HETEROCYCLES, Vol. 86, No. 1, 2012, pp. 535 - 553. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 23rd June, 2012, Accepted, 18th July, 2012, Published online, 31st July, 2012
DOI: 10.3987/COM-12-S(N)51

SYNTHESIS OF 15,28-DIDEOXY-15,28-DIDEHYDROTHYRSENOL

Mary A. Smart[1] and Frank E. McDonald*

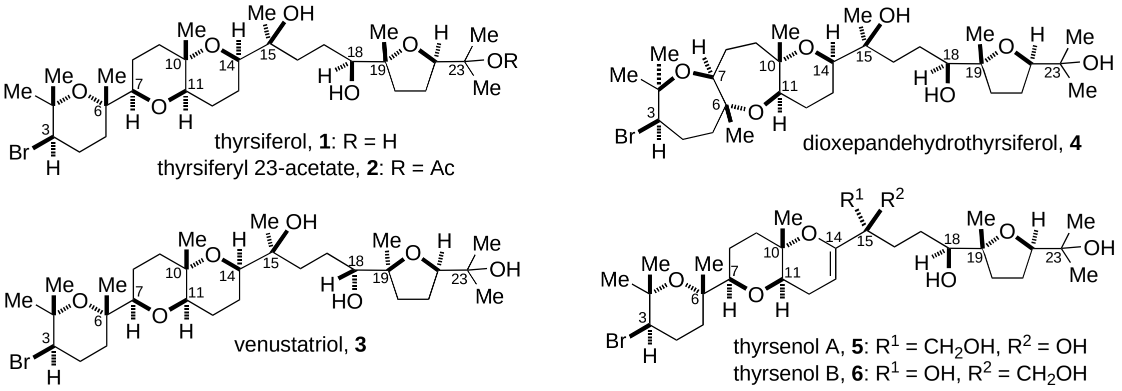
Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, GA 30322 USA; E-mail: fmcdona@emory.edu

Abstract – The tetracyclic skeleton of thyrsenols A and B has been assembled, with the construction of ring A by *exo*-selective oxacyclization of an epoxybromohydrin, B ring formation by *exo*-selective oxacyclization of hydroxyepoxide followed by solvolytic ring expansion of a tetrahydrofuran to tetrahydropyran, C ring closure by tungsten-promoted *endo*-selective oxacyclization of a hydroxyalkyne, and D ring preparation by asymmetric dihydroxylation of an epoxyalkene accompanied by *exo*-selective oxacyclization. A modified Stille coupling linked two fragments at C_{14}-C_{15} to directly provide the tetracyclic dienylether.

INTRODUCTION

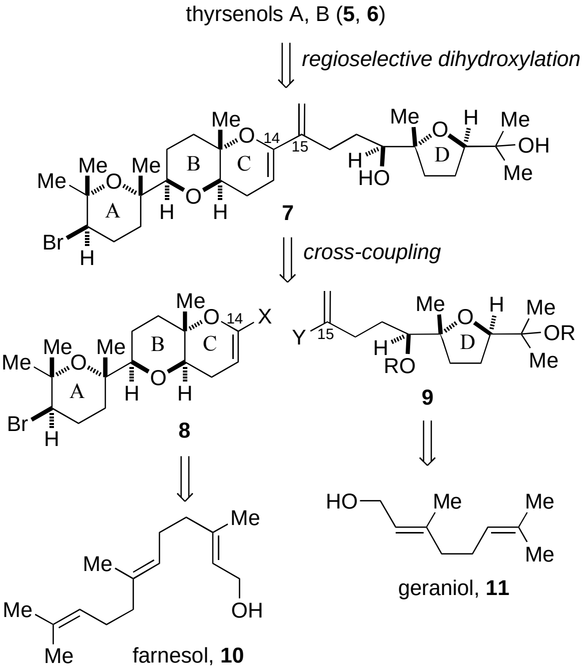
Marine polyether triterpenes encompass a large class of natural products arising from oxidative cyclizations of squalenes, exhibiting various arrangements of five, six, and even seven-membered ring ethers.[2] Pharmacologically many of these natural products display antitumor, antiinflammatory, analgesic, antiallergy, and antiviral properties, and have been the subject of numerous biological studies. In particular, thyrsiferol (**1**, Scheme 1) and especially thyrsiferyl 23-acetate (**2**) exhibit powerful inhibition of cell growth against the P388 lymphoid cancer cell line,[3] whereas the diastereomeric natural product venustatriol (**3**) shows activity against vesicular stomatitis virus (VSV) and *Herpes simples* virus type 1 (HSV-1),[4] and the structurally unique dioxepandehydrothyrsiferol (**4**) bearing two fused seven-membered rings is apparently inactive against several tumor cell lines.[5] Thyrsenols A and B (**5**, **6**) represent more highly oxidized congeners of thyrsiferol, with thyrsenol B displaying much greater cytotoxicity against than P388 cell line (IC_{50} = 0.016 μM) vs. thyrsenol A (IC_{50} = 0.40 μM).[6]

Dedicated in celebration of the 77th birthday of Prof. Ei-ichi Negishi.


thyrsiferol, **1**: R = H
thyrsiferyl 23-acetate, **2**: R = Ac
dioxepandehydrothyrsiferol, **4**
venustatriol, **3**
thyrsenol A, **5**: R^1 = CH_2OH, R^2 = OH
thyrsenol B, **6**: R^1 = OH, R^2 = CH_2OH

Scheme 1. Representative structures of fused polyether triterpenes

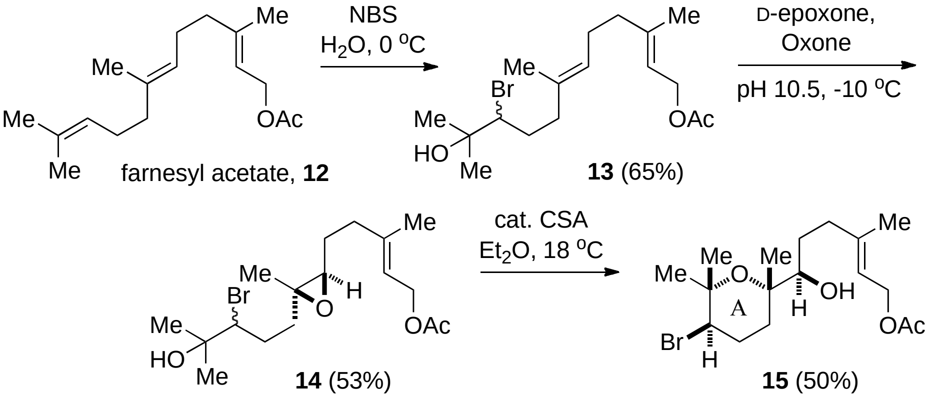
As part of our long-standing interest in the synthesis of marine polycyclic ethers including polyether triterpenes,[7] we set out to explore the preparation of thyrsiferol or one of its congeners (**2** - **6**) by regioselective and stereospecific epoxide cyclizations.[8] The total syntheses of thyrsiferols (**1**, **2**), venustatriol (**3**), and dioxepandehydrothyrsiferol (**4**) have been achieved by several different laboratories,[9-12] but to date synthetic activity directed towards the thyrsenols (**5**, **6**) has not been reported. In considering the synthesis of thyrsenols A and B (**5**, **6**), we proposed that late-stage regio- and enantioselective dihydroxylation of the dideoxydidehydrothyrsenol structure **7** would follow cross-coupling of a tricyclic enol ether derivative **8** with tetrahydrofuranyl-containing **9**, with these sectors arising from oxidative cyclization synthetic strategies beginning with farnesol (**10**) and geraniol (**11**), respectively (Scheme 2).



Scheme 2. Retrosynthetic analysis for thyrsenols via 15,28-dideoxy-15,28-didehydrothyrsenol (**7**)

RESULTS AND DISCUSSION

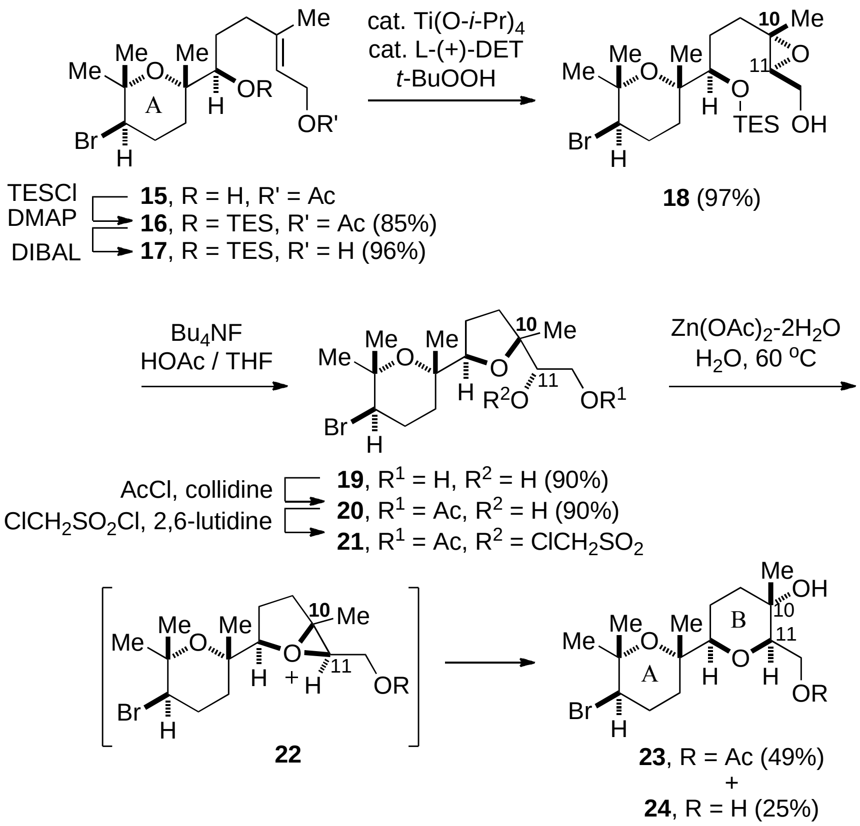
Our synthesis began with regioselective preparation of the racemic bromohydrin **13** (Scheme 3) from farnesyl acetate (**12**) as described in the literature,[13] followed by regioselective and enantioselective epoxidation utilizing the Shi ketone,[14] in which the alkene bearing the allylic acetate substituent was electronically deactivated for electrophilic epoxidation.[15] As the Shi epoxidation required a buffer system with pH 10.5, these basic reaction conditions slowly converted the bromohydrin moiety into the undesired terminal epoxide, which was minimized only by diminishing the reaction time and thus decreasing the conversion of **13** into monoepoxide **14**. Although protective groups could be introduced onto the tertiary alcohol of **13**,[16] the undesired epoxide formed upon removal of these protective groups, so in the end we judged that our original procedure of acid-catalyzed cyclization with careful control of temperature and conversion provided effective throughput of material into the desired bromotetrahydropyran diastereomer **15** as the result of kinetic resolution of the diastereomers of **14**.[17]



Scheme 3. Synthesis of ring A

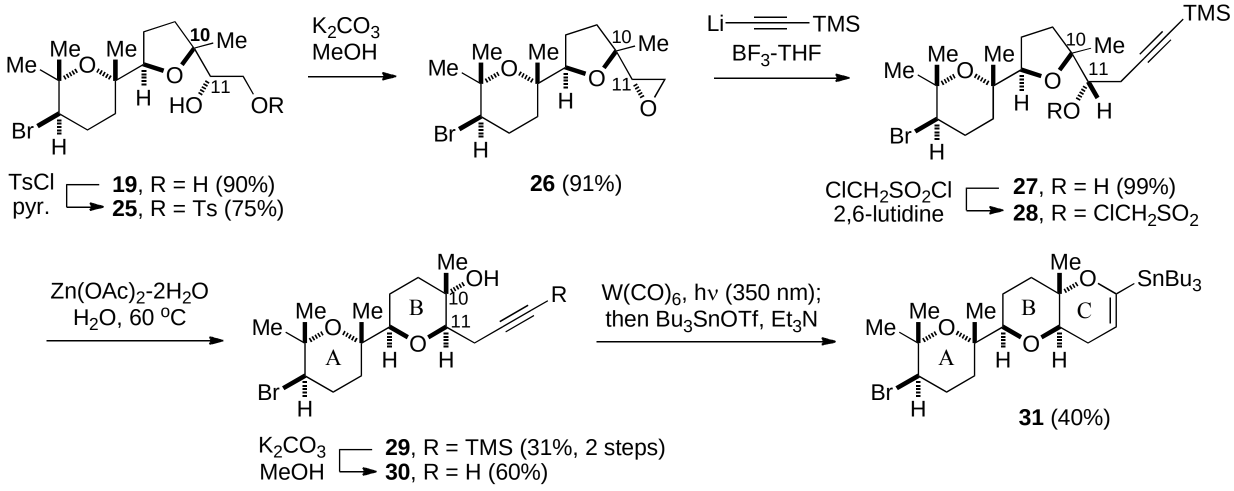
The principal challenge in constructing the B ring of thyrsenols was achieving the 6-*endo*-tet cyclization of an epoxyalcohol instead of the 5-*exo*-tet cyclization predicted by Baldwin's rules.[18] Instead, we elected to undertake a reaction sequence in which the 5-*exo*-tet cyclization tetrahydrofuranyl alcohol product would subsequently undergo isomerization to give the ring-expanded tetrahydropyranyl alcohol. The Sharpless asymmetric epoxidation[19] was conducted from the triethylsilyl ether derivative **17**, as the reaction rates and yields were diminished when the epoxidation was attempted with the corresponding diol. The triethylsilyl ether **16** was preferred over other silyl ethers for its wider range of pH stability and reduced tendency towards migration (Scheme 4). Upon deprotection of the silyl ether from the epoxidation product **18**, the tetrahydrofuranyl diol **19** was selectively produced in excellent yield. As a model system for the ring expansion step, the primary alcohol was regioselectively converted into the acetate ester **20**,[20] and then the remaining secondary alcohol was transformed to the chloromesylate **21**.

Following optimized conditions developed by the Nakata laboratory, upon heating compound **21** in the presence of water and zinc acetate, ring expansion provided the desired tetrahydropyran as a mixture of acetate **23** and diol **24**.[21,22] As the mechanism for the Nakata rearrangement involved initial generation of epoxonium ion **22** followed by addition of water at the tertiary C10, single inversion of each chiral center at C10 and C11 was anticipated to provide the stereochemistry depicted for compounds **23** and **24**.



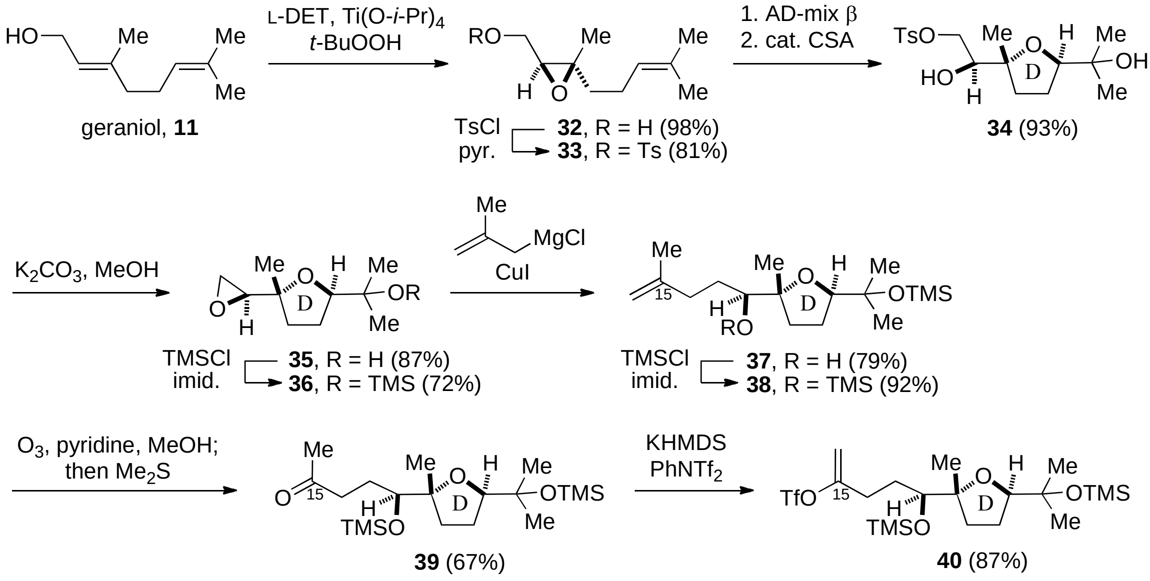
Scheme 4. Cyclization to form ring B

With the success of the model system, we incorporated the carbon atoms necessary for C-ring synthesis by converting the diol **19** into epoxide **26** (Scheme 5) via intermediacy of the primary tosylate **25**,[23] followed by addition of lithium acetylide to provide compound **27**.[24] At this stage, Nakata rearrangement converted the chloromesylate derivative **28** into the tetrahydropyranyl alcohol **29**, albeit in lower yield than we had observed in the model system in which the primary acetate had been present. Nonetheless, basic methanolysis of the trimethylsilyl group revealed the terminal alkyne of **30**. The C-ring was then formed by *endo*-selective alkynol cyclization in the presence of stoichiometric tungsten carbonyl to a cyclic Fischer oxacarbene,[25] followed by reaction with triethylamine and tributyltin triflate to install the tributyltin substituent in tricyclic compound **31** for subsequent Stille cross-coupling.



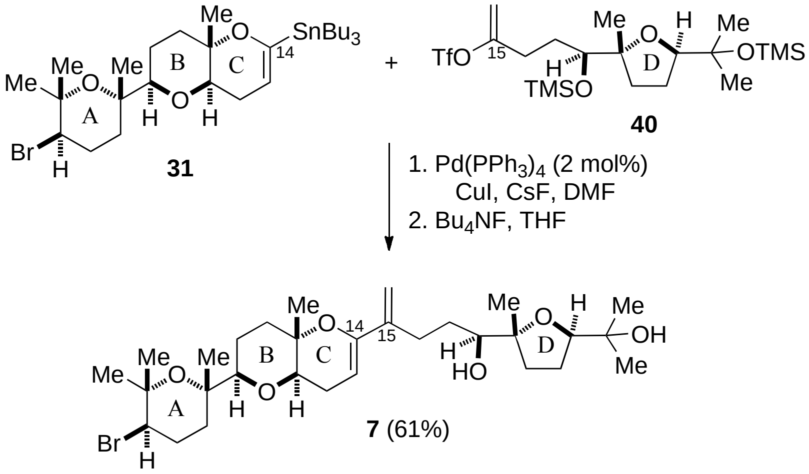
Scheme 5. Synthesis of ABC tricyclic sector

Several methods were explored for preparation of the D-ring synthon before we settled on the route depicted (Scheme 6), in which the known epoxytetrahydrofuranyl alcohol **35** was prepared in four steps from geraniol (**11**).[26] Although the literature precedent had shown that asymmetric dihydroxylation[27] of the epoxytosylate **33** with stirring for three days directly afforded the epoxytetrahydrofuran **35**, we obtained better results when the dihydroxylation was quenched after five hours, followed by acid-catalyzed cyclization for complete conversion to the tetrahydrofuranyldiol **34**, which was stable to isolation and characterization. In a separate step, basic methanolysis of **34** afforded the epoxide **35** from which the remaining tertiary alcohol was protected as silyl ether **36**. Copper-catalyzed addition of 2-methallylmagnesium chloride,[28] silylation of the resulting secondary alcohol **37**, and ozonolysis afforded the methyl ketone **39**,[29] which was converted into enol triflate **40** via the kinetic enolate of **39**.[30]



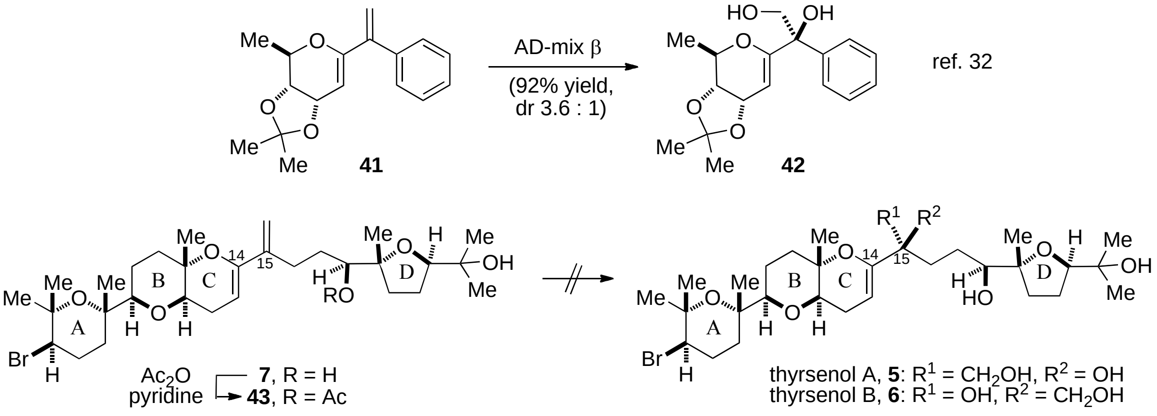
Scheme 6. Synthesis of the D ring sector

Stille coupling of the stannyl enol ether **31** and enol triflate **40** proceeded with minimal homodimerization of **31**, provided that copper iodide and cesium fluoride additives were present (Scheme 7).[31] As the fluoride salt also partially removed the silyl ethers, the dienyl ether product was best isolated as the diol **7** after complete desilylation with excess tetrabutylammonium fluoride.



Scheme 7. Palladium-catalyzed cross-coupling of ABC and D-ring sectors

At this stage, all that remained was the regioselective dihydroxylation of the C15-alkene of **7**. We were optimistic of a favorable outcome due to our precedent of a similarly regioselective dihydroxylation of a dienyl ether in a model system directed towards the branched *C*-glycoside substructure of altromycin B (**41** → **42**, Scheme 8).[32] Surprisingly, the attempted dihydroxylation of compound **7** with both AD-mix β and α gave no reaction, other than eventual decomposition of the dienyl ether after several days. The reaction of **7** with stoichiometric osmium tetraoxide[33] afforded several very polar compounds, none of which matched the proton NMR spectra of thyrsenols A or B. The reaction of osmium tetraoxide with the acetate derivative **43** provided a mixture of diastereomers exhibiting mass spectra consistent with the tetraol arising from dihydroxylation of both alkenes of **43**.[34] It appears that the aryl ring of **41** must have played an activating role in the regioselective dihydroxylation of the 1,1-disubstituted alkene, compared to the corresponding C_{15} alkene of **7** or **43**. Moreover the oxygen substituent at the allylic position of **41** may have deactivated the enol ether to dihydroxylation, whereas dihydroxylation occurred slowly but competitively with both alkenes of **43**.



Scheme 8. Attempted conversion to thyrsenols by *syn*-dihydroxylation

Although the tetracyclic skeleton of the thyrsenols was produced, unfortunately the natural product was not obtained, due to the absence of differential reactivity between the alkenes of dienyl ether **7** in the final dihydroxylation step. However, our work has demonstrated a variety of processes for the construction of cyclic ethers, including diastereoselective epoxyalcohol cyclization to form the A ring, ring expansion of a tetrahydrofuranyl alcohol to the tetrahydropyranyl alcohol isomer in the presence of an alkyne substituent, and the first example of tungsten-promoted alkynol cyclization in the presence of an alkyl bromide.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded 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 Whatman (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 Sigma-Aldrich or prepared as described in the cited literature.

Bromotetrahydropyranyl silyl ether (16): Chlorotriethylsilane (0.41 mL, 2.4 mmol) was added dropwise to a solution of bromotetrahydropyranyl alcohol **15** (0.619 g, 1.6 mmol)[17] 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 **16** (0.688 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* = 4.0 Hz, 1H), 1.70 (s, 3H), 1.81-1.89 (m, 1H), 1.99-2.30 (m, 4H), 2.07 (s, 3H), 3.25 (dd, *J* = 7.8, 3.0 Hz, 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.

Allylic alcohol (17): A solution of DIBAL (1 M in dichloromethane, 2.8 mL, 2.8 mmol) was added slowly to a -78 °C solution of allylic acetate **16** (0.688 g, 1.4 mmol) in dichloromethane (3 mL). The reaction mixture was stirred for 1 h, then allowed to warm to room temperature. After 3 h, sodium sulfate decahydrate was added gradually unti a gel formed. The gel was diluted with a saturated aqueous solution of sodium potassium tartrate (10 mL) and additional dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (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 **17** (0.602 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* = 8.0 Hz, 6H), 0.96 (t, *J* = 8.0 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, 3.0 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.

Epoxy alcohol (18): 4Å powdered, activated molecular sieves (0.686 g) were suspended in a solution of allylic alcohol **17** (0.602 g, 1.3 mmol) in dichloromethane (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 *t*-butyl hydroperoxide (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 dichloromethane (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 dichloromethane (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 **18** (0.605 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* = 8.0 Hz, 6H), 0.95 (t, *J* = 8.0 Hz, 9H), 1.17 (s, 3H), 1.28 (s, 3H), 1.30 (s, 3H), 1.42 (s, 3H), 1.49 (dt, *J* = 13.4, 4.0 Hz, 1H), 1.56-1.72 (m, 4H), 1.75-1.87 (m, 1H), 2.11 (qd, *J* = 13.6, 4.0 Hz, 1H), 2.25 (dq, *J* = 13.2, 3.6 Hz, 1H), 2.97 (dd, *J* = 7.0, 4.0 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.

Tetrahydrofuranyl diol (19): A solution of tetrabutylammonium fluoride (1 M in THF, 6 mL, 6 mmol) was added to a solution of epoxy alcohol **18** (0.605 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 dichloromethane (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 methanol : dichloromethane (v/v 2 : 98) producing diol **19** (0.410 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}; ^{1}H 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, 4.0 Hz, 1H), 2.26 (dq, *J* = 13.0, 4.0 Hz, 1H), 3.53 (dd, *J* = 10.2, 7.4 Hz, 1H), 3.64-3.71 (m, 3H), 3.88 (dd, *J* = 12.4, 4.0 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.

Primary acetate ester (20): Acetyl chloride (0.16 mL, 2.3 mmol) was added dropwise to a -78 °C solution of tetrahydrofuranyl diol **19** (0.648 g, 1.8 mmol) and 2,4,6-trimethylpyridine (0.49 mL, 3.7 mmol) in dichloromethane (3.7 mL). The reaction mixture was stirred for 2 h at -78 °C, then placed in a -25 °C freezer 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 ester **20** (0.650 g, 90%) as a clear oil. ^{1}H 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* = 12.0 Hz, 1.0 H), 2.11 (s, 3H), 2.12 (dq, *J* = 13.8, 4.2 Hz, 1H), 2.27 (dq, *J* = 13.0, 4.0 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 = 12.0, 2.4 Hz, 1H).

Bistetrahydropyran diol (24): Chloromethanesulfonyl chloride (0.16 mL, 1.8 mmol) was added dropwise to a 0 °C solution of primary acetate **20** (0.137 g, 0.35 mmol) and 2,6-lutidine (0.32 mL, 2.7 mmol) in dichloromethane (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 ester 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 diol **24** (0.0302 g, 25%) and the corresponding primary acetate **23** (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, 4.0 Hz, 1H), 2.26 (dq, J = 13.4, 4.0 Hz, 1H), 3.07 (dd, J = 17.2, 2.0 Hz, 1H), 3.31 (dd, J = 8.0, 6.6 Hz, 1H), 3.62 (dd, J = 17.2, 8.0 Hz, 1H), 3.78 (dd, J = 17.2, 6.6 Hz, 1H), 3.89 (dd, 12.4, 4.0 Hz, 1H).

Primary tosylate (25): *p*-Toluenesulfonyl chloride (0.455 g, 2.4 mmol) was added to a 0 °C solution of diol **19** (0.756 g, 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 dichloromethane (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** (0.815 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, 4.0 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 = 8.0, 2.8 Hz, 1H), 3.86 (dd, J = 12.4, 4.0 Hz, 1H), 3.98 (dd, J = 10.6, 8.0 Hz, 1H), 4.24 (dd, J = 10.6, 2.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.4 Hz, 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.

Terminal epoxide (26): Potassium carbonate (0.670 g, 4.8 mmol) was added to a solution of primary tosylate **25** (0.815 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** (0.491 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}; ^1H 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, 4.0 Hz, 1H), 2.26 (dq, *J* = 13.0, 4.0 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* = 7.0 Hz, 1H), 3.89 (dd, *J* = 12.4, 4.0 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.

Silyl alkynyl alcohol (27): 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 alkynyllithium 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** (0.491 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 room temperature 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 **27** (0.634 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, 4.0 Hz, 1H), 2.20-2.30 (m, 1H), 2.35 (dd, *J* = 16.8, 9.0 Hz, 1H), 2.50 (dd, *J* = 16.8, 3.6 Hz, 1H), 3.61-3.67 (m, 2H), 3.88 (dd, *J* = 12.8, 4.0 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.

Alkynyl alcohol (29): Chloromethanesulfonyl chloride (0.21 mL, 2.4 mmol) was added dropwise to a solution of alkynyl alcohol **27** (0.207 g, 0.48 mmol) and 2,6-lutidine (0.45 mL, 3.9 mmol) in dichloromethane (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 **28** was dissolved in dioxane (6.5 mL) and water (6.5 mL). Zinc acetate dihydrate (0.422 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 dichloromethane (10 mL) and pH 7 buffer (5 mL). The aqueous layer was extracted with additional dichloromethane (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 **29** (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}; ^{1}H 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, 4.0 Hz, 1H), 2.25 (dq, J = 13.4, 4.0 Hz, 1H), 2.34 (dd, J = 17.2, 8.0 Hz, 1H), 3.04 (dd, J = 12.4, 3.6 Hz, 1H), 3.38 (dd, J = 8.0, 6.8 Hz, 1H), 3.91 (dd, J = 12.0, 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.

Bistetrahydropyranyl alcohol (30): Potassium carbonate (0.0984 g, 0.71 mmol) was added to a solution of silyl alkynyl alcohol **29** (0.0638 g, 0.15 mmol) in methanol (3 mL) and stirred overnight. The reaction mixture was concentrated, diluted with dichloromethane (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 : dichloromethane (v/v 1 : 199) resulting in alkynyl alcohol **30** (0.0319 g, 60%) as a white solid. mp 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}; ^{1}H 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, 4.0 Hz, 2H), 1.74-1.87 (m, 4H), 2.00 (t, J = 2.6 Hz, 1H), 2.11 (qd, J = 13.6, 4.0 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, 2.0 Hz, 1H), 3.56 (dd, J = 8.2, 5 Hz, 1H), 3.90 (dd, J = 12.2, 4.0 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.

α-Stannyldihydropyran (31): A solution of alkynyl alcohol **30** (0.0319 g, 0.09 mmol) and tungsten hexacarbonyl (0.163 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 oxacarbene and stirred for 10 min. A solution of tributyltin triflate[35] (0.103 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 **31** 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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87-0.92 (m, satellite signals from coupling to

$^{117/119}$Sn were observed, $J_{\text{Sn-H}}$ = 26.0 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, 4.0 Hz, 1H), 3.08 (dd, *J* = 10.6, 2.6 Hz, 1H), 3.33 (dd, *J* =11.0, 5.6 Hz, 1H), 3.91 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.61 (dd, *J* = 5.6, 2.0 Hz, satellite signals from coupling to $^{117/119}$Sn were observed, $^3J_{\text{Sn-H}}$ = 14.0 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.

2,3-Epoxygeraniol (32):[19] 4Å powdered, activated molecular sieves (5.18 g) were suspended in anhydrous dichloromethane (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 (**11**, 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 a -25 °C freezer 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 dichloromethane (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 **32** (2.88 g, 98%) as a colorless oil. $[\alpha]^{23}_{D}$ -5.8 (CH_2Cl_2, c 0.99) {lit.,[19] $[\alpha]^{25}_{D}$ -5.3 ($CHCl_3$, c 3.0)}; IR (neat) 3430, 2968, 2925, 2859, 1673, 1453, 1384, 1251, 1222, 1076, 1037, 865 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (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* = 7.0, 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.

1-Tosyl-2,3-epoxygeraniol (33):[26] 2,3-Epoxygeraniol **32** (2.88 g, 16.9 mmol) was dissolved in pyridine (16 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (3.56 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 **33** (4.42 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}; ^{1}H 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* = 8.0 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* = 8.0 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.

Tosyltetrahydrofuran (34): Tosylepoxygeraniol **33** (2.20 g, 6.77 mmol) was dissolved in a mixture of *t*-BuOH : H$_2$O (v/v 1 : 1, 70 mL). AD mix β (9.48 g) and methanesulfonamide (0.647 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 5 h. The reaction was allowed to warm to room temperature and stirred overnight. Sodium sulfite (10.2 g, 81 mmol) was added and stirred for 1 h. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried over MgSO$_4$ and concentrated. The yellow oil was diluted with dichloromethane (100 mL); camphorsulfonic acid (0.149 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 : dichloromethane (v/v 2 : 98). The tosylated tetrahydrofuran **34** was obtained as a clear oil (2.26 g, 93%). $[\alpha]^{23}_D$ -8.8 (CH$_2$Cl$_2$, c 0.79); IR (neat) 3535, 3409, 2974, 2876, 1598, 1453, 1358, 1175, 1094, 968, 837, 816 cm^{-1}; ^{1}H 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* = 9.0, 6.6 Hz, 1H), 3.78 (dd, *J* = 8.0, 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* = 8.0 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.

Epoxytetrahydrofuranyl alcohol (35):[26] Tosyltetrahydrofuran **34** (2.26 g, 6.3 mmol) was dissolved in MeOH (30 mL) with stirring. Potassium carbonate (3.49 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 dichloromethane (50 mL) followed by an aqueous solution of NH$_4$Cl (1 M, 25 mL, 25 mmol). The aqueous layer was diluted with pH 7 buffer (50 mL) and extracted with dichloromethane (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$_3$N : EtOAc : hexanes (3 : 22 : 75) yielding epoxytetrahydrofuranyl alcohol **35** (1.03 g, 87%). $[\alpha]^{23}_D$ -2.7 (CH$_2$Cl$_2$, c 1.39) {lit.[26] $[\alpha]_D$ -2.45 (CHCl$_3$, c 6.72)}; IR (neat) 3461, 3057, 2975, 2934, 2874, 1725, 1642, 1464, 1373, 1308, 1241, 1178, 1142, 1055, 986, 943, 915, 898, 863, 814 cm^{-1}; ^{1}H 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* = 4.0, 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.

Epoxytetrahydrofuranyl silyl ether (36): Trimethylsilyl chloride was added dropwise to a solution of epoxytetrahydrofuranyl alcohol **35** (1.02 g, 5.5 mmol) and imidazole (1.51 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 **36** (1.03 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}; ^1H 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, 3.0 Hz, 1H), 3.72 (t, *J* = 7.0 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.

Alkenyl tetrahydrofuranyl alcohol (37): 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 (0.184 g, 0.97 mmol) in THF (3 mL) and stirred for 10 min. A solution of epoxytetrahydrofuran **36** (1.03 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 room temperature. 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 **47** (0.992 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, 2.0 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* = 2.0 Hz, 1H), 3.51 (dt, *J* = 10.8, 2.0 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.

Unsaturated bisilyl ether tetrahydrofuran (38): Trimethylsilyl chloride (1.3 mL, 10.3 mmol) was added dropwise to a solution of unsaturated alcohol **37** (0.992 g, 3.2 mmol) and imidazole (1.42 g, 20.9 mmol) in THF (20 mL). The reaction mixture was stirred overnight then concentrated. The resulting yellow oil was diluted with dichloromethane (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 **38** (1.12 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}; ^{1}H 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 = 9.0, 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.

Methyl ketone (39): Ozone was bubbled through a -78 °C solution of alkene **38** (1.78 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 room temperature. 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 (1.80 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 **39** (1.20 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}; ^{1}H 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 = 9.0, 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.

Enol triflate (40): 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 **39** (0.261 g, 0.67 mmol) in THF (7 mL). The enolate solution was stirred for 1 h. A solution of *N*-phenyl-bis(trifluoromethanesulfonimide) (0.362 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 room temperature. 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 **40** (0.304 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 = 9.0, 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.

Dienyl ether (7): A solution of enol triflate **40** (39.6 mg, 76 μmol) in DMF (6 mL) was degassed by three freeze-pump-thaw cycles, and then was transferred to a flask containing α-stannyl dihydropyran **31** (42.1 mg, 65 μmol), tetrakis(triphenylphosphine)palladium(0) (1.8 mg, 1.6 μmol), CuI[36] (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), dichloromethane (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 : dichloromethane (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 tetrabutylammonium fluoride (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 : dichloromethane (v/v 2 : 98) yielding the dienyl ether **7** (23.3 mg, 61%) as a waxy solid. mp 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}; ^{1}H 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, 6.0 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.

ACKNOWLEDGEMENTS

This work was supported primarily by the National Science Foundation (CHE-0516793).

REFERENCES AND NOTES

1. Based on the M.S. thesis of Mary A. Smart, Emory University, 2008.
2. J. J. Fernández, M. L. Souto, and M. Norte, *Nat. Prod. Rep.*, 2000, **17**, 235.
3. J. W. Blunt, M. P. Hartshorn, J. T. McLennan, and M. H. G. Munro, *Tetrahedron Lett.*, 1978, **19**, 69; T. Suzuki, M. Suzuki, A. Furusaki, T. Matsumoto, A. Kato, Y. Imanaka, and E. Kurosawa, *Tetrahedron Lett.*, 1985, **26**, 1329.

4. S. Sakemi, T. Higa, C. W. Jefford, and G. Bernardinelli, *Tetrahedron Lett.*, 1986, **27**, 4287.
5. C. P. Manríquez, M. L. Souto, J. A. Gavín, M. Norte, and J. J. Fernández, *Tetrahedron*, 2001, **57**, 3117.
6. M. Norte, J. J. Fernández, M. L. Souto, J. Gavín, and M. D. Gracía-Grávalos, *Tetrahedron*, 1997, **53**, 3173.
7. M. A. Boone, R. Tong, F. E. McDonald, S. Lense, R. Cao, and K. I. Hardcastle, *J. Am. Chem. Soc.*, 2010, **132**, 5300.
8. J. C. Valentine and F. E. McDonald, *Synlett*, 2006, 1816.
9. M. Hashimoto, T. Kan, K. Nozaki, M. Yanagiya, H. Shirahama, and T. Matsumoto, *Tetrahedron Lett.*, 1988, **29**, 1143; M. Hashimoto, T. Kan, K. Nozaki, M. Yanagiya, H. Shirahama, and T. Matsumoto, *J. Org. Chem.*, 1990, **55**, 5088; I. C. González and C. J. Forsyth, *J. Am. Chem. Soc.*, 2000, **122**, 9099.
10. E. J. Corey and D. Ha, *Tetrahedron Lett.*, 1988, **29**, 3171.
11. J. Tanuwidjaja, S.-S. Ng, and T. F. Jamison, *J. Am. Chem. Soc.*, 2009, **131**, 12084.
12. C. A. Broka, L. Hu, W. J. Lee, and T. Shen, *Tetrahedron Lett.*, 1987, **28**, 4993; C. A. Broka and Y. Lin, *J. Org. Chem.*, 1988, **53**, 5876; G. A. Nishiguchi, and R. D. Little, *J. Org. Chem.*, 2005, **70**, 5249; G. A. Nishiguchi, J. Graham, A. Bouraoui, R. S. Jacobs, and R. D. Little, *J. Org. Chem.*, 2006, **71**, 5936.
13. R. P. Hanzlik, *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. **VI**, 560.
14. Z. Wang, Y. Tu, M. Frohn, J. Zhang, and Y. Shi, *J. Am. Chem. Soc.*, 1997, **119**, 11224; Y. Shi, *Acc. Chem. Res.*, 2004, **37**, 488; O. A. Wong and Y. Shi, *Chem. Rev.*, 2008, **108**, 3958.
15. R. Tong, M. A. Boone, and F. E. McDonald, *J. Org. Chem.*, 2009, **74**, 8407.
16. Trimethylsilyl, *para*-methoxybenzyl, and tetrahydropyranyl ether protective groups were successfully attached to the tertiary alcohol of **13**.
17. This preparation of compound **15** was previously described: F. E. McDonald and X. Wei, *Org. Lett.*, 2002, **4**, 593. If the cyclization/resolution was not completely selective (reaction mixture too warm or reaction time too long) the desired bromotetrahydropyran **15** could be separated from the undesired diastereomer by silica column chromatography (eluent hexane : Et_2O v/v 3:1), although the yield was lower.
18. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.
19. Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.
20. K. Ishihara, H. Kurihara, and H. Yamamoto, *J. Org. Chem.*, 1993, **58**, 3791.
21. N. Hori, K. Nagasawa, T. Shimizu, and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 2145; T. Nakata, S.

Nomura, and H. Matsukura, *Tetrahedron Lett.*, 1996, **37**, 213; S. Takahashi, K. Fujisawa, N. Sakairi, and T. Nakata, *Heterocycles*, 2000, **53**, 1361; Y. Sakamoto, M. Koshizuka, H. Koshino, and T. Nakata, *Heterocycles*, 2002, **56**, 113.

22. The mesylate could be used in place of the chloromesylate **21**, but the rearrangement transformation then required refluxing in aqueous acetic acid. $Sc(OTf)_3$ was a viable alternative to $Zn(OAc)_2$, although longer reaction times were required.
23. W. S. Johnson, J. C. Collins, R. Pappo, M. B. Rubin, P. J. Kropp, W. F. Johns, J. E. Pike, and W. Bartmann, *J. Am. Chem. Soc.*, 1963, **85**, 1409.
24. M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 1983, **24**, 391; M. J. Eis, J. E. Wrobel, and B. Ganem, *J. Am. Chem. Soc.*, 1984, **106**, 3693; A. B. Evans and D. W. Knight, *Tetrahedron Lett.*, 2001, **42**, 6947.
25. F. E. McDonald and J. L. Bowman, *Tetrahedron Lett.*, 1996, **37**, 4675; J. L. Bowman and F. E. McDonald, *J. Org. Chem.*, 1998, **63**, 3680.
26. D. F. Taber, R. S. Bhamidipati, and M. L. Thomas, *J. Org. Chem.*, 1994, **59**, 3442.
27. H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
28. P. N. Devine and T. Oh, *Tetrahedron Lett.*, 1991, **32**, 883; M. A. Robbins, P. N. Devine, and T. Oh, *Organic Syntheses*; Wiley: New York, 1999; Collect. Vol. **10**, 297.
29. J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 1966, **7**, 4273.
30. J. E. McMurry and W. J. Scott, *Tetrahedron Lett.*, 1983, **24**, 979; M. W. Gilbert, A. Galkina, and J. Mulzer, *Synlett*, 2004, 2558.
31. P. H. Mee, V. Lee, and J. E. Baldwin, *Angew. Chem. Int. Ed.*, 2004, **43**, 1132; W. J. Scott and J. E. McMurry, *Acc. Chem. Res.*, 1988, **21**, 47; L. S. Liebeskind and R. W. Fengl, *J. Org. Chem.*, 1990, **55**, 5359; V. F. S. Kapadia, B. Krishnan, C. Wang, and L. S. Liebeskind, *J. Org. Chem.*, 1994, **59**, 1047; L. A. Paquette, T. Wang, and M. R. Sivik, *J. Am. Chem. Soc.*, 1994, **116**, 11323; A. M. Echavarren, O. de Frutos, N. Tamayo, P. Noheda, and P. Calle, *J. Org. Chem.*, 1997, **62**, 4524.
32. B. Koo and F. E. McDonald, *Org. Lett.*, 2005, **7**, 3621.
33. M. Schröder, *Chem. Rev.*, 1980, **80**, 187; I. Fleming, N. J. Lawrence, A. K. Sarkar, and A. P. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3303.
34. MS(FAB^+) Calcd. for $C_{32}H_{55}O_{11}{}^{79}Br_1{}^{23}Na_1$ $[(M+Na)^+]$ 717.2820, found 717.2807.
35. 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.
36. Ultrapure CuI was further purified by Soxhlet extraction with THF.
37. Supporting Information is available on the *Heterocycles* website, http://www.heterocycles.jp/.