RADICAL CATIONS IN SYNTHESIS: UTILIZING AN ELECTRON TRANSFER-INITIATED CYCLIZATION TOWARD THE NATURAL PRODUCT APICULAREN A

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B.S. in Chemistry,

University of Michigan, Ann Arbor, 2003

Submitted to the Graduate Faculty of

the School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2009

UNIVERSITY OF PITTSBURGH

SCHOOL OF ARTS AND SCIENCES

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ABSTRACT

RADICAL CATIONS IN SYNTHESIS: UTILIZING AN ELECTRON TRANSFER-INITIATED CYCLIZATION TOWARD THE NATURAL PRODUCT APICULAREN A

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Reported herein is a synthetic campaign toward the vacuolar ATPase inhibitor apicularen A through an oxidative cyclization protocol. In this protocol (termed Electron Transfer-Initiated Cyclization, or ETIC), highly reactive oxocarbenium ions are generated through benzylic carbon–carbon σ-bond cleavage under chemically mild conditions. Regioselective cleavage of one homobenzylic ether in the presence of another homobenzylic ether is achieved by selectively weakening one carbon–carbon σ-bond through substitution. This work demonstrates that if bond cleavage is sufficiently rapid following oxidation, then oxidative fragmentation reactions can be used to generate stable cations selectively in the presence of other readily oxidized functional groups

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LIST OF ABBREVIATIONS

9-I-9BBN = 9-Iodo-9-borabicyclo[3.3.1]nonane

ABC = ATP-Binding Cassette

Ac = Acetyl

ATP = Adenosine triphosphate

Ar = Aryl

Bn = Benzyl

Bu = Butyl

CAN = Ceric Ammonium Nitrate

Cp = Cyclopentadienyl

CSA = Camphorsulfonic Acid

CuTC = Copper Thiophene Carboxylate

dba = Dibenzylidene Acetone

DCC = Dicyclohexyl Carbodiimide

DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DIAD = Diisopropyl Azadicarboxylate

DIBAL = Diisobutylaluminum Hydride

DMAP = 4-Dimethylaminopyridine

DMP = Dess-Martin Periodinane

DMS = Dimethylsulfide

Et = Ethyl

ETIC = Electron Transfer-Initiated Cyclization

Fur = Furyl

HMPA = Hexamethylphosphorictriamide

Ipc = Isopinocamphenyl

KHMDS = Potassium Hexamethyldisilazide

L.A. = Lewis Acid (generic)

LDA = Lithium Diisopropylamide

mCPBA = meta-Chloroperoxybenzoic acid Me = Methyl

MOM = Methoxymethyl

NBS = N-Bromosuccinimide

NMP = N-Methylpyrrolidinone

NOESY = Nuclear Overhauser Enhancement Spectroscopy

PG = Protecting Group (generic)

Ph = Phenyl

PMB = para-Methoxybenzyl

PMP = para-Methoxyphenyl

R = generic alkyl chain

Salen = N,N'-Ethylenebis(salicylimine)

TASF = tris(Dimethyl-amino)sulfonium Difluorotrimethylsilicate

TBAF = Tetra-*n*-butylamonium Fuoride

TBDPS = tert-Butyldiphenylsilyl

TBS = tert-Butyldimethylsilyl

Tf = Trifluoromethanesulfonyl

TFAA = Trifluoroaceticanhydride

TFP = Tris(2-furyl)phosphine

THF = Tetrahydrofuran

TIPS = Triisopropylsilyl

TMS = Trimethylsilyl

Ts = Toluenesulfonyl

1.0 APICULAREN A

It is our goal to develop a synthetic route to apicularen A (**1**, Figure 1). Our route will utilize an electron transfer initiated cyclization (ETIC) reaction[1] as a key synthetic step, demonstrating the relevance of this method to total synthesis. With the complex architecture of apicularen A as a proving ground, we will apply ETIC technology in a powerful and unprecedented fashion.

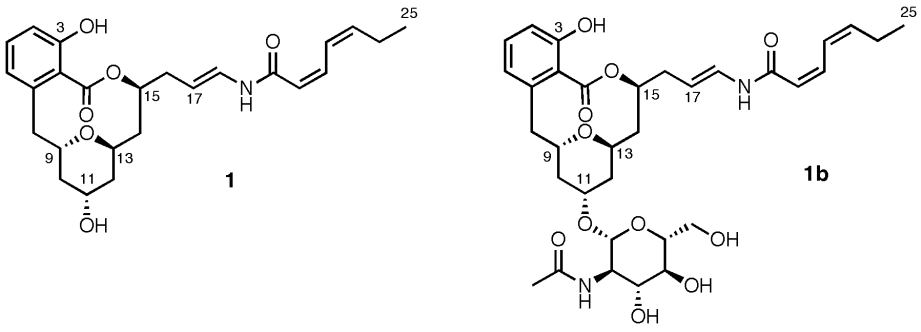


Figure 1: (−)-Apicularens A and B

1.1 BACKGROUND AND BIOLOGICAL PROFILE

The apicularens (Figure 1) are natural products isolated[2] from the myxo-bacterial genus *Chondromyces*. According to bacterial feeding experiments by Jansen and coworkers,[3] the framework is biosynethesized almost exclusively from acetate, with glycine as a precursor for the enamide side-chain (C17, C18 and N), and C25 originating from methionine. This

class of molecule has been shown to possess potent cytotoxic activity with IC_{50} values in the 0.23–6.8 nM range against nine human cancer cell lines.[2;3] The cytotoxicity of apicularen A has been attributed to its function as a vacuolar ATPase (or V-ATPase) inhibitor.

1.1.1 Vacuolar ATPases

Primary ion pumps consume ATP to facilitate ion transport across cell membranes. These proteins are highly evolutionarily conserved, found in all eukaryotic cells and tissures.[4;5;6] There are three types of ATPases[7] and a "superfamily" of ATP-Binding Cassette (ABC) transporters.[8] The P-ATPases involve a phosphorylated transition state, the F-ATPases function primarily in ATP synthesis, and the V-ATPases function only in ATP breakdown in order to move protons across cell membranes. The ABC transporters consume ATP to effect the uptake of a variety of solutes.

Malfunction of V-ATPase behavior has been implicated as the cause of the human diseases osteoporosis,[9] distal renal tubular acidosis,[10] and sensorineural deafness.[10] Furthermore, the diseases suspected of V-ATPase involvement include diabetes,[11] Alzheimer's,[12] Parkinson's,[13] cardiovascular disorders,[14] and glaucoma.[15]

1.1.2 Vacuolar ATPase Inhibitors

Known V-ATPase inhibitors fall generally into four structural classes: 1) macrolide lactones, 2) conjugated aromatics, 3) salicylate enamides, and 4) macrolide lactams.

1.1.2.1 Macrolide Lactones The earliest known V-ATPase inhibitors are the concanamycins (1982) and bafilomycins (1984), while the archazolids are a more recent discovery (2003). These compounds proved valuable tools for distinguishing among the three different types of ATPases.[16] Representative compounds from the macrolide lactone class of V-ATPase inhibitor (shown in Figure 2) include concanamycin B[17] (**2**, $IC_{50} = 5$ nM), bafilomycin A[18] (**3**, $IC_{50} = 2$ nM), and archazolid A[19] (**4**, $IC_{50} \approx 40$ nM).

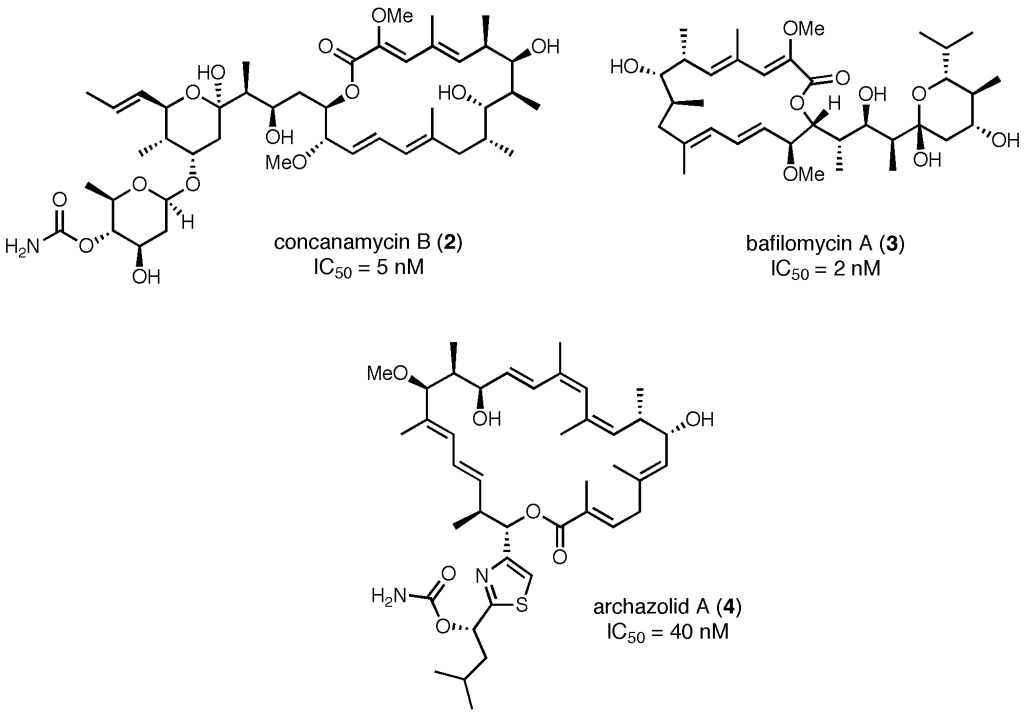


Figure 2: Macrolide lactone V-ATPase inhibitors

1.1.2.2 Conjugated Aromatics The second class of V-ATPase inhibitor discovered was the extended π-system aromatics, first seen in the compound diphyllin[20] (**5a**, $IC_{50} = 17$ nM). The Fujisawa Pharmaceutical Company compounds FR177995[21] (**5b**, $IC_{50} = 460$ nM) and FR202126[22] (**5c**, $IC_{50} = 99$ nM) also fall into this structural category (Figure 3).

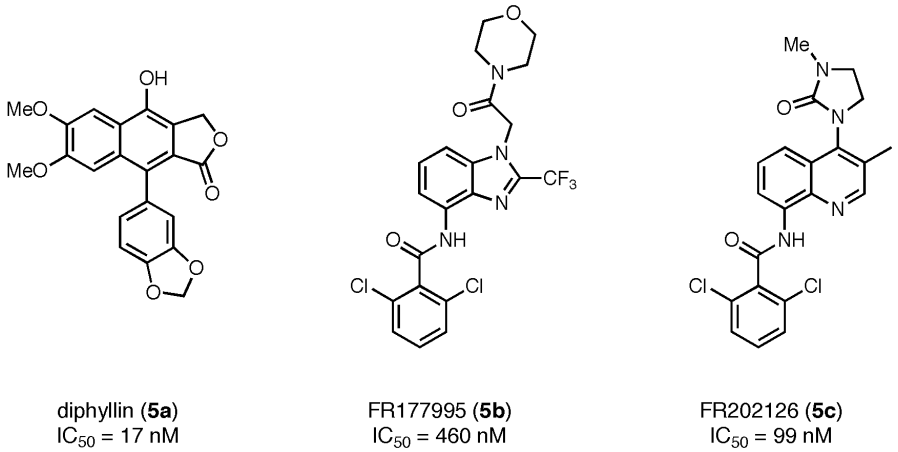


Figure 3: Conjugated aromatic V-ATPase inhibitors

1.1.2.3 Salicylate Enamides The salicylate enamide class of V-ATPase inhibitors includes the apicularens, as well as the closely related salicylihalamides, lobatamides, and oximidines. Figure 4 includes representative members salicylihalamide A[23] (**6**, $GI_{50} = 15$ nM against the NCI 60-cell human tumor assay), lobatamide A[24] (**7**, $GI_{50} \approx 9$ nM against the NCI 60-cell human tumor assay), and oximidine I[25] (**8**, $IC_50 = 16$–740 nM against normal and transformed rat 3Y1 fibroblasts).

1.1.2.4 Macrolide Lactams The final structural class of V-ATPase inhibitor is the macrolide lactams, the only presently-known members of which are the chondropsins.[26] Chondropsin A (**9**, $IC_{50} = 1$ nM) is shown in Figure 5.

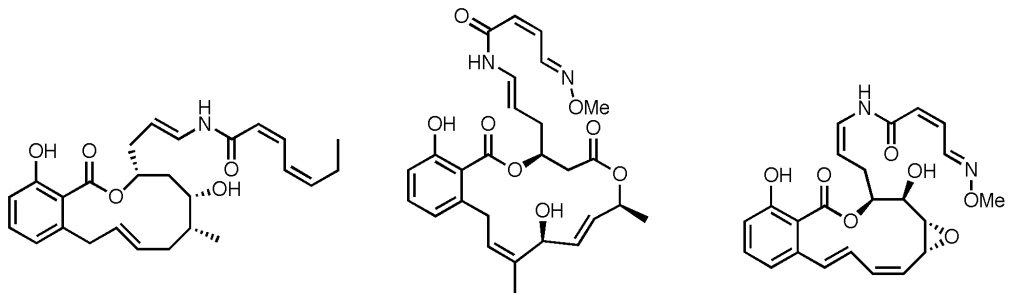


Figure 4: Salicylate enamide V-ATPase inhibitors

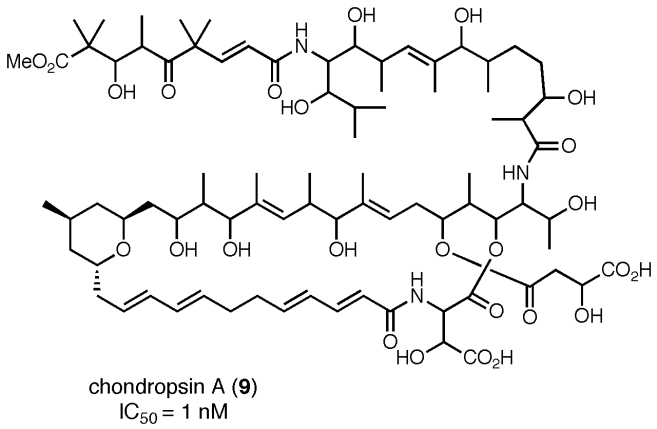


Figure 5: Macrolide lactam V-ATPase inhibitor

1.2 PREVIOUS APICULAREN SYNTHESES

Apicularen A (**1**, Figure 1) has attracted attention from the synthetic community. This section will review previous reports of synthetic work toward apicularen A.

1.2.1 De Brabander's Total Synthesis

De Brabander and co-workers[27;28] completed the first total synthesis of apicularen A. Their route (Figure 6) utilized an asymmetric hetero-Diels-Alder annulation of **163** and Danishefsky's diene **10** catalyzed by Jacobsen's chromium catalyst[29] **11** to furnish **12**. Subsequent 1,4 addition of a vinyl cuprate, $NaBH_4$ reduction and silyl ether formation produced **13**. Hydroboration/oxidation, then asymmetric Brown allylation (dr = 77:23 in favor of the 9,11-*anti*-, 13,15-*syn* diastereomer) supplied **14**. Macrolactonization was effected by treatment of **14** with NaH in THF to procure **15**. At this point the authors have accessed the apicularen A core, and their work on the side chain follows. A second silyl ether formation was performed, followed by OsO_4 dihydroxylation and successive oxidative cleavage to generate aldehyde **16**. Horner-Emmons coupling with allyl diethylphosphonoacetate and sequential Pd-catalyzed ester removal yielded carboxylic acid **17**. The epimers (differing at C11) were separated. The carboxylic acid was converted to the acyl azide, which was in turn transformed into the derivative isocyanate. Alkylation with lithiated 1-bromo-1,3-hexadiene followed by deprotection of both alcohols afforded apicularen A. Overall, the De Brabander synthesis involves 17 linear steps. The chiral induction steps in the sequence are the chromium-catalyzed asymmetric Diels-Alder annulation (C9), the diastereoselective Michael addition (C13), the stoichiometric Brown allylation (C15), and separation of epimers differing at C11. The side chain was installed via a vinyl copper addition to an isocyanate.

1.2.2 Taylor's Formal Synthesis

Taylor and co-workers reported a formal synthesis of (+)-apicularen A[30] (Figure 7). Triflate **19** (from D-glucal) was used in a Grignard addition with **18** to yield intermediate **20**. Benzofuran **20** was subjected to ozonolytic conditions with acetyl salicylaldehyde **21** as the

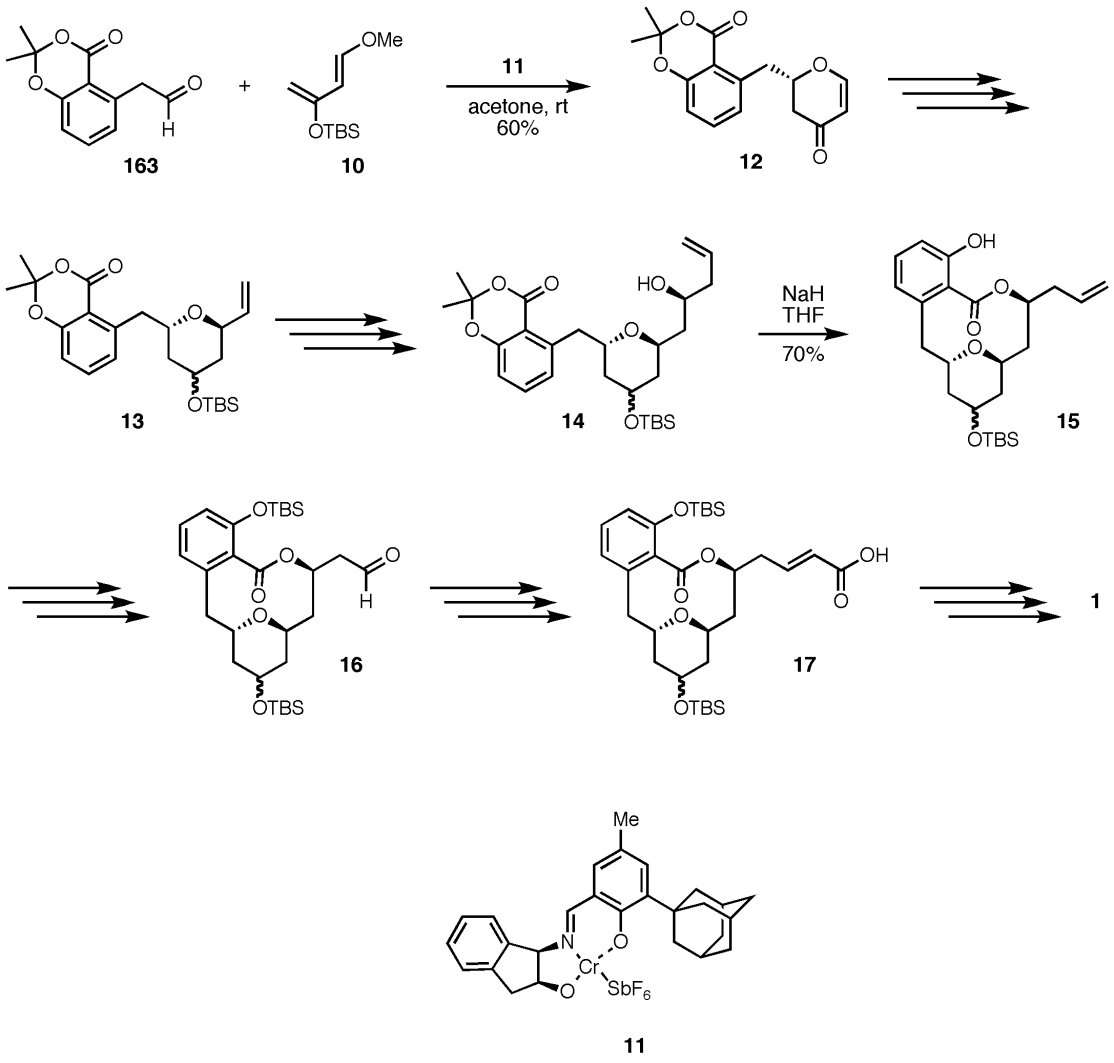


Figure 6: De Brabander's route to (−)-apicularen A

result. Oxidation of the aldehyde to a carboxylic acid, methanolysis of the acetate, and methylation of both the free phenol and carboxylic acid produced **22**. Diastereoselective allylation of hemiacetal **22** (a single diastereomer was observed) followed by complete removal of the TBDPS group with TBAF, then TBS re-protection of the secondary alcohol provided **23**. Ozonolysis of terminal olefin **23** and serial Brown allylation gave **24**, which was cyclized using DCC/DMAP to lactone **25**. Conversion of methyl ether **25** to the corresponding TBS ether was necessary to claim a formal synthesis, since **26** is a known intermediate from De Brabander's work. The Taylor synthesis involved 17 linear steps from naturally occurring D-glucal to known intermediate **26** (which by De Brabander's work is itself five steps removed from apicularen), with the stereochemical configuration at C9 and C11 deriving from D-glucal, C13 being controlled diastereoselectively by the allylation at the anomeric carbon of **22**, and C15 being established by a stoichiometric Brown allylation.

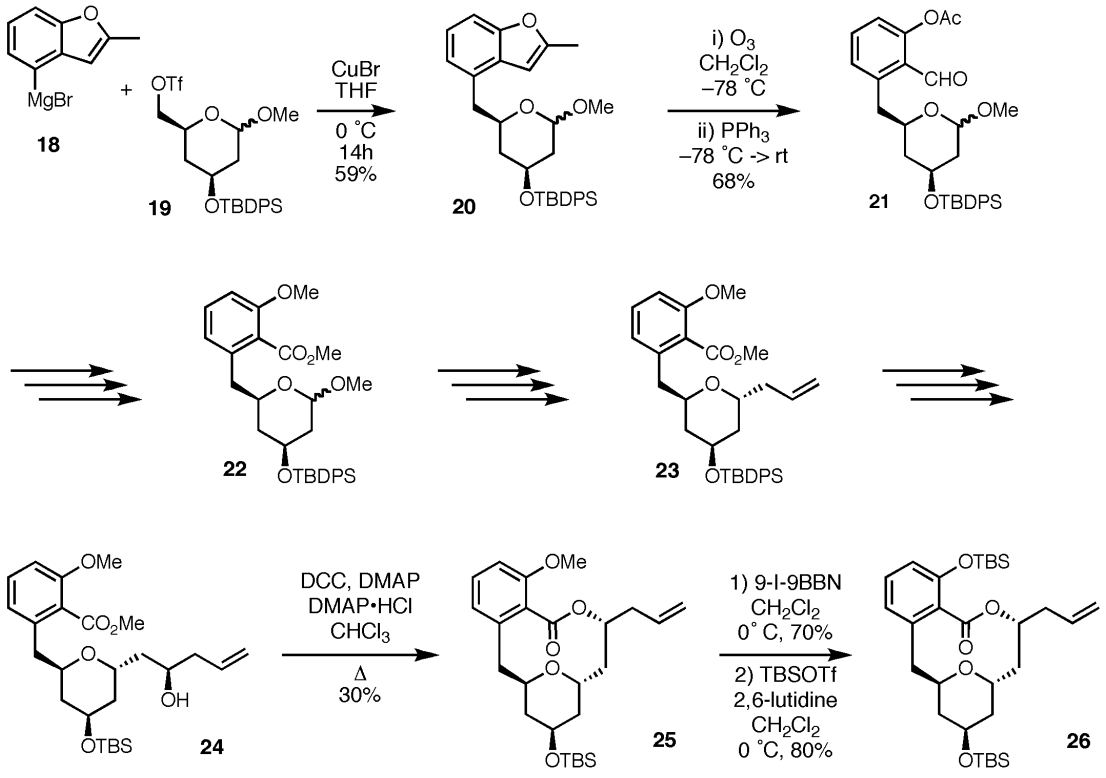


Figure 7: Taylor's route to (+)-apicularen A

1.2.3 Nicolaou's Total Synthesis

The Nicolaou group completed a total synthesis of apicularen A[31] (Figure 8) which the authors claim was "inspired by its polyacetate-based biosynthesis." The route relies heavily on an iterative allylation/ozonolysis sequence to mimic nature's use of two-carbon acetate building blocks to construct intermediate **31**. Intermediate **31** was converted to vinyl iodide **32** under Takai's conditions, and coupling with amide **33** using Rb_2CO_3 and copper(I) thiophene-2-carboxylate produced **34**. Lactonization using NaH followed by deprotection completed Nicolaou's synthesis of **1**, totaling 18 linear steps from known starting material. The chiral induction steps for this synthesis: (−)-Ipc Brown allylation, C9; (+)-Ipc Brown allylation, C11; substrate controlled diastereoselective allylations, C13; (+)-Ipc Brown allylation, C15. The side chain was appended through Rb/Cu-mediated C–N bond formation between an amide and a vinyl iodide.

1.2.4 Rychnovsky's Formal Synthesis

Rychnovsky's synthesis[32] (Figure 9) takes a more convergent approach to apicularen. Coupling nitrile **35** and iodide **36** in a highly diastereoselective manner followed by lithium ammonia reduction yielded protected polyol **37**. Oxidative cyclization and subsequent conversion of the hemiacetal to mixed acetal using DOWEX resin and MeOH followed by secondary alcohol protection provided **38**. To the anomeric carbon of **38** was added 2,4-pentadienyl-trimethylsilane, introducing the diene moiety for an impressive intramolecular Diels-Alder annulation. Otera esterification between **39** and methyl 3-bromopropynylate delivered the dienophilic fragment, and addition of DDQ, methanolysis, and TBS etherification produced arene **41** in a 44% yield (from **39**). To complete their formal synthesis, the authors converted the bromide to a phenol by treatment of **41** with *n*-BuLi/$(TMSO)_2$, and protected the phenol as the acetate. The TMS group was converted to an iodide with NIS, and the acetate and TBS groups were removed with K_2CO_3/MeOH then DOWEX / MeOH. The authors attempted to couple the resulting vinyl iodide with amide **33** (analogous to the Nicolaou route), but had no success. To complete a formal synthesis, the vinyl iodide was reduced with Bu_3SnH/AIBN to supply terminal olefin **42**, a known in-

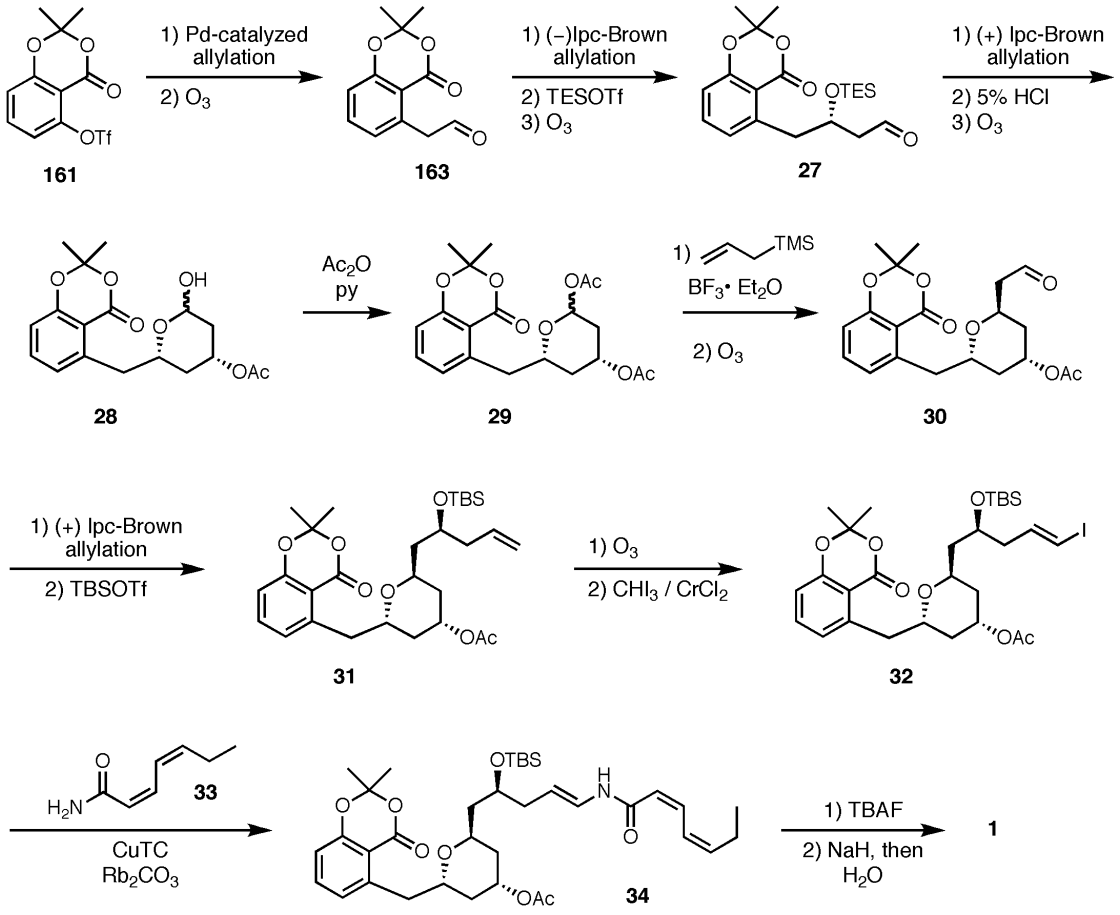


Figure 8: Nicolaou's route to (−)-apicularen A

termediate in previous apicularen A syntheses. The Rychnovsky synthesis of apicularen A involves 20 synthetic steps (17 at its longest linear sequence) to arrive at intermediate **42**, which is itself 10 steps from apicularen A by De Brabander's methods. The chiral induction steps in Rychnovsky's paper are: substrate controlled diastereoselective anomeric addition of 2,4-pentadienyl-trimethylsilane (C9), a Ru-*(R)*-(+)-BINAP catalyzed Noyroi β-ketoester reduction (C11), the substrate controlled diastereoselective nirile/iodide coupling (C13), and chiral pool reactant *(S)*-epichlorohydrin (C15).

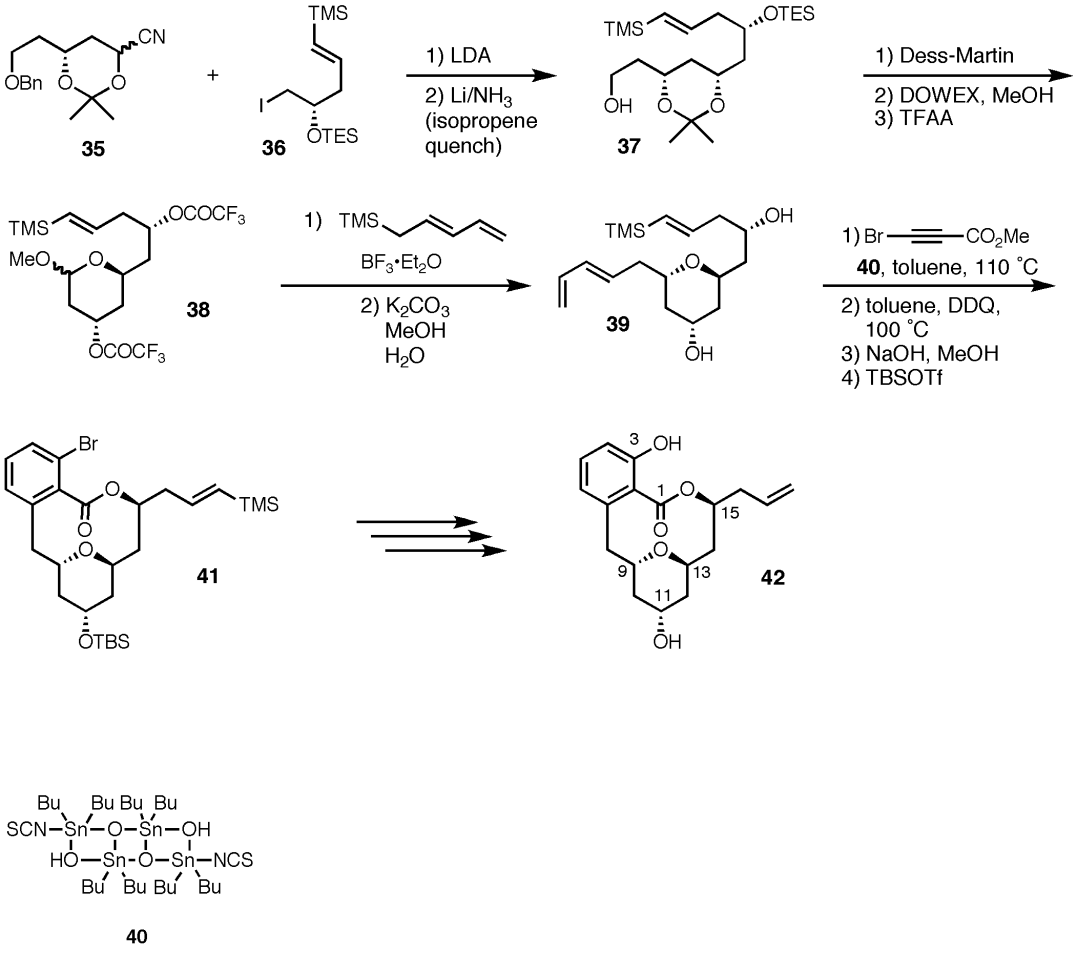


Figure 9: Rychnovsky's route to (−)-apicularen A

1.2.5 Panek's Total Synthesis

The Panek group completed a total synthesis of apicularen A[33] (Figure 10). Their route used a [4+2] annulation of aldehyde **43** and allylsilane **44** to yield **45**. Protecting group manipulations, followed by epoxidation, epoxide opening with DIBAL, and Mitsunobu inversion of the configurationally incorrect secondary alcohol led to intermediate **46**. Further protecting group manipulation, primary alcohol oxidation to an aldehyde, one-carbon homologation of the resulting aldehyde, (+)-Ipc Brown allylation of the homologated aldehyde **47**, more protecting group manipulation and formation of an activated cyanomethyl ester produced intermediate **48**. This is the lone example in the apicularen literature of this type of activated benzoate ester to effect lactonization, which proceeded in 63% yield. Lactone **49** was treated with OsO_4, then $NaIO_4$, and the resulting aldehyde was converted to a vinyl iodide using Takai's conditions. As in the Nicolaou route, the amide side chain was appended under Rb/CuTC coupling conditions. The Panek synthesis completed apicularen A in 29 synthetic steps, with the stereocenters having been set by an asymmetric [4+2] annulation of an aldehyde and chiral allyl silane (C9 and C13), a substrate controlled (and incorrect) epoxidation and subsequent Mitsunobu inversion (C11), and (+)-Ipc Brown allylation (C15). The side chain was appended in a manner virtually identical to the Nicolaou report.

1.2.6 Rizzacasa's Formal Synthesis

The Rizzacasa group reported a formal synthesis of apicularen A.[34] In one of the more convergent apicularen syntheses, bromide **51** and stannane **50** (Figure 11) were coupled under Stille conditions. Efficient macrolactonization using NaH, followed by TBAF desilylation, and MnO_2 allylic oxidation produced enone **53**. They key step in the route was a transannular etherification accomplished using Amberlyst-15 acidic resin in refluxing $CDCl_3$ to secure **54**. Notably, stereoisomers differing at C9 and C13 were shown to equilibrate to the absolute stereochemical configuration of the natural product. This demonstrates that the epimerization is under thermodynamic control, and the only stereocenter requiring an asymmetric reagent/reactant to control its absolute configuration is C15. Sodium borohydride reduction gave a 1:1 mixture of epimers at C11, and after separation of the diastereomers and methyl

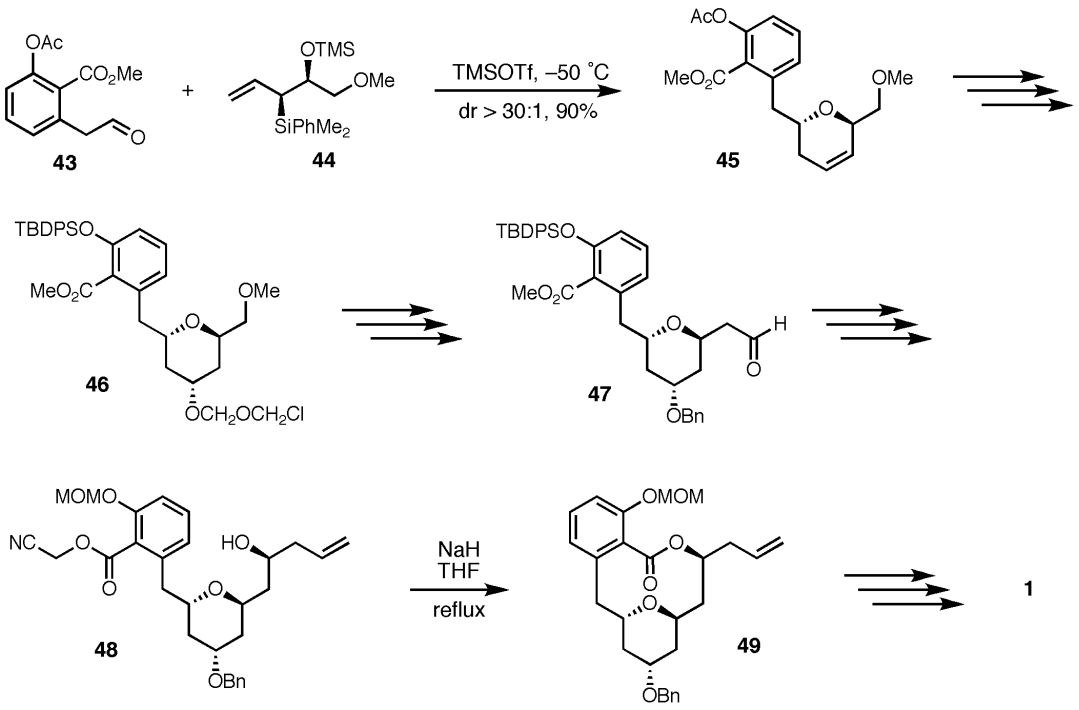


Figure 10: Panek's route to (−)-apicularen A

ether removal, the known intermediate **42** was accessed to complete the formal synthesis. The Rizzacasa synthesis used 15 synthetic steps from known material to arrive at **42**, which is itself 10 steps removed from apicularen A (by De Brabander's work). The sources of absolute stereocontrol: (+)-Ipc Brown allylation (C15) which in turn influences both C9 and C13, and a separation of epimers differing at C11.

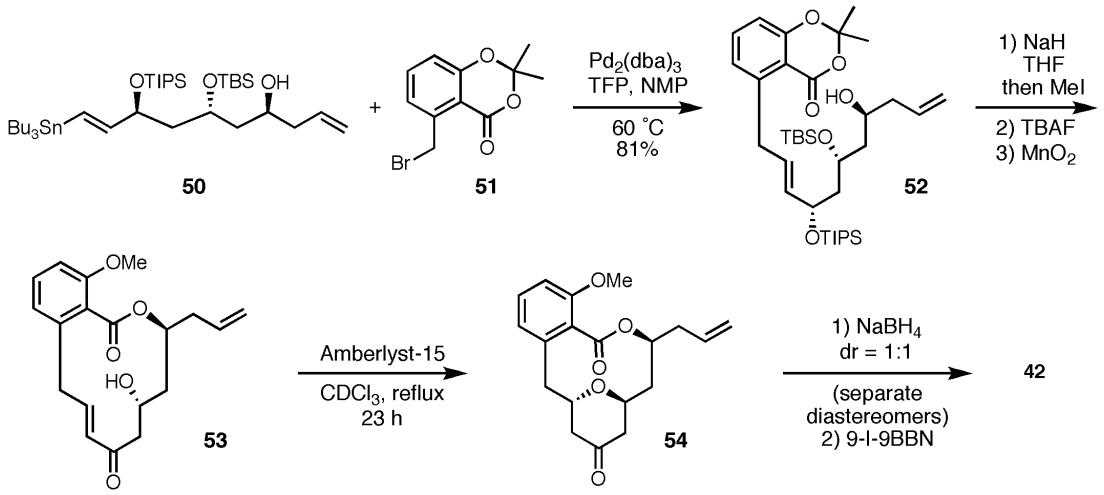


Figure 11: Rizzacasa's route to (−)-apicularen A

1.2.7 Maier's Total Synthesis

The Maier synthesis of apicularen A[35] was also convergent, and shares several themes with the Rizzacasa route. Triflate **55** and stannane **56** (Figure 12) were coupled using a Stille reaction, protecting group manipulation and installation of the mixed-acetal carboxylate provided **58**, which cyclized to give the macrolactone **59**. The key transannular etherification was accomplished through an oxy-mercuration, and subsequent reduction of the alkyl mercury to the alkane produced **60**. Further protecting group manipulation accessed aldehyde **61**, which was coupled with amide **33** to form acyl hemiaminal **62**. The hemiaminal was *O*-acylated and acetic acid was eliminated to secure **63**. Removal of the silyl protecting groups with tris(dimethyl-amino)sulfonium difluorotrimethylsilicate yielded apicularen A **1**. The Maier synthesis arrived at apicularen A in 24 synthetic steps. The chiral induction steps

were a substrate controlled oxy-mercuration (C9), chiral pool reactants (C11 and C15), and a substrate-controlled diastereoselective oxidation of a dithiane (C13). The side chain was appended by coupling an aldehyde with an amide to give an acyl hemiaminal, which was then *O*-acylated; elimination of acetic acid provided the enamide functional group.

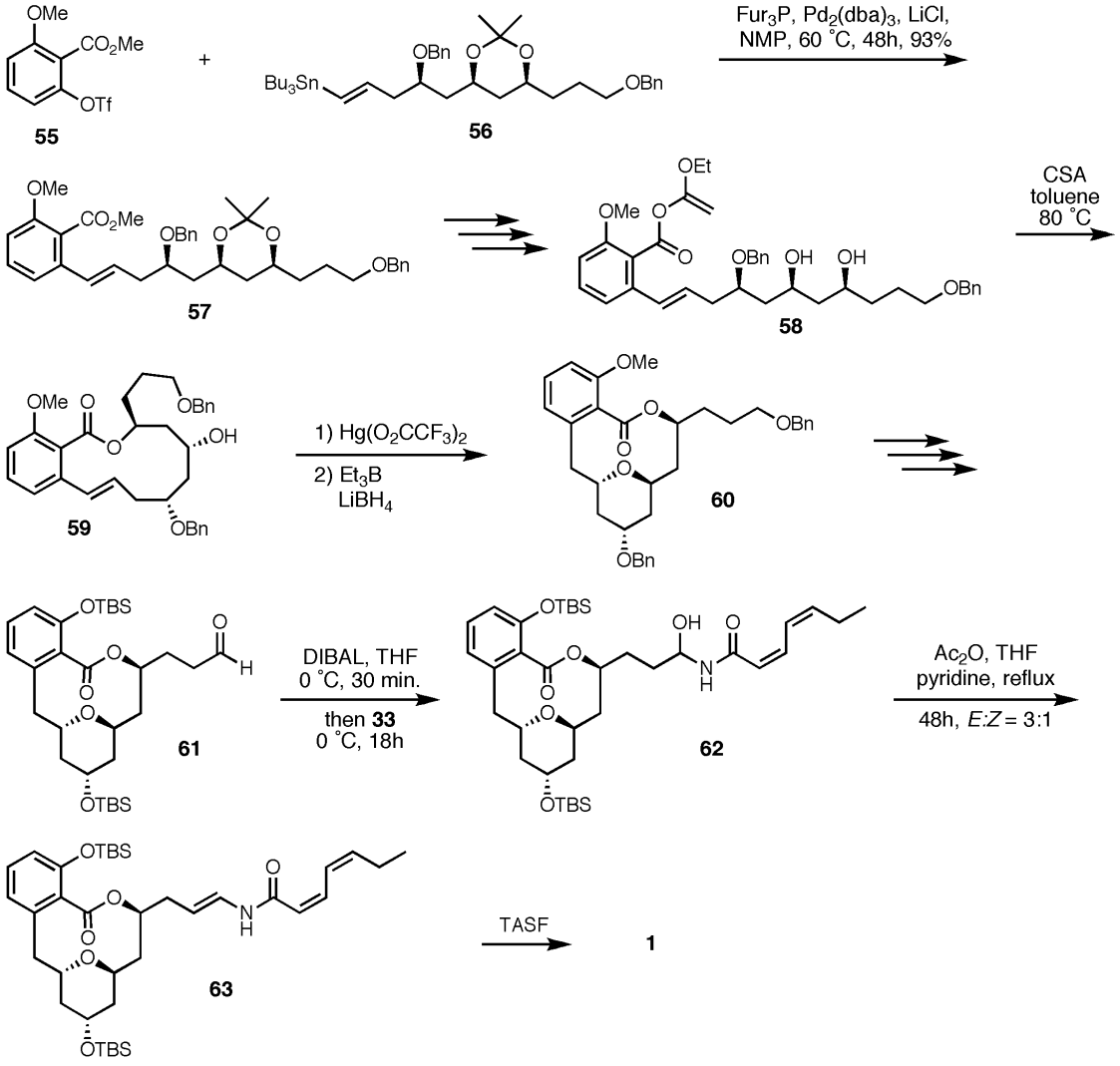


Figure 12: Maier's route to (−)-apicularen A

1.2.8 O'Doherty's Formal Synthesis

The most recent report involving synthetic studies of apicularen is from the O'Doherty group.[36] Like the Rizzacasa and Maier routes before it, the O'Doherty route is centered around a transannular etherification reaction strategy. The formal synthesis begins with the isomerization of alkynoate **64** to dieneoate **65**, followed by an asymmetric dihydroxylation to establish the first chiral center of the synthesis (C15 of apicularen). Trapping the resulting diol as the cyclic carbonate led to intermediate **66**, which was in turn converted to δ-hydroxy enoate **67**. The configuration at C13 was set by treating the hemiacetal that results from **67** and benzaldehyde with KO*t*-Bu. The carboxylate was elaborated and the desired configuration at C11 was established via an substrate-controlled diastereoselective allylation to provide **69**. Grubbs cross metathesis of **69** with styrene **70** led to the disubstituted *E*-styrene, which, when deprotected, produced **71**. The macrolactone was formed by subjecting **71** to Yamaguchi's conditions, and the product **59** is the substrate required for the key transannular etherification reaction. When **59** was treated with KO*t*-Bu in THF at 0 °C, the only observed diastereomer was the desired tetrahydropyran **60**. This significant finding lends a useful method to the apicularen literature, which compliments the existing transannular etherification methods. Furthermore, O'Doherty's report reinforces Rizzacasa's finding that there is an certain tendency to form the naturally occurring diastereomer of apicularen A through a transannular etherification. The O'Doherty route involves 21 synthetic steps from commercially available starting materials, and 18 steps at its longest linear sequence.

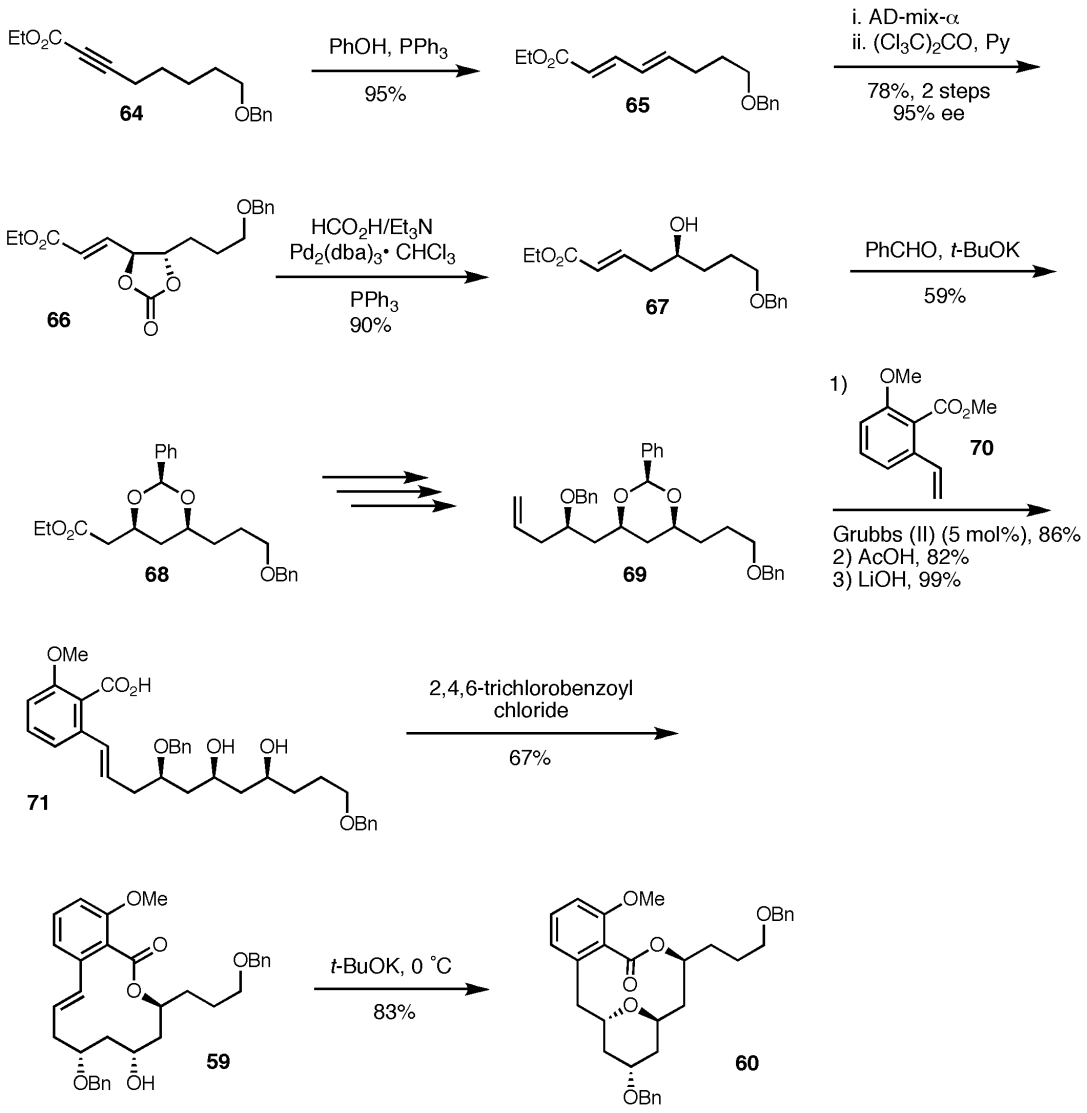


Figure 13: O'Doherty's route to (−)-apicularen A

2.0 PROPOSED ROUTE TO APICULAREN A

2.1 OUR PLANNED SYNTHESIS

We hypothesized that the tetrahydropyran ring of apicularen could be constructed using an electron transfer-initiated cyclization (ETIC) reaction, where a pendant enol acetate nucleophile attacks an oxocarbenium ion formed within the 10-membered apicularen lactone (Figure 14, lactone ring abbreviated for clarity). We further hypothesized that a measure of diastereoselectivity could be achieved in an ETIC reaction, due to the following considerations: 1) if an oxocarbenium ion can be formed within the ring, the E geometry is predicted (that is, $k^1 > k^{-1}$, not only because this orients the R groups *trans* to one another rather than *cis* as in the Z configuration, but also because the E configuration is expected to produce less added strain to the ten-membered ring than the Z configuration, and 2) we suppose that the transition state energies mimic the energies of the respective products. Figure 14 depicts the THP formation occurring through a six membered chair-type transition state wherein the presence of the lactone ring should allow for a measure of facial selectivity, as the electrophile has but one face exposed to attack in either conformation. With these hypotheses, we undertook a synthetic campaign toward apicularen A. We will incorporate convergency in our route, as the existing routes to apicularen A in the chemical literature are largely linear synthetic sequences.

In our initial retrosynthetic analysis (Figure 15), a six membered ring was imagined to be formed via ETIC chemistry, using an established ten-membered ring to establish rigidity, allowing for stereocontrol. An attractive advantage to an ETIC to construct carbon-carbon bonds is that a highly electrophilic oxocarbenium ion is generated under mild chemical conditions; strongly acidic or basic conditions are not required. This presents an opportunity

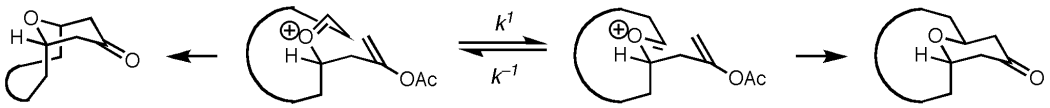


Figure 14: Envisioned THP ring formation (lactone ring abbreviated for clarity)

to chemoselectively access two different oxocarbenium ions. In the first instance, the acetal is ionized under traditional Lewis acidic conditions, and the resulting oxocarbenium ion attacked by a suitable external three-carbon nucleophile (in this example, introducing a propargyl group). In the second instance, an oxocarbenium ion is generated under chemically mild oxidizing conditions to form an oxocarbenium ion that is subsequently trapped by intramolecular delivery of a carbon nucleophile (in this example, an enol acetate) resulting in a six membered ring. The orthogonality of these methods allows for these electrophiles to be unmasked in a chemoselective manner.

Our proposed route to apicularen is shown in the forward direction in Figure 16. Known ester **116**[37] could be reduced to aldehyde **117**. The diol portion of key acetal intermediate **72** could be prepared by asymmetric allylation of known aldehyde **121**, followed by epoxidation to yield **133**. Grignard addition to epoxide **133** could lead to diol **166**, which could be converted to the bis-TMS ether derivative for use in a Noyori acetal synthesis[38] to produce acetal **72**. Addition of a propargyl group to the acetal center of **72** could yield doubly-secondary ether **73**, which could undergo hydrolysis, lactonization, and conversion to enol acetate **74**. ETIC substrate **74** could undergo cyclization to tetrahydropyrone **75**. An epimerization inspired by Rizzacasa'a work[34] could be applied to synthesize **54** and achieve a formal synthesis of the natural product. One advantage to our proposed route include a measure of convergency by rapidly establishing molecular complexity through coupling aldehyde **117** and diol **166**. The major advantage to our proposed route is the fact that the sequence is short; a formal synthesis of apicularen would be achieved in 12 synthetic steps from known compounds **116** and **121**.

The proposed mechanism for the ETIC reaction (Figure 17), involves coordination of

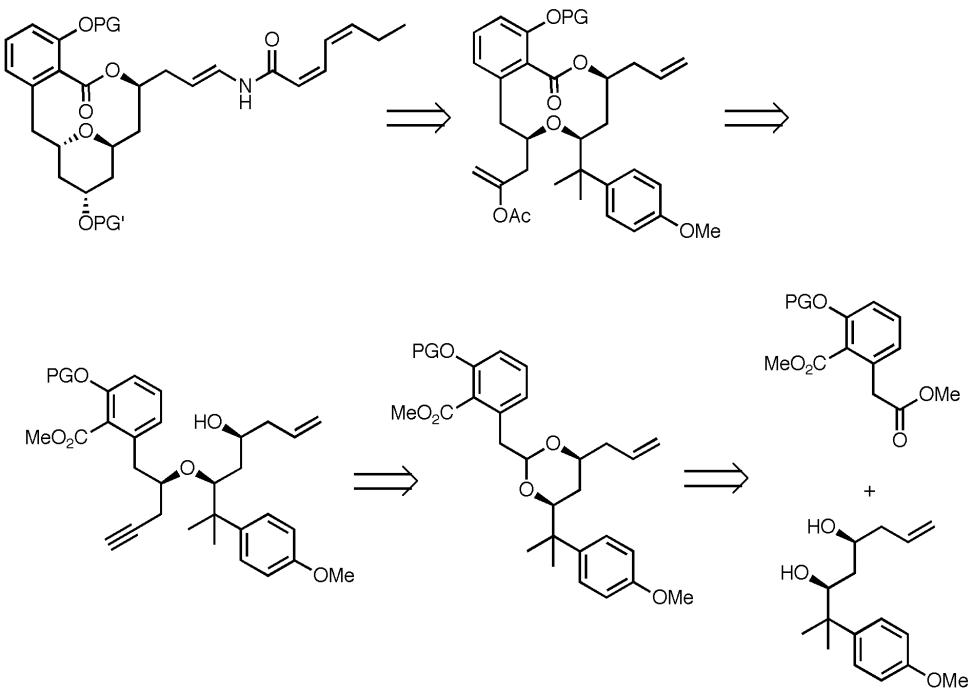


Figure 15: Initial retrosynthetic analysis

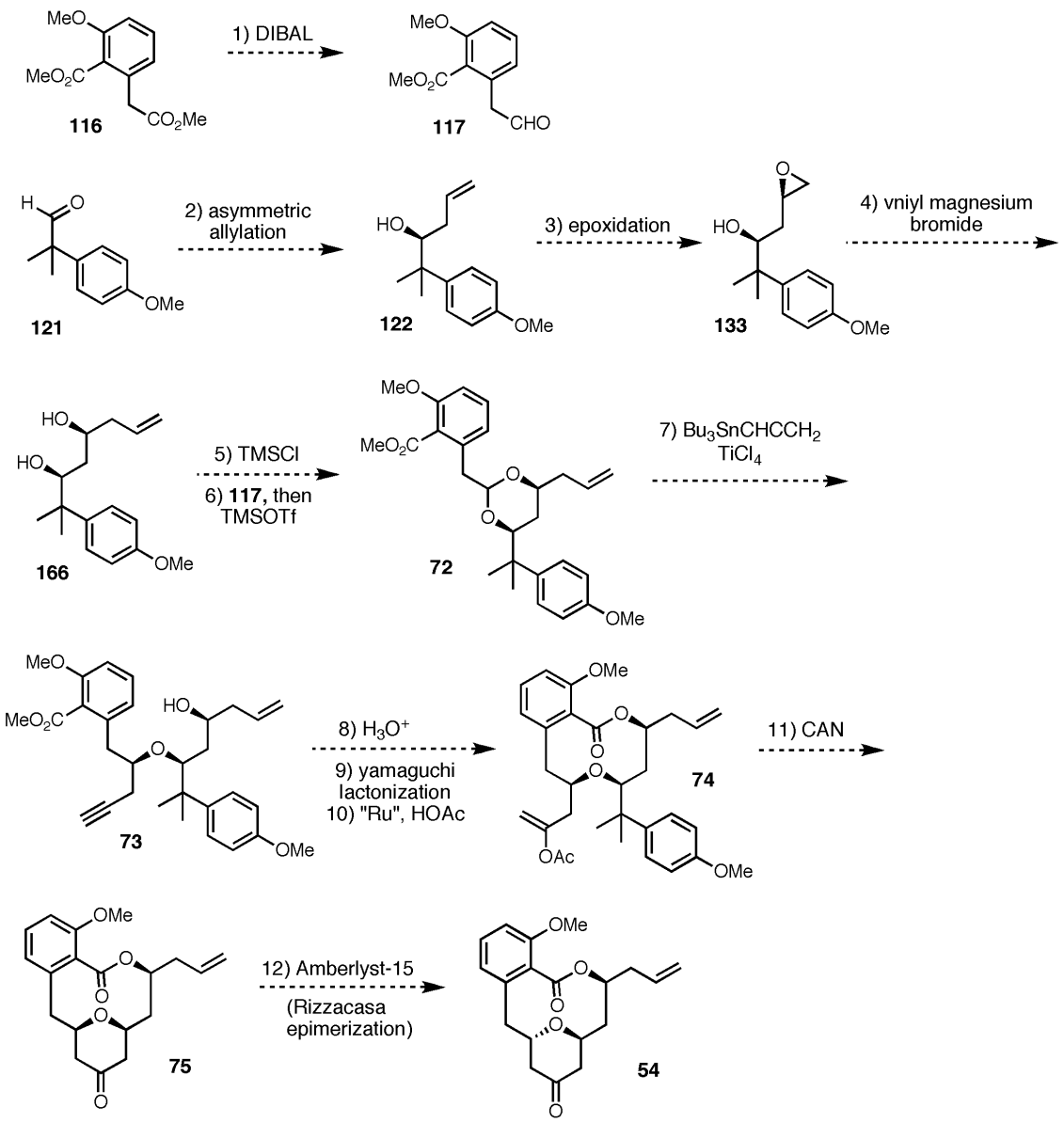


Figure 16: Proposed route to apicularen A

Ce^{IV} to the dimethyl-*p*-methoxy benzyl arene, followed by an inner-sphere electron transfer to give Ce^{III} and a radical cation of the substrate. The radical cation can undergo mesolytic cleavage to produce a radical and a cation. The resulting oxocarbenium ion is then trapped by the pendant enol acetate nucleophile to yield the desired 4-tetrahydropyrone, while the benzylic radical fragment undergoes further oxidation by Ce^{IV} and subsequent consumption of the benzylic cation by nitrate anion to produce the observed benzylnitrate by-product.

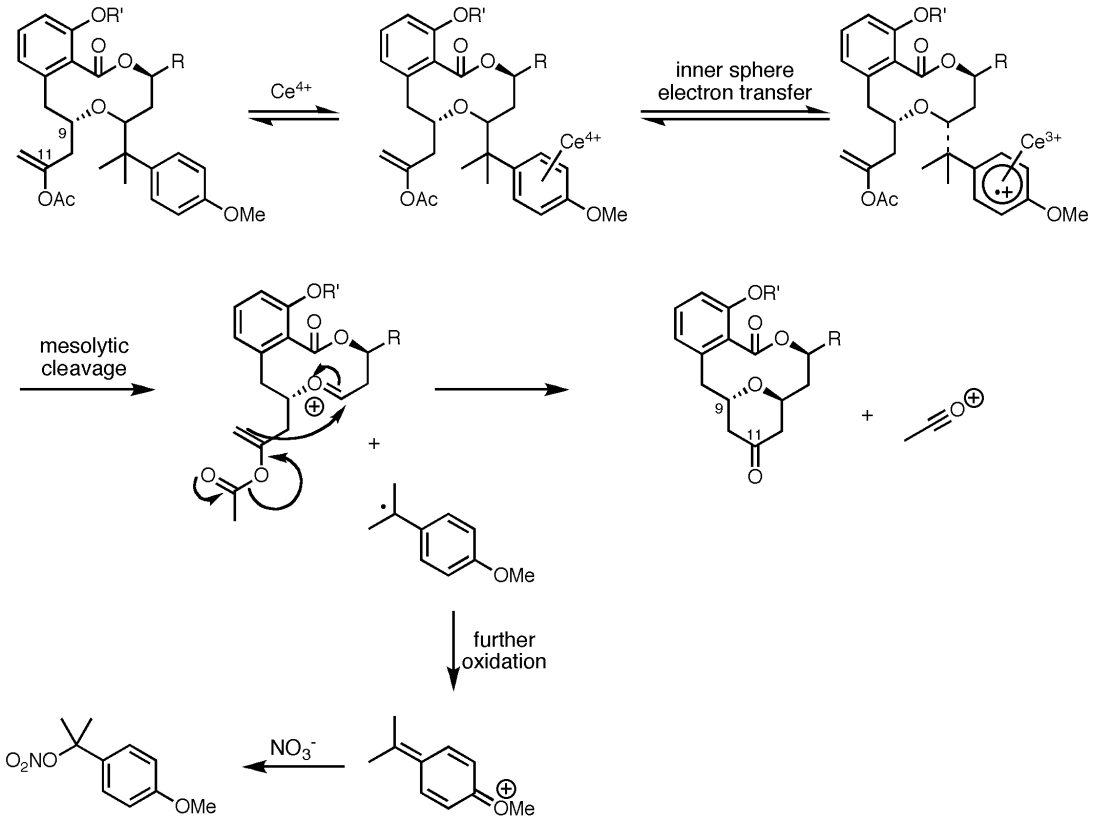


Figure 17: Proposed ETIC reaction pathway

2.2 INITIAL STUDIES: AN APICULAREN MODEL

Initially, the most pressing research issue to be addressed was whether or not our key ETIC reaction would be feasible for a synthesis of apicularen. This section describes our design

and synthesis of a model system of the apicularen A core. The model cyclization substrates were subjected to ETIC conditions, and our observations and conclusions are included.

2.2.1 Design and Synthesis of a Model System

To investigate whether the envisioned ETIC reaction would occur, we designed a truncated model of apicularen A that we could synthesize rapidly and observe for reactivity. In order to investigate any possible conformational effects (that is, whether or not any of the diastereomers show any bias over the others for fragmentation and/or cyclization due to stereochemical configuration), all four diastereomers of the apicularen core were considered and synthesized (Figure 18). Notable features of this model system are:

1. a ten-membered lactone to approximate the apicularen core
2. the dimethyl-*p*-methoxybenzyl electroauxiliary
3. an enol acetate that will act as a latent enolate
4. the absence of the C3 oxygenation, which must later be included in precursors to the natural product
5. an inert *n*-hexyl side chain, which must later be replaced with a functional handle in precursors to the natural product

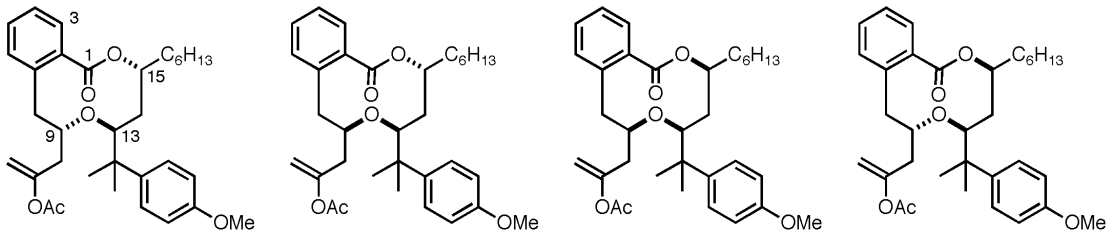


Figure 18: Model cyclization substrates

A significant challenge lies in the formation of doubly-secondary ethers. In the context of our pursuit of apicularen, an attractive tactic to achieve their synthesis is the addition of a

three-carbon nucleophile to an acetal (Figure 19). The convergent nature of synthesizing an acetal linkage allows for molecular complexity to be established in a rapid and facile manner.

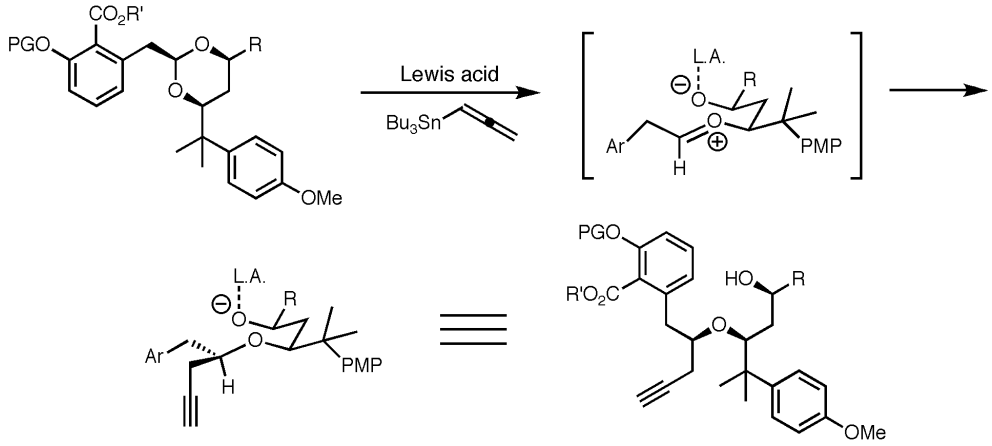


Figure 19: Acetal propargylation tactic to access doubly-secondary ethers

To secure the four diastereomers of our model system, both *anti*-diol **79** and *syn*-diol **80**, and aldehyde **85** were required. The syntheses (Figure 20) of the requisite diols commenced with the treatment of commercially available 1-(4-methoxy-phenyl)-propan-2-one (**76**) with base and iodomethane to produce bis-methylated product **77** in 82% yield. After treatment of **77** with LDA and heptanal, β-hydroxyketone **78** was available in 81% yield for either *syn*- or *anti*- reduction to diols **79** and **80**. If both isomeric diols are simultaneously desired, $NaBH_4$ serves as a suitable reducing agent, as **79** and **80** are separable via flash chromatography. The stereochemical configurations of diols **79** and **80** were determined by ^{13}C NMR analysis[39] of the derivative acetonides **81** and **82**. The synthesis of aldehyde **85** was accomplished in a two-step procedure. Commercially available ethyl-2-bromobenzoate **83** and allyltributyltin were coupled under Stille conditions[40] to yield **84** in 85% yield, and subsequent ozonolysis produced aldehyde **85** (65%).

With the configuration of the diols confirmed and aldehyde **85** in hand, acetal **87** (Figure 21) was assembled via the Noyori protocol in 90% yield.[38] The diastereomeric cyclization substrates **94** and **95** have the (13,15-*anti*-) configuration, and were available through propargylation of *anti*-acetal **87** to give **88** and **89** as a 55:45 mixture of diastereomers (70% chemical yield). Ester hydrolysis yielded *seco*-acids **90** and **91** (91% yield), and lactonization

according to the Yamaguchi[41] protocol yielded lactones **92** and **93** in 68% yield, which were separable via flash chromatography. Stereochemical assignments were made by analyzing NOESY correlations of lactones **92** and **93**. Ruthenium-catalyzed enol acetate formation[42] provided **94** (57%)and **95** (51%).

The (9,13-*syn*-, 13,15-*syn*-) diastereomer **101** was available through the *syn*-acetal **97** (Figure 22). The acetal-opening of the *syn*-acetal proceeded to **98** with excellent stereoselectivity; only one isomer, assigned by analogy to literature precedent[43] (see also Figure 19) as the (9,13-*syn*-) stereoisomer was observed in 70% yield. Hydrolysis of the ester led to *seco*-acid **99** (98%), and Yamaguchi lactonization[41] formed lactone **100** (35%). Enol acetate formation conditions[42] secured cyclization substrate **101** in 35% yield.

The synthesis of cyclization substrate **106** required special attention. The necessary (13,15-*syn*, 9,13-*anti*) relative stereochemical configuration was not available through propargylation[44] of **97**, as the only isomer of the product observed had the (9,13-*syn*, 13,15-*syn*) relationship. Thus, the synthesis of **106** (Figure 23) had to proceed through the *anti*- acetal **87**, and a Mitsunobu inversion was implemented later to establish the correct configuration at C15, confirmed by analysis NOESY correlations of lactone **105**.

2.2.2 Conclusions from Preliminary ETIC Studies

When the test cyclization substrates were subjected to ETIC conditions, none of them led to any of the desired product. We observed no fragmentation of the benzylic C–C bonds, and the major isolate when the reactions were conducted at room temperature was unreacted starting material. When the reactions were heated 100 °C or greater, the only changes in the ^{1}H NMR spectra from the starting materials to the isolated products were substitution of the PMB arene, suggesting nitration via a nucleophilic aromatic substitution reaction with nitrate anion as the nucleophile. The only other products observed when the reactions were heated to the point of thermal decomposition were spectrally unrecognizable aliphatic degradation products. These obervations led us to conclude that an oxocarbenium ion may not readily form in the ten-membered lactone of the apicularen core. In order for oxocarbenium ion formation to proceed, two sp^3 atoms in the ring must re-hybridize to sp^2.

It is likely that re-hybridization introduces too much strain to the lactone ring to make ionization feasible.

The sterically demanding dimethyl-*p*-methoxy benzyl substituent on the ten-membered ring is thought to be cumbersome with respect to the conformations the substrate can access, further restricting access to configurations that would allow for fragmentation. In order for a fragmentation event to occur, the lone pair of the oxygen atom must overlap with the σ^* orbital of the benzylic C–C bond[45] (Figure 24). The conformationally restrictive bulk of the quaternary center at the benzylic position likely prohibits certain conformations from being readily accessible. If this sterically large substituent could be replaced with a smaller electroauxiliary, benzylic C–C bond cleavage might be possible to form an oxocarbenium ion in the apicularen core. Tu and Floreancig have since shown that, under certain oxidative conditions, an oxocarbenium ion can indeed be formed in within a macrocycle.[46]

We made an acyclic version of our apicularen model where the lactone had not been established in order to eliminate the ring strain that we hypothesized was preventing oxocarbenium ion formation. The synthesis of an acyclic ETIC substrate (Figure 25) involved acylation of **98** to yield **107**, and subsequent enol acetate formation to yield acyclic cyclization substrate **108**. When subjected to ETIC conditions, **108** underwent smooth cyclization to **109** in 51% yield. A single diastereomer was observed, assigned as the syn-tetrehydropyran by NOESY. Attempted ester hydrolysis was unproductive, causing decomposition of the starting material, illustrating the base-lability of these 4-tetrahydropyrones. With this successful ETIC reaction we could move ahead in our studies, confident in our ability to complete the synthesis. Ring strain concerns likely preclude ETIC directly onto a macrolactone from being viable, but an ETIC reaction will be possible if the lactone has not yet been established in the cyclization substrate.

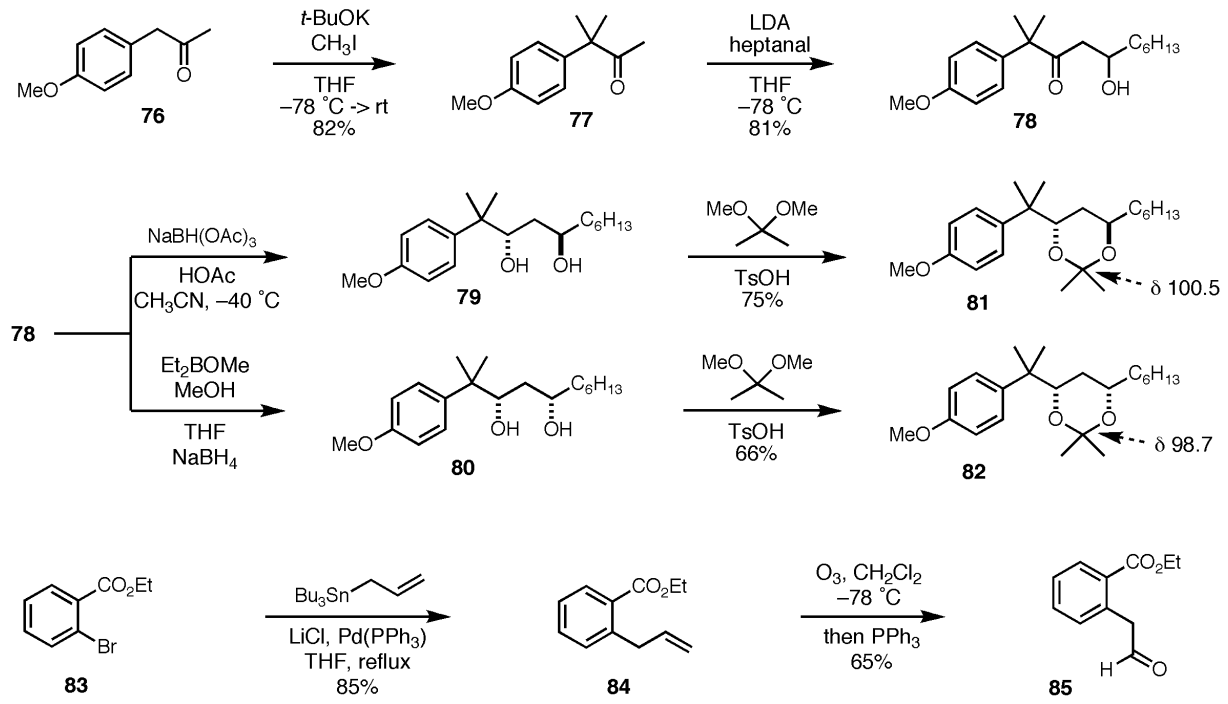


Figure 20: Synthesis of diols **79** and **80** and aldehyde **85**

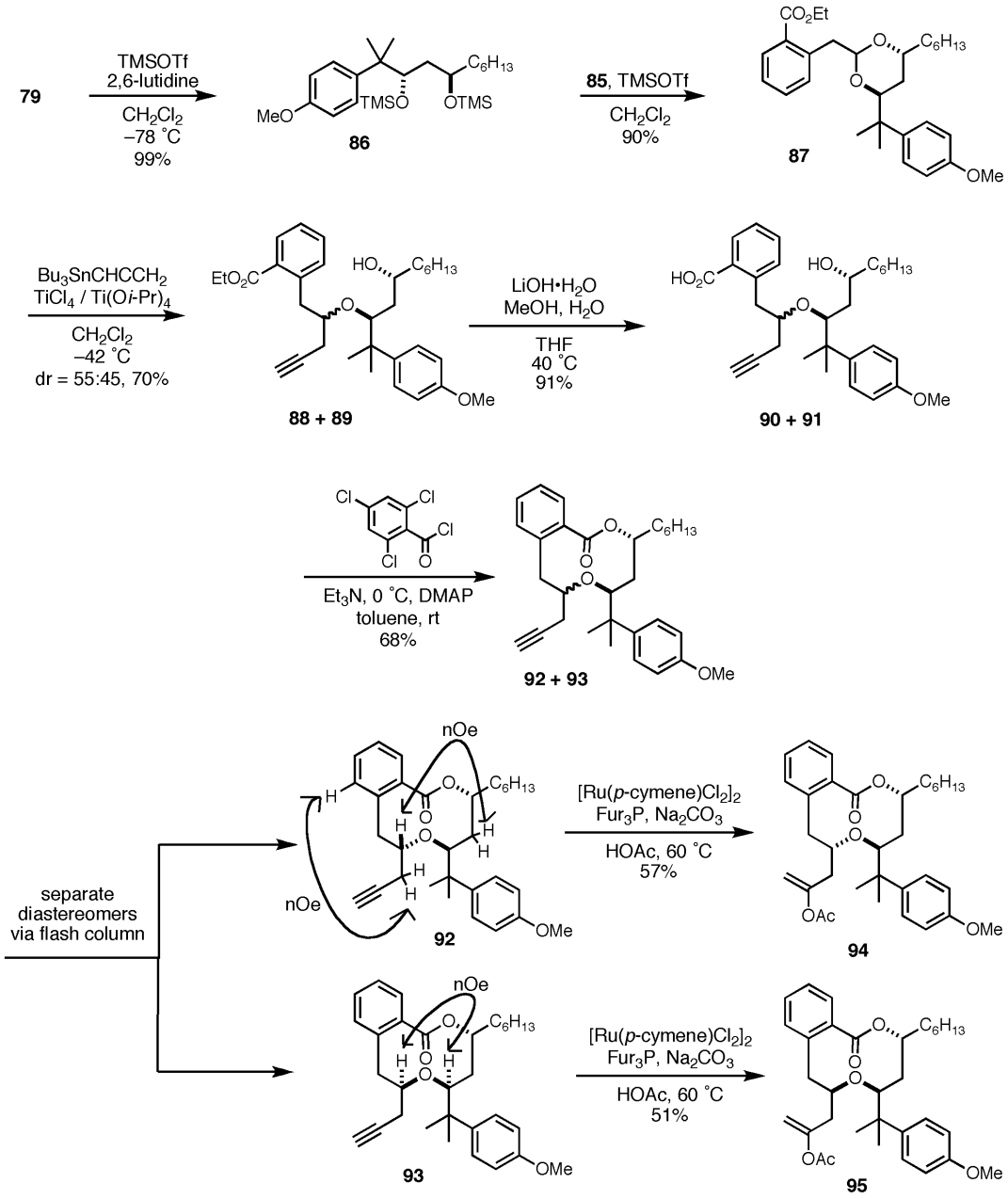


Figure 21: Synthesis of cyclization test substrates **94** and **95**

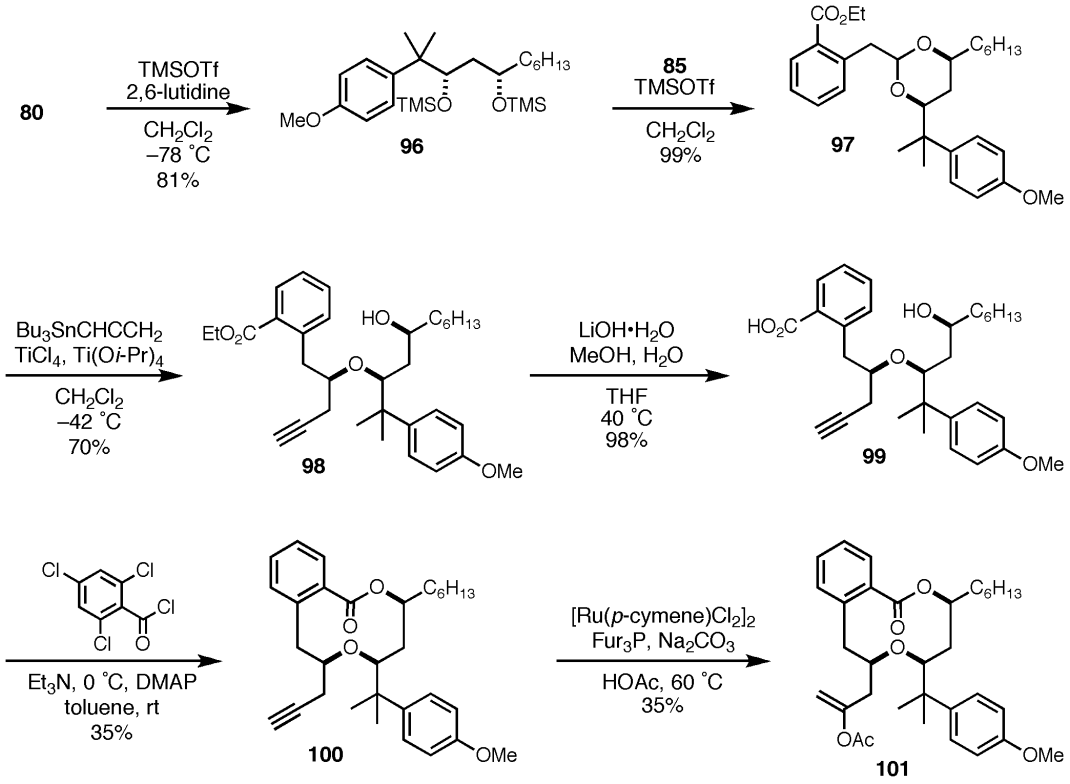


Figure 22: Synthesis of cyclization test substrate **101**

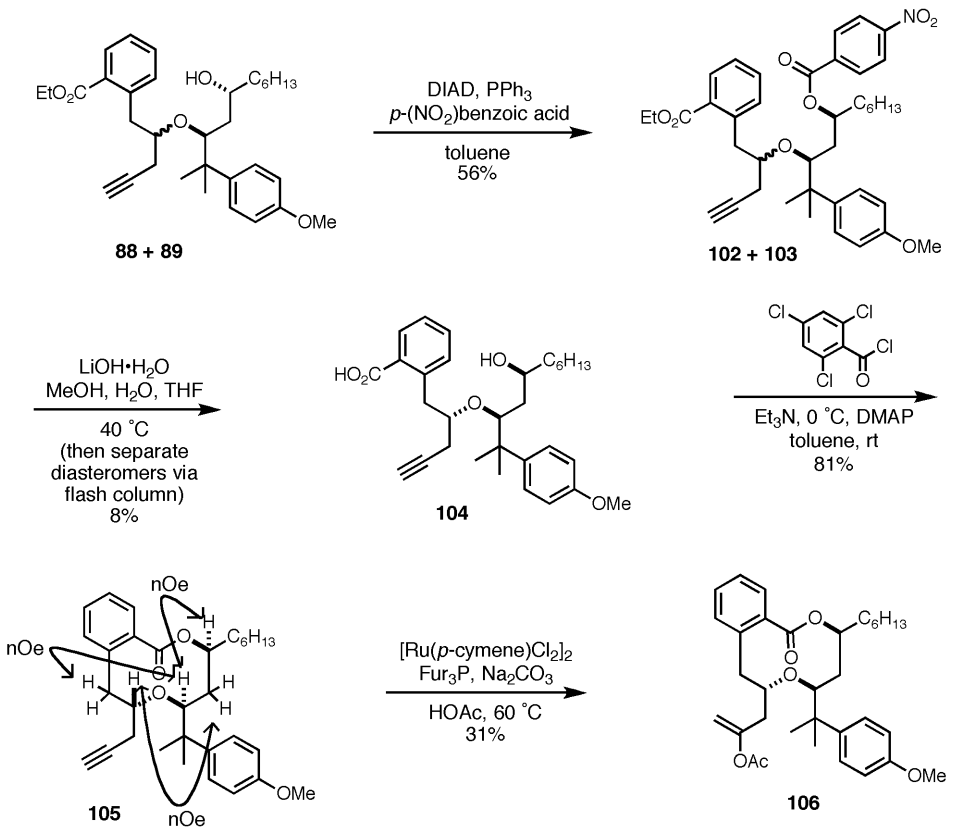


Figure 23: Synthesis of cyclization test substrate **106**

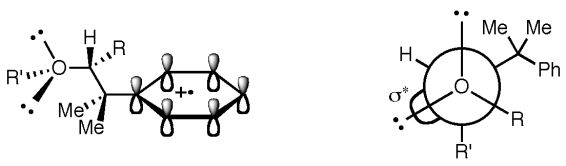


Figure 24: Preferred conformation for radical cation carbon-carbon bond cleavage

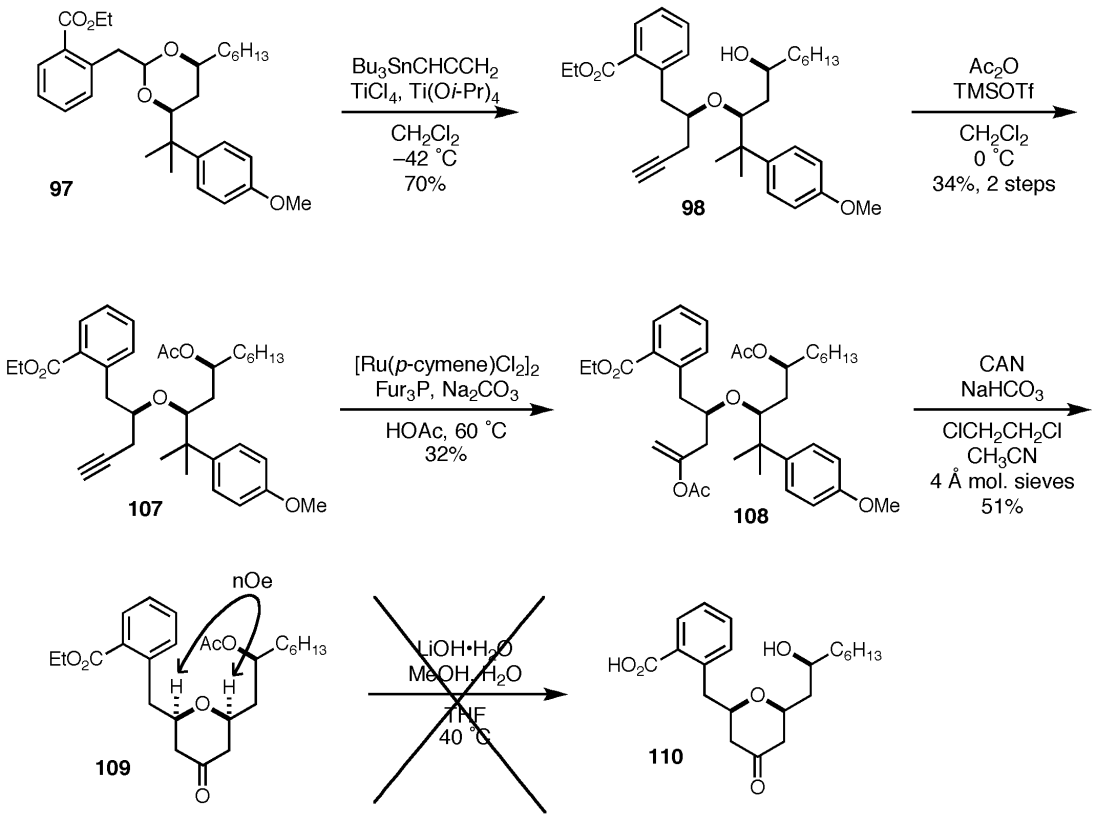


Figure 25: A successful ETIC reaction performed prior to establishing the macrolactone

3.0 CONSTRUCTION OF THE C1-C15 FRAGMENT OF APICULAREN A

3.1 CHALLENGES PRESENTED BY INCORPORATING C3 OXYGENATION

Moving toward a synthesis of apicularen A required the modification of our model system from Chapter 2. Useful intermediates for the purpose of a total synthesis require an oxygen atom at the C3 position. Furthermore, the *n*-hexyl side chain from the model system would have to be elaborated to include a functional handle that would allow us to append the apicularen side chain (or intersect a known synthetic route to arrive at a formal synthesis). Our initial efforts to modify our model system toward apicularen A are shown in Figures 26 and 27. In keeping with our acetal propargylation strategy, we prepared requisite aldehyde **117**. We envisioned introduction of the apicularen side-chain using a vinyl iodide as a functional handle,[31;33] or possibly a functionally equivalent acrylic acid.[27;30] Aldehyde **117** was synthesized (Figure 26) beginning with conversion of (*E*)-methyl but-2-enoate (**111**) to the corresponding silyl ketene acetal[47] **112** in 56% yield. Dimethyl-1,3-acetonedicarboxylate (**113**) was converted to the 1,3-allenedicarboxylate[48] (**114**) in 92% yield. Heating **112** and **114** in refluxing benzene[37] produced arenes **115**/**116** as a mixture of the phenol and methyl ether analogs. Further treatment with base and iodomethane secured **116** (19% over two steps). The low yield was due to incomplete aromatization; by-products were observed wherein annulation had occured, but a lack of aromatic proton peaks in the ^{1} NMR spectra of these side-products indicates that the acetal had not collapsed. Subsequent reduction of the desired arylmethyl carboxylate allowed for isolation of aldehyde **117**.

The *syn* diol **127** was prepared as shown in Figure 27. Synthesis of diol fragment **127** proceeded starting from fluoroanisole **118** and isobutyronitrile (**119**) to yield[49] homobenzylic

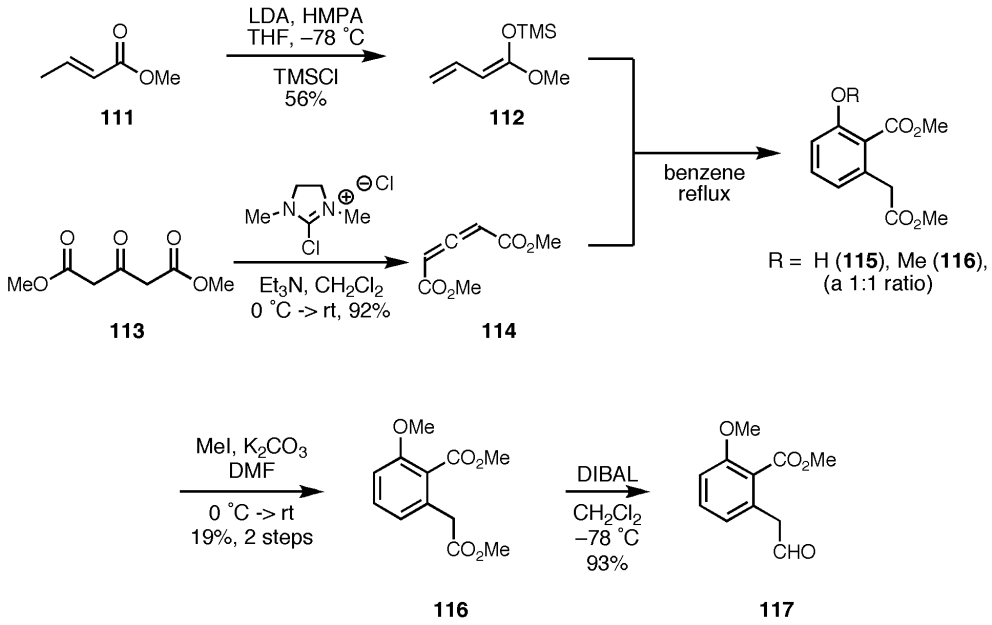


Figure 26: Preparation of aldehyde **117**

nitrile **120** (94%). Reduction and hydrolysis yielded aldehyde **121** (97%), and Grignard addition/acylation provided homoallylic acetate **123** (90%). Treatment of **123** with NBS afforded bromohydrin **124** in 63% yield as a 3:1 mixture of diastereomers (*syn-* to *anti-* confirmed by subsequent epoxidation).

A hydrolytic kinetic resolution was performed on scalemic **134** and **125** (prepared by a Leighton asymmetric allylation[50] into aldehyde **121**) to confirm the *syn-* configuration of the compound. As seen in (Figure 28), homoallylic alcohol **122** was epoxidized using achiral mCPBA, and the result was a mixture of epoxides with a dr of 1.5:1, as determined by NMR. After protection of the alcohol as the acetate, the 1.5:1 mixture of diastereomers was subjected to the (*R*, *R*) enantiomer of Jacobsen's salen-cobalt catalyst[51]. The (*R*, *R*) enantiomer of the catalyst is known to hydrolyze epoxides with the same geometry of the (*S*)-epoxide **134**. The observation that the dr had increased to 3:1 (the peaks corresponding the the major isomer were enhanced in the NMR spectrum) means that the diastereomeric mixture was enriched with the *R*-epoxide **125** by removing the *S*-epoxide **134** by selective

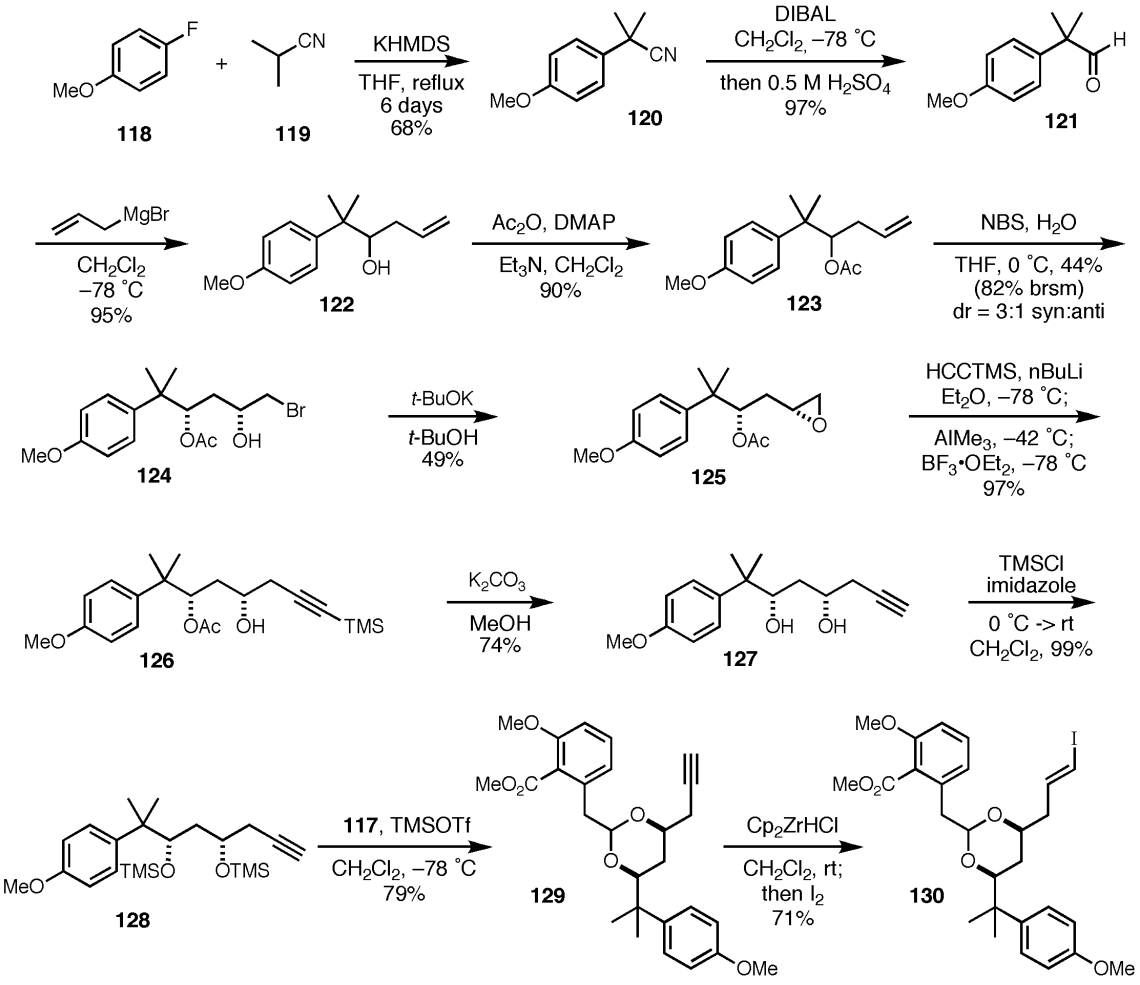


Figure 27: Synthesis of vinyliodide **130**

hydrolysis, confirming the identity of the major diastereomer as **125**.

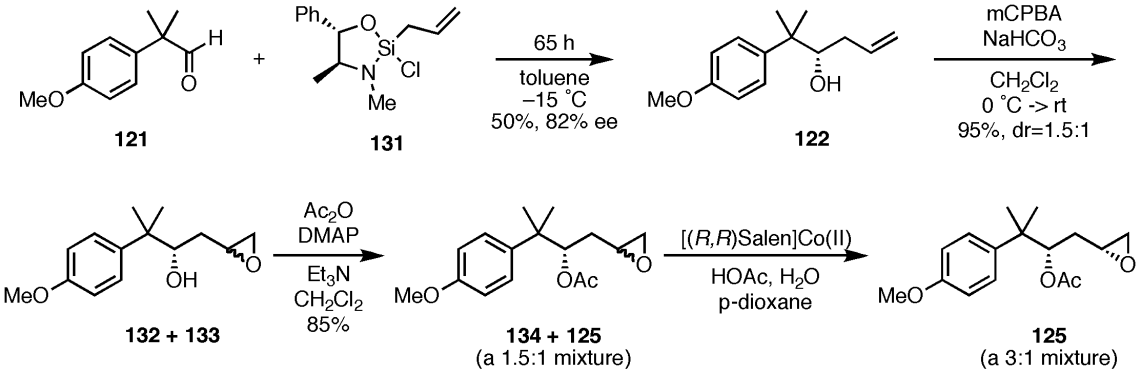


Figure 28: Hydrolytic kinetic resolution as confirmation of stereochemical configuration

Treatment of **124** with an alkoxide base provided epoxy-acetate **125** (49%). Opening the epoxide **125** (Figure 27) with trimethylsilyl acetylene[52] yielded **126** in 97% yield, and basic methanolysis provided diol **127** (74%). With aldehyde **117** and use of the Noyori protocol,[38] acetal **129** was accessed in 79% yield. Hydrozirconation and quenching with iodine[53] resulted in vinyl iodide **130** (71%). When subjected to typical Lewis acidic conditions[43;44;54;55;56;57;58;59] in the presence of allenyltributylstannane, **130** failed to undergo the desired addition reaction to the acetal center, the major isolate being unreacted starting material. Since the significant differences between substrate **130** and **98** are 1) the introduction of the C3 substituent and 2) the modification of the n-hexyl sidechain of **98** to the vinyl iodide sidechain of **130**, and since **98** underwent propargylation while **130** did not, one of these two modifications must be causing the lack of reactivity in the case of **130**.

To investigate whether the substitution at C3 was at fault, we prepared **135**, lacking an oxygen atom at C3. When subjected it to acetal-opening conditions (Figure 29), this analog underwent smooth propargylation to the desired product **136**. This result demostrated that the vinyl iodide was not causing propargylation difficulties in the case of **130**, but rather the presence of the C3 substituent was problematic. The presence of the C3 substituent likely causes a conformational change in the benzonic ester, rotating it out of conjugation with the aromatic ring. Either this conformational change itself is impeding the propargylation reaction, or the change in electronics due to a change in the π-orbital network is somehow

inhibiting formation of a proximal oxocarbenium ion. If we were to continue with our apicularen synthesis, we needed to solve this problem in order to move synthetic material through the reaction sequence.

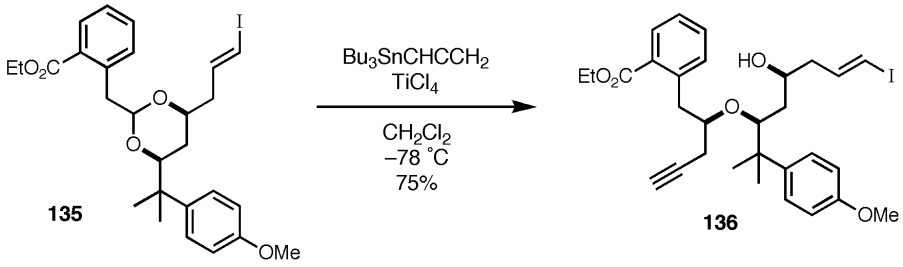


Figure 29: Evidence that substituent at C3 inhibits propargylation

In the course of our studies to investigate the acetal ionization/nucleophilic addition behavior, we arrived at acetal substrate **142**. Lacking a side-chain branch, this acetal is derived from a primary/secondary diol. Our hypothesis was that the lack of a sidechain branch would reduce steric crowding around the reactive acetal center and allow for greater access to the electrophilic site by the allene nucleophile under the reaction conditions. The fact that acetal **142** underwent the desired reaction to yield propargyl derivative **143** represented one of our initial successes in terms of reestablishing the desired propargylation reactivity. If we had been unable to access a doubly-secondary ether moiety, our synthesis would have had to have been abandoned. With **143** in hand, we were able to press forward and investigate downstream reactions and events in the synthetic sequence.

The synthesis of **143** is shown in Figure 30. We adopted Kozikowski's protocol[60] for a *de novo* synthesis of the salicylate arene; this protocol proved more reliable, reproducible, stable to ambient moisture, and higher yielding than the arene synthesis in Figure 26. Using allene 1,3-dicarboxylate **114**[48] as in our previous work, the diene was changed to 3-hydroxy-2-pyrone (**138**), which is available[61] from the potassium bisulfate-mediated double-dehydration-decarboxylation-lactonization of readily available mucic acid (**137**), though the low yield in this process is due to formation of carboxyfuran side-products. When **138** and allene **114** are heated in toluene for 72 hours, the two undergo a formal [4+2] cycloaddition followed by extrusion of CO_2 and isomerization to yield salicylate **115** in 78% yield. Protec-

tion of the phenol as the *p*-toluenesulfonate furnishes **139** in an 87% yield. The tosyl group was chosen to protect the phenol because of its stability[62] to harsh reaction conditions (LAH and pTSA for instance), and the ease of its removal with Mg^0 in methanol.[63] After reduction with one equivalent of DIBAL, aldehyde **140** was isolated (97%).

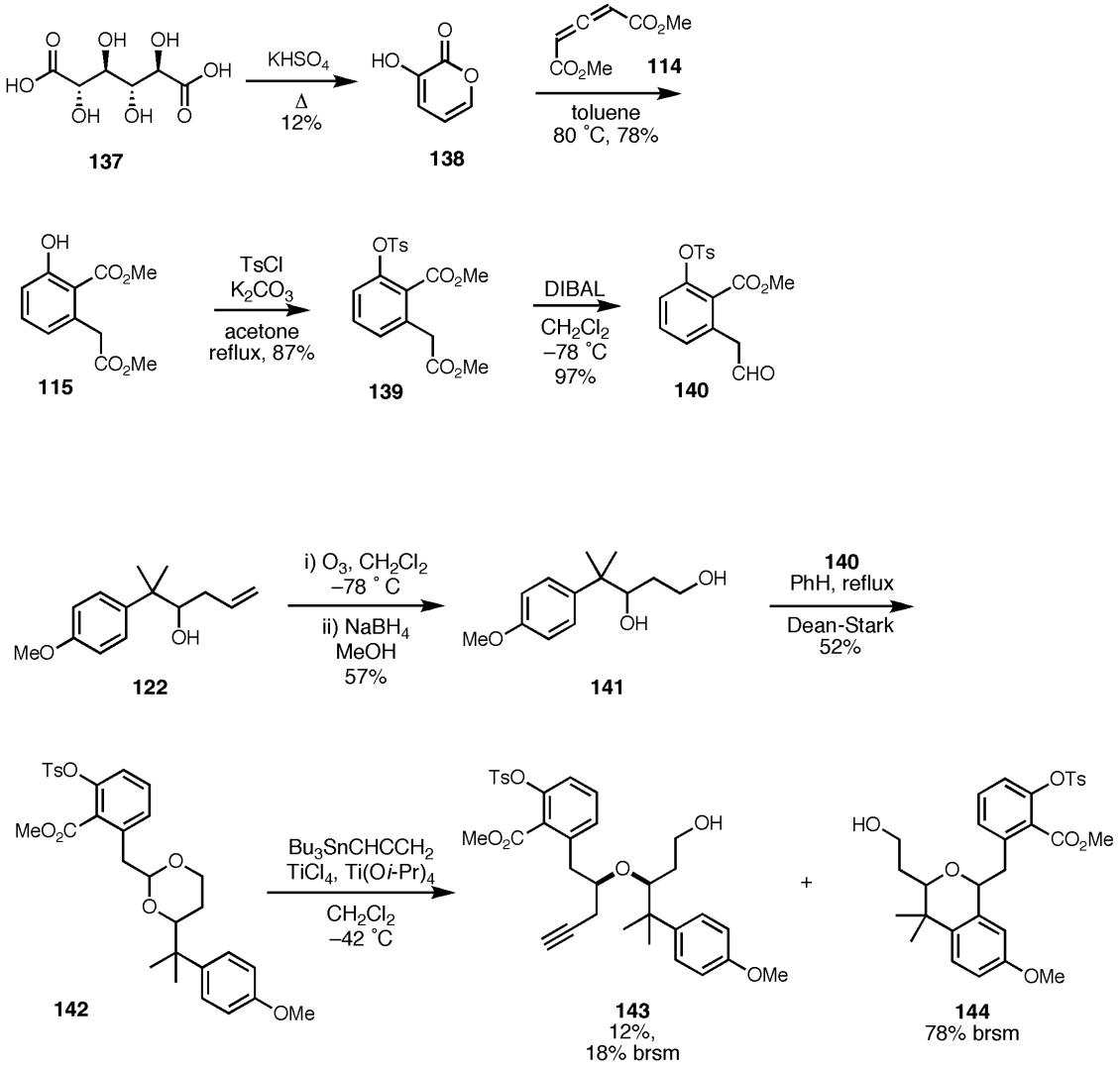


Figure 30: Synthesis and propargylation of acetal **142**

Diol **141** was chosen as a coupling partner for aldehyde **140** because it lacks an alkyl substituent at C15, which allows the Lewis acid greater physical access to the dioxane of the resulting acetal during the subsequent propargylation step. Diol **141** was available from intermediate **122** via ozonolysis and reductive breakdown of the ozonide with $NaBH_4$ (35%).

The formation of an acetal **142** via condensation of diol **141** with aldehyde **140** proceeded in a 52% yield.

When acetal **142** was subjected to acetal-opening conditions (Figure 30), three compounds were isolated: starting material, the Friedel-Crafts product **144** and the desired product **143**. Recovered starting material can be resubjected to the reaction conditions, and successive yields of **143** can be isolated in an iterative fashion. In our most successful experiment, we subjected 3.5 grams of the acetal **142** to the reaction conditions and were able to isolate 450 mg (12% isolated yield) of the desired propargylated product **143** as a single diastereomer. The resulting primary alcohol **143** was oxidized (Figure 31) using the Dess-Martin periodinane[64] to yield the corresponding aldehyde **145** in quantitative yield. This aldehyde presents an opportunity to establish the absolute stereochemical configuration at C15. A zinc-mediated allylation of aldehyde **145** did not provide any diastereoselectivity, and led to secondary alcohols **146** and **147** as a mixture of diastereomers. Subsequent enol acetate formation to **148** + **149** and TBS protection provided **150**, an ETIC substrate. Treatment of **150** with CAN formed cyclized product **151** in a 38% yield, demonstrating the feasibility of an ETIC reaction towards apicularen in the presence of the C3-oxygenated benzoic acid moiety.

In this section I have shown that we were able to overcome difficulties with the acetal propargylation technology as applied to our apicularen system. With a proof-of-concept experiment (**142** -> **143**), we were able to carry on with our synthesis to later-stage intermediates.

3.2 IMPROVED SYNTHESIS OF DOUBLY-SECONDARY ETHERS

Though the desired propargylation process had been reestablished in the case of acetal **142**, further experimentation with acetal-opening conditions was required to improve yields to acceptable levels for practical synthetic study of later-stage synthetic steps. The best results (Figure 32) were obtained using acetal **154**, containing an unprotected phenol, with allenyltrimethylsilane and a pre-cooled Ti-Lewis acid. The preparation of acetal **154**, and the

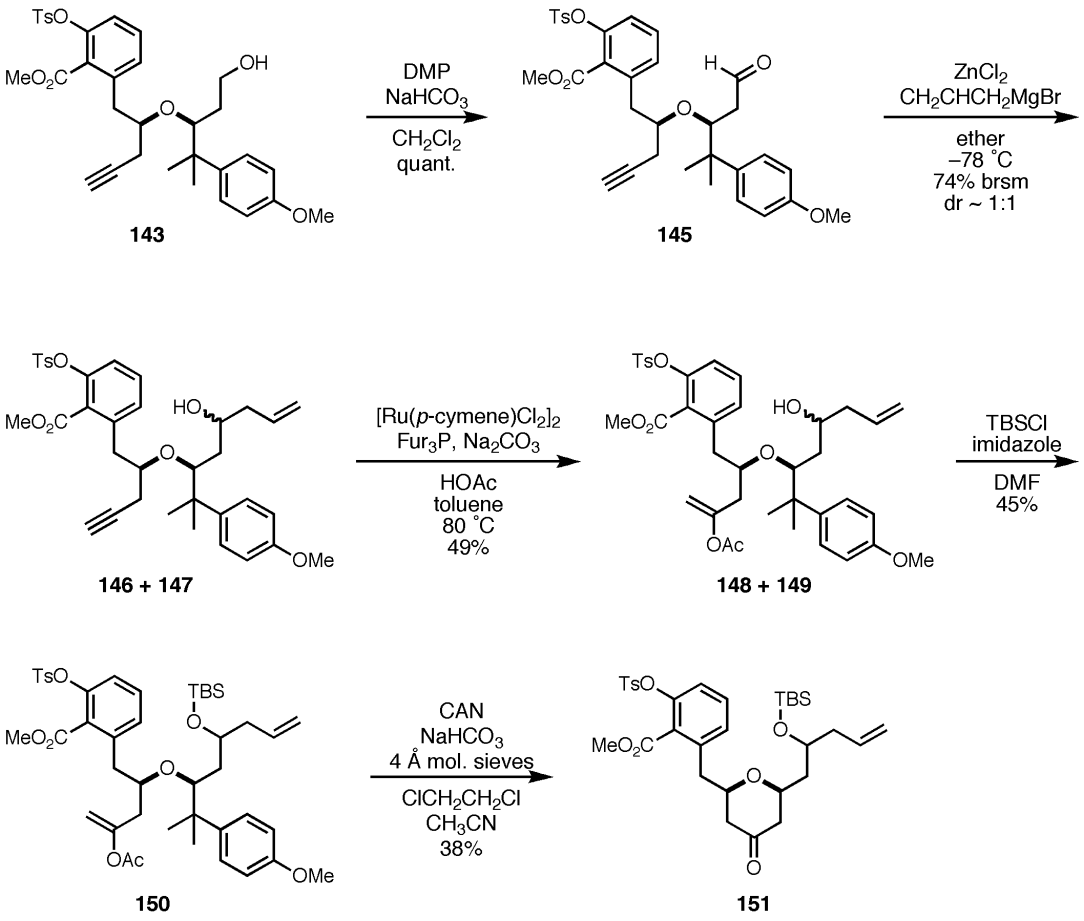


Figure 31: Probing for ETIC feasibility

subsequent application of an ETIC reaction to construct the C1–C15 fragment of apicularen A are shown in Figure 32.

While the yield of the desired doubly-secondary ether was increased to a modest 50%, the diastereomers were obtained in a ratio 6.8:1. Though the diastereomers proved inseparable, this route allowed us to synthesize enough material to investigate the ETIC reaction, and make improvements to those yields as well. This cyclization demonstrates that an ETIC reaction may be performed on a substrate possessing two potentially fragmenting (homobenzylic ether) C−C bonds. Exclusive selectivity was observed for the desired fragmentation to occur, due to differentiated rates of processes that follow the initial single-electron oxidation; the electron rich PMB electroauxiliary possesses substitutions at the benzylic position that weaken the carbon–carbon bond relative to the benzylic carbon–carbon bond of the salicylate. Extra equivalents of CAN and higher reaction temperatures were required for the first time in our group's studies of the ETIC reaction, suggesting a certain amount of reversibility in the initial oxidation step. The route shown in Figure 32 provides high enough yields in the propargylation and ETIC steps to be of practical use in continuing with the synthesis.

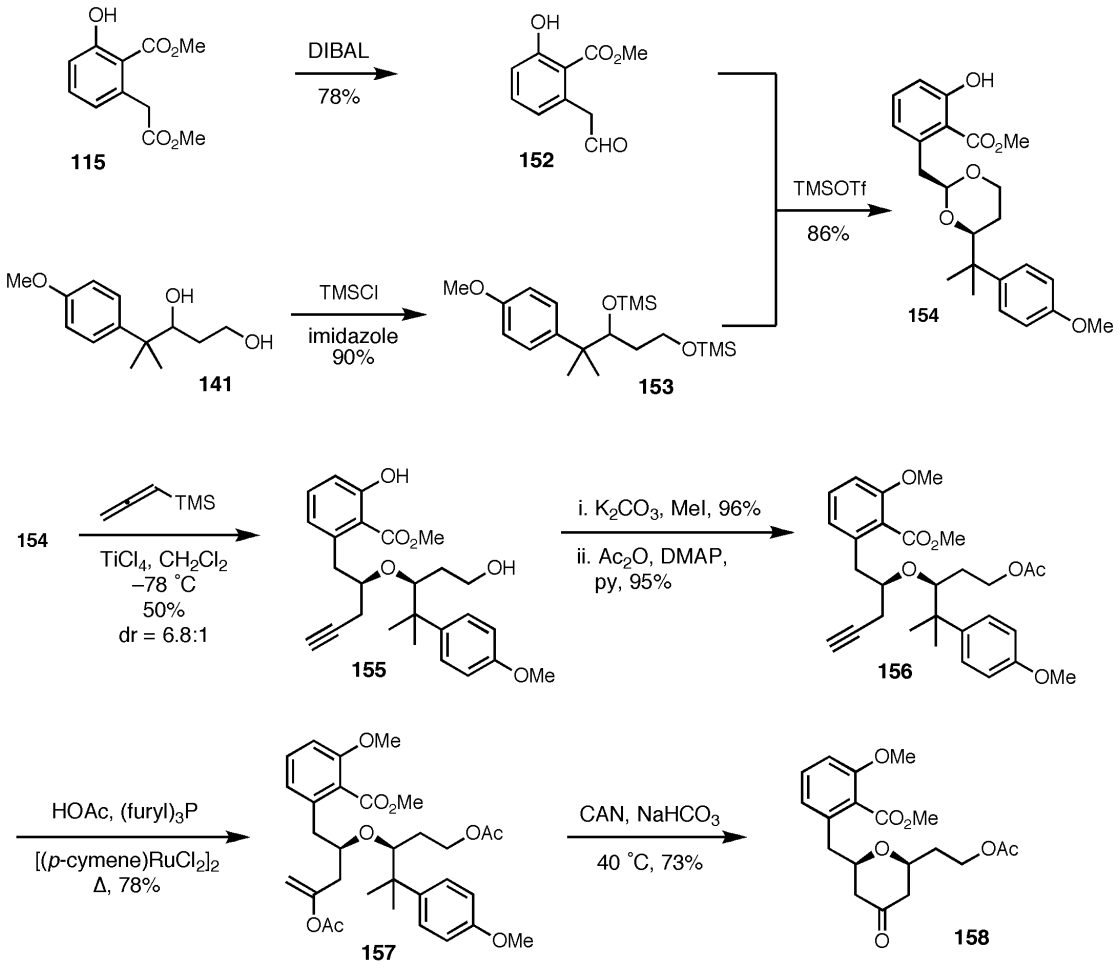


Figure 32: Synthesis of the C1–C15 fragment of apicularen

4.0 PROGRESS TOWARD COMPLETION OF AN APICULAREN SYNTHESIS

4.1 PROGRESS IN ACETAL PROPARGYLATION REACTIONS

One remaining challenge is the macrolactonization step. The protecting group scheme in substrate **158** proved undesirable due to difficulties in hydrolyzing the methyl ester to obtain the derivative carboxylic acid in good yields. The fact that the benzyl ester is doubly-*ortho* substituted likely leads the carbonyl to prefer a conformation orthogonal to the plane of the arene, thereby blocking access to the π^* orbital and inhibiting nucleophilic attack from a pendant alcohol nucleophile. Furthermore, the elaboration of the sidechain from a secondary alcohol to a primary alcohol adds undesirable synthetic steps to the route; more desirable would be to utilize an acetal derived from a doubly-secondary 1,3-diol.

In order to address concerns with the salicylate protecting group scheme, we employed the cyclic acetonide motif (see Figure 33) used by both De Brabander[28] and Nicolaou[31] in their apicularen syntheses. The cyclic acetal forces the ester carbonyl to align with the arene in a coplanar fashion, allowing for greater accessibility for incoming nucleophilic attack and therefore greater ease in eventual lactonization.

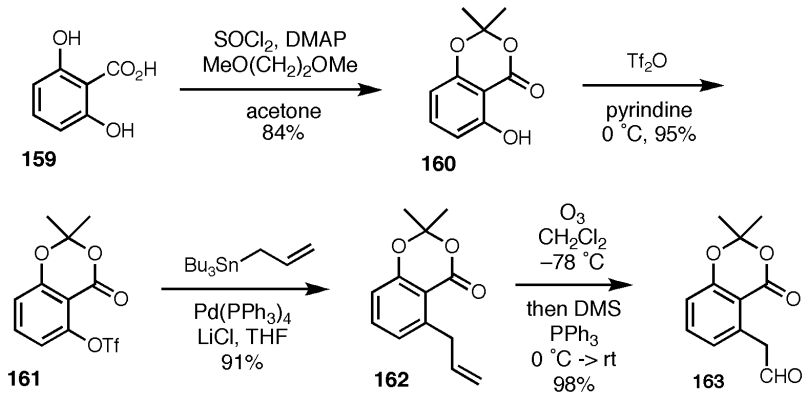


Figure 33: Synthesis of De Brabander's aldehyde **163**

As part of the further evolution of our route to apicularen, we developed conditions for the propargylation of a more complex acetal, the assembly of which is shown in Figures 34 and 35. Alkene **123** was converted to bromohydrins **164** and **124** (99% yield, dr = 3:1, diastereomers separable via flash column). The bromohydrins were converted to epoxides **132** and **133**, which were in turn elaborated to allylic alcohols **165** and **166**. ^{13}C NMR analysis of the derivative acetonides **167** and **168** confirmed the relative stereoconfiguration of both diols.

Syn diol **166** was coupled with aldehyde **163** to provide doubly-branched acetal **170**. The propargylation of **170** to **171** proceeded in a 50% yield, with a dr of 1.01:1. The advantage of this route, however, is the fact that the derivative TBS ethers **173** and **174** were readily separable by typical flash column chromatography. This is significant because separable isomers are available for the first time in our studies toward apicularen, greatly simplifying analysis, characterization and spectral interpretation of intermediates. Additionally, the synthesis of **171** and **172** establishes a doubly-secondary ether with a functional handle required for installation of the apicularen sidechain prior to the point of synthetic convergence, obviating the need to install the sidechain branch subsequent the acetal assembly point of convergence.

In this section, I have shown that we were able to move material through the synthetic sequence in good enough yields to investigate the ETIC reaction thoroughly in the context of our apicularen synthesis. Furthermore, we could move ahead to later-stage intermediates with ample material available as samples of single diastereomers.

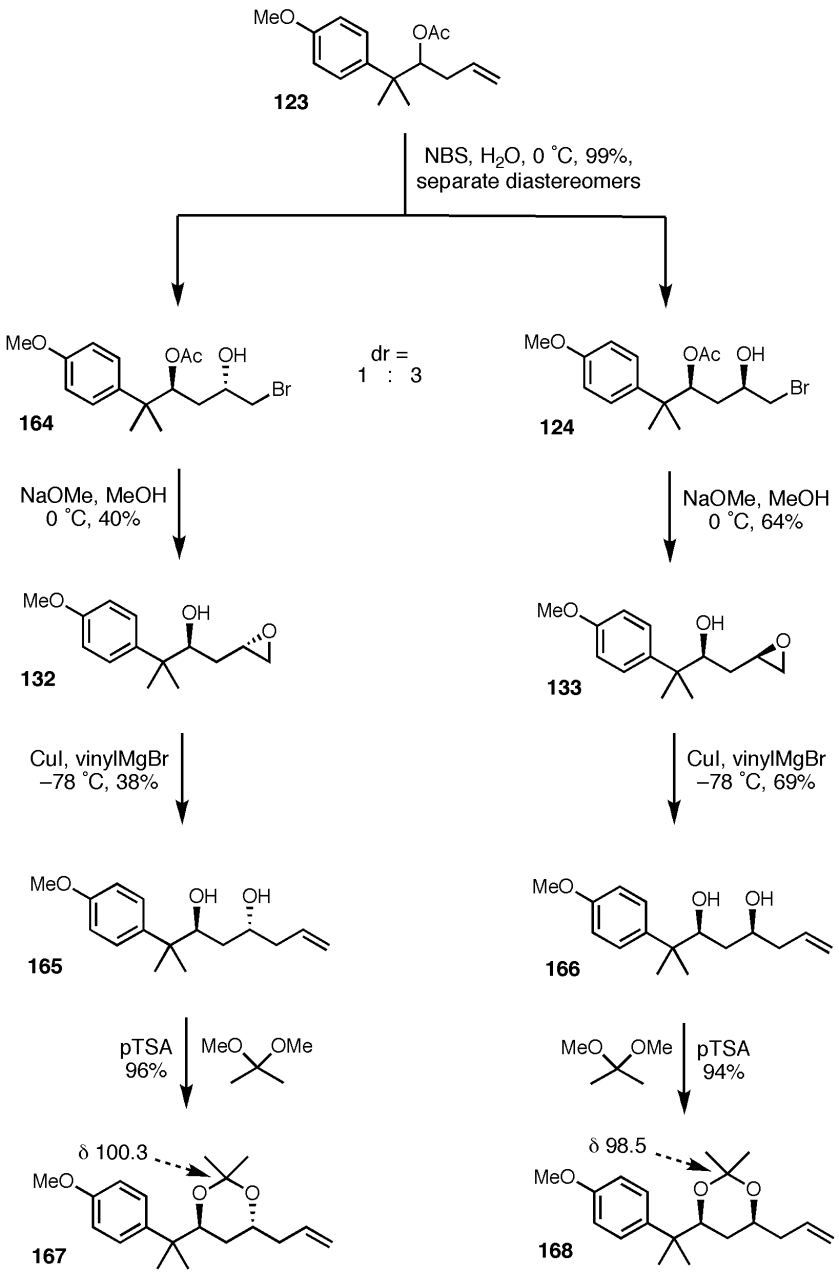


Figure 34: Synthesis of allyl diols **165** and **166**

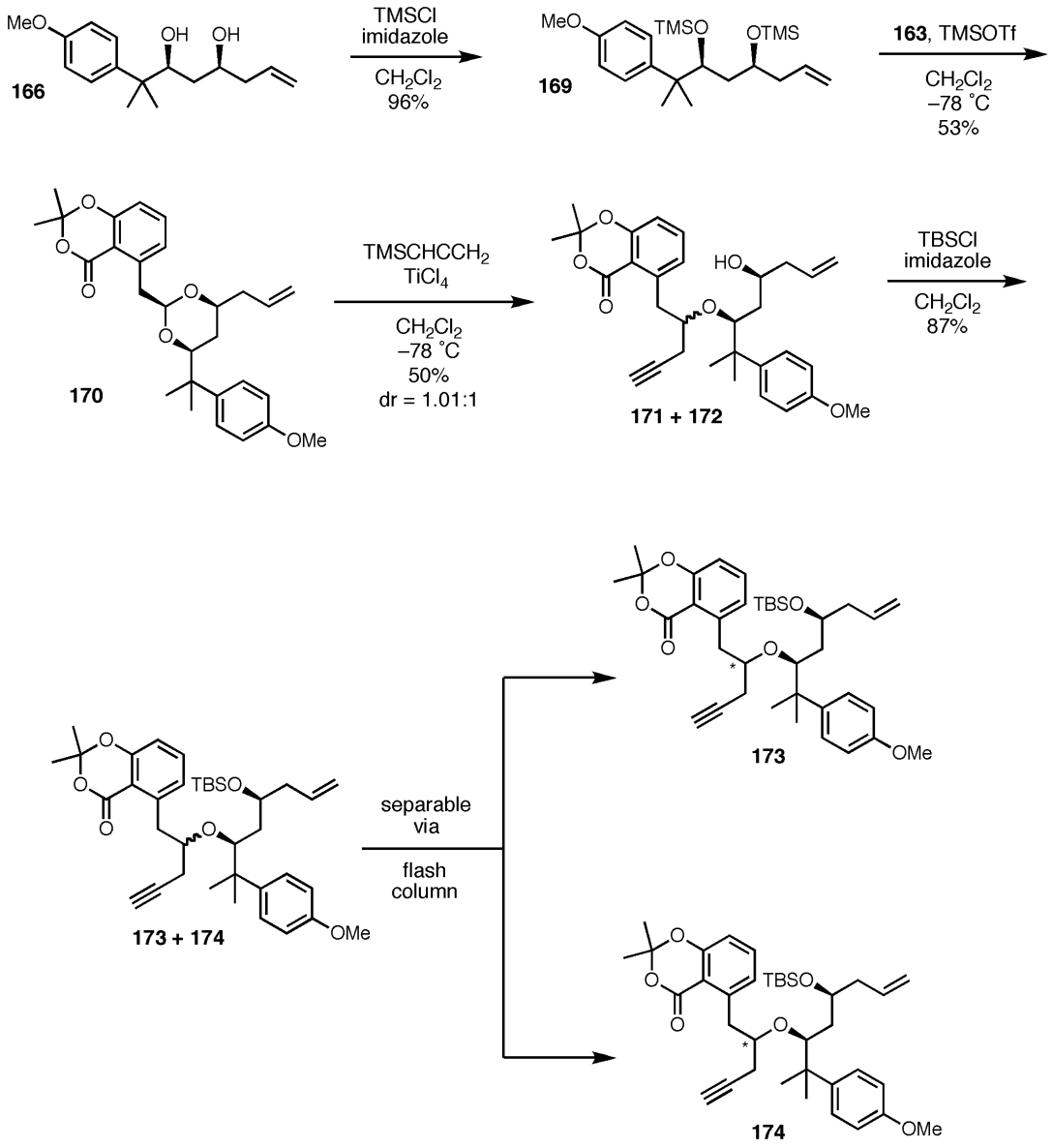


Figure 35: Route to separable doubly-secondary ether diastereomers (asterisks denote unassigned stereocenters)

4.2 LACTONIZATION STUDIES

The TBS ethers **173** and **174** were separated via flash chromatography and advanced through the synthetic scheme independently. The alkynes were converted to the enol acetates **175** and **177**, respectively (Figure 36). Both diastereomers of the enol acetate underwent ETIC processes to produce **177** and **178**, and the silyl groups were removed to yield free alcohols **179** and **180**. Despite the fact that we're dealing with two diastereomers due to the virtually nonexistent diastereoselectivity of the propargylation of acetal **170**, it is desirable to carry both diastereomers towards the macrolactone stage, based on the hypothesis that the relative stereochemical configuration of **179** and **180** will eventually be established by straightforward NOESY analysis of the derivative 10-membered lactones. According to Rizzacasa's studies,[34] the desired lactones **183** and **184** are convertible to the thermodynamically more stable (9,13-anti 13,15-syn) configuration of the natural product.

The macrolactonization step remains an active research problem. Treatment of lactonization substrates **179** and **180** with NaH in THF (in analogy to De Brabander and Nicolaou's strategies) did not yield the desired macrolactones **183** and **184**, but rather two undesired side-product lactones, the spectral data of which are consistent with structural assignments corresponding to **181** and **182**. This proposed structure is consistent with NMR data gathered, and the six-membered lactones are likely formed through opportunistic oxygen present in the basic reaction media. A proposed possible mechanism for the formation of this undesired product is shown in Figure 37. Alkoxide formation could lead to deprotonation of the proximal α-hydrogen, producing an enolate that could attack ambient atmospheric oxygen. In the basic reaction medium, the resulting α-peroxy ketone could be deprotonated to effect elimination of water. Liberated hydroxide is possibly the nucleophile that cleaves the dimethyl acetal and produces the carboxylate. At this stage, a possible intramolecular S_N2 process is invoked, due to the fact that stereochemical integrity of the starting materials was preserved in the products. That is, since **179** and **180** were subjected to the reaction conditions independently, and since the observed products were also distinguishably different diastereomers by NMR, a stereospecific rather than stereoselective lactonization event is postulated. The alternative rupture of the cyclic ether by elimination following deprontona-

tion of an α-hydrogen seems less likely, as this type of process would lead to diastereomeric scrambling. The depicted 6-*exo* cyclization was chosen rather than the presumably competitive 5-*exo* cyclization based on the fact that under these conditions, the reaction should be reversible, and the six membered ring is presumed to be thermodynamically preferred to the more strained 5-membered ring product.

4.3 VISION FOR COMPLETION OF THE SYNTHESIS

4.3.1 Macrolactonization

My hypothesis is that the lactonization of **179** and **180** will proceed in the absence of oxygen. The lactonization experiments should be repeated under rigorously deoxygenated conditions. A secondary possibility is to either reduce or otherwise suitably protect the ketones **179** and **180** and proceed with the macrolactonizations at the tetrahydropyran oxidation state. The tetrahydropyrans could be re-oxidized subsequent to lactonization in an effort to apply Rizzacasa's acid catalyzed epimerization at the ketone oxidation state.

4.3.2 Proposed Epimerization Under Acidic Conditions

Macrolactones **75** and **185** with the tetrahydropyrone oxidation state are desirable targets, as they are the closest analogies to Rizzacasa's epimerization[34] which is postulated to arrive at the thermodynamically most stable configuration based on the reversibility of Michael/retro-Michael additions under the reaction conditions (Figure 38). Alcohols **179** and **180** could be independently carried forward to macrolactone **183, 184** (Figure 39) under rigorously deoxygenated conditions, and the phenol could be protected as the methyl ethers (**75** and **185**). Based on Rizzacasa's acid-promoted epimerization, I hypothesize that intermediates **75** and **185** will undergo the same thermodynamically controlled equilibration to arrive at **54**, completing a formal synthesis of apicularen A.

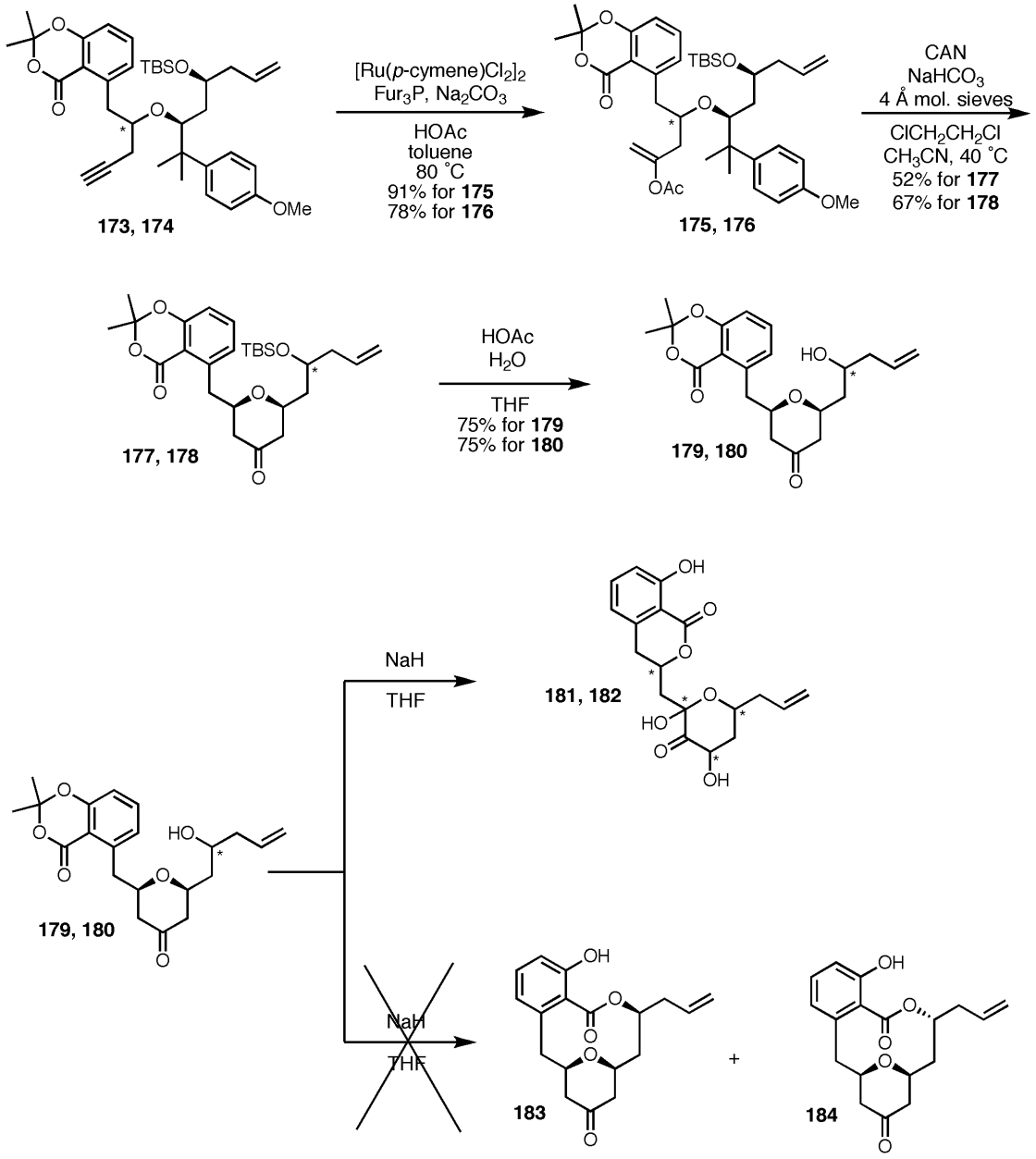


Figure 36: Undesired products from lactonization (asterisk indicates unassigned stereocenter)

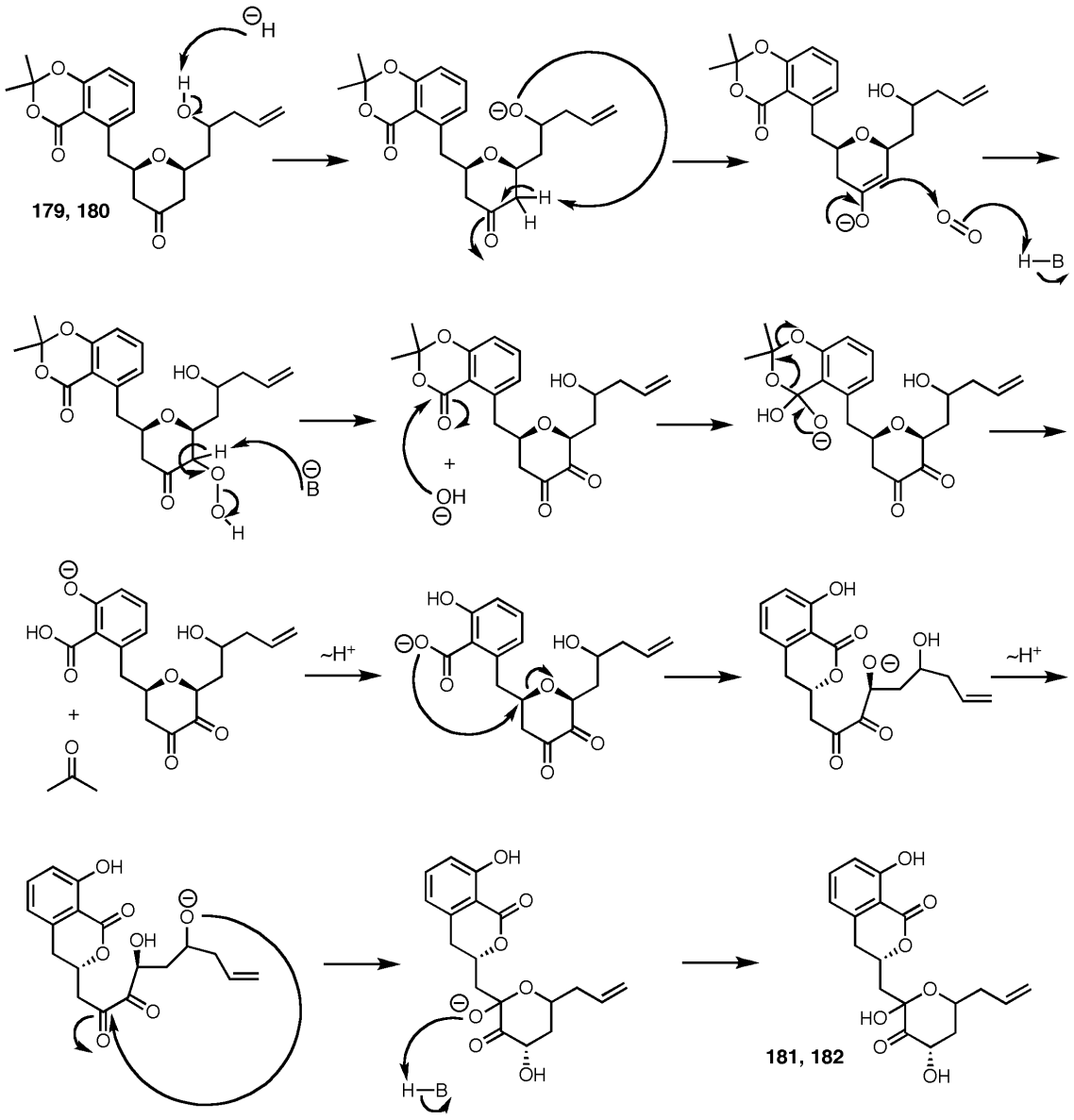


Figure 37: Proposed mechanism for formation of **181** and **182**

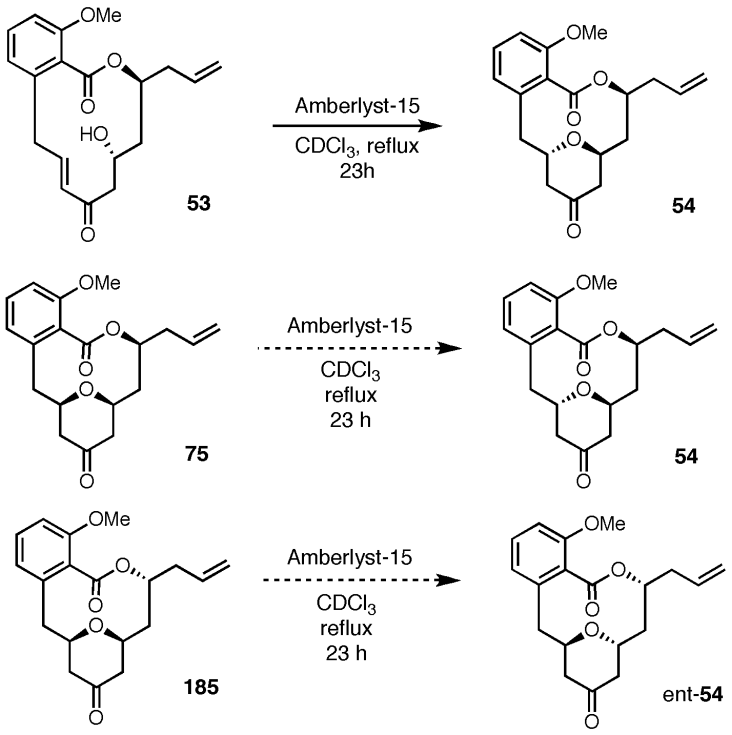


Figure 38: Proposed epimerizations based on Rizzacasa's observation

4.3.3 Proposed Epimerization Under Basic Conditions

Tetrahydropyrans **186** and **188** may be epimerizable under basic conditions (Figure 40) based on observations by O'Doherty.[36] My hypothesis is that intermediates **177** and **178** could be carried on independently through the synthetic sequence shown in Figure 41. Tetrahydropyrones **177** and **178** could be reduced to the corresponding hydroxy-tetrahydropyrans **189** and **190** by way of axial hydride delivery using L-selectride. The secondary alcohols could be protected as benzyl ethers (the benzyl group chosen to intersect Panek's route), and the TBS group removed to access **193** and **194**. Macrolactonization promoted by sodium hydride should proceed smoothly to yield **195** and **196**, as there are no longer acidic α-hydrogens present in the lactonization substrates as there were in Figure 36. The free phenol could be converted to the MOM ether (also chosen to accomodate intersection with Panek's route) to produce **197** and **198**, substrates to test the hypothesis that an O'Doherty-type epimeriza-

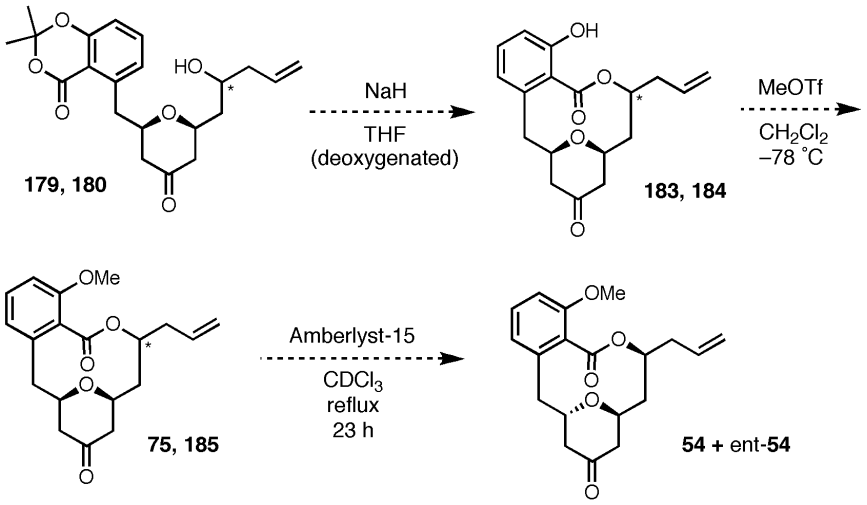


Figure 39: Proposed completion of a formal synthesis (epimerization under acidic conditions)

tion will lead to **49**, and complete a formal synthesis of apicularen A.

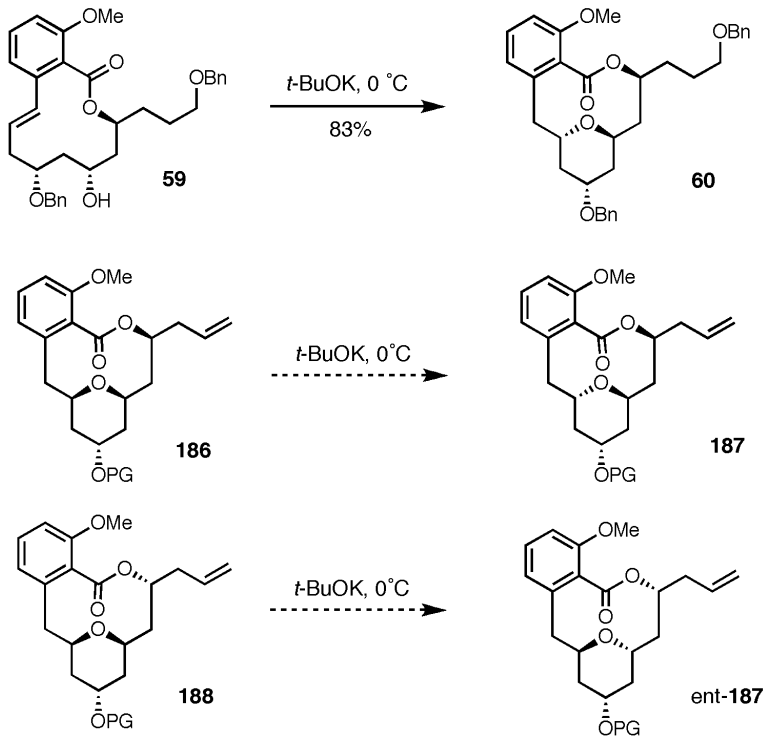


Figure 40: Proposed epimerizations based on O'Doherty's observation

4.3.4 Conclusion

An ETIC reaction has been successfully applied to access late-stage intermediates in the context of an effort towards apicularen A. Epimers **179** and **180** represent the most advanced intermediates synthesized. There remain two synthetic challenges to address before a formal synthesis can be acheived: 1) effecting macrolactonization, and 2) conducting a successful epimerization of either **75** and **185** to **54** under acidic conditions, or of **197** and **198** to **49** under basic conditions.

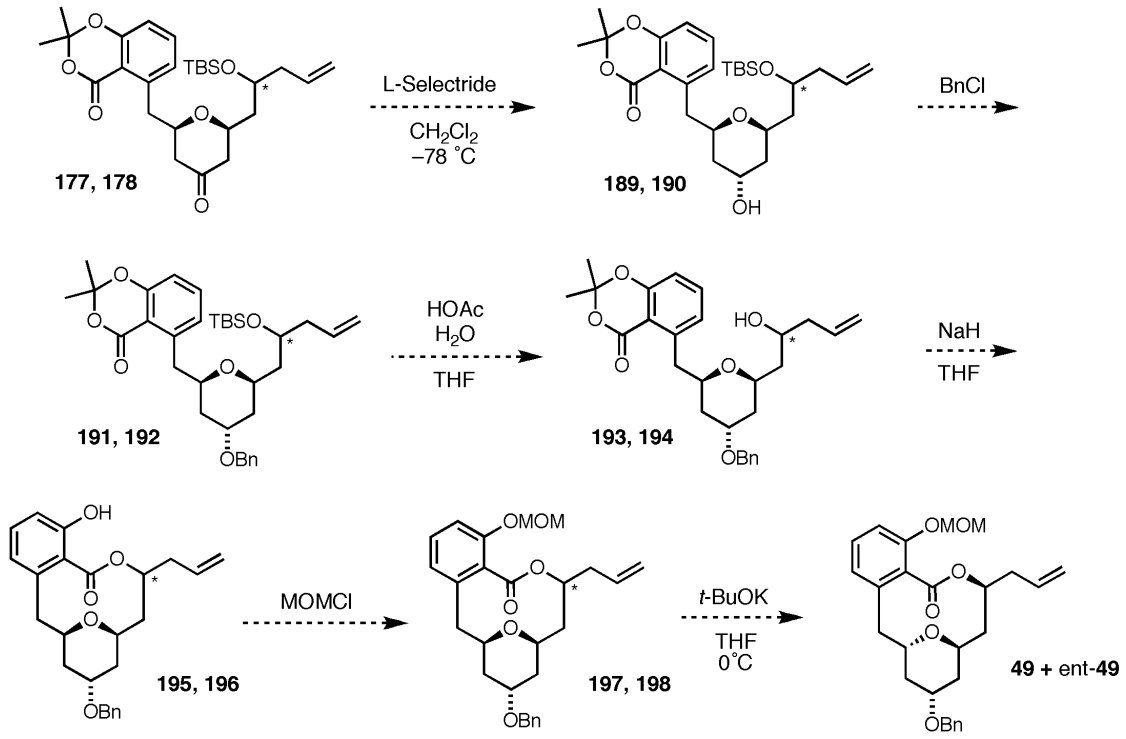


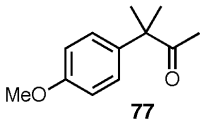
Figure 41: Proposed completion of a formal synthesis (epimerization under basic conditions)

APPENDIX A

EXPERIMENTAL PROCEDURES SUPPLEMENT TO CHAPTER 2

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometers (300 MHz and 75 MHz, respectively), and Bruker Avance 500 spectrometers (500 MHz and 125 MHz, respectively). The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as reference value. For ^{1}H NMR: $CDCl_3$ = 7.27 ppm. For ^{13}C NMR: $CDCl_3$ = 77.36 ppm. For proton data: app = apparent; br = broad; s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublets; ddt = doublet of doublet of triplets; ddq = doublet of doublet of quartets; qd = quartet of doublets; m = multiplet. High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on NaCl plates. Analytical thin layer chromatography (TLC) was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash column chromatography was performed using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, hexanes (commercial mixture), ether, dichloromethane, benzene, acetone, and toluene were purchased from EM Science and used as is for chromatography. Reagent grade methylene chloride (CH_2Cl_2) and 1,2-dichloroethane (DCE) were distilled from CaH_2 under N_2. Diethyl ether (Et_2O) was dried by passage through an aluminum drying column. THF was dried by passage through an aluminum drying column, except where noted. In these cases THF, was distilled from sodium

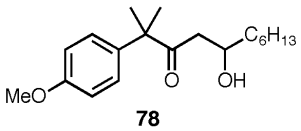
benzophenone under N_2. Anhydrous methanol (MeOH) was purchased from Aldrich and used as is. All reactions were conducted under argon or nitrogen atmosphere, in oven or flame dried glassware with magnetic stirring except were noted.



77

3-(4-Methoxyphenyl)-3-methylbutan-2-one (77)

(*Previously reported compound*[65]) To 1-(4-Methoxyphenyl)propan-2-one **(76)** (Aldrich chemical company, 10.0 g, 60.8 mmol) in THF (100 mL) at −78 °C was added iodomethane (19.0 g, 8.35 mL, 133.8 mmol). Potassium tert-butoxide (15.0 g, 133.8 mmol) was added portion-wise and the temperature was maintained at −78 °C for 30 min. The reaction warmed to room temperature and stirred for 14 hours. The reaction was quenched at 0 °C with saturated ammonium chloride (100 mL), extracted with EtOAc (3x 50 mL), washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a crude orange oil. The oil was distilled (2 torr, 98 °C) to yield the title compound as a light yellow oil (10.17 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H), 1.91 (s, 3H), 1.46 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 158.8, 136.4, 127.3, 114.4, 76.9, 55.5, 52.0, 25.5; IR (neat) 2973, 1707, 1513, 1253, 1184, 1126, 1034, 834 cm^{-1};

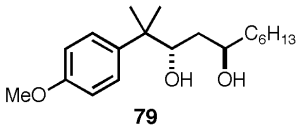


78

5-Hydroxy-2-(4-methoxyphenyl)-2-methylundecan-3-one (78).

To a solution of diisopropyl amine (6.04 g, 8.36 mL, 59.7 mmol) in 60 mL THF at 0 °C was added *n*-butyl lithium (1.6 M in hexanes, 34.19 mL, 54.7 mmol) dropwise. The solution stirred for 10 minutes then was cooled to −78 °C. To the solution of LDA at −78 °C was added ketone **77** (9.56 g, 49.7 mmol) in 40 mL THF as a slow drip. The reaction stirred at −78 °C for 45 minutes, then was quenched at 0 °C with saturated ammonium chloride (40 mL), extracted with EtOAc (3 x 40 mL). The combined organics were washed with 1 M HCl (100 mL), then brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound as an orange oil (14.89 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 3.85 (m, 1H), 3.80 (s, 3H), 3.06 (br s, 1H), 2.42 (dd, J = 17.4, 2.7 Hz, 1H), 2.27 (dd, J = 17.4, 8.7 Hz, 1H), 1.48 (s, 3H), 1.46 (s, 3H), 1.21 (br m, 10H), 0.85

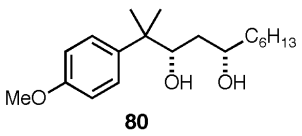
(dd, J = 6.9, 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 158.9, 135.8, 127.5, 114.5, 76.9, 68.6, 55.5, 52.0, 44.0, 36.7, 32.1, 29.5, 25.7, 25.6, 22.9, 14.4; IR (neat) 3500, 2930, 2857, 1704, 1513, 1464, 1301, 1253, 1184, 1035, 833 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{30}O_3$ (M^+) 306.2195, found 306.2244.



79

(3*S,5*R**)-2-(4-Methoxyphenyl)-2-methylundecane-3,5-diol (79).**

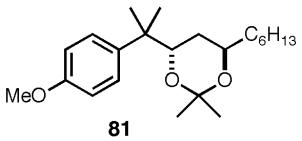
To a solution of β-hydroxyketone **78** (12.0 g, 39.16 mmol) in CH_3CN (65 mL) at -40 °C was added a solution of sodium triacetoxyborohydride (41.5 g, 195.82 mmol in 130 mL 1:1 CH_3CN:acetic acid) as a slow drip. The reaction stirred at -40 °C for 48 hours then warmed to 0 °C in a large ice bath. The ice was then allowed to melt as the reaction warmed to room temperature and stirred for an additional 24 hours. The reaction was quenched with 100 mL H_2O, then carefully with solid $NaHCO_3$. The contents were extracted with EtOAc (3x 100 mL), and the combined organics were washed with saturated $NaHCO_3$ (100 mL). The organic solvent was removed under reduced pressure and the oil that remained was suspended in ether (100 mL) and stirred with a 1:1 solution of 30% H_2O_2 : pH = 7 buffer (100 mL) for 2 hours at which time the aqueous layer had turned cloudy. The contents were extracted with EtOAc (3x 50 mL), and the combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (SiO_2, 20% EtOAc in hexanes eluent) to yield a sample that consisted of both "syn" and "anti" stereoisomers of the desired product (5.85 g) and a second sample that was the desired "anti" isomer (3.99 g, 33%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 3.96 (dd, J = 3.3, 3.2 Hz, 1H), 3.81 (s, 3H), 2.7 (br s, 1H), 2.07 (d, J = 11.7 Hz, 1H), 1.47 (m, 6H), 1.36 (m, 13H), 0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 139.3, 127.9, 113.8, 76.1, 69.9, 55.5, 41.9, 37.5, 32.1, 29.6, 26.2, 24.2, 22.9, 14.4;



80

(3*S,5*S**)-2-(4-Methoxyphenyl)-2-methylundecane-3,5-diol (80).**

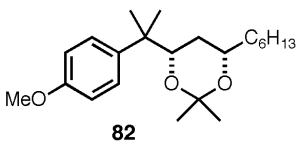
To a solution of β-hydroxyketone **78** (6.19 g, 20.2 mmol) in 100 mL THF at -78 °C was added diethylmethoxyborane (2.63 g, 26.26 mmol) dropwise, followed by MeOH (1 mL). The mixture stirred for 45 minutes at -78 °C, then sodium borohydride (2.29 g, 60.6 mmol) was added slowly. The reaction stirred for 2 hours at -78 °C, then was quenched with a 1:1:1 solution of MeOH : 30% H_2O_2 : 10% NaOH (90 mL) and was stirred vigorously at room temperature for 1 hour. The contents were extracted with EtOAc (3x 50 mL), and the combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was purified via flash column chromatograhpy (20% EtOAc in hexanes eluent) to yield a sample of both stereoisomers (2.30 g) and a sample of the desired "syn" isomer (1.81 g, 29%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 4.00 (m, 1H), 3.88 (m, 1H), 3.80 (s, 3H), 1.48 (m, 2H), 1.38 (s, 3H), 1.34 (s, 3H), 1.28 (br m, 10H), 0.884 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 138.4, 127.9, 113.5, 80.2, 72.9, 55.4, 41.3, 37.6, 33.8, 32.0, 29.4, 25.3, 22.9, 22.5, 14.3;



81

(4*R,6*S**)-4-Hexyl-6-(2-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane (81).**

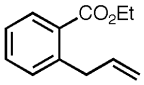
To a stirring solution of diol **79** (50 mg, 130 μmol in 2,2-dimethoxypropane (2 mL) was added a catalytic amount of tosic acid. The reaction stirred at ambient temperature for 17 hours, then was quenched with triethylamine. Contents were poured into a separatory funnel containing water and extracted thrice with EtOAc, and the combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting crude oil was purified via flash chromatography (20% EtOAc in hexanes as eluent) to yield the title compound (34 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 3.81 (m, 4H), 3.52 (m, 1H), 1.29 (br m, 24H), 0.9 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 139.3, 128.0, 113.4, 100.5, 74.0, 55.5, 40.5, 36.2, 34.6, 32.1, 29.5, 26.2, 25.7, 25.1, 24.5, 23.4, 22.9, 14.4, 5.3;



82

(4*S,6*S**)-4-Hexyl-6-(2-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane (82).**

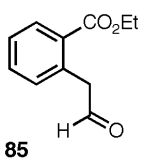
To the diol **80** (50 mg, 130 μmol) in 2,2-dimethoxypropane (2 mL) was added a catalytic amount of tosic acid. The reaction stirred for 11 hours at ambient temperature, then was quenched with triethylamine (500 μL) and poured into a separatory funnel containing 20 mL water. The contents were extracted thrice with EtOAc, and the combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting oil was purified via flash chromatography (20% EtOAc in hexanes as eluent) to yield the title compound (30 mg, 66%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 3.65 (br m, 5H), 1.28 (br m, 19H), 1.03 (m, 2H), 0.84 (br m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 139.5, 128.2, 113.5, 98.7, 69.7, 63.4, 55.5, 40.8, 36.9, 33.2, 32.1, 31.9, 31.2, 30.6, 29.5, 26.2, 25.4, 23.0, 20.0;



84

Ethyl 2-Allylbenzoate (84).

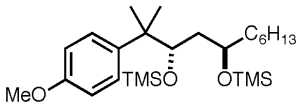
To a slurry of lithium chloride (4.44 g, 104.4 mmol) and $Pd(PPh_3)_4$ (2.02 g, 1.76 mmol) in THF (190 mL) was added ethyl-2-bromobenzoate (**83**). The mixture stirred for 25 minutes, and allyltributyltin (13.87 mL, 45.2 mmol) was added. The reaction was heated to reflux for six hours and quenched with water (80 mL). Contents were extracted thrice with EtOAc. The solvent was removed and replaced with ether. The organics were washed with 10% aqueous KF, and the white precipitate was filtered. The process of washing with 10% KF and filtering was repeated four times. The ether was evaporated *in vacuo*, and the resulting crude yellow oil was purified via flash column chromatography (10% EtOAc in hexanes eluent) to yield the title compound (5.43 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.6 Hz, 1H), 7.44 (td, J = 7.5, 7.5, 1.1 Hz, 1H), 7.27 (m, 2H), 6.03 (ddt, J = 16.9, 10.4, 6.4 Hz, 1H), 5.06 (d, J = 0.77 Hz, 1H), 5.02 (ddd, J = 8.8, 1.6, 1.1 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.78 (d, J = 6.4 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 141.7, 137.8, 132.2, 131.2, 130.8, 130.4, 126.4, 115.8, 61.1, 38.7, 14.6;



85

Ethyl 2-(2-Oxoethyl)benzoate (85).

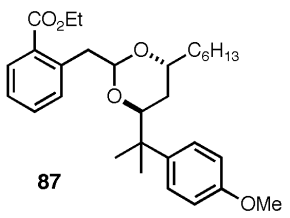
(*Previously reported compound*[66]) Alkene **84** (761 mg, 4 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C. A steady stream of ozone was bubbled through the solution for one hour. Triphenylphosphine (1.15 g, 4.4 mmol) was added and the reaction warmed to 0 °C and stirred for 45 minutes. Solvent was evaporated *in vacuo* and the resulting crude oil was purified via flash chromatography (20% EtOAc in hexanes eluent) to yield the title compound (534 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.08 (dd, J = 7.8 Hz, 1H), 7.52 (td, J = 7.5, 1.3 Hz, 1H), 7.40 (td, J = 7.5, 1.1 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 4.35 (q, J = 7.1. Hz, 2H), 4.08 (s, 2H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 166.5, 134.8, 132.3, 130.7, 129.5, 127.3, 60.7, 49.2, 13.9;



86

(4*R,6*S**)-4-Hexyl-6-(2-(4-methoxyphenyl)propan-2-yl)-2,2,8,8-tetramethyl-3,7-dioxa-2,8-disilanonane (86).**

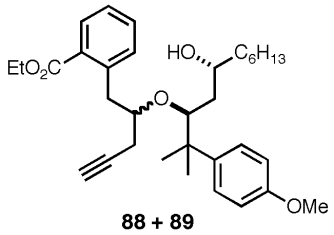
A solution of *anti*-diol **79** (380 mg, 1.23 mmol) in CH_2Cl_2 (4 mL) was cooled to −78 °C. To this solution was added 2,6-lutidine (572 μL, 4.93 mmol), and the mixture stirred for ten minutes, then TMSOTf (2 EQ) was added dropwise. The reaction stirred for 15 minutes, and was quenched with water (10 mL). Contents were extracted thrice with CH_2Cl_2, and the combined organics were washed with 1 M HCl, then brine, dried over Na_2SO_4, filtered and concentrated to yield the title compound (547 mg, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.1 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 3.90 (dd, J = 8.1, 1.6 Hz, 1H), 3.80 (s, 3H), 3.59 (m, 1H), 1.36 (m, 2H), 1.25 (br m, 16H), 0.876 (dd, J = 6.9, 6.3 Hz, 3H), 0.079 (s, 9H), 0.049 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 148.0, 140.5, 128.0, 113.4, 78.7, 71.4, 55.3, 42.4, 41.9, 38.8, 32.16, 29.78, 26.5, 25.8, 24.1, 22.9, 14.4, 1.48, 1.20;



87

Ethyl 2-(((4*R,6*S**)-4-hexyl-6-(2-(4-methoxyphenyl)propan-2-yl)-1,3-dioxan-2-yl)methyl)benzoate (87).**

To a solution of aldehyde **85** (2.51 g, 13.1 mmol) and bis-TMS ether **86** (5.92 g, 13.1 mmol) in CH_2Cl_2 (65 mL) at −78 °C was added TMSOTf (253 μL, 1.31 mmol). The reaction stirred for two hours at −78 °C, then was quenched with pyridine (160 μL, 1.96 mmol) and poured into saturated $NaHCO_3$. Contents were extracted thrice with CH_2Cl_2, and the combined organics were washed with brine, filtered, dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash chromatography (10% EtOAc in hexanes eluent) to yield the title compound (5.67 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, J = 7.7, 1.2 Hz, 1H), 7.42–7.30 (m, 3H), 7.23 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 4.97 (dd, J = 5.9, 4.3 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.93 (m, 1H), 3.80 (s, 3H), 3.67 (dd, J = 11.7, 2.2 Hz, 1H), 3.32 (dd, J = 13.3, 4.3 Hz, 1H), 3.20 (dd, J = 13.3, 6.0 Hz, 1H), 1.85–1.79 (m, 1H), 1.70 (dt, J = 12.6, 6.2 Hz, 1H), 1.39 (t, J = 7.1 Hz, 3H), 1.34–1.05 (m, 15H), 0.953 (d, J = 13.2 Hz, 1H), 0.863 (dd, J = 7.1, 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 157.7, 138.8, 138.2, 133.1, 131.3, 130.9, 130.2, 127.8, 126.3, 113.3, 95.2, 79.3, 72.3, 60.8, 55.1, 40.7, 40.1, 31.9, 30.5, 29.1, 28.6, 26.1, 25.7, 22.9, 22.6, 21.1, 14.4, 14.2;

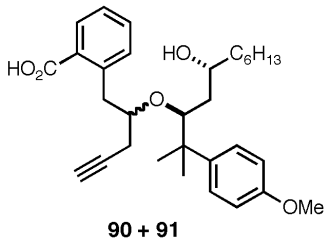


88 + 89

Ethyl 2-(2-((3*S,5*R**)-5-hydroxy-2-(4-methoxyphenyl)-2-methylundecan-3-yloxy)pent-4-ynyl) benzoate (88, 89).**

Mixed Lewis acid was prepared by addition of $TiCl_4$ (11.1 mL, 101.26 mmol) to a solution of Ti(O*i*-Pr)$_4$ (9.89 mL, 33.75 mmol) in CH_2Cl_2 (840 mL). To the acetal **87** (5.43 g, 11.25 mmol) and allenyltributyltin (10.0 mL, 33.75 mmol) in CH_2Cl_2 (280 mL) at −42 °C was added the mixed Lewis acid solution in one slow, smooth pour. After ten minutes, reaction was quenched with pyridine (45 mL) followed by methanol (45 mL). Contents were poured into 1 M HCl (450 mL), and extracted thrice with CH_2Cl_2. Combined organics were wahed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting crude brown oil was purified via flash chromatography (100% hexanes–40% EtOAc in hexanes gradient, 10% increments, as eluent)

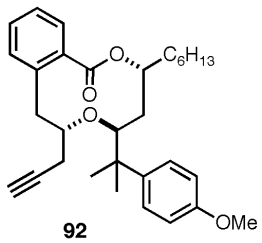
to yield the title compound as a 55:45 mixture of diastereomers, as determined by ^{1}H NMR analysis (4.13 g, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.86 (m, 1H), 7.46–7.32 (m, 3H), 7.16–7.14 (m, 2H), 6.83–6.75 (m, 2H), 4.42–4.42 (m, 2H), 3.98–3.95 (m, 1H), 3.78–3.77 (m, 5H), 3.5–3.3 (m, 1H), 3.16–3.0 (m, 1H), 2.6–2.4 (m, 1H), 2.3–2.2 (m, 1H), 2.07 (m, 1H), 1.7–1.0 (m, 18H), 0.95–0.7 (m, 5H);



90 + 91

2-(2-((3*S,5*R**)-5-Hydroxy-2-(4-methoxyphenyl)-2-methylundecan-3-yloxy)pent-4-ynyl)benzoic acid (90, 91).**

To a solution of racemic epimers **88** and **89** (4.13g, 7.90 mmol) in methanol (120 mL) and water (60 mL) was added lithium hydroxide monohydrate (18.89 g, 450 mmol). Reaction vessel was heated to 60 °C for 15 hours. Contents were acidified to pH 1 with 1 M HCl and extracted thrice with ether. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to yield the title compound as a light yellow oil (3.56 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0–7.8 (m, 1H), 7.6–7.4 (m, 1H), 7.4–7.3 (m, 2H), 7.2–7.1 (m, 1H), 7.1–7.0 (m, 1H), 6.9–6.7 (m, 2H), 4.2–4.1 (m, 1H), 4.0–3.8 (m, 1H), 3.8–3.7 (m, 4H), 3.6–3.4 (m, 2H), 3.3–3.1 (m, 1H), 2.9–2.8 (m, 1H), 2.6–2.4 (m, 1H), 2.2-2.0 (m, 2H), 1.6–0.8 (m, 21H);

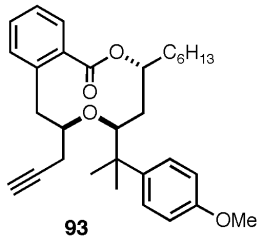


92

(3*R,5*S**,7*R**)-3-Hexyl-5-(2-(4-methoxyphenyl)propan-2-yl)-7-(prop-2-ynyl)-4,5,7,8-tetrahydrobenzo[*g*][1,5]dioxecin-1(3*H*)-one (92).**

To a solution of the *seco*-acids **90** and **91** (1.22 g, 2.47 mmol) in THF (30 mL) at 0 °C was added triehtylamine (2.07 mL, 14.82 mmol), followed by 2,4,6-trichlorobenzoyl chloride (1.93 mL, 12.35 mmol). The reaction stirred for 15 minutes at 0 °C and the contents were poured carefully, slowly and smoothly into a solution of DMAP (3.02 g, 24.7 mmol) in toluene (1200 mL) at ambient temperature, and stirred for 15 minutes. The reaction was stripped of solvent under reduced pressure, and the resulting crude white semi-solid was purified via flash chromatography (10% EtOAc in hexanes eluent) to yield 795 mg (68%) of the title compound (still as a

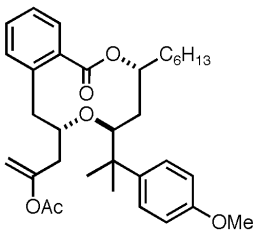
1:1 mixture of racemic epimers). A second flash column eluted with toluene separated the diastereomers, yielding 365 mg of the (9,13-*syn*-, 13,15-*anti*-) isomer **93** and 220 mg of the (9,13-*anti*-, 13,15-*anti*-) isomer **92**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 7.6 Hz, 1H), 7.5–7.3 (m, 2H), 7.29–7.20 (m, 3H), 6.86 (d, J = 8.7 Hz, 2H), 5.23 (m, 1H), 4.2–4.1 (m, 2H), 3.79 (s, 3H), 3.66 (m, 1H), 2.5–2.2 (m, 3H), 2.0–1.8 (m, 2H), 2.7–2.55 (2 singlets, 2H), 1.5–1.3 (2 singlets, 7H), 1.3–1.2 (m, 3H), 1.2–1.0 (m 6H), 0.85 (t, J = 7.0 Hz, 3H), 0.77 (m, 1H);



93

(3*R,5*S**,7*S**)-3-Hexyl-5-(2-(4-methoxyphenyl)propan-2-yl)-7-(prop-2-ynyl)-4,5,7,8-tetrahydrobenzo[*g*][1,5]dioxecin-1(3H)-one (93).**

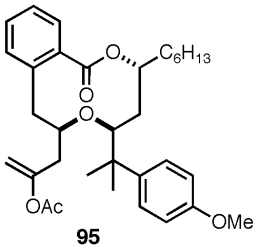
To a solution of the *seco*-acids **90** and **91** (1.22 g, 2.47 mmol) in THF (30 mL) at 0 °C was added triehtylamine (2.07 mL, 14.82 mmol), followed by 2,4,6-trichlorobenzoyl chloride (1.93 mL, 12.35 mmol). The reaction stirred for 15 minutes at 0 °C and the contents were poured carefully, slowly and smoothly into a solution of DMAP (3.02 g, 24.7 mmol) in toluene (1200 mL) at ambient temperature, and stirred for 15 minutes. The reaction was stripped of solvent under reduced pressure, and the resulting crude white semi-solid was purified via flash chromatography (10% EtOAc in hexanes eluent) to yield 795 mg (68%) of the title compound (still as a 1:1 mixture of racemic epimers). A second flash column eluted with toluene separated the diastereomers, yielding 220 mg of the (9,13-*anti*-, 13,15-*anti*-) isomer **92** and 365 mg of the (9,13-*syn*-, 13,15-*anti*-) isomer **93**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.5 Hz, 1H), 7.5–7.2 (m, 5H), 6.87 (d, J = 8.7 Hz, 2H), 4.91 (m, 1H), 4.25 (d, J = 14.2 Hz, 1H), 4.0–3.81 (m, 2H), 3.80 (s, 3H), 2.72 (dd, J = 14.2, 2.7 Hz, 1H), 2.3–2.1 (m, 2H), 2.0 (s, 1H), 1.8–1.6 (m, 2H), 1.5–1.0 (m, 15H), 0.86 (t, J = 6.8 Hz, 3H), 0.7 (m, 1H);



94

3-((3*R,5*S**,7*S**)-3-Hexyl-5-(2-(4-methoxyphenyl)propan-2-yl)-1-oxo-1,3,4,5,7,8-hexahydrobenzo[*g*][1,5]dioxecin-7-yl)prop-1-en-2-yl Ethanoate (94).**

To the alkyne (±)-**92** (199 mg, 428 μmol) in glacial acetic acid (8 mL) was added Na_2CO_3 (89 mg, 836 μmol) followed by tri-2-furyl phosphine (8 mg, 33 μmol), and then dichloro(*p*-cymene) ruthenium(II) dimer (10 mg, 17 μmol). The reaction vessel was fitted with a reflux condenser and heated to 60 °C for 30 hours. Contents were diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$, filtered through a plug of silica gel and concentrated. The resulting crude oil was purified via flash chromatography (10% EtOAc in hexanes eluent) to yield 61 mg of the starting material and 127 mg of the title compound as a colorless oil (57%, 82% brsm): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 1H), 7.35 (m, 4H), 7.16 (d, J = 7.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 5.22 (m, 1H), 4.82 (m, 2H), 4.12 (m, 2H), 3.79 (s, 3H), 3.69 (m, 1H), 2.31 (m, 2H), 2.19, (m, 1H), 1.96 (s, 3H), 1.92 (m, 1H), 1.63–1.56 (m, 2H), 1.40 (s, 3H), 1.30 (s, 3H), 1.2–0.85 (br m, 8H), 0.82–0.66 (m, 4H);

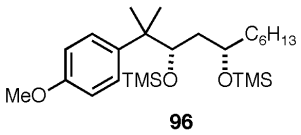


95

3-((3*R,5*S**,7*R**)-3-Hexyl-5-(2-(4-methoxyphenyl)propan-2-yl)-1-oxo-1,3,4,5,7,8-hexahydrobenzo[*g*][1,5]dioxecin-7-yl)prop-1-en-2-yl Ethanoate (95).**

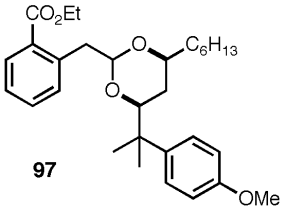
To the alkyne (±)-**93** (347 mg, 728 μmol) in glacial acetic acid (15 mL) was added Na_2CO_3 (154 mg, 1.46 mmol) followed by tri-2-furyl phosphine (14 mg, 58 μmol), and then dichloro(*p*-cymene) ruthenium(II) dimer (18 mg, 29 μmol). The reaction vessel was fitted with a reflux condenser and heated to 60 °C for 10 hours. Contents were diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$, filtered through a plug of silica gel and concentrated. The resulting crude oil was purified via flash chromatography (10% EtOAc in hexanes eluent) to yield 84 mg of the starting material and 200 mg of the title compound as a colorless oil (51%, 67% brsm): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.4 Hz, 1H), 7.35 (m, 4H), 7.17 (d, J = 7.1 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 4.87 (m, 1H), 4.80 (s, 1H), 4.60 (s, 1H), 4.27 (d, J = 14.1 Hz, 1H), 4.03 (m, 1H), 3.93 (m, 1H), 3.78 (s, 3H), 2.55 (m, 1H), 2.4–2.2 (br m, 5H), 1.66

(m, 2H), 1.25 (br m, 15H), 0.84 (m, 4H);



96

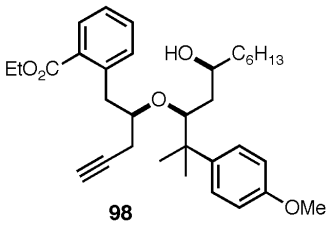
(4*S,6*S**)-4-Hexyl-6-(2-(4-methoxyphenyl)propan-2-yl)-2,2,8,8-tetramethyl-3,7-dioxa-2,8-disilanonane (96).** To the *syn*-diol **80** (1.41 g, 4.54 mmol) in 15 mL CH_2Cl_2 (15 mL) at −78 °C was added 2,6-lutidine (2.12. mL, 18.29 mmol), and the mixture stirred for five minutes. To the stirring solution at −78 °C was added TMSOTf (1.55 mL, 10.06 mmol) over the course of one minute. The reaction had consumed all starting material by TLC analysis within five minutes, so the reaction was quenched with water (20 mL), and the contents were extracted thrice with CH_2Cl_2. The combined organics were washed twice with 1 M HCl, then brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the title compound as a colorless oil (1.67 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 3.76 (m, 1H), 3.69 (m, 1H), 1.64 (m, 1H), 1.49 (m, 3H), 1.3–1.1 (m, 14H), 0.973 (dd, J = 6.9, 6.4 Hz, 3H), 0.15 (m, 18H);



97

Ethyl 2-(((4*S,6*S**)-4-hexyl-6-(2-(4-methoxyphenyl)propan-2-yl)-1,3-dioxan-2-yl)methyl)benzoate (97).** To a stirred solution of bis-TMS ether **96** (1.67 g, 3.69 mmol) and aldehyde **85** (708 mg, 3.69 mmol) in CH_2Cl_2 (18 mL) at −78 °C was added TMSOTf (67 μL, 369 μmol). The reaction stirred for five minutes then was quenched with pyridine (47 μL) and poured into saturated aqueous $NaHCO_3$ and extracted thrice with CH_2Cl_2. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude oil was purified via flash chromatography (10% EtOAc in hexanes eluent) to yield the title compound as a colorless oil (1.76 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, J = 7.8, 1.0 Hz, 1H), 7.4–7.3 (m, 2H), 7.3–7.2 (m, 1H), 7.22 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H), 4.71 (dd, J = 6.1, 4.3 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.5–3.3 (m, 3H), 3.22 (dd, J = 13.3, 6.2 Hz, 1H), 1.52–1.4 (m, 2H), 1.38 (t, J = 7.1 Hz, 3H), 1.35–1.15 (m, 14H), 1.2–1.0 (m, 2H), 0.89–0.80 (app t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 157.7,

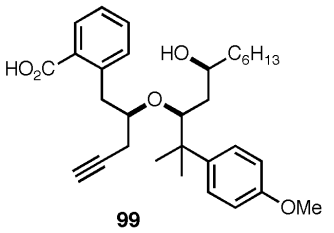
138.8, 138.1, 133.2, 131.2, 130.9, 130.3, 127.8, 126.3, 113.3, 101.6, 83.9, 76.6, 60.9, 55.1, 40.7, 39.9, 36.2, 31.9, 31.7, 29.3, 26.1, 25.1, 23.0, 22.7, 14.4, 14.2;



98

Ethyl 2-((*S)-2-((3*S**,5*S**)-5-hydroxy-2-(4-methoxyphenyl)-2-methylundecan-3-yloxy)pent-4-ynyl)benzoate (98).**

Mixed Lewis acid was prepared by addition of $TiCl_4$ (613 μL, 5.59 mmol) to a solution of Ti(O*i*-Pr)$_4$ (545 μL, 1.86 mmol) in CH_2Cl_2 (36 mL). To the acetal **97** (300 mg, 620 μmol) and allenyltributyltin (553 μL, 1.86 mmol) in CH_2Cl_2 (12 mL) at -42 °C was added the mixed Lewis acid solution in one smooth syringe-wise addition. The reaction stirred at -42 °C for 15 minutes then was quenched by addition of pyridine (3 mL) followed by methanol (3 mL). Contents were poured into 100 mL 1 M HCl and extracted thrice with EtOAc. Combined organics were washed with 1 M HCl (50 mL), then brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude oil was purified via flash column chromatography (10% EtOAc in hexanes eluent) to yield the title compound (227 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 7.6 Hz, 1H), 7.5–7.28 (m, 5H), 6.81 (d, J = 8.6 Hz, 2H), 4.42–4.36 (m, 2H), 4.07 (m, 1H), 3.78–3.70 (m, 5H), 3.3 (m, 1H), 3.15 (m, 1H), 2.8 (br s, 1H), 2.4 (m, 1H), 2.10 (m, 2H), 1.45 (t, J = 7.2 Hz, 3H), 1.3 (2 singlets, 6H), 1.2–1.0 (br m, 12H), 0.85 (t, J = 7.0 Hz, 3H);

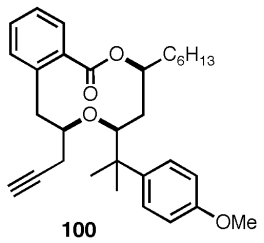


99

2-((*S)-2-((3*S**,5*S**)-5-Hydroxy-2-(4-methoxyphenyl)-2-methylundecan-3-yloxy)pent-4-ynyl)benzoic acid (99).**

To ester **98** (190 mg, 360 μmol) in methanol/water (2:1, 10 mL) was added lithiumhyroxide monohydrate (860 mg, 20.5 mmol). The reaction was heated to 60 °C for 15 hours. The reaction mixture was cooled to ambient temperature, acidified to pH 1 using 2 M HCl and extracted thrice with EtOAc. The combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the title compound as a colorless oil (175 mg, 98%):

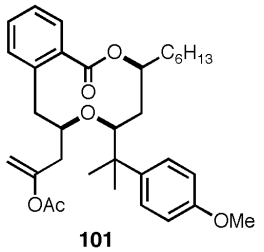
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.6 Hz, 1H), 7.5–7.2 (m, 5H), 6.78 (d, J = 8.7 Hz, 2H), 3.86 (m, 1H), 3.8–3.6 (m, 5H), 3.2–3.1 (m, 2H), 2.35–2.25 (m, 1H), 2.1–2.0 (m, 3H), 1.7–1.5 (m, 2H), 1.4–1.0 (br m, 16H), 0.826 (t, J = 7.0 Hz, 3H);



100

(3*S,5*S**,7*S**)-3-Hexyl-5-(2-(4-methoxyphenyl)propan-2-yl)-7-(prop-2-ynyl)-4,5,7,8-tetrahydrobenzo[*g*][1,5]dioxecin-1(3*H*)-one (100).**

To the *seco*-acid **99** (371 mg, 750 μmol) in THF (9 mL) at 0 °C was added triethylamine (627 μL, 4.5 mmol), followed by 2,4,6-trichlorobenzoylchloride (586 μL, 3.75 mmol). The reaction stirred at 0 °C for 30 minutes, and the reaction mixture was slowly poured into an ambient-temperature solution of DMAP (916 mg, 7.5 mmol) in toluene (375 mL). The reaction stirred for 20 minutes and was stripped of solvent under reduced pressure. The resulting white semi-solid was purified via flash chromatography (10% EtOAc in hexanes eluent) to yield the title compound (125 mg, 35%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.5, 1.3 Hz, 1H), 7.5–7.3 (m, 5H), 6.90 (d, J = 8.8 Hz, 2H), 4.81 (m, 1H), 3.85 (s, 3H), 3.72 (d, J = 13.7 Hz, 1H), 3.58 (d, J = 7.2 Hz, 1H), 3.45 (m, 1H), 3.20 (dd, J = 13.7, 7.1 Hz, 1H), 2.2–2.0 (m, 3H), 1.8 (m, 2H), 1.7 (m, 1H), 1.6 (m, 1H), 1.5–1.3 (2 singlets, 6H), 1.3–1.0 (m, 8H), 0.90 (m, 3H);

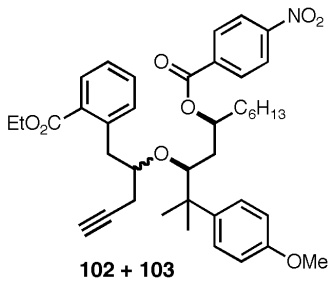


101

3-((3*S,5*S**,7*R**)-3-Hexyl-5-(2-(4-methoxyphenyl)propan-2-yl)-1-oxo-1,3,4,5,7,8-hexahydrobenzo[*g*][1,5]dioxecin-7-yl)prop-1-en-2-yl Ethanoate (101).**

To the alkyne (±)**-100** (50 mg, 96 μmol) in glacial acetic acid (2 mL) was added Na_2CO_3 (29 mg, 278 μmol) followed by tri-2-furyl phosphine (2.5 mg, 11 μmol), and then dichloro(*p*-cymene) ruthenium(II) dimer (3 mg, 55 μmol). The reaction vessel was fitted with a reflux condenser and heated to 60 °C for 6 hours, and a further 4 mol% of each dichloro(*p*-cymene) ruthenium(II) dimer and tri-2-furyl phosphine were added. The reaction was nearly complete after another 12 hours, and a spatula tip's worth of the ruthenium catalyst and phosphine ligand were added; the reaction was complete within 10 minutes. The contents were allowed to cool to ambient

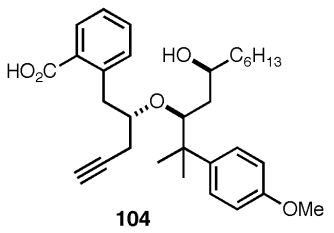
temperature, then were filtered through a plug of silica and concentrated. The resulting oil was purified via flash chromatography (10% EtOAc in hexanes eluent) to yield the title compound (18 mg, 35%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (app d, 1H), 7.32 (m, 4H), 7.16 (m, 1H), 6.85 (d, J = 8.8 Hz, 2H), 4.76 (m, 3H), 3.80 (s, 3H), 3.6–3.51 (m, 3H), 3.2 (m, 1H), 2.3 (m, 2H), 1.92 (s, 3H), 1.6 (m, 2H), 1.48 (m, 2H), 1.27 (m, 14H), 0.8 (m, 3H);



102 + 103

Ethyl 2-(2-((3*S,5*S**)-2-(4-methoxyphenyl)-2-methyl-5-(4-nitrophenylcarbonyloxy)undecan-3-yloxy)pent-4-ynyl)benzoate (102, 103).**

To a solution of alcohols **88** and **89** (3.89 g, 7.44 mmol), 4-nitrobenzoic acid (4.96 g, 29.7 mmol), and tripehenylphosphine (9.76 g, 37.2 mmol) in toluene (135 mL) was added diisopropyl azodicarboxylate (7.3 mL, 37.2 mmol). The reaction stirred at ambient temperature for two hours, and the solvent was removed *in vacuo*. The resulting crude amber oil was purified via flash column chromatography (10% EtOAc eluent) to yield the title compound as a mixture of diastereomers differing at C9 (2.74 g, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.4–8.1 (m, 2H), 8.0–7.8 (m, 1H), 7.5–7.1 (m, 6H), 6.9–6.7 (m, 3H), 5.0–4.8 (m, 1H), 4.5–4.3 (m, 2H), 4.0–3.7 (m, 4H), 3.6–3.4 (m, 1H), 3.3–3.0 (m, 2H), 2.4–1.7 (m, 5H), 1.5–1.0 (m, 19H), 0.9–0.7 (m, 3H);

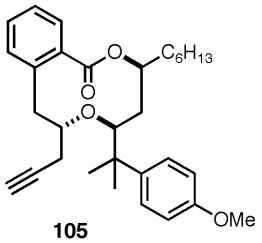


104

2-((*R)-2-((3*S**,5*S**)-5-Hydroxy-2-(4-methoxyphenyl)-2-methylundecan-3-yloxy)pent-4-ynyl)benzoic acid (104).**

To a mixture of the diesters **102** and **103** (2.73 g, 4.15 mmol) in a solution of MeOH/H_2O (2:1, 135 mL) was added lithium hydroxide monohydrate (8.79 g, 58 mmol). Reaction was warmed to 55 °C for 30 hours. The contents were acidified to pH 1 using 1 M HCl and extracted thrice with ether. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting crude yellow oil was purified via flash column chromatography (40% EtOAc in hexanes eluent) to yield 197 mg of the undesired (9,13-*anti*-, 13,15-*syn*-)

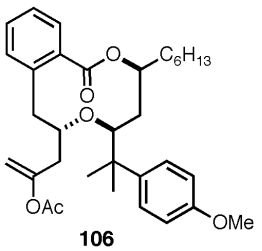
isomer and 156 mg of the title compound (8%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.8 Hz, 1H), 7.5 (m, 1H), 7.3 (m, 2H), 7.1 (d, J = 8.7 Hz, 2H), 6.7 (d, J = 8.7 Hz, 2H), 5.7 (br s, 1H), 3.9 (m, 1H), 3.78 (m, 4H), 3.6 (m, 1H), 3.4 (m, 1H), 3.3 (m, 1H), 3.1 (m, 1H), 3.0 (m, 1H), 2.4 (m, 2H), 2.1–1.8 (m, 2H), 1.6–1.5 (m, 2H), 1.5–0.7 (m, 17 H);



105

(3*S,5*S**,7*R**)-3-Hexyl-5-(2-(4-methoxyphenyl)propan-2-yl)-7-(prop-2-ynyl)-4,5,7,8-tetrahydrobenzo[*g*][1,5]dioxecin-1(3*H*)-one (105).**

To the *seco*-acid **104** (88 mg, 178 μmol) in THF (3.5 mL) at 0 °C was added triethylamine (50 μL, 356 μmol), followed by 2,4,6-trichlorobenzoyl chloride (28 μL, 178 μmol). Reaction stirred for 45 minutes, then the contents were taken up in a syringe and added dropwise to a solution of DMAP (217 mg, 178 μmol) in toluene (36 mL) over the course of 30 minutes. The solvent was removed *in vacuo* and the resulting white paste was purified via flash column chromatography (10% EtOAc in hexanes eluent) to yield the title compound (68 mg, 80%) : ^{1}H NMR (500 MHz, C_6D_6) δ 7.54 (d, J = 7.3 Hz, 1H), 7.33 (d, J = 8.6 Hz, 2H), 6.99 (m, 1H), 6.91 (m, 1H), 6.90 (m, 1H), 6.83 (d, J = 8.6 Hz, 2H); 4.75 (m, 1H), 4.40 (m, 1H), 3.92 (m, 1H), 3.36 (s, 3H), 3.27 (d, J = 14 Hz, 1H), 2.5–2.4 (m, 2H), 2.4–2.3 (m, 1H), 1.82 (s, 1H), 1.74 (d, J = 15.6 Hz, 1H), 1.53 (m, 2H), 1.45 (s, 3H), 1.44 (s, 3H), 1.5–1.15 (m, 3H), 1.1–0.9 (br m, 6H), 0.86 (m, 3H);

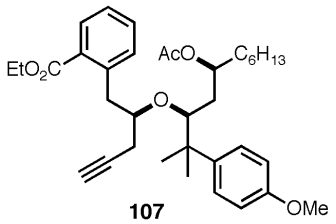


106

3-((3*S,5*S**,7*S**)-3-Hexyl-5-(2-(4-methoxyphenyl)propan-2-yl)-1-oxo-1,3,4,5,7,8-hexahydrobenzo[*g*][1,5]dioxecin-7-yl)prop-1-en-2-yl Ethanoate (106).**

To the alkyne (±)**-105** (116 mg, 243 μmol) in glacial acetic acid (4.8 mL) was added Na_2CO_3 (51 mg, 486 μmol) followed by tri-2-furyl phosphine (4.5 mg, 19 μmol), and then dichloro(*p*-cymene) ruthenium(II) dimer (6 mg, 10 μmol). The reaction vessel was fitted with a reflux condenser and heated to 60 °C for 22 hours. Contents were diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$, filtered through a plug of silica gel and concentrated. The

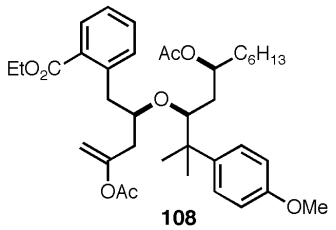
resulting crude oil was purified via flash chromatography (10% EtOAc in hexanes eluent) to yield the title compound as a colorless oil (40 mg, 31%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 7.3 Hz, 1H), 7.34 (m, 3H), 7.29 (m, 1H), 7.13 (d, J = 7.3 Hz, 1H), 6.83 (d, J = 8.6 Hz, 2H), 4.79 (m, 2H), 4.48 (m, 1H), 4.28 (m, 1H), 3.77 (m, 4H), 3.21 (d, J = 13.9 Hz, 1H), 2.59 (m, 1H), 2.43 (m, 1H), 2.27 (m, 1H), 2.00 (s, 3H), 1.65 (m, 1H), 1.57 (m, 2H), 1.30 (s, 3H), 1.28 (s, 3H), 1.12 (br m, 9H), 0.82 (dd, J = 7.0, 6.5 Hz, 3H);



107

Ethyl 2-((*S)-2-((3*S**,5*R**)-5-(ethanoyloxy)-2-(4-methoxyphenyl)-2-methylundecan-3-yloxy)pent-4-ynyl)benzoate (107).**

To alcohol **98** (505 mg, 0.955 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added acetic anhydride (255 μL, 2.69 mmol), then TMSOTf (10 μL, 54 μmol). The reaction stirred at 0 °C for one hour, and was quenched with pyridine (10 μL). The contents were washed with 1 M HCl, then brine. The organics were dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified via flash column chromatography (10% EtOAc in hexanes eluent) to yield the title compound (182 mg, 34% over 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, J = 7.8, 1.2 Hz, 1H), 7.5–7.2 (m, 5H), 6.84 (d, J = 6.9 Hz, 2H), 4.4 (m, 2H), 4.2 (m, 1H), 3.81 (m, 4H), 3.4 (m, 2H), 3.2 (m, 1H), 2.4 (m, 2H), 2.2 (s, 1H), 2.1 (s, 3H), 1.7 (m, 2H), 1.4–1.0 (m, 16H), 0.96 (t, J = 7.3 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H);

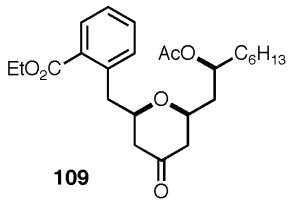


108

Ethyl 2-((*R)-4-(ethanoyloxy)-2-((3*S**,5*R**)-5-(ethanoyloxy)-2-(4-methoxyphenyl)-2-methylundecan-3-yloxy)pent-4-enyl)benzoate (108).**

To the alkyne **107** (182 mg, 0.319 mmol) in glacial acetic acid (6.4 mL) was added Na_2CO_3 (68 mg) followed by tri-2-furyl phosphine (6 mg, 25 μmol), and then dichloro(p-cymene) ruthenium(II) dimer (8 mg, 13 μmol). The reaction was warmed to 60 °C for 24 hours. A further 4 mol% of the Ru-dimer and 8 mol% of the phosphine ligand were added, and the reaction stirred at 60 °C for another 24 hours. The reaction had consumed all of the starting material

and was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The aqueous layer was back-extracted with EtOAc and the combined organics were filtered through a plug of silica gel, dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified via flash column chromatography (10% EtOAc in hexanes eluent) to yield the title compound (64 mg, 32%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.7 Hz, 1H), 7.4–7.3 (m, 1H), 7.3–7.2 (m, 4H), 6.82 (d, J = 8.9 Hz, 2H), 4.86 (m, 2H), 4.36 (m, 2H), 4.2 (m, 1H), 3.80 (m, 4H), 3.43 (m, 1H), 3.24 (m, 2H), 2.4 (m, 1H), 2.3 (m, 1H), 2.12 (s, 3H), 1.98 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.4–1.0 (m, 17H), 0.9–0.8 (m, 3H), 0.6 (m, 1H);



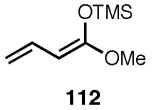
109

Ethyl 2-(((2*R,6*S**)-6-((*R**)-2-(ethanoyloxy)octyl)-4-oxotetrahydro-2*H*-pyran-2-yl)methyl)benzoate (109).**
To enol acetate **108** (29 mg, 46 μmol) in dichloroethane (3 mL) was added 4 Å molecular sieves (58 mg), then $NaCO_3$ (58 mg). To the enol acetate was added a solution of CAN (151 mg, 276 μmol in 920 μL CH_3CN). The reaction stirred for ten minutes and the contents were filtered through a plug of silica gel. The resulting oil was purified via flash column chromatography (15% EtOAc in toluene eluent) to yield the title compound (10 mg, 51%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.9, 1.1 Hz, 1H), 7.46 (m, 1H), 7.33 (m, 2H), 4.95 (m, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.83 (m, 1H), 3.5 (m, 1H), 3.36 (dd, J = 13.3, 4.2 Hz, 1H), 3.18 (m, 1H), 2.5–2.1 (m, 4H), 2.01 (s, 3H), 1.96 (m, 1H), 1.65 (m, 2H), 1.4–1.0 (m, 12H), 0.879 (t, J = 7.1 Hz, 3H);

APPENDIX B

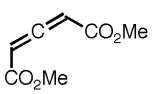
EXPERIMENTAL PROCEDURES SUPPLEMENT TO CHAPTER 3

See preface to Appendix A for standard operating procedures.



112

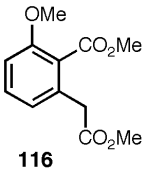
(*Z*)-(1-Methoxybuta-1,3-dienyloxy)trimethylsilane (112). (*Previously reported compound*[47]) To a solution of diisopropyl amine (14 mL, 100 mmol) in THF (75 mL) at −78 °C was added *n*-BuLi (62.5 mL of a 1.6 M solution in hexanes, 100 mmol), dropwise over 15 minutes. HMPA (21 mL, 120 mmol) was added slowly, and the reaction stirred for 10 minutes. Methyl crotonate **111** (10.6 mL, 100 mmol) was added dropwise, and the reaction stirred for 30 minutes. TMSCl (20 mL, 157 mmol) was added to the reaction mixture dropwise, and the contents stirred for 20 minutes at −78 °C. The reaction was allowed to warm to ambient temperature, and stirred for 2 hours. The solvent was evaporated under reduced pressure and replaced with pentane (250 mL). The LiCl precipitate was filtered off, and the organics were washed with water (3x 70 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting light yellow crude oil was distilled at 2 torr and collected at 30 °C to yield the title compound (9.65 g, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (dt, J = 17.2, 10.4 Hz, 1H), 4.86 (ddd, J = 17.2, 2.1, 0.6 Hz, 1H), 4.62 (ddd, J = 10.4, 2.2, 0.7 Hz, 1H), 4.50 (d, J = 10.3 Hz, 1H), 3.59 (s, 3H), 0.228 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 132.4, 106.9, 80.8, 54.7, 0.678; IR (neat) 2957, 1647, 1252, 1086, 844 cm^{-1}; MS: m/z(%): 173 (8) [$C_{14}H_{16}O_2Si^+$].



114

Dimethyl Penta-2,3-dienedioate (114).

(*Previously reported compound*[48]) To a solution of 3-oxo-pentanedioic acid dimethyl ester **113** (Aldrich Chemical Company, 8.62 mL, 59.7 mmol) and 2-chloro-1,3-dimethylimidizolinium chloride (Aldrich Chemical Company, 12.12 g, 71.66 mmol) in CH_2Cl_2 (600 mL) at 0 °C was added triethylamine (25 mL, 179 mmol). The reaction warmed to ambient temperature and stirred for 90 minutes. The solvent was removed under reduced pressure and the organics were filtered through a plug of Celite to remove the urea solid. The resulting orange oil was purified via flash column chromatography (CH_2Cl_2 eluent) to yield the title compound as a light yellow oil (8.62 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (s, 2H), 3.78 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.5, 163.4, 91.8, 52.2; IR (neat) 3028, 2956, 1966, 1724, 1439, 1394, 1268, 1164, 1025, 817 cm^{-1}; MS: m/z(%): 156 (53) [$C_7H_8O_4^+$].

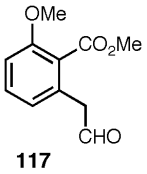


116

Methyl 2-Methoxy-6-(2-methoxy-2-oxoethyl)benzoate (116).

(*Previously reported compound*[37]) Silyl ketene acetal **112** (9.26 g, 53.7 mmol) and allene **114** (7.62 g, 48.8 mmol) were dissolved in benzene (81 mL) and heated to reflux for 20 hours. The solvent was evaporated under reduced pressure and replaced with THF. Concentrated HCl (14 drops) was added and the mixture stirred for 30 minutes. The organics were washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified via flash column chromatography (30% EtOAc in hexanes eluent) to yield a clear oil that was a two-component mixture by TLC. To this two-component sample in DMF (30 mL) at 0 °C was added K_2CO_3 (1.63 g, 11.8 mmol) followed by iodomethane (735 μL, 11.8 mmol). The reaction stirred for 15 hours and was poured into EtOAc/1 M HCl (100 mL total). The aqueous layer was extracted thrice with EtOAc. The combined organics were washed with 1 M HCl, then brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (2.17 g, 19%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (t, J = 8.0 Hz, 1H), 6.9 (m, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.69 (s, 3H), 3.67 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 167.8, 156.9, 133.1, 130.8, 123.4, 122.8, 110.3, 55.8, 52.0, 51.9, 38.8; IR (neat) 2953, 1732, 1586, 1473, 1435, 1271, 165, 1115, 1073, 1011, 760 cm^{-1}; MS: m/z(%): 238 (39) [$C_{12}H_{14}O_5^+$].

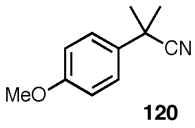
Methyl 2-Methoxy-6-(2-oxoethyl)benzoate (117).



117

(*Previously reported compound*[67]) To ester **116** (790 mg, 3.32 mmol) in CH_2Cl_2 (35 mL) at −78 °C was added DIBAL (3.32 mL of a 1 M solution in hexanes) over the course of one hour. The reaction stirred for a further 45 minutes at −78 °C then was quenched with saturated aqueous sodium potassium tartrate. The bi-phasic mixture stirred vigorously for 45 minutes. The contents were extracted with CH_2Cl_2 (3x) and the combined organics were washed with water then brine, dried over $MgSO_4$, filtered and concentrated to yield the title compound (645 mg, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.37 (m, 1H), 6.86 (m, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.69 (m, 2H);

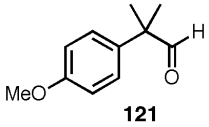
2-(4-Methoxyphenyl)-2-methylpropanenitrile (120).



120

(*Previously reported compound*[68]) To fluoroanisole **118** (Aldrich Chemical Company, 20.0 g, 158 mmol) and isobutyronitrile **119** (56.8 mL, 634 mmol) in THF (250 mL) was added KHMDS (47.4 g, 238 mmol). The reaction was heated to reflux for 6 days, then quenched at 0 °C with 200 mL 1 M HCl. The contents were extracted with EtOAc (3x 100 mL), and the combined organics were washed with brine (400 mL), dried over $MgSO_4$, filtered and concentrated to yield a crude brown oil. The oil was distilled at 2 torr and the title compound was collected at 98 °C (26.01 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 1.71 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$ δ 159.8, 133.6, 126.4, 125.0, 114.3, 55.5, 36.6, 29.4; IR (neat) 2980, 2838, 2234, 1610, 1512, 1463, 1301, 1254, 1185, 1032, cm^{-1}; MS: m/z(%): 175 (22) [$C_{11}H_{13}NO^+$].

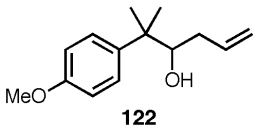
2-(4-Methoxyphenyl)-2-methylpropanal (121).



121

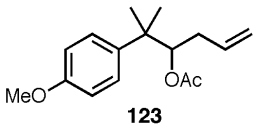
(*Previously reported compound*[69]) To nitrile **120** (12.93 g, 73.7 mmol) in CH_2Cl_2 (150 mL) at −78 °C was added DIBAL (81 mL of a 1 M solution in hexanes, 81 mmol) over the course of two hours. The reaction stirred at −78 °C for an additional 45 minutes, then was quenched with 0.5 M H_2SO_4 (150

mL), warmed to ambient temperature and stirred overnight. Contents were extracted with CH_2Cl_2 (3x 100 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (100 mL), then brine (100 mL), dried over $MgSO_4$, filtered and concentrated to yield the title compound (12.77 g, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.21 (d, $J = 6.7$ Hz, 2H), 6.92 (dd, $J = 6.7$ Hz, 2H), 3.82 (s, 3H), 1.45 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 158.6, 132.9, 127.7, 114.1, 54.8, 49.4, 22.2; IR (neat) 2970, 1723, 1513, 1253, 1185, 1034 cm^{-1}; MS: m/z(%): 178 (35) [$C_{11}H_{14}O_2^+$].



122

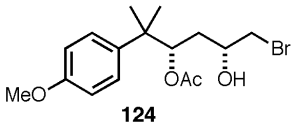
2-(4-Methoxyphenyl)-2-methylhex-5-en-3-ol (122). (*Previously reported compound*[69]) To aldehyde **121** (10.08 g, 56.6. mmol) in CH_2Cl_2 (115 mL) at -78 °C was added allyl magnesium bromide (62 mL of a 1 M solution in ether, 62 mmol) dropwise. The reaction stirred at -78 °C for one hour, then was quenched with saturated aqueous NH_4Cl and warmed to ambient temperature. The contents were extracted with CH_2Cl_2 (3x 70 mL), and the combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to yield the title compound (11.84 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, $J = 8.9$ Hz, 2H), 6.88 (d, $J = 8.9$ Hz, 2H), 5.8 (m, 1H), 5.09 (d, $J = 1.0$ Hz, 1H), 5.05 (d, $J = 1.1$ Hz, 1H), 3.81 (s, 3H), 3.64 (m, 1H), 1.9 (m, 1H), 1.6 (m, 2H), 1.34 (2 singlets, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 138.9, 136.5, 127.6, 117.3, 113.5, 78.5, 55.2, 41.7, 36.6, 24.5, 24.0; IR (neat) 3481, 2970, 2835, 1611, 113, 1252, 1185 cm^{-1}; HRMS (EI): calcd for $C_{14}H_{20}O_2$ (M^+) 220.1463, found 220.1462.



123

2-(4-Methoxyphenyl)-2-methylhex-5-en-3-yl Ethanoate (123). To a soln of alcohol **122** (11.65 g, 52.90 mmol), triethylamine (11.1 mL, 79.4 mmol) and DMAP (648 mg, 5.3 mmol) at 0 °C was added acetic anhydride (8.10 g, 79.4 mmol) dropwise. The reaction was allowed to warm to r.t. and stirred for 120 hours. The contents were poured into 1 M HCl (100 mL), extracted with CH_2Cl_2 (3x 100 mL), washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash chromatography (10% EtOAc in hexanes eluent) to yield the title compound (11.59 g, 84%): ^{1}H NMR (300 MHz,

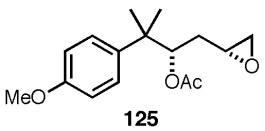
$CDCl_3$) δ 7.32 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 5.62 (m, 1H), 5.20 (dd, J = 9.6, 3.1 Hz, 1H), 4.96 (m, 1H), 4.92 (m, 1H), 3.79 (s, 3H), 2.15–2.03 (m, 2H), 2.02 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 157.9, 138.2, 135.1, 127.5, 116.8, 113.5, 79.4, 55.1, 41.1, 34.9, 26.4, 23.0, 21.0; IR (neat) 2973, 1738, 1514, 1370, 1248, 1186, 1033 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{22}O_3$ (M^+) 262.1569, found 262.1577.



124

(3*S,5*R**)-6-Bromo-5-hydroxy-2-(4-methoxyphenyl)-2-methylhexan-3-yl Ethanoate (124).**

To alkene **123** (288 mg, 1.10 mmol) in THF (6 mL) and water (40 μL) at 0 °C was added NBS (215 mg, 1.21 mmol, freshly recrystalized from H_2O). The reaction warmed to r.t. and stirred for 20 hours. Contents were partitioned between into 10 mL EtOAc and 10 mL of water. The aqueous phase was extracted with EtOAc (3x 10 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash chromatography (30% EtOAc in hexanes eluent) to yield a diastereomer, later shown to be the "syn" configuration, of the title compound (739 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 5.09 (dd, J = 8.4, 3.3 Hz, 1H), 3.79 (s, 3H), 3.58 (m, 1H), 3.44 (dd, J = 10.2, 3.3 Hz, 1H), 3.31 (dd, J = 10.5, 5.7 Hz, 1H), 2.59 (d, J = 5.1 Hz, 1H), 2.05 (s, 3H), 1.71–1.59 (m, 2H), 1.33 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 158.3, 137.8, 127.8, 113.9, 78.4, 69.4, 55.5, 41.5, 39.9, 36.3, 26.4, 22.9, 21.4; IR (neat) 3455, 2970, 1732, 1514, 1248, 1033 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{23}O_4Br$ (M^+) 358.0780, found 358.0789.

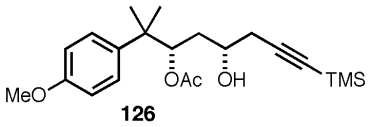


125

(*S)-3-(4-Methoxyphenyl)-3-methyl-1-((*R**)-oxiran-2-yl)butan-2-yl Ethanoate (125).**

To bromohydrin **124** (2.55 g, 22.76 mmol) in THF (250 mL) at 0 °C was added *t*-BuOK (2.55 g, 22.76 mmol) in *t*-BuOH (40 mL). The reaction stirred for one hour and the contents were partitioned between 150 mL water and 150 mL EtOAc and the layers were separated. The aqueous layer was extracted thrice with EtOAc, and the combined organics were washed with brine, dried over $MgSO_4$, filtered and

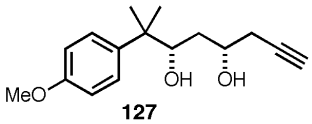
concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (20% EtOAc in hexanes eluent) to yield the title compound (3.08 g, 49%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 2H), 6.8 (m, 2H), 5.3 (m, 1H), 3.80 (s, 3H), 2.8 (m, 1H), 2.6 (m, 1H), 2.2 (m, 1H), 2.1 (s, 3H), 1.5 (m, 2H), 1.27 (2 singlets, 6H);



126

(3*S,5*S**)-5-Hydroxy-2-(4-methoxyphenyl)-2-methyl-8-(trimethylsilyl)oct-7-yn-3-yl Ethanoate (126).**

To trimethylsilyl acetylene (849 mg, 8.64 mmol) in ether (40 mL) at −78 °C was added *n*-BuLi (5.4 mL of a 1.6 M solution in hexanes, 8.64 mmol) dropwise. The reaction stirred for 35 minutes, and trimethylaluminum (4.32 mL of a 2 M solution in hexanes, 8.64 mmol) was added. The reaction warmed to −42 °C and stirred for 35 minutes. The reaction was cooled to −78 °C and epoxide **125** (1.85 g, 6.65 mmol in 5 mL ether) was added. The reaction stirred for 15 minutes, and $BF_3{\bullet}Et_2O$ (1.09 mL, 8.64 mmol) was added dropwise. The reaction stirred for 45 minutes at −78 °C, then was quenched with 0.5 M HCl (20 mL) and warmed to ambient temperature. The contents were diluted with 10 mL 0.5 M HCl/80 mL EtOAc, and the combined organics were washed with saturated $NaHCO_3$ then brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (2.43 g, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 2H), 6.8 (m, 2H), 5.1 (m, 1H), 3.8 (s, 3H), 2.3 (m, 2H), 2.1 (s, 3H), 1.7–1.5 (m, 3H), 1.3 (2 singlets, 6H), 1.2 (m, 1H), 0.1 (s, 9H);

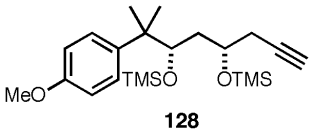


127

(3*S,5*S**)-2-(4-methoxyphenyl)-2-methyloct-7-yne-3,5-diol (127).**

To TMS alkyne **126** (2.49 g, 6.61 mmol) in MeOH (66 mL) was added K_2CO_3 (1.83 g, 13.22 mmol). The reaction stirred for three hours and the contents were partitioned between NH_4Cl/ether. The layers were separated, the organics were washed with saturated $NaHCO_3$ then brine, and the combined aqueous layers were back-extracted with ether (6x). The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was purified via flash column

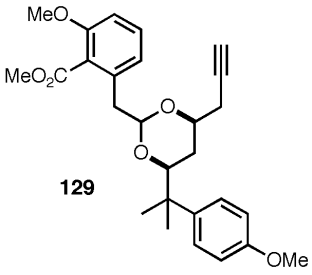
chromatography (40% EtOAc in hexanes eluent) to yield the title compound (1.29 g, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 2H), 6.8 (m, 2H), 4.0–3.85 (m, 2H), 3.8 (s, 3H), 3.6 (br s, 1H), 2.4 (br s, 1H), 2.3 (m, 2H), 2.1 (s, 1H), 1.75 (m, 1H), 1.5 (m, 1H), 1.3 (2 singlets, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 138.8, 127.7, 113.9, 81.1, 80.5, 71.3, 70.8, 55.4, 42.1, 36.3, 27.6, 24.3, 23.8;



128

(4*S,6*S**)-4-(2-(4-methoxyphenyl)propan-2-yl)-2,2,8,8-tetramethyl-6-(prop-2-ynyl)-3,7-dioxa-2,8-disilanonane (128).**

To diol **127** (903 mg, 3.44 mmol) in CH_2Cl_2 (18 mL) at 0 °C was added imidazole (1.03 g, 15.14 mmol). When the solid imidazole had dissolved (30 minutes), freshly distilled TMSCl was added. The reaction warmed to ambient temperature and stirred for 19 hours. The reaction was quenched with 20 mL water, extracted thrice with CH_2Cl_2. The combined organics were washed with 1 M HCl then brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (1.28 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2 (d, $J = 6.7$ Hz, 2H), 6.8 (d, $J = 6.7$ Hz, 2H), 3.80 (s, 3H), 3.68 (m, 2H), 2.2 (m, 1H), 2.1 (m, 1H), 1.9 (t, $J = 2.6$ Hz, 1H), 1.7–1.4 (m, 2H), 1.26 (2 singlets, 6H), 0.07 (2 singlets, 18H);

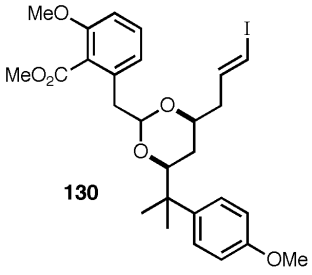


129

Methyl 2-Methoxy-6-(((2*S,4*S**,6*S**)-4-(2-(4-methoxy phenyl)propan-2-yl)-6-(prop-2-ynyl)-1,3-dioxan-2-yl) methyl)benzoate (129).**

To bis-TMS ether **128** (584 mg, 1.55 mmol) and aldehyde **117** (323 mg, 1.55 mmol) in CH_2Cl_2 (8 mL) at −78 °C was added TMSOTf (30 μL, .155 mmol). The reaction stirred for 2 minutes and was quenched with pyridine (19 μL) and poured in to saturated $NaHCO_3$. The aqueous layer was extracted thrice with CH_2Cl_2, and the combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was purified via flash column chromatography (20% EtOAc in hexanes eluent) to yield the title compound (551 mg, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 3H), 6.91 (d, $J = 7.7$

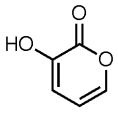
Hz, 1H), 6.8 (m, 3H), 4.67 (t, J = 4.8 Hz, 1H), 4.0–3.8 (m, 10H), 3.6 (m, 1H), 3.50 (dd, J = 11.3, 2.2 Hz, 1H), 3.0–2.8, (m, 1H), 2.45 (ddd, J = 16.7, 5.5, 2.7 Hz, 1H), 2.27 (ddd, J = 16.7, 7.4, 2.7 Hz, 1H), 1.96 (t, J = 2.7 Hz, 1H), 1.4 (m, 1H), 1.3–1.2 (m, 6H), 1.1 (m, 1H);



130

Methyl 2-(((2*S,4*S**,6*S**)-4-((*E*)-3-iodoallyl)-6-(2-(4-methoxyphenyl)propan-2-yl)-1,3-dioxan-2-yl)methyl)-6-methoxybenzoate (130).**

To alkyne **129** (369 mg, 816 μmol) in CH_2Cl_2 (4 mL) was added zirconocene hydrochloride (253 mg, 979 μmol). The reaction flask was covered in aluminum foil and stirred for 30 minutes. Freshly sublimed iodine (129 mg, 1.02 mmol) was added in one portion, the reaction stirred for 30 minutes and was quenched with 5 mL 20% $Na_2S_2O_3$. The biphasic mixture stirred vigorously for one hour and was partitioned between water/CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to yield the title compound (337 mg, 71%) : ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 3H), 6.9 (d, J = 7.3 Hz, 1H), 6.8 (m, 3H), 6.5 (m, 1H), 6.0 (d, J = 14.4 Hz, 1H), 4.6 (m, 1H), 4.0–3.7 (m, 11H), 3.5 (m, 1H), 2.8 (m, 1H), 2.2 (m, 1H), 2.1 (m, 1H), 1.28 (m, 7H), 1.1 (m, 1H);

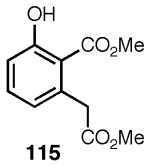


138

3-Hydroxypyran-2-one (138).

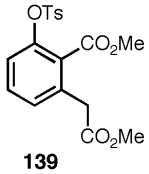
(*Previously reported compound*[61]) Solid mucic acid **137** (Acros, 50.0 g, 238 mmol) and $KHSO_4$ (50.0 g, 367 mmol) were mixed thoroughly together in a 250 mL round bottom flask. The flask was fitted with a short-path distillation condenser and receiving flask. The distillation head was left open to atmosphere in a fume hood to allow for escape of foul-smelling yellow smoke evolved during reaction. The distilling flask was heated with an open flame (Meeker burner) so that the solid mass melted from the top down. Even heating (allow for constant flame movement; flask may melt!) for 25 minutes caused collection of an orange distillate (bp = 130 °C). The distillate was partitioned between 100 mL water and 100 mL EtOAc and the layers were separated. The aqueous layer was adjusted to pH 7 with 1 M NaOH and extracted

with EtOAc (20x 20 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated to yield the title compound (2.93 g, 12%): ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.17 (dd, J = 3.6, 1.8 Hz, 1H), 6.68 (dd, J = 5.4, 1.8 Hz, 1H), 6.24 (s, 1H), 6.22 (m, 1H);



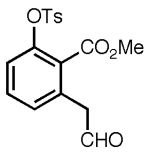
115

Methyl 2-Hydroxy-6-(2-methoxy-2-oxoethyl)benzoate (115). (*Previously reported compound*[37]) Allene **114** (8.37 g, 53.6 mmol) and pyrone **138** (6.62 g, 59.0 mmol) were dissolved in toluene (150 mL) and heated to 80 °C for 78 hours. Solvent was evaporated under reduced pressure and the crude material was purified via flash column chromatography (30% EtOAc in hexanes eluent) to yield the desired salicylate (11.1 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (s, 1H), 7.37 (dd, J = 7.5, 0.6 Hz, 1H), 6.97 (dd, J = 7.5, 1.2 Hz, 1H), 6.73 (ddd, J = 7.5, 1.2, 0.6 Hz, 1H), 3.90 (s, 5H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 171.0, 162.8, 136.5, 134.4, 123.8, 117.4, 112.1, 51.9, 51.7, 42.3; IR (neat) 2954. 1739. 1668, 1611, 1580, 1452, 1439, 1357, 1258, 1171 cm^{-1}; HRMS (EI): calcd for $C_{11}H_{12}O_5$ (M^+) 224.0685, found 224.0684.



139

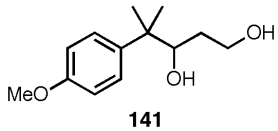
Methyl 2-(2-Methoxy-2-oxoethyl)-6-(tosyloxy)benzoate (139). To phenol **115** (2.10 g, 9.37 mmol) in acetone (50 mL) was added K_2CO_3 (2.58 g, 18.7 mmol) then tosyl chloride (1.79 g, 9.37 mmol). The reaction was heated to reflux for six hours and then partitioned between 75 mL water/75 mL EtOAc. The contents were extracted with EtOAc (3x 50 mL), and the combined organics were washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was purified via flash chromatography (30% EtOAc in hexanes) to yield the title compound (3.17 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7 (m, 2H), 7.3 (m, 3H), 7.2 (m, 1H), 7.1 (m, 1H), 3.7 (2 singlets, 5H), 3.62 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 165.8, 147.4, 145.8, 135.5, 132.6, 131.4, 130.0, 128.6, 127.6, 122.3, 52.5, 52.3, 39.3, 21.9; IR (neat) 2953, 1732, 1598, 1455, 1373, 1292, 1177 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{18}O_7S$ (M^+) 378.0773, found 378.0766.



140

Methyl 2-(2-Oxoethyl)-6-(tosyloxy)benzoate (140).

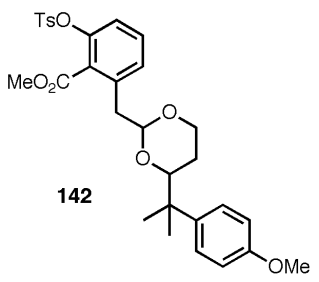
To ester **139** (272 mg, 702 μmol) in CH_2Cl_2 (10 mL) at -78 °C was added DIBAL (772 μL of a 1M solution in hexanes, 772 μmol) dropwise. The reaction stirred for one hour at -78 °C then was quenched with saturated sodium potassium tartrate and stirred vigorously for 30 minutes. Contents were extracted with CH_2Cl_2 (3x 10 mL) and the combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to yield the title compound (205 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.65 (m, 2H), 7.3 (m, 3H), 7.1 (d, $J = 7.7$ Hz, 1H), 7.0 (m, 1H), 3.8 (s, 2H), 3.7 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 165.8, 147.5, 146.0, 134.1, 132.4, 131.8, 130.3, 130.1, 128.5, 127.7, 122.5, 52.7, 48.6, 21.9; IR (neat) 1728, 1456, 1377, 1291, 1225, 1177, 1093, 911 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{16}O_6S$ (M^+) 348.0668, found 348.0654.



141

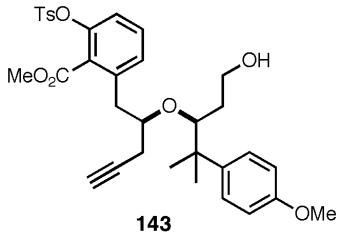
4-(4-Methoxyphenyl)-4-methylpentane-1,3-diol (141).

(*Previously reported compound*[1]) A steady stream of ozone was bubbled through a soln of 2-(4-methoxyphenyl)-2-methylhex-5-en-3-ol **122** (3.09 g, 14.0 mmol) in CH_2Cl_2 (30 mL) at -78 °C for 20 min. The soln was purged with N_2, then MeOH (30 mL) was added while the temperature was maintained at $-$ 78 °C. $NaBH_4$ (2.65 g, 70.3 mmol) was added and the reaction was warmed to 0 °C for 2 hours, then to r.t. for 16 h. The reaction was quenched by careful addition of H_2O (5 mL), then the solution was concentrated by removal of the majority of the solvent under reduced pressure. The residue was dissolved in EtOAc (200 mL) and washed with brine (2x 30 mL). The organic layer was collected, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (60% EtOAc in hexanes) to yield the title compound as a colorless oil (2.13 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, $J = 8.4$, 3.0 Hz, 2H), 6.88 (dd, $J = 8.4$, 3.0 Hz, 2H), 3.80 (m, 6H), 2.66 (br s, 1H), 2.21 (br s, 1H), 1.5 (m, 2H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 138.8, 127.6, 113.6, 79.9, 62.3, 55.2, 41.8, 32.8, 24.1, 23.7; IR (neat) 3371, 1960, 1610, 1513, 1295, 1252, 1186, 1035 cm^{-1}; HRMS (EI): calcd for $C_{13}H_{20}O_3$ (M^+) 224.1412, found 224.1402.



142

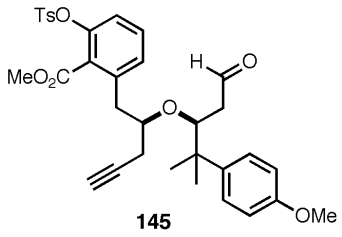
Methyl 2-(((2*R,4*R**)-4-(2-(4-Methoxyphenyl)propan-2-yl)-1,3-dioxan-2-yl)methyl)-6-(tosyloxy)benzoate (142).** Diol **141** (3.21 g, 14.3 mmol) and aldehyde **140** (5.54 g, 14.3 mmol) were dissolved in benzene (30 mL) and pTSA (272 mg, 1.43 mmol) was added. The reaction was heated to reflux in a vessel fitted with a Dean-Stark trap for five hours and the reaction was quenched with 10 mL saturated $NaCO_3$. Contents were poured into 100 mL water/100 mL EtOAc, and the layers were separated. The aqueous layer was extracted with EtOAc (3x 50 mL), the combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified via flash chromatography (30% EtOAc in hexanes) to yield the title compound (4.04 g, 51%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8 (m, 2H), 7.4 (m, 2H), 7.3–7.1 (m, 4H), 7.1 (m, 1H), 6.8 (m, 2H), 4.6 (m, 1H), 4.0 (m, 1H), 3.8 (m, 6H), 3.6 (m, 2H), 2.9 (m, 2H), 2.5 (s, 3H), 1.5 (m, 1H), 1.25 (s, 6H), 1.1 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 157.9, 146.7, 145.7, 138.9, 137.4, 132.9, 130.4, 130.1, 128.7, 128.4, 127.9, 120.9, 113.5, 101.6, 84.5, 67.1, 55.5, 52.6, 40.9, 39.4, 26.0, 25.8, 23.2, 22.0; IR (neat) 2965, 1732, 1514, 1456, 1378, 1288, 1250 cm^{-1}; HRMS (EI): calcd for $C_{30}H_{34}O_8S$ (M^+) 554.1974, found 554.1988.



143

Methyl 2-((*S)-2-((*S**)-1-Hydroxy-4-(4-methoxyphenyl)-4-methylpentan-3-yloxy)pent-4-ynyl)-6-(tosyloxy)benzoate (143).** Mixed Lewis acid was prepared by addition of Ti(O*i*Pr)$_4$ (5.48 mL, 18.7 mmol) to $TiCl_4$ (6.16 mL, 56.1 mmol) in CH_2Cl_2 (91 mL). To acetal **142** (3.46 g, 6.24 mmol) and allenyltributytin (5.56 mL, 18.7 mmol) in CH_2Cl_2 (31 mL) at -42 °C was added the mixed Lewis acid solution in one smooth pour. The reaction stirred at -42 °C for 10 minutes, then was quenched by addition of pyridine (30 mL) followed by MeOH (30 mL). Contents were poured into 1 M HCl (200 mL), extracted with CH_2Cl_2 (3x 100 mL) and the solvent was evaporated under reduced pressure and replaced with ether (300 mL). The ether solution stirred with KF on Celite (12 g) for one hour, then was filtered, dried over $MgSO_4$, filtered and concentrated.

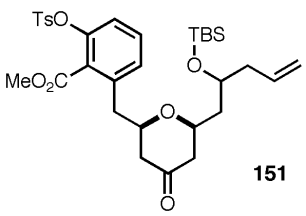
The resulting oil was purified via flash chromatography (40% EtOAc in hexanes) to yield 1.15 g of starting material, 1.8 g of a Friedel-Crafts product, and the title compound (456 mg, 18% brsm): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8 (m, 2H), 7.5–7.2 (m, 6H), 7.0 (m, 1H), 6.8 (m, 2H), 3.8 (m, 7H), 3.7 (m, 1H), 3.5 (m, 1H), 3.1 (m, 2H), 2.8 (m, 1H), 2.5 (s, 3H), 2.2 (m, 2H), 2.1 (s, 1H), 1.8 (br s, 1H), 1.4–1.2 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 158.0, 146.8, 145.9, 139.9, 139.5, 133.1, 131.1, 130.5, 130.1, 128.7, 128.3, 120.8, 113.6, 82.1, 81.5, 71.1, 60.5, 55.5, 52.9, 42.3, 38.6, 35.0, 28.1, 23.9, 23.6, 17.8; IR (neat) 3444, 3294, 2954, 1731, 1608, 1513, 1456, 1377 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{38}O_8NaS$ (M+Na$^+$) 617.2185, found 617.2127.



145

Methyl 2-((*S)-2-((*S**)-4-(4-methoxyphenyl)-4-methyl-1-oxopentan-3-yloxy)pent-4-ynyl)-6-(tosyloxy)benzoate (145).**

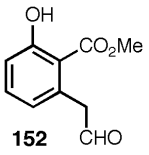
To alcohol **143** (135 mg, 227 μmol) in CH_2Cl_2 (12 mL) was added $NaHCO_3$ (286 mg, 3.4 mmol) followed by the Dess-Martin periodinane (289 mg, 681 μmol). The reaction stirred for 90 minutes, and was quenched with saturated $Na_2S_2O_3$. Contents were extracted with CH_2Cl_2 (3x 10 mL) and the combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (134 mg, >99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 7.7 (m, 2H), 7.4–7.1 (m, 6H), 7.1 (m, 1H), 6.8 (m, 2H), 4.0 (m, 1H), 3.8 (m, 6H), 3.6 (m, 1H), 3.0 (m, 1H), 2.8 (m, 1H), 2.5 (s, 3H), 2.3 (m, 2H), 2.1 (m, 1H), 1.7 (m, 2H), 1.26 (2 singlets, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 166.1, 158.1, 146.8, 145.8, 139.5, 138.5, 132.9, 130.7, 130.4, 128.7, 127.9, 120.8, 113.6, 81.0, 79.0, 71.1, 55.4, 52.7, 46.2, 41.9, 38.7, 27.1, 23.8, 22.7, 21.9; IR (neat) 3306, 2954, 1724, 1608, 1514, 1178, 732 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{36}O_6NaS$ (M+Na$^+$) 615.2129, found 615.2009.



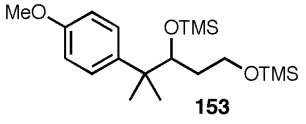
Methyl 2-(((2*R,6*S**)-6-((*R/S*)-2-(*tert*-Butyldimethylsilyloxy)pent-4-enyl)-4-oxotetrahydro-2H-pyran-2-yl)methyl)-6-(tosyloxy)benzoate (151).**

To enol acetate **150** (14 mg, 17μmol), 4 Å molecular sieves (28 mg) and $NaHCO_3$ (28 mg) in dichloroethane (3 mL) was added CAN (38 mg, 69 μmol) in 1 mL CH_3CN. The reaction strirred for 35 minutes and the contents were filtered through a plug of silica gel. The solvent was evaporated under reduced pressure and the resulting oil was purified via flash chromatography (30% EtOAc in hexanes) to yield the title compound (4 mg, 38%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8 (m, 2H), 7.4–7.1 (m, 3H), 6.8 (m, 2H), 5.7 (m, 1H), 5.0 (m, 2H), 4.0–3.7 (m, 6H), 3.0 (m, 2H), 2.5 (s, 3H), 2.2–2.0 (m, 6H), 1.7 (s, 2H), 0.8 (m, 9H), 0.1, (m, 6H);

Methyl 2-Hydroxy-6-(2-oxoethyl)benzoate (152).



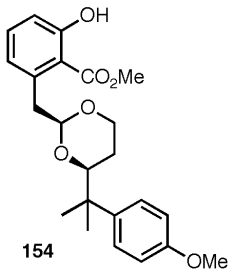
To ester **115** (8.06 g, 35.9 mmol) in CH_2Cl_2 (180 mL) at -78 °C was added, dropwise, DIBAL (54 mL of a 1.0 M solution in hexanes). The reaction warmed to 0 °C and stirred for 1 hour, at which time the reaction was quenched with 1 M HCl (200 mL). The biphasic mixture stirred vigorouslty for 1 hour. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x 100 mL). The combined organics were washed with water (200 mL), then brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash column chromatography (30% EtOAc in hexanes eluent) to yield the title compund (5.45 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.18 (s, 1H), 9.70 (s, 1H), 7.40 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 7.2 Hz, 1H), 3.94 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 171.1, 163.5, 135.5, 135.2, 124.4, 118.2, 112.6, 52.6, 51.6; IR (neat) 3052, 2956, 1719, 1670, 1609, 1577, 1449, 1319, 1247, 1219 cm^{-1}; MS: m/z(%): 194 (7) [$C_{10}H_{10}O_4^+$].



4-(2-(4-Methoxyphenyl)propan-2-yl)-2,2,8,8-tetramethyl-3,7-dioxa-2,8-disilanonane (153).

To diol **141** (5.04 g, 22.5 mol) and imidazole (6.13 g, 90.0 mmol) in CH_2Cl_2 (110 mL) at 0 °C was added TMSCl (7.33 g, 8.48 mL, 67.5

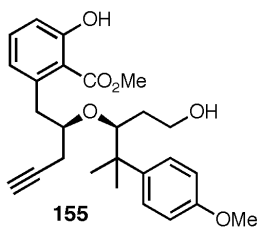
mmol) dropwise. The reaction warmed to ambient temperature and stirred for 16 hours, then was quenced with water (100 mL). The organics were washed with 1 M HCl (100 mL), then brine (100 mL), dried over $MgSO_4$, filtered and concentrated to yield the title compound (7.43 g 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 3.80 (m, 4H), 3.53 (m, 1H), 3.42 (m, 1H), 1.53 (m, 1H), 1.38 (m, 1H), 1.2 (2 singlets, 6H), 0.2 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 140.5, 128.0, 113.5, 77.9, 60.7, 55.5, 42.4, 36.1, 26.5, 23.9, 0.94, -0.14; IR (neat) 2958, 1611, 1513, 1250, 1088 cm^{-1};



154

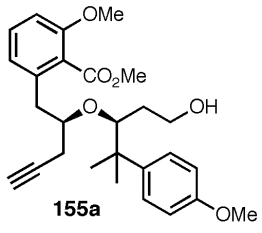
Methyl 2-Hydroxy-6-{4-[1-(4-methoxyphenyl)-1-methylethyl]-1,3-dioxan-2-ylmethyl}benzoate (154).

To a solution of aldehyde **152** (25 mg, 129 μmol) and bis-TMS ether **153** (48 mg (129 μmol) in CH_2Cl_2 (2 mL) at -78 °C was added TMSOTf (3 mg, 3 μL, 13 μmol. The reaction warmed to 0 °C and stirred for 10 minutes, then was quenched with pyridine (5 drops). Contents were poured into saturated aqueous $NaHCO_3$ (4 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 4 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash column chromatography (40% EtOAc in hexanes eluent) to yield the title compound (49 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.06 (s, 1H), 7.30 (m, 1H), 7.25 (d, $J = 9.0$ Hz, 2H), 6.89 (dd, $J = 8.4$, 1.2 Hz, 1H), 6.80 (m, 3H), 4.61 (dd, $J = 5.1$, 4.8 Hz, 1H), 4.04 (dd, $J = 11.4$, 4.2 Hz, 1H), 3.89 (s 3H), 3.79 (s, 3H), 3.58 (ddd, $J = 12.1$, 11.4, 2.4 Hz, 1H), 3.41 (dd, $J = 11.4$, 1.8 Hz, 1H), 3.31 (dd, $J = 13.5$, 5.1 Hz, 1H), 3.23 (dd, $J = 13.5$, 4.8 Hz, 1H), 1.57 (ddd, $J = 24.0$, 12.0, 5.0 Hz, 1H), 1.29 (s, 3H), 1.28 (s, 3H), 1.07 (d, $J = 12.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 162.5, 157.9, 139.0, 134.2, 127.9, 124.5, 116.6, 113.4, 112.9, 102.7, 84.7, 67.2, 55.4, 52.3, 42.2, 40.9, 26.1, 25.6, 23.2; IR (neat) 2956, 2851, 1663, 1610, 1513, 1449, 1034 cm^{-1}; MS: m/z(%): 423 (100) [$C_{23}H_{28}O_6Na^+$].



155

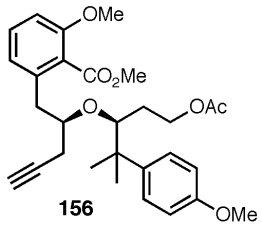
Methyl 2-Hydroxy-6-{2-[1-(2-hydroxyethyl)-2-(4-methoxyphenyl)-2-methylpropoxy]pent-4-ynyl}benzoate (155). To acetal **154** (3.13 g, 7.82 mmol) and allenyltrimethylsilane (24 wt% soln in pentane, 10.97 g, 23 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added a −78 °C solution of $TiCl_4$ (4.44 g, 23.4 mmol in 20 mL CH_2Cl_2) via cannula. The reaction had consumed all starting material within 10 minutes and was quenched with pyridine (10 mL) followed by MeOH (10 mL). The quenched mixture warmed to ambient temperature and the contents were poured into 1 M HCl (50 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3x 30 mL), the combined organics were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash column chromatography (30% EtOAc in hexanes eluent) to yield the title compound (1.74 g, dr = 6.8:1, 50%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.31 (s, 1H), 7.35 (dd, J = 8.1, 7.5 Hz, 1H), 6.95 (dd, J = 7.5, 0.9 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.79 (dd, J = 7.5, 0.9 Hz, 1H), 6.70 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.75–3.65 (m, 2H), 3.35–3.25 (m, 2H), 2.84 (dd, J = 13.8, 9.6 Hz, 1H), 2.41 (dd, J = 4.8, 2.7 Hz, 1H), 2.06 (dd, J = 2.7, 2.4 Hz, 1H), 1.7–1.5 (m, 2H), 1.35-1.20 (m, 3H), 1.04 (s, 3H), 0.936 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 162.8, 157.7, 141.6, 140.7, 134.1, 127.4, 125.6, 116.7, 113.5, 113.1, 81.6, 81.4, 76.9, 71.0, 60.6, 55.4, 52.4, 42.2, 41.9, 34.3, 26.4, 24.0, 23.3; IR (neat) 3427, 3303, 2955, 1663, 1609, 1512, 1449, 1252 cm^{-1}; MS: m/z(%): 463 (100) [$C_{26}H_{32}O_6Na^+$].



155a

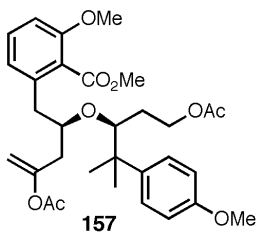
Methyl 2-{2-[1-Hydroxy-4-(4-methoxyphenyl)-4-methylpentan-3-yloxy]pent-4-ynyl}-6-methoxybenzoate (155a). To phenol **155** (603 mg, 1.37 mmol) and K_2CO_3 (567 mg, 4.10 mmol) in dry acetone (30 mL) was added iodomethane (389 mg, 171 μL, 2.74 mmol). The reaction was heated to reflux for 14 hours. The contents were partitioned between water (100 mL) and EtOAc (100 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3x 20 mL), the combined organics were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified via flash column chromatography (30% EtOAc in hexanes eluent) to yield the title compound (582 mg, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ

7.25 (dd, $J = 8.1$, 7.8 Hz, 1H), 7.19 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 7.5$ Hz, 1H), 6.8–6.72 (m, 3H), 3.89 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.75–3.50 (m, 4H), 2.82 (d, $J = 6.6$ Hz, 2H), 2.42 (ddd, $J = 17.0$, 5.4, 2.7 Hz, 1H), 2.30 (ddd, $J = 17.0$, 6.9, 2.7 Hz, 1H), 2.06 (dd, $J = 2.7$, 2.4 Hz, 1H), 1.84 (br s, 1H), 1.6–1.5 (m, 2H), 1.19 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 157.9, 156.7, 140.2, 137.0, 130.4, 127.7, 124.5, 123.7, 113.6, 109.5, 82.0, 81.7, 77.9, 71.1, 60.3, 56.2, 55.4, 52.6, 42.7, 38.1, 34.8, 26.4, 24.0, 23.5; IR (neat) 3538, 3289, 2952, 2837, 1727, 1584, 1513, 1470, 1267, 1073 cm^{-1}; MS: m/z(%): 477 (100) [$C_{27}H_{34}O_6Na^+$].



156

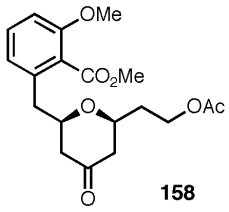
Methyl 2-{2-[1-(2-Acetoxyethyl)-2-(4-methoxyphenyl)-2-methylpropoxy]pent-4-ynyl}-6-methoxybenzoate (156). To alcohol **155a** (48 mg, 106 μmol) in CH_2Cl_2 (1 mL) was added DMAP (1.3 mg, 10.6 μmol) then pyridine (17 mg, 17 μL, 211 μmol), then acetic anhydride (32 mg, 30 μL, 211 μmol). The reaction stirred at ambient temperature for 1 hour, then was partitioned between water (20 mL) and CH_2Cl_2 (20 mL). The organics were washed with 1 M HCl (20 mL), then brine (20 mL), dried over $MgSO_4$, filtered and concentrated to yield the title compound (50 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dd, $J = 9.0$, 7.8 Hz, 1H), 7.19 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 7.8$ Hz, 1H), 6.85–6.75 (m, 3H), 4.2–4.0 (m, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.70 (m, 1H), 3.59 (dd, $J = 7.8$, 3.3 Hz, 1H), 2.86 (d, $J = 6.9$ Hz, 2H), 2.38 (ddd, $J = 16.8$, 5.4, 2.7 Hz, 1H), 2.28 (m, 1H), 2.06 (dd, $J = 2.7$, 2.1 Hz, 1H), 1.99 (s, 3H), 1.7–1.5 (m, 2H), 1.19 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 168.8, 158.0, 156.8, 139.8, 137.0, 130.4, 128.0, 127.7, 124.6, 123.8, 113.6, 109.5, 81.6, 81.3, 78.2, 71.2, 62.5, 56.2, 55.4, 52.5, 42.8, 38.2, 31.5, 26.7, 23.6, 21.3; IR (neat) 3286, 2953, 2838, 1734, 1584, 1513, 1471, 1250, 1074 cm^{-1}; HRMS (EI): calcd for $C_{29}H_{36}O_7Na$ (M + Na^+) 519.2359, found 519.2335.



157

Methyl 2-{4-Acetoxy)-2-[1-(2-acetoxyethyl)-2-(4-methoxyphenyl)-2-methylpropoxy]pent-4-enyl}-6-methoxybenzoate (157).

A solution of *n*-decyne (114 mg, 148 μL, 821 μmol), Na_2CO_3 (13 mg, 123 μmol), dicholoro(*p*-cymene)ruthenium dimer (20 mg, 33 μmol), tri-2-furyl phosphine (15 mg, 66 μmol) and acetic acid (99 mg, 94 μL, 1.64 mmol) in toluene (10 mL) was heated to 80 °C for 45 minutes. Alkyne **156** (408 mg, 821 μmol) in toluene (10 mL) was added in 10 portions. A further 2 equivalents of acetic acid (99 mg, 94 μL, 1.64 mmol) were added and the reaction stirred at 80 °C for 14 hours. The solvent was evaporated and the crude solid was purified via flash column chromatography (30% EtOAc in hexanes eluent) to yield the title compound (358 mg, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, J = 8.1 Hz, 1H), 7.12 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 7.8 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.7 Hz, 2H), 4.76 (2 singlets, 2H), 4.0–3.9 (m, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.65–3.50 (m, 2H), 2.75 (dd, J = 13.8, 7.2 Hz, 1H), 2.59 (m, 2H), 2.19 (d, J = 6.6 Hz, 1H), 2.13 (s, 3H), 2.02 (s, 3H), 1.7–1.5 (m, 2H), 1.15 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 169.2, 168.8, 157.9, 156.8, 153.6, 140.0, 137.4, 130.3, 127.7, 124.6, 123.8, 113.8, 109.4, 104.1, 80.4, 76.6, 62.6, 56.3, 55.4, 52.4, 42.5, 38.9, 38.7, 31.4, 26.5, 23.9, 21.4, 21.3; IR (neat) 2959, 2838, 1740, 1735, 1513, 1250, 1074 cm^{-1}; MS: m/z(%): 579 (100) [$C_{31}H_{40}O_9Na^+$].



158

Methyl 2-{[6-(2-Acetoxyethyl)-4-oxotetrahydro-2*H*-pyran-2-yl]methyl}-6-methoxybenzoate (158).

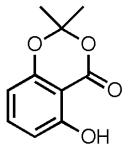
To a solution of enol acetate **157** (33 mg, 59 μmol), $NaHCO_3$ (66 mg), and powdered 4 Å molecular sieves (66 mg) in 1,2-dichloroethane (4 mL) at 40 °C was added a solution of CAN (130 mg, 237 μmol) in acetonitrile (1 mL) in one portion. The reaction turned a murky green color and stirred for 10 minutes at 40 °C. The contents were filtered through a plug of silica gel (EtOAc eluent), concentrated, and purified via flash column chromatography (40% EtOAc in hexanes eluent) to yield the title compound (16 mg, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 4.2–4.1 (m, 2H), 4.0–3.7 (m, 7H), 3.67 (m, 1H), 2.97 (dd,

$J = 13.8$, 7.2 Hz, 1H), 2.75 (dd, $J = 14.1$, 5.1 Hz, 1H), 2.4–2.2 (m, 4H), 2.02 (s, 3H), 2.0–1.8 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 171.3, 168.9, 156.9, 136.2, 130.7, 123.1, 109.8, 77.6, 74.0, 61.1, 56.3, 52.6, 47.9, 47.7, 40.1, 35.5, 21.3; IR (neat) 2954, 1732, 1585, 1471, 1267, 1073 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{24}O_7Na$ (M + Na^+) 387.1420, found 387.1432.

APPENDIX C

EXPERIMENTAL PROCEDURES SUPPLEMENT TO CHAPTER 4

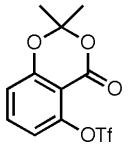
See preface to Appendix A for standard operating procedures.



160

5-Hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (160).

(*Previously reported compound*[70]) To a solution of 2,6-dihydroxybenzoic acid **159** (32.5 g, 211 mmol), DMAP (1.30 g, 10.7 mmol) and acetone (20 mL, 280 mmol) in 1,2-dimethoxyethane (70 mL) was added $SOCl_2$ (22 mL, 302 mmol) dropwise. The reaction stirred for 1 hour and was purged with N_2 for 2 hours to displace HCl gas. The volatiles were evaporated under reduced pressure and the residue was suspended in a mixture of 20 mL hexanes/20 mL CH_2Cl_2 and filtered through a pad of silica (11 g). The silica was washed with a further 80 mL of the 1:1 hexanes:CH_2Cl_2 mixture and then the solvent was evaporated. The residue was dissolved in hexanes (30 mL), and the precipitate that formed was collected to yield the title compound (35.5 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.42 (t, $J = 8.4$ Hz, 1H), 6.64 (d, $J = 8.4$ Hz, 1H), 6.45 (d, $J = 8.4$ Hz, 1H), 1.76 (s, 6H);

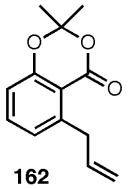


161

2,2-Dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl Trifluoromethanesulfonate (161).

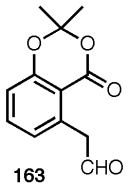
(*Previously reported compound*[71]) To phenol **160** (5.74 g, 29.5 mmol) in anhydrous pyridine (60 mL) at 0 °C was added triflic anhydride (10.0 g, 5.96 mL, 35.44 mmol) dropwise. The reaction warmed to r.t. and stirred for 2 hours, whereupon it was quenched carefully with saturated aqueous $NaHCO_3$ (60 mL). The

aqueous layer was extracted with ether (3x 30 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated. Purification via flash chromatography (20% EtOAc in hexanes eluent) yielded the title compound (11.59 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (t, $J = 8.4$ Hz, 1H), 7.07 (dd, $J = 8.4$, 0.9 Hz, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 1.77 (s, 6H);



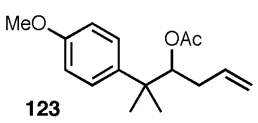
162

5-Allyl-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (162). (*Previously reported compound*[72]) A soln of triflate **161** (7.31 g, 22.4 mmol), lithium chloride (2.85 g, 67.2 mmol), palladium (tetrakis)triphenylphosphine (1.29 g, 1.12 mmol) and allyltributyltin (8.90 g, 26.9 mmol) in THF (100 mL) was heated to reflux for 3 hours. The reaction was quenched by addition of water (100 mL). The aqueous layer was separated and extracted with EtOAc (3x 100 mL). The combined organics were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified via flash chromatography (10% EtOAc in hexanes eluent) to yield the title compound (4.45 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (t, $J = 7.9$ Hz, 1H), (6.97 (d, $J = 7.5$ Hz, 1H), 6.85 (d, $J = 8.1$ Hz, 1H), 6.05 (m, 1H), 5.09 (m, 1H), 5.04 (m, 1H), 3.90 (d, $J = 6.0$ Hz, 2H), 1.71 (s, 6H);



163

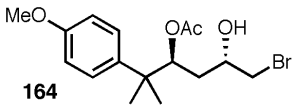
2-(2,2-Dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)ethanal (163). (*Previously reported compound*[72]) A steady stream of ozone was bubbled through a soln of alkene **162** (3.81 g, 17.5 mmol) in CH_2Cl_2 (100 mL) at 0 °C for 20 minutes. Dimethyl sulfide (25.6 mL, 349 mmol) was added and the reaction warmed to room temperature. Triphenylphosphine (4.58 g, 17.5 mmol) was added and the reaction stirred for 5 hours. The volatiles were evaporated under reduced pressure and the resulting crude material was purified via flash chromatography (30% EtOAc in hexanes eluent) to yield the title compound (3.95 g, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.94 (t, $J = 7.9$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 6.90 (d, $J = 7.5$ Hz, 1H), 4.22 (s, 2H), 1.73 (s, 6H);



123

2-(4-Methoxyphenyl)-2-methylhex-5-en-3-yl Ethanoate (123).

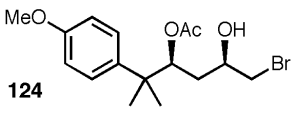
To a soln of alcohol **122** (11.65 g, 52.90 mmol), triethylamine (11.1 mL, 79.4 mmol) and DMAP (648 mg, 5.3 mmol) at 0 °C was added acetic anhydride (8.10 g, 79.4 mmol) dropwise. The reaction was allowed to warm to r.t. and stirred for 120 hours. The contents were poured into 1 M HCl (100 mL), extracted with CH_2Cl_2 (3x 100 mL), washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash chromatography (10% EtOAc in hexanes eluent) to yield the title compound (11.59 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, $J = 9.0$ Hz, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 5.62 (m, 1H), 5.20 (dd, $J = 9.6$, 3.1 Hz, 1H), 4.96 (m, 1H), 4.92 (m, 1H), 3.79 (s, 3H), 2.15–2.03 (m, 2H), 2.02 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 157.9, 138.2, 135.1, 127.5, 116.8, 113.5, 79.4, 55.1, 41.1, 34.9, 26.4, 23.0, 21.0; IR (neat) 2973, 1738, 1514, 1370, 1248, 1186, 1033 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{22}O_3$ (M^+) 262.1569, found 262.1577.



164

(3*S,5*S**)-6-Bromo-5-hydroxy-2-(4-methoxyphenyl)-2-methylhexan-3-yl Ethanoate (164).**

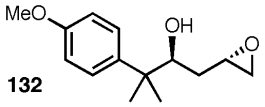
To alkene **123** (288 mg, 1.10 mmol) in THF (6 mL) and water (40 μL) at 0 °C was added NBS (215 mg, 1.21 mmol, freshly recrystalized from H_2O). The reaction warmed to r.t. and stirred for 20 hours. Contents were partitioned between into 10 mL EtOAc and 10 mL of water. The aqueous phase was extracted with EtOAc (3x 10 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash chromatography (30% EtOAc in hexanes eluent) to yield a diastereomer, later shown to be the 'anti' configuration, of the title compound (242 mg, 24%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 5.27 (m, 1H), 3.81 (s, 3H), 3.59 (m, 1H), 3.32 (m, 2H), 3.03 (d, $J = 4.5$ Hz, 1H), 2.06 (s, 3H), 1.60–1.49 (m, 2H), 1.35 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 158.0, 137.8, 135.6, 127.4, 113.6, 77.8, 76.6, 67.6, 55.2, 40.9, 38.3, 35.8, 25.7, 23.7, 21.0; IR (neat) 3488, 2967, 2360, 1734, 1513, 1372, 1250, 1034 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{23}O_4Br$ (M^+) 358.0780, found 358.0789.



124

(3*S,5*R**)-6-Bromo-5-hydroxy-2-(4-methoxyphenyl)-2-methylhexan-3-yl Ethanoate (124).**

To alkene **123** (288 mg, 1.10 mmol) in THF (6 mL) and water (40 μL) at 0 °C was added NBS (215 mg, 1.21 mmol, freshly recrystalized from H_2O). The reaction warmed to r.t. and stirred for 20 hours. Contents were partitioned between into 10 mL EtOAc and 10 mL of water. The aqueous phase was extracted with EtOAc (3x 10 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash chromatography (30% EtOAc in hexanes eluent) to yield a diastereomer, later shown to be the 'syn' configuration, of the title compound (739 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 5.09 (dd, J = 8.4, 3.3 Hz, 1H), 3.79 (s, 3H), 3.58 (m, 1H), 3.44 (dd, J = 10.2, 3.3 Hz, 1H), 3.31 (dd, J = 10.5, 5.7 Hz, 1H), 2.59 (d, J = 5.1 Hz, 1H), 2.05 (s, 3H), 1.71–1.59 (m, 2H), 1.33 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 158.3, 137.8, 127.8, 113.9, 78.4, 69.4, 55.5, 41.5, 39.9, 36.3, 26.4, 22.9, 21.4; IR (neat) 3455, 2970, 1732, 1514, 1248, 1033 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{23}O_4Br$ (M^+) 358.0780, found 358.0789.

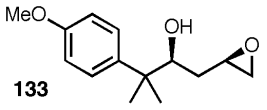


132

(*S)-3-(4-Methoxyphenyl)-3-methyl-1-[(*S**)-oxiran-2-yl]butan-2-ol (132).**

To bromohydrin **164** (770 mg, 2.14 mmol) in MeOH (10 mL) at 0 °C was added solid NaOMe (255 mg, 4.72 mmol) in one portion. The reaction warmed to r.t. and stirred for 72 hours, then was quenched with saturated aqueous amonium chloride (10 mL). Contents were partitioned between EtOAc (5 mL) and water (5 mL). The pH of the aqueous layer was adjusted to pH = 4 with 1 M HCl, and the aqueous phase was extracted with CH_2Cl_2 (3x 5 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash chromatography (40% EtOAc in hexanes eluent) to yield the title compound (later determined to be the 'anti' isomer, 204 mg, 40%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 9.0 Hz), 2H), 3.85 (ddd, J = 10.8, 3.9, 2.1 Hz, 1H), 3.81 (s, 3H),

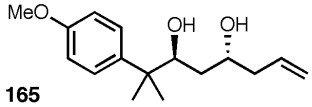
3.12 (m, 1H), 2.80 (app t, J = 4.2 Hz, 1H), 2.56 (dd, J = 4.8, 2.7 Hz, 1H), 1.71 (dd, J = 4.2, 1.2 Hz, 1H), 1.64 (m, 1H), 1.48 (m, 1H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 138.8, 127.9, 114.1, 77.8, 55.6, 51.2, 47.8, 42.0, 34.4, 24.8, 23.8; IR (neat) 3475, 2963, 1512, 1295 cm^{-1}; HRMS (EI): calcd for $C_{14}H_{20}O_3$ (M^+) 236.1412, found 236.1412.



133

(*S)-3-(4-Methoxyphenyl)-3-methyl-1-[(*R**)-oxiran-2-yl]butan-2-ol (133).**

To bromohydrin **124** (3.44 g, 9.58 mmol) in MeOH (50 mL) at 0 °C was added solid NaOMe (1.14 g, 21.1 mmol) in one portion. The reaction warmed to r.t. and stirred for 72 hours, then was quenched with saturated aqueous amonium chloride (50 mL). Contents were partitioned between EtOAc (50 mL) and water (50 mL). The pH of the aqueous layer was adjusted to pH = 4 with 1 M HCl, and the aqueous phase was extracted with CH_2Cl_2 (3x 50 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash chromatography (30% EtOAc in hexanes eluent) to yield the title compound (later determined to be the 'syn' isomer, 1.45 g, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 3.86 (ddd, J = 10.5, 3.6, 1.8 Hz, 1H), 3.81 (s, 3H), 3.04 (m, 1H), 2.72 (app t, J = 4.2 Hz, 1H), 2.41 (dd, J = 4.8, 2.7 Hz, 1H), 2.03 (d, J = 3.6 Hz, 1H), 1.66 (ddd, J = 14.4, 4.5, 1.8 Hz, 1H), 1.39 (m, 1H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 138.6, 127.5, 113.6, 78.2, 55.2, 51.7, 46.5, 41.7, 34.5, 24.5, 23.5; IR (neat) 3469, 2966, 1513, 1251, 1186 cm^{-1}; HRMS (EI): calcd for $C_{14}H_{20}O_3$ (M^+) 236.1412, found 236.1406.

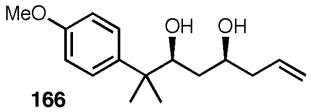


165

(3*S,5*R**)-2-(4-Methoxyphenyl)-2-methyloct-7-ene-3,5-diol (165).**

To a solution of copper(I) iodide (62 mg, 0.324 mol) in THF (2 mL) at −78 °C was added a 1.0 M soln of vinyl magnesium bromide (3.24 mL, 3.24 mmol), dropwise. The reaction stirred for 30 minutes at −78 °C, then epoxide **132** (255 mg, 1.08 mmol) in THF (3 mL) was dropwise. The reaction warmed to r.t. and stirred for 12 hours. The flask was cooled to 0 °C and the reaction was quenched

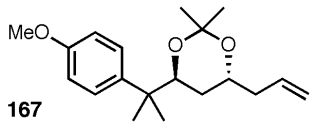
with saturated aqueous amonium chloride (5 mL). A steady stream of compressed air was bubbled gently through the suspension for 1.5 hours. Contents were partitioned between water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography yielded the title compound (66 mg, 38%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, $J = 8.7$, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 5.78 (m, 1H), 5.14 (m, 1H), 5.10 (m, 1H), 3.95 (m, 2H), 3.81 (s, 3H), 2.24 (m, 2H), 2.12 (d, $J = 4.2$ Hz, 1H), 1.88 (d, $J = 3{,}3$ Hz, 1H), 1.50 (dd, $J = 6.0$, 5.7 Hz, 2H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 138.9, 134.9, 127.6, 118.1, 113.7, 75.9, 68.5, 55.2, 41.8, 41.7, 36.9, 24.4, 23.5; IR (neat) 3413, 2958, 1512, 1250, 1036 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{24}O_3$ (M^+) 264.1725, found 264.1712.



166

(3*S,5*S**)-2-(4-Methoxyphenyl)-2-methyloct-7-ene-3,5-diol (166).**

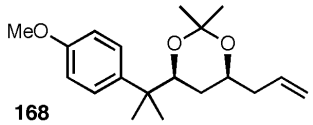
To a solution of copper(I) iodide (114 mg, 0.597 mol) in THF (4 mL) at −78 °C was added a 1.0 M soln of vinyl magnesium bromide (5.97 mL, 5.97 mmol), dropwise. The reaction stirred for 30 minutes at −78 °C, then epoxide **133** (470 mg, 1.99 mmol) in THF (6 mL) was dropwise. The reaction warmed to r.t. and stirred for 12 hours. The flask was cooled to 0 °C and the reaction was quenched with saturated aqueous amonium chloride (10 mL). A steady stream of compressed air was bubbled gently through the suspension for 1.5 hours. Contents were partitioned between water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3x 20 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography yielded the title compound (364 mg, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 5.80 (m, 1H), 5.13 (m, 1H), 5.08 (m, 1H), 3.90–3.77 (m, 5H), 3.22 (br s, 1H), 2.58 (br s, 1H), 2.20 (m, 2H), 1.58 (m, 1H), 1.39 (m, 1H), 1.33 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 139.1, 134.9, 127.9, 118.2, 114.0, 81.0, 72.4, 55.6, 42.7, 42.2, 37.1, 24.5, 23.9; IR (neat) 3379, 2964, 1513, 1297, 1073 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{24}O_3$ (M^+) 264.1725, found 264.1720.



167

(4*R,6*S**)-4-Allyl-6-[2-(4-methoxyphenyl)propan-2-yl]-2,2-dimethyl-1,3-dioxane (167).**

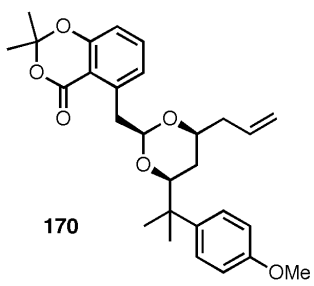
To diol **165** (33 mg, 0.124 mmol) in 2,2-dimethoxypropane (10 mL) was added a catalytic amount (<5 mg) amount of *p*-toluenesulfonic acid. The reaction stirred at r.t. for 24 hours. The reaction was concentrated to a volume of <1 mL, and the contents were purified via flash chromatography (10% EtOAc in hexanes eluent) to yield the title compound (36 mg, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 5.74 (m, 1H), 5.05 (m, 1H), 5.00 (m, 1H), 3.9–3.7 (m, 4H), 3.65 (m, 1H), 2.18 (m, 1H), 2.11 (m, 1H), 1.6–1.1 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 138.8, 134.7, 127.9, 116.5, 113.0, 100.3, 73.6, 66.8, 55.2, 40.2, 40.0, 33.6, 25.8, 24.8, 24.1, 23.2; IR (neat) 2984, 1612, 1513, 1377, 1251, 1225 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{28}O_3$ (M^+) 304.2038, found 304.2036.



168

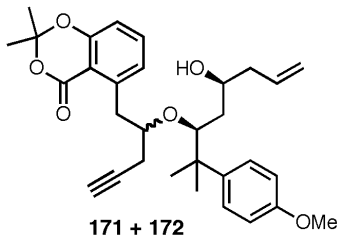
(4*S,6*S**)-4-Allyl-6-[2-(4-methoxyphenyl)propan-2-yl]-2,2-dimethyl-1,3-dioxane (168).**

To diol **166** (112 mg, 0.424 mmol) in 2,2-dimethoxypropane (20 mL) was added a catalytic amount (<5 mg) amount of *p*-toluenesulfonic acid. The reaction stirred at r.t. for 24 hours. The reaction was concentrated to a volume of <1 mL, and the contents were purified via flash chromatography (10% EtOAc in hexanes eluent) to yield the title compound (121 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0 Hz, 2H), 5.75 (m, 1H), 5.05 (m, 1H), 5.00 (m, 1H), 4.9–4.7 (m, 5H), 2.25 (m, 1H), 2.07 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H), 1.13 (m, 1H), 1.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 139.0, 134.5, 127.8, 116.8, 113.1, 98.5, 76.3, 55.2, 40.9, 40.5, 31.0, 30.1, 25.9, 22.8, 19.7; IR (neat) 2989, 1612, 1513, 1378, 1249, 1111 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{28}O_3$ (M^+) 304.2038, found 304.2034.



5-(((2*S,4*S**,6*S**)-4-Allyl-6-(2-(4-methoxyphenyl)propan-2-yl)-1,3-dioxan-2-yl)methyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (170).**

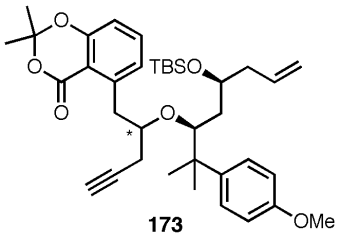
To bis-TMS ether **169** (1.14 g, 3.01 mmol) and aldehyde **163** (663 mg, 3.01 mmol) in CH_2Cl_2 (25 mL) at −78 °C was added TMSOTf (58 μL, 0.301 mmol). The reaction stirred for 10 minutes at −78 °C, then was quenched with pyrdine (5 mL) and poured into saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (10% EtOAc in hexanes eluent) yielded the title compound (738 mg, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (app t, $J = 7.9$ Hz, 1H), 7.20 (d, $J = 9.0$ Hz, 2H), 7.03 (dd, $J = 7.8$, 0.9 Hz, 1H), 6.85 (dd, $J = 8.4$, 1.2 Hz, 1H), 6.77 (d, $J = 9.0$ Hz, 2H), 5.74 (m, 1H), 5.05–4.95 (m, 2H), 4.81 (dd, $J = 6.3$, 4.2 Hz, 1H), 3.78 (s, 3H), 3.63 (dd, $J =$ 13.2, 3.9 Hz, 1H), 3.53 (m, 1H), 3.46 (m, 1H), 3.36 (dd, $J = 13.5$, 6.3, 1H), 2.28 (m ,1H), 2.12 (m, 1H), 1.69 (s, 3H), 1.68 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 1.2–1.1 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 157.6, 156.7, 141.6, 138.8, 134.6, 134.2, 127.7, 127.6, 116.9, 115.7, 113.2, 112.8, 105.1, 100.6, 83.8, 76.7, 76.0, 55.1, 40.6, 40.4, 39.5, 31.1, 25.7, 25.6, 23.3; IR (neat) 2958, 2838, 1737, 1607, 1583, 1513, 1448, 1315, 1295, 1252, 1131, 1053 cm^{-1}; HRMS (EI): calcd for $C_{28}H_{34}O_6$ (M^+) 466.2355, found 466.2362.



5-((*epi*-2-((3*S,5*S**)-5-Hydroxy-2-(4-methoxyphenyl)-2-methyloct-7-en-3-yloxy)pent-4-ynyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (171, 172).**

To acetal **170** (385 mg, 0.825 mmol) in CH_2Cl_2 (5 mL) was was added a 68 wt% soln of allenyltrimethylsilane(409 mg), and the flask was cooled to −78 °C. In a separate flask, a solution of freshly distilled $TiCl_4$ (470 mg, 2.48 mmol) in CH_2Cl_2 (5 mL) was cooled to −78 °C. The pre-cooled $TiCl_4$ solution was transferred via cannula to the −78 °C soln containing the substrate and nucleophile. Upon completion of addition, the reaction had consumed all starting material and was quenched by addition of pyridine (1 mL) followed by MeOH (1

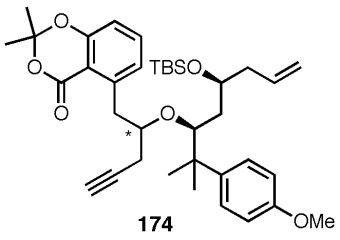
mL). The contents were poured into 1 M HCl (10 mL) and extracted with CH_2Cl_2 (3x 10 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash chromatography to yield the title compound as a mixture of in separable epimers differing at C9 (323 mg, dr = 1.008:1 (as determined by separating subsequent derivatives), 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47.–7.35 (m, 4H), 7.2–7.15 (m, 2H), 7.1–7.0 (m, 2H), 6.9–6.75 (m, 6H), 5.8–5.6 (m, 2H), 5.1–4.9 (m, 4H), 4.35–4.25 (m, 1H), 4.0–3.9 (m, 2H), 3.9–3.8 (m, 1H), 3.8–3.7 (m, 6H), 3.7–3.5 (m, 2H), 3.5–3.3 (m, 3H), 3.3–3.2 (m, 1H), 3.1–3.0 (m, 1H), 2.8–2.7 (m, 1H), 2.6–2.5 (m, 1H), 2.4–2.2 (m, 2H), 2.1–1.9 (m, 7H), 1.8–1.6 (m, 12H), 1.6–1.4 (m, 3H), 1.4–1.3 (m, 6H), 1.3–1.2 (m, 3H), 1.2–1.0 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 160.3, 157.7, 157.6, 157.2, 157.1, 143.4, 142.7, 139.9, 139.7, 135.4, 135.1, 127.8, 127.5, 127.4, 127.2, 117.1, 117.0, 116.2, 116.1, 113.4, 113.3, 112.5, 112.1, 105.3, 105.2 83.5, 82.2, 81.2, 80.8, 76.7, 75.8, 75.7, 71.3, 70.9, 70.4, 69.7, 55.2, 55.1, 42.6, 42.4, 42.1, 42.0, 39.5, 39.0, 37.6, 37.5, 25.9, 25.8, 25.6, 25.5, 23.9, 23.6, 23.5, 23.3, 22.0; IR (neat) 3525, 3300, 2937, 1732, 1606, 1581, 1511, 1476, 1314, 1251, 1048 cm^{-1}; HRMS (EI): calcd for $C_{31}H_{39}O_6$ (M + H$^+$) 507.2747, found 507.2739.



173

5-((*R*/S)-2-((3*S**,5*S**)-5-(tert-Butyldimethylsilyloxy)-2-(4-methoxyphenyl)-2-methyloct-7-en-3-yloxy)pent-4-ynyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (173).** To a solution of epimeric alcohols **171** and **172** (489 mg, 0.965 mmol) and imidazole (138 mg, 2.03 mmol) in CH_2Cl_2 (10 mL) was added TBSCl (291 mg, 1.93 mmol). The reaction stirred for 48 h and was quenched with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash chromatography (gradient of 5% to 10% to 20% EtOAc in hexanes eluent),whereupon the diastereomers proved separable, to yield 263 mg of the higher-Rf diastereomer and 261 mg of the lower-Rf diastereomer (87%). Spectral details for the diastereomer with higher Rf: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (app t, J = 7.9 Hz, 1H), 7.31 (d, J = 9.0 Hz, 2H), 7.02 (dd, J = 7.5, 0.9 Hz, 1H), 6.9–6.8 (m, 3H), 5.98 (m, 1H), 4.9–4.8 (m, 2H), 3.78 (s, 3H), 3.7–3.5 (m, 3H), 3.23 (dd, J

= 12.0, 5.7 Hz, 1H), 3.2–3.1 (m, 1H), 2.34 (ddd, J = 16.8, 5.4, 2.7 Hz, 1H), 2.20 (m, 1H), 2.05–1.96 (m, 2H), 1.95–1.85 (m, 1H), 1.73 (s, 3H), 1.66 (s, 3H), 1.35 (m, 4H), 1.27 (s, 3H), 0.87 (m, 10H), 0.03 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 157.9, 157.3, 144.2, 140.1, 135.2, 135.0, 128.3, 127.7, 116.9, 116.0, 113.5, 112.8, 105.3, 81.8, 80.7, 75.1, 70.7, 70.2, 55.6, 42.6, 42.1, 39.7, 38.8, 26.6, 26.5, 26.3, 25.5, 24.0, 23.3, 18.4, −3.8, −4.2; IR (neat) 3309, 2954, 2932, 1736, 1607, 1582, 1513, 1476, 1297, 1253, 1080, 1044 cm^{-1}; HRMS (EI): calcd for $C_{33}H_{43}O_6Si$ (M − C_4H_9)$^+$ 563.2829, found 563.2826.

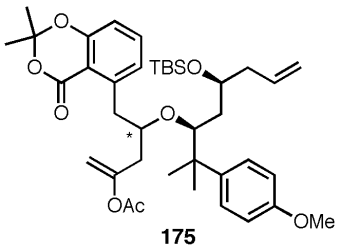


174

5-((*R*/S)-2-((3*S**,5*S**)-5-(tert-Butyldimethylsilyloxy)-2-(4-methoxyphenyl)-2-methyloct-7-en-3-yloxy)-pent-4-ynyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (174).**

To a solution of epimeric alcohols **171** and **172** (489 mg, 0.965 mmol) and imidazole (138 mg, 2.03 mmol) in CH_2Cl_2 (10 mL) was added TBSCl (291 mg, 1.93 mmol). The reaction stirred for 48 h and was quenched with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3x 10 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified via flash chromatography (gradient of 5% to 10% to 20% EtOAc in hexanes eluent),whereupon the diastereomers proved separable, to yield 263 mg of the higher-Rf diastereomer and 261 mg of the lower-Rf diastereomer (87%). Spectral details for the diastereomer with lower Rf: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (app t, J = 7.9 Hz, 1H), 7.15–7.07 (m, 3H), 6.87 (dd, J = 8.1, 0.9 Hz, 1H), 6.78 (d, J = 8.7 Hz, 2H), 5.65 (m, 1H), 5.0–4.9 (m, 2H), 3.8–3.75 (m, 4H), 3.55 (m, 1H), 3.48 (dd, J = 12.9, 4.8 Hz, 1H), 3.38 (m, 1H), 3.27 (dd, J = 12.9, 7.5 Hz, 1H), 2.58 (ddd, J = 16.8, 5.4, 2.7 Hz, 1H), 2.41 (dt, J = 16.8, 3.0 Hz, 1H), 2.23–2.13 (m, 1H), 2.04 (app t, J = 2.7, 2.4 Hz, 1H), 1.98–1.86 (m, 1H), 1.72 (s, 3H), 1.69 (s, 3H), 1.52 (m, 2H), 1.13 (s, 3H), 1.05 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 157.9, 157.4, 144.3, 140.1, 135.4, 135.1, 128.1, 127.8, 117.0, 116.2, 113.7, 112.9, 105.4, 81.8, 81.6, 71.2, 70.3, 55.6, 42.9, 42.0, 41.0, 39.6, 26.6, 26.3, 26.2, 25.8, 24.2, 23.2, 18.4, −3.7, −4.2; IR (neat) 3309, 2954, 2856, 1735, 1607, 1582, 1513, 1476, 1388, 1299, 1078, 1046 cm^{-1}; HRMS (EI): calcd for $C_{37}H_{52}O_6Si$

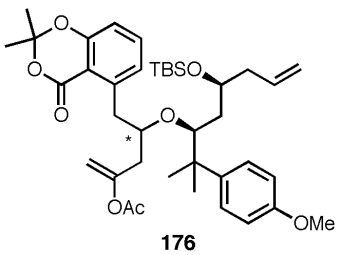
(M^+) 620.3533, found 620.3535.



175

(*R*/S)-4-((3*S**,5*S**)-5-(tert-Butyldimethylsilyloxy)-2-(4-methoxyphenyl)-2-methyloct-7-en-3-yloxy)-5-(2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)pent-1-en-2-yl Ethanoate (175).**

A solution of *n*-decyne (59 mg, 77 μL, 424 μmol), Na_2CO_3 (7 mg, 64 μmol), dicholoro(*p*-cymene)ruthenium dimer (10 mg, 17 μmol), tri-2-furyl phosphine (8 mg, 34 μmol) and acetic acid (102 mg, 97 μL, 1.69 mmol) in toluene (5 mL) was heated to 80 °C for 45 minutes. Alkyne **173** (263 mg, 424 μmol) in toluene (5 mL) was added in 5 portions and the reaction stirred at 80 °C for 14 hours. The solvent was evaporated and the crude solid was purified via flash column chromatography (10% EtOAc in hexanes eluent) to yield the title compound (264 mg, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4–7.3 (m, 3H), 6.93 (dd, J = 7.5, 0.9 Hz, 1H), 6.86–6.80 (m, 3H), 5.56 (m, 1H), 4.92–4.78 (m, 4H), 3.87–3.75 (m, 5H), 3.66–3.58 (m, 1H), 3.42–3.33 (m, 1H), 3.0–2.92 (m, 1H), 2.4–2.2 (m, 2H), 2.08 (s, 3H), 1.87–1.81 (m, 1H), 1.75 (s, 3H), 1.67 (s, 3H), 1.4–1.2 (m, 7H), 1.04–0.97 (m, 1H), 0.9–0.78 (m, 10H), 0.0 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 160.4, 157.9, 157.4, 153.7, 143.9, 140.4, 135.4, 135.1, 128.2, 127.9, 116.9, 116.2, 113.6, 112.7, 105.4, 104.6, 80.2, 75.5, 70.1, 55.6, 43.1, 41.6, 40.1, 39.9, 38.6, 27.0, 26.8, 26.3, 25.2, 23.0, 21.6, 18.4, −3.8, −4.2; IR (neat) 2954, 2931, 1755, 1735, 1607, 1513, 1252, 1203, 1079, 1042 cm^{-1}; HRMS (EI): calcd for $C_{35}H_{47}O_8Si$ (M − C_4H_9)$^+$ 623.3040, found 623.3063.

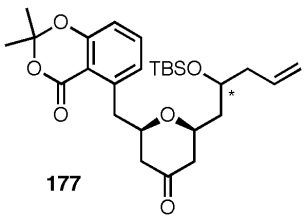


176

(*R*/S)-4-((3*S**,5*S**)-5-(tert-Butyldimethylsilyloxy)-2-(4-methoxyphenyl)-2-methyloct-7-en-3-yloxy)-5-(2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)pent-1-en-2-yl Ethanoate (176).**

A solution of *n*-decyne (48 mg, 63 μL, 349 μmol), Na_2CO_3 (5.5 mg, 52 μmol), dicholoro(*p*-cymene)ruthenium dimer (8.5 mg, 14 μmol), tri-2-furyl phosphine (6.5 mg, 28 μmol) and acetic acid (84 mg, 80 μL, 1.40 mmol)

in toluene (5 mL) was heated to 80 °C for 45 minutes. Alkyne **174** (217 mg, 349 μmol) in toluene (5 mL) was added in 5 portions and the reaction stirred at 80 °C for 14 hours. The solvent was evaporated and the crude solid was purified via flash column chromatography (10% EtOAc in hexanes eluent) to yield the title compound (186 mg, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (app t, J = 7.9 Hz, 1H), 7.11 (d, J = 9.0 Hz, 2H), 6.98 (m, 1H), 6.86 (dd, J = 8.1, 0.9 Hz, 1H), 6.78 (d, J = 9.0 Hz, 2H), 5.67 (m, 1H), 5.03–4.78 (m, 4H), 3.9–3.8 (m, 1H), 3.78 (s, 3H), 3.65–3.55 (m, 1H), 4.5–3.3 (m, 2H), 3.2–3.0 (m, 1H), 2.7–2.6 (m, 1H), 2.3–2.15 (m, 2H), 2.12 (s, 3H), 2.0–1.88 (m, 1H), 1.73 (s, 3H), 1.67 (s, 3H), 1.5–1.4 (m, 2H), 1.11 (s, 3H), 1.08 (s, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 160.4, 157.9, 157.3, 153.4, 144.2, 140.3, 135.5, 134.9, 128.2, 127.8, 117.0, 116.1, 113.7, 113.0, 112.7, 105.3, 103.9, 81.0, 80.6, 77.8, 77.4, 76.9, 75.8, 70.3, 55.5, 42.8, 41.7, 40.8, 39.7, 39.3, 26.7, 26.6, 26.3, 25.4, 23.6, 21.6, 21.0, 18.5, −3.7, −4.3; IR (neat) 2954, 2931, 1737, 1607, 1582, 1513, 1314, 1253, 1210, 1076, 1046 cm^{-1}; HRMS (EI): calcd for $C_{39}H_{56}O_8Si$ $(M + Na)^+$ 703.3642, found 703.3604.

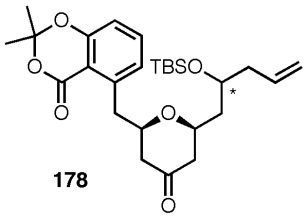


177

5-(((2*R,6*S**)-6-((*R*/S**)-2-(tert-Butyldimethylsilyloxy)pent-4-enyl)-4-oxotetrahydro-2*H*-pyran-2-yl)methyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (177).**

To a solution of enol acetate **175** (264 mg, 388 μmol), $NaHCO_3$ (250 mg), and powdered 4 Å molecular sieves (250 mg) in 1,2-dichloroethane (16 mL) at 40 °C was added a solution of CAN (850 mg, 1.55 mmol) in acetonitrile (4 mL) in one portion. The reaction turned a murky green color and stirred for 45 minutes at 40 °C. The contents were filtered through a plug of silica gel (EtOAc eluent), concentrated, and purified via flash column chromatography (40% EtOAc in hexanes eluent) to yield the title compound (98 mg, 52%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (app t, J = 7.9 Hz, 1H), 7.00 (dd, J = 7.5, 0.6 Hz, 1H), 6.87 (dd, J = 8.4, 0.9 Hz, 1H), 5.62 (m, 1H), 4.97–4.82 (m, 2H), 3.9–3.7 (m, 2H), 3.65–3.5 (m, 2H), 3.07 (dd, J = 13.2, 8.7 Hz, 1H), 2.6–2.5 (m, 1H), 2.4–2.25 (m, 2H), 2.25–2.1 (m, 1H), 2.07–1.95 (m, 1H), 1.94–1.85 (m, 1H), 1.84–1.75 (m, 1H), 1.69 (s, 6H), 1.55 (ddd, J = 14.1, 7.8, 4.2 Hz, 1H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 160.9, 157.4, 143.2, 135.3, 135.2, 127.3, 117.2,

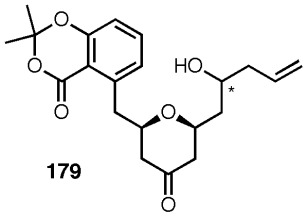
116.4, 112.4, 105.6, 73.7, 68.8, 48.4, 47.9, 43.6, 41.2, 41.1, 26.1, 26.0, 25.9, 18.3, −4.2, −4.3; IR (neat) 2929, 2856, 1733, 1607, 1583, 1477, 1448, 1316, 1297, 1059 cm^{-1}; HRMS (EI): calcd for $C_{27}H_{40}O_6NaSi$ $(M + Na)^+$ 511.2492, found 511.2472.



178

5-(((2*R,6*S**)-6-((*R*/S**)-2-(tert-Butyldimethylsilyloxy)pent-4-enyl)-4-oxotetrahydro-2*H*-pyran-2-yl)methyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (178).**

To a solution of enol acetate **176** (209 mg, 307 μmol), $NaHCO_3$ (200 mg), and powdered 4 Å molecular sieves (200 mg) in 1,2-dichloroethane (16 mL) at 40 °C was added a solution of CAN (673 mg, 1.23 mmol) in acetonitrile (4 mL) in one portion. The reaction turned a murky green color and stirred for 45 minutes at 40 °C. The contents were filtered through a plug of silica gel (EtOAc eluent), concentrated, and purified via flash column chromatography (40% EtOAc in hexanes eluent) to yield the title compound (100 mg, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (t, $J = 7.8$, 1H), 7.02 (d, $J = 7.5$ Hz, 1H), 6.87 (dd, $J = 8.1$, 0.6 Hz, 1H), 5.77 (m, 1H), 5.1–5.0 (m, 2H), 3.9–3.78 (m, 2H), 3.69–3.55 (m, 2H), 3.06 (dd, $J = 12.9$, 8.1 Hz, 1H), 2.50 (m, 1H), 2.35–2.25 (m, 2H), 2.25–2.14 (m, 3H), 1.75–1.63 (m, 7H), 1.44 (m, 1H), 0.78 (s, 9H), −0.12 (s, 3H), −0.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 160.7, 157.4, 143.0, 135.1, 134.8, 127.5, 117.5, 116.5, 112.9, 105.5, 76.9, 73.2, 67.9, 48.5, 47.9, 44.3, 43.1, 40.9, 26.7, 26.0, 25.4, 18.2, −4.3, −5.0; IR (neat) 2953, 2930, 2856, 1734, 1606, 1583, 1477, 1381, 1318, 1299, 1269, 1213, 1079 cm^{-1}; HRMS (EI): calcd for $C_{23}H_{31}O_6Si$ $(M - C_4H_9)^+$ 431.1890, found 431.1870.

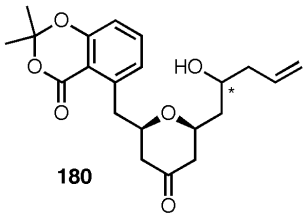


179

5-(((2*R,6*S**)-6-((*R*/S**)-2-Hydroxypent-4-enyl)-4-oxotetrahydro-2*H*-pyran-2-yl)methyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (179).**

To TBS ether **177** (98 mg, 0.200 mmol) in THF (1 mL) was added water (1 mL) followed by glacial acetic acid (3 mL). The reaction stirred for 12 hours and was partitioned between water (10 mL) and EtOAc (10 mL). The organics were washed with water (2x 10 mL), then saturated aqueous

$NaHCO_3$ (20 mL). The combined aqueous layers were back-extracted with EtOAc (3x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. Purification via flash chromatography (50% EtOAc in hexanes eluent) yielded the title compound (56 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (app t, J = 7.9 Hz, 1H), 6.97 (dd, J = 7.5, 0.6 Hz, 1H), 6.91 (dd, J = 8.1, 0.9 Hz, 1H), 5.73 (m, 1H), 5.07 (d, J = 0.9 Hz, 1H), 5.02 (m, 1H), 4.05–3.95 (m, 1H), 3.78–3.6 (m, 3H), 3.07 (dd, J = 13.2, 8.4 Hz, 1H), 2.87 (s, 1H), 2.63–2.55 (m, 1H), 2.42–2.27 (m, 3H), 2.25–2.06 (m, 2H), 1.72 (s, 3H), 1.69 (s, 3H), 1.68–1.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 160.9, 157.7, 142.4, 135.9, 134.8, 126.8, 117.9, 117.1, 112.4, 105.7, 70.8, 48.2, 47.8, 42.4, 41.9, 41.4, 26.2, 25.7; IR (neat) 3523, 2926, 1728, 1606, 1583, 1479, 1317, 1299, 1270, 1208, 1061 cm^{-1}; HRMS (EI): calcd for $C_{21}H_{26}O_6$ (M^+) 374.1729, found 374.1722.



180

5-(((2*R,6*S**)-6-((*R*/S**)-2-Hydroxypent-4-enyl)-4-oxo-tetrahydro-2*H*-pyran-2-yl)methyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (180).**

To TBS ether **178** (98 mg, 0.200 mmol) in THF (1 mL) was added water (1 mL) followed by glacial acetic acid (3 mL). The reaction stirred for 12 hours and was partitioned between water (10 mL) and EtOAc (10 mL). The organics were washed with water (2x 10 mL), then saturated aqueous $NaHCO_3$ (20 mL). The combined aqueous layers were back-extracted with EtOAc (3x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. Purification via flash chromatography (50% EtOAc in hexanes eluent) yielded the title compound (56 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (app t, J = 7.9 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.88 (dd, J = 8.4, 0.9 Hz, 1H), 5.73 (m, 1H), 5.1–5.0 (m, 2H), 3.97–3.86 (m, 1H), 3.85–3.75 (m, 2H), 3.58 (dd, J = 13.2, 3.9 Hz, 1H), 3.16 (dd, J = 13.2, 8.1 Hz, 1H), 2.53 (dd, J = 15.0, 2.4 Hz, 1H), 2.39–2.25 (m, 4H), 2.17–2.10 (m, 2H), 1.8–1.55 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 160.8, 157.6, 142.8, 135.5, 134.9, 126.9, 118.1, 116.8, 112.5, 105.7, 76.9, 74.4, 67.9, 47.9, 47.7, 42.1, 42.0, 41.1, 26.1, 25.8; IR (neat) 3489, 2922, 1727, 1606, 1583, 1479, 1317, 1270, 1209, 1062 cm^{-1}; HRMS (EI): calcd for $C_{21}H_{26}O_6Na$ (M + Na)$^+$ 397.1627, found 397.1651.

APPENDIX D

BIBLIOGRAPHY

[1] Wang, L.; Seiders, J. R., II; Floreancig, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 12596–12603.

[2] Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075.

[3] Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, *6*, 913–919.

[4] Finbow, M. E.; Harrison, M. A. *Biochem. J.* **1997**, *324*, 697–712.

[5] Stevens, T. H.; Forgac, M. *Annu. Rev. Cell. Dev. Biol.* **1997**, *13*, 779–808.

[6] Nelson, N.; Harvey, W. R. *Physiol. Rev.* **1999**, *79*, 361–385.

[7] Pedersen, P. L.; Carafoli, E. *Trends biochem. Sci.* **1987**, *12*, 146–150.

[8] Higgins, C. F. *Annu. Rev. Cell. Dev. Biol.* **1992**, *8*, 67–113.

[9] Frattini, A.; Orchard, P. J.; Sobacchi, C.; Giliani, S.; Abinun, M.; Mattsson, J. P.; Keeling, D. J.; Andersson, A.-K.; Wallbrandt, P.; Zecca, L.; Notarangelo, L. D.; Vezzoni, P.; Villa, A. *Nat. Genet.* **2000**, *25*, 343–346.

[10] Karet, F. E. et al. *Nat. Genet.* **1999**, *21*, 84–90.

[11] Rojas, J. D.; Sennoune, S. R.; Martinez, G. M.; Bakunts, K.; Meininger, C. J.; Wu, G.; Wesson, D. E.; Seftor, E. A.; Hendrix, M. J. C.; Martínez-Zaguilán, R. *J. Cell. Physiol.* **2004**, *201*, 190–200.

[12] Haass, C.; Capell, A.; Citron, M.; Teplow, D. B.; Selkoe, D. J. *J. Biol. Chem.* **1995**, *270*, 6186–6192.

[13] Kosenko, E.; Llansola, M.; Montoliu, C.; Monfort, P.; Rodrigo, R.; Hernandez-Viadel, M.; Erceg, S.; Sánchez-Perez, A. M.; Felipo, V. *Neurochem. Int.* **2003**, *42*, 493–498.

[14] Otani, H.; Yamamura, T.; Nakao, Y.; Hattori, R.; Fujii, H.; Ninomiya, H.; Kido, M.; Kawaguchi, H.; Osako, M.; Imamura, H.; Ohta, T.; Ohkuma, S. *Circulation* **2000**, *102*, 269–274.

[15] Wax, M. B.; Saito, I.; Tenkova, T.; Krupin, T.; Becker, B.; Nelson, N.; Brown, D.; Gluck, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 6752–6757.

[16] Bowman, E. J.; Siebers, A.; Altendorf, K. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7972–7976.

[17] Yilla, M.; Tan, A.; Ito, K.; Miwa, K.; Ploegh, H. L. *J. Biol. Chem.* **1993**, *268*, 19092–19100.

[18] Mattsson, J. P.; Keeling, D. J. *Biochim. Biophys. Acta* **1996**, *1280*, 98–106.

[19] Huss, M.; Sasse, F.; Kunze, B.; Jansen, R.; Steinmetz, H.; Ingenhorst, G.; Zeeck, A.; Wieczorek, H. *BMC Biochem.* **2005**, *6*, 1–10.

[20] Sørensen, M. G.; Henriksen, K.; Neutzsky-Wulff, A. V.; Dziegiel, M. H.; Karsdal, M. A. *J. Bone Miner. Res.* **2007**, *22*, 1640–1648.

[21] Farina, C.; Gagliardi, S. *Curr. Pharm. Des.* **2002**, *8*, 2033–2048.

[22] Niikura, K.; Takeshita, N.; Chida, N. *J. Toxicol. Sci.* **2005**, *30*, 297–304.

[23] Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188–8192.

[24] McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, J. H., II; Laakso, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805–7810.

[25] Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153–155.

[26] Chevallier, C.; Laprévote, O.; Bignon, J.; Debitus, C.; Guénard, D.; Sévenet, T. *Nat. Prod. Res.* **2004**, *18*, 479–484.

[27] Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217–1220.

[28] Bhattacharjee, A.; De Brabander, J. K. *Tetrahedron Lett.* **2000**, *41*, 8069–8073.

[29] Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2398–2400.

[30] Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5549–5552.

[31] Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 3701–3704.

[32] Graetz, B. R.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3357–3360.

[33] Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430.

[34] Hilli, F.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1289–1292.

[35] Petri, A. F.; Bayer, A.; Maier, M. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 5821–5823.

[36] Li, M.; O' Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087–6090.

[37] Caliskan, E.; Cameron, D. W.; Griffiths, P. G. *Aust. J. Chem.* **1999**, *52*, 1013–1020.

[38] Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248–3249.

[39] Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 917.

[40] Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992–4998.

[41] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

[42] Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 2230–2239.

[43] Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458–6467.

[44] Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925–3929.

[45] Perrott, A. L.; Lijser, H. J. P. D.; Arnold, D. R. *Can. J. Chem.* **1997**, *75*, 384–397.

[46] Tu, W.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2009**, *121*, 4637–4641.

[47] Grunwell, J. R.; Karpides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 9195.

[48] Node, M.; Fujiwara, T.; Ichihashi, S.; Nishide, K. *Tetrahedron Lett.* **1998**, *39*, 6331–6334.

[49] Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712–713.

[50] Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920 –7921.

[51] Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *124*, 1307–1315.

[52] Skrydstrup, T.; Bénéchie, M.; Khuong-Huu, F. *Tetrahedron Lett.* **1990**, *31*, 7145–7148.

[53] Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679–680.

[54] Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088–2089.

[55] Silverman, I. R.; Edington, C.; Elliott, J. D.; Johnson, W. S. *J. Org. Chem.* **1987**, *52*, 180–183.

[56] Denmark, S. E.; Willson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258–9260.

[57] Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 80898110.

[58] Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485–6487.

[59] Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477–511.

[60] Kozikowski, A. P.; Floyd, W. C.; Kuniak, M. P. *J. Chem. Soc. Chem. Comm.* **1977**, *17*, 582–583.

[61] Wiley, R. H.; Jarboe, C. H. *J. Am. Chem. Soc.* **1956**, *78*, 2398–2401.

[62] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, Third ed.; John Wiley & Sons, Inc., 1999.

[63] Sridhar, M.; Kumar, B. A.; Narender, R. *Tetrahedron Lett.* **1998**, *39*, 2847–2850.

[64] Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

[65] Gopalakrishnan, G.; Kasinath, V.; Singh, N. D. P. *Org. Lett.* **2002**, *4*, 781–782.

[66] Lee, P. H.; yung Sung, S.; Lee, K. *Org. Lett.* **2001**, *3*, 3201–3204.

[67] Herb, C.; Maier, M. E. *J. Org. Chem.* **2003**, *68*, 8129–8135.

[68] Chen, G.; Wang, Z.; Wu, J.; Ding, K. *Org. Lett.* **2008**, *10*, 4573–4576.

[69] Seiders, J. R., II; Wang, L.; Floreancig, P. E. *J. Am. Chem. Soc.* **2003**, *125*, 2406–2407.

[70] Hadfield, A.; Schweitzer, H.; Trova, M. P.; Green, K. *Synth. Commun.* **1994**, *24*, 1025–1028.

[71] Furstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071–15078.

[72] Nicolaou, K. C.; Kim, D. W.; Baati, R.; O'Brate, A.; Giannakakou, P. *Chem. Eur. J.* **2003**, *9*, 6177–6191.