

# **Total Synthesis of Pyranicin**

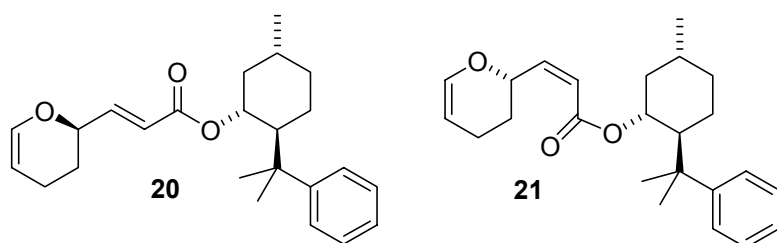
Daniel Strand and Tobias Rein

*Supporting information*

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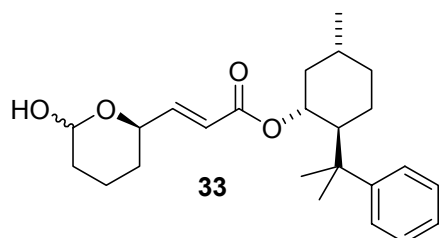
**General methodology.** All solvents were distilled before use unless otherwise stated. Diethyl ether (Et<sub>2</sub>O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone under a nitrogen atmosphere. Dichloromethane (DCM), dichloroethane (DCE), toluene and triethylamine (Et<sub>3</sub>N) were distilled from CaH<sub>2</sub> under a nitrogen atmosphere. All reactions were carried out in oven-dried or flame-dried glassware and under a nitrogen atmosphere unless water was used as a reaction medium. For reactions run in sealed vessels a thick-walled testtube fitted with a screw cap was used. Commercially available compounds were used without further purification unless otherwise indicated. Potassium and sodium hexamethyldisilazide (KHMDs, NaHMDs) were purchased as stock solutions (0.5 M, 0.6 M in toluene respectively) and titrated according to the method of Ireland and Meissner.<sup>1</sup> 18-crown-6 was recrystallized from anhydrous acetonitrile and dried under vacuum. Neocuproine was sublimated at 120 °C, 0.01 mmHg. Zinc triflate was dried at 0.01 mmHg using a heat gun for 5 min. Acrolein dimer was bulb-to-bulb distilled, oven temperature 60 °C, 0.15 mmHg. LDA was purchased as a stock solution (2 M) in THF/heptane/ethyl benzene. TLC analyses were performed on aluminium-backed F<sub>254</sub> silica gel plates, using UV and a solution of 5% phosphomolybdic acid in ethanol for visualisation. Flash chromatography was performed as described by Still and coworkers<sup>2</sup> using silica gel 60 (40-63 µm). Proton (<sup>1</sup>H) and carbon (<sup>13</sup>C) NMR spectra were recorded on a 400 or 500 MHz instrument using the residual signals from CHCl<sub>3</sub>, δ 7.26 ppm and δ 77.0 ppm, as internal references for <sup>1</sup>H and <sup>13</sup>C respectively. IR-spectra were recorded from DCM films using NaCl plates. Optical rotations were determined using the sodium-D line (589 nm).



**(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2E)-3-[(2R)-3,4-dihydro-2H-pyran-2-yl]acrylate (16) and (1R,2S,5R)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2Z)-3-[(2S)-3,4-dihydro-2H-pyran-2-yl]acrylate (20).** To a stirred solution of phosphonate **19** (1.97 g, 3.80 mmol) and 18-crown-6 (2.61 g, 9.88 mmol) in THF (150 mL) was added KHMDs (7.24 mL, 3.62 mmol, 0.5 M in toluene) dropwise at -78 °C. The resulting solution was stirred for 30 min and then added via a cannula to a precooled solution of acrolein dimer

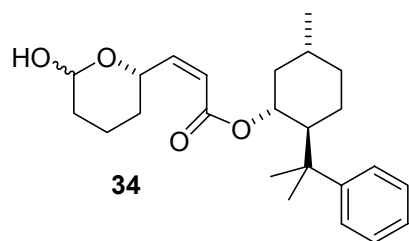
*rac*-**7** (533 mg, 4.94 mmol) in THF (70 mL) over 5 h at -78 °C. After an additional 2 h the reaction was quenched by addition of AcOH (1 M, MeOH) followed by phosphate buffer (pH 7) and partitioned between EtOAc and phosphate buffer (pH 7). The combined organic phases were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (3.13-6.25% EtOAc in heptane) afforded a 60:40 mixture of (2*Z*,4*S*)-**21** and (2*E*,4*R*)-**20** as a clear oil (1.54 g, 77% based on **19**): *dr* **21**, (2*Z*,4*S*): (2*Z*,4*R*) = 96:4; **20**, (2*E*,4*R*):(2*E*,4*S*) = 98:2.<sup>3</sup>

**General procedure for preparation of hemiacetals **33** and **34**.** To a solution of vinyl ether **20** or **21** (or a mixture of the two) in THF (0.02 M) was added *p*-toluenesulfonic acid monohydrate (5.0 equiv., 0.4 M in water) dropwise over 30 min at 0 °C. The resulting solution was heated at 32 ± 2 °C,<sup>4</sup> and stirred for 20 h. The reaction was quenched by addition of NaOH (2 M, aq) and partitioned between EtOAc and NaOH (2 M, aq) followed by repeated basic wash until the aqueous phase was clearly basic (tested with pH paper). The organic phase was dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (12.5-25% EtOAc/heptane) afforded the hemiacetals (clear oils) as inseparable diastereomeric mixtures. Isolated yields were 81% from **20**, 89% from **21** and 85% from a mixture.



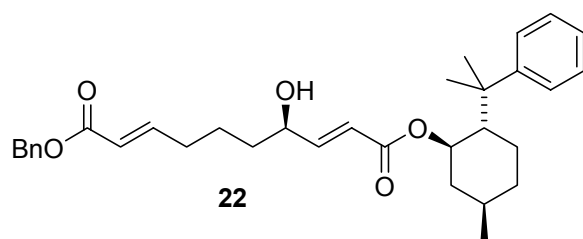
**(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2*E*)-3-[(2*R*,6*RS*)-6-hydroxytetrahydro-2*H*-pyran-2-yl]acrylate (**33**).** Diastereomeric ratio (major epimer/minor epimer) = 67:33; [ $\alpha$ ]<sub>D</sub><sup>23</sup> -0.75 (c = 1.0, DCM); IR (film) 3411 (br s), 2950 (s), 2869 (m), 1710 (s), 1658 (m), 1442 (m), 1442 (m), 1297 (s), 1270 (s); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28-7.18 (m, 4H), 7.13-7.03 (m, 1H), 6.56-6.61 (m, 1H), 5.60-5.46 (m, 1H), 5.32 (s, 1H major epimer), 4.83 (dt, *J* = 10.7, 4.4 Hz, 1H), 4.74 (ddd, *J* = 9.3, 2.0, 6.3 Hz, 1H minor epimer), 4.50 (tdd, *J* = 11.6, 2.0, 4.2, 1H major epimer), 4.00 (tdd, *J* = 11.4, 4.1, 2.0 Hz, 1H minor epimer), 2.84 (d, *J* = 6.3 Hz, 1H minor epimer), 2.45 (dd, *J* = 3.0, 1.9 Hz, 1H major epimer), 2.08-0.57 (m, 14H), 1.28 (s, 3H), 1.20 (s, 3H), 0.83 (d, *J* = 6.5 Hz, 3H); <sup>13</sup>C NMR (100.6

MHz, CDCl<sub>3</sub>)  $\delta$  165.7, 165.6, 151.1, 147.6, 146.2, 127.8, 125.2, 124.8, 120.6, 120.2, 96.2, 91.5, 74.5, 74.39, 74.35, 67.3, 50.3, 41.5, 39.6, 34.3, 32.0, 31.7, 31.1, 30.3, 29.6, 29.3, 28.8, 26.6, 26.5, 26.1, 22.5, 21.8, 21.6, 17.1, 14.0; HRMS (FAB, M+Na<sup>+</sup>) calcd for C<sub>24</sub>H<sub>34</sub>O<sub>4</sub>Na 409.2355, found 409.2352.

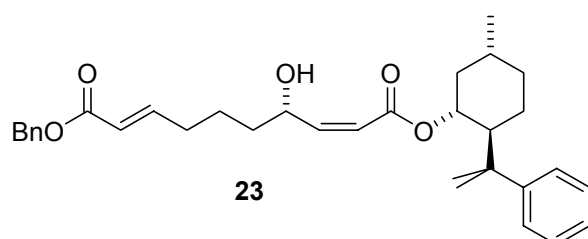


**(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2Z)-3-[(2S,6RS)-6-hydroxytetrahydro-2H-pyran-2-yl]acrylate (34).** Diastereomeric ratio (major epimer/minor epimer) = 67:33;  $[\alpha]_D^{23} +14.5$  (c = 1.0, DCM); IR (film) 3407 (br s), 2952 (s), 2874 (s), 1712 (s), 1650 (m), 1415 (m), 1186 (s); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.31-7.19 (m, 4H), 7.16-7.08 (m, 1H), 6.05 (dd, J=11.7, 7.3 Hz, 1H major epimer), 5.97 (dd, J=11.7, 7.5 Hz, 1H minor epimer), 5.51-5.41 (m, 1H minor epimer), 5.29 (s, 1H minor epimer), 5.16-4.90 (m, 1H plus 1H major epimer), 4.88-4.66 (m, 1H plus 1H major epimer), 3.58 (br s, 1H major epimer), 2.86 (br s, 1H minor epimer), 2.08-0.56 (m, 23H); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  165.3, 165.2, 151.8, 149.5, 148.7, 128.4, 125.85, 125.81, 125.5, 120.2, 119.8, 96.3, 92.1, 74.7, 74.6, 74.1, 66.8, 50.9, 42.1, 40.17, 40.11, 34.9, 32.6, 32.3, 31.8, 30.5, 29.8, 29.6, 29.4, 28.1, 27.9, 27.08, 27.05, 25.9, 25.6, 23.1, 22.5, 22.2, 17.5, 14.5; HRMS (FAB, M+H<sup>+</sup>) calcd for C<sub>24</sub>H<sub>35</sub>O<sub>4</sub> 387.2535, found 387.2547.

**General procedure for HWE reactions with hemiacetals **33** and **34**.** To a solution of (EtO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Bn<sup>5</sup> (5.0 equiv., 0.4 M) in THF at 0 °C was added LiHMDS (1.5 equiv., 1.0 M in toluene). After 1 h the resulting solution was transferred via a cannula to a precooled solution of hemiacetal **33** or **34** (or a mixture of the two) in THF (1.0 equiv., 0.1 M) and stirred at this temperature for 14 h. The reaction was then quenched with phosphate buffer (pH 7) and partitioned between EtOAc and phosphate buffer (pH 7). The combined organic phases were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (12.5-25% EtOAc/heptane) furnished the olefinated product as a clear oil. Isolated yields were 81% from **33**, 74% from **34** and 80% from a mixture.



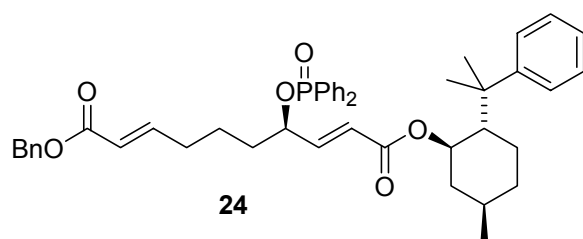
**10-Benzyl 1-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl] (2*E*,4*R*,8*E*)-4-hydroxydeca-2,8-dienedioate (22).**  $[\alpha]_{\text{D}}^{23} +1.5$  ( $c = 1.0$ , DCM); IR (film) 3455 (br, s), 2952 (s), 2919 (s), 1714 (s), 1652 (s), 1267 (m), 1174 (m);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38-7.29 (m, 5H), 7.29-7.20 (m, 5H), 7.12-7.05 (m, 1H), 6.99 (td,  $J = 15.6, 6.9$  Hz, 1H), 6.51 (dd,  $J = 15.7, 5.3$  Hz, 1H), 5.89 (td,  $J = 15.5, 1.4$  Hz, 1H), 5.39 (dd,  $J = 15.7, 1.5$  Hz, 1H), 5.30 (s, 1H), 5.17 (s, 2H), 4.85 (dt,  $J = 10.6, 4.2$  Hz, 1H), 4.16 (br s, 1H), 2.24 (dd,  $J = 12.4, 6.3$  Hz, 2H), 2.11-1.99 (m, 1H), 1.94-1.08 (m, 1H), 1.79-0.79 (m, 9H), 1.29 (s, 3H), 1.20 (s, 3H), 0.87 (d,  $J = 6.5$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.7, 165.8, 152.2, 149.4, 148.9, 136.5, 128.9, 128.6, 128.5, 128.3, 125.8, 125.1, 121.9, 121.4, 74.8, 71.2, 66.5, 50.8, 42.0, 40.1, 36.1, 34.9, 32.3, 31.7, 30.1, 28.4, 26.9, 25.2, 24.0, 22.2; HRMS (FAB,  $\text{M}+\text{H}^+$ ) calcd for  $\text{C}_{33}\text{H}_{43}\text{O}_5$  519.3110, found 519.3114.



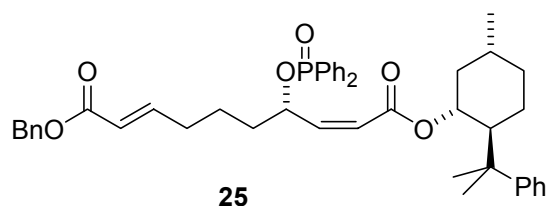
**10-Benzyl 1-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl] (2*Z*,4*S*,8*E*)-4-hydroxydeca-2,8-dienedioate (23).**  $[\alpha]_{\text{D}}^{23} +3.1$  ( $c = 1.0$ , DCM); IR (film) 3440 (br, m), 2950 (s), 2923 (s), 1712 (s), 1650 (m), 1182 (s);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42-7.32 (m, 4H), 7.31-7.23 (m, 5H), 7.17-7.10 (m, 1H), 7.05 (td,  $J = 15.6, 6.9$  Hz, 1H), 6.04 (dd,  $J = 11.9, 6.9$  Hz, 1H), 5.92 (td,  $J = 15.7, 1.3$  Hz, 1H), 5.32 (s, 1H), 5.21-5.16 (m, 1H), 5.19 (s, 2H), 4.84 (dt,  $J = 10.8, 4.4$  Hz, 1H), 4.74 (dd,  $J = 11.9, 6.5$  Hz, 1H), 3.27 (br s, 1H), 2.29 (q,  $J = 6.6$  Hz, 2H), 2.06 (ddd,  $J = 12.6, 10.9, 3.7$  Hz, 1H); 1.79-0.80 (m, 10H), 1.30 (s, 3H), 1.20 (s, 3H), 0.87 (d,  $J = 6.5$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.4, 165.9, 151.5, 151.0, 149.5, 128.5, 128.1, 128.0, 127.9, 125.3, 124.9, 121.2, 121.0, 74.8, 67.6, 66.0, 50.5, 41.6, 39.6, 35.7,

34.5, 32.0, 31.3, 28.0, 26.5, 24.7, 23.7, 21.7; HRMS (FAB,  $M+H^+$ ) calcd for  $C_{33}H_{43}O_5$  519.3110, found 519.3114.

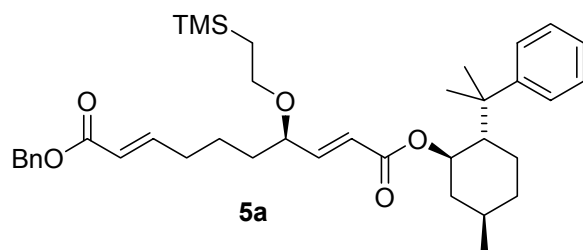
**General procedure for the preparation of diphenylphosphinate esters.** To a stirred solution of **22** or **23** (or a mixture of the two) in DCE/THF (0.1 M, 1:1) was added imidazole (5 equiv.) followed by dropwise addition of diphenylphosphinic chloride (3 equiv.) at room temperature. The resulting slurry was stirred at 60 °C for 16 h, then quenched with phosphate buffer (pH 7) and partitioned between DCM and phosphate buffer (pH 7). The combined organic phases were dried ( $MgSO_4$ ), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (25-37.5% EtOAc/heptane) afforded the phosphinate esters. Isolated yields were 91% from **22**, 86% from **23** and 96% from a mixture.



**10-Benzyl 1-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl] (2*E*,4*R*,8*E*)-4-[(diphenylphosphoryl)oxy]deca-2,8-dienedioate (**24**).  $[\alpha]_D^{23} +34.8$  ( $c = 1.0$ , DCM); IR (film) 3060 (m), 2952 (s), 2925 (s), 1714 (s), 1654 (m), 1438 (m);  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.82-7.70 (m, 4H), 7.56-7.14 (m, 16H), 7.00 (t,  $J = 7.1$  Hz, 1H), 6.92 (td,  $J = 15.4$ , 6.9 Hz, 1H), 6.51 (dd,  $J = 15.7$ , 5.9 Hz, 1H), 5.82 (d,  $J = 15.6$  Hz, 1H), 5.37 (dd,  $J = 15.6$ , 0.9 Hz, 1H), 5.16 (s, 2H), 4.93 (qd,  $J = 12.4$ , 6.1 Hz, 1H), 4.82 (dt,  $J = 10.6$ , 4.3 Hz, 1H), 2.17 (q,  $J = 7.1$  Hz, 2H), 2.03-1.95 (m, 1H), 1.86 (d,  $J = 12.4$  Hz, 1H), 1.80-0.74 (m, 9H), 1.27 (s, 3H), 1.20 (s, 3H), 0.87 (d,  $J = 6.5$  Hz, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  166.6, 165.3, 151.7, 149.1, 144.9, 144.8, 136.4, 132.8, 132.7, 132.2, 132.1, 131.8, 131.7, 129.0, 128.91, 128.87, 128.8, 128.6, 128.5, 128.3, 125.8, 125.4, 123.2, 121.9, 75.1, 74.5, 74.4, 66.5, 50.8, 42.0, 40.1, 35.4, 35.4, 34.9, 32.1, 31.7, 27.5, 27.0, 26.3, 23.1, 22.2; HRMS (FAB,  $M+H^+$ ) calcd for  $C_{45}H_{52}O_6P$  719.3502, found 719.3527.**



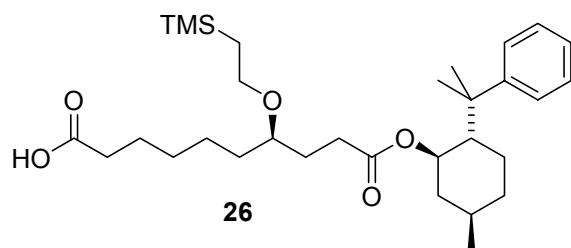
**10-Benzyl 1-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl] (2*Z*,4*S*,8*E*)-4-[(diphenylphosphoryl)oxy]deca-2,8-dienedioate (**25**).**  $[\alpha]_D^{23} +1.2$  ( $c = 1.0$ , DCM); IR (film) 3058 (m), 2952 (s), 2925 (s), 1714 (s), 1652 (m), 1440 (m), 1230 (s), 1199 (s);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87-7.72 (m, 4H), 7.50-7.16 (m, 16H), 7.13-7.07 (m, 1H), 7.02 (td,  $J = 15.4$ , 6.8 Hz, 1H), 6.13 (dd,  $J = 11.6$ , 7.9 Hz, 1H), 5.90 (d,  $J = 15.6$  Hz, 1H), 5.92-5.83 (m, 1H), 5.18 (s, 2H), 4.95 (d,  $J = 11.6$  Hz, 1H), 4.68 (dt,  $J = 10.6$ , 4.3 Hz, 1H), 2.24 (q,  $J = 7.0$  Hz, 2H), 2.03-1.85 (m, 2H), 1.82-0.78 (m, 9H), 1.24 (s, 3H), 1.18 (s, 3H), 0.91 (d,  $J = 6.5$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.7, 164.6, 151.8, 149.7, 147.6, 147.5, 136.5, 132.58, 132.54, 132.52, 132.2, 132.1, 132.0, 131.9, 131.5, 131.4, 128.9, 128.86, 128.84, 128.7, 128.6, 128.5, 128.3, 125.7, 125.4, 121.7, 120.6, 74.6, 73.09, 73.05, 66.4, 50.8, 42.0, 40.0, 35.76, 35.72, 34.9, 32.1, 31.6, 28.3, 26.9, 25.3, 23.7, 22.3; HRMS (FAB,  $\text{M}+\text{H}^+$ ) calcd for  $\text{C}_{45}\text{H}_{52}\text{O}_6\text{P}$  719.3502, found 719.3506.



**10-Benzyl 1-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl] (2*E*,4*R*,8*E*)-4-[2-(trimethylsilyl)ethoxy]deca-2,8-dienedioate (**5a**).** Neocuproine (427 mg, 0.608 mmol) and  $\text{Pd}_2\text{dba}_3$  (15.7 mg, 0.015 mmol) were dissolved in DCM (1 mL) at rt and stirred for 30 minutes. The resulting clear orange-red solution was transferred to a stirred solution of **24** or **25** (or a mixture of the two), dissolved in 2-(trimethylsilyl)ethanol (2 mL) and DCM (1 mL) at rt. The resulting clear yellow solution was then stirred at rt for 3 h during which time the colour changed to light brown. The reaction mixture was poured onto phosphate buffer (pH 7) and partitioned between DCM and phosphate buffer (pH 7). The combined organic phases were dried ( $\text{MgSO}_4$ ) followed by removal of DCM under reduced pressure. Recovery of 2-(trimethylsilyl)ethanol was accomplished using bulb-to-bulb distillation (0.01 mmHg, 60 °C).

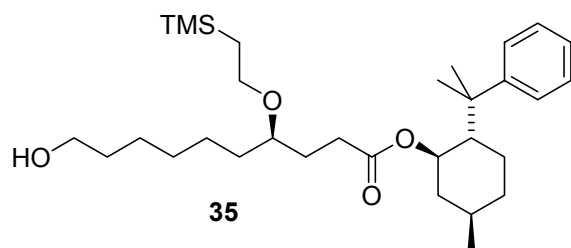


to give 1.50 g, 80%. Repeated purification by flash chromatography (10% Et<sub>2</sub>O/heptane) furnished the (2*E*, 8*E*)-diene as a clear oil (263.4 mg, 72%): Diastereomeric ratio (4*R*):(4*S*) = 97:3;  $[\alpha]_D^{23} +16.4$  (c = 1.0, DCM); IR (film) 3058 (w), 2952 (s), 2925 (s), 1714 (s), 1652 (m), 1440 (m), 1230 (m), 1230 (s), 1199 (s); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40-7.20 (m, 9H), 7.13-7.07 (m, 1H), 7.01 (td, *J* = 15.6, 6.9 Hz, 1H), 6.53 (dd, *J* = 15.8, 6.5 Hz, 1H major diastereomer), 6.35 (dd, *J* = 15.8, 6.3 Hz, 1H minor diastereomer), 5.89 (td, *J* = 15.6, 1.5, 1H), 5.44 (dd, *J* = 15.8, 1.1 Hz, 1H), 5.18 (s, 2H), 4.87 (dt, *J* = 10.7, 4.4 Hz, 1H), 3.70 (q, *J* = 5.5 Hz, 1H), 3.49 (ddd, *J* = 10.1, 9.4, 6.1 Hz, 1H), 3.29 (ddd, *J* = 10.2, 9.4, 6.3 Hz, 1H), 2.26-2.18 (m, 2H), 2.03 (ddd, *J* = 12.3, 10.6, 3.2 Hz, 1H), 1.96-1.89 (m, 1H), 1.76-0.74 (m, 12H), 1.31 (s, 3H), 1.23 (s, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.00 (s, 9H); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ 167.7, 166.7, 152.7, 150.6, 149.3, 137.4, 129.8, 129.55, 129.50, 129.2, 126.7, 126.3, 123.6, 122.7, 79.4, 75.9, 67.9, 67.4, 51.8, 43.0, 41.1, 35.9, 35.8, 33.4, 32.6, 28.3, 28.0, 27.4, 25.1, 23.1, 19.7, 0.0; HRMS (FAB, M+H<sup>+</sup>) calcd for C<sub>38</sub>H<sub>54</sub>O<sub>5</sub>Si 619.3819, found 619.3822.

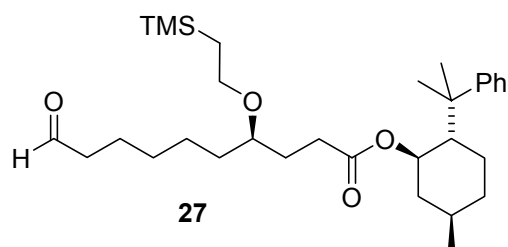


**(4*R*)-4-[2-(Trimethylsilyl)ethoxy]decanedioic acid 1-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl] ester (26).** To a solution of diene **5a** (20.0 mg, 0.032 mmol) in hexanes (2.5 mL) was added palladium (10 wt. % on activated carbon, cat.) under a nitrogen atmosphere and the atmosphere was then changed to hydrogen (purged 5 times). After 48 h at rt, the reaction was passed through a short plug of celite and concentrated *in vacuo*. Purification by flash chromatography (12.5-25% EtOAc/heptane) furnished the saturated acid **26** as a clear oil (15.3 mg, 90%):  $[\alpha]_D^{23} +0.15$  (c = 1.0, DCM); IR (film) 3058 (br, m), 2950 (s), 2923 (s), 1727 (s), 1710 (s); 1247 (s), 1174 (s), 1091 (s); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ The acid proton is not reported, 7.31-7.22 (m, 4H), 7.15-7.08 (m, 1H), 4.81 (dt, *J* = 10.7, 4.5 Hz, 1H), 3.48-3.36 (m, 2H), 3.14-3.05 (m, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.03-1.96 (m, 1H), 1.92-1.80 (m, 2H), 1.79-0.75 (m, 19H), 1.30 (s, 3H), 1.20 (s, 3H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.00 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 179.2, 173.0, 151.68, 151.62, 127.8, 125.3, 124.9, 77.8, 73.9, 65.9, 50.3, 41.8, 39.7, 34.5, 33.8, 33.6, 31.2, 30.2, 29.2, 28.6, 27.7, 26.5,

25.1, 25.0, 24.6, 21.7, 18.6, -1.3; HRMS (FAB,  $M+H^+$ ) calcd for  $C_{31}H_{53}O_5Si$  533.3662, found 533.3663.

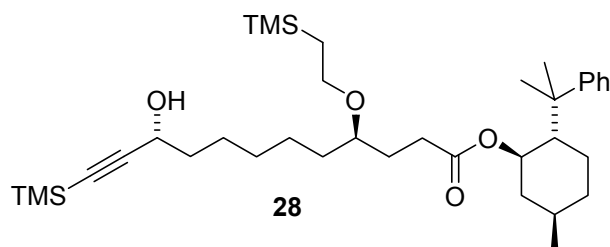


**(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (4R)-10-hydroxy-4-[2-(trimethylsilyl)ethoxy]decanoate (35).** To a solution of **26** (475 mg, 0.029 mmol) in THF (10 mL) at 0 °C was added  $BH_3 \cdot DMS$  (90  $\mu$ L, mmol, 1.0 M in DCM). The temperature was raised to rt over 12 h and the reaction was quenched by careful addition of phosphate buffer (pH 7). The resulting solution was partitioned between EtOAc and phosphate buffer (pH 7). The combined organic phases were dried ( $MgSO_4$ ), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (12.5-25% EtOAc/heptane) furnished the reduced product **35** as a clear oil (460 mg, quant.):  $[\alpha]_D^{23}$  -1.32 ( $c = 0.87$ , DCM); IR (film) 3429 (br, s), 2938 (s), 2856 (s), 1727 (s), 1456 (m), 1248 (m), 1177 (m), 1091 (m);  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.31-7.24 (m, 4H), 7.15-7.10 (m, 1H), 4.81 (dt,  $J = 10.7, 4.5$  Hz, 1H), 3.64 (t,  $J = 6.6$  Hz, 2H), 3.48-3.37 (m, 2H), 3.14-3.06 (m, 1H), 2.05-1.94 (m, 1H), 1.94-1.79 (m, 2H), 1.78-0.77 (m, H), 1.31 (s, 3H), 1.20 (s, 3H), 0.00 (s, 9H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  173.1, 151.6, 127.8, 125.3, 124.9, 77.8, 73.9, 65.9, 63.0, 50.3, 41.7, 39.6, 34.5, 33.7, 32.7, 31.2, 30.2, 29.5, 28.6, 27.7, 26.5, 25.7, 25.3, 25.1, 21.7, 18.6, -1.3; HRMS (FAB,  $M+H^+$ ) calcd for  $C_{31}H_{55}O_4Si$  519.3870, found 519.3873.



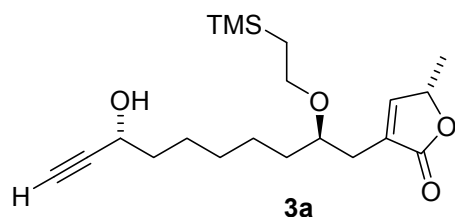
**(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (4R)-10-oxo-4-[2-(trimethylsilyl)ethoxy]decanoate (27).** Dess-Martin periodinane (508 mg, 1.20 mmol) was added in one portion to a solution of **35** (478 mg, 0.92 mmol) and pyridine (15  $\mu$ L, 0.18 mmol) in DCM (8 mL) at 0 °C. The resulting suspension was stirred for 4 h followed by

addition of NaOH (2 M, aq). After stirring for an additional 5 min the reaction was partitioned between DCM and water. The combined organic phases were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (6.25% EtOAc/heptane) afforded aldehyde **27** as a clear oil (392 mg, 82%):  $[\alpha]_D^{23}$  -1.2 (*c* = 1.0, DCM); IR (film) 2950 (s), 2929 (s), 2863 (m), 1727 (s), 1247 (m), 1174 (m), 1089 (m); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.80 (t, *J* = 1.8 Hz, 1H), 7.32-7.27 (m, 4H), 7.15 (m, 1H), 4.84 (dt, *J* = 10.7, 4.4 Hz, 1H), 3.44 (m, 2H), 3.13 (m, 1H), 2.46 (dt, *J* = 7.3, 1.8 Hz, 1H), 2.02 (m, 1H), 1.96-1.83 (m, 2H), 1.82-0.81 (m, 23H), 1.34 (s, 3H), 1.23 (s, 3H), 0.03 (s, 9H); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  203.1, 173.4, 152.0, 128.2, 125.8, 125.4, 78.2, 74.4, 66.4, 50.7, 44.2, 42.2, 40.1, 34.9, 34.1, 32.3, 31.7, 30.6, 29.7, 29.1, 28.1, 27.0, 25.6, 25.5, 23.1, 22.4, 22.2, 19.0, 14.5, -0.9; HRMS (ES<sup>+</sup>, M+Na<sup>+</sup>) calcd for C<sub>31</sub>H<sub>52</sub>NaO<sub>4</sub>Si 539.3532, found 539.3533.



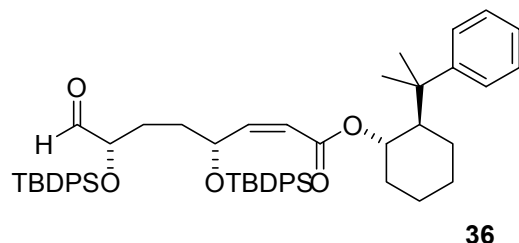
**(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (4*R*,10*R*)-10-hydroxy-12-(trimethylsilyl)-4-[2-(trimethylsilyl)ethoxy]dodec-11-ynoate (28).** To a solution of zinc triflate (79.7 mg, 0.21 mmol) and (1*R*,2*S*)-*N*(+)-methylephedrine (46.9 mg, 0.26 mmol) in toluene (1 mL) was added Et<sub>3</sub>N (73  $\mu$ L, 0.52 mmol) through a septum<sup>6</sup>. The resulting slurry was stirred 1 h 45 min and then trimethylsilylacetylene (246  $\mu$ L, 1.744 mmol) was added. After 15 min a solution of aldehyde **27** (90 mg, 0.17 mmol) in toluene (1 mL) was added via a cannula (rinsed with 0.5 mL toluene). The reaction vessel was then sealed with a screw cap and heated to 60 °C. After 20 h the reaction mixture was evaporated onto silica. Purification by flash chromatography (12.5-25% EtOAc/heptane) afforded propargylic alcohol **28** as a clear oil (80 mg, 75%): Diastereomeric ratio (10*R*:10*S*) = 98:2;<sup>7</sup>  $[\alpha]_D^{23}$  -2.8 (*c* = 1.0, DCM); IR (film) 3436 (br, s), 2952 (s), 2929 (s), 2961 (s), 2169 (w), 1727 (s), 1249 (s), 1174 (m), 840 (s); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.33-7.27 (m, 4H), 7.18-7.11 (m, 1H), 4.84 (dt, *J* = 10.7, 4.4 Hz, 1H), 4.38 (t, *J* = 6.5 Hz, 1H), 3.52-3.40 (m, 2H), 3.17-3.08 (m, 1H), 2.06-1.98 (m, 1H), 1.97-0.81 (m, 27H), 1.34 (s, 3H), 1.23 (s, 3H), 0.20 (s, 9H), 0.03 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  173.5, 152.0, 128.3, 125.8, 125.4, 107.2, 89.7, 78.3, 74.3, 66.3, 63.2,

50.7, 42.2, 40.1, 38.1, 34.9, 34.2, 31.7, 30.7, 29.8, 29.1, 28.1, 27.0, 25.7, 25.6, 25.5, 22.2, 19.0, 0.3, -0.8; HRMS (FAB, M+H<sup>+</sup>) calcd for C<sub>36</sub>H<sub>63</sub>O<sub>4</sub>Si<sub>2</sub> 615.4265, found 615.4269.

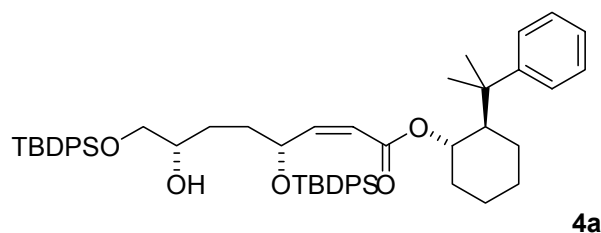


**(5S)-3-[(2R,8R)-8-Hydroxy-2-[(trimethylsilyl)ethoxy]dec-9-yn-1-yl]-5-methylfuran-2(5H)-one (3a).** To a solution of ester **28** (100 mg, 0.17 mmol) in THF (5 mL) at -78 °C was added LDA (249  $\mu$ L, 0.499 mmol, 2 M). The resulting mixture was stirred for 35 min and a pre-cooled solution (-78 °C) of **31** (131 mg, 0.83 mmol) in THF (3 mL) was added dropwise via a cannula. After stirring for 1 h the reaction was quenched by addition of MeOH (2 mL). The reaction was then brought to rt and K<sub>2</sub>CO<sub>3</sub> (200 mg, 1.44 mmol) was added. The resulting suspension was stirred another 12 h after which the reaction mixture was poured into HCl (1 M, aq). The mixture was partitioned between EtOAc and HCl (1 M, aq). The combined organic phases were then dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The crude product **29** was dissolved in MeOH and 10-camphorsulfonic acid (cat.) was added. The resulting mixture was heated to reflux. After 60 min the reaction was cooled to room temperature and partitioned between EtOAc and NaHCO<sub>3</sub> (sat., aq). The combined organic phases were dried (MgSO<sub>4</sub>) and filtered through a short plug of silica (50% EtOAc/heptane) to remove (-)-8-phenylmenthol. The resulting crude oil (59.9 mg) was isolated as a mixture of diastereomers. Of this crude lactone 44 mg was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and Et<sub>3</sub>N (159.2  $\mu$ L, 0.572 mmol) was added, followed by trichloroacetyl chloride (38.3  $\mu$ L, 0.343 mmol) at 0 °C. The resulting mixture was stirred at rt for 24 hours after which THF (6 mL) followed by NaHCO<sub>3</sub> (5 mL, sat. aq) was added. The resulting mixture was stirred for 3 h and then partitioned between EtOAc and water. The combined organic phases were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (12.5-50% EtOAc/heptane) afforded butenolide **3a** as a clear oil (33 mg, 79% overall from **28**):  $[\alpha]_D^{23}$  +17.7 (c = 0.82, DCM); IR (film) 3430 (br, m), 3297 (w), 2935 (s), 2859 (m), 1752 (s), 1319 (m), 1247 (m), 1076 (s), 1076 (s), 837 (s); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.16 (d, *J* = 1.3 Hz, 1H), 5.08-5.00 (m, 1H), 4.39 (dq, *J* = 6.6, 2.1 Hz, 1H), 3.58-3.46 (m, 3H), 2.50-2.45 (m, 3H), 1.85 (d, *J* = 5.6 Hz, 1H), 1.80-1.66 (m, 2H), 1.58-1.25 (m, 11H), 0.99-0.82 (m, 2H), 0.02 (s,

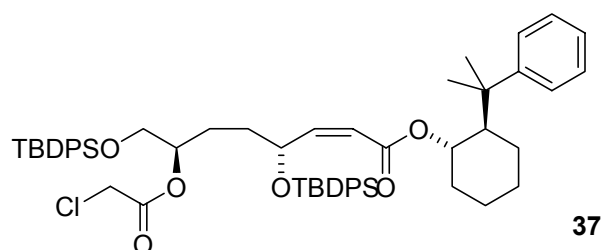
9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  174.0, 151.4, 130.7, 84.9, 77.5, 76.6, 72.8, 66.3, 62.2, 37.5, 34.0, 29.8, 29.2, 25.1, 24.8, 19.1, 18.6, -1.3; HRMS (FAB,  $\text{M}+\text{H}^+$ ) calcd for  $\text{C}_{20}\text{H}_{35}\text{O}_4\text{Si}$  367.2305, found 367.2308.



**(1*S*,2*R*)-2-(1-Methyl-1-phenylethyl)cyclohexyl (2*Z*,4*R*,7*S*)-4,7-bis{[*tert*-butyl(diphenyl)silyl]oxy}-8-oxooct-2-enoate (36).** To a stirred solution of phosphonate **8**<sup>8</sup> (1.48 g, 2.94 mmol) in THF (130 mL) was added NaHMDS (4.45 mL, 2.67 mmol, 0.6 M in toluene) dropwise at -78 °C. The resulting solution was stirred for 30 min and then transferred to a precooled solution of dialdehyde **6a** (2.00 g, 3.21 mmol) in THF (70 mL). After 4 h the reaction was quenched by addition of AcOH (1 M in MeOH) followed by phosphate buffer (pH 7) and partitioned between EtOAc and phosphate buffer (pH 7). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (6.25% EtOAc/heptane) furnished olefin **36**, a single detected stereoisomer, as a clear oil (2.00 g, 77% based on **8**<sup>9</sup>):  $[\alpha]_{\text{D}}^{23}$  -21.8 ( $c = 0.91$ , DCM); IR (film) 3072 (w), 2931 (s), 2858 (s), 1753 (s), 1710 (s), 1427 (s), 1191 (s), 1110 (s), 700 (s);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.53 (d,  $J = 1.4$  Hz, 1H), 7.63-7.70 (m, 4H), 7.62-7.55 (m, 4H), 7.49-7.42 (m, 2H), 7.43-7.35 (m, 6H), 7.35-7.19 (m, 8H), 7.27-7.18 (m, 1H), 5.95 (dd,  $J = 11.7, 8.0$  Hz, 1H), 5.43-5.35 (m, 1H), 4.83 (dd,  $J = 11.7, 0.7$  Hz, 1H), 4.64 (dt,  $J = 10.4, 4.2$  Hz, 1H), 4.07 (t,  $J = 4.7$  Hz, 1H), 2.02-1.94 (m, 1H), 1.88-0.81 (m, 12H), 1.23 (s, 3H), 1.18 (s, 3H), 1.15 (s, 9H), 1.06 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  203.7, 164.8, 151.9, 151.8, 136.25, 136.22, 136.1, 134.4, 134.2, 133.5, 133.4, 130.3, 130.0, 129.9, 128.3, 128.2, 128.1, 127.9, 127.8, 125.7, 125.4, 118.9, 78.4, 74.6, 69.8, 51.3, 40.2, 33.7, 32.5, 28.4, 27.6, 27.49, 27.42, 26.3, 26.0, 25.1, 19.8, 19.7; HRMS (ES<sup>+</sup>,  $\text{M}+\text{Na}^+$ ) calcd for  $\text{C}_{55}\text{H}_{68}\text{O}_5\text{Si}_2\text{Na}$  887.4503, found 887.4523.

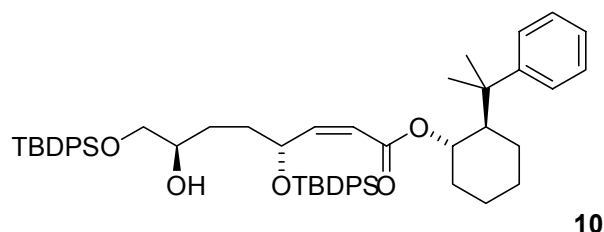


**(1S,2R)-2-(1-Methyl-1-phenylethyl)cyclohexyl (2Z,4R,7S)-4,8-bis{[tert-butyl(diphenyl)silyl]oxy}-7-hydroxyoct-2-enoate (4a).** To a solution of aldehyde **36** (1.86 g, 2.11 mmol) in isopropanol/THF (100 mL, 1:1) was added sodium borohydride (240.1 mg, 6.35 mmol) in one portion at 0 °C. After 3 h the solution was poured into phosphate buffer (pH 7) and partitioned between EtOAc and phosphate buffer (pH 7). The combined organic phases were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (3.13-12.5% EtOAc/heptane) afforded the secondary alcohol **4a** as a clear oil (1.289, g 70%);<sup>10</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> -19.6 (c = 0.8, DCM); IR (film) 3579 (br, s), 3070 (w), 2931 (s), 2858 (s), 1719 (s), 1428 (s), 1193 (s), 1110 (s) 700 (s); <sup>1</sup>H NMR (MHz, CDCl<sub>3</sub>)  $\delta$  7.70-7.66 (m, 4H), 7.64-7.60 (m, 2H), 7.60-7.56 (m, 2H), 7.48-7.32 (m, 8H), 7.33-7.25 (m, 4H), 7.25-7.15 (m, 4H), 7.11-7.06 (m, 1H), 5.98 (dd, *J* = 11.6, 8.0 Hz, 1H), 5.40 (dd, *J* = 13.1, 6.3 Hz, 1H), 4.81 (dd, 11.7, 1.0 Hz, 1H), 4.59 (dt, *J* = 10.3, 4.2 Hz, 1H), 3.73-3.65 (m, 1H), 3.63 (dd, *J* = 10.1, 3.5 Hz, 1H), 3.48 (dd, *J* = 10.0, 7.4 Hz, 1H), 2.60 (d, *J* = 3.5 Hz, 1H), 2.00-1.92 (m, 1H), 1.78-0.86 (m, 12H), 1.17 (s, 3H), 1.14 (s, 3H), 1.09 (s, 9H), 1.05 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  164.9, 152.2, 151.7, 136.24, 136.21, 135.9, 134.5, 134.4, 133.7, 133.6, 130.2, 129.9, 129.9, 128.3, 128.2, 127.9, 127.8, 125.7, 125.4, 118.7, 74.6, 72.5, 70.0, 68.4, 51.3, 40.2, 33.9, 33.7, 28.3, 27.6, 27.49, 27.46, 27.3, 26.3, 25.9, 25.1, 19.7; HRMS (FAB, M+Na<sup>+</sup>) calcd for C<sub>55</sub>H<sub>70</sub>NaO<sub>5</sub>Si<sub>2</sub> 889.4659, found 889.4661.



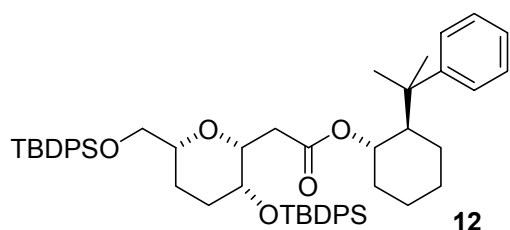
**(1S,2R)-2-(1-Methyl-1-phenylethyl)cyclohexyl (2Z,4R,7R)-4,8-bis{[tert-butyl(diphenyl)silyl]oxy}-7-[(chloroacetyl)oxy]oct-2-enoate (37).** To a stirred solution of secondary alcohol **4a** (918 mg, 1.06 mmol), triphenylphosphine (556 mg, 2.12 mmol) and

chloroacetic acid (200 mg, 2.12 mmol) was added DIAD (0.395 mL, 2.01 mmol) dropwise over 10 min at rt. The yellowish mixture turned clear over 5 min and was stirred for 3 h. The reaction was then quenched by evaporation onto silica. Purification by flash chromatography (1.56-6.25% EtOAc/heptane) afforded ester **37** as a clear oil (995 mg, 95%):  $[\alpha]_D^{23}$  -21.8 ( $c = 1.25$ , DCM); IR (film) 3070 (w), 2931 (s), 2858 (s), 1762 (m), 1710 (s), 1427 (m), 1187 (s), 1112 (s), 701 (s);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73-7.66 (m, 4H), 7.65-7.56 (m, 4H), 7.49-7.33 (m, 8H), 7.33-7.26 (m, 4H), 7.25-7.17 (m, 4H), 7.16-7.09 (m, 1H), 5.97 (dd,  $J = 11.6, 7.9$  Hz, 1H), 5.38 (dd,  $J = 11.9, 5.2$  Hz, 1H), 5.13-5.05 (m, 1H), 4.84 (d,  $J = 11.6$  Hz, 1H), 4.63 (dt,  $J = 10.3, 4.2$  Hz, 1H), 3.99 (dd, 34.9, 14.8 Hz, 2H), 2.74-3.62 (m, 2H), 2.00 (dt,  $J = 11.1, 2.2$  Hz, 1H), 1.86-0.85 (m, 13H), 1.23 (s, 3H), 1.20 (s, 3H), 1.09 (s, 9H), 1.06 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.8, 164.3, 151.6, 151.3, 135.75, 135.70, 135.6, 135.5, 134.0, 133.8, 133.2, 133.1, 129.76, 129.72, 129.59, 129.51, 127.8, 127.7, 127.4, 127.3, 125.3, 124.9, 118.4, 76.5, 74.2, 69.3, 64.9, 50.8, 41.0, 39.7, 33.2, 32.8, 27.3, 27.0, 26.9, 26.7, 25.9, 25.5, 25.4, 24.6, 19.2, 19.1; HRMS (FAB,  $\text{M}+\text{Na}^+$ ) calcd for  $\text{C}_{57}\text{H}_{71}\text{NaO}_6\text{Si}_2$  965.4375, found 965.4383.



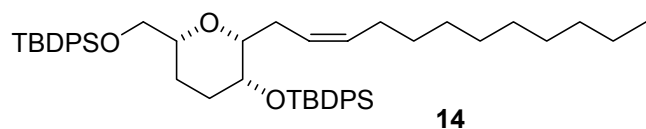
**(1S,2R)-2-(1-Methyl-1-phenylethyl)cyclohexyl (2Z,4R,7R)-4,8-bis{[tert-butyl(diphenyl)silyl]oxy}-7-hydroxyoct-2-enoate (10).** To a stirred solution of chloroacetate **37** (1.30 g, 0.837 mmol) in THF (50 mL) was added LiOH (30 mL, 0.4 M aq) dropwise at 0 °C. The reaction was then stirred for 2.5 h, poured into phosphate buffer (pH 7) and partitioned between EtOAc and phosphate buffer (pH 7). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (3.13-12.5% EtOAc/heptane) furnished a separable mixture of secondary and primary alcohols, **10:11** (92:8), as a clear oil (1.10 g, 92%):  $[\alpha]_D^{23}$  -31.5 ( $c = 1.0$ , DCM); IR (film) 3567 (br, s), 3070 (w), 2931 (s), 2858 (s), 1712 (s), 1427 (s), 1193 (s), 1112 (s), 701 (s);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77-7.71 (m, 4H), 7.67-7.58 (m, 4H), 7.54-7.35 (m, 8H), 7.26-7.20 (m, 8H), 7.18-7.11 (m, 1H), 6.04 (dd,  $J = 11.7, 7.8$  Hz, 1H), 5.46-5.46-5.39 (m, 1H), 4.81 (dd,  $J = 11.7, 1.0$  Hz, 1H), 4.66 (dt,  $J = 10.3, 4.2$ , 1H), 3.78-3.70 (m,

1H), 3.64 (dd,  $J = 10.1, 3.6$  Hz, 1H), 3.52 (dd,  $J = 10.0, 7.3$  Hz, 1H), 2.69 (br s, 1H), 2.02 (dt,  $J = 11.3, 2.2$  Hz, 1H), 1.93-0.87 (m, 12H), 1.25 (s, 3H), 1.21 (s, 3H), 1.13 (s, 9H), 1.08 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  165.0, 152.7, 151.8, 136.27, 136.22, 136.0, 134.6, 134.3, 133.7, 130.2, 130.0, 129.9, 128.3, 128.2, 127.9, 127.8, 125.8, 125.4, 118.5, 74.6, 72.0, 70.0, 68.5, 51.3, 40.2, 33.7, 28.4, 27.8, 27.4, 27.3, 26.3, 25.8, 25.1, 19.76, 19.73; HRMS (FAB,  $\text{M}+\text{Na}^+$ ) calcd for  $\text{C}_{55}\text{H}_{70}\text{NaO}_5\text{Si}_2$  889.4659, found 889.4643.

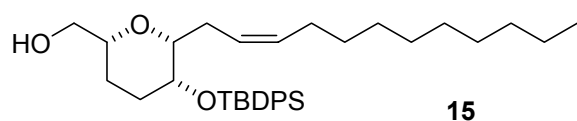


**{(2R,3R,6R)-3-[[*tert*-Butyl(diphenyl)silyl]oxy]-6-[[*tert*-butyl(diphenyl)silyl]oxymethyl]-tetrahydro-2H-pyran-2-yl}-acetic acid (1S,2R)-2-(1-Methyl-1-phenylethyl)cyclohexyl ester (12).** To a solution of secondary alcohol **10** (or a mixture of secondary/primary alcohol **10:11** (92:8)) (440 mg, 0.597 mmol) in toluene (10 mL) at 0 °C was added *t*-BuOK (99  $\mu\text{L}$ , 0.1 mmol, 1.0 M in THF) dropwise over 5 min. The reaction was stirred for 50 min, then quenched by addition of phosphate buffer (pH 7) and partitioned between EtOAc and phosphate buffer (pH 7). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo* to afford the cyclised product **12** as clear a oil, pure by NMR (440 mg, quant.): Diastereomeric ratio (2R:2S) = 96:4;  $[\alpha]_{\text{D}}^{23}$  -0.8 ( $c = 1.0$ , DCM); IR (film) 3070 (w), 2931 (s), 2851 (s), 1725 (s), 1427 (m), 1110 (s), 701 (s);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75-7.65 (m, 8H), 7.50-7.34 (m, 13 H), 7.26-7.22 (m, 2H), 7.18-7.12 (m, 2H), 4.71 (dt,  $J = 10.5, 4.3$  Hz, 1H), 3.96 (td,  $J = 9.2, 4.6$  Hz, 1H minor diastereomer), 3.72 (dd,  $J = 10.2, 4.8$  Hz, 1H), 3.61-3.54 (m, 2H), 3.44-3.36 (m, 1H major diastereomer), 3.20 (dd,  $J = 9.1, 3.5$  Hz, 1H), 2.28 (dd,  $J = 15.7, 9.0$  Hz, 1H), 2.02 (dt,  $J = 11.8, 3.4$ , 1H), 1.86-0.86 (m, 11H), 1.28 (s, 3H), 1.16 (s, 3H), 1.08 (s, 9H), 1.07 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 151.9, 135.97, 135.95, 135.6, 135.5, 134.4, 133.89, 133.85, 133.6, 129.6, 129.55, 129.52, 129.4, 127.7, 127.59, 127.53, 127.4, 125.3, 124.8, 78.0, 76.6, 74.4, 67.8, 67.2, 50.8, 39.6, 38.3, 33.0, 31.8, 30.2, 28.0, 27.1, 26.9, 26.8, 26.0, 24.6, 24.3, 22.6, 22.3, 19.6, 19.2; HRMS (FAB,  $\text{M}+\text{H}^+$ ) calcd for  $\text{C}_{55}\text{H}_{71}\text{O}_5\text{Si}_2$  867.4840, found 867.4852.



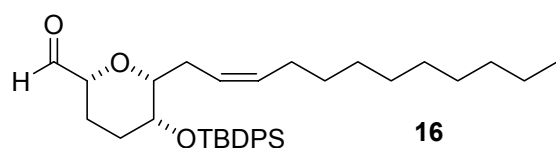


**(2R,3R,6R)-3-{{tert-Butyl(diphenyl)silyl}oxy}-6-{{tert-butyl(diphenyl)silyl}oxymethyl}-2-[(E)-dodec-2-enyl]-tetrahydro-2H-pyran (14).** To a stirred solution of ester **12** (100 mg, 0.116 mmol) in DCM (2 mL) at  $-78\text{ }^{\circ}\text{C}$  was added DIBAL-H (90.8  $\mu\text{L}$ , 0.136 mmol, 1.5 M in toluene) dropwise over 5 min. The resulting mixture was stirred for 35 min, after which a preformed (30 min) solution of decyl triphenylphosphonium bromide (164 mg, 0.340 mmol) and NaHMDS (0.45 mL, 0.227 mmol, 0.6 M in toluene) in THF (4 mL) at  $0\text{ }^{\circ}\text{C}$  was added via a cannula. The temperature was raised to  $0\text{ }^{\circ}\text{C}$  over 12 h and the reaction was then quenched by evaporation onto silica. Purification by flash chromatography (0.78-3.13% EtOAc/heptane) furnished olefin **14** as a clear oil (69 mg, 75%): (*E*):(*Z*)  $\sim 1:10$ ;  $[\alpha]_{\text{D}}^{23} +19.0$  ( $c = 1.0$ , DCM); IR (film) 3070 (w), 2927 (s), 2856 (s), 1471 (m), 1427 (m), 1112 (s), 701 (s);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.82-7.63 (m, 8H), 7.48-7.29 (m, 12H), 5.39-5.21 (m, 2H), 3.82 (dd,  $J = 10.3, 5.3$  Hz, 1H), 3.71 (s, 1H), 3.66 (dd,  $J = 10.2, 5.4$  Hz, 1H), 3.51-3.42 (m, 1H), 3.17 (dd,  $J = 8.3, 5.2$  Hz, 1H), 2.48-2.24 (m, 1H), 2.21-1.98 (m, 1H), 1.95-1.68 (m, 4H), 1.57-1.35 (m, 3H), 1.35-0.99 (m, 13H), 1.10 (s, 9H), 1.09 (s, 9H), 0.90 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) 136.0, 135.7, 136.0, 134.5, 134.0, 133.9, 133.88, 133.81, 133.6, 132.7, 132.6, 131.1, 129.4, 128.6, 128.5, 128.48, 128.44, 128.3, 127.53, 127.47, 127.40, 127.3, 126.2, 80.5, 78.1, 68.0, 67.3, 31.9, 30.7, 30.5, 29.6, 29.57, 29.56, 29.35, 29.33, 27.4, 27.1, 26.8, 22.6, 22.5, 19.6, 19.2, 14.1; HRMS (FAB,  $\text{M}+\text{Na}^+$ ) calcd for  $\text{C}_{50}\text{H}_{70}\text{NaO}_3\text{Si}_2$  797.4761, found 797.4762.

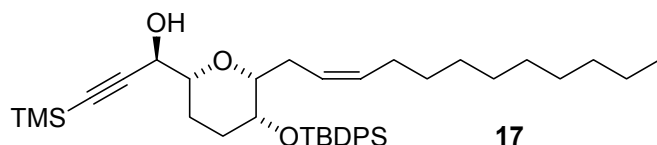


**{{(2R,3R,6R)-5-{{tert-Butyl(diphenyl)silyl}oxy}-6-[(E)-dodec-2-enyl]-tetrahydro-2H-pyran-2-yl}-methanol (15).** To a solution of bis-silyl ether **14** (270 mg, 0.336 mmol) in hexanes (20 mL, HPLC grade) was added activated  $\text{Al}_2\text{O}_3$  (11.34 g, dried 18 h at  $120\text{ }^{\circ}\text{C}$ , 0.01 mmHg). The mixture was stirred for 24 h and MeOH (20 mL) was added. After stirring an additional 15 min the mixture was filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (12.5-25% EtOAc/heptane) afforded the primary

alcohol **15** as a clear oil (157 mg, 83%):  $[\alpha]_D^{23} +28.2$  ( $c = 1.0$ , DCM); IR (film) 3421 (br, m), 2925 (s), 2854 (s), 1457 (w), 1427 (w), 1110 (s), 1031 (s);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78-7.62 (m, 4H), 7.48-7.31 (m, 6H), 5.46-5.15 (m, 2H), 3.76-3.73 (m, 1H), 3.54-3.64 (m, 2H), 3.52-3.44 (m, 1H), 3.21 (dd,  $J = 8.6, 4.9$  Hz, 1H), 2.46 (td,  $J = 15.8, 8.0$  Hz, 1H), 2.69 (br s, 1H), 2.04-1.66 (m, 5H), 1.52-1.40 (m, 1H), 1.38-1.059 (m, 15H), 1.13 (s, 9H), 0.90 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  136.00, 135.97, 134.4, 133.9, 131.6, 129.5, 127.5, 127.4, 125.7, 80.3, 77.7, 67.9, 66.2, 31.9, 30.5, 30.4, 29.6, 29.55, 29.53, 29.33, 29.31, 27.4, 27.1, 22.6, 21.5, 19.6, 14.1; HRMS (FAB,  $\text{M}+\text{Na}^+$ ) calcd for  $\text{C}_{34}\text{H}_{53}\text{O}_3\text{Si}$  537.3764, found 537.3754.

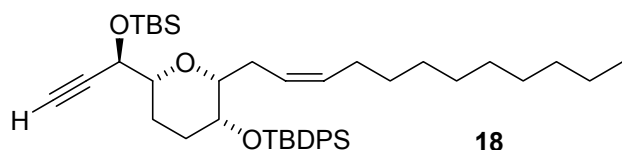


**(2R,3R,6R)-5-{{tert-Butyl(diphenyl)silyl}oxy}-6-[(E)-dodec-2-enyl]-tetrahydro-2H-pyran-2-carbaldehyde (**16**)**. To a solution of primary alcohol **15** (147 mg, 0.259 mmol) and pyridine (64  $\mu\text{L}$ , 0.778 mmol) in DCM (3.0 mL) was added, in one portion, Dess-Martin periodinane (165 mg, 0.390 mmol) at 0 °C. The reaction mixture was stirred 3 h, after which  $\text{Na}_2\text{S}_2\text{O}_3$  (5 mL, 20% aq) was added and the reaction was stirred for an additional 10 min. The reaction mixture was then partitioned between EtOAc and  $\text{Na}_2\text{S}_2\text{O}_3$  (20%, aq). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Purification by flash chromatography (6.25-12.5% EtOAc/heptane) afforded aldehyde **16** as a clear oil (125 mg, 81%):  $[\alpha]_D^{23} +55.0$  ( $c = 1.0$ , DCM); IR (film) 2927 (s), 2856 (s), 1739 (s), 1427 (m), 1110 (s), 701 (s);  $^1\text{H}$  NMR (MHz,  $\text{CDCl}_3$ )  $\delta$  9.72 (s, 1H), 7.77-6.60 (m, 4H), 7.49-7.32 (m, 6H), 5.46-5.17 (m, 2H), 3.82-3.72 (m, 2H), 3.25 (dd,  $J = 8.3, 4.5$  Hz, 1H), 2.56-2.46 (m, 1H), 2.11-1.78 (m, 5H), 1.61-1.40 (m, 3H), 1.37-1.00 (m, 13H), 1.10 (s, 9H), 0.89 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  202.6, 136.0, 135.9, 135.2, 134.1, 133.6, 131.9, 129.7, 127.6, 127.58, 127.55, 125.4, 81.6, 80.7, 67.5, 31.9, 30.4, 30.3, 29.6, 29.57, 29.54, 29.3, 27.4, 27.1, 22.6, 20.5, 19.6, 14.1; HRMS ( $\text{ES}^+$ ,  $\text{M}+\text{Na}^+$ ) calcd for  $\text{C}_{34}\text{H}_{50}\text{NaO}_3\text{Si}$  557.3427, found 557.3442.



**17**

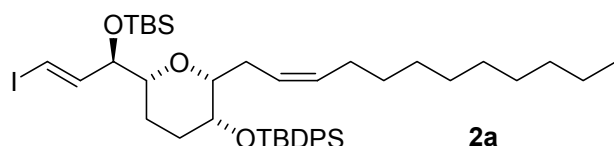
**(1R)-1-((2R,5R,6R)-5-((tert-Butyl(diphenyl)silyl)oxy)-6-[(E)-dodec-2-en-1-yl]tetrahydro-2H-pyran-2-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (17).** To a solution of zinc triflate (97 mg, 0.256 mmol) and (1*S*, 2*R*)-*N*-(*-*)-methylephedrine (57 mg, 319 mmol) in toluene (1 mL) was added Et<sub>3</sub>N (88.8  $\mu$ L, 0.637 mmol). The resulting slurry was stirred 1 h 45 min, and the trimethylsilylacetylene (150  $\mu$ L, 1.06 mmol) was added. After 15 min a solution of aldehyde **16** (120 mg, 0.212 mmol) in toluene (1 mL) was added via a cannula (rinsed with 0.5 mL toluene).<sup>11</sup> After stirring for 20 h at rt the reaction mixture was evaporated onto silica. Purification by flash chromatography (6.25% EtOAc/heptane) afforded propargylic alcohol **17** as a clear oil (110 mg, 83%);  $[\alpha]_D^{23} +19.8$  ( $c = 1.0$ , DCM); IR (film) 3478 (br, w), 2956 (s), 2927 (s), 2856 (s), 2177 (w), 1427 (w), 1249 (m), 1110 (s), 842 (s), 701 (s); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.78-7.65 (m, 4H), 7.50-7.37 (m, 6H), 5.43-5.20 (m, 2H), 4.32 (d,  $J = 7.7$  Hz, 1H), 3.76-3.70 (m, 1H), 3.40 (ddd,  $J = 10.1, 7.9, 2.0$  Hz, 1H), 3.23 (dd,  $J = 9.1, 4.3$  Hz, 1H), 2.98 (s, 1H), 2.53-2.44 (m, 1H), 2.02-1.68 (m, 5H), 1.67-1.52 (m, 2H), 1.41-0.99 (m, 14H), 1.13 (s, 9H), 0.92 (t,  $J = 6.9$  Hz, 3H), 0.20 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  136.4, 134.2, 132.1, 130.0, 128.00, 127.96, 126.0, 103.4, 91.2, 81.1, 80.7, 68.2, 66.8, 32.3, 30.9, 30.8, 30.06, 30.00, 29.79, 29.76, 27.8, 27.5, 23.1, 22.1, 20.0, 14.5, 0.2; HRMS (FAB, M+Na<sup>+</sup>) calcd for C<sub>39</sub>H<sub>61</sub>O<sub>3</sub>Si<sub>2</sub> 633.4159, found 633.4153.



**18**

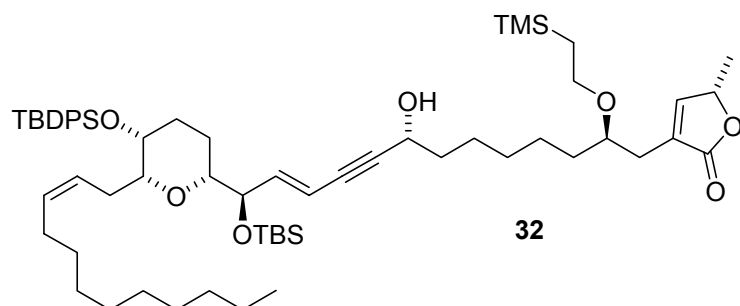
**(2R,3R,6R)-3-((tert-Butyl(diphenyl)silyl)oxy)-6-((R)-1-((tert-butyl(dimethyl)silyl)oxy)prop-2-ynyl)-2-[(E)-dodec-2-enyl]-tetrahydro-2H-pyran (18).** To a stirred solution of propargylic alcohol **17** (105 mg, 0.166 mmol) in DCM (2.5 mL) at rt, was added *t*-butyldimethylsilyl chloride (49 mg, 0.332 mmol) and imidazole (56.5 mg, 0.829 mmol) in one portion respectively at rt. The resulting suspension was stirred for 2 h, and then MeOH (2.5 mL) followed by K<sub>2</sub>CO<sub>3</sub> (120 mg, 0.868 mmol) was added. The resulting mixture was stirred a further 14 h, after which the reaction was quenched by addition of phosphate buffer (pH 7) and partitioned between EtOAc and phosphate buffer (pH 7). The combined organic phases

were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Purification by flash chromatography (1.56% EtOAc/heptane) furnished alkyne **18** as a clear oil (105 mg, 93%):  $[\alpha]_D^{23} +29.1$  (c = 1.0, DCM); IR (film) 3070 (w), 2927 (s), 2856 (s), 1608 (w), 1471 (m), 1253 (m), 1110 (s), 836 (m), 701 (s); <sup>1</sup>H NMR (MHz, CDCl<sub>3</sub>)  $\delta$  7.79-7.64 (m, 4H), 7.48-7.31 (m, 6H), 5.37-5.12 (m, 2H), 4.43 (dd, *J* = 6.4, 2.1 Hz, 1H), 3.75-3.71 (m, 1H), 3.39 (ddd, *J* = 11.4, 6.4, 2.2 Hz, 1H), 3.14 (dd, *J* = 8.1, 5.4 Hz, 1H), 2.41 (d, *J* = 2.1 Hz, 1H), 2.40-2.30 (m, 1H), 2.01-1.75 (m, 5H), 1.62-1.55 (m, 1H), 1.51-1.41 (m, 1H), 1.38-0.92 (m, 14H), 1.11 (s, 9H), 0.94 (s, 9H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.19 (s, 3H), 0.15 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  136.5, 136.4, 134.5, 131.5, 130.0, 129.9, 127.8, 126.6, 83.5, 81.1, 80.4, 73.7, 68.2, 67.0, 32.3, 31.0, 30.9, 30.08, 30.02, 29.9, 29.80, 29.77, 27.8, 27.5, 26.2, 23.1, 21.1, 20.1, 18.8, 14.5, -4.41, -4.45; HRMS (FAB, M+Na<sup>+</sup>) calcd for C<sub>42</sub>H<sub>66</sub>NaO<sub>3</sub>Si<sub>2</sub> 697.4448, found 697.4431.

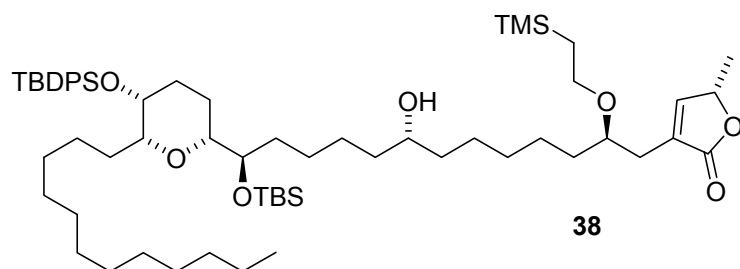


**(2R,3R,6R)-6-[(E)-(R)-1-[(tert-Butyl(dimethyl)silyl]oxy)-3-iodo-allyl]-3-[(tert-butyl(diphenyl)silyl]oxy]-2-[(E)-dodec-2-enyl]-tetrahydro-2H-pyran (2a).** To a stirred suspension of Schwartz reagent (24 mg, 0.092 mmol) in DCM (1 mL) was added alkyne **18** (52 mg, 0.0770 mmol) in DCM (1.5 mL). The resulting yellowish solution was stirred for 15 min and then cooled to 0 °C. A solution of I<sub>2</sub> in DCM (0.2 M) was added until a brownish colour persisted (~1 equiv.). The reaction was stirred a further 10 min after which Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (20%, aq) was added. The brownish colour disappeared and the reaction mixture was partitioned between DCM and Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (20%, aq). The combined organic phases were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Purification by flash chromatography (3.13-6.25% EtOAc/heptane) afforded vinyl iodide **2a** as a clear oil (53 mg, 86%):  $[\alpha]_D^{23} +35.8$  (c = 1.0, DCM); IR (film) 3070 (w), 2927 (s), 2856 (s), 1608 (w), 1471 (m), 1427 (m), 1253 (m), 1110 (s), 863 (m), 701 (s); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.77-7.62 (m, 4H), 7.46-7.32 (m, 6H), 6.77 (dd, *J* = 14.4, 4.5 Hz, 1H), 6.30 (dd, *J* = 14.4, 1.6 Hz, 1H), 5.37-5.06 (m, 2H), 4.23-4.18 (m, 1H), 3.73-3.68 (m, 1H), 3.33-3.27 (m, 1H), 3.11 (dd, *J* = 8.1, 5.2 Hz, 1H), 2.36 (td, *J* = 14.7, 7.2, 1H), 2.20-1.61 (m, 6H), 1.46-0.8 (m, 15H), 1.11 (s, 9H), 0.94-0.86 (m, 12H), 0.081 (s, 3H), 0.077 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  145.7, 136.0, 134.4, 134.1, 131.2, 129.5, 129.4, 127.4, 126.1, 80.5, 79.7, 76.6, 76.2, 67.8, 31.9, 30.57, 30.52, 29.65,

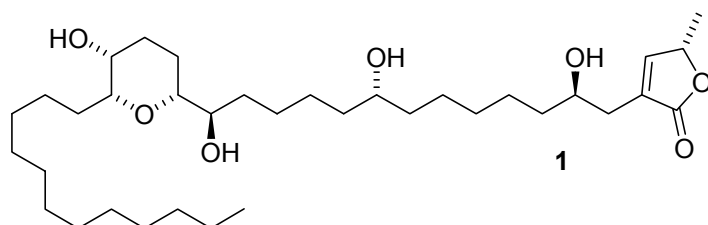
29.60, 29.3, 27.4, 27.2, 25.8, 22.7, 19.68, 19.63, 18.2, 14.1, -4.8, -4.9; HRMS (FAB, M+Na<sup>+</sup>) calcd for C<sub>42</sub>H<sub>67</sub>INaO<sub>3</sub>Si<sub>2</sub> 825.3571, found 825.3571.



**(5S)-3-[(2R,8R,11E,13R)-13-[(tert-Butyl(dimethyl)silyl]oxy]-13-[(2R,5R,6R)-5-[(tert-butyl(diphenyl)silyl]oxy)-6-[(E)-dodec-2-en-1-yl]tetrahydro-2H-pyran-2-yl]-8-hydroxy-2-[2-(trimethylsilyl)ethoxy]tridec-11-en-9-yn-1-yl]-5-methylfuran-2(5H)-one (32).** To a solution of vinyl iodide **2a** (26.3 mg, 0.033 mmol) in Et<sub>3</sub>N (0.5 mL) was added CuI (1.29 mg, 0.0068 mmol) and dichlorobis(triphenylphosphine)-palladium(II) (1.91 mg, 0.0027 mmol). The reaction mixture was stirred for 35 min at rt, after which a solution of acetylene **3a** (12 mg, 0.0328 mmol) in Et<sub>3</sub>N (1 mL) was added dropwise over 10 min (rinsed with 0.5 mL Et<sub>3</sub>N). After 2.5 h, the volatiles were removed *in vacuo*. Purification by flash chromatography (12.5-25% EtOAc/heptane) afforded ene-yne **32** as a yellowish oil (30.4 mg, 89%): [α]<sub>D</sub><sup>23</sup> +36.4 (c = 1.0, DCM); IR (film) 3436 (br, s), 2929 (s), 2856 (s), 1758 (m), 1249 (m), 1103 (s), 1027 (m), 836 (m); 703 (m); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.76-7.60 (m, 4H), 7.46-7.31 (m, 6H), 7.13 (d, *J* = 1.1 Hz, 1H), 6.36 (dd, *J* = 15.9, 4.2 Hz, 1H), 5.81 (td, *J* = 16.0, 1.8 Hz, 1H), 5.36-5.13 (m, 2H), 5.05-4.96 (m, 1H), 4.50-4.42 (m, 1H), 4.32-4.25 (m, 1H), 3.73-3.68 (m, 1H), 3.56-3.42 (m, 3H), 3.31 (ddd, *J* = 11.4, 5.8, 1.7 Hz, 1H), 3.10 (dd, *J* = 8.0, 5.6 Hz, 1H), 2.43 (d, *J* = 5.4 Hz, 2H), 2.39-2.26 (m, 1H), 1.54-0.70 (m, 35H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.09 (s, 9H), 0.90 (s, 9H), 0.08 (s, 6H), 0.00 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 173.9, 151.3, 143.6, 136.0, 134.4, 134.1, 131.2, 130.7, 129.5, 129.4, 127.4, 126.0, 109.0, 90.1, 83.5, 80.4, 80.1, 77.4, 74.1, 67.8, 66.3, 62.9, 37.8, 34.0, 31.9, 30.5, 29.8, 29.6, 29.5, 29.4, 29.35, 29.32, 27.3, 27.1, 25.8, 25.2, 25.1, 22.6, 19.6, 19.1, 18.6, 18.2, 14.1, -1.3, -4.82, -4.89; HRMS (FAB, M+Na<sup>+</sup>) calcd for C<sub>62</sub>H<sub>100</sub>NaO<sub>7</sub>Si<sub>3</sub> 1063.6675, found 1063.6689.



**(5*S*)-3-{(2*R*,8*R*,13*R*)-13-[[*tert*-Butyl(dimethyl)silyl]oxy}-13-[(2*R*,5*R*,6*R*)-5-[[*tert*-butyl(diphenyl)silyl]oxy]-6-dodecyltetrahydro-2*H*-pyran-2-yl)-8-hydroxy-2-[2-(trimethylsilyl)ethoxy]tridecyl}-5-methylfuran-2(5*H*)-one (38).** A solution of ene-yne **32** (17.5 mg, 0.017 mmol) and tosylhydrazine (300 mg, 1.6 mmol) in 1,2-DME (2.4 mL) was heated to reflux and sodium acetate (160 mg, 2.0 mmol) in water (3.0 mL) was added over 4 h using a syringe pump. The reaction was then poured onto water and partitioned between EtOAc and water and the combined organic phases were dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo. Purification by flash chromatography (12.5-25% EtOAc/heptane) furnished triprotected pyranicin **38** as a clear oil (15.0 mg, 85%):  $[\alpha]_D^{23} +19.4$  ( $c = 1.0$ , DCM); IR (film) 3399 (br, w), 2927 (s), 2856 (s), 1758 (m), 1461 (m), 1429 (m), 1089 (s), 1027 (m); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.74-7.62 (m, 4H), 7.45-7.28 (m, 6H), 7.13 (d,  $J = 1.3$  Hz, 1H), 5.01 (dq,  $J = 6.6, 1.4$  Hz, 1H), 3.70-3.62 (m, 2H), 3.62-3.55 (m, 1H), 3.55-3.42 (m, 3H), 3.29-3.23 (m, 1H), 3.05 (t,  $J = 6.6$  Hz, 1H), 2.49-2.36 (m, 3H), 1.88-1.61 (m, 3H), 1.60-0.73 (m, 44H), 1.41 (d,  $J = 6.8$  Hz, 3H), 1.08 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.00 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  173.9, 151.3, 136.0, 135.9, 134.7, 134.2, 130.8, 129.4, 129.1, 128.0, 127.4, 127.3, 80.7, 80.4, 77.4, 76.6, 74.5, 71.9, 67.7, 66.3, 37.6, 37.4, 34.1, 32.2, 31.9, 29.87, 29.83, 29.69, 29.63, 29.5, 29.3, 27.1, 25.9, 25.8, 25.6, 25.5, 25.3, 22.6, 19.6, 19.1, 18.6, 14.1, -1.3, -4.2, -4.5; HRMS (FAB, M+Na<sup>+</sup>) calcd for C<sub>62</sub>H<sub>108</sub>NaO<sub>7</sub>Si<sub>3</sub> 1071.7301, found 1071.7296; The product contained traces of tosylhydrazine.

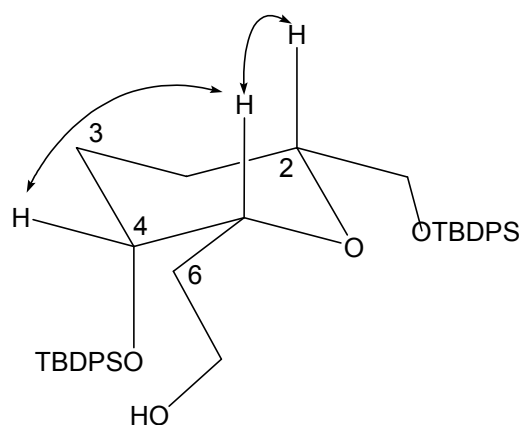


**Pyranicin (1).** To a stirred solution of tri-protected pyranicin **38** (12.0 mg, 0.0114 mmol) in MeCN (1.2 mL) was added HF (50  $\mu$ L, 40%, aq) at rt. The reaction was heated to 45 °C during 22 h and then quenched by addition of NaHCO<sub>3</sub> (sat., aq) and partitioned between EtOAc and NaHCO<sub>3</sub>. The combined organic phases were dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo. Purification by flash chromatography (3-5% MeOH/EtOAc) afforded

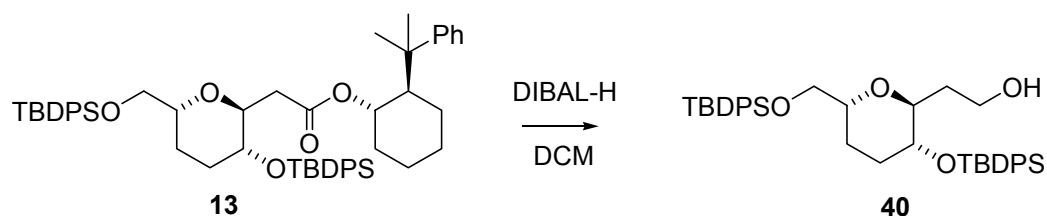
### Determination of the relative configuration of the stereocenters of the THP-rings in 12 and 13

S - 22

Diagnostic NOESY correlations of *cis-cis* THP **39**:



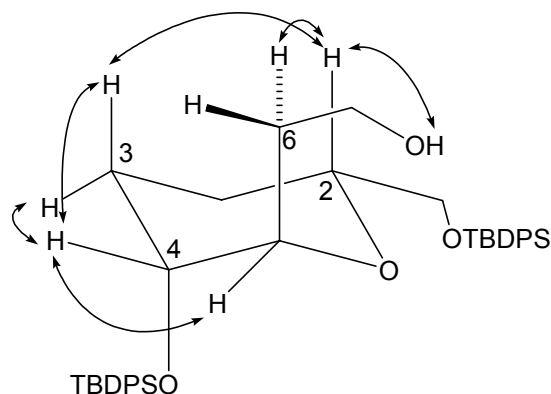
#### b) Preparation of, and analytical data for compound **40**



In order to confirm the stereochemical assignment of compound **13**, it was converted to alcohol **40** by reduction with DIBAL-H; **40**:  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.86-7.79 (m, 4H), 7.79-7.40 (m, 2H), 7.74-7.68 (m, 2H), 7.29-7.13 (m, 12H), 3.93 (td,  $J = 10.5, 3.6$  Hz, 1H), 3.85 (dd,  $J = 10.4, 7.4$  Hz, 1H), 3.75 (qd,  $J = 11.6, 3.9$  Hz, 1H), 3.65 (dd,  $J = 10.5, 5.1$  Hz, 2H), 3.56 (dd,  $J = 10.4, 4.2$  Hz, 1H), 3.51 (td,  $J = 5.4, 3.7$  Hz, 1H), 2.60 (t,  $J = 5.5$  Hz, 1H), 1.78-1.67 (m, 1H), 1.62-1.48 (m, 2H), 1.46-1.35 (m, 1H), 1.22 (s, 9H), 1.16 (s, 9H), 1.10-0.98 (m, 1H).



*Diagnostic NOESY correlations of trans-trans THP 40:*



<sup>1</sup> Ireland, R. E.; Meissner, R. S. *J. Org. Chem.* **1991**, *56*, 4566-4568.

<sup>2</sup> Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

<sup>3</sup> For analytical data of **20** and **21**, see: Pedersen, T. M.; Jensen, J. F.; Humble, R. E.; Rein, T.; Tanner, D.; Bodmann, K.; Reiser, O. *Org. Lett.* **2000**, *2*, 535-538.

<sup>4</sup> A pre-heated oilbath was used since precise temperature control was critical to avoid byproduct formation.

<sup>5</sup> Prepared using an Arbuzov protocol similar to that used in: Nagata, W.; Wakabayashi, T.; Hayase, Y. *Org. Synth.* **1973**, *53*, 44-48.

<sup>6</sup> Sealing the reaction vessel using only a septum was not sufficient to prevent TMS-acetylene from escaping from the reaction.

<sup>7</sup> As determined by <sup>1</sup>H and <sup>19</sup>F analysis of the corresponding (+)- and (-)-MTPA derivatives.

<sup>8</sup> Prepared using a similar protocol to that used in: Hatakeyama, S.; Satoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2713-2716. Selected data: Yield 93%; IR (film) 2964, 2918, 1730, 1300, 1268, 1180, 1070, 960; <sup>1</sup>H NMR (500 MHz, selected data)  $\delta$  7.31-7.28 (m, 4H), 7.16-7.11 (m, 1H), 4.81 (ddd [app td],  $J$  = 10.5, 4.5, 1H), 4.45-4.27 (m, 4H), 2.27 (ddd,  $J$  = 26.0, 20.5, 16 Hz, 2H), 2.12 (app td,  $J$  = 11.5, 3.5 Hz, 1H), 1.94 (br d,  $J$  = 13 Hz, 1H), 1.87-1.82 (m, 1H), 1.77-1.67 (m, 2H), 1.30 (s, 3H), 1.18 (s, 3H); <sup>13</sup>C NMR (125 MHz)  $\delta$  164.1, 151.9, 128.1, 125.3, 125.1, 123.7, 121.1, 76.3, 62.4 (qd,  $J$  = 19.6, 5.5 Hz), 62.3 (qd,  $J$  = 19.6, 5.5 Hz), 50.5, 39.5, 39.5, 33.4, (d,  $J$  = 14.4 Hz), 32.9, 30.0, 26.6, 25.8, 24.6, 22.1. See also; Vares, L. Ph.D. Thesis, Tartu University, Estonia, 2000.

<sup>9</sup> Alternatively, the crude **36** obtained after filtration through a short plug of silica could be directly subjected to reduction/protective group migration. This protocol afforded **4a** in 70% overall yield, based on **8**.

<sup>10</sup> In addition, 224 mg (12%) of a mixture of primary and secondary alcohol was recovered. This mixture could be re-equilibrated under the following conditions: A mixture of primary alcohol **9** and secondary alcohol **4a** was dissolved in EtOH followed by addition of catalytic amounts of DMAP. The resulting solution was refluxed for 14 h and then subjected to a similar workup as described above to give an additional 159 mg (70 %) of secondary alcohol, thus increasing the overall yield.

<sup>11</sup> Due to the higher reactivity of aldehyde **16** compared to that of aldehyde **27**, the reaction could be run at rt using standard inert techniques.