Ru Catalyzed Alkene-Alkyne Coupling. Total Synthesis of Amphidinolide P

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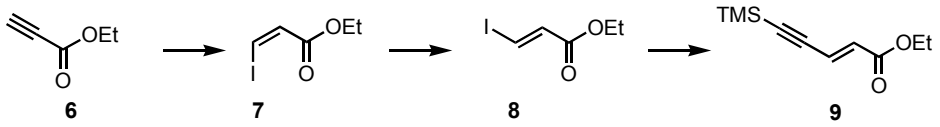
Experimentals.

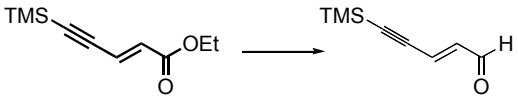


A stirred suspension of sodium iodide (dried for 12 h at 100 ºC under vacuum, 22.5 g, 0.15 mol) and acetic acid (100 mL) was heated to 70 ºC until all the solid material was dissolved. To this pale yellow solution was added ethyl propynoate (9.81 g, 0.10 mol) and the mixture was stirred for 12 h at 70 ºC. The dark brown solution was cooled to room temperature and diethyl ether (100 mL) and water (100 mL) were added. The organic layer was separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The pH of the combined organic layer was adjusted to 7 with 3 M aqueous KOH, and it was then washed with 10% aqueous $Na_2S_2O_3$ (30 mL) and brine (30 mL). The clear colorless solution was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to afford **7** (21.5 g, 0.095 mol, 95%) as a pale yellow oil and a single isomer; ν_{max}/cm^{-1} 3063, 2980, 2937, 2904, 1725, 1599, 1445, 1366, 1323, 1198, 1165, 1027, 942, 806; δ_H (300 MHz, $CDCl_3$) 1.32 (3 H, t, *J* 7.1), 4.25 (2 H, q, *J* 7.1), 6.89 (1 H, d, *J* 8.8), 7.44 (1 H, d, *J* 8.8). The spectroscopic data was consistent with the data reported in the literature (Beruben, D.; Marek, I.; Normant, J.-F.; Platzer, N. *J. Org, Chem.* **1995**, *60*, 2488)

A solution of **7** (21.5 g, 0.95 mol) in benzene (55 mL) was treated with a 47% aqueous solution of hydroiodic acid (1.6 mL) under nitrogen. The resulting mixture was heated to 80 ºC for 8 h, whereupon the dark brown solution was cooled to room temperature and diluted with diethyl ether (120 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (30 mL), 10% aqueous solution of $Na_2S_2O_3$ (30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to afford **8** (20.5 g, 0.090 mol, 95%, 16:1 *E*/*Z*) as a pale yellow oil; ν_{max}/cm^{-1} 3063, 2980, 2937, 2904, 1720, 1580, 1445, 1366, 1323, 1198, 1165, 1027, 942, 806; δ_H (300 MHz, $CDCl_3$) 1.29 (3 H, t, *J* 7.1), 4.19 (2 H, q, *J* 7.1), 6.87 (1 H, d, *J* 15.0), 7.87 (1 H, d, *J* 15.0). The spectroscopic data was consistent

with the data reported in the literature (Takeuchi, R.; Tanabe, K. ; Tanaka, S. *J. Org Chem.* **2000**, *65*, 1558).

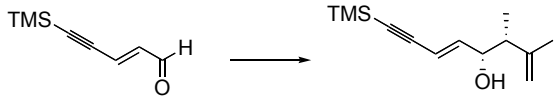
To a solution of **8** (6.87 g, 30.0 mmol) in dry triethylamine (100 mL) was added dichlorobis(triphenylphosphine)palladium (0.210 g, 0.300 mmol) and copper(I) iodide (0.028 g, 0.15 mmol). The pale yellow suspension was heated to 50 ºC and stirred until the palladium complex was dissolved (*ca.* 10 min). Trimethylsilylacetylene (3.25 g, 33.0 mmol) was added and the resulting yellow reaction mixture was stirred for 9 h at 50 ºC, during which a precipitate was formed. The dark brown mixture was cooled to room temperature, the precipitate was removed by filtration and the filter cake was washed several times with diethyl ether (40 mL). The solvent was removed under reduced pressure and the brown residue was dissolved with diethyl ether (150 mL), washed with saturated aqueous NH_4Cl (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (petroleum ether-ethyl acetate, 20:1) providing **9** (5.3 g, 26.7 mmol, 89%) as a colorless oil; R_f 0.50 (petroleum ether-ethyl acetate, 20:1); ν_{max}/cm^{-1} 2962, 2902, 2168, 2124, 1720, 1619, 1367, 1303, 1268, 1178, 1071, 960, 845, 761; δ_H (300 MHz, $CDCl_3$) 0.21 (9 H, s), 1.28 (3 H, t, *J* 7.2), 4.21 (2 H, q, *J* 7.2), 6.24 (1 H, d, *J* 15.6), 6.74 (1 H, d, *J* 15.6); δ_C (75 MHz, $CDCl_3$) –0.4, 14.1, 60.7, 101.3, 104.8, 124.8, 131.2, 165.7. The spectroscopic data was consistent with the data reported in the literature (Iijima, T.; Endo, Y.; Tsuji, M.; Kawachi, E.; Kagechika, H.; Shudo, K. *Chem. Pharm. Bull.* **1999**, *47*, 398).



9 **10**

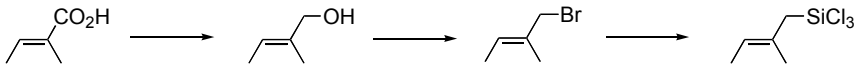
To a stirred solution of **9** (3.93 g, 20.0 mmol) in dry toluene (80 mL) was added DIBAL-H (1 M in hexane, 23.0 mL, 23.0 mmol) over a period of 30 min at –95 ºC. After the addition was complete, the reaction mixture was stirred for 30 min at this temperature and then poured into ice-cold 1M hydrochloric acid (100 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with 1M hydrochloric acid (50 mL), water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash

chromatography on silica gel (petroleum ether-diethyl ether, 20:1) to give **10** (2.10 g, 14.0 mmol, 70%) as a pale yellow oil; R_f 0.43 (petroleum ether-diethyl ether, 20:1); ν_{max}/cm^{-1} 2962, 2901, 2818, 2729, 2229, 2169, 2121, 1689, 1600, 1585, 1411, 1251, 1119, 1076, 961, 845, 761, 702, 647; δ_H (500 MHz, $CDCl_3$) 0.24 (9 H, s), 6.48 (1 H, dd, *J* 15.8, 7.6), 6.58 (1 H, dd, *J* 15.8, 0.7), 9.56 (1 H, dd *J* 7.6, 0.7); δ_C (75 MHz, $CDCl_3$) –0.6, 100.5, 111.4, 132.2, 140.1, 193.2.



10 ***syn*-11**

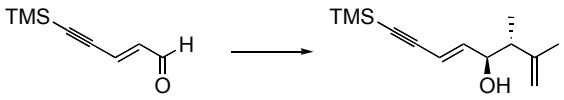
To a solution of **12** (1.13 g, 3.15 mmol) and aldehyde **10** (0.40 g, 2.37 mmol) in CH_2Cl_2 (20 mL) was added $BF_3.Et_2O$ (0.38 g, 2.68 mmol) at –78 °C. After 5 min stirring, the mixture was quenched with methanol (0.35 mL) and warmed to r.t. Ether was added and the mixture was washed with saturated aqueous $NaHCO_3$, half-saturated aqueous KF and brine, and dried over $MgSO_4$. The volatiles were removed *in vacuo* and the residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 19:1 to 9:1) to give alcohol ***syn*-11** as a colorless oil (586 mg, quant.) and as an inseparable 2.6:1 *syn*/*anti* mixture (Found: C, 69.96; H, 9.76. $C_{13}H_{22}OSi$ requires C, 70.21; H, 9.97%); R_f 0.26 (petroleum ether-ethyl acetate, 9:1); ν_{max}/cm^{-1} 3417, 2964, 1453, 1376, 1251, 955, 844, 760; δ_H (300 MHz, $CDCl_3$, minor isomer in brackets) 0.17 (9 H, s), 1.04 (0.98) (3 H, d, *J* 7.0), 1.73 (1.71) (3 H, s), 2.22-2.30 (1 H, m), 4.11-4.18 (3.92) (1 H, m), 4.80 (4.85) (1 H, s), 4.90 (4.92), (1 H, s), 5.76 (1 H, dd, *J* 16.0, 1.5), 6.19 (6.17) (1 H, dd, *J* 16.0, 5.0); δ_C (75 MHz, $CDCl_3$, minor isomer in brackets) –0.1, 13.5 (15.4), 21.4 (18.8), 46.3 (47.9), 72.7 (73.6), 94.9, 103.3, 109.9 (111.4), 112.4 (113.7), 145.1 (144.5), 146.6 (146.3).



14

To a suspension of lithium aluminium hydride in ether (400 mL) at 0 °C was added a solution of tiglic acid (8.66 g, 86.49 mmol) in ether (100 mL) dropwise over 45 min. The mixture was stirred for another 1.5 h, allowed to gradually warm to *ca.* 10 °C and recooled to 0 °C. Water (4 mL) was added followed with 15% aqueous NaOH (4 ml) and water (12 mL). After stirring for

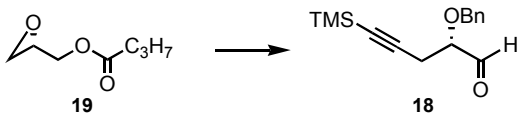
30 min, the mixture was filtered through a sintered funnel and the cake was well washed with ether. The combined filtrate was washed with saturated aqueous sodium bicarbonate and dried over $MgSO_4$. The diethyl ether was distilled through a 15 inches packed column and the residue was distilled using a short path distillation apparatus to give *E*-2-methylbut-2-en-1-ol (2.46 g, 28.56 mmol, 33%) as a colorless oil (bp 129-133 °C). A portion (1.0 g, 11.35 mmol) was redissolved in ether (20 mL), cooled to –12 °C (ice+brine) and PBr_3 (1.37 g, 5.09 mmol) was added. After 2 h, the solution was diluted with ether, washed with saturated aqueous sodium bicarbonate and brine. After drying the mixture over Na_2SO_4, the diethyl ether was distilled through a 15 inches packed column. Bromo-2-methylbut-2-ene (Haynes, R. K.; Katsifis, A. G.; Vonwiller, S. C.; Hambleyf, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5423) was obtained as a 78% w/w solution in ether (1.54 g, 7.5 mmol, 73%), as judged by ^{1}H NMR spectroscopy analysis; δ_H (300 MHz, $CDCl_3$) 1.63 (3 H, br. d, *J* 7.0), 1.76 (3 H, br. s), 3.98 (2 H, s), 5.69 (1 H, d, *J* 7.0). To a suspension of CuCl (12 mg, 0.12 mmol) and triethylamine (0.38 g, 3.73 mmol) in ether (2 mL) at 0 °C was added a mixture of trichlorosilane (0.51 g, 3.76 mmol) and bromo-2-methylbut-2-ene (78% w/w solution in ether, 0.64 g, 3.09 mmol) in ether (2.5 mL). After 75 min, the mixture was warmed to r.t. and after another 2.5 h, it was filtered under argon (a two-neck flask was fitted with a Schlenk filter and a short path distillation apparatus) and the solvent was distilled off. The residue was transferred to a bulb-to-bulb distillation apparatus under argon. Distillation (*ca.* 30 Torr, oven temperature 110 °C) gave the title compound (0.25 g, 1.16 mmol, 37%) as a colorless oil, which gradually turns cloudy and then lumpy; δ_H (300 MHz, $CDCl_3$) 1.65 (3 H, d, *J* 7.0), 1.78 (3 H, s), 2.33 (2 H, br. s), 5.37 (1 H, q, *J* 7.0). The data was consistent with the data reported in the literature (Aoki, S.; Mikami, K.; Terada, M.; Nakai, T. *Tetrahedron* **1993**, *49*, 1783).



10 ***anti*-11**

To a solution of aldehyde **10** (30 mg, 0.197 mmol) in CH_2Cl_2 (0.4 mL) was added HMPA (35 mg, 0.195 mmol). The solution was cooled to –78 °C and silane **14** (84 mg, 0.39 mmol) was added. After 12 h at –78 °C, the mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The volatiles were removed *in vacuo* and

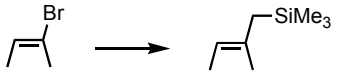
the residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 19:1 to 9:1) to give alcohol ***anti*-11** as a colorless oil (10 mg, 0.045 mmol, 23%) and as an inseparable 1:19 *syn*/*anti* mixture of diastereomers; ν_{max}/cm^{-1} 3417, 2964, 1453, 1376, 1251, 955, 844, 760; δ_H (300 MHz, $CDCl_3$) 0.17 (9 H, s), 0.98 (3 H, d, *J* 7.0), 1.71 (3 H, s), 2.22-2.30 (1 H, m), 3.92 (1 H, m), 4.85 (1 H, s), 4.92, (1 H, s), 5.76 (1 H, dd, *J* 16.0, 1.5), 6.17 (1 H, dd, *J* 16.0, 5.0); δ_C (75 MHz, $CDCl_3$) –0.1, 15.4, 18.8, 47.9, 73.6, 94.9, 103.3, 111.4, 113.7, 144.5, 146.3.



To a solution of trimethylsilylacetylene (9.44 g, 96.14 mmol) in ether (400 mL) at –78 °C was added *n*BuLi (2.58 M in hexanes, 35.5 mL, 91.6 mmol) dropwise over 20 min and the mixture was stirred for another 25 min, whereupon $AlMe_3$ (2.0 M in hexanes, 45.8 mL, 91.6 mL) was added dropwise over 25 min. The mixture was warmed up to –40 °C and stirred at this temperature for 35 min, whereupon it was recooled to –78 °C. (*S*)-Glycidyl butyrate (**19**) (10.15 g, 70.40 mmol) in ether (70 mL) was added *via* cannula over 15 min and after 10 min, $BF_3.Et_2O$ (12.99 g, 91.6 mmol) was added over 10 min. The mixture was stirred at –78 °C for 25 min, whereupon 0.5M aqueous HCl (200 mL) was carefully added and the cooling bath was removed. Upon reaching r.t., 0.5M aqueous HCl (100 mL) and EtOAc (800 mL) were added. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine. The combined organic phase was dried over $MgSO_4$ and the volatiles were removed *in vacuo* to give alcohol **20** (16.97 g) as a colorless oil. A portion (16.36 g) was redissolved in dry dioxane (200 mL). Freshly prepared crude benzyl trichloroacetimidate (33.9 g, 134 mmol) was added, followed with triflic acid (1.96 g, 13.08 mmol). An exothermic reaction ensued and after 15 min, TLC analysis showed complete conversion. After 25 min, water (100 mL) and ether (400 mL) were added and the mixture was stirred for 15 min. After further dilution with ether (300 mL), the combined organic phase was washed with saturated aqueous $NaHCO_3$ and brine. The combined aqueous phase was back-extracted once with ether. After drying the combined organic phase over $MgSO_4$, the volatiles were removed *in vacuo* to give a residue (22.5 g, quant.) which was used without further purification. An analytical sample was obtained by purification by silica

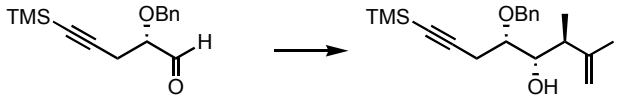
gel flash chromatography (petroleum ether-ethyl acetate, 19:1) to afford the alkyne **21** as a colorless oil (Found: C, 68.82; H, 8.70. $C_{19}H_{28}O_3Si$ requires C, 68.63; H, 8.49%); $[\alpha]_D^{22}$ +10.9 (*c* 0.68, $CHCl_3$); R_f 0.60 (petroleum ether-ethyl acetate, 4:1); ν_{max}/cm^{-1} 2962, 1740, 1250, 1176, 1101, 843, 698; δ_H (400 MHz, $CDCl_3$) 0.15 (9 H, s), 0.95 (3 H, t, *J* 7.0), 1.66 (2 H, sex, *J* 7.0), 2.31 (2 H, t, *J* 7.0), 2.52 (1 H, dd, *J* 17.0, 7.0), 2.57 (1 H, dd, *J* 17.5, 6.0), 3.78 (1 H, m), 4.17 (1 H, dd, *J* 11.5, 5.5), 4.31 (1 H, dd, *J* 11.5, 4.0), 4.64 (1 H, d, *J* 12.0), 4.68 (1 H, d, *J* 12.0), 7.28-7.42 (5 H, m); δ_C (100 MHz, $CDCl_3$) 0.0, 13.7, 18.4, 23.0, 36.1, 64.6, 71.9, 75.2, 87.0, 102.5, 127.6, 127.8, 128.4, 138.0, 173.4.

To a mixture of crude **21** (23.4 g, 70.4 mmol) in CH_2Cl_2 (300 mL) at –78 °C was added DIBAL-H (1.0M in hexane, 93 mL, 93 mmol) over 30 min. The mixture was stirred at –78 °C for another 15 min, whereupon a saturated solution of Rochelle salt (300 mL) was added. The mixture was allowed to warm up to r.t. and after 2 h of vigorous stirring, the two phases were separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and the volatiles were removed *in vacuo* to give the alcohol **22** (18.5 g) as a colorless oil. A portion (223 mg) was redissolved in CH_2Cl_2 (1 mL). To a solution of DMSO (265 mg, 3.39 mmol) in CH_2Cl_2 (4 mL) at –78 °C was added oxalyl chloride (215 mg, 1.70 mmol) and the mixture was stirred for 20 min, whereupon the solution of alcohol was added dropwise. After another 20 min at –78 °C, triethylamine (0.43 g, 4.23 mmol) was added and the cooling bath was removed. Upon reaching 0 °C, the mixture was partitioned between ether and saturated aqueous NH_4Cl. The organic phase was washed with saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. Concentration *in vacuo* and purification by flash silica gel column chromatography (petroleum ether-ethyl acetate, 9:1 to 4:1) afforded aldehyde **18** (163 mg, 0.63 mmol, 71%) as a yellow oil (Found: *[M–H]*$^+$, 259.1144. $C_{15}H_{20}OSi$ requires *[M–H]* 259.1154, 3.9 ppm, EIMS); $[\alpha]_D^{22}$ +32.6 (*c* 2.00, $CHCl_3$); R_f 0.14 (petroleum ether-ethyl acetate, 9:1); ν_{max}/cm^{-1} 2959, 2342, 2179, 1738, 1455, 1250, 1112, 1030, 845, 760, 698; δ_H (300 MHz, $CDCl_3$) 0.17 (9 H, s), 2.63 (1 H, dd, *J* 17.5, 7.0), 2.72 (1 H, dd, *J* 17.5, 6.0), 3.94 (1 H, dt, *J* 7.0, 6.0), 4.75 (2 H, s), 7.28-7.42 (5 H, m), 9.68(1 H, br. s); δ_C (100 MHz, $CDCl_3$) –0.1, 21.8, 72.7, 80.8, 87.8, 100.9, 128.0, 128.1, 128.5, 137.0, 201.2; EIMS *m/z* 259 [$(M–H)^+$, 6], 231 [$(M–CHO)^+$, 42), 91 ($PhCH_2$, 100).



17

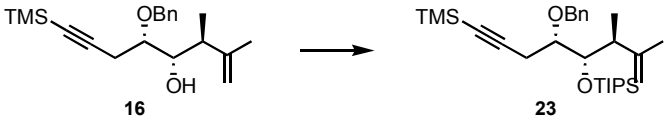
To a mixture of 2-bromo-2-butene (Aldrich, 7:3 mixture of isomers, 5.04 g, 37.37 mmol) and $Ni(acac)_2$ (0.58 g, 2.25 mmol) in ether (20 mL) at 0 °C was added trimethylsilylmagnesium chloride (1.0M in ether, 49 mL, 49 mmol) over 15 min. The mixture was warmed up to r.t. and stirred for another 21 h, whereupon saturated aqueous NH_4Cl was added. The solids were dissolved by vigorous stirring for 10 min and the aqueous phase was extracted several times with pentane. The combined organic phase was dried over $MgSO_4$, filtered and concentrated by distillation using a 10 cm Vigreux column. The residue was distilled with a Kugelrohr apparatus (oven temperature 170 °C) to give the product as a colourless oil (0.80 g). The viscous brown residue was further distilled while applying a slight vacuum (oven temperature 170 °C) to afford a pale yellow oil (1.99 g). Both fractions were of satisfactory purity as judged using ^1H NMR spectroscopy and were combined to give the title compound **17** (2.79 g, 19.6 mmol, 52%) as a pale yellow oil and a 1:1 *E*/*Z* mixture; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.03 (9 H, s), 1.46-1.67 (8 H, m), 4.95-5.05 and 5.06-5.14 (1 H, m). These data were consistent with those reported in the literature (Ishiara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490).



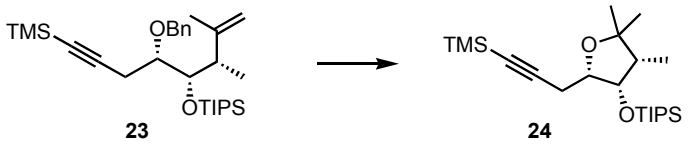
18 **16**

To a solution of **18** (1.07 g, 4.10 mmol) in CH_2Cl_2 (12 mL) and pentane (11 mL) at –110 °C (ethanol- liquid N_2 bath) was added $SnCl_4$ (1.0M in CH_2Cl_2, 4.1 mL, 4.1 mmol) over 5 min. The bath was removed and the dark orange mixture was stirred until it became homogeneous (*ca.* 3 min), whereupon it was lowered back into the cooling bath and stirred for 10 min. Silane **17** (1.17 g, 8.22 mmol) was added neat dropwise. After 15 min, saturated aqueous $NaHCO_3$ (5 mL) was added and the cooling bath was removed. Upon reaching r.t. the mixture was diluted with ethyl acetate (50 mL) and saturated aqueous $NaHCO_3$ (25 mL). The white precipitate that formed was filtered off through celite. The two phases were separated and the organic phase was washed with brine and dried over $MgSO_4$. Concentration *in vacuo* and purification by flash

silica gel column chromatography (petroleum ether-ethyl acetate, 19:1) afforded the alcohol **16** (1.04 g, 3.15 mmol, 77%) as a pale yellow oil and an inseparable 9:1 mixture of diastereomers (Found: C, 72.80; H, 9.37. $C_{20}H_{30}O_2Si$ requires C, 72.67; H, 9.15%); $[\alpha]_D^{22}$ +13.8 (*c* 0.55, $CHCl_3$); R_f 0.13 (petroleum ether-ethyl acetate, 19:1); ν_{max}/cm^{-1} 3565, 2962, 2342, 2176, 1738, 1542, 1250, 1063, 1029, 843, 760, 698; δ_H (500 MHz, $CDCl_3$, minor diastereomer in brackets) 0.15 (0.14) (9 H, s), 0.91 (1.16) (3 H, d, *J* 7.0), 1.71 (1.68) (3 H, s), 2.47 (1 H, dq, *J* 9.0, 7.0), 2.65 (1 H, dd, *J* 17.0, 7.0), 2.69 (1 H, dd, *J* 17.0, 6.0), 3.58 (1 H, dd, *J* 9.0, 2.0), 3.65 (1 H, ddd, *J* 7.0, 6.0, 2.0), 4.54 (4.50) (1 H, d, *J* 11.5), 4.80 (4.70) (1 H, d, *J* 11.5), 4.80-4.84 (4.72-4.77) (2 H, m), 7.30-7.37 (5 H, m); δ_C (125 MHz, $CDCl_3$) 0.0, 15.7, 18.7, 22.3, 44.0, 72.3, 73.5, 76.5, 86.8, 104.1, 112.6, 127.9, 128.1, 128.4, 137.9, 147.7.

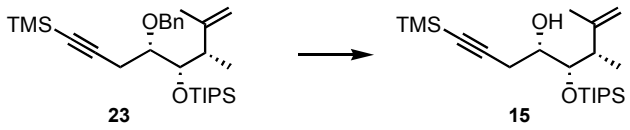


To a solution of **16** (3.0 g, 9.07 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added 2,6-lutidine (3.9 g, 36.05 mmol) and TIPSOTf (8.3 g, 27.16 mmol). The solution was warmed up to 24 °C and stirred for 6 h, whereupon it was diluted with ether and washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$ and brine. After drying over $MgSO_4$, the mixture was concentrated *in vacuo*, and the residue was purified by flash silica gel column chromatography (petroleum ether-ethyl acetate, 1 to 3%) to give the alkyne **23** (3.63 g, 7.45 mmol, 82%) as a colorless oil (Found: *[M–C_3H_7]*$^+$, 443.2808. $C_{29}H_{50}O_2Si_2$ requires *[M–C_3H_7]* 443.2802, 1.4 ppm, EIMS); $[\alpha]_D^{23}$ +26.7 (*c* 1.07, $CHCl_3$); R_f 0.20 (petroleum ether-ethyl acetate, 49:1); ν_{max}/cm^{-1} 2945, 2867, 1464, 1250, 1094, 884, 843, 679; δ_H (400 MHz, $CDCl_3$) 0.15 (9 H, s), 1.05 (21 H, s), 1.17 (3 H, d, *J* 7.0), 1.80 (3 H, s), 2.42-2.50 (1 H, m), 2.49 (1 H, dd, *J* 17.0, 5.0), 2.69 (1 H, dd, *J* 17.0, 5.0), 3.51 (1 H, q, *J* 5.0), 4.13 (1 H, t, *J* 5.0), 4.51 (1 H, d, *J* 12.0), 4.68 (1 H, d, *J* 12.0), 4.77 (1 H, br. s), 4.79 (1 H, br. s), 7.23-7.38 (5 H, m); δ_C (125 MHz, $CDCl_3$) 0.0, 13.1, 15.9, 18.3, 21.2, 21.8, 44.3, 71.4, 75.0, 79.5, 86.1, 104.6, 112.0, 127.2, 127.4, 128.0, 138.9, 147.9; ESIMS *m/z* 509 [$(M+Na)^+$, 100), 487 (MH+, 40).



23 **24**

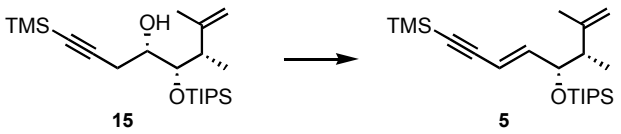
To a stirred solution of **23** (19 mg, 0.039 mmol) in CH_2Cl_2 (0.4 mL) at –78 °C was added 9-Br-9-BBN (1.0 M in CH_2Cl_2, 0.05 mL, 0.05 mmol) and the mixture was stirred for 5 min, whereupon acetic acid (15 μl) was added and the resulting red solution was warmed up to 0 °C. 1M Aqueous $Na_2S_2O_3$ was added, followed with brine, and the mixture was extracted with ether. After drying over $MgSO_4$, the mixture was concentrated *in vacuo*, and the residue was purified by flash silica gel column chromatography (petroleum ether-ether, 0 to 3%) to give **24** (9 mg, 0.022 mmol, 59%) as a colorless oil; $[\alpha]_D^{23}$ +29.3 (*c* 1.39, $CHCl_3$); R_f 0.10 (petroleum ether-ether, 9:1); ν_{max}/cm^{-1} 2962, 2868, 2168, 1465, 1249, 1168, 1140, 1059, 1014, 843, 680; δ_H (500 MHz, $CDCl_3$) 0.13 (9 H, s), 1.01 (3 H, d, *J* 7.5), 1.13 (21 H, s), 1.17 (3 H, s), 1.20 (3 H, s), 2.00 (1 H, qd, *J* 7.5, 4.5), 2.47 (1 H, dd, *J* 17.0, 5.5), 2.63 (1 H, dd, *J* 17.0, 8.0), 4.00 (1 H, ddd, *J* 8.0, 5.5, 4.0), 4.43 (1 H, dd, *J* 4.5, 4.0).



23 **15**

To a solution of **23** (3.63 g, 7.45 mmol) in a 9:1 mixture of dichloroethane-aqueous buffer 7 (50 mL) was added DDQ (3.38 g, 14.89 mmol), and the solution was heated to reflux for 45 min. After allowing the mixture to cool down to r.t., it was partitionned between water and ether. The organic phase was washed three times with water and brine. The combined aqueous phase was back-extracted once with ether. After drying over $MgSO_4$, the combined organic phase was concentrated *in vacuo*, and the residue was purified by flash silica gel column chromatography (petroleum ether-ether, 2 to 3%) to give alcohol **15** (2.43 g, 6.12 mmol, 82%) as a colorless oil (Found: C, 66.61; H, 11.36. $C_{22}H_{44}O_2Si_2$ requires C, 66.60; H, 11.18%); $[\alpha]_D^{23}$ +3.5 (*c* 0.72, $CHCl_3$); R_f 0.32 (petroleum ether-ether, 19:1); ν_{max}/cm^{-1} 3452, 2945, 2868, 2175, 1464, 1250, 1104, 1053, 1016, 883, 844, 680, 652; δ_H (500 MHz, C_6D_6) 0.17 (9 H, s), 1.09 (21 H, s), 1.32 (3 H, d, *J* 7.0), 1.87 (3 H, s), 2.43-2.50 (1 H, m), 2.51 (1 H, dd, *J* 16.5, 9.5), 2.59 (1 H, dd, *J* 16.5, 5.0), 2.75 (1 H, d, *J* 9.5), 3.94 (1 H, tdd, *J* 9.5, 5.0, 1.5), 4.44 (1 H, dd, *J* 3.5, 1.5), 4.87 (1 H, br.

s), 4.95 (1 H, br. s); δ_C (100 MHz, $CDCl_3$) 0.0, 12.3, 12.9, 18.2, 23.2, 27.3, 46.0, 67.8, 71.7, 86.7, 103.6, 112.2, 145.8.

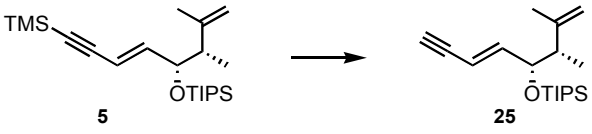


15 **5**

To a solution of **15** (1.73 g, 4.36 mmol) and triphenylphosphine (3.46 g, 13.19 mmol) in dry toluene (20 mL) was added diisopropyl azodicarboxylate (2.67 g, 13.20 mmol) and the flask was lowered into a preheated oil bath (80 °C). After stirring at this temperature for 20 min, the volatiles were removed *in vacuo* and the residue was purified by flash silica gel column chromatography (petroleum ether) to give alkyne **5** (1.37 g, 3.61 mmol, 83%) as a colorless oil and an 8:1 inseparable *E*/*Z* mixture (Found: C, 69.59; H, 11.14. $C_{22}H_{42}OSi_2$ requires C, 69.77; H, 11.18%); $[\alpha]_D^{23}$ +1.7 (*c* 3.41, $CHCl_3$); R_f 0.40 (petroleum ether); ν_{max}/cm^{-1} 2945, 2868, 2361, 2134, 1464, 1250, 1059, 958, 883, 843, 760, 679, 654;

***E* isomer**: δ_H (500 MHz, $CDCl_3$) 0.18 (9 H, s), 0.97 (3 H, d, *J* 7.0), 1.07 (21 H, s), 1.76 (3 H, s), 2.40 (1 H, br. quin., *J* 6.0), 4.46 (1 H, td, *J* 5.0, 2.0), 4.75 (1 H, s), 4.85 (1 H, s), 5.70 (1 H, dd, *J* 16.0, 2.0), 6.09 (1 H, dd, *J* 16.0, 5.0); δ_C (125 MHz, $CDCl_3$) 0.0, 12.3, 12.5, 18.1, 22.2, 47.1, 74.1, 94.1, 103.8, 110.0, 111.9, 144.5, 146.0.

***Z* isomer**: δ_H (500 MHz, $CDCl_3$) 0.17 (9 H, s), 0.97 (3 H, d, *J* 7.0), 1.06 (21 H, s), 1.80 (3 H, s), 2.40 (1 H, masked), 4.46 (1 H, masked), 4.75 (1 H, s), 4.85 (1 H, s), 5.49 (1 H, d, *J* 11.5), 5.89 (1 H, dd, *J* 11.5, 9.0).



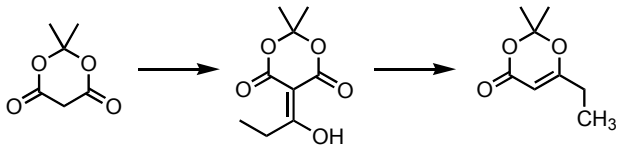
5 **25**

To a stirred solution of **5** (1.60 g, 4.22 mmol) in methanol (60 mL) was added potassium carbonate (0.59 g, 4.26 mmol) and the slurry was stirred for 2 h (a homogeneous solution was obtained after 1 h). Evaporation to dryness gave a residue that was partitioned between ether and saturated aqueous ammonium chloride. The organic phase was washed with water and brine. The aqueous phase was back-extracted once with ether. The combined organic phase was dried over $MgSO_4$ and concentrated in vacuo to give alkyne **25** (1.24 g, 4.04 mmol, 96%) as a

colorless oil and an 8:1 inseparable *E*/*Z* mixture (Found: M^+, 306.2385. $C_{19}H_{34}OSi$ requires *M* 306.2379, 2.1 ppm, EIMS); $[\alpha]_D^{23}$ +7.6 (*c* 1.56, $CHCl_3$); R_f 0.40 (petroleum ether); ν_{max}/cm^{-1} 3315, 2944, 2868, 1464, 1374, 1127, 1061, 959, 883; EIMS *m/z* 306 (M^+, 19), 237 [$(M–C_5H_9)^+$, 100].

***E* isomer**: δ_H (400 MHz, $CDCl_3$) 0.98 (3 H, d, *J* 7.2), 1.07 (21 H, s), 1.77 (3 H, s), 2.42 (1 H, broad quin., *J* 6.5), 2.85 (1 H, d, *J* 2.5), 4.46 (1 H, td, *J* 5.0, 1.5), 4.74 (1 H, s), 4.85 (1 H, s), 5.66 (1 H, ddd, *J* 16.0, 2.5, 1.5), 6.17 (1 H, dd, *J* 16.0, 5.0); δ_C (100 MHz, $CDCl_3$) 12.3, 12.4, 18.0, 22.1, 47.0, 74.1, 77.1, 82.2, 108.9, 112.0, 144.5, 145.9.

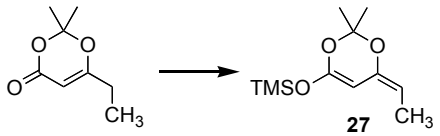
***Z* isomer**: δ_H (400 MHz, $CDCl_3$) 0.98 (3 H, d, *J* 7.2), 1.06 (21 H, s), 1.79 (3 H, s), 2.42 (1 H, masked), 2.85 (1 H, d, *J* 2.5), 4.46 (1 H, masked), 4.74 (1 H, s), 4.85 (1 H, s), 5.48 (1 H, dd, *J* 11.0, 2.5), 5.95 (1 H, dd, *J* 11.0, 9.0).



To a solution of meldrum's acid (7.20 g, 50.0 mmol) and pyridine (7.95 g, 100.0 mmol) in dry dichloromethane (40 mL) at 0 ºC was added neat propionyl chloride (5.10 g, 55.0 mmol) over a period of 10 min. The resulting mixture was stirred for 1 h at 0 ºC and then 1 h at room temperature. The reaction mixture was poured into an ice-cold solution of 2M aqueous hydrochloric acid (50 mL), diluted with dichloromethane (80 mL) and the phases were separated. The organic layer was washed with 2M aqueous hydrochloric acid (50 mL), water (2 x 50 mL), dried over $MgSO_4$ and filtered. Evaporation of the solvent under reduced pressure afforded the alkylated product (9.1 g, 48.5 mmol, 97%) as a yellow solid, which was directly used for the next step without further purification; m.p. 53-54 ºC (lit. 55 ºC); δ_H (300 MHz, $CDCl_3$) 1.24 (3 H, t, *J* 7.0), 1.72 (6 H, s), 3.08 (2 H, q, *J* 7.0), 15.37 (1 H, s). The data was consistent with the data reported in the literature (Oikawa, Y.; Sugano, K.;Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087).

A portion (5.0 g, 25.0 mmol) was dissolved in dry toluene (25 mL), dry acetone (0.71 g, 12.5 mmol) was added and the mixture was refluxed for 1 h. After the dark yellow solution was cooled to room temperature the solvent was evaporated under reduced pressure. The resulting

yellow oil was fractionally distilled to afford 6-ethyl-2,2-dimethyl-[1,3]-dioxin-4-one (3.2 g, 20.5 mmol, 82%) as a colorless oil; b.p. 52-54 ºC, 0.15 mmHg (lit. 64-65 ºC, 0.2 mmHg); ν_{max}/cm^{-1} 3102, 2991, 2944, 1731, 1633, 1463, 1392, 1300, 1205, 1079, 1014; δ_H (300 MHz, $CDCl_3$) 1.13 (3 H, t, *J* 7.5), 1.69 (6 H, s), 2.25 (2 H, q, *J* 7.5), 5.24 (1 H, s); δ_C (75 MHz, $CDCl_3$) 9.9, 24.9, 26.8, 92.3, 106.2, 161.5, 173.1. The data was consistent with the data reported in the literature (Oikawa, Y.; Sugano, K.;Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087).



27

Method A: to a solution of diisopropylamine (1.22 g, 12.0 mmol) in dry THF (20 mL) at –30 ºC was added *n*-butyllithium (1.6 M in hexanes, 7.5 mL, 12.0 mmol) dropwise. The resulting solution was stirred for 15 min and then allowed to warm to 0 ºC over a period of 30 min. To this LDA solution was added a solution of dioxenone (1.56 g, 10.0 mmol) in dry THF (5 ml) at –78 ºC and the resulting reaction mixture was stirred for 2 h –40 ºC. The yellow solution was recooled to –78 ºC and neat chlorotrimethylsilane (1.63 g, 15.0 mmol) was added. After 30 min the cooling bath was removed and the pale yellow solution was warmed to room temperature. The solvent was then evaporated *in vacuo* and the remaining solid was suspended with dry hexane (20 mL) and filtered under nitrogen. The clear yellow filtrate was concentrated *in vacuo* to a volume of approximately 5 mL and transferred into a distillation apparatus under nitrogen. Fractional distillation of the residue yielded **27** (1.91 g, 8.4 mmol, 84%) as a colorless oil and an inseparable 1.6:1 *E*/*Z* mixture; b.p. 39-41 ºC, 0.15 mm Hg (lit. 50 ºC, 0.1 mm Hg); ν_{max}/cm^{-1} 2996, 2962, 2862, 1741, 1681, 1640, 1598, 1386, 1373, 1339, 1253, 1232, 1207, 1183, 1125, 1020, 954, 875, 850, 759;

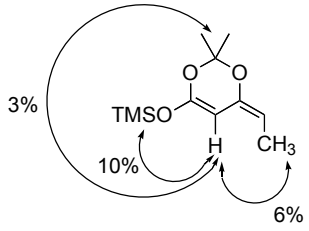
***E* isomer:** δ_H (300 MHz, $CDCl_3$) 0.27 (9 H, s), 1.51 (6 H, s), 1.57 (3 H, d, *J* 7.1), 4.58 (1 H, q, *J* 7.1), 4.76 (1 H, s); δ_C (75 MHz, $CDCl_3$) 0.3, 10.4, 24.5, 73.6, 95.7, 102.5, 145.3, 153.2.

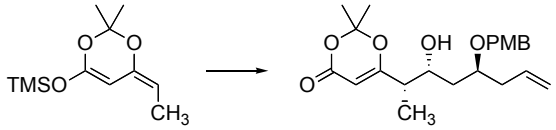
***Z* isomer**: δ_H (300 MHz, $CDCl_3$) 0.25 (9 H, s), 1.54 (6 H, s), 1.61 (3 H, d, *J* 7.1), 4.29 (1 H, q, *J* 7.1), 4.55 (1 H, s); δ_C (75 MHz, $CDCl_3$) 0.2, 9.7, 24.7, 77.5, 96.5, 102.4, 145.3, 152.0.

Method B: a schlenk-tube was charged with 1,1,1,3,3,3-hexamethyldisilazane (1.92 g, 12.0 mmol) and dry DME (30 mL) and *n*-butyllithium (1.6 M in hexanes, 7.5 mL, 12.0 mmol) was added dropwise at –30 ºC. The resulting solution was stirred for 15 min and then allowed to warm to 0 ºC over a period of 30 min. The resulting solution of LHMDS was cooled to –78 ºC and neat chlorotrimethylsilane (1.63 g, 15.0 mmol) was added *via* syringe within 2 min followed immediately by a solution of dioxenone (1.56 g, 10.0 mmol) in dry DME (5 mL). The reaction mixture was stirred for 90 min at –50 ºC and then worked up as described in method A to give **27** (1.70 g, 7.4 mmol, 74%) as a colorless oil and an inseparable 10:1 *E*/*Z* mixture.

Method C (isomerization of **27**): an NMR tube was placed under nitrogen and charged with **27** (*E*/*Z* 2:1, 50.0 mg, 0.22 mmol) and CD_2Cl_2 (0.7 mL). The resulting solution was treated with iodide (1.0 mg, 0.004 mmol) and the isomerization was followed by ^1H NMR spectroscopy at room temperature. An *E*/*Z*-ratio of 1:2 was reached after 20 min and no change of this ratio was observed after 12 h at room temperature. This material was not isolated, since all attempts to isolate the product of the reaction resulted in the decomposition of the material.

Saturation of the proton at 4.76 ppm in the 10:1 *E*/*Z* mixture of **27** gave the following nOe's:





27 **26a**

Representative procedure (Table 1, entry 8): to a solution of **28a** (70 mg, 0.30 mmol) in dry toluene (3 mL) at –78 ºC was added dropwise diisopropoxytitanium(IV) dichloride ($TiCl_2(OiPr)_2$) (1 M in toluene, 0.32 mL, 0.32 mmol). The resulting colorless solution was stirred for 10 min and then neat **27** (75 mg, 0.33 mmol) was added. The bright yellow reaction mixture was stirred at –78 ºC for 20 min before being quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was diluted with diethyl ether (20 mL), the layers were

separated and the aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (dichloromethane-ethyl acetate, 5:1) to afford the desired product (85 mg, 0.22 mmol, 73%) as a colorless oil and an inseparable mixture of all possible diastereoisomers (Found: C, 67.89; H, 7.90. $C_{22}H_{30}O_6$ requires C, 67.67; H, 7.74%); R_f 0.29 (dichloromethane/ethyl acetate, 5:1); ν_{max}/cm^{-1} 3469, 3074, 2997, 2941, 2837, 1727, 1629, 1586, 1514, 1462, 1391, 1377, 1301, 1274, 1249, 1204, 1177, 1072, 1033, 1000, 904, 861, 819;

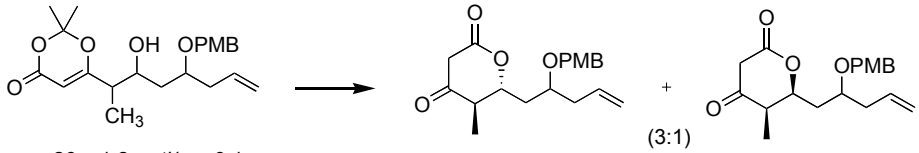
The 2,4-*anti*/*syn* diasteromeric ratio was determined by integration of proton signals of the methylene group of the PMB ether: 2,4-*anti* 4.57 (d), 2,4-*syn* 4.65 (d). The 1,2-*anti*/*syn* diasteromeric ratio was determined by integration of proton signals of the methyl group in α position of the hydroxyl group: 1,2-*anti* 1.07 (d), 1,2-*syn* 1.16 (d).

The NMR data is given for the major 2,4-*anti* diastereomer.

Major diastereomer, 1,2-*anti*: δ_H (500 MHz, $CDCl_3$) 1.07 (3 H, d, *J* 7.1), 1.66 (8 H, br s), 2.28-2.36 (2 H, m), 2.44-2.52 (1 H, m), 2.73 (1 H, d, *J* 4.9), 3.73-3.78 (1 H, m), 3.80 (3 H, s), 3.90-3.97 (1 H, m), 4.41 (1 H, d, *J* 11.3), 4.57 (1 H, d, *J* 11.3), 5.08-5.14 (2 H, m), 5.25 (1 H, s), 5.73-5.81 (1 H, m), 6.88 (2 H, d, *J* 8.6), 7.26 (2 H, d, *J* 8.6 Hz); δ_C (125 MHz, $CDCl_3$) 13.6, 24.7, 25.2, 36.6, 37.7, 44.5, 55.2, 69.6, 70.8, 75.2, 93.8, 106.4, 113.9, 117.8, 129.6, 133.9, 159.2, 161.4, 173.5.

Minor diastereomer, 1,2-*syn*: δ_H (500 MHz, $CDCl_3$) 1.16 (3 H, d, *J* 7.1), 1.67 (8 H, br s), 2.23 (1 H, quin, *J* 6.7), 2.28-2.36 (2 H, m), 2.44-2.52 (1 H, m), 2.82 (1 H, d, *J* 4.4), 3.73-3.78 (1 H, m), 3.80 (3 H, s), 3.90-3.97 (1 H, m), 4.41 (1 H, d, *J* 11.3), 4.57 (1 H, d, *J* 11.3), 5.08-5.14 (2 H, m), 5.22 (1 H, s), 5.73-5.81 (1 H, m), 6.88 (2 H, d, *J* 8.6), 7.26 (2 H, d, *J* 8.6 Hz); δ_C (125 MHz, $CDCl_3$) 12.6, 24.4, 25.4, 37.3, 37.6, 44.2, 55.2, 69.0, 70.7, 75.4, 93.5, 106.3, 113.9, 117.8, 129.6, 133.9, 159.2, 161.2, 173.3.

Proof for the relative 1,2-*anti*/*syn* stereochemistry of 26a.



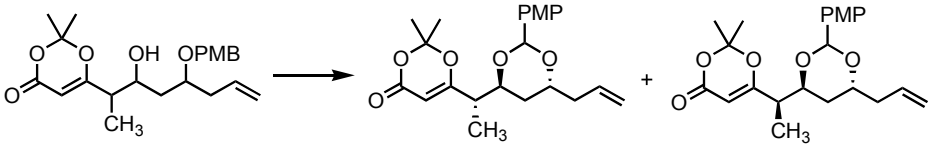
26a, 1,2-*anti*/*syn* 3:1

To a solution of **26a** (1,2-*anti*/*syn* 3:1, 100 mg, 0.25 mmol) in dry methanol (5 mL) was added at room temperature K_2CO_3 (34.5 mg, 0.25 mmol) in one portion. The resulting suspension was stirred for 6 h, during which it became a clear solution. The mixture was diluted with dichloromethane (100 mL) washed with saturated aqueous NH_4Cl (10 mL) and with brine (10mL), dried over $MgSO_4$ and filtered. After the solvent was evaporated under reduced pressure, the resulting yellow residue was purified by flash chromatography on silica gel (petroleum ether-ethyl acetate, 1:1) to afford the *anti*-lactone (44 mg, 0.132 mmol, 53 %), the *syn*-lactone (18 mg, 0.055 mmol, 22%), and a mixed fraction (10 mg, 0.030 mmol, 12 %) as colorless oils (Found: C, 68.64; H, 7.50. $C_{19}H_{24}O_5$ requires C, 68.66; H, 7.28%).

***anti*-lactone**: R_f 0.37 (petroleum ether-ethyl acetate, 1:1); ν_{max}/cm^{-1} 3075, 2928, 1759, 1727, 1667, 1612, 1513, 1463, 1392, 1351, 1249, 1174, 1076, 1034, 916, 821; δ_H (300 MHz, $CDCl_3$) 1.10 (3 H, d, *J* 7.3), 1.63-1.88 (2 H, m), 2.25 (1 H, dq, *J* 10.7, 7.3), 2.32-2.48 (2 H, m), 3.32 (2 H, s), 3.80 (3 H, s), 3.85-3.92 (1 H, m), 4.24 (1 H, dt, *J* 10.7, 2.0), 4.35 (1 H, d, *J* 11.5), 4.63 (1 H, d, *J* 11.5), 5.11-5.17 (2 H, m), 5.77-5.91 (1 H, m), 6.87 (2 H, d, *J* 8.6), 7.26 (2 H, d, *J* 8.6); δ_C (75 MHz, $CDCl_3$) 10.9, 37.8, 38.7, 45.9, 46.9, 55.2, 71.5, 72.8, 75.6, 113.8, 118.1, 129.8, 130.4, 133.7, 159.3, 166.8, 202.6.

***syn*-lactone**: R_f 0.21 (petroleum ether-ethyl acetate, 1:1); ν_{max}/cm^{-1} 3070, 2925, 1667, 1612, 1513, 1458, 1366, 1301, 1248, 1173, 1078, 1035, 916, 821; δ_H (300 MHz, $CDCl_3$) 1.03 (3 H, d, *J* 7.5), 1.65-1.79 (2 H, m), 2.36-2.49 (2 H, m), 2.50 (1 H, qd, *J* 7.5, 3.2), 3.30 (2 H, d, *J* 8.7), 3.80 (4 H, br. s), 4.35 (1 H, d, *J* 11.5), 4.63 (1 H, d, *J* 11.5), 4.60-4.67 (1 H, m), 5.11-5.17 (2 H, m), 5.76-5.87 (1 H, m), 6.87 (2 H, d, *J* 8.5), 7.26 (2 H, d, *J* 8.5); δ_C (75 MHz, $CDCl_3$) 9.5, 36.0, 38.5, 45.4, 45.7, 55.3, 71.5, 73.2, 74.8, 113.8, 118.2, 129.9, 130.4, 133.5, 159.3, 166.8, 203.6.

Proof for the relative 2,4-*anti*/*syn* stereochemistry of 26a.



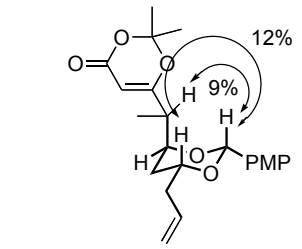
26a, 1,2-*anti/syn* 3:1
2,4-*anti/syn* 8:1

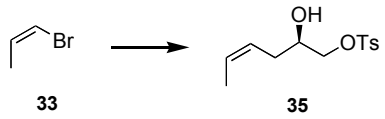
A **B**

4Å powdered molecular sieves (150 mg) and **26a** (200 mg, 0.51 mmol) were stirred in THF (10 mL) for 15 min, and DDQ (145 mg, 0.64 mmol) was added. The mixture was stirred for 8 h at room temperature, then diluted with diethyl ether (100 mL), washed with saturated aqueous

$NaHCO_3$ (3 × 15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 5:1) to afford benzylidene **B** (36 mg, 0.092 mmol, 18%) as a 3:1 mixture of 2,4-*anti*/*syn* diastereomers, a mixed fraction of **A** and **B** (30 mg, 0.076 mmol, 15%) and **A** (91.0 mg, 0.234 mmol, 46%) as colorless oils (Found: MH^+, 389.1957. $C_{22}H_{28}O_6$ requires *MH* 389.1964, EIMS);

A: R_f 0.44 (petroleum ether-ethyl acetate, 5:1); ν_{max}/cm^{-1} 3076, 2938, 2855, 1728, 1633, 1615, 1517, 1462, 1394, 1368, 1274, 1248, 1204, 1179, 1117, 1032, 1004, 903, 827; δ_H (500 MHz, $CDCl_3$) 1.16 (3 H, d, *J* 6.8), 1.52 (3 H, s), 1.61 (3 H, s), 1.68 (1 H, br. d, *J* 14.2), 1.92-1.98 (1 H, m), 2.25-2.31 (1 H, m), 2.42-2.49 (1 H, m), 3.00 (1 H, dq, *J* 11.0, 6.8), 3.78 (3 H, s), 3.95-4.03 (1 H, m), 4.18 (1 H, dd, *J* 11.0, 5.1), 5.08-5.16 (2 H, m), 5.35 (1 H, s), 5.70 (1 H, s), 5.81-5.90 (1 H, m), 6.85 (2 H, d, *J* 8.8), 7.33 (2 H, d, *J* 8.8); δ_C (125 MHz, $CDCl_3$) 14.7, 24.1, 25.7, 30.1, 38.2, 40.3, 55.2, 71.6, 74.0, 93.8, 95.2, 106.8, 113.5, 117.7, 127.3, 130.7, 133.4, 159.8, 161.4, 173.0.

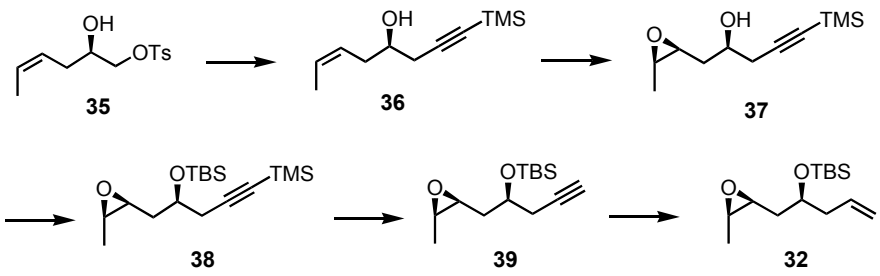




33 **35**

A dry flask was charged with Mg (5.70 g, 234 mmol) and THF (6 mL). Z-1-bromopropene (**33**, 2.80 g, 23 mmol) was added, and after 30 s, a sharp temperature rise was observed and THF (194 mL) was added. The flask was placed in an ice- water bath. Additional **33** (25.66 g, 212 mmol) was added at such a rate that the internal temperature was maintained between 28-30 ºC (*ca.* 15 min). The ice-bath was needed for another 15 min in order to maintain the temperature around 25 ºC, then it was removed. The temperature stayed at 28 ºC for another 40 min then gradually decreases to 23 ºC (r.t.). The mixture was stirred for another 1 h, then stirring was discontinued and the salts were allowed to settle for 3 h. Titration with *sec*-butanol indicated

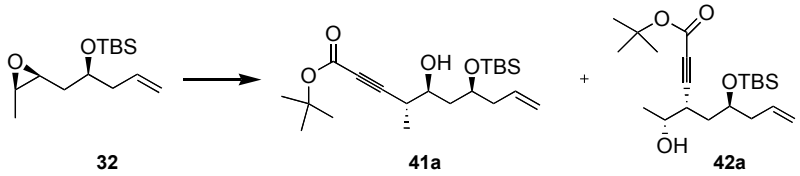
0.89 M. A dry flask was charged with Li_2CuCl_4 (Aldrich, 0.1 M in THF, 60 mL, 6.0 mmol), diluted with THF (350 mL) and cooled to –35 ºC (internal temperature). The solution of Z-1-propenyl magnesium bromide (0.89 M, 135 mL, 120.1 mmol) was added *via* syringe over 20 min. After another 35 min, (*R*)-glycidyl tosylate (**34**, 18.25 g, 80.0 mmol) in THF (30 mL + 5 mL rinse) was added *via* cannula over 15 min. After another 10 min, saturated aqueous NH_4Cl (100 mL) was added, followed with ether (300 mL). The mixture was warmed to 10 ºC with vigorous stirring over 30 min. The organic phase was washed with brine and the combined aqueous phase was back-extracted once with ether. The combined organic phase was dried over $MgSO_4$. The volatiles were removed *in vacuo*, to give a residue that was purified by silica gel flash chromatography (petroleum ether-dichloromethane-ethyl acetate, 5:4:1) to afford alcohol **35** (21.1 g, 77.9 mmol, 97%) as a colorless oil and a single isomer (Found: C, 57.57; H, 6.89. $C_{13}H_{18}O_4S$ requires C, 57.76; H, 6.71 %); $[\alpha]_D^{22}$ –9.6 (*c* 1.00, $CHCl_3$); R_f 0.19 (petroleum ether-dichloromethane-ethyl acetate, 5:4:1); ν_{max}/cm^{-1} 3528, 2923, 1598, 1354, 1173, 1096, 969, 811; δ_H (400 MHz, $CDCl_3$) 1.57 (3 H, dt, *J* 7.0, 1.5), 2.17-2.27 (2 H, m), 2.34 (1 H, s), 2.43 (3 H, s), 3.86 (1 H, qd, *J* 7.0, 3.0), 3.91 (1 H, dd, *J* 10.0, 7.0), 4.03 (1 H, dd, *J* 10.0, 3.0), 5.31 (1 H, dtq, *J* 11.5, 7.0, 1.5), 5.59 (1 H, dqt, *J* 11.5, 7.0, 1.5), 7.34 (1 H, br. s), 7.35 (1 H, br. s), 7.77 (1 H, br. s), 7.79 (1 H, br. s); δ_C (100 MHz, $CDCl_3$) 12.9, 21.6, 30.4, 69.1, 73.1, 124.1, 127.9, 129.9, 132.5, 145.0.



To a suspension of potassium hydride (washed with hexane, 1.70 g, 42.4 mmol) in THF (50 mL) at 0 °C was added **35** (9.48 g, 35.0 mmol) in THF (30 mL + 5 mL rinse) *via* cannula over 20 min. The mixture was warmed to r.t. and stirred for 22 h. To a solution of trimethylsilylacetylene (6.95 g, 70.7 mmol) in THF (250 mL) at –78 °C was added *n*Buli (2.50 M in hexanes, 28.0 mL, 70 mmol) dropwise and the mixture was stirred for 20 min, whereupon the epoxide mixture was added *via* syringe over 40 min. After 10 min, $BF_3.Et_2O$ (5.70 g, 40.2

mmol) was added over 10 min. After another 30 min, saturated aqueous NH_4Cl (100 mL) was added, followed with ether (300 mL). The mixture was warmed to 10 ºC with vigorous stirring over 30 min. The organic phase was washed with saturated aqueous sodium bicarbonate and brine. The combined organic phase was dried over $MgSO_4$. The volatiles were removed *in vacuo* and the residue (**36**, 6.82 g) was redissolved in CH_2Cl_2 (175 mL) and cooled to 0 ºC. $VO(acac)_2$ (0.65 g, 2.45 mmol) was added, followed by *tert*-butylhydroperoxide (6.3 M, 8.3 mL, 52.3 mmol). After 2 h *tert*-butylhydroperoxide (6.3 M, 4.1 mL, 25.8 mmol) was added and the mixture was stirred for a further 14 h, whereupon it was poured into ethyl acetate (400 mL), washed twice with 10% aqueous $Na_2S_2O_3$ and brine. The aqueous phase was back-extracted once. The combined organic phase was dried over $MgSO_4$. The volatiles were removed *in vacuo*, to give a residue that was purified by silica gel flash chromatography (dichloromethane-petroleum ether- ethyl acetate, 5:4:1) to afford epoxide **37** (5.31 g, 24.9 mmol, 71%) as a colorless oil and a 19:1 mixture of diastereomers. A portion (0.56 g, 2.62 mmol)) was dissolved in dry DMF (13 mL) and *tert*-butyldimethylsilyl chloride (0.80 g, 5.30 mmol) was added followed with TMEDA (0.98 g, 8.48 mmol) in at r.t. The mixture was stirred for 13 h, whereupon it was diluted with ether, washed twice with 0.5 M aqueous HCl, saturated aqueous sodium bicarbonate, water and brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give a colorless oil (**38**) that was redissolved in methanol (13 mL). Potassium carbonate (0.40 g, 2.89 mmol) was added and the mixture was stirred at r.t. for 6 h. Ether was added and the solid was filtered off through celite. The filtrate was washed with saturated ammnonium chloride and brine (twice), and dried over $MgSO_4$. Concentration *in vacuo* gave a colorless oil (**39**) that was redissolved in dry hexane (50 mL). Quinoline (0.81 g, 6.26 mmol) was added, followed with Lindlar catalyst (Aldrich 5% wt Pd, 134 mg, 0.063 mmol) and the flask was flushed with H_2 for 15 min. The catalyst was filtered off through celite. After copious rinsing with ether, the organic phase was washed with 0.5M aqueous HCl (twice), saturated aqueous sodium bicarbonate, water and brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give a residue that was purified by silica gel flash chromatography (petroleum ether-ether, 19:1) to afford epoxide **32** (582 mg, 2.27 mmol, 86%) as a colorless oil (Found: C, 65.71; H, 10.81. $C_{14}H_{28}O_2Si$ requires C, 65.57; H, 11.00%); $[\alpha]_D^{22}$ +8.4 (*c* 1.00, $CHCl_3$); R_f 0.40 (petroleum ether-ether, 9:1); ν_{max}/cm^{-1} 2930, 1468, 1257, 1100,

910, 837, 776; δ_H (400 MHz, $CDCl_3$) 0.05 (3 H, s), 0.06 (3 H, s), 0.88 (9 H, s), 1.24 (3 H, d, *J* 5.5), 1.64-1.70 (2 H, m), 2.24-2.36 (2 H, m), 2.99-3.07 (2 H, m), 3.88 (1 H, quin, *J* 6.0), 5.03-5.09 (2 H, m), 5.81 (1 H, ddt, *J* 17.0, 10.0, 7.0); δ_C (100 MHz, $CDCl_3$) –4.7, –4.5, 13.4, 18.0, 25.8, 34.6, 41.9, 52.0, 53.9, 70.2, 117.2, 134.8.

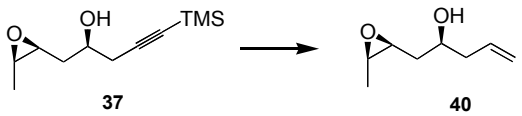


32 **41a** **42a**

To a solution of *tert*-butylpropiolate (0.30 g, 2.40 mmol) in THF (10 mL) at –78 °C was added *n*Buli (1.6M in hexanes, 1.50 mL, 2.40 mmol) dropwise over 15 min and the mixture was stirred for 30 min, whereupon **32** (373 mg, 1.45 mmol) in THF (2 mL) was added *via* cannula. After 2 min, $BF_3.Et_2O$ (0.34 g, 2.36 mmol) was added dropwise. The mixture was stirred at –78 °C for 5 h, warmed to 0 ºC and quenched with saturated aqueous NH_4Cl with vigorous stirring. When two clear phases were obtained, the two phases were separated and the aqueous phase was extracted with ether. The combined organic phase was dried over $MgSO_4$ and the volatiles were removed *in vacuo* to give a residue that was purified by silica gel flash chromatography (petroleum ether-ether, 19:1 to 7:3) to afford some starting material **32** (16 mg, 0.062 mmol, 4%), the undesired regioisomer **42a** (192 mg, 0.501 mmol, 34%) and **41a** (324 mg, 0.847 mmol, 58%) as a colorless oil (Found: C, 66.12; H, 9.83. $C_{21}H_{38}O_4Si$ requires C, 65.92; H, 10.01%); $[\alpha]_D^{22}$ +20.1 (*c* 1.73, $CHCl_3$); R_f 0.40 (petroleum ether-ether, 7:3); ν_{max}/cm^{-1} 3490, 2931, 2231, 1709, 1370, 1257, 1163, 1092, 838, 776; δ_H (500 MHz, $CDCl_3$) 0.11 (6 H, s), 0.89 (9 H, s), 1.23 (3 H, d, *J* 7.0), 1.48 (9 H, s), 1.65 (1 H, ddd, *J* 14.0, 9.0, 9.0), 1.73 (1 H, ddd, *J* 14.0, 4.5, 2.5), 2.27-2.31 (2 H, m), 2.69 (1 H, qd, *J* 7.0, 4.0), 3.09 (1 H, br. s), 3.74-3.78 (1 H, m), 3.99 (1 H, dtd, *J* 9.0, 6.5, 4.5), 5.04-5.10 (2 H, m), 5.78 (1 H, ddt, *J* 16.5, 9.5, 7.0); δ_C (125 MHz, $CDCl_3$) –4.8, –4.1, 15.1, 17.9, 25.8, 28.0, 32.6, 39.5, 42.2, 72.1, 72.3, 78.5, 83.0, 87.2, 117.7, 133.8, 152.8.

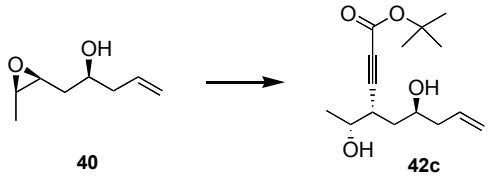
42a: (Found: C, 66.21; H, 9.99. $C_{21}H_{38}O_4Si$ requires C, 65.92; H, 10.01%); $[\alpha]_D^{22}$ +41.3 (*c* 2.01, $CHCl_3$); R_f 0.22 (petroleum ether-ether, 7:3); ν_{max}/cm^{-1} 3440, 2930, 2232, 1709, 1370, 1257, 1163, 1092, 837, 776; δ_H (500 MHz, $CDCl_3$) 0.10 (3 H, s), 0.11 (3 H, s), 0.89 (9 H, s), 1.29 (3 H, d, *J* 6.5), 1.48 (9 H, s), 1.58 (1 H, ddd, *J* 13.5, 10.0, 4.0), 1.72 (1 H, ddd, *J* 13.5, 11.5, 2.5),

2.28 (2 H, br. t, *J* 7.0), 2.70 (1 H, dt, *J* 11.5, 4.0), 3.74-3.78 (1 H, m), 3.97 (1 H, dtd, *J* 10.0, 5.5, 2.5), 5.03-5.08 (2 H, m), 5.80 (1 H, ddt, *J* 16.5, 9.5, 7.0); δ_C (125 MHz, $CDCl_3$) –4.8, –4.2, 18.1, 21.6, 25.9, 28.0, 37.4, 37.7, 42.6, 69.5, 78.2, 78.5, 83.1, 85.7, 117.5, 134.1, 152.6.



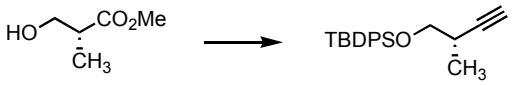
37 **40**

Potassium carbonate (2.35 g, 17.00 mmol) was added to **37** (3.61 g, 17.00 mmol) in methanol (100 mL) and the mixture was stirred at r.t. for 3 h. Ether was added and the solid was filtered off through celite. The filtrate was washed with saturated ammnonium chloride (twice), water and brine. The aqueous phase was saturated with NaCl and back-extracted three times with dichloromethane. The combined organic phase was ried over $MgSO_4$ and concentrated *in vacuo* to give a colorless oil that was redissolved in dry hexane (330 mL) and methanol (11 mL). Quinoline (2.18 g, 16.92 mmol) was added, followed with Lindlar catalyst (Aldrich 5 %wt Pd, 360 mg, 0.17 mmol) and the flask was flushed with H_2 for 15 min. The mixture was stirred for 8 h under H_2 and left to stand under H_2 overnight. The catalyst was filtered off through a plug of intimately mixed celite and powdered sodium bisulfate to remove the quinoline. Evaporation of the solvent *in vacuo* gave a residue that was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 7:3) to afford epoxide **40** (1.84 g, 12.93 mmol, 76%) as a colorless oil (Found: C, 67.38; H, 9.86. $C_8H_{14}O_2$ requires C, 67.57; H, 9.92%); $[\alpha]_D^{22}$ +6.2 (*c* 1.00, $CHCl_3$); R_f 0.14 (petroleum ether-ethyl acetate, 7:3); ν_{max}/cm^{-1} 3424, 2977, 2926, 1432, 1394, 1369, 1075, 1030, 996, 917, 779; δ_H (500 MHz, $CDCl_3$) 1.28 (3 H, d, *J* 5.5), 1.57 (1 H, dt, *J* 14.5, 8.0), 1.81 (1 H, ddd, *J* 14.5, 5.0, 4.0), 2.25-2.35 (2 H, m), 2.35 (1 H, d, *J* 2.5), 3.07 (1 H, qd, *J* 5.5, 4.0), 3.11 (1 H, ddd, *J* 8.0, 4.0, 4.0), 3.92-3.98 (1 H, m), 5.12-5.17 (2 H, m), 5.83 (1 H, dddd, *J* 18.0, 10.5, 7.5, 6.5); δ_C (125 MHz, $CDCl_3$) 13.3, 33.8, 41.8, 51.9, 55.0, 69.6, 118.2, 134.3.



40 **42c**

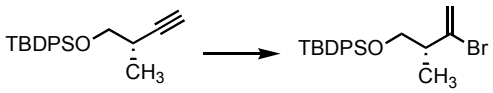
To a solution of *tert*-butylpropiolate (66 mg, 0.524 mmol) in THF (2 mL) at –78 °C was added *n*Buli (2.26 M in hexanes, 0.23 mL, 0.52 mmol) dropwise over 5 min and the mixture was stirred for 10 min, whereupon $BF_3.Et_2O$ (74 mg, 0.52 mmol) was added dropwise. After 10 min, epoxide **40** (30 mg, 0.21 mmol) in THF (0.4 mL) was added. The mixture was stirred at –78 °C for 3 h, warmed to 0 ºC and quenched with saturated aqueous NH_4Cl with vigorous stirring. When two clear phases were obtained, the two phases were separated and the aqueous phase was extracted with ether. The combined organic phase was dried over $MgSO_4$ and the volatiles were removed *in vacuo* to give a residue that was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 7:3 to 3:2) to afford alkyne **42c** (42 mg, 0.156 mmol, 74%) as a colorless oil; $[\alpha]_D^{26}$ +35.2 (*c* 4.60, $CHCl_3$); R_f 0.17 (petroleum ether-ethyl acetate, 3:2); ν_{max}/cm^{-1} 3397, 2978, 2926, 2230, 1706, 1370, 1277, 1161, 844; δ_H (400 MHz, $CDCl_3$) 1.31 (3 H, d, *J* 7.5), 1.49 (9 H, s), 1.64 (1 H, ddd, *J* 14.0, 10.5, 4.5), 1.81 (1 H, ddd, *J* 14.0, 10.5, 2.0), 2.16-2.36 (2 H, m), 2.87 (1 H, dt, *J* 10.5, 4.5), 3.78-3.96 (2 H, m), 3.99 (1 H, dtd, *J* 9.0, 6.5, 4.5), 5.10-5.17 (2 H, m), 5.78-5.88 (1 H, m); δ_C (125 MHz, $CDCl_3$) 21.2, 28.0, 29.7, 37.3, 42.6, 68.4, 69.2, 77.7, 83.4, 85.6, 118.8, 134.2; ESIMS *m/z* 291 (MNa^+, 20), 269 (MH^+, 53), 153 (100).



48 **50**

To a solution of (*R*)-hydroxyisobutyric acid methyl ester (**48**, 9.34 g, 79.06 mmol) and imidazole (7.06 g, 102.82 mmol) in CH_2Cl_2 (90 mL) was added TBDPSCl (21.7 g, 79.09 mmol) at 0 ºC. The mixture was warmed up to r.t. and stirred for 30 min, whereupon saturated aqueous $NaHCO_3$ (200 mL) was added. The mixture was vigorously stirred for one minute and extracted with CH_2Cl_2. The organic layer was washed with brine, dried and the volatiles were removed *in vacuo* to give the ester **49** (28.0 g, quant.) as a colorless oil; R_f 0.35 (petroleum ether-ethyl acetate, 9:1); δ_H (300 MHz, $CDCl_3$) 1.03 (9 H, s), 1.16 (3 H, d, *J* 7.0), 2.71 (1 H, sex, *J* 7.0), 3.68 (3 H, s), 3.72 (1 H, dd, *J* 9.5, 5.5), 3.82 (1 H, dd, *J* 9.5, 7.0), 7.35-7.43 (6 H, m), 7.64 (4 H, d, *J* 6.5). A portion (4.10 g) was redissolved in CH_2Cl_2 (60 mL), cooled to –78 ºC and DIBAL-H (1.0M in hexanes, 13.4 mL, 13.4 mmol) was added *via* syringe pump over 30 min. After another 30 min, methanol (0.50 g, 15.6 mmol) was added. The cooling bath was removed and

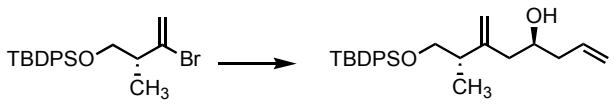
the mixture was allowed to warm to r.t. A solution of (1-diazo-2-oxo-propyl)-phosphonic acid dimethyl ester (5.53 g, 28.78 mmol) in THF (100 mL) was cooled to –78 ºC and sodium methoxide (25%wt in methanol, 6.6 mL, 28.84 mmol) in THF (20 mL) was added over 15 min, followed by the aldehyde solution, which was cannulated over 10 min. The cooling bath was removed, and after 20 min, a saturated aqueous solution of Rochelle's salt (200 mL) was added. The mixture was vigorously stirred for 30 min, and the two phases were separated. The aqueous phase was extracted twice with ether and the combined organic phase was dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a residue which was purified by silica gel flash chromatography (petroleum ether-ether, 2 to 4%) to afford the alkyne **50** (3.07 g, 9.52 mmol, 83%) as a colorless oil (Found: M^+, 322.1749. $C_{21}H_{26}OSi$ requires M 322.1753, 1.3 ppm, EIMS); $[\alpha]_D^{26}$ –5.3 (*c* 4.10, $CHCl_3$); R_f 0.28 (petroleum ether-ether, 2%); ν_{max}/cm^{-1} 3309, 2932, 2859, 1472, 1428, 1389, 1112, 824, 740, 702; δ_H (400 MHz, $CDCl_3$) 1.06 (9 H, s), 1.23 (3 H, d, *J* 7.0), 2.02 (1 H, d, *J* 2.5), 2.56 (1 H, sexd, *J* 7.0, 2.5), 3.54 (1 H, dd, *J* 9.5, 7.5), 3.73 (1 H, dd, *J* 9.5, 6.0), 7.35-7.43 (6 H, m), 7.67-7.70 (4 H, m); δ_C (100 MHz, $CDCl_3$) 17.3, 19.3, 26.8, 28.8, 67.4, 69.0, 86.5, 127.6, 129.6, 133.5, 135.6; EIMS *m/z* 322 (M^+, 0.2), 265 [$(M–C_4H_9)^+$, 100].



50 **47**

To a solution of alkyne **50** (15.59 g, 48.34 mmol) in CH_2Cl_2 (150 mL) and hexane (150 mL) at –20 ºC was added 9-Br-9-BBN (unopened commercial batch, 1.0M in CH_2Cl_2, 100 mL, 100 mmol) over 10 min. The mixture was stirred for a further 6 h at 0 ºC and acetic acid was added (39.9 g, 664 mmol). After a further 1 h at 0 ºC, 1 M aqueous $Na_2S_2O_3$ (400 mL) was added, followed with brine (400 mL). The milky aqueous phase was extracted with ether until it was clear (3×300 mL). The combined organic phase was dried over $MgSO_4$ and evaporation of the solvent *in vacuo* gave a residue that was purified by silica gel flash chromatography (petroleum ether-ether, 1 to 2%) to afford the bromide **47** (18.76 g, 46.50 mmol, 96%) as a colorless oil (Found: C, 62.38; H, 6.82. $C_{21}H_{27}BrOSi$ requires C, 62.52; H, 6.75%); $[\alpha]_D^{26}$ –5.3 (*c* 3.6, $CHCl_3$); R_f 0.40 (petroleum ether-ether, 2%); ν_{max}/cm^{-1} 2931, 2858, 2360, 2342, 1428, 1112, 823, 739, 701; δ_H (400 MHz, $CDCl_3$) 1.05 (9 H, s), 1.08 (3 H, d, *J* 7.0), 2.60 (1 H, sex, *J* 7.0), 3.55 (1 H, dd, *J* 10.0, 6.0), 3.69 (1 H, dd, *J* 10.0, 7.0), 5.48 (1 H, d, *J* 1.5), 5.67 (1 H, dd, *J* 1.5,

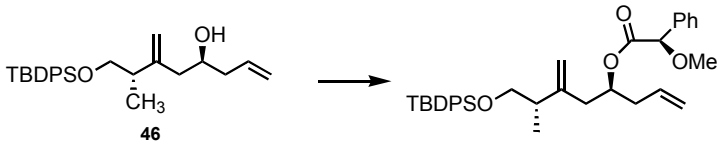
0.5), 7.36-7.44 (6 H, m), 7.66 (2 H, dd, *J* 3.0, 1.5), 7.68 (2 H, dd, *J* 3.0, 1.0); δ_C (100 MHz, $CDCl_3$) 16.2, 19.3, 26.8, 46.7, 66.3, 117.0, 127.6, 129.6, 133.6, 133.7, 135.6 (2), 137.9.



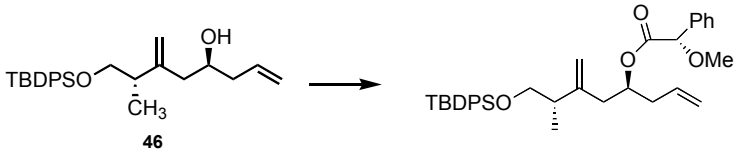
To a solution of thiophene (0.76 g, 9.03 mmol) in THF (8 mL) at –30 °C was added *n*-BuLi (2.58 M, 3.50 mL, 9.03 mmol) dropwise. The mixture was stirred for 30 min, whereupon it was cannulated into a slurry of CuCN (99.99%, 809 mg, 9.03 mmol) in THF (8 mL) at –78 °C. The cooling bath was removed and upon reaching r.t., a clear brown solution was obtained. This solution was kept at *ca.* –20 °C until the the vinyl lithium reagent was ready (*vide infra*).

To a solution of vinyl bromide **47** (2.79 g, 6.91 mmol) in ether (28 mL) was added *t*-BuLi (1.44 M, 10 mL, 14.4 mmol) at –78 °C over 10 min. After another 45 min, the freshly prepared solution of 2-thienyl lithiumcyanocuprate was cannulated into it. The pale brown heterogeneous mixture was warmed up to –45 °C (chlorobenzene/dry ice bath), and stirred at this temperature for 1 h. A solution of (*R*)-glycidyl tosylate (TCI America, 3.1 g, 13.58 mmol) in THF (11 mL) was then cannulated into the mixture, and the the resulting slurry was warmed up to 0 °C over 10 min. After an additional 5 h at 0 °C, the mixture was recooled to –78 °C and a vinyl lithium solution (13.93 mmol, prepared from *n*BuLi and tetravinyltin at –78 °C, 45 min then warming to 24 °C) in THF (14 mL) was added, followed after 5 min, with $BF_3.Et_2O$ (1.97 g, 13.93 mmol). The resulting mixture was stirred for 20 min, then quenched with a 9:1 solution of saturated aqueous NH_4Cl solution/NH_4OH and diluted with ether. After 20 min of vigorous stirring followed by filtration through Celite, the organic phase was washed with brine. The combined aqueous phase was back-extracted twice with ether. After drying the combined organic phase over $MgSO_4$, the volatiles were removed *in vacuo* to give a residue that was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 19:1 to 9:1) to afford the alcohol **46** (2.01 g, 4.92 mmol, 71%) as a colorless oil (Found: C, 76.43; H, 9.02. $C_{26}H_{36}O_2Si$ requires C, 76.42; H, 8.88%); $[\alpha]_D^{22}$ –13.1 (*c* 3.22, $CHCl_3$); R_f 0.30 (petroleum ether-ethyl acetate, 9:1); ν_{max}/cm^{-1} 3448, 2960, 2931, 2858, 1472, 1428, 1121, 1080, 823, 740, 702, 614; δ_H (400 MHz, $CDCl_3$) 1.05 (9 H, s), 1.07 (3 H, d, *J* 7.0), 2.04 (1 H, dd, *J* 14.0, 9.5), 2.19-2.23 (3 H, m), 2.35 (1

H, broad sex, *J* 7.0), 3.49 (1 H, dd, *J* 10.0, 7.0), 3.62 (1 H, dd, *J* 10.0, 6.0), 3.71 (1 H, dddd, *J* 9.5, 6.0, 6.0, 4.5), 4.93 (1 H, s), 4.94 (1 H, s), 5.09-5.14 (2 H, m), 5.83 (1 H, ddt, *J* 17.0, 10.5, 7.0), 7.35-7.43 (6 H, m), 7.64-7.68 (4 H, m); δ_C (100 MHz, $CDCl_3$) 16.7, 19.2, 26.8, 41.4, 43.6, 68.2, 68.5, 112.7, 117.5, 127.6, 129.6, 133.6, 133.7, 134.9, 135.6, 135.6, 148.8.

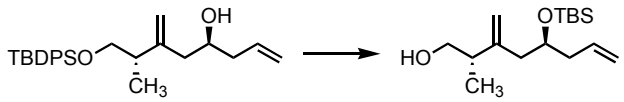


A dry tube was charged with alcohol **46** (7 mg, 0.017 mmol), (*R*)-methoxyphenylacetic acid (6 mg, 0.036 mmol) and DMAP (0.2 mg, 0.002 mmol). CH_2Cl_2 (0.2 mL) was added, and after cooling to 0 °C, DCC (7.0 mg, 0.034 mmol) was added, followed by warming to r.t. After 20 min, the solvent was blown off with argon, the residue was taken up in petroleum ether and placed on a plug of silica gel. Elution with petroleum ether, then with 5% petroleum ether-ethyl acetate gave the mandelate ester (9 mg, 0.016 mmol, 95%) as a colorless oil; R_f 0.41 (petroleum ether-ethyl acetate, 9:1); δ_H (500 MHz, $CDCl_3$) 1.03 (9 H, s), 1.04 (3 H, d, *J* 6.5), 2.05-2.18 (2 H, m), 2.15 (1 H, dd, *J* 14.5, 5.0), 2.22 (1 H, dd, *J* 14.5, 9.0), 2.27-2.34 (1 H, m), 3.38 (3 H, s), 3.43 (1 H, dd, *J* 9.5, 6.5), 3.58 (1 H, dd, *J* 9.5, 5.5), 4.65 (1 H, s), 4.74-4.81 (4 H, m), 5.07 (1 H, ddt, *J* 10.0, 7.0, 4.5), 5.39 (1 H, ddt, *J* 17.5, 10.0, 7.0), 7.29-7.44 (11 H, m), 7.63-7.67 (4 H, m).



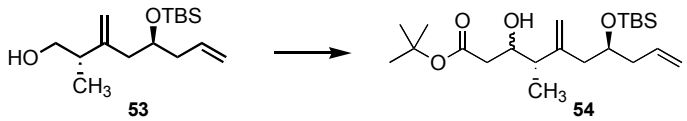
A dry tube was charged with alcohol **46** (7 mg, 0.017 mmol), (*S*)-methoxyphenylacetic acid (6 mg, 0.036 mmol) and DMAP (0.2 mg, 0.002 mmol). CH_2Cl_2 (0.2 mL) was added, and after cooling to 0 °C DCC (7.0 mg, 0.034 mmol) was added, followed by warming to r.t. After 20 min, the solvent was blown off with argon, the residue was taken up in petroleum ether and placed on a plug of silica gel. Elution with petroleum ether, then with 5% petroleum ether-ethyl acetate gave the the mandelate ester (9 mg, 0.016 mmol, 95%) as a colorless oil; R_f 0.41 (petroleum ether-ethyl acetate, 9:1); δ_H (500 MHz, $CDCl_3$) 0.88 (3 H, d, *J* 7.0), 1.01 (9 H, s), 2.05-2.30 (5 H, m), 3.32 (1 H, dd, *J* 10.0, 7.0), 3.38 (3 H, s), 3.46 (1 H, dd, *J* 10.0, 5.5), 4.43 (1

H, d, *J* 1.0), 4.47 (1 H, s), 4.66 (1 H, s), 4.99-5.09 (3 H, m), 5.66 (1 H, ddt, *J* 17.5, 10.5, 7.5), 7.25-7.30 (3 H, m), 7.35-7.43 (8 H, m), 7.61-7.66 (4 H, m).



46 **53**

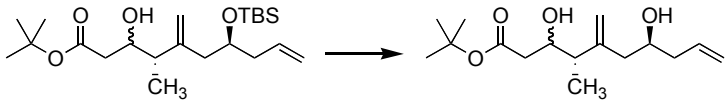
To a solution of **46** (3.08 g, 7.53 mmol) and 2,6-lutidine (3.22 g, 30.05 mmol) in CH_2Cl_2 (40 mL) was added TBSOTf (3.57 g, 13.49 mmol) at 0 °C. The mixture was stirred for 5 min, diluted with ether and washed with saturated aqueous NH_4Cl and brine. After drying the combined organic phase over $MgSO_4$, the volatiles were removed *in vacuo* to give a residue which was redissolved in anhydrous DMF (150 mL). Acetic acid (0.51 g, 8.55 mmol) was added, followed with solid TBAF.$3H_2O$ (2.66 g, 8.43 mmol). The solution was stirred for 13 h, whereupon it was diluted with ether, washed with saturated NH_4Cl, saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. The volatiles were removed *in vacuo* to give a residue that was purified by silica gel flash chromatography (petroleum ether-ether, 9:1 to 4:1) to afford the alcohol **53** (1.65 g, 5.80 mmol, 77%) as a colorless oil (Found: *[M–^{t}Bu]*$^+$, 227.1457. $C_{12}H_{23}O_2Si$ requires *M–^{t}Bu* 227.1467, 4.5 ppm, EIMS); $[\alpha]_D^{22}$ –8.4 (*c* 0.81, $CHCl_3$); R_f 0.16 (petroleum ether-ethyl acetate, 9:1); ν_{max}/cm^{-1} 3355, 2957, 2929, 2857, 1472, 1255, 1085, 836, 774; δ_H (500 MHz, $CDCl_3$) 0.04 (3 H, s), 0.06 (3 H, s), 0.88 (9 H, s), 1.06 (3 H, d, *J* 7.0), 2.17-2.23 (2 H, m), 2.25-2.31 (2 H, m), 2.37 (1 H, broad sex, *J* 6.0), 3.51 (1 H, dd, *J* 11.0, 5.5), 3.55 (1 H, dd, *J* 11.0, 6.5), 3.88 (1 H, quin, *J* 7.0), 4.92 (1 H, t, *J* 1.0), 4.94 (1 H, td, *J* 1.5, 1.0), 5.02-5.06 (2 H, m), 5.82 (1 H, ddt, *J* 15.0, 11.0, 6.5); δ_C (100 MHz, $CDCl_3$) –4.4, 16.1, 18.1, 25.9, 41.6, 41.9, 42.3, 66.0, 71.0, 112.6, 117.1, 135.0, 147.9.



53 **54**

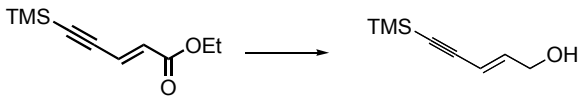
To a solution of DMSO (0.73 g, 9.30 mmol) in CH_2Cl_2 (19 mL) at –78 °C was added oxalyl chloride (0.60 g, 4.70 mmol) and the mixture was stirred for 10 min, whereupon a solution of alcohol **53** (666 mg, 2.34 mmol) in CH_2Cl_2 (4 mL) was added dropwise. After another 30 min at –78 °C, triethylamine (1.09 g, 10.76 mmol) was added and the mixture was allowed to gradually

warm to –20 °C over 20 min. A precooled (0 °C) 3:1 mixture of hexane/toluene was added and the resulting slurry was poured onto flash silica gel. Elution with petroleum ether-ether 5 % afforded aldehyde **45** (550 mg) as a pale yellow oil, which was redissolved in dry THF (5 mL). To a solution of diisopropylamine (797 mg, 7.87 mmol) in THF (14 mL) at 0 °C was added *n*-BuLi (2.58 M in hexanes, 2.70 mmol, 6.97 mmol). The solution was stirred for 15 min and cooled to –78 °C, whereupon a solution of *t*-butyl acetate (914 mg, 7.87 mmol) in THF (10 mL) was added dropwise. After 1 h, the solution of **45** was added (+1 mL THF rinse) *via* cannula and after 10 min, the mixture was quenched with saturated aqueous NH_4Cl and diluted with ether. The organic phase was washed with brine and dried over $MgSO_4$. The volatiles were removed *in vacuo* to give a residue that was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 5 to 10%) to afford ester **54** (730 mg, 1.83 mmol, 78%) as a colorless oil and an inseparable 2.8:1 mixture of diastereomers (Found: C, 66.48; H, 10.90. $C_{22}H_{42}O_4Si$ requires C, 66.28; H, 10.62%); $[\alpha]_D^{22}$ –13.3 (*c* 2.26, $CHCl_3$); R_f 0.25 (petroleum ether-ethyl acetate, 9:1); ν_{max}/cm–1 3498, 2958, 2930, 2858, 1716, 1368, 1255, 1154, 1090, 912, 836, 775; δ_H (400 MHz, $CDCl_3$, minor isomer in brackets) 0.02 (3 H, s), 0.04 (3 H, s), 0.87 (9 H, s), 1.09 (1.02) (3 H, d, *J* 7.0), 1.45 (9 H, s), 2.14-2.43 (7 H, m), 3.82-4.00 (2 H, m), 4.90-4.93 (2 H, m), 5.00-5.05 (2 H, m), 5.77-5.87 (1 H, m); δ_C (100 MHz, $CDCl_3$, minor isomer in brackets) –4.4, –4.5, 14.5 (14.6), 18.0, 25.8, 28.1, 40.2 (38.9), 41.6 (41.6), 43.0 (42.7), 44.5 (44.9), 69.9 (70.3), 70.8, 81.0, 113.1, 117.0, 134.8 (135.0), 148.2 (147.8), 172.4 (172.6).



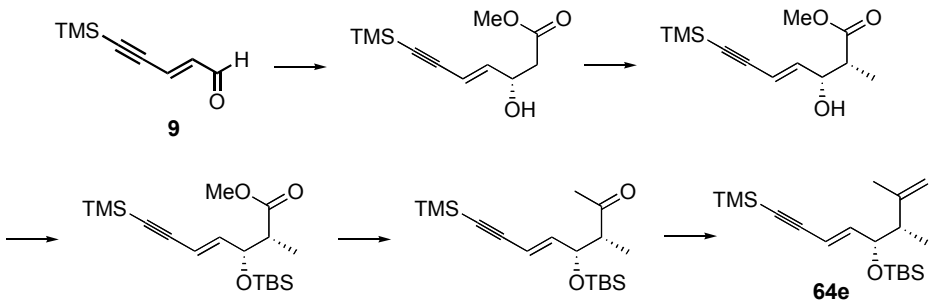
To a solution of **54** (2.8:1 mixture, 310 mg, 0.777 mmol) in THF (3 mL) was added TBAF (1.0M in THF, 1.20 mL, 1.20 mmol) at r.t. The mixture was stirred for 4 h, diluted with ether and washed with water. The combined aqueous phase was back-extracted with ether and the combined organic phase was dried over $MgSO_4$. The volatiles were removed *in vacuo* to give a residue that was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 7:3) to afford ester **55** (197 mg, 0.69 mmol, 89%) as a colorless oil and an inseparable 2.8:1 mixture of diastereomers (Found: C, 67.43; H, 10.10. $C_{16}H_{28}O_4$ requires C, 67.57; H, 9.92%); $[\alpha]_D^{22}$

–12.5 (*c* 1.24, $CHCl_3$); R_f 0.11 (petroleum ether-ethyl acetate, 7:3); ν_{max}/cm^{-1} 3426, 2978, 2932, 1726, 1368, 1256, 1154, 1040, 912; δ_H (500 MHz, $CDCl_3$, minor isomer in brackets) 1.08 (1.00) (3 H, d, *J* 7.0), 1.43 (1.44) (9 H, s), 2.10 (2.07) (1 H, dd, *J* 14.5, 9.5), 2.19-2.32 (4 H, m), 2.34 (1 H, dd, *J* 16.0, 9.0), 2.40 (1 H, dd, *J* 16.0, 3.5), 3.76-3.84 (1 H, m), 3.96 (1 H, ddd, *J* 9.0, 5.5, 3.5), 4.96-5.13 (4 H, m), 5.79-5.88 (1 H, m); δ_C (125 MHz, $CDCl_3$, minor isomer in brackets) 14.9 (16.1), 28.0, 39.8 (39.6), 41.6 (41.8), 43.6 (43.3), 43.9 (45.3), 68.6 (69.4), 70.2 (71.2), 81.2, 113.5 (113.7), 117.8 (117.5), 134.6 (134.8), 148.7 (148.8), 172.5.



9 **64b**

To a stirred solution of **9** (0.94 g, 4.8 mmol) in dry hexane (5 mL) was added dropwise DIBAL-H (1 M in hexane, 10.0 mL, 10.0 mmol) at –78 ºC. After the addition was completed the reaction was stirred for 30 min and then poured into 1M aqueous hydrochloric acid (50 mL) and diluted with diethyl ether (20 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Purification by silica gel flash chromatography (petroleum ether-ethyl acetate, 5:2) yielded (0.68 g, 4.42 mmol, 92%) of **64b** as a colorless oil; R_f 0.23 (petroleum ether-diethyl ethyl, 5:2). ν_{max}/cm^{-1} 3333, 2960, 2899, 2178, 2134, 1632, 1448, 1409, 1370, 1250, 1084, 1009, 953, 842, 760, 700; δ_H (300 MHz, $CDCl_3$) 0.19 (9 H, s), 1.45 (1 H, br. t, *J* 5.9), 4.21 (2 H, m), 5.77, (1 H, dt, *J* 15.9, 2.0), 6.31 (1 H, dt, *J* 15.9, 5.1. The data was consistent with the data reported in the literature (Carpita, A. ; Neri, D. ; Rossi, R. *Gazz. Chim. Ital.* **1987**, *117*, 481).



To a stirred solution of diisopropylamine (5.0 g, 50.0 mmol) in dry THF (70 mL) was added dropwise *n*-butyllithium (1.6M in hexane, 31.3 mL, 50.0 mmol) at –30 ºC. The resulting solution was stirred for 15 min and then allowed to warm to 0 ºC over a period of 30 min. To this LDA solution was added dropwise a solution of dry ethyl acetate (4.4 g, 50.0 mmol) in dry THF (10 mL) at –78 ºC. The reaction mixture was stirred for 30 min at this temperature and then a solution of **9** (3.8 g, 25.0 mmol) in dry THF (10 mL) was added dropwise and the reaction was stirred for 60 min at –78 ºC. At that time, the reaction mixture was poured into 1M hydrochloric acid (100 mL) and the aqueous phase was extracted with diethyl ether (3 × 70 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 5:1) yielded (5.22 g, 22.0 mmol, 88%) of aldol product as a pale yellow oil (Found: C, 61.10; H, 8.45. $C_{12}H_{20}O_3Si$ requires C, 59.96; H, 8.38%); R_f 0.30 (petroleum ether/ethyl acetate, 5:1); ν_{max}/cm^{-1} 3459, 2961, 2900, 2138, 1732, 1407, 1373, 1250, 1175, 1089, 1029, 956, 844, 760; δ_H (500 MHz, $CDCl_3$) 0.18 (9 H, s) 1.28 (3 H, t, *J* 7.3), 2.48 (1 H, dd, *J* 16.3, 8.5), 2.57 (1 H, dd, *J* 16.3, 3.6), 3.05 (1 H, d, *J* 4.4), 4.18 (2 H, q, *J* 7.3), 4.57-4.60 (1 H, m), 5.83 (1 H, dd, *J* 15.8, 1.7), 6.18 (1 H, dd, *J*`15.8, 10.7); δ_C (125 MHz, $CDCl_3$) –0.1, 14.1, 40.7, 60.9, 67.9, 95.8, 102.7, 110.6, 143.9, 171.9.

A portion (2.88 g, 12.0 mmol), was redissolved in THF (20 mL) and cooled to –78 ºC. To a stirred solution of diisopropylamine (2.6 ml, 26.0 mmol) in dry THF (50 mL) was added dropwise *n*-butyllithium (1.6M in hexane, 16.3 mL, 6.0 mmol) at –30 ºC. The resulting solution was stirred for 15 min and then allowed to warm to 0 ºC over a period of 30 min. To this LDA solution was added dropwise the solution of alcohol. The reaction mixture was stirred for 60 min at this temperature and then allowed to warm to –20 ºC over a period of 4 h to complete the deprotonation. The mixture was recooled to –78 ºC and methyl iodide (4.26 g, 30.0 mmol) was added neat *via* syringe. After the addition was completed, the resulting reaction mixture was stirred at –70 ºC to –50 ºC for 18 h and then allowed to warm to –10 ºC over a period of 8 h. Then, the reaction mixture was poured into 1M aqueous hydrochloric acid (50 mL) and the aqueous phase was extracted with diethyl ether (3 × 70 mL). The combined organic layers were washed with water (30 mL) and brine (2 × 30 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Analysis of the ^1H NMR spectrum of the crude product

showed a *ca*. 33:1 mixture of both diastereomers. Purification by silica gel flash chromatography (petroleum ether-ethyl acetate, 5:1) yielded the methylated product (2.27 g, 9.0 mmol, 75%) as a colorless oil and the single *anti* diastereomer (Found: C, 61.17; H, 8.60. $C_{13}H_{22}O_3Si$ requires C, 61.38; H, 8.72%); R_f 0.33 (petroleum ether-ethyl acetate, 5:1); ν_{max}/cm^{-1} 3458, 2962, 2900, 2166, 2134, 1732, 1629, 1459, 1377, 1250, 1184, 1104, 1041, 957, 844, 760, 699, 652; δ_H (500 MHz, $CDCl_3$) 0.18 (9 H, s), 1.20 (3 H, d, *J* 7.3), 1.28 (3 H, t, *J* 7.1), 2.55 (1 H, quint., *J* 7.1), 2.77 (1 H, d, *J* 5.8), 4.17 (2 H, q, *J* 7.3), 4.24 (1 H, q, *J* 7.1), 5.80 (1 H, dd, *J* 15.8, 1.5), 6.17 (1 H, dd, *J* 15.8, 6.1); δ_C (125 MHz, $CDCl_3$) –0.2, 14.1, 14.2, 45.1, 60.8, 73.7, 95.8, 102.7, 111.8, 143.4, 175.2.

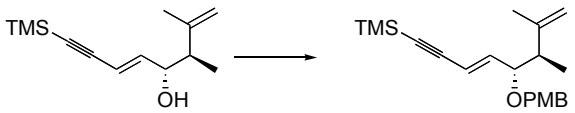
To a portion of alcohol (1.27 g, 5.0 mmol) in dry dichloromethane (25 mL) was added 2,6-lutidine (0.80 g, 7.5 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.39 g, 5.5 mmol) at –50 ºC. After 10 min, the cooling bath was removed and the reaction mixture was stirred for additional 20 min and then poured into a 10% aqueous solution of NH_4Cl (30 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 50:1) to give the silyl ether (1.72 g, 4.6 mmol, 92%) as a colorless oil (Found: C, 61.73; H, 9.94. $C_{19}H_{36}O_3Si_2$ requires C, 61.90; H, 9.84%); R_f 0.14 (petroleum ether-ethyl acetate, 50:1); ν_{max}/cm^{-1} 2958, 2898, 2858, 2165, 2135, 1738, 1629, 1472, 1372, 1251, 1178, 1112, 1063, 957, 840, 777, 698, 651; δ_H (300 MHz, $CDCl_3$) 0.03 (6 H, s), 0.19 (9 H, s), 0.86 (9 H, s), 1.04 (3 H, d, *J* 7.1), 1.26 (3 H, t, *J* 7.1), 2.55 (1 H, quint., *J* 7.1), 4.12 (2 H, q, *J* 7.1), 4.35 (1 H, t, *J* 6.8), 5.68 (1 H, d, *J* 15.8, 1.5), 6.06 (1 H, dd, *J* 15.8, 6.4); δ_C (75 MHz, $CDCl_3$) –5.2, –4.3, –0.1, 12.5, 14.2, 17.9, 25.6, 46.8, 60.4, 74.4, 95.2, 102.9, 111.4, 143.9, 174.3.

To a stirred solution of ester (1.10 g, 3.0 mmol) in dry hexane (30 mL) was added (trimethylsilyl)methyllithium (1 M in pentane, 9.0 mL, 9.0 mmol) at 0 ºC, and the resulting reaction mixture was stirred for 90 min at this temperature. Dry methanol (5 mL) was added at once to the rapidly stirred solution while the deep orange color of the solution changed to pale yellow. This mixture was stirred for 2 min (exceeding this reaction time results in a dramatic decrease of the yield of the desired product) and then immediately poured into a stirred 10%

aqueous solution of NH_4Cl (50 mL). The mixture was diluted with diethyl ether (30 mL), the layers were separated and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 20:1) to give the methyl ketone (0.82 g, 2.37 mmol, 79 %) as a colorless oil (Found: C, 63.64; H, 9.98. $C_{18}H_{34}O_2Si_2$ requires C, 63.84; H, 10.12%); R_f 0.48 (petroleum ether-ethyl acetate, 20:1); ν_{max}/cm^{-1} 2958, 2831, 2897, 2858, 2165, 2134, 1719, 1628, 1472, 1359, 1250, 1168, 1113, 1058, 957, 840, 777, 699, 651; δ_H (500 MHz, $CDCl_3$) 0.01 (3 H, s), 0.02 (3 H, s), 0.19 (9 H, s), 0.86 (9 H, s), 0.96 (3 H, d, *J* 7.1), 2.18 (3 H, s), 2.67 (1 H, quint., *J* 7.3), 4.27 (2 H, t, *J* 7.3), 5.66 (1 H, dd, *J* 15.8, 1.2), 6.05 (1 H, dd, *J* 15.8, 6.6); δ_C (125 MHz, $CDCl_3$) –5.2, –4.2, –0.1, 12.7, 18.0, 25.7, 30.9, 52.8, 75.1, 95.3, 102.8, 111.3, 144.4, 211.2.

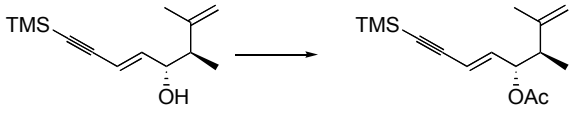
To a suspension of dry methyltriphenylphosphonium bromide (dried for 12 h at 110 ºC under vacuum, 3.5 g, 10.0 mmol) in dry THF (15 mL) was added dropwise *n*-butyllithium (1.6M in hexane, 3.75 mL, 6.0 mmol) at –40 ºC. After 30 min the resulting yellow mixture was allowed to warm to room temperature and stirred for an additional 90 min. The yellow suspension was recooled to –20 ºC and a solution of methyl ketone (0.67 g, 2.0 mmol) in dry THF (5 mL) was added *via* syringe and stirred for 30 min. The cooling bath was removed and the mixture was stirred for an additional 60 min, poured into a stirred 10% aqueous solution of NH_4Cl (20 mL) and diluted with diethyl ether (30 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Purification of the residue by silica gel flash chromatography (petroleum ether-ethyl acetate, 30:1) gave **64e** (0.61 g, 1.82 mmol, 91%) as a pale yellow oil (Found: C, 68.00; H, 10.74. $C_{19}H_{32}OSi_2$ requires C, 67.78; H, 10.78%); R_f 0.54 (petroleum ether-ethyl acetate, 30:1); ν_{max}/cm^{-1} 2959, 2930, 2897, 2858, 2170, 2133, 1647, 1472, 1362, 1250, 1110, 1065, 957, 892, 840, 775, 760, 735; δ_H (300 MHz, $CDCl_3$) 0.02 (3 H, s), 0.04 (3 H, s), 0.18 (9 H, s), 0.89 (9 H, s), 0.95 (3 H, d, *J* 7.1), 1.73 (3 H, s), 2.27 (1 H, quint., *J* 7.1), 4.19 (1 H, dt, *J* 5.3, 1.2), 4.74 (1 H, br. s), 4.82 (1 H, br. s), 5.67 (1 H, dd, *J* 15.8, 1.4), 6.10 (1 H, dd, *J*

15.8, 5.3); δ_C (75 MHz, $CDCl_3$) –5.1, –4.4, –0.1, 13.8, 18.1, 21.5, 25.8, 47.2, 74.5, 94.1, 103.6, 109.7, 111.9, 145.2, 146.3, 211.2.



***syn*-11** **64f**

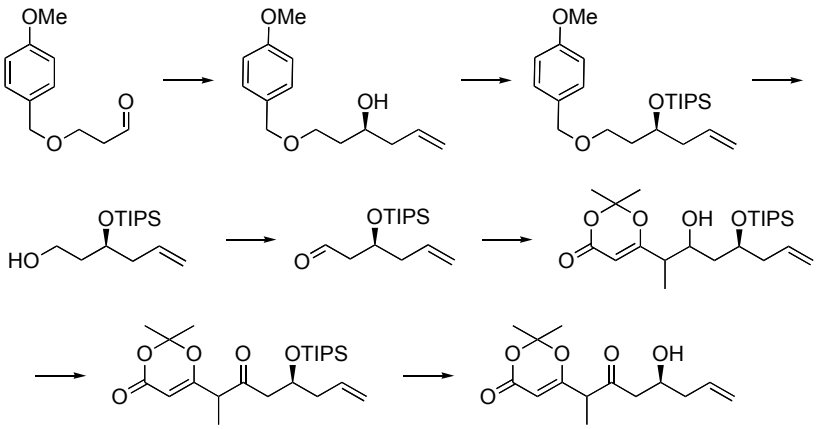
To a solution of ***syn*-11** (*syn*/*anti* 2.6:1, 85 mg, 0.382 mmol) and *p*-methoxybenzyltrichloroacetimidate (130 mg, 0.460 mmol) in ether (4 mL) at 0 °C was added triflic acid (0.01 M in ether, 0.115 mL, 1.1 μmol). The solution was allowed to warm to r.t. overnight and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 19:1 to 9:1) to give some recovered alcohol ***syn*-11** (44 mg, 0.198 mmol, 51%) and **64f** (63 mg, 0.184 mmol, 49%) as a colorless oil and as an inseparable 2.6:1 mixture of diastereomers; R_f 0.50 (petroleum ether-ethyl acetate, 9:1); ν_{max}/cm^{-1} 2961, 1514, 1302, 1249, 1173, 1037, 959, 844, 760; δ_H (300 MHz, $CDCl_3$, minor isomer in brackets) 0.22 (0.23) (9 H, s), 1.11 (0.97) (3 H, d, *J* 7.0), 1.66 (1.64) (3 H, s), 2.32 (2.40) (1 H, quin, *J* 7.0), 3.68 (1 H, t, *J* 7.5), 3.81 (3.81) (3 H, s), 4.25 (1 H, d, *J* 11.5), 4.53 (1 H, d, *J* 11.5), 4.76-4.81 (2 H, m), 5.69 (5.71) (1 H, d, *J* 16.0), 6.09 (6.08) (1 H, dd, *J* 16.0, 7.5); δ_C (125 MHz, $CDCl_3$, minor isomer in brackets) –0.1 (–0.4), 15.7 (14.3), 20.5 (20.2), 46.2 (45.5), 55.2 (53.6), 70.4 (70.1), 94.8, 103.1, 111.7 (111.6), 112.0 (112.8), 113.6 (113.7), 129.3 (129.7), 135.8, 143.8 (143.5), 146.7 (147.0), 159.1.



***syn*-11** **64g**

To a solution of ***syn*-11** (*syn*/*anti* 2.6:1, 222 mg, 1.00 mmol) in pyridine (8 mL) was added acetic anhydride (0.32 g, 3.18 mmol) at r.t. The mixture was stirred for 18 h, diluted with ether, washed three times with 10% aqueous $CuSO_4$, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The volatiles were removed *in vacuo* and the residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 97:3) to give **64g** (198 mg, 0.749 mmol, 75%) as a colorless oil and as an inseparable 2.6:1 mixture of diastereomers; R_f 0.28 (petroleum ether-ethyl acetate, 19:1); ν_{max}/cm^{-1} 2967, 1743, 1372, 1231, 1019, 954, 897, 844, 760; δ_H (300

MHz, $CDCl_3$, minor isomer in brackets) 0.18 (0.18) (9 H, s), 1.05 (1.00) (3 H, d, *J* 7.0), 1.71 (3 H, s), 2.05 (2.02) (3 H, s), 2.37 (2.43) (1 H, quin, *J* 7.0), 4.77-4.83 (2 H, m), 5.31 (5.25) (1 H, td, *J* 6.5, 1.0), 5.68 (5.73) (1 H, dd, *J* 16.0, 1.0), 6.07 (6.04) (1 H, dd, *J* 16.0, 6.5); δ_C (75 MHz, $CDCl_3$, minor isomer in brackets) –0.2, 15.1, 20.7 (19.8), 21.0, 44.8 (44.7), 75.3 (75.2), 95.8, 102.6, 112.1 (112.5), 112.7 (113.2), 140.8 (140.1), 145.4 (145.5), 170.1.



65b

A dry flask was charged with (–)-*i*pc$_2$BOMe (2.50 g, 7.90 mmol) in the dry box. Ether (22 mL) was added and the solution was cooled to 0 ºC. Allyl magnesium bromide (1.0M in ether, 7.7 mL, 7.7 mmol) was added dropwise over 10 min, whereupon the suspension was allowed to warm to r.t. After 1 h at r.t., stirring was discontinued for 15 min and the suspension was filtered through a Schlenk filter. The cake was washed with ether (2 mL). The resulting solution was cooled to –95 ºC, and 3-(4-methoxy-benzyloxy)-propionaldehyde (1.0 g, 5.15 mmol) (Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1-20) in ether (5 mL) was added dropwise along the walls of the flask. A 20% EtOAc in CH_2Cl_2 system was necessary to follow the reaction by TLC. After stirring for 45 min at –95 ºC, methanol (0.45 mL) was added and the mixture was warmed to r.t. Aqueous 2.5M NaOH (4 mL) was added, followed by 30% aqueous H_2O_2 (6.5 mL), and the mixture was vigorously stirred at r.t. overnight. After dilution with EtOAc, the two phases were separated and the organic phase was washed with saturated aqueous NH_4Cl and dried over $MgSO_4$. The volatiles were removed *in vacuo*, to give a residue that was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 4:1 to 7:3) to afford the homoallylic alcohol (875 mg, 3.70 mmol, 72%) as a colorless oil (Found: C, 71.43; H, 8.78. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%); $[\alpha]_D^{22}$ –1.9 (*c* 1.02, $CHCl_3$); R_f 0.23 (petroleum ether-ethyl

acetate, 7:3); ν_{max}/cm^{-1} 3440, 2936, 2863, 1612, 1514, 1248, 1174, 1090, 1034, 916, 820; δ_H (300 MHz, $CDCl_3$) 1.71-1.78 (2 H, m), 2.22-2.26 (2 H, m), 2.90 (1 H, d, *J* 2.5), 3.57-3.72 (2 H, m), 3.80 (3 H, s), 3.80-3.88 (1 H, m), 4.45 (2 H, s), 5.07-5.13 (2 H, m), 5.76-5.90 (1 H, m), 6.86-6.91 (2 H, m), 7.23-7.31 (2 H, m); δ_C (100 MHz, $CDCl_3$) 35.8, 41.9, 55.3, 68.7, 70.5, 72.9, 113.8, 113.9, 128.6, 129.3, 130.0, 134.9.

To a portion (757 mg, 3.20 mmol) dissolved in CH_2Cl_2 (16 mL) at 0 °C was added 2,6-lutidine (0.69 g, 6.44 mmol) and TIPSOTf (1.48 g, 4.83 mmol). The solution was stirred at 0 °C for 5 min, poured in hexane and washed four times with 1M aqueous HCl and twice with brine. After drying over $MgSO_4$, the mixture was concentrated *in vacuo* to give a residue (1.47 g) that was redissolved in CH_2Cl_2 (18 mL). Buffer pH 7 (2 mL) was added, followed by DDQ (0.90 g, 3.96 mmol), and the mixture was stirred for 45 min. Evaporation of the solvent gave a residue that was passed through a flash silica gel column (petroleum ether-ethyl acetate, 9:1) to give an oil that was redissolved in CH_2Cl_2 (10 mL). To a solution of oxalyl chloride (0.81 g, 6.4 mmol) in CH_2Cl_2 (18 mL) at –78 °C was added DMSO (1.00 g, 12.8 mmol) and the mixture was stirred for 20 min, whereupon the solution of alcohol was added dropwise. After another 20 min at –78 °C, triethylamine (1.45 g, 14 .3 mmol) was added and the cooling bath was removed. Upon reaching r.t., the mixture was partitioned between ether and 1M aqueous HCl. The organic phase was washed with 1M aqueous HCl, saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. Concentration *in vacuo* and purification by flash silica gel column chromatography (petroleum ether-ethyl acetate, 49:1 to 93:7) afforded the aldehyde (532 mg, 1.97 mmol, 61%) as a colorless oil (Found: *[M–C_3H_7]*$^+$, 227.1456. $C_{15}H_{30}O_2Si$ requires *[M–C_3H_7]* 227.1467, 5.0 ppm); $[\alpha]_D^{22}$ +12.0 (*c* 0.76, $CHCl_3$); R_f 0.45 (petroleum ether-ethyl acetate, 9:1); ν_{max}/cm^{-1} 2944, 2868, 1726, 1464, 1106, 1066, 918, 883, 680; δ_H (400 MHz, $CDCl_3$) 1.05 (21 H, s), 2.32-2.44 (2 H, m), 2.54 (1 H, ddd, *J* 16.0, 5.5, 3.0), 2.62 (1 H, dd, *J* 16.0, 5.5, 2.0), 4.39 (1 H, quin., *J* 5.5), 5.05-5.10 (2 H, m), 5.73-5.84 (1 H, m), 9.84 (1 H, dd, *J* 3.0, 2.0); δ_C (100 MHz, $CDCl_3$) 12.4, 18.0, 42.3, 50.1, 68.0, 118.3, 133.6, 202.1.

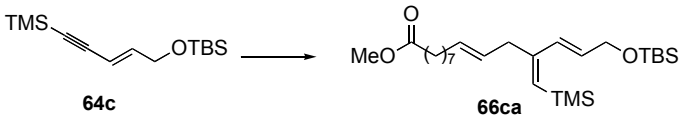
To a solution of ketene silyl acetal **27** (*E*/*Z* 10:1, 360 mg, 1.3 mmol) and a portion of the aldehyde (235 mg, 0.869 mmol) in CH_2Cl_2 (5 mL) was added $BF_3.Et_2O$ (145 mg, 1.02 mmol) at –78 °C. After 5 min stirring, the mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with ether. The organic phase was washed with brine, dried over $MgSO_4$ and

concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 17:3) to give a mixture of alcohol product and 6-ethyl-2,2-dimethyl-[1,3]dioxin-4-one (383 mg). The mixture was dissolved in CH_2Cl_2 (4 mL) and Dess-Martin periodinane (15% wt in CH_2Cl_2, 2.8 mL, 1.29 mmol) was added at r.t. After 45 min, a 1:1 mixture of 1M aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (1 mL) was added, and the suspension was diluted with ether and stirred until the two phases were clear (15 min). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 17:3) to give the ketone (248 mg, 0.584 mmol, 67%) as a colorless oil and a 1:1 mixture of epimers (Found: *[M–C_3H_7]*$^+$, 381.2089. $C_{23}H_{40}O_5Si$ requires *[M–C_3H_7]* 381.2097, 2.2 ppm); R_f 0.39 (petroleum ether-ethyl acetate, 3:1); ν_{max}/cm^{-1} 2944, 2867, 1732, 1633, 1463, 1390, 1272, 1204, 1096, 1062, 1014; δ_H (300 MHz, $CDCl_3$) 1.04 (21 H, s), 1.28 (3 H, d, *J* 7.5), 1.66 (6 H, s), 2.31 (2 H, br. t, *J* 7.0), 2.64 (1 H, dd, *J* 16.0, 5.5, one dia.), 2.66 (2 H, d, *J* 5.5, other dia.), 2.77 (1 H, dd, *J* 16.0, 5.5, one dia.), 3.34/3.35 (1 H, q, *J* 7.0), 4.35-4.44 (1 H, m), 5.01-5.08 (2 H, m), 5.34/5.35 (1 H, s), 5.70-5.86 (1 H, m); δ_C (75 MHz, $CDCl_3$) 12.4/12.8, 18.0/18.1, 24.3/24.4, 41.7/41.9, 47.9, 51.5/51.9, 67.7/68.0, 94.8/94.9, 106.9, 118.0/118.0, 133.8/133.9, 160.7, 168.9, 204.4/204.7.

HF.pyridine (*ca.* 70% HF, 1.0 g, 35 mmol) was dissolved in THF (5 mL) and pyridine (2.8 mL). A portion (4.5 mL) of this solution was added to the ketone (82 mg, 0.193 mmol) and the mixture was stirred at r.t. for 22 h, whereupon another portion of the stock solution (1.5 mL) was added. After another 21 h, the solution was diluted with ether, washed three times with 10% aqueous $CuSO_4$, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 1:1) to give the alcohol **65b** (40 mg, 0.149 mmol, 77%) as a colorless oil and a 1:1 mixture of epimers (Found: *MH*$^+$, 269.1383. $C_{14}H_{20}O_5$ requires *MH* 269.1389, 2.2 ppm); R_f 0.20 (petroleum ether-ethyl acetate, 1:1); ν_{max}/cm^{-1} 3453, 2998, 2925, 1715, 1631, 1391, 1274, 1203, 1016, 904, 864, 815; δ_H (500 MHz, $CDCl_3$) 1.32/1.32 (3 H, d, *J* 7.0), 1.67/1.68/1.69 (6 H, s), 2.24-2.27 (2 H, m), 2.65-2.68 (2 H, m), 3.38 (1 H, q, *J* 7.0), 4.11-4.15 (1 H, m), 5.11-5.15 (2 H, m), 5.38/5.39 (1 H, s), 5.75-5.84 (1 H, m); δ_C (125 MHz, $CDCl_3$) 12.8/12.8, 24.4/24.4/25.3/25.4,

40.8/40.9, 47.2, 51.2/51.5, 66.6/66.9, 94.5, 107.0/107.1, 118.5/118.5, 133.7/133.8, 160.6, 168.4/168.5, 206.6/206.6.

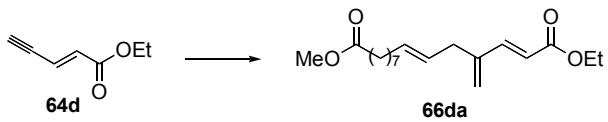
To a stirred solution of $[CpRu(CH_3CN)_3]PF_6$ (13.0 mg, 0.03 mmol) in acetone (0.5 mL) was added a solution of methyl undecenoate (59 mg, 0.3 mmol) and **64a** (37 mg, 0.3 mmol) in acetone (2.5 mL). The resulting orange solution was stirred at room temperature for 2 h. The reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to afford a 1:1 mixture of recovered started material (54 mg) and **66aa** (30 mg, 0.094 mmol, 31%) as a colorless oil (Found: C, 67.16; H, 9.55. $C_{22}H_{38}O_4Si$ requires C, 66.96; H, 9.71%); R_f 0.30 (petroleum ether-ethyl acetate, 10:1); ν_{max}/cm^{-1} 2930, 2856, 1739, 1629, 1568, 1367, 1252, 1181, 1035, 979, 845; δ_H (500 MHz, $CDCl_3$) 0.19 (9 H, s), 1.25-1.38 (11 H, m), 1.58-1.65 (2 H, m), 2.01 (2 H, q, *J* 6.8), 2.30 (2 H, t, *J* 7.6), 2.96 (2 H, d, *J* 6.1), 3.66 (3 H, s), 4.21 (2 H, q, *J* 7.1), 5.37-5.46 (2 H, m), 5.94 (1 H, d, *J* 15.6), 5.98 (1 H, s), 7.61 (1 H, d, *J* 15.6); δ_C (125 MHz, $CDCl_3$) 0.3, 14.2, 27.9, 28.9, 29.1, 29.2, 29.3, 32.5, 34.1, 38.5, 51.4, 60.3, 118.8, 127.7, 133.0, 141.5, 144.7, 150.4, 167.3, 174.3.



To a stirred solution of $[CpRu(CH_3CN)_3]PF_6$ (13.0 mg, 0.03 mmol) in acetone (0.5 mL) was added a solution of methyl undecenoate (59 mg, 0.3 mmol) and **64c** (80.5 mg, 0.3 mmol) in acetone (2.5 mL). The resulting orange solution was stirred at room temperature for 2 h. The reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether-ethyl acetate, 20:1) to afford recovered **64c** (16 mg) and a mixture of methyl undecenoate and **66ca**. Methyl undecenoate was removed using high-vacuum to give **66ca** (63 mg, 0.135 mmol, 45%) as a colorless oil (Found: C, 64.35; H, 10.01. $C_{26}H_{50}O_3Si_2$ requires C, 66.89; H, 10.79%); R_f 0.45 (petroleum ether-ethyl acetate, 20:1); ν_{max}/cm^{-1} 2952, 2928, 2856, 1743, 1571, 1463, 1435, 1249, 1127, 969, 838, 776; δ_H (500 MHz, $CDCl_3$) 0.08 (6 H, s), 0.14 (9 H, s), 0.92 (9 H,

s), 1.27-1.36 (8 H, m), 1.58-1.63 (2 H, m), 1.98-2.02 (2 H, m), 2.30 (2 H, t, *J* 7.3), 2.95 (2 H, br. s), 3.66 (3 H, s), 4.26 (2 H, dd, *J* 4.8, 1.7), 5.41-5.44 (2 H, m), 5.48 (1 H, s), 5.84 (1 H, dt, *J* 15.4, 4.8), 6.55 (1 H, dt, *J* 15.4, 1.7); δ_C (75 MHz, $CDCl_3$) –5.2, 0.4, 18.4, 24.9, 25.9, 28.9, 29.1, 29.3, 32.5, 34.1, 38.9, 51.4, 63.7, 127.8, 129.6, 129.9, 130.4, 132.3, 152.1, 174.3.

To a stirred solution of $[CpRu(CH_3CN)_3]PF_6$ (13.0 mg, 0.03 mmol) in acetone (0.5 mL) was added a solution of methyl undecenoate (59 mg, 0.3 mmol) and **64e** (100 mg, 0.3 mmol) in acetone (2.5 mL). The resulting orange solution was stirred at room temperature for 2 h. The reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether-ethyl acetate, 20:1) to afford recovered **64e** (14 mg) and a mixture of methyl undecenoate and **66ea**. Methyl undecenoate was removed using high-vacuum to give **66ea** (73 mg, 0.137 mmol, 46%) as a colorless oil (Found: C, 69.50; H, 10.24. $C_{31}H_{58}O_3Si_2$ requires C, 69.60; H, 10.93%); R_f 0.37 (petroleum ether-ethyl acetate, 20:1); ν_{max}/cm^{-1} 3072, 2953, 2926, 2856, 1743, 1647, 1570, 1462, 1436, 1248, 11060, 966, 837, 774; δ_H (500 MHz, $CDCl_3$) 0.00 (3 H, s), 0.04 (3 H, s), 0.13 (9 H, s), 0.87 (9 H, s), 0.93 (3 H, d, *J* 7.1), 1.23-1.35 (8 H, m), 1.58-1.62 (2 H, m), 1.73 (3 H, s), 1.97-1.99 (2 H, m), 2.26-2.28 (2 H, m), 2.29 (2 H, t, *J* 7.3), 2.90 (2 H, d, *J* 3.7), 3.66 (3 H, s), 4.10 (1 H, t, *J* 7.1), 4.70 (1 H, br. s), 4.77 (1 H, br. s), 5.41-5.43 (2 H, m), 5.48 (1 H, s), 5.65 (1 H, dd, *J* 15.6, 7.1), 6.35 (1 H, d, *J* 15.6); δ_C (75 MHz, $CDCl_3$) –5.1, –4.0, 0.4, 14.6, 18.2, 21.1, 24.9, 25.8, 28.9, 29.1, 29.3, 32.5, 34.1, 39.1, 47.7, 51.4, 76.5, 111.5, 127.8, 130.4, 131.1, 132.0, 132.1, 147.1, 152.2, 174.3.

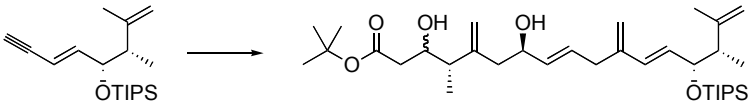


General Procedure (Table 3, entries 6-10): to a stirred solution of $[CpRu(CH_3CN)_3]PF_6$ (13.0 mg, 0.03 mmol) or CpRuCODCl (4.7 mg, 0.015 mmol) in an appropriate solvent (0.5 ml) was added a solution of methyl undecenoate (59.0 mg, 0.3 mmol) and of **64d** (37 mg, 0.3 mmol) in an appropriate solvent (3 ml) *via* syringe. The resulting solution was stirred at the indicated

temperature (preheated oil bath) for 3 h. The reaction mixture was cooled to room temperature, diluted with diethyl ether (60 ml), washed with water (10 ml), dried over $MgSO_4$, filtered, and the solvent was evaporated. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 10:1) gave a mixture of both recovered starting materials, as well as the product **66da** as a colorless oil and an inseparable mixture of branched to linear products (Found: C, 70.54; H, 9.18. $C_{19}H_{30}O_4$ requires C, 70.77; H, 9.38%); R_f 0.27 (petroleum ether-ethyl acetate, 10:1); ν_{max}/cm^{-1} 2928, 2855, 1739, 1715, 1642, 1617, 1436, 1367, 1305, 1269, 1174, 1135, 1038, 1002, 972, 867; δ_H (500 MHz, $CDCl_3$) 1.25-1.43 (10 H, m), 1.58-1.64 (2 H, m), 2.00 (2 H, apparent q, *J* 7.1), 2.30 (3 H, overlapping t, *J* 7.6), 2.91 (2 H, d, *J* 6.1), 3.66 (3 H, s), 4.21 (2 H, overlapping q, *J* 7.1), 5.34 (1 H, d, *J* 1.2), 5.40 (1 H, d, *J* 1.2), 5.41-5.52 (2 H, m), 5.92 (1 H, d, *J* 15.8), 7.32 (1 H, d, *J* 15.8);

Additional signals attributed to the linear isomer were: 2.85 (1 H, t, *J* 6.0), 4.19 (2 H, overlapping q, *J* 7.1), 5.79 (1 H, d, *J* 15.4), 6.09-6.17 (2 H, m), 7.26 (1 H. dd, *J* 15.4, 10.3).

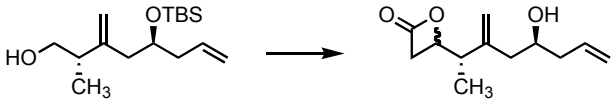
δ_C (125 MHz, $CDCl_3$) 14.3, 24.9, 28.8, 28.9, 29.1, 29.2, 29.3, 29.6, 32.4, 32.5, 34.1, 34.8, 35.8, 51.4, 60.1, 60.3, 118.4, 119.5, 123.8, 126.1, 128.5, 132.7, 133.2, 142.5, 143.6, 144.8, 146.2, 167.3, 174.3.



25 **70**

A dry flask was charged with alkene **55** (2.8:1 d.r., 83 mg, 0.292 mmol) and alkyne **25** (20 mg, 0.065 mmol) and flushed with argon. Methanol (1.1 mL) was added, followed with CpRu(COD)Cl (1.0 mg, 0.003 mmol) and NH_4PF_6 (1.0 mg, 0.006 mmol) and the mixture was heated to reflux over 10 min. After 75 min, the mixture was allowed to cool and concentrated *in vacuo*. Purification by flash silica gel column chromatography (petroleum ether-ethyl acetate, 4:1 to 7:3) afforded some recovered alkene **55** (72 mg, 0.252 mmol) and the ester **70** (24 mg, 0.040 mmol, 61%) as a yellow oil and an inseparable 2.8:1 mixture of *C*-3 epimers (Found: C, 71.01; H, 10.77. $C_{35}H_{62}O_5Si$ requires C, 71.14; H, 10.57 %); $[\alpha]_D^{22}$ –6.0 (*c* 4.06, $CHCl_3$); R_f 0.39 (petroleum ether-ethyl acetate, 7:3); ν_{max}/cm^{-1} 3427, 2966, 2942, 2867, 1729, 1462, 1368, 1255, 1154, 1059, 970, 884; δ_H (500 MHz, $CDCl_3$, minor diastereomer in brackets) 0.97 (3 H, d,

J 7.0), 1.05 (21 H, s), 1.10 (3 H, d, *J* 7.0), 1.45 (1.46) (9 H, s), 1.75 (3 H, s), 2.21 (1 H, dd, *J* 14.5, 9.0), 2.18-2.40 (3 H, m), 2.36 (1 H, dd, *J* 16.0, 9.0), 2.42 (2.49) (1 H, dd, *J* 16.0, 3.5 (2.5)), 2.90 (2 H, d, *J* 6.5), 3.97 (1 H, ddd, *J* 9.0, 5.5, 3.5), 4.21-4.30 (1 H, m), 4.36 (1 H, broad t, *J* 5.5), 4.70 (1 H, s), 4.78 (1 H, s), 4.93 (1 H, s), 4.98 (1 H, s), 4.99 (1 H, s), 5.04 (5.02) (1 H, s), 5.53-5.58 (1 H, m), 5.62 (1 H, dd, *J* 16.0, 7.0), 5.73-5.79 (1 H, m), 6.16 (1 H, d, *J* 16.0); δ_C (125 MHz, $CDCl_3$, minor diastereomer in brackets) 12.5, 13.3, 14.9 (15.6), 18.1 (18.1), 21.8, 28.1(29.7), 35.0, 39.9 (39.5), 44.0 (43.9), 44.2 (45.3), 47.8, 70.3 (71.2), 70.4 (70.9), 75.5, 81.2, 111.5, 113.8 (114.1), 115.7, 129.2 (128.8), 130.5, 131.9, 133.8 (133.9), 143.9, 146.9, 148.2 (148.3), 172.5.

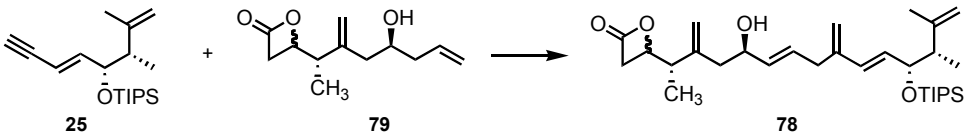


To a solution of DMSO (1.68 g, 21.56 mmol) in CH_2Cl_2 (75 mL) at –78 °C was added oxalyl chloride (1.36 g, 10.77 mmol) and the mixture was stirred for 20 min, whereupon a solution of alcohol **53** (1.54 g, 5.41 mmol) was added dropwise. After another 20 min at –78 °C, triethylamine (3.26 g, 32.29 mmol) was added and the cooling bath was removed. Upon reaching 0 °C, the mixture was partitioned between ether and saturated aqueous NH_4Cl. The organic phase was washed with saturated aqueous NH_4Cl, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude aldehyde, which was obtained as a yellow oil (1.55 g), was immediately redissolved in CH_2Cl_2 (50 mL) and cooled to –78 °C. Me_2AlCl (1.0M in hexanes, 5.4 mL, 5.4 mmol) was added over 5 min. The bright yellow mixture was stirred for 3 min, whereupon neat trimethylsilylketene (0.65 g, 5.72 mmol) was added dropwise. After another 30 min, 0.5M aqueous $NaHSO_4$ (20 mL) and ether (100 mL) were added and the mixture was allowed to warm to r.t. with vigorous stirring. Additional 0.5M aqueous $NaHSO_4$ (150 mL) and ether (100 mL) were added and the two clear phases were separated. The organic phase was washed with brine (100 mL) and the combined organic phase was back-extracted with ether (2 × 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The yellow residue (2.15 g) was taken up in acetonitrile (60 mL) and $KF.2H_2O$ (0.76 g, 8.06 mmol) was added. The mixture was vigorously stirred for 1 h, whereupon it was cooled to 0 °C. Aqueous 49% HF (13 mL, 364 mmol) was added dropwise and the mixture was stirred at 0 °C for 30 min. After dilution with

ether (100 mL), solid $NaHCO_3$ (30 g) was added portionwise over 5 min. After stirring for another 5 min, the mixture was filtered through a sintered funnel packed with $MgSO_4$. The solids were well rinsed with ether and the combined filtrate was concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 7:3 to 3:2) to afford the lactone **79** (0.78 g, 3.71 mmol, 69%) as a yellow oil and a 1.6:1 mixture of separable diastereomers (Found: M^+, 210.1254. $C_{12}H_{18}O_3$ requires M 210.1256, 0.7 ppm, EIMS);

1 diastereomer: $[\alpha]_D^{26}$ +20.8 (*c* 1.73, $CHCl_3$); R_f 0.19 (petroleum ether-ethyl acetate, 7:3); ν_{max}/cm^{-1} 3417, 2924, 1827, 1642, 1412, 1278, 1127, 914, 867; δ_H (400 MHz, $CDCl_3$) 1.22 (3 H, d, *J* 7.0), 2.14-2.35 (4 H, m), 2.50 (1 H, br. quin, *J* 7.0), 3.15 (1 H, dd, *J* 16.5, 4.5), 3.45 (1 H, dd, *J* 16.5, 6.5), 3.77-3.83 (1 H, m), 4.45 (1 H, ddd, *J* 8.5, 6.5, 4.5), 4.94 (1 H, s), 5.04 (1 H, s), 5.16 (1 H, d, *J* 18.0), 5.17 (1 H, d, *J* 11.0), 5.33 (1 H, dddd, *J* 18.0, 11.0, 7.5, 7.0); δ_C (100 MHz, $CDCl_3$) 16.1, 41.6, 41.8, 43.1, 43.7, 68.9, 73.8, 113.9, 118.6, 134.2, 146.5, 168.1.

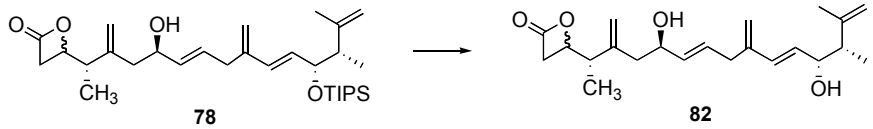
other diastereomer: $[\alpha]_D^{26}$ –14.4 (*c* 1.4, $CHCl_3$); R_f 0.13 (petroleum ether-ethyl acetate, 7:3); ν_{max}/cm^{-1} 3417, 2933, 1827, 1642, 1412, 1278, 1127, 913, 869; δ_H (500 MHz, $CDCl_3$) 1.10 (3 H, d, *J* 7.0), 2.16-2.26 (3 H, m), 2.29-2.34 (2 H, m), 2.52-2.58 (1 H, m), 3.13 (1 H, dd, *J* 16.5, 4.5), 3.48 (1 H, dd, *J* 16.5, 6.0), 3.78-3.83 (1 H, m), 4.46 (1 H, ddd, *J* 8.0, 6.0, 4.5), 5.05 (1 H, s), 5.06 (1 H, s), 5.12-5.17 (2 H, m), 5.80-5.89 (1 H, m); δ_C (125 MHz, $CDCl_3$) 14.7, 41.4, 41.6, 43.0, 43.1, 68.6, 73.4, 114.0, 118.2, 134.4, 146.3, 167.8.



25 **79** **78**

To a solution of alkyne **25** (42 mg, 0.137 mmol) and alkene **79** (100 mg, 0.475 mmol) in dry acetone (2.5 mL) at 0 °C was added $[CpRu(CH_3CN)_3]PF_6$ (6.0 mg, 0.0138 mmol). The mixture was warmed up to r.t. and stirred for 13 h, whereupon it was concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 20 to 40%) to afford some recovered **79** (62 mg, 0.295 mmol, 87%) and the lactone **78** (52 mg, 0.100 mmol, 75%) as a yellow oil and a 1.6:1 mixture of *C*-3 epimers (Found: *[M+Na]*$^+$, 539.3517. $C_{31}H_{52}O_4NaSi$ requires *M+Na* 539.3533, 2.9 ppm, ESIMS); $[\alpha]_D^{26}$ –0.2 (*c* 0.85, $CHCl_3$); R_f 0.40

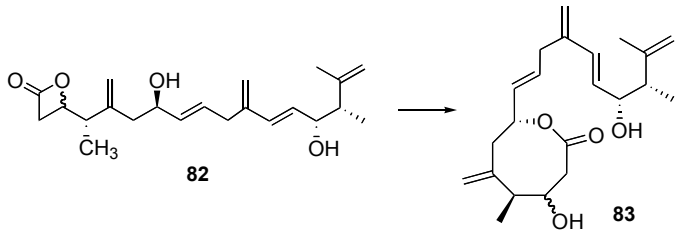
(petroleum ether-ethyl acetate, 7:3); ν_{max}/cm^{-1} 3441, 2943, 2866, 1831, 1645, 1462, 1374, 1125, 1059, 970, 882; δ_H (500 MHz, $CDCl_3$, minor diastereomer in brackets) 0.97 (3 H, d, *J* 7.0), 1.05 (21 H, s), 1.20 (1.09) (3 H, d, *J* 7.0), 1.75 (3 H, s), 2.18-2.33 (2 H, m), 2.38 (1 H, br quin., *J* 7.0), 2.90 (2 H, d, *J* 6.5), 3.12 (3.13) (1 H, dd, *J* 16.5, 4.5), 3.42 (3.45) (1 H, dd, *J* 16.5, 5.5), 4.20-4.25 (1 H, m), 4.35-4.38 (1 H, m), 4.43 (4.46) (1 H, ddd, *J* 7.0, 5.5, 4.5), 4.69 (1 H, s), 4.78 (1 H, s), 4.91 (2 H, s), 4.98 (5.03) (1 H, s), 5.02 (5.06) (1 H, s), 5.53 (5.55) (1 H, dd, *J* 15.0, 7.0), 5.61 (5.62) (1 H, dd, *J* 16.0, 6.5), 5.76 (5.76) (1 H, dt, *J* 15.0, 7.0), 6.16 (1 H, d, *J* 16.0); δ_C (125 MHz, $CDCl_3$, minor diastereomer in brackets) 12.4, 13.2 (13.3), 16.0, 18.1, 21.8, 35.0, 41.6 (41.2), 43.4 (42.9), 43.8 (43.6), 47.7, 71.1 (70.6), 73.8 (73.3), 75.3 (75.4), 111.4, 113.9 (114.1), 115.7, 129.6 (129.3), 130.5 (130.4), 131.8 (131.9), 133.7 (133.6), 143.7 (143.8), 146.0 (145.7), 146.9, 168.1 (167.8).



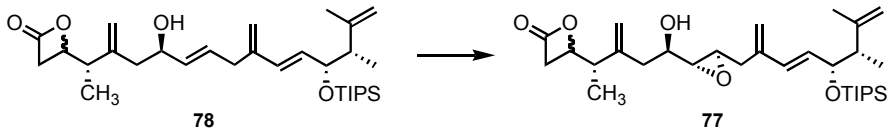
78 **82**

To a solution of lactone **78** (15 mg, 0.029 mmol) in THF (3 mL) at 0 °C was added TBAF (1.0M in THF, 0.12 mL, 0.12 mmol). The solution was stirred for 5 h, whereupon it was diluted with ether, washed with water, brine and dried over $MgSO_4$. The volatiles were removed *in vacuo* to give a residue that was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 3:2) to afford the alcohol **82** (7.5 mg, 0.021 mmol, 71%) as a colorless oil and a 1.6:1 mixture of *C*-3 epimers (Found: M^+, submitted. $C_{22}H_{32}O_4$ requires *M* 360.2301, ppm, EIMS); $[\alpha]_D^{26}$ +3.8 (*c* 0.47, $CHCl_3$); R_f 0.19 (petroleum ether-ethyl acetate, 3:2); ν_{max}/cm^{-1} 3417, 2965, 2922, 2851, 1827, 1456, 1376, 1278, 1124, 1020, 969, 894; δ_H (500 MHz, $CDCl_3$, minor diastereomer in brackets) 0.97 (3 H, d, *J* 7.0), 1.21 (1.10) (3 H, d, *J* 7.0), 1.73 (3 H, s), 2.22-2.36 (2 H, m), 2.48 (2.55) (1 H, br quin., *J* 7.0), 2.96 (2 H, d, *J* 6.5), 3.13 (3.14) (1 H, dd, *J* 16.5, 4.5), 3.44 (3.48) (1 H, dd, *J* 16.5, 6.0), 3.92 (1 H, br. t, *J* 8.0), 4.22-4.28 (1 H, m), 4.45 (4.47) (1 H, ddd, *J* 8.0, 6.0, 4.5), 4.88 (1 H, s), 4.92 (1 H, s), 4.93 (4.93) (1 H, s), 4.99 (1 H, br. s), 5.03 (5.04) (1 H, s), 5.07 (1 H, s), 5.53-5.59 (1 H, m), 5.64 (5.65) (1 H, dd, *J* 16.0, 7.5), 5.73-5.79 (1 H, m), 6.30 (1 H, d, *J* 16.0); δ_C (125 MHz, $CDCl_3$, minor diastereomer in brackets)

15.7, 16.0, 29.7, 35.0, 41.7 (41.4), 43.5, 43.8, 48.3, 71.0, 73.8, 74.4, 113.6, 114.1, 117.0, 129.6 (129.3), 130.4, 133.8 (133.9), 143.5, 145.9 (145.7), 146.8, 168.1.



Lactone **82** (1.6:1 mixture of *C*-3 epimers, 4.0 mg, 0.011 mmol) and distannoxane **85** (1.3 mg, 0.001 mmol) were placed in a dry flask, and dry hexane (7.5 mL) was added. The mixture was stirred at reflux for 20 min, cooled and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 3:2) to afford the lactone **83** (4.0 mg, 0.011 mmol, quant.) as a colorless oil and an inseparable 1.6:1 mixture of *C*-3 epimers; $[\alpha]_D^{26}$ +9.2 (*c* 0.40, $CHCl_3$); R_f 0.12 (petroleum ether-ethyl acetate, 3:2); ν_{max}/cm^{-1} 3425, 2925, 2854, 1716, 1643, 1456, 1375, 1259, 1163, 1041, 970, 899; δ_H (500 MHz, $CDCl_3$, minor diastereomer in brackets) 0.97 (0.96) (3 H, d, *J* 7.0), 1.22 (1.19) (3 H, d, *J* 7.0), 1.74 (3 H, s), 2.13 (1 H, dq, *J* 9.5, 7.0), 2.26 (1 H, dq, *J* 9.0, 7.0), 2.41 (1 H, dd, *J* 14.0, 10.5), 2.50 (1 H, dd, *J* 14.0, 2.5), 2.51 (1 H, dd, *J* 12.5, 4.5, one dia.), 2.57 (1 H, dd, *J* 11.5, 6.5, one dia.), 2.71 (1 H, dd, *J* 11.5, 5.0, other dia.), 2.99 (2 H, d, *J* 6.5), 3.06 (1 H, dd, *J* 12.5, 3.5, other dia.), 3.68 (4.10) (1 H, m), 3.93 (1 H, t, *J* 8.0), 4.88 (1 H, br. s), 4.93 (1 H, br. s), 4.93-4.98 (1 H, m), 5.00 (1 H, s), 5.02 (1 H, s), 5.09 (1 H, br. s), 5.12 (5.20) (1 H, s), 5.64 (5.63) (1 H, dd, *J* 16.0, 7.0), 5.58-5.64 (1 H, m), 5.83-5.91 (1 H, m), 6.31 (1 H, d, *J* 16.0); δ_C (125 MHz, $CDCl_3$, minor diastereomer in brackets) 15.7, 18.2, 29.7, 34.9, 38.0, 45.0, 46.4, 48.3, 74.3, 75.0, 81.8, 113.6, 116.0 (118.7), 117.3, 129.6, 130.3 (130.4), 131.1 (131.0), 133.6, 143.0, 143.1, 146.8, 172.4.



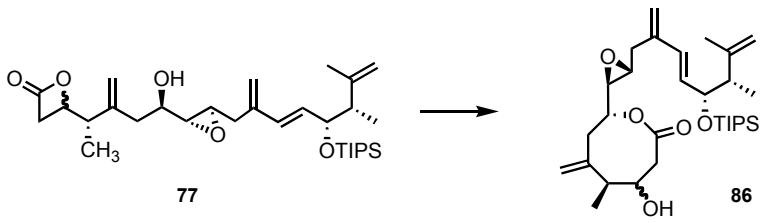
A dry flask was charged with freshly activated powdered 4Å molecular sieves (1.5 g) and CH_2Cl_2 (10 mL) and cooled to –20 °C (tetrachloroethylene/dry ice). (–)-Diethyl tartrate (102 mg, 0.495 mmol) in CH_2Cl_2 (1 mL) was added, followed with Ti(O*i*Pr)$_4$ (117 mg, 0.413 mmol)

in CH_2Cl_2 (1 mL). The mixture was stirred for 30 min, whereupon *tert*-butylhydroperoxide (6.2 M in decane, 0.13 mL, 0.806 mmol) in CH_2Cl_2 (3 mL, the solution was dried for 30 min over freshly activated powdered 4Å molecular sieves) was added. After another 30 min, a solution of alkene **78** (213 mg, 0.412 mmol) in CH_2Cl_2 (3 mL) was added. The mixture was stirred at –20 °C for 2 h, whereupon citric acid (0.036 M in ether-acetone 10% v/v, 12.0 mL, 0.432 mmol) was added and the cooling bath was removed. Upon reaching r.t. the mixture was filtered through celite and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 17:3 to 4:1) to afford one epoxide **77** epimeric at *C*-3 (45 mg, 0.084 mmol, 20%) as a pale yellow oil and a 1:1 mixture of both *C*-3 epimers (138 mg, 0.259 mmol, 63%) (Found: $[M+Na]^+$, 555.3459. $C_{31}H_{52}O_5NaSi$ requires $M+Na$ 555.3482, 4.1 ppm, ESIMS);

one *C*-3 epimer: $[\alpha]_D^{25}$ +8.7 (*c* 1.26, $CHCl_3$); R_f 0.33 (petroleum ether-ethyl acetate, 7:3); ν_{max}/cm^{-1} 3473, 2943, 2867, 1830, 1644, 1462, 1374, 1125, 1060, 969, 883; δ_H (500 MHz, $CDCl_3$) 0.98 (3 H, d, *J* 7.0), 1.05 (21 H, s), 1.20 (3 H, d, *J* 7.0), 1.76 (3 H, s), 2.22 (1 H, dd, *J* 15.0, 9.0), 2.33 (1 H, dd, *J* 15.0, 3.0), 2.36 (1 H, dd, *J* 15.0, 6.0), 2.40 (1 H, br. quin, *J* 6.5), 2.48 (1 H, dd, *J* 15.0, 6.0), 2.51 (1 H, br. quin, *J* 7.5), 2.81 (1 H, dd, *J* 3.7, 2.2), 3.17 (1 H, td, *J* 6.0, 2.2), 3.17 (1 H, dd, *J* 16.5, 4.5), 3.44 (1 H, dd, *J* 16.5, 5.5), 3.84 (1 H, br. dt, *J* 9.0, 3.7), 4.40 (1 H, td, *J* 6.0, 1.0), 4.46 (1 H, ddd, *J* 8.2, 5.5, 4.5), 4.69 (1 H, br. s), 4.79 (1 H, br. s), 4.92 (1 H, s), 5.05 (2 H, s), 5.07 (1 H, s), 5.63 (1 H, dd, *J* 16.5, 6.5), 6.21 (1 H, d, *J* 16.5); δ_C (125 MHz, $CDCl_3$) 12.4, 13.0, 16.0, 18.1, 21.9, 34.3, 39.8, 41.6, 43.6, 47.6, 54.0, 60.5, 68.1, 73.7, 75.1, 111.5, 113.8, 116.5, 130.7, 131.8, 141.2, 145.7, 146.7, 168.1.

other *C*-3 epimer: R_f 0.25 (petroleum ether-ethyl acetate, 7:3); the NMR data for this epimer was deduced from the spectrum of the pure epimer and that of the mixture δ_H (500 MHz, $CDCl_3$) 0.98 (3 H, d, *J* 7.0), 1.05 (21 H, s), 1.10 (3 H, d, *J* 7.0), 1.76 (3 H, s), 2.25 (1 H, dd, *J* 15.0, 9.0), 2.33 (1 H, dd, *J* 15.0, 3.0), 2.36 (1 H, dd, *J* 15.0, 6.0), 2.40 (1 H, br. quin, *J* 6.5), 2.47 (1 H, dd, *J* 15.0, 6.0), 2.57 (1 H, br. quin, *J* 7.5), 2.83 (1 H, dd, *J* 3.7, 2.2), 3.17 (1 H, td, *J* 6.0, 2.2), 3.13 (1 H, dd, *J* 16.5, 4.5), 3.47 (1 H, dd, *J* 16.5, 5.5), 3.86 (1 H, br. dt, *J* 9.0, 3.7), 4.39 (1 H, td, *J* 6.0, 1.0), 4.47 (1 H, ddd, *J* 8.2, 5.5, 4.5), 4.69 (1 H, br. s), 4.79 (1 H, br. s), 4.92 (1 H, s), 5.04 (1 H, s), 5.06 (1 H, s), 5.09 (1 H, s), 5.63 (1 H, dd, *J* 16.5, 6.5), 6.21 (1 H, d, *J* 16.5); δ_C

(125 MHz, $CDCl_3$) 12.4, 13.1, 16.0, 18.1, 21.9, 34.4, 39.8, 41.4, 42.9, 47.6, 54.1, 60.5, 67.6, 73.3, 75.1, 111.5, 114.1, 116.4, 130.6, 131.9, 141.3, 145.3, 146.7, 167.7.

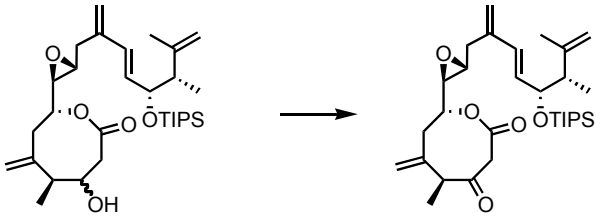


Lactone **77** (1:1 mixture of *C*-3 epimers, 128 mg, 0.240 mmol) and distannoxane **85** (14 mg, 0.011 mmol) were placed in a dry flask, and dry hexane (120 mL) was added. The mixture was stirred at reflux for 1 h, cooled down and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 17:3) to afford the lactone **86** (119 mg, 0.223 mmol, 93%) as a pale yellow oil and an inseparable 1:1 mixture of *C*-3 epimers (Found: M^+, 532.3567. $C_{31}H_{52}O_5Si$ requires *M* 532.3584, 3.2 ppm, EIMS); $[\alpha]_D^{25}$ +26.0 (*c* 1.93, $CHCl_3$); R_f 0.21 (petroleum ether-ethyl acetate, 7:3); ν_{max}/cm^{-1} 3448, 2943, 2886, 1732, 1644, 1462, 1373, 1251, 1162, 1127, 1102, 1059, 1014, 992, 987, 884; EIMS *m/z* 532 (M^+, 3), 463 [$(M–C_5H_9]^+$, 100);

one *C-3* epimer: δ_H (500 MHz, $CDCl_3$) 0.98 (3 H, d, *J* 7.0), 1.05 (21 H, s), 1.18 (3 H, d, *J* 7.0), 1.76 (3 H, s), 2.10 (1 H, dq, *J* 9.5, 7.0), 2.37-2.54 (4 H, m), 2.52 (1 H, dd, *J* 11.5, 7.0), 2.55 (1 H, dd, *J* 13.5, 3.0), 2.71 (1 H, dd, *J* 11.5, 5.0), 2.89 (1 H, dd, *J* 5.5, 2.5), 3.11 (1 H, td, *J* 5.5, 2.0), 3.66 (1 H, m), 4.25 (1 H, ddd, *J* 11.0, 5.5, 2.0), 4.40 (1 H, br. t, *J* 6.0), 4.68 (1 H, br. s), 4.78 (1 H, br. s), 5.03 (1 H, br. s), 5.06 (1 H, br. s), 5.07 (1 H, br. s), 5.12 (1 H, br. s), 5.60 (1 H, dd, *J* 16.0, 6.5), 6.20 (1 H, d, *J* 16.0); δ_C (125 MHz, $CDCl_3$) 12.4, 13.0, 18.1, 21.9, 34.17, 37.9, 41.2, 42.7, 45.0, 47.6, 56.4, 58.4, 73.3, 75.1, 81.1, 111.5, 116.7, 118.9, 130.64, 131.8, 140.8, 144.9, 146.8, 171.7.

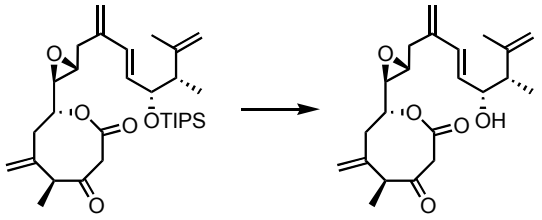
other *C-3* epimer: δ_H (500 MHz, $CDCl_3$) 0.98 (3 H, d, *J* 7.0), 1.05 (21 H, s), 1.23 (3 H, d, *J* 7.0), 1.76 (3 H, s), 2.01 (1 H, dq, *J* 9.5, 7.0), 2.37-2.54 (4 H, m), 2.49 (1 H, dd, *J* 12.5, 5.0), 2.61 (1 H, dd, *J* 14.0, 1.5), 2.91 (1 H, dd, *J* 5.0, 2.0), 2.97 (1 H, dd, *J* 12.5, 4.0), 3.14 (1 H, ddd, *J* 6.0, 5.0, 2.0), 4.10 (1 H, m), 4.40 (1 H, br. t, *J* 6.0), 4.59 (1 H, ddd, *J* 11.0, 5.0, 2.5), 4.68 (1 H, br. s), 4.78 (1 H, br. s), 5.07 (2 H, br. s), 5.12 (1 H, br. s), 5.21 (1 H, br. s), 5.60 (1 H, dd, *J* 16.0, 6.5),

6.20 (1 H, d, *J* 16.0); δ_C (125 MHz, $CDCl_3$) 12.4, 13.0, 18.1, 21.9, 34.21, 37.9, 41.2, 42.8, 43.7, 47.6, 55.8, 58.5, 73.3, 75.1, 79.3, 111.5, 116.1, 118.9, 130.68, 131.8, 140.8, 144.9, 147.4, 172.2.



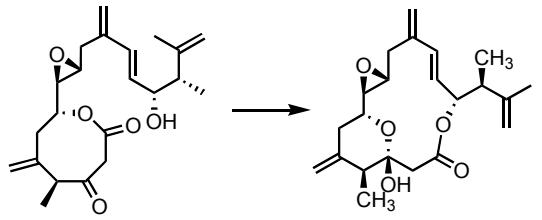
86 **87**

To a solution of alcohol **86** (86 mg, 0.161 mmol) in CH_2Cl_2 (2 mL) was added (1,1,1-triacetoxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one (102 mg, 0.240 mmol). The mixture was stirred for 1 h, whereupon CH_2Cl_2 (2 mL) and (1,1,1-triacetoxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one (102 mg, 0.240 mmol) were added. After another 15 min, ether (50 mL) was added and the mixture was washed with a 1:1 v/v solution of saturated aqueous $NaHCO_3$/1 M aqueous $Na_2S_2O_3$ (25 mL), water (25 mL), brine (25 mL) and dried over $MgSO_4$. The volatiles were removed *in vacuo* to give a residue that was purified by silica gel flash chromatography (petroleum ether-ether, 9:1) to afford the ketone **87** (70 mg, 0.132 mmol, 82%) as a pale yellow oil (Found: M^+, 530.3420. $C_{31}H_{50}O_5Si$ requires *M* 530.3427, 1.4 ppm, EIMS); $[\alpha]_D^{23}$ +31.7 (*c* 1.33, $CHCl_3$); R_f 0.27 (petroleum ether-ether, 4:1); ν_{max}/cm^{-1} 2943, 2867, 1756, 1715, 1645, 1463, 1374, 1301, 1229, 1175, 1059, 1014, 989, 884; δ_H (500 MHz, $CDCl_3$) 0.99 (3 H, d, *J* 7.0), 1.05 (21 H, s), 1.19 (3 H, d, *J* 7.0), 1.76 (3 H, s), 2.39-2.47 (4 H, m), 2.52 (1 H, dd, *J* 16.5, 5.5), 3.04 (1 H, dd, *J* 4.0, 2.0), 3.08 (1 H, td, *J* 5.5, 2.0), 3.34 (1 H, d, *J* 13.5), 3.51 (1 H, q, *J* 7.0), 3.56 (1 H, d, *J* 13.5), 4.42 (1 H, br. t, *J* 6.0), 4.69 (1 H, br. s), 4.79 (1 H, br. s), 5.04 (1 H, s), 5.06 (1 H, s), 5.09 (1 H, s), 5.10 (1 H, s), 5.08-5.12 (1 H, masked), 5.63 (1 H, dd, *J* 16.0, 6.5), 6.21 (1 H, d, *J* 16.0); δ_C (125 MHz, $CDCl_3$) 12.4, 13.0, 16.8, 18.1, 21.9, 34.2, 38.7, 47.6, 52.1, 52.4, 54.9, 57.9, 75.0, 78.7, 111.5, 116.9, 120.6, 130.7, 131.8, 140.8, 143.6, 146.8, 168.2, 200.2; EIMS *m/z* 530 (M^+, 6), 461 [$(M–C_5H_9)^+$, 94], 115 (100).



87 88

To a solution of lactone **87** (33 mg, 0.062 mmol) in THF (8 mL) at 0 °C was added TBAF (1.0M in THF, 0.3 mL, 0.3 mmol) and the cooling bath was removed. The solution was stirred for 1 h, whereupon it was diluted with ether, washed with water, brine and dried over $MgSO_4$. The volatiles were removed *in vacuo* to give a residue that was purified by silica gel flash chromatography (petroleum ether-ethyl acetate, 3:1) to afford the alcohol **88** (22 mg, 0.059 mmol, 95%) as a colorless oil (Found: *[M+Na]*$^+$, 397.1982. $C_{22}H_{30}O_5Na$ requires *M+Na* 397.1982, 2.3 ppm, ESIMS); $[\alpha]_D^{25}$ +46.2 (*c* 2.08, $CHCl_3$); R_f 0.20 (petroleum ether-ethyl acetate, 7:3); ν_{max}/cm^{-1} 3446, 2964, 2931, 1751, 1711, 1645, 1456, 1232, 1176, 1045, 1021, 986, 894; δ_H (500 MHz, $CDCl_3$) 0.99 (3 H, d, *J* 7.0), 1.19 (3 H, d, *J* 7.0), 1.73 (3 H, s), 2.27 (1 H, dq, *J* 9.0, 7.0), 2.45 (2 H, d, *J* 8.0), 2.48 (1 H, dd, *J* 15.5, 5.5), 2.54 (1 H, dd, *J* 15.5, 5.5), 3.05 (1 H, dd, *J* 4.5, 2.0), 3.09 (1 H, td, *J* 5.5, 2.0), 3.35 (1 H, d, *J* 13.5), 3.51 (1 H, q, *J* 7.0), 3.56 (1 H, d, *J* 13.5), 3.95 (1 H, br. t, *J* 8.0), 4.88 (1 H, br. s), 4.93 (1 H, br. s), 5.04 (1 H, s), 5.07 (1 H, dt, *J* 8.0, 4.5), 5.11 (1 H, s), 5.12 (1 H, s), 5.16 (1 H, s), 5.67 (1 H, dd, *J* 16.0, 7.0), 6.35 (1 H, d, *J* 16.0); δ_C (125 MHz, $CDCl_3$) 15.6, 16.8, 18.7, 36.2, 39.0, 48.2, 52.1, 52.4, 55.0, 58.0, 74.2, 78.8, 113.7, 117.9, 120.6, 130.6, 133.8, 140.8, 143.5, 146.7, 168.2, 200.2.



88 amphidinolide P (**1**)

Lactone **88** (14.0 mg, 0.037 mmol) and distannoxane **85** (9 mg, 0.007 mmol) were placed in a dry flask, and dry hexane (37 mL) was added. The mixture was stirred at reflux for 8 h, cooled down and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (petroleum ether-ether, 17:3) to afford amphidinolide P (**1**) (11.7 mg, 0.031 mmol, 84%) as a colorless oil; $[\alpha]_D^{23}$ –27.4 (*c* 0.17, MeOH); R_f 0.35 (petroleum ether-ethyl acetate, 17:3);

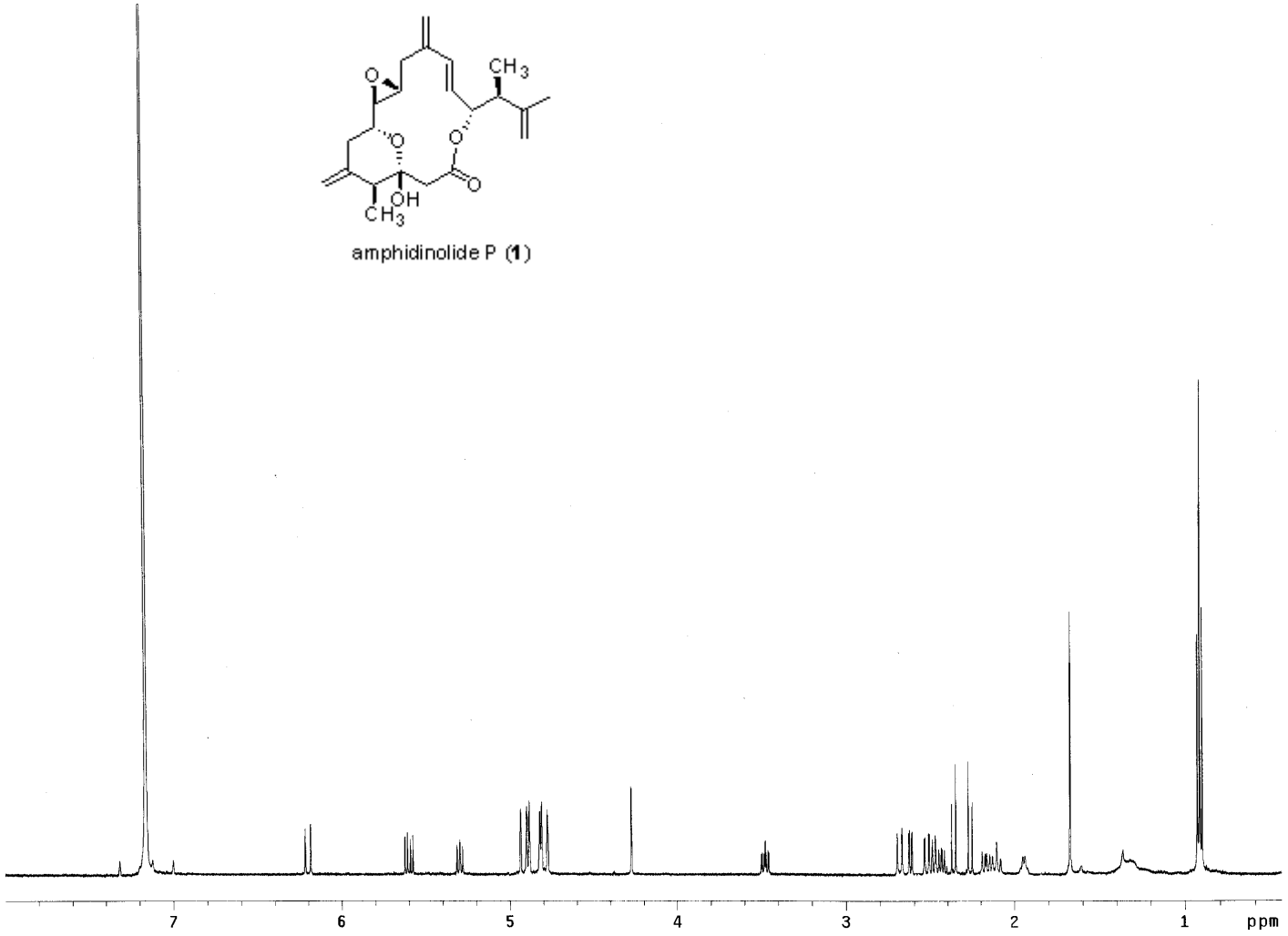
ν_{max}/cm^{-1} 3482, 3084, 2971, 2942, 1712, 1650, 1433, 1376, 1361, 1291, 1243, 1189, 1111, 988, 967, 896; δ_H (500 MHz, $CDCl_3$) 0.91 (3 H, d, *J* 7.0), 0.92 (3 H, d, *J* 7.0), 1.67 (3 H, br. s), 1.93-1.96 (1 H, m), 2.10 (1 H, dd, *J* 12.7, 11.5), 2.17 (1 H, br. dd, *J* 13.5, 9.5), 2.27 (1 H, d, *J* 12.0), 2.36 (1 H, d, *J* 12.0), 2.43 (1 H, dq, *J* 9.5, 7.0), 2.48 (1 H, dt, *J* 9.5, 1.5), 2.52 (1 H, dd, *J* 12.7, 2.7), 2.62 (1 H, dd, *J* 8.5, 1.5), 2.68 (1 H, br. d, *J* 13.5), 3.47 (1 H, ddd, *J* 11.5, 8.5, 2.7), 4.27 (1 H, d, *J* 2.0), 4.77 (1 H, m), 4.81 (1 H, br. s), 4.81-4.82 (1 H, m), 4.87-4.89 (1 H, m), 4.89-4.90 (1 H, m), 4.94 (1 H, m), 5.29 (1 H, br. t, *J* 8.5), 5.60 (1 H, dd, *J* 16.2, 7.5), 6.20 (1 H, d, *J* 16.2); δ_C (125 MHz, $CDCl_3$) 11.8, 16.1, 19.5, 36.3, 39.4, 45.0 (_ 2), 45.2, 58.2, 62.7, 73.5, 78.5, 99.2, 110.0, 112.3, 118.2, 129.1, 133.6, 142.2, 143.7, 146.5, 172.4.

Note: Data for synthetic **1** was identical to the data reported for the natural product, except for the optical rotation: $[\alpha]_D^{23}$ –27.4 (*c* 0.17, MeOH), lit. $[\alpha]_D^{20}$ +31 (*c* 0.098, MeOH) (Ishibashi, M.; Takahashi, J.; Kobayashi, J. *J. Org. Chem*. **1995**, *60*, 6062). Four optical rotation measurements in absolute methanol at slightly different concentrations gave consistent values. Concentrations of 0.09, 0.17, 0.19, 0.23 gave $[\alpha]_D^{23}$ values of –27.2, –27.4, –31.7 and –28.3, respectively. We did not observe any change of optical rotation after 5 h of storage in methanol, and the ^{1}H NMR spectra of **1** in C_6D_6 and CD_3OD were also unchanged.

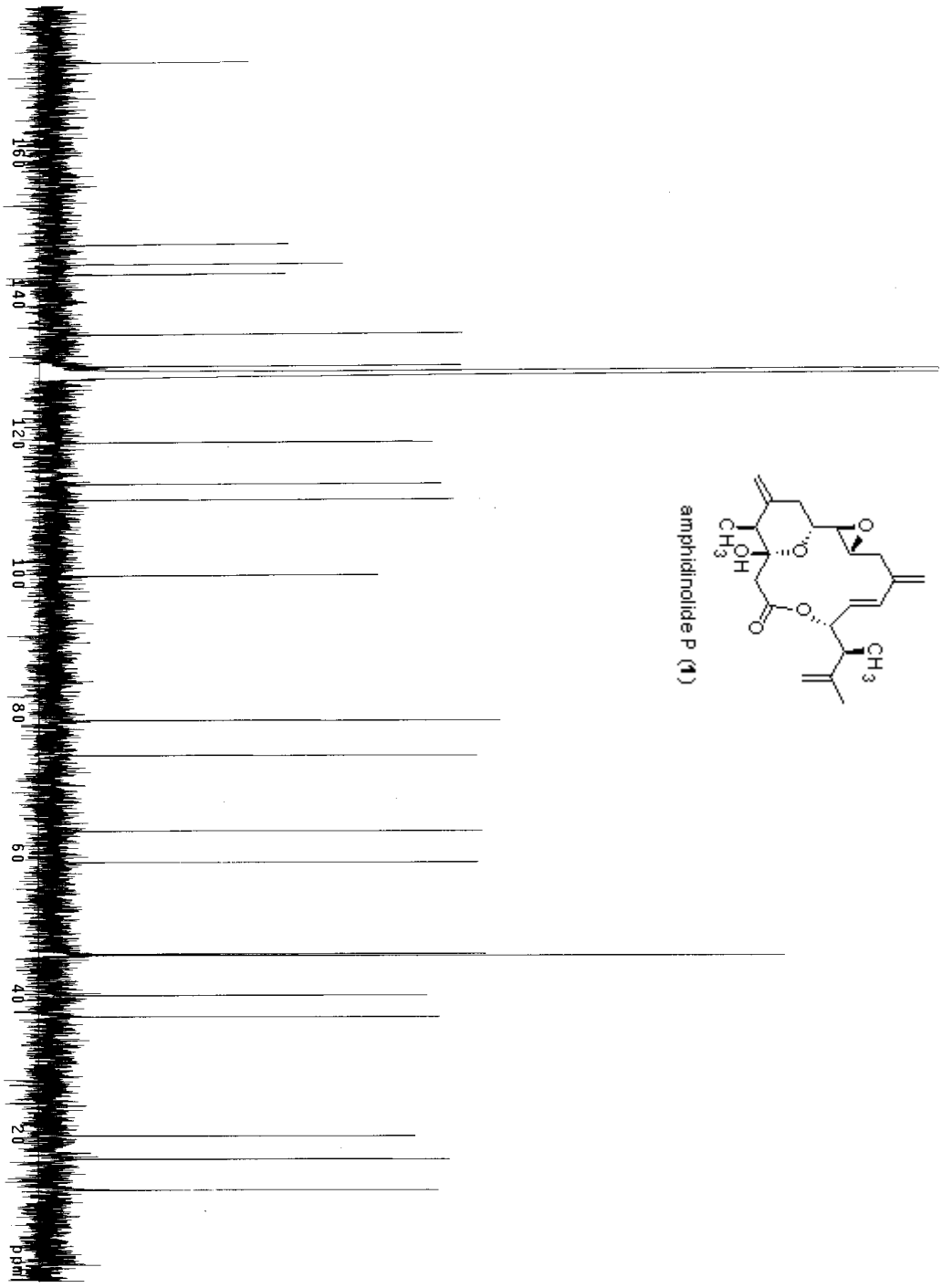
Williams *et al.* reported a synthesis of **1** which relied on two Sharpless asymmetric epoxidations to introduce the chirality, both of them using the (+)-diethyl tartrate ligand, and which should give synthetic **1** of opposite absolute configuration to the one reported herein. Yet they also reported a negative optical rotation, $[\alpha]_D^{23}$ –30 (*c* 0.09, MeOH) (Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945). Unfortunately, Professor Williams was not able to provide us with a sample of synthetic **1**, and no direct comparative measurement could be done.

assignment	natural amphidinolide P ^{1}H NMR spectrum (C_6D_6)	adjusted chemical shift* (= value - 0.04)	synthetic amphidinolide P ^{1}H NMR (C_6D_6)	natural amphidinolide P ^{13}C NMR (C_6D_6)	synthetic amphidinolide P ^{13}C NMR (C_6D_6)
1				172.4	172.4
2a	2.41 (d, 12)	2.37	2.36 (d, 12)	45.0	45.0
2b	2.31 (d, 12)	2.27	2.27 (d, 12)		
3				99.2	99.2
OH-3	4.31 (d, 1.5)	4.27	4.27 (d, 2.0)		
4	1.99 (br. q, 6.9)	1.95	1.93-1.96 (m)	45.2	45.2
5				143.7	143.7
6a	2.56 (dd, 12.7, 2.5)	2.52	2.52 (dd, 12.7, 2.7)	39.4	39.4
6b	2.14 (dd, 12.7, 11.7)	2.10	2.10 (dd, 12.7, 11.5)		
7	3.51 (ddd, 11.7, 8.3, 2.5)	3.47	3.47 (ddd, 11.5, 8.5, 2.7)	73.5	73.5
8	2.66 (dd, 8.3, 1.4)	2.62	2.62 (dd, 8.5, 1.5)	62.8	62.7
9	2.52 (dd, 9.5, 1.4)	2.48	2.48 (dt, 9.5, 1.5)	58.2	58.2
10a	2.72 (d, 13.9)	2.68	2.68 (br. d, 13.5)	36.4	36.3
10b	2.21 (dd, 13.9, 9.5)	2.17	2.17 (br. dd, 13.5, 9.5)		
11				142.3	142.2
12	6.24 (d, 16.2)	6.20	6.20 (d, 16.2)	133.6	133.6
13	5.64 (dd, 16.2, 7.5)	5.60	5.60 (dd, 16.2, 7.5)	129.1	129.1
14	5.34 (dd, 9.3, 7.5)	5.30	5.29 (br. t, 8.5)	78.5	78.5
15	2.47 (qd, 9.3, 7.3)	2.43	2.43 (dq, 9.5, 7.0)	45.0	45.0
16				146.5	146.5
17a	4.93 (br. s)	4.89	4.89-4.90 (m)	112.3	112.3
17b	4.92 (br. s)	4.88	4.87-4.89 (m)		
18 (3 H)	0.96 (d, 6.9)	0.92	0.92 (d, 7.0)	16.1	16.1
19a	4.86 (br. s)	4.82	4.81-4.82 (m)	110.0	110.0
19b	4.81 (br. s)	4.77	4.77 (m)		
20 (3 H)	0.95 (d, 7.3)	0.91	0.91 (d, 7.0)	11.8	11.8
21 (3 H)	1.71 (s)	1.67	1.67 (br. s)	19.5	19.5
22a	4.98 (br. s)	4.94	4.94 (m)	118.1	118.2
22b	4.85 (br. s)	4.81	4.81 (br. s)		

* The scale of the ^{1}H NMR spectrum for natural amphidinolide P had the benzene chemical shift off by 0.04 ppm from the accepted value. The values in this column are adjusted to place the benzene peak at its accepted value of 7.16 ppm.



amphidinolide P (**1**)


160
140
120
100
80
60
40
20
ppm
amphidinolide P (1)
CH3
OH
CH3
O
O
O
O
O
CH3