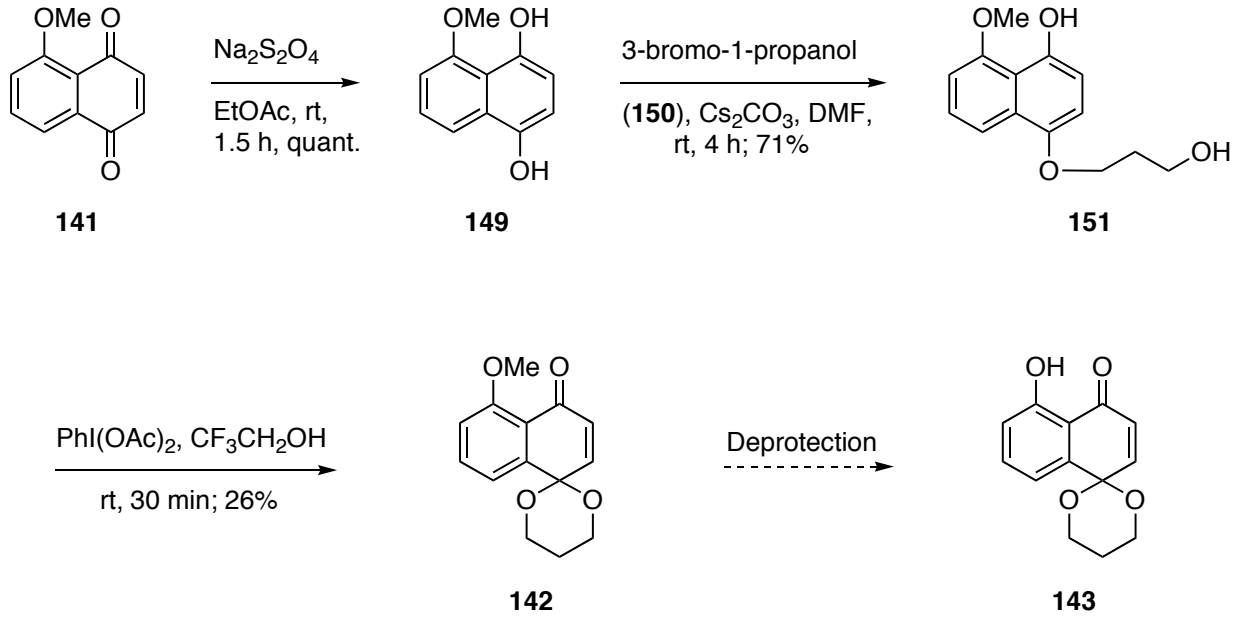
Entry	Equiv. of 145 vs 146	Rxn Conditions	Yield of 141 [%]
1	1	0.5 eq Ag_2O, toluene, rt, 20 h	19
2	1	0.5 eq Ag_2O, toluene, rt, 65 h	20
3	2	1.0 eq Ag_2O, toluene, rt, 20 h	14
4	1	toluene, rt, 20 h	16
5	1.5	H_2O, rt, 4 h	10
6	1.5	H_2O, rt, 15 h	9
7	3.5	toluene, rt, 6 d	33
8	5	H_2O, 110 °C, microwave conditions, 45 min	<10
9	5	toluene, 130 °C, microwave conditions, 45 min	15

The diene **146** posed two distinct challenges. First, it was an extremely sensitive substrate. For example, Lewis acids commonly employed to enhance the rate and/or efficiency of the cycloaddition reaction often resulted in the decomposition of the starting diene (**146**). In fact, boron trifluoride etherate, aluminum chloride and zinc chloride rapidly destroyed DMBU (**146**). Oxidants had to be carefully selected as well. We suspected that DMBU's exposure to air facilitated its decomposition on silica gel during TLC analyses. Studies indicated that the

electron rich diene **146** was completely destroyed by both selenium dioxide and lead tetracetate. Most notably, Miller *et al*. claimed that DMBU suffered from dehydrogenation by 1,4-quinones, *i.e.* tetrachlorobenzoquinone and benzoquinone, the dienophile of choice for our cycloaddition studies. It appeared as though silver (I) oxide was the oxidant of choice in the presence of DMBU (**146**). The donor diene **146** also survived treatment with mercury (II) oxide. The second potential challenge associated with the preparation of **146** was the complete lack of stereospecificity. On average, gas chromatography and ^{1}H NMR indicated that the (*Z*,*Z*)/(*Z*,*E*)/(*E*,*E*) ratio was no better than (60 ± 3)/(34 ± 3)/(6 ± 2). Thus, the less reactive (*Z*,*Z*) isomer predominated. Nonetheless, due to the ease of preparation, **146** perhaps still should be regarded as an inexpensive and abundant starting material.[81]

Scheme 25 features the modified strategy for the synthesis of additional site A analogs. Juglone methyl ether[81] **141** was quantitatively reduced to naphthalene derivative **149**[85] with excess sodium dithionite. The very air-sensitive bis-phenol **149** was submitted to an alkylation reaction with 3-bromo-1-propanol (**150**) and cesium carbonate. Previously, 4-methoxyphenol had been used as a model system to determine the optimal alkylation conditions. A "melt," consisting of neat phenol, bromoalcohol **150** and sodium hydroxide gave the desired ether product in a yield of 63%. Treatment of 4-methoxyphenol with K_2CO_3 in acetone provided both the desired *O*-alkylated product in addition to a large percentage of unreacted starting material. The best conversion of the model substrate to the corresponding ether was achieved with Cs_2CO_3 as a base. The starting material was consumed in less than 4 hours at room temperature. The desired 4-methoxyphenyl ether was isolated in 86% yield following purification by column chromatography. Fortunately, the reaction conditions translated well from the model system to the real system and as a result, naphthol **149** was selectively alkylated with **150** in 71% yield.

The resultant ether **151** was submitted to a phenolic oxidation with iodobenzene diacetate in dry trifluoroethanol.[43] However, only 26% of the spirocycle (**142)** was isolated following purification. We attempted to optimize the reaction conditions by conducting a short study on solvent effects (Table 5). The use of trifluoroethanol and acetonitrile generated the best results (Entries 3 and 5). Cleaner product mixtures were obtained from the latter set of reaction conditions.



141 **149** **151**

142 **143**

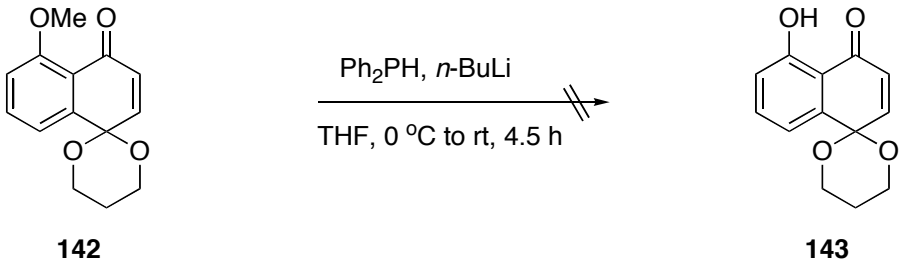
Scheme 25. Modified Strategy Towards the Synthesis of Site A Analogs.

Table 5. Influence of Solvent on Oxidative Spirocyclization Efficiency.

Entry	Conditions for 151 → 142	Yield of 142 [%]
1	$PhI(OAc)_2$, 1,1,1,3,3,3-hexafluoro-2-propanol, 4Å MS, rt, 20 min	12
2	$PhI(OAc)_2$, CH_2Cl_2, 4Å MS, rt, 30 min	8
3	$PhI(OAc)_2$, CH_3CN, 4Å MS, rt, 20 min	~26
4	$PhI(OAc)_2$, $NaHCO_3$, CH_3CN, 4Å MS, rt, 20 min	Complex mixture
5	$PhI(OAc)_2$, CF_3CH_2OH, 4Å MS, rt, 1 h, 25 min	26

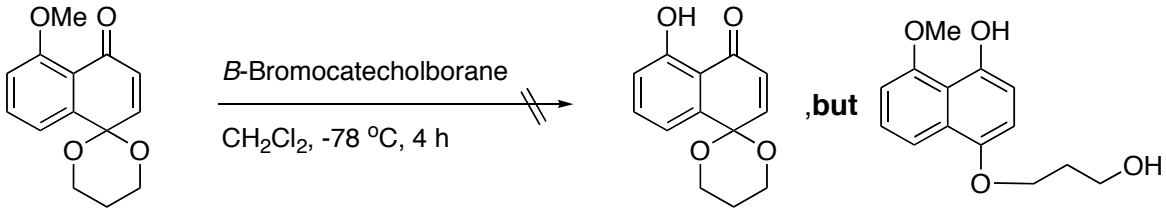
A single deprotection step separated **142** from the desired target **143**. Unfortunately, the demethylation of **142** proved to be an extremely difficult task. Two attempts with lithium diphenylphosphide[52] led to a mixture of several different products (Scheme 26). By ^{1}H NMR, a phenolic proton signal was clearly evident in a small percentage of the purified mixture. In fact, the chemical shift corresponded specifically to a phenol in close proximity to a carbonyl group. However, there were far too many extraneous peaks in the aliphatic region to definitively support the formation of the desired product, **143**. By ^{1}H NMR, the other remaining fractions contained too many aromatic and/or aliphatic signals in addition to multiple singlets in the methoxy region. The use of *B*-bromocatecholborane resulted in the formation of the spirocyclization precursor **151** by way of acetal C-O bond cleavage in preference to methyl ether C-O cleavage, followed by facile oxidation/aromatization (Scheme 27). Several other reaction conditions were attempted

in an effort to effect late-stage demethylation of spiroketal **142**. Unfortunately, all trials met with little to no success. Table 6 features a complete list of the conditions investigated.



142 **143**

Scheme 26. Attempted Deprotection with Lithium Diphenylphosphide.



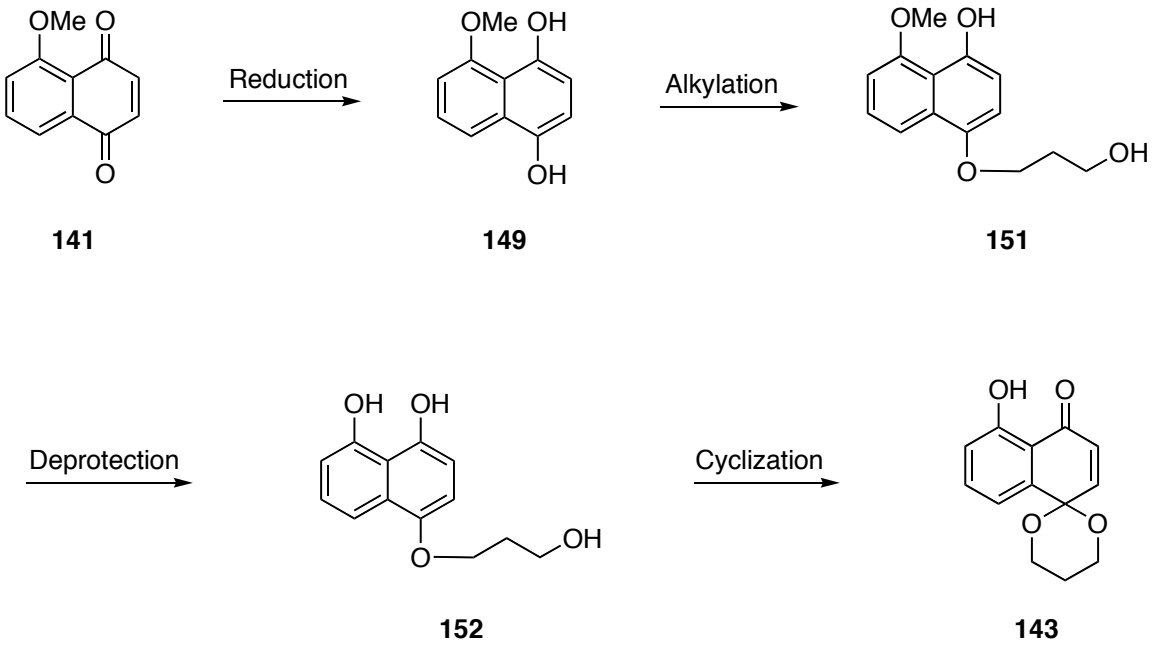
142 **143** **151**

Scheme 27. Attempted Deprotection with *B*-Bromocatecholborane.

Table 6. Attempted Deprotection of Methyl Ether **142**.

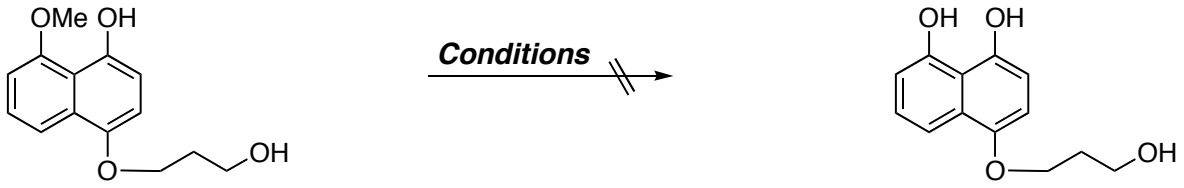
Entry	Conditions for 142 → 143	Results
1	BBr_3 (1.8 equiv), CH_2Cl_2, -78 °C, 30 min	-
2	*B*-Bromo-9-BBN (1.1 equiv), CH_2Cl_2, -78 °C, 1 h, 45 min	SM consumption, low mass balance, acetal cleavage
3	EtSH (5.0 equiv), NaH, DMF, 135 °C (o.b.t.),[a] 3 h	SM consumption, low mass balance, deprotection in addition to conjugate addition
4	$AlCl_3$ (2.0 equiv), CH_2Cl_2, 0 °C (30 min) to rt, (30 min)	SM consumption, low mass balance, acetal cleavage
5	$MgBr_2 \bullet Et_2O$ (1.2 equiv), toluene, 52 °C (o.b.t.), 7 h to 90 °C (o.b.t.), 5 h	-
6	LiI (2.2 equiv), pyridine, reflux, 8 h	-
7	PhSH (1.0 equiv), cat. K_2CO_3, NMP, 195 °C (o.b.t.), 2 h	-
8	Ph_2PH (5.0 equiv), *n*-BuLi, THF, 0 °C to rt, 4.5 h	Complex mixture
9	*B*-bromocatecholborane (1.0 equiv), CH_2Cl_2, -78 °C, 4 h	Diol **151**

[a]Oil bath temperature



Scheme 28. Early-stage Deprotection Strategy.

Scheme 28 depicts a possible alternative sequence to circumvent late-stage deprotection issues. Diol **151** could be subjected to demethylation conditions prior to oxidative spirocyclization. In fact, several attempts were made to convert diol **151** to triol **152**. As indicated in Scheme 29, after 8 hours in a mixture of lithium iodide and pyridine at 90 °C,[86] the starting material was recovered unchanged. Heating at 105 °C for six days also met with no success. Attempts at early deprotection under Lewis acidic conditions with *B*-bromocatecholborane and BBr_3 led to the recovery of starting material **151** in both cases.



151 **152**

Conditions: 1) LiI, deoxygenated pyridine, rt to 90 °C, 8 h; 105 °C, 6 d
2) BBr_3, CH_2Cl_2, -78 °C, 1 h; -78 °C, 2 h 20 min; -78 °C to rt, 2 h
3) *B*-bromocatecholborane, CH_2Cl_2, -78 °C to 0 °C to rt, 6 h

Scheme 29. Attempted Triol Formation.

1.5.2. Biological Evaluation of Site A and Site C Analogs

All site C analogs (**120-132**, Schemes 19 and 20) were submitted for biological testing[42] for trx and/or TR activity and antiproliferative activity against two human breast cancer cell lines. Site A modifications led to the free phenol (**140**, *TH-126*, Scheme 21) and the methylated spiroketal derivative (**142**, *TH-223*, Scheme 25). Both compounds were submitted for testing, despite the presence of the protected phenol in **142**. Table 7 summarizes the results from a trx/TR differential assay. It also includes the growth inhibition or antiproliferative activity against MCF-7 and MDA-MB-231 human breast cancer cells. Entries 1-15 correspond to compounds that belong to the TH-series. Entries 16 and 17 correspond to compounds that belong to the SR-series and are included in Table 7 for comparison. Furanyl derivatives **125-129** did not prove to be particularly potent or selective against trx or TR. However, allyl ether **121** and propargyl ether **122** demonstrated specificity for trx at very low levels with IC_{50}'s of 4.7 μM and 13.4 μM, respectively.

The diminished activity revealed in the trx/TR differential assay associated with analogs alkylated at the phenol was clearly established in the SR-series, with two very notable

exceptions-compounds **70** and **74** (Tables 1 and 7). The trend was also evident in the TH-series. However, exceptions were noted here as well. The derivatives **121**, **122** and **125** demonstrated significant affinity to the thioredoxin-thioredoxin reductase system. The first two are closely related to the allylated phenol from the SR-series, **74**. Thus, the enhanced biological activity (*i.e.* aforementioned specificity for trx at very low levels) is not entirely surprising. However, the activity associated with the furanyl derivative **125** is quite unexpected considering the obvious lack of activity associated with structurally related compounds, *i.e.* **126-129**. The beneficial effects of the free phenol for trx/TR inhibition are far more pronounced in a comparison of **140** to **142**. The former displays significant activity (Entry 14). The methylated derivative, **142**, on the other hand, appears to be virtually inactive (Entry 15). Analog **140** is more active against thioredoxin reductase (TR) as compared to that of the natural product palmaruymcin CP_1 (**2**). However, an evaluation of thioredoxin (trx) activity reveals that **140** is approximately 10-fold less reactive than **2**. Furthermore, the trx selectivity is less pronounced for **140** as compared to **2**. The less impressive activity of **140** could be attributed to the replacement of the naphthalenediol ketal with a 1,2-dioxolane moiety.

Table 7. IC_{50} Values [μM] for 2 Cancer Cell Lines and TR and TR/trx Inhibition.

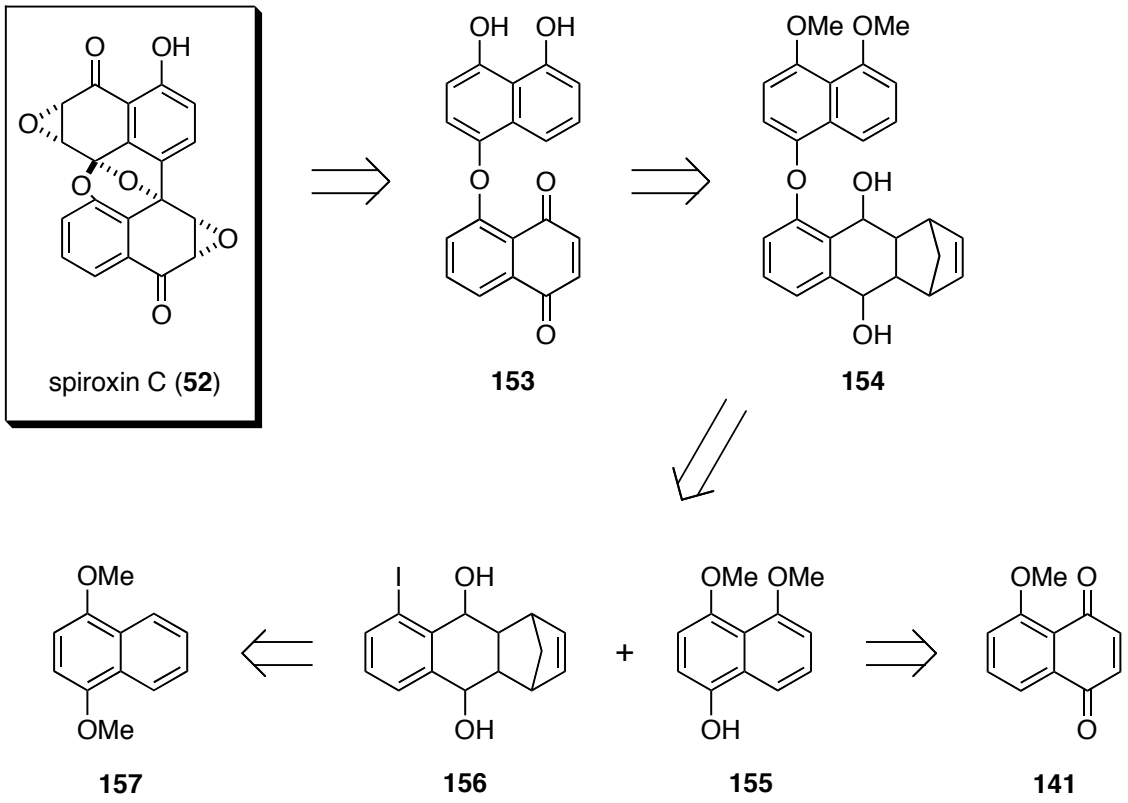
Entry	Compound	MCF-7	MDA-MB-231	TR	TR/trx
1	**120**, *TH-39*	0.7	2.2	>50	>50
2	**121**, *TH-40*	7.8	8.2	>50	4.8
3	**122**, *TH-44*	4.3	4.7	>50	13.4
4	**123**, *TH-48*	>10	9.3	>50	>50
5	**124**, *TH-49*	>10	8.0	>50	>50
6	**125**, *TH-62*	5.7	7.8	20.1	10.2
7	**126**, *TH-63*	>10	>10	>50	>50
8	**127**, *TH-64*	>10	>10	>50	>50
9	**128**, *TH-65*	5.0	4.9	>50	>50
10	**129**, *TH-66*	5.5	5.2	>50	42.4
11	**130**, *TH-126*	2.0	3.6	nd[a]	>50
12	**131**, *TH-139*	4.3	5.3	nd	>50
13	**132**, *TH-140*	1.9	4.5	nd	>50
14	**140**, *TH-169*	4.2	4.3	8.8	3.4
15	**142**, *TH-223*	4.4	5.0	>50	40.2
16	**70** (*SR*-Series)	2.0	2.0	>50	23.2
17	**74** (*SR*-Series)	2.0	2.7	>50	23.2
18	**Diepoxin σ (37)**	1.5	2.0	13.5	4.5
19	**Palmarumycin CP_1 (2)**	0.9	2.4	12.0	0.35

[a]nd, not determined.

Surprisingly, the parent natural product **2** and the majority of the synthetic analogs from the TH-series possess IC_{50}'s of less than 10 μM for both MCF-7 and MDA-MB-231 cancer cell lines. It is readily apparent that the TH-series (in addition to the SR-and JK-series) consist of a large percentage of cytotoxic compounds. Unfortunately, there is no direct evidence that the observed high levels of cytotoxicity are a direct consequence of inhibition of the trx/TR system. As expected, both compounds that inhibit trx *in vitro* with an IC_{50} of less than 10 μM, **121** and **140**, show an IC_{50} for growth inhibition for the two human breast cancer cell lines of less than 10 μM. However, several of the analogs that lack trx or trx/TR inhibitory activity (*i.e.* **122**, **123**, **126**, **137**) possess IC_{50} values for growth inhibition in excess of 10 μM.

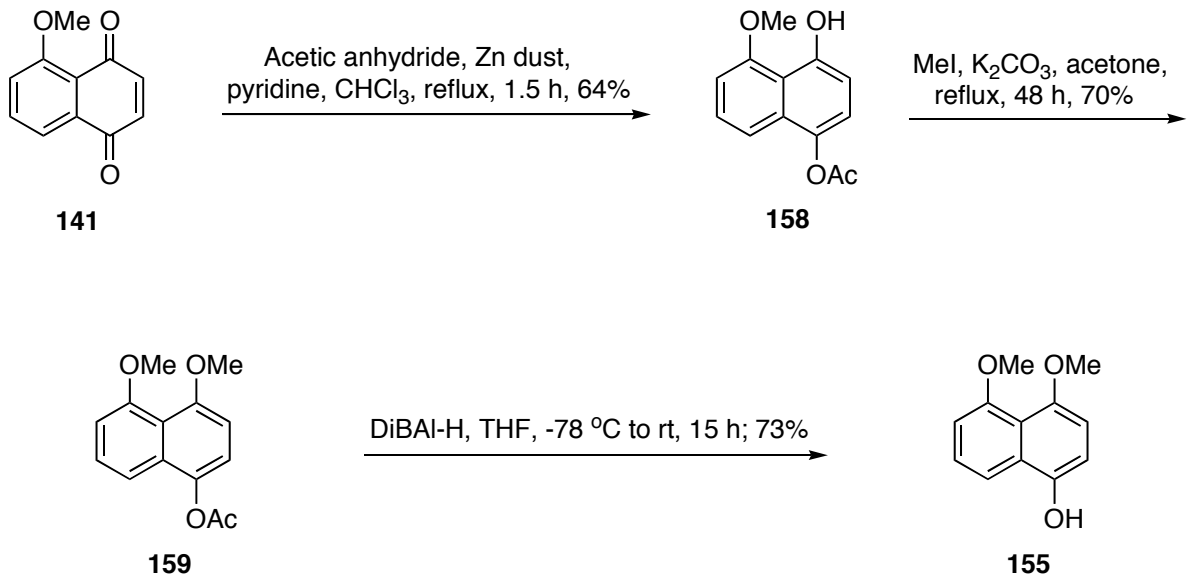
1.6. Efforts Toward the Synthesis of the Spiroxin Core

We also embarked upon the total synthesis of the novel octacycle, spiroxin C (**52**). The (retro)synthetic analysis (Scheme 30) features an Ullmann[56] ether coupling between naphthaline **155** and iodo derivative **156** for the assembly of the spiroxin scaffold. The conversion of the resultant ether **154** to the naphthoquinone derivative **153** required a retro-Diels-Alder reaction, benzylic oxidation and global deprotection. Our plans for the conversion of **153** to the natural product **52** featured the following tandem sequence: hypervalent-iodine-mediated phenolic oxidation of the more electron rich aromatic system followed by the interception of the electrophilic intermediate by the quinone carbonyl to form the requisite bridged acetal. We envisioned the C-C bond formation to occur by the trapping of the second electrophilic intermediate with the remaining nucleophilic phenol. The only remaining functionalization consisted of the late-stage introduction of oxygen via the bis-epoxidation of the two enone functions. Perhaps, such a sequence of events mimics Nature's way of assembling the unique binaphthyl linkage.



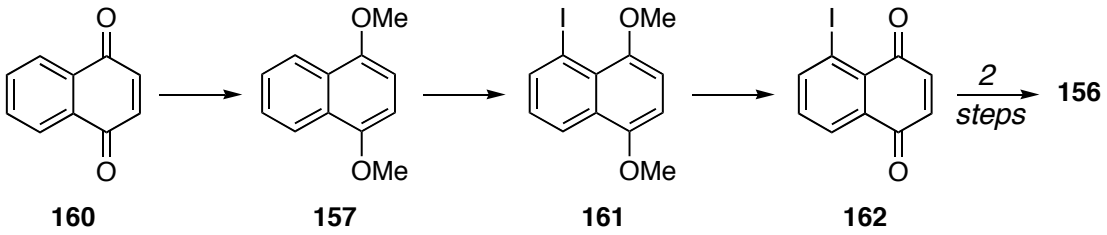
Scheme 30. Retrosynthetic Analysis of Spiroxin C (**52**).

Fragment **155** was derived from juglone methyl ether[81] **141** in three steps by an established protocol[87,88] (Scheme 31). The starting ether **141** was reduced with elemental zinc and trapped selectively *in situ* as the monoacetate[87] **158** in 64% yield. Alkylation with methyl iodide led to the clean conversion of the remaining hydroxyl group to the methyl ether **159**[87,88] in 70% yield. The free phenol at C(4) was unmasked by the hydride-mediated removal of the acetate ester in 73% yield to afford fragment **155**.[88]



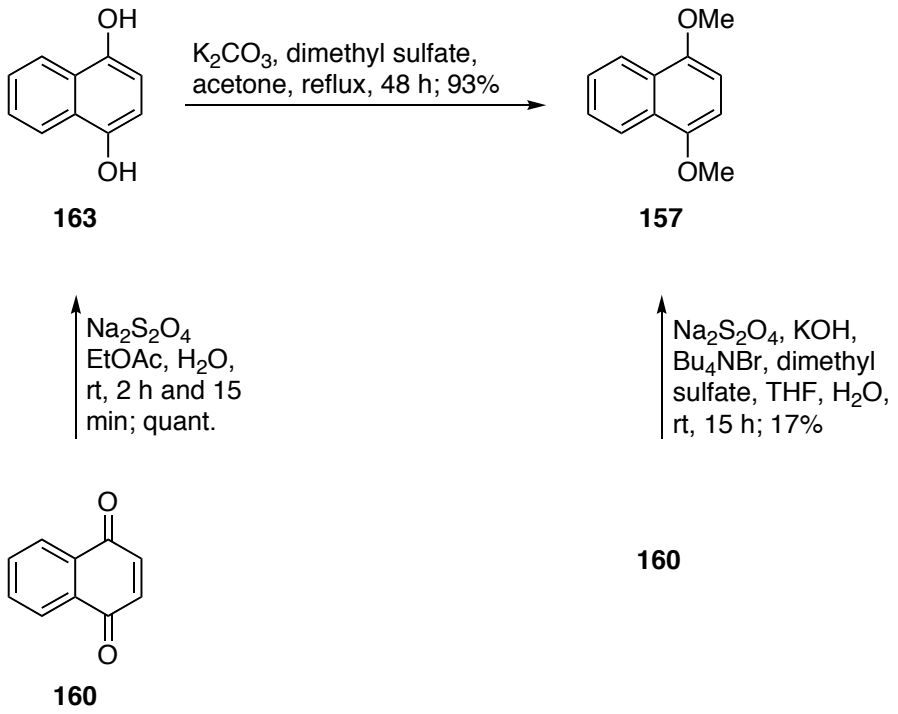
Scheme 31. Preparation of the Key Naphthaline Intermediate **155** from **141**.

The planned sequence for the construction of fragment **156** is depicted in Scheme 32. A one-pot reductive methylation[89] of 1,4-naphthoquinone **160** provided 1,4-dimethoxynaphthalene **157**. Following the selective iodination of **157**, the resultant 8-iodo isomer **161** could be converted to the corresponding naphthoquinone **162** with ceric ammonium nitrate (CAN)[90]. Then, treatment of **162** with cyclopentadiene should deliver the desired Diels-Alder adduct. Finally, we intended to access the Ullmann ether coupling partner **156** by hydride reduction of the benzylic ketones of the cycloaddition product.



Scheme 32. Planned Synthesis of **156**.

The first transformation proved to be particularly low-yielding and messy. After 15 hours, the reaction still had not reached completion, nor did it appear to be progressing at a reasonable rate. Furthermore, the separation of the desired bis-methylated product **157** from the mono-methylated compound and other impurities was also not trivial. Consequently, the two-step protocol was adopted (Scheme 33). First, the starting naphthoquinone **160** was reduced quantitatively to the air-sensitive bisphenol **163** with excess sodium dithionite.[85] Then, treatment of **163** with potassium carbonate and dimethylsulfate in refluxing acetone cleanly delivered 1,4-dimethoxynaphthalene **157**[89,91] in an overall yield of 93%.



Scheme 33. Two-step Protocol for the Preparation of **157**.

The stereospecific iodination of 1,4-dimethoxynaphthalene **157** presented serious problems as well. Table 8 summarizes the conditions employed to access **161** in useful synthetic yields.

We learned early on that the optimal conditions for the preparation of 1-iodo-8-methoxynaphthalene (**97**, Scheme 9)[52,53,54] did not suit our new, slightly modified substrate.

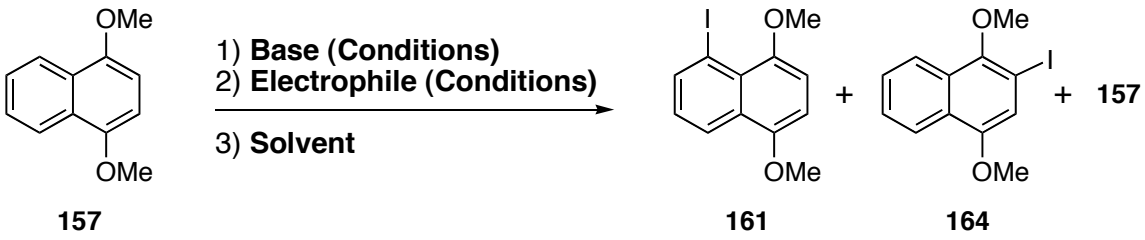
As is depicted in the Table shown below, most of the reactions were carried out in a 4:1 mixture of pentane and ether. The second solvent system (listed behind the semi-colon), indicated in Entries 2-4, 6-9 and 11, refers to the solvent(s) reintroduced to the reaction medium upon complete or partial loss of solvent due to the extended reaction times. In addition, the "product distributions" column is the result of ^{1}H NMR analysis of each crude reaction mixture.

The worst-case scenario is clearly illustrated in Entries 6 and 7. Only starting material **157** was recovered from both trials. In each case, the electrophile (iodine) was introduced as a solution. It is not likely that the mode of addition (perhaps resulting in a disruption of the effective concentration by slight dilution) played a significant role in the outcome of the reactions. For example, both the 2-and 8-iodo isomers were formed under similar conditions, as is evident by Entry 9. The more likely culprit, no doubt, was the short reaction time following the addition of the electrophile. Furthermore, the total reaction time was inclusive of the time required for the reaction to reach room temperature from a starting point of 0 °C for Entry 6 and –78 °C for Entry 7. Clearly, in the latter case, the reaction was not at room temperature for much of the total "reported time." The results imply the need for extended reaction times at effective temperatures, *i.e.* room temperature. Entries 1, 3 and 4 gave a mixture of the undesired isomer **164** and unreacted starting material **157** in a ratio of approximately 1:1. The first two results pointed to the need for more than 0.5 equivalents of electrophile. In addition, Entries 3 and 4 suggested the need for a longer "deprotonation" period prior to the addition of the electrophile. In general, the best product distributions were obtained when ether was employed as the solvent

(for the *t*-BuLi series only). In fact, an investigation of other bases (Entries 19-21 and 23) confirmed the notion that *t*-BuLi was indeed superior.

It is readily apparent that none of the results were truly outstanding. However, the most noteworthy reactions (*i.e.* best ratios of **161**:**164**, Entries 14 and 16) shared the following common elements: The starting naphthalene derivative **157** was treated with three equivalents of *t*-BuLi in diethyl ether at 0 °C. The reaction was maintained at room temperature in excess of 20 hours. In both cases, the electrophile (*i.e.* 1.5 equivalents of iodine) was introduced as a solid at 0 °C. Once again, the final reaction mixture was maintained at room temperature for an extended period, *i.e.* 24-36 hours. Despite the preference for the desired isomer **161** over **164** in many of the trials listed in Table 8, it was difficult not to notice the large quantities of unreacted starting material so common to all of the Entries. If one were to assume a perfect mass throughput, no single trial provided even 50% of the desired product! Entry 17 was the closest contender, at approximately 42% of **161**.

Table 8. Optimization of Lithiation/Iodination Reaction Conditions.



157 **161** **164**

Entry	Base; Equivalents, Conditions	Electrophile; Equivalents, Conditions	Solvent(s); Pentane: Ether	Products[a] (161:164:157)
1	*t*-BuLi; 3.0, 0 °C to rt (2 h, 20 h)	I_2, 0.5 equiv., 0 °C to rt, 4 h	4:1	0:1:1
2	*t*-BuLi; 3.0, 0 °C to rt (1.5 h, 22 h)	I_2, 1.0 equiv., 0 °C to rt, 5.5 h	4:1; then, 0:1	2.1:1.8:1
3	*t*-BuLi; 3.0, 0 °C to rt (30 min, 2 h)	I_2, 0.5 equiv., 0 °C to rt, 5 h	4:1; then, 0:1	0:1:1
4	*t*-BuLi; 3.0, 0 °C to rt (30 min, 2 h)	I_2, 1.2 equiv., 0 °C to rt, 5 h	4:1; then, 0:1	0:1:1.4
5	*t*-BuLi; 2.0, 0 °C to rt (1 h, 24 h)	I_2, 0.5 equiv., 0 °C to rt, 5 h	4:1	1:2.9:2
6	*t*-BuLi; 6.0, 0 °C to rt (1 h, 24 h)	0.29 M sol'n of I_2, 1.0 equiv., -78 °C to rt, 5 h	4:1; then, 0:1	0:0:1
7	*t*-BuLi; 6.0, 0 °C to rt (1 h, 24 h)	0.33 M sol'n of I_2, 1.1 equiv., 0 °C to rt, 5 h	4:1; then, 0:1	0:0:1
8	*t*-BuLi; 3.0, 0 °C to rt (1 h, 24 h)	ICl, 1.5 equiv., 0 °C to rt, 4 h	4:1; then, 0:1	1:3.3:2.7
9	*t*-BuLi; 3.0, 0 °C to rt (1 h, 24 h)	0.22 M sol'n of I_2, 2.1 equiv., 0 °C to rt, 15 h	4:1; then, 0:1	7:5:1
10	*t*-BuLi; 3.0, 0 °C to rt (1.5 h, 14 h)	I_2, 1.5 equiv., 0 °C to rt, 4.5 h	0:1	2:1:5.3
11	*t*-BuLi; 3.0, -78 °C to rt (1 h, 14 h)	I_2, 1.6 equiv., 0 °C to rt, 4.5 h	4:1; then, 0:1	2:1[c]

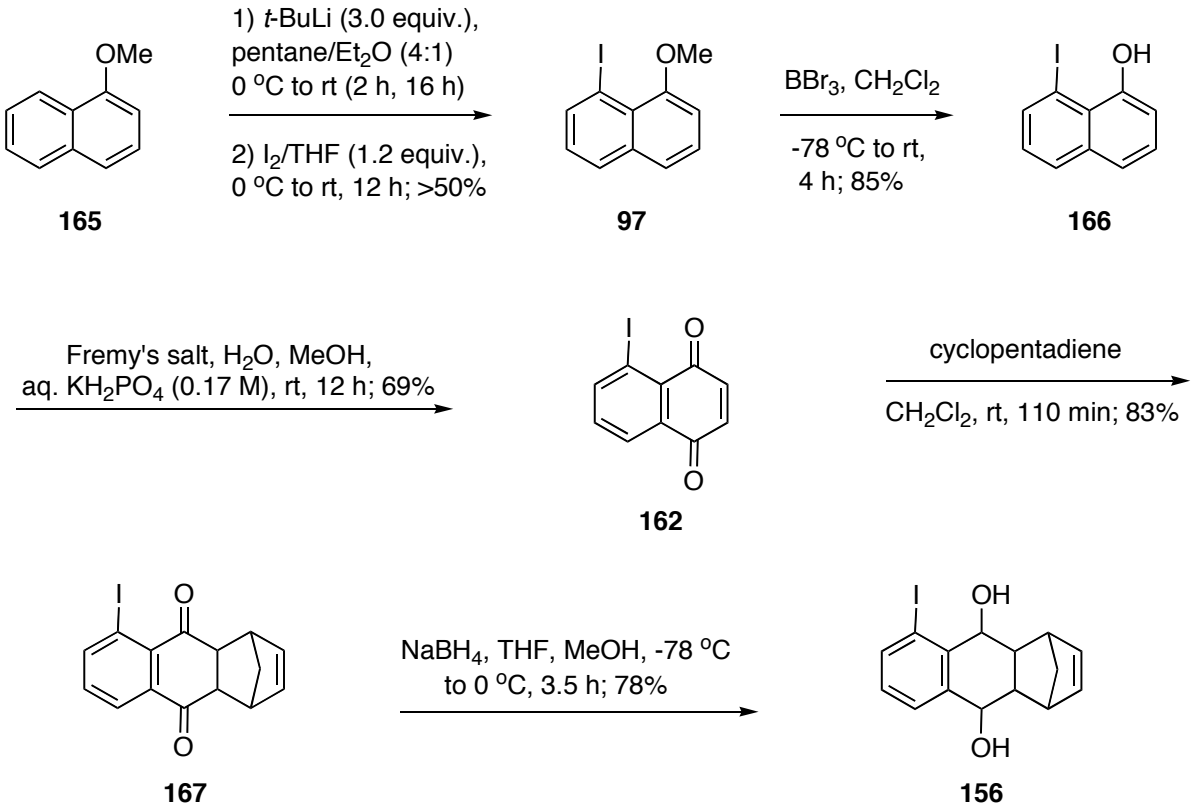
12	*t*-BuLi; 3.0, 0 °C to rt (1.5 h, 14 h)	I_2, 1.5 equiv., 0 °C to rt, 4.5 h	1:0	1.5:1[c]
13	*t*-BuLi; 3.0, 0 °C to rt (1.5 h, 14 h)	I_2, 1.5 equiv., 0 °C to rt, 4.5 h	0:1	2:1:5.3
14	*t*-BuLi; 3.0, 0 °C to rt (1.5 h, 28.5 h)	I_2, 1.5 equiv., 0 °C to rt, 36 h	0:1	5.8:1:17
15	*t*-BuLi; 3.0, 0 °C to rt (1.5 h, 28.5 h)	I_2, 1.5 equiv., 0 °C to rt, 36 h	0:1	4:1:16
16	*t*-BuLi; 1.8, 0 °C to rt (1.5 h, 22 h)	I_2, 1.5 equiv., 0 °C to rt, 24 h	0:1	9:1:17
17	*t*-BuLi; 3.0, 0 °C to rt (1.5 h, 22 h)	I_2, 3.0 equiv., 0 °C to rt, 24 h	0:1	2.3:1:2.2
18	*t*-BuLi; 6.0, 0 °C to rt (1.5 h, 22 h)	I_2, 3.0 equiv., 0 °C to rt, 24 h	0:1	1:0:3
19	*s*-BuLi; 3.0, 0 °C to rt (1 h, 14 h)	0.31 M sol'n of I_2, 3.0 equiv., 0 °C to rt, 7.5 h	0:1	0:0:1[d]
20	*n*-BuLi; 3.0, 0 °C to rt (1 h, 14 h)	0.34 M sol'n of I_2, 3.0 equiv., 0 °C to rt, 8 h	0:1	0:0:1[d]
21	LDA; 1.2, -78 °C to rt (16.5 h)	0.38 M sol'n of I_2, 1.5 equiv., 0 °C to rt, 4 h	0:1	0:0:1[d]
22	*t*-BuLi; 1.2, -78 °C to rt (18 h)	0.42 M sol'n of I_2, 1.2 equiv., -78 °C to rt, 48 h	0:1	0:0:1[d]
23	*n*-BuLi-LiDMAE; 3.0, -60 °C (1 h)	0.50 M sol'n of I_2, 4.0 equiv., -60 °C to rt, 48 h	THF, Hexane[b]	0:0:1[d]

[a]The listed ratios are +/- 10%. They were derived from ^{1}H NMR analysis of the crude material.
[b]We used this solvent system for the reaction conditions listed above.
[c]The ratio shown refers only to a comparison between **161** and **157**. The relative quantity of **164** could not be determined by ^{1}H NMR due to overlapping signals from an additional (4^{th}) compound.
[d]Mostly starting material was observed. The results do not "rigorously" account for trace product formation.

Thus, the low yields and subsequent separation ills that plagued this sequence led to its eventual abandonment. We devised a new and more efficient route for the preparation of **162**.

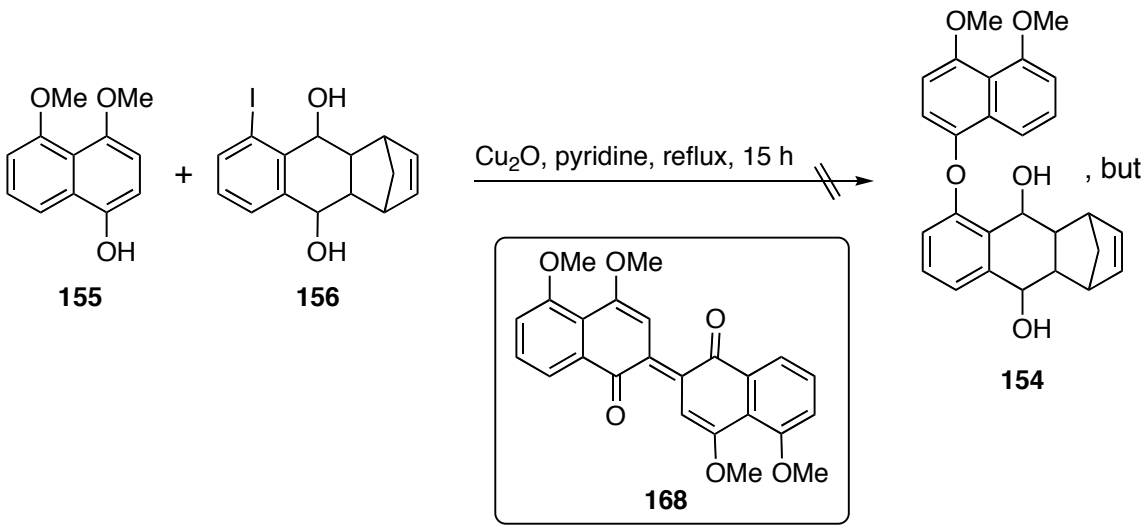
We turned our attention to a familiar substrate, 1-methoxynaphthalene (**97**, Schemes 9 and 39), previously used in the total syntheses of palmarumycin CP_1 (**2**)[43,44] and diepoxin σ[52] (**37**, Figure 9). After extensive experimentation, it was determined that the optimal reaction conditions (Scheme 34) were similar to those utilized for the lithiation/iodination of 1,4-dimethoxynaphthalene **157**. The iodine was incorporated into the naphthalene nucleus in a regioselective manner in moderate yield. Then, the methyl ether of **97** was deprotected with boron tribromide to liberate the free iodophenol **166**. Treatment of **166** with excess Fremy's salt[92] in an aqueous medium delivered the requisite iodonaphthoquinone **162** in a yield of 80%. Thus, the Diels-Alder precursor **162** could be accessed in one fewer step as compared to the original strategy (Scheme 32) and in a significantly higher overall yield.

Finally, the Diels-Alder cycloadduct was prepared in high yield from a facile cycloaddition between **162** and cyclopentadiene. Sodium borohydride reduction of the two benzylic ketones finally delivered the desired iodo derivative **156** in nearly 80% yield. Both fragments were accessed in five steps or less from commercially available starting materials. The stage was now set for the coupling of segments **155** and **156**.



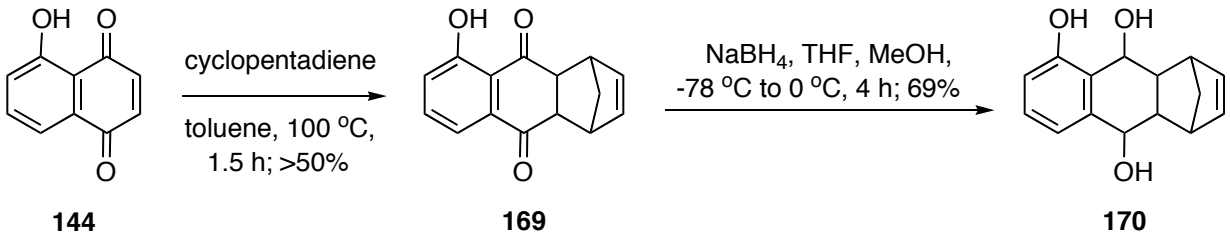
Scheme 34. Efficient Synthesis of the Aryl Iodide Segment **156**.

We initiated our synthetic studies with an investigation of the Ullmann ether coupling conditions previously used for the assembly of the palmarumycin CP_1 (**2**) and diepoxin σ (**37**) scaffold (Scheme 35). Unfortunately, subjection of **155** and **156** to Cu_2O[43,44,52,54] in refluxing pyridine for 15 hours did not deliver the expected biaryl ether **154** or unreacted starting material. Instead, a structurally related, highly conjugated compound was observed as the exclusive product by ^1H NMR. Chromatographic purification led to the isolation of a bright blue solid. ^1H, ^{13}C and MS data supported the formation of dimer **168**.[93] Apparently, the electron rich naphthol moiety **155** preferred to homocouple as opposed to couple to aryl iodide **156**.



Scheme 35. First Ullmann Ether Coupling Attempt.

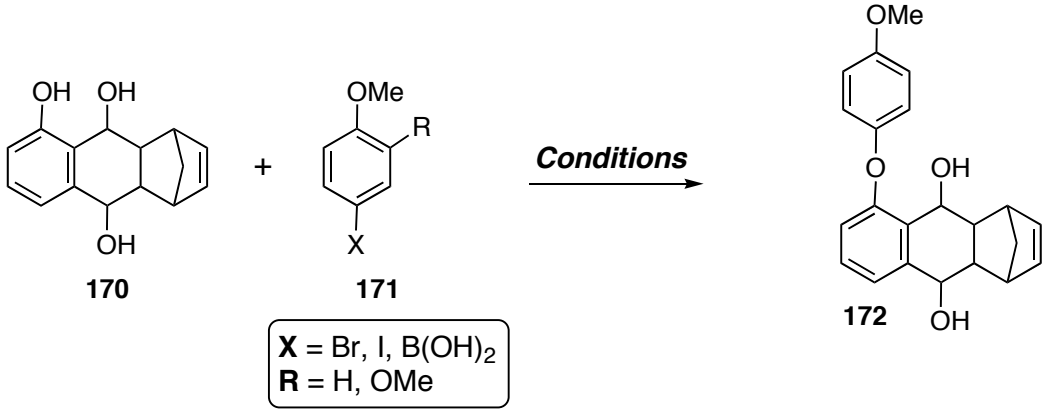
Due to the problems encountered with the electron rich naphthol **155** in coupling model studies, we decided to probe the reactivity of the hydroxyl analog of **156**. The known phenol derivative **169**[94] was prepared by a Diels-Alder reaction (Scheme 36) in an analogous fashion to **167** (Scheme 34). The subsequent sodium borohydride reduction liberated the desired triol **170** in approximately 70% yield. Table 9 details several *O*-arylation attempts, inclusive of the cupric acetate-mediated, boronic acid coupling methodology.[95]



Scheme 36. Preparation of the Hydroxyl Analog of **156**.

The conditions[96] that had proven to be successful for the first model study[97] led predominantly to the recovery of starting materials (Entry 1, Table 9). Following purification of the crude mixture by column chromatography, other miscellaneous products were also isolated. The ^{1}H NMR of one batch of material revealed the presence of a methoxy signal, albeit small, and other potentially promising diagnostic signals. Thus, the possibility of a small percentage of product **172** having been formed cannot be completely ruled out. An analysis of the crude material from the copper oxide-mediated[43,44,52,54] coupling reactions (Entries 2 and 3) revealed mostly unreacted phenol **170**. The boronic acid methodology[95] also failed to deliver the desired ether product **172** (Entry 4). Furthermore, a survey of the copper bronze/sodium carbonate and CuBr•DMS/NaH[98] conditions met with no success, as indicated by Entries 6 and 7. Surprisingly, a product mixture comprised of three distinct compounds was isolated from the CuCl, TDA-1, anisole conditions detailed in Entry 5. However, there was absolutely no incorporation of the requisite methoxy function in any of the products.

Table 9. Coupling Attempts with Modified Phenol Substrate.



Entry	170, Equiv.	171; X, R; Equiv.	*Conditions*[a]	Product Description
1	1.0	X = Br, R = H; 3.0 equiv.	CuCl (5 mol%), Cs_2CO_3, EtOAc (5 mol%), tol., reflux, 15 h	**170**, **171**, minor products
2	1.0	X = Br, R = H; 1.7 equiv.	Cu_2O (1.0 equiv.), pyr., reflux, 15 h	no product, recovered **170**
3	1.0	X = I, R = H; 1.7 equiv.	Cu_2O (1.0 equiv.), pyr., reflux, 15 h	no product, recovered **170**
4	1.0	X = $B(OH)_2$, R = OMe; 2.0 equiv.	$Cu(OAc)_2$ (1.0 equiv.), Et_3N, CH_2Cl_2, rt, 15 h	-
5	1.0	X = Br, R = H; 3.0 equiv.	CuCl (50 mol%), TDA-1, anisole, reflux, 15 h	3 distinct products, no methoxy groups
6	1.0	X = I, R = H; 3.0 equiv.	copper bronze (50 mol%), Na_2CO_3, pyr., reflux, 15 h	no product, recovered **170**
7	1.0	X = I, R = H; 1.5 equiv.	CuBr•DMS (2.0 equiv.), NaH, pyr., reflux, 12 h	-

[a]All reaction solvents were degassed (at least 3 freeze/pump/thaw cycles) prior to use.

1.7. Conclusion

We prepared new site C and site A analogs of the natural product, palmarumycin CP_1. Several derivatives demonstrated potent and selective inhibition of thioredoxin or thioredoxin reductase. Furthermore, antiproliferative activity against MCF-7 and/or MDA-MB-231 human breast cancer cell lines was observed in several cases. The sequence used to access the site A analogs is a general one, highly amenable to development of additional palmarumycin derivatives. Progress was also made towards the synthesis of the structurally related naphthalenediol spiroacetal, spiroxin C. We developed efficient, facile syntheses for the preparation of the two building blocks required for the key Ullmann ether coupling reaction.

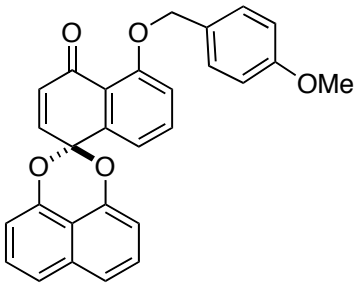
1.8. Experimental

1.8.1. General

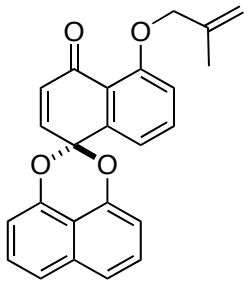
All moisture-sensitive reactions were performed under an atmosphere of N_2. All glassware was dried in an oven at 140 °C prior to use. THF and Et_2O were dried by distillation over Na/benzophenone. Dry toluene and CH_2Cl_2 were obtained by distillation from CaH_2 or from a purification system. Unless otherwise noted, solvents or reagents were used without further purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with a basic $KMnO_4$ solution (1.0 g of $KMnO_4$, 1.0 g of K_2CO_3, and 2.0 mL of 5% aq. NaOH in 100 mL of water), an anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 3.5 mL of concentrated H_2SO_4 and 2.0 mL of glacial HOAc in 92 mL of 95% ethanol), or Vaughn's reagent (4.8 g of ammonium molybdate, 0.2 g of $CeSO_4$, and 10 mL of H_2SO_4 in 90 mL of water).

NMR spectra were recorded at either 300 MHz/75 MHz ($^1H/^{13}C$ NMR) or 500 MHz/125 MHz ($^1H/^{13}C$ NMR) in $CDCl_3$ unless stated otherwise using either a Bruker AVANCE 300 MHz or Bruker DRX 500 MHz spectrometer at 21 °C. Chemical shifts (δ) are reported in parts per million and the residual solvent peak was used as an internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, m=multiplet, *br*=broad), integration and coupling constants. IR spectra were obtained on a Nicolet AVATAR 360 FT-IR E.S.P. spectrometer. Mass spectra were obtained on a VG-70-HF.

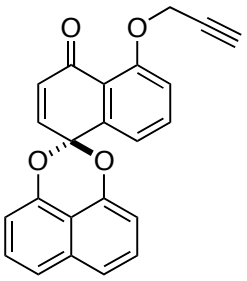
1.8.2. Experimental Procedures



General procedure for Mitsunobu reactions. **8-(4-Methoxybenzyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphto[1",8"-de][1',3']dioxin (120, *TH-39*)**.[42] A solution of palmarumycin CP_1 (20.1 mg, 0.0635 mmol), diphenylphosphino-polystyrene (230 mg, 1.41 mmol/g, 0.230 mmol) and 4-methoxybenzyl alcohol (39.6 μL, 0.318 mmol) in dry CH_2Cl_2 (2 mL) was stirred for 45 min at room temperature and cooled to 0 °C. Then, DEAD (50.0 μL, 0.318 mmol) was added dropwise to the reaction mixture at 0 °C. The solution was warmed to room temperature, stirred for 35 h, diluted with additional CH_2Cl_2, and washed with 5% aqueous KOH solution followed by 5% HCl. The organic extracts were filtered. The resin was washed further with CH_2Cl_2 and the combined extracts were concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 25:1 → 10:1 → 4:1) gave 6.1 mg (69%) of **120**: ^{1}H NMR δ 7.70-7.45 (m, 8 H), 7.21 (dd, 1 H, J = 8.1, 0.8 Hz), 6.98 (t, 4 H, J = 8.2 Hz), 6.87 (d, 1 H, J = 10.5 Hz), 6.31 (d, 1 H, J = 10.5 Hz), 5.26 (s, 2 H), 3.84 (s, 3 H); ^{13}C NMR δ 182.7, 159.2, 158.8, 147.4, 141.0, 135.1, 134.7, 134.1, 132.2, 128.4, 128.3, 127.6, 121.2, 120.4, 115.9, 114.1, 109.8, 93.4, 70.7, 55.3; MS (EI) *m/z* (rel intensity) 436 (M^+, 12), 316 (4), 287 (2), 202 (2), 169 (3), 144 (2), 121 (100), 69 (8); HRMS (EI) calcd for $C_{28}H_{20}O_5$ 436.1311, found 436.1323.

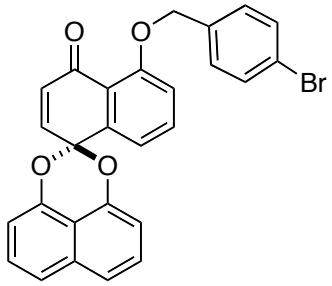


8-(2-Methylallyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphtho[1",8"-de][1',3']dioxin (121, *TH-40*).[42] According to the general procedure, palmarumycin CP_1 (16.5 mg, 0.0522 mmol), diphenylphosphino-polystyrene (189 mg, 1.41 mmol/g, 0.266 mmol), methylallyl alcohol (22 μL, 0.26 mmol) and DEAD (41 μL, 0.26 mmol) in dry CH_2Cl_2 (1.7 mL) provided after 5 d 9.7 mg (50%) of **121**: ^{1}H NMR δ 7.69 (t, 1 H, *J* = 8.1 Hz), 7.61-7.57 (m, 3 H), 7.48 (t, 2 H, *J* = 7.5 Hz), 7.16 (dd, 1 H, *J* = 8.2, 0.7 Hz), 6.99 (d, 2 H, *J* = 7.1 Hz), 6.86 (d, 1 H, *J* = 10.5 Hz), 6.29 (d, 1 H, *J* = 10.5 Hz), 5.36 (s, 1 H), 5.08 (s, 1 H), 4.63 (s, 2 H), 1.92 (s, 3 H); MS (EI) *m/z* (rel intensity) 370 (M^+, 99), 329 (5), 316 (15), 211 (30), 173 (41), 144 (100), 132 (58), 114 (91), 88 (40), 69 (27), 55 (85); HRMS (EI) calcd for $C_{24}H_{18}O_4$ 370.1205, found 370.1207.

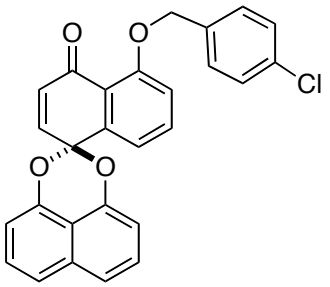


8-(2-Propynyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphtho[1",8"-de][1',3']dioxin (122, *TH-44*).[42] According to the general procedure, palmarumycin CP_1 (12.8 mg, 0.0404 mmol), diphenylphosphino-polystyrene (146 mg, 1.41 mmol/g, 0.206 mmol), propargyl alcohol (11.7 μL, 0.201 mmol) and DEAD (31.9 μL, 0.203 mmol) in dry CH_2Cl_2 (2.0

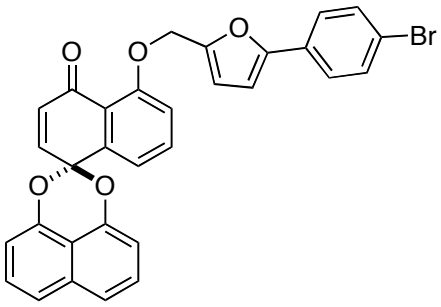
mL) provided after 37 h 6.4 mg of starting material and 1.9 mg (24% based on recovered starting material) of **122**: ^{1}H NMR δ 7.76-7.66 (m, 2 H), 7.58 (dd, 2 H, *J* = 8.4, 0.7 Hz), 7.48 (t, 2 H, *J* = 7.5 Hz), 7.36 (dd, 1 H, *J* = 7.9, 1.5 Hz), 6.99 (dd, 2 H, *J* = 7.5, 0.7 Hz), 6.88 (d, 1 H, *J* = 10.5 Hz), 6.30 (d, 1 H, *J* = 10.5 Hz), 4.92 (d, 2 H, *J* = 2.4 Hz), 2.57 (t, 1 H, *J* = 2.4 Hz); MS (EI) *m/z* (rel intensity) 354 (M^+, 39), 202 (9), 179 (6), 149 (10), 126 (100), 114 (34), 107 (16), 98 (18), 77 (18), 69 (26); HRMS (EI) calcd for $C_{23}H_{14}O_4$ 354.0892, found 354.0898.



8-(4-Bromobenzyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphtho[1",8"-de][1',3']dioxin (123, *TH-48*).[42] According to the general procedure, palmarumycin CP_1 (11.5 mg, 0.0364 mmol), diphenylphosphino-polystyrene (132 mg, 1.41 mmol/g, 0.186 mmol), 4-bromobenzyl alcohol (34 mg, 0.18 mmol) and DEAD (29 μL, 0.18 mmol) in dry CH_2Cl_2 (2.0 mL) provided after 41 h 6.7 mg (38%) of **123**: ^{1}H NMR δ 7.69-7.46 (m, 10 H), 7.18 (d, 1 H, *J* = 7.2 Hz), 6.99 (d, 2 H, *J* = 7.4 Hz), 6.89 (d, 1 H, *J* = 10.5 Hz), 6.32 (d, 1 H, *J* = 10.5 Hz), 5.28 (s, 2 H); MS (EI) *m/z* (rel intensity) 484 (M^+, 61), 316 (8), 287 (12), 231 (6), 202 (15), 169 (100), 114 (37), 90 (31), 63 (10); HRMS (EI) calcd for $C_{27}H_{17}BrO_4$ 484.0310, found 484.0313.

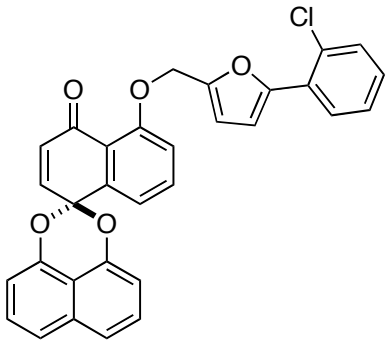


8-(4-Chlorobenzyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphtho[1",8"-de][1',3']dioxin (124, *TH-49*).[42] According to the general procedure, palmarumycin CP_1 (12 mg, 0.038 mmol), diphenylphosphino-polystyrene (137 mg, 1.41 mmol/g, 0.193 mmol), 4-chlorobenzyl alcohol (27 mg, 0.19 mmol) and DEAD (30 μL, 0.19 mmol) in dry CH_2Cl_2 (2.0 mL) provided after 87 h 6.3 mg (38%) of starting material contaminated with an impurity and 1.4 mg (8%) of **124**: ^{1}H NMR δ 7.69-7.51 (m, 6 H), 7.48 (t, 2 H, *J* = 7.7 Hz), 7.40 (d, 2 H, *J* = 7.5 Hz), 7.19 (d, 1 H, *J* = 8.0 Hz), 6.99 (d, 2 H, *J* = 7.3 Hz), 6.89 (d, 1 H, *J* = 10.5 Hz), 6.32 (d, 1 H, *J* = 10.5 Hz), 5.28 (s, 2 H); MS (EI) *m/z* (rel intensity) 440 (M^+, 20), 316 (100), 287 (25), 149 (15), 127 (17), 114 (52); HRMS (EI) calcd for $C_{27}H_{17}ClO_4$ 440.0815, found 484.0831.

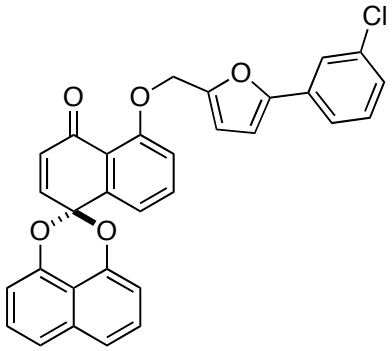


8-[5-(4-Bromophenyl)-furan-2-ylmethoxy]-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphtho[1",8"-de][1',3']dioxin (125, *TH-62*).[42] According to the general procedure, palmarumycin CP_1 (6.3 mg, 0.020 mmol), diphenylphosphino-polystyrene (72 mg, 1.41 mmol/g, 0.102 mmol), 5-(4-bromophenyl)furfuryl alcohol (25 mg, 0.010 mmol) and DEAD (16 μL, 0.082

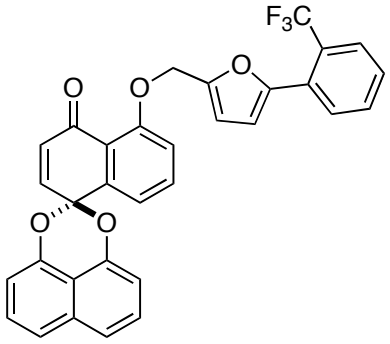
mmol) in dry CH_2Cl_2 (0.70 mL) provided after 30 h 2.8 mg (25%) of **125**: ^{1}H NMR δ 7.71-7.60 (m, 2 H), 7.57-7.45 (m, 8 H), 7.34-7.31 (m, 1 H), 6.98 (d, 2 H, *J* = 7.3 Hz), 6.87 (d, 1 H, *J* = 10.5 Hz), 6.65 (d, 2 H, *J* = 9.2 Hz), 6.30 (d, 1 H, *J* = 10.5 Hz), 5.28 (s, 2 H); MS (EI) *m/z* (rel intensity) 550 (M^+, 72), 339 (18), 316 (62), 237 (100), 235 (96), 183 (24), 160 (17), 128 (31), 114 (45), 91 (12), 77 (15); HRMS (EI) calcd for $C_{27}H_{19}BrO_5$ 550.0416, found 550.0406.



8-[5-(2-Chlorophenyl)-furan-2-ylmethoxy]-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphtho[1",8"-de][1',3']dioxin (126, *TH-63*).[42] According to the general procedure, palmarumycin CP_1 (6.0 mg, 0.019 mmol), diphenylphosphino-polystyrene (68.6 mg, 1.41 mmol/g, 0.097 mmol), 5-(2-chlorophenyl)furfuryl alcohol (20 mg, 0.094 mmol) and DEAD (15 μL, 0.095 mmol) in dry CH_2Cl_2 (0.80 mL) provided after 35 h 1.1 mg (11%) of **126**: ^{1}H NMR δ 7.88 (dd, 1 H, *J* = 7.8, 1.6 Hz), 7.71-7.66 (m, 2 H), 7.58 (d, 2 H, *J* = 8.1 Hz), 7.50-7.43 (m, 3 H), 7.37-7.31 (m, 2 H), 7.26-7.21 (m, 1 H), 7.13 (d, 1 H, *J* = 3.4 Hz), 6.99 (d, 2 H, *J* = 7.4 Hz), 6.87 (d, 1 H, *J* = 10.4 Hz), 6.67 (d, 1 H, *J* = 3.4 Hz), 6.30 (d, 1 H, *J* = 10.5 Hz), 5.31 (s, 2 H); MS (EI) *m/z* (rel intensity) 506 (M^+, 7), 400 (11), 368 (40), 351 (25), 316 (16), 208 (35), 191 (80), 163 (11), 149 (38), 128 (31), 115 (25), 97 (37), 84 (79), 69 (57), 57 (100); HRMS (EI) calcd for $C_{31}H_{19}ClO_5$ 506.0921, found 506.0939.

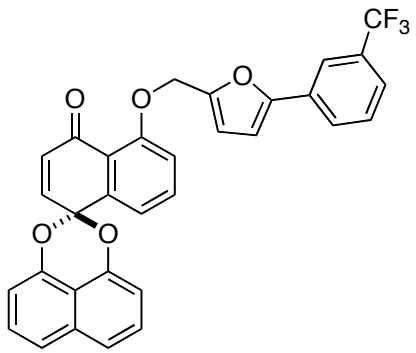


8-[5-(3-Chlorophenyl)-furan-2-ylmethoxy]-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphtho[1",8"-de][1',3']dioxin (127, *TH-64*).[42] According to the general procedure, palmarumycin CP_1 (6.9 mg, 0.022 mmol), diphenylphosphino-polystyrene (78.9 mg, 1.41 mmol/g, 0.111 mmol), 5-(3-chlorophenyl)furfuryl alcohol (22.8 mg, 0.109 mmol) and DEAD (17 μL, 0.11 mmol) in dry CH_2Cl_2 (0.80 mL) provided after 36 h 2.5 mg (23%) of **127**: ^{1}H NMR δ 7.72-7.68 (m, 3 H), 7.68-7.55 (m, 3 H), 7.48 (t, 3 H, *J* = 7.7 Hz), 7.34-7.30 (m, 2 H), 6.98 (d, 2 H, *J* = 7.5 Hz), 6.88 (d, 1 H, *J* = 10.5 Hz), 6.73 (d, 2 H, *J* = 10.9 Hz), 6.30 (d, 1 H, *J* = 10.5 Hz), 5.29 (s, 2 H); MS (EI) *m/z* (rel intensity) 506 (M^+, 25), 316 (100), 287 (27), 225 (20), 191 (48), 160 (25), 139 (37), 128 (21), 114 (56), 77 (22), 57 (25); HRMS (EI) calcd for $C_{31}H_{19}ClO_5$ 506.0921, found 506.0926.



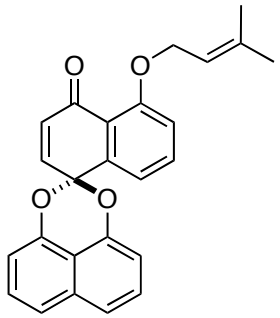
8-[5-(2-Trifluoromethylphenyl)-furan-2-ylmethoxy]-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphtho[1",8"-de][1',3']dioxin (128, *TH-65*).[42] According to the general

procedure, palmarumycin CP_1 (10 mg, 0.032 mmol), diphenylphosphino-polystyrene (114 mg, 1.41 mmol/g, 0.161 mmol), 5-[2-(trifluoromethyl)phenyl]furfuryl alcohol (42 mg, 0.17 mmol) and DEAD (25 μL, 0.16 mmol) in dry CH_2Cl_2 (1.0 mL) provided after 30 h 3.9 mg (23%) of **128**: ^{1}H NMR δ 7.78-7.73 (m, 2 H), 7.71-7.62 (m, 2 H), 7.58 (d, 2 H, *J* = 8.2 Hz), 7.48 (t, 3 H, *J* = 7.6 Hz), 7.34 (dd, 2 H, *J* = 7.6, 1.7 Hz), 6.98 (d, 2 H, *J* = 7.4 Hz), 6.87 (d, 1 H, *J* = 10.5 Hz), 6.69 (dd, 2 H, *J* = 14.9, 3.2 Hz), 6.30 (d, 1 H, *J* = 10.5 Hz), 5.31 (s, 2 H); MS (EI) *m/z* (rel intensity) 540 (M^+, 13), 316 (31), 287 (7), 225 (100), 177 (9), 114 (15); HRMS (EI) calcd for $C_{32}H_{19}F_3O_5$ 540.1196, found 540.1196.

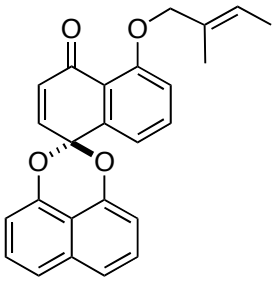


8-[5-(3-Trifluoromethyl)-furan-2-ylmethoxy]-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphtho[1",8"-de][1',3']dioxin (129, *TH-66*).[42] According to the general procedure, palmarumycin CP_1 (10 mg, 0.032 mmol), diphenylphosphino-polystyrene (115 mg, 1.41 mmol/g, 0.162 mmol), 5-[3-(trifluoromethyl)phenyl]furfuryl alcohol (38 mg, 0.16 mmol) and DEAD (25 μL, 0.16 mmol) in dry CH_2Cl_2 (1.0 mL) provided after 30 h 5.8 mg (34%) of **129**: ^{1}H NMR δ 7.92-7.85 (m, 2 H), 7.75-7.69 (m, 2 H), 7.58 (d, 2 H, *J* = 8.3 Hz), 7.53-7.43 (m, 3 H), 7.33 (dd, 2 H, *J* = 7.7, 1.3 Hz), 6.98 (d, 2 H, *J* = 7.4 Hz), 6.88 (d, 1 H, *J* = 10.5 Hz), 6.71 (dd, 2 H, *J* = 25.8, 3.3 Hz), 6.30 (d, 1 H, *J* = 10.5 Hz), 5.31 (s, 2 H); MS (EI) *m/z* (rel intensity) 540 (M^+, 17), 316

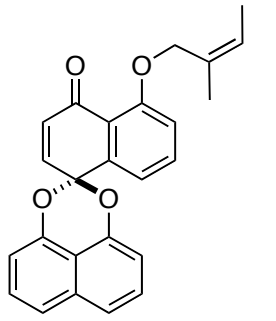
(12), 225 (100), 173 (9), 128 (7), 114 (10), 57 (6); HRMS (EI) calcd for $C_{32}H_{19}F_3O_5$ 540.1185, found 540.1182.



8-(3-Methylbut-2-enyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphtho[1",8"-de][1',3']dioxin (130, *TH-126*).[42] According to the general procedure, palmarumycin CP_1 (12.5 mg, 0.0395 mmol), diphenylphosphino-polystyrene (143 mg, 1.41 mmol/g, 0.202 mmol), 3-methyl-2-buten-1-ol (20 μL, 0.20 mmol) and DEAD (31 μL, 0.20 mmol) in dry CH_2Cl_2 (1.3 mL) provided after 67 h 7.8 mg (51%) of **130**: ^{1}H NMR δ 7.68 (t, 1 H, *J* = 8.0 Hz), 7.59 (d, 3 H, *J* = 9.5 Hz), 7.48 (t, 2 H, *J* = 7.7 Hz), 7.17 (d, 1 H, *J* = 8.3 Hz), 6.98 (d, 2 H, *J* = 7.3 Hz), 6.85 (d, 1 H, *J* = 10.6 Hz), 6.28 (d, 1 H, *J* = 10.6 Hz), 5.58 (t, 1 H, *J* = 6.5 Hz), 4.75 (d, 2 H, *J* = 6.4 Hz), 1.81 (s, 3 H), 1.79 (s, 3 H); MS (EI) *m/z* (rel intensity) 384 (M^+, 6), 369 (4), 316 (63), 287 (21), 271 (6), 259 (12), 231 (11), 202 (14), 114 (59), 102 (6), 88 (9), 69 (100); HRMS (EI) calcd for $C_{25}H_{20}O_4$ 384.1362, found 384.1361.

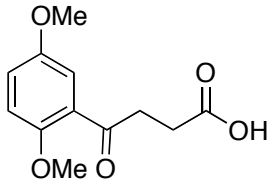


(*E*)-8-(2-Methylbut-2-enyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphtho[1",8"-de][1',3']dioxin (131, *TH-139*).[42] According to the general procedure, palmarumycin CP_1 (14.5 mg, 0.0458 mmol), diphenylphosphino-polystyrene (163 mg, 1.41 mmol/g, 0.230 mmol), 2-methyl-2-buten-1-ol (tiglic alcohol 20 mg, 0.23 mmol) and DEAD (36 μL, 0.23 mmol) in dry CH_2Cl_2 (1.5 mL) provided after 36 h 9.9 mg (56%) of **131**: ^{1}H NMR δ 7.68 (t, 1 H, *J* = 8.0 Hz), 7.58 (d, 3 H, *J* = 8.7 Hz), 7.48 (t, 2 H, *J* = 7.6 Hz), 7.16 (d, 1 H, *J* = 8.0 Hz), 6.98 (d, 2 H, *J* = 7.2 Hz), 6.85 (d, 1 H, *J* = 10.5 Hz), 6.29 (d, 1 H, *J* = 10.5 Hz), 5.79 (m, 1 H), 4.59 (s, 2 H), 1.82 (s, 3 H), 1.71 (d, 3 H, *J* = 6.4 Hz); MS (EI) *m/z* (rel intensity) 384 (M^+, 64), 369 (20), 316 (100), 287 (22), 273 (8), 259 (9), 231 (6), 202 (9), 172 (6), 160 (8), 114 (7); HRMS (EI) calcd for $C_{25}H_{20}O_4$ 384.1362, found 384.1364.

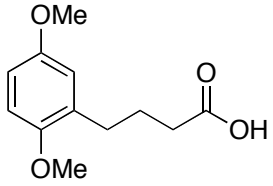


(*Z*)-8-(2-Methylbut-2-enyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2'-naphtho[1",8"-de][1',3']dioxin (132, *TH-140*).[42] According to the general procedure, palmarumycin CP_1 (14.6 mg, 0.0462 mmol), diphenylphosphino-polystyrene (167 mg, 1.41

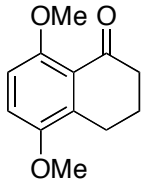
mmol/g, 0.235 mmol), 2-methyl-2-buten-1-ol (angelic alcohol 20 mg, 0.23 mmol) and DEAD (36 μL, 0.23 mmol) in dry CH_2Cl_2 (1.5 mL) provided after 36 h 6.4 mg (36%) of **132**: ^{1}H NMR δ 7.69 (t, 1 H, *J* = 8.0 Hz), 7.61-7.57 (m, 3 H), 7.48 (t, 2 H, *J* = 7.6 Hz), 7.17 (d, 1 H, *J* = 8.2 Hz), 6.98 (d, 2 H, *J* = 7.6 Hz), 6.85 (d, 1 H, *J* = 10.5 Hz), 6.28 (d, 1 H, *J* = 10.6 Hz), 5.55 (m, 1 H), 4.76 (s, 2 H), 1.93 (s, 3 H), 1.75 (d, 3 H, *J* = 6.6 Hz); MS (EI) *m/z* (rel intensity) 384 (M^+, 59), 369 (18), 316 (87), 287 (16), 271 (7), 259 (10), 231 (9), 202 (13), 155 (5), 114 (100), 84 (60), 69 (86), 55 (22); HRMS (EI) calcd for $C_{25}H_{20}O_4$ 384.1362, found 384.1364.



4-(2', 5'-Dimethoxyphenyl)-4-oxobutyric acid.[76] To a 0 °C suspension of $AlCl_3$ (23.16 g, 0.1737 mol) in nitrobenzene (85 mL) was added *p*-dimethoxybenzene **133** (10.0 g, 0.0724 mol) and succinic anhydride **134** (8.69 g, 0.0868 mol). The brown solution was allowed to stir at 0 °C for 3.5 h, gradually warmed to room temperature over 2.5 h, and then poured into ice water (500 mL). After addition of 10% NaOH until aqueous pH > 9, the aqueous phase was extracted with diethyl ether (3 × 125 mL) and then acidified with 10% HCl to induce precipitation. The resulting tan clumpy solid was filtered, dried and recrystallized from methanol/water (1:1) to give 12.0 g (70%) of 4-(2', 5'-dimethoxyphenyl)-4-oxo-butyric acid as tan needles: mp 101.1-104.0 °C; ^{1}H NMR δ 7.36 (d, 1 H, *J* = 3.2 Hz), 7.06 (dd, 1 H, *J* = 8.9, 3.2 Hz), 6.93 (d, 1 H, *J* = 9.1 Hz), 3.89 (s, 3 H), 3.80 (s, 3H), 3.35 (t, 2 H, *J* = 6.5 Hz), 2.76 (t, 2 H, *J* = 6.5 Hz).

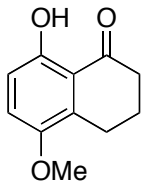


4-(2',5'-Dimethoxyphenyl)butyric acid (135).[76] A solution of 4-(2', 5'-dimethoxyphenyl)-4-oxo-butyric acid (31.5 g, 0.132 mol) in triethylene glycol (360 mL) containing sodium hydroxide (19.6 g, 0.489 mol), hydrazine monohydrate (18.5 g, 0.370 mol) and water (19 mL) was heated at reflux for 3 h. It was heated further without a condenser until the temperature rose to 210 °C. The temperature was lowered to 190 °C through the addition of water and heating was continued for 4 h. Then, the reaction mixture was cooled, poured into a mixture of concentrated HCl (100 mL) and ice (1000 g), and extracted with ether (3 × 250 mL). The combined ether layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1 → 1:1) gave 14.6 g (49%) of **135** as white crystals with a slight yellowish hue and 7.3 g (25%) of a mixture of the desired product **135** and a minor impurity: ^{1}H NMR δ 6.78 (d, 2 H, J = 8.6 Hz), 6.73 (s, 1 H), 6.72 (d, 2 H, J = 8.3 Hz), 3.78 (s, 3 H), 3.77 (s, 3 H), 2.67 (t, 2 H, J = 7.2 Hz), 2.39 (t, 2 H, J = 7.5 Hz), 1.94 (p, 2 H, J = 7.3 Hz).

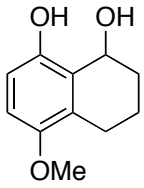


5,8-Dimethoxy-3,4-dihydro-2*H*-naphthalen-1-one (136).[75,76,77] A solution of **135** (1.16 g, 5.17 mmol) in 78% H_2SO_4 (1.1 M, 4.7 mL, 5.17 mmol) was stirred for 1.5 h at 98 °C. The resulting red solution was poured into ice water (100 g) and extracted with ether (3 × 50 mL).

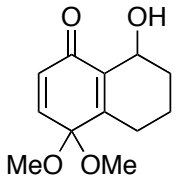
The ether extracts were washed with 1 M NaOH (2 × 25 mL) and brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 4:1 → 2:1 → 1:1) afforded 730 mg (68%) of **136** as a solid: ^{1}H NMR δ 6.99 (d, 1 H, *J* = 9.1 Hz), 6.80 (d, 1 H, *J* = 9.1 Hz), 3.87 (s, 3 H), 3.83 (s, 3 H), 2.89 (t, 2 H, *J* = 6.1 Hz), 2.62 (dd, 2 H, *J* = 8.5, 4.7 Hz), 2.06 (p, 2 H, *J* = 6.5 Hz).



8-Hydroxy-5-methoxy-3,4-dihydro-2*H*-naphthalen-1-one.[78] To a solution of tetralone **145** (49.2 mg, 0.239 mmol) in CH_2Cl_2 (3.0 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 120 μL, 0.703 mmol) dropwise at –78 °C. After 2 h, the dry ice/acetone bath was removed and the mixture was warmed to room temperature over 75 min. The organic phase was washed with water (10 mL), 5% Na_2CO_3 (2.5 mL), 5% $Na_2S_2O_3$ and another aliquot of water (10 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/Et_2O, 25:1) afforded 39.6 mg (80%) of 8-hydroxy-5-methoxy-3,4-dihydro-2*H*-naphthalen-1-one as a yellow solid: mp 92.1-93.0 °C; ^{1}H NMR δ 11.93 (s, 1 H), 7.08 (d, 1 H, *J* = 9.0 Hz), 6.79 (d, 1 H, *J* = 8.9) 3.82 (s, 3 H), 2.90 (t, 2 H, *J* = 6.2 Hz), 2.68 (dd, 2 H, *J* = 13.1, 6.6 Hz), 2.09 (p, 2 H, *J* = 6.5 Hz).

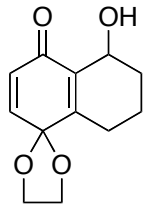


5-Methoxy-1,2,3,4-tetrahydronaphthalene-1,8-diol (137).[42,52] To a 0 °C solution of 8-hydroxy-5-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (0.162 g, 0.842 mmol) in Et_2O (6.0 mL) was added LAH (0.150 g, 3.95 mmol) batchwise over 12 min. The ice bath was removed immediately following the addition of the reducing agent. After 10 min, the clear, colorless solution was quenched with water (200 μL) at 0 °C, and diluted with Et_2O (17 mL) and 10% $NaHSO_4$ (6 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 2:1) gave 154 mg (94%) of **137** as an oil which crystallized upon storage at –20 °C: ^{1}H NMR δ 6.68 (s, 2 H), 5.00 (t, 1 H, *J* = 6.6 Hz), 3.76 (s, 3 H), 2.62-2.58 (m, 2 H), 2.11-2.09 (m, 1 H), 1.89-1.65 (m, 4 H), 1.26 (*br* s, 1 H).



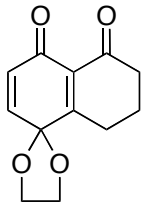
8-Hydroxy-4,4-dimethoxy-5,6,7,8-tetrahydro-4*H*-naphthalen-1-one (138).[42,79] To a 0 °C solution of diol **137** (0.0938 g, 0.483 mmol) in MeOH (9.7 mL) was added iodobenzene diacetate (0.180 g, 0.559 mmol) batchwise over 6 min. The ice bath was removed immediately following the addition of oxidant. After 20 min, solid $NaHCO_3$ (0.140 g, 1.67 mmol) was added at 0 °C, and the reaction mixture was allowed to stir for another 15 min, diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with

brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 4:1 → 2:1 → 1:1) afforded 0.0758 g (70%) of **138** as a yellow solid: IR (neat) 3497, 2943, 2832, 1674, 1643, 1620, 1456, 1404, 1295, 1104, 1064, 1019, 990, 968, 843 cm^{-1}; ^1H NMR δ 6.81 (d, 1 H, *J* = 10.3 Hz), 6.45 (d, 1 H, *J* = 10.4 Hz), 4.8-4.7 (m, 1 H), 3.34 (d, 1 H, *J* = 2.3 Hz), 3.23 (s, 6 H), 2.5-2.1 (m, 2 H), 1.88-1.83 (m, 3 H), 1.7-1.6 (m, 1 H); ^{13}C NMR δ 185.8, 154.6, 144.4, 137.4, 132.2, 94.9, 62.2, 51.1, 51.0, 29.9, 23.7, 17.4; MS (EI) *m/z* (rel intensity) 224 (M^+, 16), 209 (18), 193 (49), 164 (40), 150 (33), 137 (100), 131 (19), 121 (24), 115 (17), 107 (56), 91 (36), 77 (77), 65 (48), 55 (57); HRMS (EI) calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1055.

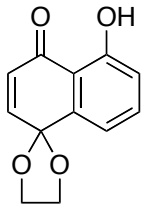


8-Hydroxy-5,6,7,8-tetrahydro-4*H*-naphthalen-1-one-4-spiro-2'-dioxolane (139).[42,80] To a solution of dienone **138** (40 mg, 0.18 mmol) in DME (1.8 mL) was added ethylene glycol (78.0 mg, 70 μL, 1.3 mmol) followed by the dropwise addition of $BF_3 \bullet Et_2O$ (26 mg, 30 μL, 0.18 mmol). After 20 min, the dark yellow solution was diluted with CH_2Cl_2 and washed with water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 2:1 → 1:1) afforded **139** in quantitative yield: mp 116.6–119.1 °C; IR (neat) 3514, 2945, 2893, 1677, 1647, 1625, 1404, 1292, 1172, 1112, 1019, 967, 843 cm^{-1}; ^1H NMR δ 6.68 (d, 1 H, *J* = 10.1 Hz), 6.11 (d, 1 H, *J* = 10.1 Hz), 4.66 (*br* s, 1 H),

4.19-4.12 (m, 4 H), 3.29 (d, 1 H, J = 2.0 Hz), 2.38-2.21 (m, 2 H), 1.85-1.78 (m, 3 H), 1.67-1.62 (m, 1 H); ^{13}C NMR δ 186.7, 154.0, 143.6, 135.4, 127.7, 99.6, 66.5, 66.5, 62.8, 29.8, 23.6, 17.7.

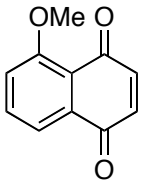


3,4-Dihydro-2*H*,5*H*-naphthalene-1,8-dione-5-spiro-2'-dioxolane.[42] To a solution of acetal **139** (40 mg, 0.18 mmol) in CH_2Cl_2 (3.0 mL) was added Dess-Martin periodinane (118 mg, 0.278 mmol) batchwise over 5 min at room temperature. The reaction mixture was stirred for 75 min and diluted with Et_2O. The solution was concentrated to a slurry *in vacuo*, dissolved in Et_2O (35 mL) and washed with a 1:1 mixture of saturated $NaHCO_3$, 10% aqueous sodium thiosulfate solution (10 mL), water (10 mL) and brine (10 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 8.5 mg (21%) of 3,4-dihydro-2*H*,5*H*-naphthalene-1,8-dione-5-spiro-2'-dioxolane that was used without further purification.



8-Hydroxy-4*H*-naphthalene-1-one-4-spiro-2'-dioxolane (140).[42] A solution of crude 3,4-dihydro-2*H*,5*H*-naphthalene-1,8-dione-5-spiro-2'-dioxolane (8.5 mg, 0.039 mmol) in CH_2Cl_2 (1.0 mL) was added to MnO_2 (Aldrich, 85% activated, 35 mg, 0.40 mmol, dried over P_2O_5 for 3 h just before use). The reaction mixture was stirred at room temperature for 18 h, filtered through a small pad of celite and washed repeatedly with CH_2Cl_2 (25 mL). The combined

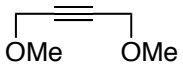
organic layers were concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 4:1) gave 1.5 mg (18%) of **140** as a yellow solid: mp 96.2-100.5 °C; IR (neat) 2956, 2919, 2852, 1662, 1617, 1460, 1393, 1344, 1296, 1240, 1157, 1083, 967, 843, 806, 746 cm^{-1}; ^1H NMR δ 12.16 (s, 1 H), 7.54 (t, 1 H, *J* = 8.7 Hz), 7.12 (d, 1 H, *J* = 7.6 Hz), 7.01 (d, 1 H, *J* = 8.3 Hz), 6.85 (d, 1 H, *J* = 10.3 Hz), 6.33 (d, 1 H, *J* = 10.3 Hz), 4.4-4.2 (m, 4 H); ^{13}C NMR δ 189.6, 161.8, 144.1, 141.4, 136.2, 128.3, 118.9, 118.0, 114.6, 99.9, 65.9; MS (EI) *m/z* (rel intensity) 218 (M^+, 100), 187 (12), 164 (8), 162 (47), 146 (7), 134 (25), 118 (21), 102 (15), 92 (15), 76 (9), 63 (15), 57 (9); HRMS (EI) calcd for $C_{12}H_{10}O_4$ 218.0579, found 218.0571.



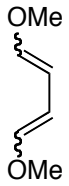
5-Methoxy-1,4-napthoquinone (juglone methyl ether, **141)**.[81] To a solution of 1,4-dimethoxybutadiene **146** (40 mg, 0.35 mmol) in toluene (1.0 mL) was added an excess of benzoquinone **145** (133 mg, 1.23 mmol). The reaction mixture was stirred at room temperature for 6 d. Then, it was filtered and the remaining solids were washed repeatedly with toluene. The filtrate was concentrated *in vacuo*. Chromatography on neutral Al_2O_3 (toluene) gave a crude residue that was recrystallized from MeOH to give 22 mg (33%) of **141** as an orange solid: ^1H NMR δ 7.77-7.68 (m, 2 H), 7.33 (d, 1 H, *J* = 7.9 Hz), 6.89 (s, 2 H), 4.03 (s, 3 H).

Alternatively, a solution of juglone **144** (2.55 g, 14.64 mmol) in CH_2Cl_2 (50 mL) was treated with Ag_2O (2.8 g, 12.1 mmol) followed by excess MeI (2.2 mL, 5.0 g, 35.3 mmol).[85] After 31.5 h at room temperature, the ratio of starting material to product was 2:1 by ^1H NMR. Consequently, more Ag_2O (2.8 g, 12.1 mmol) and MeI (0.760 mL, 1.73 g, 12.2 mmol) were

added. After an additional 21.5 h, the dark brown solution was filtered through a pad of celite. The celite pad was washed repeatedly with CH_2Cl_2 and then the solvent was concentrated *in vacuo* to give **141** in nearly quantitative yield. Approximately 6-8% of starting juglone **144** was detected by ^{1}H NMR. Juglone **144** can be separated from juglone methyl ether **141** via recrystallization from MeOH.

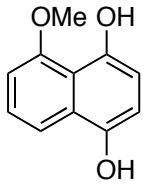


1,4-Dimethoxy-2-butyne (148).[84] To a solution of 2-butyne-1,4-diol **147** (10.0 g, 0.116 mol) in water (19 mL) was added dimethyl sulfate (28 mL) and sodium hydroxide pellets (12 g, 0.29 mol) in approximately 15 portions each over 1.5 h. The temperature of the reaction mixture was maintained between 30 and 40 °C throughout the addition process by cooling occasionally with an ice bath. Following the addition, the solution was heated at 90 °C for 3.5 h, treated with water (75 mL), cooled to room temperature and extracted with Et_2O (5 × 50 mL). Finally, the organic phase was dried (K_2CO_3), filtered and concentrated *in vacuo*. Purification by distillation gave 8.5 g (64%) of **148**: bp 50-52 °C (15 mm) [lit.[84] bp 54 °C (12mm)]; ^{1}H NMR δ 4.15 (s, 4 H), 3.39 (s, 6 H).

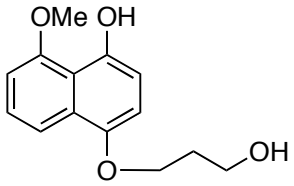


1,4-Dimethoxy-1,3-butadiene (DMBU, 146).[81,84] To a solution of **148** (3.43 g, 0.0301 mol) in DMSO (7.0 mL) was added potassium *tert*-butoxide (314 mg, 2.80 mmol) in three batches at 0 °C. The reaction mixture was heated at 65-70 °C for 2.5 h, poured into water (50

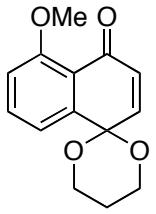
mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under vacuum to remove Et_2O. The remaining orange oil was purified by distillation to give 1.9 g (54%) of **146**: bp 72-76 °C (25 mm) [lit.[99] bp 71-72 °C (30 mm)]; (*Z*,*Z*)-isomer: ^{1}H NMR δ 5.85-5.81 (m, 2 H), 5.34 (dd, 2 H, *J* = 3.6, 1.4 Hz), 3.62 (s, 6 H); (*E*,*Z*)-isomer: 6.56 (d, 1 H, *J* = 12.8 Hz), 5.78-5.72 (m, 2 H), 4.94 (dd, 1 H, *J* = 10.7, 6.0 Hz), 3.56 (s, 6 H); (*E*,*E*)-isomer: 6.43 (dd, 2 H, *J* = 9.1, 2.7 Hz), 5.39 (dd, 2 H, *J* = 8.9, 2.7), 3.53 (s, 3 H).



5-Methoxynaphthalene-1,4-diol (149).[85] A solution of juglone methyl ether **141** (50 mg, 0.27 mmol) in EtOAc (6.0 mL) was added to a solution of sodium dithionite (389 mg, 2.23 mmol) in water (4.0 mL). The reaction mixture was stirred at room temperature for 1.5 h. Then, the aqueous phase was separated from the organic and subsequently extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The air-sensitive solid **149** (50 mg, 100%) was used immediately without further purification or stored under vacuum: ^{1}H NMR δ 8.97 (s, 1 H), 7.77 (d, 1 H, *J* = 8.6 Hz), 7.36 (t, 1 H, *J* = 8.0 Hz), 6.85 (d, 1 H, *J* = 7.7 Hz), 6.78 (d, 1 H, *J* = 8.3 Hz), 6.72 (d, 1 H, *J* = 8.2 Hz), 4.86 (s, 1 H), 4.08 (s, 3 H).

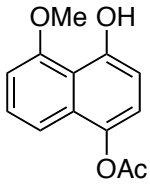


4-(3-Hydroxypropyl)-8-methoxy-naphthalen-1-ol (151).[42] A solution of **149** (125 mg, 0.659 mmol) in deoxygenated DMF (1.0 mL) was added to solid Cs_2CO_3 (280 mg, 0.856 mmol). The reaction mixture was stirred at room temperature for 30 min, treated with 3-bromo-1-propanol **150** (75 μL, 0.79 mmol), stirred for 4 h, diluted with water (20 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1 → 1:1) afforded 116 mg (71%) of **151** as a solid: mp 126.5-127.8 °C; IR (neat) 3375, 3267, 2945, 1636, 1606, 1412, 1071, 1026, 753 cm^{-1}; ^1H NMR δ 8.81 (s, 1 H), 7.66 (dd, 1 H, J = 8.5, 0.9 Hz), 7.17 (t, 1 H, J = 8.1 Hz), 6.67 (dd, 1 H, J = 7.8, 0.6 Hz), 6.63 (d, 2 H, J = 1.4 Hz), 4.05 (t, 2 H, J = 5.9 Hz), 3.89 (s, 3 H), 3.79 (t, 2 H, J = 6.0 Hz), 1.99 (p, 2 H, J = 5.9 Hz), 1.80 (*br* s, 1 H); ^{13}C NMR δ 156.2, 148.4, 147.4, 128.2, 125.5, 115.9, 115.8, 109.3, 108.0, 105.1, 66.8, 60.9, 56.3, 32.5; MS (EI) *m/z* (rel intensity) 248 (M^+, 61), 190 (50), 189 (100), 175 (28), 174 (19), 147 (7), 118 (6), 103 (6), 84 (9).



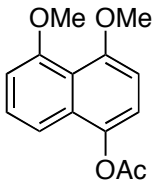
8-Methoxy-4*H*-naphthalene-1-one-4-spiro-2'-dioxolane (142).[42] To a solution of **151** (243 mg, 0.979 mmol) in CF_3CH_2OH (33 mL) containing 4Å MS was added excess solid $NaHCO_3$ (272 mg, 3.24 mmol) followed by iodobenzene diacetate (350 mg, 1.09 mmol)

batchwise over 5 min at room temperature. The reaction mixture was stirred at room temperature for 85 min. It underwent a variety of color changes beginning at dark blue and ultimately persisting at bright yellow. Upon the completion of the reaction, the solids were removed via filtration and the remaining solution was concentrated *in vacuo*. The resultant residue was diluted with CH_2Cl_2 (40 mL) and washed with 5% $NaHCO_3$ (15 mL) followed by brine (20 mL). Finally, the organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 4:1 → 2:1 → 1:1) gave 63.8 mg (26%) of **142** as an orange solid: mp 147.5-152.1 °C; IR (neat) 2960, 2919, 2840, 1670, 1636, 1595, 1475, 1322, 1258, 1281, 1094, 1060 cm^{-1}; ^1H NMR δ 7.69-7.55 (m, 3 H), 7.03 (dd, 1 H, *J* = 7.8, 1.5 Hz), 6.37 (d, 1 H, *J* = 10.8 Hz), 4.33 (td, 2 H, *J* = 12.6, 2.5 Hz), 4.09 (dd, 2 H, *J* = 7.2, 4.6 Hz), 3.95 (s, 3 H), 2.5-2.2 (m, 1 H), 1.65-1.60 (m, 1 H); ^{13}C NMR δ 183.4, 159.4, 145.0, 134.6, 134.5, 130.9, 119.3, 118.6, 112.5, 90.8, 61.3, 56.2, 25.1; MS (EI) *m/z* (rel intensity) 246 (M^+, 40), 217 (23), 216 (35), 198 (15), 189 (46), 188 (100), 160 (27), 159 (38), 149 (9), 131 (28), 130 (29), 114 (12), 104 (34), 102 (32), 89 (10), 76 (37), 63 (9); HRMS (EI) calcd for $C_{14}H_{14}O_4$ 246.0892, found 246.0896.

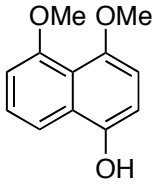


1-Acetoxy-5-methoxy-4-naphthol (158).[87] To a solution of **141** (2.10 g, 11.16 mmol) in $CHCl_3$ (70 mL) was added dropwise acetic anhydride (2.9 mL, 30.68 mmol) followed by pyridine (2.9 mL, 35.86 mmol) and zinc dust (8.10 g, 0.124 mol). The reaction mixture was heated to a gentle reflux (60-65 °C) for 1.5 h, cooled and then filtered. The resulting filtrate was

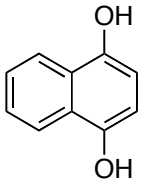
poured into water (150 mL) and stirred for 10 min. The organic phase was separated and washed with 1.1 M HCl (~25 mL) followed by water (2 × 75 mL). Then, it was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 1:1) gave 1.65 g (64%) of **158** as a yellow/orange viscous oil: ^{1}H NMR δ 9.30 (s, 1 H), 7.42-7.34 (m, 2 H), 7.13 (d, 1 H, J = 8.3 Hz), 6.85 (d, 1 H, J = 8.2 Hz), 6.83 (dd, 1 H, J = 6.2, 2.0 Hz), 4.07 (s, 3 H), 2.43 (s, 3 H).



1-Acetoxy-4,5-dimethoxynaphthalene (159).[87,88] To a solution of **158** (740 mg, 3.19 mmol) in acetone (80 mL) was added solid K_2CO_3 (2.2 mg, 15.92 mmol) and excess MeI (2.0 mL, 27.90 mmol). The reaction mixture was stirred at reflux for 24 h before a second portion of MeI (2.0 mL, 27.90 mmol) was introduced in an effort to drive the reaction to completion. After an additional 20 h at reflux, the solution was cooled to room temperature. The salts were removed by vacuum filtration and the acetone was concentrated *in vacuo*. The resultant residue was diluted with EtOAc (75 mL) and washed with water (30 mL) followed by brine (30 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a bright yellow oil. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1) provided 546 mg (70%) of **159** as a viscous yellow oil which solidified upon standing: ^{1}H NMR δ 7.43-7.38 (m, 2 H), 7.16 (d, 1 H, J = 8.4 Hz), 6.90 (dd, 1 H, J = 6.6, 2.2 Ha), 6.82 (d, 1 H, J = 8.5 Hz), 3.99 (s, 3 H), 3.98 (s, 3 H), 2.44 (s, 3 H).

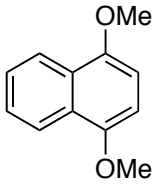


4,5-Dimethoxy-1-naphthol (155).[88] To a –78 °C solution of **159** (546 mg, 2.22 mmol) in THF (20 mL) was added dropwise diisobutylaluminum hydride (1.0 M in hexanes, 7.0 mL, 7.0 mmol). After 1 h at –78 °C, the dry ice/acetone bath was replaced by a 0 °C ice bath and the solution was allowed to warm to room temperature gradually over the next couple of hours. Following an additional 12 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (65 mL) and treated with an aqueous AcOH solution (0.600 mL of acid in 60.0 mL of water). The resultant biphasic mixture was stirred vigorously for 1.5 h. Then, the aqueous phase was separated from the organic and the latter was washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1 → 1:1) gave 330 mg (73%) of **155**: ^{1}H NMR δ 7.77 (d, 1 H, J = 8.5 Hz), 7.42 (t, 1 H, J = 8.1 Hz), 6.92 (d, 1 H, J = 7.7 Hz), 6.78 (d, 1 H, J = 8.3 Hz), 6.73 (d, 1 H, J = 8.3 Hz), 4.97 (s, 1 H), 4.00 (s, 3 H), 3.93 (s, 3 H).

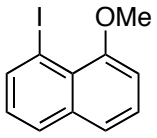


Naphthalene-1,4-diol (163).[89] To an aqueous solution of sodium dithionite (19.4 g, 0.111 mol) in water (190 mL) was added a solution of naphthoquinone **160** (2.0 g, 12.7 mmol) in EtOAc (150 mL) via an addition funnel over 30 min. The reaction mixture was stirred at room temperature for 2 h and 15 min. Then, the aqueous phase was separated from the organic phase

and subsequently extracted with EtOAc (3 x 75 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 2.0 g (100%) of **163** as a pinkish purple solid. The bisphenol **163** should not be further purified due to the ease with which it succumbs to (air) oxidation. Consequently, the diol should be placed under vacuum upon isolation and used shortly thereafter. Batches of **163** were stable for up to 8 days.

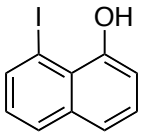


1,4-Dimethoxynaphthalene (157).[89,91] To a solution of **163** (550 mg, 3.43 mmol) in acetone (45 mL) was added solid K_2CO_3 (2.49 g, 18.02 mmol) followed by dimethyl sulfate (2.0 mL). The reaction mixture was heated at reflux for 48 h, cooled and poured into water (100 mL). The aqueous phase was extracted with $CHCl_3$ (3 x 150 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a reddish purple oil which solidified upon standing. Chromatography on SiO_2 (Hexanes/Et_2O, 1:0 → 100:1 → 50:1) delivered 600 mg (93%) of **157** as a white crystalline solid: ^{1}H NMR δ 8.23-8.20 (m, 2 H), 7.53-7.50 (m, 2 H), 6.71 (s, 2 H), 3.97 (s, 3 H).



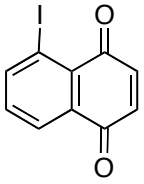
1-Iodo-8-methoxynaphthalene (97).[52,53,54] To a 0 °C solution of **165** (300 mg, 1.90 mmol) in Et_2O (800 μL) was added *t*-BuLi (1.7 M in pentane, 3.40 mL, 5.78 mmol) dropwise. The resultant thick, orange slurry was allowed to stir at 0 °C for 2 h prior to the removal of the

ice bath. After approximately 16 h at room temperature, the reaction mixture was re-cooled to 0 °C and a solution of I_2 (593 mg, 2.34 mmol) in THF (4.0 mL) was introduced dropwise over 10 min. The thick orange paste was transformed into a homogeneous solution during the course of the addition of the electrophile. The solution was gradually warmed to room temperature and stirred for at least 12 h. Finally, the reaction mixture was quenched by the addition of water (3-5 mL) at 0 °C (or more accurately, between 0 °C and +5 °C). Following the quench, the contents of the reaction vessel were poured into 30 mL of water. The heterogeneous mixture was diluted further with water and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Chromatography on SiO_2 (Hexanes/Et_2O, 1:0 → 100:1 → 50:1) provided 200.3 mg (>37%) of **97** as a white solid. At least 70 mg of the desired iodo compound **97** could be found in other batches of mixed material following the column purification: ^{1}H NMR δ 8.20 (dd, 1 H, J = 7.4, 1.2 Hz), 7.78 (dd, 1 H, J = 11.9, 1.2 Hz), 7.43-7.41 (m, 2 H), 7.05 (dd, 1 H, J = 8.1, 7.4 Hz), 6.93 (dd, 1 H, J = 5.9, 2.9 Hz), 3.96 (s, 3 H).

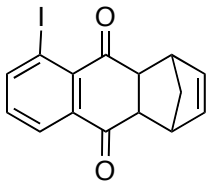


8-Iodonaphthalen-1-ol (166). To a –78 °C solution of **97** (2.80 g, 9.86 mmol) in CH_2Cl_2 (120 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 20 mL, 20 mmol) dropwise via an addition funnel over 75 min. The reaction mixture was gradually warmed to room temperature during the course of the next 2.5 h. The reaction mixture was diluted with CH_2Cl_2 and quenched with 5% Na_2CO_3 (~25 mL). The aqueous phase was separated from the organic phase and extracted with additional aliquots of CH_2Cl_2 (3 x 50 mL). The combined organic extracts were then washed

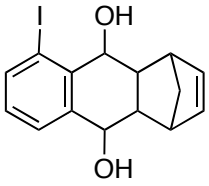
with water (75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/Et_2O, 100:1 → 50:1 → 20:1 → 8:1) delivered 2.25 (85%) of phenol **166**: ^1H NMR δ 8.05 (d, 1 H, *J* = 7.4 Hz), 7.82 (d, 1 H, *J* = 8.2 Hz), 7.46 (*app* td, 1 H, *J* = 8.5, 1.4 Hz), 7.40 (*app* t, 1 H, *J* = 8.0 Hz), 7.14 (s, 1 H), 7.09-7.03 (m, 2 H).



5-Iodonaphthalene-1,4-dione (crude, 162).[92] To a solution of Fremy's salt (1.50 g, 5.59 mmol) in aqueous KH_2PO_4 (30 mL of ~0.19 M solution) and water (108 mL) was added a solution of iodophenol **166** (440 mg, 1.63 mmol) in MeOH (44 mL) dropwise at room temperature. As Fremy's salt dissolved in the aqueous medium, the solution turned purple. Upon the addition of **166**, the purple color dissipated and a reddish orange color developed. This red color persisted throughout the course of the reaction. After 12 h at room temperature, the reaction mixture was extracted with Et_2O (3 x 50 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a dark brown solid. Chromatography on SiO_2 (Hexanes/Et_2O, 100:1 → 50:1 → 20:1 → 8:1) provided 318.2 mg (69%) of the desired iodonaphthoquinone **162** as an orange solid: ^1H NMR δ (diagnostic signals) 8.40 (dd, 1 H, *J* = 7.9, 1.3 Hz), 8.19 (dd, 1 H, *J* = 7.7, 1.3 Hz), 7.38 (t, 1 H, *J* = 7.8 Hz), 7.05 (AB, 1 H, *J* = 10.3 Hz), 6.97 (AB, 1 H, *J* = 10.3 Hz).

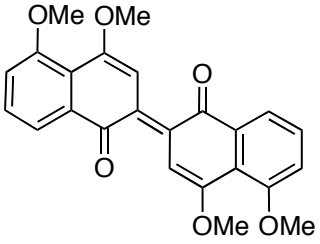


(1*RS,4*RS**,4a*RS**,9a*RS**)-1,4,4a,9a-Tetrahydro-5-iodo-1,4-methano-9,10-anthraquinone (167)**. To a solution of iodonaphthoquinone **162** (580 mg, 2.05 mmol) in CH_2Cl_2 (44 mL) was added cyclopentadiene (1.40 mL, 1.38 g, 10.44 mmol) at room temperature. The resultant orange solution lightened in color to yellow over the course of the first hour. The reaction was maintained at room temperature for a total of 110 min. Subsequently, the volatiles were removed *in vacuo* to give a thick yellow oil. Chromatography on SiO_2 (Hexanes/EtOAc, 4:1 → 2:1) delivered 559.1 mg (78%) of the Diels-Alder adduct **167** as a yellow foam: ^{1}H NMR δ 8.26 (ddd, 1 H, *J* = 7.8, 0.8, 0.5 Hz), 7.94 (ddd, 1 H, *J* = 7.8, 0.8, 0.4 Hz), 7.30-7.24 (m, 1 H), 6.06 (d of AB, 1 H, *J* = 5.7, 2.7 Hz), 5.99 (d of AB, 1 H, *J* = 5.4, 2.6 Hz), 3.62-3.45 (m, 4 H), 1.61 (ddd, 1 H, *J* = 8.7, 1.7, 1.7 Hz), 1.52 (dd, 1 H, *J* = 8.7, 0.4 Hz).

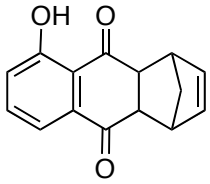


(5*RS,8*RS**,8a*RS**,9*RS**,10*RS**,10a*RS**)-9,10-Dihydroxy-1-iodo-5,8,8a,9,10,10a-hexahydro-5,8-methanoanthracene (156)**. To a –78 °C suspension of $NaBH_4$ (96.0 mg, 2.54 mmol) in THF (25 mL) was added dropwise a solution of **167** (559.1 mg, 1.592 mmol) in THF (6.4 mL). Then, MeOH (9.5 mL) was added. The reaction mixture was stirred at –78 °C for 2.5 h, and gradually warmed to 0 °C over the span of the next 60 min. As the solution warmed up, the bright yellow color dissipated. Finally, the mixture was quenched with saturated aqueous

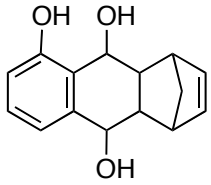
NH_4Cl (4.8 mL) at 0 °C, concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1 → 1:1) gave 440 mg (78%) of **156** as a white solid: ^{1}H NMR δ 7.78 (dd, 1 H, *J* = 8.0, 1.2 Hz), 7.24 (dd, 1 H, *J* = 7.3, 0.9 Hz), 6.97 (dd, 1 H, *J* = 7.9, 7.4 Hz), 6.23-6.21 (m, 2 H), 5.18 (d, 1 H, *J* = 3.4 Hz), 4.69 (d, 1 H, *J* = 3.3 Hz), 3.02-3.00 (m, 4 H), 2.59-2.50 (m, 2 H), 1.55 (*app* dt, 1 H, *J* = 8.0, 1.8 Hz), 1.47 (d, 1 H, *J* = 8.0 Hz).



2,3-Bijuglone-dimethylether (168).[93] A solution of phenyl iodide **156** (44.4 mg, 0.125 mmol) in distilled pyridine (2.0 mL) was added to a Schlenk flask already containing naphthol **155** (15.0 mg, 0.0734 mmol) and Cu_2O (12.0 mg, 0.0838 mmol). Both **155** and the Cu_2O were pumped on under full vacuum for 20 min prior to the introduction of **156**. The mixture was degassed immediately following the addition, and then heated at reflux for 15 h. The pyridine was removed *in vacuo* and the crude residue was loaded directly onto a column. Chromatography on SiO_2 (CH_2Cl_2/EtOAc, 9:1) provided dimer **168** as a bright blue solid: ^{1}H NMR δ 8.40 (s, 1 H), 7.88 (d, 1 H, *J* = 8.0 Hz), 7.42 (t, 1 H, *J* = 8.0 Hz), 7.18 (d, 1 H, *J* = 8.2 Hz), 4.07 (s, 3 H), 3.94 (s, 3 H); ^{13}C NMR δ 188.8, 159.4, 156.3, 133.9, 130.4, 129.8, 121.2, 120.5, 117.5, 104.0, 57.0, 56.3; MS (EI) *m/z* (rel intensity) 404 (M^+, 100), 389 (94), 388 (84), 373 (81).



(1*RS,4*RS**,4a*RS**,9a*RS**)-1,4,4a,9a-Tetrahydro-5-hydroxy-1,4-methano-9,10-anthraquinone (169)**.[94] A suspension of juglone **144** (555.7 mg, 3.19 mmol) in toluene (3.0 mL) was treated with excess cyclopentadiene (1.20 mL, 1.18 g, 8.95 mmol) at room temperature. The reaction mixture became more homogeneous during the course of the diene addition. The solution was heated at 100 °C for 1.5 h. Then, the solvent and excess reagents (*i.e.* cyclopentadiene) were removed *in vacuo*. Upon recrystallization from EtOH, the orange residue was transformed into a tan solid. This slightly discolored batch of material was not submitted to additional purification. Furthermore, the resultant mother liquor from the first recrystallization was not submitted to a second recrystallization. Thus, the first crop only yielded 376.7 mg (49%) of the desired cycloadduct **169**: ^{1}H NMR δ 12.6 (s, 1 H), 7.64-7.54 (m, 2 H), 7.21 (dd, 1 H, J = 7.9, 1.5 Hz), 6.03 (d, 2 H, J = 1.6 Hz), 3.71-3.67 (m, 2 H), 3.49 (d of AB, 1 H, J = 8.8, 3.8 Hz), 3.41 (d of AB, 1 H, J = 8.8, 3.9 Hz), 1.61-1.53 (m, 2 H).



(5*RS,8*RS**,8a*RS**,9*RS**,10*RS**,10a*RS**)-1,9,10-Trihydroxy-5,8,8a,9,10,10a-hexahydro-5,8-methanoanthracene (170, crude)**.[100] To a –78 °C suspension of $NaBH_4$ (52.2 mg, 1.38 mmol) in THF (13.8 mL) was added dropwise a solution of **169** (165.8 mg, 0.6905 mmol) in THF (2.8 mL). Then, MeOH (4.1 mL) was added. The reaction mixture was stirred at

–78 °C for 3 h and 10 min, gradually warmed to 0 °C over the span of the next 50 min, and quenched with saturated aqueous NH_4Cl (2.1 mL) at 0 °C. The resulting mixture was concentrated *in vacuo*. Finally, the resulting residue was diluted with water and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Crude diol **170** was used for the next step without purification: ^{1}H NMR δ (CD_3OD, characteristic signals) 6.99 (t, 1 H, J = 7.8 Hz), 6.74 (d, 1 H, J = 7.5 Hz), 6.52 (d, 1 H, J = 7.9 Hz), 5.44-5.31 (m, 1 H), 5.25-5.13 (m, 3 H), 4.70-4.56 (m, 1 H), 2.97 (*br* s, 1 H), 2.90 (*br* s, 1 H), 2.77 (*br* s, 2 H); MS (EI) *m/z* (rel intensity) 244 (M^+, 10), 226 (16), 208 (21), 160 (100), 144 (21), 131 (65), 115 (28), 91 (44); HRMS (EI) calcd for $C_{15}H_{16}O_3$ 244.1099, found 244.1106.

2. The Total Synthesis and Structure Validation of Bistramide C

2.1. Introduction

2.1.1. Historical and Biological Background of the Bistramides

The bistramides (A (**1**), B (**2**), C (**3**), D (**4**) and K (**5**)) constitute a novel class of bioactive cyclic polyethers and were isolated from the marine ascidian *Lissoclinum bistratum*.[101,102] Bistramides A and C were isolated near the Ua islet, New Caledonia in 1988 by Gouiffès, *et al*.[101] The Gouiffès research group is also credited with providing a preliminary biological evaluation of bistramide A (**1**, Figure 20). Their studies led to the determination that **1** exhibited cytotoxicity towards P388 murine leukemia, KB and human epithelial cell lines with IC_{50}'s ranging from 0.01 to 0.1 μg/mL.[103] Furthermore, it was determined (rather recently) that bistramide A (**1**) induced atypical differentiation in HL-60 and NSCLC-N6 cells in addition to growth arrest at G_2/M in the former cell line.[104] The parent compound (**1**) also possessed the ability to enhance the phospholipid-dependent activity of type II protein kinase C.[105]

The Gouiffès group employed modern two-dimensional ^1H and ^{13}C NMR techniques for the structure elucidation of bistramide A (**1**). For example, ^1H-^1H and ^1H-^{13}C COSY in concert with relayed ^1H-^1H -^{13}C COSY and ^1H -^{13}C COLOC experiments were used to determine critical bond connections. The relay ^1H-^1H -^{13}C transfer provided useful correlations (^1H-^{13}C) from distant protons via H-H couplings. Based on the significant correlations obtained from their NMR analyses, the French research group suggested a completely linear array for the structure of bistramide A. They were unable to deduce a definitive 3-D structure of the target molecule due to the inherent shortcomings of the existing 2-D NMR technology.[101]

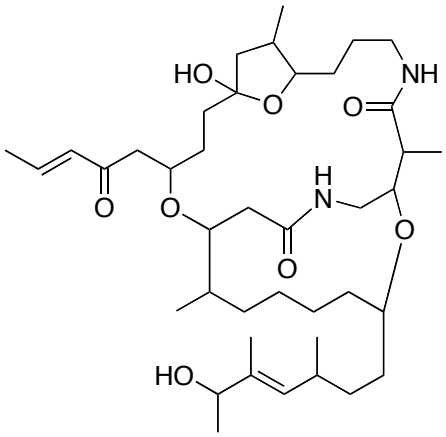


Figure 19. Original Proposal for the Structure of Bistramide A.

Shortly thereafter, the Hawkins group from the University of Queensland in Australia isolated two allegedly new macrocyclic ethers from the aplousobranch ascidian *Lissoclinum bistratum*.[106] They determined the structures of the two compounds (bistratene A and bistratene B) through the use of detailed ^{1}H and ^{13}C spectral analyses and 2-D COSY 45 and ^{1}H-^{13}C shift correlation experiments. Bistratene B is simply an acetylated derivative of bistratene A. The acetyl group resides on the secondary allylic alcohol function. Their 2-D NMR experiments (*i.e.* COSY 90, COSY 45, HETCOR and long-range ^{1}H-^{13}C correlations) were entirely consistent with the linear structure presented by Gouiffès, *et al.* two years prior. Thus, it soon became apparent that bistratene A was indeed identical to bistramide A (**1**). The Hawkins research team claimed that their consideration of three key long-range ^{1}H-^{13}C correlations allowed them to propose a three-dimensional structure for the natural product in question (Figure 19). The so-called key coupling information was obtained from a standard ^{1}H-^{13}C shift correlation pulse sequence with delay times optimized for long-range couplings as opposed to a COLOC pulse sequence.[106]

Hawkins, *et al.* also probed the cytotoxicity of the bistratenes towards the following two human cell lines, MR5CV1 fibroblasts and T24 bladder carcinoma cells. They were pleased to

discover that both bistratenes A and B possessed low IC_{50} values, 0.07 μg/mL and 0.09 μg/mL, respectively.[106] In fact, the new isolates clearly rivaled the highly cytotoxic bryostatins.[107] Unfortunately, neither compound displayed preferential cytotoxicity towards the tumor cell line T24. Other preliminary biological studies (employing flow cytometry) revealed that the bistratenes were capable of killing cells at all phases of the cell cycle. The results from the Hawkins research group suggested that the bistratenes acted at the cell membrane level as opposed to the protein level via the inhibition of protein or nucleic acid synthesis.[106]

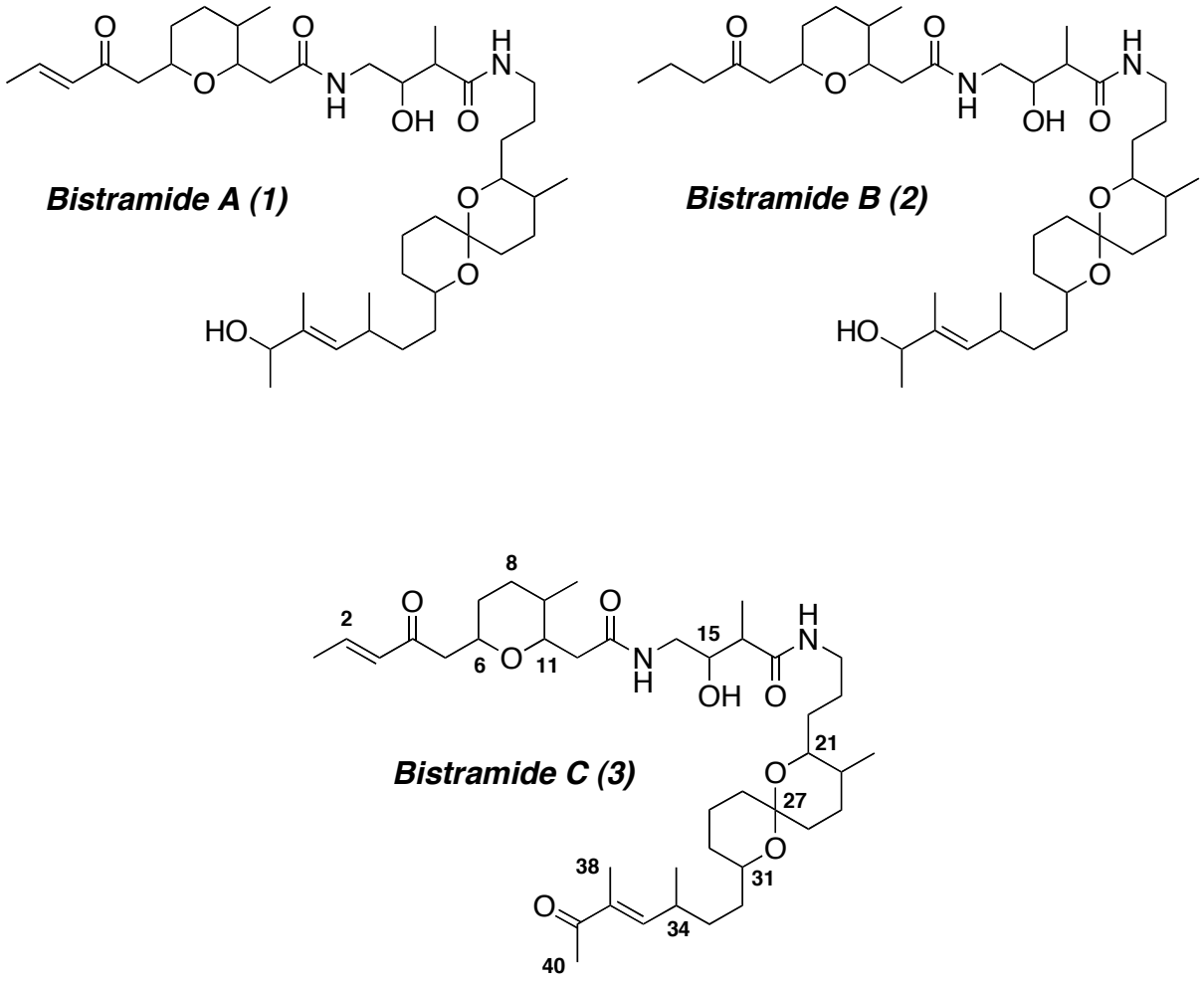


Figure 20. Structures of Bistramides A-C.

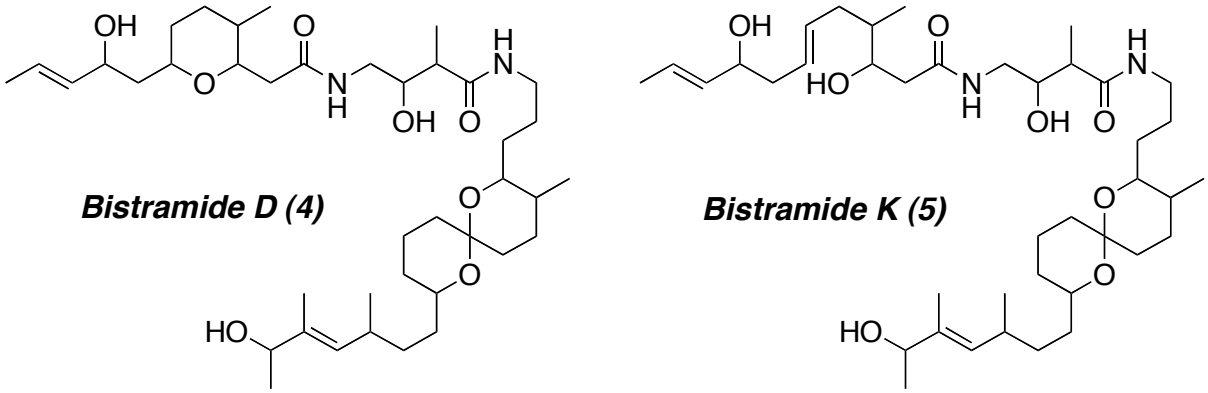


Figure 21. Structures of Bistramides D and K.

In 1992, the Ireland group at the University of Utah revised the macrocyclic structure proposed by Hawkins *et al.* for bistramide A (Figure 19), also known as bistratene A. The compound that they isolated from a Fijian *Lissoclinum* species possessed the same molecular formula and similar spectral data to those reported previously for the natural product. It soon became apparent that severe overlap in the ^{1}H NMR spectrum precluded the definitive structural assignment of bistramide A based exclusively upon ^{1}H correlation methods. Consequently, Ireland *et al*. used a 2-D INADEQUATE experiment (optimized for sp^3-sp^3 couplings) for the elucidation of the carbon backbone. The resulting spectral data were then analyzed by a new automated procedure. The above analysis, in conjunction with other 2-D methods (*i.e.* HMBC, COSY, INAPT) allowed for the unambiguous structural determination of bistramide A. The modified structure (**1**) is depicted in Figure 20. As an added bonus, the biological profile of **1** was expanded upon. Ireland's studies revealed that bistramide A (**1**) displayed *in vitro* cytotoxicity against the human colon tumor HCT116 and murine leukemia L1210 cell lines with an IC_{50} of 0.1 μg/mL.[108]

In 1994, Biard *et al*. reported the isolation, characterization and pharmacological properties of four new bistramides, B-D (**2**-**4**) and K (**5**), all of which are depicted in Figures 20 and 21.[102] Unfortunately, the relative and absolute configurations were not determined at this time. Six tumor cell lines were used to test the *in vitro* cytotoxicity of compounds **1**-**5**: KB, P388, P388/dox., B16, HT29 and NSCLC-N6. The differential cytotoxicity against the P388 and P388/dox. cell lines was especially pronounced for bistramide D (**4)** and bistramide K (**5)**. Cytofluorimetric analysis was used to probe the influence of the bistramides on the cell cycle. Following 48 hours of growth in the presence of **5**, a complete block of the NSCLC-N6 cells was observed. The remaining compounds (**1**-**4**) displayed a significant decrease in the S phase and partial block in the G_1 phase of the cell cycle. Compounds **4** and **5** were tested for their *in vivo* antitumor activity in nude mice engrafted sc with NSCLC-N6. After a 30 day period, T/C values of 53% and 49% were found for **4** and **5**, respectively. Bistramide A (**1**) was determined to be too toxic for the accurate determination of antitumor activity (*i.e.* T/C value of 118%).[102]

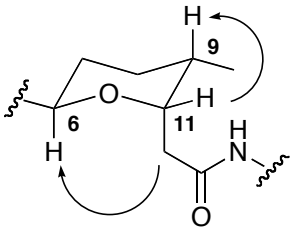
Despite its clarification of the constitution of the natural product, Ireland's structural reassignment[108] shed no light on the relative or absolute configuration of the bistramides, which possess either ten or eleven undefined stereogenic carbons. As a direct consequence, the number of possible diastereomeric and enantiomeric target structures exceeds 1000 in all cases and 2000 in some. Despite the clear dearth of structural information, the biological profile of the bistramides renders them attractive synthetic targets. Preliminary biological studies indicate that compounds **1**-**5** possess potent cytotoxic, antiproliferative[109,110,111] and neurotoxic[112,113,103] activities. Consequently, from a pharmacological standpoint, they offer great promise as chemotherapeutic agents. The high *in vitro* cytotoxic activity coupled to the diminished *in vivo*

activity make the bistramides particularly well suited for the treatment of slowly evolving tumors, such as non-small cell pulmonary carcinoma.[102]

In order to fully probe the biological activity of these marine natural products and initiate SAR studies, a complete structure assignment was required. Thus, several years ago, we began our quest to elucidate the structure and (subsequently) complete the total synthesis of bistramide C (**3**). Our combined use of chiroptical tools, organic synthesis and NMR spectroscopy led to an early prediction for the relative and absolute configuration of (+)-bistramide C (**3**) in addition to a highly convergent total synthesis of a stereoisomer of the natural product (**6**).[114]

2.1.2. Determination of the Relative Stereochemistry

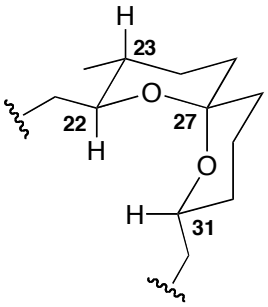
Other researchers were also working to gain information about the structure of the natural product target. Solladie's 2-D 500 MHz ^{1}H NMR analyses of a bistramide D derivative (bisacetylated at C(15) and C(39)) established the relative configuration at carbons 6, 9, 11 and 22, 23, 27, 31. The NOESY spectrum also revealed a strong long-range correlation between protons H(6) and H(12); thus, providing evidence for a *trans*-substituted pyran. In addition, a *cis*-relationship between H(9) and H(11) was based on a clear long-range correlation between these two nuclei. Solladie's spectroscopic studies suggested two possible relative configurations for the pyran moiety, (6*R*,9*S*,11*S*) or (6*S*,9*R*,11*R*).[115]



(6*R*,9*S*,11*S*)

Figure 22. Possible Relative Configuration for the Pyran Moiety.

Further NOESY analyses indicated a very clear correlation between H(22) and H(31), suggesting an axial orientation between these two hydrogens in the spiroketal portion of the molecule. In addition, H(22) appeared to be in very close proximity to the neighboring methyl substituent, C(24). The lack of a correlation between H(22) and H(23) added further credence to the possibility of an *anti*-relationship or *trans*-configuration. The two possible relative configurations for the spiroketal moiety were (22*S*,23*R*,27*R*,31*R*) or (22*R*,23*S*,27*S*,31*S*).[115]



(22*S*,23*R*,27*R*,31*R*)

Figure 23. Possible Relative Configuration for the Spiroketal Moiety.

2.2. Total Synthesis of a Bistramide C Stereoisomer

The structural assignments made by Solladie *et al.*[115] were confirmed by NMR analyses of a natural product sample by Dr. Seiji Yoshimura in our group and therefore, the total number of possible stereostructures of bistramide C (**3**, Figure 20) could be significantly reduced. The absolute configuration for the two major fragments (Figures 22 and 23) had to be selected randomly,[114] however. Due to the fact that we also lacked sufficient information about the absolute configuration of the remote stereocenter on the spiroketal tether, the stereochemistry at C(34) had to be selected at random as well. We initiated our studies with the (*R*)-configured center. Dr. Yoshimura also determined that the *anti*-stereochemistry at C(15) and C(16) was more likely than the *syn*-configuration by the comparison of both stereoisomers of an *N*-acetamide methyl amide derivative of the β-hydroxy-γ-amino acid segment. Our synthetic efforts finally culminated in the total synthesis of the (6*S*,9*R*,11*R*,15*S*,16*R*,22*R*,23*S*,27*S*,31*S*,34*R*)-stereoisomer of bistramide C (**6**, Figure 24).[114]

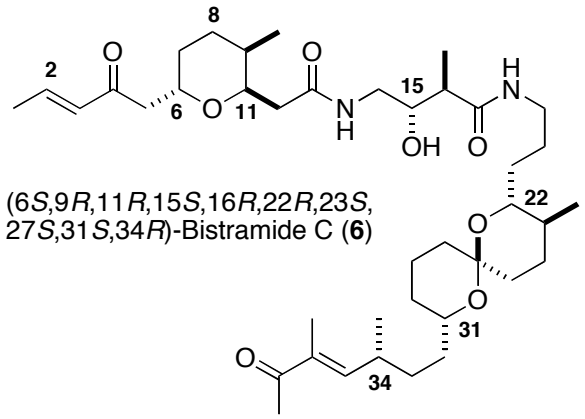
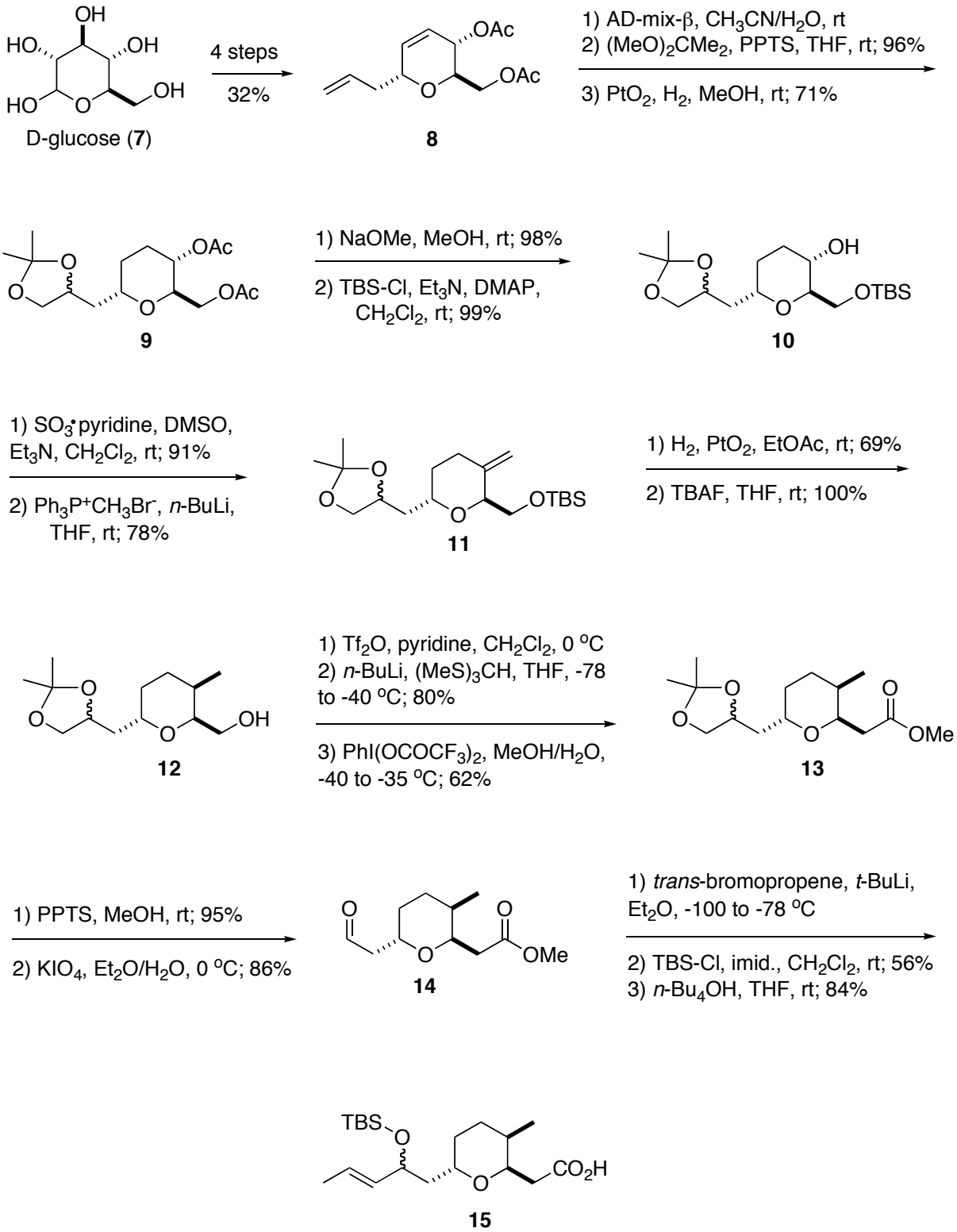


Figure 24. Stereoisomer of Bistramide C.

The two amide bonds were the two obvious points of disconnection for the retrosynthetic analysis of **6** (Figure 24). The synthesis of the left-hand fragment is depicted in Scheme 37. The

pyran acid **15** (Scheme 1) was accessed in 21 steps from (*D*)-glucose (**7)** in an overall yield of 2%. Conveniently, both the left-hand fragment and the spiroketal moiety were derived from **7**.[114]

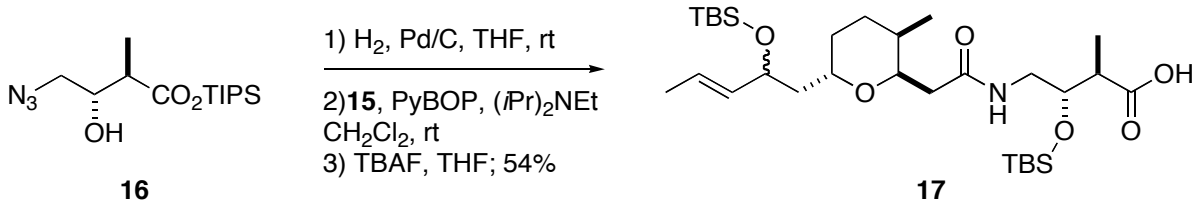


Scheme 37. Synthesis of Pyran Acid **15**.

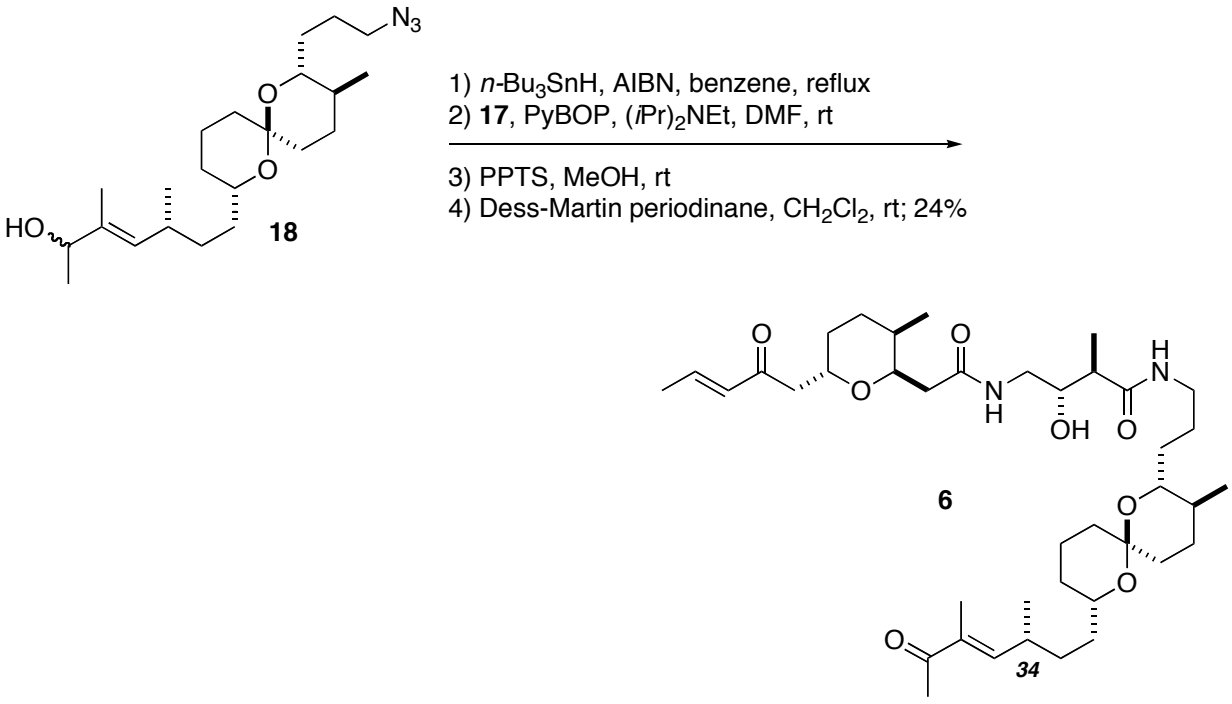
The synthesis of the pyran acid segment (**15**)[114] commenced with a chemoselective dihydroxylation of diene **8** with AD-mix β.[116,117] Following the protection of the resultant diol as an acetonide with 2,2-dimethoxypropane and catalytic acid, the olefin was reduced via standard catalytic hydrogenation conditions to provide diacetate **9** in a three-step yield of 68%. After the saponification of both esters with sodium methoxide in methanol, the primary alcohol was selectively protected as *tert*-butyldimethylsilyl ether **10** in high overall yield. The secondary hydroxyl group was transformed into the requisite β-oriented methyl ether via a three-step sequence. A Parikh-Doering oxidation[118] followed by a Wittig olefination with methyltriphenylphosphonium bromide provided exocyclic olefin **11** in 71% yield. Then, a stereoselective hydrogenation reaction delivered hydrogen from the more sterically accessible α-face. Deprotection of the silyl ether under basic fluoride conditions set the stage for the preparation of the key trithioorthoester. First, treatment of **12** with triflic anhydride delivered the unstable triflate intermediate. Subsequent to that, it was displaced with the *in situ* generated anion of tris(methylthio)methane[119,120] in a yield of 80%. The resultant trithioorthoester was converted to methyl ester **13** via the Stork protocol[121] in 62% yield (three-step yield of 50%). The aldehyde moiety of **14** was revealed upon deprotection of the acetonide and oxidative cleavage of the resultant diol with potassium periodate.[122] Treatment of **14** with *trans*-propenyl lithium[123] at –100 °C resulted in the exclusive addition of the organolithium reagent to the aldehyde function. The secondary allylic alcohol of the chain-extended product was protected as a silyl ether prior to the unmasking of the carboxylic acid **15** via saponification.

The final coupling strategy featured a PyBOP-mediated[124] coupling between pyran acid **15** and azido ester **16** (Scheme 38).[114] The short linker **16** was prepared in six steps and 17% overall yield from the chiral pool precursor, (*D*)-malic acid. As depicted in Scheme 39, similar

coupling conditions were used to link acid **17** with the amine generated from a tributyltinhydride reduction[125,126] of spiroketal azide **18**. The resultant bisamide was transformed into the desired target molecule **6** in just two additional steps.[114]



Scheme 38. First Amide Bond Construction Towards the Synthesis of **6**.



Scheme 39. Completion of the Total Synthesis of the Bistramide C Stereoisomer **6**.

2.3. Comparison of 6 to the Natural Product

The spectroscopic data (^{1}H and ^{13}C) for **6**[114] were in close agreement to those[102] published for the natural product, with the exception of the chemical shift at C(34) (Tables 10 and 11). It appeared as though the ^{1}H and ^{13}C shifts for the synthetic material correlated quite well to those of natural bistramide, specifically for C(1)-C(18). Thus, we reasoned that the relative configuration of the pyran, γ-amino acid-coupled fragment **17** was indeed correct. Such an important conclusion led to the reduction in the total number of stereoisomeric target structures from 32 to 8. In addition, the total synthesis of **6** provided key fragments for a chiroptical analysis in accordance with van't Hoff's principle of optical superposition.[127,128,129,130,131] We have successfully utilized this methodology in the past to accurately assign the absolute configuration of natural products.[127,129]

Table 10. Comparison of ^{1}H NMR Data for Natural Bistramide C vs. the Synthetic Bistramide C Stereoisomer **6** ($CDCl_3$).

	Natural bistramide C (600 MHz)[102]			Synthetic stereoisomer **6** (600 MHz)		
Hydrogen #	δ [ppm]	mult	J [Hz]	δ [ppm]	mult	J [Hz]
1-H	1.90	dd	6.8, 1.5	1.92	dd	6.8, 1.4
2-H	6.88	dq	15.9, 6.8	6.91	dq	15.7, 6.9
3-H	6.12	dd	15.9, 1.7	6.13	dd	15.8, 1.5
4-H	-	-	-	-	-	-
5-Ha	2.92	dd	16.9, 8.8	2.91	dd	17.0, 9.0
5-Hb	2.58	dd	16.9, 3.1	2.53	dd	17.0, 2.8
6-H	4.17	m		4.20	t	9.6
7-Ha	1.68	m		N/A	-	
7-Hb	1.37	m		N/A	-	
8-Ha	1.62	m		N/A	-	
8-Hb	1.33	m		N/A	-	
9-H	1.90	m		N/A	-	
10-H	0.82	d	7.1	0.86	d	7.0
11-H	4.06	dd	11.8, 4.8	4.07	dd	11.2, 4.9
12-Ha	2.73	dd	15.4, 11.7	2.76	dd	15.2, 11.7
12-Hb	2.15	m		2.14	d	15.2
13-H	-	-	-	-	-	-
14-Ha	3.48	m		3.50	m	
14-Hb	3.22	m		3.24	dt	13.8, 5.8
15-H	3.69	m		3.73	m	
16-H	2.38	m		2.39	m	
17-H	1.22	d	7.1	1.27	d	7.6
18-H	-	-	-	-	-	-
19-H	3.30	m		3.30	m	

20-Ha	1.83	m		N/A	-	
20-Hb	1.55	m		N/A	-	
21-Ha	1.74	m		N/A	-	
21-Hb	1.36	m		N/A	-	
22-H	3.15	dt	2.2, 9.4	3.14	dt	2.0, 9.7
23-H	1.26	m		N/A	-	
24-H	0.77	d	6.3	0.82	d	6.5
25-Ha	1.58	m		N/A	-	
25-Hb	1.44	m		N/A	-	
26-Ha	1.58	m		N/A	-	
26-Hb	1.42	m		N/A	-	
27-H	-	-	-	-	-	-
28-Ha	1.52	m		N/A	-	
28-Hb	1.38	m		N/A	-	
29-Ha	1.83	m		N/A	-	
29-Hb	1.56	m		N/A	-	
30-Ha	1.40	m		N/A	-	
30-Hb	1.14	m		N/A	-	
31-H	3.44	m		3.43	m	
32-Ha	1.34	m		N/A	-	
32-Hb	1.34	m		N/A	-	
33-Ha	1.49	m		N/A	-	
33-Hb	1.55	m		N/A	-	
34-H	2.58	m		2.60	m	
35-H	1.01	d	7.1	1.05	d	6.7
36-H	6.37	dq	9.8, 1.2	6.40	d	9.8
37-H	-	-	-	-	-	-
38-H	1.73	fd	1.2	1.78	*br* d	

39-H	-	-	-	-	-	-
40-H	2.28	s		2.32	s	
NH, 13/14	7.31	*br* t	5.9	7.32	*br* t	5.5
NH, 18/19	6.97	*br* t	5.7	6.96	*br* t	5.5
OH	4.59	*br* s		4.61	*br* s	

Table 11. Comparison of ^{13}C NMR Data for Natural Bistramide C vs. the Synthetic Bistramide C Stereoisomer **6** ($CDCl_3$).

	Natural bistramide C (100 MHz)[102]	Synthetic **6** (151 MHz)	$\Delta\delta_{nat.-synth.}$
Carbon #	δ [ppm]	δ [ppm]	Δδ [ppm]
1	18.4	18.6	-0.2
2	144.2	144.8	-0.6
3	132.2	132.3	-0.1
4	198.4	199.2	-0.8
5	45.4	45.4	0.00
6	64.9	64.9	0.00
7	30.8	31.0	-0.2
8	26.6	26.7	-0.1
9	33.0	33.5	-0.5
10	17.1	17.4	-0.3
11	74.8	75.0	-0.2
12	32.5	32.5	0.0
13	173.4	173.7	-0.3
14	44.7	44.9	-0.2
15	73.8	74.0	-0.2
16	43.4	43.5	-0.1
17	15.6	15.7	-0.1
18	175.1	175.4	-0.3
19	39.6	39.7	-0.1
20	29.9	29.9	0.00
21	30.6	30.7	-0.1
22	74.3	74.5	-0.2
23	34.9	35.1	-0.2
24	18.1	18.2	-0.1

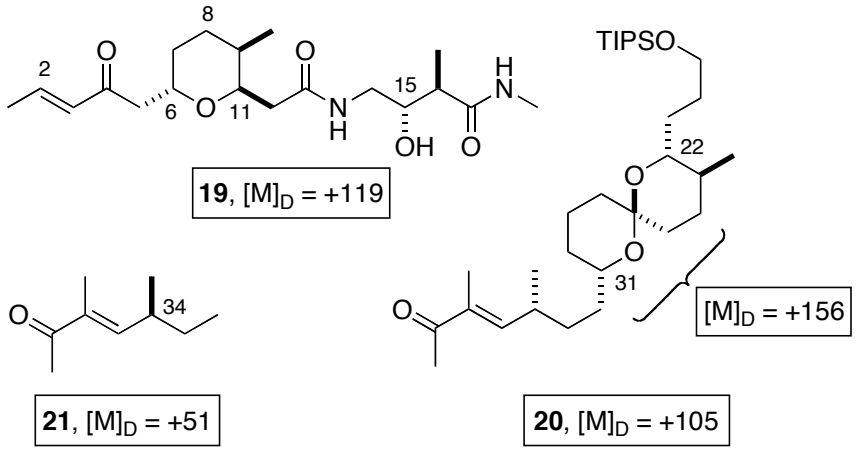
25	28.0	28.1	-0.1
26	36.2	36.3	-0.1
27	95.2	95.7	-0.5
28	35.5	35.6	-0.1
29	19.2	19.3	-0.1
30	31.4	31.5	-0.1
31	68.9	69.6	-0.7
32	34.8	34.6	+0.2
33	33.4	33.5	-0.1
34	**31.8**	**34.2**	**-2.4**
35	20.1	20.4	-0.3
36	149.3	149.6	-0.3
37	136.3	136.6	-0.3
38	11.5	11.6	-0.1
39	200.2	200.6	-0.4
40	25.5	25.8	-0.3

Average $\Delta\delta[\text{ppm}]_{\text{nat.-synth.}} = 0.28$

2.4. Chiroptical Analyses

Experimental molar rotations ($[M]_D$)were measured for two synthetic fragments, **19** and **20**, as shown in Figure 25.[114] The (*S*)-configuration at C(34) of the spiroketal moiety was taken into consideration through the use of (+)-normanicone (**21**)[132,133,134] in the $[M]_D$ summation process. The addition of the molar rotation value increments for the eight remaining stereoisomeric bistramides generated the following results: $[M]_D$ = -326, +326, -224, +224, -88, +88, -14, +14 (Figure 25). The predicted value of $[M]_D$ = +224 for the synthetic material matched the experimentally determined value of $[M]_D$ = +239 to an acceptable degree of

accuracy. The $[M]_D$ of the natural product, $[M]_D$ = +70,[102] was in relatively close agreement with one of the molar rotation values obtained from the van't Hoff analysis,[127,128,131] $[M]_D$ = +88, for stereostructure **22** with the configuration (6*R*,9*S*,11*S*,15*R*,16*S*,22*R*,23*S*,27*S*,31*S*,34*S*). The $[M]_D$ for **22** was calculated by adding the $[M]_D$ corresponding to the enantiomer of **19** to both the $[M]_D$ of the spiroketal moiety and the $[M]_D$ of **21**, to account for the (*S*)-configured stereocenter at C(34). The following summation, -119 + 156 + 51, delivered a $[M]_D$ of +88. Gratifyingly, the revised structure also addresses the stereochemical discrepancy at C(34) observed in the NMR analyses of **6**.[114] A recent (2004) total synthesis of bistramide A by the Kozmin research group[135] confirmed our stereochemical prediction for the parent structure!



Configuration, Van't Hoff Sum of $[M]_D$ Increments

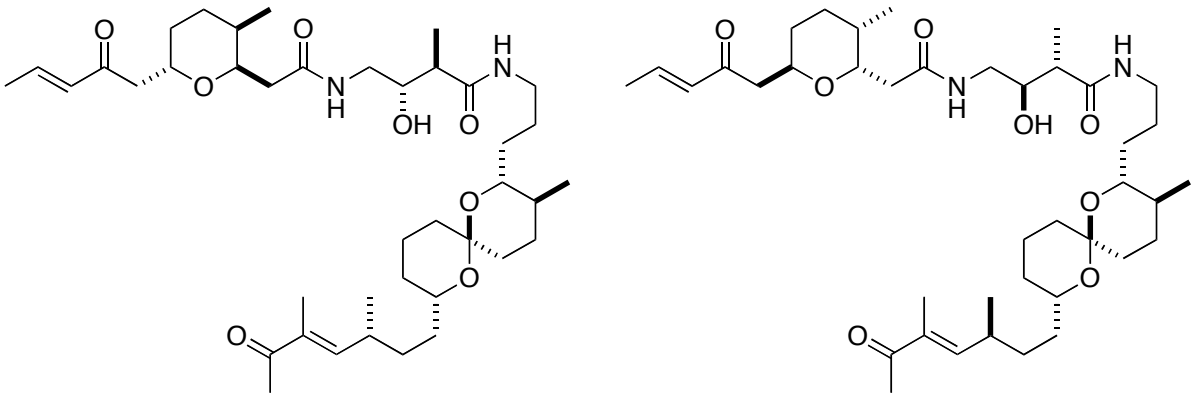
(6*S*,9*R*,11*R*,15*S*,16*R*,22*R*,23*S*,27*S*,31*S*,34*R*), $[M]_D$ = +224
(6*S*,9*R*,11*R*,15*S*,16*R*,22*S*,23*R*,27*R*,31*R*,34*R*), $[M]_D$ = -88
(6*S*,9*R*,11*R*,15*S*,16*R*,22*S*,23*R*,27*R*,31*R*,34*S*), $[M]_D$ = +14
(6*S*,9*R*,11*R*,15*S*,16*R*,22*R*,23*S*,27*S*,31*S*,34*S*), $[M]_D$ = +326
(6*R*,9*S*,11*S*,15*R*,16*S*,22*S*,23*R*,27*R*,31*R*,34*S*), $[M]_D$ = -224
(6*R*,9*S*,11*S*,15*R*,16*S*,22*R*,23*S*,27*S*,31*S*,34*S*), $[M]_D$ = +88
(6*R*,9*S*,11*S*,15*R*,16*S*,22*R*,23*S*,27*S*,31*S*,34*R*), $[M]_D$ = -14
(6*R*,9*S*,11*S*,15*R*,16*S*,22*S*,23*R*,27*R*,31*R*,34*R*), $[M]_D$ = -326

Figure 25. Determination of the Absolute Stereochemistry of Bistramide C Through the Application of Van't Hoff's Principle of Optical Superposition.

2.5. Retrosynthetic Analysis of the Revised Target

Clearly, the $[M]_D$ (experimentally determined or predicted via $[M]_D$ summation) for the bistramide C stereoisomer **6** did not correspond to that of the natural product. Due to the fact that a much better correlation existed between stereostructure **2 2** ((6*R*,9*S*,11*S*,15*R*,16*S*,22*R*,23*S*,27*S*,31*S*,34*S*), $[M]_D$ = +88) and the natural product, we embarked upon the synthesis of the revised target. The stereochemical differences between **6** and **22** are

illustrated in Figure 26. The major goal of this second-generation synthesis was to test the prediction of the van't Hoff analysis. A minor goal was to improve our first-generation synthetic approach.



(6*S*,9*R*,11*R*,15*S*,16*R*,22*R*,23*S*, 27*S*,31*S*,34*R*)-Bistramide C (**6**)

(6*R*,9*S*,11*S*,15*R*,16*S*,22*R*,23*S*, 27*S*,31*S*,34*S*)-Bistramide C (**22**)

Figure 26. Stereochemical Comparison Between **6** and **22**.

The new structure assignment for bistramide C necessitated major changes in our synthetic approach: preparation of the enantiomers of both the pyran building block and the γ-amino ester linker and installation of the methyl group at C(34) of the spiroketal moiety in the proper stereochemical sense.

Once again, the retrosynthetic analysis[136] of **22** (Figure 27) utilized the two amide bonds as disconnection points. The primary amine coupling partners were masked as azides which allowed for the facile assembly of **23**, **24**, and **25** via standard coupling practices with minimal protecting group manipulations. The spiroketal azide **24** was conveniently derived from (*D*)-glucose (**7**). (*L*)-malic acid (**27**) served as the chiral pool precursor for the γ-azido ester linker **25**. As indicated previously in the synthesis of the bistramide C stereoisomer **6**,[114] both the

trans-pyran acid **15** (Scheme 37) and the spiroketal segment **18** (Scheme 39) were derived from **7**. However, the structurally modified *trans*-pyran coupling partner (Figure 27)[136] was not to be derived from the commercially available, though cost-prohibitive (*L*)-glucose. A very different approach was implemented for the synthesis of **23**.

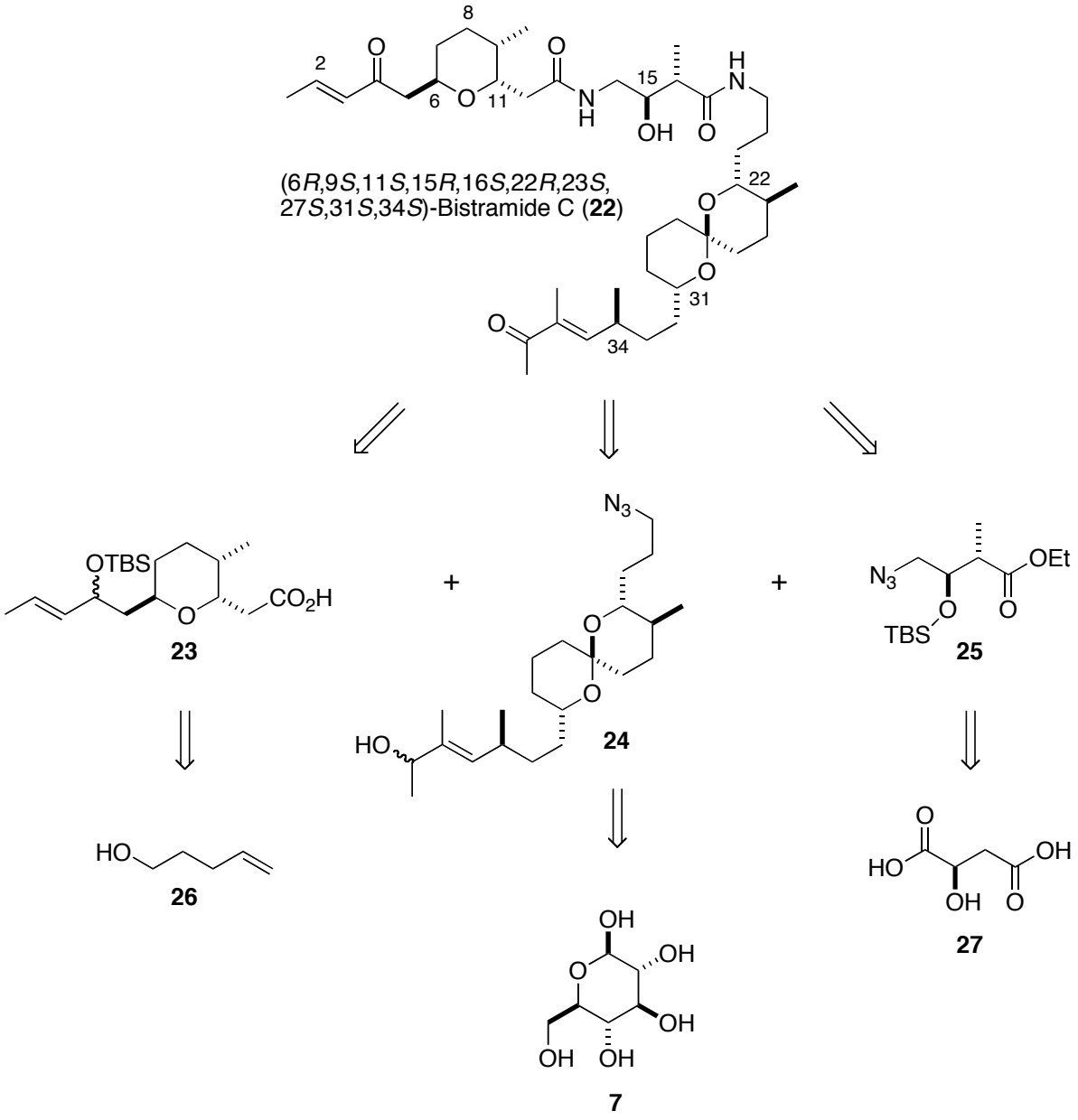


Figure 27. Retrosynthetic Analysis of the Revised Natural Product Target.

2.6. First Generation Approach to the Synthesis of the *trans*-Pyran Acid

2.6.1. Retrosynthetic Analysis

The first generation approach for the construction of the requisite *trans*-tetrahydropyran fragment **23** featured an acid-mediated, tandem acetonide deprotection/stereocontrolled intramolecular hetero-Michael[137] cyclization reaction. Several literature reports supported the feasibility of forming substituted tetrahydropyrans via hetero-Michael additions.[137] Few[137f] detailed a tandem process (*i.e.* deprotection of a protective group under acidic or basic conditions followed by an *in situ* intramolecular conjugate addition reaction), which was our initial objective. Furthermore, there were no examples of acyclic 1,3-diols employed as starting materials for tandem processes of this type. The additional challenge or level of complexity was further compounded by the fact that we needed the *trans*-pyran configuration. Unfortunately, the majority of the referenced studies depicted successful means of accessing the more thermodynamically favored products (*i.e.* 2,6-*cis*-derivatives).[137] It was very clear from the onset that we were attempting to execute an unusually difficult sequence of events.

Exposure of **29** to acidic media was thought to facilitate both the liberation of the 1,3-diol and the subsequent intramolecular conjugate addition. The secondary alcohol was envisioned to react preferentially with the enoate moiety to form a substituted pyran. The conjugate addition of the primary alcohol to the enoate appeared to be a less likely alternative due to the formation of the less than optimal eight-membered ring ether product. A retrosynthetic analysis of the pyran segment is depicted below in Figure 28. The key intermediate **29** was obtained from commercially available 4-penten-1-ol (**26**) in 11 steps and an overall yield of 35% (Schemes 40 and 42).

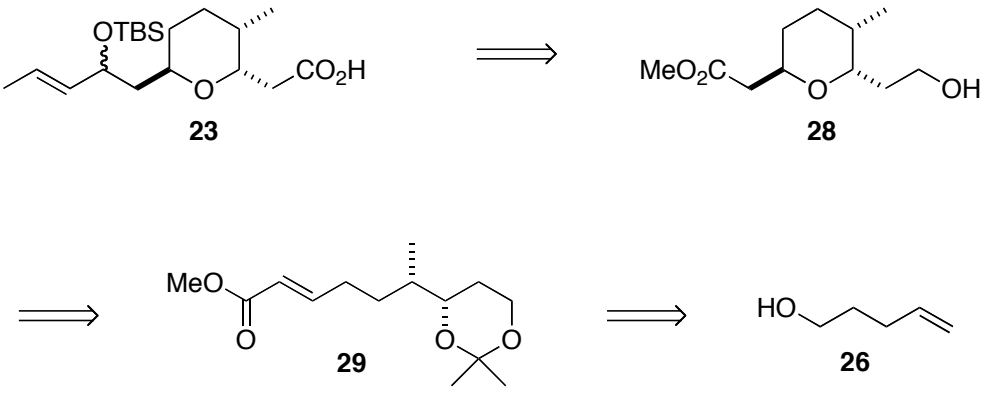


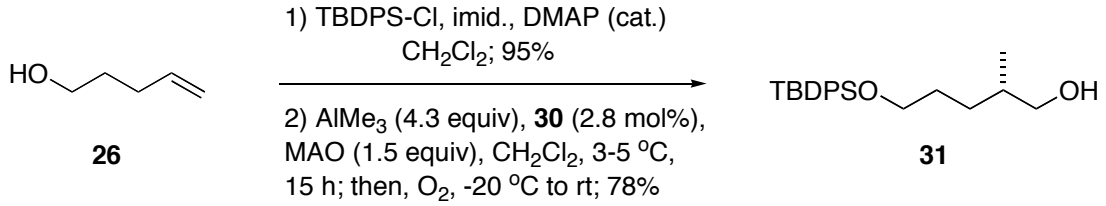
Figure 28. Retrosynthetic Analysis of the Pyran Fragment.

The benefits associated with this strategy were clear. The synthesis of **23** did not require the use of orthogonal protecting groups to differentiate between the two alcohols at positions 1 and 3 of the linear chain (**37**, Scheme 42). The tandem sequence also allowed for the rapid assembly of functionalized tetrahydropyrans in a highly stereoselective manner. Furthermore, the termini of the resulting pyran tethers (**28**, Figure 28) were easily differentiable, ultimately allowing for the selective manipulation of one terminus over the other.

2.6.2. Preparation of the (*E*)-Enoate

2.6.2.1. Key Methylalumination Reaction

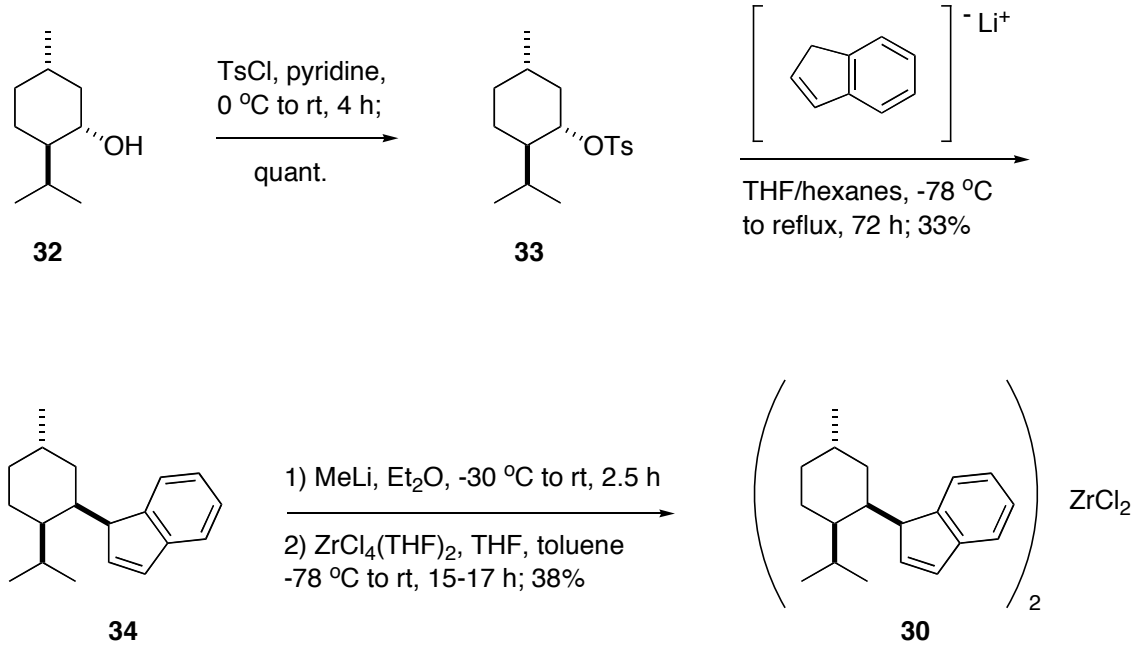
We initiated the synthesis of **23** with our MAO- or water-accelerated[138,139,140] zirconocene[141] **30**-catalyzed methylalumination[142] methodology (Scheme 40). The silyl-protected α-olefin was converted to the desired methylated product **31** in high yields (73-88%) and enantioselectivities (83-95%) using either MAO or water as the accelerant and catalyst loadings as low as 2.0 mol %. The conversion of terminal olefins to chiral branched hydrocarbons is a very powerful synthetic transformation.[138,139,142] Its synthetic utility has been clearly demonstrated in the preparation of a key segment in the total synthesis of the marine natural product pitiamide A.[143] Furthermore, the procedure is scalable and will be submitted to *Organic Synthesis* for publication. A summary of methylalumination results is compiled in Table 12.



Scheme 40. Erker's Chiral Zirconocene-catalyzed Methylalumination Methodology.

The catalyst, (+)-bis(1-neomenthylindenyl)zirconium dichloride (**30**),[141] was prepared in three steps from (+)-menthol (**32**, Scheme 41). Following the tosylation of menthol, **33** was added to a freshly prepared solution of indenyl lithium in THF at 0 °C. The nucleophilic

displacement of the secondary tosyl group required forcing conditions, *i.e.* reflux for 72 hours. The resultant ligand **34** was initially isolated as a black residue. Its transformation into a pristine white solid consisted of three discrete purification steps. First, the black residue was submitted to a Kugelrohr distillation (80 °C, ≤0.1 mm Hg) to remove all volatiles. The remaining brown residue was purified further via sublimation (100-102 °C, ≤0.1 mm Hg). The clear, colorless, oily sublimate was simply discarded. Next, the resultant yellow solid was submitted to chromatography on SiO_2 and the ligand was finally isolated in its pure form as a white solid. The technique for the purification of **30** was developed in our laboratories. It is not detailed in the Erker[141] literature reference.



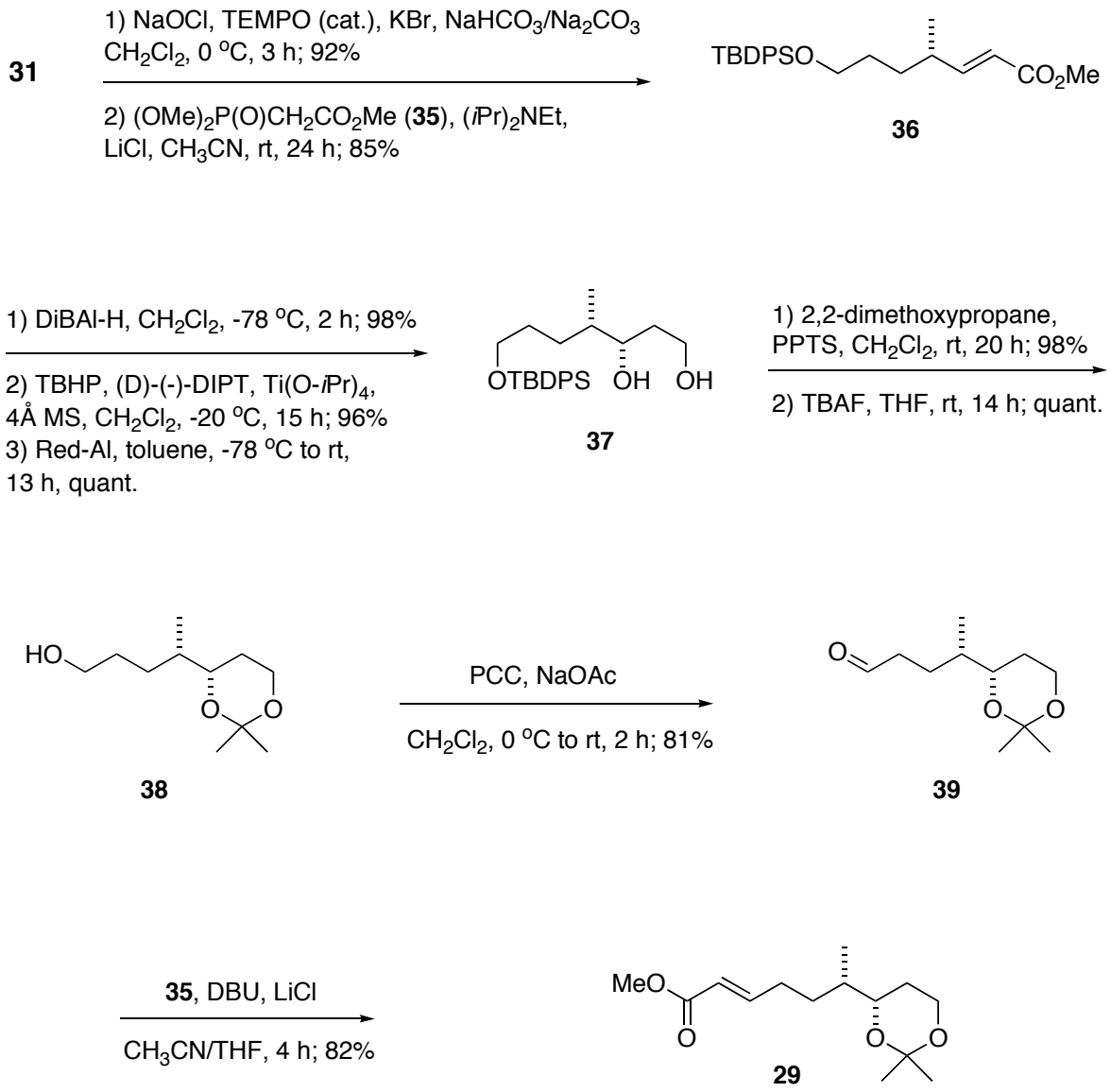
32 **33** **34** **30**

Scheme 41. Preparation of Erker's Catalyst **30**.

Table 12. Optimization of Methylalumination Reactions.

Entry	SM (quantity)	30 (mol%)	$AlMe_3$, equiv.	Additive, equiv.	Time [h]	Temp. [°C]	Isolated Yield [%]/ brsm
1	52 mg	7.0	neat, 4.2	H_2O, 1.0	20	-20	43/70
2	214 mg	7.0	neat, 4.2	H_2O, 1.0	40	-20	38/84
3	103 mg	10.0	neat, 6.0	H_2O, 1.0	14.5	-20	73
4	103 mg	5.0-7.0	neat, 5.5	H_2O, 1.0	13	-2 to 0	73
5	515 mg	5.0-6.0	neat, 4.3	MAO, 1.5	36	0	78
6	514 mg	6.0	neat, 4.3	MAO, 1.5	30	0	-
7	1.02 g	6.0	neat, 4.3	MAO, 1.5	20	0	-
8	413 mg	5.5	neat, 4.3	MAO, 4.0	20	0	81 (rxns 6-8)
9	595 mg	5.3	neat, 4.3	MAO, 4.4	15	0	63 (+ SM)
10	804 mg	5.5	neat, 4.3	MAO, 3.0	15	5	80
11	243 mg	2.5	neat, 4.3	MAO, 3.0	40	-10 to 5	35 (+ SM)
12	121 mg	7.2	neat, 4.3	H_2O, 1.0	42	5	>68
13	105 mg	7.0	neat, 4.2	H_2O, 1.0	20	5	71
14	226 mg	3.0	neat, 4.2	H_2O, 1.0	36	5	77
15	250 mg	3.0-5.0	sol'n, 4.2	H_2O, 1.0	20	0	74
16	798 mg	3.0	sol'n, 4.2	H_2O, 1.0	20	-5	53 (+ SM)
17	1.4 g	3.1	sol'n, 4.2	H_2O, 1.0	15	5	>77
18	581 mg	3.5-4.0	sol'n, 4.2	H_2O, 1.0	15	4 to 6	86
19	754 mg	3.5-4.0	sol'n, 4.2	H_2O, 1.0	20	0 to 5	
20	596 mg	5.0	neat, 4.3	MAO, 1.5	20	3 to 5	88
21	1.46 g	2.0	neat, 4.3	MAO, 1.5	15	5	87
22	230 mg	2.0	neat, 4.3	MAO, 1.5	15	1 to 5	86
23	2.02 g	2.8	neat, 4.3	MAO, 1.5	17	5	78

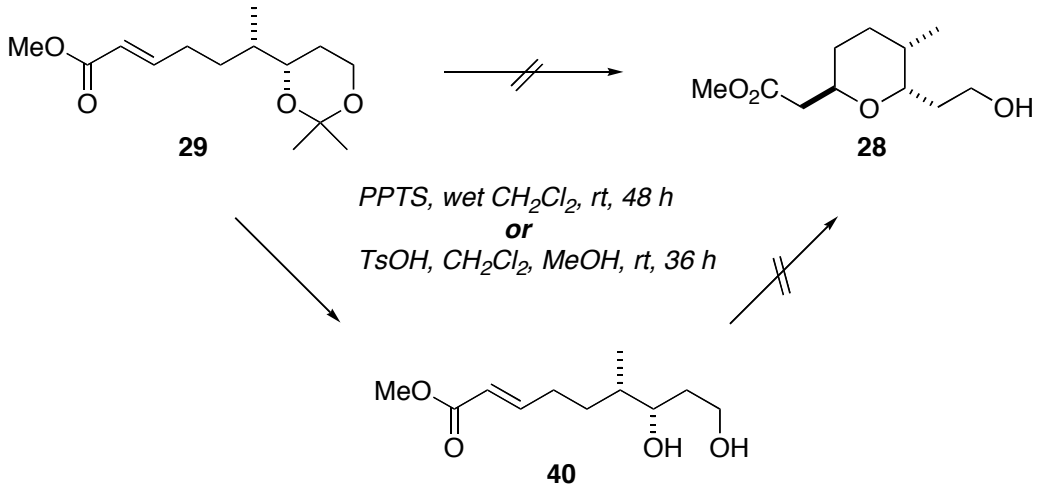
The enantiomerically enriched methyl-branched substrate **31** was oxidized under mild conditions with NaOCl and catalytic TEMPO.[144] The resultant aldehyde was submitted to a Masamune-Roush-modified Horner-Wadsworth-Emmons olefination[145] reaction with commercially available trimethylphosphonacetate **35**. Enoate **36** was ultimately isolated in a two-step yield of 78%. The acyclic chain was further elaborated into 1,3-diol **37** via a DiBAl-H reduction of **36** followed by a Sharpless Asymmetric Epoxidation[146] with (-)-diisopropyl D-tartrate. Initially, the reductive opening of the intermediate oxirane with Red-Al[147,148] in THF required a large excess of reducing agent and provided the desired product **37** in consistently low yields. A switch to toluene led to the quantitative conversion of starting epoxide to diol **37**. Following the protection of **37** as an acetonide, the chain was extended from the opposite terminus. Deprotection of the silyl ether with TBAF unmasked the primary alcohol **38**, which was then submitted to a sodium acetate-buffered PCC oxidation followed by a second Horner-Wadsworth-Emmons[145] reaction to provide the key (*E*)-enoate intermediate **29** in a two-step yield of 66%.



Scheme 42. Preparation of the Michael Acceptor.

2.6.3. Evaluation of the Michael Acceptor

Treatment of **29** with catalytic quantities of pyridinium *p*-toluenesulfonate (PPTS) in wet methylene chloride for 48 hours at room temperature led to a product mixture comprised mostly of diol **40** as opposed to the desired *trans*-pyran **28**. ^{1}H NMR analysis revealed the existence of some unreacted starting material, *i.e.* approximately 24% of the acetonide **29**. More forceful acidic conditions (*i.e. p*-toluenesulfonic acid, *p*-TsOH) led to the complete unmasking of the acetonide. Unfortunately, the reaction did not proceed beyond this point (Scheme 43).



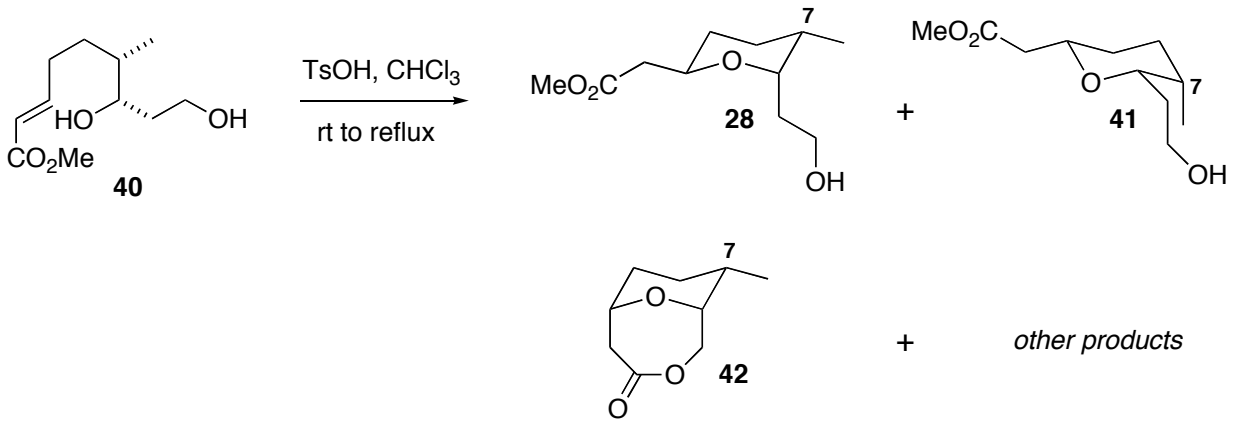
Scheme 43. Acid-mediated Acetonide Deprotection/Intramolecular Cyclization Attempts.

In an effort to further probe this reaction, diol **40** was resubmitted to protic acid conditions (*p*-TsOH, $CHCl_3$, room temperature to reflux). At first, **40** was simply dissolved in chloroform due to the possibility that additional acid was not necessary (and perhaps inhibitory) for the promotion of the cyclization. Unfortunately, a TLC analysis revealed little to no change after an extended time period. Consequently, the solution was treated with more *p*-TsOH and finally heated to reflux. Approximately 24 hours later, only 10% of the starting enoate **40** remained. Chromatographic purification revealed three major isolable batches of material (in very small

quantities due to an overall low mass balance). The material of highest R_f was mainly comprised of an approximate 1.4:1 mixture of compounds, based upon the integration of two methyl doublets in the ^{1}H NMR spectrum. No protons existed further downfield of 4.00 ppm. The olefin signals had been effectively "replaced" by a familiar AB spin system at *ca* 2.6 and 2.4 ppm, highly indicative of a mixture of *cis*-and *trans*-pyrans, **41** and **28** (Scheme 44). The methoxy singlet could easily be attributed to the desired *trans*-product or a minor compound based solely upon integration (as it related to the methyl substituent). The lack of a second methoxy signal to correlate in an analogous fashion to the major compound, in conjunction with the observable diagnostic signals, suggested the possible *in situ* lactonization of the expected *cis*-product **41** to give **42**. The exact structure of the product was not rigorously determined.

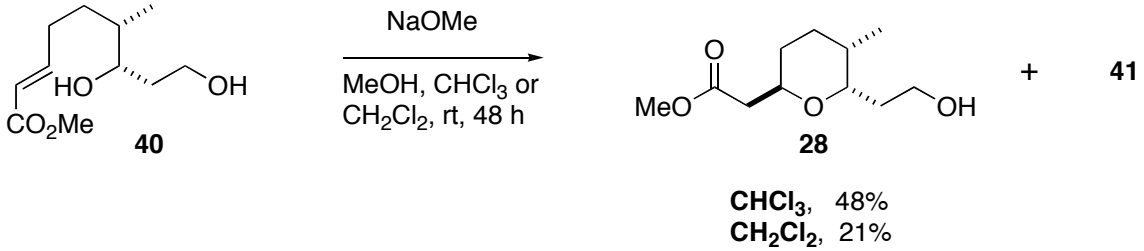
The moderately polar material (*i.e.* middle R_f spot) appeared to contain a mixture of pyrans as well. Based upon the integration of the methyl doublets, the mixture existed in a 5.5 :1 ratio. The fact that the minor methoxy singlet did not exactly correspond to the other diagnostic proton signals, specific to the minor component, spoke to the existence of a structurally closely-related third compound within the mix (*e.g.* non-lactonized *cis*-product or *cis*-pyran epimeric at C(7)). In other words, the methoxy signal appeared to integrate for more than it should, relative to the other familiar, diagnostic signals.

The most polar batch of material bore quite a bit in common with the other two batches. The only notable exception was the obvious lack of a methoxy singlet at *ca* 3.7 ppm. The protic acid conditions were clearly capable of transforming diol **40** into pyran products. However, the unacceptably low mass balance(s) spawned an investigation of other types of reaction conditions.



Scheme 44. Acid-promoted Ring Closure.

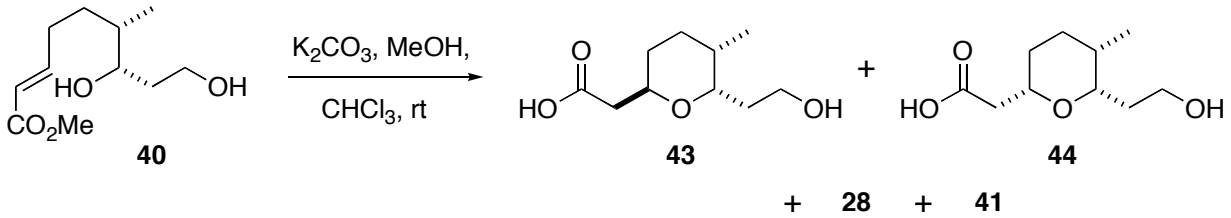
Treatment of **40** with excess sodium methoxide in a mixture of chloroform and methanol resulted in the isolation of a crude mixture of pyran products in greater than 85% yield (Scheme 45). A small percentage (8-10% of the total mass) could be attributed to unreacted starting material **40**, as indicated by ^{1}H NMR. Careful SiO_2 chromatography led to the successful separation of the *trans*-pyran **28** from the *cis*-product **41**. The desired isomer **28** was isolated in a yield of 48%. The other less polar batches of material consisted of varying distributions of *cis*-pyrans in a composite yield of 42%.



Scheme 45. Base-mediated Ring Closure.

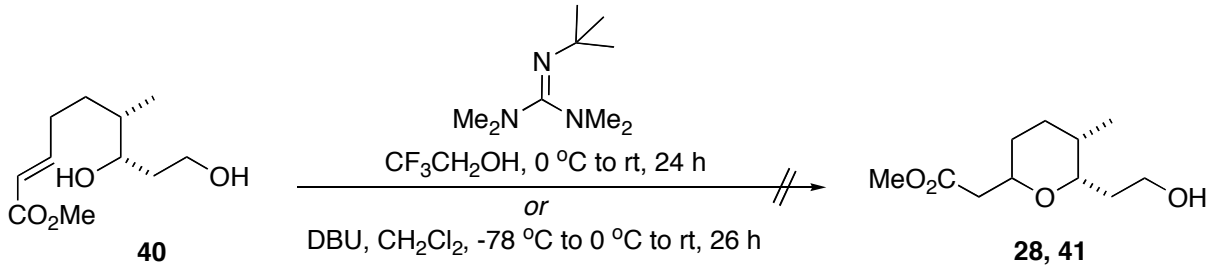
The minor products formed in the cyclization studies were most evident by the small sets of methyl doublets in the ^{1}H NMR spectrum and the accompanying methoxy signals further downfield. The minor contributors may have originated from the cyclization of a minor diastereomer, a direct outcome of the first transformation of the synthetic sequence (Scheme 40). Initial methylalumination[138,139,140] of the silyl protected 4-penten-1-ol proceeded in high yield, but with moderate selectivity; thus, allowing for an assortment of cyclization products to form from a slightly different precursor. The compounds that were not adequately characterized by a 1:1 ratio of methyl to methoxy proton signals, but were identical to the ^{1}H NMR of the *cis*-product in all other respects, suggested a *cis*-pyran derivative (*i.e.* lactone **42**, Scheme 44), as mentioned previously.

Exposure of enoate **40** to potassium carbonate,[137f,h] also in a mixture of chloroform and methanol, delivered a very low yield of both *cis* and *trans*-pyrans **41** and **28** following the initial isolation (Scheme 46). However, upon treatment of the aqueous phase with 10% hydrochloric acid and re-extraction with ethyl acetate, a mixture of carboxylic acids **43** and **44** was isolated. The structures were corroborated by ^{1}H and ^{13}C NMR data. The approximate 2:1 mixture of pyran acids with a clear preference for the *trans*-product sufficiently accounted for the missing mass balance.



Scheme 46. Synthesis of Pyran Acids and Esters.

A quest for enhanced reactivity and/or better selectivity for **28** led to the investigation of guanidine bases (Scheme 47) as viable alternatives to the inorganic bases previously evaluated. Prolonged exposure of **40** to Barton's base[149] in trifluoroethanol at room temperature resulted in the exclusive and quantitative recovery of the starting diol **40**. Starting material was also recovered from treatment of **40** with DBU in methylene chloride at –78 °C, 0 °C and room temperature.

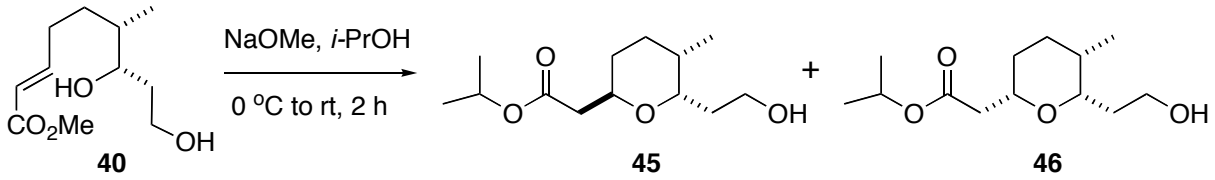


Scheme 47. Investigation of Guanidine Bases.

Finally, the sodium methoxide/anhydrous methanol reaction conditions were re-investigated (Scheme 45). The chloroform co-solvent was exchanged for methylene chloride due primarily to the potential for carbenes to form from chloroform/methanol mixtures and the possible deleterious outcome(s) that might arise on account of it. Unfortunately, the slightly modified reaction conditions led to the isolation of a crude residue in a mere 60% yield. Careful column chromatography afforded a clean batch of *cis*-pyran ester **41**, albeit in very low yield. A mixture (2-3:1) of *cis*-related products, inclusive of **41** as the major component, was isolated in 13% yield. A third batch of material existed as an approximate 1:1 mixture of **41** and another structurally-related compound X, which was not identified at this stage. As usual, the desired *trans*-pyran ester **28** was isolated in its characteristically pure form in a yield of 21%. We were more interested in the separation of the *cis*-pyran **41** from the *trans*-pyran **28**, which, quite

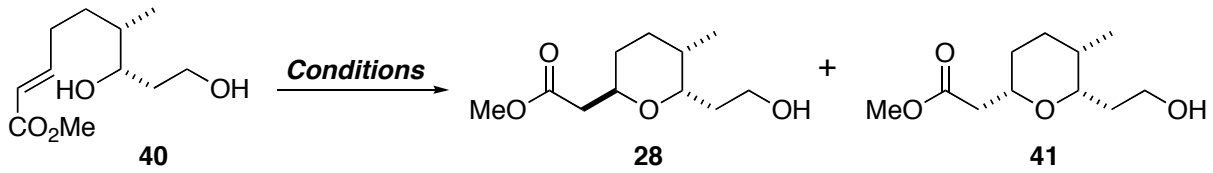
naturally, was similar in polarity to the former. The other products were systematically separated out of the mix during the purification process. However, they were rarely extensively characterized.

When the polar, protic medium was replaced by toluene, the crude pyran mixture was isolated in 66% yield (Scheme 49). The possibility of the formation of hydrolysis products was not explored. The ^{1}H NMR spectrum of the crude material revealed a mixture of *cis*-and *trans*-products in an approximate 1:1 ratio. A TBAF-promoted cyclization afforded similar results (Scheme 49). A recent literature report indicated the superiority of potassium *t*-butoxide,[137i] as compared to other common base promoters, in effecting ring closure via an intramolecular Michael addition reaction. Unfortunately, in our hands, treatment of **40** with excess potassium *t*-butoxide at 0 °C delivered a mixture of *cis*- and *trans*-substituted carboxylic acids **43** and **44** (Scheme 46) in the usual dissatisfying ratio of 1:1. Sodium methoxide in isopropanol afforded **45** and **46**, products of a successful cyclization reaction and an *in situ* trans-esterification process (Scheme 48).



40 **45** **46**

Scheme 48. Intramolecular Hetero-conjugate Addition and *In situ* Trans-esterification.



40 28 41

Conditions: NaOMe, toluene, 0 °C to rt, 3 h; TBAF, THF, 0 °C to rt, 15 h; NaH, THF, DMF, -78 °C to 0 °C to rt, 24 h

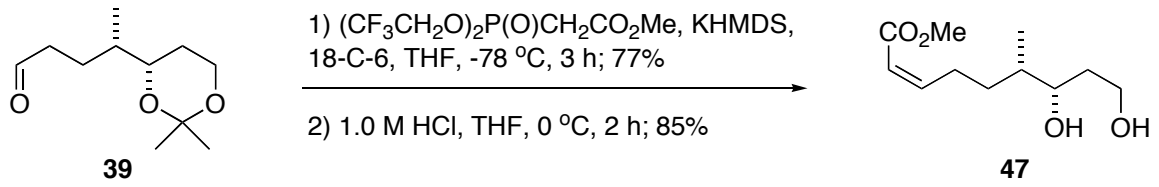
Scheme 49. Synthesis of Mixtures of *cis*- and *trans*-Pyrans.

Treatment of **40** with stoichiometric sodium hydride[137b,d,e] in THF at –78 °C led only to the recovery of starting material (Scheme 49). Excess NaH (60%) led mostly to decomposition, an outcome that is possibly attributable to the less than optimal quality of the hydride reagent. The most obvious potential problem with NaH is the presence of sodium hydroxide, which clearly poses a serious threat to the integrity of the cyclization process. Finally, treatment of the 1,3-diol **40** with excess NaH (95%) at –78 °C once again delivered only the starting material, unchanged after 5.5 hours, despite a TLC analysis that indicated the contrary (*i.e.* consumption of starting material). Treatment of **40** with NaH (60%) in a solution of THF and DMF transformed the starting diol **40** into a mixture of *cis*- and *trans*-pyran products, albeit in very low yield (Scheme 49). Furthermore, treatment of **40** with KHMDS[137d,e] in toluene at –78 °C afforded a rather complex mixture of products.

2.6.4. Preparation and Evaluation of the (Z)-Enoate

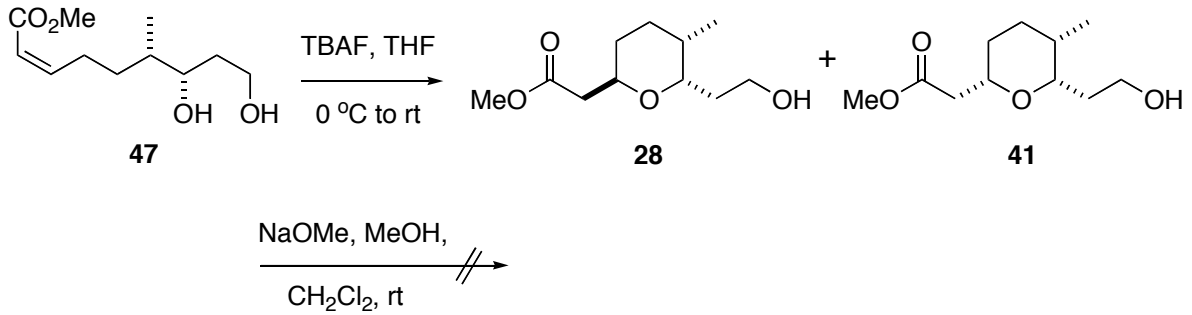
The (*Z*)-enoate **47** (Scheme 50) was prepared in an analogous fashion to **26**. Common aldehyde intermediate **39** was submitted to standard Still-Wittig olefination[150] conditions. Then, the resultant acetonide was deprotected with either *p*-toluenesulfonic acid at room temperature or

1 M HCl at 0 °C in reasonable yields. Unfortunately, neither set of reaction conditions facilitated ring closure following the deprotection.



Scheme 50. Facile Preparation of the (*Z*)-Enoate.

Treatment of **47** with TBAF delivered a mixture of *cis*- and *trans*-products in an approximate 1:1 ratio. Surprisingly, the (*Z*)-configured olefin **47** exhibited very little reactivity under the standard sodium methoxide reaction conditions successfully employed for the cyclization of **40**.



Scheme 51. Short Investigation of the Base-promoted Cyclization Potential of (*Z*)-Isomer **47**.

2.7. Second Generation Approach to the Synthesis of the *trans*-Pyran Acid

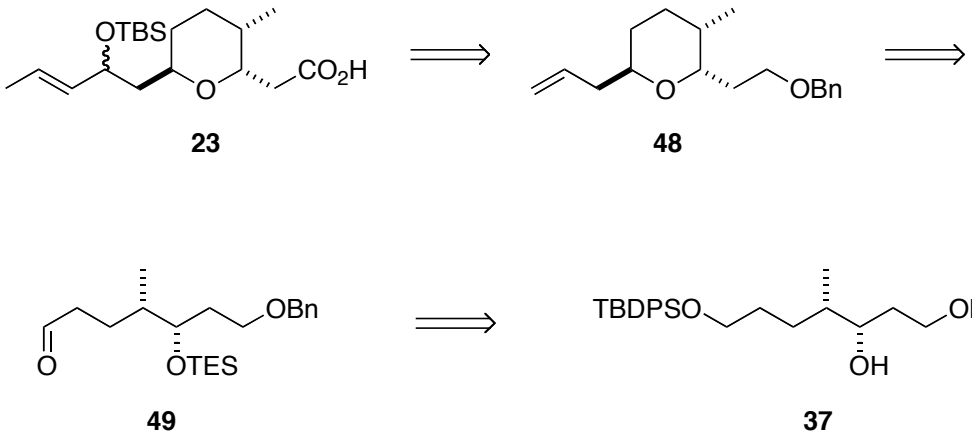
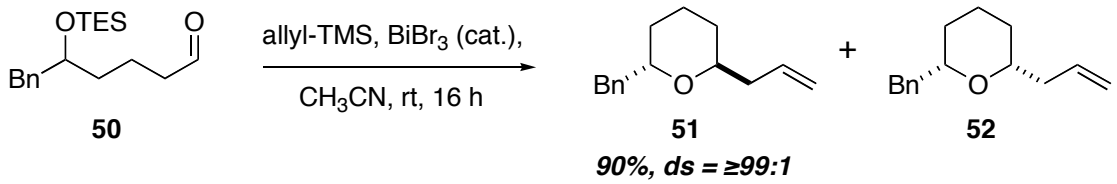


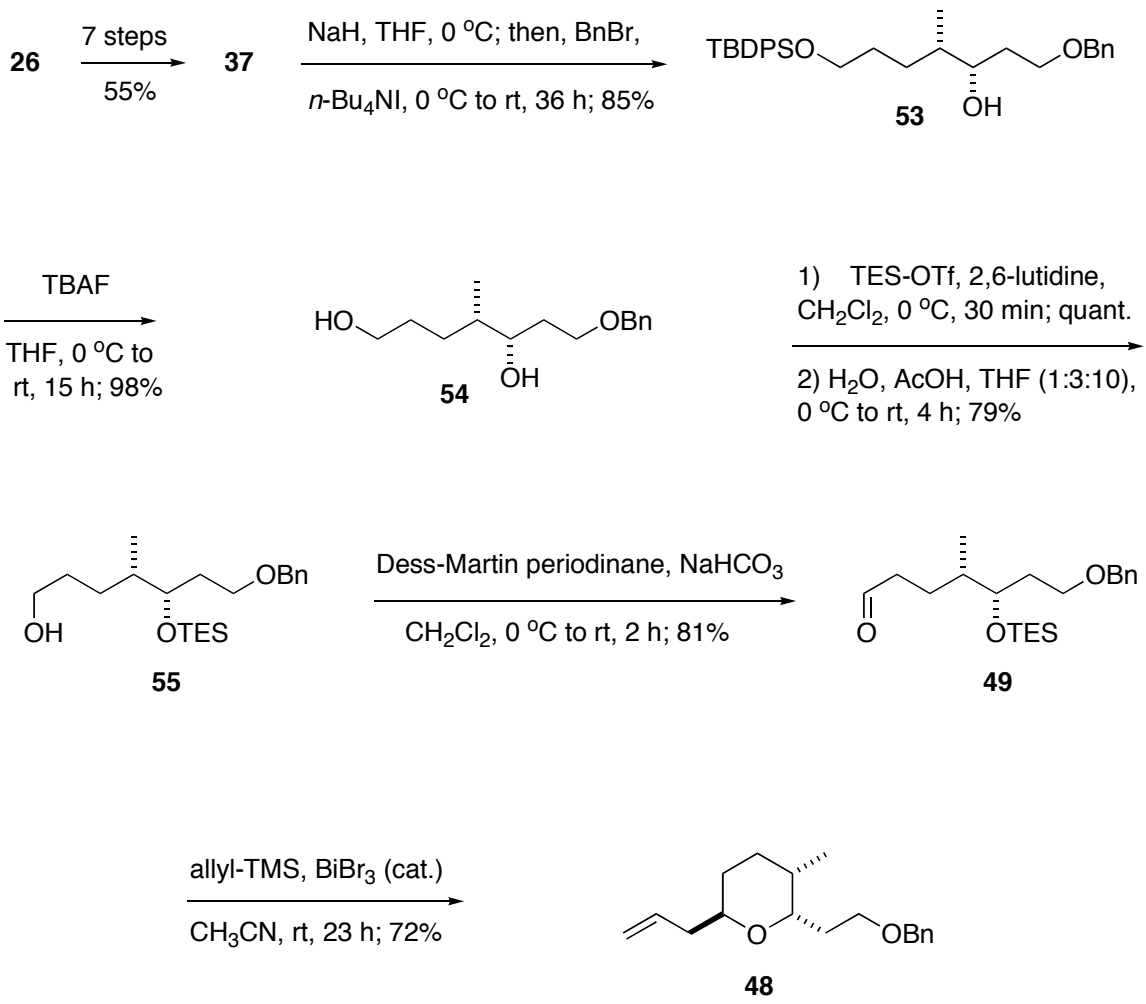
Figure 29. Retrosynthetic Analysis of the Second Generation Approach.

The second generation synthesis of pyran **23** featured P.A. Evans' methodology for the stereoselective construction of *trans*-tetrahydropyrans (Figure 29).[151] Scheme 52 illustrates the high level of efficiency the Evans group was able to achieve for the conversion of the slightly less functionalized δ-triethylsilyloxy aldehyde **50** to the corresponding *trans*-2,6-disubstituted pyran **51**.



Scheme 52. Evans' Stereoselective Construction of Cyclic Ethers.

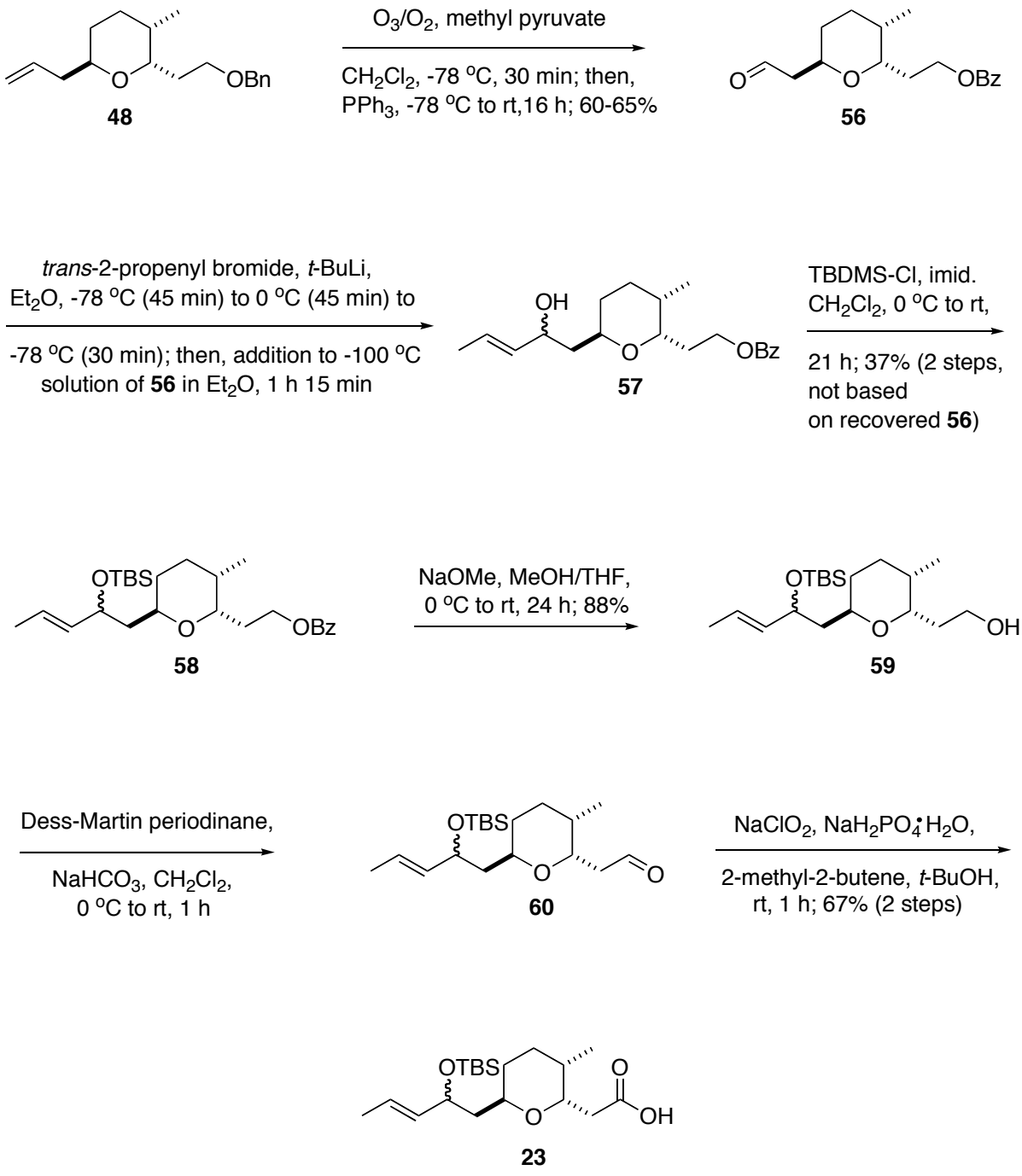
Common intermediate **37** was accessed in the usual fashion from 4-penten-1-ol **26** in 7 steps and 55% overall yield (Schemes 40 and 42). The primary alcohol function of **37** was selectively protected with benzyl bromide in 85% yield (8 steps; 46%). Following a TBAF deprotection of silyl ether **53**, the resultant 1,5-diol **54** was bis-protected with triethylsilyl triflate (Scheme 53). The primary silyl ether was preferentially cleaved upon exposure to a dilute solution of acetic acid in a mixture of THF and water.[152,153] Subsequently, the alcohol product **55** was oxidized to the key aldehyde intermediate **49** by sodium bicarbonate-buffered Dess-Martin periodinane[154] reaction conditions. Treatment of **49** with catalytic $BiBr_3$ and excess allyltrimethylsilane afforded **48** in 72% yield and >5:1 diastereomeric ratio. The stereochemistry of *trans*-pyran **48** was assigned by ^{1}H and ^{13}C NMR chemical shift comparisons of **48** to other structurally related compounds (*i.e.* similarly substituted *trans*- and *cis*-pyrans) documented in the literature.



Scheme 53. Synthesis of the Key Pyran Intermediate.

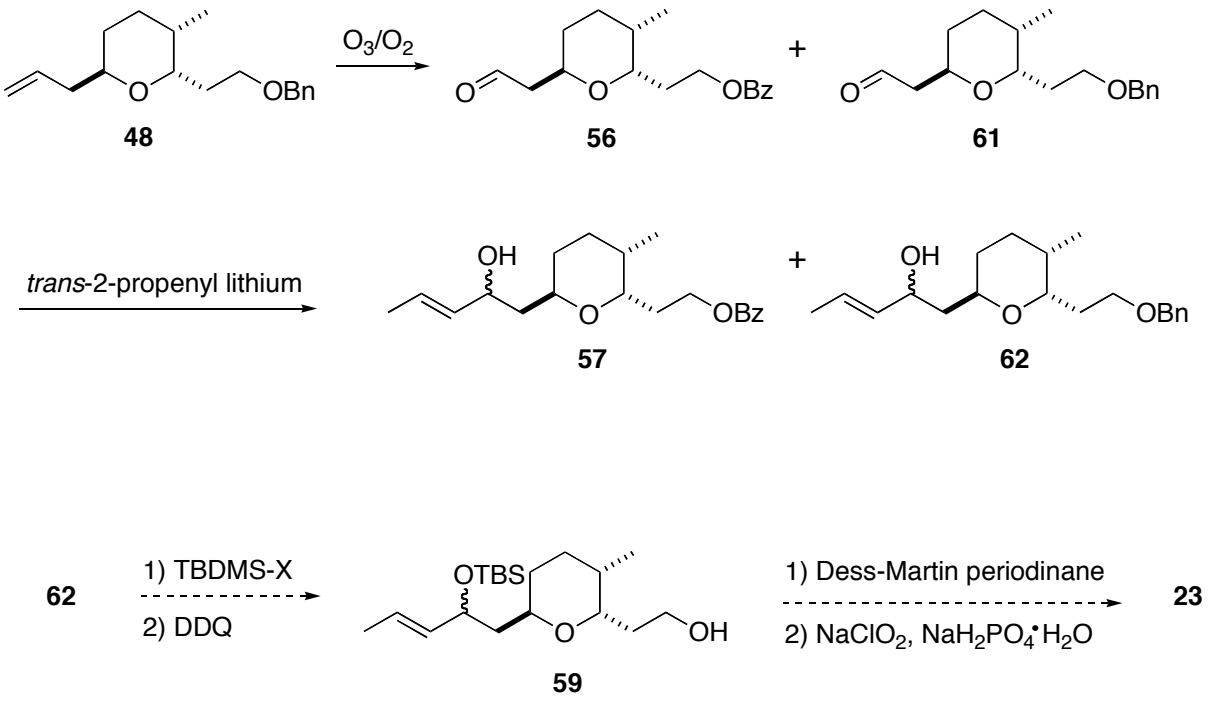
We recognized the potential to manipulate the termini of both pyran side chains simultaneously. Thus, oxidation of **48** with ozone followed by *in situ* reduction of the resultant ozonides with triphenylphosphine transformed the benzyl ether into the benzoate ester and the allyl group into the aldehyde in 60-65% yield. Treatment of a –100 °C solution of aldehyde-ester **56** with a –78 °C solution of propenyl lithium in degassed diethyl ether led to the exclusive addition of the organolithium reagent to the aldehyde function. The secondary allylic alcohol **57** was isolated as a >10:1 mixture of epimers. We chose not to assign the stereochemistry of the

major isomer, due to the fact that its configuration was inconsequential for the synthesis of the natural product. However, assuming chelation control in the addition step, protection of the secondary alcohol function as a *tert*-butyldimethylsilyl ether followed by cleavage of the benzoate with sodium methoxide in methanol afforded pyran **59** in a three-step yield of 33%. The three-step yield does not account for the percentage of unreacted aldehyde **56** recovered from the first transformation. The requisite carboxylic acid fragment **23** was easily accessed from **59** via a two-step oxidation sequence.[155] The intermediate aldehyde **60** was simply isolated from the Dess-Martin periodinane[154] reaction and submitted as a crude mixture to the sodium hypochlorite conditions.[156]



Scheme 54. Completion of the Synthesis of the *trans*-Pyran Building Block.

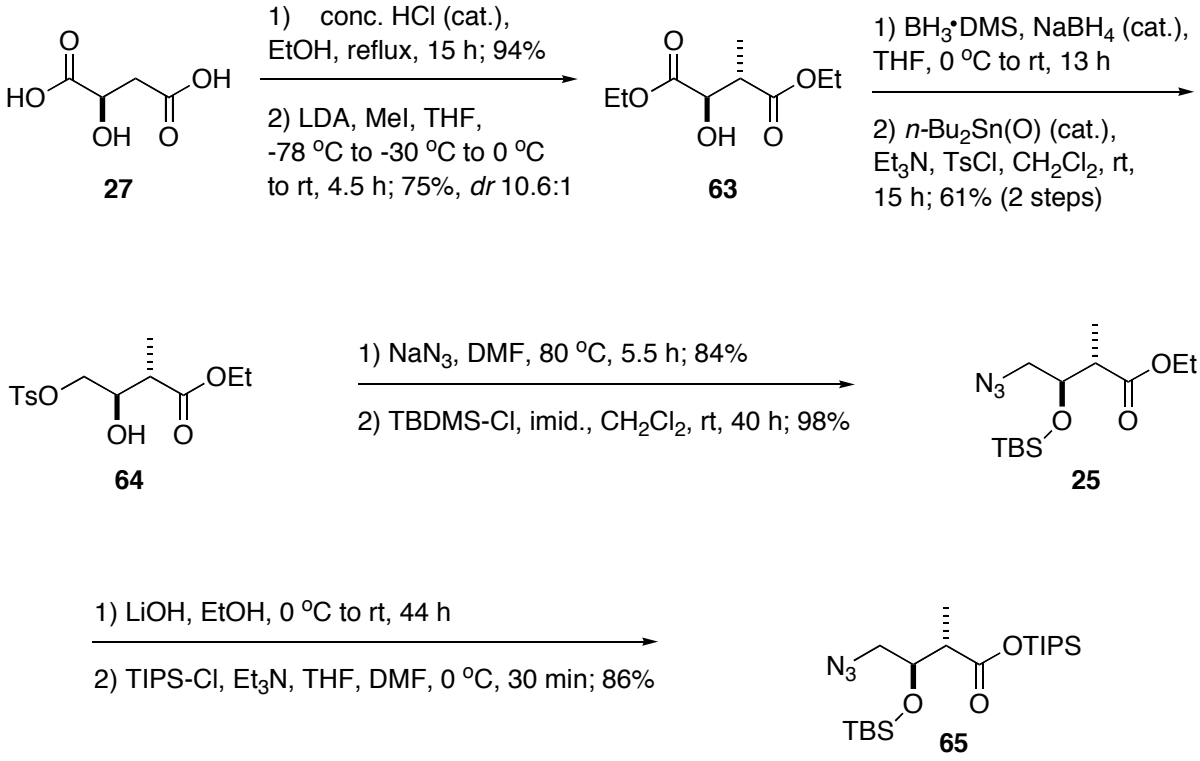
A small percentage of **61** was often isolated from the ozonolysis reaction. It proved to be far more prudent to stop the reaction prior to its completion as opposed to subjecting the potentially labile aldehyde to prolonged ozonolysis conditions. Aldehydes **56** and **61** were routinely separated from each other immediately following the oxidation reaction. However, due to the fact that alcohols **57** and **62** possessed a much greater difference in polarity relative to their aldehyde precursors, separation by column chromatography was often postponed until after the organolithium addition. Pyran **62** could be fed back into the synthetic sequence following silylation of the allylic alcohol and deprotection of the benzyl ether, as illustrated in Scheme 55.



Scheme 55. Transformation of the Benzyl Derivative into the *trans*-Pyran Building Block.

2.8. Synthesis of the γ-Amino Ester Fragment

The synthesis of the enantiomer of the previously prepared (Scheme 38) γ-amino ester building block, **25** (Figure 27 and Scheme 56), commenced with Fischer esterification of the chiral pool precursor (*D*)-malic acid (**27**). Seebach alkylation[157] conditions were employed for the diastereoselective introduction of the requisite methyl group at C(16) of diethyl malate to provide **63** in a yield of 75% as a mixture of two diastereomers. ^{1}H NMR analysis of the crude material revealed a diastereomeric ratio (dr) of approximately 9:1 (*trans*/*cis*). Upon purification by column chromatography, 62% of the methylated diester **63** could be isolated with a dr of up to 10.6 :1 (*trans*/*cis*). Following a chelation-controlled selective reduction[158] of one of the ethyl esters of (2*R*,3*S*)-3-methyl malate **63**, the resultant crude 1,2-diol was converted in 61% yield to the primary tosylate **64** via Martinelli's stannylidene acetal methodology.[159] Azide displacement of the mono-tosylate followed by *tert*-butyldimethylsilyl protection of the β-hydroxy group furnished **25** in a two-step yield of 82%. Finally, the ethyl ester was exchanged for the triisopropylsilyl ester to give **65** in 86% yield. Previous synthetic efforts[114,132] in our group revealed late-stage problems associated with *ent*-**25**. For example, reduction of the azide group in *ent*-**25** followed by coupling to *ent*-**23** delivered the corresponding amide in good yield. Unfortunately, under a variety of reaction conditions intended only for the saponification of the ethyl ester, the newly formed amide bond was rather unexpectedly hydrolyzed.



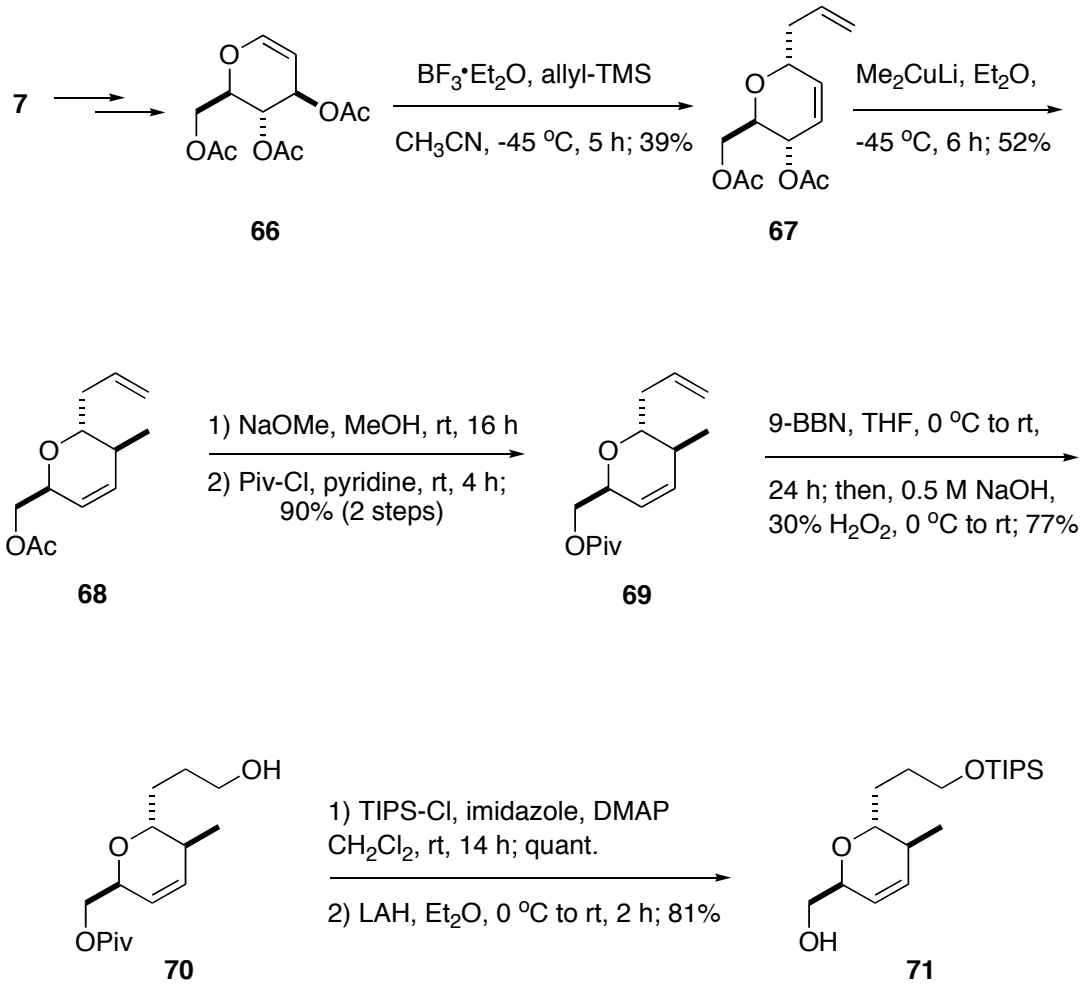
Scheme 56. Synthesis of the γ-Amino Ester Fragment.

2.9. Synthesis of the Spiroketal Fragment

2.9.1. Synthesis of the Spirocyclization Precursor

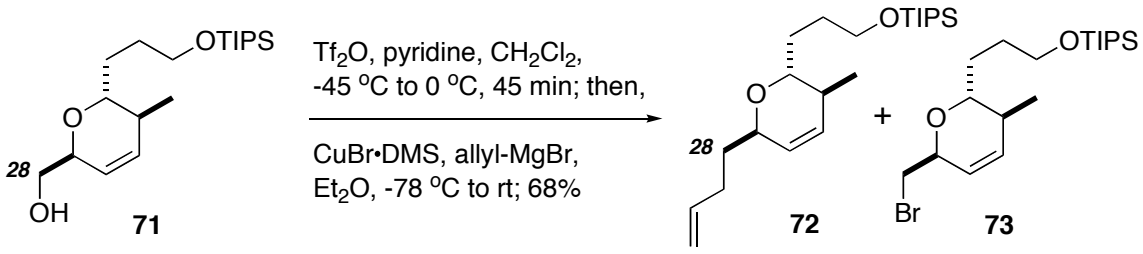
The synthesis of the structurally revised spiroketal fragment **24** commenced with the elaboration of tri-*O*-acetyl-D-glucal **66**[160] into diene **67** by a carbon-Ferrier rearrangement[161] with allyltrimethylsilane and BF_3•Et_2O in acetonitrile (Scheme 57).[162,163] An S_N2' displacement of the resultant allylic acetate with lithium dimethylcuprate provided pyran **68**.[164] The primary acetate was converted to the more robust trimethylacetyl derivative **69** via ester saponification followed by acylation of the resultant crude alcohol. The protecting group switch was initiated primarily due to the susceptibility of the primary acetate to undergo partial hydrolysis during the

course of the cuprate reaction. In addition, the potentially labile acetate was anticipated to be problematic during the oxidation step of the hydroboration[165] sequence. Fortunately, hydroboration of the terminal olefin with the sterically encumbered 9-borabicyclco[3.3.1]nonane (9-BBN)[165] proceeded smoothly. Silylation of the newly installed alcohol of **70** with triisopropylsilyl chloride and reductive removal of the pivaloate with lithium aluminum hydride afforded **71** in 29% yield from diacetate **67**.



Scheme 57. Preparation of Alcohol Intermediate **71**.

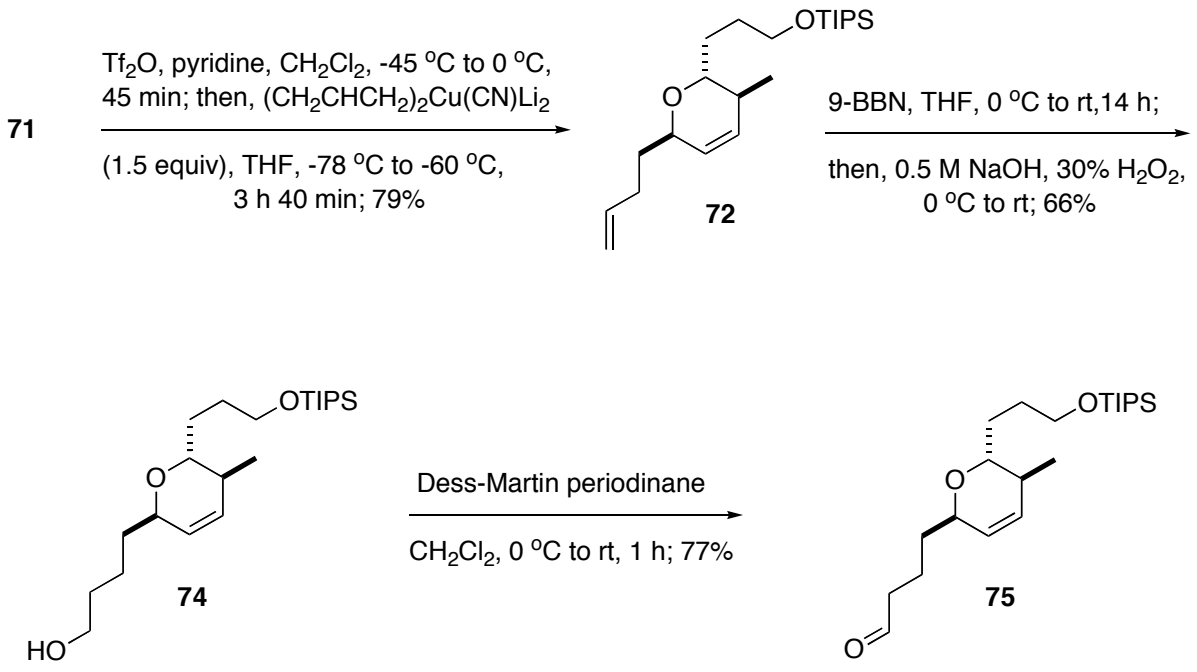
Nucleophilic displacement reactions at the C(6) position of tetrahydropyrans with organometallic reagents are particularly problematic due to the strong electron-withdrawing effect of the β-oxygen.[166] The strategy employed for the synthesis of the bistramide stereoisomer **6**[114,132] featured a non-trivial chain extension at C(28) via a nucleophilic displacement of the intermediate 1° triflate[167] with allylmagnesium bromide in the presence of a catalytic quantity of CuBr•DMS complex.[168] Despite a systematic variation of reaction conditions, the desired product **72** was always accompanied by bromide **73** (Scheme 58). More often than not, the quantity of **73** exceeded that of the desired compound. The formation of **73** was thought to be a direct consequence of the variable quality of the commercial Grignard source. The relative ratios of **72** and **73** were determined by ^{1}H NMR. The two pyrans proved to be inseparable by chromatography.



Scheme 58. Chain Extension Via Lower-order Allyl Cuprate Methodology.

Thus, after extensive experimentation, we determined that the corresponding higher-order allyl cuprate[169] was a far more reliable method for the extension of the side chain (Scheme 59). The organometallic species of interest was prepared via transmetallation of the higher-order methyl cuprate ($Me_2Cu(CN)Li_2$) with allyltributylstannane at –78 °C. The methyl cuprate was prepared *in situ* from methyl lithium and copper cyanide. Following the treatment of **71** with

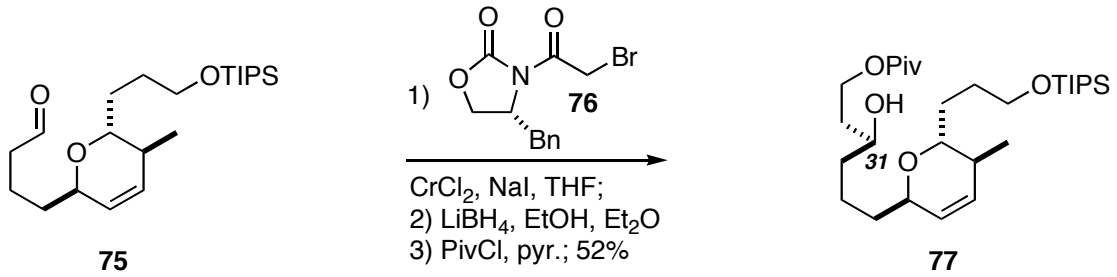
triflic anhydride and pyridine at –45 °C, the resultant triflate[167] was transferred via cannula to a cold solution (–78 °C) of the allyl cuprate in THF. The starting material was completely consumed in less than four hours at –78 °C → –60 °C. The cuprate displacement reactions were routinely performed on gram quantities (1.0-3.3 g) of **71**. The desired allylated product **72** was isolated in approximately 80% yield following purification by chromatography. Selective hydroboration-oxidation of the terminal olefin and subsequent Dess-Martin oxidation[154] of the resultant 1° alcohol provided the key aldehyde intermediate **75** in 40% yield from **71**.



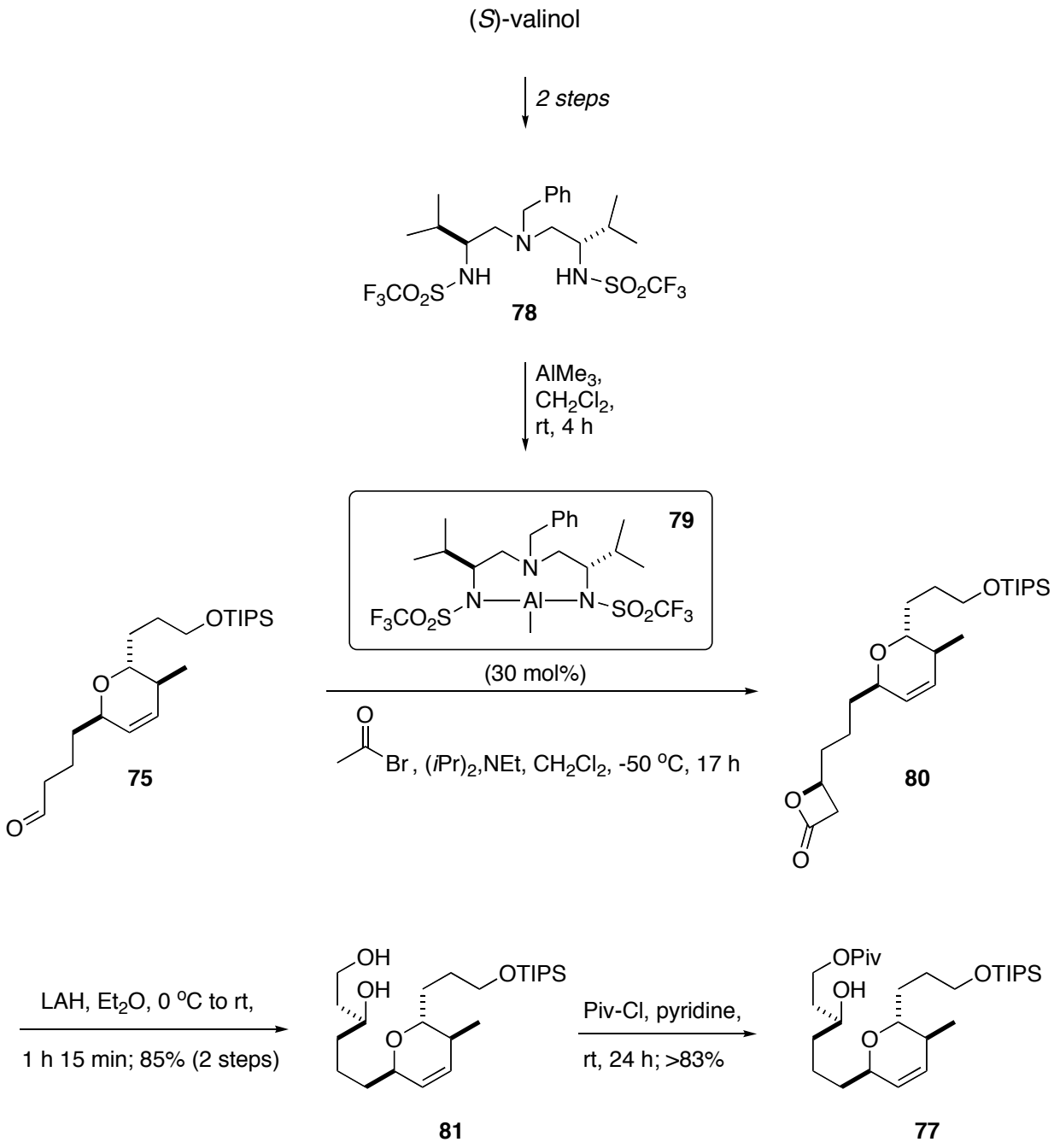
Scheme 59. Synthesis of Aldehyde **75** Via Higher-order Allyl Cuprate Methodology.

Scheme 60 depicts the original strategy invoked for the preparation of the spirocycle precursor **77** in the total synthesis of **6**.[114,132] The chromium (II) mediated Reformatsky reaction[170] between **75** and 2-bromopropionyl oxazolidinone **76** afforded a 13:4 mixture of

diastereomers in a yield of 68%. The reductive removal of the chiral auxiliary with lithium borohydride in ethanol[171] unmasked the intermediate 1,3-diol. It was then selectively protected as a mono-ester with pivaloyl chloride to provide the unsaturated pyran **77** in a 52% overall yield from **75**.



Scheme 60. Former Strategy[114,132] for the Construction of Spirocycle Precursor **77**.

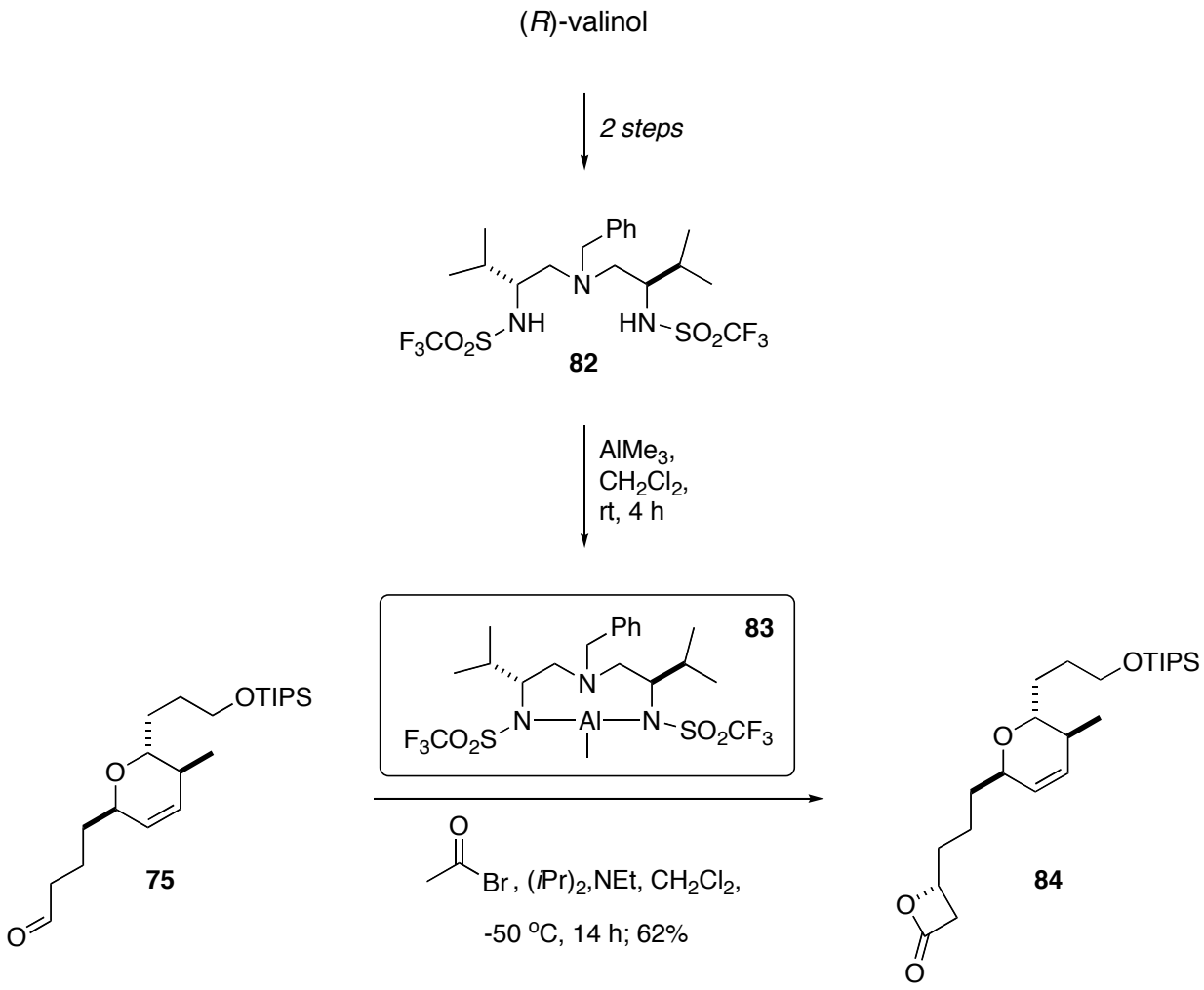


Scheme 61. Improved Strategy for the Preparation of Spirocycle Precursor **77**.

We recognized the need to improve upon the aldol strategy for the installation of the (*S*)-configured stereocenter at C(31). Nelson's acyl halide-aldehyde condensation (AAC)

methodology proved to be a suitable solution (Scheme 61).[172] The appropriate (*S*,*S*)-triamine ligand **78** was prepared from (*S*)-valinol in two steps.[173] Subsequently, the Al(III)-triamine complex **79** was prepared from **78** and $AlMe_3$ at room temperature in four hours. Catalyst **79** proved to be quite effective in facilitating the condensation of acetyl bromide with aldehyde **75** in high yield (>90%) and excellent diastereoselectivity (>95% de). Reduction of the β-lactone **80** with lithium aluminum hydride liberated the 1,3-diol **81**. Selective acylation of the primary alcohol delivered the desired spirocycle precursor **77** as a single diastereomer in (greater than) 71% overall yield from **75**. It was more beneficial to subject the semi-pure β-lactone **80** to the reductive opening conditions. Careful chromatography could and should be postponed until after the opening of the β-lactone in order to maximize material throughput.

The (*R*)-valinol-derived catalyst[172] was also explored (Scheme 62). Treatment of the aldehyde **75** with the (*R*,*R*)-Al(III)-triamine complex **83**[173] delivered the β-lactone product **84**,[174] albeit in slightly lower yield as compared to the diastereomer prepared previously (**80**, Scheme 61). A higher catalyst loading was required to effect the condensation reaction. An initial attempt with only 25 mol% of **83** met with no success. More noteworthy, however, was the fact that the two lactone products were indistinguishable by ^1H and ^{13}C NMR analyses! The optical rotation measurements were more useful. The (*S*)-derived β-lactone **80** showed an $[\alpha]_D$ -0.0043 (*c* = 0.50, $CHCl_3$, 22 °C). The (*R*)-derived β-lactone product **84** was characterized by a very different value, $[\alpha]_D$ +13.5 (*c* = 0.65, CH_2Cl_2, 22 °C). The parent triamine ligands **78** and **82** were submitted to the same analysis. The $[\alpha]_D$ measurements for the (*S*,*S*)-and (*R*,*R*)-triamine ligands were +6.0 and –5.2, respectively. The samples were prepared in methylene chloride at 10 mg/mL and subsequently analyzed at 22 °C.

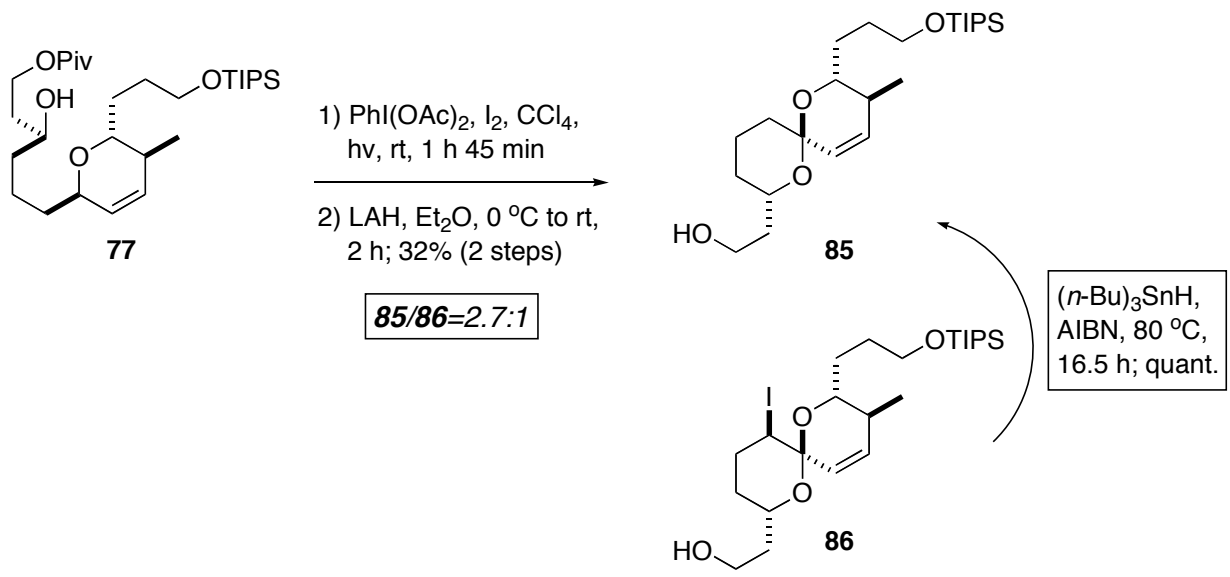


Scheme 62. Preparation of the (*R*)-Configured β-Lactone.

2.9.2. Spirocyclization

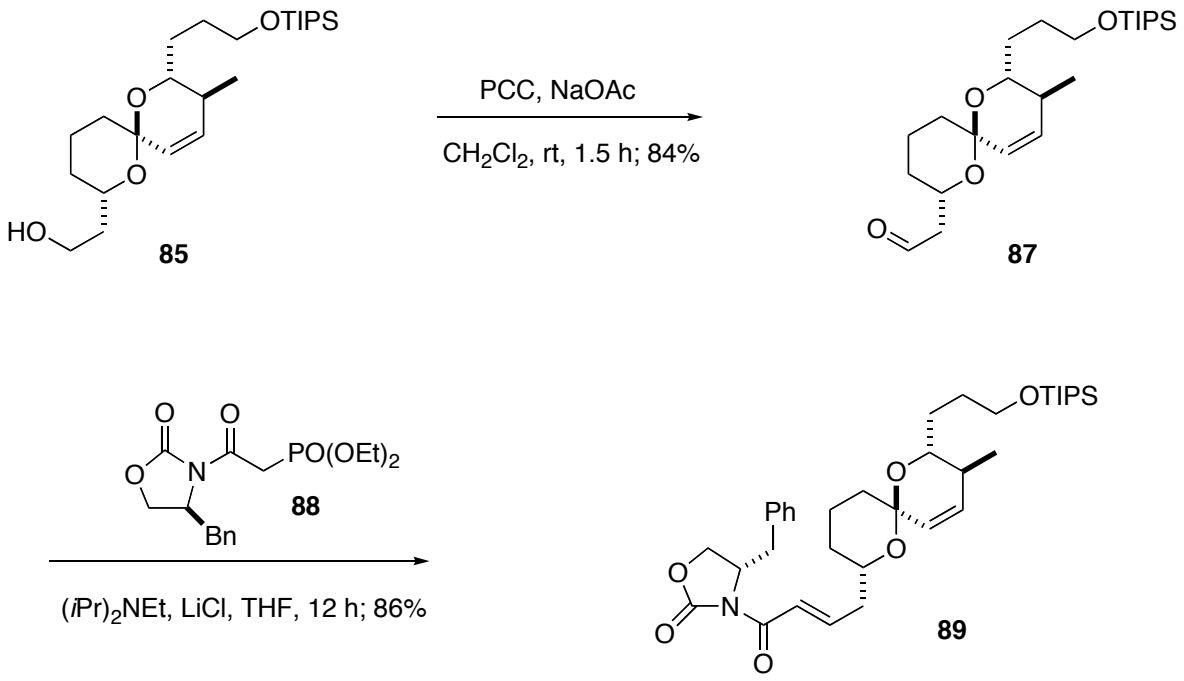
Oxidative spirocyclization[175,176,177,178] in the presence of iodobenzene diacetate and iodine transformed **77** into a mixture[114,132,177] of partially iodinated spiroketals upon irradiation with a 250 W tungsten lamp (Scheme 63). Following the C-H insertion reaction, the crude mixture was directly subjected to the reductive removal of the pivaloate with lithium aluminum hydride. The resultant spiroketals, **85** and **86**, were separated by chromatography. The iodide of **86**, which was installed regio-and stereoselectively,[114,132] was reductively removed via tributyltin hydride[179]

in nearly quantitative yield. Spiroketal **85** proved to be structurally identical to material that was isolated during the preparation of the bistramide C stereoisomer **6** (Figure 24).[114,132]



Scheme 63. Oxidative Spirocyclization.

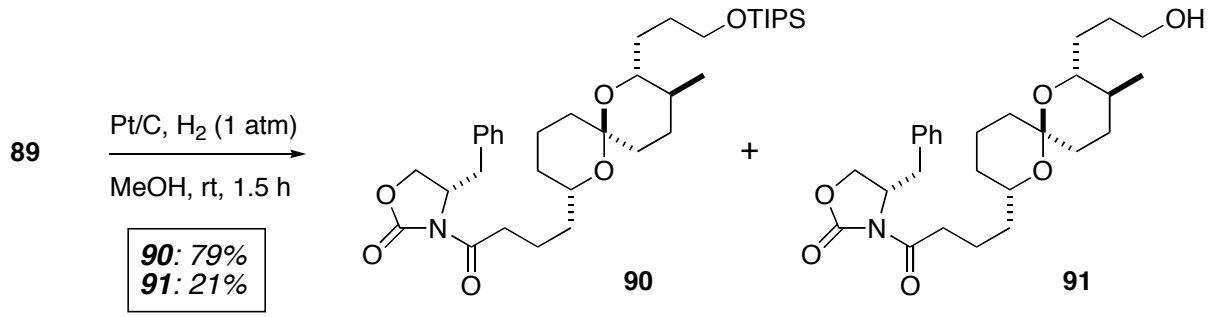
Oxidation of **85** with PCC[180] in the presence of sodium acetate as buffer afforded aldehyde **87** in a yield of 84%. Spirocycle **87** was readily converted to the desired α,β-unsaturated oxazolidinone **89** in 86% yield via a Horner-Wadsworth-Emmons reaction with phosphonate **88**[181,182] under standard Masumune-Roush[145] conditions. The (*S*)-phenylalanine-derived oxazolidinone **88** was prepared by an Arbuzov reaction[181,183] between triethylphosphite and the appropriate bromopropionyl oxazolidinone.[184]



Scheme 64. Spiroketal Chain Extension.

Catalytic hydrogenation of both alkenes with Pt/C in MeOH delivered the precursor for the late-stage diastereoselective alkylation. However, we were first interested in optimizing the reaction conditions for the double hydrogenation. Previously, *en route* to **6**, the saturated product **90** had been isolated in 63% yield upon exposure to hydrogen and Pt/C in methanol at room temperature for 2.5 hours. Unfortunately, the desired spirocycle **90** was accompanied by 19% of **91**, a product obtained from both the cleavage of the silyl protecting group (due most likely to the acidic nature of the metal catalyst) in addition to the expected saturation. Prolonged exposure of **89** to Pd/C under a hydrogen atmosphere gave only 33% of **90**. As expected, the remaining mass balance could be attributed to the formation of **91**. Treatment of spirocycle **89** with Wilkinson's catalyst in methanol for two days at room temperature delivered neither desired product **90** nor unwanted by-product **91**. It was finally determined that Pt was indeed the best metal for the hydrogenation reaction and sodium bicarbonate buffered conditions were not necessary. However, slightly shorter reaction times (*i.e.* 1-1.5 h as opposed to ≥2.5 h) were

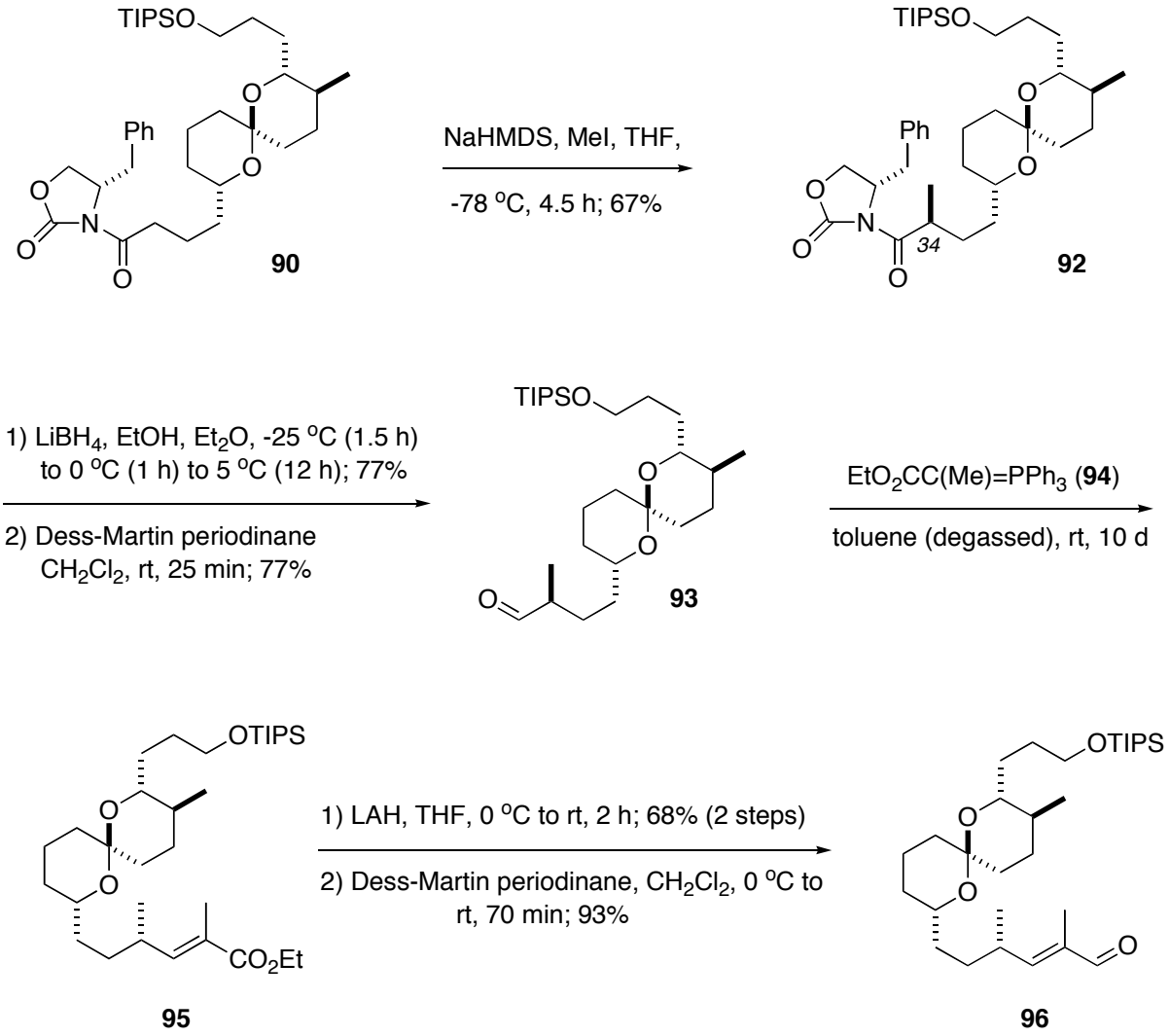
required to maximize the conversion of **89** to **90**. Thus, treatment of **89** with catalytic Pt on carbon and 1 atm of hydrogen gas for 1.5 hours at room temperature afforded the fully saturated spirocycle **90** in a yield of 79% following purification via chromatography. A flush of the column revealed 21% of the alcohol by-product **91** (Scheme 65).



Scheme 65. Improved Conversion of **89** to Saturated Spirocycle **90**.

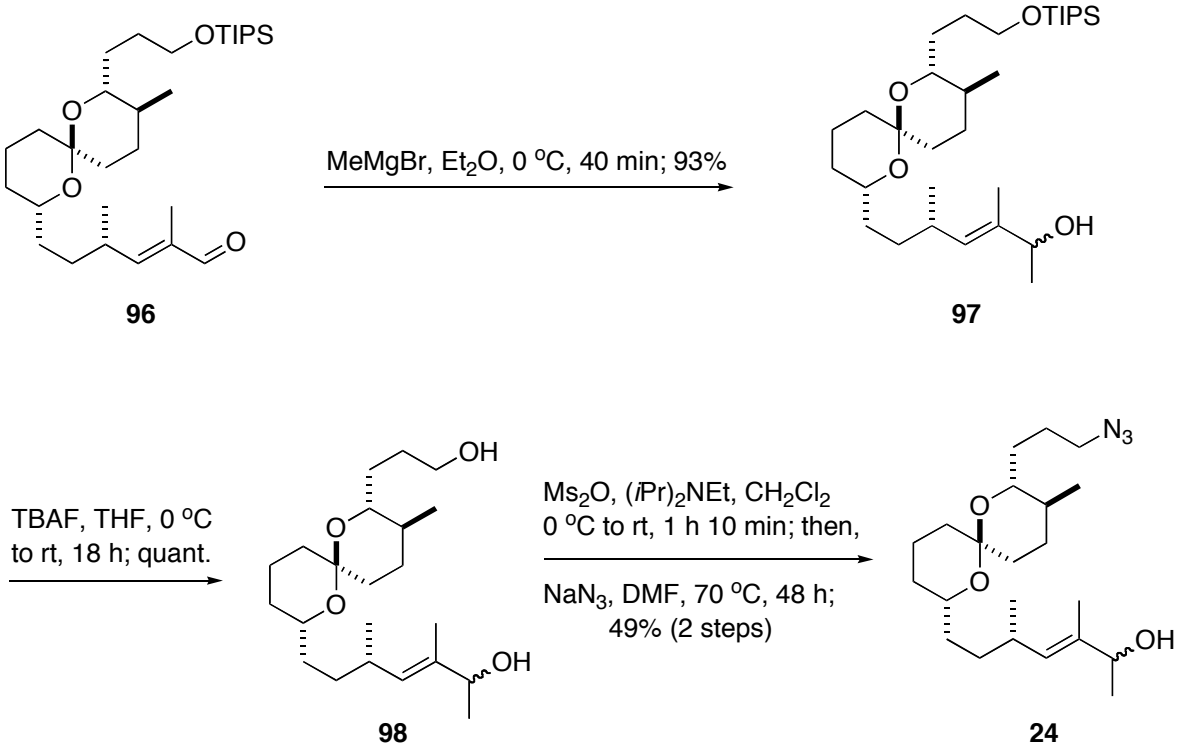
Finally, the key methyl group at C(34) was installed in 67% yield using the alkylation conditions reported by Evans.[185] Only a single diastereomer was identified. The chiral auxiliary in **92** was reductively removed with lithium borohydride in ethanol[171] in a yield of 77%. Oxidation[154] of the resultant alcohol delivered the Wittig precursor **93**, also in 77% yield. The end-game strategy[114,132] was maintained, despite the lengthy sequence necessary for the manipulation of the remaining side chain of the spiroketal moiety. It had been previously reported by Wipf *et al.* that the α-branched aldehyde posed some difficulty in the attempted elaboration of the spiroketal. The most obvious choice for the construction of the C(36) to C(40) segment, *i.e.* 3-triphenylphosphoranylidene-2-butanone, provided low yields of the desired enone even in the presence of a large excess of the Wittig reagent, increased reaction times and/or increased temperatures. Furthermore, little to no success was met with the use of Horner-

Wadsworth-Emmons-type phosphonate reagents under a variety of reaction conditions. Alternatively, aldehyde **93** was carried through a sequence of four steps for the preparation of the intermediate secondary allylic alcohol **97** (Schemes 66 and 67). Wittig condensation with carbethoxyethylidenetriphenylphosphorane **94** and lithium aluminum hydride reduction of the resultant enoate **95** followed by oxidation of the allylic alcohol to the α,β-unsaturated aldehyde with Dess-Martin periodinane[154] transformed **93** into enal **96** in an overall yield of 63% (Scheme 66).



Scheme 66. Further Functionalization of the Spiroketal Moiety.

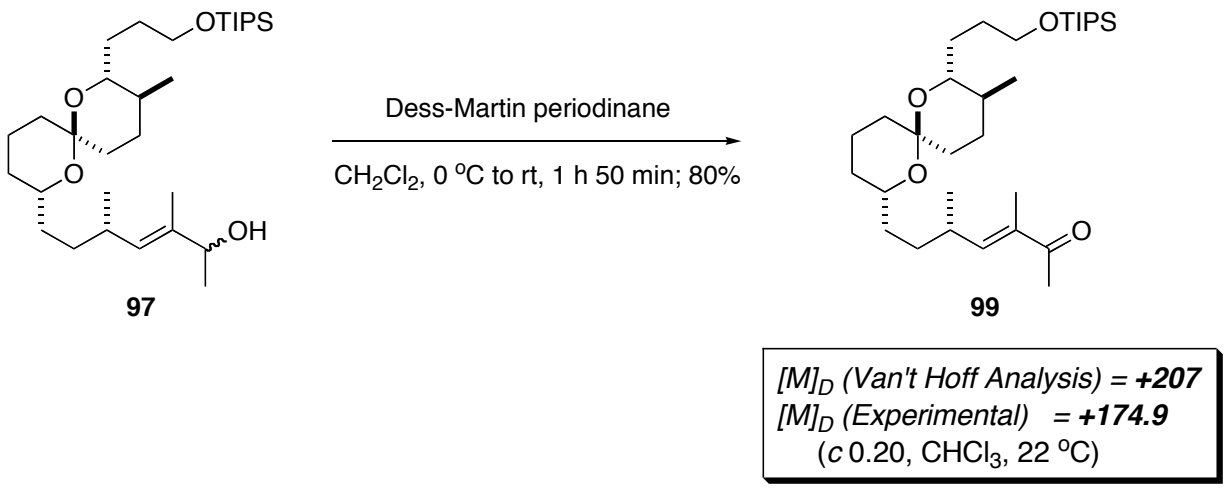
A low temperature addition of methylmagnesium bromide to **96** furnished the secondary alcohol **97** as a mixture of diastereomers in 93% yield. Following the removal of the triisopropylsilyl group with TBAF, diol **98** was isolated in a two-step yield of 85%. Finally, the key azide fragment **24** was accessed by selective mesylation[186,114,132] of the primary alcohol followed by an S_N2-displacement of the crude mesylate with sodium azide. Either methanesulfonic anhydride or methanesulfonyl chloride[114,132,186] could be used to effect the conversion of **98** to the intermediate mesylate in comparable yields. The anhydride provided us with more reproducible results, however.



Scheme 67. Completion of the Synthesis of the Spiroketal Building Block.

2.10. Van't Hoff Analysis, Revisited

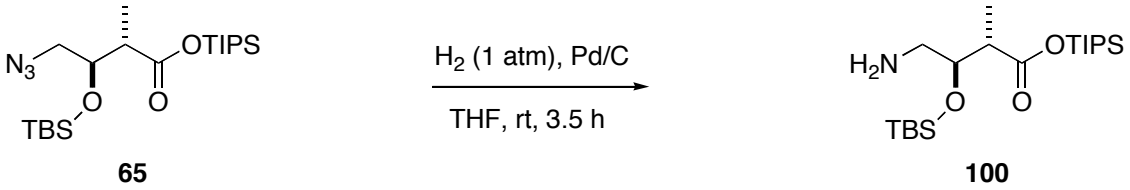
Upon completion of the synthesis of **97**, the van't Hoff principle of optical superposition[127,128,129,130,131] was revisited. Previously, a computational analysis provided a means for predicting $[M]_D$ for methyl ketone **99** (Figure 25 and Scheme 68).[114] We decided to test the accuracy of our chiroptical tools by comparing the computationally derived value with that obtained from the optical rotation analysis of a synthetic sample. Thus, **97** was transformed into the requisite enone **99** in a facile manner upon treatment with Dess-Martin periodinane. Gratifyingly, the experimentally determined value of $[M]_D$ = +174.9 (*c* = 0.20, $CHCl_3$, 22 °C) matched the predicted value of $[M]_D$ = +207 within an acceptable degree of accuracy. We continued our synthetic quest with renewed confidence.



Scheme 68. Comparison of Computationally and Experimentally Derived $[M]_D$ Results.

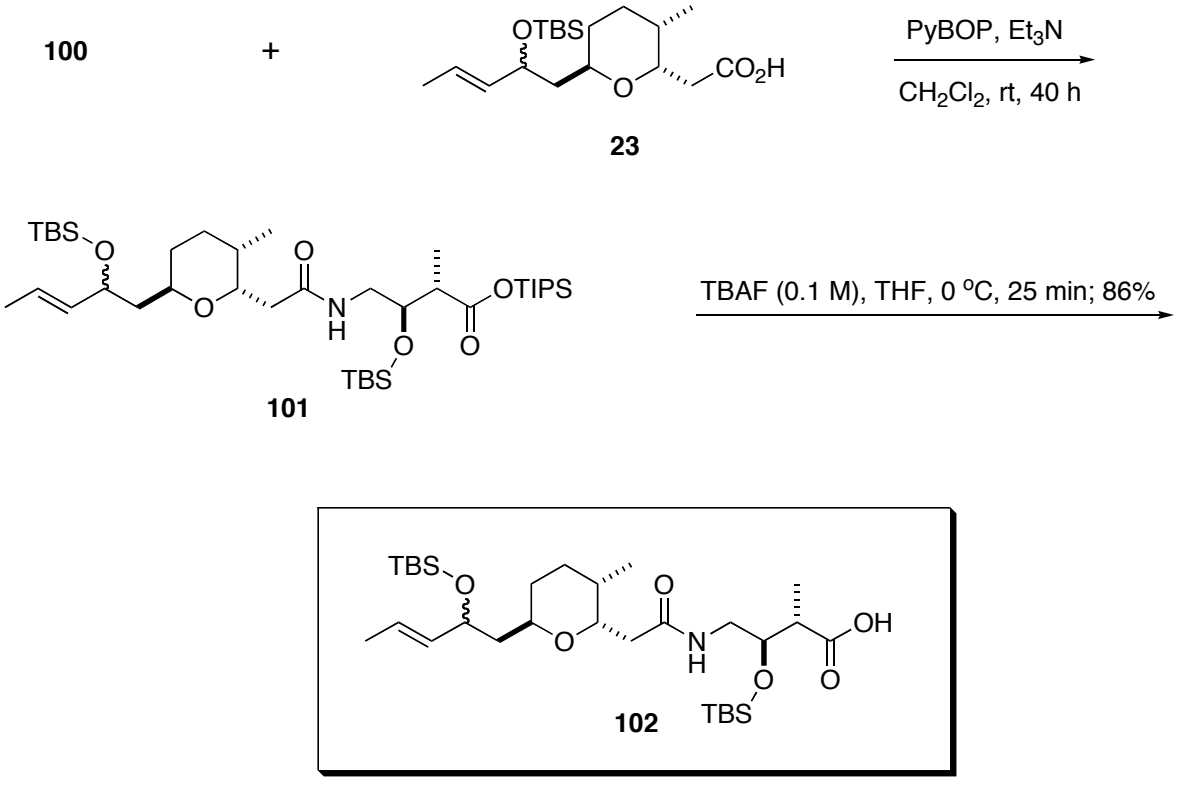
2.11. Synthesis of the Intermediate Amide

We initiated the final segment condensation sequence with the reduction of azide **65** (Scheme 56) by standard catalytic hydrogenation[187] conditions. The labile amino ester intermediate **100** was isolated briefly and then submitted to a PyBOP-mediated[124] coupling reaction with pyran acid **23**. Following a fluoride-induced deprotection of the TIPS ester, carboxylic acid **102** was obtained in an overall yield of 86% (Scheme 70).



65 **100**

Scheme 69. Azide Reduction.



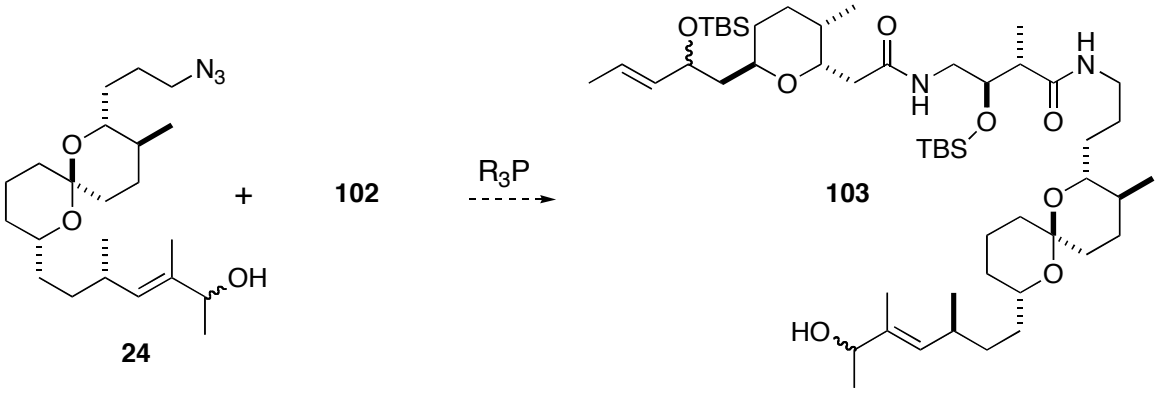
23 **101** **102**

Scheme 70. Coupling of *trans*-Pyran Acid **23** with γ-Amino Ester **100**.

2.12. Model Studies for the Construction of the Second Amide Bond

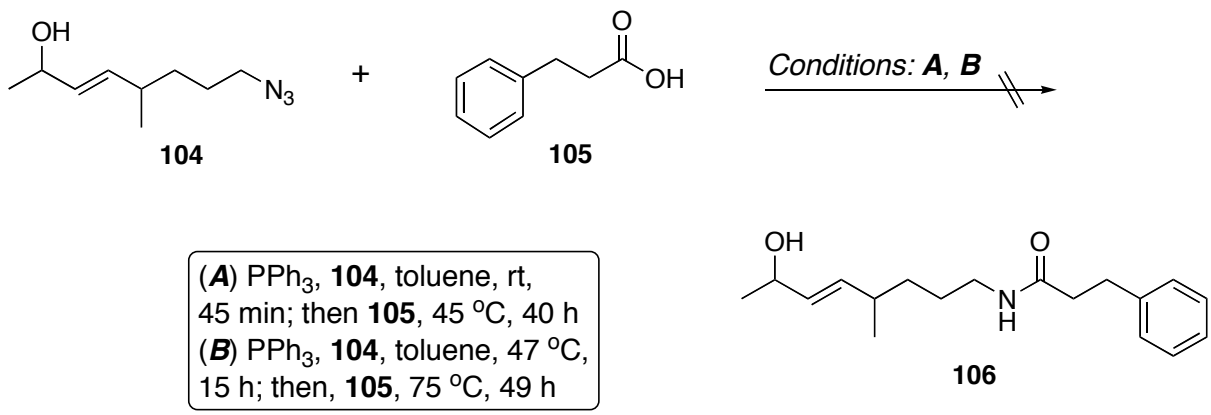
2.12.1. One Pot Segment Coupling Sequence

We were very intrigued by the possibility of accessing the requisite bisamide **103** via a one-pot reaction of **24**, **102** and an aryl or alkyl phosphine (Scheme 71).[188,189] Obviously, the phosphine-mediated amide bond construction pathway represented a more efficient process. Plus, it eliminated the need to isolate the highly lipophilic amino alcohol intermediate.



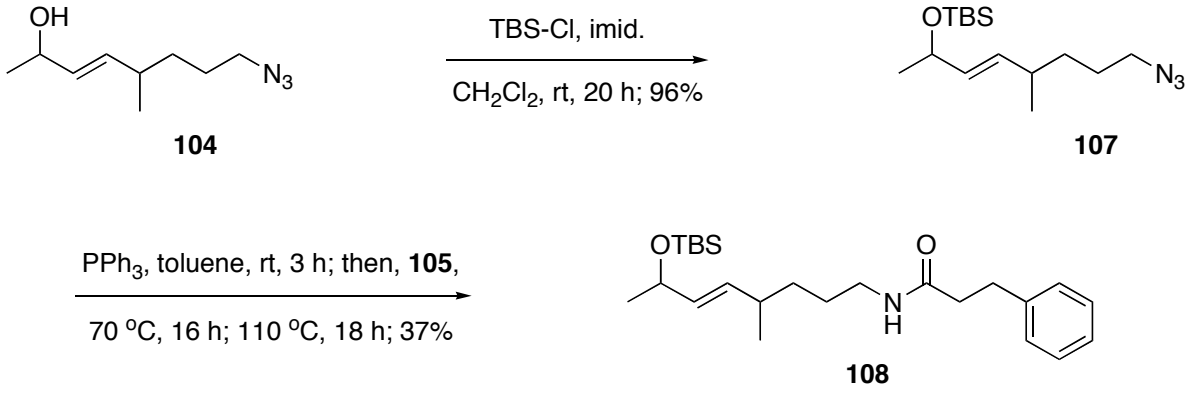
Scheme 71. Synthetic Plan for the Final Amide Coupling Reaction.

Our first synthetic attempt (Scheme 72) featured a 45-minute pre-mix of **104** and triphenylphosphine in degassed toluene followed by the addition of neat **105** in excess. The ^{1}H NMR analysis of an aliquot removed after 24 and 40 hours at 45 °C revealed a complete absence of amide product. In an effort to address the obvious question of iminophosphorane formation, the azide/phosphine mixture was heated to 47 °C and maintained for 15 hours prior to the addition of a solution of hydrocinnamic acid (**105**) in degassed toluene. An additional 49 hours at 75 °C led to an assortment of spots by TLC, but no clear indication of product formation.



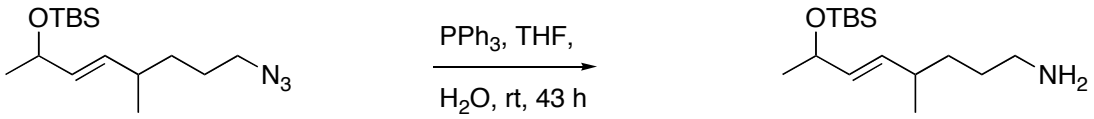
Scheme 72. Initial Phosphine-mediated, One-pot Coupling Attempts.

We speculated that the lack of reactivity was due to the presence of a free hydroxyl group. Consequently, the alcohol function of **104** was capped as a silyl ether (Scheme 73). Azide **107** was then treated with triphenylphosphine and maintained at room temperature for three hours prior to the addition of a solution of **105** in degassed toluene. The resultant reaction mixture was heated at 70 °C for 16 hours. The ^{1}H NMR spectrum of an aliquot revealed, once again, a complete absence of product. Finally, the reaction was heated at 110 °C for an additional 18 hours. After purification by chromatography, the desired amide **108** was finally isolated in 37% yield.



Scheme 73. Successful Coupling Attempt with TBS-protected **107**.

We next investigated the ability of azide **107** to undergo reduction to the corresponding amine **109** via standard Staudinger reduction[190] conditions (Scheme 74). The starting azide was cleanly and "quantitatively" converted to **109**. The diagnostic triplet at 3.25 ppm had been replaced by an equally as diagnostic triplet at 2.68 ppm. The ^{1}H NMR also revealed a complete absence of starting material. This observation confirmed that coupling, and not iminophosphorane formation was the rate-limiting step in the sequence.



107 **109**

Scheme 74. Staudinger Reduction of Azide **107**.

Treatment of **104** with **105** and triphenylphosphine at elevated temperatures for extended periods of time resulted in the successful conversion of **104** to amide **106** (Scheme 75). Unfortunately, the amide product **106** co-eluted with triphenylphosphine oxide. Thus, **106** was clearly identified by ^{1}H NMR, but never quantified. Excess acid (*i.e.* 1.2-1.5 equivalents, total) resulted in the further conversion of **106** to the bis-acylated product **110**.

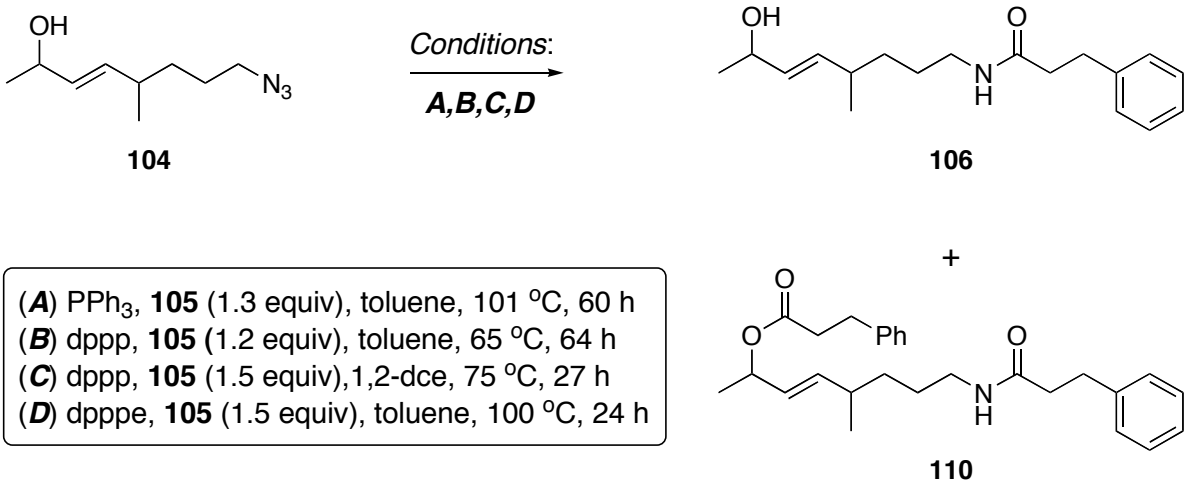
2.12.2. An Investigation of Bisphosphines

Our study of alkyl bisphosphines was initiated in an effort to exploit their enhanced reactivity vs. triphenylphosphine. We also wanted to explore the potential benefits of bidentate coupling reagents that could conceivably interact with the carboxylate component.

We began our studies with 1,3-bis(diphenylphosphino)propane (dppp) (Scheme 75). After 45 minutes at room temperature, the mixture of **104** and dppp was treated with excess acid **105**. No

obvious change could be discerned by TLC after 15 hours at room temperature. An aliquot removed after 10 hours at 65 °C revealed trace product **106** and no starting azide **104**. After 40 additional hours of mild heating, the reaction was quenched. Purification by chromatography on SiO_2 revealed two major compounds **106** and **110** (Scheme 75). Once again, the more polar amide **106** co-eluted with the oxidized form of the bisphosphine. More notable, however, was the fact that the reaction had been promoted at far lower temperatures with dppp as compared to PPh_3. Unfortunately, once again, due to the contamination problem, the amide product **106** was never properly quantified.

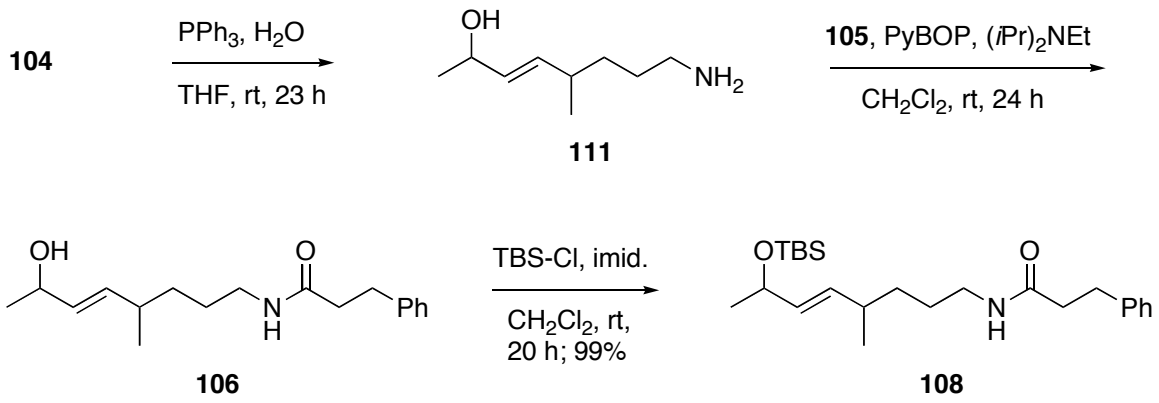
Comparable results were obtained from treatment of azide **104** with hydrocinnamic acid (**105**) and dppp in 1,2-dichloroethane at 75 °C for an extended time period (Scheme 75). A switch to a bisphosphine bearing a slightly longer tether, 1,5-bis(diphenylphosphino)pentane (dpppe), generated similar results. In both cases, the bis-acylated compound **110** was isolated very cleanly following purification by chromatography, while the amide suffered from the usual contamination issues.



Scheme 75. Successful Phosphine-mediated Coupling Reactions with **104**.

2.12.3. Two Pot Segment Coupling Sequence

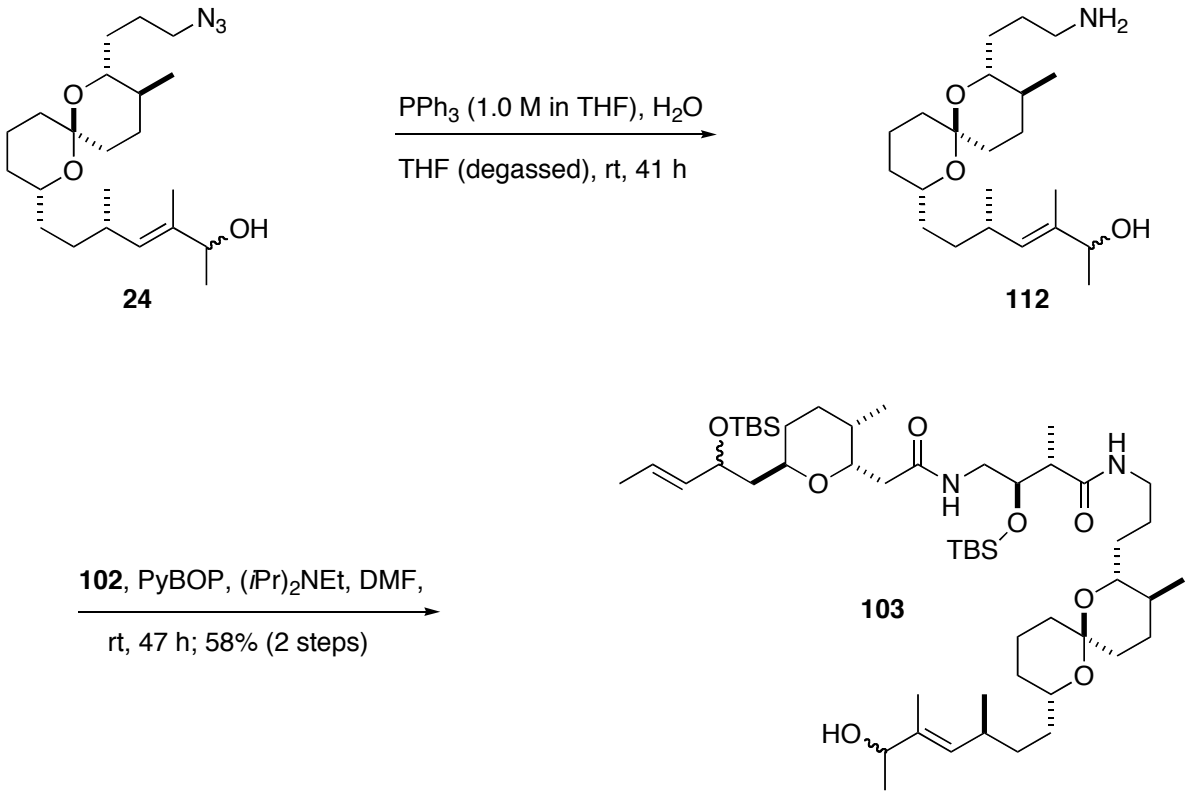
Although the results from the bisphosphine studies were quite encouraging, the temperatures required to promote the formation of the amide bond were generally too high. Since the Staudinger reaction[190] proceeded quite smoothly at room temperature in (degassed) THF (Scheme 76), we thought that it might be best to isolate the amine **111** after the reduction and subsequently submit the crude mixture to a separate coupling reaction. The two-step strategy would allow for both reactions to be run under relatively mild conditions. In order to fully assess the efficiency of the reduction/coupling sequence, the free hydroxyl group of **106** was protected as a *tert*-butyldimethylsilyl ether immediately after the coupling step. After purification by chromatography, which finally allowed for the facile removal of triphenylphosphine oxide, **108** was isolated in nearly quantitative yield. This sequence was selected for the bistramide target synthesis.



Scheme 76. Two Pot Reduction/Coupling Sequence.

2.13. Final Segment Coupling

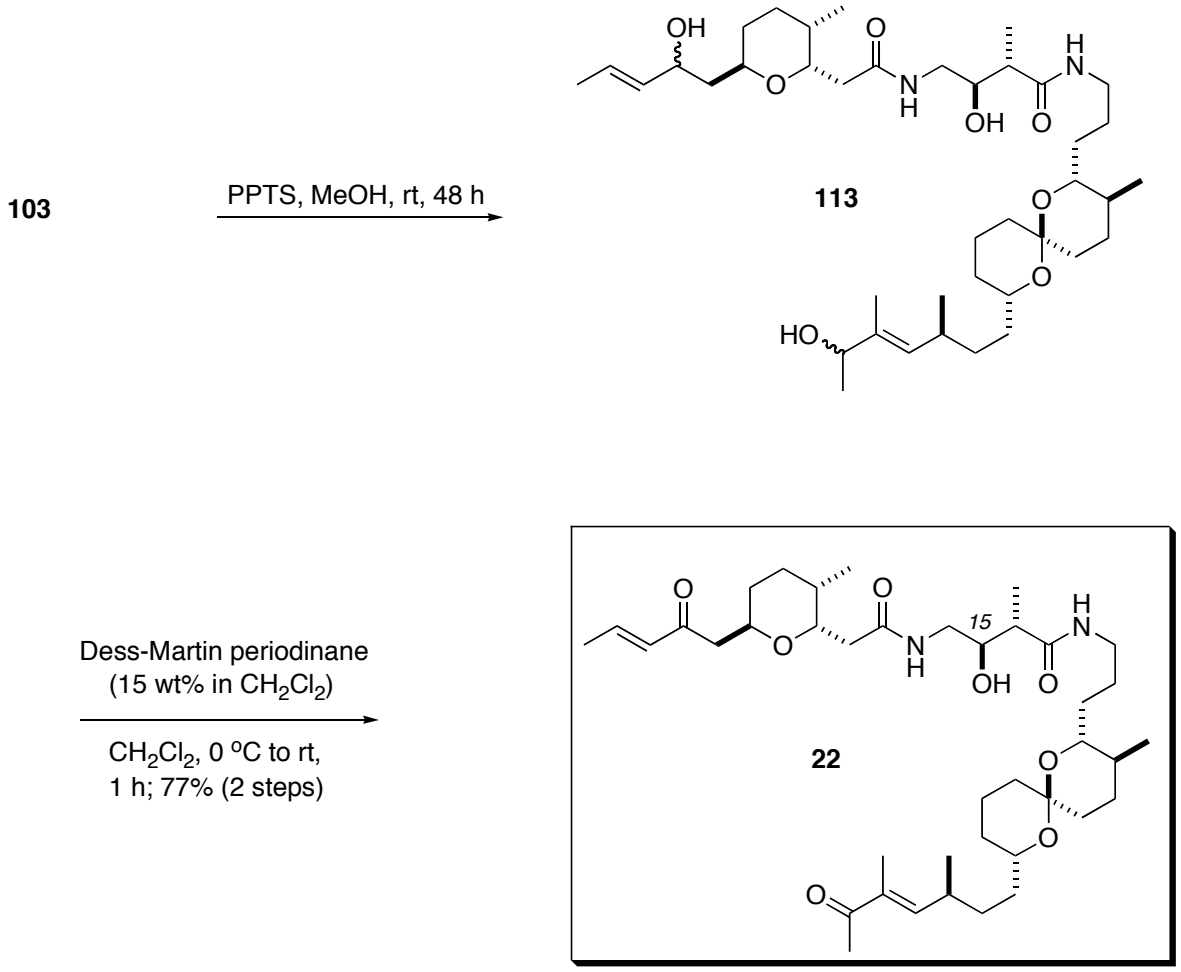
Analogous to the model study, spiroketal azide **24** was treated with triphenylphosphine in degassed THF at room temperature (Scheme 77). Upon completion of the redox reaction, the solvent was removed *in vacuo*. The completion of the reaction was determined by a ^{1}H NMR analysis of an aliquot. The highly hydrophilic amino alcohol **112** was not exposed to or treated with water at any point during its isolation. Finally, the crude amine was treated with a DMF solution of **102**, followed by PyBOP[124] and Hünig's base. The diamide product **103** was isolated in a two-step yield of 58%.



Scheme 77. Final Segment Coupling.

2.14. Completion of the Total Synthesis of Bistramide C

Global deprotection of **103** under mildly acidic conditions[191] furnished triol **113**. Following the removal of pyridinium *p*-toluenesulfonate via basic extraction, crude **113** was submitted to the final oxidation reaction. The secondary allylic alcohols were selectively oxidized to the corresponding enones with Dess-Martin periodinane[154] to give the target molecule **22** in a two-step yield of 77% (Scheme 78). This oxidation typically required more than two equivalents of Dess-Martin[154] in order to minimize the recovery of starting material. Unfortunately, C(15) was also quite prone to oxidation under these reaction conditions. Consequently, the fully oxidized trione was often isolated as a major by-product.



Scheme 78. Completion of the Total Synthesis of Bistramide C.

2.15. Comparison of Synthetic Bistramide to Authentic Bistramide

An authentic sample of bistramide C (**22**) was generously provided to us by Professor Biard from the Université de Nantes. Thus, we were able to physically analyze both the natural bistramide C sample[192] and the synthetic material[193] **22**. A comparison of the ^{1}H NMR data revealed no significant differences, as indicated in Table 13. Ironically, the ^{1}H NMR data of the bistramide C stereoisomer[114,132] and the authentic sample were also in very close agreement.

Clearly, the ^{1}H NMR spectroscopic data, alone, were not powerful enough to provide sufficient evidence in support of either **6** or synthetic **22**[136] as the unambiguous structural match to the authentic sample.

Table 13. Comparison of ^{1}H NMR Data for Natural Bistramide C ($CDCl_3$, ~5 mg/0.6 mL) vs. Synthetic Bistramide C **22** ($CDCl_3$, 1.3 mg/0.18 mL).

	Natural bistramide C (600 MHz)[192]			Synthetic bistramide C **22** (600 MHz)		
Hydrogen #	δ [ppm]	mult	J [Hz]	δ [ppm]	mult	J [Hz]
1-H	1.93	dd	6.9, 1.6	1.93	d	6.8
2-H	6.92	dq	13.7, 6.8	6.91	dq	15.5, 7.0
3-H	6.13	dd	15.8, 1.6	6.13	d	15.8
4-H	-	-	-	-	-	-
5-Ha	2.94-2.87	m		2.91	dd	17.1, 9.3
5-Hb	2.57-2.51	m		2.54	d	17.3
6-H	4.20	t	9.7	4.20	t	8.5
7-Ha	1.76-1.50	m		1.76-1.66	m	
7-Hb	1.45-1.30	m		1.45-1.30	m	
8-Ha	1.76-1.50	m		1.66-1.61	m	
8-Hb	1.45-1.30	m		1.45-1.30	m	
9-H	1.96-1.90	m		1.96-1.90	m	
10-H	0.87	d	7.0	0.86	d	6.9
11-H	4.10-4.05	m		4.06	dd	11.1, 4.3
12-Ha	2.83-2.73	m		2.78	dd	14.8, 12.0
12-Hb	2.14	d	12.5	2.14	d	15.1
13-H	-	-	-	-	-	-
14-Ha	3.52	ddd	13.8, 6.4, 5.5	3.52	ddd	13.3, 6.1, 5.9
14-Hb	3.23	ddd	12.7, 6.9, 5.7	3.23	ddd	13.2, 5.8, 5.6

15-H	3.73	*br* s		3.73	(app) t	4.9
16-H	2.43-2.35	m		2.42-2.36	m	
17-H	1.27	d	7.1	1.27	d	7.1
18-H	-	-	-	-	-	-
19-H	3.35-3.28	m		3.37-3.26	m	
20-Ha	1.90-1.80	m		1.90-1.79	m	
20-Hb	1.76-1.50	m		1.61-1.50	m	
21-Ha	1.76-1.50	m		1.76-1.66	m	
21-Hb	1.45-1.30	m		1.45-1.30	m	
22-H	3.14	dt	8.5, 2.0	3.13	(app) t	9.8
23-H	1.45-1.30	m		1.45-1.30	m	
24-H	0.82	d	6.5	0.82	d	6.3
25-Ha	1.76-1.50	m		1.61-1.50	m	
25-Hb	1.50-1.45	m		1.49-1.45	m	
26-Ha	1.76-1.50	m		1.66-1.61	m	
26-Hb	1.50-1.45	m		1.49-1.45	m	
27-H	-	-	-	-	-	-
28-Ha	1.76-1.50	m		1.61-1.50	m	
28-Hb	1.45-1.30	m		1.45-1.30	m	
29-Ha	1.90-1.80	m		1.90-1.79	m	
29-Hb	1.76-1.50	m		1.61-1.50	m	
30-Ha	1.76-1.50	m		1.61-1.50	m	
30-Hb	1.20-1.08	m		1.20-1.10	m	
31-H	3.50-3.40	m		3.49-3.42	m	
32-Ha	1.45-1.30	m		1.45-1.30	m	
32-Hb	1.45-1.30	m		1.45-1.30	m	
33-Ha	1.76-1.50	m		1.61-1.50	m	
33-Hb	1.45-1.30	m		1.45-1.30	m	

34-H	2.60-2.57	m		2.61-2.56	m	
35-H	1.05	d	6.6	1.05	d	6.5
36-H	6.42	d	9.7	6.41	d	9.8
37-H	-	-	-	-	-	-
38-H	1.77	d	1.2	1.77	*br* s	
39-H	-	-	-	-	-	-
40-H	2.33	s		2.33	*br* s	
NH, 13/14	7.35	*br* t		7.36	*br* t	5.4
NH, 18/19	7.00	*br* t		7.00	*br* t	5.1
OH	4.63	*br* s		4.64	d	5.2

The ^{13}C NMR analysis was quite illustrative (Table 14). The largest carbon chemical shift discrepancy between the natural (authentic) and the synthetic (**22)** samples proved to be a mere 0.06 ppm. This deviation was observed for only one carbon-C(2). In fact, more than 50% of all carbons in the molecule differed by 0.02 ppm or less! Obviously, the ^{13}C NMR analysis provided very strong support for the authenticity of synthetic **22**.[136] In addition, the dept135, in conjunction with the dept90 analysis revealed that **22** contained 6 quaternary centers, 12 sp carbons, 15 sp^2 carbons and 7 sp^3 carbons.

Table 14. Comparison of ^{13}C NMR Data for Natural Bistramide C ($CDCl_3$, ~5 mg/0.6 mL) vs. Synthetic Bistramide C **22** ($CDCl_3$, 1.3 mg/0.18 mL).

	Natural bistramide C (151 MHz)[192]	Synthetic bistramide **22** (151 MHz)	$\Delta\delta_{nat.-synth.}$
Carbon #	δ [ppm]	δ [ppm]	Δδ [ppm]
1	18.42	18.45	-0.03
2	**144.55**	**144.61**	**-0.06**
3	132.05	132.05	0.00
4	198.92	198.95	-0.03
5	45.23	45.24	-0.01
6	64.63	64.60	0.03
7	30.80	30.82	-0.02
8	26.46	26.46	0.00
9	33.32	33.34	-0.02
10	17.17	17.21	-0.04
11	74.84	74.87	-0.03
12	32.19	32.17	0.02
13	173.55	173.58	-0.03
14	44.67	44.70	-0.03
15	73.87	73.89	-0.02
16	43.28	43.28	0.00
17	15.52	15.54	-0.02
18	175.11	175.12	-0.01
19	39.52	39.52	0.00
20	25.86	25.88	-0.02
21	30.46	30.46	0.00
22	74.34	74.36	-0.02
23	34.80	34.81	-0.01
24	18.01	18.02	-0.01
25	27.85	27.85	0.00

26	36.02	36.02	0.00
27	95.43	95.44	-0.01
28	35.41	35.42	-0.01
29	19.08	19.08	0.00
30	31.32	31.33	-0.01
31	68.92	68.94	-0.02
32	34.26	34.28	-0.02
33	32.89	32.90	-0.01
34	33.80	33.82	-0.02
35	20.07	20.09	-0.02
36	149.46	149.50	-0.04
37	136.20	136.20	0.00
38	11.38	11.40	-0.02
39	200.39	200.43	-0.04
40	25.57	25.60	-0.03

Average $\Delta\delta[\text{ppm}]_{\text{nat.-synth.}} = 0.018$

More notable, however, were the differences (Table 15) between the ^{13}C NMR literature data for bistramide C[102] and our ^{13}C NMR data[192] for an authentic sample of bistramide C (**22**). Of course, these data should be nearly identical. Surprisingly, the ^{13}C NMR data reported for bistramide C[102] and our independent analysis of an authentic sample[192] do not match. The chemical shifts corresponding to C(20) and C(34) differ greatly. Our analysis of the authentic material revealed carbon chemical shifts of 25.86 ppm for C(20) and 33.80 ppm for C(34) as compared to the literature report of 29.89 and 31.80 ppm, respectively. Ironically, the discrepancy at C(34) had greatly influenced our earlier analysis. Clearly, we had been under the

incorrect impression that this specific data point corroborated our van't Hoff analysis conclusions (Figure 25). However, in light of our recent spectroscopic findings, NMR differences between diastereomer **6** and the natural product do not reflect configurational isomerisms at specific carbons.

Table 15. Comparison of ^{13}C NMR Data for Literature Reported Bistramide C vs. Our Independent Analysis of an Authentic Sample of Bistramide C ($CDCl_3$, ~5 mg/0.6 mL).

	Natural bistramide C-obs. (151 MHz)	Natural bistramide C-lit. (151 MHz)[102]	$\Delta\delta_{obs.-lit.}$
Carbon #	δ [ppm]	δ [ppm]	Δδ [ppm]
1	18.42	18.38	0.10
2	144.55	144.20	0.35
3	132.05	132.16	-0.11
4	198.92	198.39	0.53
5	45.23	45.36	-0.13
6	64.63	64.94	-0.31
7	30.80	30.82	-0.02
8	26.46	26.60	-0.14
9	33.32	32.96	0.36
10	17.17	17.09	0.08
11	74.84	74.80	0.04
12	32.19	32.53	-0.34
13	173.55	173.40	0.15
14	44.67	44.73	-0.06
15	73.87	73.80	0.07
16	43.28	43.37	-0.09
17	15.52	15.55	-0.03
18	175.11	175.10	0.01

19	39.52	39.58	-0.06
20	**25.86**	**29.89**	**-4.03**
21	30.46	30.56	-0.10
22	74.34	74.30	0.04
23	34.80	34.86	-0.06
24	18.01	18.05	-0.04
25	27.85	28.00	-0.15
26	36.02	36.16	-0.14
27	95.43	95.20	0.23
28	35.41	35.53	-0.12
29	19.08	19.20	-0.12
30	31.32	31.41	-0.09
31	68.92	68.90	0.02
32	34.26	34.84	-0.58
33	32.89	33.38	-0.49
34	**33.80**	**31.80**	**2.00**
35	20.07	20.10	-0.03
36	149.46	149.26	0.20
37	136.20	136.29	-0.09
38	11.38	11.46	-0.08
39	200.39	200.17	0.22
40	25.57	25.54	0.03

Average $\Delta\delta[\text{ppm}]_{\text{nat.-synth.}} = 0.030$

The ^{13}C NMR data for the stereoisomer **6**[114,132] as compared to the ^{13}C NMR data[192] for the authentic sample revealed a different set of discrepancies (Table 16). Ironically, the chemical shifts at C(34) corresponded reasonably well, since a mere difference of 0.40 ppm is generally

regarded as acceptable. However the chemical shifts at C(20) differed drastically. The bistramide C stereoisomer **6** is characterized by a chemical shift of 29.9 ppm for C(20). Our ^{13}C NMR analysis of the authentic sample of the natural product revealed a chemical shift of 25.86 ppm. Clearly, a difference of 4.04 ppm is highly unusual. The next largest deviation was only 0.68 ppm for C(31), which is relatively close to stereocenter C(34). In fact, on average, the carbon chemical shifts differed by 0.35 ppm as compared to only 0.018 ppm for synthetic **22** versus that of the natural sample (Table 14).

Both C(20) and C(31) were introduced as part of the spiroketal fragment. Upon the completion of the synthesis of **6**, our chiroptical analyses indicated that the spiroketal segment (as compared to the other two fragments) needed to undergo the least amount of stereochemical revision. The current ^{13}C NMR comparison suggests that there is no intuitive correlation between bistramide C stereoisomers and their corresponding ^{13}C chemical shifts. We currently do not understand the reason for this lack of correlation.

Table 16. Comparison of ^{13}C NMR Data for Bistramide C Steroisomer **6** vs. Our Independent Analysis of an Authentic Sample of Bistramide C ($CDCl_3$, ~5 mg/0.6 mL).

	Bistramide C stereoisomer **6** (151 MHz)	Natural bistramide C-obs. (151 MHz)[192]	$\Delta\delta_{\mathbf{6}\text{-nat.}}$
Carbon #	δ [ppm]	δ [ppm]	δ [ppm]
1	18.6	18.4	0.2
2	144.8	144.6	0.2
3	132.3	132.1	0.2
4	199.2	198.9	0.3
5	45.4	45.2	0.2
6	64.9	64.6	0.3
7	31.0	30.8	0.2
8	26.7	26.5	0.2
9	33.5	33.3	0.2
10	17.4	17.2	0.2
11	75.0	74.8	0.2
12	32.5	32.2	0.3
13	173.7	173.6	0.1
14	44.9	44.7	0.2
15	74.0	73.9	0.1
16	43.5	43.3	0.2
17	15.7	15.5	0.2
18	175.4	175.1	0.3
19	39.7	39.5	0.2
20	**29.9**	**25.9**	**4.0**
21	30.7	30.5	0.2
22	74.5	74.3	0.2
23	35.1	34.8	0.3
24	18.2	18.0	0.2

25	28.1	27.9	0.2
26	36.3	36.0	0.3
27	95.7	95.4	0.3
28	35.6	35.4	0.2
29	19.3	19.1	0.2
30	31.5	31.3	0.2
31	69.6	68.9	0.7
32	34.6	34.3	0.3
33	33.5	32.9	0.6
34	34.2	33.8	0.4
35	20.4	20.1	0.3
36	149.6	149.5	0.1
37	136.6	136.2	0.4
38	11.6	11.4	0.2
39	200.6	200.4	0.2
40	25.8	25.6	0.2

Average $\Delta\delta[\text{ppm}]_{\text{nat.-synth.}} = 0.3$

The optical rotations were compared as well. As expected, the $[\alpha]_D$ of synthetic **22**, +7.3 (*c* 0.05, CH_2Cl_2, 22 °C), was in closer agreement to the literature value[102] for natural bistramide C, +10 (*c* 0.05, CH_2Cl_2, 20 °C), as compared to that of the stereoisomer **6**,[114,132] +34 (*c* 0.05, CH_2Cl_2, 22 °C). Our independent measurement[136] of the optical rotation of the natural product revealed a different value, $[\alpha]_D$ 3.9 (*c* 0.05, CH_2Cl_2, 22 °C). There is still some question with regards to the validity of the reported $[\alpha]_D$ values due to the surprising (and perhaps, coincidental) similarity in the measurements for bistramides A-D: +10 (A), +10 (B), +10 (C) and

+8 (D). The $[\alpha]_D$ for bistramide K is reported to be +20. All measurements were reported in CH_2Cl_2 at 20 °C and at a concentration of 0.05 mg/mL.

A circular dichroism (CD) analysis provided additional spectroscopic support for the equivalency of synthetic **22** and natural bistramide. The CD's for synthetic **22**, an authentic sample of the natural product and stereoisomer **6** are depicted below (Figures 30-32, respectively). The similarities between synthetic **22** and the natural sample are quite pronounced. The spectrum corresponding to the bistramide C stereoisomer **6** differs greatly from the former compounds.

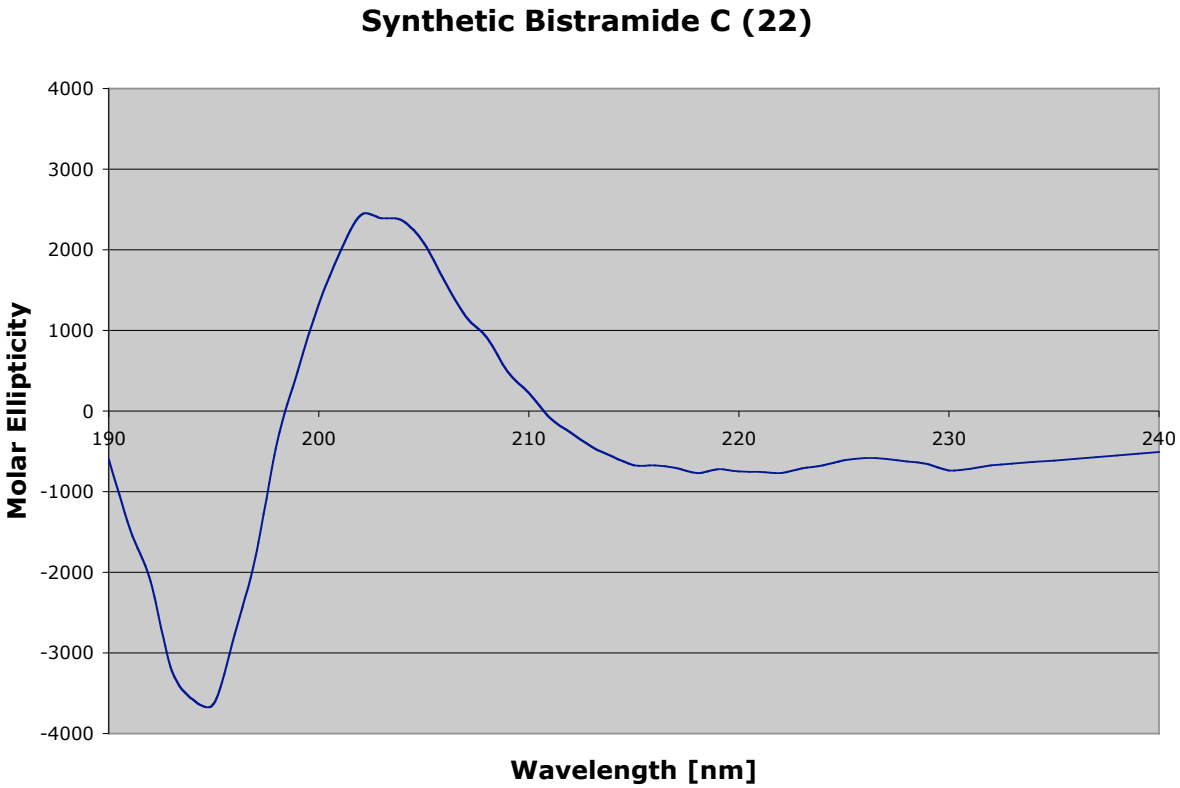
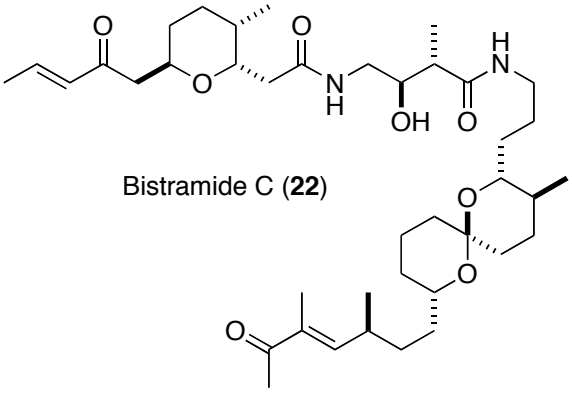


Figure 30. CD Spectrum of the Synthetic Bistramide C **22** (MeOH, *c* 0.712 mM).



Bistramide C (**22**)

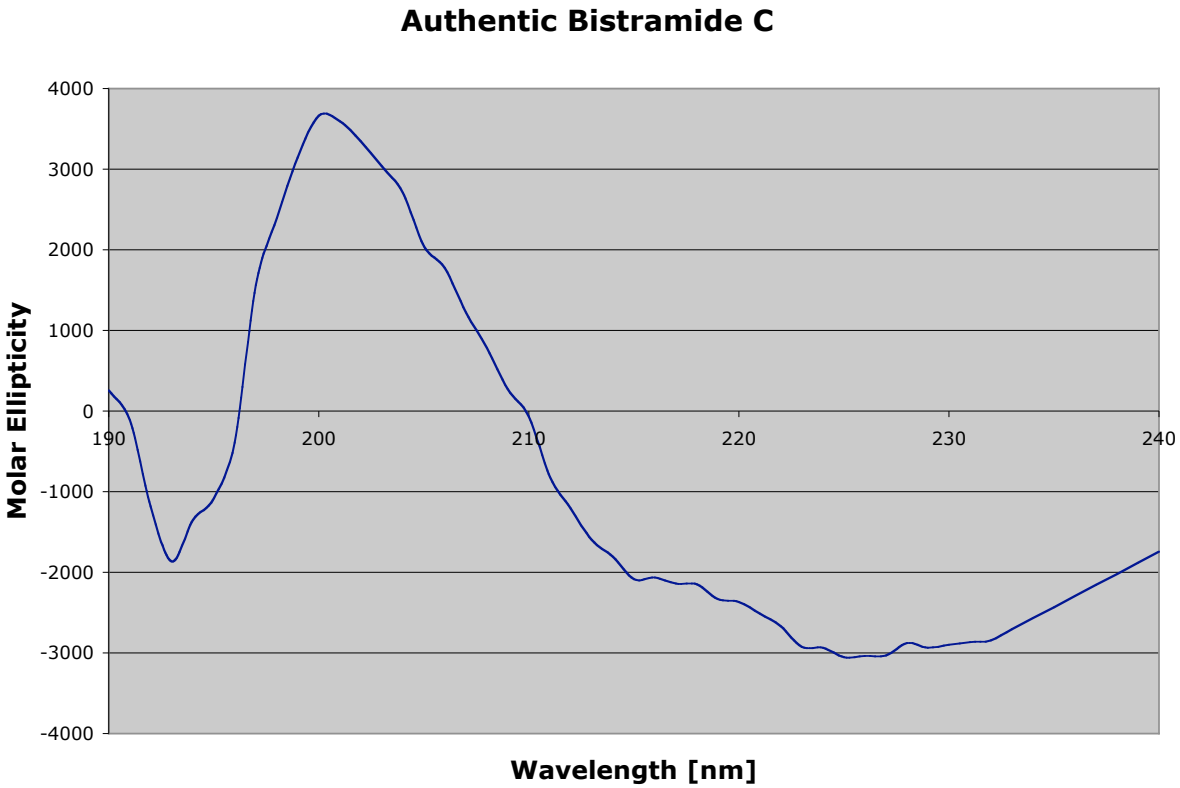
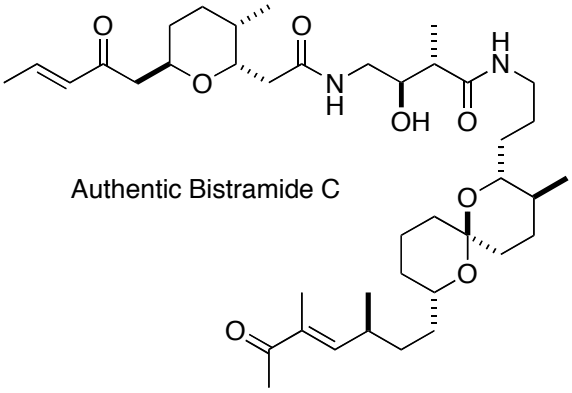


Figure 31. CD Spectrum of an Authentic Sample of Bistramide C (MeOH, *c* 0.723 mM).



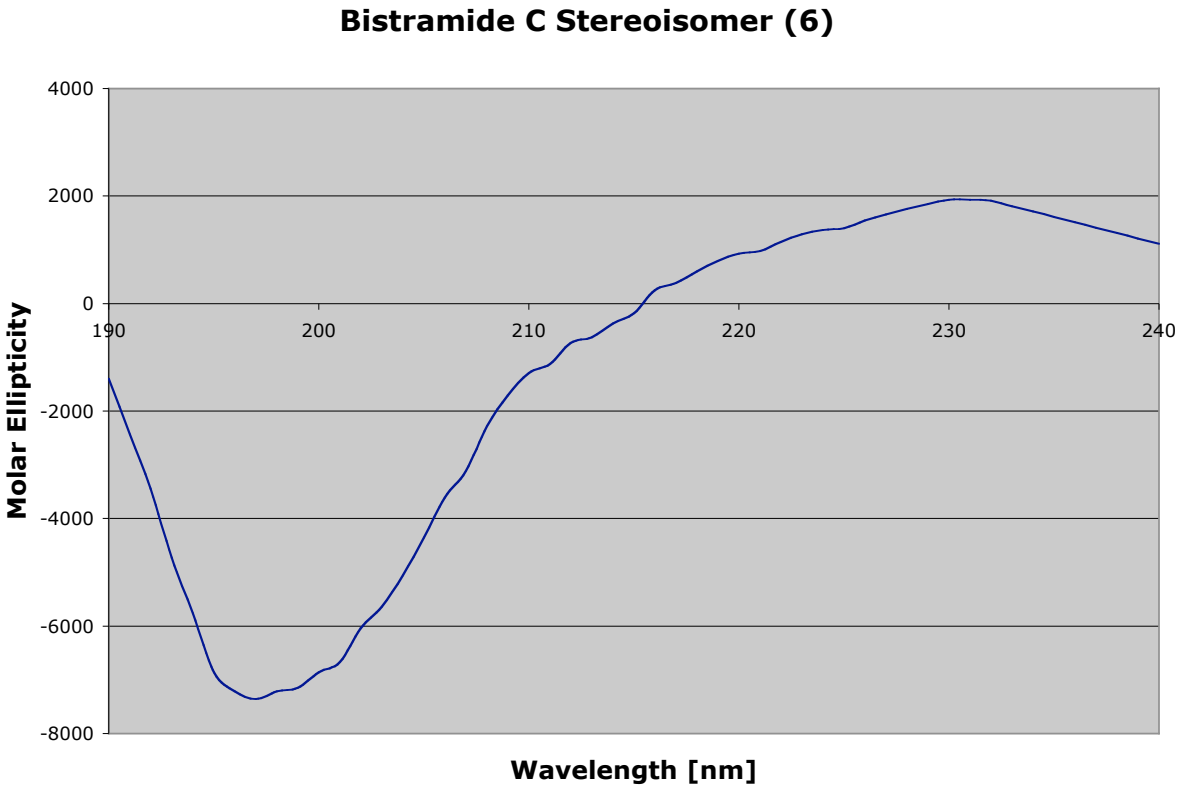
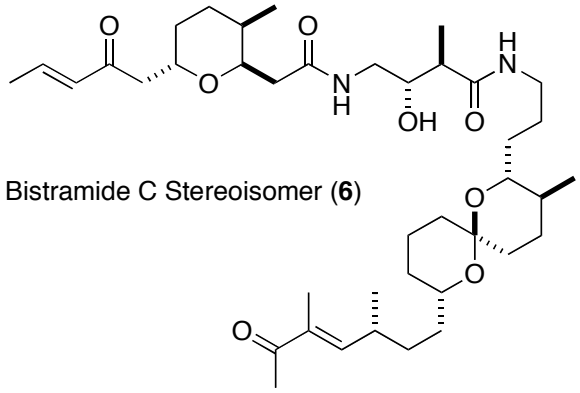


Figure 32. CD Spectrum of the Bistramide C Stereoisomer **6** (MeOH, c 0.712 mM).



2.16. Conclusion

We successfully completed the first total synthesis of the *Lissoclinum bistratum* natural product bistramide C. We relied upon a highly convergent three-component coupling strategy for the synthesis of the target molecule. The primary amine precursors to the two key amide bonds were masked as azides. The use of azides ultimately allowed for the facile assembly of the three segments via standard coupling practices with minimal protecting group manipulations. Some of the key synthetic highlights include our water-accelerated, chiral zirconocene-catalyzed methylalumination methodology. We also employed P.A. Evans' tandem $BiBr_3$-initiated cyclization-allylation methodology for the construction of the 2,6-*trans*-substituted tetrahydropyran of the pyran-acid fragment. The synthesis of the spiroketal featured both a hypervalent iodine-mediated C-H insertion reaction and Nelson's acyl halide-aldehyde condensation (AAC) chemistry.

The ^{1}H and ^{13}C spectroscopic properties of synthetic bistramide C **22** are in exact agreement with those corresponding to a measurement of an authentic sample of the natural product. A comparison of the optical rotations also revealed a close agreement between both synthetic **22** and the literature value and synthetic **22** and our $[\alpha]_D$ measurement for the authentic material. In addition, a CD analysis further corroborated the fact that the configuration of our synthetic material **22** was analogous to that of the natural product, bistramide C and that the previously prepared **6** was indeed a stereoisomer. Thus, our current synthetic efforts in conjuction with NMR methodology and an assortment of chiroptical tools culminated in the first total synthesis of the target molecule. The total synthesis of bistramide C also provided additional validation for our original stereochemical predictions. Furthermore, it demonstrated the power and importance total synthesis plays in the structure elucidation of natural products.

2.17. Experimental

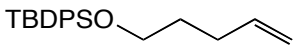
2.17.1. General

All moisture-sensitive reactions were performed under an atmosphere of N_2. All glassware was dried in an oven at 140 °C prior to use. THF and Et_2O were dried by distillation over Na/benzophenone. Dry toluene and CH_2Cl_2 were obtained by distillation from CaH_2 or from a purification system. Unless otherwise noted, dry solvents were used. However, reagents were used without further purification, unless otherwise specified. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with a basic $KMnO_4$ solution (1.0 g of $KMnO_4$, 1.0 g of K_2CO_3 and 2.0 mL of 5% aq. NaOH in 100 mL of water), an anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 3.5 mL of concentrated H_2SO_4 and 2.0 mL of glacial HOAc in 92 mL of 95% EtOH), a PMA solution (5.0 g of phosphomolybdic acid in 100 mL of EtOH), ninhydrin (0.3 g of ninhydrin, 3.0 mL glacial HOAc in 100 mL of *n*-butyl alcohol) or Vaughn's reagent (4.8 g of ammonium molybdate, 0.2 g of $CeSO_4$ and 10 mL of H_2SO_4 in 90 mL of water).

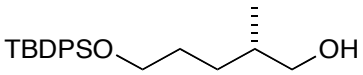
NMR spectra were recorded at 300 MHz/75 MHz ($^1H/^{13}C$ NMR), 500 MHz/125 MHz ($^1H/^{13}C$ NMR) or 600 MHz/150 MHz ($^1H/^{13}C$ NMR) in $CDCl_3$ unless stated otherwise using a Bruker AVANCE 300 MHz, a Bruker DRX 500 MHz or a Bruker 600 MHz spectrometer at 21 °C. Chemical shifts (δ) are reported in parts per million and the residual solvent peak was used as an internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, sx=sextet, m=multiplet, *br*=broad), integration and coupling constants. Melting points were measured on a MelTemp melting point apparatus with a

digital temperature read-out. IR spectra were obtained on a Nicolet AVATAR 360 FT-IR E.S.P. spectrometer. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. CD measurements were obtained on a JASCO J715 spectrometer.

2.17.2. Experimental Procedures



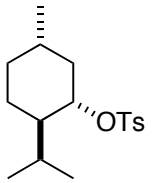
1-(*tert*-Butyldiphenylsilanyloxy)-4-pentene.[194] To a solution of 4-penten-1-ol **26** (1.0 g, 12 mmol) in CH_2Cl_2 (30 mL) was added DMAP (142 mg, 1.16 mmol), imidazole (1.20 g, 17.6 mmol) and TBDPS-Cl (3.8 g, 3.6 mL, 14 mmol) at 0 °C. After 3 h at 0 °C, the reaction mixture was diluted with Et_2O (100 mL) and washed with saturated aqueous $NaHCO_3$ followed by brine. Then, the organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 100:1) delivered 3.6 g (95%) of 1-(*tert*-butyldiphenylsilanyloxy)-4-pentene: ^{1}H NMR δ 7.68 (*app* d, 4 H, J = 6.9 Hz), 7.44-7.37 (m, 6 H), 5.88-5.71 (m, 1 H), 5.01 (d, 1 H, J = 17.1 Hz), 4.95 (d, 1 H, J = 9.0 Hz), 3.69 (t, 2 H, J = 6.4 Hz), 2.17 (*app* q, 2 H, J = 7.1 Hz), 1.67 (p, 2 H, J = 6.5 Hz), 1.06 (s, 9 H).



(2*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-2-methylpentan-1-ol (31).[195] A slight excess of methylaluminoxane (MAO) (10 weight % solution in toluene (Aldrich), 6.2 mL, 5.4 g, 9.3 mmol) was transferred to a 50 mL Schlenk flask containing a stir bar. Toluene and other volatiles were removed under reduced pressure (≤0.1 mm Hg) and the remaining solid was

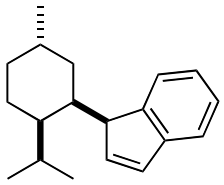
dissolved in degassed[196] CH_2Cl_2 (6.8 mL). Neat $AlMe_3$ (1.90 g, 26.8 mmol) was transferred from the glovebox to another 100 mL round bottom flask possessing a sidearm. The flask was then reattached to the manifold line and the $AlMe_3$ was subsequently diluted with degassed CH_2Cl_2 (6.0 mL). Then, a solution of (+)-bis(1-neomenthylindenyl)zirconium dichloride **30** (118 mg, 0.176 mmol) in degassed CH_2Cl_2 (14.0 mL) was added via cannula to the aforementioned $AlMe_3$ solution at 0 °C. The resultant bright yellow solution was warmed to room temperature over 30 min and then re-cooled to 0 °C prior to the dropwise addition via cannula of the previously prepared MAO solution. The catalyst/$AlMe_3$ solution darkened in color upon the introduction of MAO and a red color persisted shortly thereafter (*i.e.* through the midpoint of the addition). The resultant dark red (or purple solution) was warmed to room temperature and stirred for at least 30 min prior to the addition of a solution of 1-(*tert*-butyldiphenylsilanyloxy)-4-pentene (2.02 g, 6.22 mmol) in degassed CH_2Cl_2 via cannula (6.0 mL + 1.0 mL rinse of flask and cannula). The reaction mixture was stirred at +5 °C for 17 h, cooled to –20 °C, and O_2 gas[197] was bubbled into the solution at a rapid rate. The reaction mixture was gradually warmed to room temperature during this process. Following the removal of all volatiles, the remaining yellow sludge was dissolved in a minimal quantity of CH_2Cl_2 (50 mL), transferred to an Erlenmeyer flask and cooled to 0 °C prior to the addition of a solution of 10% NaOH (30 mL). The heterogeneous mixture was stirred vigorously at 0 °C for approximately 1 h. Finally, the aqueous phase was separated from the organic phase and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Chromatography on SiO_2 (Hexanes/EtOAc, 1:0 → 20:1 → 8:1 → 4:1 → 2:1) delivered 1.73 g (78%) of **31** in 83.4% ee as a clear, colorless oil. The enantiomeric excess was determined by chiral HPLC on a Chiralcel

OD column (1% *i*-PrOH/Hexane, 0.5 mL/min, UV detection, λ =254 nm, R_t(**31**): 27.71 min and R_t(minor): 25.58 min): $[\alpha]_D$ -3.4 (*c* 0.50, $CHCl_3$, 22 °C); IR (neat) 3346, 3071, 3049, 2931, 2858, 1589, 1472, 1427, 1389, 1361, 1111, 938, 823, 793, 740, 701, 688 cm^{-1}; ^1H NMR δ 7.74-7.71 (m, 4 H), 7.49-7.39 (m, 6 H), 3.71 (t, 2 H, *J* = 6.4 Hz), 3.51 (dd, 1 H, *J* = 10.5, 5.8 Hz), 3.43 (dd, 1 H, *J* = 10.5, 6.5 Hz), 1.76-1.44 (m, 3 H), 1.26-1.16 (m, 2 H), 1.11 (s, 9 H), 0.94 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 135.5, 134.0, 129.5, 127.5, 68.1, 64.1, 35.4, 29.8, 29.2, 26.8, 19.2, 16.5; MS (EI) *m/z* (rel intensity) 299 ($[M–C_4H_9]^+$, 6), 281 (6), 229 (6), 221 (4), 217 (3), 213 (2), 200 (19), 199 (64), 197 (14), 181 (13), 139 (24), 135 (13); HRMS (EI) calcd for $C_{22}H_{36}O_2Si$ (M-C_4H_9) 299.1467, found 299.1478.



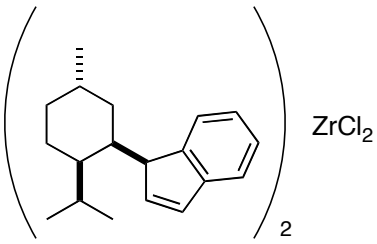
(+)-(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl *p*-toluenesulfonate (33).[141] A solution of (+)-menthol (**32)** (20.43 g, 0.1307 mol) in pyridine (46 mL) was cooled to 0 °C prior to the portion wise addition of *p*-toluenesulfonyl chloride (27.40 g, 0.1438 mol) over 20 min. The reaction mixture was warmed to room temperature and allowed to stir for an additional 4 h. Then, it was added to an aqueous acid solution (170 g of ice/90 mL of concentrated HCl) and the resulting solid precipitate was collected by vacuum filtration. To ensure maximum dryness in a relatively short time period, the white crystalline solid was dissolved in Et_2O and washed with water. The organic phase was dried ($MgSO_4$), filtered (gravity filtration) and concentrated *in vacuo* to give 40.6 g (100%) of **33** as a white crystalline solid: ^1H NMR δ 7.81 (d, 2 H, *J* = 8.3 Hz), 7.33 (d, 2 H, *J* = 8.0 Hz), 4.40 (*app* td, 1 H, *J* = 10.8, 4.6 Hz), 2.45 (*br* s, 3 H), 2.22-2.09

(m, 1 H), 1.97-1.84 (m, 1 H), 1.72-1.58 (m, 2 H), 1.50-1.31 (m, 2 H), 1.20 (*app* dd, 2 H, J = 12.0, 7.0 Hz), 1.06-0.91 (m, 1 H), 0.89 (d, 3 H, J = 6.5 Hz), 0.84 (d, 3 H, J = 7.0 Hz), 0.53 (d, 3 H, J = 6.9 Hz).



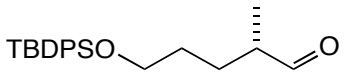
(-)-3-[(1'*R*,2'*R*,5'*S*)-2'-Isopropyl-5'-methylcyclohexyl]indene (34).[141] A solution of indene (8.33 g, 71.7 mmol) in THF (65 mL) was cooled to –78 °C prior to the dropwise addition (via an addition funnel) of *n*-BuLi (1.6 M in hexanes, 44.8 mL, 71.7 mmol). The freshly prepared indenyl lithium solution was stirred at –78 °C for approximately 1 h and then warmed to 0 °C prior to the dropwise addition of a solution of **33** (19.4 g, 62.4 mmol) in THF (93 mL). The resulting mixture was warmed to room temperature and then heated at reflux for 72 h. Then, the purple/black solution was cooled to room temperature, hydrolyzed with water (100 mL) and diluted with Et_2O (50 mL). The organic phase was separated from the aqueous phase and washed with water (3 x 100 mL). The aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Ligand purification consisted of three stages. First, the black residue was submitted to a Kugelrohr distillation (80 °C, ≤0.1 mm Hg) to remove all volatiles. The clear, colorless oily distillate was discarded and the brown residue remaining in the pot was purified further via sublimation (100-102 °C, ≤0.1 mm Hg). Finally, the resultant yellow solid was submitted to column chromatography on SiO_2 (Hexanes) to give 6.09 g (33%) of **34** as a colorless solid: ^{1}H NMR δ 7.48 (d, 1 H, J = 7.4 Hz), 7.38 (*app* d, 1 H, J = 7.3 Hz), 7.35-7.27 (m, 1 H), 7.23-7.20

(m, 1 H), 6.38 (*br* s, 1 H), 3.37 (*br* s, 2 H), 3.37-3.30 (m, 1 H), 1.94-1.87 (m, 1 H), 1.85-1.75 (m, 2 H), 1.70-1.40 (m, 3 H), 1.29-1.08 (m, 2 H), 1.05-1.01 (m, 1 H), 0.92 (d, 3 H, J = 6.6 Hz), 0.79 (d, 3 H, J = 6.5 Hz), 0.72 (d, 3 H, J = 6.6 Hz).



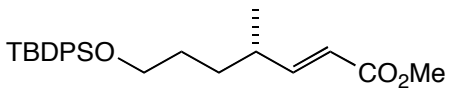
(+)-Bis(1-neomenthylindenyl)zirconium dichloride (30).[141] A solution of **34** (855 mg, 3.36 mmol) in degassed Et_2O (18 mL) was cooled to –30 °C prior to the dropwise addition of MeLi (1.4 M in Et_2O, 2.6 mL, 3.6 mmol). The reaction mixture was warmed to room temperature and allowed to stir for 2.5 h. Then, the volatiles were removed under reduced pressure.[198] The resulting red/purple solid was dissolved in degassed THF (45 mL) and cooled to –78 °C prior to its dropwise addition via cannula to a –78 °C suspension of $ZrCl_4(THF)_2$ (643 mg, 1.70 mmol) in degassed toluene (11 mL). The heterogenous mixture was warmed to room temperature gradually over 2 h, stirred at room temperature under N_2 and shielded from light for an additional 12 to 15 h. The reaction solvents were removed under reduced pressure and the remaining solid was washed with degassed pentane (2 x 20 mL). (pentane was added via syringe to the residue under N_2 with stirring. The solid was allowed to settle and the orange (ligand-containing) solution was decanted via cannula): The remaining (catalyst-containing) solid was treated with degassed CH_2Cl_2 (5-6 mL) and the organic solution was subsequently decanted via cannula into another tared, dry round bottom flask, leaving behind the LiCl precipitate. The CH_2Cl_2 was removed under reduced pressure and the yellow solid was treated once more with CH_2Cl_2, decanted and concentrated. Schlenk techniques can also be employed for this catalyst

isolation. The complex **30** was isolated in a yield of 38% (420 mg): ^{1}H NMR δ 7.76 (d, 1 H, *J* = 8.7 Hz), 7.68 (d, 1 H, *J* = 8.5 Hz), 7.37-7.32 (m, 1 H), 7.19-7.14 (m, 1 H), 6.61 (d, 1 H, *J* = 2.9 Hz), 5.56 (d, 1 H, *J* = 2.8 Hz), 3.81-3.67 (m, 1 H), 2.25-2.00 (m, 2 H), 2.00-1.67 (m, 2 H), 1.67-1.38 (m, 2 H), 1.38-1.13 (m, 2 H), 1.13-0.83 (m, 1 H), 0.98 (d, 3 H, *J* = 6.3 Hz), 0.63 (d, 3 H, *J* = 6.6 Hz), -0.02 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR (125 MHz) δ 128.3, 126.6, 126.1, 125.8, 125.1, 124.5, 122.4, 97.9, 48.0, 39.0, 36.0, 34.1, 28.8, 23.5, 22.2 (2C), 18.2.

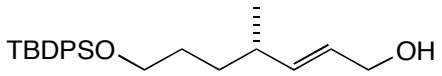


(2*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-2-methylpentanal.[199] To a solution of alcohol **31** (0.350 g, 0.983 mmol) in CH_2Cl_2 (10 mL) was added 10 mL of a pH 8.6 aqueous buffer, a solution of $NaHCO_3$ (4.20 g, 50.0 mmol) and Na_2CO_3 (0.530 g, 5.00 mmol) in 100 mL of H_2O, and solid KBr (11.7 mg, 98.3 μmol). Then, catalytic TEMPO (15.4 mg, 98.5 μmol) was introduced followed by NaOCl (1.65 mL) at 0 °C. The sodium hypochlorite solution was added in roughly equimolar quantities every 15 min over the span of 1.5 h. The biphasic mixture was maintained at 0 °C for an additional 1.5 h. Then, the organic phase was separated from the aqueous phase and the latter was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic extracts were washed with 1.0 M HCl containing KI (65.4 mg, 0.394 mmol), 1.0 M $Na_2S_2O_3$, water and brine. Finally, the organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an orange oil. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1) afforded 320 mg (92%) of **(**2*S*)-5-(*tert*-butyldiphenylsilanyloxy)-2-methylpentanal: $[\alpha]_D$ +10.5 (*c* 1.0, $CHCl_3$, 22 °C); IR (neat) 3070, 3050, 2929, 2858, 2708, 1962, 1897, 1834, 1727, 1589, 1462, 1428, 1390, 1112, 826, 703 cm^{-1}; ^{1}H NMR δ 9.61 (s, 1 H), 7.68-7.65 (m, 4 H), 7.44-7.38 (m, 6 H), 3.68 (t, 3 H, *J* = 6.1 Hz), 2.34 (*app* sxd, 1 H, *J* = 6.8, 1.9 Hz), 1.80-1.75 (m, 1 H), 1.64-157 (m, 2 H), 1.49-

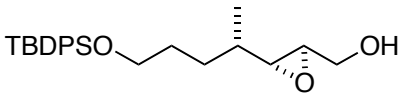
1.40 (m, 1 H), 1.09 (d, 3 H, J = 7.0 Hz), 1.06 (*br* s, 9 H); ^{13}C NMR δ 205.2, 135.5, 133.8, 129.6, 127.6, 63.5, 45.9, 29.7, 26.8, 26.8, 19.2, 13.3; MS (EI) *m/z* (rel intensity) 297 ($[M-C_4H_9]^+$, 35), 279 (38), 267 (53), 235 (58), 219 (59), 201 (66), 189 (58), 179 (57), 159 (88), 135 (65), 123 (98), 117 (79), 105 (52), 91 (100), 81 (69), 78 (66), 69 (58), 61 (61), 55 (65); HRMS (EI) calcd for $C_{18}H_{21}O_2Si$ ($M-C_4H_9$) 297.1311, found 297.1312.



(*S*,*E*)-Methyl 7-(*tert*-butyldiphenylsilanyloxy)-4-methylhept-2-enoate (36).[136] To a suspension of (*S*)-5-(*tert*-butyldiphenylsilanyloxy)-2-methylpentanal (1.20 g, 3.44 mmol) and LiCl (5-10 equivalents, previously dried under vacuum at 140 °C for 15 h and flame-dried (x 3) directly before use) in dry acetonitrile (41 mL) was added trimethylphosponoacetate **35** (0.956 g, 0.850 mL, 5.25 mmol) at room temperature followed by diisopropylethylamine (0.534 g, 0.720 mL, 4.13 mmol) at 0 °C. The ice bath was removed immediately following the addition of the amine base. After an additional 24 h, the yellow, cloudy solution was diluted with brine and the aqueous phase was subsequently extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (x 3) (Hexanes/EtOAc, 1:0 → 200:1 → 100:1 → 75:1) gave 1.18 g (85%) of **36** as a light yellow oil: $[\alpha]_D$ +15.1 (*c* 0.80, $CHCl_3$, 22 °C); IR (neat) 3063, 2932, 2858, 1725, 1655, 1428, 1271, 1174, 1111, 815, 738, 702, 687 cm^{-1}; ^{1}H NMR δ 7.72-7.69 (m, 4 H), 7.48-7.38 (m, 6 H), 6.90 (dd, 1 H, J = 15.7, 7.9 Hz), 5.80 (dd, 1 H, J = 15.7, 0.6 Hz), 3.76 (s, 3 H), 3.69 (t, 2 H, J = 6.1 Hz), 2.32 (septet, 1 H, J = 6.7 Hz), 1.64-1.44 (m, 4 H), 1.10 (*br* s, 9 H), 1.07 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 167.2, 154.6, 135.5, 133.9, 129.5, 127.6, 119.3, 63.7, 51.9, 36.2, 32.1, 30.0, 26.8, 19.4, 19.1; HRMS (ESI) calcd for $C_{25}H_{34}O_3SiNa$ (M+Na) 433.2175, found 433.2180.



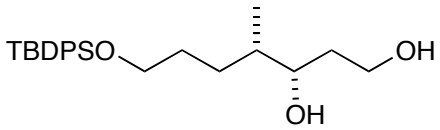
(*S*,*E*)-7-(*tert*-Butyldiphenylsilanyloxy)-4-methylhept-2-en-1-ol.[136] To a –78 °C solution of enoate **36** (1.53 g, 3.73 mmol) in CH_2Cl_2 (80 mL) was added diisobutylaluminum hydride (1.0 M solution in hexanes, 12.0 mL, 12.0 mmol) dropwise over the span of 17 min. The reaction mixture was stirred at –78 °C for 1.5 h. Then, 1.0 M tartaric acid (16 mL) and brine (16 mL) were added to the solution. The dry ice/acetone bath was removed during the course of the aqueous quench. The heterogeneous mixture was allowed to stir for 15 h. Finally, the organic layer was extracted into EtOAc (3 x 75 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1) gave 1.40 g (98%) of (*S*,*E*)-7-(*tert*-butyldiphenylsilanyloxy)-4-methylhept-2-en-1-ol as a clear, colorless oil: IR (neat) 3333, 3071, 3049, 2998, 2931, 2858, 1659, 1589, 1472, 1428, 1389, 1188, 1110, 1007, 972, 823, 797, 740, 701 cm^{-1}; ^1H NMR δ 7.78-7.75 (m, 4 H), 7.62-7.41 (m, 6 H), 5.69-5.56 (m, 2 H), 4.20-4.10 (m, 2 H), 3.74 (t, 2 H, J = 6.5 Hz), 2.19 (septet, 1 H, J = 6.6 Hz), 1.99 (*br* s, 1 H, OH), 1.69-1.57 (m, 2 H), 1.50-1.39 (m, 2 H), 1.15 (*br* s, 9 H), 1.05 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 138.6, 135.5, 134.0, 129.5, 127.5, 127.3, 64.0, 63.6, 36.0, 32.8, 30.2, 26.8, 20.4, 19.1; MS (EI) *m/z* (rel intensity) 325 ($[M-C_4H_9]^+$, 11), 307 (25), 229 (22), 200 (27), 199 (84), 197 (18), 183 (25), 182 (17), 139 (18), 135 (15), 110 (16), 109 (100), 81 (26), 77 (15), 67 (67); HRMS (EI) calcd for $C_{24}H_{34}O_2Si$ ($M-C_4H_9$) 325.1624, found 325.1639.



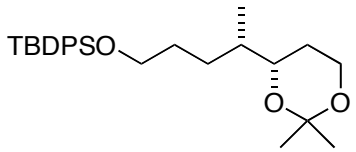
{(2*R*,3*R*)-3-[(*S*)-5-(*tert*-Butyldiphenylsilanyloxy)pentan-2-yl]oxiran-2-yl}methanol.[136]

To a –20 °C slurry of 4Å MS and D-(-)-DIPT (1.05 g, 0.950 mL, 3.83 mmol) in CH_2Cl_2 (40 mL) was added Ti(O-*i*Pr)$_4$ (1.06 g, 1.10 mL, 3.19 mmol). Approximately 35 min later, an excess of TBHP (6.0 M in isooctane,[200] 1.5 mL, 9.0 mmol) was introduced. The resultant mixture was stirred at –20 °C for 40 min prior to the dropwise addition of a solution of (*S*,*E*)-7-(*tert*-butyldiphenylsilanyloxy)-4-methylhept-2-en-1-ol (1.40 g, 3.66 mmol) in CH_2Cl_2 (23 mL) via cannula. After 24 h at –20 °C, H_2O was added to the reaction mixture to hydrolyze the Ti(O-*i*Pr)$_4$ (20 x's the weight of the Lewis acid, 21.2 g, 1.18 mol). The mixture was warmed to room temperature during the course of the addition. Then, a 30% aqueous solution[146] of NaOH/saturated NaCl (3.5 mL) was introduced in an effort to saponify the tartrate ester. The biphasic mixture was allowed to stir for several hours until phase separation was observed. Then, the organic phase was removed and the remaining aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered through a pad of celite and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1 → 1:1) gave a minor diastereomer and 1.40 g (96%) of {(2*R*,3*R*)-3-[(*S*)-5-(*tert*-butyldiphenylsilanyloxy)pentan-2-yl]oxiran-2-yl}methanol as a clear, colorless oil in a ratio of ~5:1 (NMR): $[\alpha]_D$ +13.6 (*c* 0.8, $CHCl_3$, 22 °C); IR (neat) 3448, 3070, 3044, 2956, 2931, 2858, 1473, 1428, 1379, 1111, 951, 928, 887, 823, 799, 702 cm^{-1}; ^{1}H NMR δ (*Major Isomer*) 7.67 (d, 4 H, *J* = 7.5 Hz), 7.44-7.36 (m, 6 H), 4.00-3.83 (m, 1 H), 3.66 (t, 2 H, *J* = 6.3 Hz), 3.64-3.58 (m, 1 H), 2.93 (*app* dt, 1 H, *J* = 4.8, 2.5 Hz), 2.71 (dd, 1 H, *J* = 6.9, 2.3 Hz), 1.67-1.50 (m, 3 H), 1.50-1.31 (m, 3 H), 1.05 (s, 9 H), 1.02 (d, 3 H, *J* = 6.2 Hz); ^{13}C NMR δ (*Major Isomer*) 135.5, 133.9,

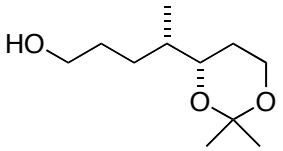
129.5, 127.5, 63.8, 61.8, 60.4, 58.4, 35.2, 30.0, 29.7, 26.8, 19.1, 17.0. (*Minor Isomer*) 57.1, 34.9, 30.5; HRMS (ESI) calcd for $C_{24}H_{34}O_3SiNa$ (M+Na) 421.2175, found 421.2188.



(3*S*,4*S*)-7-(*tert*-Butyldiphenylsilanyloxy)-4-methylheptane-1,3-diol (37).[136] To a –78 °C solution of {(2*R* ,3*R*)-3-[(*S*)-5-(*tert*-butyldiphenylsilanyloxy)pentan-2-yl]oxiran-2-yl}methanol (1.40 g, 3.52 mmol) in toluene (35 mL) was added a solution of Red-Al (3.5 M in toluene, 4.0 mL, 14.0 mmol) dropwise over 15 min. The dry ice/acetone bath was replaced with a 0 °C bath immediately following the addition. The reaction mixture was gradually warmed to room temperature and allowed to stir for 15 h. Then, it was diluted with diethyl ether (30 mL) and cooled to 0 °C prior to the slow addition of water (1.9 mL) followed by 1.0 M tartaric acid (32 mL). Following the partitioning of the heterogeneous mixture into two distinct phases (*i.e.* stirring for 2 h at room temperature), the aqueous phase was extracted with EtOAc (3 x 75 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resultant oil was purified via chromatography on SiO_2 (Hexanes/EtOAc, 4:1 → 2:1 → 1:1 → 0:1) to give 1.40 g (100%) of **37** as a pale yellow oil: $[\alpha]_D$ -7.9 (*c* 0.80, $CHCl_3$, 22 °C); IR (neat) 3357, 3070, 3049, 2932, 2858, 1472, 1428, 1389, 1111, 1007, 939, 823, 798, 740, 701, 688 cm^{-1}; ^1H NMR δ 7.69-7.66 (m, 4 H), 7.44-7.37 (m, 6 H), 3.92-3.78 (m, 2 H), 3.75 (ddd, 1 H, *J* = 9.9, 3.6, 3.0 Hz), 3.68 (t, 2 H, *J* = 6.3 Hz), 2.70-2.20 (m, 2 H, OH region), 1.80-1.45 (m, 5 H), 1.30-1.15 (m, 2 H), 1.06 (*br* s, 9 H), 0.90 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 135.6, 134.1, 129.5, 127.6, 75.6, 64.2, 62.3, 38.7, 35.5, 30.2, 29.0, 26.9, 19.2, 14.2; HRMS (ESI) calcd for $C_{24}H_{36}O_3SiNa$ (M+Na) 423.2331, found 423.2346.

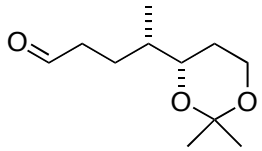


***tert*-Butyl{(*S*)-4-[(*S*)-2,2-dimethyl-1,3-dioxan-4-yl]pentyloxy}diphenylsilane**. To a solution of diol **37** (337 mg, 0.842 mmol) in CH_2Cl_2 (17 mL) was added excess 2,2-dimethoxypropane (2.10 mL, 17.1 mmol) and catalytic PPTS (21.0 mg, 0.0835 mmol) at 0 °C. The ice bath was removed immediately following the addition of acid. After approximately 20 h, the reaction mixture was diluted with Et_2O (50 mL) and washed with saturated aqueous $NaHCO_3$ followed by brine. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Chromatography on SiO_2 (Hexanes/EtOAc containing 0.5% Et_3N, 8:1 → 4:1 → 2:1) afforded 363 mg (98%) of *tert*-butyl{(*S*)-4-[(*S*)-2,2-dimethyl-1,3-dioxan-4-yl]pentyloxy}diphenylsilane: ^{1}H NMR δ 7.69-7.66 (m, 4 H), 7.46-7.35 (m, 6 H), 3.94-3.85 (m, 2 H), 3.66 (*app* t, 2 H, J = 6.2 Hz), 3.63-3.61 (m, 1 H), 1.69-1.49 (m, 7 H), 1.44 (s, 3 H), 1.38 (s, 3 H), 1.06 (s, 9 H), 0.88 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 135.5, 134.1, 129.5, 127.6, 98.1, 72.4, 64.2, 60.1, 37.6, 30.1, 29.9, 28.1, 27.9, 26.9, 19.2, 14.9.

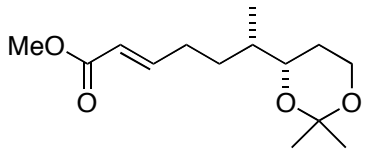


(*S*)-4-[(*S*)-2,2-Dimethyl-1,3-dioxan-4-yl]pentan-1-ol (38). To a solution of *tert*-butyl{(*S*)-4-[(*S*)-2,2-dimethyl-1,3-dioxan-4-yl]pentyloxy}diphenylsilane (823 mg, 1.87 mmol) in THF (46 mL) was added TBAF (1.0 M in THF, 3.80 mL, 3.80 mmol) at 0 °C. The ice bath was removed immediately following the dropwise addition of TBAF. After an additional 15 h at room temperature, the reaction mixture was diluted with Et_2O and washed successively with

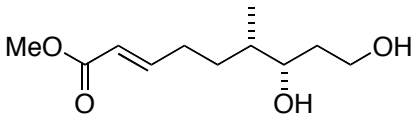
saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by chromatography on SiO_2 (Hexanes/EtOAc containing 0.5% Et_3N, 8:1 → 4:1 → 2:1 → 1:1) delivered a minor diastereomer and 378 mg (100%) of the desired alcohol **38** in a ratio of ~5:1 (NMR): ^{1}H NMR δ (*Major Isomer*) 3.95 (dd of AB, 1 H, *J* = 11.8, 11.8, 2.9 Hz), 3.86 (dd of AB, 1 H, *J* = 11.7, 5.6, 1.8 Hz), 3.73-3.63 (m, 3 H), 1.71-1.47 (m, 3 H), 1.44 (s, 3 H), 1.41-1.31 (m, 3 H), 1.38 (s, 3 H), 1.22-1.06 (m, 1 H), 0.92 (d, 3 H, *J* = 6.8 Hz). (*Minor Isomer*) 0.88 (d, 3 H, *J* = 6.8 Hz).



(*S*)-[(*S*)-2,2-Dimethyl-1,3-dioxan-4-yl]pentanal (39). A solution of alcohol **38** (34.1 mg, 0.169 mmol) in CH_2Cl_2 (8.0 mL) was added to a suspension of PCC (109 mg, 0.507 mmol) and NaOAc (83.1 mg, 1.01 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C. The orange heterogeneous mixture was warmed to room temperature and stirred for a total of 2 h. Finally, the reaction mixture was diluted with Et_2O (50 mL) and quenched with Na_2SO_4. The solid reagents were removed via filtration through a short pad of celite. The remaining organic solvents were removed *in vacuo*. The resulting orange/brown oil was purified by chromatography on SiO_2 (Hexanes/EtOAc containing 0.5% Et_3N, 8:1 → 4:1 → 2:1 → 1:1) to give a minor diastereomer and 27.3 mg (81%) of the desired aldehyde **39** in a ratio of ~6:1 (NMR): ^{1}H NMR δ 9.78 (t, 1 H, *J* = 1.7 Hz), 3.94 (dd of AB, 1 H, *J* = 11.8, 11.8, 2.9 Hz), 3.85 (dd of AB, 1 H, *J* = 11.6, 7.4, 1.8 Hz), 3.71 (ddd, 1 H, *J* = 11.6, 4.8, 2.6 Hz), 2.56-2.38 (m, 2 H), 1.91-1.78 (m, 1 H), 1.75-1.56 (m, 2 H), 1.56-1.45 (m, 2 H), 1.42 (*br* s, 3 H), 1.36 (*br* s, 3 H), 0.90 (d, 3 H, *J* = 6.6 Hz).

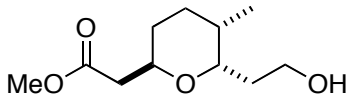


(*S*,*E*)-Methyl 6-[(*S*)-2,2-dimethyl-1,3-dioxan-4-yl]hept-2-enoate (29). To a suspension of aldehyde **39** (25.1 mg, 0.126 mmol) and LiCl (10 equivalents, previously dried under vacuum at 130 °C for 15 h and flame-dried (x 3) directly before use) in a 1:1 mixture of acetonitrile and THF (2.0 mL) was added trimethylphosponoacetate **35** (34.9 mg, 31.0 μL, 0.192 mmol) at room temperature followed by DBU (23.4 mg, 23.0 μL, 0.154 mmol) at 0 °C. The ice bath was removed immediately following the addition of base. The reaction was stirred at room temperature for 3 h and 45 min. Finally, the solution was treated with brine and the aqueous phase was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 20:1) gave ≥ 26.3 mg (82-95%) of enoate **29** (the exact amount of product in a batch of mixed fractions containing both the (*E*)- and (*Z*)-isomers was not specifically quantified): ^{1}H NMR δ (*Major Isomer*) 6.98 (dt, 1 H, *J* = 15.7, 6.9 Hz), 5.84 (dt, 1 H, *J* = 15.6, 1.6 Hz), 3.95 (dd of AB, 1 H, *J* = 11.8, 11.8, 2.8 Hz), 3.86 (dd of AB, 1 H, *J* = 11.6, 5.6, 1.8 Hz), 3.73 (s, 3 H), 3.69 (ddd, 1 H, *J* = 11.5, 5.1, 2.6 Hz), 2.38-2.09 (m, 2 H), 1.75-1.47 (m, 3 H), 1.43 (s, 3 H), 1.38 (s, 3 H), 1.34-1.13 (m, 2 H), 0.91 (d, 3 H, *J* = 6.7 Hz). (*Minor Isomer*) 0.87 (d, 3 H, *J* = 6.8 Hz).



(6*S*,7*S*,*E*)-Methyl 7,9-dihydroxy-6-methylnon-2-enoate (40). To a solution of (*E*)-enoate **29** (17.9 mg, 0.0699 mmol) (slightly contaminated with the (*Z*)-isomer) in THF (1.2 mL) was added an aqueous solution of 1.0 M HCl (700 μL) at 0 °C dropwise over 13 min.

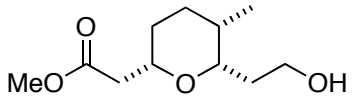
Approximately 2 h and 10 min later, saturated aqueous $NaHCO_3$ (700 μL) was added to the mixture at 0 °C. Finally, the aqueous phase was extracted first with Et_2O (3 x 15 mL) followed by CH_2Cl_2 (1 x 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by chromatography on SiO_2 (Hexanes/EtOAc, 4:1 → 2:1 → 1:1 → 0:1) provided 13.8 mg (91%) of the desired diol **40**: ^{1}H NMR δ 6.96 (dt, 1 H, *J* = 15.6, 7.0 Hz), 5.83 (dt, 1 H, *J* = 15.7, 1.5 Hz), 3.96-3.72 (m, 3 H), 3.72 (s, 3 H), 2.86 (*br* s, 2 H), 2.38-2.09 (m, 2 H), 1.78-1.44 (m, 4 H), 1.38-1.22 (m, 1 H), 0.90 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ (*Major Isomer*) 167.2, 149.4, 121.1, 75.2, 62.2, 51.4, 38.4, 35.3, 31.1, 30.0, 13.9. (*Minor Isomer*) 76.0, 38.6, 29.8.



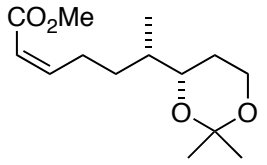
Methyl 2-[(2*R*,5*S*,6*S*)-6-(2-hydroxyethyl)-5-methyltetrahydro-2*H*-pyran-2-yl]acetate (28). To a solution of diol **40** in a mixture of anhydrous MeOH (700 μL) and $CHCl_3$ (300 μL) was added excess NaOMe (5.0 mg, 0.093 mmol) at 0 °C. The NaOMe was not introduced all at once. One batch was introduced at the onset of the reaction and a second batch was added approximately 16 h after its initiation, due to the seemingly large quantity of unreacted starting material evident by TLC. After 44 h at room temperature, the MeOH was removed *in vacuo*. The remaining residue was diluted with H_2O and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed successively with water and brine. Then, the organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by chromatography on SiO_2 afforded 4.0 mg (48%) of the desired *trans*-isomer **28**. The other less polar batch of

material, inclusive of *cis*-pyran **41**, was isolated in a combined yield of 42%. The ^{1}H NMR of the crude material also revealed the presence of unreacted starting material in 8-10%.

Alternatively, mixtures of *cis*- and *trans*-pyrans, **41** and **28**, respectively, were obtained from the treatment of **40** with NaOMe in a MeOH/CH_2Cl_2 (1.8:1, 0.45 M) solvent system. The chloroform co-solvent was exchanged for methylene chloride due primarily to the potential for carbenes to form in basic chloroform media. **28**: ^{1}H NMR δ 4.18-4.09 (m, 1 H), 3.97 (dt, 1 H, *J* = 7.2, 4.2 Hz), 3.77 (*app* q, 2 H, *J* = 5.7 Hz), 3.70 (*br* s, 3 H), 2.67-2.59 (m, 1 H), 2.63 (d of AB, 1 H, *J* = 15.1, 9.3 Hz), 2.40 (d of AB, 1 H, *J* = 15.2, 4.0 Hz), 2.03-1.81 (m, 2 H), 1.81-1.72 (m, 1 H), 1.72-1.56 (m, 1 H), 1.53-1.41 (m, 2 H), 1.41-1.31 (m, 1 H), 0.86 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz) δ 172.3, 75.5, 66.7, 60.9, 51.9, 40.2, 32.9, 29.7, 28.9, 26.5, 16.3.

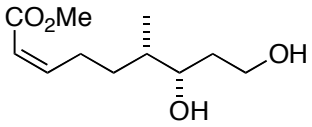


Methyl 2-[(2*S*,5*S*,6*S*)-6-(2-hydroxyethyl)-5-methyltetrahydro-2*H*-pyran-2-yl]acetate (41, crude): ^{1}H NMR δ 3.86-3.73 (m, 4 H), 3.70 (s, 3 H), 2.84 (dd, 1 H, *J* = 8.5, 3.1 Hz), 2.58-2.37 (m, 2 H), 1.91-1.75 (m, 2 H), 1.70-1.60 (m, 2 H), 1.50-1.35 (m, 3 H), 0.97 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 172.0, 81.6, 75.0, 62.5, 51.8, 41.1, 35.2, 31.0, 30.7, 25.8, 11.9.



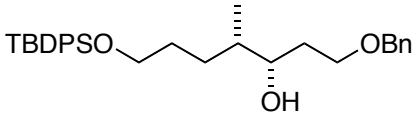
(*S*,*Z*)-Methyl 6-[(*S*)-2,2-dimethyl-1,3-dioxan-4-yl]hept-2-enoate. A solution of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (102 μL, 153 mg, 0.482 mmol) and 18-crown-6 (383 mg, 1.45 mmol) in THF (3.4 mL) was cooled to –78 °C prior to the

dropwise addition of a solution of KHMDS (0.25 M in THF, 1.30 mL, 0.325 mmol) over 7 min. The solution of amide base was prepared directly before use from solid KHMDS, stored in the glovebox, and anhydrous THF. After approximately 10 min, a solution of the aldehyde **39** (50.9 mg, 0.255 mmol) in THF (9.0 mL) was added dropwise, albeit at a rapid rate. The reaction mixture was stirred at –78 °C for 3 h. Then, the solution was treated with brine and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 20:1 → 8:1) gave ≥39.2 mg (≥77%) of (*S*,*Z*)-methyl 6-[(*S*)-2,2-dimethyl-1,3-dioxan-4-yl]hept-2-enoate. Once again, a small batch of mixed fractions was not purified further. Thus, the contribution from the desired (*Z*)-isomer was not specifically quantified: ^{1}H NMR δ (*Major Isomer*) 6.24 (dt, 1 H, *J* = 10.5, 7.4 Hz), 5.78 (dt, 1 H, *J* = 11.5, 1.7 Hz), 3.95 (dd of AB, 1 H, *J* = 11.8, 11.8, 2.9 Hz), 3.85 (dd of AB, 1 H, *J* = 11.7, 5.6, 1.9 Hz), 3.72 (s, 3 H), 3.70 (ddd, 1 H, *J* = 11.2, 5.3, 2.5 Hz), 2.84-2.53 (m, 2 H), 1.75-1.47 (m, 3 H), 1.44 (s, 3 H), 1.41-1.31 (m, 1 H), 1.38 (s, 3 H), 1.31-1.13 (m, 1 H), 0.94 (d, 3 H, *J* = 6.7 Hz). (*Minor Isomer*) 0.90 (d, 3 H, *J* = 6.8 Hz).



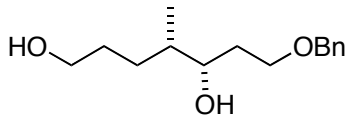
(6*S*,7*S*,*Z*)-Methyl 7,9-dihydroxy-6-methylnon-2-enoate (47). To a solution of (*S*,*Z*)-methyl 6-[(*S*)-2,2-dimethyl-1,3-dioxan-4-yl]hept-2-enoate (14.5 mg, 56.6 μmol) in THF (950 μL) was added an aqueous solution of 1.0 M HCl (570 μL) at 0 °C dropwise over 7 min. Approximately 2 h later, saturated aqueous $NaHCO_3$ (400 μL) was added to the solution at 0 °C. Finally, the aqueous phase was extracted first with Et_2O (3 x 15 mL) followed by CH_2Cl_2 (1 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Purification by chromatography on SiO_2 (Hexanes/EtOAc, 4:1 → 2:1 → 1:1 → 0:1) provided 10.4 mg (85%) of the desired diol **47**: ^{1}H NMR δ 6.31-6.21 (m, 1 H), 5.77 (dd, 1 H, *J* = 11.4, 1.3 Hz), 3.90-3.75 (m, 3 H), 3.70 (s, 3 H), 2.81-2.50 (m, 2 H), 2.73 (*br* s, 2 H), 1.81-1.44 (m, 3 H), 1.44-1.24 (m, 2 H), 0.92 (d, 3 H, *J* = 6.7 Hz).

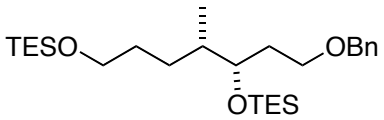


(3*S*,4*S*)-1-(Benzyloxy)-7-(*tert*-butyldiphenylsilylanyloxy)-4-methylheptan-3-ol (53).[136] To a suspension of NaH (8.1 mg, 0.34 mmol) in THF (0.4 mL) was added a solution of diol **37** (61.1 mg, 0.150 mmol) in THF (1.9 mL + 0.3 mL rinse) at 0 °C via cannula. The ice bath was removed immediately following the addition. Approximately 15 min later, the reaction mixture was re-cooled to 0 °C and stirred for an additional 35 min prior to the dropwise addition of benzyl bromide (26.0 μL, 37.4 mg, 0.219 mmol). After 17.5 h at room temperature, catalytic tetrabutylammonium iodide (22.4 mg, 0.061 mmol) was added to the reaction in an effort to drive it to completion. Approximately 14.5 h later, the reaction mixture was diluted with Et_2O and treated with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 25 mL). Then, the organic phase was washed with brine and the combined aqueous extracts were washed with Et_2O. Finally, the combined Et_2O extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 6:1 → 4:1 → 1:1) gave 63.3 mg (85%) of **53** as an oil: $[\alpha]_D$ -8.8 (*c* 1.0, $CHCl_3$, 22 °C); IR (neat) 3481, 3070, 2931, 2858, 1472, 1428, 1389, 1361, 1111, 1028, 1007, 823, 739, 701 cm^{-1}; ^{1}H NMR δ (*Major Isomer*) 7.72 (dd, 4 H, *J* = 7.5, 1.9 Hz), 7.46-7.15 (m, 1 H), 4.56 (s, 2 H), 3.80-364 (m, 5 H), 2.78 (*br* d, 1 H (OH), *J* = 2.4 Hz), 1.90-1.45 (m, 5 H), 1.33-1.18 (m, 2 H), 1.11 (*br* s, 9 H), 0.93 (d, 3 H, *J* =

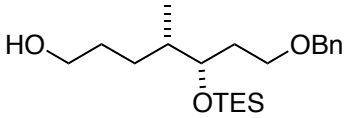
6.7 Hz); ^{13}C NMR δ (*Major Isomer*) 137.9, 135.5, 134.1, 129.5, 128.4, 127.6, 127.5, 74.6, 73.3, 69.7, 64.2, 38.4, 33.6, 30.3, 29.0, 26.9, 19.2, 14.2; HRMS (ESI) calcd for $C_{31}H_{42}O_3SiNa$ (M+Na) 513.2801, found 513.2819.



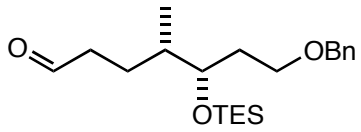
(4*S*,5*S*)-7-(Benzyloxy)-4-methylheptane-1,5-diol (54).[136] To a 0 °C solution of alcohol **53** (1.29 g, 2.63 mmol) in THF (58 mL) was added TBAF (1.0 M in THF, 3.95 mL, 3.95 mmol). The ice bath was removed immediately following the addition and the reaction mixture was maintained at room temperature for an additional 15 h. Finally, it was further diluted with Et_2O (50 mL) and washed with saturated aqueous $NaHCO_3$, water and brine. The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 4:1 → 1:1 →0:1) gave 646.1 mg (98%) of **54** as a colorless oil: mp 53.4-54.9 °C; $[\alpha]_D$ -0.27 (*c* 1.0, CH_2Cl_2, 22 °C); IR (neat) 3385, 3083, 3064, 3030, 2934, 2867, 1454, 1417, 1365, 1205, 1074, 1028, 736, 698 cm^{-1}; ^{1}H NMR δ 7.36-7.29 (m, 5 H), 4.50 (s, 2 H), 3.78-3.72 (m, 2 H), 3.70-3.62 (m, 3 H), 2.90 (*br* s, 1 H), 1.88-1.74 (m, 2 H), 1.71-1.44 (m, 5 H), 1.28-1.16 (m, 1 H), 0.92 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR δ (*Major Isomer*) 137.9, 128.4, 127.7, 74.7, 73.4, 69.8, 63.1, 38.3, 33.3, 30.5, 28.8, 14.3. (*Minor Isomer*) 75.6, 38.5, 32.8, 30.2, 28.3, 15.3; HRMS (ESI) calcd for $C_{15}H_{24}O_3Na$ (M+Na) 275.1623, found 275.1608.



(3*S*,4*S*)-[3,7-Bis-(triethylsilanyloxy)-4-methylheptyloxymethyl]benzene.[136] To a 0 °C solution of diol **54** (646 mg, 2.57 mmol) in CH_2Cl_2 was added 2,6-lutidine (2.02 g, 2.20 mL, 18.9 mmol) over 5 min. After 10 min, triethylsilyl triflate (2.3 mL, 2.7 g, 10.2 mmol) was added dropwise over 7-10 min at 0 °C. Approximately 1 h after the introduction of excess silylating reagent, the reaction mixture was diluted with Et_2O and treated with saturated aqueous $NaHCO_3$. The biphasic mixture was allowed to stir for 15 min prior to the extraction of the aqueous layer with Et_2O. The combined organic layers were washed with additional saturated aqueous $NaHCO_3$, water and brine. Finally, the organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc containing 0.5% Et_3N, 1:0 → 50:1 → 20:1 → 10:1 → 6:1 → 0:1) gave 1.23 g (100%) of (3*S*,4*S*)-[3,7-bis-(triethylsilanyloxy)-4-methylheptyloxymethyl]benzene as a light yellow oil: $[\alpha]_D$ -18.5 (*c* 0.8, $CHCl_3$, 22 °C); IR (neat) 3093, 3070, 3036, 2954, 2911, 2876, 1458, 1420, 1381, 1364, 1238, 1097, 1006, 803, 733, 696, 671 cm^{-1}; ^1H NMR δ 7.36-7.15 (m, 5 H), 4.52,4.51 (AB, 2 H, *J* = 11.9 Hz), 3.78 (dt, 1 H, *J* = 7.7, 3.8 Hz), 3.64-3.60 (m, 2 H), 3.55 (t, 2 H, *J* = 6.7 Hz), 1.84-1.45 (m, 6 H), 1.02-0.95 (m, 18 H), 0.87 (d, 3 H, *J* = 6.8 Hz), 0.67-0.57 (m, 12 H); ^{13}C NMR δ (*Major Isomer*) 138.6, 128.2, 127.6, 127.4, 73.1, 72.9, 67.6, 63.3, 38.7, 33.2, 31.3, 27.9, 14.8, 6.9, 6.7, 5.2, 4.4. (*Minor Isomer*) 72.7, 63.1, 39.0, 31.0, 14.0; HRMS (ESI) calcd for $C_{27}H_{52}O_3Si_2Na$ (M+Na) 503.3141, found 503.3134.

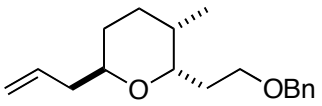


(4*S*,5*S*)-7-Benzyloxy-4-methyl-5-(triethylsilanyloxy)-heptan-1-ol (55).[136] To a mixture of (3*S*,4*S*)-[3,7-bis-(triethylsilanyloxy)-4-methyl-heptyloxymethyl]benzene (82.5 mg, 0.172 mmol) in THF (2.0 mL) and water (200 μL) was added concentrated acetic acid dropwise at 0 °C. The ice bath was removed immediately following the addition of acid. Approximately 3.5 h later, the reaction mixture was re-cooled to 0 °C and treated very carefully (*i.e.* dropwise addition) with a solution of saturated aqueous $NaHCO_3$ (4.3 mL) over 1.5 h. The heterogeneous mixture was diluted with Et_2O, warmed gradually to room temperature and allowed to stir vigorously for 2 h. The aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine and the combined aqueous extracts were extracted once more with Et_2O (1 x 25 mL). Finally, the combined Et_2O extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc containing 0.5% Et_3N, 1:0 → 50:1 → 20:1 → 8:1 → 4:1 → 1:1 → 0:1) gave 49.4 mg (79%) of **55** as a colorless oil. The remaining mass balance could be attributed to unreacted starting material and fully (silyl) deprotected material. Both of these substrates were isolated and recycled accordingly: **55**: $[\alpha]_D$ +30.3 (*c* 0.63, $CHCl_3$, 22 °C); IR (neat) 3408, 2954, 2875, 1455, 1419, 1363, 1240, 1105, 1067, 1005 cm^{-1}; ^1H NMR δ 7.72-7.28 (m, 5 H), 4.51, 4.49 (AB, 2 H, *J* = 11.9 Hz), 3.75 (dt, 1 H, *J* = 7.8, 3.9 Hz), 3.67-3.61 (m, 2 H), 3.55-3.48 (m, 2 H), 1.79-1.40 (m, 8 H), 0.95 (t, 9 H, *J* = 7.9 Hz), 0.86 (d, 3 H, *J* = 6.8 Hz), 0.58 (*app* q, 6 H, *J* = 7.9 Hz); ^{13}C NMR δ 133.4, 128.2, 127.6, 127.4, 73.1, 72.9, 67.5, 63.1, 38.6, 33.0, 30.9, 27.6, 14.9, 6.9, 5.1; HRMS (ESI) calcd for $C_{21}H_{38}O_3SiNa$ (M+Na) 389.2488, found 389.2498.

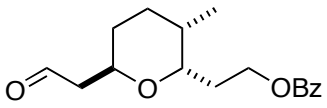


(4*S*, 5*S*)-7-Benzyloxy-4-methyl-5-(triethylsilanyloxy)-heptenal (49).[136] To a solution of alcohol **55** (180 mg, 0.493 mmol) in CH_2Cl_2 (10 mL) was added solid $NaHCO_3$ (211 mg, 2.51 mmol) followed by Dess-Martin periodinane (379 mg, 894 mmol) at 0 ^oC. The oxidant was added in 3 batches over 2 min and the ice bath was removed after 10 min. It was necessary to add water (6-8 μL) to accelerate the oxidation process. After a total of 2 h, the reaction mixture was diluted with Et_2O (25-30 mL) and treated at 0 ^oC with a 1:1 mixture (by volume) of saturated aqueous $NaHCO_3$ (6.0 mL) and saturated aqueous $Na_2S_2O_3$ (6.0 mL). The ice bath was removed immediately following the addition and the heterogeneous mixture was allowed to stir for approximately 1 h or until clear phase separation was observed. Then, the aqueous phase was extracted with Et_2O (2 x 15 mL) and EtOAc (1 x 15 mL). The combined organic extracts were washed with an additional batch of saturated aqueous $NaHCO_3$ followed by brine. Finally, they were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a clear, colorless oil. Chromatography on SiO_2 (Hexanes/EtOAc, 50:1 → 20:1 → 8:1 → 4:1) provided 145 mg (81%) of **49** as a clear, colorless oil: $[\alpha]_D$ -20.8 (*c* 0.8, $CHCl_3$, 22 °C); IR (neat) 2958, 2865, 2716, 1725, 1454, 1403, 1385, 1230, 1086, 1017, 740 cm^{-1}; ^1H NMR δ (*Major Isomer*) 9.76 (t, 1 H, *J* = 1.6 Hz), 7.41-7.29 (m, 5 H), 4.52, 4.48 (AB, 2 H, *J* = 11.9 Hz), 3.78 (dt, 1 H, *J* = 7.8, 3.9 Hz), 3.53 (t, 2 H, *J* = 6.6 Hz), 2.55-2.33 (m, 2 H), 1.95-1.84 (m, 1 H), 1.82-1.62 (m, 2 H), 1.60-1.49 (m, 1 H), 1.46-1.33 (m, 1 H), 0.98-0.93 (m, 9 H), 0.86 (d, 3 H, *J* = 6.8 Hz), 0.59 (q, 6 H, *J* = 7.9 Hz); ^{13}C NMR δ (*Major Isomer*) 202.9, 138.4, 128.3, 127.7, 127.5, 73.0, 72.8, 67.4, 42.3, 38.3, 32.9, 24.1, 14.7, 7.0, 5.1. (*Minor Isomer*) 202.6, 72.6, 67.3, 42.0, 32.5, 24.7, 14.2; MS (EI) *m/z* (rel intensity) 335 ($[M–C_2H_5]^+$, 56), 279 (65), 243 (35), 229 (57), 227 (100), 215 (30), 199 (44),

173 (49), 159 (35), 131 (35), 129 (60), 117 (84), 115 (61), 105 (46), 103 (80), 101 (52), 92 (45), 87 (55); HRMS (EI) calcd for $C_{19}H_{31}O_3Si$ (M-C_2H_5) 335.2042, found 335.2042.

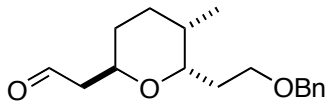


(2*S*,3*S*,6*R*)-6-Allyl-2-[2-(benzyloxy)ethyl]-3-methyltetrahydro-2*H*-pyran (48).[136] To a solution of aldehyde **49** (145 mg, 0.398 mmol) in CH_3CN (5.0 mL) was added a solution of $BiBr_3$ (26.4 mg, 0.0588 mmol) in CH_3CN (290-300 μL) at room temperature. The Lewis acid was prepared as a solution in CH_3CN in an approximate concentration of 1 mg/10 μL. Then, excess allyltrimethylsilane (180 mg, 0.250 mL, 1.57 mmol) was rapidly introduced following the first addition. After 24 h[201,202] at room temperature, the solvent was removed under reduced pressure and the resulting yellow residue was purified by chromatography on SiO_2 (Hexanes/EtOAc, 50:1 → 20:1 → 10:1) to give 79.1 mg (72%) of **48** as a clear, colorless oil. This oil was comprised of an inseparable mixture of diastereomers in a ratio of approximately 5:1 as indicated by ^{1}H NMR:[203] $[\alpha]_D$ -61.0 (*c* 0.806, $CHCl_3$, 22 °C); IR (neat) 3070, 3032, 2928, 2857, 1456, 1369, 1101, 909 cm^{-1}; ^{1}H NMR δ (*Major Isomer*) 7.40-7.25 (m, 5 H), 5.78 (ddt, 1 H, *J* = 17.2, 10.1, 7.1 Hz), 5.05 (d, 1 H, *J* = 19.6 Hz), 5.00 (d, 1 H, *J* = 9.9 Hz), 4.54 (s, 2 H), 3.93 (ddd, 1 H, *J* = 11.2, 4.5, 4.0 Hz), 3.70-3.40 (m, 3 H), 2.26 (ddd, 1 H, *J* = 14.1, 7.1, 7.0 Hz), 2.19-1.96 (m, 2 H), 1.96-1.83 (m, 1 H), 1.75-1.50 (m, 3 H), 1.48-120 (m, 2 H), 0.84 (d, 3 H, *J* = 7.0 Hz). (*Minor Isomer*) 5.38-5.20 (m, 1 H), 3.88-3.79 (m, 1 H), 2.54-2.41 (m, 1 H), 0.95 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR δ (*Major Isomer*) 138.5, 135.4, 128.3, 127.7, 127.5, 116.4, 73.7, 73.2, 68.6, 67.5, 40.1, 33.0, 30.4, 26.8, 25.7, 16.8. (*Minor Isomer*) 73.0, 71.2, 34.1, 27.4, 18.2; HRMS (ESI) calcd for $C_{18}H_{26}O_2Na$ (M+Na) 297.1831, found 297.1821.

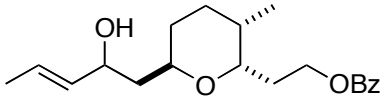


2-[(2*S*,3*S*,6*R*)-3-Methyl-6-(2-oxoethyl)tetrahydro-2*H*-pyran-2-yl]ethyl benzoate (56).[136] Ozone was bubbled into a solution of pyran **48** (88.0 mg, 0.321 mmol) and excess methyl pyruvate (170 mg, 0.150 mL, 1.66 mmol) in CH_2Cl_2 (9.0 mL) at –78 °C for a total of 27 min. The reaction was monitored by TLC (Hexanes/EtOAc, 4:1). When TLC plates were being developed, only oxygen was bubbled into the reaction mixture. Thus, ozone was introduced intermittently for the following time intervals: 8, 3, 3, 3, 3, and 7 min. Comparable yields were obtained for an ozonolysis reaction featuring a steady, continuous supply of ozone for 13 min followed by 25 min. Upon completion of the ozonolysis reaction, oxygen was bubbled into the reaction mixture for 5-10 min at –78 °C. Alternatively, the reaction flask was vented with a needle and N_2 was bubbled rapidly into the reaction mixture at –78 ^{o}C. Finally, excess PPh_3 was added to the reaction mixture at –78 °C. The dry ice/acetone bath was removed 45 min after the addition of the reducing agent. Approximately 15 h later, the solvent was removed *in vacuo*. The resultant yellow residue was purified via chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1 → 1:1 → 1:2 → 0:1) to give 3.2 mg of **61** and app. 51.8 mg **(**56%) of **56**[204] and a minor diastereomer in a ratio of ~7.9:1 (NMR): $[\alpha]_D$ -57.7 (*c* 0.30, $CHCl_3$, 22 °C); IR (neat) 3061, 2919, 2848, 2734, 1729, 1455, 1374, 1270, 1175, 1104, 800, 748, 710 cm^{-1}; ^{1}H NMR δ (*Major Isomer*) 9.81 (t, 1 H, *J* = 1.6 Hz), 8.05 (d, 2 H, *J* = 8.3 Hz), 7.60-7.53 (m, 1 H), 7.49-7.40 (m, 2 H), 4.57-4.49 (m, 1 H), 4.39-4.31 (m, 1 H), 4.25-4.13 (m, 1 H), 3.97 (dt, 1 H, *J* = 12.0, 4.0 Hz), 2.64 (ddd, 1 H, *J* = 16.3, 7.9, 2.6 Hz), 2.47 (dd, 1 H, *J* = 16.3, 4.8 Hz), 2.30-2.15 (m, 1 H), 2.10-1.88 (m, 1 H), 1.84-1.61 (m, 3 H), 1.53-1.34 (m, 2 H), 0.87 (d, 3 H, *J* = 7.0 Hz). (*Minor Isomer*) 9.79 (*br* s, 1 H), 7.38-7.33 (m, 5 H), 4.48-4.42 (m, 1 H), 2.87 (ddd, 1 H, *J* = 15.9, 8.9,

3.1 Hz), 0.98 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ (*Major Isomer*) 201.2, 166.6, 132.9, 130.4, 129.6, 128.3, 73.9, 64.5, 62.3, 49.3, 32.8, 30.7, 26.5, 24.5, 16.9. (*Minor Isomer*) 73.4, 66.9, 33.6, 31.9, 29.4, 22.7, 14.1; HRMS (ESI) calcd for $C_{17}H_{22}O_4Na$ (M+Na) 313.1416, found 313.1401.



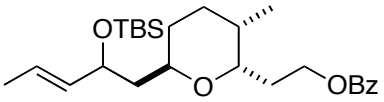
2-{(2*R*,5*S*,6*S*)-6-[2-(Benzyloxy)ethyl]-5-methyltetrahydro-2*H*-pyran-2-yl}acetaldehyde (61): $[\alpha]_D$ -47.2 (*c* 0.61, $CHCl_3$, 22 °C); IR (neat) 3061, 3032, 2929, 2857, 2728, 1721, 1452, 1368, 1271, 1095, 1051, 1031, 738, 698 cm^{-1}; ^{1}H NMR δ (*Major Isomer*) 9.71 (dd, 1 H, *J* = 2.7, 1.8 Hz), 7.36-7.27 (m, 5 H), 4.52 (s, 2 H), 4.14-4.02 (m, 1 H), 3.93 (ddd, 1 H, *J* = 12.0, 4.1, 3.8 Hz), 3.64-3.48 (m, 2 H), 2.59 (ddd, 1 H, *J* = 16.1, 8.4, 2.8 Hz), 2.40 (ddd, 1 H, *J* = 16.1, 4.3, 1.8 Hz), 2.12-1.97 (m, 1 H), 1.97-1.86 (m, 1 H), 1.76-1.52 (m, 3 H), 1.52-1.24 (m, 2 H), 0.86 (d, 3 H, *J* = 7.0 Hz). (*Minor Isomer*) 9.75 (dd, 1 H, *J* = 3.2, 2.0 Hz), 3.79 (d, 1 H, *J* = 3.2 Hz), 2.85 (ddd, 1 H, *J* = 15.9, 9.1, 3.1), 0.96 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ (*Major Isomer*) 201.3, 138.6, 128.4, 127.7, 127.5, 74.0, 73.2, 67.4, 64.6, 49.3, 33.0, 30.7, 26.6, 25.8, 16.7. (*Minor Isomer*) 137.7, 132.2, 132.1, 131.9, 127.8, 73.8, 73.1, 67.2, 66.9, 46.4, 33.7, 32.9, 29.7, 27.8, 22.4, 18.1; HRMS (ESI) calcd for $C_{17}H_{24}O_3Na$ (M+Na) 299.1623, found 299.1606.



2-{(2*S*,3*S*,6*R*)-6-[(*E*)-2-Hydroxypent-3-enyl]-3-methyltetrahydro-2*H*-pyran-2-yl]ethyl benzoate (57).[136] To a –78 °C solution of *trans*-2-propenylbromide (43.0 μL, 60.5 mg, 0.499 mmol) in degassed Et_2O (6.5 mL) was added *tert*-butyllithium (1.7 M in hexanes, 0.650

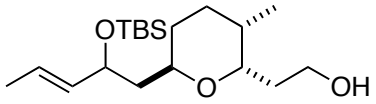
mL, 1.11 mmol) over a 4 min period. The clear, colorless solution was maintained at –78 °C for 40 min and then the dry ice/acetone bath was replaced with a 0 °C bath. Approximately 45 min later, the organolithium solution was re-cooled to –78 °C and maintained for 15 min prior to its transfer via cannula over 15 min to a pre-cooled (-110 °C to –100 °C) solution of **56** mixed with a small percentage of **61** (48.3 mg, 0.166 mmol) in degassed Et_2O (4.4 mL). The mixture was stirred at approximately –105 °C (temperature range: -110 °C to –100 °C) for an additional 50 min. Finally, the reaction mixture was quenched with saturated aqueous NH_4Cl and the aqueous layer was extracted with Et_2O (3 x 25 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The first few drops of NH_4Cl were added to the reaction mixture at –100 °C. The heterogeneous mixture was allowed to warm to room temperature gradually from this point on. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1 → 1:1 → 0:1) provided 27.9 mg (50%) of **57**. Most of the benzyl derivative **62** and unreacted aldehyde **56** were separated out at this stage. The R_f's of the 3 compounds were quite similar (Hexanes/EtOAc, 2:1). Thus, the desired allylic alcohol **57** was contaminated to a slight degree with **56** and **62**. The batch of **57** used for characterization purposes contained a negligible quantity of the other isomers: $[\alpha]_D$ -69.3 (*c* 0.33, $CHCl_3$, 22 °C); IR (neat) 3464, 2962, 2927, 2856, 1720, 1668, 1599, 1452, 1378, 1279, 1117, 1068, 1028, 979, 802, 718 cm^{-1}; ^1H NMR δ 8.08-8.03 (m, 2 H), 7.60-7.53 (m, 1 H), 7.48-7.41 (m, 2 H), 5.71 (ddq, 1 H, *J* = 15.3, 0.8, 6.2 Hz), 5.48 (ddq, 1 H, *J* = 15.3, 6.8, 1.5, Hz), 4.65-4.57 (m, 1 H), 4.42- 4.27 (m, 2 H), 4.02 (dt, 1 H, *J* = 11.7, 4.2 Hz), 3.83 (*app* tt, 1 H, *J* = 9.8, 2.6 Hz), 3.42 (d, 1 H, OH, *J* = 1.1 Hz), 2.28-2.16 (m, 1 H), 2.04-1.91 (m, 1 H), 1.83-1.73 (m, 2 H), 1.69 (d, 3 H, *J* = 6.0 Hz), 1.65-1.55 (m, 2 H), 1.48-1.24 (m, 3 H), 0.85 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 166.5, 133.8, 132.8, 130.5, 129.6,

128.3, 126.3, 73.9, 72.2, 69.3, 62.2, 43.1, 33.0, 31.8, 26.5, 24.5, 17.6, 17.1; HRMS (ESI) calcd for $C_{20}H_{28}O_4Na$ (M+Na) 355.1885, found 355.1869.

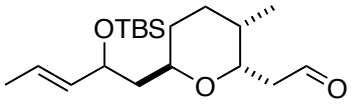


2-{(2*S*,3*S*,6*R*)-6-[(*E*)-2-(*tert*-Butyldimethylsilanyloxy)pent-3-enyl]-3-methyltetrahydro-2*H*-pyran-2-yl}ethyl benzoate (58).[136] To an ice-cooled solution of allylic alcohol **57** (27.9 mg, 0.839 mmol) and imidazole (38.5 mg, 0.566 mmol) in CH_2Cl_2 (700 μL) was added *tert*-butyldimethylsilyl chloride (55.6 mg, 0.369 mmol). After 24 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The minor component comprised less than 10% of the mixture by ^1H NMR. It most likely could be attributed to the epimer at C(4). Chromatography on SiO_2 (Hexanes/EtOAc, 1:0 → 50:1 → 20:1 → 8:1) provided 27.6 mg (74%)[205] of **58** as a clear, colorless oil: $[\alpha]_D$ -58.1 (*c* 0.52, $CHCl_3$, 22 °C); IR (neat) 3062, 3031, 2949, 2928, 2856, 1723, 1609, 1460, 1377, 1274, 1089, 965, 841, 774, 713 cm^{-1}; ^1H NMR δ (*Major Isomer*) 8.08-8.00 (m, 2 H), 7.60-7.53 (m, 1 H), 7.48-7.40 (m, 2 H), 5.61 (dq, 1 H, *J* = 12.9, 6.3 Hz), 5.41 (ddq, 1 H, *J* = 15.3, 7.4, 1.5 Hz), 4.59-4.34 (m, 2 H), 4.19 (*app* q, 1 H, *J* = 7.0 Hz), 3.95 (dt, 1 H, *J* = 11.4, 4.0 Hz), 3.70-3.55 (m, 1 H), 2.19-2.03 (m, 1 H), 2.02-1.89 (m, 1 H), 1.89-1.75 (m, 2 H), 1.75-1.70 (m, 1 H), 1.67 (dd, 3 H, *J* = 6.3, 1.2 Hz), 1.65-1.60 (m, 1 H), 0.94-0.79 (m, 12 H), 0.04 (s, 3 H), 0.02 (s, 3 H). (*Minor Isomer*) 0.13 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR δ (*Major Isomer*) 166.6, 134.6, 132.7, 130.6, 129.6, 128.3, 126.2, 73.3, 71.0, 65.9, 62.6,

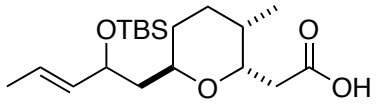
44.2, 33.1, 30.7, 26.9, 25.9, 25.2, 18.1, 17.5, 16.6, -4.4, -4.7; HRMS (ESI) calcd for $C_{26}H_{42}O_4SiNa$ (M+Na) 469.2750, found 469.2722.



2-{(2*S*,3*S*,6*R*)-6-[(*E*)-2-(*tert*-Butyldimethylsilanyloxy)pent-3-enyl]-3-methyltetrahydro-2*H*-pyran-2-yl]ethanol (59).[136] To a 0 °C solution of pyran **58** (21.1 mg, 47.2 μmol) in MeOH/THF (830 μL, app. 2.8:1) was added excess NaOMe (16.7 mg, 0.309 mmol). Initially, only 1.2 mg of NaOMe was introduced. Additional base was added during the course of the reaction. The ice bath was removed approximately 5 min following the addition of NaOMe. After 24 h at room temperature, the reaction mixture was cooled to 0 °C and treated with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 25 mL) and then the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1) provided 14.2 mg (88%) of the desired alcohol **59**: $[\alpha]_D$ -48.8 (*c* 0.473, $CHCl_3$, 22 °C); IR (neat) 3415, 2930, 2860, 1675, 1470, 1380, 1255, 1055, 965, 835, 770 cm^{-1}; ^1H NMR δ 5.57 (dq of AB, 1 H, *J* = 15.3, 0.49, 6.4 Hz), 5.40 (dq of AB, 1 H, *J* = 15.2, 7.2, 1.5 Hz), 4.15 (q, 1 H, *J* = 6.9 Hz), 3.93 (dt, 1 H, *J* = 11.3, 4.1 Hz). 3.84-3.74 (m, 2 H), 3.74-3.68 (m, 1 H), 2.30-2.18 (m, 1 H), 2.00-1.81 (m, 3 H), 1.81-1.70 (m, 1 H), 1.70-1.60 (m, 2 H), 1.68 (dd, 3 H, *J* = 6.3, 1.4 Hz), 1.52-1.41 (m, 3 H), 1.39-1.19 (m, 3 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR 134.3, 126.0, 74.8, 70.9, 66.9, 61.4, 43.1, 32.9, 29.1, 26.6, 25.9, 18.1, 17.6, 15.9, -4.1, -4.8; HRMS (ESI) calcd for $C_{24}H_{36}O_3SiNa$ (M+Na) 365.2488, found 365.2499.

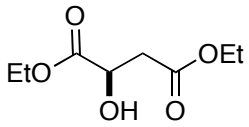


2-{(2*S*,3*S*,6*R*)-6-[(*E*)-2-(*tert*-Butyldimethylsilanyloxy)pent-3-enyl]-3-methyltetrahydro-2*H*-pyran-2-yl}acetaldehyde (60). To a solution of **59** (14.2 mg, 41.4 μmol) in CH_2Cl_2 (1.0 mL) was added solid $NaHCO_3$ (14.0 mg, 0.167 mmol) followed by Dess-Martin periodinane (29.0 mg, 68.3 μmol) at 0 °C. The ice bath was removed approximately 10 min after the introduction of the oxidant. After an additional 2 h, the reaction mixture was diluted with Et_2O (4.0 mL) at 0 °C. Then, a 1:1 mixture of saturated aqueous $NaHCO_3$ (400 μL) and saturated aqueous $Na_2S_2O_3$ (400 μL) was introduced dropwise, also at 0 °C. The heterogeneous mixture was warmed to room temperature and allowed to stir for 2 h. Then, the mixture was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 11.9 mg (84%) of a yellow residue. The crude aldehyde **60** was used for the next step without further purification: ^{1}H NMR δ 9.79 (dd, 1 H, *J* = 3.3, 1.8 Hz), 5.53 (dq of AB, 1 H, *J* = 12.8, 6.4, 15.1 Hz), 5.34 (dq of AB, 1 H, *J* = 7.3, 1.5, 15.1 Hz), 4.42 (dt, 1 H, *J* = 9.7, 4.5 Hz), 4.12 (q, 1 H, *J* = 7.7 Hz), 3.66-3.47 (m, 1 H), 2.74 (dd of AB, 1 H, *J* = 16.0, 10.4, 3.4 Hz), 2.32 (dd of AB, 1 H, *J* = 16.0, 4.2, 1.8 Hz), 2.03-1.88 (m, 1 H), 1.79 (dd of AB, 1 H, *J* = 13.7, 8.2, 5.6 Hz), 1.68 (dd, 3 H, *J* = 6.3, 1.5 Hz), 1.46 (dd of AB, 1 H, *J* = 13.3, 8.0, 4.6 Hz), 1.38-1.19 (m, 4 H), 0.87 (*br* s, 9 H), 0.82 (d, 3 H, *J* = 7.0 Hz), 0.03 (s, 3 H), 0.01 (s, 3 H).

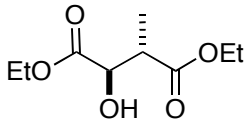


{(2*S*,3*S*,6*R*)-6-[(*E*)-2-(*tert*-Butyldimethylsilanyloxy)pent-3-enyl]-3-methyltetrahydro-2*H*-pyran-2-yl}acetic acid (23). To a solution of aldehyde **60** (11.9 mg, 34.9 μmol) in *tert*-butanol (3.6 mL) and 2-methyl-2-butene (200 μL) was added a solution of $NaClO_2$ (40.5 mg, 0.448 mmol) and $NaH_2PO_4 \bullet H_2O$ (52.0 mg, 0.377 mmol) in H_2O (1.0 mL) dropwise at room temperature over the span of 8 min. The mixture turned yellow during the course of the addition of the oxidant. The color persisted for the duration of the reaction. After 1.5 h, the volatiles were removed *in vacuo*. Then, EtOAc was added to the remaining slurry. Additional (cold) water was added to the heterogeneous mixture and then, the aqueous phase was extracted with EtOAc (2 x 25 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 9.8 mg (67% over 2 steps) of the desired acid **23**: $[\alpha]_D$ -94.3 (*c* 0.175, CH_2Cl_2, 22 °C); IR (neat) 3158, 2928, 2857, 1719, 1243, 1079, 959, 838, 773 cm^{-1}; ^1H NMR δ 5.57 (dq of AB, 1 H, *J* = 15.1, 12.6, 6.4 Hz), 5.38 (dq of AB, 1 H, *J* = 15.3, 1.4, 7.1 Hz), 4.28 (dt, 1 H, *J* = 9.3, 4.4 Hz), 4.15 (q, 1 H, *J* = 7.0 Hz), 3.75-3.63 (m, 1 H), 2.68 (d of AB, 1 H, *J* = 15.5, 10.0 Hz), 2.39 (d of AB, 1 H, *J* = 15.5, 4.2 Hz), 2.00-1.91 (m, 1 H), 1.84 (dd of AB, 1 H, *J* = 13.6, 7.6, 5.9 Hz), 1.68 (dd, 3 H, *J* = 6.3, 1.1 Hz), 1.75-1.63 (m, 2 H), 1.49 (dd of AB, 1 H, *J* = 13.1, 7.6, 5.2 Hz), 1.42-1.24 (m, 4 H), 0.87 (*br* s, 9 H), 0.87-0.85 (m, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR δ 176.4, 134.3, 126.2, 73.1, 70.9, 67.4, 43.6, 32.9, 32.7, 29.8, 26.6, 26.0, 18.3, 17.8, 16.3, -4.0, -4.7; HRMS (ESI) calcd for $C_{19}H_{36}O_4SiNa$ (M+Na) 379.2281, found 379.2296.

γ-Amino Ester Fragment

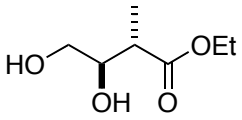


(*R*)-Diethyl malate.[206] A solution of D-malic acid (10.0 g, 74.6 mmol) in absolute ethanol (70 mL) was treated with concentrated HCl (250 μL) at room temperature. Then, the solution was heated at reflux for 15 h, concentrated and purified by chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1) to provide 13.4 g (94%) of the desired (*R*)-diethyl malate as a yellow oil: ^{1}H NMR δ 4.47 (q, 1 H, *J* = 5.4 Hz), 4.27 (d of AB, 1 H, *J* = 7.2, 1.5 Hz), 4.22 (d of AB, 1 H, *J* = 7.1, 1.4 Hz), 4.15 (q, 2 H, *J* = 7.1 Hz), 3.32 (d, 1 H, *J* = 5.4 Hz), 2.83 (d of AB, 1 H, *J* = 16.3, 4.6 Hz), 2.75 (d of AB, 1 H, *J* = 16.3, 6.0 Hz), 1.28 (t, 3 H, *J* = 7.1 Hz), 1.25 (t, 3 H, *J* = 7.1 Hz).



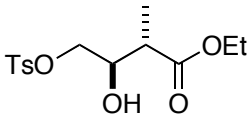
Diethyl (2*R*,3*S*)-3-methylmalate (63).[207] To a solution of diisopropylamine (4.30 mL, 30.7 mmol) in THF (14 mL) was added *n*-BuLi (1.6 M in hexane, 17.8 mL, 28.5 mmol) slowly via an addition funnel at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then cooled to –78 °C prior to the slow addition of a dilute solution of (*R*)-diethyl malate (2.36 g, 12.4 mmol) in THF (3.0 mL). The resulting orange solution was stirred for 50 min at –78 °C, slowly warmed to –20 °C over a period of 2 h, stirred at –20 °C for 20 min and then re-cooled to –78 °C prior to the slow addition of MeI (1.20 mL, 2.74 g, 19.28 mmol). After an additional 30 min at –78 °C, the reaction mixture was warmed to –30 °C over the course of the next hour. Then, the

dry ice/acetone bath was replaced by a 0 °C bath. After 1 h at 0 °C, the reaction mixture was warmed to room temperature over the course of 1 h and maintained at this temperature for an additional hour. Finally, the yellow solution was quenched with 1.0 M citric acid (60 mL) and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude material by chromatography on SiO_2 (Hexanes/EtOAc, 15:1 → 8:1 → 4:1 → 2:1) afforded 1.88 g (75%, as a mixture of 2 diastereomers) of **63**. A ^{1}H NMR analysis of the crude material revealed a diastereomeric ratio (dr) of approximately 9:1. Upon purification by chromatography on SiO_2, 62% of the methylated diester **63** could be isolated with a dr of 10.6 :1: ^{1}H NMR δ (*Major Isomer*) 4.33-4.19 (m, 3 H), 4.18 (d of AB, 1 H, *J* = 7.1, 1.6 Hz), 4.13 (d of AB, 1 H, *J* = 7.2, 1.6 Hz), 3.15 (d, 1 H, *J* = 6.3 Hz), 3.03 (dq, 1 H, *J* = 7.3, 3.6 Hz), 1.31 (t, 3 H, *J* = 7.1 Hz), 1.30 (d, 3 H, *J* = 7.2 Hz), 1.26 (t, 3 H, *J* = 7.1 Hz). (*Minor Isomer)* 4.61 (dd, 1 H, *J* = 5.3, 3.7 Hz), 4.33-4.19 (m, 2 H), 4.19-4.12 (m, 2 H), 3.06 (d, 1 H, *J* = 7.1 Hz), 2.93 (dq, 1 H, *J* = 7.2, 3.6 Hz), 1.34-1.23 (m, 6 H), 1.18 (d, 3 H, *J* = 7.2 Hz).

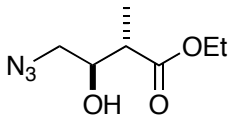


(2*S*,3*R*)-3,4-Dihydroxy-2-methylbutyric acid ethyl ester.[114] To a solution of diester **63** (0.400 g, 1.96 mmol) in THF (4.8 mL) was added BH_3•DMS (0.200 mL, 0.160 g, 2.11 mmol) slowly at 0 °C. The reaction was maintained at 0 °C during the course of the H_2 gas evolution, which was immediately evident following the borane addition. Approximately 45 min later, the ice bath was removed and the reaction mixture was warmed to room temperature. After 15 additional min, $NaBH_4$ (5.0 mg, 0.13 mmol) was introduced at 0 °C. The reaction mixture was

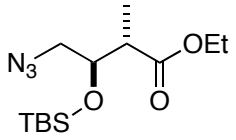
stirred at room temperature for 12 h and quenched with MeOH (7.0 mL) at 0 °C. The ice bath was removed immediately following the quench and the reaction mixture was stirred for an additional 20 min prior to the removal of all volatiles *in vacuo*. The crude (2*S*,3*R*)-3,4-dihydroxy-2-methylbutyric acid ethyl ester was used for the next step without further purification: ^{1}H NMR δ 4.19 (q, 2 H, *J* = 7.1 Hz), 3.84-3.70 (m, 2 H), 3.64-3.54 (m, 1 H), 3.30 (d, 1 H, *J* = 5.4 Hz), 2.65 (p, 1 H, *J* = 7.2 Hz), 2.27 (*app* t, 1 H, *J* = 5.9 Hz), 1.28 (t, 3 H, *J* = 7.1 Hz), 1.22 (d, 3 H, *J* = 7.2 Hz).



(2*S*,3*R*)-3-Hydroxy-2-methyl-4-(toluene-4-sulfonyloxy)-butyric acid ethyl ester (64). To a solution of the previously prepared (2*S*,3*R*)-3,4-dihydroxy-2-methylbutyric acid ethyl ester (321 mg, 1.98 mmol) in CH_2Cl_2 (5.0 mL) was added dibutyltin oxide (25.0 mg, 0.100 mmol), followed by TsCl (381 mg, 2.00 mmol) and freshly distilled Et_3N (280 μL, 0.203 g, 2.01 mmol) at room temperature. After 15 h, the reaction mixture was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude material by chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1 → 1:1 → 0:1) provided 376.2 mg (61%) of **64**[208] as a pale yellow oil: ^{1}H NMR δ 7.79 (d, 2 H, *J* = 8.3 Hz), 7.35 (d, 2 H, *J* = 8.0 Hz), 4.17-4.02 (m, 4 H), 3.90 (ddd, 1 H, *J* = 9.6, 4.7, 1.2 Hz), 3.00 (*br* s, 1 H), 2.65 (p, 1 H, *J* = 7.2 Hz), 2.44 (s, 3 H), 1.24 (t, 3 H, *J* = 7.1 Hz), 1.19 (d, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ (*Major Isomer*) 174.9, 145.0, 132.5, 129.9, 127.9, 71.2, 71.1, 61.0, 41.5, 21.6, 14.0. (*Minor Isomer*) 70.8, 69.6, 11.3.

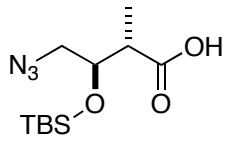


(2*S*,3*R*)-4-Azido-3-hydroxy-2-methylbutyric acid ethyl ester.[114] A mixture of **6 4** (380.4 mg, 1.202 mmol) and NaN_3 (156 mg, 2.40 mmol) in DMF (4.0 mL) was heated at 80 °C (oil bath temperature) for 5.5 h. The reaction mixture was diluted with EtOAc and then washed with water (2 x 25 mL) and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification via chromatography on SiO_2 (Hexanes/EtOAc, 15:1 → 8:1 → 4:1) provided 190 mg (84%) of (2*S*,3*R*)-4-azido-3-hydroxy-2-methylbutyric acid ethyl ester as a yellow oil: ^{1}H NMR δ 4.20 (q, 2 H, *J* = 7.1 Hz), 3.88 (ddd, 1 H, *J* = 10.1, 6.2, 3.9 Hz), 3.44 (d of AB, 1 H, *J* = 12.7, 3.9 Hz), 3.35 (d of AB, 1 H, *J* = 12.7, 6.1 Hz), 3.17 (d, 1 H, *J* = 6.1 Hz), 2.67 (p, 1 H, *J* = 7.1 Hz), 1.29 (t, 3 H, *J* = 7.1 Hz), 1.23 (d, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 175.3, 72.6, 61.0, 54.3, 42.5, 14.1, 14.0.

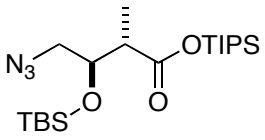


(2*S*,3*R*)-4-Azido-3-(*tert*-butyldimethylsilanyloxy)-2-methylbutyric acid ethyl ester (25).[114,136] To a solution of (2*S*,3*R*)-4-azido-3-hydroxy-2-methylbutyric acid ethyl ester (176 mg, 0.940 mg) and imidazole (154 mg, 2.26 mmol) in CH_2Cl_2 (1.0 mL) was added TBS-Cl (283 mg, 1.88 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for an additional 40 h. Then, it was diluted with Et_2O (50 mL) and washed with water and brine. Finally, the organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by chromatography on SiO_2 (Hexanes/EtOAc, 1:0 → 15:1 → 8:1) afforded 276 mg (98%) of a minor diastereomer and azide **25** as a yellow oil in a ratio of ~5.4:1 (NMR): ^{1}H NMR δ (*Major Isomer*) 4.14 (q, 2 H, *J* = 7.1 Hz), 4.04 (ddd, 1 H, *J* = 6.2, 5.4, 3.7 Hz), 3.41 (d of AB, 1

H, *J* = 12.8, 3.7 Hz), 3.23 (d of AB, 1 H, *J* = 12.8, 5.4 Hz), 2.76 (p, 1 H, *J* = 7.1 Hz), 1.28 (t, 3 H, *J* = 7.1 Hz), 1.13 (d, 3 H, *J* = 7.2 Hz), 0.90 (s, 9 H), 0.13 (s, 3 H), 0.09 (s, 3 H). *(Minor Isomer)* ^{1}H NMR δ 3.41 (dd, 1 H, *J* = 10.6, 5.7 Hz), 1.17 (d, 3 H, *J* = 7.1 Hz).



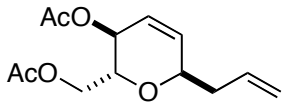
(2*S*,3*R*)-4-Azido-3-(*tert*-butyldimethylsilanyloxy)-2-methylbutyric acid.[114,136] To a 0 °C solution of **25** (203.8 mg, 0.6760 mmol) in EtOH (3.5 mL) was added LiOH (1.0 M in H_2O, 1.6 mL). The reaction mixture was warmed to room temperature following the addition of base and stirred for a total of 44 h. Then, it was cooled to 0 °C and acidified with 1.0 M HCl (1.6 mL). The aqueous phase was extracted with EtOAc (3 x 25 mL) and the organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 177 mg (96%) of crude (2*S*,3*R*)-4-azido-3-(*tert*-butyldimethylsilanyloxy)-2-methylbutyric acid in a dr of 2.9-3.5:1: ^{1}H NMR δ (*Major Isomer*) 4.02 (*app* q, 1 H, *J* = 4.8 Hz), 3.45 (d of AB, 1 H, *J* = 12.8, 4.1 Hz), 3.28 (d of AB, 1 H, *J* = 12.8, 5.4 Hz), 2.81 (dq, 1 H, *J* = 12.9, 7.2 Hz), 1.20 (d, 3 H, *J* = 7.2 Hz), 0.91 (s, 9 H), 0.16 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR δ (*Major Isomer*)173.3, 72.6, 54.3, 45.6, 25.8, 17.9, 12.0, -4.6, -4.8. (*Minor Isomer*) 66.0, 18.1, 15.4, 11.4.



(2*S*,3*R*)-4-Azido-3-(*tert*-butyldimethylsilanyloxy)-2-methylbutyric triisopropylsilanyl ester (65).[114,136] To an ice-cooled solution of (2*S*,3*R*)-4-azido-3-(*tert*-butyldimethylsilanyloxy)-2-methylbutyric acid (177 mg, 0.647 mmol) in a 1:1 mixture of THF and DMF (2.8 mL) was

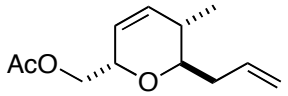
added Et_3N (144 μL, 105 mg, 1.03 mmol) followed by TIPS-Cl (180 μL, 162 mg, 0.841 mmol). The reaction mixture was stirred at 0 °C for 30 min. The yellow solution was diluted with Et_2O (40 mL) and washed with H_2O, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification of the crude material by chromatography on SiO_2 (Hexanes/EtOAc, 1:0 → 25:1) provided 239 mg (86% over 2 steps) of ester **65** as a pale yellow oil with a dr of ~16:1 (NMR): $[\alpha]_D$ +15.2 (*c* 0.53, $CHCl_3$, 22 °C); IR (neat) 2950, 2862, 2102, 1719, 1467, 1380, 1260, 1183, 1101, 1046, 838, 773 cm^{-1}; ^1H NMR δ 4.15 (dq, 1 H, *J* = 7.0, 4.1 Hz), 3.38 (d of AB, 1 H, *J* = 12.5, 4.2 Hz), 3.30 (d of AB, 1 H, *J* = 12.5, 7.0 Hz), 2.75 (ddd, 1 H, *J* = 14.5, 11.3, 7.3 Hz), 1.37-1.23 (m, 3 H, *J* = 7.5 Hz), 1.18 (d, 3 H, *J* = 7.2 Hz), 1.09 (d, 18 H, *J* = 6.5 Hz), 0.92 (s, 9 H), 0.15 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR δ (*Major Isomer*) 173.1, 72.6, 54.3, 45.6, 25.8, 17.8, 12.0, -4.7, -4.9. (*Minor Isomer*) 55.4, 45.1, 18.0, 11.3; HRMS (ESI) calcd for $C_{20}H_{43}N_3O_3Si_2Na$ (M+Na) 452.2741, found 452.2763.

Spiroketal Fragment



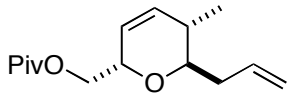
[(2*R*,3*S*,6*R*)-3-Acetoxy-6-allyl-3,6-dihydro-2*H*-pyran-2-yl]methyl acetate (67).[114,136] To a -45 °C solution of BF_3•Et_2O (28.5 mL, 0.227 mol) in CH_3CN (100 mL) was added a solution of (slightly impure or crude) tri-*O*-acetyl-D-glucal **66**[114] (51.3 g, 0.189 mol) and allyltrimethylsilane (30.0 mL, 0.188 mol) in CH_3CN (300 mL) via an addition funnel over a 4 h

period. After an additional hour, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by chromatography on SiO_2 (Hexanes/EtOAc, 20:1 → 10:1 → 4:1) provided 18.9 g (39%) of **67** as a pale yellow oil: ^{1}H NMR δ 5.96-5.79 (m, 3 H), 5.18-5.11 (m, 3 H), 4.30-4.24 (m, 1 H), 4.24-4.13 (m, 2 H), 4.03-3.94 (m, 1 H), 2.48 (t of AB, 1 H, J = 14.5, 7.9 Hz), 2.34 (t of AB, 1 H, J = 14.3, 6.9 Hz), 2.10 (s, 6 H).



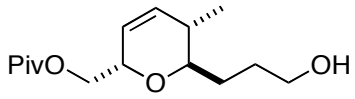
[(2*S*,5*S*,6*R*)- 6-Allyl-5-methyl-5,6-dihydro-2*H*-pyran-2-yl]methyl acetate (68).[114,136] MeLi (1.6 M in Et_2O, 22.0 mL, 35.2 mmol) was added dropwise to a suspension of CuBr•SMe_2 (3.60 g, 17.5 mmol) in Et_2O (50 mL) at –30 °C under a N_2 atmosphere. After approximately 15 min at –30 °C, the solution was warmed to 0 °C. The cuprate solution was added very slowly, in batches via syringe pump over a period of 4 h and 40 min, to a -45 °C solution of diene **67** (2.25 g, 8.84 mmol) in Et_2O (126 mL). Approximately 1 h later, the reaction mixture was quenched with saturated aqueous NH_4Cl. The organic layer was washed with 0.5 M aqueous NaOH, followed by brine. Then, the Et_2O layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude material by column chromatography on SiO_2 (Hexanes/EtOAc, 20:1 → 15:1 → 8:1 → 4:1 → 2:1) provided 960 mg (52%) of **68**: ^{1}H NMR δ 5.97-5.81 (m, 1 H), 5.78 (dt of AB, 1 H, J= 10.3, 2.5 Hz), 5.62 (dt of AB, 1 H, J = 10.2, 2.4 Hz), 5.11 (d, 1 H, J = 15.9 Hz), 5.07 (d, 1 H, J = 9.7 Hz), 4.44-4.36 (m, 1 H), 4.29 (d of AB, 1 H, J = 11.5, 8.0 Hz), 4.00 (d of

AB, 1 H, J = 11.5, 3.4 Hz), 3.42 (ddd, 1 H, J = 7.5, 7.5, 4.0), 2.47-2.38 (m, 1 H), 2.38-2.22 (m, 1 H), 2.10 (s, 3 H), 1.00 (d, 3 H, J = 7.1 Hz).

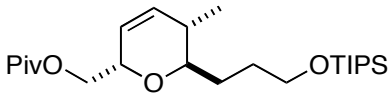


[(2*S*,5*S*,6*R*)-6-Allyl-5-methyl-5,6-dihydro-2*H*-pyran-2yl]methyl pivalate (69).[114,136] To a solution of acetate **68** (23.3 g, 0.111 mol) in MeOH (210 mL) was added NaOMe (209 mg, 3.87 mmol) at room temperature. After 16 h, the reaction mixture was concentrated and subsequently dried *in vacuo*. The crude residue (18.5 g) was used for the next step without further purification.

To a solution of the previously prepared orange oil in pyridine (60 mL) was added pivaloyl chloride (15.0 mL, 14.7 g, 0.122 mol) dropwise, over the span of 30 min. A cool water bath was placed under the reaction mixture during the course of the addition due to the slight exotherm that resulted. After 3.5 h at room temperature, the solution was diluted with EtOAc (400 mL) and then washed with water, 1.0 M HCl, saturated aqueous $NaHCO_3$ and brine. Finally, the organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by chromatography on SiO_2 (Hexanes/EtOAc, 50:1 → 20:1 → 8:1) gave 25.1 g (90% over 2 steps) of **69** as a pale yellow oil: ^{1}H NMR δ 5.97-5.81 (m, 1 H), 5.77 (t of AB, 1 H, J = 10.2, 2.3 Hz), 5.62 (t of AB, 1 H, J = 10.2, 2.5 Hz), 5.14-5.03 (m, 2 H), 4.42-4.36 (m, 1 H), 4.32 (d of AB, 1 H, J = 11.2, 7.5 Hz), 3.96 (d of AB, 1 H, J = 11.2, 3.2 Hz), 3.43 (ddd, 1 H, J = 7.8, 7.8, 3.7 Hz), 2.45-2.34 (m, 1 H), 2.33-2.19 (m, 1 H), 2.16-2.06 (m, 1 H), 1.23 (s, 9 H), 1.00 (d, 3 H, J = 7.1 Hz).

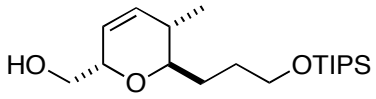


[(2*S*,5*S*,6*R*)-6-(3-hydroxypropyl)-5-methyl-5,6-dihydro-2*H*-pyran-2-yl]methyl pivalate (70).[114,136] To a solution of starting pyran **69** (12.64 g, 50.15 mmol) in THF (200 mL) was added 9-BBN (0.5 M in THF, 201 mL, 101 mmol) dropwise via an addition funnel over 40 min at room temperature. The material from the previous reaction was split into two batches, 12.64 g and 12.43 g, for the hydroboration/oxidation sequence. The two reactions were run in parallel to accommodate the large scale. Approximately 24 h later, the reaction mixture was cooled to 0 °C prior to the slow, dropwise addition of 0.5 M NaOH (200 mL) via an addition funnel over 1 h. Next, 30% aqueous H_2O_2 (200 mL) was introduced dropwise via an addition funnel over 1.5 h. Due to the exotherm, only half (100 mL) of the aqueous H_2O_2 solution was added during the first hour. The remaining 100 mL was introduced in the last 30 min. By this point (*i.e.* last half hour), the heterogeneous mixture was no longer exothermic. After an additional 14 h at room temperature, the mixture was diluted with EtOAc and the organic layer was washed with brine and the aqueous layer was extracted with $CHCl_3$ (3 x 100 mL). Finally, the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1 → 1:1) delivered 20.76 g (77%) of the desired alcohol **70** as a colorless oil. The two reactions were worked up independently. However, the crude material was combined for the purpose of purification. The yield reflects the combination of the two approximately equimolar batches: ^{1}H NMR δ 5.76 (t of AB, 1 H, J = 10.3, 2.0 Hz), 5.61 (t of AB, 1 H, J = 10.3, 2.5 Hz), 4.44-4.38 (m, 1 H), 4.33 (d of AB, 1 H, J = 11.3, 7.8 Hz), 3.96 (dd, 1 H, J = 11.3, 2.8 Hz), 3.67 (t, 2 H, J = 5.9 Hz), 3.34 (dt, 1 H, J = 7.5, 2.2 Hz), 2.16-2.00 (m, 2 H), 1.88-1.63 (m, 3 H), 1.63-1.47 (m, 1 H), 1.22 (s, 9 H), 0.98 (d, 3 H, J = 7.1 Hz).

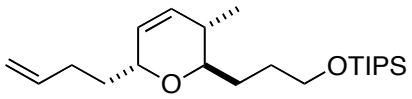


{(2*S*,5*S*,6*R*)-5-Methyl-6-[3-(triisopropylsilanyloxy)propyl]-5,6-dihydro-2*H*-pyran-2-yl}methyl pivalate.[114,136] To a solution of **70** (20.76 g, 76.89 mmol), imidazole (10.5 g, 154.2 mmol) and DMAP (939 mg, 7.69 mmol) in CH_2Cl_2 (200 mL) was added TIPS-Cl (17.8 g, 19.7 mL, 92.3 mmol) at room temperature. After approximately 14 h, the solids were removed via filtration and the remaining solution (or filtrate) was concentrated *in vacuo*. The resulting white residue was diluted with EtOAc (150 mL) and washed with 10% citric acid (2 x 25 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*.

Alternatively, upon completion of the reaction, the heterogenous mixture was diluted with EtOAc and subsequently washed with saturated aqueous $NaHCO_3$, followed by brine. As indicated previously, the organic layer was then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the yellow oil via chromatography on SiO_2 (Hexanes/EtOAc, 80:1 → 40:1 → 20:1) gave 32.8 g (100%) of {(2*S*,5*S*,6*R*)-5-methyl-6-[3-(triisopropylsilanyloxy)propyl]-5,6-dihydro-2*H*-pyran-2-yl}methyl pivalate: ^{1}H NMR δ 5.76 (t of AB, 1 H, J = 10.3, 2.2 Hz), 5.61 (t of AB, 1 H, J = 10.2, 2.4 Hz), 4.40-4.34 (m, 2 H), 4.28 (d of AB, 1 H, J = 11.4, 7.7 Hz), 3.97 (d of AB, 1 H, J = 11.4, 3.4 Hz), 3.78-3.63 (m, 1 H), 3.32 (dt, 1 H, J = 8.2, 2.4 Hz), 2.13-1.97 (m, 1 H), 1.88-1.69 (m, 2 H), 1.69-1.34 (m, 2 H), 1.22 (s, 9 H), 1.07-1.03 (m, 21 H), 0.98 (d, 3 H, J = 7.1 Hz).



{(2*S*,5*S*,6*R*)-5-Methyl-6-[3-(triisopropylsilanyloxy)propyl]-5,6-dihydro-2*H*-pyran-2-yl}methanol (71).[114,136] A solution of {(2*S*, 5*S*,6*R*)-5-methyl-6-[3-(triisopropylsilanyloxy)propyl]-5,6-dihydro-2*H*-pyran-2-yl}methyl pivalate (10.14 g, 23.80 mmol) in Et_2O (100 mL) was added dropwise via an addition funnel over the span of 65 min to a 0 °C suspension of LAH (1.98 g, 52.17 mmol) in Et_2O (60 mL). The ice bath was removed immediately following the addition. After an additional 50 min at room temperature, the reaction mixture was re-cooled to 0 °C and treated with water (2.0 mL) followed by a solution of 15% aqueous NaOH (2.0 mL). The heterogeneous mixture was warmed to room temperature and maintained for 1 h prior to the slow addition of a second aliquot of water (6.0 mL) at 0 °C. Finally, the resulting white granular material was removed via vacuum filtration after additional stirring (1 h) at room temperature. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by chromatography on SiO_2 (Hexanes/EtOAc, 20:1 → 8:1 → 4:1) delivered 6.56 g (81%) of **71** as a colorless oil: ^{1}H NMR δ 5.76 (t of AB, 1 H, *J* = 10.3, 2.5 Hz), 5.59 (t of AB, 1 H, *J* = 10.3, 2.4 Hz), 4.25 (ddd, 1 H, *J* = 10.8, 5.7, 2.5 Hz), 3.81-3.70 (m, 2 H), 3.65 (d of AB, 1 H, *J* = 11.5, 8.5 Hz), 3.54 (d of AB, 1 H, *J* = 11.5, 3.6 Hz), 3.34 (dt, 1 H, *J* = 7.7, 2.4 Hz), 2.19-2.00 (m, 1 H), 1.88-1.47 (m, 5 H), 1.08-1.04 (m, 21 H), 1.00 (d, 3 H, *J* = 7.1 Hz).

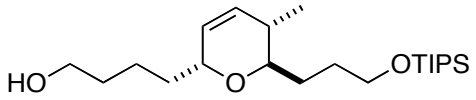


(2*R*,3*S*,6*R*)-[3-(6-But-3-enyl)-3-methyl-3,6-dihydro-*2H*-pyran-2-yl)-propoxy]triisopropylsilane (72).[114,136] To a –45 °C solution of **71** (3.26 g, 9.53 mmol) and

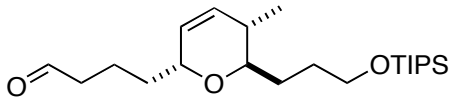
pyridine (1.0 mL, 0.98 g, 12.4 mmol) in CH_2Cl_2 (73 mL) was slowly added trifluoromethanesulfonic anhydride (1.88 mL, 3.23 g, 11.5 mmol) dropwise. After 30 min, the –45 °C bath was replaced with a 0 °C ice bath. Approximately 15 min later, the reaction mixture was diluted with Et_2O. The Et_2O solution was washed with ice-cold 0.5 M HCl, followed by water, saturated aqueous $NaHCO_3$ and brine. Finally, the organic layer was dried (Na_2SO_4), filtered through a small pad of silica gel and concentrated *in vacuo*. The resulting pale yellow oil was used for the next step within 1.5 h after its initial isolation and without additional purification.

To a –78 °C suspension of CuCN (1.9 g, 21.0 mmol) in THF (78 mL) was added MeLi (1.6 M in Et_2O, 26.2 mL, 41.9 mmol) dropwise. After 15 min at –78 °C, the dry ice/acetone bath was replaced with a 0 °C ice bath. The preparation of the triflate should be initiated at this point in time. After 30 min at 0 °C, the now homogeneous solution was re-cooled to –78 °C and subsequently treated with allyltributylstannane (13.9 g, 13.0 mL, 42.0 mmol) dropwise. The dry ice/acetone bath was replaced with a 0 °C ice bath approximately 10 min after the introduction of the stannane. The yellow solution was stirred at this temperature for the next 1.5-2 h. Finally, a –78 °C solution of the previously prepared triflate (4.52 g, 9.54 mmol, theoretical yield) in THF (51 mL) was added via cannula to a –78 °C solution of the higher order allyl cuprate. After 3 h and 40 min between –60 °C and –78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl. Subsequently, the organic layer was washed with 0.5 M aqueous NaOH followed by brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude material by chromatography on SiO_2 (Hexanes/EtOAc, 1:0 → 100:1 → 50:1) gave 2.76 g (79%) of **72** as a clear, colorless oil: ^{1}H NMR δ 5.94-5.75 (m, 1 H), 5.65 (t of AB, 1 H, J = 10.1, 1.9 Hz), 5.60 (t of AB, 1 H, J = 10.1, 1.7 Hz), 5.04 (dq, 1 H, J = 17.1, 1.6 Hz), 4.96 (dq, 1 H, J =

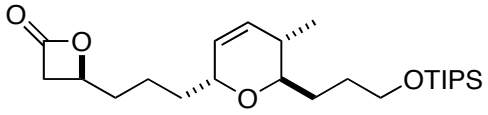
10.1, 0.9 Hz), 4.13-4.06 (m, 1 H), 3.79-3.66 (m, 2 H), 3.24 (*app* td, 1 H, J = 7.2, 2.5 Hz), 2.31-2.06 (m, 2 H), 2.06-1.94 (m, 1 H), 1.91-1.38 (m, 6 H), 1.19-1.00 (m, 21 H), 0.96 (d, 3 H, J = 7.1 Hz); ^{13}C NMR δ 138.4, 130.8, 128.7, 114.7, 74.1, 71.0, 63.2, 34.3, 33.1, 30.2, 29.4, 29.2, 18.0, 12.0.



4-{(2*R*,5*S*,6*R*)-5-Methyl-6-[3-(triisopropylsilanyloxy)propyl]-5,6-dihydro-2*H*-pyran-2-yl}butan-1-ol (74).[114,136] To a 0 °C solution of diene **72** (2.32 g, 6.33 mmol) in THF (26 mL) was added 9-BBN (0.5 M in THF, 25.0 mL, 12.5 mmol). The reaction mixture was stirred for approximately 14.5 h at room temperature. Then, it was cooled to 0 °C and treated with 0.5 M NaOH (24 mL) followed by 30% aqueous H_2O_2 (24 mL). The resulting heterogeneous mixture was warmed to room temperature and stirred for a total of 7 h and 15 min. The aqueous phase was extracted with EtOAc (3 x 50 mL). Finally, the combined organic layers were washed with water and brine, and then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude material by chromatography on SiO_2 (Hexanes/EtOAc, 50:1 → 15:1 → 8:1 → 4:1 → 2:1 → 1:1) provided >1.6 g (>66%) of the desired alcohol **74** as a clear, colorless oil. A significant quantity (450 mg total mass of mixture) of the desired product **74** co-eluted with an impurity: ^{1}H NMR δ 5.66 (t of AB, 1 H, J = 11.2, 1.9 Hz), 5.60 (t of AB, 1 H, J = 11.1, 1.8 Hz), 4.16-4.06 (m, 1 H), 3.78-3.69 (m, 2 H), 3.66 (t, 2 H, J = 6.3 Hz), 3.28-3.22 (m, 1 H), 2.09-1.94 (m, 1 H), 1.88-1.69 (m, 2 H), 1.69-1.38 (m, 9 H), 1.13-1.00 (m, 21 H), 0.97 (d, 3 H, J = 7.1 Hz).

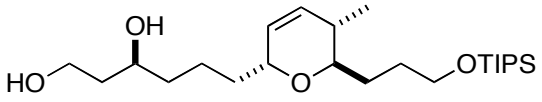


4-{(2*R*,5*S*,6*R*)-5-Methyl-6-[3-(triisopropylsilanyloxy)propyl]-5,6-dihydro-2*H*-pyran-2-yl}butanal (75).[114,136] To a 0 °C solution of starting alcohol **74** (231 mg, 0.600 mmol) in CH_2Cl_2 (8.0 mL) was added Dess-Martin periodinane (383 mg, 0.903 mmol) in one single batch. Approximately 5 min later, the reaction mixture was warmed to room temperature and stirred at this temperature for an additional 1.5 h. Finally, the mixture was diluted with EtOAc (20 mL) and washed sequentially with saturated aqueous $NaHCO_3$ (2 x 15 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a white residue. Purification of the crude material by chromatography on SiO_2 (Hexanes/EtOAc, 50:1 → 20:1) gave 176.3 mg (77%) of aldehyde **75** as an oil: ^{1}H NMR δ 9.77 (t, 1 H, *J* = 1.8 Hz), 5.62 (s, 2 H), 4.13-4.06 (m, 1 H), 3.76-3.65 (m, 2 H), 3.23 (ddd, 1 H, *J* = 11.7, 9.6, 3.0 Hz), 2.47 (*app* t, 2 H, *J* = 7.4 Hz), 2.06-1.94 (m, 1 H), 1.94-1.38 (m, 8 H), 1.19-1.00 (m, 21 H), 0.96 (d, 3 H, *J* = 7.1 Hz).



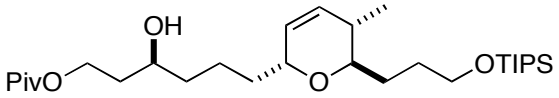
(*S*)-4-{3-((2*R*,5*S*,6*R*)-5-Methyl-6-[3-(triisopropylsilanyloxy)propyl]-5,6-dihydro-*2H*-pyran-2-yl)propyl}oxetan-2-one (80).[136] To a solution of (*S*,*S*)-triamine ligand **78**[173] (1.03 g, 1.90 mmol) in CH_2Cl_2 (10 mL) was added $AlMe_3$ (2.0 M in toluene, 1.1 mL, 2.2 mmol) dropwise at room temperature. After 3 h and 15 min, the temperature was lowered to –50 °C. Then, both diisopropylethylamine (1.80 mL, 1.34 g, 10.28 mmol) and acetyl bromide (0.860 mL, 1.42 g, 11.63 mmol) were introduced dropwise, respectively. Finally, a solution of aldehyde **75** (2.32 g, 6.08 mmol) in CH_2Cl_2 (14 mL) was added slowly via an addition funnel over 35 min.

The reaction mixture was stirred at –50 °C for an additional 16.5 h. Following the addition of cold Et_2O (60 mL) to the yellow solution at –50 °C, the mixture was warmed to room temperature and subsequently filtered through a pad of silica gel. The silica gel plug was washed repeatedly with Et_2O (100 mL) and EtOAc (200 mL). The solvent was removed *in vacuo* and the remaining yellow oil was submitted to purification by chromatography on SiO_2 (Hexanes/EtOAc, 75:1 → 20:1 → 17:1 → 8:1 → 4:1 → 1:1). The purification step was intended for the sole purpose of removing from the crude material most, if not all, triamine ligand **78**. Thus, slightly impure β-lactone **80** (2.83 g) was isolated and used directly for the next step: $[\alpha]_D$ 0 (*c* 0.50, $CHCl_3$, 22 °C); IR (neat) 3024, 2941, 2865, 1829, 1461, 1377, 1199, 1106, 1073, 1012, 998, 882, 723, 676 cm^{-1}; ^1H NMR δ 5.63 (*br* s, 2 H), 4.52 (dt, 1 H, *J* = 11.5, 5.8 Hz), 4.12-4.09 (m, 1 H), 3.78-3.66 (m, 2 H), 3.52 (d of AB, 1 H, *J* = 16.2, 5.7 Hz), 3.24 (*app* dt, 1 H, *J* = 6.6, 2.8 Hz), 3.08 (d of AB, 1 H, *J* = 16.2, 4.3 Hz), 2.10-1.95 (m, 1 H), 1.95-1.73 (m, 3 H), 1.73-1.40 (m, 7 H), 1.13-1.02 (m, 21 H), 0.98 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 168.2, 130.9, 128.3, 74.4, 71.2, 70.8, 63.2, 42.9, 34.5, 34.1, 33.3, 29.4, 29.0, 21.4, 18.2, 18.0, 12.0; HRMS (ESI) calcd for $C_{24}H_{44}O_4SiNa$ (M+Na) 447.2907, found 447.2899.



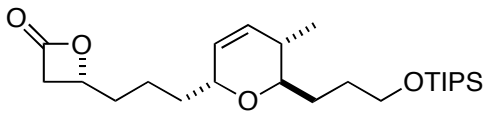
(*S*)-6-{(2*R*,5*S*,6*R*)-5-Methyl-6-[3-(triisopropylsilanyloxy)propyl]-5,6-dihydro-*2H*-pyran-2-yl}hexane-1,3-diol (81).[136] To a 0 °C suspension of excess LAH (526 mg, 13.9 mmol) in Et_2O (8.0 mL) was added a solution of β-lactone **80** (app. 2.83 g, 6.67 mmol) in Et_2O (14 mL). The reaction was stirred at 0 °C for 40 min prior to the removal of the ice bath. After 15 additional min, water (530 μL) was introduced dropwise at 0 °C over 1 h. Then, a solution of

15% aqueous NaOH[209] (530 μL) was added dropwise at 0 °C. The heterogeneous mixture was warmed to room temperature over 1 h prior to the addition of a second aliquot of H_2O (1.6 mL) at 0 °C. The final mixture was warmed to room temperature prior to the removal of the aluminum salts via vacuum filtration. The Et_2O layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude material by chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1 → 1:1 → 0:1) provided 2.2 g (85% over 2 steps) of diol **81** as a clear, colorless oil: ^{1}H NMR δ 5.65 (*app* t of AB, 1 H, *J* = 10.3, 1.8 Hz), 5.59 (*app* t of AB, 1 H, *J* = 10.3, 1.9 Hz), 4.16-4.06 (m, 1 H), 3.94-3.78 (m, 3 H), 3.75 (*app* d of AB, 1 H, J = 9.9. 6.1 Hz), 3.68 (*app* d of AB, 1 H, *J* = 9.9, 6.3 Hz), 3.25 (*app* td, 1 H, *J* = 7.2, 2.5 Hz), 2.67 (*br* s, 2 H), 2.06-1.94 (m, 1 H), 1.88-1.38 (m, 12 H), 1.19-0.95 (m, 21 H), 0.87 (d, 3 H, *J* = 7.2 Hz).

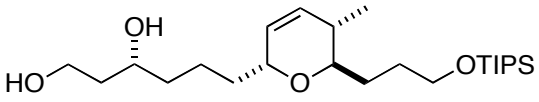


(*S*)-3-Hydroxy-6-{(2*R*,5*S*,6*R*)-5-methyl-6-[3-(triisopropylsilanyloxy)propyl]-5,6-dihydro-2*H*-pyran-2-yl}hexyl pivalate (77).[136] To a 0 °C solution of diol **81** (271 mg, 0.635 mmol) in pyridine (4.2 mL) was added pivaloyl chloride (85.0 μL, 83.3 mg, 0.697 mmol). The reaction mixture was warmed to room temperature over 30 min and kept at this temperature for an additional 4 h. Then, the solution was diluted with EtOAc (40 mL) and subsequently washed with 1.0 M HCl (2 x 15 mL), saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by chromatography on SiO_2 (Hexanes/EtOAc, 20:1 → 8:1 → 4:1 → 2:1 → 1:1) gave 271 mg (83%)[210] of **77** as a clear, colorless oil: ^{1}H NMR δ 5.65 (t of AB, 1 H, *J* = 10.3, 2.0 Hz), 5.60 (t of AB, 1 H, *J* = 10.4, 1.8 Hz), 4.38 (ddd, 1 H, *J* = 11.1, 8.6, 4.8 Hz), 4.23-4.09 (m, 2 H), 3.76-

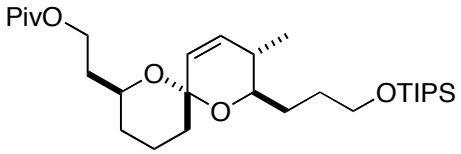
3.62 (m, 3 H), 3.25 (*app* t, 1 H, *J* = 6.9 Hz), 2.05-1.94 (m, 1 H), 1.91-1.38 (m, 13 H), 1.21 (*br* s, 9 H), 1.13-1.00 (m, 21 H), 0.97 (d, 3 H, *J* = 7.1 Hz).



(*R*)-4-{3-((2*R*,5*S*,6*R*)-5-Methyl-6-[3-(triisopropylsilanyloxy)propyl]-5,6-dihydro-*2H*-pyran-2-yl)propyl}oxetan-2-one (84).[136] To a solution of (*R*,*R*)-triamine ligand **82** (24.9 mg, 0.0460 mmol) in CH_2Cl_2 (250 μL) was added $AlMe_3$ (2.0 M in toluene, 25.3 μL, 0.0506 mmol) dropwise at room temperature. After 3 h, the temperature was lowered to –50 °C. Then, both diisopropylethylamine (24.0 μL, 17.8 mg, 0.137 mmol) and acetyl bromide (11.2 μL, 18.6 mg, 0.151 mmol) were introduced dropwise. Next, a solution of aldehyde **75** (30.6 mg, 0.0801 mmol) in CH_2Cl_2 (320 μL) was slowly added to the cold reaction mixture. Finally, after 14 h at –50 °C, cold Et_2O (10 mL) was added to the yellow solution. The resultant mixture was warmed to room temperature and subsequently filtered through a pad of silica gel. The silica gel plug was washed repeatedly with Et_2O (25 mL) and EtOAc (50 mL). The solvent was removed *in vacuo* and the remaining yellow oil was submitted to purification by chromatography on SiO_2 (Hexanes/EtOAc, 75:1 → 20:1 → 17:1 → 8:1 → 4:1 → 1:1) to afford 20.5 mg (62%) of the desired (*R*)-configured β-lactone **84** as a pale yellow oil: $[\alpha]_D$ +13.5 (*c* 0.7, CH_2Cl_2, 22 °C); ^{1}H NMR δ 5.63 (*br* s, 2 H), 4.55-4.48 (m, 1 H), 4.16-4.06 (m, 1 H), 3.78-3.66 (m, 2 H), 3.52 (d of AB, 1 H, *J* = 16.2, 5.8 Hz), 3.25 (*app* dt, 1 H, *J* = 7.0, 2.9 Hz), 3.07 (d of AB, 1 H, *J* = 16.2, 4.3 Hz), 2.06-1.85 (m, 2 H), 1.85-1.42 (m, 9 H), 1.15-1.03 (m, 21 H), 0.98 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 168.3, 131.0, 128.4, 74.6, 71.2, 71.1, 63.3, 43.0, 34.8, 34.3, 33.6, 29.5, 29.2, 21.6, 18.1 (2C), 12.1.

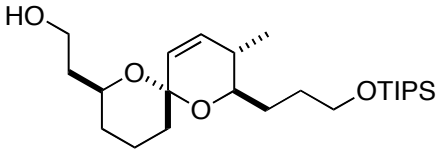


(*R*)-6-{(2*R*,5*S*,6*R*)-5-Methyl-6-[3-(triisopropylsilanyloxy)propyl]-5,6-dihydro-2*H*-pyran-2-yl}hexane-1,3-diol. To a 0 °C suspension of excess LAH (3.2 mg, 0.085 mmol) in Et_2O (100 μL) was added a solution of β-lactone **84** (18.0 mg, 0.0425 mmol) in Et_2O (100 μL). The reaction was maintained at 0 °C for 45 min prior to the removal of the ice bath. After an additional 45 min at room temperature, water (100 μL) was introduced at 0 °C followed by 15% aqueous NaOH (100 μL). More Et_2O was added to the reaction mixture to facilitate the mixing process. The heterogeneous mixture was warmed to room temperature and subsequently treated with water (300 μL) at 0 °C. The final mixture was warmed to room temperature prior to the removal of the aluminum salts via vacuum filtration. The Et_2O layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude material by chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1 → 1:1 → 0:1) provided 12.0 mg (66%) of (*R*)-6-{(2*R*,5*S*,6*R*)-5-methyl-6-[3-(triisopropylsilanyloxy)propyl]-5,6-dihydro-*2H*-pyran-2-yl}hexane-1,3-diol as an oil: ^{1}H NMR δ 5.65 (*app* t of AB, 1 H, *J* = 10.3, 1.9 Hz), 5.58 (*app* t of AB, 1 H, J = 10.3, 1.9 Hz), 4.16-4.06 (m, 1 H), 3.97-3.78 (m, 3 H), 3.75 (*app* d of AB, 1 H, *J* = 9.9, 6.2 Hz), 3.68 (*app* d of AB, 1 H, *J* = 9.8, 6.2 Hz), 3.26 (*app* td, 1 H, *J* = 7.0, 2.5 Hz), 2.31 (*br* s, 2 H), 2.05-1.94 (m, 1 H), 1.88-1.38 (m, 12 H), 1.19-1.02 (m, 21 H), 0.97 (d, 3 H, *J* = 7.1 Hz).



2-{(2*S*,6*S*,8*R*,9*S*)-9-Methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undec-10-en-2-yl}ethyl pivalate.[114,136] To a suspension of iodobenzene

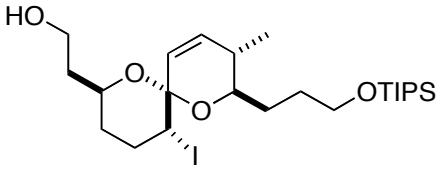
diacetate (2.70 g, 8.38 mmol) and iodine (2.13 g, 8.39 mmol) in CCl_4 (210 mL) was added a solution of alcohol **77** (2.15 g, 4.20 mmol) in CCl_4 (60 mL) at room temperature. The reaction was initiated by light (250W infrared heat lamp with a tungsten filament) and the mixture was continuously irradiated for 1 h and 45 min. The reaction mixture was cooled to 0 °C prior to a quench with saturated aqueous $Na_2S_2O_3$ (300 mL). The resultant heterogeneous mixture was warmed to room temperature and stirred for a total of 1.5 h. Finally, the aqueous layer was extracted with EtOAc (2 x 150 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The red residue (comprised of both an oil and solid material) was purified by chromatography through a short, wide plug of SiO_2 (Hexanes/EtOAc, 75:1 → 50:1 → 20:1 → 8:1 → 4:1 → 1:1) to give a crude mixture of spiroketals that was used without further purification.



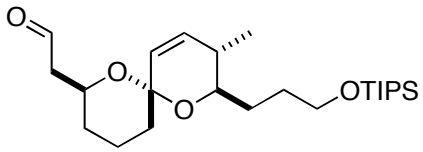
2-{(2*S*,6*S*,8*R*,9*S*)-9-Methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undec-10-en-2-yl}ethanol (85).[114,136] To a 0 °C suspension of LAH (295 mg, 7.77 mmol) in Et_2O (24 mL) was added a solution of the crude spiroketals prepared above (1.80 g) in Et_2O (30 mL) via an addition funnel over 35 min. Then, the reaction mixture was warmed to room temperature, stirred for an additional 1.5 h, quenched at 0 °C with 0.5 M NaOH and stirred for another 30-45 min. The solids were removed via vacuum filtration and the remaining solvent was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by chromatography on SiO_2 (Hexanes/EtOAc, 20:1 → 15:1 → 10:1 → 8:1 → 4:1 → 2:1) provided

574 mg (32% over 2 steps) of **85** as a colorless oil and 269 mg (12% over 2 steps) of **86** as a colorless oil.

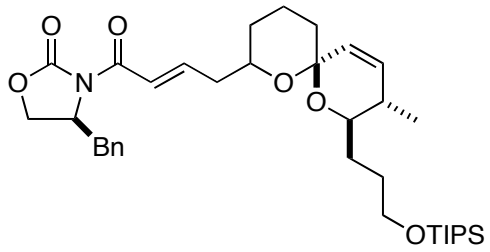
A solution of **86** (269 mg, 0.487 mmol) and AIBN (30 mg, 0.18 mmol) in tributyltin hydride (3.0 mL) was heated at 80 °C for approximately 16.5 h. The mixture was purified by chromatography on SiO_2 (Hexanes/EtOAc, 1:0 → 50:1 → 20:1 → 8:1 → 4:1) to give 211.3 mg (quant.) of spiroketal **85**, slightly contaminated by tin-derived impurities: ^{1}H NMR δ 5.66 (d of AB, 1 H, *J* = 9.9, 1.7 Hz), 5.56 (d of AB, 1 H, *J* = 9.9, 2.4 Hz), 4.03 (ddt, 1 H, *J* = 10.5, 10.5, 3.4 Hz), 3.83-3.43 (m, 4 H), 3.39 (dt, 1 H, *J* = 9.6, 2.0 Hz), 2.99 (dd, 1 H, *J* = 5.9, 4.9 Hz), 2.13-1.78 (m, 5 H), 1.78-1.53 (m, 7 H), 1.53-1.38 (m, 2 H), 1.38-1.25 (m, 2 H), 1.25-1.00 (m, 18 H), 0.96 (d, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 134.7, 129.2, 94.0, 73.8, 71.6, 63.4, 62.1, 37.9, 34.5, 30.8, 29.9, 29.7, 29.2, 18.6, 18.0, 16.9, 12.0.



2-{(2*S*,6*S*,8*R*,9*S*)-5-Iodo-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undec-10-en-2-yl}ethanol (86):[114,136] ^{1}H NMR δ 5.77 (dd, 1 H, *J* = 9.9, 1.7 Hz), 5.45 (dd, 1 H, *J* = 9.9, 2.7 Hz), 4.17-4.10 (m, 1 H), 4.07 (dd, 1 H, *J* = 12.9, 4.4 Hz), 3.81-3.71 (m, 4 H), 3.42 (*br* t, 1 H, *J* = 8.7 Hz), 2.63-2.47 (m, 2 H), 2.28-2.13 (m, 2 H), 2.00-1.81 (m, 2 H), 1.81-1.44 (m, 5 H), 1.14-1.04 (m, 22 H), 0.97 (d, 3 H, *J* = 7.2 Hz).

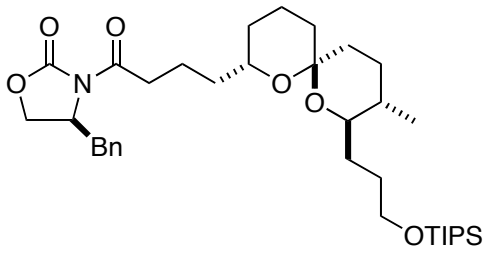


2-{(2*S*,6*S*,8*R*,9*S*)-9-Methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undec-10-en-2-yl}acetaldehyde (87).[114,136] To a suspension of PCC (410 mg, 1.90 mmol) and NaOAc (312 mg, 3.80 mmol) in CH_2Cl_2 (13 mL) was added a solution of alcohol **85** (135 mg, 0.317 mmol) in CH_2Cl_2 (14 mL) at room temperature. After 1.5 h, the reaction mixture was quenched with Et_2O and $MgSO_4$. The solids were removed by vacuum filtration and the organic phase (CH_2Cl_2 and Et_2O) was concentrated *in vacuo*. The resulting orange oil was purified by column chromatography on SiO_2 (Hexanes/EtOAc, 20:1 → 10:1 → 4:1 → 2:1 → 1:1) to give 112.7 mg (84%) of **87**: ^{1}H NMR δ 9.78 (t, 1 H, *J* = 1.9 Hz), 5.67 (d of AB, 1 H, *J* = 9.9, 1.7 Hz), 5.54 (d of AB, 1 H, *J* = 9.9, 2.5 Hz), 4.41-4.25 (m, 1 H), 3.82-3.69 (m, 2 H), 3.40 (dt, 1 H, *J* = 9.6, 2.1 Hz), 2.56 (dd of AB, 1 H, *J* = 16.4, 8.4, 2.9 Hz), 2.42 (dd of AB, 1 H, *J* = 16.1, 4.4, 1.8 Hz), 2.09-1.81 (m, 4 H), 1.75-1.41 (m, 6 H), 1.34-1.25 (m, 1 H), 1.16-1.00 (m, 21 H), 0.94 (d, 3 H, *J* = 7.2 Hz).



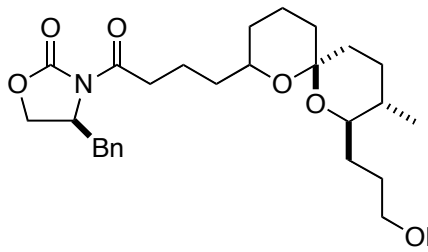
(4*S*)-4-Benzyl-3-((*E*)-4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-10-en-2-yl}-but-2-enoyl)-oxazolidin-2-one (89).[136] To a suspension of aldehyde **87** (511 mg, 1.21 mmol), LiCl (10 equiv, 511mg, 1.21 mmol, previously dried under vacuum at 140 °C for 15 h and flame-dried (x 3) directly before use) and (*S*)-diethyl 2-(4-benzyl-

2-oxooxazolidin-3-yl)-2-oxoethylphosphonate **88**[181,182] (513 mg, 1.45 mmol) in THF (15 mL) was added diisopropylethylamine (252 μL, 187 mg, 1.45 mmol) dropwise at room temperature. The reaction mixture was maintained at room temperature for 4.5 d. Finally, it was diluted with brine and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (Hexanes/EtOAc, 20:1 → 8:1 → 4:1) provided 647.2 mg (86%, not based on recovered starting material) of pure **89** as a clear, colorless oil. The reaction did not proceed to completion. A significant quantity of unreacted aldehyde **87** still existed (63 mg, mixture comprised of a 4.5:1 ratio of starting material **87** to product **89** via ^{1}H NMR analysis): ^{1}H NMR δ 7.34-7.19 (m, 7 H), 5.66 (d of AB, 1 H, *J* = 9.9, 1.6 Hz), 5.56 (d of AB, 1 H, *J* = 9.9, 2.4 Hz), 4.70 (ddd, 1 H, *J* = 13.1, 6.9, 3.4 Hz), 4.41-4.13 (m, 2 H), 3.92 (ddd, 1 H, *J* = 10.9, 6.2, 5.0 Hz), 3.80-3.68 (m, 2 H), 3.42 (dt, 1 H, *J* = 9.7, 1.5 Hz), 3.33 (dd, 1 H, *J* = 13.3, 3.2 Hz), 2.76 (dd, 1 H, *J* = 13.3, 9.6 Hz), 2.56-2.34 (m, 2 H), 2.13-2.00 (m, 1 H), 1.91-1.81 (m, 3 H), 1.69-1.53 (m, 4 H), 1.53-1.34 (m, 2 H), 1.34-1.16 (m, 1 H), 1.16-0.91 (m, 21 H), 0.97 (d, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 164.7, 153.3, 148.0, 135.4, 134.7, 129.4, 129.3, 128.9, 127.3, 122.0, 94.2, 73.3, 68.9, 63.3, 60.4, 55.3, 39.4, 37.9, 34.6, 30.3, 29.6, 29.2, 18.6, 18.0, 16.8, 12.0.



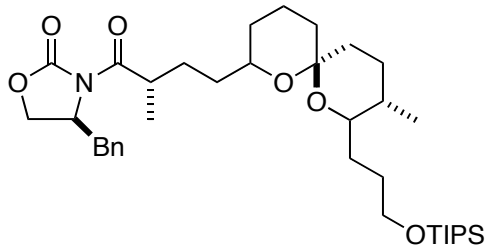
(*S*)-4-Benzyl-3-(4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilylanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}butanoyl)oxazolidin-2-one (90).[136] A solution of spiroketal

89 (15.0 mg, 24.0 μmol) in MeOH (2.0 mL) was transferred to a round bottom flask already containing Pt/C (5%, 6.0 mg). The heterogeneous mixture was treated with H_2 gas for 1.5 h at room temperature. Then, it was filtered through a pad of celite and washed thoroughly with CH_2Cl_2. The solvent was removed *in vacuo* and the resultant residue was purified via chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 1:1) to provide ~3.2 mg (21%) of **91** 11.9 mg (79%) of **90** as a colorless oil: $[\alpha]_D$ +48.9 (*c* 1.2, $CHCl_3$, 22 °C); IR (neat) 3065, 3026, 2955, 2862, 1796, 1697, 1456, 1380, 1347, 1210, 1095, 986, 877 cm^{-1}; ^1H NMR δ 7.37-7.25 (m, 3 H), 7.23-7.20 (m, 2 H), 4.68 (dddd, 1 H, *J* = 13.2, 6.9, 3.4 Hz), 4.22-4.11 (m, 2 H), 3.80-3.66 (m, 2 H), 3.63-3.51 (m, 1 H), 3.31 (dd, 1 H, *J* = 13.3, 3.2 Hz), 3.18 (*app* t, 1 H, *J* = 9.8 Hz), 3.09-2.90 (m, 2 H), 2.76 (dd, 1 H, *J* = 13.3, 9.7 Hz), 2.00-1.67 (m, 6 H), 1.67-1.41 (m, 9 H), 1.41-1.23 (m, 3 H), 1.23-1.16 (m, 1 H), 1.16-0.97 (m, 21 H), 0.84 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 173.1, 153.4, 135.4, 129.4, 128.9, 127.3, 95.4, 74.5, 68.9, 66.1, 63.7, 55.1, 38.0, 36.1, 35.8, 35.6, 35.5, 35.1, 31.3, 29.5, 29.4, 28.0, 20.6, 19.0, 18.0 (2), 12.0; MS (EI) *m/z* (rel intensity) 586 ([M-C_3H_7]$^+$, 12), 343 (17), 178 (25), 131 (21), 117 (36), 95 (64), 69 (54); HRMS (EI) calcd for $C_{33}H_{52}NO_6Si$ (M-C_3H_7) 586.3564, found 586.3593.



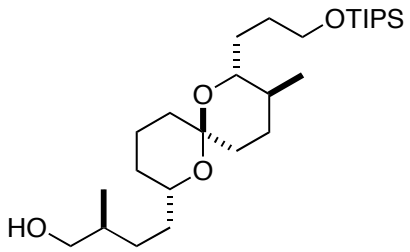
(*S*)-4-Benzyl-3-(4-{(2*S*,6*S*,8*R*,9*S*)-8-[3-hydroxypropyl]-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl}butanoyl)oxazolidin-2-one (91):[136] ^1H NMR δ 7.37-7.21 (m, 5 H), 4.69 (ddd, 1 H, *J* = 13.1, 6.9, 3.3 Hz), 4.24-4.15 (m, 2 H), 3.74-3.55 (m, 3 H), 3.32 (d of AB,

1 H, *J* = 13.4, 3.2 Hz), 3.27-3.21 (m, 1 H), 2.99 (*app* t, 2 H, *J* = 7.3 Hz), 2.77 (d of AB, 1 H, *J* = 13.3, 9.7 Hz), 2.35 (*br* s, 1 H), 2.00-1.31 (m, 17 H), 1.23-1.13 (m, 2 H), 0.85 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR δ 173.5, 153.7, 135.5, 129.6, 129.2, 127.6, 76.2, 71.4, 71.2, 66.4, 63.6, 55.4, 38.2, 37.7, 37.0, 35.6, 34.0, 32.6, 29.4, 29.1, 28.2, 27.0, 22.2, 20.6, 18.6, 18.3, 12.3.



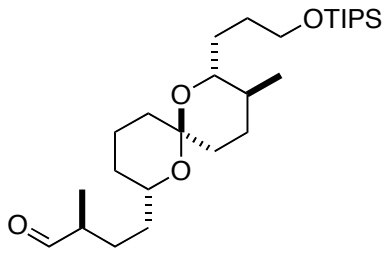
(*S*)-4-Benzyl-3-((*S*)-2-methyl-4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}butanoyl)-oxazolidin-2-one (92).[136] To a –78 °C solution of NaHMDS (1.0 M in THF, 0.850 mL, 0.850 mmol) in THF (1.0 mL) was added a –78 °C solution of oxazolidinone **90** (0.463 g, 0.736 mmol) in THF (5.5 mL) via cannula. The solution was stirred for 30 min prior to the introduction of excess MeI (0.230 mL, 0.524 g, 3.68 mmol) at –78 °C. The reaction mixture was maintained at –78 °C for an additional 3 h and 35 min. Finally, it was quenched with saturated aqueous NH_4Cl and the aqueous phase was extracted with EtOAc (3 x 35 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification (x 2) via chromatography on SiO_2 (Hexanes/EtOAc, 20:1 → 15:1 → 8:1 → 4:1) provided 316.8 mg (67%) of **92** as a clear, colorless oil: $[\alpha]_D$ +57.6 (*c* 0.50, $CHCl_3$, 22 °C); IR (neat) 2924, 2866, 1785, 1697, 1451, 1379, 1210, 1099, 988 cm^{-1}; ^{1}H NMR δ 7.36-7.21 (m, 5 H), 4.70 (ddd, 1 H, *J* = 12.6, 6.4, 3.2 Hz), 4.22-4.14 (m, 2 H), 3.79-3.66 (m, 3 H), 3.56-3.47 (m, 1 H), 3.27 (dd, 1 H, *J* = 13.3, 3.1 Hz), 3.15 (*br* t, 1 H, *J* = 9.3 Hz), 2.77 (dd, 1 H, *J* = 13.3, 9.6 Hz), 2.06-1.75 (m, 4 H),

1.75-1.37 (m, 13 H), 1.37-1.28 (m, 1 H), 1.25 (d, 3 H, J = 6.9 Hz), 1.19-1.11 (m, 1 H), 1.09-1.03 (m, 21 H), 0.84 (d, 3 H, J = 6.5 Hz); ^{13}C NMR δ 177.1, 152.9, 135.3, 129.4, 128.9, 127.3, 95.4, 74.5, 68.8, 65.9, 63.7, 55.2, 37.9, 37.7, 36.0, 35.4, 35.0, 33.9, 31.0, 29.4, 29.3, 28.0, 19.0, 18.0, 17.5, 12.0; MS (EI) *m/z* (rel intensity) 600 ([M-C_3H_7]$^+$, 13), 357 (19), 233 (19), 178 (21), 159 (14), 131 (31), 117 (100), 95 (84), 75 (52); HRMS (EI) calcd for $C_{34}H_{54}NO_6Si$ (M-C_3H_7) 600.3720, found 600.3742.

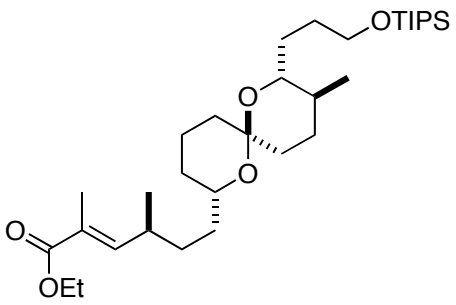


(*S*)-2-Methyl-4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}butan-1-ol.[136] To a solution of oxazolidinone **92** (17 mg, 26 μmol) in Et_2O (1.0 mL) and absolute EtOH (10-15 μL) was slowly added $LiBH_4$ (2.0 M in THF, 30 μL, 60 μmol) at –25 °C. The hydride solution was prepared from solid $LiBH_4$ prior to use. Comparable yields were obtained with a commercially available solution. The reaction mixture was kept below 0 °C (*i.e.* -25 °C to –10 °C) for 1.5 h, warmed slowly to 0 °C, and stirred for an additional 12 h at +5 °C. The mixture was quenched with 0.5 M NaOH (2.0 mL) and brine (2.0 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow residue. Chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 6:1 → 4:1 → 2:1) provided 9.6 mg (77%) of (*S*)-2-methyl-4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}butan-1-ol as a clear, colorless oil: $[\alpha]_D$ +36.6 (*c* 0.50, $CHCl_3$, 22

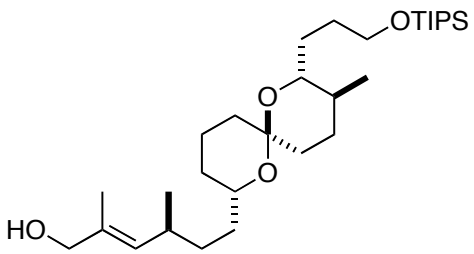
°C); IR (neat) 3387, 2938, 2866, 1461, 1384, 1098, 986, 882 cm^{-1}; ^1H NMR δ 3.81-3.69 (m, 2 H), 3.54-3.41 (m, 3 H), 3.16 (*br* t, 1 H, *J* = 9.6 Hz), 1.88-1.75 (m, 3 H), 1.69-1.42 (m, 15 H), 1.42-1.17 (m, 3 H), 1.17-0.97 (m, 21 H), 0.93 (d, 3 H, *J* = 6.4 Hz), 0.83 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 95.5, 74.5, 69.4, 68.2, 63.6, 36.1, 35.9, 35.6, 35.1, 33.6, 31.3, 29.5, 29.4, 29.2, 28.1, 19.1, 18.0, 16.8, 12.1; MS (EI) *m/z* (rel intensity) 452 ($[M-H_2O]^+$, 2), 471 (25), 453 (31), 427 (82), 409 (18), 184 (20), 155 (23), 131 (43), 117 (100), 95 (91), 85 (66), 69 (71); HRMS (EI) calcd for $C_{27}H_{52}O_3Si$ (M-H_2O) 452.3686, found 452.3698.



(*S*)-2-Methyl-4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}butanal (93).[136] To a solution of (*S*)-2-methyl-4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}butan-1-ol (9.6 mg, 20 μmol) in CH_2Cl_2 (300 μL) was added Dess-Martin periodinane (14.0 mg, 33.0 μmol) at room temperature. After 25 min, the reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. Finally, the organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by chromatography on SiO_2 (Hexanes/EtOAc, 15:1 → 8:1 → 4:1) provided 7.4 mg (77%) of **93** as a clear, colorless oil: ^1H NMR δ 9.64 (d, 1 H, *J* = 1.9 Hz), 3.78-3.68 (m, 2 H), 3.50 (dt, 1 H, *J* = 5.2, 10.5 Hz), 3.13 (dt, 1 H, *J* = 1.7, 9.5 Hz), 2.45-2.30 (m, 1 H), 1.98-1.81 (m, 4 H), 1.63-1.25 (m, 18 H), 1.11 (d, 3 H, *J* = 7.0 Hz), 1.09-1.05 (m, 18 H), 0.84 (d, 3 H, *J* = 6.5 Hz).

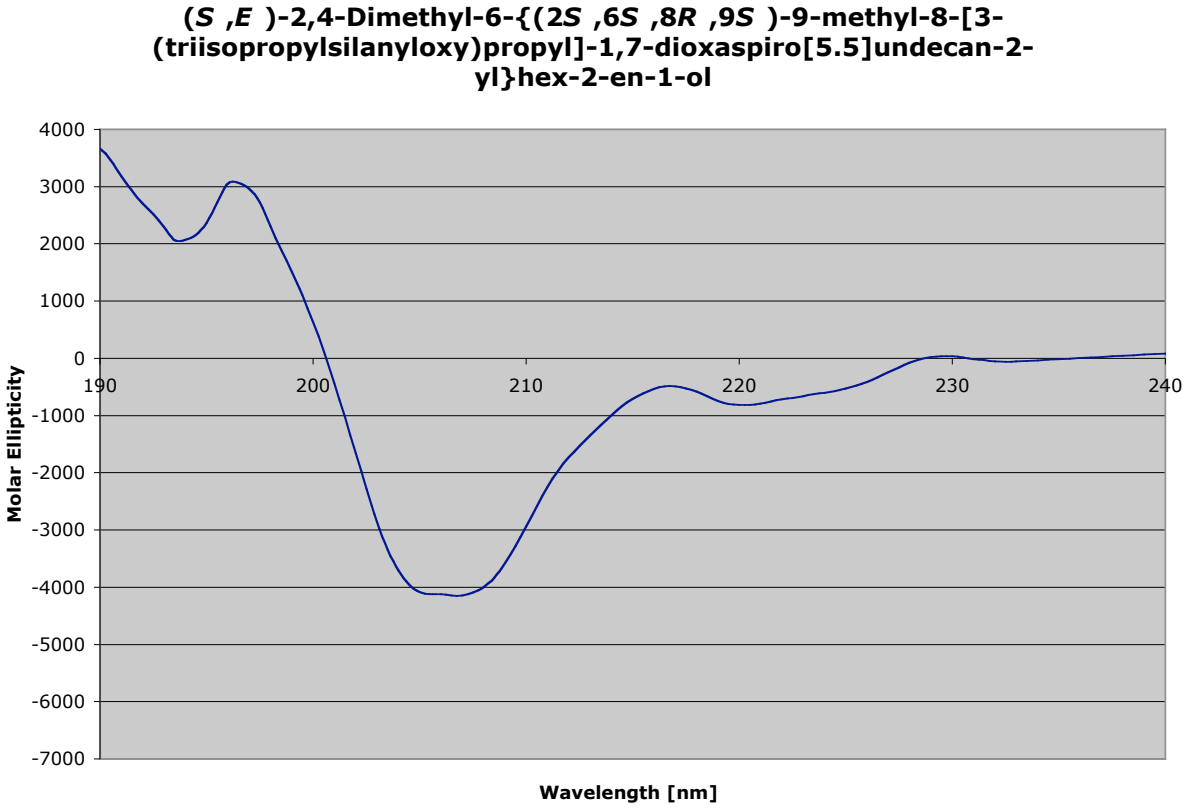


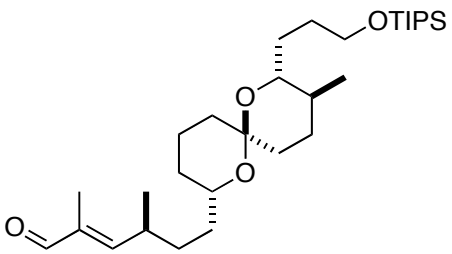
(*S*, *E*) - E t h y l 2 , 4 - d i m e t h y l - 6 - { (2 *S* , 6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}hex-2-enoate (95).[136] A solution of aldehyde **93** (88.0 mg, 0.188 mmol) in degassed (3 freeze/pump/thaw cycles) toluene (4.3 mL) was added to a round bottom flask containing a large excess of (carbethoxyethylidene)triphenylphosphorane **94** (2.70 g, 7.45 mmol). Then, the resulting heterogeneous mixture was submitted to 2 additional freeze/pump/thaw cycles, and stirred at room temperature for 10 d. Finally, the yellow slurry was filtered through a short pad of SiO_2 (Hexanes/EtOAc, 8:1 → 6:1). Upon removal of the organic solvents *in vacuo*, the desired enoate **95** (contaminated with reagent impurities) was isolated as a pale yellow oil. The crude material was submitted to the next step without additional purification: ^{1}H NMR δ 6.55 (dd, 1 H, *J* = 10.0, 1.4 Hz), 4.19 (q, 2 H, *J* = 7.1 Hz), 3.79-3.65 (m, 2 H), 3.55-3.44 (m, 1 H), 3.14 (dt, 1 H, *J* = 9.9, 1.9 Hz), 2.59-2.41 (m, 1 H), 2.05-1.75 (m, 3 H), 1.83 (d, 3 H, *J* = 1.4 Hz), 1.69-1.45 (m, 9 H), 1.45-1.34 (m, 3 H), 1.33-1.20 (m, 4 H), 1.30 (t, 3 H, *J* = 7.1 Hz), 1.20-1.04 (m, 21 H), 1.01 (d, 3 H, *J* = 6.6 Hz), 0.83 (d, 3 H, *J* = 6.5 Hz).



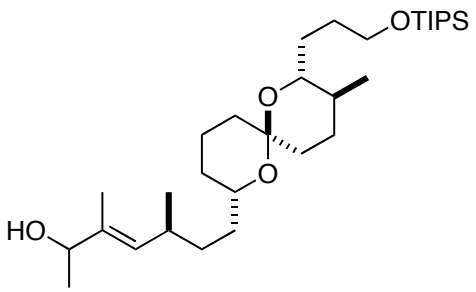
(*S*,*E*)-2,4-Dimethyl-6-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}hex-2-en-1-ol.[136] To a flame-dried, 3-neck round bottom flask containing excess LAH (18.0 mg, 2.68 mmol) was added a solution of slightly impure **95** (97.6 mg, 0.177 mmol) in THF (6.0 mL) at 0 °C via an addition funnel. Approximately 5 min later, the ice bath was removed and the reaction mixture was warmed to room temperature and stirred for a total of 2 h. Then, the mixture was cooled to 0 °C prior to the slow introduction of water (20 μL) followed by a 15% aqueous NaOH solution (20 μL). The resulting mixture was warmed to room temperature and stirred for 45 min prior to the dropwise addition of another aliquot of water (60 μL) at 0 °C. Finally, after 30 min of additional stirring, the remaining salts were removed via gravity filtration. Purification by chromatography on SiO_2 (Hexanes/EtOAc, 15:1 → 8:1 → 4:1) provided 64.9 mg (68% over 2 steps) of (*S*,*E*)-2,4-dimethyl-6-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}hex-2-en-1-ol as a clear, colorless oil: $[\alpha]_D$ +33.8 (*c* 0.50, $CHCl_3$, 22 °C); CD (λ (nm), θ) (206.5, -4146.8), (220, -812.2), (237, 25.1), (*c* 9.80 x 10^{-4}, MeOH, 22 °C); IR (neat) 3374, 2939, 2866, 1459, 1384, 1225, 1095, 985, 879 cm^{-1}; ^1H NMR δ 5.18 (dd, 1 H, *J* = 9.5, 1.2 Hz), 4.10 (*br* s, 2 H), 3.79-3.65 (m, 2 H), 3.52-3.46 (m, 1 H), 3.15 (dt, 1 H, *J* = 9.7, 1.9 Hz), 2.45-2.26 (m, 1 H), 1.93-1.75 (m, 3 H), 1.66 (d, 3 H, *J* = 1.2 Hz), 1.59-1.45 (m, 10 H), 1.45-1.25 (m, 7 H), 1.13-1.04 (m, 21 H), 0.95 (d, 3 H, *J* = 6.7 Hz), 0.83 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 133.4, 132.7, 95.4, 74.5, 69.0, 68.9, 63.6, 36.1, 35.5, 35.1, 34.2, 33.5, 32.0, 31.5, 29.5, 29.4, 28.0, 21.0, 19.1,

18.0, 13.9, 12.0; MS (EI) *m/z* (rel intensity) 492 ([M-H_2O]$^+$, 0.2), 474 (0.4), 465 (0.2), 449 (1.9), 431 (0.9), 383 (2.3), 365 (1.0), 302 (17), 284 (21), 213 (17), 185 (16), 149 (16), 131 (58), 103 (60), 75 (100), 64 (68); HRMS (EI) calcd for $C_{30}H_{56}O_3Si$ (M-H_2O) 492.3999, found 492.4010.

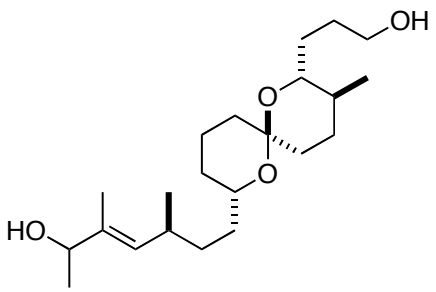




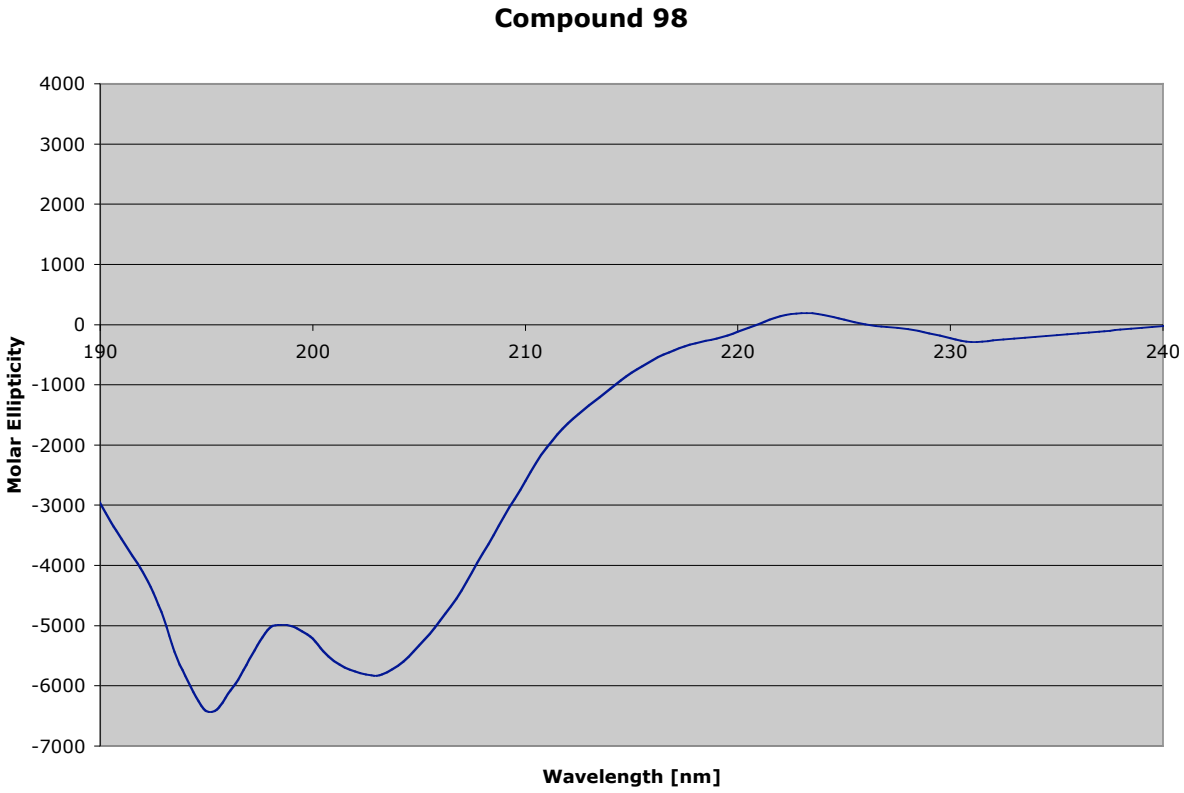
(*S*,*E*)-2,4-Dimethyl-6-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}hex-2-enal (96). To a 0 °C solution of (*S*,*E*)-2,4-dimethyl-6-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}hex-2-en-1-ol (11.2 mg, 22.0 μmol) in methylene chloride (0.850 mL) was added Dess-Martin periodinane (13.1 mg, 30.8 μmol) in two batches. Approximately two minutes later, the ice bath was removed and the reaction mixture was warmed to room temperature. After a total of 70 min, the mixture was diluted with EtOAc and subsequently washed with saturated aqueous $NaHCO_3$ and brine. The resulting EtOAc extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by chromatography through a plug of SiO_2 (Hexanes/EtOAc, 50:1 → 15:1 → 8:1) and used in the next step without any additional purification. The desired aldehyde **96** was isolated as a clear, colorless oil (10.4 mg, 93%): ^{1}H NMR δ 9.64 (d, 1 H, *J* = 1.8 Hz), 6.28 (dd, 1 H, *J* = 9.9, 1.1 Hz), 3.80-3.65 (m, 2 H), 3.56-3.44 (m, 1 H), 3.13 (*app* t, 1 H, *J* = 9.6 Hz), 2.81-2.63 (m, 1 H), 2.00-1.78 (m, 3 H), 1.76 (d, 3 H, *J* = 1.1 Hz), 1.69-1.44 (m, 10 H), 1.44-1.19 (m, 6 H), 1.19-1.00 (m, 23 H), 0.84 (d, 3 H, *J* = 6.5 Hz).

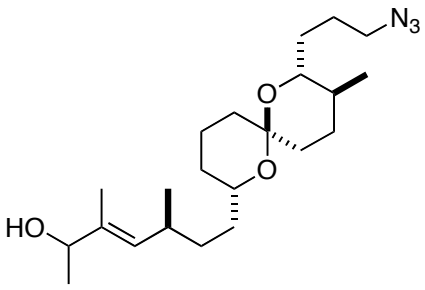


(5*S*,*E*)-3,5-Dimethyl-7-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}hept-3-en-2-ol (97).[136] Methylmagnesium bromide (3.0 M in Et_2O, 80.0 μL, 0.240 mmol) was added dropwise to a 0 °C solution of aldehyde **96** (20.4 mg, 40.2 μmol) in diethyl ether (800 μL). After 40 min at 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl. The heterogeneous mixture was warmed to room temperature and the aqueous phase was subsequently extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow residue. Chromatography on SiO_2 (Hexanes/EtOAc, 50:1 →15:1 → 8:1) gave 19.5 mg (93%) of **97** as a clear, colorless oil and a 1:1 mixture of diastereomers at C(39): $[\alpha]_D$ +32.3 (*c* 0.50, $CHCl_3$, 22 °C); IR (neat) 3437, 2934, 2866, 1465, 1378, 1219, 1095, 986, 876 cm^{-1}; ^1H NMR δ 5.18 (d, 1 H, *J* = 9.4 Hz), 4.25-4.19 (m, 1 H), 3.78-3.65 (m, 2 H), 3.56-3.44 (m, 1 H), 3.16 (*br* t, 1 H, *J* = 9.7 Hz), 2.47-2.28 (m, 1 H), 1.97-1.75 (m, 3 H), 1.63 (d, 3 H, *J* = 1.3 Hz), 1.63-1.44 (m, 10 H), 1.44-1.31 (m, 3 H), 1.26 (d, 3 H, *J* = 6.4 Hz), 1.19-1.00 (m, 22 H), 0.96 (d, 3 H, *J* = 6.5 Hz), 0.93 (d, 3 H, *J* = 6.1 Hz), 0.83 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 137.1, 131.7, 131.5, 95.4, 74.5, 73.5, 73.4, 68.9, 63.6, 36.1, 35.5, 35.1, 34.2, 33.5, 31.9, 31.5, 29.7, 29.5, 29.4, 28.0, 21.7, 21.0, 19.1, 18.0, 12.0, 11.7, 11.5; MS (EI) *m/z* (rel intensity) 506 ($[M–H_2O]^+$, 0.6), 481 (0.6), 464 (1.4), 463 (3.8), 445 (1.3), 423 (0.5), 391 (0.6), 282 (12), 163 (43), 109 (61), 95 (100), 75 (71); HRMS (EI) calcd for $C_{31}H_{58}O_3Si$ (M–H_2O) 506.4155, found 506.4160.



(5*S*,*E*)-7-[(2*S*,6*S*,8*R*,9*S*)-8-(3-Hydroxypropyl)-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl]-3,5-dimethylhept-3-en-2-ol (98).[136] A solution of alcohol **97** (6.5 mg, 12 μmol) in THF (660 μL) was treated with TBAF (0.5 M in THF, 37.2 μL, 18.6 μmol) at 0 °C. The ice bath was removed immediately following the addition. After 40 h at room temperature, the yellow solution was diluted with EtOAc (25 mL) and washed with saturated aqueous $NaHCO_3$, water and brine. Finally, the organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification via chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1 → 2:1 → 1:1) provided 4.6 mg (quant.) of diol **98** as a clear, colorless oil and a 1:1 mixture of diastereomers at C(39): $[\alpha]_D$ +39.4 (*c* 0.10, $CHCl_3$, 22 °C); CD (λ (nm), θ) (203, -5833.0), (223.5, 189.3), (231, -288.3), (*c* 1.36 x 10^{-3}, MeOH, 22 °C); IR (CH_2Cl_2) 3368, 2929, 2867, 1665, 1446, 1387, 1259, 1216, 1040, 880, 805 cm^{-1}; ^1H NMR δ 5.19 (d, 1 H, *J* = 8.9 Hz), 4.21 (dq, 1 H, *J* = 6.5, 2.9 Hz), 3.78-3.60 (m, 2 H), 3.56-3.41 (m, 1 H), 3.23 (*app* t, 1 H, *J* = 9.2 Hz), 2.46-2.24 (m, 2 H), 1.94-1.73 (m, 3 H), 1.73-1.30 (m, 18 H), 1.63 (*br* s, 3 H), 1.26 (d, 3 H, *J* = 6.4 Hz), 1.24-1.05 (m, 2 H), 0.96 (d, 1.5 H, *J* = 6.3 Hz), 0.94 (d, 1.5 H, *J* = 6.2 Hz), 0.85 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR δ 137.3 (2C), 131.5, 131.3, 95.8, 74.6 (2C), 73.5, 73.4, 69.2, 63.3 (2C), 36.2, 35.4, 34.5, 34.1, 33.5, 31.9, 31.3, 29.7, 29.6, 28.7, 27.9, 21.8 (2C), 21.0, 19.1, 18.0, 11.8, 11.6; HRMS (ESI) calcd for $C_{22}H_{40}O_4Na$ (M+Na) 391.2824, found 391.2842.

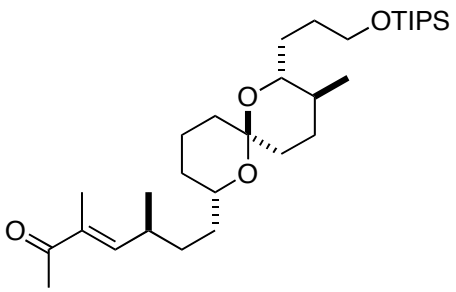




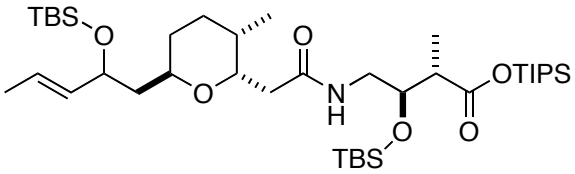
(5*S*,*E*)-7-[(2*S*,6*S*,8*R*,9*S*)-8-(3-Azidopropyl)-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl]-3,5-dimethylhept-3-en-2-ol (24).[136] To a 0 °C solution of diol **98** (4.6 mg, 12.6 μmol) in CH_2Cl_2 (650 μL) was added dropwise diisopropylethylamine (7.0 μL, 5.2 mg, 39 μmol) followed by a solution of Ms_2O (5.1 mg, 29 μmol) in CH_2Cl_2 (200 μL). The ice bath was removed 25 min after the addition of the electrophile. Approximately 35 min later, the solution

was cooled to 0 °C and additional Ms_2O (1.4 mg, 8.0 μmol) was introduced as a solution in CH_2Cl_2 (200 μL) in an effort to drive the reaction to completion. After 25 min at 0 °C, the reaction mixture was diluted with EtOAc and washed sequentially with saturated aqueous $NaHCO_3$, 10% citric acid and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*.

A mixture of the crude mesylate and the corresponding bis-mesylate (5.58 mg, 12.5 μmol) and NaN_3 (1.8 mg, 28 μmol) in DMF (300 μL) was heated to 68 °C (oil bath temperatue) for approximately 24 h. To facilitate the completion of the reaction, additional NaN_3 (3.5 mg, 54 μmol) was introduced at this time. Then, the reaction mixture was heated to 75-80 °C (oil bath temperature) and stirred for another 24 h. Finally, it was diluted with EtOAc and washed with H_2O (2 x 25 mL) followed by brine. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude residue via chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 4:1) provided 2.4 mg (49%) of azide **24** as a clear, colorless oil: ^{1}H NMR δ 5.19 (d, 1 H, J = 9.3 Hz), 4.28-4.16 (m, 1 H), 3.50-3.39 (m, 1 H), 3.38 (d of AB, 1 H, J = 12.4, 7.0 Hz), 3.29 (d of AB, 1 H, J = 12.1, 7.0 Hz), 3.17 (*app* t, 1 H, J = 9.7 Hz), 2.47-2.28 (m, 1 H), 2.06-1.88 (m, 2 H), 1.88-1.69 (m, 4 H), 1.64 (*br* s, 3 H), 1.62-1.61 (m, 1 H), 1.56-1.47 (m, 2 H), 1.47-1.28 (m, 9 H), 1.26 (d, 3 H, J = 6.4 Hz), 1.25-1.06 (m, 1 H), 0.97 (d, 1.5 H, J = 6.2 Hz), 0.94 (d, 1.5 H, J = 6.3 Hz), 0.85 (d, 3 H, J = 6.5 Hz).

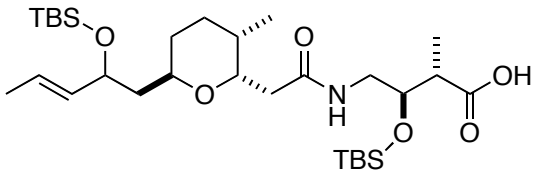


(*S*,*E*)-3,5-Dimethyl-7-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)propyl]-1,7-dioxaspiro[5.5]undecan-2-yl}hept-3-en-2-one (99). To a solution of allylic alcohol **97** (9.1 mg, 17 μmol) in CH_2Cl_2 (0.800 mL) was added Dess-Martin periodinane (10.8 mg, 25.4 μmol) in two batches at 0 °C. The reaction mixture was stirred at 0 °C for 78 min and warmed to room temperature over the next 30 min. Then, it was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified via chromatography on SiO_2 (Hexanes/EtOAc, 20:1 → 8:1 → 4:1) to give 7.3 mg (80%) of **99** as an oil: $[\alpha]_D$ +33.5 (*c* 0.20, $CHCl_3$, 22 °C); ^{1}H NMR δ 6.40 (dd, 1 H, *J* = 9.7, 1.3 Hz), 3.80-3.66 (m, 2 H), 3.56-3.44 (m, 1 H), 3.15 (dt, 1 H, *J* = 9.8, 1.9 Hz), 2.69-2.50 (m, 1 H), 2.32 (s, 3 H), 1.97-1.81 (m, 3 H), 1.78 (d, 3 H, *J* = 1.3 Hz), 1.66-1.47 (m, 10 H), 1.47-1.28 (m, 5 H), 1.14-1.04 (m, 21 H), 0.84 (d, 3 H, *J* = 6.5 Hz).



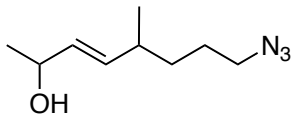
(2*S*,3*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4-(2-{(2*R*,3*S*,6*R*)-6-[2-(*tert*-butyldimethylsilanyloxy)-pent-3-enyl]-3-methyltetrahydropyran-2-yl}-acetylamino)-2-methylbutyric triisopropylsilanyl ester (101).[136] A solution of γ-azidoester **65** (54.8 mg, 0.128 mmol) in THF (7.0 mL) was transferred via cannula to a flask already containing Pd/C (3%, 57.0

mg). The heterogeneous mixture was treated with H_2 gas (1 atm) at room temperature for 3.5 h, filtered through a short plug of celite and washed thoroughly with CH_2Cl_2. The solvent was removed *in vacuo*. The resultant aminoester **100** was dissolved in CH_2Cl_2 (1.0 mL) and subsequently treated with a solution of acid **23** (16.9 mg, 0.0169 mmol) in CH_2Cl_2 (5.7 mL). To this clear, colorless solution was added excess PyBOP (34.2 mg, 65.7 μmol), followed by distilled Et_3N (10.5 μL, 75.3 μmol). After 40 h at room temperature, the mixture was diluted with Et_2O and washed with water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude material via chromatography on SiO_2 (Hexanes/Et_2O, 20:1 → 15:1 → 8:1 → 4:1) provided 30.3 mg (86%) of amide **101** as a >10:1 mixture of diastereomers at C(4): ^{1}H NMR δ 6.57 (*br* t, 1 H, *J* = 5.6 Hz), 5.55 (q of AB, 1 H, *J* = 14.9, 6.4 Hz), 5.39 (dd of AB, 1 H, *J* = 15.2, 6.8, 1.4 Hz), 4.19-4.10 (m, 2 H), 4.05 (dd, 1 H, *J* = 10.4, 6.1 Hz), 3.81-3.69 (m, 1 H), 3.59 (dt, 1 H, *J* = 13.4, 6.5 Hz), 3.23 (dt, 1 H, *J* = 13.5, 5.6 Hz), 2.67 (dq, 1 H, *J* = 7.2, 4.1 Hz), 2.50 (d of AB, 1 H, *J* = 15.6, 10.0 Hz), 2.19 (d of AB, 1 H, *J* = 15.5, 3.4 Hz), 1.88-1.71 (m, 4 H), 1.67 (dd, 3 H, *J* = 6.3, 1.1 Hz), 1.56-1.44 (m, 2 H), 1.41-1.24 (m, 7 H), 1.18 (d, 3 H, *J* = 7.1 Hz), 1.09 (d, 18 H, *J* = 7.3 Hz), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H), 0.04 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR δ 173.7, 171.5, 134.4, 125.5, 72.5, 72.3, 70.7, 67.5, 44.8, 42.6, 42.5, 35.4, 32.7, 28.1, 26.4, 25.9, 25.8, 18.1, 18.0, 17.9, 17.6, 15.5, 13.1, 11.9, -4.1, -4.5, -4.8.



(2*S*,3*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4-(2-{(2*R*,3*S*,6*R*)-6-[2-(*tert*-butyldimethylsilanyloxy)-pent-3-enyl]-3-methyltetrahydropyran-2-yl}-acetylamino)-2-methylbutyric acid (102).[136] To a 0 °C solution of amide **101** (6.7 mg, 0.090 mmol) in THF (2.4 mL) was added TBAF (0.1 M in THF, 100 μL, 10.0 μmol). Approximately 13 min later, the solution was diluted with EtOAc and washed with 0.01 M HCl, followed by brine. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow residue (7.9 mg, >100%) as a mixture of diastereomers at C(4). The crude material was used for the next coupling reaction without purification.

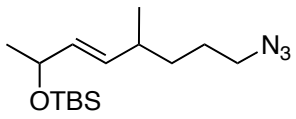
Racemic Series



(*E*)-8-Azido-5-methyloct-3-en-2-ol (104). To a 0 °C solution of (*E*)-4-methyloct-5-ene-1,7-diol (0.127 g, 0.801 mmol) in CH_2Cl_2 (6.0 mL) was added dropwise distilled diisopropylethylamine (0.250 mL, 0.181 g, 1.40 mmol) followed by a solution of Ms_2O (0.167 g, 0.959 mmol) in CH_2Cl_2 (900 μL) also dropwise and by cannula. After 20 min at 0 °C, the reaction mixture was diluted with Et_2O and treated with saturated aqueous $NaHCO_3$. The heterogeneous mixture was warmed to room temperature and the aqueous phase was extracted with Et_2O (2 x 20 mL) and EtOAc (1 x 20 mL). The combined organic extracts were washed

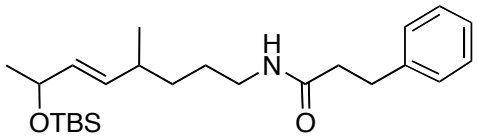
sequentially with 1.0 M citric acid and brine. Finally, the organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the corresponding primary mesylate, (*E*)-7-hydroxy-4-methyloct-5-enyl methanesulfonate, as a yellow oil and a mixture of diastereomers at C(5).

A solution of the crude mesylate in DMF (10.0 mL) was treated with NaN_3 (80.0 mg, 1.23 mmol) and heated to 38 °C for 15 h and 45 °C for 4 h. After an additional 27 h at 55 °C, the reaction mixture was first cooled to room temperature and then diluted with EtOAc. The organic phase was washed with water (x 3) followed by brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a very fluid oil. Purification of the crude material via chromatography on SiO_2 (Hexanes/EtOAc, 8:1 → 6:1 → 4:1) provided 113.4 mg (78%) of **104** as a clear, colorless oil and a 1:1 mixture of diastereomers at C(2) and C(5): ^{1}H NMR δ 5.51-5.36 (m, 2 H), 4.31-4.13 (m, 1 H), 3.21 (t, 2 H, *J* = 6.8 Hz), 2.19-2.00 (m, 1 H), 1.94 (*br* s, 1 H), 1.56-1.51 (m, 2 H), 1.36-1.29 (m, 2 H), 1.22 (d, 3 H, *J* = 6.3 Hz), 0.97 (d, 1.5 H, *J* = 6.7 Hz), 0.96 (d, 1.5 H, *J* = 6.7 Hz); ^{13}C NMR δ 135.5, 133.1, 68.6, 51.4, 35.9, 33.6, 26.5, 23.4, 20.4.

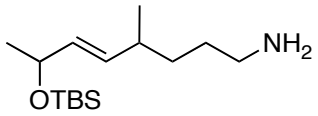


(*E*)-(8-Azido-5-methyloct-3-en-2-yloxy)(*tert*-butyl)dimethylsilane (107). To a solution of azide **104** (21.9 mg, 0.121 mmol) in CH_2Cl_2 (700 μL) was added imidazole (25.0 mg, 0.367 mmol) at room temperature and TBS-Cl (35.0 mg, 0.232 mmol) at 0 °C. The ice bath was removed immediately following the addition of the silylating reagent. After 20 h at room temperature, the reaction mixture was diluted with Et_2O and washed with water followed by brine. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting residue was purified via chromatography on SiO_2 (Hexanes/EtOAc, 1:0 → 50:1 → 20:1 → 8:1

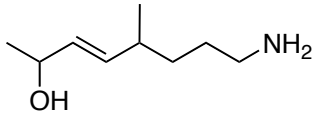
→ 4:1) to give 34.2 mg (96%) of crude **107** as an oil and a mixture of diastereomers at C(2) and C(5): IR (neat) 2957, 2929, 2857, 2096, 1472, 1463, 1368, 1256, 1086, 974, 835, 776 cm^{-1}; ^1H NMR δ 5.48-5.31 (m, 2 H), 4.25 (dt, 1 H, *J* = 11.6, 6.1 Hz), 3.25 (t, 2 H, *J* = 6.9 Hz), 2.18-2.05 (m, 1 H), 1.63-1.50 (m, 2 H), 1.50-1.29 (m, 2 H), 1.20 (d, 3 H, *J* = 6.3 Hz), 1.00 (d, 1.5 H, *J* = 6.7 Hz), 0.99 (d, 1.5 H, *J* = 6.7 Hz), 0.94-0.89 (m, 9 H), 0.06 (*br* s, 6 H).



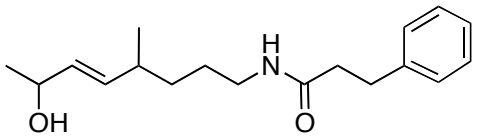
(*E*)-*N*-[7-(*tert*-Butyldimethylsilanyloxy)-4-methyloct-5-enyl]-3-phenylpropanamide (108). A solution of azide **107** (18.3 mg, 0.619 mmol) and PPh_3 (19.5 mg, 0.0743 mmol) in degassed toluene (750 μL) was stirred for 3 h at room temperature. The reaction mixture was treated with a solution of hydrocinnamic acid **105** (13.5 mg, 0.0898 mmol) in degassed toluene (400 μL) and heated to 70 °C for 16 h and 110 °C for an additional 18 h. The solvent was removed *in vacuo* and the crude yellow residue was purified via chromatography on SiO_2 (Hexanes/EtOAc, 20:1 → 8:1 → 4:1 → 2:1 → 1:1 → 0:1) to give 9.1 mg (37%) of **108** as a mixture of diastereomers: ^1H NMR δ 7.31-7.17 (m, 5 H), 5.45-5.30 (m, 3 H), 4.24 (dt, 1 H, *J* = 11.8, 6.3 Hz), 3.16 (*app* q, 2 H, *J* = 6.0 Hz), 2.96 (*app* t, 2 H, *J* = 7.7 Hz), 2.46 (*app* t, 2 H, *J* = 7.7 Hz), 2.13-2.00 (m, 1 H), 1.50-1.31 (m, 2 H), 1.26-1.18 (m, 2 H), 1.19 (d, 3 H, *J* = 6.3 Hz), 0.96 (d, 1.5 H, *J* = 6.7 Hz), 0.95 (d, 1.5 H, *J* = 6.7 Hz), 0.90 (*br* s, 9 H), -0.06 (s, 3 H), -0.05 (s, 3 H); ^{13}C NMR δ 171.9, 140.9, 134.3, 133.5, 128.5, 126.2, 69.4, 39.5, 38.5, 35.9, 34.0, 31.8, 27.3, 25.9, 24.7, 20.5, 18.3, -4.5, -4.7.



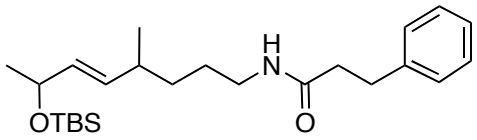
(*E*)-7-(*tert*-Butyldimethylsilanyloxy)-4-methyloct-5-en-1-amine (109). To a solution of **107** (14.4 mg, 0.0487 mmol) in THF (500 μL) was added water (2.5 μL) followed by excess PPh_3 (20.0 mg, 0.0762 mmol). After 43 h at room temperature, the reaction mixture was treated with brine and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The amine, isolated as a mixture of diastereomers, was not submitted to purification. The experiment was conducted in an effort to determine whether or not the azide function of **107** was susceptible to reduction with PPh_3 and to what extent (if any) the resultant amine could be isolated. The NMR data listed correspond to the crude material, still contaminated with PPh_3 and $Ph_3P(O)$: ^{1}H NMR δ 5.47-5.34 (m, 2 H), 4.29-4.21 (m, 1 H), 2.68 (t, 2 H, *J* = 7.0 Hz), 2.13-2.01 (m, 1 H), 1.79 (*br* s, 2 H), 1.50-1.39 (m, 2 H), 1.34-1.25 (m, 2 H), 1.20 (d, 3 H, *J* = 6.3 Hz), 0.99 (d, 1.5 H, *J* = 6.7 Hz), 0.97 (d, 1.5 H, *J* = 6.7 Hz), 0.93-0.86 (m, 9 H), 0.08-0.03 (m, 6 H).



(*E*)-8-Amino-5-methyloct-3-en-2-ol (111). To a solution of azide **104** (27.8 mg, 0.153 mmol) in THF (780 μL) was added water (4.0 μL) followed by PPh_3 (48.3 mg, 0.184 mmol). After 23 h at room temperature, the THF and water were removed *in vacuo* (*i.e.* azeotroping with toluene followed by pumping under full vacuum). The labile aminoalcohol **111**, isolated as a mixture of diastereomers, was submitted to the coupling reaction without a formal work-up or purification.

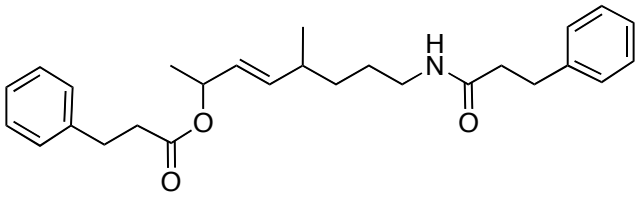


(*E*)-*N*-(7-Hydroxy-4-methyloct-5-enyl)-3-phenylpropanamide (106). To a solution of the crude amine **111** (24.1 mg, 0.153 mmol, assuming a quantitative yield in the previous step) in CH_2Cl_2 (1.25 mL) was added hydrocinnamic acid **105** (20.8 mg, 0.139 mmol), PyBOP (80.0 mg, 0.154 mmol) and diisopropylethylamine (33.0 μL, 23.9 mg, 0.185 mmol). After 24 h at room temperature, the reaction mixture was diluted with Et_2O (15 mL) and washed with saturated aqueous $NaHCO_3$ and water. The aqueous phase was back-extracted with EtOAc (25 mL) and the organic extracts were washed with brine. Then, the (combined) aqueous phase was extracted with an additional aliquot of EtOAc (25 mL). Finally, the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give **106** as an oil contaminated with $Ph_3P(O)$ and the by-product from PyBOP and a mixture of diastereomers. The efficiency of the coupling reaction was determined after the protection of the secondary allylic alcohol as a *tert*-butyldimethylsilyl ether; **106**: ^{1}H NMR δ 7.31-7.25 (m, 2 H), 7.25-7.13 (m, 3 H), 5.53-5.38 (m, 3 H), 4.31-4.19 (m, 1 H), 3.18 (*app* q, 2 H, J = 6.7 Hz), 2.96 (t, 2 H, J = 7.6 Hz), 2.45 (*app* td, 2 H, J = 8.0, 1.7 Hz), 2.08 (ddd, 1 H, J = 13.6, 6.9, 6.9 Hz), 1.91 (d, 1 H, J = 3.2 Hz), 1.50-1.31 (m, 2 H), 1.31-1.13 (m, 2 H), 1.26 (d, 3 H, J = 6.3 Hz), 0.97 (d, 1.5 H, J = 6.7 Hz), 0.96 (d, 1.5 H, J = 6.7 Hz).

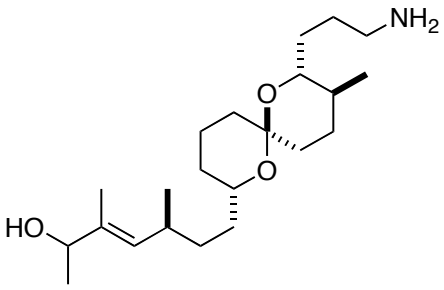


(*E*)-*N*-[7-(*tert*-Butyldimethylsilanyloxy)-4-methyloct-5-enyl]-3-phenylpropanamide (108). To a solution of crude **106** in CH_2Cl_2 (2.1 mL) was added imidazole (48.1 mg, 0.707

mmol) at room temperature and TBS-Cl (46.7 mg, 0.310 mmol) at 0 °C. The ice bath was removed immediately following the addition of the silylating reagent. After 20 h at room temperature, the reaction mixture was diluted with Et_2O and washed with water followed by brine. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification via chromatography on SiO_2 (Hexanes/EtOAc, 4:1 → 2:1 → 1:1) provided 55.0 mg (99%) of **108** as an oil and a mixture of diastereomers.

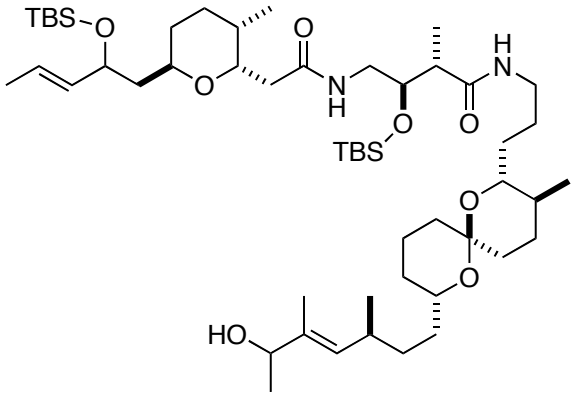


(*E*)-5-Methyl-8-(3-phenylpropanamide)oct-3-en-2-yl 3-phenylpropanoate (110, diastereomeric mixture): ^{1}H NMR δ 7.31-7.27 (m, 4 H), 7.22-7.19 (m, 6 H), 5.51-5.25 (m, 4 H), 3.24-3.08 (m, 2 H), 2.96 (*app* q, 4 H, *J* = 7.4 Hz), 2.62 (td, 2 H, *J* = 8.2, 1.8 Hz), 2.46 (t, 2 H, *J* = 7.4 Hz), 2.11-2.00 (m, 1 H), 1.50-1.32 (m, 2 H), 1.28-1.18 (m, 2 H), 1.27 (d, 3 H, *J* = 5.9 Hz), 0.95 (d, 1.5 H, *J* = 6.7 Hz), 0.95 (d, 1.5 H, *J* = 6.7 Hz).



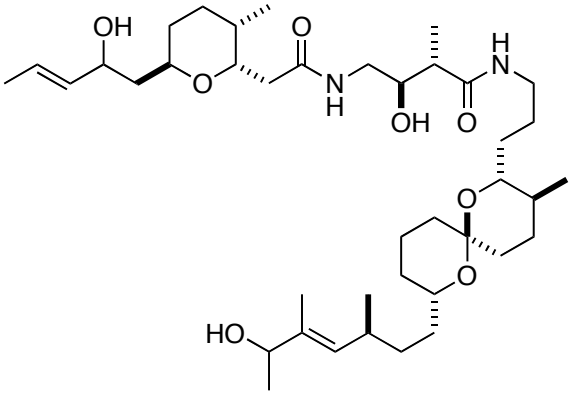
(5*S*,*E*)-7-[(2*S*,6*S*,8*R*,9*S*)-8-(3-Aminopropyl)-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl]-3,5-dimethylhept-3-en-2-ol (112). To a solution of azidoalcohol **24** (2.4 mg, 6.1 μmol) in degassed (3 freeze/pump/thaw cycles) THF (150 μL) was added PPh_3 (1.0 M in degassed THF,

8.0 μL, 8.0 μmol) followed by H_2O (0.6-1.0 μL) at room temperature. After 41 h, the reaction mixture was concentrated *in vacuo* and the crude residue was isolated as a 1:1 mixture of diastereomers at C(2) and used directly for the next step.



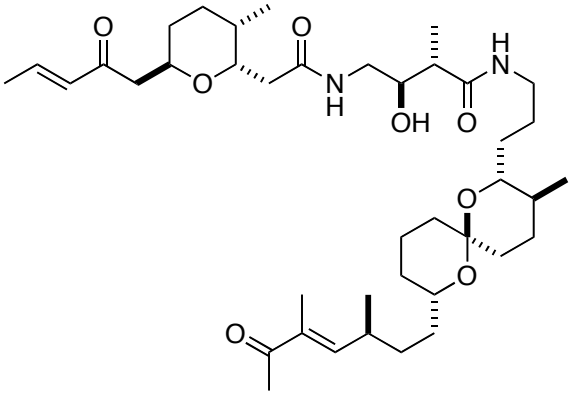
(2*S*,3*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4-(2-{(2*S*,3*S*,6*R*)-6-[(*E*)-2-(*tert*-butyldimethylsilanyloxy)pent-3-enyl]-3-methyltetrahydro-2*H*-pyran-2-yl}acetamido)-*N*-(3-{(2*R*,3*S*,6*S*,8*S*)-8-[(3*S*,*E*)-6-hydroxy-3,5-dimethylhept-4-enyl]-3-methyl-1,7-dioxaspiro[5.5]undecan-2-yl}propyl)-2-methylbutanamide (103). Aminoalcohol **112** (2.42 mg, 6.59 μmol) was treated with a solution of acid **102** (5.0 mg, 8.5 μmol) in DMF (550 μL) followed by PyBOP (3.8 mg, 7.3 μmol) and diisopropylethylamine (1.7 μL, 1.2 mg, 9.7 μmol) at room temperature. After 47 h, the reaction mixture was diluted with EtOAc (20 mL) and washed with 10% citric acid, saturated aqueous $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude material via chromatography on SiO_2 (Hexanes/EtOAc, 4:1 → 2:1 → 1:1 → 0:1) provided 3.5 mg (58% over 2 steps) of **103** as a >10:1 mixture of diastereomers at C(4) and a 1:1 mixture of diastereomers at C(39): ^{1}H NMR (600 MHz) δ 6.86 (*br* s, 1 H), 6.31-6.29 (m, 1 H), 5.55 (dq, 1 H, *J* = 12.9, 6.2 Hz), 5.40 (dd, 1 H, *J* = 15.5, 6.8 Hz), 5.19 (*app* t, 1 H, *J* = 9.9 Hz), 4.25-4.10 (m, 3 H), 3.95-3.85

(m, 1 H), 3.80-3.65 (m, 2 H), 3.48-3.38 (m, 1 H), 3.33-3.25 (m, 2 H), 3.18 (*br* t, 1 H, *J* = 9.8 Hz), 2.89 (ddd, 1 H, *J* = 13.0, 7.6, 4.4 Hz), 2.48 (d of AB, 1 H, *J* = 15.5, 9.6 Hz), 2.46-2.42 (m, 1 H), 2.40-2.33 (m, 1 H), 2.22 (d of AB, 1 H, *J* = 15.5, 3.8 Hz), 1.93-1.85 (m, 1 H), 1.85-1.78 (m, 2 H), 1.78-1.70 (m, 2 H), 1.70-1.65 (m, 2 H), 1.67 (d, 3 H, *J* = 6.3 Hz), 1.65-1.60 (m, 1 H), 1.63 (d, 3 H, *J* = 7.3 Hz), 1.60-1.50 (m, 6 H), 1.50-1.35 (m, 5 H), 1.35-1.20 (m, 11 H), 1.17 (d, 3 H, *J* = 7.2 Hz), 0.95-0.94 (m, 3 H), 0.92 (*br* s, 9 H), 0.87 (*br* s, 9 H), 0.85 (d, 3 H, *J* = 6.8 Hz), 0.81 (d, 1.5 H, *J* = 6.5 Hz), 0.81 (d, 1.5 H, *J* = 6.5 Hz), 0.19 (d, 3 H, *J* = 3.1 Hz), 0.12 (*br* s, 3 H), 0.04 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (150 MHz) δ 174.4, 171.8, 137.3, 137.2, 134.4, 131.4, 130.6, 125.4, 95.4, 73.7, 73.6, 73.4, 72.9, 72.6, 72.3, 70.6, 69.4 (2C), 67.3 (2C), 44.5, 43.1 (2C), 43.0 (2C), 39.0, 36.1, 35.5, 35.0, 34.0, 33.7, 32.7, 31.9, 31.2, 30.2, 28.6, 27.9, 26.5, 25.9 (2C), 25.7, 25.6, 21.8, 21.7, 20.9, 20.8, 19.2, 18.1, 18.0, 17.9, 17.6, 15.7 (2C), 12.2, 11.7, 1.0, -4.1, -4.4, -4.8, -5.0.



(2*S*,3*R*)-3-Hydroxy-*N*-(3-{(2*R*,3*S*,6*S*,8*S*)-8-[(3*S*,*E*)-6-hydroxy-3,5-dimethylhept-4-enyl]-3-methyl-1,7-dioxaspiro[5.5]undecan-2-yl}propyl)-4-(2-{(2*S*,3*S*,6*R*)-6-[(*E*)-2-hydroxypent-3-enyl]-3-methyltetrahydro-2*H*-pyran-2-yl}acetamido)-2-methylbutanamide (113). To a solution of bisamide **103** (1.8 mg, 1.9 μmol) in MeOH (160 μL) was added PPTS

(2.2 mg, 8.7 μmol) at room temperature. After 48 h, the reaction mixture was diluted with CH_2Cl_2 and treated with saturated aqueous $NaHCO_3$. After 45 min, the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 1.4 mg of a yellow residue as a >10:1 mixture of diastereomers at C(4) and a 1:1 mixture of diastereomers at C(39), which was used for the next reaction without purification: ^{1}H NMR δ 7.06-6.97 (m, 1 H), 6.67 (*app* t, 1 H, *J* = 5.2 Hz), 5.65 (*app* dq, 1 H, *J* = 15.3, 6.4 Hz), 5.47 (ddd, 1 H, *J* = 15.3, 6.6, 1.4 Hz), 5.19 (*br* d, 1 H, *J* = 8.5 Hz), 4.67 (*br* t, 1 H, *J* = 5.9 Hz), 4.28-4.08 (m, 3 H), 3.96-3.84 (m, 1 H), 3.84-3.77 (m, 1 H), 3.77-3.63 (m, 1 H), 3.63-3.38 (m, 2 H), 3.38-3.24 (m, 3 H), 3.24-3.13 (m, 1 H), 2.71 (dd, 1 H, *J* = 15.1, 11.8 Hz), 2.44-2.26 (m, 3 H), 2.19 (dd, 1 H, *J* = 15.2, 2.5 Hz), 2.13-1.88 (m, 4 H), 1.88-1.69 (m, 5 H), 1.68 (d, 3 H, *J* = 6.2 Hz), 1.68-1.50 (m, 10 H), 1.50-1.31 (m, 7 H), 1.30-1.21 (m, 4 H), 1.19-1.06 (m, 2 H), 0.98 (d, 3 H, *J* = 6.3 Hz), 0.94 (d, 3 H, *J* = 6.3 Hz), 0.85 (d, 3 H, *J* = 7.1 Hz), 0.82 (d, 3 H, *J* = 6.5 Hz).

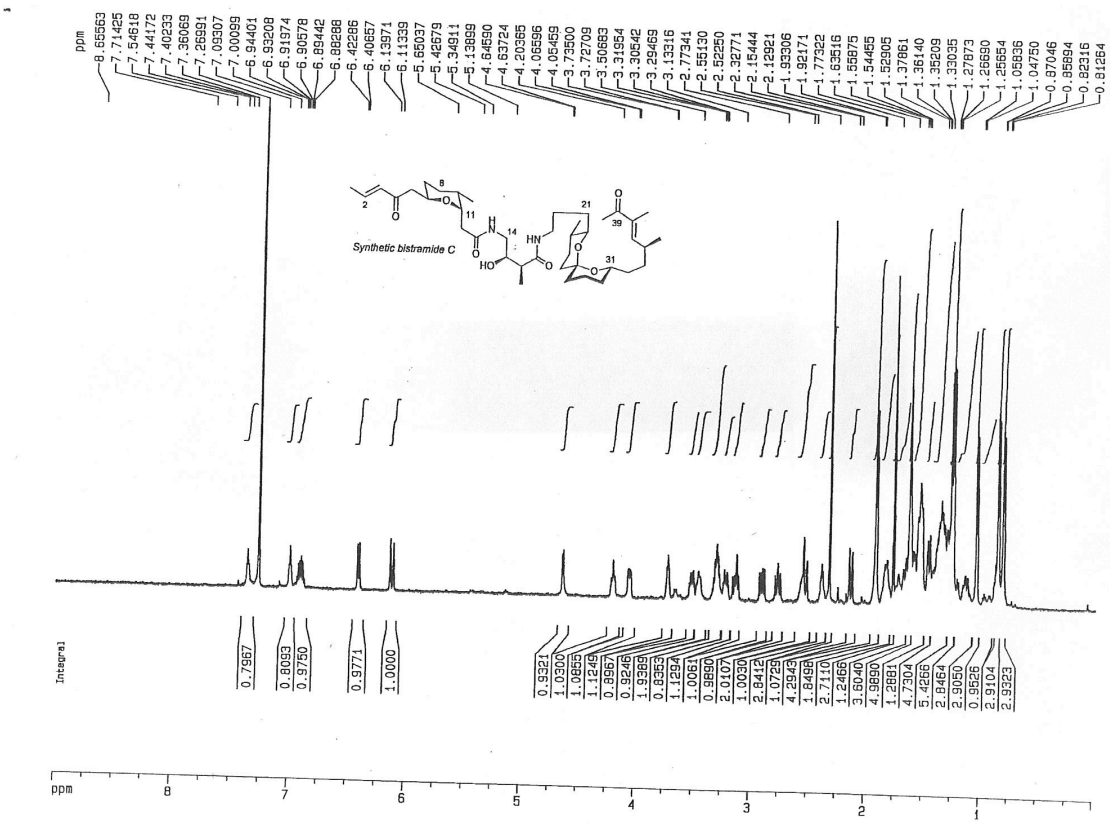


(6*S*,9*S*,11*S*,15*R*,16*S*,22*R*,23*S*,27*S*,31*S*,34*S*)-Bistramide C (22). To a solution of crude triol **113** (1.4 mg, 2.0 μmol) in CH_2Cl_2 (180 μL) was added Dess-Martin periodinane (15 weight % in CH_2Cl_2, 12 μL, 1.8 mg, 4.2 μmol) at 0 °C. The ice bath was removed 17 min after the

addition of the oxidant. Approximately 39 min later, the reaction mixture was diluted with EtOAc and treated with saturated aqueous $NaHCO_3$ at 0 °C. After 45 min of stirring at room temperature, the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic extracts were then washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 2.9 mg (quant.) of a yellow residue. Purification of the crude material by preparative HPLC on SiO_2 (10 mm x 25 mm, CH_2Cl_2/MeOH, 99:1 to 96:4 over 60 min, 5.0 mL/min,[211] UV detection at λ = 242 nm) provided approximately 1.0 mg (77% over 2 steps) of **22**: $[\alpha]_D$ +7.3 (*c* 0.053, CH_2Cl_2, 22 °C); ^{1}H NMR δ 7.36 (*br* t, 1 H, *J* = 5.4 Hz), 7.00 (*br* t, 1 H, *J* = 5.1 Hz), 6.91 (*app* dq, 1 H, *J* = 15.5, 7.0 Hz), 6.41 (d, 1 H, *J* = 9.8 Hz), 6.13 (d, 1 H, *J* = 15.8 Hz), 4.64 (d, 1 H, *J* = 5.2 Hz), 4.20 (t, 1 H, *J* = 8.5 Hz), 4.06 (dd, 1 H, *J* = 11.1, 4.3 Hz), 3.73 (*app* t, 1 H, *J* = 4.9 Hz), 3.52 (ddd, 1 H, *J* = 13.3, 6.1, 5.9 Hz), 3.49-3.42 (m, 1 H), 3.37-3.26 (m, 2 H), 3.23 (ddd, 1 H, *J* = 13.2, 5.8, 5.6 Hz), 3.13 (*app* t, 1 H, *J* = 9.8 Hz), 2.91 (dd, 1 H, *J* = 17.1, 9.3 Hz), 2.78 (dd, 1 H, *J* = 14.8, 12.0 Hz), 2.61-2.56 (m, 1 H), 2.54 (d, 1 H, *J* = 17.3 Hz), 2.42-2.36 (m, 1 H), 2.33 (*br* s, 3 H), 2.14 (d, 1 H, *J* = 15.1 Hz), 1.93 (d, 4 H, *J* = 6.8 Hz), 1.90-1.79 (m, 2 H), 1.77 (*br* s, 3 H), 1.76-1.66 (m, 1 H), 1.66-1.61 (m, 4 H), 1.61-1.50 (m, 5 H), 1.49-1.45 (m, 1 H), 1.44-1.30 (m, 6 H), 1.27 (d, 5 H, *J* = 7.1 Hz), 1.23-1.08 (m, 2 H), 1.05 (d, 3 H, *J* = 6.5 Hz), 0.86 (d, 3 H, *J* = 6.9 Hz), 0.82 (d, 3 H, *J* = 6.3 Hz); ^{13}C NMR δ 200.4 (q), 199.0 (q), 175.1 (q), 173.6 (q), 149.5 (s), 144.6 (s), 136.2 (q), 132.1 (s), 95.4 (q), 74.9 (s), 74.4 (s), 73.9 (s), 68.9 (s), 64.6 (s), 45.2 (d), 44.7 (d), 43.3 (s), 39.5 (d), 36.0 (d), 35.4 (d), 34.8 (s), 34.3 (d), 33.8 (s), 33.3 (s), 32.9 (d), 32.2 (d), 31.3 (d), 30.8 (d), 30.5 (d), 27.9 (d), 26.5 (d), 25.9 (d), 25.6 (t), 20.1 (t), 19.1 (d), 18.5 (t), 18.0 (t), 17.2 (t), 15.5 (t), 11.4 (t); HRMS (ESI) calcd for $C_{40}H_{66}N_2O_8$ (M+Na) 725.4746, found 725.4741, calcd for $C_{40}H_{66}N_2O_8$ (M+H) 703.4930, found 703.4897.

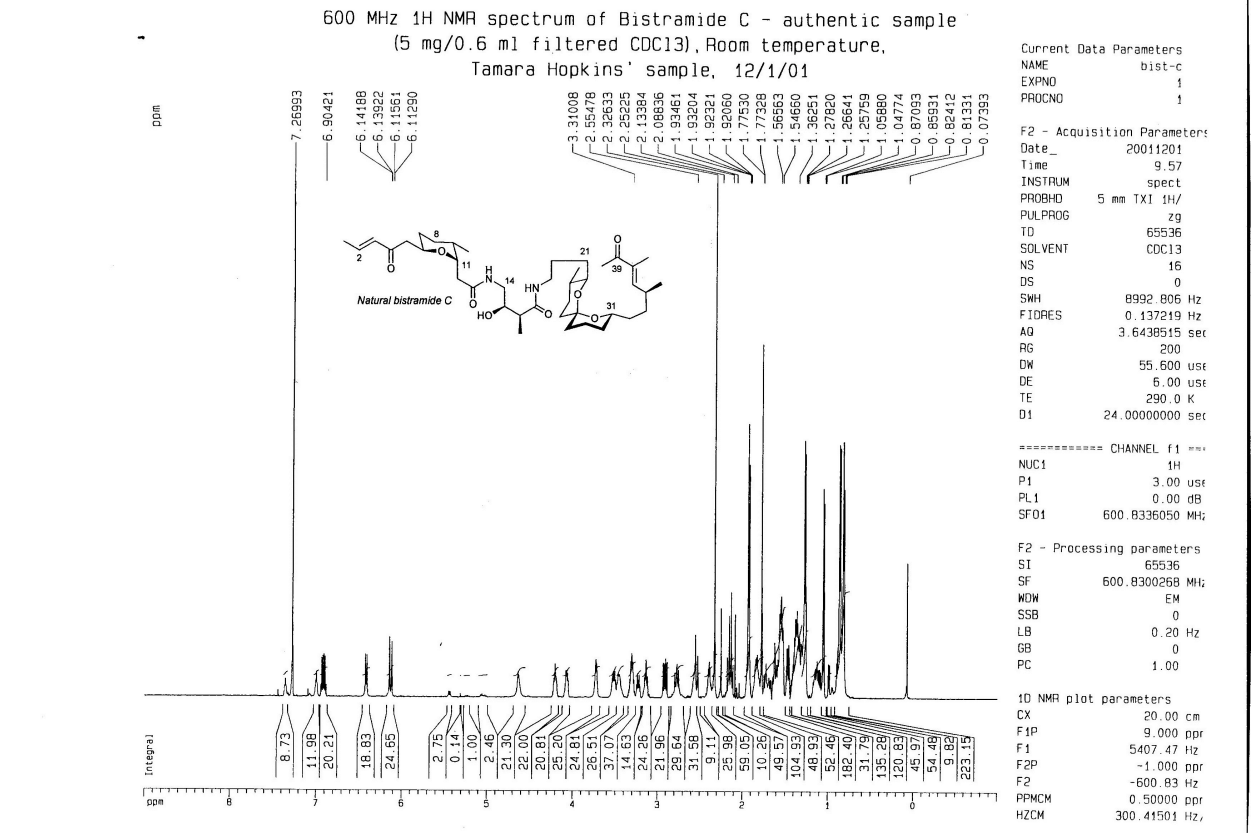
APPENDIX A

[1]H NMR Spectrum of Bistramide C (**22**)



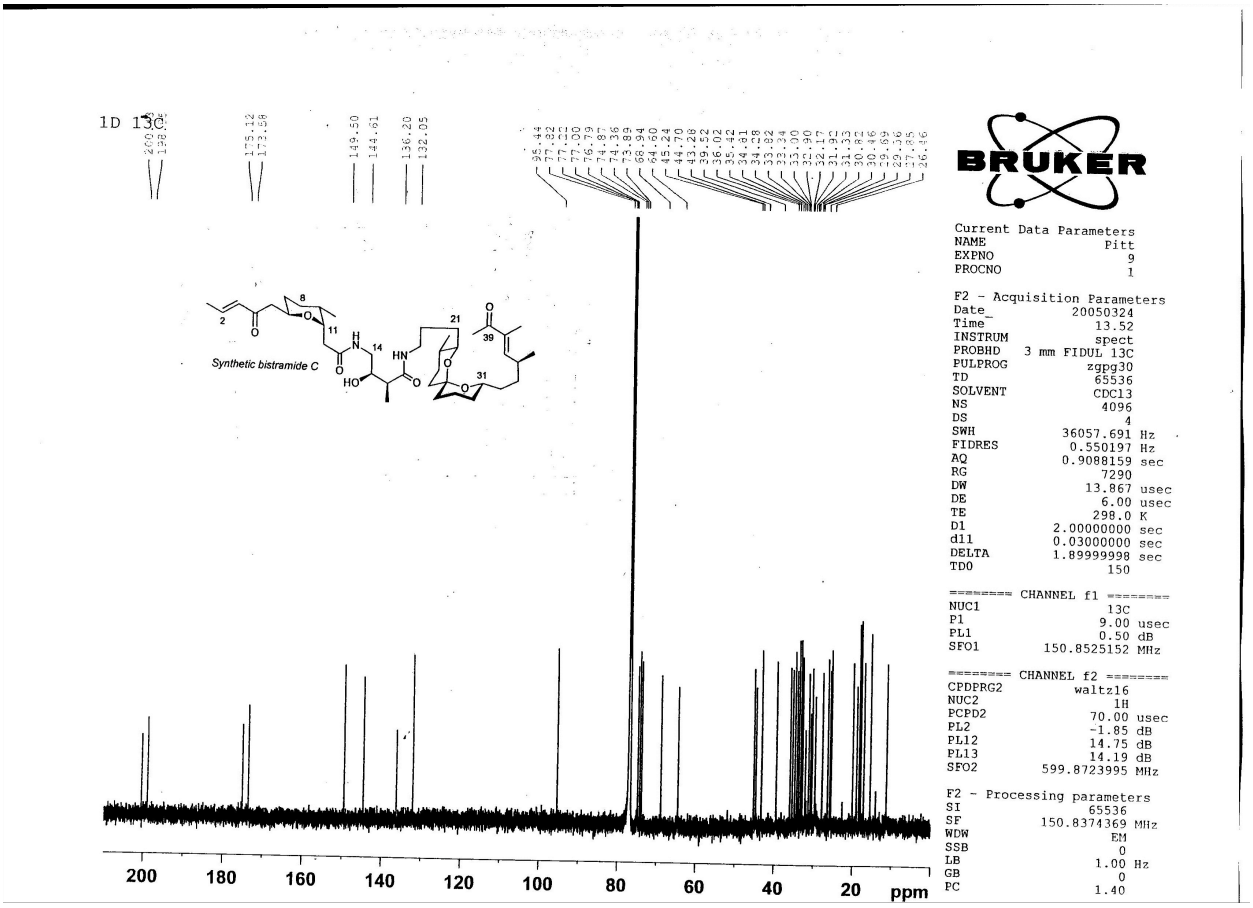
APPENDIX B

^{1}H NMR Spectrum of an Authentic Sample of Bistramide C



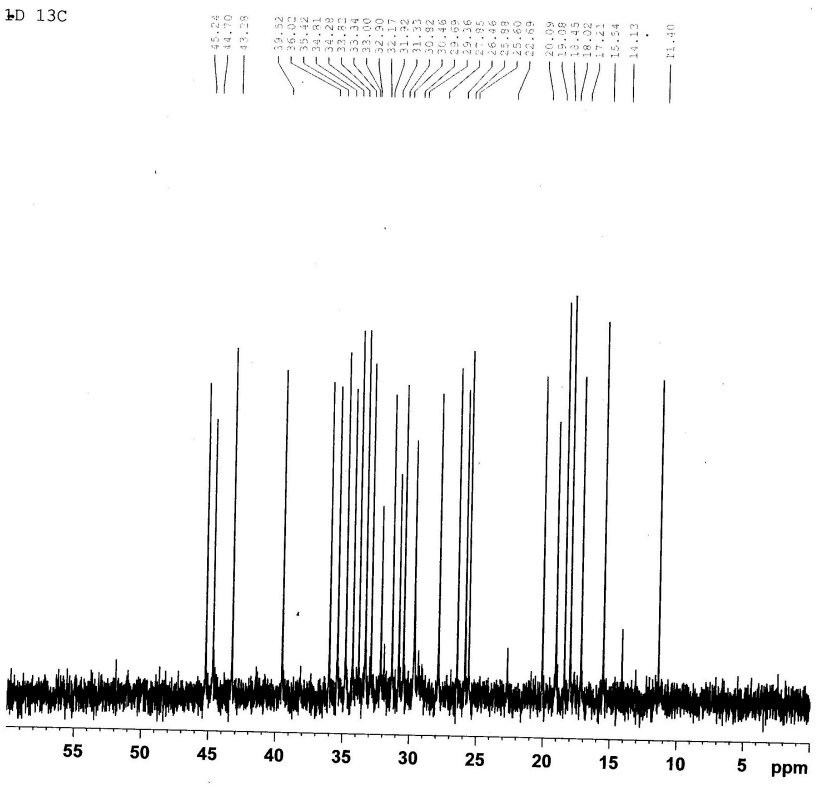
APPENDIX C

^{13}C NMR Spectrum of Bistramide C (**22**)



APPENDIX D

^{13}C NMR Spectrum of Bistramide C (**22**)



BRUKER

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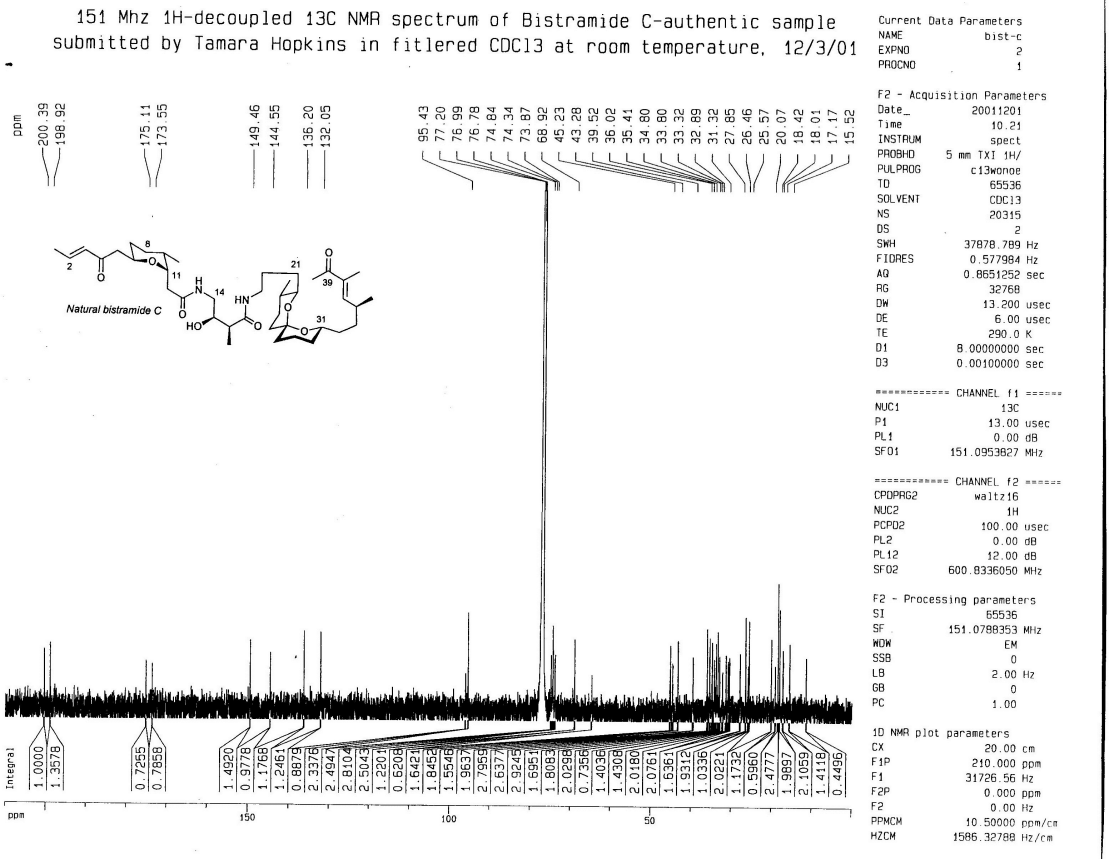
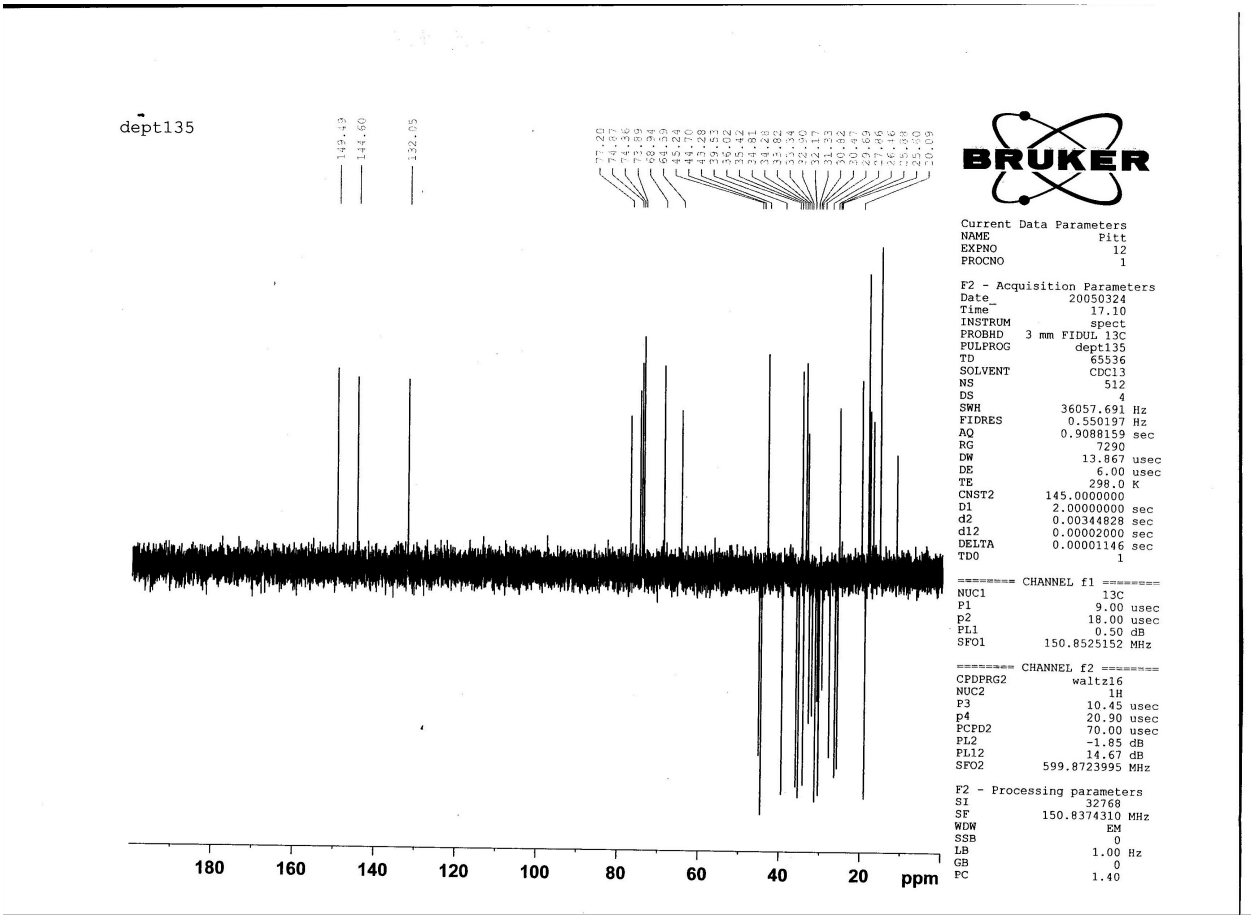
APPENDIX E

^{13}C NMR Spectrum of an Authentic Sample of Bistramide C



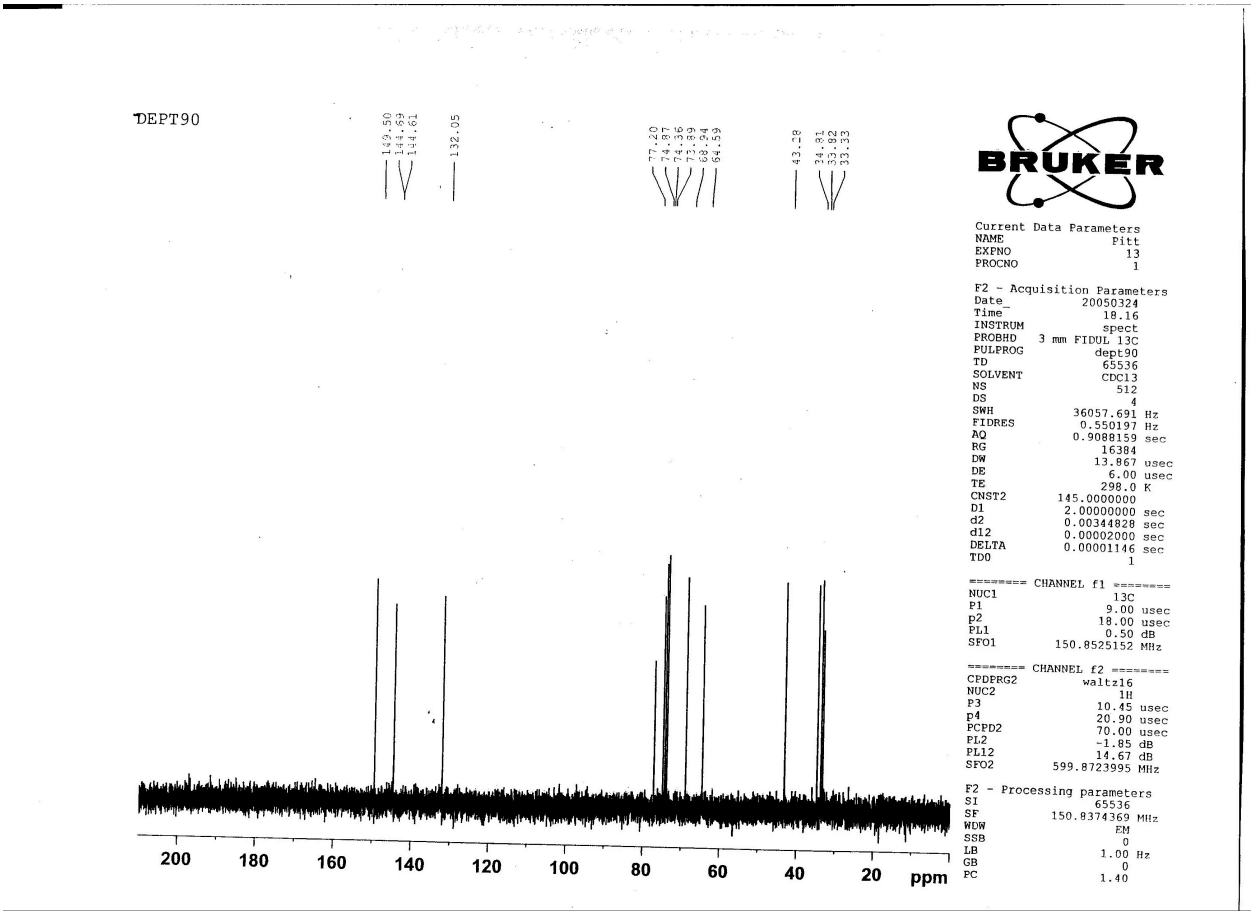
APPENDIX F

dept135 Spectrum of Bistramide C (**22**)



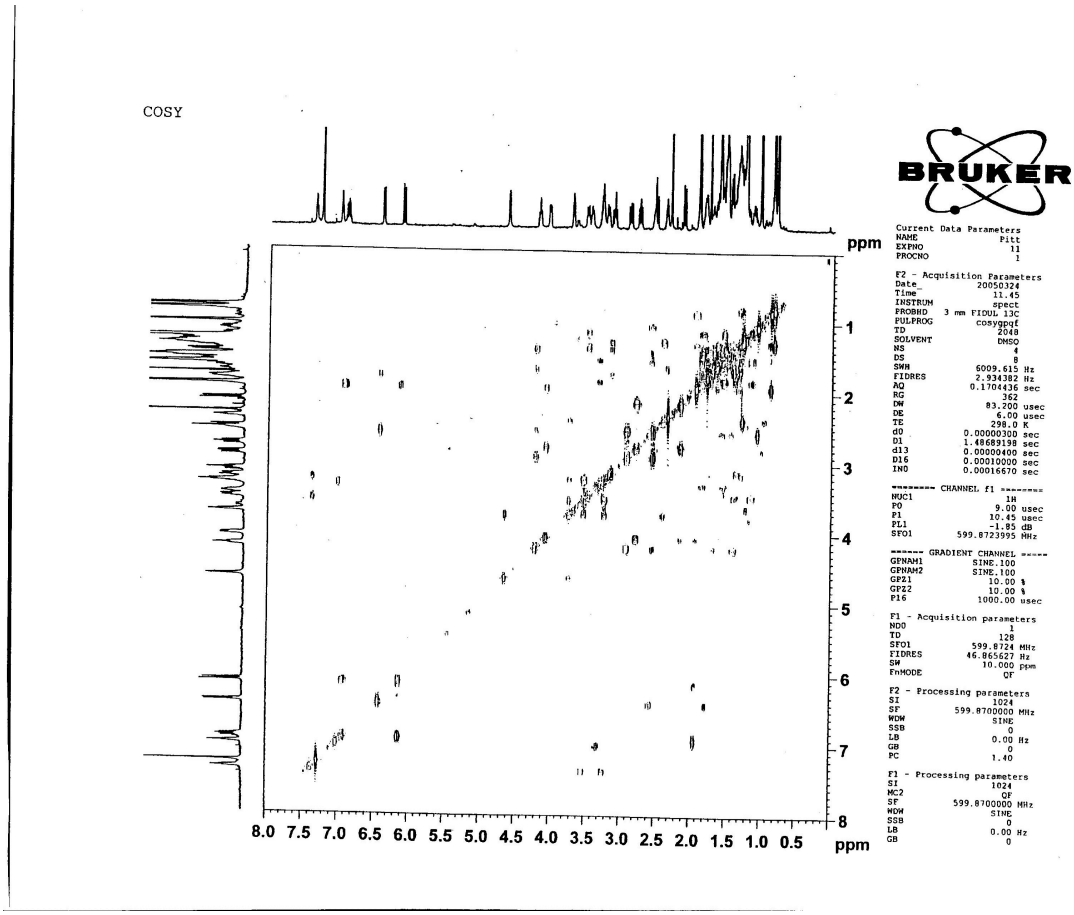
APPENDIX G

dept90 Spectrum of Bistramide C (**22**)



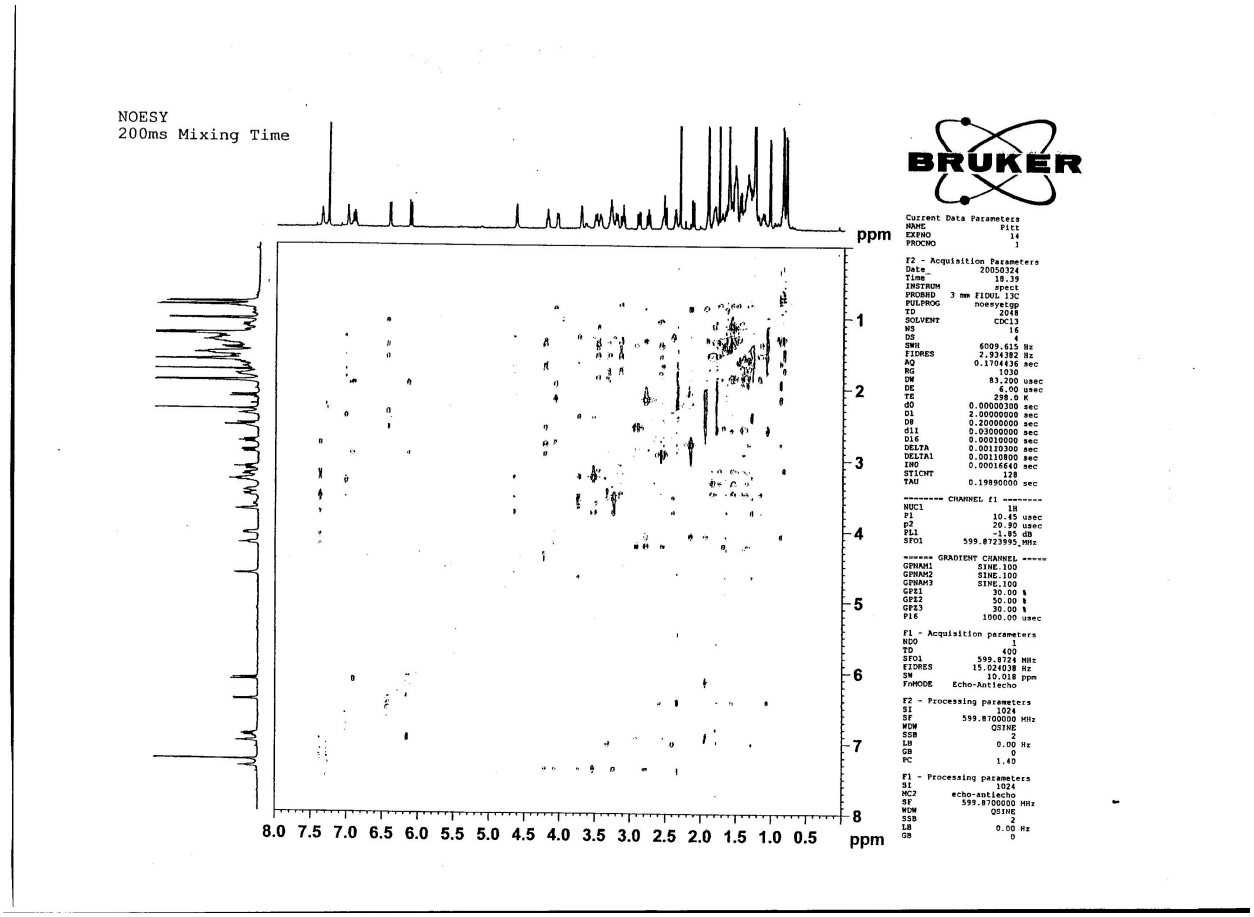
APPENDIX H

^{1}H-^{1}H COSY Spectrum of Bistramide C (**22**)



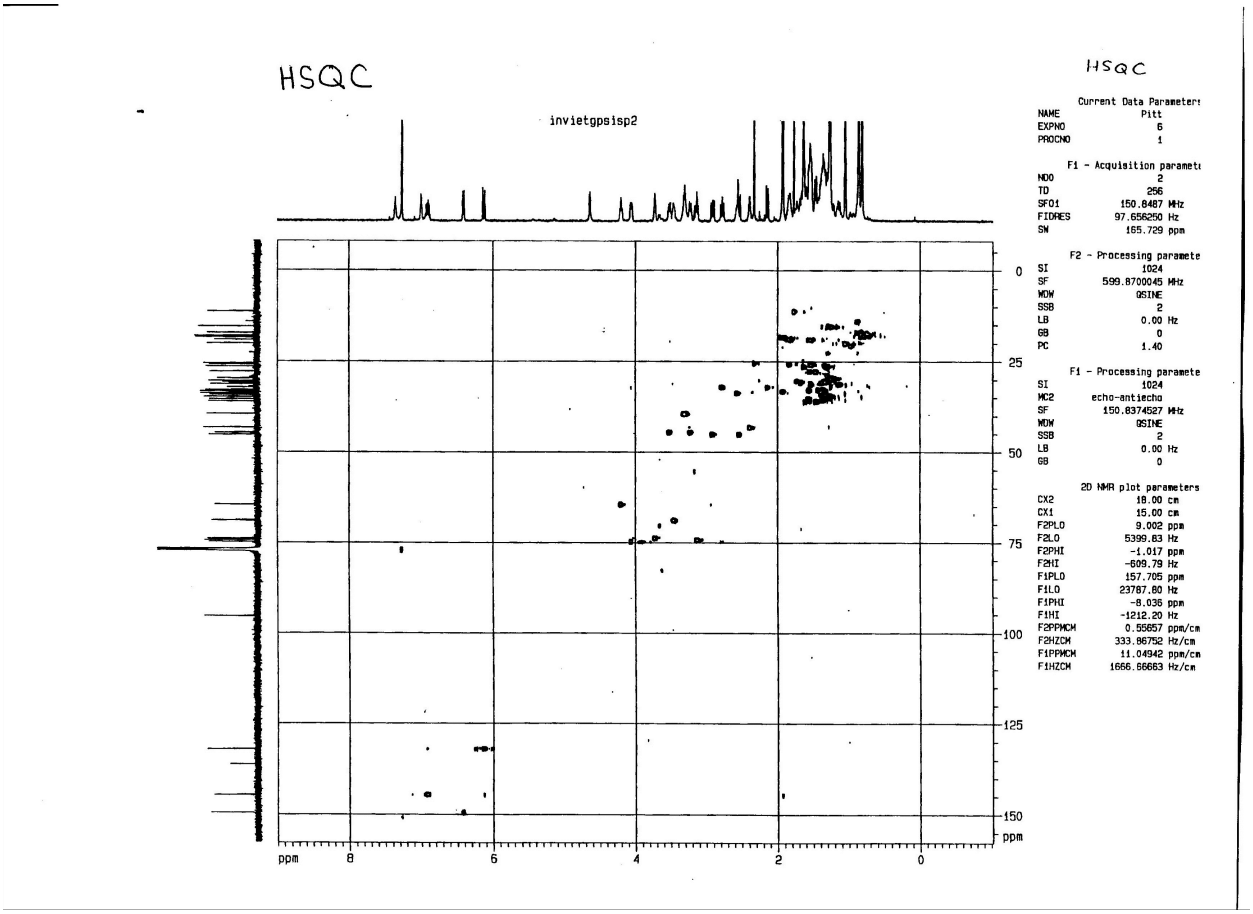
APPENDIX I

^{1}H-^{1}H NOESY Spectrum of Bistramide C (**22**)



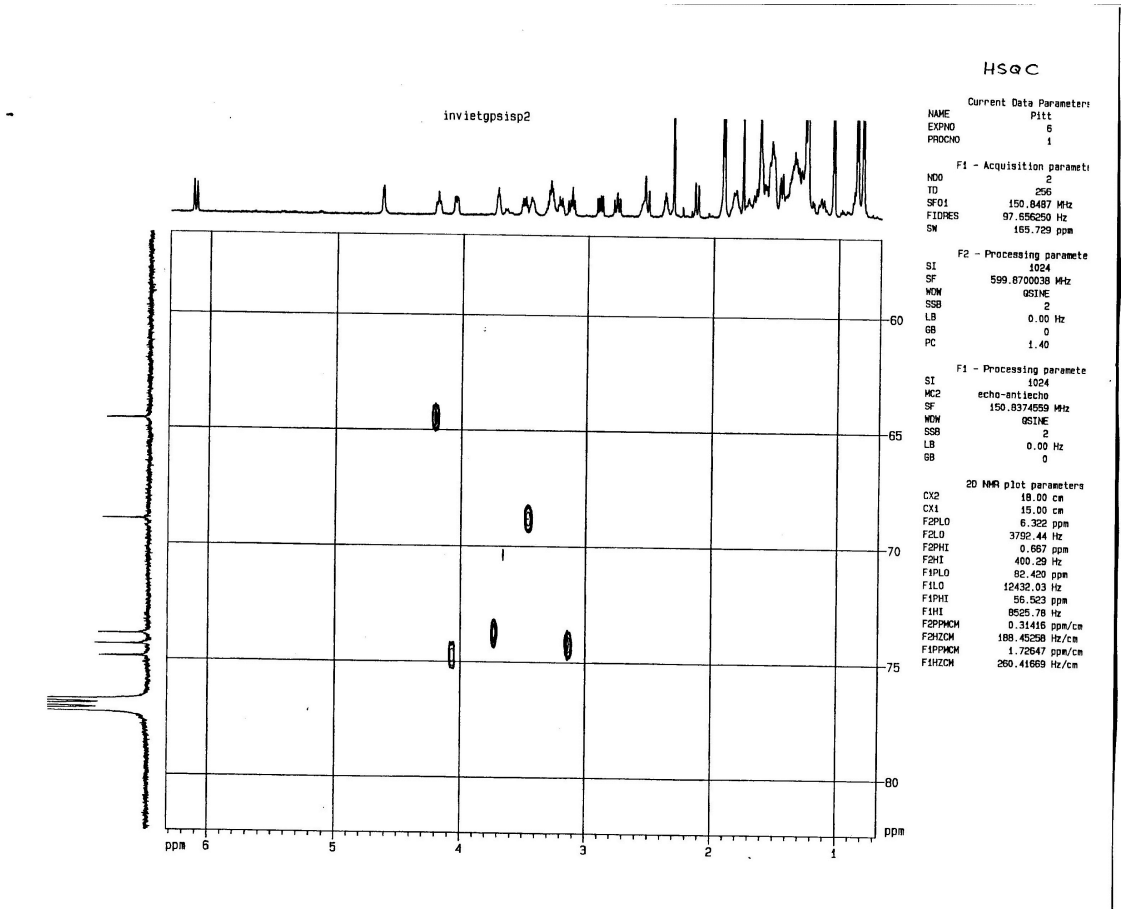
APPENDIX J

^{1}H-^{13}C HSQC Spectrum of Bistramide C (**22**)



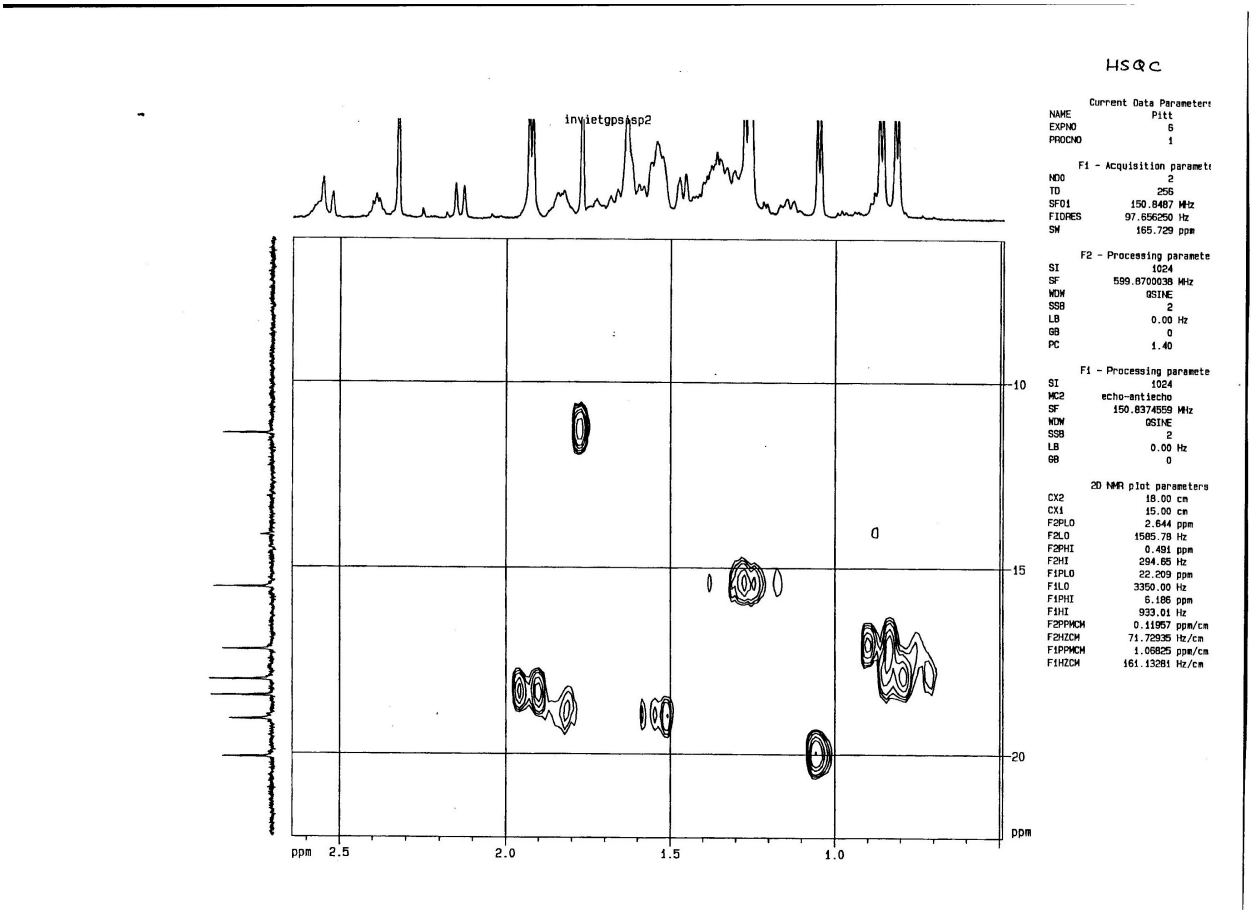
APPENDIX K

^{1}H-^{13}C HSQC Spectrum of Bistramide C (**22**)



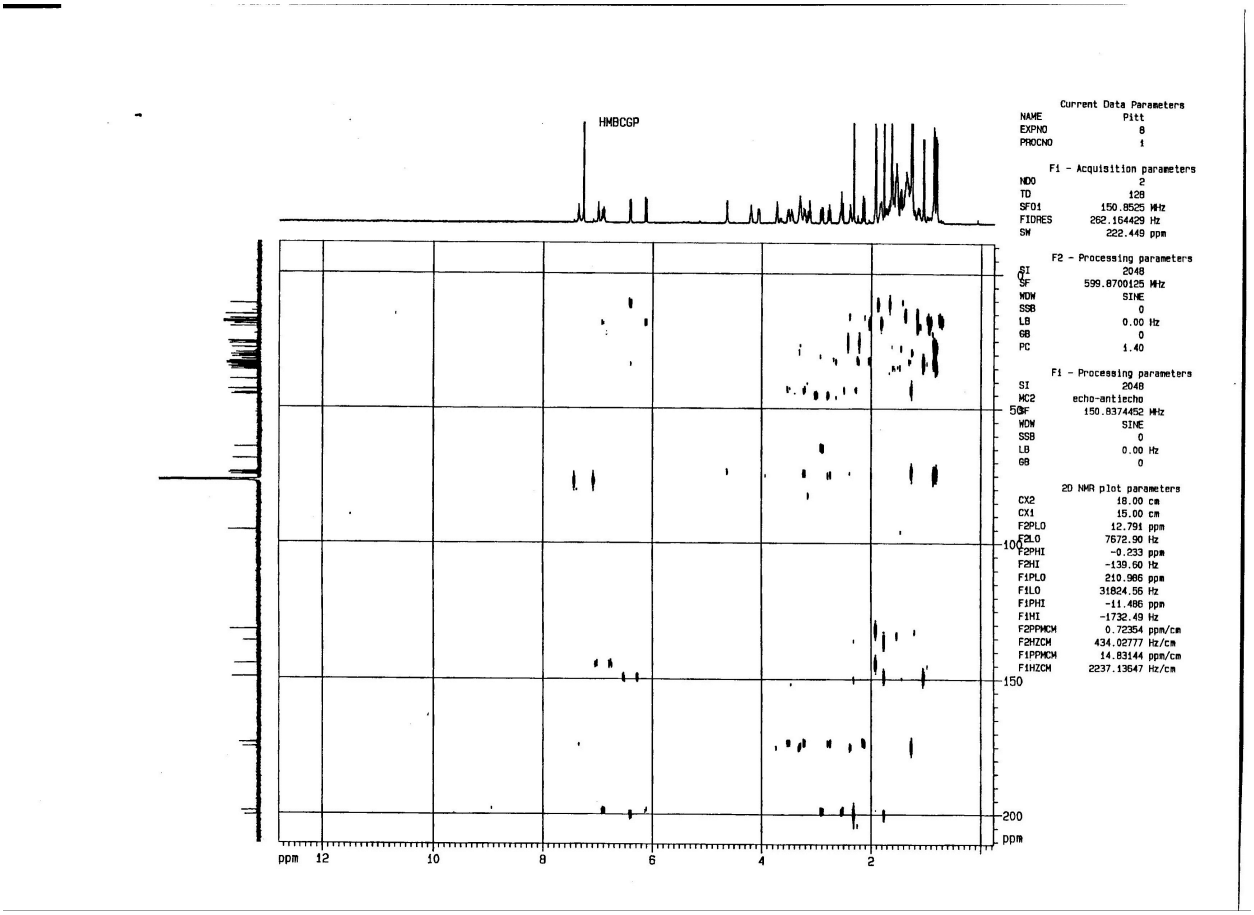
APPENDIX L

^{1}H-^{13}C HSQC Spectrum of Bistramide C (**22**)



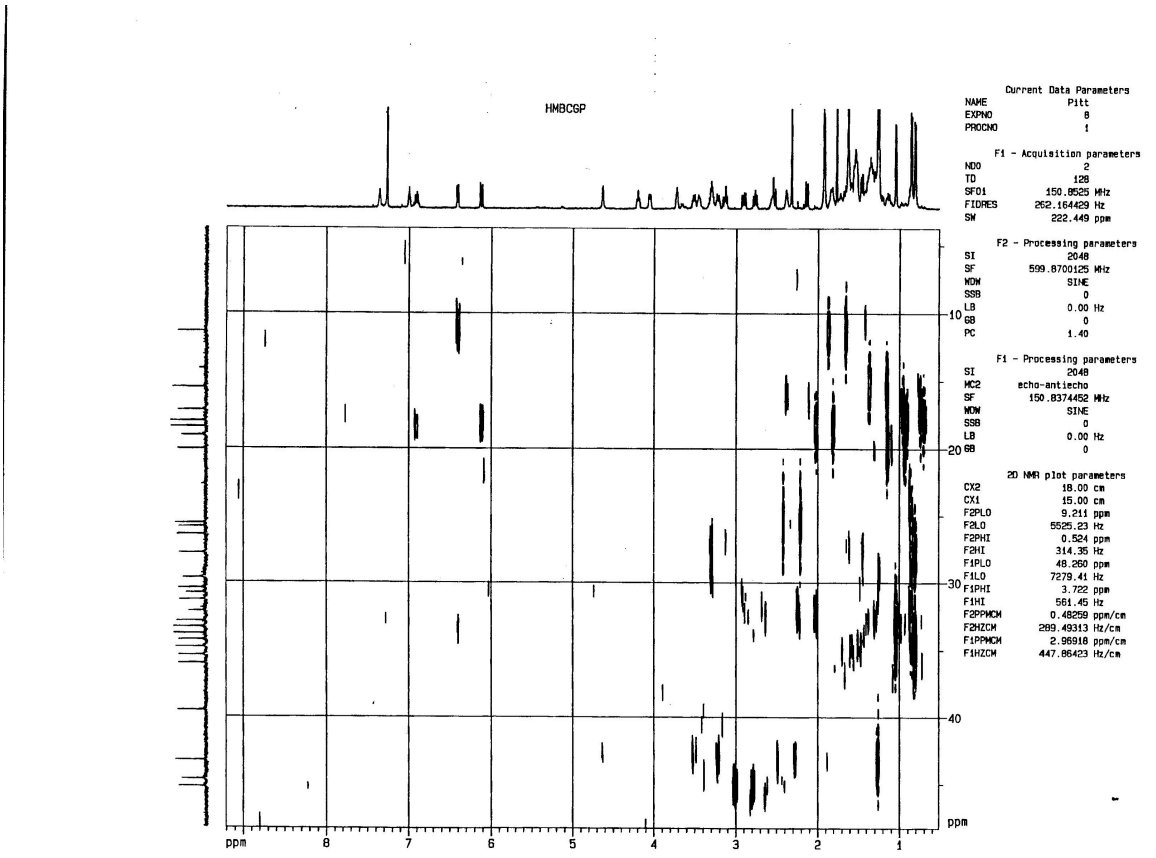
APPENDIX M

^{1}H-^{13}C HMBC Spectrum of Bistramide C (**22**)



APPENDIX N

^{1}H-^{13}C HMBC Spectrum of Bistramide C (**22**)



2.18. REFERENCES AND NOTES

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197) O_2 was bubbled directly into the flask from a gas cylinder. An in-line bubbler was used to monitor the flow rate. The flask should be equipped with a vent needle during the oxidation process.

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202) It was not uncommon for the two-component etherification process to stop before completion. If and/or when this occurred, the introduction of a small quantity of water facilitated the completion of the cycle, *i.e.* product formation. Several microliters of water were added to the current reaction to effect the desired pyran formation in a timely fashion.

203) It was not entirely clear whether or not the diastereomeric mixture was a mixture of *cis*- and *trans*- pyrans or a mixture of *trans*-pyrans. The former would be a direct outcome of a moderately selective etherification process. The other alternative would arise from the reaction of the minor diastereomer from the carboalumination sequence in a highly stereoselective (*trans*) fashion during the etherification process. The latter outcome

seemed very unlikely, as it was not at all apparent (by ^{1}H and/or ^{13}C NMR) that 20% of a minor component still existed by this point in the synthetic sequence. Attempts at separating the diastereomers by HPLC were unsuccessful. Also, attempts at definitively assigning the major product as a *trans*-pyran using common 2D spectroscopic methods generated ambiguous results.

204) A very small percentage of **61** also exists in this mixture, as indicated by ^{1}H NMR.

205) Often, the material used for the silyl protection was contaminated with minor quantities of the benzyl-protected pyran **62** and unreacted aldehyde **56** from the previous propenyl lithium addition. Since the R_f's of the desired benzoate **57**, **62** and **56** were quite similar, a slightly impure batch of material was often used in an effort to maximize the throughput of **57**. As a result, the isolated yield of **58** was slightly lower than normal.

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208) The dr ratio could not be determined from the ^{1}H NMR.

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210) The reported yield does not account for the bisacylated by-product which can be recycled and the small percentage of recovered starting material (**81**).

211) Bistramide C has also been purified by HPLC on SiO_2 using a 20 min gradient (99:1 to 96:4, CH_2Cl_2/MeOH) and a flow rate of 7 mL/min.