Reductive Spiroannulation of Nitriles with Secondary Electrophiles

Matthew D. Morin and Scott D. Rychnovsky*

Department of Chemistry, 516 Rowland Hall, University of California, Irvine, California 92697-2025

Table of Contents

1	General Methods	1
2	Preparation of 2-cyano-THP 1	3
3	Preparation of chloride and phosphate side chains 2a-h	4
4	Preparation of cyclization precursors 3a-d and 16	10
5	Cyclization of precursors 3a-d and 16	13
6	Preparation of dioxolane side chains 2e-h	17
7	Preparation of precursors 3e-h and 5a-d	21
8	Cyclization of precursors 5a-d	29
9	Correlation Studies	33

1 General Methods

Moisture- and air-sensitive reactions were carried out in flame- or oven-dried glassware that had been cooled under an argon atmosphere. Thin layer chromatography was performed using Whatman Partisil K6F 60Å silica gel (250µm layer thickness on glass support). Flash column chromatography was performed on Sorbent Technologies 32-63µm silica gel. Optical rotations were taken on a JASCO DIP-370 digital polarimeter at 23°C, unless otherwise stated. Infrared spectra were acquired on a MIDAC Grams/Prospect FT-IR. Melting points were determined on an Electrothermal apparatus and are reported uncorrected. NMR spectra were obtained on Bruker 400 or 500 MHz FT-NMR spectrometers. All ¹H and ¹³C NMR spectra were recorded in ppm and referenced to the residual solvent peaks (7.27 and 77.0 ppm, respectively). Some spectra

were additionally referenced to a TMS spike at 0.00 ppm. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, dd = doublet of doublet, m = multiplet), coupling constant(s) in Hertz (Hz) and integration. Multiplets (m) are recorded over the indicated range (in ppm) at which they appear. ^{13}C NMR data are presented in order of decreasing chemical shift. Infrared data are reported in order of decreasing frequency (wavenumbers). High resolution mass spectral data were recorded on either a MicroMass 7070E-HF, a MicroMass Autospec, or a Waters LCT premier spectrometer. Low resolution GCMS data were obtained on a Thermo-Finnigan Trace MS^{PLUS} spectrometer equipped with a 30 m J&W Scientific DB-5 capillary column, employing a temperature range of 50-290 °C and a ramp of 10 °C/min. Capillary GC analysis was performed on a Hewlett Packard model 6890 instrument with a 30m X 0.25 μm Restek RTX-1701 capillary column equipped with FID detector. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ). All commercial reagents were used as supplied from the manufacturer with exception of the following: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) and diisopropylamine (DIPA) were distilled from CaH_2 onto baked 4Å molecular sieves; 1,2-epoxy-5-bromopentane was distilled (44-46 °C, 0.9 torr); boron trifluoride diethyl etherate complex was distilled from CaH_2 (50 °C, 40 torr); di-*tert*-butylbiphenyl (DBB) was recrystallized from ethanol. Tetrahydrofuran (THF), Et_2O , CH_2Cl_2 , and toluene were degassed with argon and then passed through two 4 × 36 inch columns of anhydrous neutral alumina A-2 alumina (8 × 14 mesh; LaRoche Chemicals; activated under a flow of Ar at 350 °C for 12 h to remove H_2O , according to the procedure described by Grubbs.¹ Molarities of organolithium reagents were determined by titration against *N*-benzylbenzamide as an indicator.²

¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

² Burchat, A. F.; Chong, J. M.; Nielsen, N. J. *Organomet. Chem.* **1997**, *542*, 281.

Compounds not explicitly numbered in the main body of this publication have been assigned a number in sequence, beginning with 100.

2 Preparation of 2-cyano-THP **1**

(6*S*)-6-Methyltetrahydropyran-2-carbonitrile (**1**)

(2*R*,6*S*)-6-Methyltetrahydropyran-2-yl acetate³ (0.310 g, 1.96 mmol) was dissolved in CH₂Cl₂ (10 mL) and cooled to −78 °C. Trimethylsilyl cyanide (0.372 g, 3.79 mmol) was added dropwise to the stirring solution, followed immediately by boron trifluoride-diethyl ether complex (0.414 g, 2.91 mmol). The solution was stirred at −78 °C for 2.5 h, after which NaHCO₃ (saturated aqueous, 5 mL) was added. After warming to room temperature over 30 min, the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 194 mg (80%) of (6*S*)-6-Methyl-tetrahydro-pyran-2-carbonitrile **1** as a 3:1 mixture of diastereomers. The product was not purified further.

Data for **1**: R_f 0.49 (20% EtOAc:hexanes); IR (neat) 2942, 2664, 1445, 1385, 1207, 1048 cm^{−1}; Major Diastereomer: ¹H NMR (500 MHz, CDCl₃) δ 4.84 (s, 1H), 3.89 (dtd, *J* = 2.1, 6.1, 12.3 Hz, 1H), 1.93-1.26 (m, 6H), 1.20 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 118.0, 70.9, 64.9, 32.4, 28.2, 21.6, 19.7; Minor Diastereomer: ¹H NMR (500 MHz, CDCl₃) δ 4.23 (dd, *J* = 2.3, 11.7 Hz, 1H), 3.50 (dtd, *J* = 2.0, 6.1, 12.3 Hz, 1H), 1.93-1.26 (m, 6H), 1.22 (d, *J* = 6.2 Hz, 3H); ¹³C NMR (500 MHz, CDCl₃) 118.0, 75.2, 65.9, 32.0, 29.8, 22.6, 21.7 ppm; HRMS (EI) *m/z*

³ Prepared by the sequence given herein: Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc. Perk. Trans. I* **2000**, 2385-2394.

major diastereomer calcd for C₇H₁₁NO 125.0841, found 125.0847, *m/z* minor diastereomer calcd for 125.0841, found 125.0849; Anal. calcd C: 67.17, H: 8.86, found C: 67.35, H: 9.04.

3 Preparation of chloride and phosphate side chains 2a-h

(*S*)-Phosphoric acid diethyl ester 1-methyl-4-pentenyl ester (**100**)

Optically pure (*S*)-hex-5-en-2-ol (1.00 g, 10.0 mmol) was dissolved in CH₂Cl₂ (100 mL) and cooled to 0 °C. *N*-Methylimidazole (1.65 g, 20.0 mmol) was added by syringe and the solution was stirred for 20 min. Diethyl chlorophosphate (3.45 g, 20.0 mmol) was then added by syringe and the solution was stirred for 15 minutes at 0 °C. After warming to room temperature, saturated NH₄Cl (20 mL) was added, and the aqueous phase was extracted with CH₂Cl₂ (3 × 15 mL). The organic extracts were washed with brine (10 mL), dried with Na₂SO₄, filtered, and concentrated *in vacuo* to give 3.96 g of unpurified oil. Flash column chromatography of the crude oil (50:50-70:30 diethyl ether:petroleum ether gradient) afforded 1.98 g (84%) of phosphate ester (*S*)-**100**.

Data for (*S*)-**100**: R_f 0.07 (1:1 Et₂O:Pet. Ether); [α]_D = +15.2 (*c* 1.37, CHCl₃); IR (neat) 3486, 3079, 2982, 2936, 1447, 1385 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.86-5.78 (tdd, *J* = 6.6, 10.2, 17.0 Hz, 1H), 5.05 (dd, *J* = 3.4, 17.1 Hz, 1H), 4.98 (dd, *J* = 3.0, 10.2 Hz, 1H), 4.50 (apparent septet, *J* = 6.3 Hz, 1H), 4.11 (dq, *J* = 4.7, 7.1 Hz, 4H), 2.18-2.12 (m, 2H), 1.80-1.74 (m, 1H), 1.64-1.62 (m, 1H), 1.35 (d, *J* = 6.3 Hz, 6H), 1.33 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 137.6, 115.0, 75.3 (d, *J*_{PC} = 6.3 Hz), 63.5 (d, *J*_{PC} = 3.8 Hz), 63.4 (d, *J*_{PC} = 3.8

Hz), 36.6 (d, $J_{\text{PC}} = 6.3$ Hz), 29.3, 21.5 (d, $J_{\text{PC}} = 2.5$ Hz), 16.2 (d, $J_{\text{PC}} = 2.5$ Hz) 16.1 (d, $J_{\text{PC}} = 3.8$ Hz) ppm; HRMS (CI/NH₃) m/z calcd for C₁₀H₂₂O₄P [M+H]⁺ 237.1255, found 237.1258.

The (*R*)-diethyl ester **100** was prepared by the identical method. (*R*)-hex-5-en-2-ol (2.50 g, 25.0 mmol) yielded 4.81 g (82 %) of (*R*)-ethyl ester **100**. Data for (*R*)-**100**: $[\alpha]_{\text{D}} = -16.8$ (c 1.45, CHCl₃).

(*S*)-Phosphoric acid diethyl ester 4-hydroxy-1-methylbutyl ester (101**)**

A solution of (*S*)-diethyl ester **100** (1.50 g, 6.34 mmol) in a 1:1 mixture of CH₂Cl₂:EtOH (30 mL each) was cooled to -78 °C. Ozone was passed through the solution until a blue color persisted, after which the solution was purged with O₂ until the color vanished. Sodium borohydride (0.483 g, 12.7 mmol) was added and the mixture was warmed to room temperature. The solution was stirred at room temperature for 8 hours. The solvent was then removed *in vacuo* and the impure oil taken up in CH₂Cl₂ (20 mL). The organic layer was washed with saturated NH₄Cl until gas evolution ceased. The layers were partitioned and the aqueous phase was extracted with CH₂Cl₂ (5 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried with Na₂SO₄, filtered and concentrated to afford 1.52 g of oil. Flash column chromatography (75% EtOAc:hexanes) afforded 1.34 g (88%) of (*S*)-alcohol **101**.

Data for (*S*)- **101**: R_f 0.05 (75% EtOAc:hexanes); $[\alpha]_{\text{D}}$ (*S*)-**101** = +5.3 (c 1.44, CHCl₃); IR (neat) 3427, 2983, 2937, 2873, 1446, 1385, 1258, 1166, 1030 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.56 (m, 1H), 4.13-4.03 (m, 4H), 3.71-3.62 (m, 2H), 2.07 (s, 1H), 1.75-1.65 (m, 4H), 1.35 (d, $J = 6.2$ Hz, 6H), 1.33 (d, $J = 7.1$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 75.7, 63.6, 62.4, 33.9,

28.0, 21.6, 16.1 ppm; HRMS (CI/NH₃) m/z calcd for C₉H₂₂O₅P [M+H]⁺ 241.1205, found 241.1198.

(*R*)-alcohol **101** was prepared by the identical method. (*R*)-diethyl ester **100** (4.50 g, 19.0 mmol) provided 3.98 g (87 %) of (*R*)-alcohol **101**. Data for (*R*)-**101**: $[\alpha]_D = -5.5$ (*c* 1.34, CHCl₃).

(S)-Phosphoric acid diethyl ester 4-iodo-1-methylbutyl ester (2b)

Alcohol **101** (0.027 g, 0.11 mmol) was dissolved in dry Et₂O (1 mL) and cooled to 0° C with an ice bath. Triphenylphosphine (0.058 g, 0.22 mmol) and imidazole (0.015 g, 0.22 mmol) were successively introduced to the flask. The mixture was thoroughly stirred until a homogenous solution was observed. Iodine (0.056 g, 0.22 mmol, solution in 1 mL Et₂O) was then added dropwise to the reaction mixture by syringe, during which time a thick precipitate formed. The mixture was stirred at room temperature for 20 min, then diluted with Et₂O (5 mL). NaHSO₃ (3 mL, 40% aqueous solution) was added to reduce the iodine. The aqueous phase was extracted with Et₂O (3 × 5 mL), and the combined ethereal extracts were washed with brine (5 mL), dried with Na₂SO₄, filtered and concentrated. The resulting residue was subjected to flash column chromatography (50% EtOAc:hexanes) to give 0.027 g (71%) of iodide (*S*)-**2b**.

Data for (*S*)-**2b**: R_f 0.42 (75% EtOAc:hexanes); $[\alpha]_D = +8.2$ (*c* 2.04, CHCl₃); IR (neat) 2981, 2935, 2910, 1445, 1384, 1270, 1167, 1100, 1032 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.51 (app. sept, *J* = 6.3 Hz, 1H), 4.11 (quintet of doublets, *J* = 4.7, 7.2 Hz, 4H), 3.22 (t, *J* = 6.8 Hz, 2H), 1.94-1.90 (m, 2H), 1.73-1.69 (m, 2H), 1.36-1.32 (m, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 74.6 (d, *J*_{PC} = 6.0 Hz), 63.6 (d, *J*_{PC} = 4.0 Hz), 63.5 (d, *J*_{PC} = 5.5 Hz), 38.1 (d, *J*_{PC} = 6.4 Hz), 29.0,

21.6 (d, $J_{\text{PC}} = 2.3$ Hz), 16.2 (d, $J_{\text{PC}} = 6.4$ Hz), 16.1 (d, $J_{\text{PC}} = 6.4$ Hz), 6.1 ppm; HRMS (EI) m/z calcd for $\text{C}_9\text{H}_{20}\text{IO}_4\text{P}$ [M^+] 350.0144, found 350.0144. Anal. calcd C: 30.87, H: 5.67, found C: 30.68, H: 5.40.

The (*R*)-iodide **2d** was prepared in the identical manner. (*R*)-alcohol **101** (3.70 g, 15.4 mmol) provided 3.81 g (71 %) of (*R*)-iodide **2d**. Data for **2d**: $[\alpha]_{\text{D}} = -8.6$ (c 2.18, CHCl_3).

(*S*)-4-Chloropentanal (**102**)

(*R*)-5-hexen-2-ol (2.00 g, 19.96 mmol) and triphenylphosphine (7.85 g, 29.9 mmol) were dissolved in carbon tetrachloride (16.0 g, 103 mmol) and heated to reflux for 3 h. After cooling to room temperature, CH_2Cl_2 was added (10 mL) and the reaction mixture was cooled to -78 °C. The solution was sparged with O_2 gas for 5 min and then subjected to ozone until a blue color persisted. O_2 was again passed through the reaction mixture until the blue color was no longer apparent. Triphenylphosphine (7.85 g, 29.9 mmol) was added and the reaction mixture was slowly warmed to room temperature. After stirring for 12 h, the precipitated phosphorus compounds were removed by filtration and the filtrate was concentrated under reduced pressure to give a mixture of solids. Flash column chromatography (10%-30% Et_2O :pentane) gave 934 mg (39%) of (*S*)-4-chloropentanal **102** with trace amounts of polymerized aldehyde.

Data for (*S*)-**102**: R_f 0.36 (25% Et_2O :Pentane); $[\alpha]_{\text{D}} = +74.9$ (c 1.14, CHCl_3); IR (neat) 2973, 2930, 1713, 1446, 1381, 1123 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.83 (s, 1H), 4.08 (m, 1H), 2.70 (m, 2H), 2.13 (m, 1H), 1.93 (m, 1H), 1.55 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.2, 57.7, 41.0, 32.2, 25.4 ppm; HRMS (EI-GCMS) calcd for $\text{C}_5\text{H}_9\text{ClO}$ [M] $^+$ 120.0342, found 120.0343.

The (*R*)-aldehyde **102** was prepared in an identical manner. (*S*)-5-hexen-2-ol (2.50 g, 25.0 mmol) yielded 1.04 g (34 %) of (*R*)-aldehyde **102**. Data for **102**: $[\alpha]_D = -75.4$ ($c = 1.095$, CHCl_3).

(*S*)-4-Chloropentanol-1-ol (103**)**

(*S*)-4-Chloropentanal **102** (900 mg, 7.46 mmol) was dissolved in methanol (37 mL) and cooled to 0 °C. Sodium borohydride (282 mg, 7.46 mmol) was added in one portion and the solution was warmed to room temperature. After 1 h the mixture was concentrated *in vacuo* to give a clear oil accompanied by white solids. Flash column chromatography of the oil (10%-25% Et_2O :Petroleum Ether) afforded 784 mg (86%) of (*S*)-4-chloropentanol-1-ol **103**.

Data for compound (*S*)-**103**: R_f 0.08 (25% Et_2O :petroleum ether); $[\alpha]_D = +42.5$ (c 1.30, CHCl_3); IR (neat) 3342, 2929, 1446, 1380, 1060, 899 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.08 (m, 1H), 3.69 (t, $J = 5.8$ Hz, 2H), 1.85-1.68 (m, 4H), 1.53 (dd, $J = 0.4, 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 62.3, 58.6, 36.6, 29.7, 25.4; HRMS (EI-GCMS) m/z calcd for $\text{C}_5\text{H}_9\text{Cl}$ $[\text{M}-\text{H}_2\text{O}]^+$ 104.0392, found 104.0394.

The (*R*)-alcohol **103** was prepared in an identical fashion. (*R*)-aldehyde **102** (900 mg, 7.46 mmol) afforded 873 mg (95 %) of (*R*)-alcohol **103**. Data for (*R*)-**103**: $[\alpha]_D = -45.0$ (c 1.00, CHCl_3).

Optical purity of (*S*)- and (*R*)-alcohols **103** was determined by chiral GC analysis: β -cyclodextrin dialkyl column, 1.0 mL/min, ramp 2.0 °C/min from 50-120 °C, (*R*)-alcohol $t_R = 27.949$ min (86% ee), (*S*)-alcohol $t_R = 30.384$ min (92% ee).

(S)-4-Chloro-1-iodopentane (2a)

(S)-4-chloropentan-1-ol **103** (600 mg, 4.89 mmol) was dissolved in Et₂O (20 mL) and cooled to 0 °C. Triphenylphosphine (1.41 g, 5.38 mmol) and imidazole (366 mg, 5.38 mmol) were successively added to the flask. Upon complete dissolution, iodine (1.37 g, 5.38 mmol, as a solution in 20 mL of Et₂O) was added dropwise by syringe to the stirring mixture. A precipitate was observed with the addition of each drop. The pale yellow reaction mixture was transferred to a separatory funnel and the thick precipitates were triturated with Et₂O (10 × 10 mL) to ensure complete transfer of product. The yellow solution was washed with 10% NaHSO₃ (40 mL), and the aqueous phase was extracted with Et₂O (3 x 20 mL). Combined organic extracts were dried with Na₂SO₄, filtered, and concentrated under reduced pressure to give a yellow oil. Flash column chromatography (pentane eluent) afforded 962 mg (84 %) of (S)-4-chloro-1-iodopentane **2a**.

Data for **2a**: *R_f* 0.50 (Pentane); [α]_D = +45.9 (*c* 2.05, CHCl₃); IR (neat) 2969, 2927, 1443, 1379, 1256, 1216, 1175, 1019 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.05 (m, 1H), 3.22 (t, *J* = 6.6 Hz, 2H), 2.08 (m, 1H), 1.99-1.78 (m, 3H), 1.54 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 57.4, 40.8, 30.3, 25.4, 5.8 ppm; HRMS (EI-GCMS) calcd for C₅H₁₀I [M-Cl]⁺ 196.9827, found 196.9826.

The (*R*)-iodide **2c** was prepared in a congruent fashion. (*R*)-alcohol **103** (680 mg, 5.55 mmol) gave 1.02 g (79 %) of (*R*)-iodide **2c**. Data for **2c**: [α]_D = -46.1 (*c* 1.05, CHCl₃).

4 Preparation of cyclization precursors 3a-d and 16

Phosphoric acid (2*S*,6*S*,1'*R*)- and (2*S*,6*S*,1'*S*)-4'-(2-cyano-6-methyltetrahydropyran-2-yl)-1'-methylbutyl ester diethyl esters (3d) and (3b), respectively

(6*S*)-2-Cyanotetrahydropyran **1** (65 mg, 0.52 mmol) and iodide **2d** (150 mg, 0.43 mmol) were dissolved in dry THF (2.1 mL) and cooled to $-40\text{ }^{\circ}\text{C}$. DMPU (118 mg, 1.04 mmol) was added to the stirring solution by syringe. Lithium diisopropylamide (1.49 mL, 0.38 M in THF, prepared from freshly distilled DIPA and *n*-butyllithium) was added dropwise and the solution was stirred for 3.5 hours. The reaction mixture was diluted with Et₂O (10 mL) and washed with saturated NH₄Cl (10 mL) and H₂O (10 mL). The aqueous phase was extracted with Et₂O (3 $\times$ 5 mL), and the combined ethereal extracts were dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Flash column chromatography of the unpurified oil (40%-60% EtOAc:hexanes) gave 95 mg (64 %) of ester (2*S*,6*S*,1'*R*)-**3d**.

Data for (2*S*,6*S*,1'*R*)-**3d**: R_f 0.21 (50% EtOAc:hexanes); $[\alpha]_D = -67.9$ (c 2.07, CHCl₃); IR (neat) 2978, 2936, 1446, 1384, 1263, 1035, 1004 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.48 (sept, $J = 6.7$ Hz, 1H), 4.08 (dtd, $J = 5.6, 7.1, 7.5$ Hz, 4H), 3.82 (dtd, $J = 2.2, 6.7, 11.3$ Hz, 1H), 1.84-1.44 (m, 12H), 1.32 (d, $J = 6.6$ Hz, 6H), 1.30 (d, $J = 7.3$ Hz, 3H), 1.17 (d, $J = 7.6$ Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 119.4, 75.2 (d, $J_{PC} = 3.0$ Hz), 75.1, 71.5, 63.5 (d, $J_{PC} = 5.0$ Hz), 63.4 (d, $J_{PC} = 4.0$ Hz), 40.2, 36.9 (d, $J_{PC} = 6.0$ Hz), 34.3, 32.0, 21.5, 21.4 (d, $J_{PC} = 3.0$ Hz), 20.5, 19.3, 16.1 (d, $J_{PC} = 3.0$ Hz), 16.0 (d, $J_{PC} = 3.0$ Hz); HRMS (CI/NH₃) m/z calcd for C₁₆H₃₁NO₅P [M+H]⁺ 348.1940, found 348.1943; Anal. calcd C: 55.32, H: 8.70, found C: 55.52, H: 8.81.

The identical procedure generated (2*S*,6*S*,1'*S*)-ester **3b**. Alkylation of 2-cyanotetrahydropyran **1** (54 mg, 0.43 mmol) with (*S*)-iodide **2b** (120 mg, 0.34 mmol) bore 78 mg (66 %) of ester (2*S*,6*S*,1'*S*)-**3b**.

Data for ester (2*S*,6*S*,1'*S*)-**3b**: R_f 0.21 (50% EtOAc:hexanes); $[\alpha]_D = -32.8$ (c 2.12, CHCl₃); IR (neat) 2983, 2936, 1457, 1384, 1265, 1166, 1037 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.50 (sept, $J = 5.4$ Hz, 1H), 4.10 (app. sext, $J = 7.0$ Hz, 4H), 3.84 (dtd, $J = 2.2, 6.1, 11.3$ Hz, 1H), 1.85-1.59 (m, 11H), 1.47-1.41 (m, 1H), 1.35-1.32 (m, 9H), 1.18 (d, $J = 6.1$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 119.5, 75.4 (d, $J_{PC} = 6.3$ Hz), 75.3, 71.6, 63.6 (d, $J_{PC} = 6.3$ Hz), 63.5 (d, $J_{PC} = 5.0$ Hz) 40.4, 37.1 (d, $J_{PC} = 6.3$ Hz), 34.4, 32.1, 21.6, 21.5 (d, $J_{PC} = 2.5$ Hz), 20.6, 19.5, 16.2 (d, $J_{PC} = 4.3$ Hz), 16.1 (d, $J_{PC} = 4.3$ Hz); HRMS (CI) m/z calcd for C₁₄H₂₅NO₄P⁺ 302.1516, found 302.1520. Anal. calcd C: 55.32, H: 8.70, found C: 53.47, H: 8.86.

(2*S*,6*S*,4'*S*)- and (2*S*,6*S*,4'*R*)-2-(4'-Chloropentyl)-6-methyltetrahydropyran-2-carbonitrile precursors **3a and **3c**, respectively**

2-Cyanotetrahydropyran **1** (283 mg, 2.26 mmol) and (*S*)-4-chloro-1-iodopentane **2a** (500 mg, 2.15 mmol) were dissolved in dry THF (11 mL) under argon atmosphere and cooled to -40 °C. DMPU (580 mg, 4.52 mmol) was added by syringe, followed by slow addition of LDA (3.51 mL, 0.71 M solution in THF/hexanes). After stirring for 3 h, the reaction mixture was warmed to 0 °C, and the reaction was quenched with saturated NH₄Cl (10 mL) and diluted with H₂O (10 mL). The organic phase was extracted with Et₂O (3 × 15 mL) and the combined extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated. Flash column

chromatography of the residual oil (30% – 50% CH₂Cl₂:pentane) returned starting iodide **2a** (50 mg) and 342 mg (77% based on recovered starting material) of (2*S*,6*S*,4'*S*)-chloride **3a**.

Data for (2*S*,6*S*,4'*S*)-**3a**: *R_f* 0.46 (50% CH₂Cl₂:pentane); [α]_D = – 29.1 (*c* 1.03, Et₂O); IR (neat) 2937, 2870, 2659, 1445, 1219, 1079 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.05 (m, 1H), 3.87 (dtd, *J* = 2.2, 6.1, 11.3 Hz, 1H), 1.89-1.66 (m, 11H), 1.53 (d, *J* = 6.6 Hz, 3H), 1.47 (m, 1H), 1.19 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 119.5, 75.3, 71.7, 58.3, 40.2, 40.0, 34.3, 32.1, 25.3, 21.7, 21.2, 20.6 ppm; GCMS (EI) *t_R* = 13.32 min, *m/z* 203 [M – CN], 194 [M – Cl];

The same procedure produced the epimeric chloride **3c**. Alkylation of 2-cyanotetrahydropyran **1** (283 mg, 2.26 mmol) with (*R*)-iodide **2c** (500 mg, 2.15 mmol) afforded 130 mg of starting iodide **2c** and 232 mg (63 % based on recovered starting material) of chloride **3c**.

Data for (2*S*,6*S*,4'*R*)-**3c**: *R_f* 0.46 (50% CH₂Cl₂/pentane); [α]_D = –119 (*c* 1.02, Et₂O); IR (neat) 2938, 2870, 2659, 1445, 1383, 1218, 1079 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.05 (sext, *J* = 6.4 Hz, 1H), 3.87 (dtd, *J* = 2.2, 6.1, 11.2 Hz, 1H), 1.88-1.66 (m, 11H), 1.53 (d, *J* = 6.6 Hz, 3H), 1.47 (m, 1H), 1.20 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 119.5, 75.4, 71.6, 58.1, 40.0, 39.9, 34.3, 32.1, 25.3, 21.7, 21.0, 20.7; HRMS (APCI) *m/z* calcd for C₁₁H₂₀ClO 203.1203 [M – CN], found 203.1199; Anal. calcd C: 62.73, H: 8.77, found C: 62.77, H: 8.89.

(2*R*,6*S*)-6-Methyl-2-pent-4-enyltetrahydropyran-2-carbonitrile (16)

(6*S*)-2-Cyanotetrahydropyran **1** (200 mg, 1.60 mmol) was dissolved in dry THF (4 mL) and cooled to –40 °C. DMPU (410 mg, 3.20 mmol) was added by syringe, followed by LDA

(2.28 mL, 1.76 mmol, 0.77M solution in THF/hexanes). The solution was stirred for 10 min, after which 5-bromo-1-pentene (226 mg, 1.44 mmol, solution in 4 mL THF) was added dropwise. The orange mixture was allowed to stir for 2.5 h and then was quenched with saturated NH_4Cl (5 mL). After dilution with Et_2O (10 mL), water (10 mL) was added to dissolve the salts. The aqueous phase was extracted with Et_2O (3×10 mL), and the ethereal extracts were washed with brine (20 mL). The extracts were then dried with MgSO_4 , filtered and concentrated *in vacuo* to give a yellow oil. Flash column chromatography (10%-33% CH_2Cl_2 :pentane gradient) afforded 205 mg (74%) of olefin **16**.

Data for **16**: R_f 0.20 (25% CH_2Cl_2 :pentane); $[\alpha]_D = -78.8$ (c 2.39, CHCl_3); IR (neat) 3078, 2938, 2869, 2360, 1445, 1218, 915 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.80 (dddd, $J = 6.7, 6.8, 10.2, 16.9$ Hz, 1H), 5.04 (dd, $J = 1.9, 17.1$ Hz, 1H), 4.99 (dd, $J = 2.0, 10.1$ Hz, 1H), 3.86 (dtd, $J = 2.2, 6.1, 11.3$ Hz, 1H), 2.11 (m, 2H), 1.87-1.45 (m, 10H), 1.19 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.9, 119.6, 115.1, 75.4, 71.6, 40.2, 34.3, 33.4, 32.1, 22.9, 21.7, 20.7; HRMS (EI-GCMS) calcd for $\text{C}_{12}\text{H}_{18}\text{NO}$ $[\text{M}-\text{H}]^+$ 192.1389, found 192.1386.

5 Cyclization of precursors 3a-d and 16

(1R,5S,7S)-Dimethyl-6-oxaspiro[4.5]decane (**6**)

Phosphate ester **3b** (100 mg, 0.29 mmol) was dissolved in dry THF (2.0 mL) with phenanthroline (0.5 mg). The solution was cooled to -40 $^{\circ}\text{C}$ and *n*-butyllithium (1.41 M in hexanes) was added dropwise until a pale red color persisted. Lithium di-*tert*-butylbiphenylide (ca. 0.4 M solution in THF, freshly prepared) was then titrated into the reaction flask until the dark green color persisted. The reaction mixture was stirred for 2 hours at -40 $^{\circ}\text{C}$, and the

reaction was quenched with MeOH (0.3 mL). The solution was then carefully concentrated *in vacuo* to give a thin film of crude oil mixed with white crystalline non-polar byproducts. Flash column chromatography (5%-10% CH₂Cl₂:pentane gradient) yielded 36 mg (75%) of spirocycle **6**.

Data for **6**: R_f 0.24 (10% CH₂Cl₂:pentane); [α]_D = −107 (c 0.430, CHCl₃); IR (neat) 2930, 2871, 1461, 1379, 1215, 1086, 1046, 887 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 3.46 (dtd, *J* = 2.2, 6.2, 12.5 Hz, 1H), 2.24 (quint, *J* = 6.8 Hz, 1H), 1.88-1.17 (complex, m, 12H), 1.13 (d, *J* = 6.2 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 84.0, 68.9, 37.6, 34.2, 33.8, 33.1, 30.8, 22.3, 20.6, 18.1, 15.5 ppm; Capillary GC t_R = 10.387 min; HRMS (EI-GCMS) *m/z* calcd for C₁₁H₂₀O [M⁺] 168.1514, found 168.1515.

(1R,5S,7S)-Dimethyl-6-oxaspiro[4.5]decane (6)

Olefin **16** (100 mg, 0.52 mmol) was dissolved in dry THF (3 mL) with phenanthroline (0.5 mg) and cooled to −40 °C. *n*-Butyllithium (1.40 M in hexanes) was titrated into the mixture until a deep red color persisted. Lithium di-*tert*-butyl-biphenylide (ca. 0.4 M solution in THF, freshly prepared) was titrated into the reaction mixture until the solution remained dark green. After stirring for 1.5 h, the reaction was quenched with MeOH (0.3 mL). Slow evaporation of the quenched solution under reduced pressure gave a thin film of clear oil, along with white crystalline byproducts. Flash column chromatography (0%-25% CH₂Cl₂:pentane) produced 56 mg of a clear oil. Second purification (0-10% CH₂Cl₂:pentane) gave 40 mg (45%) of spirocycle **6** contaminated with ~5% protonated byproduct. Capillary GC analysis: t_R = 10.376 min.

(1R,5S,7S)-Dimethyl-6-oxaspiro[4.5]decane (6)

Chloride **3a** (100 mg, 0.44 mmol) and phenanthroline (0.5 mg) were dissolved in dry THF (2 mL) under argon atmosphere. The solution was cooled to $-78\text{ }^{\circ}\text{C}$ and *n*-butyllithium (0.45 M in hexanes/THF) was added dropwise until a reddish brown color persisted. LiDBB (ca. 0.4 M solution in THF, freshly prepared) was then added dropwise until the meniscus of the solution remained a dark green color for a few seconds. The solution was stirred 15 min, then transferred to a $-40\text{ }^{\circ}\text{C}$ bath and stirred for 1.5 h. After quenching with MeOH (0.2 mL) and concentrating under mild vacuum, flash column chromatography (10% CH_2Cl_2 pentane) produced 33 mg of oxaspirocycle **6**. Capillary CG analysis: $t_R = 10.491\text{ min}$.

(1S,5S,7S)-Dimethyl-6-oxaspiro[4.5]decane (7)

Chloride **3c** (100 mg, 0.44 mmol) and phenanthroline (0.5 mg) were dissolved in dry THF (2 mL) under argon atmosphere. The solution was cooled to $-78\text{ }^{\circ}\text{C}$ and *n*-butyllithium (0.45 M in hexanes/THF) was added dropwise until a reddish brown color persisted. LiDBB (ca. 0.4 M solution in THF, freshly prepared) was then added dropwise until the meniscus of the solution remained a dark green color for a few seconds. The solution was stirred 15 min, then transferred to a $-40\text{ }^{\circ}\text{C}$ bath and stirred for 1.5 h. After quenching with MeOH (0.2 mL) and concentrating under vacuum, flash column chromatography (10% CH_2Cl_2 :pentane) produced 16 mg (22%) of oxaspirocycle **7**.

Data for **7**: R_f 0.30 (25% CH_2Cl_2 :Pentane); $[\alpha]_D = +70.9$ ($c = 0.285$, Et_2O); IR (neat) 2959, 2855, 1444, 1377, 1088, 1017 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.65 (dtd, $J = 2.1, 6.2, 13.4$ Hz, 1H), 2.40 (quint., $J = 7.1$ Hz, 1H), 2.05-1.99 (m, 1H), 1.73-1.23 (m, 11H), 1.11 (d, $J = 6.1$ Hz, 3H), 0.82 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 86.3, 66.2, 38.6, 35.1, 33.5, 32.2, 29.8, 22.8, 21.2, 20.3, 17.7 ppm; GCMS (EI) $t_R = 8.25$ min, m/z 168 $[\text{M}]^+$ Capillary GC $t_R = 10.233$ min.

(2S,6S,2'S)- and (2S,6S,2'R)-6-Methyl-2-(1',2'-epoxypent-5'-yl)-tetrahydropyran-2-carbonitrile (104)

2-Cyanotetrahydropyran **1** (200 mg, 1.60 mmol) and ($\pm$)-2-(3-bromopropyl)-oxirane (252 mg, 1.52 mmol, racemic) were dissolved in dry THF (6 mL) under Ar atmosphere and cooled to -40 $^{\circ}\text{C}$. DMPU (414 mg, 3.23 mmol) was added by syringe, followed by dropwise addition of LDA (2.28 mL, 0.77M in THF/hexanes). The reaction mixture was stirred for 2.5 h, warming gradually to -10 $^{\circ}\text{C}$, at which point the reaction was quenched with saturated NH_4Cl (5 mL). H_2O (10 mL) was added to dissolve the salts. The aqueous phase was extracted with Et_2O (3×10 mL) and the combined extracts were washed with brine (10 mL), dried (MgSO_4), filtered and concentrated *in vacuo* to give a yellow oil. Flash column chromatography (30% CH_2Cl_2 :pentane) produced 214 mg (67%) of epoxides **104** as a 1:1 mixture of diastereomers.

Data for **104**: R_f 0.08 (50% CH_2Cl_2 :pentane); IR (neat) 3048, 2937, 2869, 1458, 1446, 1384 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.78 (dtd, $J = 1.9, 6.1, 11.4$ Hz, 1H), 2.86 (dtd, $J = 4.3, 6.8, 8.7$ Hz, 1H), 2.68 (t, $J = 4.7$ Hz, 1H), 2.41 (ddd, $J = 1.6, 2.6, 4.4$ Hz, 1H), 1.81-1.35 (m,

12H), 1.12 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 119.3, 75.1, 71.4, 51.7, 51.6, 46.6, 40.2, 40.1, 34.1, 32.0, 31.9, 21.4, 20.4, 20.3, 20.1 ppm; HRMS (CI/NH_3) calcd for 183.1380 $[\text{M}-\text{CN}]^+$, found 183.1388.

6 Preparation of dioxolane side chains 2e-h

(S)-4-But-3-enyl-2,2-dimethyl[1,3]dioxolane (**105**)

(S)-Hex-5-ene-1,2-diol⁴ (4.00 g, 34.4 mmol) was dissolved in CH_2Cl_2 (70 mL). 2,2-Dimethoxypropane (5.15 g, 49.4 mmol) was added *via* syringe, followed by *p*-toluenesulfonic acid (650 mg, 3.44 mmol). Reaction progress was monitored by TLC until complete consumption of the starting diol. Water (30 mL) and saturated NaHCO_3 (30 mL) were added, and the aqueous phase was extracted with CH_2Cl_2 (3×35 mL). The extracts were dried with Na_2SO_4 , filtered and concentrated to give 5.32 g (99%) of (S)-4-but-3-enyl-2,2-dimethyl[1,3]dioxolane **105**, which required no further purification.

Data for dioxolane (S)-**105**: R_f 0.69 (50% Et_2O :pentane); $[\alpha]_D = +29.7$ (c 1.05, benzene); IR (neat) 3078, 2986, 1642, 1371, 1217, 1063 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.82 (tdd, $J = 6.6, 10.2, 16.9$ Hz, 1H), 5.04 (qd, $J = 1.7, 17.1$ Hz, 1H), 4.98 (qd, $J = 1.3, 10.2$ Hz, 1H), 4.10 (quint, $J = 6.1$ Hz, 1H), 4.04 (dd, $J = 5.9, 7.8$ Hz, 1H), 3.53 (t, $J = 7.6$ Hz, 1H), 2.19-2.09 (m, 2H), 1.75 (m, 1H), 1.60 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.9, 115.0, 108.7, 75.5, 69.4, 32.8, 29.9, 26.9, 25.7 ppm; GCMS (EI) $t_R = 5.79$ min, m/z 141 $[\text{M} - \text{CH}_3]$.

⁴ Obtained in high optical purity by hydrolytic kinetic resolution. See: Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.*, **2002**, *124*, 1307-1315.

The (*R*)-dioxolane **105** was prepared by this same method. (*R*)-Hex-5-ene-1,2-diol (4.5 g, 38.7 mmol) and 2,2-dimethoxypropane (5.65 g, 54.2 mmol) reacted in the presence of (1*S*)-(+)-camphorsulfonic acid⁵ (900 mg, 3.87 mmol) to afford 6.04 g (99 %) of (*R*)-dioxolane **105**. Data for (*R*)-**105**: $[\alpha]_D = -29.1$ (*c* 1.02, benzene).

The optical purity of (*R*)- and (*S*)-dioxolanes **105** was determined by chiral GC analysis: β -cyclodextrin dialkyl column, 1.0 mL/min, isothermal 50 °C, (*R*)-**105** $t_R = 14.849$ min (97% ee), (*S*)-**105** $t_R = 14.098$ min (99% ee).

(*S*)-3-(2,2-Dimethyl[1,3]dioxolan-4-yl)propan-1-ol (106**):**

(*S*)-4-But-3-enyl-2,2-dimethyl[1,3]dioxolane **105** (4.00 g, 25.6 mmol) was dissolved in CH₂Cl₂/MeOH (1:1 mixture, 100 mL) and cooled to −78 °C. K₂CO₃ (1.00 g) was added and the reaction mixture was subjected to ozone until a light blue color persisted. The solution was sparged with O₂ until a clear solution was obtained, after which sodium borohydride (1.07 g, 28.2 mmol) was added. The mixture was warmed to rt and allowed to stir for 24 h. After concentration *in vacuo* the residual oil was dissolved in CH₂Cl₂ (50 mL) and washed with H₂O (40 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 15 mL), and the combined extracts were dried with Na₂SO₄, filtered and concentrated to give 3.87 g (94%) of the crude (*S*)-3-(2,2-dimethyl[1,3]dioxolan-4-yl)-propan-1-ol **106**, which was not further purified.

⁵ Used in lieu of *p*-toluenesulfonic acid.

The (*R*)-enantiomer of this compound was prepared identically. (*R*)-Dioxolane **105** (5.00 g, 32.0 mmol) produced 4.72 g (92 %) of (*R*)-alcohol **106**. Physical data matched that reported in the literature.⁶

(*S*)-4-(3-Iodopropyl)-2,2-dimethyl[1,3]dioxolane (2g)

(*S*)-3-(2,2-dimethyl[1,3]dioxolan-4-yl)propan-1-ol **106** (1.00 g, 6.24 mmol) was dissolved in dry CH₂Cl₂ (16 mL) and cooled to 0 °C. Triphenylphosphine (1.72 g, 6.86 mmol) and imidazole (850 mg, 12.5 mmol) were successively added to the solution, and the solution was stirred until all reagents had completely dissolved. Iodine (1.74 g, solution in 40 mL CH₂Cl₂) was added dropwise to the reaction mixture, during which a cloudy yellow solution was generated. The reaction mixture was diluted with CH₂Cl₂ (20 mL) and washed with 20% NaHSO₃ (30 mL). The aqueous phase was extracted with CH₂Cl₂ (3 X 20 mL), dried with MgSO₄, filtered and concentrated to give a mixture of oily white solids. Flash column chromatography (pentane – 15% Et₂O:pentane) gave 1.34 g (79%) of (*S*)-4-(3-iodopropyl)-2,2-dimethyl[1,3]dioxolane **2g**.

The (*R*)-enantiomer was prepared identically. (*R*)-Alcohol **106** (4.00 g, 25.0 mmol) afforded 5.54 g (82 %) of (*R*)-iodide **2e**. Physical data matched that reported in the literature.⁷

⁶ Physical data was found to match that reported in the literature. For the (*S*)-enantiomer: Sugai, T.; Ikeda, H.; Ohta, H. *Tetrahedron*, **1996**, 52, 8123-8134. Brimble, M. A.; Park, I. H.; Taylor, C. M. *Tetrahedron*, **2003**, 59, 5861-5868. For the (*R*)-enantiomer: Yang, W.-Q.; Kitahara, T. *Tetrahedron*, **2000**, 56, 1451-1461. Larcheveque, M.; Lalande, J. *Tetrahedron*, **1984**, 40, 1061.

⁷ Physical data was found to match that reported in the literature. For the (*S*)-enantiomer: Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.*, **1989**, 54, 5153-5161. For the (*R*)-enantiomer: Yang, W.-Q.; Kitahara, T. *Tetrahedron*, **2000**, 56, 1451-1461.

(S)-4-(2,2-Dimethyl[1,3]dioxolan-4-yl)butan-1-ol (107)

(S)-4-But-3-enyl-2,2-dimethyl[1,3]dioxolane **105** (3.00 g, 19.2 mmol) was dissolved in dry THF (40 mL) and cooled to 0 °C. Borane-THF complex (10.4 mL, 1.0 M solution in THF) was added dropwise to the reaction mixture. After stirring for 20 min, the reaction was quenched with water (15 mL), and the mixture was diluted with Et₂O (15 mL), which resulted in a cloudy solution. NaHSO₃ (20 mL, 20% w/v) was added and the solution was shaken in a separatory funnel until a clear biphasic mixture was observed. The aqueous layer was extracted with Et₂O (3 × 20 mL). The extracts were washed with brine, dried with Na₂SO₄, filtered and concentrated. Flash column chromatography (50% Et₂O:pentane – Et₂O) gave 2.07 g of (S)-4-(2,2-dimethyl[1,3]dioxolan-4-yl)butan-1-ol **107** (62%).

Data for alcohol (S)-**107**: *R_f* 0.11 (50% Et₂O:pentane); [α]_D = +27.4 (*c* 1.06, Et₂O); IR (neat) 3429, 2937, 1456, 1370, 1056 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.09 (m, 1H), 4.04 (dd, *J* = 5.9, 7.7 Hz, 1H), 3.66 (m, 2H), 3.51 (t, *J* = 7.5 Hz, 1H), 1.69-1.45 (m, 6H), 1.41 (s, 3H), 1.36 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 108.7, 76.0, 69.4, 62.7, 33.3, 32.6, 26.9, 25.7, 22.0 ppm; HRMS (ESI) calcd for C₉H₁₈O₃Na⁺ 197.1154, found 197.1147.

The (*R*)-enantiomer was prepared by the same method as above. (*R*)-Dioxolane **105** (3.00 g, 19.2 mmol) underwent hydroboration/oxidation to give 2.42 g (72 %) of (*R*)-alcohol **107**. Data for (*R*)-alcohol **107**: [α]_D = -27.9 (*c* 1.06, Et₂O).

(S)-4-(4-Iodobutyl)-2,2-dimethyl[1,3]dioxolane (2h)

(*S*)-4-(2,2-Dimethyl[1,3]dioxolan-4-yl)butan-1-ol **107** (1.50 g, 8.60 mmol) was dissolved in dry CH₂Cl₂ (20 mL) and cooled to 0 °C. Triphenylphosphine (2.37 g, 9.03 mmol) and imidazole (1.17 g, 17.2 mmol) were successively added to the flask. Iodine (2.40 g, 9.46 mmol, solution in 20 mL CH₂Cl₂) was added dropwise to the reaction mixture, resulting in a yellow solution. The solution was diluted with CH₂Cl₂ (30 mL) and washed with NaHSO₃ (30 mL, 20% aq. solution). The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL). The extracts were dried with MgSO₄, filtered and concentrated to give a mixture of oil and white solids. Flash column chromatography (pentane – 35% Et₂O:pentane) afforded 2.24 g (92 %) of (*S*)-4-(4-iodobutyl)-2,2-dimethyl[1,3]dioxolane **2h**.

Data for (*S*)-iodide **2h**: *R_f* 0.45 (20% Et₂O:pentane); [α]_D = +8.18 (*c* 1.10, Et₂O); IR (neat) 2934, 2865, 1378, 1214, 1062, 857 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.10-4.03 (m, 2H), 3.52 (t, *J* = 7.1 Hz, 1H), 3.20 (t, *J* = 7.0 Hz, 2H), 1.87 (quint., *J* = 7.1 Hz, 2H), 1.65-1.43 (m, 4H), 1.42 (s, 3H), 1.36 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 108.8, 75.7, 69.4, 33.4, 32.5, 26.9, 26.7, 25.7, 6.5 ppm; GCMS (EI) *t_R* = 13.02 min, *m/z* 213 [*M* – C₄H₈O], 155 [*M* – I].

The (*R*)-iodide **2f** was prepared by the same method. (*R*)-Alcohol **107** (1.50 g, 8.60 mmol) gave 2.27 g (93 %) of (*R*)-iodide **2f**. Data for (*R*)-iodide **2f**: [α]_D = –8.79 (*c* 1.15, Et₂O).

7 Preparation of precursors 3e-h and 5a-d

(2*S*,6*S*,4'*S*)-2-[3-(2',2'-Dimethyl-[1',3']dioxolan-4'-yl)-propyl]-6-methyltetrahydropyran-2-carbonitriles (**3g**)

(*S*)-4-(3-Iodopropyl)-2,2-dimethyl[1,3]dioxolane **2g** (1.78 g, 6.60 mmol) and 2-cyanotetrahydropyran **1** (870 mg, 6.94 mmol) were dissolved in dry THF (30 mL) under argon atmosphere. DMPU (1.78 g, 13.9 mmol) was added and the solution cooled to $-40\text{ }^{\circ}\text{C}$. LDA (11.7 mL, 0.65 M solution in hexanes/THF) was added dropwise over 10 min. The reaction mixture was stirred 2 h, then quenched with saturated NH_4Cl (20 mL). After warming to rt, H_2O (20 mL) was added and the aqueous phase was extracted with Et_2O ($3 \times 30\text{ mL}$). The extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography (15 % Et_2O :Pentane) produced 1.33 g (76 %) of (2*S*,6*S*,4'*S*)-dioxolane **3g**.

Data for (2*S*,6*S*,4'*S*)-**3g**: R_f 0.24 (20% Et_2O /pentane); $[\alpha]_D = -64.1$ (c 1.12, Et_2O); IR (neat) 2982, 2937, 2660, 1457, 1371, 1218 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.10 (app. quint., $J = 6.9\text{ Hz}$, 1H), 4.05 (dd, $J = 6.0, 7.7\text{ Hz}$, 1H), 3.85 (dtd, $J = 3.9, 6.1, 12.2\text{ Hz}$, 1H), 3.53 (t, $J = 7.5\text{ Hz}$, 1H), 1.87-1.45 (m, 12H), 1.41 (s, 3H), 1.36 (s, 3H), 1.19 (d, $J = 6.1\text{ Hz}$, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 119.5, 108.8, 75.7, 75.3, 71.6, 69.3, 40.7, 34.3, 33.3, 32.1, 26.9, 25.7, 21.7, 20.6, 20.1 ppm; HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 290.1727, found 290.1727.

(2*S*,6*S*,4'*R*)-Dioxolane **3e** was prepared by the same procedure. 2-Cyanotetrahydropyran **1** (1.27 g, 10.1 mmol) was alkylated with (*R*)-iodide **2e** (2.60 g, 9.64 mmol) to give 1.83 g (70 %) of (2*S*,6*S*,4'*R*)-dioxolane **3e**. Data for (2*S*,6*S*,4'*R*)-dioxolane **3e**: R_f 0.25 (20% Et_2O /pentane); $[\alpha]_D = -71.6$ (c 1.03, Et_2O); IR (neat) 2982, 2937, 2870, 2660, 1457, 1372, 1218 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.11-4.03 (m, 2H), 3.86 (dtd, $J = 2.2, 6.1, 15.3\text{ Hz}$, 1H), 3.52 (t, 7.2 Hz, 1H), 1.87-1.45 (m, 12H), 1.41 (s, 3H), 1.36 (s, 3H), 1.19 (d, $J = 6.1\text{ Hz}$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 119.5, 108.8, 75.9, 75.4, 71.6, 69.4, 40.8, 34.3, 33.4, 32.1, 26.9, 25.7, 21.7, 20.6, 20.3 ppm; HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 290.1727, found 290.1690.

(2*R*,6*S*,2'*R*)-2-(1',2'-Dihydroxypent-5'-yl)-6-methyltetrahydropyran-2-carbonitrile (4)

(2*S*,6*S*,4'*R*)-Dioxolane **3e** (2.10 g, 7.83 mmol) was dissolved in MeOH (40 mL) with stirring. Pyridinium *p*-toluenesulfonate (PPTS, 2.17 g, 8.64 mmol) was added, and the mixture stirred at r.t. for 18 h. After diluting with EtOAc (30 mL), H₂O (20 mL) and brine (20 mL) were added. The aqueous phase was extracted with EtOAc (8 × 20 mL), and the extracts were dried (Na₂SO₄), filtered and concentrated to give a viscous oil. Flash column chromatography (50-80% EtOAc:Hexanes) afforded 1.30 g (99% based on recovered starting material) of (2*R*,6*S*,2'*R*)-diol **4** as a viscous yellow oil and 571 mg of starting dioxolane **3e**.

Data for (2*R*,6*S*,2'*R*)-**4**: *R_f* 0.05 (50% EtOAc:Hexanes); [α]_D = −54.4 (*c* 1.135, Et₂O); IR (neat) 3391, 2936, 1446, 1384, 1077 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 3.86 (dtd, *J* = 4.0, 6.1, 12.2 Hz, 1H), 3.75 (dt, *J* = 3.1, 6.5 Hz, 1H) 3.66 (dd, *J* = 3.1, 11.0 Hz, 1H), 3.45 (dd, *J* = 7.5, 11.0 Hz, 1H), 2.10 (s, 2H), 1.87-1.48 (m, 11H), 1.20 (d, *J* = 6.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 119.6, 75.5, 71.9, 71.7, 66.7, 40.5, 34.4, 32.7, 32.1, 21.7, 20.6, 20.0 ppm; HRMS (ESI) *m/z* calcd for C₁₂H₂₁NO₃Na⁺ 250.1419 [*M*+Na]⁺, found 250.1419.

(2*R*,6*S*,2'*S*)-Diol **4** was prepared equivalently. (2*S*,6*S*,4'*S*)-**3g** (700 mg, 2.62 mmol) produced 423 mg of (2*R*,6*S*,2'*S*)-diol **4** and 200 mg of starting dioxolane **3g**. Data for (2*R*,6*S*,2'*S*)-**4**: *R_f* 0.05 (50% EtOAc:hexanes); [α]_D = −85.2 (*c* 0.92, Et₂O); IR (neat) 3368, 2928, 1445, 1220, 1077 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 3.86 (dtd, *J* = 4.0, 6.1, 12.0 Hz, 1H), 3.75 (dt, *J* = 3.1, 7.0 Hz, 1H), 3.66 (dd, *J* = 3.1, 11.0 Hz, 1H), 3.45 (dd, *J* = 7.5, 11.0 Hz, 1H), 2.10 (s, 2H), 1.87-1.48 (m, 11H), 1.19 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 119.6, 75.4, 71.9, 71.7, 66.7, 40.6, 34.3, 32.7, 32.1, 21.7, 20.6, 19.9 ppm; HRMS (ESI) *m/z* calcd for

C₁₂H₂₁NO₃Na⁺ [M+Na]⁺ 250.1419, found 250.1419; Anal. calcd C: 63.41, H: 9.31, found C: 63.29, H: 9.16.

(2*S*,6*S*,2'*S*)-6-Methyl-2-(1',2'-epoxypent-5'-yl)-tetrahydropyran-2-carbonitrile (5b)⁸

(2*R*,6*S*,2'*S*)-Diol **4** (297 mg, 1.31 mmol) was dissolved in CH₂Cl₂ (2 mL). PPTS (33 mg, 0.13 mmol) and trimethyl orthoacetate (189 mg, 1.57 mmol) were added and the mixture stirred for 1.5 h. Solvent was removed *in vacuo* and the residual volatile compounds removed by placing the reaction flask under high vacuum (~0.1 torr) for 2 min. The remaining residue was redissolved in CH₂Cl₂ (2 mL) and acetyl bromide (1.61 mg, 1.31 mmol) was added *via* syringe. After 30 min. the solvent was again removed and the remaining oil concentrated. MeOH (10 mL) and K₂CO₃ (235 mg, 1.70 mmol) were added and the reaction mixture stirred overnight. The reaction was quenched with saturated NH₄Cl (5 mL) and the mixture was diluted with CH₂Cl₂ (5 mL). The aqueous phase was extracted with CH₂Cl₂ (4 × 10 mL), and the extracts were dried (MgSO₄), filtered and concentrated. Flash column chromatography (20% Et₂O:pentane) gave 203 mg (74 %) of the desired epoxide **5b** as a white solid.

Data for (2*S*,6*S*,2'*S*)-epoxide **5b**: R_f 0.55 (50% Et₂O/pentane); mp 54-55 °C; [α]_D = -110 (c 0.955, Et₂O); IR (thin film) 2978, 2951, 2659, 1383, 1217, 847 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.85 (dtd, *J* = 4.0, 6.1, 12.2 Hz, 1H), 2.93 (m, 1H), 2.76 (t, *J* = 4.8 Hz, 1H), 2.48 (dd, *J* = 2.7, 5.0 Hz, 1H), 1.86-1.45 (m, 11H), 1.19 (d, *J* = 6.1 Hz, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 119.5, 75.3, 71.6, 51.9, 46.9, 40.4, 34.3, 32.1, 32.1, 21.6, 20.6, 20.3 ppm; HRMS (ESI) calcd for

⁸ Procedure adopted from the following: Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, 48, 10515-10530.

$\text{C}_{12}\text{H}_{19}\text{NO}_2\text{Na}^+$ 232.1308 $[\text{M}+\text{Na}]^+$, found 232.1313; Anal. calcd C: 68.87, H: 9.15, found C: 69.02, H: 9.29.

(2*S*,6*S*,2'*R*)-epoxide **5a** was prepared by the identical procedure. Ring closure was effected on (2*R*,6*S*,2'*R*)-diol **4** (356 mg, 1.57 mmol) to afford 258 mg (78 %) of (2*S*,6*S*,2'*R*)-epoxide **5a**. Data for (2*S*,6*S*,2'*R*)-**5a**: R_f 0.55 (50% Et_2O :pentane); mp 38-39 °C; $[\alpha]_D = -83.9$ (c 1.03, Et_2O); IR (thin film) 2937, 2659, 1558, 1218, 1075, 917 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.85 (dtd, $J = 4.0, 6.1, 12.2$ Hz, 1H), 2.92 (dtd, $J = 4.6, 6.6, 8.9$ Hz, 1H), 2.75 (t, $J = 4.7$ Hz, 1H), 2.48 (dd, $J = 2.7, 5.0$ Hz, 1H), 1.87-1.45 (m, 11H), 1.18 (d, $J = 6.1$ Hz, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 119.5, 75.3, 71.6, 51.9, 46.9, 40.4, 34.3, 32.2, 32.1, 21.6, 20.6, 20.5 ppm; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2\text{Na}^+$ 232.1308 $[\text{M}+\text{Na}]^+$, found 232.1313; Anal. calcd C: 68.87, H: 9.15, found C: 68.78, H: 8.97.

(2*R*,6*S*,4'*R*)-2-[4-(2',2'-Dimethyl[1',3']dioxolan-4'-yl)-butyl]-6-methyltetrahydropyran-2-carbonitrile (3f)

(*R*)-4-(4-Iodobutyl)-2,2-dimethyl[1,3]dioxolane **2f** (1.19 g, 4.20 mmol) and 2-cyanotetrahydropyran **1** (500 mg, 4.00 mmol) were dissolved in dry THF (20 mL) under argon atmosphere. DMPU (1.02 g, 8.00 mmol) was added and the solution cooled to -40 °C. LDA (5.00 mL, 4.00 mmol, 0.80 M solution in hexanes/THF) was added dropwise over 10 min. The reaction mixture was stirred 2 h, then warmed to 0 °C and diluted with saturated NH_4Cl (15 mL). After warming to rt, H_2O (10 mL) was added and the aqueous phase was extracted with Et_2O (3×15 mL). The extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and

concentrated *in vacuo*. Flash column chromatography (15-20% Et₂O:pentane) gave 860 mg (83%) of (2*R*,6*S*,4'*R*)-carbonitrile **3f** and 144 mg of starting iodide **2f**.

Data for (2*R*,6*S*,4'*R*)-carbonitrile **3f**: *R*_f 0.29 (20% Et₂O:pentane); [α]_D = −69.0 (*c* 1.05, Et₂O); IR (neat) 2936, 2867, 1456, 1379, 1218, 1064 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 4.07 (m, 1H), 4.02 (dd, *J* = 6.0, 7.6 Hz, 1H), 3.84 (dtd, *J* = 2.2, 6.1, 12.3 Hz, 1H), 3.49 (t, *J* = 7.4 Hz, 1H), 1.85-1.41 (m, 13H), 1.39 (s, 3H), 1.34 (s, 3H), 1.17 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 119.6, 108.6, 75.8, 75.4, 71.5, 69.4, 40.6, 34.3, 33.3, 32.1, 26.9, 26.7, 25.5, 23.7, 21.6, 20.6 ppm; HRMS (APCI) *m/z* calcd for C₁₆H₂₈NO₃ [M+H]⁺ 282.2069, found 282.2061.

(2*R*,6*S*,4'*S*)-carbonitrile **3h** was prepared by the same procedure as above. 2-Cyanotetrahydropyran **1** (500 mg, 4.00 mmol) was alkylated with (*S*)-iodide **2h** (1.19 g, 4.20 mmol) to afford 697 mg (67 %) of carbonitrile **3h**. Data for (2*R*,6*S*,4'*S*)-carbonitrile **3h**: *R*_f 0.29 (20% Et₂O:pentane); [α]_D = −46.2 (*c* 1.07, Et₂O); IR (neat) 2936, 2867, 1456, 1369, 1219, 1065 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 4.07 (m, 1H), 4.02 (m, 1H), 3.84 (dtd, *J* = 2.0, 6.1, 12.2 Hz, 1H), 3.50 (t, *J* = 7.5 Hz, 1H), 1.85-1.41 (m, 13H), 1.40 (s, 3H), 1.35 (s, 3H), 1.18 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 119.6, 108.6, 75.8, 75.4, 71.6, 69.4, 40.6, 34.3, 33.4, 32.1, 26.9, 25.7, 25.6, 23.7, 21.6, 20.6 ppm; HRMS (APCI) *m/z* calcd for C₁₆H₂₈NO₃ [M+H]⁺ 282.2069, found 282.2060.

(2*R*,6*S*,2'*R*)-2-(1',2'-Dihydroxyhex-6-yl)-6-methyltetrahydropyran-2-carbonitrile (108)

(2*R*,6*S*,4'*R*)-carbonitrile **3f** (600 mg, 2.13 mmol) was dissolved in THF (12 mL). HCl (2*N*, 12 mL) was added, and the reaction was monitored by TLC for disappearance of starting

material. After 5 min the reaction mixture was diluted with Et₂O (20 mL), and the acid was neutralized with saturated NaHCO₃. The aqueous phase was extracted with Et₂O (5 × 10 mL), and the combined extracts were dried with Na₂SO₄, filtered and concentrated to give 392 mg of (2*R*,6*S*,2'*R*)-diol **108**. The diol was not further purified.

Data for (2*R*,6*S*,2'*R*)-diol **108**: *R*_f 0.08 (50% EtOAc:hexanes); [α]_D = −38.3 (*c* 1.15, Et₂O); IR (neat) 3305, 2933, 2866, 1445, 1219, 1180 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 3.83 (dtd, *J* = 2.0, 6.1, 12.2 Hz, 1H), 3.69 (m, 1H), 3.62 (apparent d, *J* = 11.0 Hz, 1H), 3.42 (m, 1H), 2.69 (br s, 1H), 2.59 (br s, 1H), 1.85-1.38 (m, 14H), 1.18 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 119.6, 75.4, 72.0, 71.6, 66.7, 40.6, 34.3, 32.8, 32.1, 25.3, 23.7, 21.6, 20.6 ppm; HRMS (ESI) *m/z* calcd for C₁₃H₂₃NO₃Na [M+Na]⁺ 264.1576, found 264.1570.

The (2*R*,6*S*,2'*S*)-diol **108** was prepared similarly. (2*R*,6*S*,4'*S*)-carbonitrile **3h** (600 mg, 2.13 mmol) was deprotected to give 351 mg of (2*R*,6*S*,2'*S*)-diol **108**. Data for (2*R*,6*S*,2'*S*)-diol **108**: *R*_f 0.08 (50% EtOAc:hexanes); [α]_D = −63.5 (*c* 1.02, Et₂O); IR (neat) 3322, 2935, 2866, 1445, 1383, 1219 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 3.83 (dtd, *J* = 2.1, 6.1, 12.2 Hz, 1H), 3.69 (m, 1H), 3.62 (m, 1H), 3.42 (m, 1H), 2.71 (br s, 1H), 2.62 (br s, 1H), 1.85-1.38 (m, 14H), 1.18 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 119.6, 75.4, 72.0, 71.6, 66.7, 40.6, 34.3, 32.8, 32.1, 25.3, 23.7, 21.6, 20.6 ppm; HRMS (ESI) *m/z* calcd for C₁₃H₂₃NO₃Na [M+Na]⁺ 264.1576, found 264.1566.

(2*R*,6*S*,2'*S*)-6-Methyl-2-(1',2'-epoxyhex-6'-yl)-tetrahydro-pyran-2-carbonitrile (**5d**)⁸

(2*R*,6*S*,2'*S*)-Diol **108** (250 mg, 1.04 mmol) was dissolved in CH₂Cl₂ (2 mL). PPTS (25 mg, 0.10 mmol) and trimethyl orthoacetate (150 mg, 1.24 mmol) were added and the mixture stirred for 1.5 h. Solvent was removed *in vacuo* and the residual volatile compounds removed by placing the reaction flask under high vacuum (~0.1 torr) for 2 min. The remaining residue was redissolved in CH₂Cl₂ (2 mL) and acetyl bromide (128 mg, 1.04 mmol) was added *via* syringe. After 20 min. the solvent was again removed and the remaining oil concentrated. MeOH (10 mL) and K₂CO₃ (185 mg, 1.35 mmol) were added and the reaction mixture stirred overnight. The reaction was quenched with saturated NH₄Cl (5 mL) and diluted with CH₂Cl₂ (5 mL). The aqueous phase was extracted with CH₂Cl₂ (4 × 10 mL), and the extracts were dried (MgSO₄), filtered and concentrated. Flash column chromatography (20% Et₂O:pentane) afforded 198 mg (85%) of epoxide **5d** as a slightly yellow oil.

Data for (2*R*,6*S*,2'*S*)-epoxide **5d**: R_f 0.26 (20% Et₂O:pentane); [α]_D = −103 (*c* 1.17, Et₂O); IR (neat) 3046, 2936, 1482, 1383, 1220, 1075 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 3.86 (dtd, *J* = 2.2, 6.0, 11.3 Hz, 1H) 2.92 (m, 1H), 2.76 (t, *J* = 4.9 Hz, 1H), 2.47 (dd, *J* = 2.7, 5.0 Hz, 1H), 1.86-1.45 (m, 14H), 1.19 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 119.6, 75.4, 71.6, 52.1, 47.1, 40.7, 34.4, 32.3, 32.1, 25.8, 23.6, 21.7, 20.7 ppm; HRMS (ESI) calcd for C₁₃H₂₁O₂NNa⁺ 246.1470, found 246.1471.

(2*R*,6*S*,2'*R*)-epoxide **5c** was prepared by the same procedure as above. (2*R*,6*S*,2'*R*)-Diol **108** (275 mg, 1.14 mmol) was converted to 190 mg (75 %) of epoxide **5c**. Data for (2*R*,6*S*,2'*R*)-epoxide **5c**: R_f 0.26 (20% Et₂O:pentane); [α]_D = −62.4 (*c* 1.09, Et₂O); IR (neat) 3047, 2867, 1457, 1383, 1220, 1076 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ 3.85 (dtd, *J* = 2.1, 6.1, 11.3 Hz, 1H), 2.92 (m, 1H), 2.76 (t, *J* = 4.7 Hz, 1H), 2.47 (dd, *J* = 2.7, 5.0 Hz, 1H), 1.86-1.45 (m, 14H), 1.18 (d, *J* =

6.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 119.6, 75.4, 71.6, 52.1, 47.1, 40.6, 34.4, 32.2, 32.1, 25.8, 23.5, 21.7, 20.7 ppm; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{21}\text{O}_2\text{NNa}^+$ 246.1470, found 246.1472.

8 Cyclization of precursors 5a-d

(1R,5R,7S)-(7-Methyl-6-oxaspiro[4.5]dec-1-yl)methanol (10) and (2S,6S,8S)-2-Methyl-1-oxaspiro[5.5]undecan-8-ol (11)

A sample of (2*S*,6*S*,2'*S*)-epoxide **5b** (253 mg, 1.19 mmol) was dissolved in dry THF (10 mL) with phenanthroline crystals (0.5 mg) and cooled to $-78\text{ }^\circ\text{C}$. *n*-Butyllithium (0.4 M in hexanes/THF) was added dropwise until a red color persisted. LiDBB (~ 0.4 M in THF) was then added dropwise until the meniscus remained green for ca. 20 sec. The mixture was stirred for 1 hr, then quenched with MeOH (0.5 mL). The solution was diluted with Et_2O (10 mL) and washed with half saturated NH_4Cl (25 mL). The aqueous phase was extracted with Et_2O (3×15 mL), and washed with brine (30 mL). The combined extracts were dried with Na_2SO_4 , filtered and concentrated to give yellow solids. The remaining solids were submitted to flash column chromatography (20% Et_2O :pentane) to give 158 mg (72%) of alcohol **10** and 46 mg (21%) of alcohol **11**.

Data for alcohol **10**: R_f 0.36 (50% Et_2O :pentane); $[\alpha]_D = +51.4$ (c 1.055, Et_2O); IR (neat) 3368, 2926, 1446, 1214, 1026 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.69-3.61 (m, 2H), 3.28 (t, $J = 9.1$ Hz, 1H), 2.47 (q, $J = 7.1$ Hz, 1H), 1.93, (m, 1H), 1.79-1.48 (complex m, 12H), 1.12 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 84.8, 66.6, 63.7, 43.9, 39.9, 33.2, 29.9, 26.7, 22.6, 21.3, 20.5 ppm; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{19}\text{O}_2^+ [\text{M} - \text{H}]^+$ 183.1385, found 183.1394.

Data for alcohol **11**: R_f 0.27 (50% Et₂O:pentane); $[\alpha]_D = +46.4$ (c 1.250, Et₂O); IR (neat) 3363, 2931, 1449, 1202, 1009 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.74 (tt, $J = 4.2, 11.1$ Hz, 1H), 3.66 (dtd, $J = 2.1, 6.1, 12.1$ Hz, 1H), 2.67 (dddd, 1.6, 1.9, 3.9, 13.2 Hz, 1H), 1.98 (m, 1H), 1.79-1.49 (m, 8H), 1.40-1.31 (m, 2H), 1.25-1.12 (m, 3H), 1.09 (d, $J = 6.1$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 73.8, 67.0, 65.4, 39.1, 38.4, 36.1, 36.0, 33.4, 22.5, 19.5, 19.4 ppm; GCMS (EI) $t_R = 11.36$ min, m/z 184 [M]⁺, 166 [M – H₂O].

(1S,5R,7S)-(7-Methyl-6-oxaspiro[4.5]dec-1-yl)methanol (8) and (2S,6S,8R)-2-Methyl-1-oxaspiro[5.5]undecan-8-ol (9)

(2S,6S,2'R)-Epoxide **5a** (508 mg, 2.43 mmol) was dissolved in dry THF (20 mL) with a few 1,10-phenanthroline crystals and cooled to –78 °C. *n*-Butyllithium (0.4 M in hexanes/THF) was added dropwise until a red color persisted. LiDBB (~0.4 M in THF) was then added dropwise until the meniscus remained green for ca. 20 sec. The mixture was stirred for 1 h, and then the reaction was quenched with MeOH (0.5 mL). The solution was diluted with Et₂O (10 mL) and washed with half saturated NH₄Cl (25 mL). The aqueous phase was extracted with Et₂O (3 × 15 mL) and washed with brine (30 mL). The combined extracts were dried with Na₂SO₄, filtered and concentrated to give a pale yellow mixture of solids. Flash column chromatography (20% Et₂O:pentane) gave 130 mg (29%) of alcohol **8** and 183 mg (41%) of alcohol **9**.

Data for alcohol **8**: R_f 0.23 (50% Et₂O:pentane); $[\alpha]_D = -88.4$ (c 1.31, Et₂O); IR (neat) 3391, 2928, 1459, 1368, 1081 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.72-3.68 (m, 2H), 3.58 (dd, $J = 7.3, 11.2$ Hz, 1H), 2.23 (m, 2H), 1.89-1.51 (complex m, 12H), 1.13 (d, $J = 6.2$ Hz, 3H); ¹³C

NMR (125 MHz, CDCl₃) δ 84.5, 69.7, 63.7, 42.9, 39.4, 34.4, 32.7, 26.1, 22.3, 19.9, 19.0 ppm; GCMS (EI) t_R = 11.75 min, m/z 184 [M]⁺.

Data for alcohol **9**: R_f 0.27 (50% Et₂O:pentane); $[\alpha]_D$ = +16.0 (c 1.065, Et₂O); IR (neat) 3429, 2934, 1449, 1077, 1025 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.95 (m, 1H), 3.86 (dtd, J = 2.1, 6.1, 12.2 Hz, 1H), 3.69 (m, 1H), 2.44 (d, J = 13.7 Hz, 1H), 1.96 (m, 1H), 1.77 – 1.35 (m, 10H), 1.26 (td, J = 13.4, 4.3 Hz, 2H), 1.11 (d, J = 6.1, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 74.1, 67.7, 66.8, 39.9, 36.4, 34.1, 33.3, 33.2, 22.4, 19.2, 15.9 ppm; HRMS (ESI) calcd for C₁₁H₁₉O₂⁺ 183.1385, found 183.1384.

(2S,6R,8S)-2-Methyl-1-oxaspiro[5.6]dodecan-8-ol (13)

Epoxide **5d** (100 mg, 0.45 mmol) was dissolved in dry THF (5 mL) with 1,10-phenanthroline (~0.5 mg) and cooled to -78 °C. *n*-BuLi (1.6 M in hexane) was titrated into the reaction mixture until a light red color persisted. LiDBB (~0.4 M solution in THF) was then added dropwise until the meniscus of the solution remained green for at least 20 sec. The reaction flask was transferred to a -40 °C bath and allowed to stir for 18 h. The reaction was quenched with CD₃OD (1 mL), and the mixture was warmed to room temperature. Et₂O (10 mL) was added and the mixture was washed with saturated NH₄Cl (10 mL). The aqueous phase was extracted with Et₂O (3 × 5 mL). The extracts were washed with brine (5 mL), dried with Na₂SO₄, filtered and concentrated to give a crude mixture of white and yellow solids. Flash column chromatography (15-40% Et₂O:pentane) gave 40 mg (45%) of spirocycle **13**.

Data for spirocycle **13**: R_f 0.24 (50% Et₂O:pentane), $[\alpha]_D = +34.4$ (c 1.11, Et₂O), IR (neat) 3331, 2928, 2861, 1453, 1371, 1211 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.96 (m, 1H), 3.68 (dtd, $J = 2.2, 6.1, 12.2$ Hz, 1H), 2.53 (d, $J = 14.5$ Hz, 1H), 2.03 (m, 1H), 1.70-1.24 (m, 14H), 1.11 (d, $J = 6.1$ Hz, 3H) 1.16-1.07 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 73.7, 67.7, 66.0, 44.7, 40.8, 38.8, 37.5, 33.2, 24.6, 22.6, 22.3, 19.7 ppm; GCMS (EI) $t_R = 13.07$ min, m/z 198 [M]⁺, 180 [M – H₂O].

Stereochemical Assignment of Alcohol **13** by nOe studies

(2*S*,6*R*,8*R*)-2-Methyl-1-oxa-spiro[5.6]dodecan-8-ol (**12**)

Epoxide **5c** (100 mg, 0.45 mmol) was submitted to reaction conditions identical to those employed for the epoxide epimer **5d**. Flash column chromatography (15-40% Et₂O:pentane) gave 25 mg (28%) of (2*S*,6*R*,8*R*)-2-methyl-1-oxaspiro[5.6]dodecan-8-ol **12**, contaminated with ~10% of the alcohol epimer and <5% of an unidentified compound.

Data for spirocycle **12**: R_f 0.24 (50% Et₂O:pentane), IR (neat) 3377, 2929, 2862, 1454, 1077, 1024 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.69 (m, 2H), 2.20 (d, $J = 13.9$ Hz, 1H), 1.93-1.20 (m, 15H), 1.10 (d, $J = 6.1$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 74.4, 69.8, 66.0, 44.3,

42.0 40.1, 35.2, 33.1, 26.6, 22.7, 21.6, 19.8 ppm; GCMS (EI) t_R = 13.28 min, m/z 198 $[M]^+$, 180 $[M - H_2O]$.

9 Correlation Studies

7-Methyl-6-oxaspiro[4.5]dec-1-ylmethyl-4-nitrobenzoate (**15**)

To a solution of alcohol **10** (70 mg, 0.38 mmol) in CH_2Cl_2 (2.5 mL) was added 4-(dimethylamino)pyridine (93 mg, 0.76 mmol) and 4-nitrobenzoyl chloride (141 mg, 0.76 mmol) at room temperature. The solution was stirred overnight, during which time a white ppt formed. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL), and the combined extracts were dried with $MgSO_4$, filtered and concentrated. Flash column chromatography (20% Et_2O :pentane) gave 120 mg (94 %) of *p*-nitrobenzoate **15** as a white solid.

Data for **15**: R_f 0.73 (50% Et_2O :pentane); mp 67-68 °C; $[\alpha]_D = +76.8$ (c 1.14, CH_2Cl_2); IR (thin film) 3111, 2932, 1725, 1529, 1273, 1109 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 8.28 (td, J = 2.1, 8.9 Hz, 2H), 8.18 (td, J = 2.0, 9.0 Hz, 2H), 4.35 (dd, J = 5.6, 10.9 Hz, 1H), 4.02 (dd, J = 8.7, 10.9 Hz, 1H), 3.64 (m, 1H), 2.77 (q, J = 7.7 Hz, 1H), 2.04 (m, 1H), 1.85-1.53 (m, 10H), 1.22-1.12 (m, 1H), 1.11 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 150.4, 135.5, 130.5, 123.5, 84.7, 66.9, 66.7, 40.3, 39.7, 33.1, 30.1, 27.3, 22.5, 21.4, 20.4 ppm; HRMS (ESI) calcd for $C_{18}H_{23}O_5Na^+$ 356.1474, found 356.1482.

Crystal structures and the corresponding data for *p*-nitrobenzoates **14** and **15** have been deposited at the Cambridge Crystallographic Data Centre with the deposition numbers CCDC 267282 and 267283.

Spirocycle 6 from alcohol 8

Alcohol **8** (58 mg, 0.31 mmol), triphenylphosphine (87 mg, 0.33 mmol) and imidazole (43 mg, 0.62 mmol) were dissolved in CH₂Cl₂ (3 mL) and cooled to 0 °C. Iodine (87 mg, 0.34 mmol as a solution in 5 mL CH₂Cl₂) was added dropwise to the reaction mixture. Upon complete addition of the I₂ solution, NaHSO₃ (5 mL, 20% w/v aqueous solution) was added to the yellow reaction mixture. The aqueous phase was extracted with CH₂Cl₂ (3 × 3 mL). The extracts were dried with MgSO₄, filtered and concentrated. Flash column chromatography (pentane – 20% Et₂O:pentane) gave 56 mg (62%) of the corresponding iodinated compound. This intermediate was not fully characterized. The intermediate iodide (50 mg, 0.17 mmol) was dissolved in dry Et₂O (2 mL) and cooled to –78 °C. *tert*-butyllithium (360 µL, 0.51 mmol, 1.4 M solution in pentane) was added dropwise to the reaction mixture. After 30 min, the mixture was quenched with MeOH (0.5 mL), and the solution warmed to rt and concentrated. Flash column chromatography (pentane – 20% Et₂O/pentane) gave 27 mg (93 %) of spirocycle **6**. Capillary GC: *t*_R = 10.475 min.

Spirocycle 7 from alcohol 10

When applied to alcohol **10** (50 mg, 0.27 mmol), the identical procedure as above furnished 20 mg (44 %) spirocycle **7** contaminated with elimination product. Capillary GC: t_R = 10.242 min.

2-Methyl-1-oxaspiro[5.5]undecan-8-one (**17**)

Dimethylsulfoxide (33 mg, 0.39 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and cooled to -78°C . Oxalyl chloride (30 mg, 0.23 mmol) was added dropwise, and the mixture was stirred for 15 min. Alcohol **9** (30 mg, 0.16 mmol, solution in 1 mL CH_2Cl_2) was added dropwise, followed by triethylamine (82 mg, 0.81 mmol). The reaction mixture was warmed to rt and allowed to stir for 30 min. H_2O (3 mL) and saturated NH_4Cl (1 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The extracts were washed with brine, dried with MgSO_4 , filtered and concentrated. Flash column chromatography (10-25% Et_2O :pentane) gave 28 mg (97%) of ketone **17**.

Data for ketone **17**: R_f 0.24 (25% Et_2O :pentane); $[\alpha]_D = +14.3$ (c 1.40, Et_2O); IR (neat) 2934, 2870, 1714, 1444, 1229, 1094 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.67 (dtd, $J = 2.2, 6.1, 12.1$ Hz, 1H), 2.94 (td, $J = 1.7, 13.8$ Hz, 1H), 2.36-2.24 (m, 3H), 2.12 (m, 1H), 1.83-1.52 (m, 7H), 1.38 (m, 1H), 1.14-1.08 (m, 1H), 1.07 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 210.4, 76.6, 66.0, 46.4, 40.9, 38.9, 34.8, 33.1, 22.3, 20.6, 19.1 ppm; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{18}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 205.1205, found 205.1212.

Oxidation of the epimeric starting alcohol **11** (27 mg, 0.15 mmol) under identical conditions afforded 26 mg of ketone **17** in 96 % yield.

Stereochemical Assignment for ketone **17 by nOe studies** **2-Methyl-1-oxaspiro[5.6]dodecan-8-one (109)**

Dimethylsulfoxide (39 mg, 0.49 mmol) was dissolved in dry CH₂Cl₂ (1 mL) and cooled to -78 °C. Oxalyl chloride (58 mg, 0.44 mmol) was added dropwise, and the solution was allowed to stir until gas evolution ceased (~10 min). A mixture of oxaspiro[5.6]alcohols **12** and **13** (40 mg, 0.20 mmol, solution in 1 mL CH₂Cl₂) was added slowly, followed by Et₃N (100 mg, 1.0 mmol). The solution was allowed to warm to rt and stirred for 45 min, at which time H₂O (3 mL) and saturated NH₄Cl (2 mL) were added. Extraction of the aqueous phase with CH₂Cl₂ (3 × 5 mL) followed by drying with MgSO₄, filtration and concentration *in vacuo* afforded a clear oil. Flash column chromatography (10-25% Et₂O:petroleum ether) gave 20 mg (51%) of 2-methyl-1-oxaspiro[5.6]dodecan-8-one **109**.

Data for 2-methyl-1-oxaspiro[5.6]dodecan-8-one **109**: R_f 0.51 (50% Et₂O:petroleum ether); [α]_D = +16.2 (*c* 1.00, Et₂O); IR (neat) 2932, 2864, 1699, 1445, 1207, 1086 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.69 (dtd, *J* = 2.2, 6.1, 12.2 Hz, 1H), 3.08 (dd, *J* = 1.6, 13.4 Hz, 1H), 2.66 (d, *J* = 13.4 Hz, 1H), 2.44 (m, 2H), 1.90-1.43 (m, 10H), 1.30 (dt, *J* = 4.8, 13.3 Hz, 1H), 1.09 (m, 1H), 1.04 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 212.2, 73.2, 66.5, 48.1, 46.0, 44.0,

35.9, 32.7, 24.0, 23.9, 22.3, 19.4 ppm; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2\text{Na}^+$ 219.1361, found 219.1356.