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Towards the Synthesis of Marine Polyether Triterpenes

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Date

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B.S., Montana State University, 2001

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An Abstract of

A thesis submitted to the Faculty of the Graduate School of

Emory University in partial fulfillment of

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Master of Science

Department of Chemistry

2008

Abstract: The carbon skeleton of marine polyether triterpenes: thyrsiferol, dehydrothyrsiferol, thyrsenols A and B has been constructed. Carbon-carbon bonds were successfully created by nucleophilic opening of terminal epoxides and palladium catalyzed cross coupling. Oxygen containing stereocenters were set by asymmetric epoxide formation and asymmetric dihydroxylation. Cyclic ethers were formed by acid catalyzed hydroxyepoxide oxacyclizations, tungsten promoted alkynol endocyclization, and the Nakata rearrangement.

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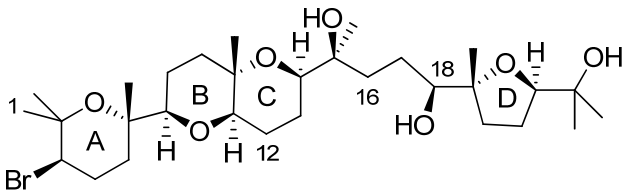
1.0) Introduction:

Oceanic life has produced a wide range of structurally diverse biologically active natural products.[1] The majority of these compounds are isolated from algae, bacteria, soft corals, and sponges. Pharmacologically these natural products display anti-tumor, anti-inflammatory, analgesia, allergy, and anti-viral properties. Despite significant synthetic and pharmacological research/interest in marine natural products, none are currently on the market as pharmaceutical drugs.

Marine derived polyether compounds exhibit a large diversity of ring sizes and show strong biological activity.[2] These polyethers originate from derivatives of fatty acids or terpenoids from squalene.[2a] This thesis will focus entirely on polyether triterpenes. These metabolites have been isolated from red algae (largely from the genus *Laurencia*) found in a variety of geographic locations.

Figure 1: Thyrsiferol

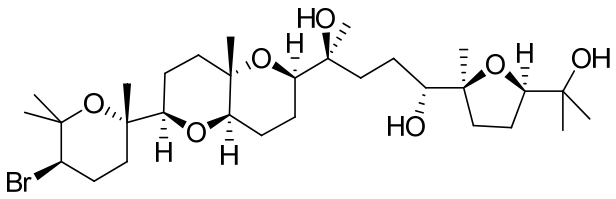


Thyrsiferol **1**

Thyrsiferol (**1)** was the first marine polyether triterpenoid possessing the BC ring structure (dioxabicyclo[4.4.0]decane) reported.[3] It was isolated from *Laurencia thyrsifera* collected off the coast of New Zealand.[3] The structure and relative stereochemistry was determined by X-ray crystallographic analysis of the derivative thyrsiferyl 18-acetate but the absolute stereochemistry was not determined until venustatriol (**2**) was isolated and characterized.[4] Thyrsiferol and its acetate derivatives were tested against the P-388

lymphoid cancer cell line.[2b] While thyrsiferol (**1**) showed some activity (ED_{50} = 10 ng/mL), thyrsiferol 23-acetate was a powerful cell growth inhibitor (ED_{50} = 0.3 ng/mL).[2b]

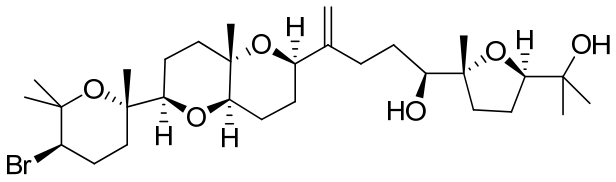
Figure 2: Venustatriol



Venustatriol **2**

Venustatriol (**2**) was isolated from *Laurencia venusta* off the coast of Okinawa.[4] It shares the ABC ring structure of thyrsiferol but varies in stereochemistry at positions C_{18} and C_{19}. This slight change in stereostructure results in significant changes in biological activity. The crude extract from *L. venusta* exhibited activity against vesicular stomatitis virus (VSV) and *Herpes simplex* type 1 (HVS-1).[4]

Figure 3: Dehydrothyrsiferol



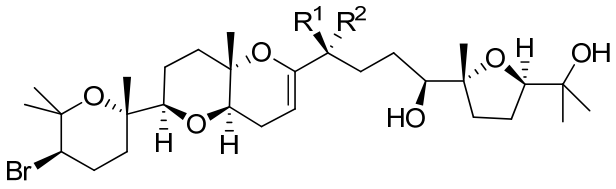
Dehydrothysiferol **3**

Dehydrothyrsiferol (**3**) was isolated from *Laurencia pinnatifida* collected off the coast of the Canary Islands of Spain.[5] Dehydrothyrsiferol's structure was determined by chemical transformation to thyrsiferol (**1**).[5] Dehydrothyrsiferol shows anticancer activity against P-388 cell line (IC_{50} = 0.017 μM)[2a] and antimitotic activity by inhibiting PP2A.[6]

Thyrsenols A (**4**) and B (**5**) were isolated from *Laurencia viridis* off the coast of the Canary Islands of Spain.[7] Thyrsenol B (**5**) displays much greater cytotoxicity against P388 cell line (IC_{50} = 0.016 μM) compared to thyrsenol A (**4**) (IC_{50} = 0.40 μM).[7] It is

theorized that the orientation of the side chain containing the D ring in relation to the ABC ring structure greatly affects the cytotoxic activity of this family of compounds.[6]

Figure 4: Thyrsenols A and B



Thyrsenol A: R^1= OH, R^2= CH_2OH **4**
Thyrsenol B: R^1= CH_2OH, R^2= OH **5**

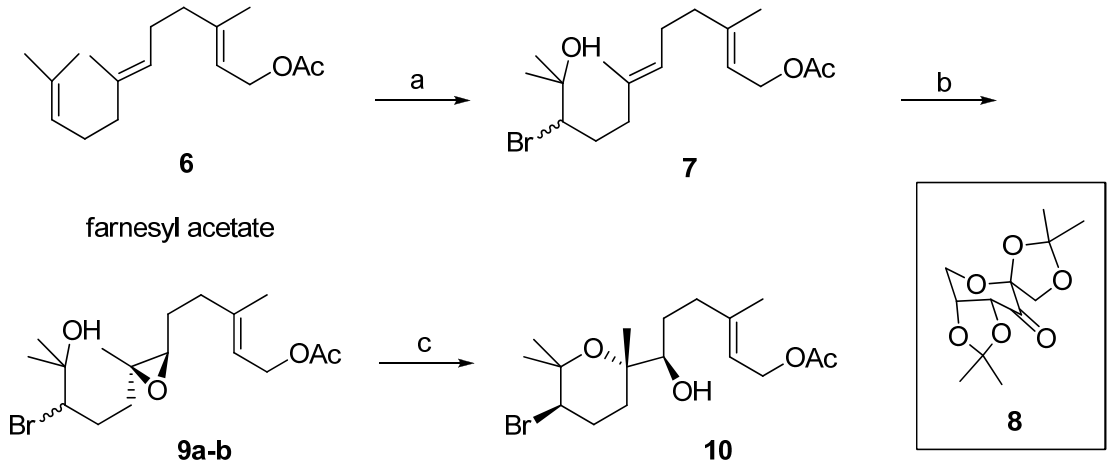
Total syntheses of thyrsiferol (**1**) and venustatriol (**2**) have been achieved by the Corey,[8] Forsyth,[9] Shirahama and Matsumoto[10] groups, while a number of partial[11,12] or unnatural analog[6a] syntheses have been published. It is our aim in this thesis to illustrate the evolution of our goal from the total synthesis of thyrsiferol (**1**) and venustatriol (**2**) to exploring the construction of the shared framework of dehydrothyrsiferol (**3**) and thyrsenols A (**4**) & B (**5**).

2.0) Previous Synthesis of the ABC Tristetrahydropyran Ring System:

The McDonald group previously synthesized the ABC tristetrahydropyran ring system of thyrsiferol (**1**) and venustatriol (**2**).[12] The synthesis began with the regioselective construction of racemic bromohydrin (**7**) from farnesyl acetate (**6**).[13] The subsequent regioselective and enantioselective epoxidation utilizing the Shi ketone[14] (**8**) was inherently problematic. The Shi epoxidation required a buffer system with a pH of 10.5. Exposure to basic conditions converted the bromohydrin moiety to the corresponding epoxide, leading to the challenge of choosing longer reaction times and obtaining a larger percentage of diepoxide, or selecting shorter reaction times and lower conversion of starting materials.[15] A variety of hydroxyl protecting groups[16] were

explored to prevent the conversion of the bromohydrin to epoxide during exposure to the Shi conditions, but unfortunately upon removal under a variety of conditions the undesired epoxide formed. The inseparable diastereomers (**9a-b**) underwent an acid-catalyzed cyclization under carefully controlled conditions resulting in the kinetic resolution of the desired bromotetrahydropyran diasteromer (**10**).[17] This reaction sequence was conserved in our synthesis.

Scheme 1: Synthesis of the bromotetrahydropyran ring A

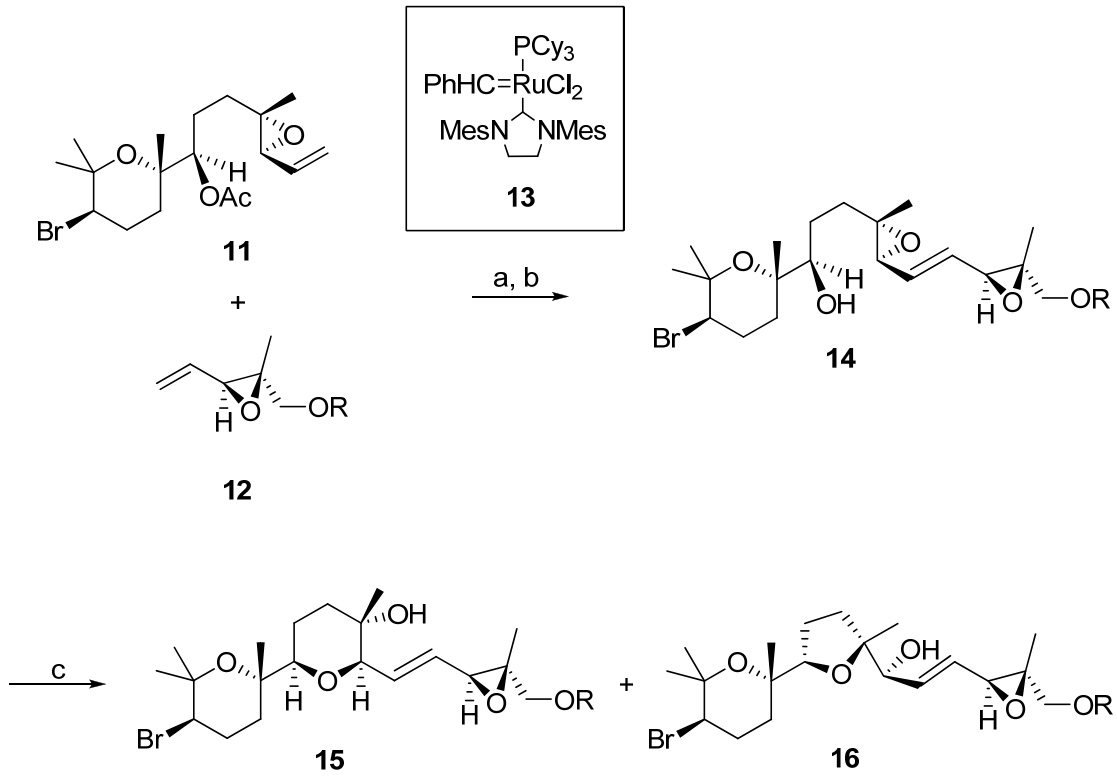


(a) NBS, H_2O, tBuOH, 65%; (b) **8**, Oxone, K_2CO_3 buffer, CH_3CN, CH_2Cl_2, 0°C, 53%; (c) CSA, Et_2O, 19 °C, 50%.

The previously published McDonald synthesis of the ABC tristetrahydropyran ring system of thyrsiferol and venustatriol utilized the second generation Grubbs catalyst (**13**) in an alkene cross-metathesis. Although this method accomplished the goal of carbon-carbon bond formation, it did require recycling of unconsumed starting material and homodimers produced in the first cycle. In our attempts to increase the scale of the reaction sequence we observed that acid-catalyzed cyclization of hydroxydiepoxide (**14**) was not completely *endo*-regioselective. The adjacent alkene was intended to stabilize developing partial positive charge at the *endo* position, thus biasing production of the

endo product.[18] However, a mixture of desired bistetrahydropyran (**15**) and *exo*-tetrahydrofuran (**16**) were produced. This lack of selectivity combined with the inefficiency of the cross-metathesis triggered our search for a new synthetic plan.

Scheme 2: Unselective formation of B ring



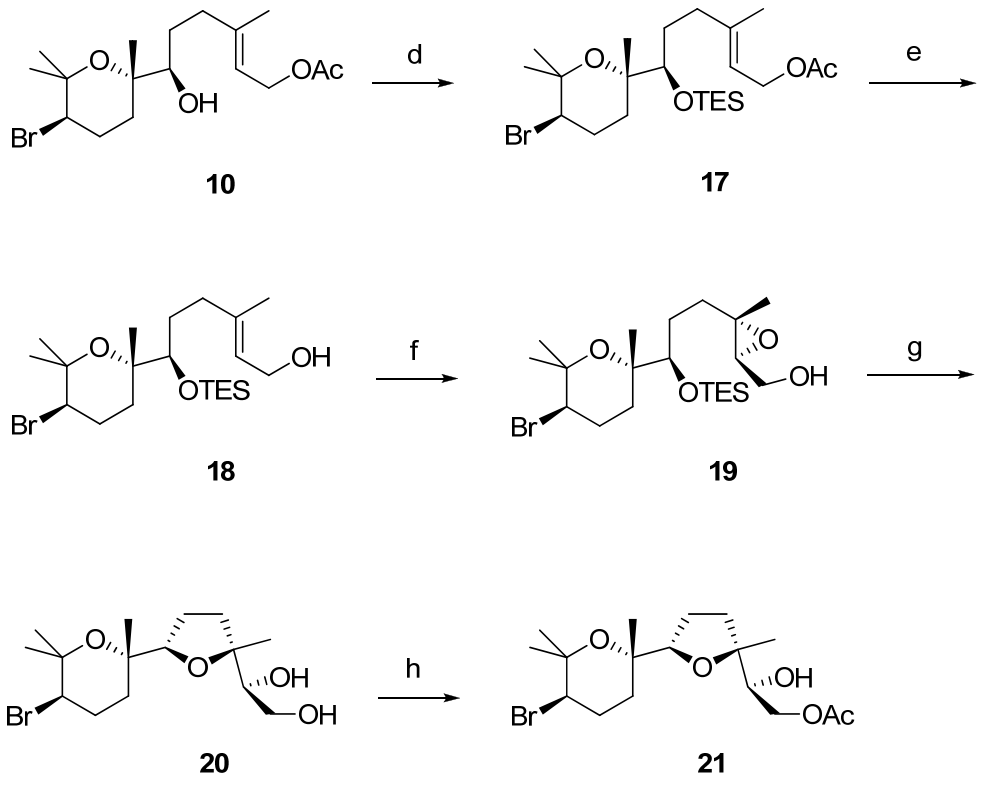
(a) **13**, CH_2Cl_2, 44% + 20% with recycle; (b) LiOH, MeOH, H_2O, 79%; (c) PPTs, CH_2Cl_2,

2.1) Revised Synthesis of B Ring:

Baldwin's rules predict that 5-*exo*-tet cyclization is favorable to 6-*endo*-tet.[19] Consequently we decided to explore a reaction sequence that would allow us to form the tetrahydrofuran initially and rearrange to the tetrahydropyran in later steps. Bromo-tetrahydropyranyl alcohol (**10**) was protected as triethylsilyl ether (**17**). Protection of the secondary alcohol was necessary to increase the reaction rate and yield of the subsequent Sharpless asymmetric epoxidation. The triethylsilyl ether was preferred over other silyl

ethers for its wider range of pH stability and reduced tendency toward migration.[20] The allylic acetate of (**17**) was reductively removed by diisobutylaluminum hydride, producing allylic alcohol (**18**) in excellent yield. The Sharpless asymmetric epoxidation[21] furnished epoxy alcohol (**19**) in excellent yield and diastereomeric purity > 95%,[22] indicating that both Shi and Sharpless epoxidations proceeded with high enantioselectivity. Removal of the silyl ether under buffered conditions generated tetrahydrofuranyl diol (**20**). The primary alcohol was selectively protected[23] as acetate (**21**) in preparation for exploration of rearrangement conditions.

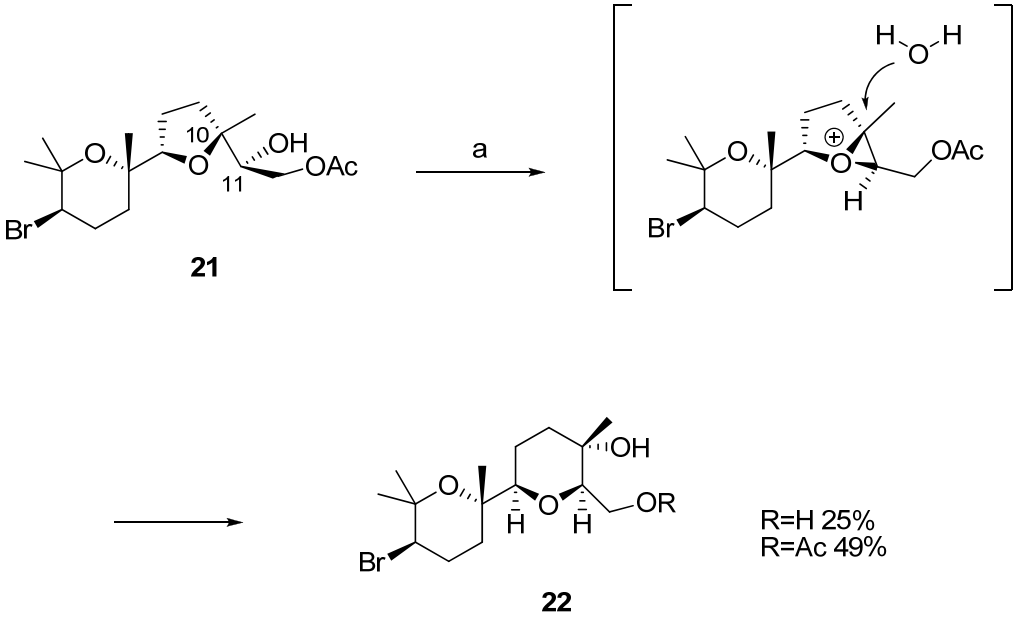
Scheme 3: Synthesis of ring expansion precursor



(d) TESCl, DMAP (cat.), Pyridine, 85%; (e) DIBAL, CH_2Cl_2, -78°C, 96%; (f) L (+)-diethyl tartrate, $Ti(OiPr)_4$, *t*BuOOH, CH_2Cl_2, -20°C, 97%; (g) TBAF, AcOH, THF, 90%; (h) AcCl, collidine, CH_2Cl_2, -25°C, 90%.

With primary acetate (**21**) in hand we were able to investigate the modified Nakata rearrangement.[24] The Nakata rearrangement was originally developed with *trans*-fused polycyclic ether ring systems in mind and could be used for ring expansion as well as contraction.[25] Initially the secondary alcohol of (**21**) was converted to the chloromesylate (monochlate, Mc)[26] quantitatively. Upon heating in the presence of water and zinc acetate[27] an epoxonium ion intermediate was formed. It was postulated that an antiperiplanar conformation between the C_{10}-O and the C_{11}-OMc was necessary for effective epoxonium ion generation.[c] Water attacked the C_{10} position of the epoxonium ion from the back. The regioselective attack of water resulted from the greater distribution of partial positive charge on the tertiary carbon center. The rearrangement generated a mixture of the desired diol (**22**) and the corresponding primary acetate.

Scheme 4: Nakata rearrangement

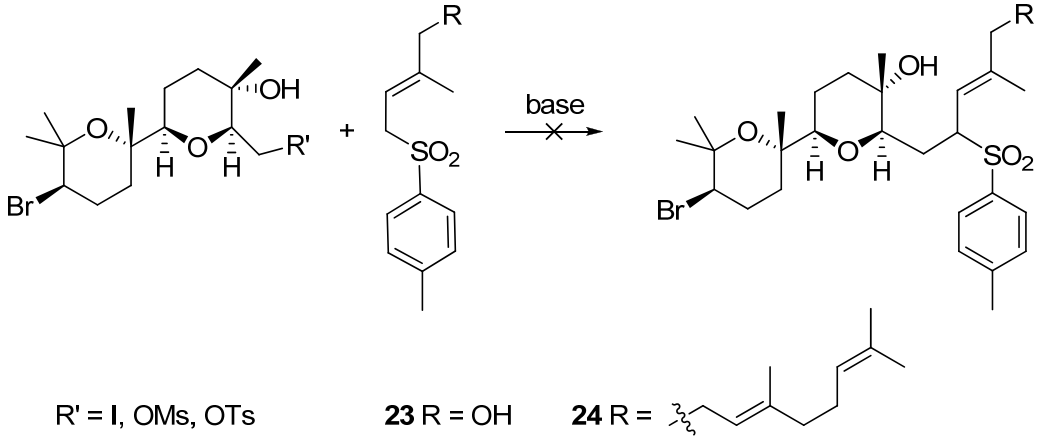


(a) $ClCH_2SO_2Cl$, 2,6-lutidine, CH_2Cl_2 then $Zn(OAc)_2$, H_2O, 1,4-dioxane, 72 °C.

2.2) Attempted Carbon-Carbon Bond Construction via Sulfur Mediated Anions:

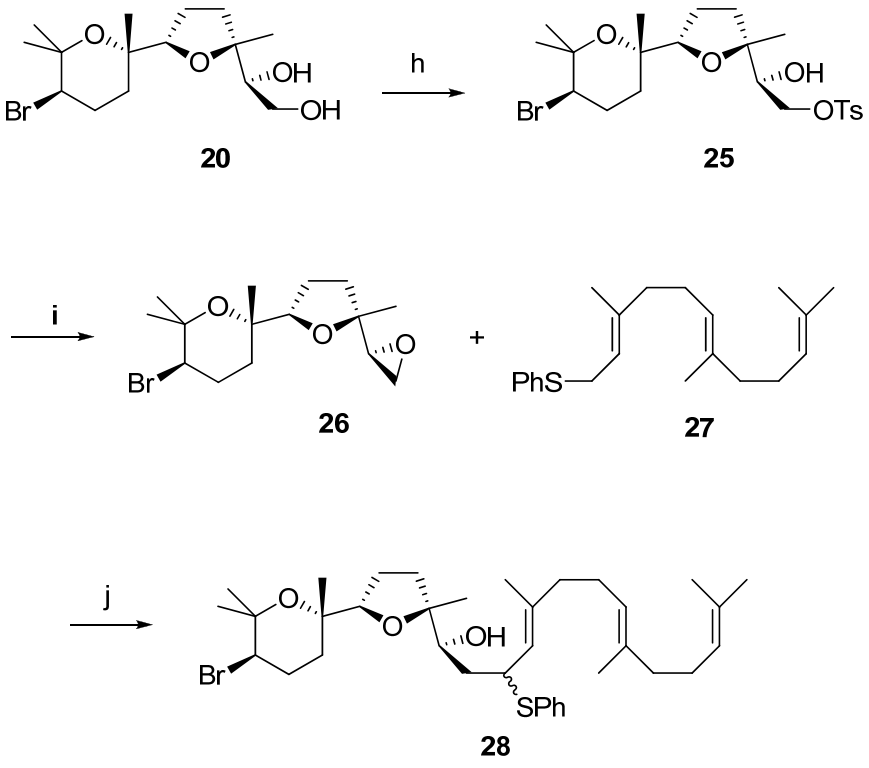
With the AB ring system in hand our next challenge was the carbon-carbon bond formation necessary to construct the third tetrahydropyran ring. Initially our goal was to couple anionic allylic sulfones to the bistetrahydropyran ring system through a S_N2 type displacement[28] followed by palladium catalyzed reductive desulfonylation.[29] The Mori group had previously demonstrated the viability of similar tetrahydropyran ring systems[30] as electrophilic coupling partners with anionic epoxy sulfones.[31] Bistetrahydropyranyl iodide, mesylate, and tosylate were all screened against sulfone (**23**)[28b] under a variety of base and solvent conditions recovering starting materials and/or decomposition products. It was theorized that Coulombic repulsion might prevent the doubly deprotonated sulfone (**23**) from reaching the necessary proximity to the deprotonated bistetrahydropyran electrophile. Attempts to reduce the Coulombic repulsion and facilitate carbon-carbon bond formation between farnesyl sulfone (**24**) and bistetrahydropyranyl iodide were ultimately unsuccessful. Steric congestion and Coulombic repulsion both contributed to the lack of desired reactivity.

Scheme 5: Attempted anionic coupling



In an effort to reduce both steric congestion and Coulombic repulsion during carbon-carbon bond formation, the use of a terminal epoxide as the electrophilic coupling partner was explored. The Morimoto group successfully opened terminal epoxides with an allylic carbanion stabilized by sulfur, twice in their synthesis of (+)-aurilol.[32] Construction of the terminal epoxide began by selective primary tosylation of tetrahydrofuranyl diol (**20**).[33] Exposure to basic conditions provided the terminal epoxide (**26**) in good yield. Addition of the farnesyl thioether (**27**) anion was successful[32] however, more complex (containing the tetrahydrofuran D ring) thioethers decomposed under reaction conditions. Since the coupled farnesyl thioether was not a great candidate for regioselective functionalization, other carbon nucleophiles were considered.

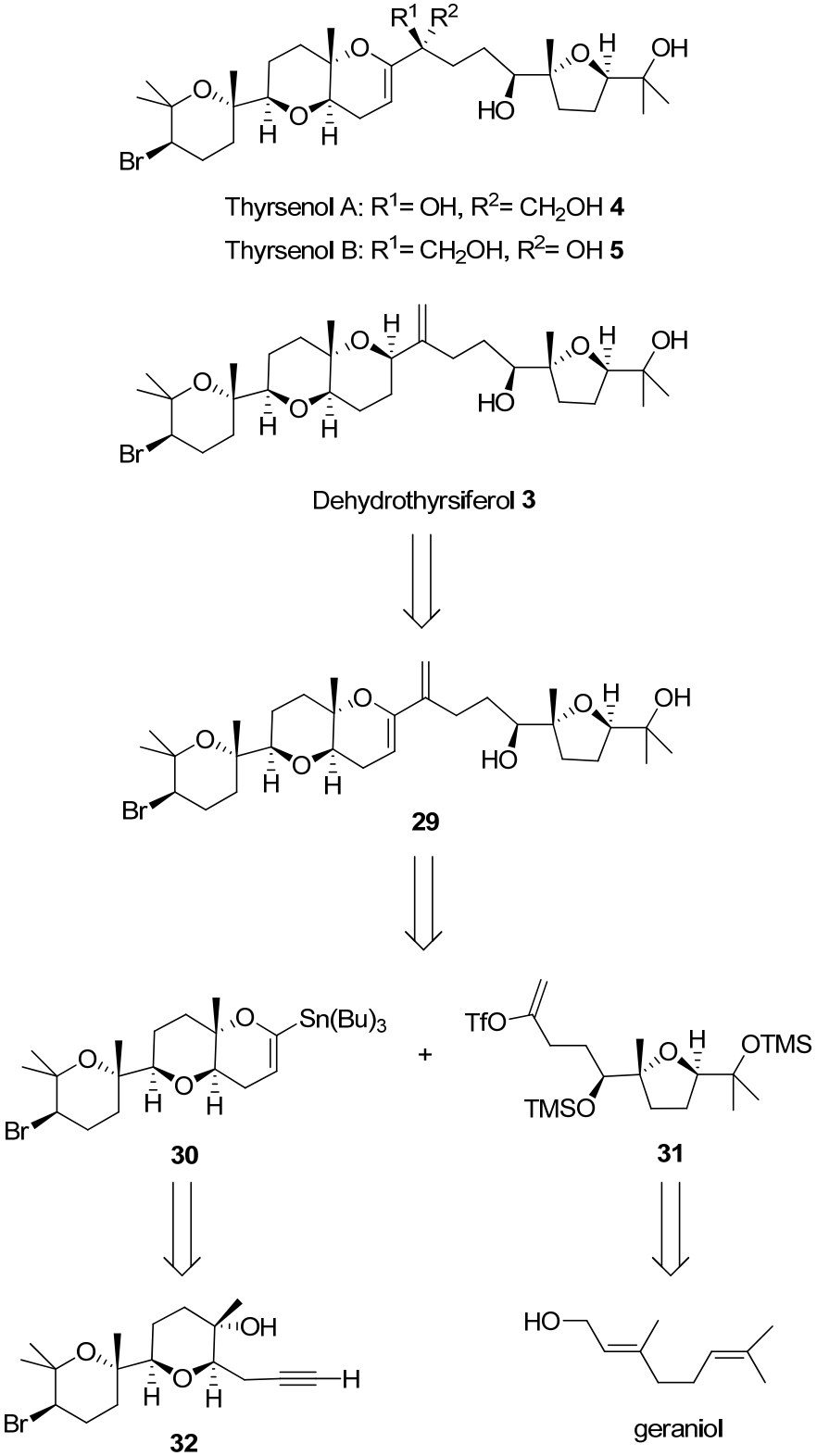
Scheme 6: Sulfur mediated addition to a terminal epoxide



(h) TsCl, pyridine, 4 °C, 75%; (i) K_2CO_3, MeOH, 91%; (j) nBuLi, TMEDA, THF.

2.3) Revised Retrosynthetic Strategy:

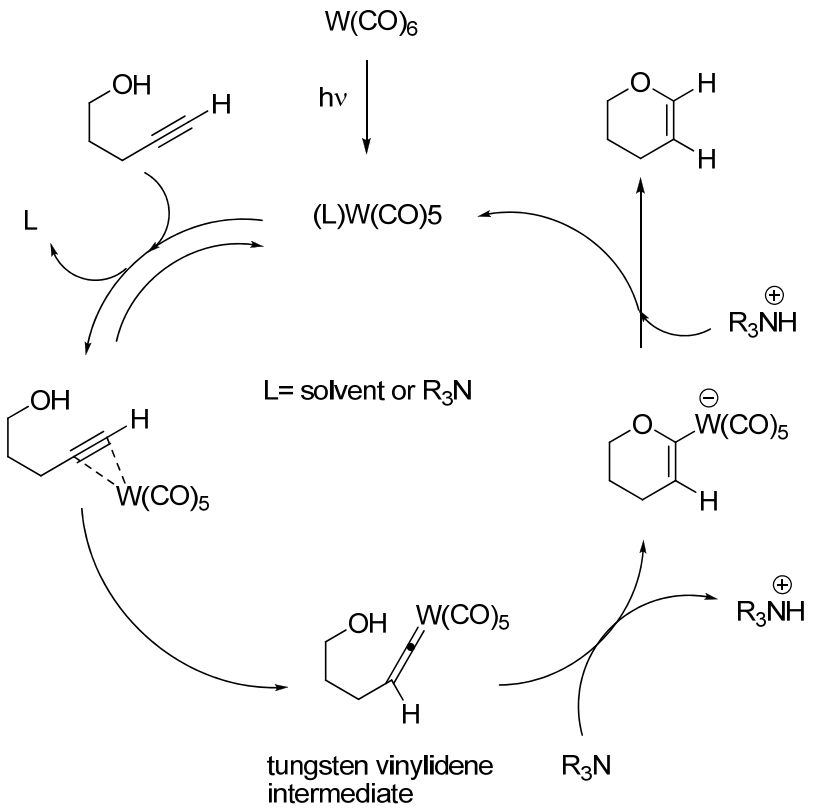
Scheme 7: Retrosynthesis of Thyrsenols and Dehydrothyrsiferol



Thyrsenols A (**4**), B (**5**) and dehydrothyrsiferol (**3**) could arise from a common dienyl ether precursor (**29**). Regioselective dihydroxylation of dienyl ether (**29**) would provide thyrsenols A (**4**) and B (**5**),[34] although enantioselective and regioselective reduction of the dihydropyran C ring of (**29**) could supply dehydrothyrsiferol (**3**).[35] Dienyl ether (**30**) would be synthesized by a Stille coupling of α–stannyl dihydropyran (**29**) and enol triflate (**31**).[36,34] Enol triflate (**31**) would be generated from geraniol through a sequence of enantioselective epoxidation and dihydroxylation followed by side chain extension. α–Stannyl dihydropyran (**30**) originated from alkynyl alcohol (**32**) through stoichiometric tungsten chemistry developed by the McDonald group. [37] Alkyne addition to terminal epoxide (**26**) followed by the Nakata rearrangement produced alkynyl alcohol (**32**). Selection of an alkynyl nucleophile to open the terminal epoxide would reduce the steric bulk of the nucleophile while possibly increasing the yield of the coupling.

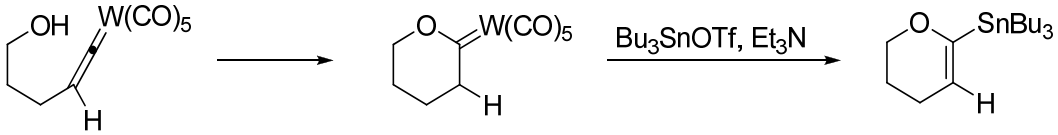
The catalytic cycle of tungsten cycloisomerization began by irradiation with ultraviolet light which caused tungsten hexacarbonyl to lose a carbon monoxide ligand generating a coordinatively unsaturated species,[38] although recently Koo and McDonald have developed a stable tungsten Fischer carbene precatalyst that does not require photolysis of the reaction mixture.[39] This open coordination site was probably stabilized by ethereal solvent or amine present in the reaction mixture. Ligand exchange produced an η^2 metal alkyne complex which underwent an irreversible rearrangement to a tungsten vinylidene. Base induced attack of the tethered oxygen nucleophile on the internal electrophilic carbon of the vinylidene, furnished the anionic vinyl tungsten species. Protonation induced production of the metal free enol ether.

Scheme 8: Tungsten catalyzed cycloisomerization mechanism



However in the absence of amine and presence of stoichiometric tungsten it was possible to generate and isolate a relatively stable tungsten carbene. Exposure of the tungsten carbene to tributyltin triflate in the presence of triethylamine produced the α–stannyl dihydropyran.[37]

Scheme 9: Generation of α-stannyl dihydropyran

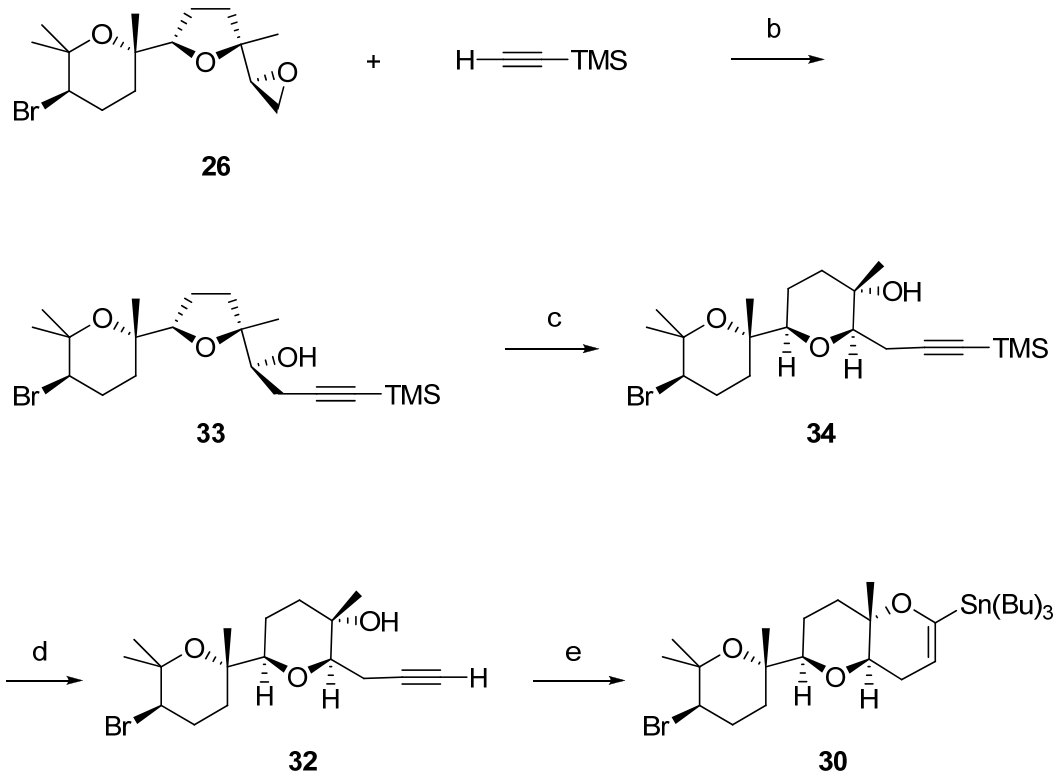


2.4) Construction of C Ring:

Burova and McDonald have previously demonstrated the vigor and synthetic utility of acetylide addition to terminal epoxides.[40] Following their precedent, addition of the lithium trimethylsilyl acetylide to terminal epoxide (**26**) supplied the

tetrahydrofuranyl alcohol (**33**) in excellent yield. The Nakata rearrangement provided bistetrahydropyran (**34**) in low yield.[24] It is unclear why the propargyl side chain adversely affected the outcome of the Nakata rearrangement. Removal of the trimethyl-silyl protecting group under basic conditions afforded the free alkyne (**32**). Photolysis of alkynyl alcohol (**32**) in the presence of stoichiometric tungsten hexacarbonyl followed by treatment with tributylstannyl triflate and triethylamine resulted in a moderate yield of α–stannyl dihydropyran (**30**). This low yield was expected since substitution at the propargyl position is essential for high conversion rates.

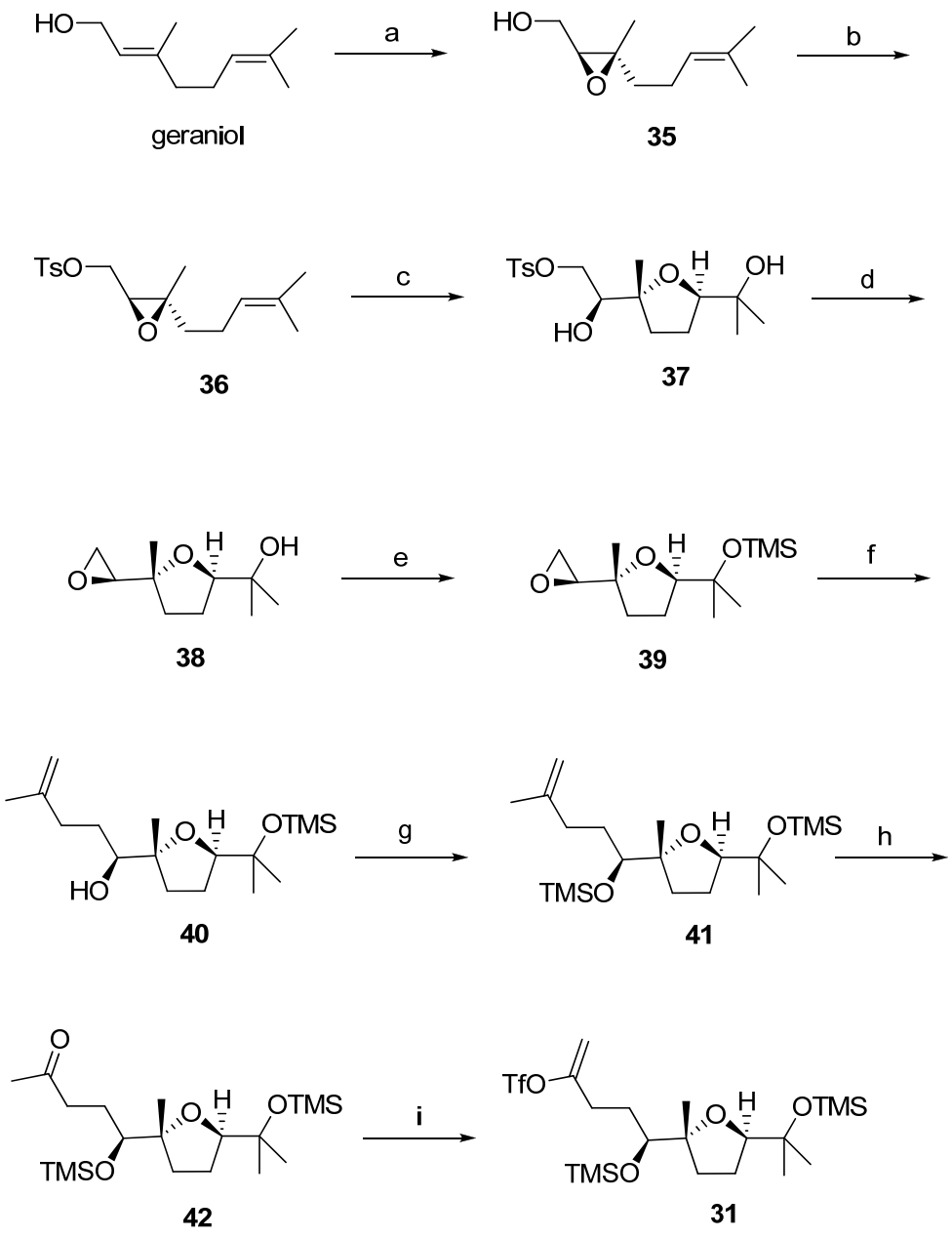
Scheme 10: Synthesis of the C ring



(b) nBuLi, BF_3•THF, THF,-78°C, 99%; (c) $ClCH_2SO_2Cl$, pyridine, CH_2Cl_2,0°C; then $Zn(OAc)_2$•$2H_2O$, H_2O, dioxane, 60°C, 31%; (c) K_2CO_3, MeOH, 60%; (e) $W(CO)_6$, hν, THF; then Bu_3SnOTf, Et_3N, Et_2O, 40%.

2.5) Assembly of the D Ring:

Scheme 11: Synthesis of tetrahydrofuranyl D ring



(a) L-diethyl tartrate, $Ti(OiPr)_4$, *t*BuOOH, 98%. (b) TsCl, pyr, -25°C, 81%. (c) AD mix β, tBuOH, H_2O, 93%. (d) K_2CO_3, MeOH, 87%, (e) TMSCl, imid., THF, 72%. (f) methylallyl-magnesiumchloride, CuI, THF, 79%. (g)TMSCl, imid., THF, 92%. (h) O_3, pyr, MeOH, *i*PrOH, Me_2S, 67%. (i) KHMDS, $PhN(Tf)_2$, THF, -78°C, 87%.

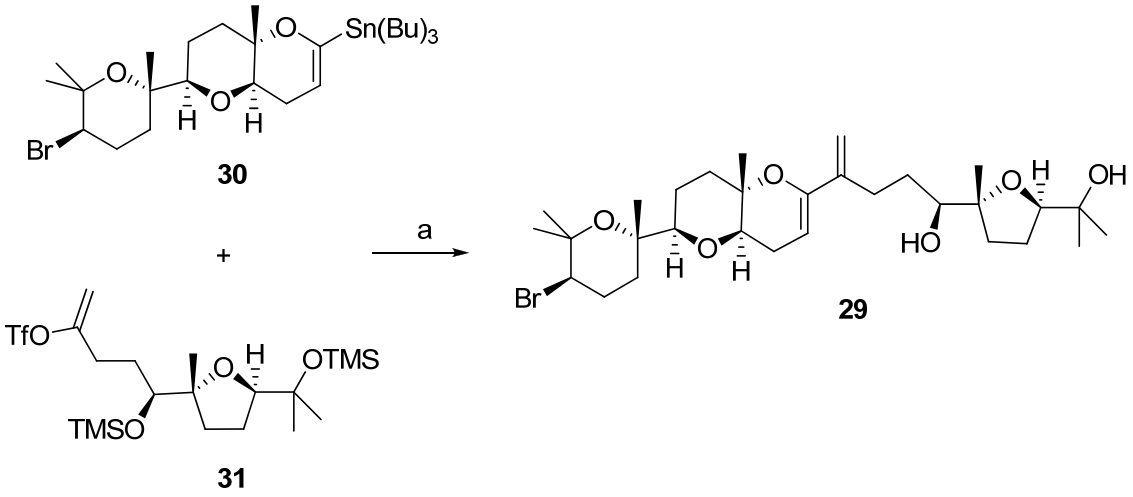
Synthesis of the D ring began with an enantioselective epoxidation of geraniol following Sharpless' precedent.[21] Geranyl acetone was also explored as a possible starting material for the D ring. However, the presence of the methyl ketone during the enantioselective Shi epoxidation[14] led to a significant decrease in enantiopurity. Hydrazone protective groups were examined but were ultimately incompatible with reaction conditions.[41] The hydroxyl group of 2,3-epoxygeraniol (**35**) was protected as tosylate. This tosylate not only served the purpose of installing the terminal epoxide functionality later in the synthesis but also decreased the polarity of the dihydroxylation product, allowing for much greater ease in purification and in turn higher yields. Asymmetric dihydroxylation of tosyl geranyl epoxide (**36**) produced tetrahydrofuran (**37**) in good yield.[42] Transformation to the terminal epoxide (**38**) followed by protection as the trimethylsilyl ether (**39**) set the stage for the copper mediated Grignard addition to the terminal epoxide.[43] This carbon-carbon bond forming step proceeded smoothly and in good yield furnishing (**40**). After protection of the free secondary alcohol as silyl ether (**41**), ozonolysis was performed generating methyl ketone (**42**).[44] Coupling partner enol triflate (**31**) was regioselectively produced by trapping the kinetic enolate of (**42**) with triflating agent.[45]

2.6) Stille Cross Coupling:

The Stille coupling proceeded smoothly with the addition of copper iodide and cesium fluoride salts, with minimal homodimerization of α–stannyl dihydropyran (**30**).[36a] Copper iodide and fluoride ion may have an synergistic effect on the Stille coupling.[36a] Copper underwent a transmetalation with the stannane to provide a more reactive organocopper intermediate, increasing the rate of the reaction as well as generating

tributyltin iodide. This byproduct was converted to insoluble tributyltin fluoride which increased the formation of the organocopper species further enhancing the rate. Exposure to fluoride ion during the Stille coupling partially removed the silyl ethers, and treatment with additional fluoride provided the free diol (**29**).

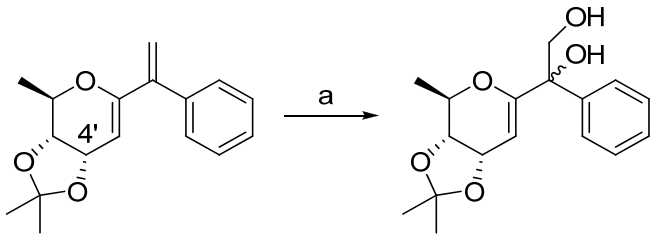
Scheme 12: Stille coupling



(a) 2% $Pd(PPh_3)_4$, CuI, CsF, DMF then TBAF, THF, 61%

2.7) Efforts to Functionalize Unsaturated Centers:

Scheme 13: Regioselective dihydroxylation of dienyl ether[34]

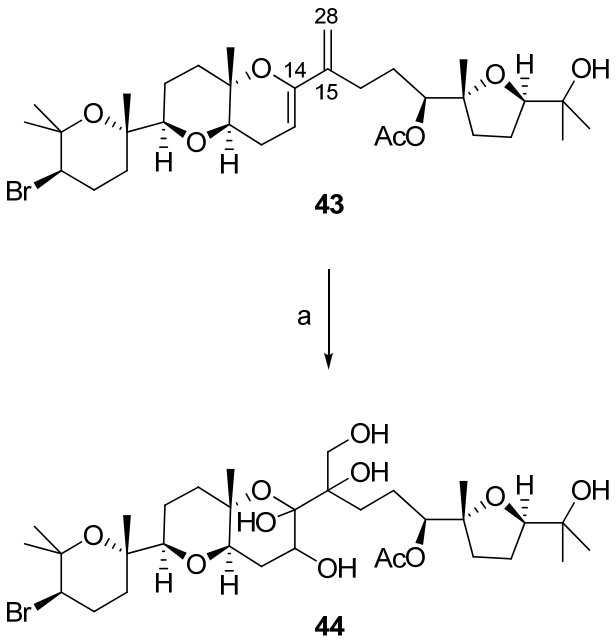


(a) AD mix α or β, 92-93%

Koo and McDonald successfully utilized commercially available AD mix to perform a regioselective dihydroxylation in a similar conjugated dienyl ether system.[34] The 1,1-disubstituted alkene reacted exclusively under the dihydroxylation conditions

although a mixture of diastereomers was obtained.[34] Substitution at the 4′ position of the glycal appeared to provide a significant steric barrier against dihydroxylation of the more electron rich double bond.

Scheme 14: Dihydroxylation of dienyl ether (43)



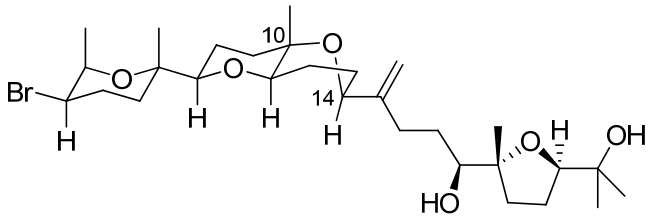
(a) OsO_4, pyridine, $Na_2S_2O_5$

Exposure of dienyl ether (**29**) to asymmetric dihydroxylation conditions for 3 days produced no reaction, and after this time period decomposition of the dienyl ether began.[42] Treatment of dienyl ether (**29**) with stoichiometric osmium tetroxide[46] followed by reduction of the resultant osmate esters produced several very polar compounds, none of which matched the proton spectra of thyrsenol A (**4**) or B (**5**).[7,47] Dienyl ether (**29**) was monoacylated in order to reduce polarity and improve isolation of the products resulting from treatment with osmium tetroxide followed by reductive conditions. High resolution mass spectrometry identified monoacetate pentahydroxyl tristetrahydropyran (**44**) as the product resulting from treatment with stoichiometric osmium tetroxide. While steric

factors prevented dienyl ether (**29**) from fitting into the congested alkaloid pocket necessary for catalytic asymmetric dihydroxylation, they did not present a sufficient barrier to overcome the electronic bias towards reaction with the more electron rich enol ether. In fact the steric bulk did not prevent the formation of a second osmate ester. Oxidation of the 1,1-disubstituted alkene has remained an unsolved challenge.

Attempts to synthesize dehydrothyrsiferol (**3**) from dienyl ether (**43**) by treatment with sodium cyanoborohydride under moderately acidic conditions (pH 4) were not successful.[35] It was our hope that under acidic conditions the enol ether would be protonated generating an oxonium ion followed by delivery of a hydride to the α-carbon opposite the axial methyl group at C_{10} supplying the desired stereochemistry at C_{14}. Torsional strain prevented delivery of the hydride to the desired face. The C ring of dehydrothyrsiferol (in addition to venustatriol and thyrsiferol) exists in a twist-boat conformation to avoid 1,3-diaxial interactions.[3] This conformational strain makes construction of the fused bistetrahydropyran system a formidable goal.

Figure 5: Twist-boat conformation of the C ring



3

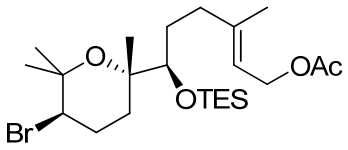
3.0) Conclusion:

The complete carbon skeleton of marine polyether triterpenes: thyrsiferol (**1**), dehydrothyrsiferol (**3**), thyrsenols A (**4**) and B (**5**) has been constructed. Carbon-carbon bonds were successfully created by nucleophilic opening of terminal epoxides and palladium catalyzed cross coupling. Oxygen containing stereocenters were set by

asymmetric epoxide formation and asymmetric dihydroxylation. However, functionalization of the 1,1-disubstituted alkene to provide thyrsenols A and B or the enol ether to provide dehydrothyrsiferol remain unsolved synthetic challenges.

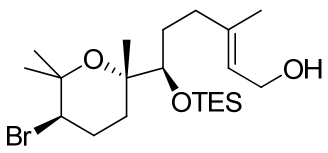
Experimental

General: ^{1}H and ^{13}C NMR spectra were recorded on a on a VNMR-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) or an INOVA-600 spectrometer (600 MHz for ^{1}H, 150 MHz for ^{13}C). NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$) with residual chloroform (δ 7.27 ppm for ^{1}H NMR and δ 77.23 ppm for ^{13}C NMR) taken as the internal standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows s, singlet; b, broad; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were collected on a Mattson Genesis II FT-IR spectrometer as neat films. Mass spectra (high resolution FAB) were recorded on a VG 70-S Nier Johason Mass Spectrometer. Analytical Thin Layer Chromatography (TLC) was performed on precoated glass backed plates purchased from Whitman (silica gel 60 F_{254}; 0.25mm thickness). Flash chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from EM Science. All reactions were carried out with anhydrous solvents in oven-dried or flame-dried and argon-charged glassware. All anhydrous solvents were dried over molecular sieves and water content assayed by Karl Fischer titration prior to use. The pH 7 buffer solution used in aqueous workups was prepared by diluting Na_2HPO_4 (18.9 g, 133 mmol) and KH_2PO_4 (9.1 g, 67 mmol) with deionized water to a volume of 1L. All reagents were purchased from Aldrich Chemical or prepared as described in the cited literature.



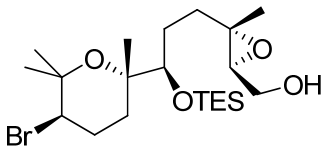
17

Bromotetrahydropyranyl silyl ether (17): Chlorotriethyl silane (0.41 mL, 2.4 mmol) was added dropwise to a solution of bromotetrahydropyranyl alcohol **10**[12] (0.6190 g, 1.6 mmol) and DMAP (0.0649 g, 0.5 mmol) in pyridine (4 mL). The reaction mixture was stirred overnight, diluted with Et_2O (50 mL) and washed with pH 7 buffer (50 mL). The aqueous layer was extracted with additional Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by silica gel column chromatography eluted with a gradient of 3% Et_3N in hexanes to 9% Et_3N in hexanes yielding the silyl ether **17** (0.6876 g, 85%) as a clear oil. $[\alpha]^{23}_D$ = +23.0 (CH_2Cl_2, c = 1.03); IR (neat) 3583, 3434, 2955, 2876, 1740, 1657, 1456, 1381, 1232, 1115, 1019, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.61 (q, *J* = 7.6 Hz, 6H), 0.96 (t, *J* = 7.6 Hz, 9H), 1.17 (s, 3H), 1.26-1.36 (m, 1H), 1.28 (s, 3H), 1.42 (s, 3H), 1.49 (dt, *J* = 13.2, 4.4 Hz, 1H), 1.67 (t, *J* = 4 Hz, 1H), 1.70 (s, 1H), 1.81-1.89 (m, 1H), 1.99-2.30 (m, 4H), 2.07 (s, 3H), 3.25 (dd, *J* = 7.8, 3Hz, 1H), 3.88 (dd, *J* = 12.6, 4.2 Hz, 1H), 4.60 (d, *J* = 7.2 Hz, 2H), 5.36 (dt, *J* = 7.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.8, 7.3, 16.7, 19.4, 21.3, 23.8, 28.6, 30.7, 31.3, 37.1, 37.2, 59.2, 61.7, 75.3, 76.4, 81.0, 118.1, 143.1, 171.4; MS(FAB^+) Calcd. for $C_{23}H_{44}O_4{}^{79}Br_1{}^{28}Si_1$ [$(M+H)^+$] 491.2187, found 491.2189.



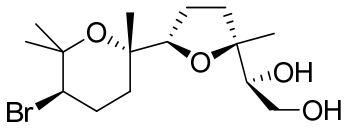
18

Allylic alcohol (18): A solution of DIBAL (1 M in DCM, 2.8 mL, 2.8 mmol) was added slowly to a -78 ˚C solution of allylic acetate **17** (0.6876 g, 1.4 mmol) in DCM (3 mL). The reaction mixture was stirred for 1h. then allowed to warm to RT. After 3 h. sodium sulfate decahydrate was added gradually till a gel formed. The gel was diluted with a saturated aqueous solution of sodium potassium tartrate (10 mL) and additional DCM (10 mL). The aqueous layer was extracted with DCM (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$. After concentration, the crude product was purified by silica gel column chromatography eluted with Et_2O : hexanes (v/v 2 : 8) resulting in allylic alcohol **18** (0.6023 g, 96%) as a clear oil. $[\alpha]^{23}_D$ = +23.2 (CH_2Cl_2, c = 1.74); IR (neat) 3413, 2955, 2876, 2359, 2092, 1640, 1456, 1372, 1237, 1115, 1011, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.61 (q, *J* = 8 Hz, 6H), 0.96 (t, *J* = 8 Hz, 9H), 1.17 (s, 3H) 1.26-1.40 (m, 2H), 1.28 (s, 3H), 1.42 (s, 3H), 1.50 (dt, *J* = 13.2, 4.4 Hz, 1H), 1.68 (s, 3H), 1.81-1.89 (m, 1H), 1.97-2.04 (m, 1H), 2.08-2.19 (m, 2H), 2.25 (dq, *J* = 13.2, 3.6 Hz, 1H), 3.25 (dd, *J* = 7.8, 3 Hz), 3.88 (dd, *J* = 12.6, 3.8 Hz, 1H), 4.17 (d, *J* = 6.8 Hz, 2H), 5.44 (dt, *J* = 6.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.8, 7.3, 16.6, 19.4, 23.8, 28.6, 30.9, 31.3, 37.2, 37.3, 59.2, 59.7, 75.3, 76.4, 81.1, 123.2, 140.7; MS(FAB^+) Calcd. for $C_{21}H_{41}O_3{}^{79}Br_1{}^{23}Na_1{}^{28}Si_1$ [$(M+Na)^+$] 471.1901, found 471.1899.



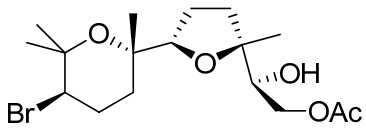
19

Epoxy alcohol (19): 4 Å powdered, activated molecular sieves (0.6855 g) were suspended in a solution of allylic alcohol **18** (0.6023 g, 1.3 mmol) in DCM (11 mL) with stirring. The suspension was cooled to -20 ˚C and L-(+)-diethyl tartrate (0.07 mL, 0.41 mmol) followed by Ti(O*i*-Pr)$_4$ (0.09 mL, 0.30 mmol) were added. The precatalyst mixture was stirred for 30 min. An anhydrous solution of TBHP (5.5 M in decane, 0.7 mL, 3.9 mmol) was added slowly to the mixture and stirred at -20 ˚C for 1 h. then placed in the freezer (-25 ˚C) overnight. The reaction mixture was filtered though celite to remove the sieves and diluted with additional DCM (50 mL) and an aqueous KOH solution (1.5 M, 50 mL). The biphasic mixture was stirred for 1 h. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by silica gel column chromatography eluted with Et_2O : hexanes (v/v 1: 3) producing epoxy alcohol **19** (0.6046 g, 97%) as a clear oil. $[\alpha]^{23}_D$ = +19.1 (CH_2Cl_2, c = 1.07); IR (neat) 3435, 2955, 2876, 1641, 1456, 1382, 1237, 1116, 1017, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (q, *J* = 8 Hz, 6H), 0.95 (t, *J* = 8 Hz, 9H), 1.17 (s, 3H), 1.28 (s, 3H), 1.30 (s, 3H), 1.42 (s, 3H), 1.49 (dt, *J* = 13.4, 4 Hz, 1H), 1.56-1.72 (m, 4H), 1.75-1.87 (m, 1H), 2.11 (qd, *J* = 13.6, 4 Hz, 1H), 2.25 (dq, *J* = 13.2, 3.6 Hz, 1H), 2.97 (dd, *J* = 7, 4 Hz, 1H), 3.25 (dd, *J* = 7.4, 3.4 Hz, 1H), 3.67-3.73 (m, 1H), 3.82-3.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.8, 7.3, 17.0, 19.4, 23.8, 28.0, 28.6, 31.3, 36.2, 37.2, 59.1, 61.7, 61.7, 62.8, 75.4, 76.4, 81.2; MS(FAB$^+$) Calcd. for $C_{21}H_{42}O_4{}^{79}Br_1{}^{28}Si_1$ [(M+H)$^+$] 465.2030, found 465.2024.



20

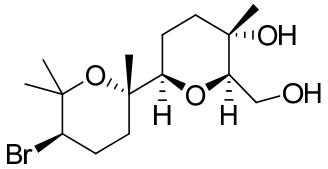
Tetrahydrofuranyl diol (20): A solution of TBAF (1 M in THF, 6 mL, 6 mmol) was added to a solution of epoxy alcohol **19** (0.6046 g, 1.3 mmol) and glacial acetic acid (0.3 mL, 5.2 mmol) in THF (1 mL). The reaction was monitored by TLC. After starting material was fully consumed, the reaction was diluted with DCM (10 mL) and washed with a saturated brine solution (3 x 10 mL). The organic layer was dried over $MgSO_4$ and purified by silica gel column chromatography eluted with MeOH : DCM (v/v 2: 98) producing diol **20** (0.4098 g, 90%) as a clear oil. $[\alpha]^{23}_{D} = +30.7$ (CH_2Cl_2, c = 1.47); IR (neat) 3400, 2975, 2939, 2875, 2359, 2340, 1646, 1455, 1380, 1130, 1089, 1111, 1035, 901, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.22 (s, 3H), 1.29 (s, 3H), 1.41 (s, 3H), 1.53-1.60 (m, 2H), 1.65 (dt, *J* = 13.2, 4.4 Hz, 1H), 1.76-1.89 (m, 2H), 1.96-2.04 (m, 1H), 2.11 (qd, *J* = 13.2, 4 Hz, 1H), 2.26 (dq, *J* = 13, 4 Hz, 1H), 3.53 (dd, *J* = 10.2, 7.4 Hz, 1H), 3.64-3.71 (m, 3H), 3.88 (dd, *J* = 12.4, 4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 23.3, 23.8, 26.6, 28.1, 31.1, 33.0, 34.7, 58.6, 63.5, 74.8, 75.3, 76.7, 65.0, 88.4; MS(FAB$^+$) Calcd. for $C_{15}H_{28}O_4{}^{79}Br_1{}^{28}$ [$(M+H)^+$] 351.1166, found 351.1166.



21

Primary acetate (21): Acetyl chloride (0.16 mL, 2.3 mmol) was added dropwise to a -78 ˚C solution of tetrahydrofuranyl diol **20** (0.6484 g, 1.8 mmol) and 2,4,6-trimethyl pyridine (0.49 mL, 3.7 mmol) in DCM (3.7 mL). The reaction mixture was stirred for 2 h. at -78 ˚C then placed in the freezer (-25 ˚C) overnight. The reaction was quenched by the

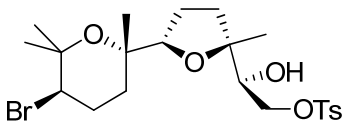
addition of an aqueous HCl solution (1 M, 2 mL, 2 mmol). The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography eluted with Et_2O : hexanes (v/v 1 :1) yielding primary acetate **21** (0.6498 g, 90%) as a clear oil. ^1H NMR (600 MHz, $CDCl_3$) δ 1.18 (s, 3H), 1.25 (s, 3H), 1.30 (s, 3H), 1.43 (s, 3H), 1.58-1.61 (m, 3H), 1.88-1.91 (m, 2H), 2.04 (q, *J* = 12 Hz, 1H), 2.11 (s, 3H), 2.12 (dq, *J* = 13.8, 4.2 Hz, 1H), 2.27 (dq, *J* = 13, 4 Hz, 1H), 3.66 (t, *J* = 7.8 Hz, 1H), 3.76 (dd, *J* = 7.8, 2.4 Hz, 1H), 3.87 (dd, *J* = 12.6, 4.2 Hz, 1H), 4.00 (dd, *J* = 11.7, 8.7 Hz, 1H), 4.27 (dd, *J* = 12, 2.4 Hz, 1H).



22

Bistetrahydropyran diol (22): Chloromethanesulfonyl chloride (0.16 mL, 1.8 mmol) was added dropwise to a 0 ˚C solution of primary acetate **21** (0.1365 g, 0.35 mmol**)** and 2,6-lutidine (0.32 mL, 2.7 mmol) in DCM (0.94 mL). The mixture was stirred for 30 min. then diluted with Et_2O (10 mL) and an aqueous HCl solution (0.5 M, 5 mL). The aqueous layer was extracted with additional Et_2O (2 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude chloromesylate product and zinc acetate dihydrate were dissolved in 1,4-dioxane (5 mL) and water (5 mL). The reaction mixture was heated to 72 ˚C and stirred for 3 h. The reaction mixture was diluted with aqueous HCl solution (0.5 M, 5 mL) and Et_2O (10 mL). The aqueous layer was extracted with additional Et_2O (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by silica gel column chromatography eluted with a gradient of

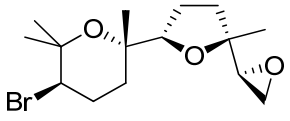
EtOAc : hexanes (v/v 1: 3 to 5 : 7) yielding a mixture of free diol **22** (0.0302 g, 25 %) and corresponding primary acetate (0.0673 g, 49 %) . The primary acetate was removed by treatment with LiOH (0.012 g, 0.5 mmol) in a mixture of water (1 mL) and methanol (3 mL). After monitoring the reaction by TLC, the mixture was diluted with water (1 mL) and Et_2O (5 mL). The aqueous layer was extracted with additional Et_2O (2 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated, and no additional purification was necessary. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.21 (s, 3H), 1.27 (s, 3H), 1.38-1.47 (m, 1H), 1.41 (s, 3H), 1.53-1.62 (m, 2H), 1.75-1.86 (m, 3H), 2.11 (qd, *J* = 13.6, 4 Hz, 1H), 2.26 (dq, *J* = 13.4, 4 Hz, 1H), 3.07 (dd, *J* = 17.2, 2 Hz, 1H), 3.31 (dd, *J* =8, 6.6 Hz, 1H), 3.62 (dd, *J* = 17.2, 8 Hz, 1H), 3.78 (dd, *J* = 17.2, 6.6 Hz, 1H), 3.89 (dd, 12.4, 4 Hz, 1H).



25

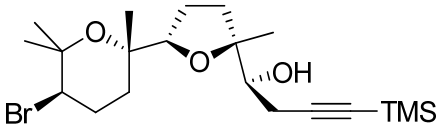
Primary tosylate (25): *p*-Toluenesulfonyl chloride (0.4550 g, 2.4 mmol) was added to a 0 ˚C solution of diol **20** (0.7560g, 2.2 mmol) in pyridine (31 mL). The reaction was stirred for 1 h., then placed in the refrigerator (4 ˚C) for 24 h. The reaction mixture was diluted with DCM (50 mL) and washed with aqueous saturated brine (3 x 50 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography eluted with Et_2O : hexanes (v/v 1 : 3) yielding primary tosylate **25** (0.8154 g, 75%) as a clear oil. $[\alpha]^{23}_D$ = +7.6 (CH_2Cl_2, c = 5.57); IR (neat) 3522, 3442, 2980, 2876, 2359, 1599, 1454, 1362, 1176, 1128, 1094, 1034, 970, 909, 835, 815, 765, 732, 662, 554 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.19 (s, 3H), 1.27 (s, 3H), 1.40 (s, 3H), 1.51-1.60 (m, 2H), 1.81-1.87 (m, 2H), 1.92-2.00 (m, 1H), 2.09 (qd, *J* =

13.6, 4 Hz, 1H), 2.19-2.30 (m, 1H), 2.45 (s, 3H), 2.60 (d, *J* = 3.2 Hz, 1H), 3.58 (t, *J* = 7.4 Hz, 1H), 3.72 (dt, *J* = 8, 2.8 Hz, 1H), 3.86 (dd, *J* = 12.4, 4 Hz, 1H), 3.98 (dd, *J* = 10.6, 8 Hz, 1H), 4.24 (dd, *J* = 10.6, 2.8 Hz, 1H), 7.35 (d, *J* = 8 Hz, 2H), 7.81 (d, *J* = 8.4, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.9, 22.7, 23.8, 26.3, 28.1, 31.1, 33.8, 35.4, 58.7, 71.9, 74.7, 74.7, 75.1, 83.8, 88.5, 128.2, 130.1, 133.0, 145.1; MS(FAB$^+$) Calcd. for $C_{22}H_{34}O_6{}^{79}Br_1{}^{32}S_1$ [(M+H)$^+$] 505.1254, found 505.1254.



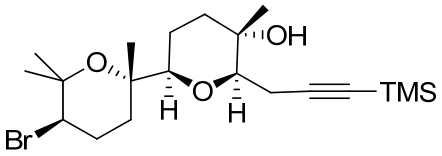
26

Terminal epoxide (26): Potassium carbonate (0.6700 g, 4.8 mmol) was added to a solution of primary tosylate **25** (0.8154 g, 1.6 mmol) in methanol (16 mL) and stirred for 1 h. The reaction mixture was concentrated, diluted with Et_2O (50 mL) and washed with pH 7 buffer (3 x 50 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography eluted with Et_2O : hexanes (v/v 1 : 3) producing terminal epoxide **26** (0.4905 g, 91%) as a clear oil. $[\alpha]^{23}{}_D$ = +23.2 (CH_2Cl_2, c = 0.94); IR (neat) 3583, 2980, 2873, 2359, 1462, 1452, 1381, 1370, 1242, 1130, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.24 (s, 3H), 1.29, (s, 3H), 1.42 (s, 3H), 1.54-1.67 (m, 2H), 1.87-1.92 (m, 2H), 2.12 (qd, *J* = 13.6, 4 Hz, 1H), 2.26 (dq, *J* = 13, 4 Hz, 1H), 2.58 (dd, *J* = 5.2, 2.8 Hz, 1H), 2.72 (t, *J* = 4.6 Hz, 1H), 2.97 (dd, *J* = 4.4, 2.8 Hz, 1H), 3.66 (t, *J* = 7 Hz, 1H), 3.89 (dd, *J* = 12.4, 4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 23.9, 24.0 26.5, 28.2, 31.1, 33.1, 36.1, 44.4, 57.4, 59.0, 75.1, 81.6, 88.3; MS(FAB$^+$) Calcd. for $C_{15}H_{26}O_3{}^{79}Br_1{}^{28}$ [(M+H)$^+$] 333.1060, found 333.1060.



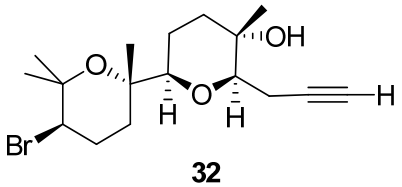
33

Silyl alkynyl alcohol (33): A solution of *n*-butyllithium (1.6 M in hexanes, 3.5 mL, 5.6 mmol) was added to a -78 ˚C solution of trimethylsilyl acetylene (0.69 mL, 4.9 mmol) in THF (10 mL). The lithiate solution was allowed to warm to -55 ˚C and stirred for 1 h. The mixture was cooled to -78 ˚C, boron trifluoride tetrahydrofuran complex (0.69 mL, 6.3 mmol) was added and the acetylide mixture stirred for 20 min. A solution of terminal epoxide **26** (0.4905 g, 1.5 mmol) in THF (8 mL) was added via cannula to the acetylide solution. The reaction mixture was stirred for -78 ˚C for 2 h. then allowed to warm slowly to RT over the period of 2 h. The reaction mixture was diluted with Et_2O (75 mL) and washed with pH 7 buffer (3 x 30 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography eluted with Et_2O : hexanes (v/v 1 : 10) yielding alkynyl alcohol **33** (0.6338 g, 99%) as a clear oil. $[\alpha]^{23}_D$ = +31.0 (CH_2Cl_2, c = 3.19); IR (neat) 3436, 2973, 2898, 2877, 2175, 1642, 1456, 1381, 1250, 1132, 1076, 1034, 844, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.15 (s, 3H), 1.22 (s, 3H), 1.29 (s 3H), 1.41 (s, 3H), 1.56-1.63 (m, 2H), 1.83-1.89 (m, 2H), 1.98-2.05 (m, 1H), 2.11 (qd, *J* = 13.6, 4 Hz, 1H), 2.20-2.30 (m, 1H), 2.35 (dd, *J* = 16.8, 9 Hz, 1H), 2.50 (dd, *J* = 16.8, 3.6 Hz, 1H), 3.61-3.67 (m, 2H), 3.88 (dd, *J* = 12.8, 4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.26, 21.2, 22.9, 23.8, 24.0, 26.6, 28.2, 31.1, 33.0, 35.7, 58.9, 74.8, 75.1, 75.2, 85.2, 86.9, 88.6, 104.5; MS(FAB^+) Calcd. for $C_{20}H_{35}O_3{}^{79}Br_1{}^{23}Na_1{}^{28}Si_1$ [$(M+Na)^+$] 453.1431, found 453.1432.



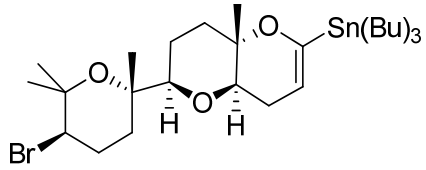
34

Alkynyl alcohol (34): Chloromethanesulfonyl chloride (0.21 mL, 2.4 mmol) was added dropwise to a solution of alkynyl alcohol **33** (0.2071 g, 0.48 mmol) and 2,6-lutidine (0.45 mL, 3.9 mmol) in DCM (1.3 mL) at 0 ˚C. The reaction mixture was stirred for 1 h., diluted with ethyl acetate (10 mL) and washed with saturated aqueous brine (2 x 5 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude chloromesylate was dissolved in dioxane (6.5 mL) and water (6.5 mL). Zinc acetate dihydrate (0.4223 g, 1.9 mmol) was added to the solution and the reaction mixture was heated to 60 ˚C for 5 h. The reaction mixture was diluted with DCM (10 mL) and pH 7 buffer (5 mL). The aqueous layer was extracted with additional DCM (2 x 10 mL), the combined organic layers were dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography eluted with Et_2O : hexanes (v/v 1 : 10) yielding bistetrahydropyranyl alcohol **34** (0.0638 g, 31 %) as a clear oil. $[\alpha]^{23}_D = +40.8$ (CH_2Cl_2, c = 0.25); IR (neat) 3413, 2959, 2859, 2361, 2178, 1718, 1631, 1470, 1380, 1249, 1129, 1103, 1072, 1017, 843,760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 9H), 1.19 (s, 3H), 1.20 (s, 3H), 1.27 (s, 3H), 1.40 (s, 3H), 1.50-1.64 (m, 2H), 1.75-1.87 (m, 4H), 2.10 (qd, *J* = 13.6, 4 Hz, 1H), 2.25 (dq, *J* = 13.4, 4 Hz, 1H), 2.34 (dd, *J* = 17.2, 8 Hz, 1H), 3.04 (dd, *J* = 12.4, 3.6 Hz, 1H), 3.38 (dd, *J* = 8, 6.8 Hz, 1H), 3.91 (dd, *J* = 12, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.2, 20.2, 20.3, 21.4, 23.2, 23.9, 28.4, 29.9, 31.2, 37.2, 39.2, 59.2, 70.6, 74.6, 75.2, 82.3, 86.5, 86.9, 104.8; MS(FAB$^+$) Calcd. for $C_{20}H_{36}O_3{}^{79}Br_1{}^{28}Si_1$ [$(M+H)^+$] 431.1612, found 431.1600.



32

Bistetrahydropyranyl alcohol (32): Potassium carbonate (0.0984 g, 0.71 mmol) was added to a solution of silyl alkynyl alcohol **34** (0.0638 g, 0.15 mmol) in methanol (3 mL) and stirred overnight. The reaction mixture was concentrated, diluted with DCM (10 mL) and washed with pH 7 buffer (3 x 5 mL). The organic layer was dried over $MgSO_4$, concentrated, purified by silica gel column chromatography eluted with methanol : DCM (v/v 1 : 199) resulting in alkynyl alcohol **32** (0.0319 g, 60%) as a white solid. m.p. = 61-62 ˚C; $[\alpha]^{23}_D$ = +46.4 (CH_2Cl_2, c = 0.83); IR (neat) 3413, 3307, 2924, 2856, 1462, 1381, 1265, 1128, 1103, 1072, 1028, 980, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.19 (s, 3H), 1.27 (s, 3H), 1.40 (s, 3H), 1.56 (tt, *J* = 13.2, 4 Hz, 2H), 1.74-1.87 (m, 4H), 2.00 (t, *J* = 2.6 Hz, 1H), 2.11 (qd, *J* = 13.6, 4 Hz, 1H), 2.19-2.30 (m, 2H), 2.49 (ddd, *J* = 16.8, 5.2, 2.8 Hz, 1H), 3.05 (dd, *J* = 11.6, 2 Hz, 1H), 3.56 (dd, *J* = 8.2, 5 Hz, 1H), 3.90 (dd, *J* = 12.2, 4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.2, 20.2, 23.3, 23.8, 28.4, 29.9, 31.2, 37.0, 39.5, 59.2, 69.7, 70.4, 74.6, 75.1, 82.4, 82.6, 86.4; MS(FAB^+) Calcd. for $C_{17}H_{28}O_3{}^{79}Br_1$ [$(M+H)^+$] 359.1216, found 359.1218.



30

α-Stannyl dihydropyran (30): A solution of alkynyl alcohol **32** (0.0319 g, 0.09 mmol) and tungsten hexacarbonyl (0.1631 g, 0.5 mmol) in anhydrous degassed THF (4 mL) was irradiated at 350 nm for 2 h. The reaction mixture was stirred for 16 h. then irradiated for

an additional 2 h. After stirring for an additional 24 h., the reaction mixture was concentrated. Powdered, activated 4 Å molecular sieves (0.6 g) and Et_2O were added to the crude tungsten carbene and stirred for 10 min. A solution of tributyltin triflate[48] (0.1034 g, 0.24 mmol) in Et_2O (0.5 mL) was added and stirred for 10 min, followed by the addition of Et_3N (0.86 mL, 6.2 mmol). After stirring overnight the mixture was filtered to remove the sieves and concentrated. The crude yellow solid was purified by silica gel column chromatography eluted with Et_2NH : hexanes (v/v 2 : 98), producing stannyl dihydropyran **30** as an off white solid (0.0229 g, 40 %). $[\alpha]^{23}_D$ = -2.5 (CH_2Cl_2, c = 0.49); IR (neat) 2954, 2926, 2852, 1600, 1455, 1375, 1132, 1101, 1044, 1022, 952, 903. 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87-0.92 (m, satellite signals from coupling to $^{117/119}Sn$ were observed, J_{Sn-H} = 26 Hz, 15H), 1.10, (s, 3H), 1.21 (s, 3H), 1.26-1.36 (m, 6H), 1.28 (s, 3H), 1.41 (s, 3H), 1.47-1.58 (m, 9H), 1.76-1.92 (m, 4H), 2.00-2.14 (m, 2H), 2.25 (dq, *J* = 13.6, 4 Hz, 1H), 3.08 (dd, *J* = 10.6, 2.6 Hz, 1H), 3.33 (dd, *J* =11, 5.6 Hz, 1H), 3.91 (dd, *J* = 12, 4 Hz, 1H), 4.61 (dd, *J* = 5.6, 2 Hz, satellite signals from coupling to $^{117/119}Sn$ were observed, $^3J_{Sn-H}$ = 14 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8, 14.0, 15.8, 20.2, 23.2, 23.9, 26.0, 27.4, 28.4, 29.1, 29.2, 31.2, 36.9, 37.4, 59.3, 73.9, 74.5, 75.1, 86.4, 108.7, 160.0; MS(FAB$^+$) Calcd. for $C_{29}H_{54}O_3{}^{79}Br_1{}^{120}Sn_1$ [$(M+H)^+$] 649.2273, found 649.2258.

35

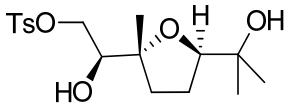
2,3-Epoxygeraniol (35)[21]: 4 Å powdered, activated molecular sieves (5.1797 g) were suspended in anhydrous DCM (50 mL) in a 100 mL 3-necked round bottom flask equipped with a thermometer. The suspension was cooled to -20 ˚C and L-(+)-diethyl

tartrate (0.22 mL, 1.28 mmol) and Ti(O*i*-Pr)$_4$ (0.25 mL, 0.84 mmol) were added with stirring. A solution of anhydrous TBHP (5.5M in decane, 4.8 mL, 26.4 mmol) was added dropwise and the catalyst mixture was aged for 30 min. at -20 ˚C. Geraniol (3 mL, 17.3 mmol) was added over a period of 20 min. The reaction mixture was stirred for 5 h. at -20 ˚C then placed in the freezer (-25 ˚C) overnight. The cold mixture was filtered through celite and stirred with a solution of KOH (1.5 M, 50 mL) for 1 h. The biphasic mixture was separated and the aqueous layer was extracted with additional DCM (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resultant oil was purified by silica gel column chromatography eluted with diethyl ether : hexanes (v/v 1:3) yielding 2,3-epoxygeraniol **35** (2.8799 g, 98%) as a colorless oil. $[\alpha]^{23}_D = -5.8$ (CH_2Cl_2, c = 0.99); IR (neat) 3430, 2968, 2925, 2859, 1673, 1453, 1384, 1251, 1222, 1076, 1037, 865 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.31 (s, 3H), 1.44-1.52 (m, 1H), 1.62 (s, 3H), 1.65-1.73 (m, 1H), 1.69 (s, 3H), 2.09 (bq, *J* = 7.6 Hz, 2H), 2.99 (dd, *J* = 6.4, 4.4 Hz, 1H), 3.67-3.72 (m, 1H), 3.81-3.87 (m, 1H), 5.09 (tt, *J* = 7, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 17.9, 23.9, 25.9, 38.7, 61.4, 61.7, 63.1, 123.5, 132.4; MS(FAB$^+$) Calcd. for $C_{10}H_{19}O_2$ [(M+H)$^+$] 171.1380, found 171.1375.

36

1-Tosyl-2,3-epoxygeraniol (36): 2,3-Epoxygeraniol **35** (2.8799 g, 16.9 mmol) was dissolved in pyridine (16 mL) and cooled to 0 ˚C. *p*-Toluenesulfonyl chloride (3.5574 g, 18.7 mmol) was added and stirred until just dissolved. The reaction mixture was then placed in the freezer (-25 ˚C) overnight. The cold mixture was filtered to remove the solids and the solids were rinsed with cold Et_2O. The filtrate was washed with pH 7

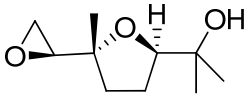
buffer (3 x 50 mL) and the organic layers were dried over $MgSO_4$ and concentrated. The resultant oil was purified by silica gel column chromatography eluted with Et_2O : hexanes (v/v 1:10) yielding tosylepoxygeraniol **36** (4.4235 g, 81%) as a clear oil. $[\alpha]^{23}_D$ = -4.6 (CH_2Cl_2, c = 0.99); IR (neat) 2968, 2925, 2859, 1598, 1452, 1364, 1177, 1097, 966, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.40-1.47 (m, 1H), 1.60 (s, 3H), 1.60-1.68 (m, 1H), 1.68 (s, 3H), 2.04 (bq, *J* = 8 Hz, 2H), 2.46 (s, 3H), 2.98 (t, *J* = 5.6 Hz, 1H), 4.12 (dq, *J* = 11.2, 5.6 Hz, 2H), 5.04 (tt, *J* = 7.2, 1.4 Hz, 1H), 7.37 (d, *J* = 8 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 17.9, 21.9, 23.7, 25.9, 38.2, 58.9, 61.1, 68.8, 123.2, 128.2, 130.2, 132.6, 132.8, 145.3; MS(FAB^+) Calcd. for $C_{17}H_{24}O_4{}^{23}Na_1{}^{32}S_1$ [$(M+Na)^+$] 347.1288, found 347.1284.



37

Tosyltetrahydrofuran (37): Tosylepoxygeraniol **36** (2.1976 g, 6.77 mmol) was dissolved in a mixture of *t*-BuOH : H_2O (v/v 1:1, 70 mL). AD mix β (9.4849 g) and methanesulfonamide (0.6468 g, 6.8 mmol) were added to the solution. After the solids had dissolved completely, the biphasic mixture was cooled to 0 ˚C and stirred for 5h. The reaction was allowed to warm to room temperature and stirred overnight. Sodium sulfite (10.2082 g, 81 mmol) was added and stirred for 1h. The layers were separated and the aqueous layer was extracted with DCM (3 x 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The yellow oil was diluted with DCM (100 mL); CSA (0.1493 g, 0.6 mmol) was added and stirred for 10 min. The acid solution was concentrated producing a yellow oil which was purified by silica gel column chromatography eluted with MeOH : DCM (v/v 2 : 98). The tosylated tetrahydrofuran **37**

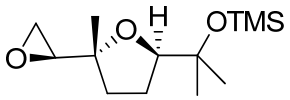
was obtained as a clear oil (2.2564 g, 93%). $[\alpha]^{23}_{D}$ = -8.8 (CH_2Cl_2, c = 0.79); IR (neat) 3535, 3409, 2974, 2876, 1598, 1453, 1358, 1175, 1094, 968, 837, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.13 (s, 3H), 1.18 (s, 3H), 1.64-1.70 (m, 1H), 1.82-1.88 (m, 2H), 2.02-2.09 (m, 1H), 2.46 (s, 3H), 3.72 (dd, *J* = 9, 6.6 Hz, 1H), 3.78 (dd, *J* = 8, 2.8 Hz, 1H), 4.01 (dd, *J* = 10.4, 7.6 Hz, 1H), 4.25 (dd, *J* = 10.4, 2.2 Hz, 1H), 7.37 (d, *J* = 8 Hz, 2H), 7.82 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 22.9, 24.2, 26.4, 27.7, 34.3, 70.7, 71.7, 74.9, 83.8, 87.4, 128.2, 130.2, 132.9, 145.3; MS(FAB^+) Calcd. for $C_{17}H_{27}O_6{}^{32}S_1$ [$(M+H)^+$] 359.1523, found 359.1513.



38

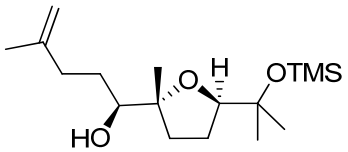
Epoxytetrahydrofuranyl alcohol (38): Tosyltetrahydrofuran **37** (2.2564 g, 6.3 mmol) was dissolved in MeOH (30 mL) with stirring. Potassium carbonate (3.4870 g, 25.2 mmol) was added and the suspension was stirred for 15 min. The reaction mixture was concentrated to 5 mL, the residue was diluted with DCM (50 mL) followed by an aqueous solution of NH_4Cl (1 M, 25 mL, 25 mmol). The aqueous layer was diluted with pH 7 buffer (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography eluted with Et_3N : EtOAc : hexanes (3 : 22: 75) yielding epoxytetrahydrofuranyl alcohol **38** (1.0300 g, 87%). $[\alpha]^{23}_{D}$ = -2.7 (CH_2Cl_2, c = 1.39); IR (neat) 3461, 3057, 2975, 2934, 2874, 1725, 1642, 1464, 1373, 1308, 1241, 1178, 1142, 1055, 986, 943, 915, 898, 863, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.23 (s, 3H), 1.28 (s, 3H), 1.61-1.64 (m, 2H), 1.82-1.87 (m, 2H), 2.59 (dd, *J* = 5.2, 2.8 Hz, 1H), 2.75, (t, *J* = 4.4 Hz, 1H), 3.04 (dd, *J* = 4, 2.8 Hz, 1H), 3.78 (t, *J* = 7.6 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 24.5, 26.4, 27.7, 32.9, 44.1, 57.3, 70.8, 81.5, 87.0; MS(FAB$^+$) Calcd. for $C_{10}H_{19}O_3$ [(M+H)$^+$] 187.1329, found 187.1327.



39

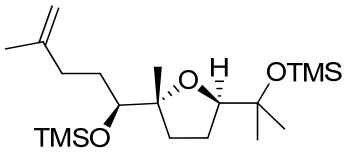
Epoxytetrahydrofuranyl silyl ether (39): Trimethylsilyl chloride was added dropwise to a solution of epoxytetrahydrofuranyl alcohol **38** (1.0205 g, 5.5 mmol) and imidazole (1.5073 g, 22.1 mmol) in THF (5 mL). The solution was stirred overnight. The reaction mixture was diluted with Et_2O (50 mL) and pH 7 buffer (50 mL). The organic layer was washed with additional pH 7 buffer (2 x 50 mL), then dried over $MgSO_4$. After concentration of the crude product, purification by silica gel column chromatography eluted with Et_3N : hexanes (v/v 3 : 97) yielded the silyl ether **39** (1.0263 g, 72%). $[\alpha]^{23}_D$ = -2.9 (CH_2Cl_2, c = 1.41); IR (neat) 3436, 3052, 2974, 2897, 2874, 1632, 1462, 1382, 1369, 1250, 1174, 1101, 1063, 1044, 916, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.18 (s, 3H), 1.22 (s, 3H), 1.24 (s, 3H), 1.57-1.63 (m, 1H), 1.75-1.81 (m, 1H), 1.86-1.93 (m, 2H), 2.59 (dd, *J* = 5.2, 2.8 Hz, 1H), 2.73 (bt, *J* = 4.6 Hz, 1H), 3.00 (dd, *J* = 4.2, 3 Hz, 1H), 3.72 (t, *J* = 7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.8, 24.0, 25.9, 26.7, 27.8, 33.2, 44.4, 57.4, 75.0, 81.7, 87.7; MS(FAB$^+$) Calcd. for $C_{13}H_{27}O_3{}^{28}Si_1$ [(M+H)$^+$] 259.1724, found 259.1721.



40

Alkenyl tetrahydrofuranyl alcohol (40): A solution of 2-methylallylmagnesium chloride (0.5 M in THF, 13 mL, 6.5 mmol) was added dropwise to a -40 ˚C suspension of

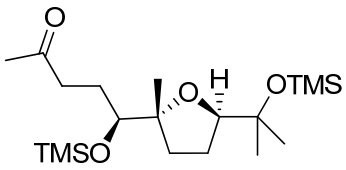
CuI[49] (0.1841 g, 0.97 mmol) in THF (3 mL) and stirred for 10 min. A solution of epoxytetrahydrofuran **39** (1.0263 g, 5.0 mmol) in THF (4 mL) was added to the Grignard solution. The reaction was warmed to 0 ˚C and stirred for 30 min, then allowed to warm to RT. The reaction was stirred for an additional 30 min, then diluted with Et_2O (50 mL) and pH 7 buffer (50 mL). The aqueous layer was extracted with additional Et_2O (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by neutral alumina column chromatography eluted with Et_2O : toluene (v/v 1 : 199) yielding unsaturated alcohol **40** (0.9918 g, 79%) as a clear oil. $[\alpha]^{23}_D$ = +6.8 (CH_2Cl_2, c = 0.27); IR (neat) 3462, 2970, 2872, 2095, 1648, 1454, 1380, 1250, 1176, 1131, 1040, 909, 883, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.13 (s, 3H), 1.17 (s, 3H), 1.24 (s, 3H), 1.36-1.45 (m, 1H), 1.51 (ddd, *J* = 11.4, 7.4, 2 Hz, 1H), 1.55-1.63 (m, 1H), 1.75 (s, 3H), 1.80-1.96 (m, 2H), 2.01-2.15 (m, 2H), 2.29-2.36 (m, 1H), 2.44 (t, *J* = 2 Hz, 1H), 3.51 (dt, *J* = 10.8, 2 Hz, 1H), 3.69 (dd, *J* = 9.8, 5.8 Hz, 1H), 4.72-4.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.8, 22.8, 24.1, 26.5, 26.9, 27.3, 29.8, 31.1, 35.1, 74.5, 76.4, 86.3, 88.6, 110.1, 146.2; MS(FAB$^+$) Calcd. for $C_{17}H_{38}O_3N_1{}^{28}Si_1$ [$(M+NH_4)^+$] 332.2616, found 332.2614.



41

Unsaturated bisilyl ether tetrahydrofuran (41): Trimethylsilyl chloride (1.3 mL, 10.3 mmol) was added dropwise to a solution of unsaturated alcohol **40** (0.9918 g, 3.2 mmol) and imidazole (1.4220 g, 20.9 mmol) in THF (20 mL). The reaction mixture was stirred overnight then concentrated. The resulting yellow oil was diluted with DCM (50 mL) and

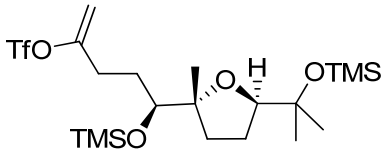
pH 7 buffer (50 mL). The organic layer was washed with additional pH 7 buffer (2 x 50 mL) then dried over $MgSO_4$. The crude product was purified by silica gel column chromatography eluted with Et_3N : hexanes (v/v 3 : 97) yielding silyl ether **41** (1.1189 g, 92%). $[\alpha]^{23}_D = +0.5$ (CH_2Cl_2, c = 1.26); IR (neat) 3076, 2960, 2873, 1650, 1454, 1373, 1250, 1173, 1131, 1102, 1066, 1042, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 9H), 0.13 (s, 9H), 1.09 (s, 3H), 1.17 (s, 3H), 1.21 (s, 3H), 1.35-1.44 (m, 1H), 1.50-1.55 (m, 1H), 1.66-1.73 (m, 1H), 1.74 (s, 3H), 1.76-2.00 (m, 4H), 2.14-2.21 (m, 1H), 3.52 (dd, *J* = 9.8, 2.6 Hz, 1H), 3.66 (dd, *J* = 9, 5.8 Hz, 1H), 4.71 (bd, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.2, 2.8, 22.9, 23.5, 26.2, 26.7, 27.6, 31.5, 33.6, 35.2, 74.8, 78.2, 85.9, 87.3, 109.8, 146.5; MS(FAB$^+$) Calcd. for $C_{20}H_{46}O_3N_1{}^{28}Si_2$ [$(M+NH_4)^+$] 404.3011, found 404.3011.



42

Methyl ketone (42): Ozone was bubbled through a -78 ˚C solution of alkene **41** (1.7765 g, 4.6 mmol), pyridine (9 mL), methanol (15 mL), and isopropanol (15 mL) with stirring. The reaction was monitored by TLC. After complete consumption of alkene, dimethyl sulfide (1.4 mL, 19.1 mmol) was added and the solution was warmed to RT. The reaction mixture was stirred overnight, then concentrated. The crude product mixture was diluted with Et_2O (50 mL), washed with pH 7 buffer (3 x 50 mL), then dried over $MgSO_4$ and concentrated. Trimethylsilyl chloride (1.4 mL, 11.1 mmol) was added dropwise to a solution of the resultant oil and imidazole (1.7995 g, 26.4 mmol) in THF (7 mL). The reaction mixture was stirred overnight then concentrated. The yellow oil was dissolved in

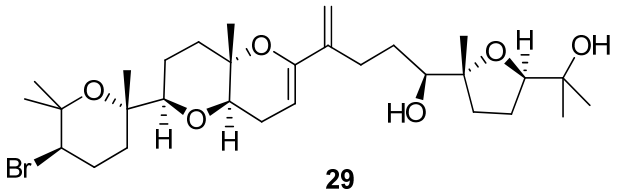
Et_2O (50 mL), washed with pH 7 buffer (3 x 50 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography eluted with Et_3N : hexanes (v/v 3 : 97) resulting in methyl ketone **42** (1.1990 g, 67%). $[\alpha]^{23}_D$ = +1.1 (CH_2Cl_2, c = 1.69); IR (neat) 2962, 2899, 2873, 1720, 1454, 1410, 1362, 1250, 1174, 1103, 1041, 912, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 9H), 0.12 (s, 9H), 1.09 (s, 3H), 1.15 (s, 3H), 1.20 (s, 3H), 1.47-1.56 (m, 2H), 1.75-1.97 (m, 4H), 2.15 (s, 3H), 2.39-2.47 (m, 1H), 2.57-2.65 (m, 1H), 3.52 (dd, *J* =9.4, 3.4 Hz, 1H), 3.63 (dd, *J* = 9, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0, 2.8, 23.5, 26.2, 26.5, 27.5, 27.6, 30.1, 33.4, 41.2, 74.7, 85.9, 87.5, 209.4; MS(FAB^+) Calcd. for $C_{19}H_{41}O_4{}^{28}Si_2$ [$(M+H)^+$] 389.2538, found 389.2539.



31

Enol triflate (31): A solution of KHMDS (0.5 M in toluene, 1.5 mL, 0.75 mmol) was added dropwise to a -78 ˚C solution of methyl ketone **42** (0.2606 g, 0.67 mmol) in THF (7 mL). The enolate solution was stirred for 1 h. A solution of *N*-phenyl-bis(trifluoro-methanesulfonimide) (0.3620 g, 1.0 mmol) in THF (2 mL) was added dropwise to the enolate solution. The reaction was stirred at -78 ˚C for 10 min, then allowed to warm to RT. After 1 h. the reaction mixture was concentrated, diluted with Et_2O (10 mL), washed with pH 7 buffer (2 x 5 mL), and dried over $MgSO_4$. After concentration the crude product was purified by silica gel column chromatography eluted with Et_3N : hexanes (v/v 3 : 97) yielding enol triflate **31** (0.3036 g, 87%). $[\alpha]^{23}_D$ = +1.1 (CH_2Cl_2, c = 0.51); IR (neat) 2962, 2900, 2873, 1670, 1419, 1252, 1213, 1176, 1146, 1101, 1066, 1041, 939,

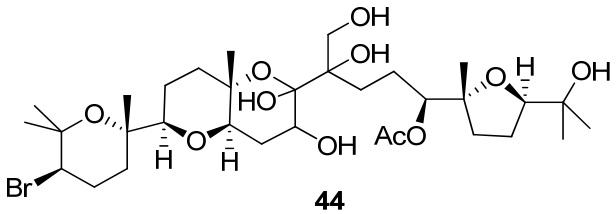
883, 841 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 9H), 0.13 (s, 9H), 1.09 (s, 3H), 1.16 (s, 3H), 1.21 (s, 3H), 1.47-1.61 (m, 2H), 1.75-1.95 (m, 4H), 2.27-2.35 (m, 1H), 2.48-2.56 (m, 1H), 3.52 (dd, *J* = 9.4, 3.4 Hz, 1H), 3.64 (dd *J* = 9, 5.8 Hz, 1H), 4.97 (d, *J* = 3.6 Hz, 1H), 5.11 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.0, 2.8, 23.0, 26.2, 26.5, 27.5, 29.9, 30.0, 31.4, 34.2, 74.6, 85.6, 87.5, 104.3, 113.9, 117.1, 120.3, 123.5, 157.4; MS(FAB$^+$) Calcd. for $C_{20}H_{39}O_6F_3{}^{23}Na_1{}^{32}S_1{}^{28}Si_2$ [(M+Na)$^+$] 543.1850, found 543.1860.



29

Dienyl ether (29): A degassed solution[50] of enol triflate **31** (39.6 mg, 76 μmol) in DMF (6 mL) was transferred to a flask containing α-stannyl dihydropyran **30** (42.1 mg, 65 μmol), tetrakis(triphenylphosphine)palladium(0) (1.8 mg, 1.6 μmol), CuI[49] (10.4 mg, 55 μmol), and CsF (0.02 g, 0.13 mmol). The reaction mixture was degassed an additional 2 cycles. The mixture was heated to 50 ˚C and stirred for 22 h. After cooling, the solution was diluted with EtOAc (20 mL), DCM (20 mL) and water (10 mL) and stirred for an additional 1 h. The biphasic mixture was filtered through celite and diluted with saturated brine (20 mL). The aqueous layer was extracted with a EtOAc : DCM (1 : 1) solution (20 mL x 3). The combined organic layers were dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography eluted with a gradient of Et_2O : hexanes (v/v 1 : 4 to 1 : 1) resulting in a mixture of monosilyl product and free diol. The mixture was diluted with THF (1 mL) and a solution of TBAF (1 M in THF, 1 mL, 1 mmol) and stirred for 1 h. The crude diol solution was concentrated and purified by silica gel column

chromatography eluted with methanol : DCM (v/v 2 : 98) yielding the dienyl ether **29** (23.3 mg, 61 %) as a waxy solid. m.p. = 119-122 ˚C; $[\alpha]^{23}_{D}$ = -7 (CH_2Cl_2, c = 0.145); IR (neat) 3435, 2972, 2926, 2852, 1641, 1458, 1377, 1321, 1180, 1122, 1105, 1022, 895 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.13 (s, 6H), 1.22 (s, 6H), 1.28 (s, 3H), 1.41 (s, 3H), 1.50-1.58 (m, 3H), 1.62-1.70 (m, 2H), 1.82-1.89 (m, 3H), 1.93-1.98 (m, 3H), 2.07-2.14 (m, 2H), 2.17-2.28 (m, 3H), 2.32 (bt, *J* = 1.8 Hz, 1H), 2.50-2.55 (m, 1H), 3.10 (dd, *J* = 11.4, 1.8 Hz, 1H), 3.36 (dd, *J* = 10.8, 6 Hz, 1H), 3.54 (bd, *J* = 10.2 Hz, 1H), 3.76 (dd, *J* = 10.5, 5.7 Hz, 1H), 3.91 (dd, *J* = 12.6, 4.2 Hz, 1H), 4.92-4.93 (m, 2H), 5.41 (bd, *J* = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 20.2, 23.0, 23.9, 24.1, 24.1, 25.2, 26.8, 28.0, 28.4, 30.1, 31.1, 31.2, 31.4, 36.7, 37.4, 59.2, 70.6, 73.5, 74.6, 75.2, 76.5, 76.7, 86.3, 86.5, 87.9, 96.0, 111.4, 142.8, 149.1; MS(FAB$^+$) Calcd. for $C_{30}H_{50}O_6{}^{79}Br_1$ [$(M+H)^+$] 585.2785, found 585.2783.



44

Monoacetate pentahydroxyl tristetrahydropyran (44): Acetic anhydride (1 mL, 10.6 mmol) was added to a solution of dienyl ether **29** (5.1 mg, 8.7 μmol) in pyridine (2 mL) and stirred overnight. The reaction mixture was concentrated and purified by preparative TLC eluted with Et_3N : EtOAc : hexanes (v/v 3 : 27 : 70) yielding the secondary acetate **43** (5.4 mg, 99 %). A solution of secondary acetate **43** (5.4 mg, 8.6 μmol) and osmium tetroxide (10 mg, 39 μmol) in pyridine (2 mL) were stirred overnight. A solution of sodium metabisulfite (19.3 mg, 102 μmol) in water (0.5 mL) was added and stirred an additional 5 h. The biphasic mixture was diluted with pH 7 buffer (2 mL) and the

aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated resulting in a crude diastereomeric mixture of monoacetate pentahydroxyl **44**. MS(FAB^+) Calcd. for $C_{32}H_{55}O_{11}{}^{79}Br_1{}^{23}Na_1$ [$(M+Na)^+$] 717.2820, found 717.2807.

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[15] The unreacted alkene of **9a-b** is deactivated to epoxidation by the electron-withdrawing acetoxymethylene sustituent.

[16] Trimethylsilyl ether, *para*-methoxybenzyl ether, and tetrahydropyranyl ether were successfully synthesized.

[17] If the resolution was not completely selective (reaction mixture too warm or reaction time too long) it was possible to separate the desired bromotetrahydropyran (**5**) from the undesired diasteromer by silica column chromatography eluted with Et_2O : hexanes (v/v 1:3), although the yield was lower.

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[22] Only the desired diastereomer was observed by ^{1}H NMR, undesired diastereomers therefore must be below the 5% detection limit of ^{1}H NMR.

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[26] Mesylate could be used in place of the chloromesylate, but required reflux in aqueous acetic acid.

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[47] We give special thanks to Dr. J. J. Fernández for assistance in providing electronic copies of the original spectra and Dr. M. L. Souto's thesis.

[48] Tributyltin triflate was freshly prepared by dropwise addition of triflic anhydride (0.03 mL, 0.18 mmol) to neat bistributyltin oxide (0.06 mL, 0.12 mmol). The neat solution was stirred for 1 h. then excess triflic anhydride was removed by vacuum. The white solid was used without purification.

[49] Ultra pure CuI was further purified by soxhlet extraction with THF.

[50] The DMF solution was degassed by 3 cycles of the freeze-pump-thaw method.