Supporting Information

Synthesis of the C16-C28 Spiroketal Fragment of Spongistatin 1 (Altohyrtin A): The Pyrone Approach

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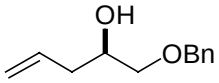
Experimental Section

Materials and Methods: General. Infrared (IR) spectra were obtained using a Perkin-Elmer 283 infrared spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on the following instruments: Bruker model Avance 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz) and Bruker model Avance 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz). Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Thin layer chromatography (TLC) was conducted on silica gel F_{254} TLC plates purchased from Scientific Adsorbents, Inc. Flash chromatography was carried out using silica gel (32 to 63 μm) purchased from Scientific Adsorbents, Inc. Diethyl ether, tetrahydrofuran (THF), and dichloromethane were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Alkyamines were distilled from calcium hydride immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled under reduced pressure from calcium hydride and stored over 4 Å molecular sieves. All air and water sensitive reactions were performed in flasks flame dried under a positive flow of nitrogen and conducted under a nitrogen atmosphere.

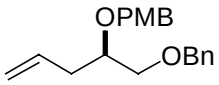
Certain compounds contain inseparable mixtures of diastereomers, but the various resonances are distinct in the ^{1}H NMR spectra. In these instances we have reported the signal in the following manner: [1.00 (s), 1.10 (s), 3H]. This particular example would represent an isolated methyl group in a mixture of diastereomeric compounds. In one diastereomer the methyl group has a δ 1.00 and is a singlet, where in the other diastereomer it appears at δ 1.10 as a singlet.

All reactions of the spirocyclic compounds **11-20** were performed on a diastereomeric mixture of C17 since the stereochemistry is inconsequential in the CD ketone fragment. Separation of these C17 diastereomers was not always trivial and often impossible. As a result, the characterization data for these compounds is for one diastereomer of an undetermined configuration about C17.



(*2R*)-1-Benzyloxy-pent-4-en-2-ol. Into a flask equipped with a mechanical stirrer, an addition funnel, and a low-temperature thermometer was added anhydrous copper iodide (1.23g, 6.48 mmol). Then 200 mL of THF were added and the flask was cooled to –30 °C. Vinyl magnesium bromide (1.0 M in THF, 324 mL, 324 mmol) was added via addition funnel at such a rate as to maintain the temperature below –30 °C. After stirring for 30 min at –30 °C, (*S*)-benzyl glycidyl ether **6** (10.64 g, 64.80 mmol) in 10 mL of THF was added dropwise via addition funnel at such a rate as to maintain the temperature below –30 °C. After stirring for 1.5 h at –30 °C, the reaction was quenched by the addition of saturated NH_4Cl and warmed to room temperature. The reaction was filtered through a fritted funnel containing celite and the THF was removed under reduced pressure. The mixture was brought up in 500 mL of diethyl ether and the

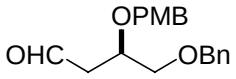
organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (10-20% EtOAc in hexanes) provided 12.33 g (99%) of homoallylic alcohol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (dd, J = 6, 6, Hz, 2H), 3.43 (AB portion of ABX, J_{AB} = 9.5 Hz, J_{AX} = 3.3 Hz, J_{BX} = 7.7 Hz, $\Delta\nu_{AB}$ = 53.6 Hz, 2H), 3.84-3.90 (m, 1H), 4.54 (s, 3H), 5.05-5.14 (m, 2H), 5.75-5.87 (m, 1H), 7.26-7.37 (band, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.84, 69.65, 73.31, 73.83, 117.63, 127.68, 127.73, 128.40, 134.18, 137.90; IR(film) 3400, 1200, 1080, 900 cm^{-1}; $[\alpha]^{23}_D$ = +3.8° (*c* 1.34, CH_2Cl_2).



7

(*2R*)-1-Benzyloxy-2-(4-methoxy-benzyloxy)-pent-4-ene (7). Into a flask equipped with a mechanical stirrer, addition funnel, and a thermometer was added potassium hydride (30% dispersion in oil, 12.72 g, 95.4 mmol). The potassium hydride was rinsed with pentanes then diluted in 150 mL THF and cooled to 0 °C. Homoallylic alcohol (9.17 g, 47.7 mmol) in 60 mL of THF was added dropwise via addition funnel. After stirring for 15 min at 0°C, *p*-methoxybenzylbromide (1.99M solution in THF, 26.5 mL, 52.47 mmol) in 20 mL of THF was added dropwise via addition funnel. The orange slurry was then allowed to warm to room temperature and stirred for 1.5 h. The reaction was quenched with saturated NH_4Cl diluted with diethyl ether. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (5% EtOAc in hexanes) provided 12.52 g (84%) of alkene **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27-2.40 (m, 2H), 3.52 (AB portion of ABX, J_{AB} = 5.5 Hz, J_{AX} = 10.5 Hz, J_{BX} = 9.9 Hz, $\Delta\nu_{AB}$ = 10.4 Hz, 2H), 3.60-3.67 (m, 1H), 3.78 (s, 3H),

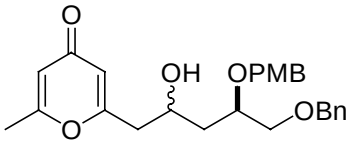
4.53 (s, 2H), 4.55 (AB_q, J_{AB} = 11.6 Hz, $\Delta\nu_{AB}$ =17.7 Hz, 2H), 5.01-5.11 (m, 2H), 5.75-5.81 (m, 1H), 6.84 (d, J = 8.9 Hz, 2H), 7.26(d, J = 8.9 Hz, 2H), 7.28-7.35 (band, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.21, 55.11, 71.37, 72.13, 73.20, 77.19, 113.59, 116.99, 127.43, 127.49, 128.24, 129.20, 130.76, 134.57, 138.30, 159.00; IR(film) 1510, 1250, 1080 cm^{-1}; $[\alpha]^{23}_D$ = +1.2° (*c* 1.15, CH_2Cl_2).



5

(*3R*-)4-Benzyloxy-3-(4-methoxy-benzyloxy)-butyraldehyde (5). Alkene **7** (16.3g, 52.18 mmol), osmium tetraoxide(1g / 100mL in water,13.27 mL, 0.52 mmol), and N-methylmorpholine oxide monohydrate (8.46 g, 62.62 mmol) was dissolved in 260 mL of a 3 : 1 THF : water mixture and allowed to stir for 18 h. The reaction was quenched with 100 mL of saturated Na_2SO_3, diluted with 300 mL of ethyl acetetate, and the organic layer was washed with saturated $NaHCO_3$, water, and brine, then concentrated in vacuo. The crude diol was then diluted in 260 mL of a 1.25 : 1 THF : water mixture and sodium periodate (15.59 g, 72.91 mmol) was added. After two h, the reaction was filtered through celite and the organic layer was washed three times with 10% $Na_2S_2O_3$, water, and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (15-20% EtOAc in hexanes) provided 14.76 g (90%) of aldehyde **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60-2.73 (m, 2H), 3.55 (AB portion of ABX, J_{AB} = 11.0 Hz, J_{AX} = 5.3 Hz, J_{BX} = 4.7 Hz, $\Delta\nu_{AB}$ = 24.1 Hz, 2H), 3.78 (s, 3H), 4.07-4.13 (m, 1H), 4.52 (AB_q, J_{AB} = 12.1 Hz, $\Delta\nu_{AB}$ =5.3 Hz, 2H), 4.54 (AB_q, J_{AB} = 12.1 Hz, $\Delta\nu_{AB}$ = 29.7 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H) 7.21 (d, J = 8.4 Hz, 2H), 7.25-7.36 (band, 5H), 9.73 (t, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.31, 55.11, 71.36, 71.61, 72.71, 73.26, 113.69,

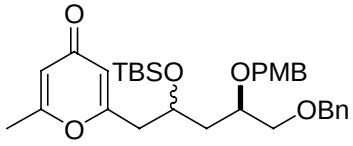
127.53, 127.61, 128.30, 129.35, 130.02, 137.83, 159.18, 200.81; IR(film) 2710, 1720, 1610, 1245, 1090, 1030 cm^{-1}; $[\alpha]^{23}_D$ = +14.6° (*c* 1.84, CH_2Cl_2).



8

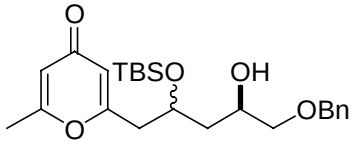
2-[(*4R*)-5-Benzyloxy-2-hydroxy-4-(4-methoxy-benzyloxy)-pentyl]-6-methyl-pyran-4-one (8). Into a flask equipped with a mechanical stirrer, addition funnel, and a low-temperature thermometer was added anhydrous lithium chloride (52 g, 1.23 mmol), diisopropyl amine (40 mL, 229 mmol) and 400 mL of THF. The mixture was cooled to –78 °C and *n*-butyl lithium (1.6 M in THF, 132 mL, 211 mmol) was added dropwise via addition funnel. After stirring for 5 min at –78 °C, the reaction flask was placed in an ice bath until the internal temperature reached 0 °C. After stirring at 0 °C for 5 min, the reaction was cooled to –78 °C and 2,6-dimethyl-pyran-4-one **4** in 500 mL of THF was added via addition funnel to afford a blood red solution. After stirring for 2 h at –78 °C, aldehyde **5** (55.16g, 175.5 mmol) in 50 mL of THF was added via addition funnel so as to maintain the temperature below –70 °C. After stirring for 20 min at –78 °C, the reaction was quenched with 200 mL of saturated NH_4Cl and allowed to warm to room temperature. The THF was removed under reduced pressure and then the mixture was diluted in 500 mL of ethyl acetate. The organic layer was washed with water and brine, and the aqueous layers were back extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (1-5% CH_3OH in CH_2Cl_2) provided 56.28 g (73%) of pyrone aldol adduct **8** as an approximately 1:1 mixture of diastereomers: ^1H NMR (400 MHz, $CDCl_3$)

δ 1.61-1.84 (m, 2H), [2.19 (s), 2.20 (s), 3H], 2.48-2.63 (m, 2H), 3.55 (m, 2H), 3.77 (s, 3H), 3.79-3.90 (m, 1H), 4.12 (m, 1H), 4.53 (s, 2H), [4.45 (d, J_{obs} = 9.3 Hz), 4.48 (d, J_{obs} = 9.3 Hz), 1H], [4.63 (d, J_{obs} = 11.8 Hz), 4.67 (d, J_{obs} = 11.8 Hz), 1H], 6.03 (br. s, 1H), [6.07 (d, J = 1.9 Hz), 6.09 (d, J = 1.9 Hz), 1H], [6.84 (d, J = 2.9 Hz), 6.85 (d, J = 2.9 Hz), 2H], 7.18-7.37 (band, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.68, 38.66, 38.87, 41.62, 41.89, 55.17, 66.04, 68.03, 71.51, 71.88, 71.96, 72.13, 73.29, 73.38, 74.63, 77.23, 113.77, 113.83, 114.55, 114.62, 127.52, 127.61, 127.72, 128.32, 128.37, 129.53, 128.58, 129.70, 130.18, 137.74, 137.92, 159.23, 159.28, 165.63, 165.72, 166.12, 166.40, 180.08, 180.15; IR(film) 3380, 1665, 1610, 1515, 1255, 1095 cm^{-1}; $[\alpha]^{23}_D$ = +30.6° (*c* 1.60, CH_2Cl_2).



2-[(*4R*)-5-Benzyloxy-2-(tert-butyl-dimethyl-silanyloxy)-4-(4-methoxy-benzyloxy)-pentyl]-6-methyl-pyran-4-one. Alcohol **5** (60.79 g, 139.1 mmol) and 2,6-lutidine (72.9 mL, 626.0 mmol) were dissolved in 400 mL of dichloromethane and cooled to –10 °C. Tertbutyldimethylsilyl trifluoromethanesulfonate (63.9 mL, 278.2 mmol) was added dropwise via syringe and the reaction was allowed to stir at –10 °C for 4 h. The reaction was quenched with 100 mL of methanol, allowed to warm to room temperature, and then diluted with 1.2 L of ethyl acetate. The organic layer was washed with 10% H_2SO_4, saturated $NaHCO_3$, water and brine, then dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (30-60% EtOAc in hexanes) provided 53.77 g (70%) of a diastereomeric mixture of silyl ethers: ^{1}H NMR (400 MHz, $CDCl_3$) δ [-0.15 (s), -0.08 (s), -0.05 (s), 0.00 (s), 6H], [0.79 (s), 0.83 (s), 9H], 1.64-185 (m, 2H), 2.17 (s, 3H), 2.40-2.69 (m, 2H), 3.60 (AB portion of ABX, J_{AB} = 9.7 Hz, J_{AX} = 3.5 Hz,

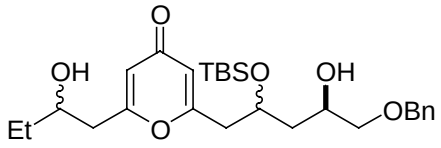
J_{BX} = 4.8 Hz, $\Delta\nu_{AB}$ = 15.9 Hz, 2H), 3.67-3.75 (m, 1H), 3.78 (m, 3H), 4.10-4.20 (m, 1H), [4.42 (d, J_{obs} = 11.8 Hz), 4.45 (d, J_{obs} = 10.9 Hz), 1H], 4.52 (br. s, 1H), 4.53 (AB_q, J_{AB} = 11.8 Hz, $\Delta\nu_{AB}$ = 8 Hz, 2H), 4.64 (d, J_{obs} = 10.5 Hz, 1H), [5.99 (d, J = 2 Hz), 6.05 (d, J = 2 Hz), 1H], 6.02-6.04 (m, 1H), [6.83 (d, J = 1.4 Hz), 6.85 (d, J = 1.4 Hz), 1H], 7.20-7.36 (band, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.27, -4.76, -4.72, -4.68, 17.76, 17.82, 19.61, 19.64, 25.59, 25.67, 39.81, 40.57, 41.22, 42.52, 55.15, 67.36, 67.68, 71.09, 71.28, 72.45, 73.21, 73.26, 73.87, 74.77, 113.64, 113.66, 113.92, 113.95, 115.17, 127.51, 127.54, 128.27, 129.03, 129.39, 130.38, 130.58, 138.02, 138.05, 159.00, 159.09, 165.21, 165.32, 166.04, 166.49, 179.85; IR(film) 1670, 1620, 1515, 1255, 1100, 840 cm^{-1}; $[\alpha]^{23}_D$ = +19.2° (*c* 1.97, CH_2Cl_2).



9

2-[(*4R*)-5-Benzyloxy-2-(tert-butyl-dimethyl-silanyloxy)-4-hydroxy-pentyl]-6-methyl-pyran-4-one (9). The *p*-methoxybenzyl protected pyrone (55.77 g, 100.88 mmol) and pyridine (0.82 mol, 10.1 mmol) were dissolved in 500 mL of dichloromethane and 25 mL of water. The reaction was cooled to 0 °C and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (34.35 g, 151.32 mmol) was added. The reaction was stirred for 20 min at 0 °C, then allowed to warm to room temperature. After 2 h the reaction was quenched with 250 mL of saturated $NaHCO_3$, and then diluted in 1 L of dichloromethane. The organic layer was washed four times with saturated $NaHCO_3$ and brine, then the aqueous layers were back extracted two times with dichloromethane. The organic layers were combined and dried over Na_2SO_4 and then concentrated in vacuo. Purification by flash

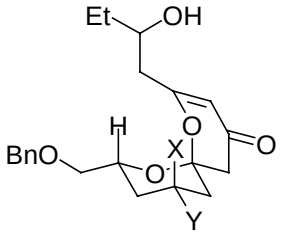
chromatography (45-85% EtOAc in hexanes) provided 40.11 g (92%) of alcohol 9 as a mixture of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ [-0.09 (s), -0.04 (s), 0.01 (s), 0.06 (s), 6H], [0.81 (s), 0.84 (s), 9H], 1.48-1.74 (m, 2H), 2.22 (s, 3H), 2.58-2.75 (m, 2H), 3.32 (app. dt, *J* = 8.4, 0.8 Hz, 1H), 3.44 (app. dt, *J* = 9.2, 3.6 Hz, 1H), 3.93-4.04 (m, 1H), 4.20-4.33 (m, 1H), 4.53 (app. d, *J* = 2.3 Hz, 2H), 6.05-6.10 (m, 2H), 7.25-7.36 (band, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.11, -5.02, -4.89, -4.78, 17.76, 17.84, 19.70, 25.60, 25.67, 40.05, 40.33, 41.37, 42.23, 66.73, 67.35, 67.58, 68.06, 73.27, 74.46, 74.62, 113.98, 113.99, 115.28, 115.32, 127.65, 127.72, 127.74, 128.37, 137.75, 137.80, 165.39, 165.49, 165.77, 166.22, 179.87, 179.89; IR(film) 3360, 1655, 1600, 1395, 1250, 1075, 835 cm^{-1}; $[\alpha]^{23}_{D}$ = +12.3° (*c* 2.01, CH_2Cl_2).



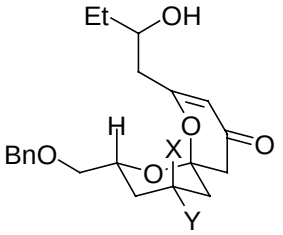
10

2-[(*4R*)-5-Benzyloxy-2-(tert-butyl-dimethyl-silanyloxy)-4-hydroxy-pentyl]-6-(2-hydroxy-butyl)-pyran-4-one (10). Into a flask equipped with a mechanical stirrer, addition funnel, and a low-temperature thermometer was added anhydrous lithium chloride (7.47 g, 176.26 mmol), diisopropyl amine (5.48 mL, 31.48 mmol) and 240 mL of THF. The mixture was cooled to –78 °C and *n*-butyl lithium (1.6 M in THF, 18.9 mL, 30.22 mmol) was added dropwise via addition funnel. After stirring for 5 min at –78 °C, the reaction flask was placed in an ice bath until the internal temperature reached 0 °C. After stirring at 0°C for 5 min, the reaction was cooled to –98°C and alcohol **9** (5.448 g, 12.59 mmol) in 10 mL of THF was added via addition funnel to afford an orange solution. After stirring for 40 min at –98 °C, a pre-cooled solution (-78 °C) of

propionaldehyde (10.3 mL, 151.08 mmol) in 10 mL of THF was added via cannula so as to maintain the temperature below –90 °C. After stirring for 20 min at –98 °C, the reaction was quenched with saturated NH_4Cl and allowed to warm to room temperature. The reaction was diluted in 500 mL of ethyl acetate, the organic layer was washed with water and brine, and then the aqueous layers were back extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (1-4% CH_3OH in CH_2Cl_2) provided 3.84 g (63%) of aldol adduct **10** as a mixture of diastereomers along with 0.91 g (17%) of recovered starting material **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ [-0.04 (s), 0.02 (s), 0.03 (s), 0.04 (s), 0.08 (s), 0.09 (s), 6H], [0.83 (s), 0.86 (s), 0.87 (s), 9H], 0.91-0.98 (m, 3H), 1.40-1.56 (m, 2H), 1.57-1.75 (m, 2H), 2.40-2.90 (band, 6H), 3.25-3.36 (m, 1H), 3.40-3.46 (m, 1H), 3.75-3.87 (m, 1H), 3.90-4.00 (m, 1H), 4.22-4.37 (m, 1H), 4.57 (br. s, 2H), 6.04-6.13 (m, 2H), 7.24-7.36 (band, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.99, -4.97, -4.92, -4.83, 9.88, 9.93, 10.03, 17.75, 17.78, 17.81, 25.59, 25.66, 30.06, 30.14, 40.14, 40.39, 41.17, 41.46, 41.53, 41.69, 42.32, 66.73, 67.06, 67.16, 67.31, 67.79, 68.38, 69.81, 70.10, 70.26, 70.32, 73.21, 73.25, 74.54, 74.68, 74.79, 114.63, 114.67, 114.73, 114.88, 114.95, 115.01, 127.65, 128.32, 137.72, 137.75, 137.82, 166.11, 166.73, 167.25, 167.49, 180.20, 180.29; IR(film) 3380, 1665, 1605, 1255, 1095, 840 cm^{-1}; $[\alpha]^{23}_D$ = +12.0° (*c* 1.68, CH_2Cl_2).



11e X = H, Y = OTBS

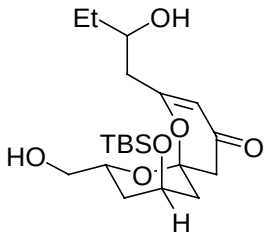


11a X = OTBS, Y = H

Spiroenones 11e and 11a. To a stirred solution of diol **10** (10.93 g, 22.27 mmol) in 560 mL of benzene was added trifluoroacetic acid (90 drops from a 20.5 gauge needle). After stirring for 3 days the reaction was quenched with 10 mL of triethyl amine and then concentrated in vacuo. Purification by flash chromatography (35% EtOAc in hexanes then 3% CH_3OH in CH_2Cl_2) provided 5.32 g (48%) of recovered pyrone **10** along with 4.81 g (44%) of a 1.5:1 mixture of spiroenones **11e:11a.** After three recycles the spiroenones could be isolated in >80% overall yield.

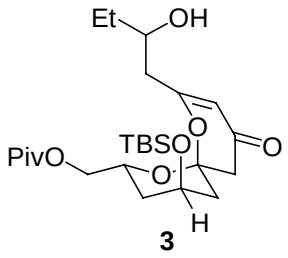
(*6R, 8R, 10R*)-8-Benzyloxymethyl-10-(tert-butyl-dimethyl-silanyloxy)-2-(2-hydroxy-butyl)-1,7-dioxa-spiro[5.5]undec-2-en-4-one (11e): (mixture of C17 diastereomers) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), [0.06 (s), 0.07 (s), 3H], 0.86 (s, 9H), [0.87 (t, J = 7.4 Hz), 0.96 (t, J = 7.4 Hz), 3H], 1.22-1.34 (m, 1H), 1.38-1.57 (band, 3H), 1.79-1.87 (m, 1H), 2.17-2.29 (m, 2H), [2.41 (d, J = 5.0 Hz), 2.44 (d, J = 3.1 Hz), 1H], 2.61 (AB portion of ABX, J_{AB} = 16.7 Hz, J_{AX} = 8.1 Hz, J_{BX} = 5.0 Hz, $\Delta\nu_{AB}$ = 50.0 Hz, 2H), [2.38 (d, J = 3.1 Hz), 2.66 (d, J = 4.0 Hz), 1H], 3.39 (d, J = 6.0 Hz, 2H), 3.43-3.46 (m, 1H), [3.54-3.62 (m), 3.74-3.82 (m), 1H], [4.00-4.08 (m), 4.10-4.20 (m), 1H], [4.48 (br. s), 4.50 (AB_q, J_{AB} = 12.5 Hz, $\Delta\nu_{AB}$ = 17.2 Hz), 2H], [5.40 (s), 5.47 (s), 1H], 7.24-7.35 (band, 5H);^{13}C NMR (100 MHz, $CDCl_3$) δ -4.70, -4.65, -4.61, -4.59, 9.86, 10.04, 17.93, 25.68, 25.70, 30.09, 36.67, 36.76, 42.67, 42.97, 43.11, 43.25, 46.50, 46.60, 64.32, 64.45, 69.94, 70.89, 71.19, 71.59, 72.07, 72.62, 73.23, 73.50, 104.27, 104.64, 105.52, 106.94, 127.64, 127.68, 127.70, 128.32, 128.35, 137.62, 137.84, 169.57, 170.85, 191.18, 19.27; IR(film) 3420, 1650, 1615, 1255, 1100, 1055, 975, 835 cm^{-1}; $[\alpha]^{23}_D$ = -98.0° (*c* 1.64, CH_2Cl_2).

(*6R, 8R, 10S*)-8-Benzyloxymethyl-10-(tert-butyl-dimethyl-silanyloxy)-2-(2-hydroxy-butyl)-1,7-dioxa-spiro[5.5]undec-2-en-4-one (11a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 0.95 (t, J = 7.7 Hz, 3H), 1.40-1.57 (band, 4H), 1.67 (dd, J = 14.4, 3.6 Hz, 1H), 2.10 (dd, J = 14.4, 2.3 Hz, 1H), 2.30 (AB portion of ABX, J_{AB} = 18.5 Hz, J_{AX} = 10.3 Hz, J_{BX} = 2.1 Hz, $\Delta\nu_{AB}$ = 57.2 Hz, 2H), 2.55 (AB_q, J_{AB} = 17.5 Hz, $\Delta\nu_{AB}$ = 96.3 Hz, 2H), 3.36 (AB portion of ABX, J_{AB} = 10.8 Hz, J_{AX} = 8.1 Hz, J_{BX} = 2.7 Hz, $\Delta\nu_{AB}$ = 21.8 Hz, 2H), 3.44 (d, J = 5.4 Hz, 1H), 3.89-3.98 (m, 1H), 4.17-4.22 (m, 1H), 4.32-4.43 (m, 1H), 4.52 (s, 2H), 5.49 (s, 1H), 7.21-7.33 (band, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.10, 10.06, 17.89, 25.64, 30.05, 33.80, 40.05, 43.66, 47.14, 63.66, 66.91, 69.34, 72.03, 72.96, 102.71, 106.75, 127.53, 128.28, 137.56, 170.60, 191.39; IR(pellet) 3510, 1670, 1620, 1255, 835 cm^{-1}; $[\alpha]^{23}_{D}$ = -162.8° (*c* 1.71, CH_2Cl_2).



(*6R, 8R, 10S*)-10-(tert-Butyl-dimethyl-silanyloxy)-2-(2-hydroxy-butyl)-8-hydroxymethyl-1,7-dioxa-spiro[5.5]undec-2-en-4-one. A flask containing spiroenone **11a** (548 mg, 1.12 mmol) and $Pd(OH)_2$ / C (20 wt% Pd, 181 mg, 0.31 mmol) in 15 mL of ethyl acetate was evacuated under aspirator and placed under a hydrogen atmosphere. After 30 min the reaction was filtered through celite and concentrated in vacuo to provide 445 mg (91%) of diol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 0.96 (t, J = 7.3 Hz, 3H), 1.42-1.58 (band, 4H), 1.70 (dd, J = 15.0, 4.0 Hz, 1H), 2.13 (app. d, J = 16.5 Hz, 1H), 2.17-2.22 (m, 1H), 2.33 (AB portion of ABX, J_{AB} =

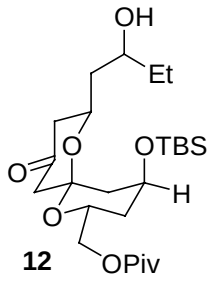
14.0 Hz, J_{AX} = 10.2 Hz, J_{BX} = 1.9 Hz, $\Delta\nu_{AB}$ = 54.0 Hz, 2H), 2.44 (d, *J* = 15.9 Hz, 1H), 2.70 (d, *J* = 15.9 Hz, 1H), 3.10 (d, *J* = 4.3 Hz, 1H), 3.46-3.59 (m, 2H), 3.91-4.00 (m, 1H), 4.22-4.26 (m, 1H), 4.26-4.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.04, 9.96, 17.96, 25.69, 30.32, 33.49, 40.25, 43.41, 46.99, 63.68, 65.08, 68.14, 69.51, 102.74, 106.57, 171.29, 191.99; IR(pellet) 3350, 1645, 1620, 1255, 1080, 835 cm^{-1}; $[\alpha]^{23}_D$ = -173.9° (*c* 1.61, CH_2Cl_2).



3

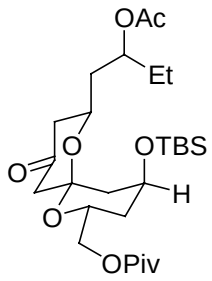
2,2-Dimethyl-propionic acid-(*2R, 4S, 6R*)-4-(tert-butyl-dimethyl-silanyloxy)-8-(2-hydroxy-butyl)-10-oxo-1,7-dioxa-spiro[5.5]undec-8-en-2-ylmethyl ester (3). To a flask containing diol (393 mg, 0.981 mmol) and triethyl amine (0.29 mL, 2.08 mmol) in 20 mL of dichloromethane was added pivalyl chloride (0.14 mL, 1.09 mmol) dropwise via syringe, followed by the addition of N,N-dimethylaminopyridine (12 mg, 0.1 mmol) After stirring for 1.5 h the reaction was quenched with saturated $NaHCO_3$ and diluted in 40 mL of diethyl ether. The organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (25% EtOAc in hexanes) provided 385 mg (81%) of pivalate ester **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H), 1.15 (s, 9H), 1.43-1.56 (band, 3H), 1.62-1.68 (m, 1H), 1.70 (dd, *J* = 14.6, 4.2 Hz, 1H), 2.12 (app. dt, *J* = 15.4, 1.9 Hz, 1H), 2.35 (AB portion of ABX, J_{AB} = 14.4 Hz, J_{AX} = 9.4 Hz, J_{BX} = 2.9 Hz, $\Delta\nu_{AB}$ = 30.6 Hz, 2H), 2.54 (AB_q, J_{AB} = 15.8 Hz, $\Delta\nu_{AB}$ = 78.8 Hz,

2H), 2.97 (d, J = 9.8, 1H), 3.80 (dd, J = 11.2, 5.6 Hz, 1H), 3.85-3.93 (m, 1H), 4.18 (dd, J = 11.2, 5.6 Hz, 1H), 4.23-4.27 (m, 1H), 4.36-4.44 (m, 1H), 5.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.07, 9.91, 18.09, 25.73, 27.02, 30.24, 34.37, 38.71, 40.10, 42.73, 46.97, 63.50, 63.88, 66.10, 69.70, 102.56, 105.96, 170.66, 178.50, 191.13; IR(pellet) 3480, 1720, 1665, 1620, 1255, 980, 830 cm^{-1}; $[\alpha]^{23}_D$ = -130.0° (*c* 2.13, CH_2Cl_2).



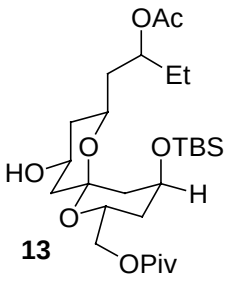
2,2-Dimethyl-propionic acid-(*2R, 4S, 6S, 8R*)-4-(tert-butyl-dimethyl-silanyloxy)-8-(2-hydroxy-butyl)-10-oxo-1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester (12). A flask containing spiroenone **3** (322 mg, 0.664 mmol) and Pd / C (10 wt% Pd, 106 mg, 0.1 mmol) in 6.6 mL of absolute ethanol was evacuated under aspirator and placed under a hydrogen atmosphere. After 12 h the reaction was filtered through celite and concentrated in vacuo. Purification by flash chromatography (10-35% EtOAc in hexanes) provided 291 mg (90%) of ketone **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 0.93 (t, J = 7.1 Hz, 3H), 1.18 (s, 9H), 1.32-1.75 (band, 7H), 2.00 (app. dt, J = 14.0, 2.2 Hz, 1H), 2.33 (dd, J = 17.7, 2.9 Hz, 1H), 2.53 (AB_q, J_{AB} = 16.0 Hz, $\Delta\nu_{AB}$ = 48.9 Hz, 2H), 2.85 (dd, J = 17.1, 12.5 Hz, 1H), 3.68-3.76 (m, 1H), 3.98 (AB portion of ABX, J_{AB} = 12.0 Hz, J_{AX} = 7.7 Hz, J_{BX} = 3.4 Hz, $\Delta\nu_{AB}$ = 23.8 Hz, 2H), 4.17 (br. s, 1H), 4.20-4.24 (m, 1H), 4.27-4.35 (m, 1H), 4.61-4.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.31, -4.64, 10.23, 18.79, 26.15, 27.26, 30.48, 33.95, 38.71, 40.42,

44.34, 44.57, 50.00, 63.34, 64.64, 66.93, 71.74, 73.03, 98.38, 178.23, 205.81; IR(film) 3530, 1725, 1155, 830 cm^{-1}; $[\alpha]^{23}_D$ = -99.1° (*c* 2.11, CH_2Cl_2).



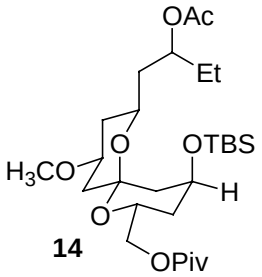
2,2-Dimethyl-propionic acid-(*2R, 4S, 6S, 8R*)-8-(2-acetoxy-butyl)-4-(tert-butyl-dimethyl-silanyloxy)-10-oxo-1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester. Ketone **12** (239 mg, 0.491 mmol) and triethyl amine (0.35 mL, 2.48 mmol) were dissolved in 5 mL of dichloromethane. Acetic anhydride (0.14 mL, 1.48 mmol) was added via syringe, followed by the addition of N,N-dimethylaminopyridine (6 mg, 0.05 mmol). After stirring for 2.5 h the reaction was quenched with saturated $NaHCO_3$ and diluted in diethyl ether. The organic layer was washed with saturated $NaHCO_3$ and brine, then dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (15% EtOAc in hexanes) provided 259 mg (99%) of acetate ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.86 (t, *J* = 7.5 Hz, 3H), 0.88 (s, 9H), 1.16 (s, 9H), 1.44-1.65 (band, 5H), 1.70 (ddd, *J* = 13.9, 8.0, 1.4 Hz, 1H), 1.91 (ddd, *J* = 14.3, 3.4, 1.1 Hz, 1H), 1.99 (s, 3H), 2.10 (ddd, *J* = 13.7, 8.6, 5.1 Hz, 1H), 2.47 (AB_q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 25.5 Hz, 2H), 2.51 (AB portion of ABX, J_{AB} = 15.5 Hz, J_{AX} = 3.6 Hz, J_{BX} = 11.3 Hz, $\Delta\nu_{AB}$ = 55.4 Hz, 2H), 4.00 (AB portion of ABX, J_{AB} = 11.3 Hz, J_{AX} = 6.6 Hz, J_{BX} = 3.7 Hz, $\Delta\nu_{AB}$ = 11.9 Hz, 2H), 4.01-4.10 (m, 1H), 4.10-4.15 (m, 1H), 4.52-4.60 (m, 1H), 4.87-4.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.97, -4.81, 9.16, 18.12, 21.15, 25.84, 27.18, 27.22, 34.64, 38.75, 39.75, 40.48, 44.14, 51.34, 63.61, 63.89, 66.82, 68.43, 71.51,

98.74, 170.45, 178.22, 206.28; IR(film) 1730, 1245, 1155, 835 cm^{-1}; $[\alpha]^{23}_D$ = -67.4° (*c* 1.55, CH_2Cl_2).



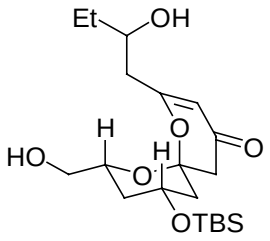
13

2,2-Dimethyl-propionic acid-(*2R, 4S, 6R, 8S, 10S*)-8-(2-acetoxy-butyl)-4-(tert-butyl-dimethyl-silanyloxy)-10-hydroxy-1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester (13). A flask containing the spirocyclic ketone (234 mg, 0.443 mmol) was dissolved in 4.5 mL of THF and cooled to –78 °C. L-Selectride (1 M in THF, 0.57 mL, 0.57 mmol) was added dropwise slowly via syringe. After 1.5 h the reaction was quenched with 10 mL of saturated potassium/sodium tartrate solution, diluted in 15 mL of diethyl ether and allowed to warm to room temperature. After 1.5 h the organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (20-40% EtOAc in hexanes) provided 193 mg (82%) of alcohol **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.86 (t, *J* = 7.6 Hz, 3H), 0.89 (s, 9H), 1.19 (s, 9H), 1.22-1.35 (m, 1H), 1.44-1.67 (band, 5H), 2.01 (s, 3H), 1.89-2.05 (m, 3H), 2.01 (s, 3H), 2.15 (ddd, *J* = 12.2, 6.1, 2.0 Hz, 1H), 3.51-3.58 (m, 1H), 3.84-3.92 (m, 1H), 4.07 (AB portion of ABX, J_{AB} = 11.2 Hz, J_{AX} = 5.4 Hz, J_{BX} = 5.4 Hz, $\Delta\nu_{AB}$ = 23.1 Hz, 2H), 4.10 (m 1H), 4.49-4.58 (m, 1H), 4.88-4.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.02, -4.71, 9.25, 18.10, 21.20, 25.92, 27.16, 27.76, 35.03, 37.26, 38.79, 39.22, 39.84, 45.01, 63.42, 64.02, 64.92, 66.51, 67.36, 71.95, 98.29, 170.71, 178.30; IR(film) 3450, 1735, 1240, 1155, 1035, 830 cm^{-1}; $[\alpha]^{23}_D$ = -15.1° (*c* 1.76, CH_2Cl_2).

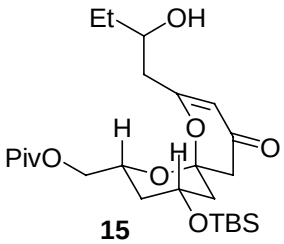


14

2,2-Dimethyl-propionic acid-(*2R, 4S, 6R, 8R, 10S*)-8-(2-acetoxy-butyl)-4-(tert-butyl-dimethyl-silanyloxy)-10-methoxy-1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester (14). Trimethyloxonium tertrafluoroborate (277 mg, 1.87 mmol) and 2,6-di-tert-butyl-4-methylpyridine (766 mg, 3.73 mmol) were dissolved in 5 mL of dichloromethane and allowed to stir for 10 min. Alcohol **13** (198 mg, 0.373 mmol) in 2.5 mL of dichloromethane was added via syringe and the reaction was allowed to stir for 1.5 h. The reaction was quenched with saturated $NaHCO_3$ and diluted with diethyl ether. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (8% EtOAc in hexanes) provided 130 mg of methyl ether **14** (64%, 82% brsm): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.89 (s, 9H), 1.04 (app. dt, *J* = 11.7, 11.7 Hz, 1H), 1.17 (s, 9H), 1.31 (dd, *J* = 11.7, 11.7 Hz, 1H), 1.44 (dd, *J* = 14.0, 3.5 Hz, 1H), 1.52-1.68 (band, 5H), 1.95-2.09 (m, 3H), 2.00 (s, 3H), 2.18 (ddd, *J* = 12.2, 2.3, 1.9 Hz, 1H), 3.30 (s, 3H), 3.34-3.42 (m, 1H), 3.46-3.54 (m, 1H), 4.07 (AB portion of ABX, J_{AB} = 11.3 Hz, J_{AX} = 5.4 Hz, J_{BX} = 5.4 Hz, $\Delta\nu_{AB}$ = 32.3 Hz, 2H), 4.11 (m, 1H), 4.51-5.49 (m, 1H), 4.88-4.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.03, -4.63, 9.29, 18.15, 21.22, 26.00, 27.15, 27.96, 35.20, 35.60, 36.25, 38.78, 39.78, 43.35, 55.39, 63.50, 64.12, 66.45, 67.45, 71.97, 73.94, 98.03, 170.70, 178.17; IR(film) 1735, 1450, 1355, 1230, 825 cm^{-1}; $[\alpha]^{23}_D$ = -12.4° (*c* 1.15, CH_2Cl_2).

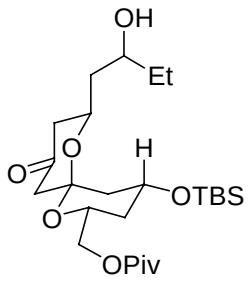


(*6R, 8R, 10R*)-10-(tert-Butyl-dimethyl-silanyloxy)-2-(2-hydroxy-butyl)-8-hydroxymethyl-1,7-dioxa-spiro[5.5]undec-2-en-4-one. A flask containing spiroenone **11e** (1.207 g, 2.46 mmol) and $Pd(OH)_2$ / C (20 wt% Pd, 394 mg, 0.741 mmol) in 30 mL of ethyl acetate was evacuated under aspirator and placed under a hydrogen atmosphere. After 30 min the reaction was filtered through celite and concentrated in vacuo to provide 934 mg (95%) of diol: (mixture of C17 diastereomers) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), [0.86 (s), 0.87 (s), 9H], [0.96 (t, *J* = 7.5 Hz), 0.97 (t, *J* = 7.5 Hz), 3H], 1.28-1.40 (m, 1H), 1.45-1.59 (m, 4H), 1.75-1.83 (m, 1H), [2.05 (m), 2.47 (m), 1H], 2.23-2.32 (m, 3H), 2.44 (ddd, *J* = 14.2, 7.1, 3.6 Hz, 1H), 2.62 (AB portion of ABX, J_{AB} = 16.5 Hz, J_{AX} = 4.5 Hz, J_{BX} = 2.7 Hz, $\Delta\nu_{AB}$ = 59.6 Hz, 2H), 3.49-3.57 (m, 1H), 3.75-3.94 (m, 1H), 4.12-4.23 (m, 1H), [5.43 (s), 5.44(s), 1H]; ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.70, -4.65, -4.61, -4.58, 9.89, 9.95, 17.94, 25.69, 30.25, 30.39, 36.03, 36.11, 42.37, 42.77, 43.24, 43.45, 46.30, 46.41, 64.10, 64.32, 65.08, 65.17, 69.98, 71.03, 72.02, 72.50, 104.17, 104.44, 105.36, 106.73, 170.19, 171.05, 191.65, 191.75; IR(film) 3380, 1655, 1615, 1255, 1065, 835 cm^{-1}; $[\alpha]^{23}_D$ = -108.3° (*c* 1.61, CH_2Cl_2).

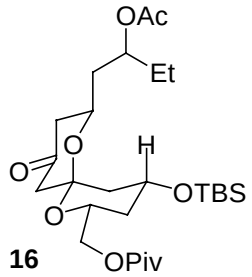


15

2,2-Dimethyl-propionic acid-(*2R, 4R, 6R*)-4-(tert-butyl-dimethyl-silanyloxy)-8-(2-hydroxy-butyl)-10-oxo-1,7-dioxa-spiro[5.5]undec-8-en-2-ylmethyl ester (15). To a flask containing diol (864 mg, 2.16 mmol) and triethyl amine (0.61 mL, 4.34 mmol) in 40 mL of dichloromethane was added pivalyl chloride (0.31 mL, 2.39 mmol) dropwise via syringe, followed by the addition of N,N-dimethylaminopyridine (27 mg, 0.22 mmol) After stirring for 3.5 h the reaction was quenched with saturated $NaHCO_3$ and diluted in ethyl acetate. The organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (25% EtOAc in hexanes) provided 960 mg (92%) of pivalate ester **15**: (mixture of C17 diastereomers) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), [0.86 (s), 0.87 (s), 9H], 0.96 (t, J = 7.4 Hz, 3H), 1.14 (s, 9H), 1.22-1.37 (m, 1H), 1.43-1.59 (m, 3H), [1.82-1.89 (m), 2.15 (d, J = 4.0 Hz), 2 H], 2.20-2.33 (m, 2H), 2.34-2.43 (m, 1H), [2.58 (AB_q, J_{AB} = 16.6 Hz, $\Delta\nu_{AB}$ = 43.7 Hz), 2.59 (AB_q, J_{AB} = 16.6 Hz, $\Delta\nu_{AB}$ = 40.4 Hz), 2H], 3.74-3.82 (m, 1H), 3.96-4.04 (m, 3H), 4.13-4.21 (m, 1H), [5.39 (s), 5.40 (s), 1H]; ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.70, -4.61, 9.78, 9.90, 17.99, 25.70, 27.02, 27.05, 30.16, 30.22, 36.49, 36.62, 38.70, 38.72, 42.31, 43.13, 43.35, 46.35, 63.97, 65.91, 66.01, 68.53. 68.90, 70.32, 70.88, 104.15, 104.39, 105.82, 106.21, 169.32, 169.59, 178.27, 178.61, 190.92, 191.00; IR(film) 3430, 1725, 1655, 1615, 1255, 1150, 835 cm^{-1}; $[\alpha]^{23}_D$ = -11.1° (*c* 1.39, CH_2Cl_2).



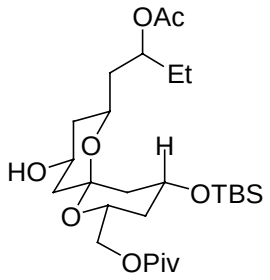
2,2-Dimethyl-propionic acid-(*2R, 4R, 6S, 8R*)-4-(tert-butyl-dimethyl-silanyloxy)-8-(2-hydroxy-butyl)-10-oxo-1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester. A flask containing spiroenone **15** (900 mg, 1.86 mmol) and Pd / C (10 wt% Pd, 596 mg, 0.28 mmol) in 19 mL of absolute ethanol was evacuated under aspirator and placed under a hydrogen atmosphere. After 4 h the reaction was filtered through celite and concentrated in vacuo. Purification by flash chromatography (10-35% EtOAc in hexanes) provided 769 mg (85%) of ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.86 (s, 9H), 0.96 (t, *J* = 7.2 Hz, 3H), 1.17 (s, 9H), 1.22-1.36 (m, 2H), 1.47-1.61 (m, 2H), 1.71 (dd, *J* = 9.0, 7.6 Hz, 1H), 1.74 (dd, *J* = 9.0, 7.6 Hz, 1H), 1.77-1.85 (m, 1H), 2.07 (ddd, *J* = 12.8, 4.5, 1.5 Hz, 1H), 2.47 (AB portion of ABX, J_{AB} = 16.8 Hz, J_{AX} = 2.6 Hz, J_{BX} = 12.6 Hz, $\Delta\nu_{AB}$ = 128.0 Hz, 2H), 2.57 (AB_q, J_{AB} = 16.8 Hz, $\Delta\nu_{AB}$ = 27.9 Hz, 2H), 3.77-3.84 (m, 1H), 3.95 (dd, *J* = 11.8, 6.9 Hz, 1H), 4.04-4.16 (m, 3H), 4.27-4.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.70, -4.66, 9.91, 18.05, 25.76, 27.20, 30.60, 36.87, 38.73, 43.15, 43.41, 44.99, 50.03, 64.46, 66.56, 67.71, 68.83, 69.64, 100.03, 178.21, 205.64; IR(film) 3450, 1730, 1140, 1060, 830 cm^{-1}; $[\alpha]^{23}_{D}$ = -67.8° (*c* 1.08, CH_2Cl_2).



16

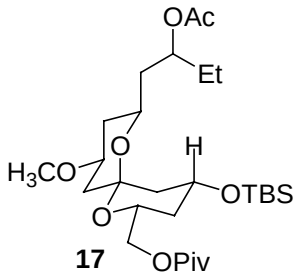
2,2-Dimethyl-propionic acid-(*2R, 4R, 6S, 8R*)-8-(2-acetoxy-butyl)-4-(tert-butyl-dimethyl-silanyloxy)-10-oxo-1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester (16). Spirocyclic ketone (192 mg, 0.394 mmol) and triethyl amine (0.11 mL, 1.18 mmol) were dissolved in 4 mL of dichloromethane. Acetic anhydride (0.33 mL, 2.36 mmol) was

added via syringe, followed by the addition of N,N-dimethylaminopyridine (5 mg, 0.04 mmol). After stirring for 1.5 h the reaction was quenched with saturated $NaHCO_3$ and diluted in diethyl lether. The organic layer was washed with saturated $NaHCO_3$ and brine, then dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (10% EtOAc in hexanes) provided 194 mg (93%) of acetate ester: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 0.89 (t, *J* = 7.1 Hz, 3H), 1.16 (s, 9H), 1.20-1.33 (m, 2H), 1.58-1.82 (band, 5H), 1.99-2.04 (m, 1H), 2.02 (s, 3H), 2.29 (dd, *J* = 15.7, 2.9 Hz, 1H), 2.54 (AB_q, J_{AB} = 15.7 Hz, $\Delta\nu_{AB}$ = 23.9 Hz, 2H), 2.62 (dd, *J* = 17.2, 12.9 Hz, 1H), 3.94 (dd, *J* = 11.2, 7.4 Hz, 1H), 4.04-4.15 (m, 4H), 4.98-5.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.74, -4.70, 9.42, 10.03, 21.17, 25.77, 27.23, 27.67, 36.94, 38.73, 41.11, 43.96, 44.73, 49.63, 64.38, 66.71, 67.59, 68.53, 72.06, 99.89, 170.40, 178.20, 205.47; IR(film) 1725, 1245, 1140, 830 cm^{-1}; $[\alpha]^{23}_D$ = -70.7° (*c* 0.99, CH_2Cl_2).



2,2-Dimethyl-propionic acid-(*2R, 4R, 6R, 8S, 10S*)-8-(2-acetoxy-butyl)-4-(tert-butyl-dimethyl-silanyloxy)-10-hydroxy-1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester. A flask containing spirocyclic ketone **16** (175 mg, 0..331 mmol) was dissolved in 4 mL of THF and cooled to –78 °C. L-Selectride (1 M in THF, 0.40 mL, 0.40 mmol) was added dropwise slowly via syringe. After 1.5 h the reaction was quenched with 4 mL of saturated potassium/sodium tartrate solution, diluted in 10 mL of diethyl ether and

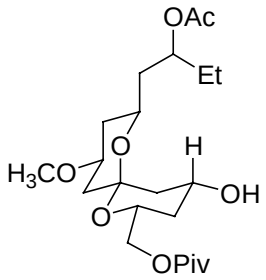
allowed to warm to room temperature. After 1.5 h the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (17.5-40% EtOAc in hexanes) provided 141 mg (80%) of alcohol: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.85 (s, 9H), 0.87 (t, J = 7.3 Hz, 3H), 1.19 (s, 9H), 1.21-1.32 (m, 2H), 1.35-1.43 (m, 1H), 1.52-1.74 (band, 6H), 1.78-1.82 (m, 1H), 1.94-2.06 (m, 2H), 2.02 (s, 3H), 3.52-3.58 (m, 1H), 3.93-4.02 (m, 2H), 4.07 (AB portion of ABX, J_{AB} = 10.1 Hz, J_{AX} = 5.5 Hz, J_{BX} = 3.9 Hz, $\Delta\nu_{AB}$ = 96.2 Hz, 2H), 4.09-4.16 (m, 1H), 4.91-4.97 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.66, -4.64, 9.34, 17.96, 21.25, 25.75, 27.19, 27.62, 37.27, 38.79, 40.41, 40.78, 41.78, 43.25, 64.31, 64.35, 66.37, 67.34, 67.55, 72.76, 99.97, 170.53, 178.32; IR(film) 3490, 1735, 1245, 1145, 835 cm^{-1}; $[\alpha]^{23}_D$ = -9.0° (*c* 0.61, CH_2Cl_2).



17

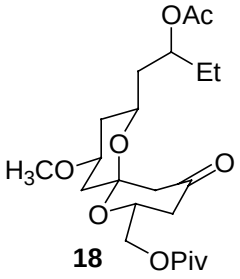
2,2-Dimethyl-propionic acid-(*2R, 4R, 6R, 8R, 10S*)-8-(2-acetoxy-butyl)-4-(tert-butyl-dimethyl-silanyloxy)-10-methoxy-1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester (17). Trimethyloxonium tertrafluoroborate (287 mg, 1.34 mmol) and 2,6-di-tert-butyl-4-methylpyridine (822 mg, 2.67 mmol) were dissolved in 2.5 mL of dichloromethane and allowed to stir for 10 min. Spirocyclic alcohol (141 mg, 0.259 mmol) in 2.5 mL of dichloromethane was added via syringe and the reaction was allowed to stir for 1.5 h. The reaction was quenched with saturated $NaHCO_3$ and diluted with diethyl ether. The organic layer was washed with saturated $NaHCO_3$ and brine, dried

over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (8% EtOAc in hexanes) provided 127 mg (79%) of methyl ether **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.85 (s, 9H), 0.87 (t, *J* = 7.3 Hz, 3H), 1.18 (s, 9H), 1.09-1.25 (m, 2H), 1.28-1.38 (m, 2H), 1.54-1.77 (band, 4H), 1.81-1.86 (m, 1H), 1.92-1.98 (m, 1H), 2.02 (s, 3H), 2.07 (ddd, *J* = 15.5, 5.5, 1.4 Hz, 1H), 2.19 (ddd, *J* = 16.4, 5.5, 0.9 Hz, 1H), 3.31 (s, 3H), 3.40-3.54 (m, 2H), 3.85-3.94 (m, 1H), 4.06-4.10 (m, 2H), 4.11-4.18 (m, 1H), 4.89-4.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.62, 9.27, 17.89, 21.31, 25.71, 27.12, 27.59, 37.52, 37.77, 38.76, 39.29, 40.74, 42.09, 55.43, 64.32, 66.16, 67.45, 67.70, 72.81, 73.52, 99.63, 170.55, 178.13; IR(film) 1730, 1455, 1370, 1240, 1130, 1080, 830 cm^{-1}; $[\alpha]^{23}_D$ = -6.8° (*c* 0.60, CH_2Cl_2).



2,2-Dimethyl-propionic acid-(*2R, 4R, 6S, 8R, 10S*)-8-(2-acetoxy-butyl)-4-hydroxy-10-methoxy-1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester. Silyl ether **17** (121 mg, 0.222 mmol) was dissolved in 3 mL of THF and then tetrabutylammonium fluoride (1 M in THF, 0.44 mL, 0.44 mmol) was added via syringe. After 2 h the reaction was quenched with saturated NH_4Cl and diluted in ethyl acetate. The organic layer was washed with saturated NH_4Cl, saturated $NaHCO_3$ and brine, then dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (40-60% EtOAc in hexanes) provided 83 mg (87%) of equatorial alcohol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.3 Hz, 3H), 1.19 (s, 9H), 1.11-1.21 (m, 2H), 1.28-1.41 (m, 2H), 1.52-1.62

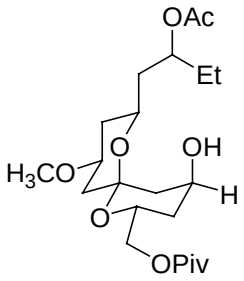
(m, 2H), 1.64-1.79 (m, 2H), 1.90-1.98 (m, 2H), 2.04 (s, 3H), 2.09 (ddd, *J* = 13.0, 4.9, 1.2 Hz, 1H), 2.31 (ddd, *J* = 13.0, 4.1, 1.2 Hz, 1H), 3.31 (s, 3H), 3.40-3.50 (m, 2H), 3.93-4.01 (m, 1H), 4.10 (d like, *J* = 5Hz, 2H), 4.16-4.22 (m, 1H), 4.99-5.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.26, 21.21, 27.15, 27.80, 37.20, 37.70, 38.43, 38.81, 40.45, 41.96, 55.50, 63.50, 66.07, 67.01, 67.77, 73.28, 73.80, 99.62, 171.20, 178.20; IR(film) 3450, 1725, 1455, 1375, 1250, 1155, 1145, 1035 cm^{-1}; $[\alpha]^{23}_D$ = +5.6° (*c* 0.54, CH_2Cl_2).



18

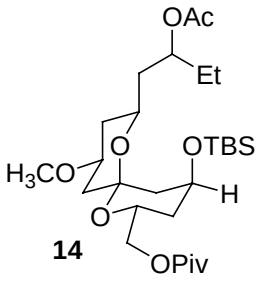
2,2-Dimethyl-propionic acid-(*2R, 6R, 8R, 10S*)-8-(2-acetoxy-butyl)-10-methoxy-4-oxo-1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester (18). A flask containing oxalyl chloride (2 M in CH_2Cl_2, 1.48 mL, 2.96 mmol) in 7 mL of dichloromethane was cooled to –78 °C and then dimethyl sulfoxide (0.42 mL, 5.92 mmol) was added dropwise via syringe. After stirring for 15 min at –78 °C, equatorial alcohol (637 mg, 1.48 mmol) in 3 mL of dichloromethane was added slowly dropwise via syringe. The solution was allowed to stir for an additional 20 min at –78 °C, then triethyl amine (1.03 mL, 7.40 mmol) was added dropwise via syringe and the reaction was allowed to slowly warm to room temperature. The reaction was quenched with saturated $NaHCO_3$ and diluted in diethyl ether. The organic layer was washed with saturated $NaHCO_3$, water and brine, then dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (20-35% EtOAc in hexanes) provided 548 mg (87%) of ketone **18**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.3 Hz, 3H), 1.08-1.19 (m, 1H), 1.18 (s, 9H), 1.42-1.56 (m, 3H),

1.65-1.72 (m, 2H), 1.94-2.01 (m, 1H), 2.04 (s, 3H), 2.19 (ddd, J = 12.4, 4.4, 1.2 Hz, 1H), 2.28-2.42 (m, 3H), 2.77 (d, J = 15.0 Hz, 1H), 3.31 (s, 3H), 3.34-3.42 (m, 1H), 3.46-3.55 (m, 1H), 4.17 (AB portion of ABX, J_{AB} = 11.1 Hz, J_{AX} = 4.4 Hz, J_{BX} = 4.1 Hz, $\Delta\nu_{AB}$ = 24.2 Hz, 2H), 4.54-4.61 (m, 1H), 4.85-4.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.10, 21.24, 27.14, 27.37, 37.47, 38.86, 39.72, 41.60, 42.30, 46.20, 55.61, 65.45, 67.14, 68.10, 70.87, 73.31, 100.53, 170.68, 178.03, 203.42; IR(film) 1735, 1715, 1700, 1355, 1230, 1145 cm^{-1}; $[\alpha]^{23}_D$ = +8.5° (*c* 0.95, CH_2Cl_2).



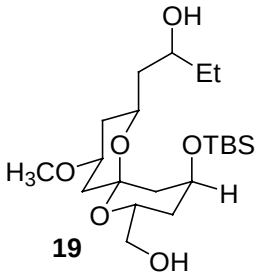
2,2-Dimethyl-propionic acid-(*2R, 4S, 6S, 8R, 10S*)-8-(2-acetoxy-butyl)-4-hydroxy-10-methoxy-1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester. A flask containing spirocyclic ketone **16** (51 mg, 0.119 mmol) was dissolved in 2.5 mL of THF and cooled to –78 °C. L-Selectride (1 M in THF, 0.15 mL, 0.15 mmol) was added dropwise slowly via syringe. After 30 min the reaction was quenched with 2.5 mL of saturated potassium/sodium tartrate solution, diluted in 5 mL of diethyl ether and allowed to warm to room temperature. After 1.5 h the organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (20-50% EtOAc in hexanes) provided 50 mg (97%) of axial alcohol**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.0 Hz, 3H), 1.17 (s, 9H), 1.21-1.34 (m, 2H), 1.39-1.47 (m, 2H), 1.51-1.62 (m, 2H), 1.70-1.80 (m, 2H), 1.91 (ddd, J = 13.6, 8.2, 5.4 Hz, 1H), 2.01 (ddd, J = 12.2, 4.8, 1.4 Hz, 1H), 2.04 (s, 3H), 2.10-2.20 (m, 2H), 3.30 (s, 3H), 3.33-3.47

(m, 1H), 3.54 (d, *J* = 10.9 Hz, 1H), 3.61-3.69 (m, 1H), 4.04-4.11 (m, 3H), 4.41-4.49 (m, 1H), 4.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.93, 21.64, 27.60, 28.15, 34.65, 35.67, 36.48, 39.24, 41.17, 42.64, 55.99, 63.87, 64.71, 66.92, 69.80, 72.79, 73.51, 100.08, 171.41, 178.62; IR(film) 3510, 1720, 1320, 1240, 1140 cm^{-1}; $[\alpha]^{23}_D$ = -28.0° (*c* 0.75, CH_2Cl_2).



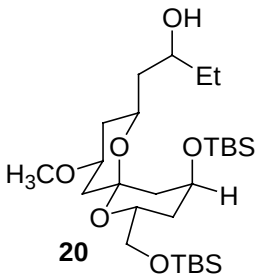
14

2,2-Dimethyl-propionic acid-(*2R, 4S, 6R, 8R, 10S*)-8-(2-acetoxy-butyl)-4-(tert-butyl-dimethyl-silanyloxy)-10-methoxy-1,7-dioxa-spiro[5.5]undec-2-ylmethyl ester (14). Axial alcohol (465 mg, 1.08 mmol) and 2,6-lutidine (0.125 mL, 1.08 mmol) were dissolved in 17 mL of dichloromethane and the solution was cooled to –78 °C. A solution of t-butyldimethylsilyl trifluoromethanesulfonate (0.50 mL, 2.16 mmol) and 2,6-lutidine (0.625 mL, 5.4 mmol) in 3 mL of dichloromethane was added very slowly via syringe. After stirring for 1 h at –78 °C the reaction was quenched with saturated $NaHCO_3$, diluted in diethyl ether, and allowed to warm to room temperature. The organic layer was washed with saturated $NaHCO_3$, water and brine, then dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography provided 555 mg (94%) of axial silyl ether **14**.



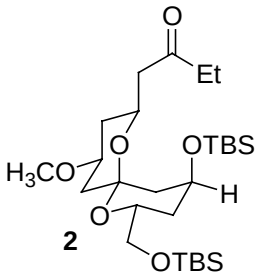
19

(*1R*)-1-[(*4S, 6R, 8R, 10S*)-10-(tert-Butyl-dimethyl-silanyloxy)-8-hydroxymethyl-4-methoxy-1,7-dioxa-spiro[5.5]undec-2-yl]-butan-2-ol (19). Diester **14** (1.19 g, 2.18 mmol) was dissolved in 40 mL of CH_3OH and 5 mL of 6M NaOH. After 5 h the reaction was diluted in ethyl acetate, washed with saturated NH_4Cl, saturated $NaHCO_3$ and brine, then dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (75% EtOAc in hexanes) provided 879 mg (96%) of diol **19**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.13 (s, 3H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.91 (s, 9H), 1.24 (app. dt, *J* = 11.8, 11.8Hz, 1H), 1.35-1.53 (band, 5H), 1.57 (ddd, *J* = 14.2, 3.0, 1.8 Hz, 1H), 1.64-1.75 (m, 2H), 1.96-2.05 (m, 2H), 2.18 (ddd, *J* = 14.6, 3.3, 1.3 Hz, 1H), 3.32 (s, 3H), 3.41-3.47 (m, 1H), 3.47 (dd, *J* = 11.6, 5.3 Hz, 1H), 3.71 (dd, *J* = 11.6, 3.1 Hz, 1H), 3.69-3.77 (m, 2H), 4.17-4.21 (m, 1H), 4.25-4.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.27, -4.49, 10.07, 18.97, 26.39, 30.17, 33.86, 35.62, 37.87, 43.03, 43.07, 55.37, 64.87, 65.61, 65.91, 71.98, 72.59, 73.25, 98.37; IR(film) 3470, 1245, 1050, 820 cm^{-1}; $[\alpha]^{23}_D$ = +0.6° (*c* 0.70, CH_2Cl_2).



20

(*1R*)-1-[(*4S, 6R, 8R, 10S*)-10-(tert-Butyl-dimethyl-silanyloxy)-8-(tert-butyl-dimethyl-silanyloxymethyl)-4-methoxy-1,7-dioxa-spiro[5.5]undec-2-yl]-butan-2-ol (20). Imidazole (286 mg, 4.20 mmol) and *t*-butyldimethylsilyl chloride (380 mg, 2.52 mmol) were dissolved in 35 mL of dichloromethane and allowed to stir for 5 min. The slurry was cooled to 0 °C and diol **19** (879 mg, 2.10 mmol) in 3 mL of dichloromethane was added dropwise via syringe. After 1.5 h the reaction was quenched with saturated $NaHCO_3$ and diluted in diethyl ether. The organic layer was washed with saturated $NaHCO_3$ and brine, then dried over Na_2SO_4 and concentrated in vacuo. Purification via flash chromatography (10% EtOAc in hexanes) provided 1.018 g (91%) of silyl ether **20**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 0.91 (t, J = 7.1 Hz, 3H), 1.22-1.55 (band, 5H), 1.58-1.64 (m, 3H), 1.69-1.75 (m, 1H), 1.95 (ddd like, J = 12.5, 4.2, 2.1 Hz, 1H), 2.00 (ddd, J = 12.5, 4.2, 1.0 Hz, 1H), 2.15 (ddd, J = 14.6, 3.1, 1.0 Hz, 1H), 3.31 (s, 3H), 3.39-3.49 (m, 1H), 3.62 (AB portion of ABX, J_{AB} = 10.3 Hz, J_{AX} = 6.0 Hz, J_{BX} = 4.3 Hz, $\Delta\nu_{AB}$ = 52.6 Hz, 2H), 3.74-3.82 (m, 1H), 3.82-3.88 (m, 1H), 4.13-4.17 (m, 1H), 4.26-4.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.22, -5.17, -4.72, -4.61, 10.22, 18.29, 18.69, 25.89, 26.31, 30.08, 34.80, 35.49, 36.90, 42.05, 43.61, 55.41, 64.90, 65.91, 66.15, 68.03, 68.51, 73.99, 98.27; IR(film) 3510, 1460, 1250, 1130, 1080, 830 cm^{-1}; $[\alpha]^{23}_D$ = +4.6° (*c* 1.75, CH_2Cl_2).



2

(*1S*)-1-[(*4S, 6R, 8R, 10S*)-10-(tert-Butyl-dimethyl-silanyloxy)-8-(tert-butyl-dimethyl-silanyloxymethyl)-4-methoxy-1,7-dioxa-spiro[5.5]undec-2-yl]-butan-2-one (2). A flask containing oxalyl chloride (2 M in CH_2Cl_2, 0.51 mL, 1.02 mmol) in 3 mL of dichloromethane was cooled to –78 °C and then dimethyl sulfoxide (0.14 mL, 2.04 mmol) was added dropwise via syringe. After stirring for 15 min at –78 °C, alcohol **20** (271 mg, 0.509 mmol) in 2 mL of dichloromethane was added slowly dropwise via syringe. The solution was allowed to stir for an additional 20 min at –78°C, then triethyl amine (0.35 mL, 2.55 mmol) was added dropwise via syringe and the reaction was allowed to slowly warm to room temperature. The reaction was quenched with saturated $NaHCO_3$ and diluted in diethyl ether. The organic layer was washed with saturated $NaHCO_3$, water and brine, then dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (5-7.5% EtOAc in hexanes) provided 244 mg (90%) of ketone **2**. ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.01 (s, 3H), 0.02 (s, 6H), 0.83 (s, 9H), 0.86 (s, 9H), 0.94-1.01 (m, 1H), 1.02 (t, J = 7.1 Hz, 3H), 1.30 (dd, J = 11.7, 11.7 Hz, 1H), 1.43 (dd, J = 14.1, 3.7 Hz, 1H), 1.56 (ddd, J = 14.1, 11.1, 3.7 Hz, 1H), 1.59-1.70 (m, 1H), 1.98 (ddd, J = 12.4, 4.4, 1.5 Hz, 1H), 2.13 (ddd, J = 14.6, 3.7, 1.1 Hz, 1H), 2.18-2.23 (m, 1H), 2.39 (AB_q, J_{AB} = 6.9 Hz, $\Delta\nu_{AB}$ = 14.1 Hz, 2H), 2.72 (AB portion of ABX, J_{AB} = 17.5 Hz, J_{AX} = 8.8 Hz, J_{BX} = 3.8 Hz, $\Delta\nu_{AB}$ = 86.5 Hz, 2H), 3.30 (s, 3H), 3.42-3.50 (m, 1H), 3.62 (AB portion of ABX, J_{AB} = 10.8 Hz, J_{AX} = 6.0 Hz, J_{BX} = 4.8 Hz, $\Delta\nu_{AB}$ = 66.3 Hz, 2H), 3.86-3.94 (m, 1H), 4.07-4.11 (m, 1H), 4.29-4.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.23, -5.18, -4.99, -4.91, 7.72, 18.08, 18.28, 25.81, 25.87, 35.00, 35.53, 36.88, 37.09, 43.37, 48.62, 55.55, 64.33, 66.20, 66.22, 66.49, 73.85,

98.21, 209.32; IR(film) 1720, 1465, 1385, 1365, 1255, 1045, 840 cm^{-1}; $[\alpha]^{23}_{D}$ = +4.6° (*c* 0.8, CH_2Cl_2).