Enantioselective Synthesis of α-Methylene-β-hydroxy Carboxylic Acid Derivatives via a Diastereoselective Aldol-β-Elimination Sequence: Application to the C(15)-C(21) Fragment of Tedanolide C

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Experimental Procedures and Tabulated Spectroscopic Data

1. General Procedures:

All reactions were performed in flame-dried glassware under a slightly positive pressure of argon. Air and moisture sensitive reagents and solutions were transferred with a syringe or cannula through rubber septa.

Thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} glass plates (obtained from Merck) with a 0.25 mm thickness. TLC plates were visualized with UV light and/or by staining with a solution of cerium molybdate [prepared from 20 g $(NH_4)Mo_7O_{24}{\cdot}7H_2O$, 1 g $Ce(SO_4)_2$ and 400 mL 10% H_2SO_4]. Column Chromatography was performed on Kieselgel 60 (230-400 mesh). HPLC purifications were performed using an HPLC system composed of two pumps connected to a normal phase column, using either RI or UV detection.

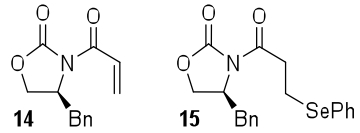
Solvents and Reagents: Dichloromethane, tetrahydrofuran, toluene, and diethyl ether were purified by pressure filtration through activated alumina. Dimethylformamide, ethanol, *t*-butanol, dimethyl sulfoxide were purchased as grade solvents and used without any further purification. Triethylamine, pyridine, 2,6-lutidine, diisopropylethylamine were distilled under argon form calcium hydride. Powdered molecular sieves 3Å were flame-dried under vacuum and used immediately.

Instrumentation: ^1H and ^{13}C NMR spectra were recorded on a commercial 400 MHz spectrometer. ^1H NMR chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.26 ppm). Coupling constants are given in Hertz (Hz). ^{13}C NMR chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane (with the $CHCl_3$ peak at 77.0 ppm).

Infrared spectra (IR) were recorded on a commercially available FT-IR spectrometer by dropping a solution of the sample on a NaCl plate. Optical rotations were measured using a quartz cell with 0.5 mL capacity and a 10 cm path length. Melting points (m. p.) were measured with a capillary melting point apparatus and are uncorrected.

High resolution mass spectra (HRMS) were recorded using an Agilent 6210 TOF mass spectrometer at the University of Florida (Gainesville).

2. Synthesis of α-Methylene-β-hydroxy Carboxylic Acid Derivatives



β-(Phenylselenyl)propionyl imide 15:

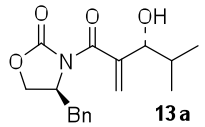
Triethylamine (17.7 mL, 127.0 mmol) was added to a stirred solution of acrylic acid (4.7 mL, 68.5 mmol) in THF (250 mL) at -25 °C followed by the slow addition of acryloyl chloride (5.2 mL, 64.0 mmol). The reaction mixture was stirred for 40 min at -20 °C. LiCl (2.82 g, 66.5 mmol) was added in one portion followed by the addition of (*S*)-4-benzyl oxazolidinone (8.5 g, 48.2 mmol). The slightly yellow cloudy reaction mixture was allowed to warm to room temperature and stirred for 36 h before being quenched with 0.2 M HCl (100 mL). The mixture was concentrated under reduced pressure and poured into ethyl acetate (200 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with a saturated solution of $NaHCO_3$ (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexanes-ethyl acetate, gradient from 5:1 to 2:1) and re-crystallization (hexane-ethyl acetate ~ 8:1) gave acryloyl imide **14** (5.7 g – 6.7 g, 51% – 60% yield) as colorless needles. The spectroscopic data were in complete agreement with the data from literature.[1]

$NaBH_4$ (783 mg, 20.7 mmol) was added in small portions to a stirred suspension of diphenyl diselenide (3.10 g, 9.93 mmol) in EtOH (85 mL) at room temperature over 5-10 min. The resulting colorless clear solution was stirred additionally for 3 min. AcOH (0.90 mL, 15.7 mmol) was added dropwise and stirring was continued for 2 min. The solution of benzeneselenol was then added slowly to a vigorously stirred solution of imide **14** (3.78 g, 16.3 mmol) in THF (55 mL) at -35 °C with a cannula over 10-15 min. After complete addition the reaction mixture turned into a thick white suspension which was stirred for 40 min with the temperature being allowed to warm to -20 °C. The reaction was quenched by the addition of a saturated solution of NH_4Cl (70 mL) and poured into dichloromethane (200 mL). The slightly yellow organic phase was separated and the aqueous phase was extracted with dichloromethane (3x). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting yellow solid was taken up in ~50 mL hexane and 2 mL dichloromethane, refluxed for 5 min and cooled to room temperature. The product was filtered, washed twice with cold hexane and dried under vacuum. Compound **15** (6.09 g, 96%) was obtained as fine white needles: m. p. = 121 °C; $[\alpha]_D^{25}$ = +65.9 (*c* = 0.735, CH_2Cl_2); IR (thin film) 3026, 1779, 1695, 1386, 1251, 1213, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.55 (m, 2H, $H_{arom.}$), 7.26 – 7.35 (m, 6H, $H_{arom.}$) 7.21 (m, 2H, $H_{arom.}$), 4.66 (m, 1H, NCH), 4.20 (dd ~ t, *J* = 9.1 Hz, 1H, C$\underline{H_A}H_B$Ph), 4.16 (dd, *J* = 9.1, 3.4 Hz, 1H, C$\underline{H_B}H_A$Ph), 3.33 – 3.48 (m, 2H, $CH_2C(O)$), 3.29 (dd, *J* = 13.4, 3.2 Hz, 1H, C$\underline{H_A}H_B$O), 3.20 (t, *J* = 6.9 Hz, 2H, CH_2Se), 2.78 (dd, *J* = 13.4, 9.5 Hz, 1H, C$\underline{H_B}H_A$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.8, 153.3, 135.1, 133.1, 129.8, 129.4, 129.2, 129.0, 127.4, 127.2, 66.3, 55.1, 37.8, 36.8, 21.3; HRMS: $[M+NH_4]^+$ calcd.: 407.0869, found: 407.0842.

General procedure for aldol reaction and β-elimination to give α-methylene-β-hydroxy imides:

A solution of Bu_2BOTf (1.20 mL, 1.20 mmol, 1.0 M in CH_2Cl_2) was added to a stirred solution of β-(phenylselenyl)propionyl imide **15** (390 mg, 1.00 mmol) in CH_2Cl_2 (5.0 mL, *c* = 0.2 M) at -78 °C. Stirring was continued for 10 min. Triethylamine (0.25 mL, 1.79 mmol) was added dropwise and the reaction mixture was stirred for 75 min at -78 °C and for 15 min at 0 °C before being re-cooled to -78 °C.

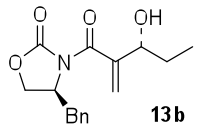
All commercially available aldehydes (1.10 mmol) were freshly distilled and used either directly or as a solution in CH_2Cl_2 (1.0 mL). The aldehyde was added dropwise, the reaction mixture was stirred for 6 h and was allowed to warm to -10 °C. Alternatively, the reaction mixture can be stirred overnight to room temperature in most instances without diminished yield. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and diluted with CH_2Cl_2 (10 mL). The organic phase was separated and the aqueous phase was extracted once with CH_2Cl_2. The combined organic layers were cooled to 0 °C. Pyridine (0.16 mL, 2.0 mmol) was added followed by the addition of H_2O_2 (0.18 mL, 3.1 mmol, 50 w% in H_2O) and the reaction mixture was stirred vigorously. The reaction progress was monitored by TLC and in cases where the oxidation did not go to completion an additional aliquot of H_2O_2 (0.09 mL, 50 w% in H_2O) was added. After TLC analysis indicated the complete consumption of the starting material, the reaction mixture was poured into the remaining aqueous phase, the organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified via column chromatography.



13a

Compound 13a from isobutyraldehyde:

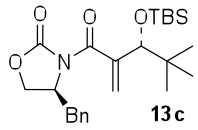
Compound **13a** was prepared by the general procedure from imide **15** (505 mg, 1.30 mmol), Bu_2BOTf (2.0 mL, 2.0 mmol, 1.0 M in CH_2Cl_2), NEt_3 (0.50 mL, 3.59 mmol) and isobutyraldehyde (0.20 mL, 2.19 mmol) in 7 mL of CH_2Cl_2. Purification of the crude product by column chromatography (hexane-ethyl acetate = 2:1) gave allylic alcohol **13a** (318 mg, 81%) as a viscous oil: $[\alpha]_D^{26}$ = +18.1 (*c* = 0.585, CH_2Cl_2); IR (thin film) 3522 (br), 2962, 2873, 1782, 1682, 1391, 1353, 1215, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.22 – 7.37 (m, 5H, $H_{arom.}$), 5.68 (s, 1H, C$\underline{H}_A$$H_B$C), 5.55 (s, 1H, C$\underline{H}_B$$H_A$C), 4.79 (m, 1H, NCH), 4.28 (dd ~ t, *J* = 8.9 Hz, 1H, C$\underline{H}_A$$H_B$Ph), 4.21 (dd, *J* = 9.1, 5.0 Hz, 1H, C$\underline{H}_B$$H_A$Ph), 4.09 (d, *J* = 7.0 Hz, 1H, C$\underline{H}$OH), 3.36 (dd, *J* = 13.4, 3.4 Hz, 1H, C$\underline{H}_A$$H_B$O), 2.95 (br s, 1H, OH), 2.83 (dd, *J* = 13.4, 9.4 Hz, 1H, C$\underline{H}_B$$H_A$O), 1.89 (octett, *J* = 6.8 Hz, 1H, C$\underline{H}$$CH_3$), 1.03 (d, *J* = 6.7 Hz, 3H, CH_3), 0.98 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ =169.6, 153.7, 147.3, 134.7, 129.2, 128.9, 127.3, 119.9, 77.2, 66.6, 54.8, 37.7, 33.5, 18.7, 18.0; HRMS: $[M+NH_4]^+$ calcd.: 321.1809, found: 321.1819.



13b

Compound 13b from propionaldehyde:

Compound **13b** was prepared by the general procedure from imide **15** (394 mg, 1.01 mmol), Bu_2BOf (1.50 mL, 1.50 mmol, 1.0 M in CH_2Cl_2), NEt_3 (0.30 mL, 2.15 mmol) and propionaldehyde (0.09 mL, 1.25 mmol) in 5 mL of CH_2Cl_2. Purification of the crude product by column chromatography (hexane-ethyl acetate = 1:1) gave allylic alcohol **13b** (273 mg, 93%) as a viscous oil: $[\alpha]_D^{24}$ = +48.2 (*c* = 0.845, CH_2Cl_2); IR (thin film) 3502 (br), 2968, 2932, 1783, 1684, 1391, 1353, 1312, 1214 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.35 (m, 3H, $H_{arom.}$), 7.22 (m, 2H, $H_{arom.}$), 5.64 (s, 1H, $C\underline{H}_AH_BC$), 5.46 (s, 1H, $C\underline{H}_BH_AC$), 4.78 (m, 1H, NCH), 4.30 (m, 2H, $C\underline{H}_AH_BPh$ and overlapping $C\underline{H}OH$), 4.21 (dd, *J* = 9.1, 4.6 Hz, 1H, $C\underline{H}_BH_APh$), 3.34 (dd, *J* = 13.5, 3.4 Hz, 1H, $C\underline{H}_AH_BO$), 2.88 (dd, *J* = 13.5, 9.1 Hz, 2H, $C\underline{H}_BH_AO$ and overlapping OH), 1.72 (dq ~ quint, *J* = 7.5 Hz, 2H, CH_2), 1.01 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.5, 153.7, 147.8, 134.7, 129.3, 128.9, 127.4, 118.4, 73.4, 66.6, 54.9, 37.6, 29.2, 9.8; HRMS: $[M+NH_4]^+$ calcd.: 307.1652, found: 307.1663.

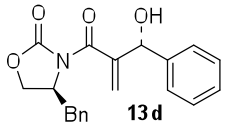


13c

Compound 13c from pivaldehyde:

Compound **13c** was prepared as follows. Bu_2BOTf (3.0 mL, 3.0 mmol, 1.0 M in CH_2Cl_2) was added to a stirred solution of imide **15** (810 mg, 2.09 mmol) in CH_2Cl_2 (10 mL) at -78 °C and stirring was continued for 10 min. Et_3N (1.0 mL, 7.17 mmol) was added dropwise and the mixture was stirred for 75 min at -78 °C and 10 min at 0 °C before being re-cooled to -78 °C. Pivaldehyde (0.30 mL, 2.76 mmol) was added dropwise, the reaction mixture was stirred overnight and was allowed to warm to room temperature. The reaction was quenched with a saturated solution of NH_4Cl (5 mL), the organic phase was separated and the aqueous phase was extracted 1 time with CH_2Cl_2 (10 mL). The combined organic layers were cooled to 0 °C, pyridine (0.10 mL) was added and 3 aliquots of H_2O_2 (0.20 mL each, 50 wt% in H_2O) were added every 15 min until TLC analysis indicated complete consumption of the intermediate aldol. The reaction mixture was poured into the original aqueous phase, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). Purification of the crude product by column chromatography (hexane-ethyl acetate = 3:1) gave the corresponding allylic alcohol which could not be separated from imide **14** (formed after oxidation of remaining imide **15**). Therefore, TBSOTf (0.46 mL, 2.0 mmol) was added to a stirred solution of the impure allylic alcohol and 2,6-lutidine (0.50 mL, 4.29 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction was stirred overnight and was allowed to warm to room temperature. The reaction mixture was diluted with a saturated solution of $NaHCO_3$ (10 mL), the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification of the crude product by column chromatography (hexane-ethyl acetate = 10:1) gave TBS-ether **13c** (503 mg, 56%) as a colorless, viscous oil which was, in turn, contaminated with small amounts of

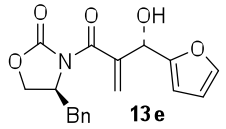
TBSOH. $[\alpha]_D^{25}$ = +54.2 (*c* = 0.45, CH_2Cl_2); IR (thin film) 2956, 2858, 1790, 1682, 1361, 1213, 1105, 1083, 874, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.24 – 7.34 (m, 3H, $H_{arom.}$), 7.17 (m, 2H, $H_{arom.}$), 6.00 (s, 1H, $C\underline{H}_AH_BC$), 5.79 (s, 1H, $C\underline{H}_BH_AC$), 4.85 (m, 1H, NCH), 4.53 (s, 1H, CHOSi), 4.28 (dd ~ t, *J* = 8.8 Hz, 1H, $C\underline{H}_AH_BPh$), 4.15 (dd, *J* = 9.0, 7.0 Hz, 1H, $C\underline{H}_BH_APh$), 3.25 (dd, *J* = 13.5, 3.5 Hz, 1H, $C\underline{H}_AH_BO$), 2.86 (dd, *J* = 13.5, 8.8 Hz, 1H, $C\underline{H}_BH_AO$), 0.95 (s, 9H, 3xCH_3), 0.88 (s, 9H, 3xCH_3), 0.12 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.7, 152.9, 143.6, 134.8, 129.4, 128.9, 127.4, 126.5, 77.3, 66.1, 54.9, 37.5, 36.5, 25.9, 25.4, 18.1, -4.7, -5.3; HRMS: $[M+NH_4]^+$ calcd.: 449.2836, found: 449. 2848.



13d

Compound 13d from benzaldehyde:

Compound **13d** was prepared by the general procedure from imide **15** (790 mg, 2.03 mmol), Bu_2BOTf (3.0 mL, 3.0 mmol, 1.0 M in CH_2Cl_2), NEt_3 (0.56 mL, 4.02 mmol) and benzaldehyde (0.24 mL, 2.36 mmol) in 10 mL of CH_2Cl_2. Purification of the crude product by column chromatography (hexanes-ethyl acetate = 2:1) gave allylic alcohol **13d** (590 mg, 86%) as colorless crystals: m. p. = 158 °C; $[\alpha]_D^{25}$ = +58.7 (*c* = 0.68, CH_2Cl_2); IR (thin film) 3350 (br), 3025, 1783, 1682, 1387, 1353, 1199, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.26 – 7.48 (m, 8H, $H_{arom.}$), 7.17 (m, 2H, $H_{arom.}$), 5.62 (d, *J* = 5.8 Hz, 1H, C<u>H</u>OH), 5.59 (s, 2H, overlapping CH_2C), 4.68 (m, 1H, NCH), 4.23 (dd ~ t, *J* = 9.0 Hz, 1H, $C\underline{H}_AH_BPh$), 4.17 (dd, *J* = 9.0, 4.2 Hz, 1H, $C\underline{H}_BH_APh$), 3.22 (dd, *J* = 13.5, 3.4 Hz, 1H, $C\underline{H}_AH_BO$), 3.14 (d, *J* = 5.8 Hz, 1H, OH), 2.74 (dd, *J* = 13.5, 9.2 Hz, 1H, $C\underline{H}_BH_AO$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.3, 153.6, 146.5, 140.6, 134.8, 129.4, 129.0, 128.5, 128.1, 127.4, 126.9, 120.7, 74.0, 66.6, 55.3, 37.4; HRMS: $[M+NH_4]^+$ calcd.: 355.1652, found: 355.1627.

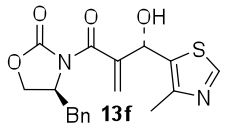


13e

Compound 13e from 2-furaldehyde:

Compound **13e** was prepared by the general procedure from imide **15** (835 mg, 2.15 mmol), Bu_2BOTf (3.30 mL, 3.3 mmol, 1.0 M in CH_2Cl_2), NEt_3 (1.0 mL, 7.17 mmol) and 2-furaldehyde (0.20 mL, 2.41 mmol, distilled from K_2CO_3) in 12 mL of CH_2Cl_2. The reaction was stirred for 5 h and then was allowed to warm to -15 °C. Purification of the crude product by column chromatography (hexane-ethyl acetate = gradient from 2:1 to 1:1) gave allylic alcohol **13e** (900 mg, 86%) as slightly yellow crystals: m. p. = 89 – 92 °C; $[\alpha]_D^{24}$ = +56.3 (*c* = 0.915, CH_2Cl_2); IR (thin film) 3468 (br), 2922, 1781, 1685, 1391, 1354, 1215, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.43 (dd, *J* = 1.8, 0.8 Hz, 1H, H_{furan}), 7.28 – 7.34 (m, 3H, $H_{arom.}$), 7.17 (m, 2H, $H_{arom.}$), 6.41 (d, *J* = 3.2 Hz, 1H, H_{furan}), 6.36 (dd, *J* = 3.2, 1.8 Hz, 1H, H_{furan}), 5.83 (d, *J* = 1.5 Hz, 1H, $C\underline{H}_AH_BC$), 5.72 (d, *J* = 1.0 Hz, 1H, CH_BH_AC), 5.66 (s, 1H, C<u>H</u>OH), 4.74 (m, 1H, NCH), 4.27 (dd ~ t, *J* = 9.0 Hz, 1H, $C\underline{H}_AH_BPh$), 4.19 (dd, *J* = 9.0, 4.6 Hz, 1H, $C\underline{H}_BH_APh$), 3.26 (br s, 1H, OH), 3.23 (dd, *J* = 13.6, 3.4

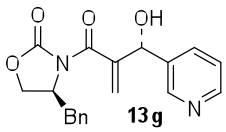
Hz, 1H, C$\underline{H_A}H_BO$), 2.80 (dd, *J* = 13.6, 9.0 Hz, 1H, C$\underline{H_B}H_AO$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.5, 153.5, 153.3, 144.3, 142.8, 134.6, 129.4, 128.9, 127.4, 121.6, 110.4, 108.3, 67.3, 66.6, 55.0, 37.3; HRMS: $[M+NH_4]^+$ calcd. 345.1445, found: 345.1446.



13f

<u>Compound 13f from 4-methylthiazole-5-carboxaldehyde</u>:

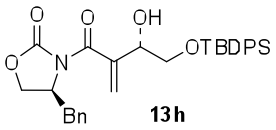
Compound **13f** was prepared by the general procedure from imide **15** (729 mg, 1.88 mmol), Bu_2BOTf (2.90 mL, 2.90 mmol, 1.0 M in CH_2Cl_2), NEt_3 (0.85 mL, 6.10 mmol) and a solution of 4-methylthiazole-5-carboxaldehyde (270 mg, 2.12 mmol, solution in 2 mL of CH_2Cl_2) in 8 mL of CH_2Cl_2. Purification of the crude product by column chromatography (hexane-ethyl acetate = gradient from 1:1 to 1:2) gave allylic alcohol **13f** (567 mg, 84%) as colorless crystals: m. p. = 144 °C (decomposition); $[\alpha]_D^{24}$ = +54.7 (*c* = 1.19, CH_2Cl_2); IR (thin film) 3200 (br), 3029, 2922, 1784, 1684, 1389, 1353, 1213, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65 (s, 1H, $H_{thiazole}$), 7.25 – 7.33 (m, 3H, $H_{arom.}$), 7.17 (m, 2H, $H_{arom.}$), 5.92 (s, 1H, C$\underline{H}$OH), 5.65 (d, *J* = 1.5 Hz, 1H, C$\underline{H_A}H_BC$), 5.62 (d, *J* = 1.0 Hz, 1H, C$\underline{H_B}H_AC$), 4.71 (m, 1H, NCH), 4.27 (dd ~ t, *J* = 9.0 Hz, 1H, C$\underline{H_A}H_BPh$), 4.19 (dd, *J* = 9.0, 4.2 Hz, 1H, C$\underline{H_B}H_APh$), 3.88 (br s, 1H, OH), 3.25 (br d, *J* = 13.4 Hz, 1H, C$\underline{H_A}H_BO$), 2.77 (dd, *J* = 13.4, 9.4 Hz, 1H, C$\underline{H_B}H_AO$), 2.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.5, 153.5, 151.8, 150.0, 145.2, 134.6, 132.3, 129.3, 129.0, 127.5, 120.9, 67.3, 66.7, 55.3, 37.5, 15.3; HRMS $[M+H]^+$ calcd.: 359.1060, found: 359.1058.



13g

<u>Compound 13g from pyridine-3-carboxaldehyde (nicotinealdehyde):</u>

Compound **13g** was prepared by the general procedure from imide **15** (420 mg, 1.08 mmol), Bu_2BOTf (1.60 mL, 1.60 mmol, 1.0 M in CH_2Cl_2), NEt_3 (0.50 mL, 3.58 mmol) and pyridine-3-carboxaldehyde (0.13 mL, 1.38 mmol) in 6 mL of CH_2Cl_2. The reaction mixture was stirred overnight and was allowed to warm to room temperature. Purification of the crude product by column chromatography (hexane-ethyl acetate = gradient from 1:1 to 1:5) gave allylic alcohol **13g** (323 mg, 88%) as a slightly yellow crystals: m. p. = 132 – 134 °C (decomposition); $[\alpha]_D^{25}$ = +60.1 (*c* = 0.50, acetone); IR (thin film) 3400 (br), 2855, 1794, 1678, 1351, 1215 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-D_6) δ = 8.67 (s, 1H, $H_{pyridine}$), 8.51 (dd, *J* = 4.8, 1.5 Hz, 1H, $H_{pyridine}$), 7.78 (m, 1H, $H_{pyridine}$), 7.40 (dd, *J* = 7.8, 4.8 Hz, 1H, $H_{pyridine}$), 7.27 – 7.36 (m, 3H, $H_{arom.}$), 7.21 (m, 2H, $H_{arom.}$), 6.08 (s, 1H, OH), 5.67 (s, 1H, C$\underline{H_A}H_BC$), 5.64 (s, 1H, C$\underline{H_B}H_AC$), 5.61 (s, 1H, C$\underline{H}$OH), 4.69 (m, 1H, NCH), 4.34 (dd ~ t, *J* = 8.6 Hz, 1H, C$\underline{H_A}H_BPh$), 4.21 (dd, *J* = 8.7, 4.6 Hz, 1H, C$\underline{H_B}H_APh$), 2.95 (dd, *J* = 13.4, 3.2 Hz, 1H, C$\underline{H_A}H_BO$), 2.83 (dd, *J* = 13.4, 8.3 Hz, 1H, C$\underline{H_B}H_AO$); ^{13}C NMR (100 MHz, DMSO-D_6) δ = 169.3, 153.5, 149.7, 147.5, 138.5, 136.4, 135.9, 130.3, 129.5, 127.8, 124.3, 119.9, 70.8, 67.3, 55.2, 37.4; HRMS: $[M+Na]^+$ calcd.: 361.1191, found: 361.1178.

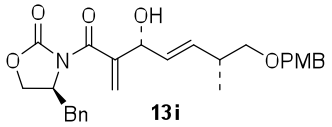


13h

Compound 13h from aldehyde 16:

Aldehyde **16** was prepared from 2-butene-1,4-diol following a literature procedure.[2]

Compound **13h** was prepared by the general procedure from imide **15** (312 mg, 0.80 mmol), Bu_2BOTf (1.20 mL, 1.20 mmol, 1.0 M in CH_2Cl_2), NEt_3 (0.35 mL, 2.51 mmol) and a solution of aldehyde **16** (350 mg, 1.17 mmol, solution in 1 mL of CH_2Cl_2) in 5 mL of CH_2Cl_2. Purification of the crude product by column chromatography (hexane-ethyl acetate = 3:1) gave allylic alcohol **13h** (372 mg, 88%) as colorless crystals: m. p. = 81 °C; $[\alpha]_D^{24}$ = +26.4 (*c* = 2.705, CH_2Cl_2); IR (thin film) 3504 (br), 2930, 2857, 1786, 1686, 1353, 1214, 1112, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.69 (m, 4H, $H_{arom.}$), 7.25 – 7.44 (m, 9H, $H_{arom.}$), 7.18 (m, 2H, $H_{arom.}$), 5.71 (d, *J* = 1.0 Hz, 1H, C$\underline{H}_A$$H_B$C), 5.57 (s, 1H, C$\underline{H}_B$$H_A$C), 4.70 (m, 1H, NCH), 4.64 (dd ~ t, *J* = 5.8 Hz, 1H, C$\underline{H}$OH), 4.21 (dd ~ t, *J* = 8.9 Hz, 1H, C$\underline{H}_A$$H_B$Ph), 4.14 (dd, *J* = 9.0, 4.8 Hz, 1H, C$\underline{H}_B$$H_A$Ph), 3.79 (m, 2H, CH_2OSi), 3.26 (dd, *J* = 13.4, 3.4 Hz, 1H, C$\underline{H}_A$$H_B$O), 2.98 (br s, 1H, OH), 2.70 (dd, *J* = 13.4, 9.4 Hz, 1H, C$\underline{H}_B$$H_A$O), 1.07 (s, 9H, $(CH_3)_3$C); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.8, 153.4, 144.7, 135.6, 134.9, 133.0, 133.0, 129.8, 129.3, 128.9, 127.7, 127.4, 120.3, 71.7, 67.2, 66.5, 54.9, 37.7, 26.8, 19.2; HRMS: $[M+Na]^+$: calcd.: 552.2177, found: 552.2200.



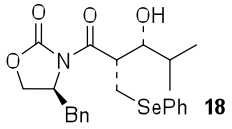
13i

Compound 13i from α,β-unsaturated aldehyde 17:

Aldehyde **17** was prepared by Parikh-Doering oxidation from alcohol **22** as described in the literature.[3]

Compound **13i** was prepared by the general procedure from imide **15** (371 mg, 0.96 mmol), Bu_2BOTf (1.40 mL, 1.40 mmol, 1.0 M in CH_2Cl_2), NEt_3 (0.35 mL, 2.51 mmol) and a solution of aldehyde **17** (195 mg, 0.83 mmol, solution in 1 mL of CH_2Cl_2) in 5 mL of CH_2Cl_2. The reaction was stirred for 4 h and was allowed to warm to -30 °C. Purification of the crude product by column chromatography (hexane-ethyl acetate = 1.25:1) gave allylic alcohol **13i** (296 mg, 76%) as colorless, highly viscous oil. $[\alpha]_D^{24}$ = +44.1 (*c* = 0.845, CH_2Cl_2); IR (thin film) 3479 (br), 2960, 2931, 2859, 1789, 1685, 1514, 1354, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.20 – 7.36 (m, 7H, $H_{arom.}$), 6.86 (m, 2H, $H_{arom.}$), 5.79 (dd, *J* = 15.6, 6.9 Hz, 1H, (*E*)-C$\underline{H}$=CH), 5.62 (ddd, *J* = 15.6, 6.8, 0.9 Hz, 1H, (*E*)-CH=C$\underline{H}$), 5.62 (d, *J* = 1.3 Hz, 1H, C$\underline{H}_A$$H_B$C), 5.44 (s, 1H, C$\underline{H}_B$$H_A$C), 4.94 (br s, 1H, C$\underline{H}$OH), 4.72 (m, 1H, NCH), 4.43 (s, 2H, PMPCH_2O), 4.26 (dd ~ t, *J* = 9.0 Hz, 1H, C$\underline{H}_A$$H_B$Ph), 4.19 (dd, *J* = 9.1, 4.1 Hz, 1H, C$\underline{H}_B$$H_A$Ph), 3.78 (s, 3H, OCH_3), 3.28 – 3.38 (m, 3H, C$\underline{H}_A$$\underline{H}_BOCH_2$ and overlapping C$\underline{H}_A$$H_B$O), 2.86 (dd, *J* = 13.5, 9.2 Hz, 1H, C$\underline{H}_B$$H_A$O), 2.67 (d, *J* = 4.7 Hz, 1H, OH), 2.54 (m, 1H, C$\underline{H}$$CH_3$), 1.06 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.3, 159.1, 153.6, 146.6, 136.6, 134.8, 130.6, 129.5, 129.1, 129.0, 128.9, 127.5, 118.7, 113.7, 74.7, 72.9, 72.6, 66.6, 55.2, 37.6, 36.5, 16.8; HRMS: $[M+NH_4]^+$ calcd.: 483.2490, found: 483.2505.

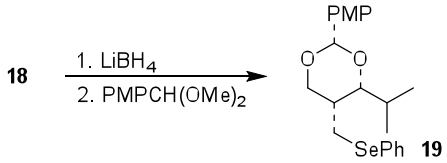
3. Stereochemicial Assignment of the Intermediate Syn Aldols



18

Aldol 18:

A solution of Bu_2BOTf (3.90 mL, 3.90 mmol, 1.0 M in CH_2Cl_2) was added to a stirred solution of compound **15** (1.01 g, 2.60 mmol) in CH_2Cl_2 (7.5 mL) at -78 °C. The mixture was stirred for 5 – 10 min, then Triethylamine (1.10 mL, 7.89 mmol) was added dropwise and stirring was continued at -78 °C for 80 min and at 0 °C for 10 min. The solution of the enol borane was re-cooled to -78 °C and isobutyraldehyde (0.37 mL, 4.05 mL) was added dropwise. The reaction mixture was stirred overnight and allowed to warm to room temperature before being quenched with a saturated solution of $KHCO_3$ (10 mL); the mixture was stirred for additional 60 min before workup. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexane-ethyl acetate = gradient from 3:1 to 1:1) gave aldol **18** (1.053 mg, 88% yield) as a highly viscous oil. $[\alpha]_D^{25}$ = -43.9 (*c* = 5.17, CH_2Cl_2); IR (thin film) 3475 (br), 2962, 1778, 1693, 1384, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.58 (m, 2H, $H_{arom.}$), 7.27 – 7.35 (m, 8H, $H_{arom.}$), 4.73 (m, 1H, NCH), 4.58 (m, 1H, CHC(O)), 4.20 (dd ~ t, *J* = 9.2 Hz, 1H, C$\underline{H}_A$H$_B$Ph), 4.17 (dd, *J* = 9.2, 3.5 Hz, 1H, C$\underline{H}_B$H$_A$Ph), 3.55 (dd, *J* = 8.1, 3.2 Hz, 1H, C$\underline{H}$OH), 3.44 (dd ~ t, *J* = 12.1 Hz, 1H, C$\underline{H}_A$H$_B$Se), 3.35 (dd, *J* = 13.5, 3.2 Hz, 1H, C$\underline{H}_A$H$_B$O), 3.19 (dd, *J* = 12.3, 3.4 Hz, 1H, C$\underline{H}_B$H$_A$Se), 2.79 (dd, *J* = 13.5, 9.6 Hz, 1H, C$\underline{H}_B$H$_A$O), 2.37 (br s, 1H, OH), 1.72 (m, 1H, C$\underline{H}$CH$_3$), 1.00 (d, *J* = 6.6 Hz, 3H, CH_3), 0.80 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.9, 152.9, 135.2, 133.3, 130.1, 129.4, 129.1, 128.9, 127.3, 127.3, 77.3, 66.0, 55.5, 46.5, 37.6, 31.4, 24.2, 18.9, 18.6; HRMS: $[M+Na]^+$ calcd.: 484.0999, found: 484.1007.



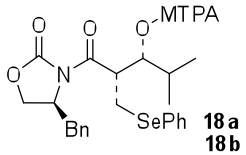
19

PMP-Acetal **19**:

$LiBH_4$ (60 mg, 2.75 mmol) was added in one portion to a stirred solution of aldol **18** (750 mg, 1.63 mmol) in Et_2O (20 mL) and H_2O (0.02 mL) at 0 °C. The reaction was stirred for 2 h, quenched with a saturated solution of NH_4Cl (10 mL) and poured into CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexane-ethyl acetate = gradient from 2:1 to 1:1) gave the corresponding diol (397 mg, 85%) as colorless crystals: m. p. = 52 °C; $[\alpha]_D^{25}$ = -59.6 (*c* = 0.85, CH_2Cl_2); IR (thin film) 3368, 2959, 2873, 1579, 1477, 1437, 1023, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.54 (m, 2H, $H_{arom.}$), 7.24 – 7.29 (m, 3H, $H_{arom.}$), 4.07 (dd, *J* = 10.8, 4.4 Hz, 1H, C$\underline{H}_A$H$_B$O), 3.81 (dd, *J* = 10.8, 3.4 Hz, 1H, C$\underline{H}_B$H$_A$O), 3.49 (dd, *J* = 8.6, 2.8 Hz, 1H,

C<u>H</u>OH), 3.15 (dd, *J* = 12.4, 3.6 Hz, 1H, C<u>H</u>$_A$H$_B$Se), 3.08 (dd, *J* = 12.4, 10.0 Hz, 1H, C<u>H</u>$_B$H$_A$Se), 2.94 (br s, 2H, 2xOH), 1.89 (m, 1H, C<u>H</u>CH$_2$), 1.74 (m, 1H, C<u>H</u>CH$_3$), 0.98 (d, *J* = 6.5 Hz, 3H, CH$_3$), 0.70 (d, *J* = 6.8 Hz, 3H, CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 133.0, 132.9, 130.2, 129.0, 127.0, 80.1, 64.9, 41.5, 30.9, 24.1, 18.9, 18.9; HRMS: [M+NH$_4$]$^+$ calcd.: 306.0967, found: 306.0966.

Freshly distilled 4-methoxybenzaldehyde dimethyl acetal (0.10 mL, 0.57 mmol) was added to a stirred solution of the latter diol (125 mg, 0.435 mmol) in CH_2Cl_2 (12 mL) at 0 °C followed by the addition of (±)-CSA (small spatula, approx. 5 mg). The reaction was stirred for 20 min and quenched with a saturated solution of $NaHCO_3$ (5 mL). The organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexane-ethyl acetate = 6:1) gave PMP-acetal **19** (171 mg, 97%) as a highly viscous oil. $[\alpha]_D^{25}$ = -57.0 (*c* = 1.15, CH_2Cl_2); IR (thin film) 2960, 2836, 1615, 1518, 1248, 1143, 1098, 1034 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.56 (m, 2H, H$_{arom.}$), 7.41 (m, 2H, H$_{arom.}$), 7.25 (m, 3H, H$_{arom.}$), 6.89 (m, 2H, H$_{arom.}$), 5.46 (s, 1H, CHPMP), 4.63 (d, *J* = 11.5 Hz, 1H, C<u>H</u>$_A$H$_B$O), 3.91 (dd ~ d, *J* = 11.5 Hz, 1H, C<u>H</u>$_B$H$_A$O), 3.81 (s, 3H, OCH$_3$), 3.42 (dd, *J* = 10.1, 1.9 Hz, 1H, CHO), 3.29 (dd ~ t, *J* = 12.2 Hz, 1H, C<u>H</u>$_A$H$_B$Se), 3.14 (dd ~ d, *J* = 12.4 Hz, 1H, C<u>H</u>$_B$H$_A$Se), 1.84 (m, 1H, C<u>H</u>CH$_3$), 1.69 (m, 1H, C<u>H</u>CH$_2$), 1.01 (d, *J* = 6.4 Hz, 3H, CH$_3$), 0.67 (d, *J* = 6.8 Hz, 3H, CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 159.8, 133.4, 131.3, 130.0, 129.0, 127.2, 127.1, 113.6, 101.9, 86.1, 70.1, 55.3, 35.7, 29.3, 24.8, 19.7, 17.1; HRMS: [M+Na]$^+$ calcd.: 429.0941, found: 429.0932.



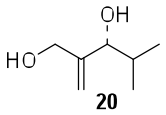
18a
18b

<u>Mosher Ester 18a from (*S*)-MTPACl</u>:

^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.60 (m, 2H, H$_{arom.}$), 7.56 (m, 2H, H$_{arom.}$), 7.27 – 7.41 (m, 11H, H$_{arom.}$), 4.96 (dd, *J* = 9.9, 2.1 Hz, 1H, CHOMTPA), 4.59 and 4.58 (m, 2H, NCH and overlapping CHC(O)), 4.37 (dd ~ t, *J* = 8.6 Hz, 1H, C<u>H</u>$_A$H$_B$Ph), 4.21 (dd, *J* = 8.8, 2.4 Hz, 1H, C<u>H</u>$_B$H$_A$Ph), 3.69 (s, 3H, OCH$_3$), 3.39 (dd ~ t, *J* = 12.2 Hz, 1H, C<u>H</u>$_A$H$_B$Se), 3.26 (dd, *J* = 13.6, 3.1 Hz, 1H, C<u>H</u>$_A$H$_B$O), 2.96 (dd, *J* = 13.6, 8.8 Hz, 1H, C<u>H</u>$_B$H$_A$O), 2.92 (dd, *J* = 12.6, 2.6 Hz, 1H, C<u>H</u>$_B$H$_A$Se), 1.83 (m, 1H, C<u>H</u>CH$_3$), 0.64 (d, *J* = 6.8 Hz, 3H, CH$_3$), 0.53 (d, *J* = 6.5 Hz, 3H, CH$_3$).

<u>Mosher Ester 18b from (*R*)-MTPACl</u>:

^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.58 (m, 4H, H$_{arom.}$), 7.27 – 7.43 (series of m, 11H, H$_{arom.}$), 5.02 (dd, *J* = 9.3, 2.3 Hz, 1H, CHOMTPA), 4.62 (m, 1H, NCH), 4.56 (ddd ~ dt, *J* = 11.7, 2.4 Hz, 1H, CHC(O)), 4.33 (dd ~ t, *J* = 8.7 Hz, 1H, C<u>H</u>$_A$H$_B$Ph), 4.20 (dd, *J* = 8.9, 2.4 Hz, 1H, C<u>H</u>$_B$H$_A$Ph), 3.53 (s, 3H, OCH$_3$), 3.35 (dd ~ t, *J* = 12.1 Hz, 1H, C<u>H</u>$_A$H$_B$Se), 3.26 (dd, *J* = 13.6, 3.0 Hz, 1H, C<u>H</u>$_A$H$_B$O), 2.92 (2x dd ~ m, 2H, C<u>H</u>$_B$H$_A$Se and overlapping C<u>H</u>$_B$H$_A$O), 1.91 (m, 1H, C<u>H</u>CH$_3$), 0.82 (d, *J* = 6.5 Hz, 3H, CH$_3$), 0.70 (d, *J* = 6.8 Hz, 3H, CH$_3$).

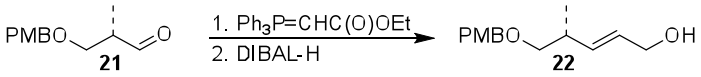


20

Diol 20:

$NaBH_4$ (30 mg, 0.793 mmol) was added in one portion to a stirred solution of **18** (160 mg, 0.527 mmol) and $CeCl_3 \cdot 7H_2O$ (240 mg, 0.644 mmol) in MeOH (8 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min before being quenched with a saturated solution of NH_4Cl (5 mL). CH_2Cl_2 (15 mL) was added, the organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexane-ethyl acetate = 2:1) gave diol **20** (38 mg, 55% yield) as colorless crystals. The spectroscopic data were in full agreement with the data reported for *ent*-**20** in literature.[4] m. p. = 47 °C; $[\alpha]_D^{24}$ = +17.6 (*c* = 1.80, $CHCl_3$); IR (thin film) 3405 (br), 2925, 2897, 1384, 1319, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.15 (d, *J* = 1.0 Hz, 1H, $C\underline{H}_AH_BC$), 5.06 (s, 1H, $C\underline{H}_BH_AC$), 4.27 (d, *J* = 13.2 Hz, 1H, $C\underline{H}_AH_BO$), 4.09 (d, *J* = 13.2 Hz, 1H, $C\underline{H}_BH_AO$), 3.83 (d, *J* = 7.8 Hz, 1H, C<u>H</u>OH), 2.74 (br s, 2H, 2xOH), 1.82 (m, 1H, CH), 0.98 (d, *J* = 6.6 Hz, 3H, CH_3), 0.83 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.7, 113.6, 80.7, 63.9, 31.8, 19.3, 18.2; HRMS: $[M+H]^+$ calcd.: 131.1067, found: 131.1073.

4. Synthesis of the C(15)-C(21) Fragment of Tedanolide C

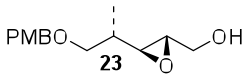


21 **22**

Allylic alcohol 22:

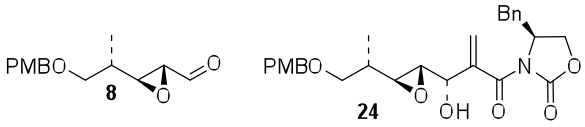
Compound **22** was prepared according to a slightly modified literature procedure.[5] Ethyl (triphenylphosphoranylidene)acetate (13.0 g, 37.3 mmol) was added to a solution of known aldehyde **21**[6] in 120 mL of toluene. The reaction mixture was flushed with argon and stirred overnight at 60 °C. The solution was cooled to ambient temperature, concentrated under reduced pressure and the crude product was purified by column chromatography (hexane-diethyl ether = gradient from 5:1 to 3:1) to give the α,β-unsaturated (*E*)-ester (8.05 g, 91%) as a colorless oil.

DIBAL-H (68.0 mL, 68.0 mmol, 1.0 M in CH_2Cl_2) was added to a stirred solution of the latter unsaturated ester (7.86 g, 28.2 mmol) in 60 mL of CH_2Cl_2 at -78 °C. The mixture was stirred for 4 h and was allowed to warm to -30 °C. The reaction was quenched by the careful addition of a saturated solution of Rochelle's salt and stirred overnight. The organic phase was separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexane-diethyl ether = 1:1) gave allylic alcohol **22** (5.87 g, 88%) as a viscous oil. The spectroscopic data of compound **22** were in complete agreement with data from literature.[6]



Epoxide 23 from Sharpless-Epoxidation of 22:

(+)-L-Diethyl tartrate (1.90 mL, 11.09 mmol) was added to a stirred suspension of 6.2 g of flame-dried molecular sieves (3Å) in 30 mL of CH_2Cl_2 at -35 °C followed by the addition of Ti(O*i*-Pr)$_4$ (2.30 mL, 7.77 mmol). The mixture was stirred for 30 min, then a solution of allylic alcohol **22** (5.25 g, 22.22 mmol) in 14 mL of CH_2Cl_2 was added dropwise in two portions and the reaction mixture was stirred for 30 min. *t*-BuOOH (6.0 mL, 33.0 mmol, 5.5 M solution in nonane) was added dropwise and the mixture was stirred for 24 h at -30 °C. The reaction was quenched by the addition of 1.80 g of tartaric acid in 15 mL of H_2O and 8.0 g of $FeSO_4 \cdot 7H_2O$ and stirred for 90 min at room temperature. The reaction mixture was then poured into 300 mL of CH_2Cl_2 and dried over Na_2SO_4 under vigorous stirring. The product was filtered through Celite, washed with CH_2Cl_2, concentrated under reduced pressure. The crude product was purified by column chromatography (hexane-ethyl acetate = gradient from 1:1 to 1:1.5) to give epoxyalcohol **23** (5.32 g, 95%, d.r. = 15:1) as a colorless, highly viscous oil. $[\alpha]_D^{24}$ = -21.0 (*c* = 1.15, $CHCl_3$); IR (thin film) 3435 (br), 2860, 1612, 1513, 1247, 1088, 1033 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 (m, 2H, $H_{arom.}$), 6.88 (m, 2H, $H_{arom.}$), 4.45 (AB-system, 2H, $PMPCH_2O$), 3.90 (ddd, *J* = 12.5, 5.3, 2.6 Hz, 1H, $C\underline{H}_AH_BOH$), 3.80 (s, 3H, CH_3O), 3.62 (ddd, *J* = 12.5, 7.0, 4.4 Hz, 1H, $C\underline{H}_BH_AOH$), 3.46 (dd, *J* = 9.2, 5.7 Hz, 1H, $C\underline{H}_AH_BOPMB$), 3.42 (dd, *J* = 9.2, 5.7 Hz, 1H, $C_{HB}H_AOPMB$), 3.00 (m, 1H, $CH_{Aepoxide}$), 2.94 (dd, *J* = 6.8, 2.4 Hz, 1H, $CH_{Bepoxide}$), 1.80 (m, 1H, $C\underline{H}CH_3$), 1.68 (t, *J* = 6.3 Hz, 1H, OH), 0.99 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.2, 130.5, 129.2, 113.8, 72.8, 72.2, 61.8, 57.8, 56.9, 55.3, 35.7, 13.4; HRMS: $[M+NH_4]^+$ calcd.: 270.1700, found: 270.1698.

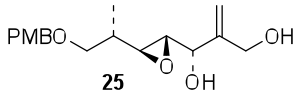


Allylic alcohol 24 from epoxyaldehyde 8:

A solution of SO_3·pyridine (6.30 g, 39.58 mmol) in 24 mL of DMSO was added over a period of 5 min to a stirred 0 °C solution of epoxyalcohol **23** (4.80 g, 19.02 mmol) and diisopropylethylamine (20.0 mL, 114.8 mmol) in 110 mL of CH_2Cl_2. The reaction mixture was stirred for 90 min before being diluted with 50 mL of a saturated solution of NH_4Cl. The aqueous phase was separated and the organic phase was washed with 100 mL of a 1.0 M solution of $KHSO_4$. The combined aqueous layers were extracted twice with ethyl acetate and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was flushed through a short column of silica gel (hexane-ethyl acetate = 2:1) to give epoxyaldehyde **8** (3.93 g, 83%) as a slightly yellow oil. The product was used immediately in the next step without further purification.

Bu_2BOTf (21.0 mL, 21.0 mmol, 1.0 M solution in CH_2Cl_2) was added slowly to a stirred solution of imide **15** (5.95 g, 15.32 mmol) in 36 mL of CH_2Cl_2 at -78 °C. The mixture was stirred for 10 min, then triethylamine (5.4 mL, 38.74 mmol) was added dropwise. The resulting was stirred at -78 °C for 75 min, at 0 °C for 15 min and re-cooled to -78 °C. A solution of freshly prepared

epoxyaldehyde **8** (3.93 g, 15.70 mmol) in 10 mL of CH_2Cl_2 was added slowly in two portions. The reaction mixture was stirred at -78 °C for 5 h and allowed to warm to room temperature overnight before being quenched with 40 mL of a saturated solution of NH_4Cl. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (1x). The combined organic layers were cooled to 0 °C. Pyridine (0.85 mL, 10.5 mmol) was added and then H_2O_2 (0.90 mL, 15.6 mmol, 50% in H_2O) was added. Two additional aliquots of H_2O_2 (0.40 mL each) were added after 15 and 30 min, respectively. After approximately 45 min, TLC analysis indicated complete consumption of the starting material. The reaction mixture was poured into the aqueous layer, the organic phase was separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexane-ethyl acetate = gradient from 2:1 to 1:1) gave compound **24** (5.83 g, 79%) as a colorless, highly viscous oil. $[\alpha]_D^{24}$ = +24.3 (*c* = 1.62, CH_2Cl_2); IR (thin film) 3468 (br), 2963, 2931, 2860, 1785, 1685, 1512, 1354, 1246, 1213, 1110, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.20 – 7.35 (series of m, 7H, $H_{arom.}$), 6.86 (m, 2H, $H_{arom.}$), 5.80 (d, *J* = 1.0 Hz, 1H, $C\underline{H}_AH_BC$), 5.59 (s, 1H, $C\underline{H}_BH_AC$), 4.72 (m, 1H, NCH), 4.44 (m, 3H, $PMPCH_2O$ and overlapping $C\underline{H}OH$), 4.25 (dd ~ t, *J* = 8.9 Hz, 1H, $C\underline{H}_AH_BPh$), 4.18 (dd, *J* = 9.0, 4.6 Hz, 1H, $C\underline{H}_BH_APh$), 3.78 (s, 3H, CH_3O), 3.48 (dd, *J* = 9.2, 5.7 Hz, 1H, $PMBOC\underline{H}_AH_B$), 3.43 (dd, *J* = 9.2, 5.8 Hz, 1H, $PMBOC\underline{H}_BH_A$), 3.33 (dd, *J* = 13.6, 3.3 Hz, 1H, $C\underline{H}_AH_BO$), 3.04 (m, 3H, $CH_{Aepoxide}H_{Bepoxide}$ and overlapping OH), 2.86 (dd, 1H, *J* = 13.6, 9.1 Hz, 1H, $C\underline{H}_BH_AO$), 1.80 (m, 1H, $C\underline{H}CH_3$), 1.01 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.7, 159.0, 153.4, 143.6, 134.8, 130.4, 129.4, 129.1, 128.9, 127.3, 120.8, 113.6, 72.7, 72.1, 70.6, 66.5, 58.3, 58.2, 55.1, 55.0, 37.3, 35.5, 13.2; HRMS: $[M+NH_4]^+$ calcd.: 499.2439, found: 499.2443.

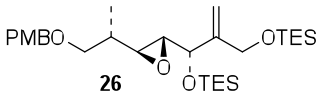


25

Double allylic alcohol 25:

$NaBH_4$ (500 mg, 13.2 mmol) was added in one portion to a stirred solution of unsaturated imide **24** (5.30 g, 11.0 mmol) and $CeCl_3{\cdot}7H_2O$ (6.20 g, 16.6 mmol) in 120 mL of methanol at 0 °C. The mixture was stirred for 30 min. A small aliquot of $NaBH_4$ (~ 50 mg) was added additionally and stirring was continued for 30 min at 0 °C. The reaction mixture was quenched by the slow addition of a saturated solution of NH_4Cl (50 mL) and poured into CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted four times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexane-ethyl acetate = gradient from 1:1 to 1:2) gave double allylic alcohol **25** (3.28g, 97%) as a highly viscous colorless oil. (Occasionally, the product could not be fully separated from remaining (*S*)-4-benzyl oxazolidinone which, however, did not affect the following protection step). $[\alpha]_D^{25}$ = +20.2 (*c* = 2.62, $CHCl_3$); IR (thin film) 3401 (br), 2962, 2863, 1612, 1513, 1247, 1088, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.25 (m, 2H, $H_{arom.}$), 6.87 (m, 2H, $H_{arom.}$), 5.20 (s, 2H, CH_2C), 4.45 and 4.42 (AB-system, 2H, $PMPCH_2O$), 4.37 (d, *J* = 3.2 Hz, 1H, $C\underline{H}OH$), 4.21 and 4.14 (AB-system, 2H, $C\underline{H}_2OH$), 3.79 (s, 3H, CH_3O), 3.44 (d, *J* = 5.5 Hz, 2H, $PMBOCH_2$), 3.04 (dd, *J* = 6.4, 2.3 Hz, 1H, $CH_{Aepoxide}$), 2.99 (dd, *J* = 3.4, 2.4 Hz, 1H, $CH_{Bepoxide}$), 2.79 (br s, 1H, OH), 2.63 (br s, 1H, OH), 1.85 (m, 1H, $C\underline{H}CH_3$), 0.97 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C

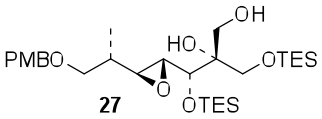
NMR (100 MHz, $CDCl_3$) δ = 159.2, 146.4, 130.2, 129.3, 114.1, 113.7, 72.8, 72.1, 71.5, 63.9, 58.5, 57.4, 55.2, 35.2, 13.0; HRMS: $[M+NH_4]^+$ calcd.: 326.1962, found: 326.1951.



26

Bis-TES ether 26:

Triethlysilyl chloride (5.0 mL, 29.79 mmol) was added dropwise to a stirred solution of diol **25** (3.28 g, 10.6 mmol), imidazole (7.0 g, 103 mmol) and DMAP (170 mg, 14.0 mmol) in 180 mL of DMF at 0 °C. The reaction mixture was stirred for 36 h and allowed to warm to room temperature during that period. The reaction mixture was re-cooled to 0 °C, then 100 mL of Et_2O was added followed by the addition of 100 mL of H_2O. The organic phase was separated and the aqueous phase was extracted three times with 50 mL of Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexane-ethyl acetate = 10:1) gave bis-silyl ether **26** (5.36 g, 94%) as a colorless oil. $[\alpha]_D^{25}$ = -2.0 (*c* = 4.12, CH_2Cl_2); IR (thin film) 2955, 2876, 1513, 1458, 1247, 1099, 1005, 821, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.26 (m, 2H, $H_{arom.}$), 6.87 (m, 2H, $H_{arom.}$), 5.23 (dd, *J* = 3.5, 1.7 Hz, 1H, $C\underline{H}_AH_BC$), 5.13 (dd ~ t, *J* = 1.2 Hz, 1H, $C\underline{H}_BH_AC$), 4.45 (s, 2H, $PMPCH_2O$), 4.27 and 4.20 (AB system, *J* = 14.8 Hz, 2H, CH_2OSi), 4.15 (d, *J* = 4.2 Hz, 1H, CHOSi), 3.81 (s, 3H, CH_3O), 3.47 (dd, *J* = 9.1, 5.3 Hz, 1H, $C\underline{H}_AH_BOPMB$), 3.39 (dd, *J* = 9.1, 6.3 Hz, 1H, $C\underline{H}_BH_AOPMB$), 2.88 (dd, *J* = 7.2, 2.1 Hz, 1H, $CH_{Aepoxide}$), 2.82 (dd, *J* = 4.2, 2.2 Hz, 1H, $CH_{Bepoxide}$), 1.70 (m, 1H, $C\underline{H}CH_3$), 0.92 – 1.00 (m, 21H, CH_3 and overlapping 6x$C\underline{H}_3CH_2Si$), 0.60 (m, 12H, 6xCH_2Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.1, 148.7, 130.7, 129.1, 113.7, 110.3, 77.2, 72.8, 72.7, 72.4, 62.3, 59.7, 57.8, 55.2, 36.1, 13.6, 6.8, 4.7, 4.4; HRMS: $[M+NH_4]^+$ calcd.: 554.3692, found: 554.3729.



27

Diol 27:

AD mix-β (1.80 g) was added to a vigorously stirred solution of alkene **26** (635 mg, 1.18 mmol) in *t*-BuOH (6 mL) and H_2O (6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 48 h. Additional OsO_4 (0.25 mL, 0.02 mmol, 2.5 w% in *t*-BuOH) and $(DHQD)_2PHAL$ (46 mg, 0.06 mmol) were added and the mixture was strirred for an additional 48 h at 0 °C. The reaction was quenched with Na_2SO_3 (1.4 g), stirred for 2 h at room temperature and poured into CH_2Cl_2 (20 mL) and H_2O (10 mL). The organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexane-ethyl acetate = 6:1) gave diol **27** (507 mg, 75% yield; 95% based on recovered starting material) as a 4.5 : 1 mixture of diastereomers (determined by ^1H NMR analysis). An analytical sample of the diastereomeric mixture was purified by HPLC (20% ethyl acetate in hexane, R_t = 13.5 min). The spectroscopic data are given for the main diastereomer. $[\alpha]_D^{23}$ = -1.3 (*c* = 2.50, CH_2Cl_2); IR (thin

film) 3487, 2954, 2876, 1513, 1247, 1086, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.26 (m, 2H, $H_{arom.}$), 6.86 (m, 2H, $H_{arom.}$), 4.45 (s, 2H, CH_2Oar), 3.79 (s, 3H, OCH_3), 3.68 – 3.79 (series of overlapping m, 5 H, CH_2OSi, CH_2OH, CHOSi), 3.51 (dd, *J* = 9.2 Hz, 5.2 Hz, 1H, $C\underline{H}_AH_BO$), 3.42 (dd, *J* = 9.2, 6.2 Hz, 1H, $C\underline{H}_BH_AO$), 3.09 (dd, *J* = 4.7, 2.3 Hz, 1H, $CH_{Aepoxide}$), 3.01 (d, *J* = 5.4 Hz, 1H, OH), 2.95 (dd, *J* = 7.2, 2.3 Hz, 1H, $CH_{Bepoxide}$), 2.91 (s, 1H, OH), 1.74 (m, 1H, $C\underline{H}CH_3$), 1.03 (d, *J* = 7.0 Hz, 3H, $C\underline{H}_3CH$), 0.96 (t, *J* = 8.1 Hz, 9H, $C\underline{H}_3CH_2Si$), 0.95 (t, *J* = 7.8 Hz, 9H, $C\underline{H}_3CH_2Si$), 0.62 (q, *J* = 7.7 Hz, 6H, $CH_3C\underline{H}_2Si$), 0.61 (q, *J* = 8.2 Hz, 6H, CH_3CH_2Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.1, 130.5, 129.14, 113.7, 74.4, 72.8, 72.6, 72.4, 63.9, 63.8, 57.4, 55.9, 55.2, 36.2, 13.4, 6.6, 4.2, 4.2; HRMS: $[M+Na]^+$ calcd.: 593.3300, found: 593.3319.

5. References in Supporting Information

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