SUPPORTING INFORMATION

A Concise Asymmetric Synthesis of (-)-Rasfonin

Yange Huang, Adriaan J. Minnaard* and Ben L. Feringa*

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

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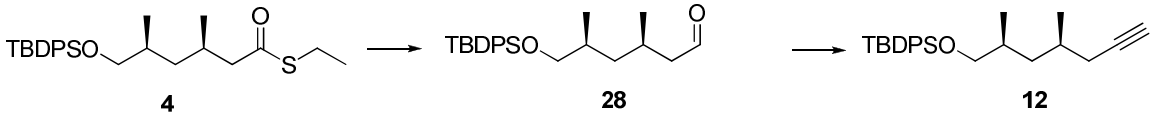
General Techniques

Starting materials were purchased from Aldrich, Alpha Aesar or Acros and used as received unless stated otherwise. All solvents were reagent grade and, if necessary, dried and distilled prior to use. Column chromatography was performed on silica gel (Aldrich 60, 230-400 mesh) or on aluminium oxide (Merck, aluminium oxide 90 neutral activated). TLC was performed on silica gel 60/Kieselguhr F_{254}.

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR300 (299.97 MHz for ^{1}H, 75.48 MHz for ^{13}C) or a Varian AMX400 (399.93 MHz for ^{1}H, 100.59 MHz for ^{13}C) spectrometer in $CDCl_3$ unless stated otherwise. Chemical shifts are reported in δ values (ppm) relative to the residual solvent peak ($CHCl_3$, ^{1}H = 7.24, ^{13}C = 77.0). Carbon assignments are based on ^{13}C and APT ^{13}C experiments. Splitting patterns are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

High resolution mass spectra (HRMS) were recorded on an AEI-MS-902 and FTMS orbitrap (Thermo Fisher Scientific) mass spectrometer. Optical rotations were measured on a *Schmidt+ Haensch* polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). Enantiomeric excess was determined by HPLC (Chiralcel OB, 250*4.6, 10 μm), (Chiralcel OD, 250*4.6, 10 μm).

Experimental procedures



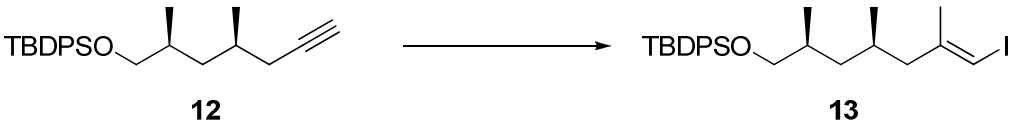
4 28 12

(–)-*tert*-butyl((2S,4R)-2,4-dimethylhept-6-ynyloxy)diphenylsilane (12)

To a stirred mixture of **4**[1] (1.98 g, 4.52 mmol) in dry DCM (100 mL) was added DIBALH (5.89 mL, 5.89 mmol, 1.0 M solution in DCM) at –65 °C under nitrogen. Stirring was continued until TLC showed complete conversion (2-3 h). The reaction mixture was quenched with 60 mL saturated aqueous Rochelle salt (potassium sodium tartrate) and stirred for 30 min. The phases were separated and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to yield crude aldehyde which was purified by flash chromatography (eluent pentane/ether) to give **28** used in the next step without complete removal of the eluent.

To a THF(45 mL) solution of trimethylsilyldiazomethane (4.53 mL, 9.06 mmol, 2.0 M solution in hexanes) was added *n*-BuLi (3.26 mL, 8.16 mmol, 2.5 M solution in hexanes) at –78 ºC. After being stirred for 30 min, crude **28**, dissolved in 20 mL of THF, was added. The mixture was stirred for 0.5 h at –78 ºC and then warmed to room temperature overnight. The mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (eluent pentane/ether) to give **12** as a colorless oil (1.46 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69- 7.67 (m, 4H), 7.41- 7.38 (m, 6H), 3.52 (dd, *J*= 5.4, 9.8 Hz, 1H), 3.43 (dd, *J*= 6.3, 9.8 Hz, 1H), 2.19- 2.13 (m, 1H), 2.04- 1.98 (m, 1H), 1.93 (t, *J*= 2.7 Hz), 1.77- 1.69 (m, 2H), 1.53 (dd, *J*= 6.6, 13.7 Hz, 1H), 1.06 (s, 9H), 0.97 (d, *J*= 6.7 Hz, 3H), 0.94 (d, *J*= 6.7 Hz, 3H); ^{13}C NMR (100

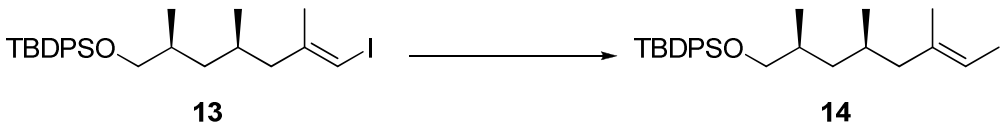
MHz, $CDCl_3$) δ 17.7, 19.6, 20.3, 25.8, 27.1, 29.9, 33.4, 40.1, 69.0, 69.4, 83.4, 127.8, 129.7, 134.3, 135.9; HRMS (APCI+) calculated for $C_{25}H_{35}OSi$: 379.2452, found: 379.2448; $[\alpha]_D$ = –9.2 (c= 1.6, $CHCl_3$).



12 **13**

(-)-*tert*-butyl((2S,4R,E)-7-iodo-2,4,6-trimethylhept-6-enyloxy)diphenyl silane (13)

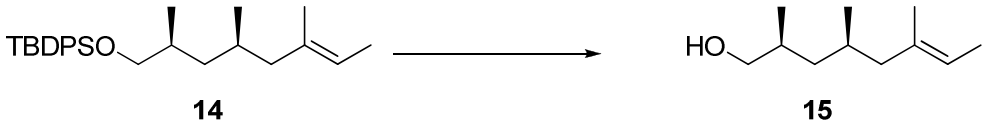
H_2O (28.6 µL, 1.59 mmol) was added to a solution of Me_3Al (7.95 mL, 15.9 mmol) and $ZrCp_2Cl_2$ (233 mg, 0.79 mmol) in DCM (20 mL) at –78°C. The mixture was warmed to room temperature and stirred for 30 min, then cooled to –78 °C again. Alkyne **12** (1.2 g, 3.18 mmol) in 12 mL DCM was added slowly to the mixture. After stirring for 3 h at room temperature, the reaction mixture was treated with a solution of I_2 (1.61 g, 6.36 mmol) in THF (10 mL) at –78°C. After stirring for 30 min at –78°C, the reaction mixture was warmed to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (eluent pentane/ether) to give **13** as a colorless oil (1.46 g, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70- 7.66 (m, 4H), 7.46- 7.37 (m, 4H), 5.82 (s, 1H), 3.50 (dd, *J*= 5.3, 9.9 Hz, 1H), 3.43 (dd, *J*= 6.2, 9.8 Hz, 1H), 2.19 (dd, *J*= 4.7, 13.3 Hz, 1H), 1.90 (dd, *J*= 9.3, 13.2 Hz, 1H), 1.77 (d, *J*= 1.0 Hz, 3H), 1.75- 1.66 (m, 2H), 1.39- 1.30 (m, 2H), 1.07 (s, 9H), 0.94 (d, *J*= 6.7 Hz, 3H), 0.77 (d, *J*= 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 19.6, 20.1, 24.0, 27.1, 28.7, 33.4, 41.3, 47.7, 68.9, 75.4, 127.8, 129.8, 134.2, 135.8, 135.9, 147.4; HRMS (APCI+) calculated for $C_{26}H_{38}OSi$: 521.1731, found: 521.1721; $[\alpha]_D$ = –8.7 (c= 6.2, $CHCl_3$).



13 **14**

(–)-*tert*-butyldiphenyl((2S,4R,E)-2,4,6-trimethyloct-6-enyloxy)silane (14)

Me_2Zn (2.3 mL, 2.67 mmol, 1.2 M in heptane) was added dropwise to a THF solution (30 mL) of vinyl iodide **13** (1.17 g, 2.22 mmol) and $Pd(PPh_3)_2Cl_2$ (79 mg, 0.112 mmol) at 0 ºC. The reaction mixture was allowed to warm to room temperature slowly, protected from light and stirred overnight. The reaction was quenched with water, diluted with ether and subsequently extracted with ether (3 x 30 mL), The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (eluent pentane/ether) to give **14** as a colorless oil (0.854 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69- 7.67 (m, 4H), 7.45- 7.35 (m, 6H), 5.16 (q, *J*= 7 Hz, 1H), 3.51 (dd, *J*= 5.1, 9.8 Hz, 1H), 3.42 (dd, *J*= 6.4, 9.8 Hz, 1H), 1.99 (d, *J*= 8.3 Hz, 1H), 1.80- 1.73 (m, 1H), 1.67- 1.61 (m, 2H), 1.57(d, *J*= 6.8 Hz, 3H), 1.53 (s, 3H), 1.38- 1.27 (m, 2H), 1.06 (s, 9H), 0.95 (d, *J*= 6.7 Hz, 3H), 0.75 (d, *J*= 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 15.8, 18.2, 19.6, 20.3, 27.1, 28.4, 33.5, 41.4, 48.0, 69.1, 119.9, 127.8, 129.7, 134.4, 135.0, 135.9; HRMS (APCI+) calculated for $C_{27}H_{41}OSi$: 409.2921, found: 409.2915; $[\alpha]_D$ = –7.8 (c= 1.0, $CHCl_3$).

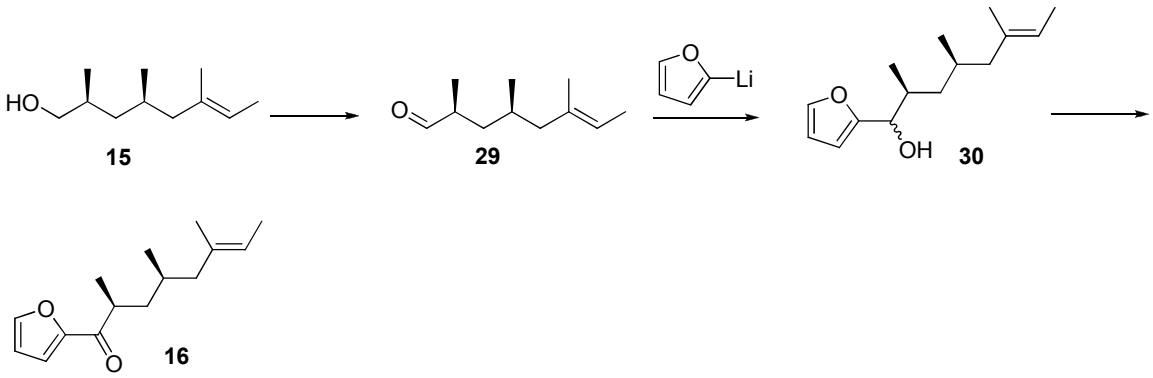


14 **15**

(-)-(2S,4R,E)-2,4,6-trimethyloct-6-en-1-ol (15)

To a stirred mixture of **14** (0.856 g, 2.1 mmol) in THF (25 mL) was added TBAF (1.0 M solution in THF, 6.29 mL, 6.29 mmol). The resulting solution was stirred for 4 h, and then quenched with sat. aq. NH_4Cl and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (eluent pentane/ether) to give **15** as a colorless oil (0.436 g, 87%): ^{1}H

NMR (400 MHz, $CDCl_3$) δ 5.17 (dd, *J*= 6.2, 12.6 Hz, 1H), 3.52 (dd, *J*= 5.1, 10.5 Hz, 1H), 3.37 (dd, *J*= 6.8, 10.5 Hz, 1H), 2.04- 1.97 (m, 1H), 1.77- 1.63 (m, 3H), 1.57 (d, *J*= 8.5 Hz, 3H), 1.55 (s, 3H), 1.53 (br, 1H), 1.33- 1.25 (m, 2H), 0.93 (d, *J*= 6.7 Hz, 3H), 0.81 (d, *J*= 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 15.8, 17.7, 20.4, 28.3, 33.4, 41.2, 47.8, 68.5, 120.1, 134.8; HRMS (APCI+) calculated for $C_{11}H_{23}O$: 171.1743, found: 171.1739; $[\alpha]_D$ = –4.2 (c= 1.1, $CHCl_3$).



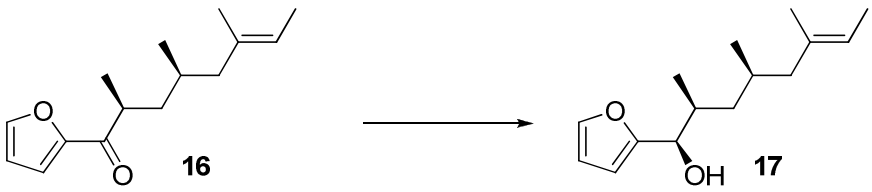
(+)-(2S,4R,E)-1-(furan-2-yl)-2,4,6-trimethyloct-6-en-1-one (16)

To a stirred solution of alcohol **15** (311 mg, 1.83 mmol) in DCM (15 mL) were added molecular sieves 4Å (1.0 g), NMO (648 mg, 5.48 mmol) and TPAP (44 mg, 128 µmol). The reaction mixture was stirred at rt for 1 h, filtered through a silica pad, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ ether) to afford **29** as a colourless oil (277 mg, 90% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (d, *J*= 2.6 Hz, 1H), 5.18 (dd, *J*= 6.6, 13.2 Hz, 1H), 2.48- 2.41 (m, 1H), 1.96 (dd, *J*= 5.8, 13.0 Hz, 1H), 1.78- 1.62 (m, 4H), 1.57 (d, *J*= 6.7 Hz, 3H), 1.54 (d, *J*= 1.0 Hz, 3H), 1.08 (d, *J*= 5.5 Hz, 3H), 0.83 (d, *J*= 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 14.5, 15.7, 19.9, 28.6, 38.3, 44.4, 47.9, 120.6, 134.2, 205.7.

To a stirred solution of distilled furan (194 mg, 2.85 mmol) in THF was added *n*-BuLi (0.61 mL, 1.52 mmol) at –78 ^oC. The reaction mixture was stirred for 3 h, and then a THF solution(3 mL) of **29** (160 mg, 0.95 mmol) was added slowly. The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was quenched with sat. aq. NH_4Cl and extracted with ether (3 x 10 mL), The combined organic layers were dried over

Na_2SO_4, filtered, concentrated and purified by flash chromatography (eluent pentane/ether) to give **30** as a brown oil (0.197 g, 88%).

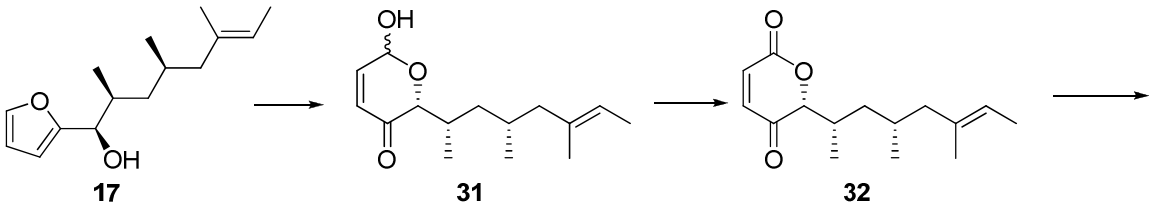
To a stirred solution of alcohol **30** (166 mg, 0.702 mmol) in DCM (15 mL) were added molecular sieves 4Å (0.6 g), NMO (249 mg, 2.11 mmol) and TPAP (12 mg, 35 µmol). The reaction mixture was stirred at rt for 1 h, filtered through a silica pad, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/ ether) to afford **16** as a brown oil (161 mg, 98% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.18 (d, *J*= 3.5 Hz, 1H), 6.52 (dd, *J*= 1.7, 3.5 Hz, 1H), 5.16 (dd, *J*= 6.6, 13.3 Hz, 1H), 3.41- 3.32 (m, 1H), 1.98 (dd, *J*= 6.1, 13.1 Hz, 1H), 1.85 (ddd, *J*= 5.4, 8.8, 14.1 Hz, 1H), 1.72 (dd, *J*= 8.2, 13.1 Hz, 1H), 1.64- 1.48 (m, 1H), 1.55(d, *J*= 6.6 Hz, 3H), 1.49 (s, 3H), 1.17 (d, *J*= 6.9 Hz, 3H), 1.13- 1.08 (m, 1H), 0.79 (d, *J*= 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 15.6, 18.4, 20.0, 28.8, 39.4, 40.9, 48.2, 112.3, 117.3, 120.2, 134.6, 146.6, 152.8, 193.8; HRMS (APCI+) calculated for $C_{15}H_{23}O_2$: 235.1693, found: 235.1685; $[\alpha]_D$ = +30.5 (c= 0.4, $CHCl_3$).

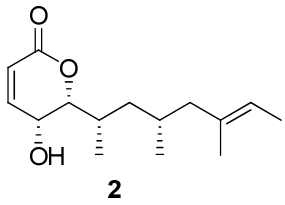


(–)-(1R,2S,4R,E)-1-(furan-2-yl)-2,4,6-trimethyloct-6-en-1-ol (17)

To a stirred solution of (*S*)-2-methyl-CBS-oxazaborolidine (43 µL , 0.043 mmol, 1.0 M solution in THF) in THF (0.6 mL) was added borane-dimethylsufide complex (47 µL, 0.094 mmol, 2 M solution in THF) followed by a solution of **16** (20 mg, 0.085 mmol) in THF (2 mL) at 0 °C and under N_2. After 4 h, the mixture was quenched with sat. aq. NH_4Cl and extracted with ether (3 x 10 mL), The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (eluent pentane/ether)

to give **17** as a colorless oil (14.9 mg, 94%, *syn*/*anti*>98/2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.33 (dd, *J*= 1.8, 3.2 Hz, 1H), 6.22 (dd, *J*= 0.6, 3.2 Hz, 1H), 5.15 (q, *J*= 7 Hz, 1H), 4.51 (d, *J*= 5.6 Hz, 1H), 2.10- 1.99 (m, 2H), 1.57 (d, *J*= 6.9 Hz, 3H), 1.54 (s, 3H), 1.33- 1.21 (m, 4H), 0.97 (d, *J*= 6.8 Hz, 3H), 0.79 (d, *J*= 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 15.6, 15.8, 20.5, 28.4, 35.8, 41.0, 47.4, 72.3, 106.5, 110.3, 120.1, 134.8, 141.8, 156.6; HRMS (ESI+) calculated for $C_{15}H_{25}O_2$: 237.1854, found: 237.0879; $[\alpha]_D$ = – 5.4 (c= 0.7, $CHCl_3$).





(-)-(5R,6R)-6-((2S,4R,E)-4,6-dimethyloct-6-en-2-yl)-5-hydroxy-5,6-dihydro-2H-pyran-2-one (2)

To a stirred solution of furyl alcohol **17** (14.9 mg, 0.063 mmol) in DCM (1 mL) at 0 °C was added vanadyl acetylacetonate (0.8 mg, 0.003 mmol) followed by dropwise addition of *tert*-butylhydroperoxide (0.012 mL, 0.063 mmol, 5.5 M in decane). The solution was warmed to room temperature and stirred for 40 min. The mixture was filtered through a silica pad, concentrated under reduced pressure and the residue was purified by flash chromatography (eluent pentane/ ether) to afford **31** as a colourless oil (7.3 mg, 69% yield).

Jones' reagent (0.021 mL, 2.7 M) was added dropwise to an ice-cold solution of hemiacetal **31** (7 mg, 0.029 mmol) in acetone (1 mL). The resulting mixture was stirred for 1 h at room temperature. The mixture was diluted with *tert*-butyl methyl ether (5 mL) and

washed with water; the organic phase was dried over Na_2SO_4, filtered, and the solvent was evaporated to give the crude product **32** which was used directly for the next step: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J*= 10.2 Hz, 1H), 6.78 (d, *J*= 10.2 Hz, 1H), 5.19 (dd, *J*= 6.6, 13.0 Hz, 1H), 4.90 (d, *J*= 2.4 Hz, 1H), 2.46- 2.37 (m, 1H), 2.02 (d, *J*= 5.2, 12.4 Hz, 1H), 1.77- 1.53 (m, 4H), 1.58 (d, *J*= 7.0 Hz, 3H), 1.56 (s, 3H), 0.88 (d, *J*= 6.8 Hz, 3H), 0.84 (d, *J*= 6.3 Hz, 3H).

To a solution of **32** in 1 mL of DCM was added $NaBH_4$ (1.5 mg, 0.039 mmol) and $CeCl_3$ (0.13 mL, 0.052 mmol, 0.4 M solution in MeOH) at –78°C. The mixture was stirred for 0.5 h, warmed to room temperature and diluted with ether. The mixture was quenched with 5 mL H_2O, and extracted with ether (3 x 3 mL), The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (eluent pentane/ether) to give **2** as a colorless oil (6 mg, 80% based on compound **31**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (dd, *J*= 6.1, 9.6 Hz, 1H), 6.10 (d, *J*= 9.6 Hz, 1H), 5.20 (dd, *J*= 6.0, 11.3 Hz, 1H), 4.22 (d, *J*= 4.1 Hz, 1H), 3.91 (dd, *J*= 2.3, 9.3 Hz, 1H), 2.27- 2.13 (m, 2H), 1.85- 1.73 (m, 1H), 1.58 (s, 6H), 1.45- 1.38 (m, 1H), 1.28- 1.22 (m, 1H), 1.14 (d, *J*= 6.5 Hz, 3H), 1.07- 0.98 (m, 1H), 0.84 (d, *J*= 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 144.6, 134.8, 123.2, 120.3, 85.6, 60.9, 46.6, 40.1, 31.5, 28.2, 21.2, 16.0, 15.8, 13.6; HRMS (ESI+) calculated for $C_{15}H_{24}O_3Na$: 275.1617, found: 275.1616; $[\alpha]_D$ = –117.1 (c= 0.6, $CHCl_3$).

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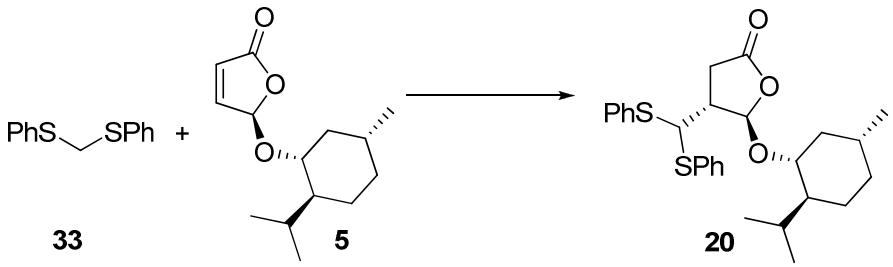
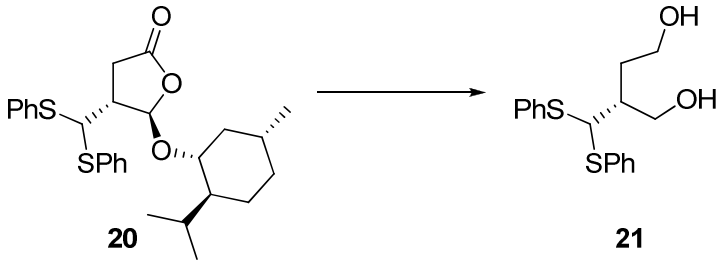


33 **5** **20**

(-)-(4R,5R)-4-(bis(phenylthio)methyl)-5-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)dihydrofuran-2(3H)-one (20)

To a stirred solution of **33** (1.95 g, 8.4 mmol) in 50 mL THF was added *n*-BuLi (4.73 mL, 7.56 mmol) dropwise at –78°C. The reaction mixture was stirred for 0.5 h, followed by the addition of **5** in 20 mL THF. The mixture was quenched with sat. aq. NH_4Cl after TLC showed complete conversion (2- 3 h). The mixture was extracted with ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and the residue was purified by flash chromatography (eluent pentane/ether) to give **20** as a white solid (1.71 g, 86% as the single diastereomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50- 7.31 (m, 10H), 5.86 (s, 1H), 4.34 (d, *J*= 5.2 Hz, 1H), 3.52 (dt, *J*= 4.2, 10.7, 10.6 Hz, 1H), 2.87- 2.68 (m, 3H), 2.11- 1.98 (m, 2H), 1.68- 1.58 (m, 2H), 1.44- 1.29 (m, 1H), 1.23- 1.16 (m, 1H), 1.06- 0.81 (m, 3H), 0.93 (d, *J*= 6.5 Hz, 3H), 0.86 (d, *J*= 7.0 Hz, 3H), 0.77 (d, *J*= 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 133.9, 133.4, 133.3,133.3, 133.1, 129.5, 129.5, 128.9, 128.7, 102.4, 77.7, 61.3, 48.0, 46.7, 40.1, 34.5, 32.4, 31.6, 25.7, 23.3, 22.5, 21.1, 15.9; HRMS (APCI+) calculated for $C_{21}H_{29}O_3S$: 361.1832, found: 361.1812; $[\alpha]_D$ = –83.5 (c= 1.3, $CHCl_3$).

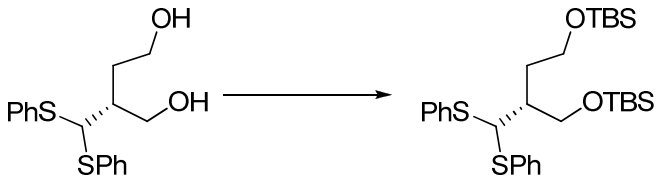


20 **21**

(+)-(R)-2-(bis(phenylthio)methyl)butane-1,4-diol (21)

To a stirred solution of **20** (1.51 g, 3.2 mmol) in 100 mL THF was added $LiAlH_4$ (3.2 mL, 12.8 mmol, 4 M solution in diethylether) dropwise at 0 °C. The mixture was stirred for an additional 0.5 h at 0 °C and then warmed to room temperature. The mixture was quenched with 10 mL H_2O after complete conversion shown by TLC. The resulting mixture was subsequently filtered, and extracted with ether (3 x 20 mL). The combined organic layers

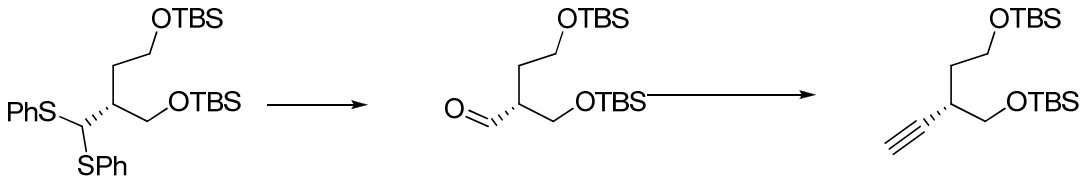
were dried over Na_2SO_4, filtered, concentrated and the residue was purified by flash chromatography (eluent pentane/ether) to give **21** as a white solid (0.856 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45- 7.24 (m, 10H), 4.67 (d, *J*= 3.5 Hz, 1H), 3.83 (t, *J*= 6.1 Hz, 2H), 3.78- 3.71 (m, 1H), 3.65- 3.58 (m, 1H), 3.22 (br, 1H), 2.92 (br, 1H), 2.23- 2.20 (m, 1H), 2.10- 2.07 (m, 1H), 1.82- 1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 134.8, 132.7, 132.5, 129.3, 128.0, 127.9, 64.6, 63.0, 61.6, 44.3, 32.5; HRMS (ESI+) calculated for $C_{17}H_{19}O_2S_2$: 319.0826, found: 319.0801; $[\alpha]_D$ = +24.5 (c= 0.2, $CHCl_3$).



21 **22**

(+)-(R)-6-(bis(phenylthio)methyl)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecane (22)

To a solution of **21** (0.752 g, 2.35 mmol) in anhydrous dichloromethane (30 mL) was added imidazole (1.28 g, 18.8 mmol) followed by *tert*-butyl-dimethylsilyl chloride (2.83 g, 18.8 mmol), and the resulting white suspension was stirred at rt overnight. The reaction mixture was quenched with 20 mL of water and extracted with ether (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (eluent pentane/ether) to give **22** as a colorless oil (1.24 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47- 7.20 (m, 10H), 5.05 (d, *J*= 2.7 Hz, 1H), 3.82- 3.79 (m, 2H), 3.66 (t, *J*= 6.1 Hz, 2H), 2.30- 2.27 (m, 1H), 2.11- 2.05 (m, 1H), 1.55- 1.44 (m, 1H), 0.87- 0.85 (m, 18H), 0.02- 0.00 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.7, 131.8, 131.3, 129.0, 127.3, 127.0, 63.2, 62.0, 60.5, 43.3, 30.5, 26.1, 26.0, 18.5, 18.3, -5.2, -5.1; HRMS (APCI+) calculated for $C_{23}H_{44}O_2SSi_2$: 440.2595, found: 440.2538; $[\alpha]_D$ = +44.9 (c= 0.8, $CHCl_3$).

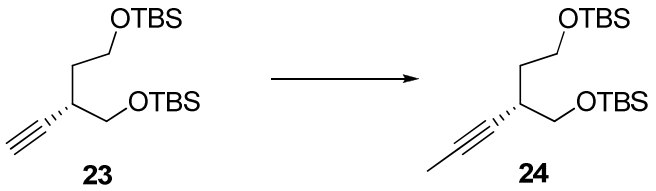


22 **34** **23**

(+)-(S)-6-ethynyl-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecane (23)

To a solution of thioacetal **22** (4 g, 7.29 mmol) in acetonitrile-water (4:1, 50 mL) at room temperature was added $HgCl_2$ (3.96 g, 14.6 mmol) and HgO (3.16 g, 14.6 mmol), and the mixture was stirred for 3 h. Subsequent fitration through Celite, followed by removal of the solvents under reduced pressure. Purification by flash chromatography (eluent pentane/ether) gave **34** as a colorless oil (2.14 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, *J*= 1.7 Hz, 1H), 3.93- 3.82 (m, 2H), 3.73- 3.62 (m, 2H), 2.63- 2.57 (m, 1H), 2.01- 1.91 (m, 1H), 1.75- 1.65 (m, 1H), 0.87 (s, 18 H), 0.04 (s, 12H).

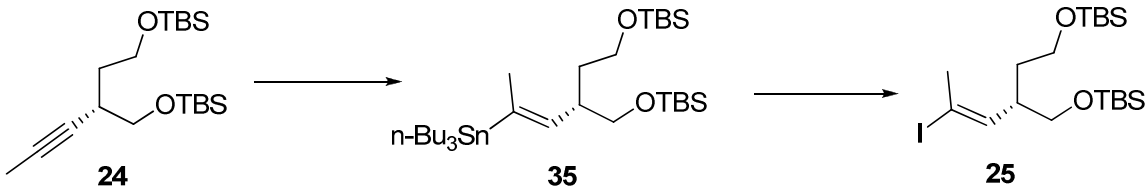
To a THF solution (45 mL) of trimethylsilyldiazomethane (10.93 mL, 21.86 mmol, 2.0 M solution in hexanes) was added *n*-BuLi (12.8 mL, 20.4 mmol, 1.6 M solution in hexanes) at –78 ºC. After being stirred for 30 min, a solution of **34** in THF (20 mL) was added. The mixture was stirred for 0.5 h at –78 ºC and then warmed to room temperature overnight. The mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and the product was purified by flash chromatography (eluent pentane/ether) to give **23** as a colorless oil (1.42 g, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80- 3.75 (m, 2H), 3.71 (dd, *J*= 5.7, 9.7 Hz, 1H), 3.58 (dd, *J*= 7.3, 9.7 Hz, 1H), 2.73- 2.63 (m, 1H), 2.03 (d, *J*= 2.4 Hz, 1H), 1.93- 1.82 (m, 1H), 1.61- 1.49 (m, 1H), 0.89 (s, 18H), 0.06 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.4, 70.1, 66.1, 60.9, 34.5, 31.6, 26.2, 26.1, 18.5, -5.1, -5.1; HRMS (APCI+) calculated for $C_{18}H_{39}O_2Si_2$: 343.2483, found: 343.2472; $[\alpha]_D$ = +5.7 (c= 0.9, $CHCl_3$).



23 **24**

(+)-(S)-2,2,3,3,10,10,11,11-octamethyl-6-(prop-1-ynyl)-4,9-dioxa-3,10-disiladodecane (24)

Alkyne **23** (1.4 g, 4.09 mmol) was dissolved in dry THF (20 mL) and *n*-BuLi (5.1 mL, 8.17 mmol) was added at –78 ^{o}C under N_2. After 10 min, MeI (1.78 mL, 4.06 g, 28.63 mmol) was added. The resulting solution was allowed to warm to 0 ^{o}C over 2 h, after which TLC showed complete conversion. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and the residue was purified by flash chromatography (eluent pentane/ether) to give **24** as a colorless oil (1.33 g, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83- 3.72 (m, 2H), 3.67 (dd, *J*= 5.6, 9.7 Hz, 1H), 3.50 (dd, *J*= 7.3, 14.1 Hz, 1H), 2.65- 2.52 (m, 1H), 1.93- 1.82 (m, 1H), 1.78 (d, *J*= 2.3 Hz, 3H), 1.53- 1.41 (m, 1H), 0.89 (s, 18H), 0.05 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.4, 80.0, 66.6, 61.3, 34.9, 31.9, 26.2, 26.1, 18.6, 3.7, -5.1; HRMS (APCI+) calculated for $C_{19}H_{40}O_2Si_2Na$: 379.2459, found: 379.2447; $[\alpha]_D$ = +30.2 (c= 0.9, $CHCl_3$).

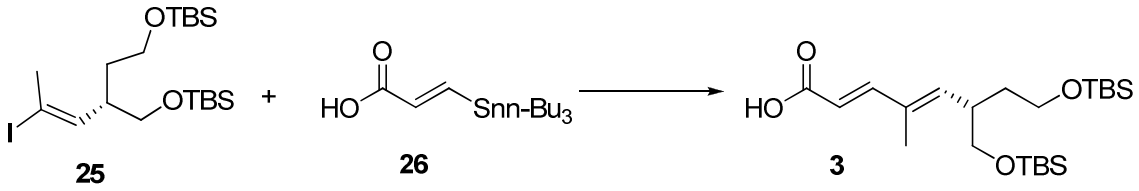


24 **35** **25**

(+)-(S,E)-6-(2-iodoprop-1-enyl)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecane (25)

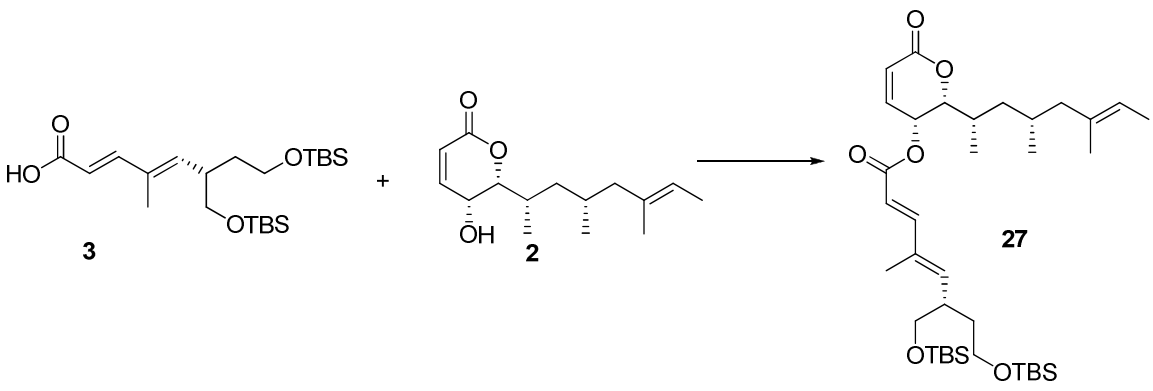
To an oven-dried, nitrogen-filled flask was added $Pd(OAc)_2$ (15.71 mg, 0.07 mmol, 5 mol%) and tricyclohexylphosphine (39.26 mg, 0.14 mmol, 10 mol%) followed by freshly distilled hexane (25 mL) and the resulting mixture was stirred for 20 min until the solids were dissolved. Alkyne **24** (500 mg, 1.40 mmol) in hexane (10 mL) was added slowly, followed by slow addition of neat Bu_3SnH (1.56 mL, 5.61 mmol) over 5 min. The reaction was finished after 20 min (TLC analysis) and the mixture was subsequently transferred to a silica gel column and rapidly eluted with hexane, followed by hexane/ether to provide **35** as a colorless oil (711 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (dd, *J*= 1.1, 9.1 Hz, 1H), 3.66- 3.41 (m, 4H), 2.86- 2.73 (m, 1H), 1.92- 1.76 (m, 2H), 1.84 (s, 3H), 1.60- 1.43 (m, 7H), 1.36- 1.24 (m, 12H), 0.91- 0.83 (m, 9H), 0.88 (s, 18H), 0.03 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 139.6, 66.9, 61.6, 37.4, 35.2, 29.4, 27.6, 26.2, 26.1, 19.9, 18.5, 13.9, 9.3, -5.1.

To a solution of **35** (622 mg, 0.96 mmol) in dichloromethane (20 mL) was added a solution of I_2 (487 mg, 1.92 mmol, 1.3 eq) in dichloromethane (15 mL) at –78 ^{o}C under nitrogen. The resulting solution was stirred for 10 min at –78 ^{o}C and then allowed to warm to room temperature. The solution was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and the product was purified by flash chromatography (eluent pentane/ether) to give **25** as a colorless oil (348.6 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (d, *J*= 10.1 Hz, 1H), 3.66- 3.52(m, 2H), 3.49- 3.46 (m,2H), 2.74- 2.61 (m, 1H), 2.39 (s, 3H), 1.75- 1.63 (m, 1H), 1.43- 1.30 (m, 1H), 0.88 (s, 18H), 0.03 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 95.5, 66.1, 60.8, 40.6, 34.3, 28.5, 26.2, 26.1, 18.5, -5.2; HRMS (ESI+) calculated for $C_{19}H_{42}O_2Si_2I$: 485.1763, found: 485.1752; $[\alpha]_D$ = +28.5 (c= 1.2, $CHCl_3$).



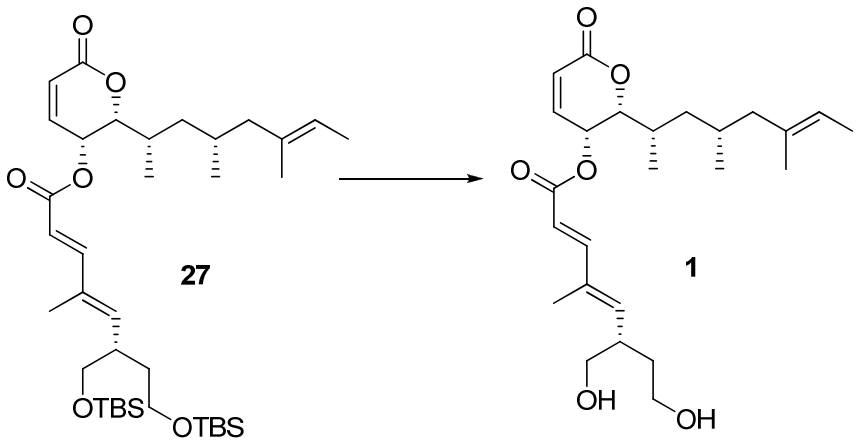
(+)-(S,2E,4E)-8-(tert-butyldimethylsilyloxy)-6-((tert-butyldimethylsilyloxy)methyl)-4-methylocta-2,4-dienoic acid (3)

To a solution of vinyl iodide **25** (188.8 mg, 0.390 mmol) and carboxylic acid **26**[2] (288 mg, 0.779 mmol) in *N*-methylpyrrolidinone (7 mL) was added diisopropylethylamine (339 µL, 1.95 mmol) and Pd_2dba_3 (38 mg, 0.039 mmol) at room temperature under nitrogen. The flask was covered with aluminum foil, and the reaction mixture was stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and the product was purified by flash chromatography (eluent pentane/ether with 1% acetic acid) to give **3** as a colorless oil (145 mg, 87%, with some acetic acid): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 15.6 Hz, 1H), 5.80 (d, *J* = 15.8 Hz, 1H), 5.75 (d, *J* = 12.4 Hz, 1H), 3.62-3.47 (m, 4H), 2.89-2.88 (m, 1H), 1.82 (s, 3H), 1.54-1.37 (m, 2H), 0.87 (s, 18H), 0.01 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 152.0, 145.2, 134.3, 115.3, 66.3, 61.0, 38.6, 34.8, 26.1, 26.0, 18.4, 13.8, 12.8, -5.1, -5.2; HRMS (ESI+) calculated for $C_{22}H_{44}O_4Si_2Na$: 451.7432, found: 451.2652; $[\alpha]_D$ = +39.4 (c= 0.6, $CHCl_3$).



(-)-(S,2E,4E)-((2R,3R)-2-((2S,4R,E)-4,6-dimethyloct-6-en-2-yl)-6-oxo-3,6-dihydro-2H-pyran-3-yl) 8-(tert-butyldimethylsilyloxy)-6-((tert-butyldimethylsilyloxy)methyl)-4-methylocta-2,4-dienoate (27)

To a solution of acid **3** (12.76 mg, 0.030 mmol, 1.5 eq) in dry toluene (0.47 mL) was added HPLC grade triethylamine (8.3 μL, 0.059 mmol, 3.0 equiv) at room temperature followed by dropwise addition of 2,4,6-trichlorobenzoyl chloride (6.4 μL, 0.040 mmol, 2.0 equiv). The resulting solution was stirred for 1 h upon which TLC showed complete conversion. Alcohol **2** (5 mg, 0.020 mmol, 1.0 eq) in dry toluene (0.5 mL) was then added, followed by DMAP (8.5 mg, 0.069 mmol, 3.5 equiv). After 2 h, the mixture was transferred to a silica gel column and eluted with pentane/ether to yield **27** as a colorless oil (10.5 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 15.7 Hz, 1H), 7.04 (dd, *J* = 6, 9.6 Hz, 1H), 6.20 (d, *J* = 9.6 Hz, 1H), 5.77 (d, *J*= 11.3 Hz, 1H), 5.73 (d, *J*= 5.5 Hz, 1H), 5.34 (dd, *J*= 2.4, 6.0 Hz, 1H), 5.11 (q, *J* = 7 Hz, 1H), 4.12 (dd, *J*= 2.4, 8.8 Hz, 1H), 3.63-3.44 (m, 4H), 2.89-2.78 (m, 1H), 2.22-2.13 (m, 1H), 2.05 (br d, *J* = 10.9 Hz, 1H), 1.79 (s, 3H), 1.74-1.61 (m, 1H), 1.52 (s, 3H), 1.48-1.36 (m, 1H), 1.30-0.94 (m, 11H), 0.87 (s, 9H), 0.86 (s, 9H), 0.78 (d, *J* = 6.5 Hz, 3H), 0.01-0.00 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 163.6, 151.8, 145.6, 140.8, 134.4, 134.2, 125.0, 120.3, 114.3, 83.5, 66.2, 61.9, 60.9, 46.6, 40.2, 38.6, 34.8, 31.7, 28.2, 26.1, 20.8, 18.5, 16.1, 15.5, 13.6, 12.8, -5.1 ; HRMS (ESI+) calculated for $C_{37}H_{66}O_6Si_2Na$: 685.4290, found: 685.4245; $[\alpha]_D$ = −157.1 (c= 0.5, $CHCl_3$).



(-)-(S,2E,4E)-((2R,3R)-2-((2S,4R,E)-4,6-dimethyloct-6-en-2-yl)-6-oxo-3,6-dihydro-2H-pyran-3-yl) 8-hydroxy-6-(hydroxymethyl)-4-methylocta-2,4-dienoate (1)

To a solution of **27** (3.9 mg, 0.0059 mmol) in MeCN (1 mL) was added one drop of HF (48 wt.% in H_2O) at room temperature. The resulting mixture was stirred for 20 min, and then quenched with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and the product was purified by flash chromatography (eluent EtOAc/Heptane) to give **1** as a colorless oil (2.6 mg, 100%, with small amount of diastereomers which are difficult to separate): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 15.7 Hz, 1H), 7.04 (dd, *J* = 5.9, 9.5 Hz, 1H), 6.21 (d, *J* = 9.6 Hz, 1H), 5.81 (d, *J* = 15.8 Hz, 1H), 5.77 (d, *J* = 11.3 Hz, 1H), 5.35 (dd, *J*= 2.4, 6.0 Hz, 1H), 5.12 (q, *J* = 7 Hz, 1H), 4.12 (dd, *J*= 2.9, 6.7 Hz, 1H), 3.77-3.71 (m, 1H), 3.65-3.57 (m, 2H), 2.93-2.84 (m, 1H), 2.25-2.13 (m, 1H), 2.05 (br d, *J* = 10.9 Hz, 1H), 1.84 (s, 3H), 1.80-1.75 (m, 1H), 1.71-1.66 (m, 1H), 1.65- 1.59 (m, 1H), 1.55 (d, *J* = 6.7 Hz, 3H), 1.53 (s, 3H), 1.44- 1.41 (m, 2H), 1.34- 1.24 (m, 5H), 1.15 (d, *J* = 6.6 Hz, 3H), 1.01, 0.78 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 160.7, 148.3, 140.7, 138.0, 132.1, 131.6, 122.4, 117.5, 112.5, 80.7, 63.3, 59.1, 58.1, 43.7, 37.4, 36.6, 32.1, 28.8, 27.7, 27.1, 18.0, 13.3, 10.8, 10.0; HRMS (ESI+) calculated for $C_{25}H_{38}O_6Na$: 457.2561, found: 457.2531; $[\alpha]_D$ = –164.8 (c= 0.1, $CHCl_3$) [Lit.[3]= –162.8 (c=0.43, DCM), Lit.[4]= –170 (c= 0.09, MeOH)]. The optical and spectroscopic data are in agreement with the reported values.[3-5]

References and Notes:

[1] Prepared in 6 grams scale by CuBr/JosiPhos catalyzed iterative asymmetric conjugate addition of MeMgBr developped by our group (97% *ee* for the first methyl group, 96/4 *de* for the second methyl group).
[2] J. Thibonnet, V. Launay, M. Abarbri, A. Duchene, J. Parrain, *Tetrahedron Lett*. **1998**,39, 4277.
[3] R. K. Boeckman, Jr., J. E. Pero, D. J. Boehmler, *J. Am. Chem. Soc*. **2006**, *128*, 11032.
[4] K. Akiyama, S. Yamamoto, H. Fujimoto, M. Ishibashi, *Tetrahedron* **2005**, *61*, 1827.
[5] T. Tomikawa, K. Shin-Ya, K. Furihato, T. Kinoshita, A. Miyajima, H. Seto, Y. Hayakawa, *J. Antibiot*. **2000**, *53*, 848.