Supporting Information

Iterative Stereospecific Reagent-Controlled Homologation Using a Functionalized α-Chloroalkyllithium: Synthesis of Cyclic Targets Related to Epibatidine

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1. Experimental Procedures

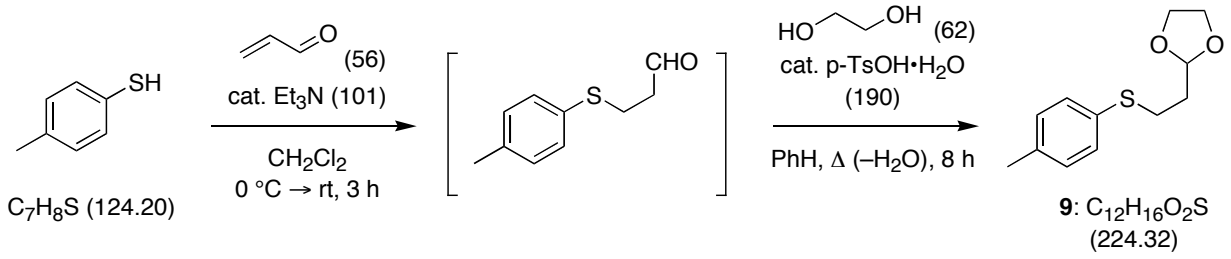
General experimental and analytical techniques

All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of N_2 or Ar. THF was either freshly distilled from sodium benzophenone ketyl immediately prior to use, or else taken from a commercially available solvent purification system (SPS) employing activated Al_2O_3 drying columns.[S1] Anhydrous CH_2Cl_2 and toluene were obtained via distillation from CaH_2 or taken from a SPS using activated Al_2O_3 drying columns. Anhydrous DMF was obtained from a SPS fitted with zeolite based (4Å MS) drying columns. Preparative chromatographic separations were performed on silica gel 60 (35-75 μm) and

S1. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K. *Organomet*. **1996**, *15*, 1518-1520.

reactions followed by TLC analysis using silica gel 60 plates (2-25 μm) with fluorescent indicator (254 nm) and visualized with UV or phosphomolybdic acid. All commercially available reagents were used as received unless otherwise noted. Melting points were determined from open capillary tubes on a melting point apparatus and are uncorrected. Infra-red (IR) spectra were recorded in Fourier transform mode using KBr disks for solids, while oils were supported between NaCl plates ("neat"). ^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified and from the indicated deuterated solvents in standard 5 mm diameter tubes. Chemical shift in ppm is quoted relative to residual solvent signals calibrated as follows: $CDCl_3$ δ_H ($CHCl_3$) = 7.26 ppm, δ_C = 77.2 ppm; $(CD_3)_2SO$ δ_H (CD_3SOCHD_2) = 2.50 ppm, δ_C = 39.5 ppm. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Numbers in parentheses following carbon atom chemical shifts refer to the number of attached hydrogen atoms as revealed by the DEPT spectral editing technique. Low (MS) and high resolution (HRMS) mass spectra were obtained using either electron impact (EI) or electrospray (ES) ionization techniques. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units.

*Synthesis of Chlorosulfoxides **12** (Scheme 3)*



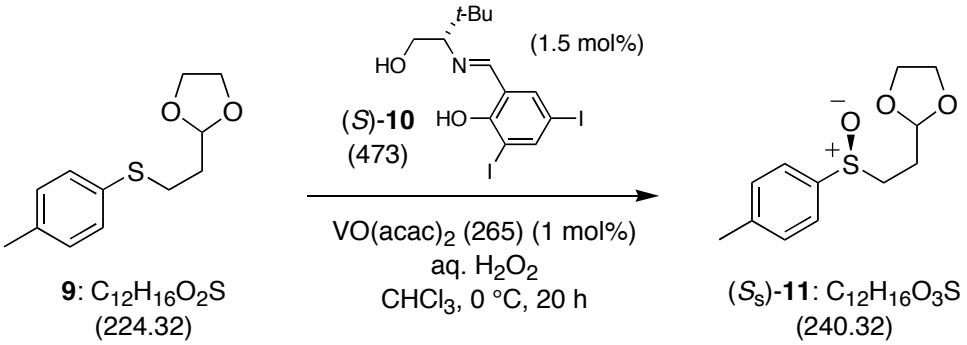
C_7H_8S (124.20)

9: $C_{12}H_{16}O_2S$ (224.32)

2-[2-(4-Methylphenyl)thioethyl]-1,3-dioxolane (9). Prepared by a modification of the method of Serra and Fuganti.[S2] A solution of acrolein (90 wt.%, 2.00 mL, d = 0.84, 1.68 g, 27.0 mmol) and Et_3N (0.17 mL, d = 0.726, 123 mg, 1.22 mmol) in CH_2Cl_2 (10 mL) at 0 °C under Ar was treated with p-thiocresol (3.10 g, 25.0 mmol) in CH_2Cl_2 (10 mL) during 2 min. The mixture was stirred for 80 min and then anhydrous solid Na_2SO_4 (10.0 g) was added. The system was then filtered, the filter cake washed with CH_2Cl_2 (2x5 mL), and the filtrate and combined washings concentrated *in vacuo* to obtain the intermediate conjugate addition adduct as a pale yellow oil (4.40 g). This residue was taken up immediately in PhH (20 mL), treated with ethylene glycol (2.10 mL, d = 1.11, 2.33 g, 37.6 mmol) and p-TsOH•H_2O (120 mg, 0.63 mmol), and the solution heated to reflux with stirring in a flask connected to a small Dean-Stark apparatus. After 5 h, no more H_2O was observed to collect in the Dean-Stark apparatus. The reaction mixture was then allowed to cool to rt and partitioned between EtOAc (20 mL) and sat. aq. $NaHCO_3$ (20 mL). The

S2. Serra, S.; Fuganti, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2191-2196.

layers were separated and the organic phase washed with H_2O (20 mL) and brine (10 mL), dried (Na_2SO_4) and then concentrated *in vacuo* to yield the desired dioxolane (5.60 g, ≤ 25.0 mmol, ≤ 100%) as a light orange oil. ^{1}H NMR analysis indicated that the material was > 95% pure and it was used without further purification in the next step. Data for **9**: IR (neat) 2948, 1894, 1495, 1440, 1395, 1138, 1015, 941, 801 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, "d", *J* = 8.1 Hz), 7.10 (2H, "d", *J* = 8.0 Hz), 4.98 (1H, t, *J* = 4.5 Hz), 3.99-3.92 (2H, m), 3.90-3.83 (2H, m), 2.98 (2H, triplet-like AA´XX´ pattern), 2.32 (3H, s), 2.00-1.95 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3 (0), 130.2 (2C, 1), 129.8 (2C, 1), 128.5 (0), 103.3 (1), 65.1 (2C, 2), 33.8 (2), 28.7 (2), 21.1 (3) ppm (a small spurious peak was observed at 132.5); MS (EI) *m/z* 224 ($M^{+\bullet}$, 100), 137 (20), 100 (65), 73 (58); HRMS (EI) *m/z* 224.0877 (calcd. for $C_{12}H_{16}O_2S$: 224.8071).



2-[(S_S)-2-(4-Methylphenyl)sulfinylethyl]-1,3-dioxolane [(S_S)-11]. Prepared by the method of Jackson and co-workers.[S3] A 100 mL RB flask equipped with a magnetic stirrer bar was charged with (S)-*tert*-leucinol derived ligand (*S*)-**10** (158 mg, 0.334 mmol)[S3] and vanadyl acetoacetonate (59 mg, 0.223 mmol) followed by $CHCl_3$ (20 mL). The resulting mixture was stirred at rt for 2 h during which time the initially emerald green solution became a caramel brown color. A solution of sulfoxide **9** (5.00 g, 22.3 mmol) in $CHCl_3$ (15 mL) was then added all at once and the mixture stirred for 30 min at rt before being cooled to 2 °C (in a refrigerator). 30 wt.% aq. H_2O_2 (2.70 mL, d = 1.11, 3.00 g, 26.5 mmol) was added and stirring at 2 °C continued until TLC analysis indicated that all of the starting material had been consumed (19.5 h). The resulting dark orange colored solution was quenched with 10 wt.% aq. $Na_2S_2O_3$ (20 mL) and the layers shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (2x20 mL) and the combined organic phases washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The dark brown residue (ca. 6.4 g) was purified by column chromatography (SiO_2, eluting with 35-75% EtOAc in hexanes) to afford sulfoxide (–)-(S_S)-**11** (4.30 g, 17.9 mmol, 80%) as a colorless oil which slowly crystallized on standing. HPLC analysis using a suitable chiral stationary phase indicated %ee > 99% for this material (Figure S1, below). X-ray diffraction analysis of enantiomeric material prepared in a like manner but using the ligand (*R*)-**10** confirmed the expected stereochemical

S3. Drago, C.; Caggiano, L.; Jackson, R. F. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 7221-7223.

outcome (i.e., (*R*)-**10** affords (+)-(R_S)-**11**, and *vice versa*, and as concluded previously by Jackson et al. in ref. S3, see Figure S2). Data for (–)-(S_S)-**11** (>99% ee): mp 53-54 °C (TBME-hexanes); $[\alpha]_D^{23}$ = – 97.3 (c = 1.00, $CHCl_3$); IR (neat) 2880, 1492, 1401, 1135, 1083, 1047, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, "d", *J* = 8.3 Hz), 7.32 (2H, "d", *J* = 8.0 Hz), 4.97 (1H, t, *J* = 4.2 Hz), 3.96-3.90 (2H, m), 3.89-3.83 (2H. m), 2.93 (1H, ddd, *J* = 13.2, 9.9, 5.8 Hz), 2.87 (1H, ddd, *J* = 13.2, 9.9, 5.7 Hz), 2.41 (3H, s), 2.09 (1H, dddd, *J* = 14.1, 9.8, 5.9, 4.2 Hz), 1.89 (1H, dddd, *J* = 14.2, 9.9, 5.7, 4.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6 (0), 140.6 (0), 130.1 (2C, 1), 124.4 (2C, 1), 102.9 (1), 65.3 (2C, 2), 51.2 (2), 26.4 (2), 21.6 (3) ppm; MS (EI) *m/z* 240 ($M^{+\bullet}$, 12), 223 (100), 137 (24), 100 (32), 73 (60); HRMS (EI) *m/z* 240.0816 (calcd. for $C_{12}H_{16}O_3S$: 240.0820).

HPLC analysis of (±)-**11**, prepared by [O] of **9** with 30 wt.% aq. H_2O_2 in MeOH, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 10% *i*-PrOH in hexanes at 0.5 mL min^{-1} and monitored by UV at 210 nm, showed resolved peaks: $t_{ret.}$ [(+)-(R_S)-**11**] = 25.6 min, $t_{ret.}$ [(–)-(S_S)-**11**] = 29.0 min. Analysis of the enantioenriched material prepared as described above revealed an enantiomeric excess of >99% in favor of the (*S*)-enantiomer (Figure S1).

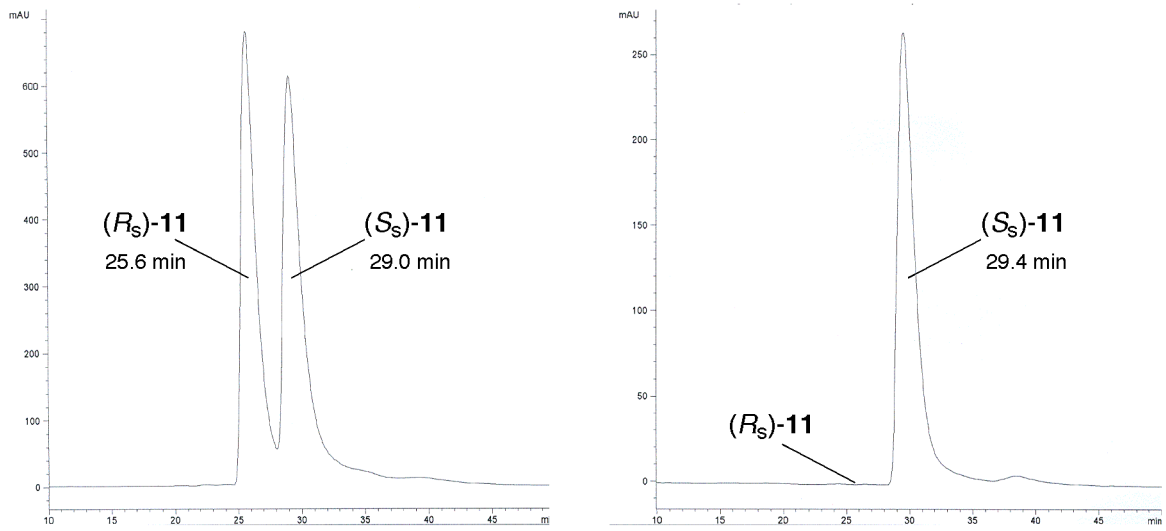


Figure S1. HPLC analysis of **11** with Daicel Chiralcel® OD column: left trace racemic standard, right trace enantioenriched sample of (–)-(S_S)-**11** with %ee > 99%.

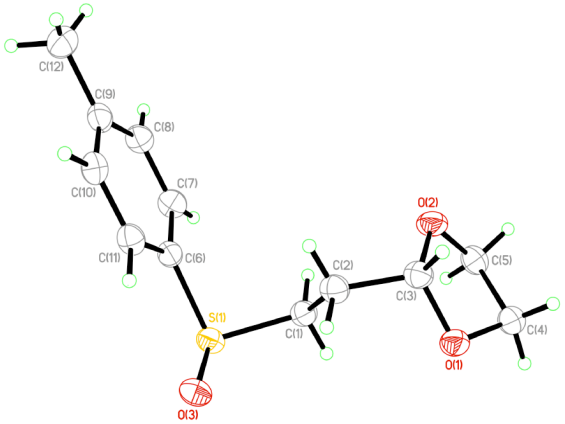
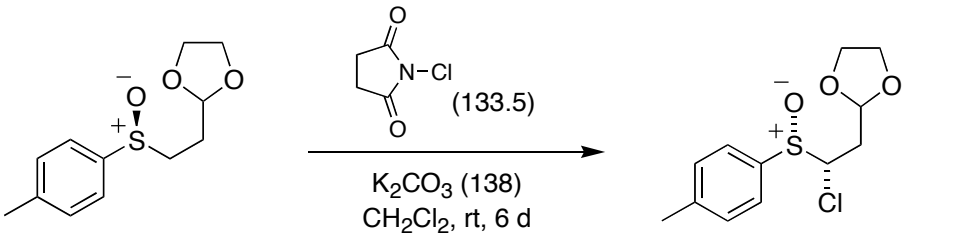


Figure S2. ORTEP diagram for (+)-(R_S)-**11** (prepared from **9** using ligand (*R*)-**10**). Full crystallographic data are available in the accompanying CIF file. 50% probability ellipsoids are plotted for non-hydrogen atoms.



(S_S)-**11**: $C_{12}H_{16}O_3S$
(240.32)

(S_S)-*syn*-H-**12**: $C_{12}H_{15}ClO_3S$
(274.76)

2-[(S_S,2*S*)-2-Chloro-2-(4-methylphenyl)sulfinylethyl]-1,3-dioxolane [(S_S)-*syn*-H-12]. Prepared by the method of Yamakawa and co-workers.[S4] A stirred solution of the scalemic sulfoxide (–)-(S_S)-**11** (4.45 g, 18.5 mmol) in anhydrous CH_2Cl_2 (50 mL) at rt was treated with solid K_2CO_3 (1.50 g, 10.9 mmol) and then *N*-chlorosuccinimide (NCS, 12.0 g, 89.9 mmol). The resulting suspension was stirred vigorously at rt until TLC analysis revealed that a majority of the starting material had been consumed (10 d). The reaction mixture was then filtered through a celite pad and the filtrate treated with 4 wt.% aq. NaI (50 mL) followed by 10 wt.% $Na_2S_2O_3$ (80 mL) to reduce excess NCS. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2x20 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and then concentrated *in vacuo* to yield 5.61 g of a brown solid. The residue was further purified by column chromatography (SiO_2, eluting with 60% EtOAc in hexanes) to afford the desired chloro-sulfoxide (+)-(S_S)-*syn*-H-**12** (4.36 g, 15.9 mmol, 86%) as a colorless solid. ^{1}H NMR analysis indicated that this material was a 84:16 mixture of *syn* and *anti* diastereoisomers, respectively. Recrystallization from *t*-BuOMe (TBME) gave (+)-(S_S)-*syn*-H-**12** with dr ≥95:5 as long colorless needles. X-ray diffraction analysis confirmed the relative and absolute stereochemical outcome of this transformation to be as illustrated (Figure S3).

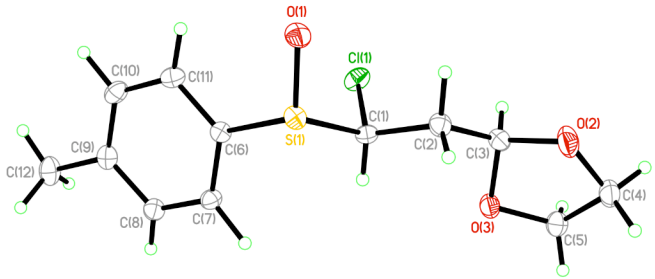
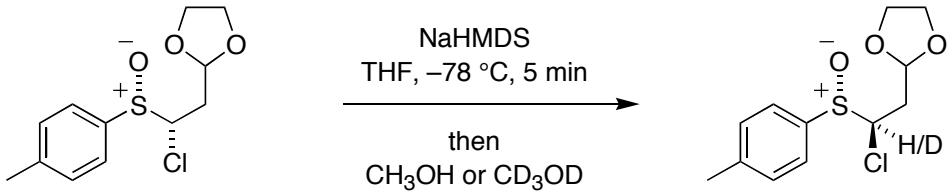


Figure S3. ORTEP diagram for (+)-(S_S)-*syn*-H-**12** (prepared from (–)-(S_S)-**11**). Full crystallographic data are available in the accompanying CIF file. 50% probability ellipsoids are plotted for non-hydrogen atoms.

Data for (+)-(S_S)-*syn*-H-**12**: mp 126-128 °C (TBME); $[\alpha]_D^{23}$ = + 108.6 (c = 1.15, $CHCl_3$); IR (KBr) 2883, 1596, 1492, 1398, 1145, 1083, 1057, 810 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, "d", *J* = 8.2 Hz), 7.34 (2H, "d", *J* = 8.3 Hz), 5.14 (1H, dd, *J* = 6.6, 3.3 Hz), 4.78 (1H, dd, *J* = 10.3, 3.4 Hz), 4.02-3.94 (2H, m), 3.93-3.85 (2H, m), 2.48 (1H, ddd, *J* = 14.3, 6.6, 3.4 Hz), 2.43

S4. Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *Tetrahedron Lett*. **1988**, *29*, 313-316.

(3H, s), 1.91 (1H, ddd, *J* = 13.8, 10.3, 3.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8 (0), 135.5 (0), 129.8 (2C, 1), 126.0 (2C, 1), 101.5 (1), 71.4 (1), 65.3 (2), 65.1 (2), 35.4 (2), 21.7 (3) ppm; ; MS (EI) *m/z* 276 (M[^{37}Cl]$^{+\bullet}$, 4), 274 (M[^{35}Cl]$^{+\bullet}$, 12), 257 (44), 134 (60), 73 (100); HRMS (EI) *m/z* 274.0430 (calcd. for $C_{12}H_{15}O_3{}^{35}ClS$: 274.0430).



(S_S)-*syn*-H-**12**: $C_{12}H_{15}ClO_3S$ (274.76)

(S_S)-*anti*-H-**12**: $C_{12}H_{15}ClO_3S$ (274.76)
(S_S)-*anti*-D-**12**: $C_{12}H_{14}DClO_3S$ (275.77)

2-[(S_S,2*R*)-2-Chloro-2-(4-methylphenyl)sulfinylethyl]-1,3-dioxolane [(S_S)-*anti*-H-12].
A stirred solution of (+)-(S_S)-*syn*-H-**12** (1.00 g, 3.64 mmol) in anhydrous THF (12 mL) at –78 °C under Ar was treated with NaHMDS (4.00 mL, 2.0 M in THF, 8.00 mmol). This reagent was added during 30 sec down the cold flask side-wall to chill it before it combined with the reaction mixture. The resulting dark orange solution of metallated sulfoxide was stirred for 5 min at –78 °C before being protonolyzed with MeOH (1.0 mL). After 2 min, sat. aq. NH_4Cl (6 mL) was added and the quenched reaction mixture was allowed to warm to rt. EtOAc (6 mL) was added and the layers shaken and separated. The aqueous phase was extracted with EtOAc (3x6 mL) and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 20% EtOAc in hexanes) to afford the epimerization product (+)-(S_S)-*anti*-H-**12** (880 mg, 3.20 mmol, 88%, *anti:syn* = 93:7) as a colorless solid. The material was triturated with THF (10 mL) resulting in precipitation of a small quantity (62 mg) of the highly insoluble racemate of *anti*-H-**12** (mp 134-136 °C (TBME)]. The THF triturate was concentrated *in vacuo* and the residue recrystallized from *t*-BuOMe (TBME) to afford (+)-(S_S)-*anti*-H-**12** with heightened stereoisomeric purity (dr ≥ 95:5). Data for (+)-(S_S)-*anti*-H-**12**: mp 86-89 °C (TBME); $[\alpha]_D{}^{23}$ = + 129.3 (c = 0.59, $CHCl_3$); IR (KBr) 2964, 2886, 1398, 1135, 1090, 1051, 817 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (2H, "d", *J* = 8.1 Hz), 7.34 (2H, "d", *J* = 8.2 Hz), 5.18 (1H, dd, *J* = 6.4, 3.3 Hz), 4.66 (1H, dd, *J* = 10.0, 3.5 Hz), 4.03-3.84 (4H, m), 2.43 (3H, s), 2.39 (1H, ddd, *J* = 14.4, 6.4, 3.5 Hz), 2.25 (1H, ddd, *J* = 14.5, 10.0, 3.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0 (0), 137.5 (0), 129.9 (2C, 1), 126.1 (2C, 1), 101.4 (1), 73.0 (1), 65.3 (2), 65.1 (2), 36.0 (2), 21.7 (3) ppm; MS (EI) *m/z* 276 (M[^{37}Cl]$^{+\bullet}$, 4), 274 (M[^{35}Cl]$^{+\bullet}$, 12), 259 (16), 257 (44), 134 (68), 73 (100); HRMS (EI) *m/z* 274.0432 (calcd. for $C_{12}H_{15}O_3{}^{35}ClS$: 274.0430).

2-[(S_S,2*R*)-2-Chloro-2-deutero-2-(4-methylphenyl)sulfinylethyl]-1,3-dioxolane [(S_S)-*anti*-D-12]. Conducting an experiment otherwise identical to that described above for the conversion of (+)-(S_S)-*syn*-H-**12** to (+)-(S_S)-*anti*-H-**12** with CD_3OD in place of CH_3OH during the quench, afforded (+)-(S_S)-*anti*-D-**12** with %D≥85%. XRD confirmed the relative and absolute stereochemical outcome of the reaction to be as illustrated above (Figure S4).

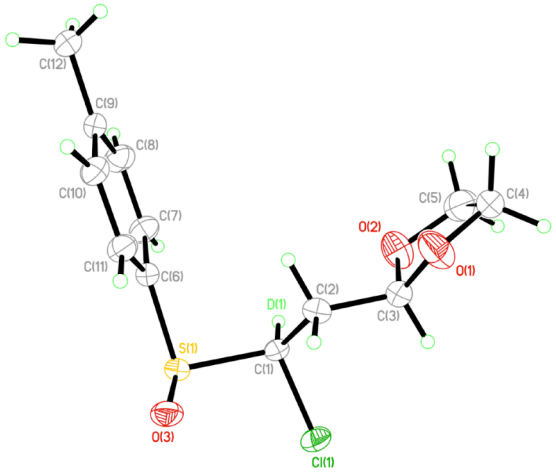
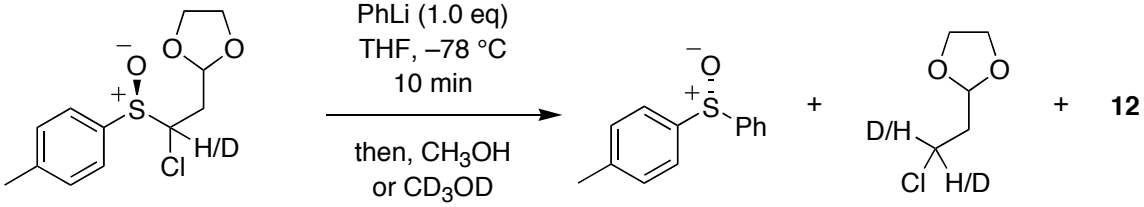


Figure S4. ORTEP diagram for (+)-(S_S)-*anti*-D-**12** (prepared from (+)-(S_S)-*syn*-H-**12**). Full crystallographic data are available in the accompanying CIF file. 50% probability ellipsoids are plotted for non-hydrogen atoms.

Data for (+)-(S_S)-*anti*-D-**12**: colorless needles; mp 86-87 °C (TBME); $[\alpha]_D^{23}$ = + 133.1 (c = 0.96, $CHCl_3$); IR (KBr) 2961, 2886, 1595, 1495, 1401, 1138, 1086, 1044, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (2H, "d", *J* = 8.2 Hz), 7.34 (2H, "d", *J* = 8.3 Hz), 5.18 (1H, dd, *J* = 6.4, 3.3 Hz), 4.03-3.84 (4H, m), 2.43 (3H, s), 2.38 (1H, dd, *J* = 14.5, 6.4 Hz), 2.24 (1H, ddm, *J* = 14.5, 3.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1 (0), 137.3 (0), 129.9 (2C, 1), 126.1 (2C, 1), 101.4 (1), 72.6 (CDCl, 1:1:1 multiplet, $^1J_{CD}$ = 25.6 Hz), 65.3 (2), 65.1 (2), 35.8 (2), 21.7 (3) ppm; HRMS (ES) *m/z* 300.0353 (calcd. for $C_{12}H_{14}DO_3Na^{37}ClS$: 300.0361), 298.0377 (calcd. for $C_{12}H_{14}DO_3Na^{35}ClS$: 298.0391).

Sulfoxide Ligand Exchange Studies (Table 1)



(*R*$_S$)-*syn*-H-**12**: $C_{12}H_{15}ClO_3S$ (274.76)
(*R*$_S$)-*anti*-H-**12**: $C_{12}H_{15}ClO_3S$ (274.76)
(*R*$_S$)-*anti*-D-**12**: $C_{12}H_{14}DClO_3S$ (275.77)

13: $C_{13}H_{12}OS$ (216.30)

14: $C_5H_9ClO_2$ (136.58)
$C_5H_8DClO_2$ (137.58)
$C_5H_7D_2ClO_2$ (138.59)

Sulfoxide ligand exchange from chlorosulfoxides 12 (Table 1). A stirred solution of the given form of chlorosulfoxide **12** (75 mg, 0.273 mmol) in anhydrous THF (1.8 mL) at –78 °C under Ar was treated with PhLi (0.17 mL, 1.60 M in Bu_2O) during 5 sec. The resulting orange solution

was stirred for 10 min and then quenched by the addition of either CH_3OH (0.25 mL) or CD_3OD (0.25 mL) as indicated. The mixture was then treated with sat. aq. NH_4Cl (1 mL) and allowed to warm to rt. EtOAc (5 mL) and H_2O (5 mL) were added and the layers shaken and separated. The aqueous phase was extracted with EtOAc (5 mL) and the combined organic phases washed with brine (2 mL), dried (Na_2SO_4), and then concentrated *in vacuo*. ^{1}H NMR spectral analysis was conducted at this stage to determine the molar ratio of **13** to **14**. The residue was then purified by column chromatography (SiO_2, eluting with 40% EtOAc in hexanes) to afford, in order of elution: inseparable non-polar components including isotopomers of **14** and sulfoxide ligand coupling adducts (e.g., Ph-Ph),[S5] the pure SLE product **13**, and a pure mixture of chlorosulfoxide diastereoisomers/isotopomers of **12**. The isolated yield determined for **13** was used to quantify an effective yield of alkylchloride **14** (since the latter could not be isolated in a wholly pure form). ^{1}H NMR spectral signatures for **13** and HH-**14** matched those previously reported by Senanayake et al.[S6] and Lugtenburg et al.,[S7] respectively. Data for **12** are given above.

Data for p-tolyl phenyl sulfoxide (**13**): colorless oil; $[\alpha]_D^{23} < 1$ (c = 1.00, $CHCl_3$: observed rotation too low to enable a meaningful determination of value or sign); IR (neat) 3052, 2915, 1596, 1489, 1443, 1093, 1041, 804 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.61 (2H, m), 7.53 (2H, dm, *J* = 8.2 Hz), 7.47-7.41 (3H, m), 7.29-7.24 (2H, m), 2.37 (3H, s) ppm.

^{1}H NMR spectral data for 2-(2-chloroethyl)-1,3-dioxolane (HH-**14**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (1H, t, *J* = 4.6 Hz), 4.00-3.92 (2H, m), 3.91-3.84 (2H, m), 3.65 (2H, t, *J* = 7.0 Hz), 2.14 (2H, td, *J* = 7.0, 4.8 Hz) ppm.

^{1}H NMR spectral data for 2-(2-chloro-2-deuteroethyl)-1,3-dioxolane (HD-**14**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (1H, t, *J* = 4.6 Hz), 4.00-3.92 (2H, m), 3.91-3.84 (2H, m), 3.63 (1H, t of 1:1:1, *J* = 6.9, 1.7 Hz), 2.13 (2H, dd of 1:1:1, *J* = 6.9, 4.8, 1.2 Hz) ppm.

^{1}H NMR spectral data for 2-(2-chloro-2,2-dideuteroethyl)-1,3-dioxolane (DD-**14**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (1H, t, *J* = 4.6 Hz), 4.00-3.92 (2H, m), 3.91-3.84 (2H, m), 2.12 (2H, d of 1:2:3:2:1, *J* = 4.7, 1.0 Hz) ppm.

Careful analysis of the integration trace for HH-**14** and HD-**14** combined multiplets at $\delta_H \sim 3.65$ ppm enabled an estimation of the ratio of HH:HD:DD as indicated in Figure S5 (below).

S5. Oae, S.; Uchida, Y. *Acc. Chem. Res.* **1991**, *24*, 202-208.
S6. Zhengxu, H.; Dhileephkumar, K.; Grover, P.; Wilkinson, S.; Fang, K.; Xiping, S.; Zhi-Hui, L.; Magiera, D.; Senanayake, C. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2032-2035.
S7. Shrestha, P. B.; Lugtenburg, J. *Eur. J. Org. Chem.* **2003**, 4654-4663.

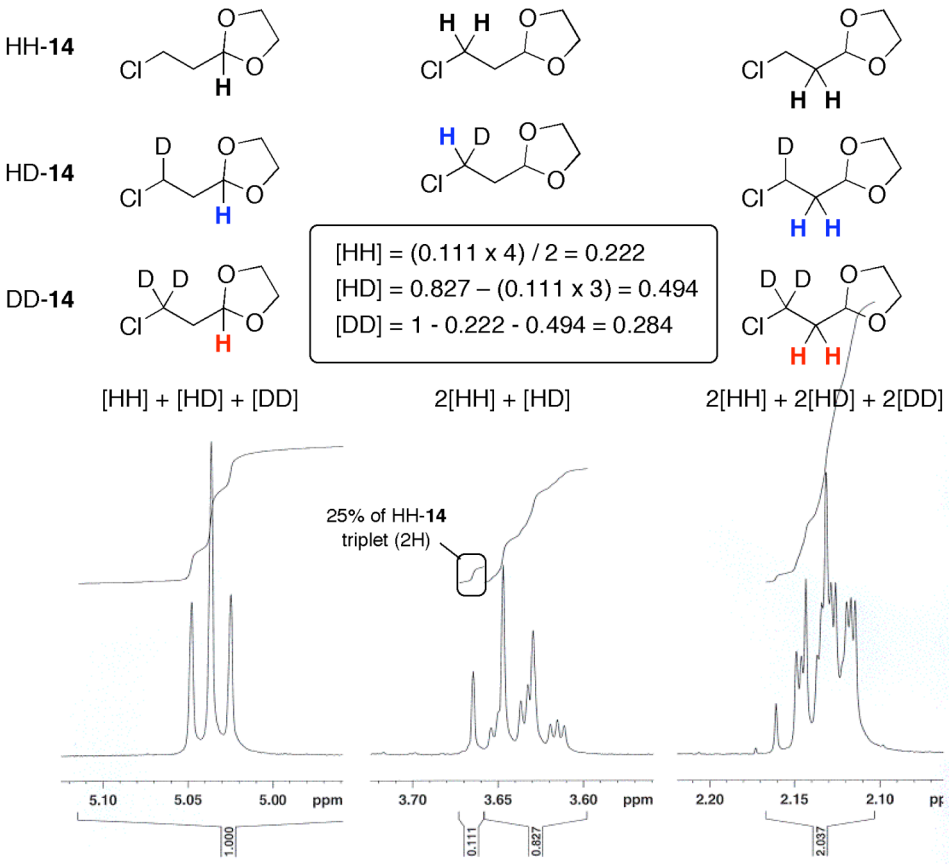
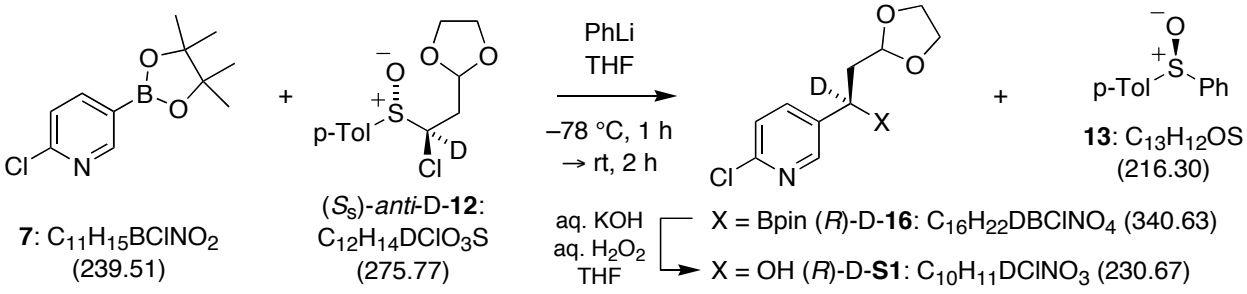


Figure S5. Detail of ^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **12** obtained from experiment summarized as Entry 3 in Table 1. The integration based method used to determine ratio of isotopomers is illustrated.

*Synthesis of Boronates **16** via StReCH and HPLC Analysis of Derived Alcohols (Table 2, Entries 1-3)*



Representative procedure for 1st StReCH Reaction (Table 2, Entry 3). A stirred solution of *B*-pyridyl pinacol boronate **7** (150 mg, 0.626 mmol)[S8] and chlorosulfoxide (S_S)-*anti*-D-**12** (207 mg, 0.751 mmol) in anhydrous THF (4.2 mL, 0.15 M in boronate) at –78 °C under Ar, was treated dropwise with PhLi (0.44 mL, 1.69 M in *n*-Bu_2O, 0.744 mmol) during 30 sec. The

S8. Boronate **7** can be obtained from a variety of chemical suppliers (including Aldrich, cat.#659843), or else prepared from inexpensive 5-bromo-2-chloro-pyridine by the method of Rault et al., see: Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885-2890.

resulting light orange mixture was allowed to stir for 1 h at –78 °C, then warmed to rt and stirred for a further 2 h during which time the color darkened significantly. Sat. aq. NH_4Cl (2 mL) was added and the quenched reaction mixture partitioned between EtOAc (5 mL) and H_2O (5 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 mL). The combined organic phases were then washed with brine (2 mL), dried (Na_2SO_4), and concentrated *in vacuo*. ^{1}H NMR analysis of the residue revealed that 79% of boronate **7** had been successfully converted into StReCH adduct D-**16** (and 90% of **12** had been converted to sulfoxide **13**). Purification by column chromatography (SiO_2, eluting with 30% EtOAc in hexanes) afforded an inseparable mixture of (*R*)-D-**16** and **13** (262 mg, 43 wt.% in **16**, effectively 113 mg, 0.331 mmol, 53%) as a colorless oil. Data for (*R*)-D-**16** (obtained from mixtures with sulfoxide **13**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, dd, *J* = 2.0, < 1 Hz), 7.55 (1H, dd, *J* = 8.2, 2.5 Hz), 7.21 (1H, dd, *J* = 8.2, < 1 Hz), 4.91 (1H, dd, *J* = 4.9, 3.1 Hz), 4.00-3.92 (2H, m), 3.88-3.81 (2H, m), 2.28 (1H, dd, *J* = 13.8, 4.8 Hz), 1.95 (1H, dd, *J* = 13.7, 3.0 Hz), 1.18 (6H, s), 1.16 (6H s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6 (1), 148.6 (0), 138.7 (1), 137.6 (0), 124.0 (1), 103.3 (1), 83.9 (2C, 0), 65.3 (2), 65.1 (2), 36.1 (2), 26.6-25.7 (m, CDBpin), 24.8 (2C, 3), 24.7 (2C, 3) ppm; HRMS (ES) *m/z* 341.1523 (calcd. for $C_{16}H_{23}D^{11}B^{35}ClNO_4$: 341.1550).

Oxidation to alcohol (*R*)-D-S1 for ee determination. A sample of the mixture of (*R*)-D-**16** and **13** obtained above (8.0 mg, 43 wt.% in **16**, effectively 3.4 mg, 0.331 mmol, 0.010 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. The solution was then treated with aq. 2M KOH (0.5 mL) and 30 wt.% aq. H_2O_2 (0.25 mL) and stirred for 1 h. After this time the mixture was partitioned between EtOAc (5 mL) and H_2O (5 mL) and layers separated. The aq. phase was extracted with EtOAc (5 mL) and combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 60% EtOAc in hexanes) to afford the carbinol (+)-(*R*)-D-**S1** (2.0 mg, 0.0086 mmol, 86%) as a colorless oil: $[\alpha]_D^{23}$ = + 20.5 (c = 1.05, $CHCl_3$); IR (neat) 3420, 2924, 1588, 1567, 1459, 1367, 1106, 1027, 944, 844 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (1H, d, *J* = 2.5 Hz), 7.71 (1H, dd, *J* = 8.2, 2.5 Hz), 7.31 (1H, d, *J* = 8.3 Hz), 5.07 (1H, dd, *J* = 4.4, 3.7 Hz), 4.11-4.03 (2H, m), 3.99-3.87 (2H, m), 3.62 (1H, br s), 2.15-2.04 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6 (0), 147.7 (1), 138.3 (0), 136.6 (1), 124.2 (1), 103.1 (1), 67.3 (CDOH, 1:1:1 multiplet, $^1J_{CD}$ = 22.2 Hz), 65.3 (2), 65.1 (2), 42.1 (2) ppm; MS (ES) *m/z* 233 $(M+H)^+$, 231 $(M+H)^+$; HRMS (ES) *m/z* 233.0611 (calcd. for $C_{10}H_{12}D^{37}ClNO_3$: 233.0617), 231.0628 (calcd. for $C_{10}H_{12}D^{35}ClNO_3$: 231.0647).

HPLC analysis of (±)-H-**S1** performed with a Daicel Chiralcel® AD column (4.6 mm ID x 250 mm), eluting with 5% *i*-PrOH in hexanes at 1.0 mL min^{-1} and monitored by UV at 210 nm, showed resolved peaks: $t_{ret.}$ [(*S*)-H-**S1**] = 58.4 min, $t_{ret.}$ [(*R*)-H-**S1**] = 63.5 min. Analysis of the

enantioenriched deuterated material D-**S1** prepared as described above revealed an enantiomeric excess of 89% in favor of the (*R*)-enantiomer (Figure S6).

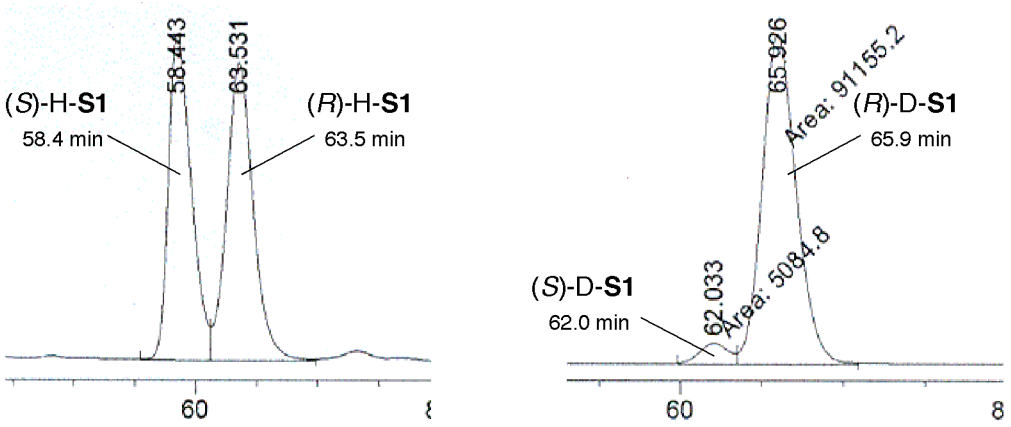
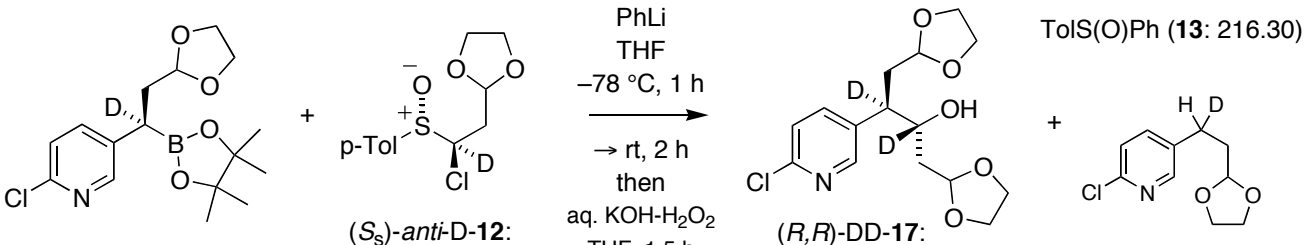


Figure S6. HPLC analysis of **S1** with Daicel Chiralcel® AD column: left trace racemic standard, right trace enantioenriched sample of (*R*)-D-**S1** with %ee = 89% (Table 2, Entry 3).

Carbinol (*R*)-H-**S1** (with 93% ee as determined by HPLC analysis) was similarly prepared from (*R*)-H-**16**, itself derived from StReCH reaction of boronate **7** with (R_S)-*syn*-**12** (Table 2, Entry 1). Data for (+)-(*R*)-H-**S1**: $[\alpha]_D^{23}$ = + 29.1 (c = 0.69, $CHCl_3$); IR (neat) 3420, 2924, 1587, 1569, 1459, 1138, 1105, 1024, 854 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (1H, d, *J* = 2.4 Hz), 7.71 (1H, dd, *J* = 8.2, 2.5 Hz), 7.31 (1H, d, *J* = 8.2 Hz), 5.11-5.04 (2H, m), 4.15-4.03 (2H, m), 3.97-3.88 (2H, m), 3.60 (1H, br s), 2.15-2.00 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6 (0), 147.8 (1), 138.4 (0), 136.6 (1), 124.2 (1), 103.1 (1), 67.7 (1), 65.3 (2), 65.1 (2), 42.2 (2) ppm; HRMS (EI) *m/z* 229.0499 (calcd. for $C_{10}H_{12}{}^{35}ClNO_3$: 229.0506).

*Synthesis of Carbinols **17** via Iterative StReCH and HPLC Analysis (Table 2, Entries 4-7)*



(*R*)-D-**16**: $C_{16}H_{22}DBClNO_4$ (340.63)

(S_S)-*anti*-D-**12**: $C_{12}H_{14}DClO_3S$ (275.77)

(*R,R*)-DD-**17**: $C_{15}H_{18}D_2ClNO_5$ (331.79)

D-**19**: $C_{10}H_{11}DClNO_2$ (214.67)

Representative procedure for 2nd StReCH Reaction (Table 2, Entry 4). A stirred solution of boronate (*R*)-D-**16** (309 mg, 41 wt.% in **16** rest **13**, 0.372 mmol, ≥ 89% ee) and chlorosulfoxide (S_S)-*anti*-D-**12** (124 mg, 0.450 mmol, dr = 96:4) in anhydrous THF (2.5 mL, 0.15 M in boronate)

at –78 °C under Ar, was treated dropwise with PhLi (0.25 mL, 1.80 M in *n*-Bu_2O, 0.450 mmol) during 30 sec. The resulting light yellow mixture was allowed to stir for 1 h at –78 °C, then warmed to rt and stirred for a further 2 h during which time the color darkened. After this time, aq. 2M KOH (0.5 mL) and 30 wt.% aq. H_2O_2 (0.25 mL) were added and the biphasic mixture stirred vigorously for 1.5 h. The mixture was then partitioned between EtOAc (5 mL) and H_2O (5 mL) and the layers separated. The aq. phase was extracted with EtOAc (5 mL) and combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 70% EtOAc in hexanes) to afford, in order of elution: an inseparable mixture of protodeboronated adduct D-**19** and **13** (299 mg, 16 wt.% in D-**19**, 0.223 mmol, 60%), alcohol D-**S1** (resulting from oxidation of D-**16**, 21 mg, 0.091 mmol, 24%), and the desired bisacetal (*R,R*)-DD-**17** (28 mg, 0.084, 23%, dr = 89:11) as a colorless solid. HPLC analysis of this chromatographed bisacetal material (**17**) revealed that the major diastereoisomer had an enantiomeric excess of ≥ 98%, while the minor diastereoisomer exhibited %ee < 24% (see below and Figure S8). Recrystallization of (*R,R*)-DD-**17** from TBME afforded excellent quality needles of the pure major diastereoisomer. X-ray diffraction analysis of this material confirmed the absolute and relative stereochemical of (*R,R*)-DD-**17** (Figure S7).

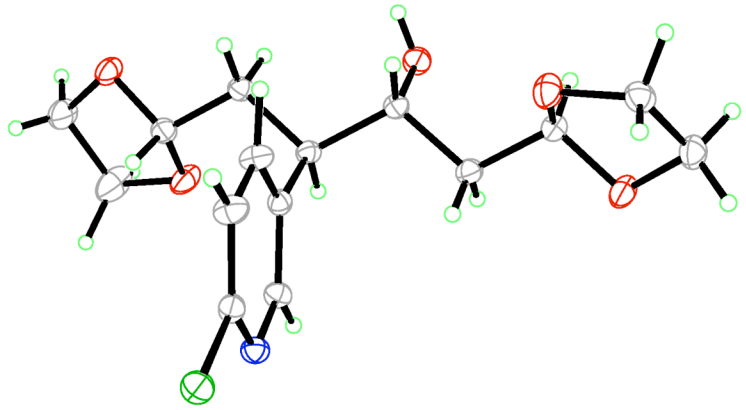
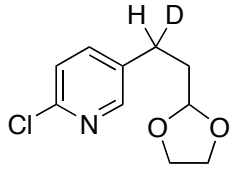


Figure S7. ORTEP diagram for (–)-(*R,R*)-DD-**17**. Full crystallographic data are available in the accompanying CIF file. 50% probability ellipsoids are plotted for non-hydrogen atoms.

Data for (–)-(*R,R*)-DD-**17**: colorless needles; mp 113-114 °C (TBME); $[\alpha]_D^{23}$ = – 52.9 (c = 0.90, $CHCl_3$); IR (KBr) 3481, 2888, 1734, 1559, 1458, 1406, 1369, 1140, 1028, 944 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, dd, *J* = 2.5, 0.7 Hz), 7.58 (1H, dd, *J* = 8.3, 2.5 Hz), 7.27 (1H, dd, *J* = 8.2, 0.7 Hz), 4.99 (1H, dd, *J* = 4.9, 3.6 Hz), 4.65 (1H, dd, *J* = 6.6, 3.3 Hz), 4.01-3.73 (8H, m), 3.29 (1H, s), 2.24 (1H, dd, *J* = 14.2, 6.6 Hz), 2.08 (1H, dd, *J* = 14.2, 3.2 Hz), 1.74 (1H, dd, *J* = 14.5, 3.5 Hz), 1.68 (1H, dd, *J* = 14.6, 5.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2 (1), 149.9 (0), 138.8 (1), 136.8 (0), 124.1 (1), 103.5 (1), 103.0 (1), 70.3 (CDOH, 1:1:1 multiplet, $^1J_{CD}$ = 20.8 Hz), 65.2 (2), 65.1 (2), 64.92 (2), 64.90 (2), 44.0 (CDR, 1:1:1 mulitplet, $^1J_{CD}$ = 19.5 Hz), 37.8 (2), 35.0 (2) ppm; HRMS (EI) *m/z* 331.11849 (calcd. for $C_{15}H_{18}D_2{}^{35}ClNO_5$: 331.11554).

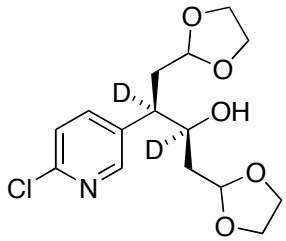
A pure sample of D-**19** was obtained by subjecting the inseparable mixture of D-**19** and **13** to aq. H_2O_2 (5 eq) and an ammonium molybdate catalyst (10 mol%) in EtOH (24 h, rt). This treatment resulted in conversion of **13** to the corresponding sulfone which was easily separated from D-**19** by chromatography (SiO_2, eluting with 40% EtOAc in hexanes). The protodeboronated adduct exhibited the following spectral characteristics.



D-**19**: $C_{10}H_{11}DClNO_2$
(214.67)

Data for D-**19**: colorless oil; IR (neat) 2885, 1559, 1458, 1139, 1107, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, d, *J* = 2.5 Hz), 7.50 (1H, dd, *J* = 8.2, 2.6 Hz), 7.25 (1H, d, *J* = 8.2 Hz), 4.89 (1H, t, *J* = 4.5 Hz), 4.03-3.94 (2H, m), 3.92-3.83 (2H, m), 2.72 (1H, t of 1:1:1, *J* = 7.5, 1.8 Hz), 1.96 (2H, dd of 1:1:1, *J* = 7.9, 4.5, <1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8 (1), 149.3 (0), 138.9 (1), 136.0 (0), 124.1 (1), 103.4 (1), 65.2 (2C, 2), 35.0 (2), 26.2 (CDH, 1:1:1 multiplet, $^1J_{CD}$ = 19.6 Hz) ppm; MS (EI) *m/z* 216 (16%), 214 (36), 169 (8), 141 (20), 127 (40), 101 (92), 73 (100); HRMS (CI) *m/z* 215.0694 (calcd. for $C_{10}H_{12}D^{35}ClNO_2$: 215.0698).

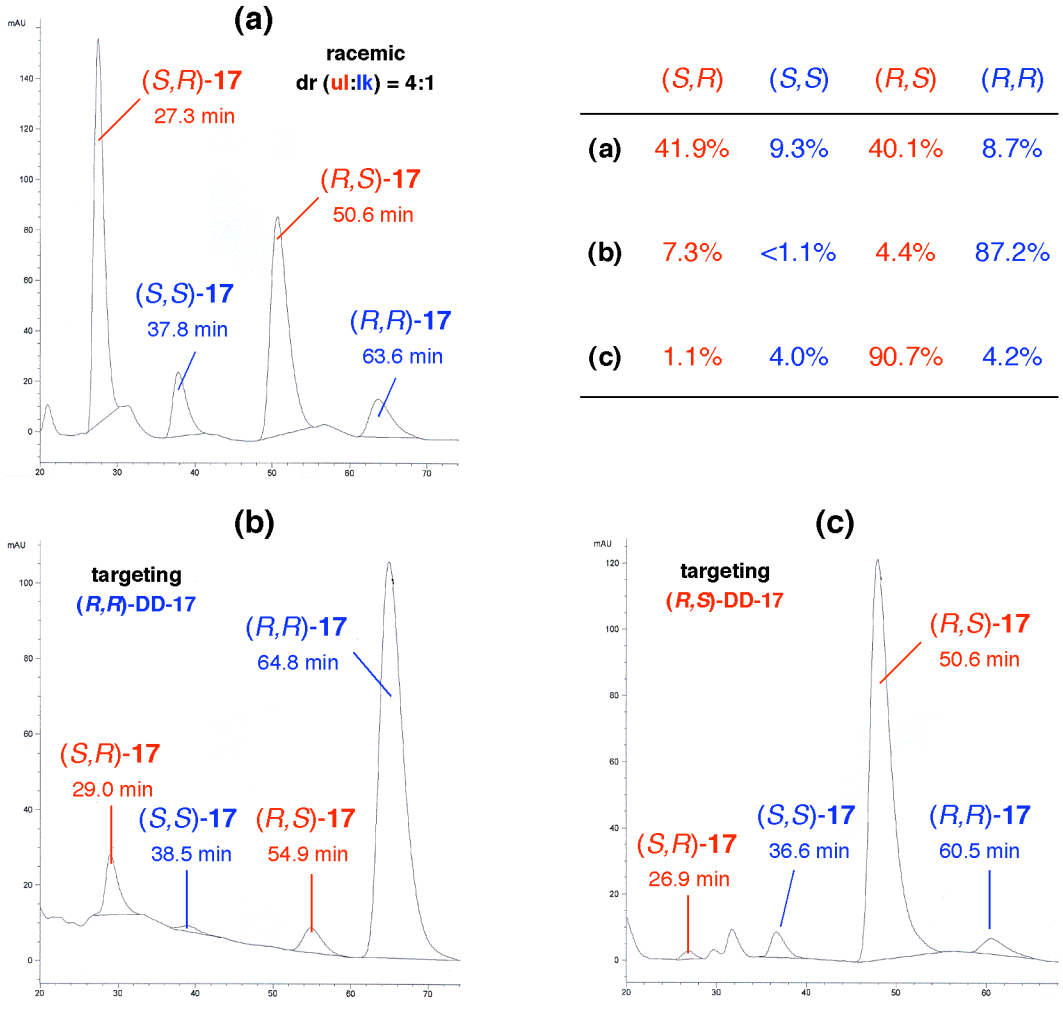
The alternate "unlike" (ul) diastereoisomer (*R,S*)-DD-**17** was targeted in an analogous manner to the "like" (lk) isomer (*R,R*)-DD-**17** (above) by using chlorosulfoxide (R_S)-*anti*-D-**12** (of dr = 93:7) in the second StReCH step from boronate (*R*)-D-**16** (of er = 89%) (Table 2, Entry 5). HPLC analysis of (*R,S*)-DD-**17** (22%, dr = 90:10) prepared in this manner indicated that the major diastereoisomer had an enantiomeric excess of ≥ 98%, while the minor diastereomer exhibited %ee ~ 2% (see below and Figure S8).



(*R,S*)-DD-**17**:
$C_{15}H_{18}D_2ClNO_5$
(331.79)

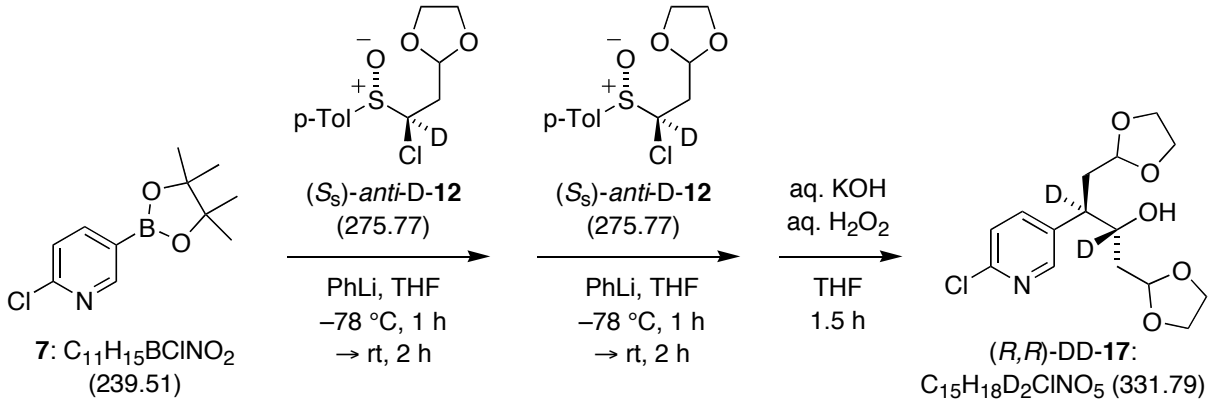
Data for (–)-(*R,S*)-DD-**17**:
colorless oil; $[\alpha]_D^{23}$ = – 35.2 (c = 0.60, $CHCl_3$); IR (neat) 3488, 2886, 1559, 1458, 1140, 1109, 1024, 944 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, dd, *J* = 2.5, 0.7 Hz), 7.73 (1H, dd, *J* = 8.3, 2.5 Hz), 7.26 (1H, dd, *J* = 8.3, 0.6 Hz), 4.98 (1H, dd, *J* = 5.2, 3.4 Hz), 4.69 (1H, dd, *J* = 6.3, 3.6 Hz), 4.01-3.77 (8H, m), 3.12 (1H, s), 2.21 (1H, ddm, *J* = 14.1, 3.4 Hz), 2.12 (1H, dd, *J* = 14.1, 6.2 Hz), 1.72 (1H, dd, *J* = 14.4, 3.4 Hz), 1.39 (1H, dd, *J* = 14.6, 5.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6 (1), 150.1 (0), 139.8 (1), 135.6 (0), 123.9 (1), 103.6 (1), 103.0 (1), 69.4 (CDOH, 1:1:1 multiplet, $^1J_{CD}$ ~ 20 Hz), 65.2 (2), 65.1 (2), 65.0 (2), 64.9 (2), 43.5 (CDR, 1:1:1 multiplet, $^1J_{CD}$ ~ 20 Hz), 38.7 (2), 36.8 (2) ppm; HRMS (CI) *m/z* 332.1223 (calcd. for $C_{15}H_{19}D_2{}^{35}ClNO_5$: 332.1234).

HPLC Analysis of Carbinols 17. A diastereomerically biased racemic sample of DD-**17** (dr ~ 4:1, favoring the "unlike" (ul) relative stereochemical configuration) was prepared from boronate **7** by two separate sequential StReCH reactions employing racemic chlorosulfoxide *anti*-D-**12** (nb. reaction sequence gave dr ~ 1:1; this ratio was deliberately perturbed by subsequent column chromatography). HPLC analysis of the racemic sample using a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 10% *i*-PrOH in hexanes and monitored by UV at 210 nm, showed resolved peaks: $t_{ret.}$ [(*S*,*R*)-DD-**17**] = 27.3 min, $t_{ret.}$ [(*S*,*S*)-DD-**17**] = 37.8 min, $t_{ret.}$ [(*R*,*S*)-DD-**17**] = 50.6 min, $t_{ret.}$ [(*R*,*R*)-DD-**17**] = 63.6 min (Figure S8, chromatogram a). Samples of **17** obtained from iterative StReCH reaction sequences using enantioenriched chlorosulfoxides were analyzed using the same HPLC conditions, results are given in Table 2 of the main manuscript. Illustrated below are chromatograms for samples of (*R*,*R*)-DD-**17** and (*R*,*S*)-DD-**17** obtained by a separate second StReCH reaction from isolated boronate **16** (Table 2, Entries 4 and 5).



	(*S*,*R*)	(*S*,*S*)	(*R*,*S*)	(*R*,*R*)
(a)	41.9%	9.3%	40.1%	8.7%
(b)	7.3%	<1.1%	4.4%	87.2%
(c)	1.1%	4.0%	90.7%	4.2%

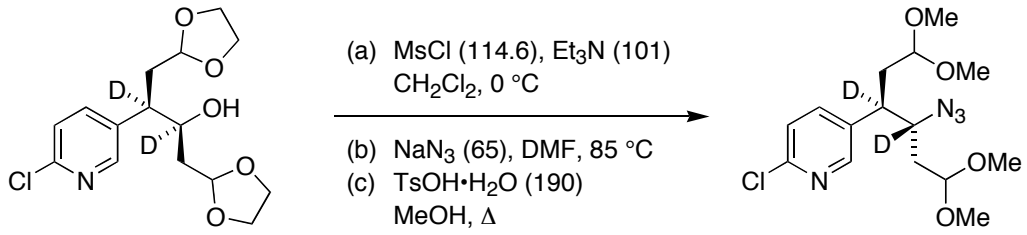
Figure S8. HPLC analysis of carbinols **17** with Daicel Chiralcel® OD column: (a) racemic sample of DD-**17** with dr (ul:lk) = 4:1; (b) enantioenriched sample of (*R*,*R*)-DD-**17** targeted by StReCH reaction of (*R*)-**16** (of 89% ee) with (S_S)-*anti*-D-**12** (of dr = 96:4) (Table 2, Entry 4); (c) enantioenriched sample of (*R*,*S*)-DD-**17** targeted by StReCH reaction of (*R*)-**16** (of 89% ee) with (R_S)-*anti*-D-**12** (of dr = 93:7) (Entry 5).



Representative procedure for one-pot iterative double StReCH reaction (Table 2, Entry 6). A stirred solution of boronate **7** (150 mg, 0.626 mmol)[S8] and chlorosulfoxide (S_S)-*anti*-D-**12** (207 mg, 0.751 mmol, dr = 95:5) in anhydrous THF (3.0 mL, 0.21 M in boronate) at –78 °C under Ar, was treated dropwise with PhLi (0.44 mL, 1.69 M in *n*-Bu_2O, 0.744 mmol) during 20 sec. The resulting light yellow mixture was allowed to stir for 1 h at –78 °C, then warmed to rt and stirred for 2 h during which time the color darkened. The reaction mixture was then re-cooled to –78 °C and (S_S)-*anti*-D-**12** (207 mg, 0.751 mmol, dr = 95:5) in dry THF (1.0 mL) added. After a period of 10 min to ensure that the flask contents had returned to ca. –78 °C, the reaction mixture was treated with a second portion of PhLi (0.44 mL, 1.69 M in *n*-Bu_2O, 0.744 mmol) during 20 sec. The reaction was again initially stirred for 1 h at –78 °C and then warmed to rt and stirred for a further 2 h. The contents of the flask, which were by now very darkly colored indeed (resembling a solution of I_2), were then cooled to 0 °C and treated with 2M aq. KOH (0.5 mL) followed by 30 wt.% aq. H_2O_2 (0.25 mL) and the biphasic mixture stirred vigorously for 1.5 h. The mixture was then partitioned between EtOAc (10 mL) and H_2O (10 mL) and the layers separated. The aq. phase was extracted with EtOAc (10 mL) and combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 70% EtOAc in hexanes) to afford the targeted carbinol (*R,R*)-DD-**17** (84 mg, 0.253 mmol, 40%) as a colorless oil which solidified on standing. ^{1}H NMR and HPLC analysis (as described above) indicated dr = 85:15 and that the major (targeted "like") diastereoisomer possessed %ee ≥ 98%, while the minor (untargeted "unlike") diastereoisomer exhibited %ee < 10%. Characterization data for (*R,R*)-DD-**17** are recorded above (p. S12).

The "unlike" diastereoisomer (*R,S*)-DD-**17** (405 mg, 1.22 mmol, 49%) was targeted in analogous fashion from boronate **7** (600 mg, 2.50 mmol)[S8] by a one-pot sequential double StReCH reaction involving initial deployment of chlorosulfoxide (S_S)-*anti*-D-**12** (827 mg, 3.00 mmol) followed by its antipode (R_S)-*anti*-D-**12** (827 mg, 3.00 mmol) in the second stage (Table 2, Entry 7). Carbinol (*R,S*)-DD-**17** prepared in this manner exhibited dr = 79:21 with diastereoisomer ee's of ≥97% and ~1%, respectively. Characterization data for (*R,S*)-DD-**17** are recorded above (p. S13).

*Advancement of Carbinol (R,S)-DD-**17** (Scheme 4)*

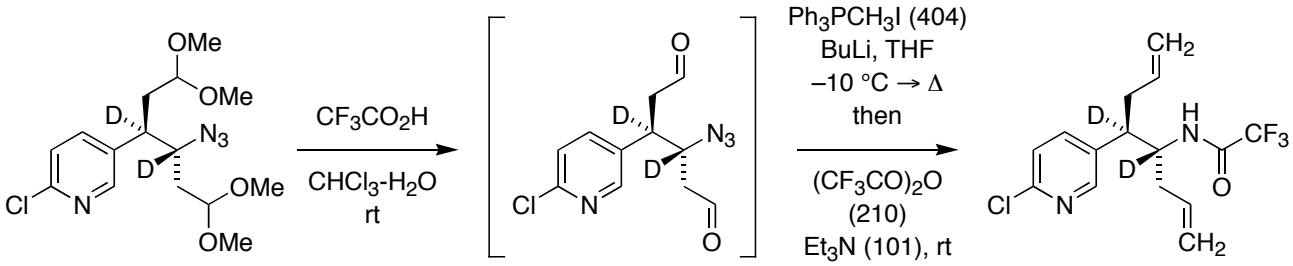


(*R,S*)-DD-**17**:
$C_{15}H_{18}D_2ClNO_5$ (331.79)

20: $C_{15}H_{21}D_2ClN_4O_4$
(360.83)

Azide 20: *Mesylation*. A stirred solution of carbinol (*R,S*)-DD-**17** (295 mg, 0.889 mmol) and Et_3N (1.24 mL, d = 0.726, 900 mg, 8.91 mmol) in CH_2Cl_2 (10 mL) at 0 °C under Ar was treated with neat MsCl (0.34 mL, d = 1.48, 503 mg, 4.39 mmol). After stirring for 35 min, the mixture was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2x5 mL) and the combined organic phases were washed with H_2O (5 mL) and brine (5 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. *Azidation*. The residue (384 mg of crude mesylate) was immediately dissolved in anhydrous DMF (5 mL), treated with powdered NaN_3 (580 mg, 8.92 mmol), and the resulting suspension stirred at 85 °C (bath temp.) under Ar for 6 h. The mixture was then cooled to rt, partitioned between EtOAc (20 mL) and H_2O (50 mL) and the layers separated. The aqueous phase was extracted with EtOAc (3x10 mL) and the combined organic phases washed with H_2O (20 mL), brine (10 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. *Transacetalization*. The resulting crude azide (253 mg) was taken up in MeOH (15 mL), treated with p-TsOH•H_2O (34 mg, 0.179 mmol), and stirred at a gently reflux for 17.5 h to effect exchange of ethylene glycol acetal groups for dimethyl acetals. The reaction mixture was then cooled to rt, treated with sat. aq. $NaHCO_3$ (1.0 mL) and ca. 80% of MeOH solvent removed *in vacuo*. The flask contents were then partitioned between EtOAc (30 mL) and H_2O (30 mL) and the layers separated. The aqueous phase was extracted with EtOAc (2x15 mL) and the combined organic phases washed with H_2O (20 mL), brine (10 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 35% EtOAc in hexanes) to afford the desired azidobisacetal **20** (168 mg, 0.466 mmol, 52%) as a colorless oil: $[\alpha]_D^{14} = -4.7$ (c = 0.28, $CHCl_3$); IR (neat) 2932, 2105, 1456, 1365, 1192, 1131, 1056, 954 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (1H, dd, *J* = 2.5, 0.6 Hz), 7.54 (1H, dd, *J* = 8.3, 2.6 Hz), 7.32 (1H, dd, *J* = 8.3, 0.6 Hz), 4.50 (1H, dd, *J* = 6.8, 4.6 Hz), 4.01 (1H, dd, *J* = 8.2, 3.6 Hz), 3.315 (3H, s), 3.310 (3H, s), 3.24 (3H, s), 3.22 (3H, s), 2.23 (1H, dd, *J* = 14.1, 8.3 Hz), 1.87 (1H, ddm, *J* = 14.1, 3.5 Hz), 1.70-1.61 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7 (0), 150.0 (1), 138.4 (1), 135.6 (0), 124.5 (1), 102.5 (1), 102.4 (1), 63.3 (CDN_3, 1:1:1 multiplet, $^1J_{CD}$ ~ 20 Hz), 53.9 (3),

53.8 (3), 53.3 (3), 53.0 (3), 43.0 (CDR, 1:1:1 multiplet, $^1J_{CD}$ = 18.7 Hz), 36.1 (2), 34.3 (2) ppm; HRMS (EI) *m/z* 360.15220 (calcd. for $C_{15}H_{21}D_2{}^{35}ClN_4O_4$: 360.15333).



20: $C_{15}H_{21}D_2ClN_4O_4$ (360.83)

S2: $C_{11}H_9D_2ClN_4O_2$ (268.70)

21: $C_{15}H_{14}D_2ClF_3N_2O$ (334.76)

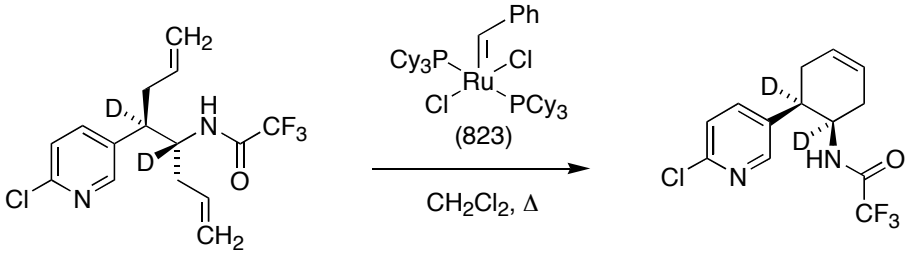
Diene 21: *Acetal hydrolysis.* A biphasic mixture of the bisacetal (19 mg, 52.7 μmol) in $CHCl_3$-H_2O (2:1, 1.5 mL) at rt was treated with CF_3CO_2H (0.5 mL) and stirred vigorously for 2 h. After this time, the reaction mixture was partitioned between EtOAc (10 mL) and H_2O (5 mL) and carefully shaken with sat. aq. $NaHCO_3$ (5 mL). The layers were separated and the aqueous phase extracted with EtOAc (2x5 mL). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4) then concentrated *in vacuo* to afford 16 mg of dialdehyde **S2** as a colorless oil which was used immediately in the subsequent step. *Wittig-Staudinger reaction.* While the acetal hydrolysis step was in progress, methylenetriphenylphosphorane was prepared by the addition of n-BuLi (75 μL, 2.13 M in hexanes, 0.160 mmol) to a stirred suspension of methyltriphenylphosphonium iodide (69 mg, 0.171 mmol) in anhydrous THF (1 mL) at 0 °C under Ar. The resulting deep yellow solution of phosphorane was allowed to stir for 1.5 h, then cooled to –10 °C and treated with the freshly prepared dialdehyde **S2** (16 mg, ≤ 52.7 μmol) in anhydrous THF (1 mL). The reaction mixture immediately became a pale yellow suspension and was allowed to warm to rt during the next 1.5 h. The resulting orange suspension was heated at a gentle reflux for 45 min, then cooled to rt and treated with Et_3N (110 μL, d = 0.726, 80 mg, 0.7911 mmol) followed by neat $(CF_3CO)_2O$ (TFAA, 73 μL, d = 1.511, 110 mg, 0.524 mmol). After stirring at rt for 17.5 h, the reaction mixture was partitioned between EtOAc (10 mL) and H_2O (5 mL) and the layers separated. The aqueous phase was extracted with EtOAc (5 mL) and the combined organic phases washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford 91 mg of a dark brown residue. Separation of the desired diene from this complex mixture of non-polar and polar components* was acheived by column chromatography (SiO_2, eluting with 15-20% EtOAc in hexanes) resulting in the isolation of **21** (2.2 mg, 6.6 μmol, 12%) as a colorless oil.

Limited data for unstable dialdehyde **S2**: colorless oil; IR (neat) 2922, 2101, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, br s), 9.71 (1H, br s), 8.30 (1H, dm, *J* = 2.6 Hz), 7.55 (1H, dd, *J* =

8.3, 2.6 Hz), 7.33 (1H, d, *J* = 8.3 Hz), 3.10 (1H, d, *J* = 18.0 Hz), 2.89 (1H, d, *J* = 18.3 Hz), 2.68 (1H, d, *J* = 18.8 Hz), 2.56 (1H, d, *J* = 18.5 Hz) ppm.

Data for diene **21**: colorless oil; $[\alpha]_D^{22} = -15.7$ (c = 0.07, $CHCl_3$); IR (neat) 3292, 2923, 1718, 1456, 1164, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H, d, *J* = 2.5 Hz), 7.49 (1H, dd, *J* = 8.3, 2.6 Hz), 7.34 (1H, d, *J* = 8.3 Hz), 6.00 (1H, br s), 5.63 (1H, ddt, *J* = 17.4, 9.9, 6.5 Hz), 5.53 (1H, ddt, *J* = 17.2, 10.4, 6.4 Hz), 5.15 (1H, dm, *J* = 10.3 Hz), 5.05 (1H, dm, *J* = 17.5 Hz), 4.98 (1H, dm, *J* = 9.5 Hz), 4.96 (1H, dm, *J* = 17.0 Hz), 2.54 (1H, dd, *J* = 14.7, 7.0 Hz), 2.40 (1H, dd, *J* = 14.5, 7.0 Hz), 2.28 (1H, ddm, *J* = 14.6, 6.3 Hz), 1.92 (1H, dd, *J* = 14.7, 8.0 Hz) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.3 ($CF_3\underline{C}ONHR$, q, $^2J_{CF}$ = 36.8 Hz), 150.7 (0), 150.1 (1), 138.3 (1), 134.6 (0), 134.4 (1), 132.1 (1), 124.7 (1), 120.1 (2), 118.4 (2), 115.9 (CF_3, q, $^1J_{CF}$ = 285.6 Hz), 36.5 (2), 35.7 (2) ppm {2xCDR signals not observed}; HRMS (CI+) *m/z* 335.1104 (calcd. for $C_{15}H_{15}D_2{}^{35}ClF_3N_2O$: 335.1107).

*Note: addition of 2 equiv. of methylenetriphenylphosphorane to azidodialdehyde **S2** (anywhere between –78 °C to 0 °C) did not result in its conversion to the expected azidodiene. Evidentally, a rapid reaction consumes the azide functional group that likely results (in part) in the ultimate generation of an iminophosphorane (quenching of which with TFAA gives the desired trifluoro-acetamide). Other as yet unidentified non-polar adducts (<5% of mass) were also generated from the above transformation; however, the vast bulk of the mass balance was very polar material (possibly polymeric) which could not be easily eluted from the SiO_2 chromatography column.



21: $C_{15}H_{14}D_2ClF_3N_2O$ (334.76)

22: $C_{13}H_{10}D_2ClF_3N_2O$ (306.71)

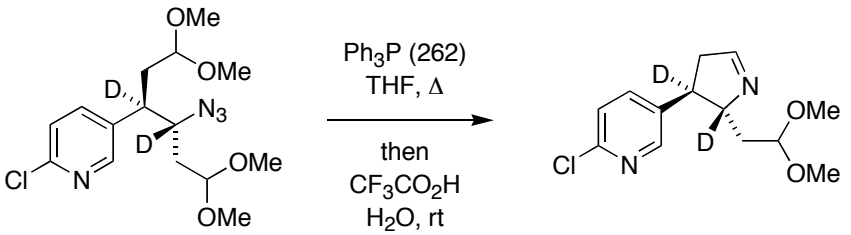
Cyclohexene 22: A stirred solution of diene **21** (1.4 mg, 4.2 μmol) in CH_2Cl_2 (0.5 mL) under Ar was heated to a gentle reflux then treated with a freshly prepared dilute solution of Grubbs' 1st generation olefin metathesis catalyst (50 μL, 8.5 mM in CH_2Cl_2, 0.43 μmol, 10 mol%).[S9] Heating of the reaction mixture was continued for 45 min and then it was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 25% EtOAc in hexanes) to afford the desired cyclohexene (**22**, 1.1 mg, 3.6 μmol, 85%) as a colorless oil: $[\alpha]_D^{22} = +39.0$ (c

S9. Schwab, P. E.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.

= 0.10, $CHCl_3$); IR (neat) 3275, 2924, 1717, 1701, 1559, 1540, 1459, 1216, 1185, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, d, *J* = 2.6 Hz), 7.53 (1H, dd, *J* = 8.3, 2.6 Hz), 7.29 (1H, d, *J* = 8.3 Hz), 6.00 (1H, br s), 5.95 (1H, dm, *J* = 10.2 Hz), 5.80 (1H, dm, *J* = 10.2 Hz), 2.68 (1H, dm, *J* = 18.8 Hz), 2.48 (1H, dm, *J* = 17.8 Hz), 2.40 (1H, dm, *J* = 18.6 Hz), 1.97 (1H, dm, *J* = 17.4 Hz) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.9 ($CF_3\underline{C}ONHR$, q, $^2J_{CF}$ = 38.9 Hz), 150.7 (0), 149.4 (1), 138.3 (1), 135.1 (0), 126.7 (1), 124.5 (1), 124.4 (1), 115.8 (CF_3, q, $^1J_{CF}$ = 287.3 Hz), 47.5 (CDN, 1:1:1 multiplet, $^1J_{CD}$ = 21.0 Hz), 37.7 (CDPy, 1:1:1 multiplet, $^1J_{CD}$ = 20.5 Hz), 29.1 (2), 28.3 (2) ppm; HRMS (CI+) *m/z* 307.0796 (calcd. for $C_{13}H_{11}D_2{}^{35}ClF_3N_2O$: 307.0794).

Spectroscopic data for **22** are in excellent agreement (baring the expected differences) with those previously reported by Corey and co-workers for the all protio isotopomer, as follows: [S10] $[\alpha]_D{}^{23}$ = + 113.5 (c = 1.57, $CHCl_3$);* IR (neat) 3299, 3028, 2919, 1708, 1564, 1451, 1208 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (1H, d, *J* = 2.5 Hz), 7.55 (1H, dd, *J* = 8.4, 2.6 Hz), 7.29 (1H, d, *J* = 8.3 Hz), 6.09 (1H, br s), 5.98-5.90 (1H, m), 5.82-5.76 (1H, m), 4.55-4.49 (1H, m), 3.38-3.32 (1H, m), 2.75-2.66 (1H, m), 2.52-2.38 (2H, m), 2.02-1.95 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4 ($CF_3\underline{C}ONHR$, q, $^2J_{CF}$ = 36.1 Hz), 150.7, 149.3, 138.1, 135.1, 126.6, 124.4, 124.3, 115.6 (CF_3, q, $^1J_{CF}$ = 285.4 Hz), 47.8, 38.2, 29.3, 28.3 ppm.

*Note: discrepancy in optical rotation magnitudes for isotopomers of **22** is a likely artifact of the significantly different concentrations employed for each measurement (c = 0.10 vs. 1.57).



20: $C_{15}H_{21}D_2ClN_4O_4$ (360.83)

23: $C_{13}H_{15}D_2ClN_2O_2$ (270.75)

Iminoacetal 23: A stirred solution of azide **20** (22 mg, 61.0 μmol) in anhydrous THF (1.5 mL) at rt under Ar was treated with Ph_3P (24 mg, 91.6 μmol) and the resulting mixture heated at a gentle reflux for 3 h. The mixture was then cooled to rt, treated with H_2O (0.5 mL) followed by TFA (0.5 mL), and stirred vigorously at rt for 3 h. After this time, EtOAc (10 mL) and H_2O (5 mL) were added and the pH of the aqueous phase adjusted to 12-13 by addition of 2 M aq. KOH (ca. 7 mL). The layers were shaken and separated and the aqueous phase extracted with EtOAc (2x5 mL). The combined organic phases were washed with H_2O (5 mL) and brine (5 mL), then dried

S10. Data reproduced from the microfiche based Supporting Information associated with: Corey, E. J.; Loh, T.-P.; AchyuthaRao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600-5602.

(Na_2SO_4) and concentrated *in vacuo*. Purification of the residue (48 mg) by column chromatography (SiO_2, eluting with 4% MeOH in CH_2Cl_2) afforded iminoacetal **23** (9 mg, 33.2 μmol, 54%) as a colorless oil: $[\alpha]_D^{18}$ = + 53.3 (c = 0.30, $CHCl_3$); IR (neat) 2930, 2829, 1560, 1459, 1365, 1124, 1104, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, dd, *J* = 2.6, 0.7 Hz), 7.65 (1H, br s), 7.45 (1H, dd, *J* = 8.2, 2.6 Hz), 7.28 (1H, dd, *J* = 8.3, 0.7 Hz), 4.62 (1H, dd, *J* = 7.0, 4.5 Hz), 3.30 (3H, s), 3.27 (3H, s), 3.14 (1H, d, *J* = 18.0 Hz), 2.60 (1H, d, *J* = 17.7 Hz), 1.93 (1H, dd, *J* = 13.8, 4.4 Hz), 1.85 (1H, dd, *J* = 13.8, 6.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9 (1), 149.9 (0), 149.0 (1), 138.7 (0), 137.2 (1), 124.6 (1), 103.0 (1), 53.8 (3), 53.2 (3), 52.9 (CDN, 1:1:1 multiplet, $^1J_{CD}$ ~ 20 Hz), 46.3 (2), 44.1 (CDPy, 1:1:1 multiplet, $^1J_{CD}$ = 19.2 Hz), 38.9 (2) ppm; HRMS (CI+) *m/z* 271.1172 (calcd. for $C_{13}H_{16}D_2{}^{35}ClN_2O_2$: 271.1182).