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Supporting Information

69451 Weinheim, Germany

Total Synthesis of (+)-Leucascandrolide A

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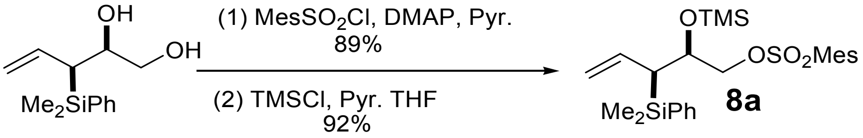
General Information: ^{1}H- and ^{13}C-NMR were recorded in $CDCl_3$ at 400 MHz and 75.0 MHz respectively unless specified otherwise. Chemical shifts are reported in parts per million using the solvent resonance internal standard chloroform (7.24 and 77.0 ppm, unless specified otherwise). Data are reported as follows: chemical shift, integration, multiplicity (app = apparent, par obsc = partially obscured, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, abq = ab quartet) and coupling constant. Ratios of diastereomers (dr) were determined by ^{1}H-NMR (400 MHz). Infrared Resonance (IR) spectra were recorded on a Nicolet Impact 400 FT-IR spectrometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and are reported as $[\alpha]_D$ (concentration in grams/100 mL solvent). Tetrahydrofuran (THF), ethyl ether (Et_2O), methylene chloride (CH_2Cl_2), benzene and toluene were dried using a solvent drying system (Al_2O_3). All other reagents were used as supplied from commercial sources. All reactions were carried out in oven-dried glassware under argon or N_2 atmosphere unless otherwise noted. Analytical thin layer chromatography was performed using Whatman Reagent silica gel 60-Å plates. Flash chromatography was performed using E. Merck silica gel (230-400 mesh).



Allylsilane 8a. 2-Mesitylenesulfonyl chloride (14.52 g, 66 mmol) was added to a solution of diol[SI1] (13.1 g, 55.5 mmol), pyridine (8.8 g, 111 mmol) and 4-(dimethylamino) pyridine (DMAP) (677 mg, 5.5 mmol) in DCM (150 mL). The mixture was stirred for 72 h at room temperature. Removal of the solvent under reduced pressure and purification by flash column chromatography (silica gel, 8% EtOAc in hexane) afforded the corresponding sulfonate as a pale yellow oil (20.6 g, 89%). A solution of the resulting sulfonate (1.67 g, 4 mmol) in THF (20 mL) was treated with pyridine (1.26 g, 16 mmol) and TMSCl (1.29 g, 12 mmol). The reaction mixture was stirred for 12h before water (20 mL) was added. The mixture was extracted with Et_2O (3 x 20 mL). And the combined organic layers were dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure and purification by flash chromatography (silica gel, 2% EtOAc in hexane) afforded the silyl ether **8a** as a pale yellow oil (1.8 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, m), 7.32-7.25 (3H, m), 6.93 (2H, s), 5.58 (1H, m), 4.88 (1H, dd, *J* = 10 Hz, 1.6 Hz), 4.74 (1H, d, *J* = 16.8 Hz), 3.97 (1H, m), 3.70 (1H, dd, *J* = 4 Hz, 10 Hz), 3.62 (1H, dd, *J* = 6.4 Hz, 10 Hz), 2.54 (6H, s), 2.30 (3H, s), 1.97 (1H, dd, *J* = 14.4 Hz, 5.2 Hz), 0.25 (6H, s), 0.00 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 139.7, 137.7, 135.9,

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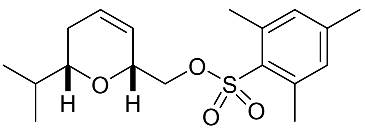
[SI1] The diol was prepared by a similar manner according to the reported procedures: H. Huang, J. S. Panek, *Org. Lett.* **2003**, *5*, 1991. For its physical data, see: D. C. Chauret, J. M. Chong, Q. Ye, *Tetrahedron: Asym.* **1999**, *10*, 3601.

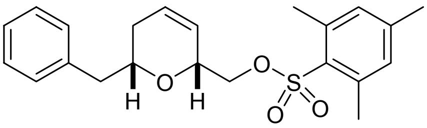
134.0, 131.6, 130.4, 128.9, 127.5, 114.8, 72.6, 71.8, 40.0, 22.3, 20.7, 0.03, -3.1, -3.5; IR (neat) νmax 2956, 1604, 1358, 1251, 977; $[\alpha]^{23}_{D}$ = -4.6^{o} (c = 0.65, CH_2Cl_2); CIHRMS $[M]^+$ calculated for $C_{25}H_{38}O_4SSi_2$ 490.2029, found: 490.2007.

General experimental procedure for Table 1.

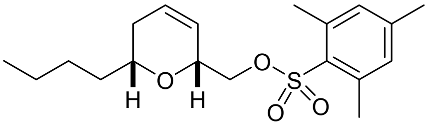
TfOH (0.0243 mL, 0.275 mmol) was slowly added to a solution of an aldehyde (0.375 mmol) and the allylsilane (0.250 mmol) in CH_2Cl_2 (2.5 mL) at –78 ^{o}C. The reaction mixture was stirred for 12 h at this temperature before an aqueous saturated solution of $NaHCO_3$ (5 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography afforded the pyran as pale yellow oil in the yield and diastereomeric ratio (dr) reported in Table 1.



9a (entry 1, Table 1) (yield = 90%, dr = 25 : 1 (*cis* : *trans*)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (2H, s), 5.89 (1H, m), 5.53 (1H, m), 4.31 (1H, m), 3.97 (1H, dd, *J* = 4 Hz, 10 Hz), 3.85 (1H, dd, *J* = 6.8 Hz, 10 Hz), 3.16 (1H, m), 2.62 (6H, s), 2.28 (3H, s), 1.89 (2H, m), 1.57 (1H, hept, *J* = 6.8 Hz), 0.86 (3H, d, *J* = 6.8 Hz), 0.82 (3H, d, *J* = 6.8 Hz) ; ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 143.1, 140.0, 131.5, 128.0, 124.8, 78.6, 72.6, 71.0, 32.8, 27.7, 22.5, 21.0, 18.4, 17.8; IR (neat) νmax 2960, 1604, 1357; $[\alpha]^{23}_{D}$ = $+14.4^{o}$ (c = 0.55, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{18}H_{26}O_4S$ 339.1585, found: 339.1626.

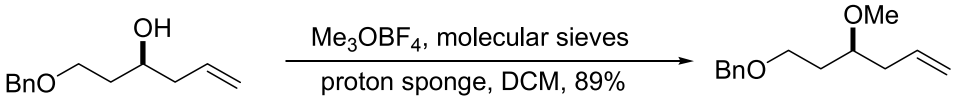


9b (entry 2, Table 1) (yield = 91%, dr = 8 : 1 (*cis* : *trans*)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.11 (5H, m), 6.96 (2H, s), 5.85 (1H, m), 5.53 (1H, m), 4.31 (1H, m), 3.95 (1H, dd, *J* = 4 Hz, 10 Hz), 3.91 (1H, dd, *J* = 4 Hz, 10 Hz), 3.70 (1H, m), 2.82 (1H, dd, *J* = 6.8 Hz, 13.6 Hz), 2.62 (6H, s), 2.59 (1H, dd, *J* = 6.4 Hz, 14 Hz), 2.30 (3H, s), 1.89 (2H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 143.1, 140.0, 138.1, 131.5, 129.2, 128.1, 127.5, 126.2, 124.8, 74.4, 72.5, 70.8, 42.0, 30.2, 22.6, 21.0; IR (neat) νmax 2938, 1604, 1355; $[\alpha]^{23}_{D}$ = $+30.0^{o}$ (c = 0.55, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{22}H_{26}O_4S$ 387.1585, found: 387.1646.

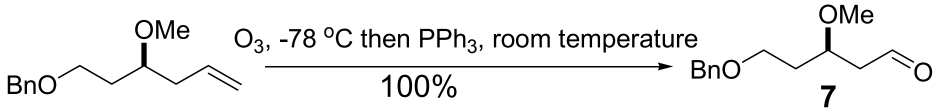


9c (entry 3, Table 1) (yield = 85%, dr = 16 :1 (*cis* : *trans*)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (2H, s), 5.87 (1H, m), 5.53 (1H, m), 4.30 (1H m), 3.97 (1H, dd, *J* = 4.4 Hz, 10.4 Hz), 3.88 (1H, dd, *J* = 6.8 Hz, 10.4 Hz), 3.43 (1H, m), 2.61 (6H, s), 2.28 (3H, s), 1.86 (2H, m), 1.46-1.19 (6H, m), 0.87 (3H, t, *J* = 6.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 143.0, 140.0, 131.6, 131.5, 127.8, 124.9, 73.6, 72.4, 71.0, 35.4, 30.7, 27.4, 22.6, 22.6, 21.0, 14.0; IR (neat) νmax 2932, 1604, 1356; $[\alpha]^{23}_{D}$ = $+15.2^{o}$ (c = 0.55, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{19}H_{28}O_4S$ 353.1742, found: 353.1776.

Aldehyde **7** is readily prepared from known alcohol: [SI2]



Trimethyloxonium tetrafluoroborate (7.8 g) was added to a solution of alcohol[SI2] (4.0 g, 19.4 mmol), molecular sieves 4Å (13.6 g) and proton sponge® (13.6 g) in DCM (400 mL). The resulting mixture was stirred for 2 hours before additional portions of proton sponge® (9.0 g) and trimethyloxonium tetrafluoroborate (5.0 g) were added. The suspension was stirred overnight before filtered through a pad of Celite®. The yellow filtrate was washed with an aqueous solution of HCl (1N) and the organic layer was dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, 5 % EtOAc in hexane) afforded the methyl ether (3.8 g, 89%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (5H, m), 5.79 (1H, m), 5.06 (1H, m), 5.03 (1H, m), 4.48 (2H, abq, J = 11.6 Hz), 3.54 (2H, m), 3.38 (1H, m), 3.32 (3H, s), 2.26 (2H, dd, J = 6 Hz, 7.2 Hz) 1.77 (2H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 138.5, 134.6, 128.3, 127.6, 127.5, 117.1, 77.5, 73.0, 66.9, 56.8, 37.9, 33.9; IR (neat) νmax 2925, 1604, 1094; $[\alpha]^{23}_D$ = +28.1° (c = 3.3, CH_2Cl_2); CIHRMS M^+ calculated for $C_{14}H_{20}O_2$ 220.1463, found: 220.1425.



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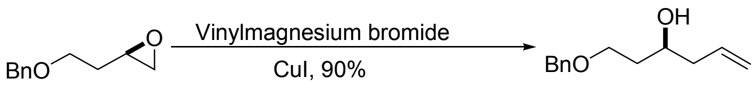
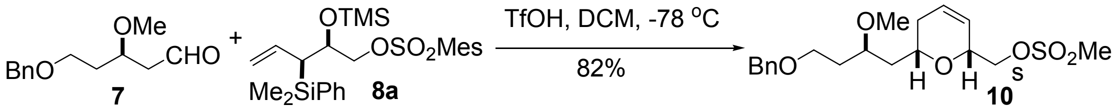
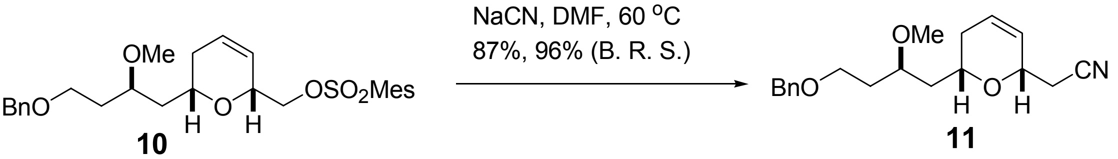
Aldehyde 7. Ozone gas was bubbled through a solution of olefin (3.5 g, 15.9 mmol) in DCM (317 mL) at -78 °C until the solution turned pale blue. Solid PPh_3 (12.5 g) was then added. The mixture was slowly warmed to room temperature and stirred overnight. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, 25% EtOAc in hexane) afforded the aldehyde **7** (3.88 g, ca.100%).^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, t, J = 3 Hz), 7.35-7.25 (5H, m), 4.47 (2H, s), 3.89 (1H, m), 3.55 (2H, m), 3.33 (3H, s), 2.59 (2H, m), 1.90 (1H, m), 1.79 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 138.3, 128.4, 127.7, 73.7, 73.0, 66.2, 56.9, 48.1, 34.0; IR (neat) νmax 2930, 1723, 1095; $[\alpha]^{23}_D$ = +13.5 ° (c = 0.93, CH_2Cl_2); CIHRMS M^+ calculated for $C_{13}H_{18}O_3$ 223.1289, found: 223.1314.

[SI2] R. P. Short, S. Masamune, *J. Am. Chem. Soc.* **1989**, *111*, 1892. The homoallylic alcohol could also be obtained using a regioselective ring opening of (*R*)-epoxide with vinyl magnesium bromide (2 equiv.) and a catalytic amount of CuI (10% mol).

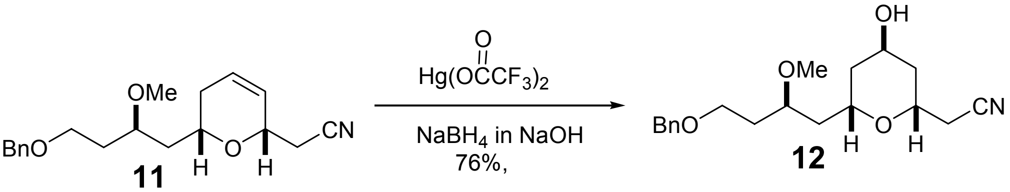




Dihydropyran 10. A solution of aldehyde **7** (930 mg, 4.2 mmol) and silane **8a** (3.56 g, 7.3 mmol) in DCM (65 mL) at -78 °C was treated with TfOH (833 mg, 5.55 mmol). The mixture was stirred for 12 h at this temperature before an aqueous saturated solution of $NaHCO_3$ (60 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 60 mL) and combined organic layers were dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, 20% EtOAc in hexane) afforded the pyran **10** as a pale yellow oil (1.67 g, 82%, dr = 12 : 1 (*cis* : *trans*)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (5H, m), 6.92 (2H, s), 5.87 (1H, m), 5.53 (1H, dd, br, *J* = 2 Hz, 10 Hz), 4.47 (2H, s), 4.29 (1H, m), 3.96 (1H, dd, *J* = 4 Hz, 10 Hz), 3.87 (1H, dd, *J* = 6 Hz, 10 Hz), 3.62 (1H, m), 3.52 (2H, m), 3.45 (1H, m), 3.25 (3H, s), 2.61 (6H, s), 2.27 (3H, s), 1.90 (2H, m), 1.77 (3H, m), 1.49 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 140.0, 138.5, 131.7, 131.6, 128.4, 127.8, 127.7, 127.6, 124.9, 74.9, 72.9, 72.3, 70.7, 70.5, 66.7, 56.3, 39.3, 33.7, 30.8, 22.4, 20.8; IR (neat) νmax 2939, 1604, 1355 1097; $[\alpha]^{23}_D$ = +20.5^o (c = 0.55, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{27}H_{36}O_6S$ 489.2266, found: 489.2333.

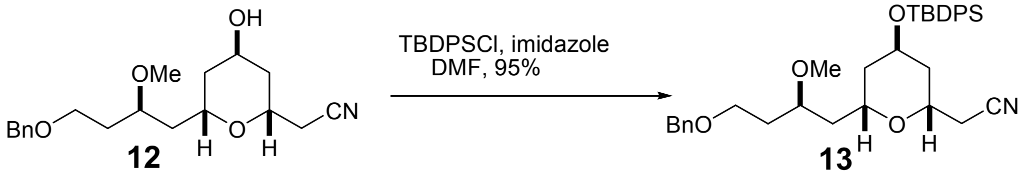


Dihydropyran 11. A solution of sulfonate **10** (1.62 g, 3.3 mmol) in DMF (11 mL) was treated with NaCN (650 mg, 13.3 mmol). The mixture was stirred for 60 h at 60 °C before the reaction was diluted with water (50 mL). The mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (4 x 20 mL), dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, 15% - 20 % EtOAc in hexane) afforded the pyran **11** as a pale yellow oil (0.91 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (5H, m), 5.97 (1H, m), 5.62 (1H, m), 4.48 (2H, s), 4.35 (1H, m), 3.72 (1H, m), 3.59-3.48 (3H, m), 3.29 (3H, s), 2.51 (2H, m), 2.00 (2H, m), 1.85 (3H, m), 1.60 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.2, 127.8, 127.5, 127.4, 126.4, 117.0, 74.7, 72.7, 70.8, 69.9, 66.6, 56.2, 39.1, 33.7, 30.5, 24.1; IR (neat) νmax 2926, 2862, 2250, 1454, 1093; $[\alpha]^{23}_D$ = +23.4^o (c = 0.44, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{19}H_{25}NO_3$ 316.1868, found: 316.1924.

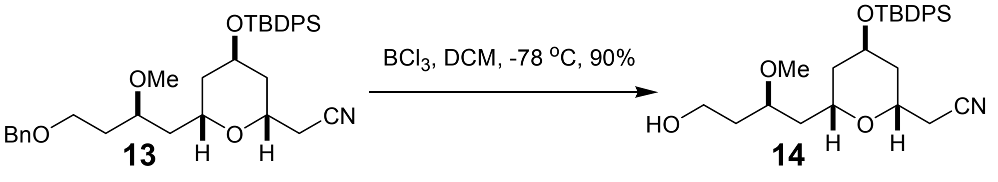


Pyran 12. A solution of olefin **11** (650 mg, 2.06 mmol) in THF (16 mL) and water (12 mL) was treated with mercury trifluoroacetate (4.38 g, 10.3 mmol). The reaction mixture was stirred for 18 h before an aqueous solution of NaOH (3N, 13.6 mL) and $NaBH_4$ (392 mg, in an aqueous solution of NaOH (3.7

mL, 3N)) were added in a sequential order. The mixture was stirred for 10 minutes and extracted with EtOAc (2 x 40 mL). The combined organic layers were dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, 50% - 60 % EtOAc in hexane) afforded the pyran **12** as a pale yellow oil (522 mg, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (5H, m), 4.48 (2H, abq, *J* = 12.8 Hz), 4.27 (1H, m), 4.03 (1H, m), 3.95 (1H, m), 3.58-3.46 (3H, m), 3.29 (3H, s), 2.45 (2H, m), 1.87-1.72 (3H, m), 1.64-1.55 (2H, m), 1.53-1.38 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.3, 127.7, 127.5, 117.3, 75.0, 72.8, 68.8, 67.0, 66.8, 63.6, 56.2, 39.3, 37.9, 37.1, 33.6, 24.3; IR (neat) νmax 3438, 2922, 2251, 1074; $[\alpha]^{23}_D = +16.7^o$ (c = 0.55, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{19}H_{27}NO_4$ 334.1974, found: 334.1990.

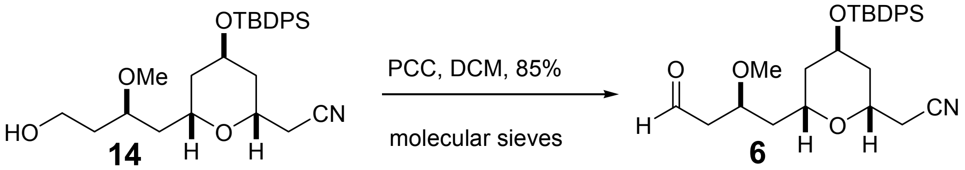


Pyran 13. A solution of alcohol **12** (630 mg, 1.89 mmol) in DMF (3.8 mL) was treated with imidazole (386 mg, 5.67 mmol) and TBDPSCl (780 mg, 2.85 mmol) in a sequential fashion. The resulting mixture was stirred for 72 h before the reaction was diluted with water (50 ml). The mixture was then extracted with EtOAc (2 x 40 mL) and the combined organic layers were washed with brine (3 x 20 mL), dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, DCM then 20 % EtOAc in hexane) afforded the pyran **13** as a pale yellow oil (1.03 g, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (4H, m), 7.44-7.25 (11H, m), 4.49 (2H, m), 4.22 (1H, m), 4.14 (2H, m), 3.55 (2H, m), 3.45 (1H, m), 3.27 (3H, s), 2.42 (2H, m), 1.82 (2H, m), 1.76 (1H, m), 1.60 (2H, m), 1.44 (1H, m), 1.35 (1H, m), 1.23 (1H, m), 1.06 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 135.7, 135.7, 133.8, 133.77, 129.9, 128.4, 127.8, 127.7, 127.69, 127.5, 117.3, 74.9, 72.9, 69.3, 67.5, 66.8, 65.5, 56.5, 39.7, 38.2, 37.8, 34.0, 26.8, 24.5, 19.1; IR (neat) νmax 2929, 2251, 1107; $[\alpha]^{23}_D = +0.65^o$ (c = 0.77, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{35}H_{45}NO_4Si$ 572.3151, found: 572.3189.

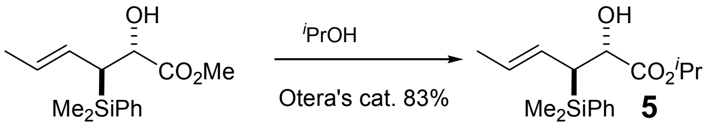


Pyran 14. A solution of benzyl ether **13** (1130 mg, 1.97 mmol) in DCM (44 mL) at -78 °C was treated with BCl_3 (13.3 mL, 1.0 M in hexane). The mixture was stirred for 20 h at this temperature before MeOH (10 ml) and a saturated aqueous $NaHCO_3$ solution (100 mL) was added. The mixture was stirred for 20 min and then extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, 45% EtOAc in hexane) afforded the pyran **14** as a pale yellow oil (957 mg, 90%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (4H, m), 7.44-7.34 (6H, m), 4.23 (1H, m), 4.16 (1H, m), 4.07 (1H, m), 3.77 (2H,

m), 3.59 (1H, m), 3.32 (3H, s), 2.59 (1H, br), 2.43 (2H, m), 1.86 (2H, m), 1.74 (1H, m), 1.61 (1H, m), 1.50 (1H, m), 1.44 (1H, m), 1.35 (1H, m), 1.27 (1H, m), 1.06 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 135.7, 133.8, 133.7, 130.0, 127.8, 127.8, 117.5, 77.8, 69.2, 67.7, 65.5, 60.9, 56.4, 38.8, 38.4, 37.8, 35.5, 26.9, 24.6, 19.1; IR (neat) νmax 3439, 2930, 2252, 1105; $[\alpha]^{23}_D = +6.91^\circ$ (c = 0.55, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{28}H_{39}NO_4Si$ 482.2682, found: 482.2696.



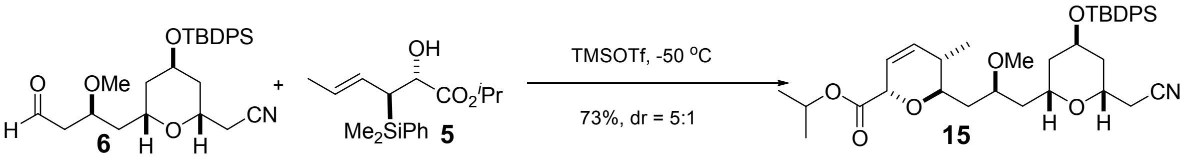
Pyran 6. A solution of alcohol **14** (475 mg, 0.99 mmol) and molecular sieves 4Å (2.4 g) in DCM (37 mL) was treated with PCC (804 mg, 2.9 mmol). The mixture was stirred for 2 h and then filtered through a short pad of silica to afford the pyran **6** as a pale yellow oil (402 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (1H, dd, J = 2.0 Hz, J = 2.4 Hz), 7.60 (4H, m), 7.44-7.34 (6H, m), 4.23 (1H, m), 4.16 (1H, m), 4.11 (1H, m), 3.88 (1H, m), 3.31 (3H, s), 2.67 (1H, d, J = 2 Hz), 2.66 (1H, d, J = 2.4 Hz), 2.43 (2H, m), 1.83 (1H, m), 1.60 (1H, m), 1.53 (1H, m), 1.49 (1H, m), 1.38-1.22 (2H, m), 1.07 (9H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 201.4, 135.5, 133.6, 135.5, 129.7, 129.6,117.2, 73.0, 68.6, 67.5, 65.4, 56.4, 47.8, 39.0, 38.2, 37.7,26.9, 24.5, 19.1; IR (neat) νmax 2930, 2251, 1724, 1427, 1105; $[\alpha]^{23}_D$ = -1.05° (c = 0.47, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{28}H_{37}NO_4Si$ 480.2525, found: 480.2587.



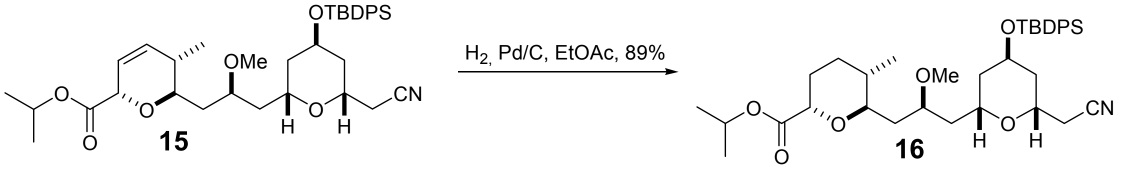
Silane 5. A solution of the methyl ester[SI3] (582 mg, 2.09 mmol) in ^{i}PrOH (15 mL) was treated with Otera's catalyst[SI4] (119 mg). The mixture was refluxed for 120 h in sealed tube (ca. 110 °C). The resulting mixture was concentrated and purified by silica column chromatography (2% EtOAc in hexane) to afford the crotyl silane **5** as a pale yellow oil (530 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, m), 7.34 (3H, m), 5.38 (1H, m), 5.25 (1H, m), 4.99 (1H, hept, J = 6.4 Hz), 4.14 (1H, m), 2.84 (1H, br d, J = 4.8 Hz), 2.06 (1H, dd, J = 2.8 Hz, 10.4 Hz), 1.59 (3H, dd, J = 2Hz, 6.8 Hz), 1.19 (3H, d, J = 6.4 Hz), 1.15 (3H, d, J = 6.4 Hz), 0.37 (3H, s), 0.31 (3H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.8, 137.7, 134.2, 128.9, 127.6, 126.8, 124.9, 71.3, 69.2, 38.2, 21.9, 21.8, 18.1, -3.8, -4.0; IR (neat) νmax 3513, 2980, 1723, 1247, 1106; $[\alpha]^{23}_D$ = +35.1° (c = 0.49, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{17}H_{26}O_3Si$ 307.1685, found: 307.1719.

[SI3] J. S. Panek, M.Yang, J. S. Solomon, *J. Org. Chem.* **1993**, *58*, 1003.

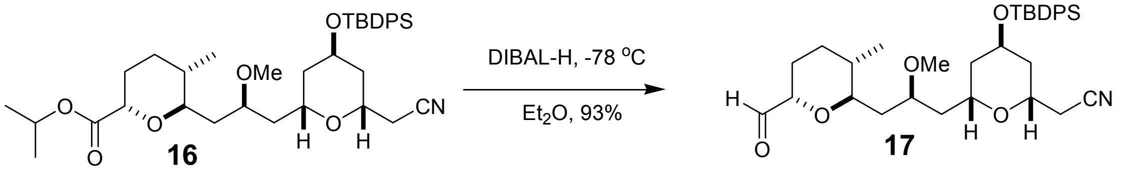
[SI4] J. Otera, N. Danoh, H. Nozaki, *J. Org. Chem.* **1991**, *56*, 5307.



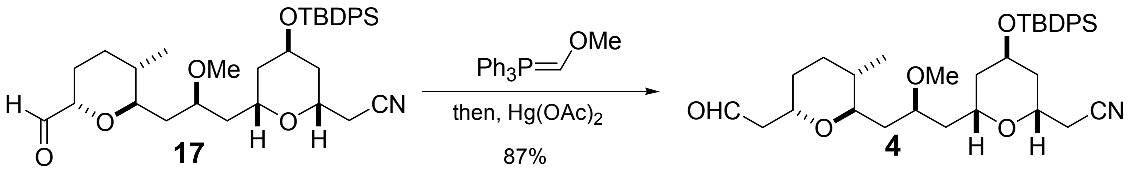
Bispyran 15. A solution of aldehyde **6** (400 mg, 0.83 mmol) and crotylsilane **5** (463 mg, 1.51 mmol) in DCM (16.7 mL) at -50 °C was treated with TMSOTf (240 mg, 1.08 mmol). The resulting mixture was stirred for 12 h at this temperature before a saturated aqueous solution of $NaHCO_3$ (50 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure provided the dihydropyrans as a mixture of diastereomers (dr = 5:1 (*trans* : *cis*), determined by ^{1}H-NMR analysis). Purification of the residue by flash chromatography (silica gel, 15-20% EtOAc in hexane) afforded the *trans*-pyran **15** (385 mg, 73%) as a single diastereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (4H, m), 7.44-7.34 (6H, m), 5.82 (1H, m), 5.72 (1H, m), 5.06 (1H, hept, *J* = 6.4 Hz), 4.63 (1H, m), 4.22 (1H, m), 4.21-4.14 (2H, m), 3.75 (1H, m), 3.65 (1H, m, *J* = 9.2 Hz), 3.4 (3H, s), 2.43 (2H, m), 2.03 (1H, m), 1.90-1.75 (3H, m), 1.66-1.49 (3H, m), 1.36- 1.29 (1H, m), 1.25 (3H, d, *J* = 6 Hz), 1.22 (3H, d, *J* = 6 Hz), 1.21 (1H, m), 1.06 (9H, s), 0.94 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.3, 135.6, 135.6, 133.8, 133.7, 133.4, 129.7, 129.7, 127.7, 127.6, 122.5, 117.3, 74.5, 74.1, 72.1, 69.4, 68.1, 67.5, 65.7, 56.7, 40.0, 39.5, 38.5, 37.9, 33.8, 26.9, 24.6, 21.8, 19.2, 17.2; IR (neat) νmax 2930, 2251, 1746, 1106; $[\alpha]^{23}_D$ = -24° (c = 0.67, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{37}H_{51}NO_6Si$ 633.3486, found: 633.3457.



Bispyran 16. A solution of olefin **15** (385 mg, 0.61 mmol) in EtOAc (23 mL) was treated with Pd/C (10 wt. %, 77 mg) and then placed under a H_2 atmosphere and stirred for 18 h. The heterogeneous solution was filtered through a pad of Celite®. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, 20% EtOAc in hexane) afforded the *trans* pyran **16** as a pale yellow oil (342 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (4H, m), 7.44-7.34 (6H, m), 5.09 (1H, hept, *J* = 6.4 Hz), 4.36 (1H, m), 4.22 (1H, m), 4.21-4.12 (2H, m), 3.66-3.59 (2H, m), 3.39 (3H, s), 2.43 (2H, m), 2.06 (1H, m), 1.87-1.72 (3H, m), 1.65-1.50 (5H, m), 1.44-1.15 (4H, m), 1.25 (3H, d, *J* = 6.8 Hz), 1.24 (3H, d, *J* = 6 Hz), 1.06 (9H, s), 0.84 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.8, 135.6, 135.6, 133.8, 133.7, 129.7, 129.7, 127.7, 127.6, 117.2, 75.7, 74.5, 72.5, 69.4, 67.9, 67.5, 65.7, 56.9, 40.4, 39.6, 38.5, 37.8, 35.1, 28.7, 27.0, 26.9, 24.6, 21.9, 21.8, 19.2, 18.2; IR (neat) νmax 2929, 2251, 1738, 1106; $[\alpha]^{23}_D$ = +14.4° (c = 0.52, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{37}H_{53}NO_6Si$ 636.3676, found: 636.3668.

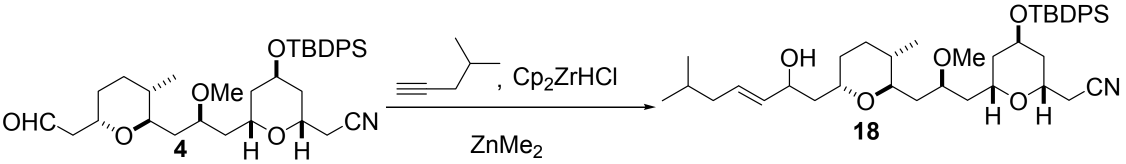


Aldehyde 17. A solution of ester **16** (110 mg, 0.17 mmol) in Et_2O (4.3 mL) at -78 °C was treated with DIBAL-H (0.363 mL, 1.0 M in hexane). The mixture was stirred for 1 h before MeOH (1 mL) was added at -78 °C followed by the addition of a saturated aqueous solution of Rochelle's salts (10 mL). The mixture was stirred for 1.5 h and slowly warmed to room temperature. The reaction mixture was acidified (5% aqueous HCl, 3 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, 40% EtOAc in hexane) afforded the aldehyde**17** as a pale yellow oil (92 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (1H, d, *J* = 2 Hz), 7.62 (4H, m), 7.44-7.33 (6H, m), 4.23 (1H, m), 4.21-4.08 (3H, m), 3.71 (1H, m), 3.41 (1H, m), 3.35 (3H, s), 2.44 (2H, m), 2.09 (1H, m), 1.87-1.69 (3H, m), 1.66- 1.45 (5H, m), 1.42-1.22 (4H, m), 1.07 (9H, s), 0.82 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 205.8, 135.6, 133.7, 133.7, 129.8, 129.7, 127.7, 127.6, 117.2, 78.8, 77.1, 73.9, 69.2, 67.5, 65.7, 56.7, 39.8, 38.7, 38.6, 37.8, 34.7, 28.9, 26.9, 24.6, 23.9, 19.2, 17.9; IR (neat) νmax 2929, 2251 1732, 1105; $[\alpha]^{23}_D$ = +35.3° (c = 0.30, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{34}H_{47}NO_5Si$ 578.3257, found: 578.3353.



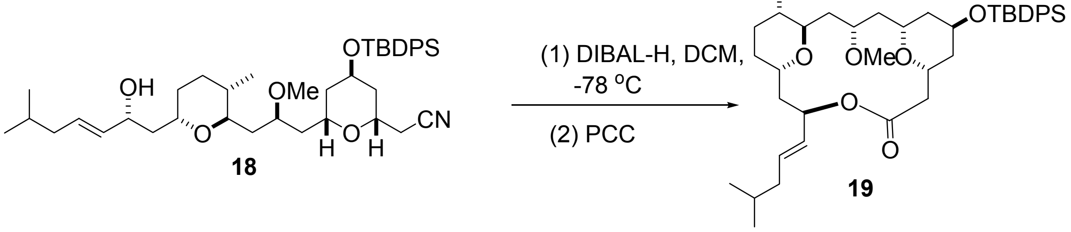
Preparation of Wittig reagent (0.25 M in THF): To a suspension of (methoxymethyl)triphenylphosphonium chloride (800 mg) in THF (6.32 mL) at -78 °C was treated with LiHMDS (2.12 mL, 1.0 M in THF). The reaction mixture was then warmed to room temperature. A deep red solution formed.

Aldehyde 4. A solution of aldehyde **17** (92 mg, 0.16 mmol) in THF (2 mL) at -78 °C was treated with the solution (1.5 mL) prepared above. The mixture was stirred for 4.5 h and slowly warmed to room temperature before it was diluted with water (10 mL). The reaction mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvents afforded the enol ether as a dark yellow oil. A solution of the crude enol ether in THF (4.8 mL) and water (2.4 mL) was treated with mercury acetate (432 mg). The reaction mixture was stirred for 15 minutes before KI solution (8% in water, 25 mL) was added. The resulting mixture was stirred for another 20 minutes and was extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvents under reduced pressure and purification of the residue by flash column chromatography (silica gel, 30-50% EtOAc in hexane) afforded the aldehyde **4** as a pale yellow oil (82 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, m), 7.62 (4H, m), 7.44-7.33 (6H, m), 4.38 (1H, m), 4.22 (1H, m), 4.18 (1H, m), 4.09 (1H, m), 3.55 (1H, m), 3.45 (1H, m), 3.26 (3H, s), 2.85 (1H, ddd, J = 2.4 Hz, 8.4 Hz, 16 Hz), 2.44 (2H, m), 2.42 (1H, ddd, ovrlp, *J* = 1.2 Hz, 4.8 Hz), 1.75- 1.23 (13H, m), 1.06 (9H, s), 0.97 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 201.6, 135.6, 133.7, 129.8, 127.7, 127.6, 117.3, 74.1, 73.2, 69.2, 67.5, 66.5, 65.7, 56.6, 46.7, 39.7, 38.6, 38.0, 37.9, 33.5, 27.6, 26.9, 26.2, 24.6, 19.2, 18.2; IR (neat) νmax 2929, 2251 1725, 1105; $[\alpha]^{23}_D = +20.4^\circ$ (c = 0.30, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{34}H_{47}NO_5Si$ 591.3380, found: 591.3379.



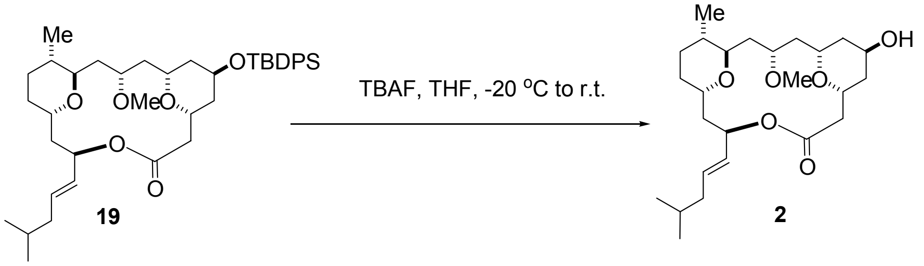
To a suspension of bis(cyclopentadienyl)zirconium chloride hydride (250 mg, 0.97 mmol) in DCM (4.4 mL) at room temperature was treated with 4-methyl-1-pentyne (114.3 μL, 0.97 mmol). The mixture was stirred for 15 minutes until a clear yellow solution formed. The resulting solution was cooled to -60 °C and was treated with $ZnMe_2$ (0.486 mL, 2.0 M in toluene). The reaction mixture was stirred for 20 minutes at this temperature and was warmed to 0 °C and stirred for another 5 minutes.

Allylic alcohol 18. A solution of aldehyde **4** (115 mg, 0.19 mmol) in DCM (5 mL) was cooled to 0 °C before being transferred to the vinyl zinc solution prepared as described above. The mixture was stirred at 0 °C for 3.5 h before a saturated aqueous solution of NH_4Cl (10 mL) was added. The reaction mixture was extracted with DCM (3 x 10 mL). The combined organic layers were washed by brine (20 mL), dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of solvent and a filtration through a short pad of silica (80% EtOAc in hexane) afforded the alcohol as a mixture of diastereomers (105 mg, 80%, dr = 2:1). The resulting mixture was subjected to careful purification by flash chromatography (10% - 12.5% - 15% EtOAc in DCM) to afford desired alcohol **18** (72 mg, 55%) as a single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.59 (4H, m), 7.44-7.33 (6H, m), 5.64 (1H, m), 5.48 (1H, dd, *J* = 6 Hz, 11.2 Hz), 4.33 (1H, m), 4.22 (1H, m), 4.18 (1H, m), 4.06 (2H, m), 3.60 (2H, m), 3.31 (3H, s), 2.42 (2H, m), 2.09 (1H, m), 1.97-1.22 (18H, m), 1.06 (9H, s), 0.97 (3H, d, *J* = 6.4 Hz), 0.86 (3H, d, *J* = 6.8 Hz) 0.85 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 135.7, 134.3, 133.9, 133.8, 129.9, 129.4, 127.8, 127.8, 117.4, 74.4, 72.9, 69.2, 68.7, 67.6, 67.4, 65.7, 56.5, 41.6, 40.0, 39.4, 38.6, 37.9, 37.6, 33.5, 28.2, 27.8, 26.9, 26.3, 24.6, 22.2, 22.2, 19.1, 18.4; IR (neat) νmax 3456, 2928, 1427, 1105; $[\alpha]^{23}_D = +16.5^\circ$ (c = 0.32, CH_2Cl_2); CIHRMS $[M]^+$ calculated for $C_{41}H_{61}NO_5Si$ 675.4319, found: 675.4334.

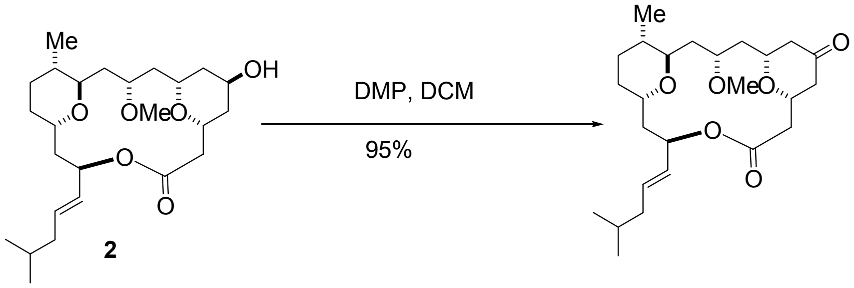


Macrolide 19. A solution of nitrile **18** (55 mg, 0.082 mmol) in DCM (2.0 mL) at -78 °C was slowly treated with DIBAL-H (0.212 mL, 1.0 M in hexane). The mixture was stirred for 2 h at this temperature before HCl (1.0 N, 3 mL) was added at -78 °C and the resulting mixture was stirred for 20 minutes and slowly warmed to room temperature. The reaction mixture was extracted with EtOAc (3 x 10 mL). The

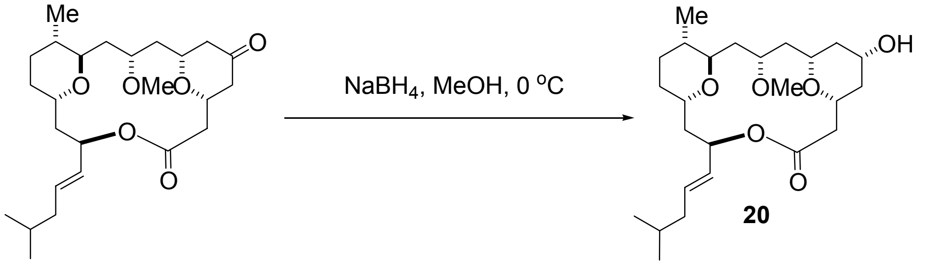
combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, EtOAc) afforded the crude aldehyde. The mixture was kept at room temperature for 18 h. Purification by flash column chromatography (silica gel, 20% EtOAc in hexane) afforded the lactol as a thick oil (29 mg, 55%) and the polar residue was kept at room temperature for another 5 days before another portion of lactol (5 mg, 9%) was isolated. A solution of lactol (25 mg) and molecular sieves (300 mg) in DCM (3 mL) was treated with PCC (50 mg, 0.18 mmol) and the reaction mixture was stirred at room temperature for 22 hours. Purification by flash chromatography (silica gel, 20% EtOAc in hexane) afforded the lactone **19** as a thick oil (22 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (4H, m), 7.44-7.33 (6H, m), 5.70 (1H, m), 5.41-5.28(2H, m), 4.28-4.25 (2H, m), 3.93-3.87 (2H, m), 3.64 (1H, m, J = 10.8 Hz), 3.51 (1H, m, J = 10.8 Hz), 3.32 (3H, s), 2.50-2.42 (2H, m), 2.23 (1H, m, J = 12.4 Hz), 1.94-1.00 (17H, m), 1.16 (3H, d, J = 7.2 Hz), 1.09 (9H, s), 0.83 (6H, d, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 135.7, 135.7, 134.1, 134.1, 132.2, 130.2, 129.9, 129.9, 127.8, 73.6, 73.5, 70.7, 69.5, 69.4, 66.2, 63.2, 57.2, 43.2, 43.0, 41.6, 38.9, 38.6, 38.5, 35.5, 30.8, 29.6, 28.0, 27.1, 26.9, 24.0, 22.2, 19.3, 18.2; IR (neat) νmax 2928, 1741, 1111; $[\alpha]^{23}_D = +41.3^o$ (c = 0.375, CH_2Cl_2); CIHRMS $[M+1]^+$ calculated for $C_{41}H_{60}O_6Si$ 677.4193, found: 677.4228.



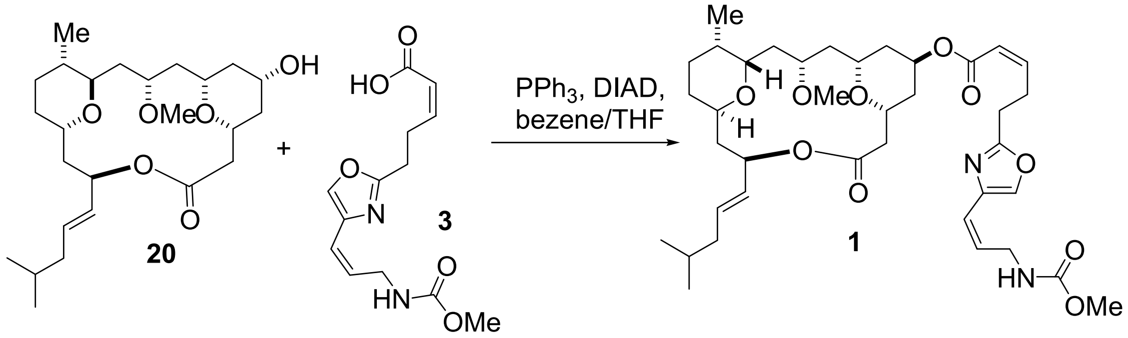
Macrolide 2. A solution of silyl ether **19** (35 mg, 0.052 mmol) in THF (3.5 mL) at -20 °C was treated with TBAF (0.26 mL, 1.0 M in THF). The mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was cooled to -20 °C and additional TBAF (0.26 mL, 1.0 M in THF) was added. The mixture was then warmed to room temperature again. This operation was repeated for another two times before the reaction mixture was diluted with an aqueous saturated solution of NH_4Cl (10 mL) and was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, 80% EtOAc in hexane) afforded the alcohol **2** as a thick oil (22.5 mg, ca. 100%). ^1H NMR (400 MHz, C_5D_5N) δ 5.85-5.76 (2H, m), 5.58 (2H, dd, J = 6.4 Hz, 15.2 Hz), 4.68 (2H, m), 4.46 (1H, m), 4.22 (1H, m, J = 11.2 Hz), 4.09 (1H, m, J = 11.2 Hz), 3.96 (1H, m), 3.78 (1H, m), 3.41 (3H, s), 2.73 (1H, dd, J = 13.2 Hz, 4 Hz), 2.57-2.49 (2H, m), 2.15 (1H, dd, J = 12.8 Hz, 10.4 Hz), 1.97-1.85 (5H, m), 1.77 (1H, m), 1.69 (2H, m), 1.55 (2H, m), 1.43-1.20 (2H, m), 1.14-1.04 (2H, m), 1.10 (3H, d, J = 6.4 Hz), 0.82 (3H, d, J = 6.8 Hz), 0.81 (3H, d, J = 6.4 Hz); ^{13}C NMR (75 MHz, C_5D_5N) δ 170.8, 132.4, 131.9, 74.3, 74.2, 71.3, 70.2, 70.0, 64.1, 63.5, 57.0, 44.2, 43.7, 42.0, 40.2, 39.9, 39.8, 36.1, 31.7, 28.6, 27.6, 24.5, 22.6, 22.5, 18.7; IR (neat) νmax 3435, 2927, 1739, 1652, 1464, 1385, 1274, 1110; $[\alpha]^{23}_D = +27^o$ (c = 0.1, EtOH); CIHRMS $[M+1]^+$ calculated for $C_{25}H_{42}O_6$ 439.3015, found: 439.3087.



A solution of alcohol **2** (19 mg, 0.043 mmol) in DCM (1.2 mL) was treated with Dess-Martin periodinane (DMP) (55.2 mg, 0.13 mmol) and pyridine (10.5 μL) in a sequential fashion. The mixture was stirred for 2 h before diluted with saturated aqueous solutions of $NaHCO_3$ and NaS_2O_3 (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and filtered through a sinter glass funnel. Removals of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, 20% EtOAc in DCM) afforded the ketone as a thick oil (18 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (1H, m), 5.33 (2H, m), 4.00 (1H, m), 3.87 (1H, m), 3.48 (3H, m), 3.35 (3H, s), 2.62 (1H, dd, *J* = 3.6 Hz, 13.2 Hz), 2.44 (2H, m), 2.36-2.22 (4H, m), 2.08 (1H, m), 1.86 (3H, m), 1.73-1.22 (6H, m), 1.28 (2H, m), 1.13 (3H, d, *J* = 7.2 Hz), 1.03 (1H, m), 0.84 (3H, s), 0.82 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 168.7, 132.9, 129.9, 74.4, 73.5, 73.4, 71.2, 63.1, 57.3, 47.8, 47.3, 43.3, 42.7, 41.5, 39.5, 35.5, 30.8, 28.0, 27.0, 24.0, 22.1, 18.1; $[\alpha]^{23}_{D}$ = +54° (c = 0.05, EtOH); IR (neat) νmax 2927, 1740, 1464, 1385, 1270, 1155; CIHRMS $[M+1]^+$ calculated for $C_{25}H_{40}O_6$ 437.2858, found: 437.2863.



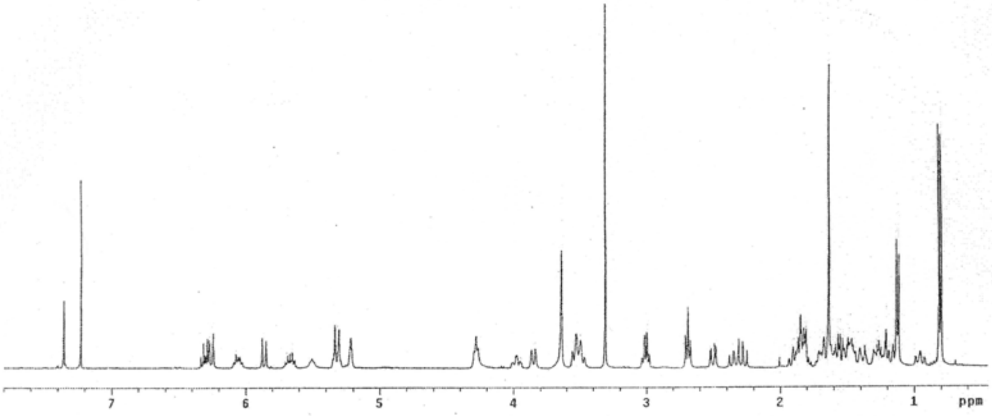
Macrolide 20. A solution of ketone prepared as described above (15 mg, 0.034 mmol) in MeOH (0.7 mL) at 0 °C was treated with $NaBH_4$ (2.6 mg, 0.068 mmol). The mixture was stirred for 0.5 h at this temperature before AcOH (19 μL) was added. The resulting mixture was concentrated and residue was purified by flash chromatography (silica gel, 80% EtOAc in hexanes) to afford the alcohol **20** as a thick oil (14 mg, 93% as a 14:1 mixture of diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ5.68 (1H, m), 5.33 (2H, m), 3.86 (2H, m), 3.68 (1H, m), 3.49 (2H, m), 3.33 (3H, s), 3.19 (1H, t, *J* = 11.2 Hz), 2.54 (1H, dd, *J* = 3.6 Hz, 13.2 Hz), 2.35 (2H, m), 2.00 (2H, m), 1.86 (4H, m), 1.69-1.39 (6H, m), 1.31- 1.18 (4H, m), 1.14 (3H, d, *J* = 5.4 Hz), 0.98 (1H, m), 0.82 (3H, d, *J* = 6.4 Hz), 0.82 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 132.4, 130.1, 73.6, 73.5, 73.0, 72.2, 70.8, 67.9, 63.0, 57.2, 43.0, 42.8, 41.5, 41.0, 40.7, 39.1, 35.4, 30.9, 28.0, 27.0, 24.0, 22.1, 18.1; $[\alpha]^{23}_{D}$ = +55° (c = 0.05, EtOH);IR (neat) νmax 3435, 2927, 1739, 1652, 1464, 1385, 1274, 1110; CIHRMS $[M+1]^+$ calculated for $C_{25}H_{42}O_6$ 439.3015, found: 439.3013.



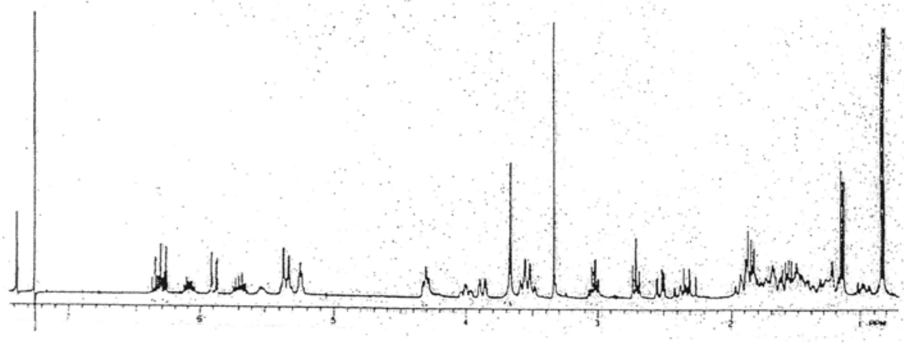
Leucascandrolide A (**1**). A solution of alcohol **20** (15 mg, 0.034 mmol), acid **3** (34.4 mg, 0.122 mmol) and triphenyl phosphine (35.53 mg, 0.135 mmol) in benzene (1.87 mL) and THF (0.5 mL) at 0 °C was treated with DIAD (26.67 μL). The mixture was stirred for 14h and warmed to room temperature. The resulting mixture was concentrated and residue was purified by flash chromatography (silica gel, 20% to 40% EtOAc in DCM) to afford the leucascandrolide A (**1**) as thick glass (18.5 mg, 77%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37 (1H, s), 6.31 (1H, m), 6.26 (1H, m), 6.07 (1H, m), 5.87 (1H, d, J = 11.6 Hz), 5.68 (1H, m), 5.52 (1H, br), 5.32 (2H, m), 5.23 (1H, t, J = 2.8 Hz), 4.29 (2H, t, J = 5.6 Hz), 3.99 (1H, m), 3.87 (1H, m), 3.66 (3H, s), 3.53 (3H, m), 3.32 (3H, s), 3.02 (2H, m), 2.70 (2H, t, J = 7.2 Hz), 2.51 (1H, dd, J = 4 Hz, 13.2 Hz), 2.32 (2H, m), 1.95-1.80 (5H, m), 1.72-1.17 (11H, m), 1.14 (3H, d, J = 7.2 Hz), 0.97 (1H, m), 0.82 (6H, d, J = 6.4 Hz) ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.5, 165.4, 160.1, 157.2, 149.4, 141.1, 136.4, 134.0, 132.5, 131.1, 120.7, 116.6, 73.6, 73.3, 70.8, 70.0, 69.6, 67.3, 63.0, 57.2, 52.1, 43.2, 42.7, 41.5, 39.3, 99.1, 35.5, 35.4, 30.9, 28.0, 27.5, 27.0, 25.6, 24.2, 22.1, 18.1; $[\alpha]^{23}_D$ = +41° (c = 0.065, EtOH); IR (neat) νmax 2953, 1717, 1276; CIHRMS $[M+1]^+$ calculated for $C_{38}H_{56}N_2O_{10}$ 700.3935, found 700.3912. The spectra data of leucascandrolide A (**1**) were in excellent agreement with those previously reported.[SI5]

[SI5] a) M. D'Ambrosio, A. Guerriero, C. Debitus, F. Pietra, *Helv. Chim. Acta.* **1996**, *79*, 51; b) K. R. Hornberger, C. L. Hamblett, J. L. Leighton, *J. Am. Chem. Soc.* **2000**, *122*, 12894.

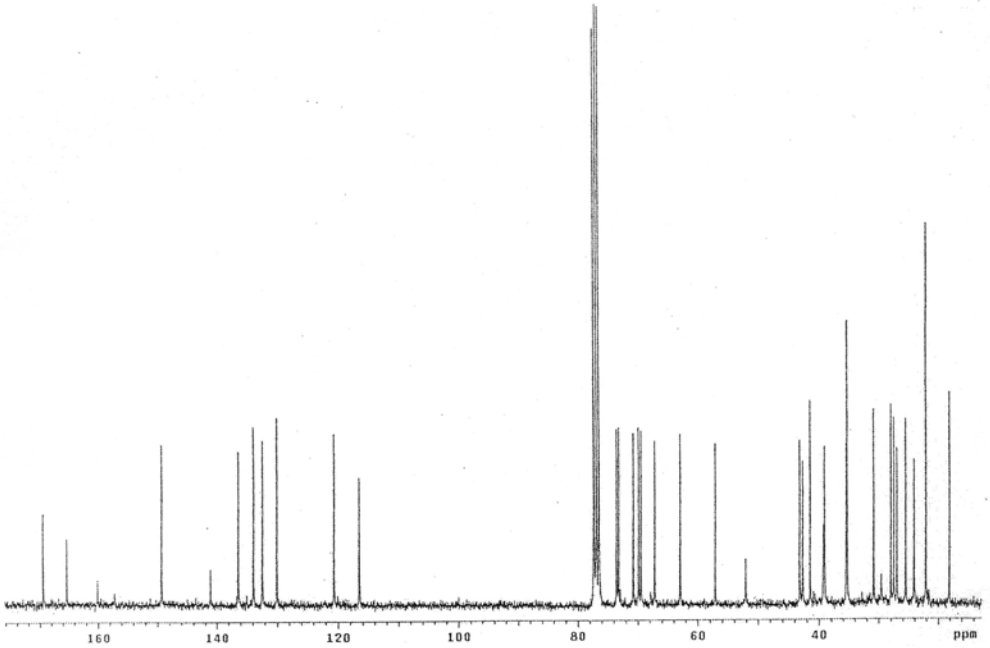
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of synthetic Leucascandrolide A



^{1}H NMR ($CDCl_3$) spectrum of natural Leucascandrolide A[SI5b]



^{13}C NMR (75 MHz, CDCl$_3$) spectrum of synthetic Leucascandrolide A



^{13}C NMR (CDCl$_3$) spectrum of natural Leucascandrolide A[SI5b]