Supporting Information

Mukaiyama-Michael Reactions with Acrolein and Methacrolein: A Catalytic Enantioselective Synthesis of the C17-C28 Fragment of Pectenotoxins

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1 General Information

All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. When needed, nonaqueous reagents were transferred under argon *via* syringe or cannula and dried prior to use. THF, Et₂O and DCM (CH₂Cl₂) were obtained by passing deoxygenated solvents through activated alumina columns (MBraun SPS-800 Series solvent purification system). MeOH was distilled from magnesium methoxide, DMF and Et₃N were distilled over CaH₂, and allylamine and MsCl were fractionally distilled, prior to their use. TBSOTf was prepared with Corey's procedure.¹ Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230-400 mesh) plates and analyzed by UV light or by staining upon heating with anisaldehyde solution (2.8 mL anisaldehyde, 2 mL conc. H₂SO₄, 1.2 mL conc. CH₃COOH, 100 mL EtOH), vanillin solution (6 g vanillin, 5 mL conc. H₂SO₄, 3 mL glacial acetic acid, 250 mL EtOH) or KMnO₄ solution (1 g KMnO₄, 6.7 g K₂CO₃, 1.7 mL 1M NaOH, 100 mL H₂O). For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230-400 mesh) and p.a. grade solvents unless otherwise noted.

The ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃, CD₃CN or CD₃OD on NMR spectrometers operating at 500 (¹H 500.13 MHz; ¹³C 125.76 MHz) or 250 (¹H 250.13 MHz; ¹³C 62.90 MHz). The chemical shifts are reported in ppm relative to CHCl₃ (δ 7.26), CHD₂CN (δ 1.94) or CHD₂OD (δ 3.31) for ¹H NMR. For the ¹³C NMR spectra, the residual CDCl₃ (δ 77.0), CD₃CN (δ 118.26) or CD₃OD (49.00) were used as the internal standards. The enantiomeric excesses (*ee*) and diastereomeric ratios (*dr*) of the products were determined by GC in comparison to the corresponding racemic samples using a SUPELCO Astec CHIRALDEX B-DM Column or by HPLC using UV detection monitored at an appropriate wavelength using CHIRALPAK IB column (ø 0.46 cm × 25 cm). Melting points (mp) were determined in open capillaries and are uncorrected.

¹ Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, 22, 3455.

2 The Mukaiyama-Michael Reactions

2.1 Screening of catalysts for the Mukaiyama-Michael reaction

General procedure: To a stirred suspension of the catalyst (0.05 mmol, 10 mol-%), 4-nitrobenzoic acid (8.4 mg, 0.05 mmol, 10 mol-%), tetradecane (as an internal standard, 22.8 mg, 30 μ L, 0.115 mmol, 23 mol-%) and water (18 mg, 18 μ L, 1 mmol, 200 mol-%) in DCM (1 mL) at rt were added methacrolein (70.1 mg, 80 μ L, 1 mmol, 200 mol-%) and silyloxyfuran **17** (106 mg, 120 μ L, 0.5 mmol, 100 mol-%). The mixture was stirred at rt and the reaction progress was monitored by GC, using the SUPELCO Astec CHIRALDEX B-DM column.

Table 1. Screening of the catalysts for the Mukaiyama-Michael reaction.

8: R¹=Bn

9: R¹=H

10: R²=3,5-(F₃C)₂C₆H₃, R³= SiMe₃

11: R²=Ph, R³= SiMe₃

12: R²=Ph, R³= SiPh₂Me

13: R²=3,5-(F₃C)₂C₆H₃, R³= SiPh₂Me

14: R²=2-naphthyl, R³= SiMe₃

15: R²=2-naphthyl, R³= SiPh₂Me

(R,R)-16

Entry	Catalyst	Duration (h)	Conversion (%) ^a	ee (18a/b)	dr (18a/b)
1	8	23	33	2.4/1.8	54/45
2	9	1,5	>95	37/23	64/36
3	10	24	65	20/28	65/35
4	11	24	94	54/53	57/43
5	12	10	>95	61/63	56/44
6	13	24	>95	29/64	59/41
7	14	20	>95	59/59	56/44
8	15	24	76	30/37	58/42
9	(R,R)-16	8	>95	-93/-93	56/44

^aConversion of the silyloxyfuran **17** was monitored by GC.

2.2 Synthesis of the Catalysts 8-15

2.2.1 (*S*)-2-(((Methyldiphenylsilyl)oxy)diphenylmethyl)pyrrolidine (**12**)

To a stirred solution of (*S*)-diphenyl(pyrrolidin-2-yl)methanol (**S1**) (500 mg, 1.97 mmol, 100 mol-%) and triethylamine (399 mg, 0.55 mL, 3.94 mmol, 200 mol-%) in DCM (5 mL) at rt was added methyldiphenylsilyl chloride (550 mg, 0.50 mL, 2.36 mmol, 120 mol-%) and 4-dimethylaminopyridine (48.1 mg, 0.39 mmol, 20 mol-%). The mixture was stirred for 20 hours at rt. The reaction was quenched by the addition of water (25 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 1:2 to 1:1) to afford the product **12** as white solid (661 mg, 1.47 mmol, 75%). Spectral data matches those reported previously in the literature.²

R_f (EtOAc/Hexane 1:1) = 0.27; mp 86-87 °C; $[\alpha]_D = -44.3$ (c 1.0, CHCl₃); IR (film, cm⁻¹): 3066, 2960, 2872, 1428, 1113, 1071, 699; ¹H NMR (500 MHz, CDCl₃): δ 7.57-7.49 (m, 6H), 7.41-7.29 (m, 8 H), 7.29-7.19(m, 6H), 4.04 (dd, 1H, J = 8.4, 6.9 Hz), 2.76 (ddd, 1H, J = 9.6, 7.9, 6.5 Hz), 2.58 (ddd, 1H, J = 9.6, 7.6, 5.1 Hz), 1.90 (br s, 1H), 1.68-1.60 (m, 1H), 1.46-1.36 (m, 2H), 1.08-0.98 (m, 1H), 0.24 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 146.4, 145.5, 139.3, 139.1, 134.3, 134.2, 128.98, 128.95, 128.4, 127.62, 127.60, 127.47, 127.46, 127.0, 126.7, 83.9, 65.2, 46.7, 27.2, 24.2, -1.0; HRMS (ESI⁺): m/z calcd for [C₃₀H₃₂ONSi] 450.2253, found 450.2260, Δ = 1.5 ppm.

² Grošelj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Beck, A. K. *Helv. Chim. Acta*, **2009**, 92, 1225.

2.2.2 (*S*)-2-(Bis(3,5-bis(trifluoromethyl)phenyl)((methyldiphenylsilyl)oxy)-methyl)pyrrolidine (**13**)

To a stirred solution of (*S*)-(-)-α,α-bis[3,5-(trifluoromethyl)phenyl]-2-pyrrolidine methanol (**S2**) (1.00 g, 1.9 mmol, 100 mol-%) and triethylamine (385 mg, 0.53 mL, 3.8 mmol, 200 mol-%) in DCM (20 mL) at rt was added methyldiphenylsilyl chloride (535 mg, 0.48 mL, 2.3 mmol, 120 mol-%) and 4-dimethylaminopyridine (61.2 mg, 0.5 mmol, 26 mol-%). The mixture was stirred for 20 hours at rt. The reaction was quenched by the addition of water (30 mL). The layers were separated and the aqueous phase was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 0:1 to 1:5) to afford the product **13** as thick yellow oil (1.16 g, 1.6 mmol, 84%).

R_f (EtOAc/Hexane 1:5) = 0.63; $[\alpha]_D = -8.1$ (*c* 1.0, CHCl₃); IR (film, cm⁻¹): 3072, 2968, 2876, 1373, 1277, 1173, 1132; ¹H NMR (500 MHz, CDCl₃): δ 8.12 (br s, 2H), 7.87 (br s, 1H), 7.77 (br s, 1H), 7.66 (br s, 1H), 7.59-7.55 (m, 1H), 7.47-7.55 (m, 10H), 4.23 (dd, 1H, *J* = 8.0, 6.5 Hz), 2.85 (app dt, 1H, *J* = 10.0, 7.0 Hz), 2.47 (ddd, 1H, *J* = 10.0, 6.7, 5.9 Hz), 1.83-1.75 (m, 1H), 1.69 (br s, 1H), 1.61-1.62 (m, 1H), 1.51-1.42 (m, 1H), 0.97-0.87 (m, 1H), 0.62 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 147.0, 145.8, 136.6, 136.1, 134.0, 133.9, 131.4 (q, ²*J*_{CF} = 33.4 Hz), 130.7 (q, ²*J*_{CF} = 33.3 Hz), 130.0, 129.9, 128.9 (q, ³*J*_{CF} = 2.8 Hz), 128.5 (q, ³*J*_{CF} = 2.6 Hz), 127.90, 127.87, 123.3 (q, ¹*J*_{CF} = 272.7 Hz), 123.1 (q, ¹*J*_{CF} = 272.9 Hz), 121.8 (sept., ³*J*_{CF} = 3.7 Hz), 121.5 (sept., ³*J*_{CF} = 3.6 Hz), 83.3, 63.9, 47.1, 27.8, 25.2, -1.0; HRMS (ESI⁺): *m/z* calcd for [C₃₄H₂₈ONF₁₂Si] 722.1749, found 722.1749, Δ = 0.1 ppm.

2.2.3 (S)-2-(Di(naphthalen-2-yl)((trimethylsilyl)oxy)methyl)pyrrolidine (**14**)

To a stirred solution of (S)-(-)- α,α -di-(2-naphthyl)-2-pyrrolidine methanol (**S3**) (217 mg, 0.61 mmol, 100 mol-%) and triethylamine (124 mg, 0.17 mL, 1.22 mmol, 200 mol-%) in DCM (5 mL) at rt was added trimethylsilyl chloride (80.4 mg, 0.09 mL, 0.74 mmol, 120 mol-%) and 4-dimethylaminopyridine (14.9 mg, 0.12 mmol, 20 mol-%). The mixture was stirred for 20 hours at rt. The mixture was then concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexane 1:5) to afford the product **14** as thick yellow oil (240 mg, 0.56 mmol, 92%). Spectral data matches those reported previously in the literature.³

R_f (EtOAc/Hexane 1:2) = 0.08; $[\alpha]_D = -59.5$ (c 1.0, CHCl₃); IR (film, cm⁻¹): 3057, 2954, 2873, 1249, 840, 794, 749, 478; ¹H NMR (500 MHz, CDCl₃): δ 8.12 (d, 1H, J = 1.4 Hz), 8.06 (d, 1H, J = 1.5 Hz), 7.93-7.75 (m, 4H), 7.72 (d, 1H, J = 4.4 Hz), 7.69 (d, 1H, J = 4.4 Hz), 7.54-7.42 (m, 5H), 7.34 (dd, 1H, J = 8.7, 1.8 Hz), 4.32 (app t, 1H, J = 7.4 Hz), 3.01-2.90 (m, 1H), 2.90-2.79 (m, 1H), 2.09 (br s, 1H), 1.85-1.57 (m, 3H), 1.56-1.35 (m, 1H), -0.02 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 144.2, 143.2, 133.0, 132.9, 132.64, 132.57, 128.6, 127.61, 127.56, 127.4, 127.3, 126.7, 126.6, 126.04, 125.99, 125.8, 83.7, 65.5, 47.4, 27.8, 25.3, 2.5; HRMS (ESI⁺): m/z calcd for [C₂₈H₃₂ONSi] 426.2253, found 426.2255, Δ = 0.4 ppm.

³ Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794.

2.2.4 (*S*)-2-(((Methyldiphenylsilyl)oxy)di(naphthalen-2-yl)methyl)pyrrolidine (**15**)

To a stirred solution of (*S*)-(-)-α,α-di-(2-naphthyl)-2-pyrrolidine methanol (**S3**) (177 mg, 0.5 mmol, 100 mol-%) and triethylamine (101 mg, 0.14 mL, 1.0 mmol, 200 mol-%) in DCM (5 mL) at rt was added methyldiphenylsilyl chloride (140 mg, 0.13 mL, 0.6 mmol, 120 mol-%) and 4-dimethylaminopyridine (12.2 mg, 0.1 mmol, 20 mol-%). The mixture was stirred for 3 days at rt. The mixture was then concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexane 0:1 to 1:5 to 1:0) to afford the product **15** as white solid (258 mg, 0.47 mmol, 94%).

R_f (EtOAc/Hexane 1:2) = 0.17; mp 77-78 °C; $[\alpha]_D = -68.7$ (c 1.0, CHCl₃); IR (film, cm⁻¹): 3054, 2961, 2872, 1428, 1116, 793, 742, 700, 478; ¹H NMR (500 MHz, CDCl₃): δ 8.07 (d, 1H, J = 1.4 Hz), 7.99 (d, 1H, J = 1.3 Hz), 7.81-7.72 (m, 4H), 7.66 (d, 1H, J = 8.7 Hz), 7.62 (d, 1H, J = 8.7 Hz), 7.55 (dd, 1H, J = 8.7, 1.8 Hz), 7.54-7.50 (m, 4H), 7.49-7.43 (m, 4H), 7.34 (dd, 1H, J = 8.6, 1.8 Hz), 7.33-7.28 (m, 2H), 7.27-7.22 (m, 4H), 4.25 (app t, 1H, J = 7.6 Hz), 2.84-2.77 (m, 1H), 2.62-2.56 (m, 1H), 1.80-1.65 (m, 2H), 1.53-1.34 (m, 2H), 1.12-1.03 (m, 1H), 0.19 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 143.6, 142.8, 139.0, 138.8, 134.4, 134.2, 132.8, 132.7, 132.6, 132.5, 129.11, 129.06, 128.49, 128.47, 127.6, 127.47, 127.46, 127.45, 127.42, 127.29, 127.27, 126.7, 126.4, 126.1, 126.0, 125.9, 125.8, 84.4, 65.2, 46.9, 27.6, 24.5, -0.8; HRMS (ESI⁺): m/z calcd for [C₃₈H₃₆ONSi] 550.2566, found 550.2574, Δ = 1.5 ppm.

2.3 Synthesis of (2*S*,5*S*)-2,5-Diphenylpyrrolidine Catalyst ((*S,S*)-**16**)

The synthesis of the catalyst (*S,S*)-**16** (Scheme 1) is based on previously reported procedures.⁴

⁴ Chong, J. M.; Clarke, I. S.; Koch, I.; Olbach, P. C.; Taylor, N. J. *Tetrahedron: Asym.* **1995**, 6, 409. Aldous, D. J.; Dutton, W. M.; Steel, P. G. *Tetrahedron: Asym.* **2000**, 11, 2455. Sato, M.; Gunji, Y.; Ikeno, T.; Yamada, T. *Synthesis* **2004**, 9, 1434.

Scheme 1. Synthesis of (2*S*,5*S*)-2,5-diphenylpyrrolidine catalyst **(S,S)-16**.

2.3.1 1,4-Diphenylbutane-1,4-dione (**S5**)

A flask was charged with 2-bromo-1-phenylethanone (**S4**) (20.2 g, 101 mmol, 100 mol-%) and sodium hydroxymethanesulfinate dihydrate (15.6 g, 101 mmol, 100 mol-%). Freshly distilled DMF (150 mL) was added and the mixture was stirred for 23 hours. Water (400 mL) was added and the mixture was filtered through a sintered funnel (porosity 4). The solid remnant was dissolved in DCM (200 mL) and the resulting solution was washed with 1M NaOH (150 mL) and brine (150 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the product **S5** as white crystalline solid (9.3 g, 39 mmol, 77%). The spectroscopic data match those reported in the literature.⁵

R_f (EtOAc/Hexane 1:1) = 0.82; mp 144-147 °C; ¹H NMR (500 MHz, CDCl₃): δ 8.08-8.01 (m, 4H), 7.62-7.44 (m, 6H), 3.47 (s, 4H).

⁵ Jarvis, W.F.; Hoey, M.D.; Finocchio, A.L.; Dittmer, D.C. *J. Org. Chem.* **1988**, *53*, 5750.

2.3.2 (1*R*,4*R*)-1,4-Diphenylbutane-1,4-diol (**S6**)⁴

To a solution of (S)-diphenyl(pyrrolidin-2-yl)methanol (1.23 g, 4.87 mmol, 20 mol-%) in THF (30 mL) at rt was added B(OMe)₃ (0.63 g, 0.69 mL, 6.09 mmol, 25 mol-%) and the resulting solution was stirred for 1 h. Borane-methyl sulfide complex (2M solution in THF, 3.70 g, 24.3 mL, 48.7 mmol, 200 mol-%) was added, followed by a solution of compound **S5** (5.80 g, 24.3 mmol, 100 mol-%) in THF (100 mL) over 30 min. After stirring the reaction mixture for another hour, it was quenched with 2M HCl (aq. 40 mL) slowly. The organic solvent was evaporated under reduced pressure and the residue was diluted with EtOAc (50 mL) and water (50 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hexane 3:2) to afford compound **S6** as colorless viscous oil, which solidified after keeping under high vacuum overnight (5.65 g, 23.3 mmol, 96%). The spectroscopic data match those reported in the literature.⁴

R_f (EtOAc/hexane 3:2) = 0.33; mp 77-78 °C; [α]_D = +57.7 (*c* 1.0, CHCl₃); ¹H NMR (250 MHz, CD₃OD): δ 7.30-7.19 (m, 10H), 4.60 (t, 2H, *J* = 6.1 Hz), 1.93-1.76 (m, 2H), 1.74-1.59 (m, 2H); ¹³C NMR (62.9 MHz, CD₃OD): δ 146.4, 129.2, 128.2, 127.0, 75.0, 36.4.

2.3.3 (2*S*,5*S*)-1-Allyl-2,5-diphenylpyrrolidine (**S7**)⁴

To a stirred solution of **S6** (1.50 g, 6.19 mmol, 100 mol-%) in DCM (50 mL) at -20 °C was added dry Et₃N (1.88 g, 2.6 mL, 18.6 mmol, 300-mol%) followed by freshly distilled MsCl (1.77 g, 1.2 mL, 15.5 mmol, 250 mol-%). After 3 h stirring at -20 °C, freshly distilled allylamine (35.3 g, 46 mL, 619 mmol, 1000 mol-%) was added and the resulting mixture was left to warm to rt and stirred for 9 h. The reaction mixture was then washed

with water (30 mL), brine (30 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography (Et₂O/Hexane 1:99) to afford the minor *meso* isomer as light yellow oil (0.2 g, 0.76 mmol, 12%) and the major compound **S7** as colorless oil (1.20 g, 4.56 mmol, 74%). The spectroscopic data match those reported in the literature.⁴

meso isomer of **S7**: *R_f* (Et₂O/hexane 5:95) = 0.5; ¹H NMR (250 MHz, CDCl₃): δ 7.53-7.49 (m, 4H), 7.39-7.33 (m, 4H), 7.28 (t, 1H, *J* = 1.5 Hz), 7.26-7.22 (m, 1H), 5.71 (ddt, 1H, *J* = 17.0, 10.2, 6.8 Hz), 4.92 (ddt, 1H, *J* = 10.2, 2.2, 0.9 Hz), 4.84 (ddt, 1H, *J* = 17.0, 2.2, 1.3 Hz), 3.93-3.81 (m, 2H), 3.06 (dt, 2H, *J* = 6.9, 1.1 Hz), 2.27-2.13 (m, 2H), 1.89-1.75 (m, 2H).

(*S,S*) isomer of **S7**: *R_f* (Et₂O/hexane 5:95) = 0.4; [α]_D = -115.9 (*c* 1.03, CHCl₃); ¹H NMR (250 MHz, CDCl₃): δ 7.34-7.21 (m, 10H), 5.65 (dddd, 1H, *J* = 17.9, 10.7, 7.3, 4.6 Hz), 4.96-4.86 (m, 2H), 4.39-4.30 (m, 2H), 2.99 (ddt, 1H, *J* = 14.7, 4.5, 1.9 Hz), 2.73 (dd, 1H, *J* = 14.7, 7.3 Hz), 2.61-2.43 (m, 2H), 2.00-1.84 (m, 2H).

2.3.4 (2*S*,5*S*)-2,5-Diphenylpyrrolidine ((*S,S*)-**16**)⁴

To a solution of **S7** (3.0 g, 11.4 mmol, 100 mol-%) in a solvent mixture of ACN/H₂O (84:16, 150 mL) at rt, was added (PPh₃)₃RhCl (Wilkinson's catalyst, 0.53 g, 0.57 mmol, 5 mol-%). The mixture was purged with nitrogen for 10 min and then refluxed at 100 °C for 5 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure (to ca 1/2 volume) and the residue was diluted with Et₂O (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 × 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Et₂O/Hexane 1:9) to afford the catalyst (*S,S*)-**16** as white solid (2.25 g, 10.08 mmol, 88%, 97% *ee*). The enantiopurity was determined by HPLC-analysis (CHIRALPAK IB column, hexane/2-propanol/diethyl amine 99.5:0.5:0.1, 0.5 ml/min flow rate). The spectroscopic data match those reported in the literature.⁴

R_f (Et₂O/hexane 3:7) = 0.5; mp 47-48 °C; [α]_D = -103.5 (*c* 0.99, CHCl₃); ¹H NMR (250 MHz, CDCl₃): δ 7.43-7.38 (m, 4H), 7.37-7.30 (m, 4H), 7.27-7.20 (m, 2H), 4.60-4.49 (m, 2H), 2.48-2.31 (m, 2H), 1.99-1.82 (m, 3H); ¹³C NMR (62.9 MHz, CDCl₃): δ 145.9, 128.4, 126.8, 126.3, 62.2, 35.5.

2.4 Preliminary Study of the Reaction scope: One-Pot Sequential Mukaiyama–Michael Addition–Luche Reduction

General procedure: To a suspension of catalyst (*S,S*)-**16** (20 mol-%) and 4-nitrobenzoic acid (20 mol-%) in DCM (0.25 mmol/mL) was added H₂O (200 mol-%), followed by Michael acceptor aldehyde (200 mol-%) and the reaction mixture was then cooled to 0 °C. After 10 min, the Michael donor silyloxyfuran (100 mol-%) was added and the reaction mixture was stirred at the same temperature for 24 h. GC-analysis of the reaction mixture was carried out using the SUPELCO Astec CHIRALDEX B-DM column, for finding the *ee* (%) and *dr* (%) of the product aldehyde(s). The reaction mixture was then diluted with MeOH (0.25 mmol/4 mL), still stirred at 0 °C, and to this resulting solution was added CeCl₃·7H₂O (150 mol-%) in one portion, followed by NaBH₄ (300 mol-%) in two equal portions. The reaction mixture was stirred at the same temperature for 2 h, and quenched by slow addition of 1M HCl (aq. 1 mL). The reaction mixture was concentrated (to ca 1/5 volume) under reduced pressure, and the crude reaction mixture was diluted with EtOAc (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hexane) to afford the primary alcohol.

Table 2. Preliminary study of the reaction scope with (2*S*,5*S*)-2,5-diphenylpyrrolidine.

1) (*S,S*)-**16**, 4-NBA,
H₂O, DCM, 0 °C, 24 h
2) NaBH₄, MeOH,
CeCl₃·7H₂O, 0 °C, 2 h

22: R¹=Me, R²=Me
S8: R¹=Me, R²=H
S9: R¹=H, R²=Me
S10: R¹=H, R²=H

Entry	R ¹	R ²	R ³	<i>ee</i> ^a (%)	<i>dr</i> ^a (a/b)	Yield (%)
1	Me	Me	TBS	97/96 ^b	55:45	80
2	Me	H	TBS	94/93 ^b	50:50	65
3	H	Me	TBS	94	-	65
4	H	H	TBS	91	-	56
5	H	H	TIPS	92	-	71

^a Determined by GC (Supelco Astec CHIRALDEX B-DM column) from the reaction mixture before reduction.

^b *ee* reported for both **22a/22b** and **S8a/S8b**.

2.4.1 Diastereomeric mixture of (*S*)-5-[(*S*)-3-Hydroxy-2-methylpropyl]-5-methylfuran-2(*5H*)-one (**22a**) and (*S*)-5-[(*R*)-3-hydroxy-2-methylpropyl]-5-methylfuran-2(*5H*)-one (**22b**)

Prepared according to the general procedure using silyloxyfuran **17** (100 mg, 109 μ L, 0.471 mmol, 100 mol-%) and methacrolein (**7**) (66 mg, 78 μ L, 0.942 mmol, 200 mol-%). The residue of the reaction mixture was purified by flash chromatography (EtOAc/hexane 3:2) to afford a diastereomeric mixture of compounds **22a** and **22b** as a light yellow oil (64 mg, 0.376 mmol, 80%, *dr* (**22a/b**) 55:45, *ee* (**22a/b**) 97%:96%).

R_f (EtOAc/hexane 3:2) = 0.4; ¹H NMR (250 MHz, CDCl₃): δ 7.40 (d, 0.45H, J = 5.6 Hz), 7.37 (d, 0.55 H, J = 5.6 Hz), 6.01 (d, 1H, J = 5.6 Hz), 3.50-3.35 (m, 2H), 2.08 (dd, 0.45H, J = 14.4, 3.9 Hz), 1.94-1.84 (m, 0.55H), 1.75 (br s, 1H), 1.72-1.57 (m, 2H), 1.48 (s, 1.65 H), 1.47 (s, 1.35H), 0.94 (d, 3H, J = 6.7 Hz).

2.4.2 Diastereomeric mixture of (*S*)-5-[(*S*)-3-Hydroxy-2-methylpropyl]furan-2(*5H*)-one (**S8a**) and (*S*)-5-[(*R*)-3-hydroxy-2-methylpropyl]furan-2(*5H*)-one (**S8b**)

Prepared according to the general procedure using silyloxyfuran **S13** (100 mg, 0.504 mmol, 100 mol-%) and methacrolein (**7**) (70.7 mg, 83 μ L, 1.01 mmol, 200 mol-%). The residue of the reaction mixture was purified by flash chromatography (EtOAc/hexane 4:1) to afford a diastereomeric mixture of compounds **S8a** and **S8b** as a light yellow oil (51 mg, 0.326 mmol, 65% *dr* (**S8a/b**) 1:1, *ee* (**S8a/b**) 94%:93%).

R_f (EtOAc/hexane 3:2) = 0.15; IR (film, cm⁻¹): 3417, 2961, 2875, 1738, 1461, 1324, 1165, 1105, 1046, 1025, 989, 908, 812; ¹H NMR (250 MHz, CDCl₃): δ 7.50-7.47 (m, 1H), 6.06 (dd, 1H, J = 5.7, 1.7 Hz), 5.21-5.12 (m, 1H), 3.62-3.42 (m, 2H), 2.37 (br s, 1H), 2.01-1.83 (m, 1.5 H), 1.76-1.39 (m, 1.5H), 0.98 (d, 1.5H, J = 6.7 Hz), 0.97 (d, 1.5H, J = 6.7 Hz); ¹³C NMR (62.9 MHz, CDCl₃): δ 173.3 and 173.2, 157.2 and 157.0, 121.1 and

121.0, 82.4 and 82.0, 67.6 and 67.0, 37.2 and 36.9, 32.8 and 32.7, 17.2 and 16.4; HRMS (ESI⁺): *m/z* calcd for [C₈H₁₂O₃Na] 179.0684, found 179.0685, Δ = 0.4 ppm.

2.4.3 (*S*)-5-(3-Hydroxypropyl)-5-methylfuran-2(5*H*)-one (**S9**)

Prepared according to the general procedure using silyloxyfuran **17** (100 mg, 109 μ L, 0.471 mmol, 100 mol-%) and acrolein (**6**) (52.8 mg, 63 μ L, 0.942 mmol, 200 mol-%). The residue of the reaction mixture was purified by flash chromatography (EtOAc/hexane 4:1) to afford compound **S9** as a light yellow oil (48 mg, 0.307 mmol, 65%, *ee* 94%).

R_f (EtOAc/hexane 3:2) = 0.15; [α]_D = +34.1 (*c* 1.15, CHCl₃); IR (film, cm⁻¹): 3421, 2979, 2873, 1732, 1452, 1378, 1315, 1263, 1183, 1144, 1115, 1059, 1030, 952, 820, 724; ¹H NMR (250 MHz, CDCl₃): δ 7.38 (d, 1H, *J* = 5.6 Hz), 6.02 (d, 1H, *J* = 5.6 Hz), 3.63 (t, 2H, *J* = 6.0 Hz), 1.98-1.73 (m, 2H), 1.71-1.50 (m, 3H), 1.48 (s, 3H); ¹³C NMR (62.9 MHz, CDCl₃): δ 172.5, 160.3, 120.6, 88.7, 62.2, 34.5, 26.7, 24.0; HRMS (ESI⁺): *m/z* calcd for [C₈H₁₂O₃Na] 179.0684, found 179.0687, Δ = -4.1 ppm.

2.4.4 (*S*)-5-(3-Hydroxypropyl)furan-2(5*H*)-one (**S10**)

Prepared according to the general procedure using silyloxyfuran **S13** (100 mg, 0.504 mmol, 100 mol-%) and acrolein (**6**) (56.5 mg, 67 μ L, 1.01 mmol, 200 mol-%). The residue of the reaction mixture was purified by flash chromatography (EtOAc/hexane 4:1) to afford compound **S10** as a light yellow oil (40 mg, 0.281 mmol, 56%, *ee* 91%).

R_f (EtOAc/hexane 3:2) = 0.2; [α]_D = +75.6 (*c* 1.12, CHCl₃); IR (film, cm⁻¹): 3417, 2954, 2872, 1734, 1447, 1331, 1275, 1162, 1108, 1066, 1056, 1014, 995, 924, 817; ¹H NMR (250 MHz, CDCl₃): δ 7.47 (dd, 1H, *J* = 5.7, 1.5 Hz), 6.08 (dd, 1H, *J* = 5.7, 2.0 Hz), 5.12-5.06 (m, 1H), 3.66 (t, 2H, *J* = 5.6 Hz), 2.19 (br s, 1H), 1.99-1.83 (m, 1H), 1.78-1.62 (m,

3H); ^{13}C NMR (62.9 MHz, CDCl_3): δ 173.2, 156.4, 121.4, 83.2, 61.8, 29.6, 27.8; HRMS (ESI^+): m/z calcd for $[\text{C}_7\text{H}_{10}\text{O}_3\text{Na}]$ 165.0528, found 165.0524, $\Delta = -2.4$ ppm.

2.4.5 (*S*)-5-(3-Hydroxypropyl)furan-2(5*H*)-one (**S10**)

Prepared according to the general procedure using silyloxyfuran **S14** (100 mg, 110 μL , 0.416 mmol, 100 mol-%) and acrolein (**6**) (70 mg, 83 μL , 1.25 mmol, 300 mol-%). The residue of the reaction mixture was purified by flash chromatography (EtOAc/hexane 4:1) to afford compound **S10** as a pale yellow oil (42 mg, 0.295 mmol, 71%, *ee* 92%).

2.4.6 Furan-2(5*H*)-one (**S12**)

To a solution of furfuraldehyde (**S11**) (15.0 g, 12.9 mL, 156 mmol, 100 mol-%) in DCM (50 mL) in a three-necked round-bottomed flask fitted with a condenser and a dropping funnel, were added Na_2SO_4 (7.5 g, 50 wt-%), *N,N*-dimethylethanolamine (4.73 g, 5.3 mL, 53.1 mmol, 34 mol-%) followed by formic acid (14.4 g, 11.8 mL, 312 mmol, 200 mol-%). H_2O_2 (49.7% aq. solution, 8.5 g, 17.1 mL, 250 mmol, 200 mol-%) was added slowly through dropping funnel. The reaction mixture started refluxing. After complete addition of H_2O_2 the reaction mixture was stirred vigorously overnight. After completion of the reaction, the biphasic reaction mixture was separated and the aqueous layer was extracted with DCM (1 $\times$ 20 mL). The combined organic layer was washed with sat. aq. NaHSO_3 (2 $\times$ 50 mL) and then tested negative with peroxide test. The organic layer was dried over Na_2SO_4 , concentrated under reduced pressure and purified by distillation at 85 °C (10 torr) to afford **S12** as light yellow oil (7.6 g, 90.4 mmol, 58%).⁶

R_f (EtOAc/hexane 1:4) = 0.2; ^1H NMR (250 MHz, CDCl_3): δ 7.57 (dt, 1H, $J = 5.8, 1.7$ Hz), 6.14 (dt, 1H, $J = 5.8, 2.2$ Hz), 4.89 (dd, 2H, $J = 2.2, 1.7$ Hz); ^{13}C NMR (62.9 MHz, CDCl_3): δ 173.7, 152.9, 121.5, 72.1.

⁶ Näsman, J. H. *Org. Syn. Coll. Vol.* 8, **1993**, 396.

2.4.7 *tert*-Butyl(furan-2-yloxy)dimethylsilane (**S13**)

To a solution of **S12** (1 g, 0.84 mL, 11.89 mmol, 100 mol-%) in DCM (10 mL) was added triethylamine (2.41 g, 3.3 mL, 23.79 mmol, 200 mol-%). The solution was chilled on ice bath and *tert*-butyl(dimethyl)silyl trifluoromethanesulfonate (3.77 g, 3.3 mL, 14.27 mmol, 120 mol-%) was added. After removal of the ice bath, the reaction mixture was stirred vigorously at rt for 5 h. The reaction mixture was then quenched with water (10 mL). The phases were separated and organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by distillation at 100 °C (10 torr) to afford the compound **S13** as colorless oil (2.10 g, 10.59 mmol, 89%). Spectral data matches those reported previously in the literature.⁷

R_f (EtOAc/hexane 1:9) = 0.8; ¹H NMR (250 MHz, CDCl₃): δ 6.81 (dd, 1H, *J* = 2.2, 1.1 Hz), 6.20 (dd, 1H, *J* = 3.1, 2.2 Hz), 5.10 (dd, 1H, *J* = 3.1, 1.1 Hz), 0.97 (s, 9H), 0.24 (s, 6H).

2.4.8 (Furan-2-yloxy)triisopropylsilane (**S14**)

To a solution of **S12** (1.0 g, 0.844 mL, 11.89 mmol, 100 mol-%) in DCM (10 mL) was added triethylamine (2.4 g, 3.32 mL, 23.79 mmol, 200 mol-%). The solution was chilled on ice bath and triisopropylsilyl trifluoromethanesulfonate (4.4 g, 3.48 mL, 14.27 mmol, 120 mol-%) was added. After removal of the ice bath, the reaction mixture was stirred vigorously at rt for 5 h. The reaction mixture was then quenched with water (10 mL). The phases were separated and organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by distillation at 100 °C (0.1 torr) to afford the compound **S14** as colorless oil (2.7 g, 11.23 mmol, 94%). Spectral data matches those reported previously in the literature.⁸

⁷ Curti, C.; Battistini, L.; Zanardi, F.; Rassu, G.; Zambrano, V.; Pinna, L.; Casiraghi, G. *J. Org. Chem.* **2010**, 75, 8681.

⁸ Boukouvalas, J.; Loach, R. P. *J. Org. Chem.* **2008**, 73, 8109.

R_f (EtOAc/hexane 1:9) = 0.8; ^1H NMR (250 MHz, CDCl_3): δ 6.80 (dd, 1H, J = 2.2, 1.1 Hz), 6.20 (dd, 1H, J = 3.1, 2.2 Hz), 5.12 (dd, 1H, J = 3.1, 1.1 Hz), 1.36-1.18 (m, 3H), 1.11 (d, 18H, J = 6.8 Hz); ^{13}C NMR (62.9 MHz, CDCl_3): δ 157.0, 131.8, 111.1, 83.4, 17.5, 12.2.

3 Synthesis and Confirmation of the Stereochemistry of the C₁₇-C₂₈ Fragment of Pectenotoxins

3.1 Synthesis of the C₁₇-C₂₈ Fragment of Pectenotoxin-2

3.1.1 *tert*-Butyldimethyl((5-methylfuran-2-yl)oxy)silane (**17**)

To a solution of 5-methylfuran-2(3*H*)-one (**S15**) (5.9 g, 5.4 mL, 60 mmol, 100 mol-%) in DCM (60 mL) was added triethyl amine (12.1 g, 16.7 mL, 120 mmol, 200 mol-%). The solution was chilled on ice bath and *tert*-butyl(dimethyl)silyl trifluoromethanesulfonate (19.0 g, 16.5 mL, 72 mmol, 120 mol-%) was added. After removal of the ice bath, the reaction mixture was stirred vigorously at rt for one hour. The reaction was quenched by the addition of water (80 mL). The layers were separated and the aqueous phase was extracted with DCM (60 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane) to afford the compound **17** as clear pale yellow oil (12.2 g, 57 mmol, 95%). The spectroscopic data match those reported in the literature.⁹

R_f (EtOAc/hexanes 1:5) = 0.88; ¹H NMR (250 MHz, CDCl₃): δ 5.75 (dq, 1H, *J* = 3.0, 1.1 Hz), 4.95 (d, 1H, *J* = 3.0 Hz), 2.16 (d, 3H, *J* = 1.1 Hz), 0.97 (s, 9H), 0.23 (s, 6H); ¹³C NMR (62.9 MHz, CDCl₃): δ 155.3, 141.4, 106.2, 83.7, 25.6, 18.2, 13.6, -4.8.

⁹ Takahashi, A.; Yanai, H.; Taguchi, T. *Chem. Commun.*, **2008**, 44, 2385-2387.

3.1.2 (*R*)-2-Methyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (**18b**) and (*S*)-2-methyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (**18a**)

To a suspension of catalyst (*S,S*)-**16** (1.05 g, 4.71 mmol, 20 mol-%) and 4-nitrobenzoic acid (0.787 g, 4.71 mmol, 20 mol-%) in DCM (80 mL) was added H₂O (0.848 g, 0.85 mL, 47.1 mmol, 200 mol-%), followed by methacrolein (3.30 g, 3.9 mL, 47.1 mmol, 200 mol-%) and the reaction mixture was cooled to 0 °C. After 10 min, **17** (5.0 g, 5.43 mL, 23.54 mmol, 100 mol-%) was added and the reaction mixture was stirred at the same temperature for 24 h. The mixture was then concentrated under reduced pressure and the residue was purified by flash chromatography (Et₂O/pentane 1:1) to afford **18a** (elutes first) followed by a mixture of **18a** and **18b** as light yellow oils (total yield 3.25 g, 21.1 mmol, 90%).

Repeated chromatographic separation (Et₂O/pentane 1:1) afforded **18a** (>99:1 *dr* by ¹H NMR, 1.69 g, 10.05 mmol, 47%) and **18b** (>95:5 *dr* by ¹H NMR, 1.33 g, 7.91 mmol, 37%) in high diastereomeric purity.¹⁰

Epimerization of **18a**: 1,8-Diazabicycloundec-7-ene (0.36 g, 0.356 mL, 2.38 mmol, 20 mol-%) was added to a solution of compound **18a** (2.00 g, 11.9 mmol, 100 mol-%) in DCM (50 mL). The reaction mixture was stirred at room temperature for 2 h, while the progress of epimerization was monitored by GC analysis. After the thermodynamic equilibrium of diastereomers was reached, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (Et₂O/pentane 1:1).

(*R*)-2-Methyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (**18b**):

R_f (Et₂O/pentane 1:1) = 0.30; [*α*]_D = +51.3 (*c* 1.13, DCM); IR (film, cm⁻¹): 2980, 2936, 1748, 1722, 1457, 1192, 1115, 954, 922, 822, 750; ¹H NMR (250 MHz, CD₃CN): δ 9.44

¹⁰ It should be noted that due to the volatility of **18a** and **18b**, an alternate protocol that we have also used involves removal of the majority of **18a** by a single flash chromatographic purification procedure, followed by Luche reduction and separation of the remaining **22a** from **22b**. This protocol was especially useful on smaller scale experiments.

(d, 1H, $J = 2.6$ Hz), 7.53 (d, 1H, $J = 5.7$ Hz), 6.01 (d, 1H, $J = 5.7$ Hz), 2.44 (dd, 1H, $J = 14.8, 7.6$ Hz), 2.30-2.16 (m, 1H), 1.69 (dd, 1H, $J = 14.8, 4.7$ Hz), 1.43 (s, 3H), 1.04 (d, 3H, $J = 7.1$ Hz); ^{13}C NMR (62.9 MHz, CD_3CN): δ 205.1, 173.4, 162.5, 121.8, 89.5, 43.2, 39.6, 25.3, 15.8; HRMS (ESI^+): m/z calcd for $[\text{C}_9\text{H}_{12}\text{O}_3\text{Na}]$ 191.0684, found 191.0690, $\Delta = 2.3$ ppm.

(*S*)-2-Methyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (**18a**):

R_f (Et_2O /pentane 1:1) = 0.40; $[\alpha]_D = -19.7$ (c 1.07, DCM); IR (film, cm^{-1}): 2980, 2935, 1745, 1719, 1456, 1193, 1115, 954, 920, 820, 703; ^1H NMR (250 MHz, CD_3CN): δ 9.47 (d, 1H, $J = 1.7$ Hz), 7.47 (d, 1H, $J = 5.7$ Hz), 5.97 (d, 1H, $J = 5.7$ Hz), 2.37-2.23 (m, 2H), 1.80 (dd, 1H, $J = 13.9, 3.5$ Hz), 1.45 (s, 3H), 1.06 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (62.9 MHz, CD_3CN): δ 204.9, 173.1, 162.1, 121.1, 89.2, 42.6, 38.7, 24.9, 15.5; HRMS (ESI^+): m/z calcd for $[\text{C}_9\text{H}_{12}\text{O}_3\text{Na}]$ 191.0684, found 191.0680, $\Delta = 3.1$ ppm.

3.1.3 (*S*)-5-((*R*)-3-Hydroxy-2-methylpropyl)-5-methylfuran-2(5*H*)-one (**22b**)

$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (5.98 g, 16.05 mmol, 150 mol-%) was added to a solution of compound **18b** (1.80 g, 10.7 mmol, 100 mol-%) in MeOH (40 mL). The reaction mixture was cooled to 0 °C and NaBH_4 (0.607 g, 16.05 mmol, 150 mol-%) was added in three equal portions. The reaction mixture was stirred at 0 °C for 2 h. After completion of the reaction (monitored by TLC), 1M HCl (aq. 5 mL) was added dropwise until effervescence ceased. The reaction mixture was concentrated under reduced pressure (to ca 1/5 volume) and the residue was diluted with 1M HCl (aq. 30 mL) and DCM (30 mL). The layers were separated and the aqueous layer was extracted with DCM (2×30 mL). The combined organic layers were dried over Na_2SO_4 , filtered, concentrated and the residue was purified by flash chromatography (Et_2O /Hexane 7:3) to afford compound **22b** as colorless viscous oil (1.64 g, 9.64 mmol, 90%).

R_f (Et_2O /hexane 4:1) = 0.3; $[\alpha]_D = +32.1$ (c 1.06, CHCl_3); IR (film, cm^{-1}): 3417, 1737, 1458, 1380, 1246, 1126, 1076, 1040, 994, 956, 823; ^1H NMR (250 MHz, CDCl_3): δ 7.39 (d, 1H, $J = 5.6$ Hz), 6.01 (d, 1H, $J = 5.6$ Hz), 3.48-3.35 (m, 2H), 2.08 (dd, 1H, $J = 14.4, 3.9$ Hz), 1.77 (br s, 1H), 1.68-1.56 (m, 1H), 1.47 (s, 3H), 1.46 (dd, 1H, $J = 14.5, 7.6$ Hz), 0.94 (d, 3H, $J = 6.7$ Hz); ^{13}C NMR (62.9 MHz, CDCl_3): δ 172.6, 160.9, 120.3, 88.9, 68.0, 41.3, 31.4, 24.5, 18.2; HRMS (ESI^+): m/z calcd for $[\text{C}_9\text{H}_{14}\text{O}_3\text{Na}^+]$ 193.0841; found 193.0842, $\Delta = 0.6$ ppm.

3.1.4 (*R*)-5-((*R*)-3-Hydroxy-2-methylpropyl)-5-methyldihydrofuran-2(3*H*)-one (**S16**)

To a solution of compound **22b** (950 mg, 5.58 mmol, 100 mol-%) in EtOAc (5 mL) at rt was added 5% Palladium-charcoal (95 mg, 10 wt-%). The reaction suspension was exposed to a H₂ atmosphere (~1atm pressure using a balloon) for 2 h. After the completion of the reaction, the mixture was filtered through a pad of celite (ø 2 cm × 3.5 cm) and concentrated to afford pure compound **S16** as colorless viscous oil (940 mg, 5.46 mmol, 98%).

R_f (EtOAc/hexane 3:2) = 0.3; $[\alpha]_D = +12.1$ (c 1.01, CHCl₃); IR (film, cm⁻¹): 3432, 1764, 1460, 1384, 1198, 1162, 1137, 1043, 960, 938; ¹H NMR (250 MHz, CDCl₃): δ 3.48-3.35 (m, 2H), 2.70-2.47 (m, 2H), 2.17-1.94 (m, 2H), 1.90-1.78 (m, 3H), 1.52- 1.43 (m, 1H), 1.40 (s, 3H), 1.00 (d, 3H, J = 6.6 Hz); ¹³C NMR (62.5 MHz, CDCl₃): δ 177.0, 87.1, 67.8, 43.6, 33.7, 31.7, 28.6, 25.2, 17.9; HRMS (ESI⁺): m/z calcd for [C₉H₁₆O₃Na⁺] 195.0997; found 195.0990, Δ = -3.8 ppm.

3.1.5 (*R*)-5-((*R*)-3-(Benzyloxy)-2-methylpropyl)-5-methyldihydrofuran-2(3*H*)-one (**23**)

To a solution of **S16** (51.8 mg, 0.30 mmol, 100 mol-%) in DMF (1.5 mL) at 0 °C was added NaH (55-65% dispersion in mineral oil, 24.0 mg, 1.0 mmol, 200 mol-%) in one portion and the resulting suspension was stirred at 0 °C for 30 min. Benzyl bromide (122 mg, 0.08 mL, 0.33 mmol, 110 mol-%) and tetrabutylammonium iodide (15.4 mg, 0.09 mmol, 30 mol-%) were added and the ice bath was removed. After 2 h of stirring at rt, the reaction mixture was quenched by the addition of water (10 mL). EtOAc (10 mL) was added and the layers were separated. The organic layer was washed with water (10 mL). The combined aqueous layers were acidified by the addition of 3M HCl (aq. ~5 mL, the acidity was measured pH-indicator paper) and extracted with EtOAc (10 mL). Combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/hexane 1:2) afforded the desired product **23** as clear pale yellow oil (61.8 mg, 0.24 mmol, 78%).

R_f (EtOAc/hexane 1:2) = 0.42; $[\alpha]_D = +12.0$ (c 0.1, CHCl_3); IR (film, cm^{-1}): 2971, 2931, 2857, 1766, 1101, 961, 739, 699; ^1H NMR (500 MHz, CDCl_3): δ 7.38–7.24 (m, 5H), 4.50 (s, 2H), 3.31 (dd, 1H, $J = 9.0, 5.7$ Hz), 3.25 (dd, 1H, $J = 9.0, 7.0$ Hz), 2.58 (ddd, 1H, $J = 17.9, 9.3, 8.3$ Hz), 2.55 (ddd, 1H, $J = 17.9, 9.3, 6.2$ Hz), 2.09 (ddd, 1H, $J = 12.8, 9.3, 8.3$ Hz), 2.01–1.91 (obs m, 1H), 1.98 (ddd, 1H, $J = 12.8, 8.3, 6.2$ Hz), 1.89 (dd, 1H, $J = 14.4, 4.0$ Hz), 1.49 (dd, 1H, $J = 14.4, 7.8$ Hz), 1.40 (s, 3H), 1.03 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, CDCl_3): δ 176.7, 138.5, 128.4, 127.55, 127.53, 87.0, 76.0, 73.1, 44.4, 34.2, 30.0, 28.8, 25.4, 18.6; HRMS (ESI⁺): m/z calcd for $[\text{C}_{16}\text{H}_{22}\text{O}_3\text{Na}]$ 285.1467, found 285.1473, $\Delta = 2.2$ ppm.

3.1.6 (6*R*,8*R*)-9-(Benzyloxy)-6,8-dimethylnon-1-ene-3,6-diol (**24**)

To a stirred solution of lactone **23** (0.439 g, 1.67 mmol, 100 mol-%) in DCM (15 mL) at -78°C was added DIBAL-H (1M solution in DCM, 2.50 mL, 2.49 mmol, 150 mol-%) dropwise. After stirring for 1 hour at -78°C , the reaction was quenched by the addition of sat. Rochelle salt solution (aq. 60 mL). The cold mixture was allowed to warm to rt and stirring was continued until both phases were clear. The mixture was diluted by DCM (15 mL) and the layers were separated. The aqueous layer was extracted with DCM (2×40 mL). The combined organic phases were washed with sat. brine (50 mL), dried over NaSO_4 , filtered and concentrated under reduced pressure to afford the crude lactol intermediate as a clear oil. This crude material was used in the next step without further purification.

R_f (EtOAc/hexanes 1:2) = 0.44.

To a stirred solution of the crude lactol (0.442 g, 1.67 mmol, 100%) in THF (10 mL) at -30°C was added vinylmagnesium bromide (1M solution in THF, 16.6 mL, 16.6 mmol, 1000 mol-%). The reaction mixture was allowed to warm to rt during one hour. The reaction was quenched by the addition of sat. NH_4Cl (aq. 40 mL) and diluted with EtOAc (15 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×25 mL). The combined organic phases were dried over NaSO_4 , filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/hexane 1:2) afforded the product **24** as a mixture of diastereomers (0.424 g, 1.45 mmol, 87 %).

R_f (EtOAc/hexane 1:2) = 0.16; IR (film, cm^{-1}): 3367, 2926, 2859, 1073, 992, 917, 735, 697; ^1H NMR (500 MHz, CDCl_3): δ 7.38–7.26 (m, 5H), 5.85 (ddd, $\frac{1}{2}\text{H}$, $J = 17.1, 10.6,$

6.2 Hz), 5.84 (ddd, $\frac{1}{2}$ H, $J = 17.1, 10.6, 6.2$ Hz), 5.21 (dt, $\frac{1}{2}$ H, $J = 10.6, 1.5$ Hz), 5.20 (dt, $\frac{1}{2}$ H, $J = 10.6, 1.5$ Hz), 5.08 (obs dt, $\frac{1}{2}$ H, $J = 17.1, 1.5$ Hz), 5.07 (obs dt, $\frac{1}{2}$ H, $J = 17.1, 1.5$ Hz), 4.52 (s, 2H), 4.10 (app tq, $\frac{1}{2}$ H, $J = 6.2, 1.5$ Hz), 4.03 (app tq, $\frac{1}{2}$ H, $J = 6.2, 1.5$ Hz), 3.41 (dd, $\frac{1}{2}$ H, $J = 9.0, 1.8$ Hz), 3.40 (dd, $\frac{1}{2}$ H, $J = 9.0, 1.8$ Hz), 3.25 (dd, $\frac{1}{2}$ H, $J = 9.0, 2.5$ Hz), 3.24 (dd, $\frac{1}{2}$ H, $J = 9.0, 2.5$ Hz), 2.13-2.02 (m, 1H), 1.73-1.45 (m, 6H), 1.17 (s, $1\frac{1}{2}$ H), 1.16 (s, $1\frac{1}{2}$ H), 0.92 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (125 MHz, CDCl_3): δ 141.31, 141.25, 137.6, 137.5, 128.45, 128.44, 127.79, 127.76, 114.3, 114.2, 77.1, 77.0, 73.5, 73.30, 73.28, 73.1, 71.51, 71.48, 48.8, 48.7, 37.4, 36.7, 32.0, 31.6, 29.21, 29.19, 27.98, 27.96, 19.54, 19.52; HRMS (ESI^+): m/z calcd for $[\text{C}_{18}\text{H}_{28}\text{O}_3\text{Na}]$ 315.1936, found 315.1936, $\Delta = 1.6$ ppm.

3.1.7 (8*R*,10*R*,*E*)-Methyl 11-(benzyloxy)-8-hydroxy-8,10-dimethylundec-4-enoate (**25**)

To a solution of alcohol **24** (21.9 mg, 0.075 mmol, 100 mol-%) in trimethyl orthoacetate (1 mL) was added propionic acid (0.4 mg, 0.4 μL , 0.005 mmol, 7 mol-%). The reaction mixture was stirred at +100 $^\circ\text{C}$ for 3 days. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexane 1:5) to afford the olefin **25** as a clear oil (17.6 mg, 0.051 mmol, 67%).

R_f (EtOAc/hexane 1:5) = 0.16; $[\alpha]_D = -0.8$ (c 1.0, CHCl_3); IR (film, cm^{-1}): 3443, 2927, 2854, 1738, 1454, 1438, 1168, 1092, 738, 699; ^1H NMR (500 MHz, CDCl_3): δ 7.37-7.25 (m, 5H), 5.51-5.37 (m, 2H), 4.52 (dd^{AB}, 2H, $|J_{AB}| = 12.1$ Hz, $\Delta\nu = 6.9$ Hz), 3.66 (s, 3H), 3.39 (dd, 1H, $J = 8.9, 4.5$ Hz), 3.37 (br s, 1H), 3.26 (t, 1H, $J = 8.9$ Hz), 2.39-2.33 (m, 2H), 2.33-2.26 (m, 2H), 2.09-1.92 (m, 3H), 1.60-1.46 (m, 4H), 1.14 (s, 3H), 0.93 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (125 MHz, CDCl_3): δ 173.6, 137.7, 131.9, 128.4, 127.8, 127.72, 127.70, 77.1, 73.3, 71.7, 51.4, 48.2, 41.2, 34.1, 29.2, 27.94, 27.86, 27.5, 19.6; HRMS (ESI^+): m/z calcd for $[\text{C}_{21}\text{H}_{32}\text{O}_4\text{Na}]$ 371.2204, found 371.2198, $\Delta = 1.6$ ppm.

3.1.8 (*S*)-5-((1*S*,4*R*,6*R*)-7-(Benzyloxy)-1,4-dihydroxy-4,6-dimethylheptyl)-dihydrofuran-2(3*H*)-one (**26**)

A flask was charged with potassium hexacyanoferrate(III) (670 mg, 2.025 mmol, 300-mol%), potassium carbonate (280mg, 2.025 mmol, 300 mol-%), potassium osmate dihydrate (5.0 mg, 0.014 mmol, 2 mol-%), methanesulfonamide (64 mg, 0.675 mmol, 100 mol-%) and (DHQ)₂PHAL (52 mg, 0.068 mmol, 10 mol-%).¹¹ Water (4.3 mL) and *tert*-butanol (2.4 mL) were added and the resulting slurry was stirred until all solids dissolved.¹² The clear solution was then cooled to 0 °C. Olefin **25** (235 mg, 0.675 mmol, 100 mol-%) in a small amount of *tert*-butanol (1 mL+1 mL for rinsing the container) was added and the mixture was stirred for 2 h 25 mins at 0 °C. Sodium sulfite (1.5 g, excess) was added in one portion to the mixture. After stirring for 1 hour at rt, the layers were separated. The aqueous phase was diluted with water and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to afford the desired product **26** as clear oil (224 mg, 0.64 mmol, 95%, *dr* 9:1).

R_f (EtOAc/hexanes 1:5) = 0.38; $[\alpha]_D^{20} = +13.9$ (c 2.0, CHCl₃); IR (film, cm⁻¹): 3416, 2957, 2928, 2870, 1765, 1496, 1190, 1076, 741, 699; ¹H NMR (500 MHz, CDCl₃): δ 7.37-7.27 (m, 5H), 4.52 (s, 2H), 4.36 (ddd, 1H, $J = 7.3, 7.3, 4.8$ Hz), 3.78 (br s, 1H), 3.55-3.49 (m, 1H), 3.43 (dd, 1H, $J = 9.0, 4.1$ Hz), 3.25 (app t, 1H, $J = 9.0$ Hz), 2.59 (ddd, 1H, $J = 17.9, 10.0, 5.0$ Hz), 2.58 (br s, 1H), 2.49 (ddd, 1H, $J = 17.9, 10.0, 8.7$ Hz), 2.20 (dddd, 1H, $J = 12.8, 10.0, 7.3, 5.0$ Hz), 2.13-2.03 (m, 1H), 2.04 (dddd, 1H, $J = 12.8, 10.0, 8.7, 7.3$ Hz), 1.70-1.50 (m, 7H), 1.16 (s, 3H), 0.93 (d, 3H, $J = 6.9$ Hz); ¹³C NMR (125 MHz, CDCl₃): δ 177.1, 137.5, 128.5, 127.86, 127.83, 83.3, 77.1, 74.1, 73.4, 71.4, 49.0, 37.0, 29.2, 28.6, 28.1, 27.5, 24.2, 19.5; HRMS (ESI⁺): m/z calcd for [C₂₀H₃₀O₅Na] 373.1995, found 373.1991, $\Delta = 1.2$ ppm.

¹¹ It is also possible to use the commercially available AD-mix α .

¹² The use of an ultrasonic bath speeds up the process.

3.1.9 (2*S*,2'*R*,5'*R*)-5'-((*R*)-3-(Benzyloxy)-2-methylpropyl)-5'-methylhexahydro-[2,2'-bifuran]-5(2*H*)-one (**27**)

To a stirred solution of diol **26** (224 mg, 0.64 mmol, 100 mol-%) and Et₃N (647 mg, 0.89 mL, 6.39 mmol, 1000 mol-%) in DCM (13 mL) at -40 °C was added methanesulfonyl chloride (220 mg, 0.15 mL, 1.92 mmol, 300 mol-%). After 15 mins of stirring at -40 °C, the reaction was quenched by the addition of MeOH (1.5 mL). The cold mixture was allowed to warm to rt and water (20 mL) was added. The layers were separated and the aqueous layer was extracted with DCM (2 × 15 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude mesylate intermediate as clear oil. This material was used directly in the next reaction without further purification.

R_f (EtOAc) = 0.58; HRMS (ESI⁺): m/z calcd for [C₂₁H₃₂O₇SNa] 451.1766, found 451.1776, Δ = 2.2 ppm.

A stirred solution of the crude mesylate intermediate (274 mg, 0.64 mmol, 100 mol-%) in 2,6-lutidine (6 mL, excess) was heated for 15 hours at +120 °C and then allowed to cool to rt. The mixture was diluted with water (20 mL) and DCM (20 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (MeOH/DCM 1:99) to afford the product **27** as clear oil (157 mg, 0.47 mmol, 73%).

R_f (1% MeOH/DCM) = 0.21; $[\alpha]_D^{25} = +19.1$ (c 2.0, CHCl₃); IR (film, cm⁻¹): 2965, 2929, 2870, 1775, 1454, 1176, 1095, 1075, 738, 699; ¹H NMR (500 MHz, CDCl₃): δ 7.36-7.31 (m, 4H), 7.30-7.25 (m, 1H), 4.50 (s, 2H), 4.38 (ddd, 1H, J = 7.3, 5.8, 5.8 Hz), 3.96 (ddd, 1H, J = 7.3, 6.3, 5.8 Hz), 3.29 (dd, 1H, J = 9.1, 6.4 Hz), 3.23 (dd, 1H, J = 9.1, 6.5 Hz), 2.55 (ddd, 1H, J = 17.7, 9.8, 6.3 Hz), 2.46 (ddd, 1H, J = 17.7, 9.8, 7.3 Hz), 2.27 (dddd, 1H, J = 13.0, 9.8, 7.4, 6.3 Hz), 2.12-2.00 (m, 1H), 2.07 (dddd, 1H, J = 13.0, 9.8, 7.3, 5.8 Hz), 1.97-1.86 (m, 1H), 1.85-1.69 (m, 3H), 1.64 (dd, 1H, J = 14.2, 4.1 Hz), 1.33 (dd, 1H, J = 14.2, 7.6 Hz), 1.22 (s, 3H), 1.00 (d, 3H, J = 6.7 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 177.2, 138.8, 128.3, 127.5, 127.4, 84.2, 82.1, 79.5, 76.6, 72.9, 44.0, 37.8, 30.3, 28.2, 28.1, 26.7, 23.9, 18.7; HRMS (ESI⁺): m/z calcd for [C₂₀H₂₈O₄Na] 355.1885, found 355.1891, Δ = 1.5 ppm.

3.1.10 (*S*)-4-((2*R*,5*R*)-5-((*R*)-3-(Benzyloxy)-2-methylpropyl)-5-methyl-tetrahydrofuran-2-yl)-4-hydroxy-*N*-methoxy-*N*-methylbutanamide (**S17**)

To a suspension of *N,O*-dimethylhydroxylamine hydrochloride (129 mg, 1.32 mmol, 280 mol-%) in THF (1.6 mL) at -10°C was slowly added *tert*-butylmagnesium chloride (2M solution in Et_2O , 1.23 mL, 2.46 mmol, 520 mol-%). The resulting mixture was stirred for 10 mins and then a solution of lactone **27** (157 mg, 0.47 mmol, 100 mol-%) in THF (1 mL+1 mL for rinsing the container) was added *via* canula. After 12 mins of stirring at -8°C , the reaction was quenched by the addition of sat. NH_4Cl (aq. 20 mL). The mixture was diluted with water (10 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×20 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to afford the product **S17** as clear oil (143 mg, 0.36 mmol, 77%).

R_f (EtOAc) = 0.43; $[\alpha]_D = +10.6$ (c 1.0, CHCl_3); IR (film, cm^{-1}): 3436, 2964, 2929, 2870, 1661, 1454, 1377, 1095, 1074, 736, 699; ^1H NMR (500 MHz, CDCl_3): δ 7.35-7.30 (m, 4H), 7.29-7.23 (m, 1H), 4.49 (s, 2H), 3.81 (ddd, 1H, $J = 8.3, 6.3, 4.5$ Hz), 3.68 (s, 3H), 3.62 (dddd, 1H, $J = 9.3, 4.5, 2.3, 2.3$ Hz), 3.30 (dd, 1H, $J = 9.0, 6.2$ Hz), 3.22 (dd, 1H, $J = 9.0, 6.8$ Hz), 3.17 (s, 3H), 2.79 (d, 1H, $J = 2.3$ Hz), 2.69-2.54 (m, 2H), 1.97-1.73 (m, 5H), 1.71-1.61 (m, 2H), 1.62 (dd, 1H, $J = 14.1, 4.1$ Hz), 1.33 (dd, 1H, $J = 14.1, 7.4$ Hz), 1.20 (s, 3H), 1.00 (d, 3H, $J = 6.7$ Hz); ^{13}C NMR (125 MHz, CDCl_3): δ 174.8, 138.7, 128.2, 127.41, 127.3, 83.3, 81.7, 76.6, 72.8, 72.0, 61.1, 44.1, 38.1, 32.2, 30.2, 28.7, 27.3, 26.7, 25.6, 18.9; HRMS (ESI $^+$): m/z calcd for $[\text{C}_{22}\text{H}_{35}\text{O}_5\text{NNa}]$ 416.2413, found 416.2405, $\Delta = -1.9$ ppm.

3.1.11 4-((2*R*,5*R*)-5-((*R*)-3-(Benzyloxy)-2-methylpropyl)-5-methyl-tetrahydrofuran-2-yl)-*N*-methoxy-*N*-methylpent-4-enamide (**S18**)

To a solution of alcohol **S17** (142 mg, 0.36 mmol, 100 mol-%) in DCM (7.2 mL) were added 4-methylmorpholine *N*-oxide (423 mg, 3.61 mmol, 1000 mol-%) and 4 Å molecular sieves (360 mg, 50 mg/mL of solvent). The slurry was cooled to 0 °C and a catalytic amount of tetrapropylammonium perruthenate (11.7 mg, 0.03 mmol, 9 mol-%) was added. The ice bath was removed and the reaction mixture was stirred for 3 h at rt. The mixture was then filtered through a silica layer (ø 2 cm × 3.5 cm) which was rinsed with EtOAc (2 × 20 mL). The filtrate was concentrated under reduced pressure to afford the crude ketone intermediate as yellow oil. This crude material was used directly in next reaction without further purification.

R_f (EtOAc/hexane 1:1) = 0.4; HRMS (ESI⁺): m/z calcd for [C₂₂H₃₃O₅NNa] 414.2256, found 414.2261, Δ = 1.2 ppm.

To a suspension of methyltriphenylphosphonium bromide (193 mg, 0.54 mmol, 150 mol-%) in THF (3.6 mL) at 0 °C was added *n*-BuLi (2.5M solution in hexane, 0.18 mL, 0.45 mmol, 125 mol-%). The mixture was stirred for 10 mins and the crude ketone (141 mg, 0.36 mmol, 100 mol-%) was added in a small amount of THF (1 mL+1 mL for rinsing the container) *via* canula. After 20 mins of stirring at 0 °C, the reaction was quenched by the addition of sat. NH₄Cl (aq. 15 mL) and diluted with EtOAc (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 1:4) to afford the product **S18** as clear oil (111 mg, 0.28 mmol, 79%).

R_f (EtOAc/hexane 1:1) = 0.55; $[\alpha]_D^{25} = +16.4$ (*c* 1.0, CHCl₃); IR (film, cm⁻¹): 2965, 2931, 2869, 1667, 1454, 1417, 1377, 1100, 740, 698; ¹H NMR (500 MHz, CDCl₃): δ 7.35-7.29 (m, 4H), 7.28-7.22 (m, 1H), 5.09 (s, 1H), 4.78 (s, 1H), 4.49 (s, 2H), 4.35 (dd, 1H, *J* = 7.3, 6.8 Hz), 3.66 (s, 3H), 3.32 (dd, 1H, *J* = 9.1, 6.2 Hz), 3.23 (dd, 1H, *J* = 9.1, 6.8 Hz), 3.16 (s, 3H), 2.64 (ddd, 1H, *J* = 16.0, 9.6, 6.3 Hz), 2.59 (ddd, 1H, *J* = 16.0, 9.3, 6.5 Hz), 2.38 (ddd, 1H, *J* = 15.7, 9.3, 6.3 Hz), 2.30 (ddd, 1H, *J* = 15.7, 9.6, 6.5 Hz), 2.11-2.01 (m, 1H), 1.99-1.88 (m, 1H), 1.84-1.67 (m, 3H), 1.64 (dd, 1H, *J* = 14.1, 4.3 Hz), 1.36 (dd, 1H, *J* = 14.1, 7.4 Hz), 1.24 (s, 3H), 1.02 (d, 3H, *J* = 6.7 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 174.0, 149.7, 138.7, 128.2, 127.33, 127.25, 108.5, 83.4, 81.4, 76.5, 72.8, 61.1, 44.3, 38.0, 32.1, 31.5, 30.5, 30.2, 26.7, 26.3, 18.9; HRMS (ESI⁺): m/z calcd for [C₂₃H₃₅O₄NNa] 412.2464, found 412.2470, Δ = 1.6 ppm.

3.1.12 5-((2*R*,5*R*)-5-((*R*)-3-(Benzyloxy)-2-methylpropyl)-5-methyl-tetrahydrofuran-2-yl)hex-5-en-2-one (**28**)

To a solution of amide **S18** (52.7 mg, 0.13 mmol, 100 mol-%) in THF (1.3 mL) at -78 °C was slowly added methylmagnesium chloride (3M solution in THF, 0.22 mL, 0.66 mmol, 500 mol-%). After 10 mins the -78 °C bath was replaced by an ice bath and the reaction mixture was stirred for another 30 mins at 0 °C. The reaction was quenched by addition of sat. NH₄Cl (aq. 15 ml). The resulting mixture was diluted with EtOAc (20 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane 1:5) to afford the product **28** as clear oil (39.6 mg, 0.11 mmol, 87%).

R_f (EtOAc/hexane 1:2) = 0.70; $[\alpha]_D^{25} = +22.7$ (c 2.3, CHCl₃); IR (film, cm⁻¹): 2965, 2927, 2853, 1717, 1454, 1360, 1095, 1042, 737, 698; ¹H NMR (500 MHz, CDCl₃): δ 7.36-7.30 (m, 4H), 7.30-7.29 (m, 1H), 5.10-5.04 (m, 1H), 4.75-4.71 (m, 1H), 4.50 (s, 2H), 4.33 (app t, 1H, $J = 7.0$ Hz), 3.33 (dd, 1H, $J = 9.0, 6.2$ Hz), 3.24 (dd, 1H, $J = 9.0, 6.8$ Hz), 2.66 (ddd^{AB}, 1H, $J = 17.2, 9.3, 6.2$ Hz), 2.60 (ddd^{AB}, 1H, $J = 17.2, 9.0, 6.3$ Hz), 2.38-2.29 (m, 1H), 2.29-2.21 (m, 1H), 2.15 (s, 3H), 2.08-2.00 (m, 1H), 1.99-1.89 (m, 1H), 1.85-1.68 (m, 3H), 1.65 (dd, 1H, $J = 14.0, 4.5$ Hz), 1.37 (dd, 1H, $J = 14.0, 7.4$ Hz), 1.24 (s, 3H), 1.03 (d, 3H, $J = 6.7$ Hz); ¹³C NMR (125 MHz, CDCl₃): δ 208.3, 149.3, 138.7, 128.2, 127.4, 127.3, 108.7, 83.4, 81.4, 76.6, 72.8, 44.3, 42.1, 38.0, 31.5, 30.2, 29.8, 26.7, 25.5, 18.9; HRMS (ESI⁺): m/z calcd for [C₂₂H₃₂O₃Na] 367.2249, found 367.2248, $\Delta = -0.3$ ppm.

3.2 Determination of Relative Stereochemistries at C25 and C27

Relative stereochemistries were determined by ¹H-NMR of compounds **S19** and **S20** (Scheme 2.). The characteristic coupling constants between the two vicinal protons in the six membered rings confirmed the relative stereochemistry. The axial-axial coupling was significantly larger (11.1 Hz) than the axial-equatorial coupling (4.7 Hz).

Scheme 2. Conformational drawings of **S20** and **S19**.3.2.1 (*S*)-5-((*S*)-3-Hydroxy-2-methylpropyl)-5-methylfuran-2(5*H*)-one (**22a**)

Following the above procedure (for compound **22b**), compound **22a** (colorless viscous liquid, 228 mg, 1.34 mmol, 90%) was synthesized from compound **18a** (250 mg, 1.49 mmol).

R_f (EtOAc/hexane 6:4) = 0.3; $[\alpha]_D = +18.8$ (c 1.03, CHCl_3); IR (film, cm^{-1}): 3417, 1735, 1455, 1381, 1277, 1188, 1147, 1095, 1046, 995, 956, 930, 820; ^1H NMR (250 MHz, CDCl_3): δ 7.38 (d, 1H, $J = 5.6$ Hz), 6.00 (d, 1H, $J = 5.6$ Hz), 3.45 (dd, 1H, $J = 10.7, 5.3$ Hz), 3.37 (dd, 1H, $J = 10.7, 6.0$ Hz), 2.20 (bs, 1H), 1.96-1.83 (m, 1H), 1.72-1.55 (m, 2H), 1.47 (s, 3H), 0.92 (d, 3H, $J = 6.5$ Hz); ^{13}C NMR (62.9 MHz, CDCl_3): δ 172.7, 161.1, 120.0, 89.3, 67.3, 40.8, 31.4, 24.4, 18.2; HRMS (ESI^+): m/z calcd for $[\text{C}_9\text{H}_{14}\text{O}_3\text{Na}]^+$ 193.0841; found 193.0837, $\Delta = 1.7$ ppm.

3.2.2 (3*aS*,6*S*,7*aS*)-6,7*a*-Dimethylhexahydro-2*H*-furo[3,2-*b*]pyran-2-one (**S19**)

To a stirred solution of alcohol **22a** (111 mg, 0.65 mmol, 100 mol-%) in THF (10 mL) at rt was added NaH (55-65% dispersion in mineral oil, 52.3 mg, 2.2 mmol 200 mol-%) in

one portion. The mixture was stirred for 40 mins at rt. The reaction was then quenched by the addition of 2M HCl (aq. 10 mL). The mixture was diluted with Et₂O (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Et₂O) to afford the product **S19** as white crystals (96.9 mg, 0.57 mmol, 87%).

R_f (Et₂O) = 0.69; mp 49-53 °C; $[\alpha]_D = -46.1$ (c 1.0, CHCl₃); IR (film, cm⁻¹): 2956, 2931, 1771, 1144, 1095, 929; ¹H NMR (500 MHz, CDCl₃): δ 3.90 (d, 1H, J = 4.2 Hz), 3.75 (ddd, 1H, J = 11.2, 3.9, 2.8 Hz), 2.93 (app t, 1H, J = 11.2 Hz), 2.85 (dd, 1H, J = 17.5, 4.2 Hz), 2.46 (dd, 1H, J = 17.5, 0.7 Hz), 2.26 (app dt, 1H, J = 14.8, 3.0 Hz), 2.01-1.90 (m, 1H), 1.29 (s, 3H), 1.21 (dd, 1H, J = 14.8, 12.2 Hz), 0.82 (d, 3H, J = 6.8 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 175.5, 82.9, 76.7, 71.7, 40.6, 38.0, 25.9, 25.5, 16.4; HRMS (ESI⁺): m/z calcd for [C₉H₁₄O₃Na] 193.0841, found 193.0838, Δ = -1.1 ppm.

3.2.3 (3a*S*,6*R*,7a*S*)-6,7a-Dimethylhexahydro-2*H*-furo[3,2-*b*]pyran-2-one (**S20**)

To a stirred solution of alcohol **22b** (79.7 mg, 0.47 mmol, 100 mol-%) in THF (10 mL) at rt was added NaH (55-65% dispersion in mineral oil, 37.4 mg, 1.56 mmol, 200 mol-%) in one portion. The mixture was stirred for 15 mins at rt. The reaction was then quenched by the addition of 1M HCl (10 mL). The mixture was diluted with Et₂O (10 mL). The layers were separated and the aqueous phase was extracted with Et₂O (2 × 10 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Et₂O) to afford the product **S20** as white solid (51.8 mg, 0.30 mmol, 65%).

R_f (Et₂O) = 0.67; mp 55-57 °C; $[\alpha]_D = +16.0$ (c 0.1 CHCl₃); IR (film, cm⁻¹): 2926, 1772, 1136, 1081, 932; ¹H NMR (500 MHz, CDCl₃): 3.94 (dd, 1H, J = 5.5, 2.2 Hz), 3.61 (dd, 1H, J = 11.3, 4.1 Hz), 3.50 (ddd, 1H, J = 11.3, 4.7, 1.2 Hz), 2.80 (dd, 1H, J = 17.7, 5.5 Hz), 2.57 (dd, 1H, J = 17.7, 2.2 Hz), 1.94-1.87 (m, 1H), 1.87-1.78 (m, 2H), 1.33 (s, 3H), 1.07 (d, 3H, J = 6.9 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 174.8, 83.1, 76.9, 69.7, 37.8, 36.0, 26.8, 25.2, 17.8; HRMS (ESI⁺): m/z calcd for [C₉H₁₄O₃Na] 193.0841, found 193.0844, Δ = 1.6 ppm.

3.3 Determination of Absolute Stereochemistry

Determination of the absolute stereochemistry of compound **27** was based on the relative stereochemistries of centers C25 and C27 of molecules **18a** and **18b**, as established in Section 3.2 (see above), and on the well-established stereochemical reliability of the Sharpless asymmetric dihydroxylation (AD) reaction for (*E*)-olefins.¹³ The AD reaction establishes the absolute stereochemistry at C21 and C22, and NOE experiments for compound **27** gave evidence for the correct stereochemistry at C25 (Scheme 3, for further details please see the spectral section). Further support for the relative stereochemistry was obtained from the crystal structure of compound **29** (Figure 1). Compound **29** was synthesized using AD-mix β ((DHQD)₂PHAL ligand) and therefore had the opposite stereochemistry at centers C21 and C22 compared to compound **27**, which was prepared using AD-mix α ((DHQ)₂PHAL ligand). The reason for using compound **29** for the X-ray studies was that compound **27** was not crystalline.

Scheme 3. Selected diagnostic NOE-enhancements of **27**.

Figure 1. Crystal structure of **29**.

¹³ For a review, see: Kolb, H.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, 94, 2483.

3.3.1 (*R*)-5-((1*R*,4*R*,6*R*)-7-(Benzyloxy)-1,4-dihydroxy-4,6-dimethylheptyl)-dihydrofuran-2(3*H*)-one (**29**)

A flask was charged with potassium hexacyanoferrate(III) (94.5 mg, 0.284 mmol, 300 mol-%), potassium carbonate (39.3 mg, 0.28 mmol, 300 mol-%), potassium osmate dihydrate (0.7 mg, 0.002 mmol, 2 mol-%), methanesulfonamide (9.0 mg, 0.095 mmol, 100 mol-%) and (DHQD)₂PHAL (7.4 mg, 0.009 mmol, 10 mol-%).¹⁴ Water (3.2 mL) and *tert*-butanol (1.8 mL) were added, and the resulting slurry was stirred until all solids dissolved.¹² The clear solution was then cooled to 0 °C. Olefin **25** (33.0 mg, 0.095 mmol, 100 mol-%) in a small amount of *tert*-butanol (1 mL+1 mL for rinsing the container) was added and the mixture was stirred 2 h 25 mins at 0 °C. Sodium sulfite (1.5 g, excess) was added in one portion to the mixture. After stirring for 1 hour at rt, the layers were separated. The aqueous phase was diluted with water and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to afford the product **29** as white crystalline solid (32.1 mg, 0.092 mmol, 97%, *dr* 9:1).

R_f (EtOAc) = 0.38; mp 93-96 °C; $[\alpha]_D = -11.3$ (*c* 2.2, CHCl₃); IR (film, cm⁻¹): 3406, 2956, 2928, 2870, 1761, 1190, 1089, 1074, 740, 699; ¹H NMR (500 MHz, CDCl₃): δ 7.37-7.27 (m, 5H), 4.52 (s, 2H), 4.39 (ddd, 1H, *J* = 7.6, 6.6, 3.6 Hz), 4.14 (br s, 1H), 3.71 (br s, 1H), 3.46 (ddd, 1H, *J* = 8.8, 6.9, 3.6 Hz), 3.43 (dd, 1H, *J* = 9.0, 4.1 Hz), 3.23 (app t, 1H, *J* = 9.0 Hz), 2.61 (ddd, 1H, *J* = 17.8, 9.9, 5.9 Hz), 2.45 (ddd, 1H, *J* = 17.8, 9.9, 8.0 Hz), 2.17 (dddd, 1H, *J* = 12.8, 9.9, 7.6, 5.9 Hz), 2.26-2.04 (obs. m, 1H), 2.12 (dddd, 1H, *J* = 12.8, 9.9, 8.0, 6.6 Hz), 1.81-1.69 (m, 2H), 1.66-1.48 (m, 4H), 1.17 (s, 3H), 0.92 (d, 3H, *J* = 7.0 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 177.7, 137.5, 128.6, 128.05, 127.98, 83.1, 77.2, 74.1, 73.6, 71.6, 49.6, 37.7, 29.3, 28.7, 28.0, 27.9, 24.1, 19.6; HRMS (ESI⁺): *m/z* calcd for [C₂₀H₃₀O₅Na] 373.1991, found 373.1986, Δ = -1.2 ppm.

¹⁴ It is also possible to use the commercially available AD-mix β.

4 Spectral Data

OEC-

3-081

OEC-3-081

13

OEC-3-167

OEC-3-167

14

OEC-3-111

14

OEC-3-111

¹H NMR spectrum of compound 10b in CDCl₃. The spectrum shows peaks from 0 to 8 ppm. Integration values are provided for several regions: 1.00, 1.03, 4.16, 2.11, 1.17, 3.92, 4.57, 1.26, 2.05, 5.14, 1.01, 0.97, 1.01, 2.30, 2.15, 1.08, and 2.98. The x-axis is labeled 'ppm' and ranges from 0 to 8.0.

15

OEC-3-103

S5

OEC-4-079

S43

S6

OEX-1-013A

S6

OEX-1-013A

S45

(S,S)-S7

OEX-1-014

(meso)-S7

OEX-1-014-top

OEX-1-016A

OEX-1-016A

(*S,S*)-16 (racemate: top, enantioenriched: bottom)

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Report Method ID: 1004
Page: 1 of 1

Project Name: Saho
Date Printed: 5/19/2011
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Report Method: Default Individual Report
Report Method ID: 1004
Page: 1 of 1

Project Name: Saho
Date Printed: 5/19/2011
3:34:03 PM Europe/Helsinki

18 (racemate: top, enantioenriched: bottom)

OEX-1-113B-Top

OEX-1-113B-Top

OEC-3-185

22 (diastereomeric mixture)

OEX-2-013

OEX-1-115-top spot

OEX-1-115-top spot

OEX-2-053

OEX-2-053

19 (racemate: top, enantioenriched: bottom)

S8 (diastereomeric mixture)

OEX-2-067

S8 (diastereomeric mixture)

OEX-2-067

20 (racemate: top, enantioenriched: bottom)

OEX-2-071

OEX-2-071

21 (racemate: top, enantioenriched: bottom)

OEX-2-069

OEX-2-069

S12

OEX-2-021

OEX-2-021

OEX-2-077

S14

OEX-2-085

S14

OEX-2-085

17

OEC-3-143

17

OEC-3-143

OEX-1-125

S16

OEX-1-125

23

OEC-5-011

23

OEC-5-011

24

OEC-4-155

24

OEC-4-155

25

OEC-5-017

25

OEC-5-017

OEC-5-019

OEC-5-019

27

OEC-5-009

27

OEC-5-009

OEC-5-009 (COSY)

OEC-5-009 (NOESY)

OEC-5-009 NOE

S17

OEC-5-041

S92

S17

OEC-5-041

S18

OEC-5-049

S94

OEC-5-049

S95

OEC-5-033

28

OEC-5-033

OEC-4-061

OEC-4-061

OEC-4-061

S20

¹H NMR spectrum of compound 10a in CDCl₃. The spectrum shows peaks from 0.8 to 7.5 ppm. Integration values are provided for several regions: 0.92, 0.98, 0.96, 0.96, 0.95, 0.919, 0.984, 0.963, 0.963, 0.954, 1.015, 1.965, 3.041, and 3.000. A list of chemical shifts (delta) is provided on the right side of the spectrum, ranging from 0.8145 to 7.2595 ppm.

S20

OEC-3-189

OEC-3-189

OEC-5-021

OEC-5-021