Supporting Information

The Total Synthesis of Phalarine via a Stereospecific Pictet–Spengler Reaction: Transfer of Chirality from L-Tryptophane

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General. All non-aqueous reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. All reagents were commercially available and used without further purification from Sigma-Aldrich, Acros, and Strem, unless indicated otherwise. Tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), benzene (PhH), and toluene ($PhCH_3$) were obtained from a dry solvent system (activated alumina columns, positive Argon pressure). All other solvents were used as received in Sure/Seal bottles (Aldrich). Triethylamine (Et_3N), pyridine, and chlorotrimethylsilane (TMSCl) were distilled from CaH_2 immediately prior to use. Reactions were magnetically stirred and monitored by thin layer chromatography on Merck silica gel 60-F_{254} coated 0.25 mm plates. All reactions were performed at room temperature (ca 23 ºC) unless indicated otherwise. Flash chromatography was performed with E. Merck silica gel (60, particle size 40-63 µm), unless indicated otherwise. Yields reported are for isolated, spectroscopically pure compounds. Microwave experiments were performed using a Biotage microwave reactor. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DRX-500 MHz or Bruker AVII+-600 MHz spectrometer. Chemical shifts are given in ppm relative to the residual undeuterated solvent peak and coupling constants are given in Hz. Residual solvent peaks were referenced as follows: acetone-d_6 (^{1}H, δ = 2.05 ppm; ^{13}C, δ = 29.9 ppm), $CDCl_3$ (^{1}H, δ = 7.26 ppm; ^{13}C, δ = 77.0 ppm), and DMSO-d_6 (^{1}H, δ = 2.50 ppm; ^{13}C, δ = 39.5 ppm). Multiplicities and peak shape are labeled as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, pt = pseudo triplet, dd = doublet of doublets, etc. IR spectra were recorded on a JASCO FTIR-6100 instrument. Optical rotations were measured on a JASCO P-2000 polarimeter. Low resolution mass spectra were acquired at the Sloan–Kettering Institute Core Facility on a Perkin Elmer Sciex API 100 spectrometer.

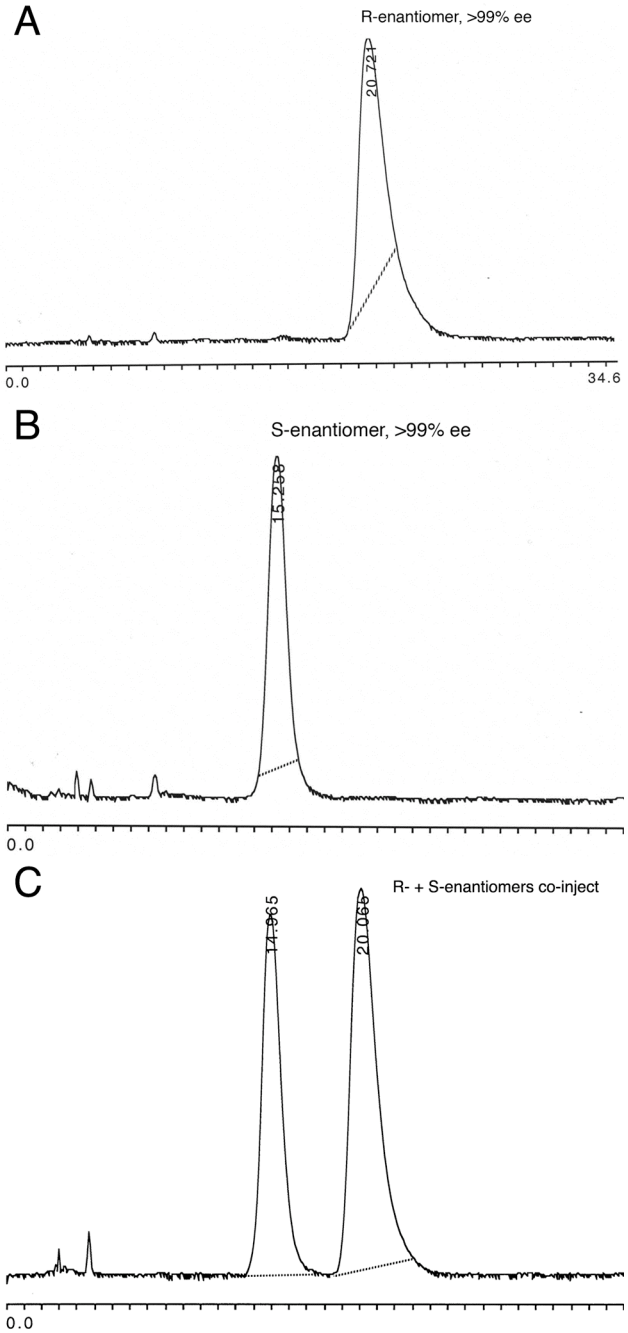
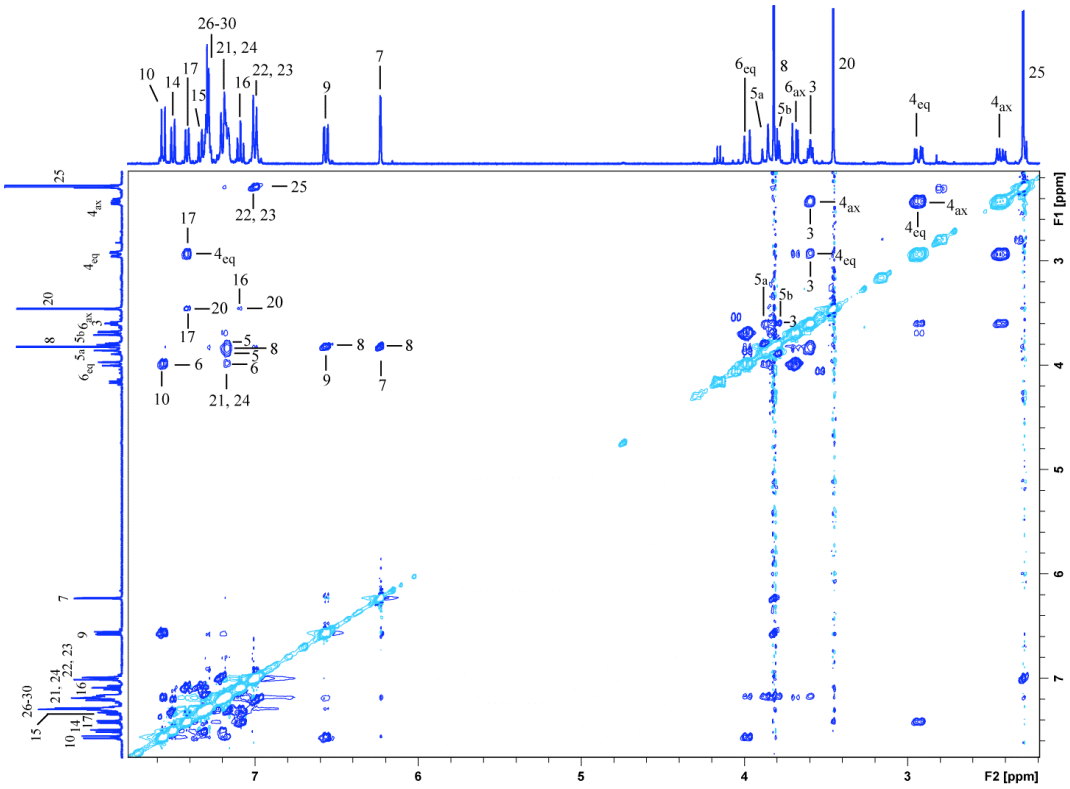
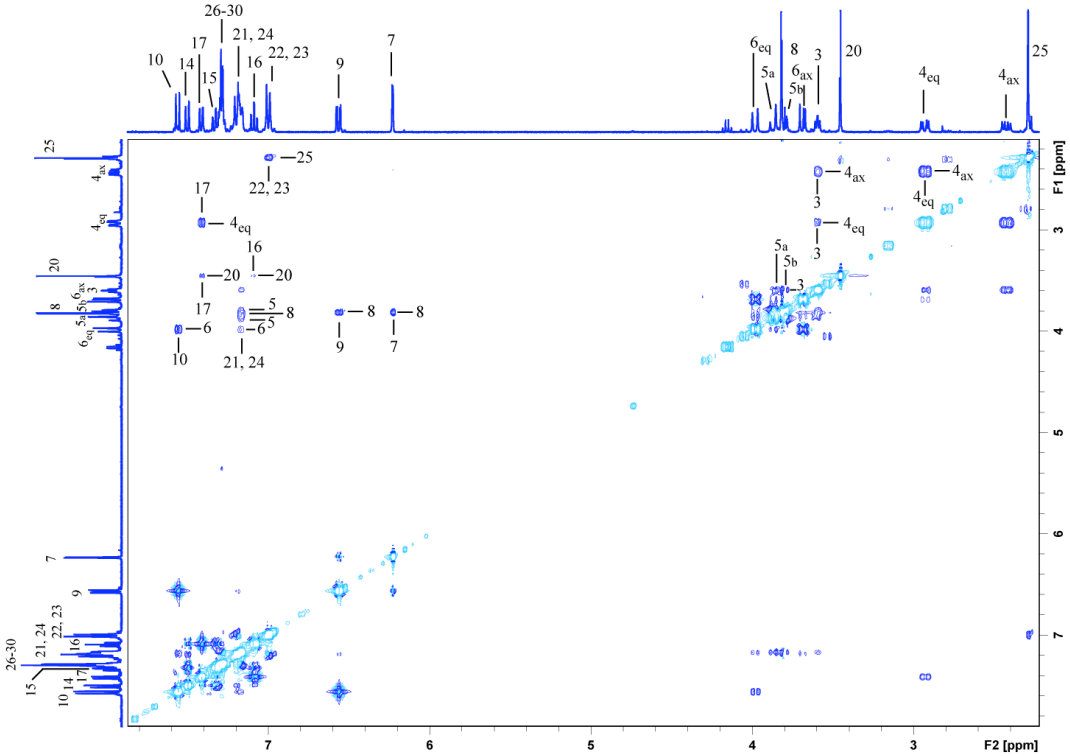


Figure S1. Analytical chiral HPLC of isolated asymmetric Pictet–Spengler reaction products (Chiracel OD-H column, 5% IPA/hexanes isocratic, 1.2 ml/min, λ = 280 nm): A) compound *ent*-**41** (*R*-enantiomer at tryptophane center), R_t = 20.7 min, B) compound **41** (*S*-enantiomer at tryptophane center), R_t = 15.3 min, C) co-inject of compounds **41** and *ent*-**41**, R_t = 15.0, 20.1 min respectively.

A. 700ms NOESY



B. 500ms NOESY



C. 250ms NOESY

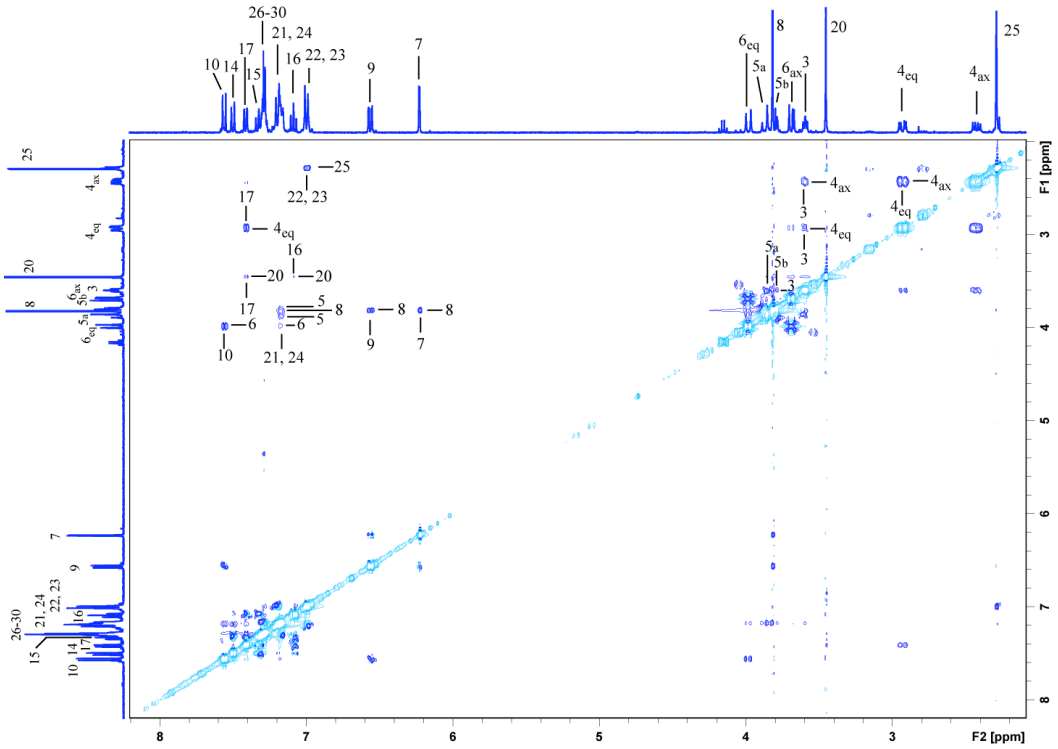
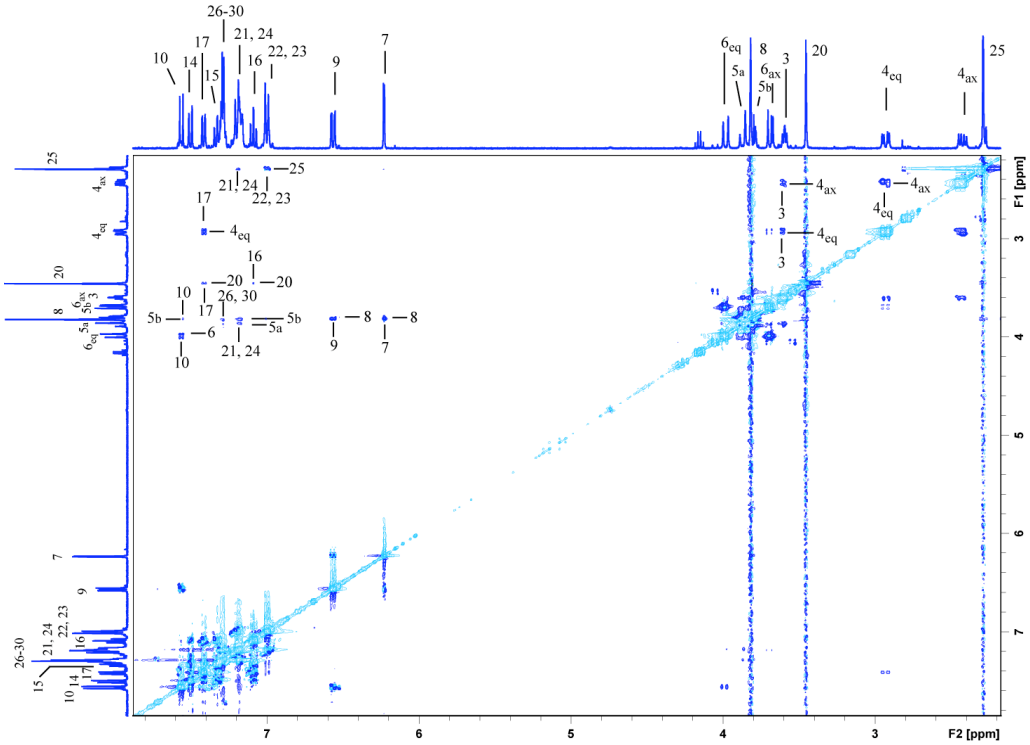


Figure-S2. The (a) 700, (b) 500, and (c) 250 ms NOESY 2D spectra of **41** in $CDCl_3$ solvent. No artifacts or spin diffusion peaks were observed.

A. 200ms T-ROESY



B. 100ms T-ROESY

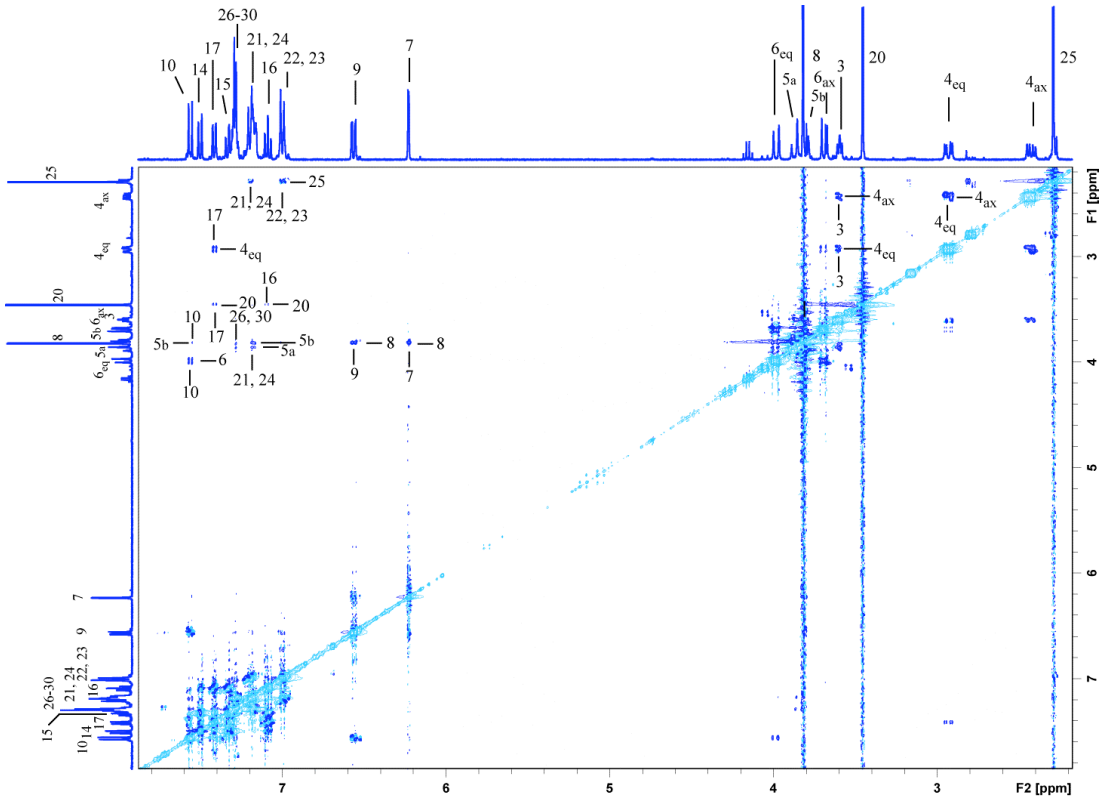
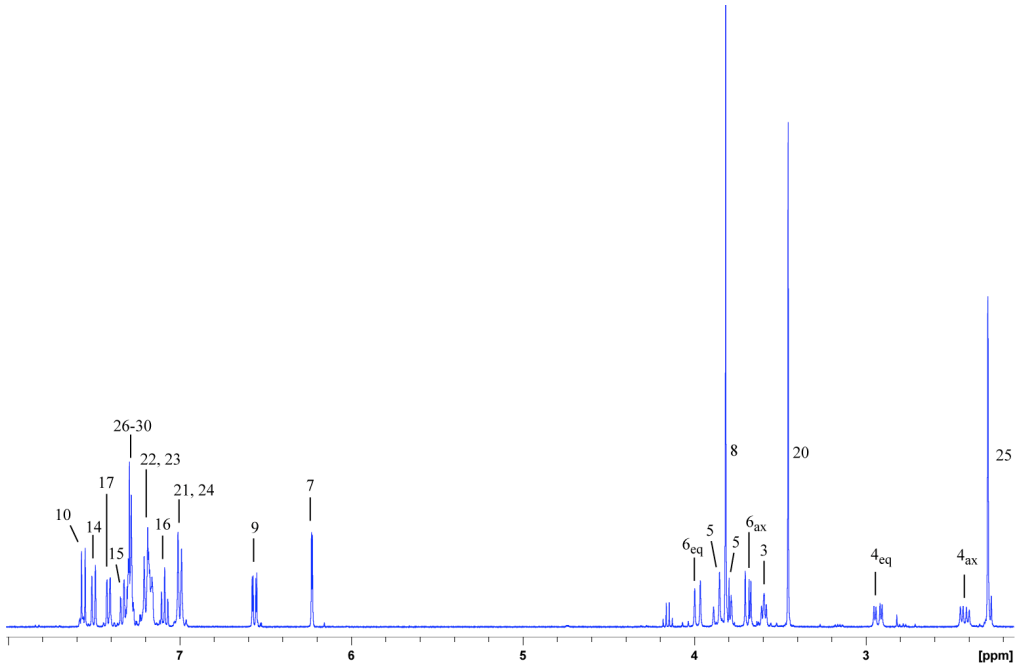
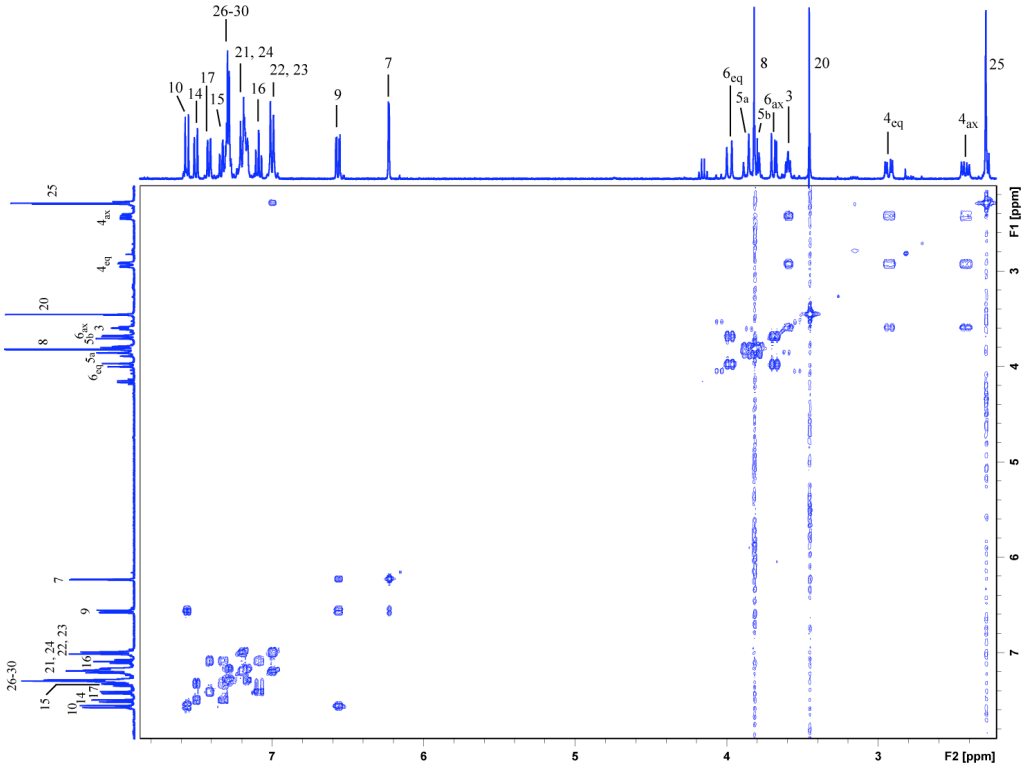


Figure-S3. (a) 200 ms T-ROESY and (b) 100 ms T-ROESY spectra of **41**. No artifacts or spin diffusion peaks were observed.

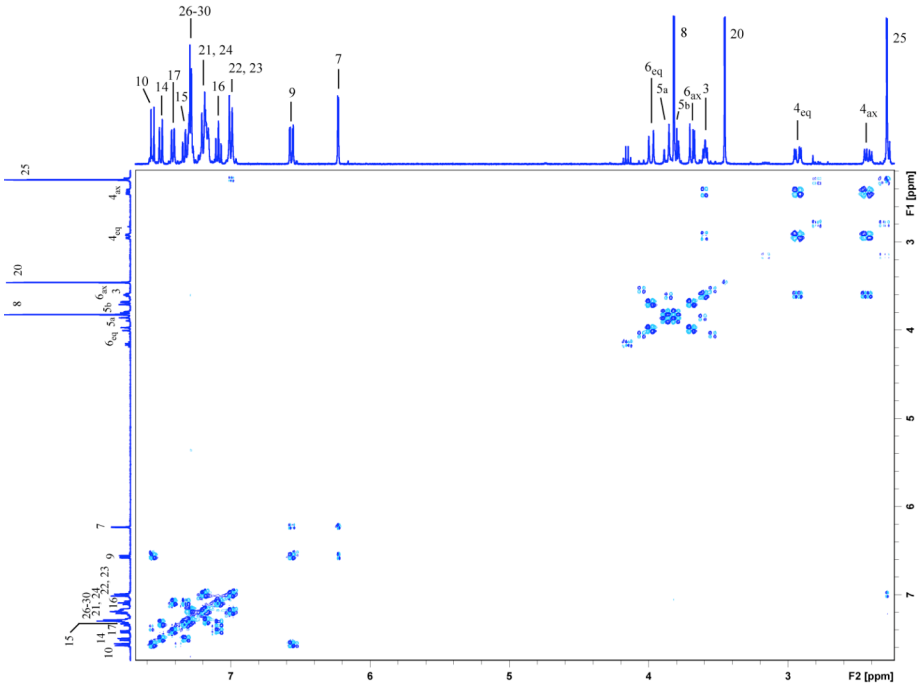
A. ^{1}H-NMR Spectrum of **41**



B. ^{1}H-^{1}H Gradient COSY Spectrum of **41**



C. ^{1}H-^{1}H DQF- COSY Spectrum of **41**



D. ^{13}C-^{1}H Gradient HSQC with Multiplicity Editing of **41**

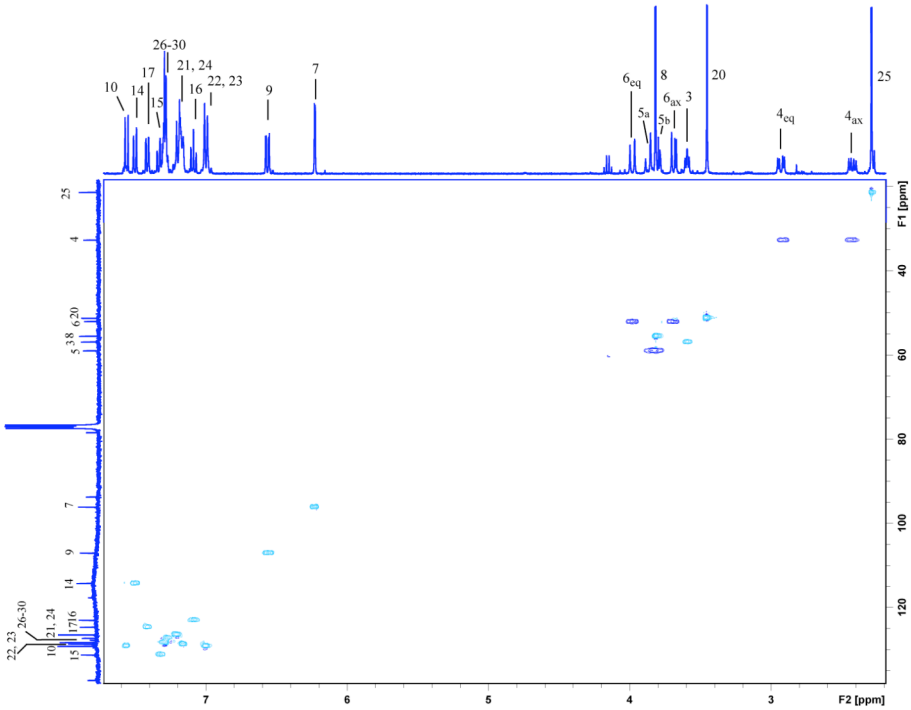


Figure-S4. (a) ^{1}H-NMR, (b) ^{1}H-^{1}H gradient COSY, (c) ^{1}H-^{1}H DQF- COSY, (d) ^{13}C-^{1}H Gradient HSQC with multiplicity editing spectra of **41**.

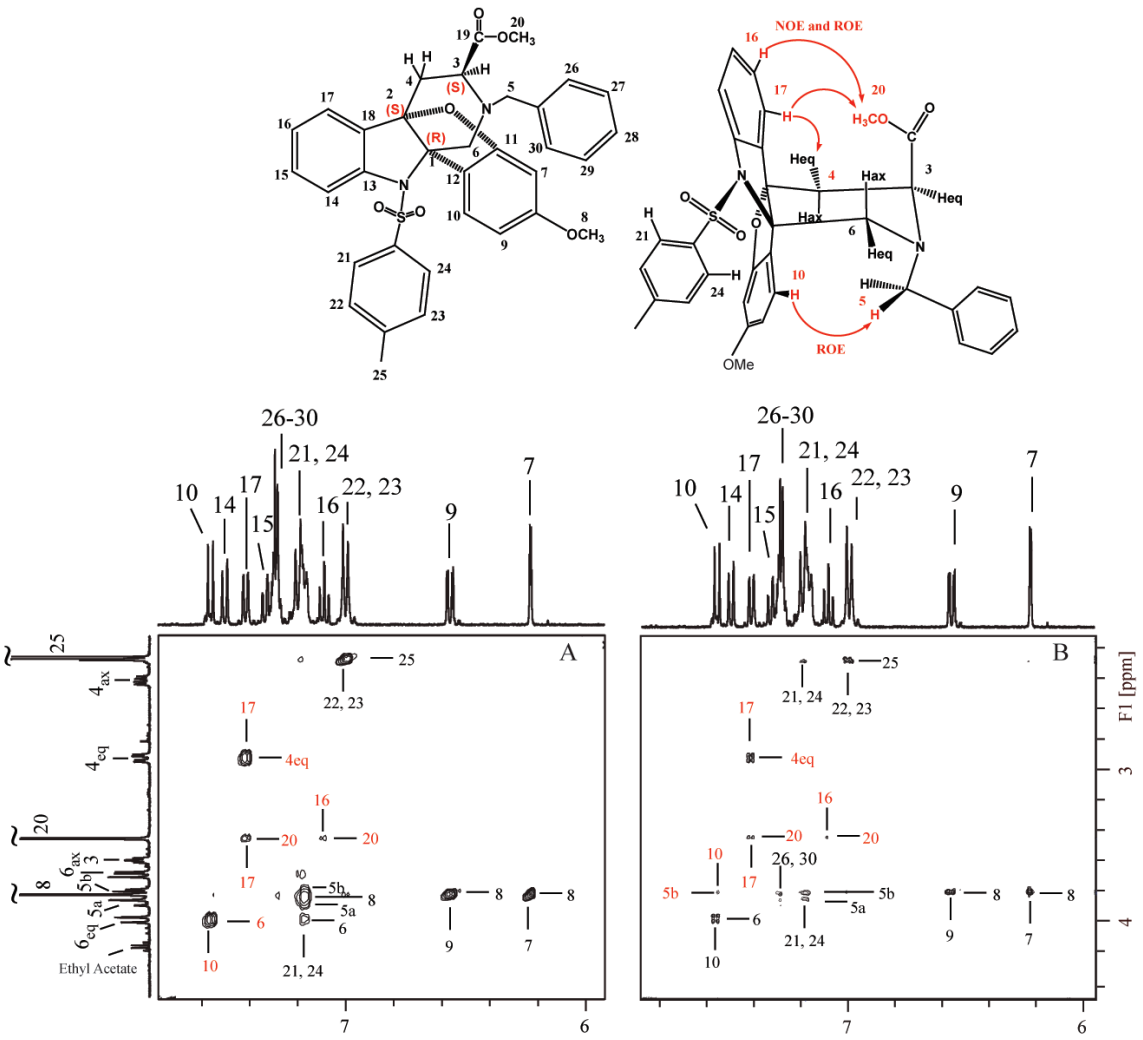


Figure S5. The structure of **41** with key NOEs and ROEs indicated by red arrows (top). The aromatic to aliphatic section of the 700 ms NOESY 2D spectra (A) and the 200 ms T-ROESY[1] 2D spectra (B) of **41** are shown. Both experiments were acquired in $CDCl_3$ solvent, and key NOE and ROE correlations are indicated in red. The T-ROESY[1] 2D experiment was used to suppress any errant TOCSY correlations, and no spin diffusion artifacts were observed in either of the two types of experiments. The resulting NOESY and T-ROESY experiments allowed for the unequivocal proton assignments of **41** and the determination of its relative stereochemistry as *SSR*.

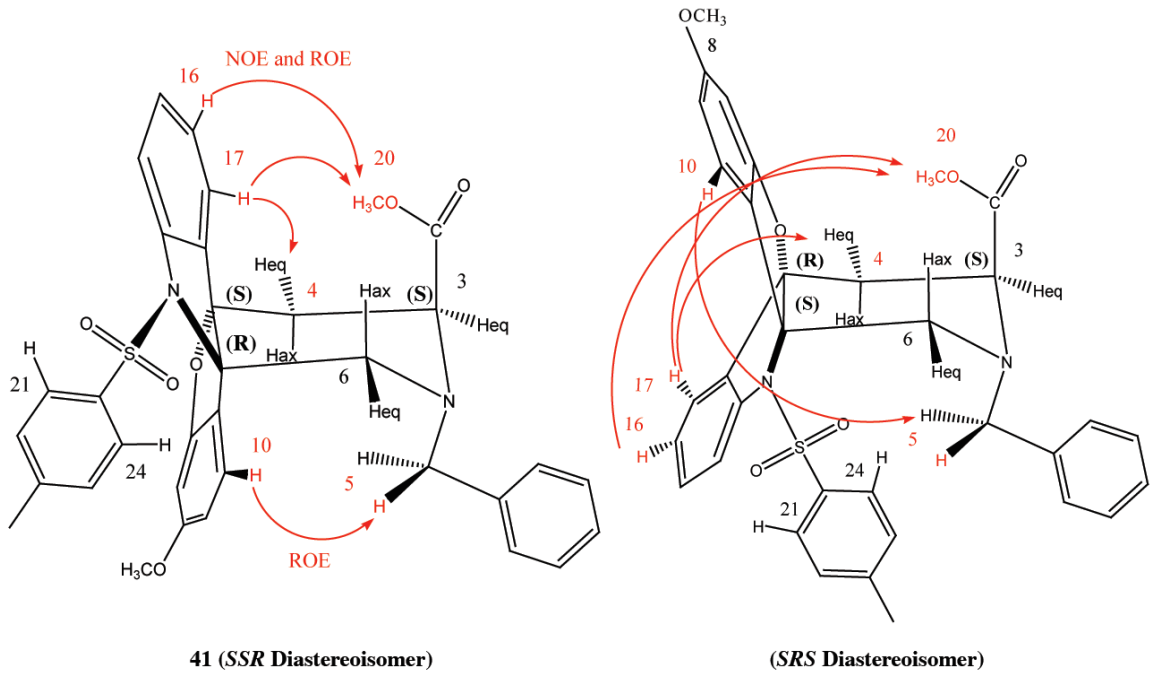
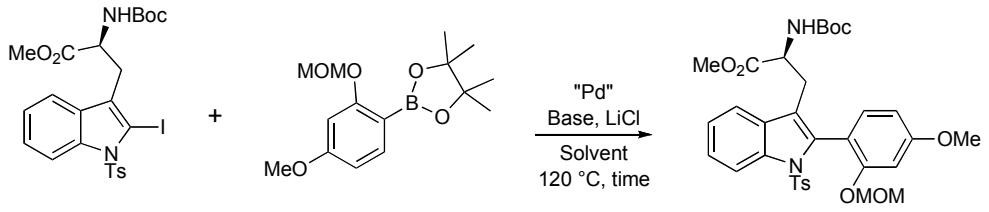


Figure S6. Key observed NOE and ROE interactions. These data are consistent with the *SSR* diastereoisomer (left) of **41** and inconsistent with the *SRS* diastereoisomer (right).

Validation of NMR methods: Because several key NOE and ROE correlations were at the $1/r^6$ limit (r = the distance between two nuclei) their intensities were weak. To validate the observed correlations and ensure they were not artifacts or spin diffusion peaks, several measures were taken. First, NOESY experiments with mixing times of 700, 500 and 250 ms were conducted. Examination of our data revealed that the NOE data follow the expected pattern, indicating that no artifacts were present.[2] Similarly, no artifacts were observed in ROESY experiments conducted at 200 and 100 ms.

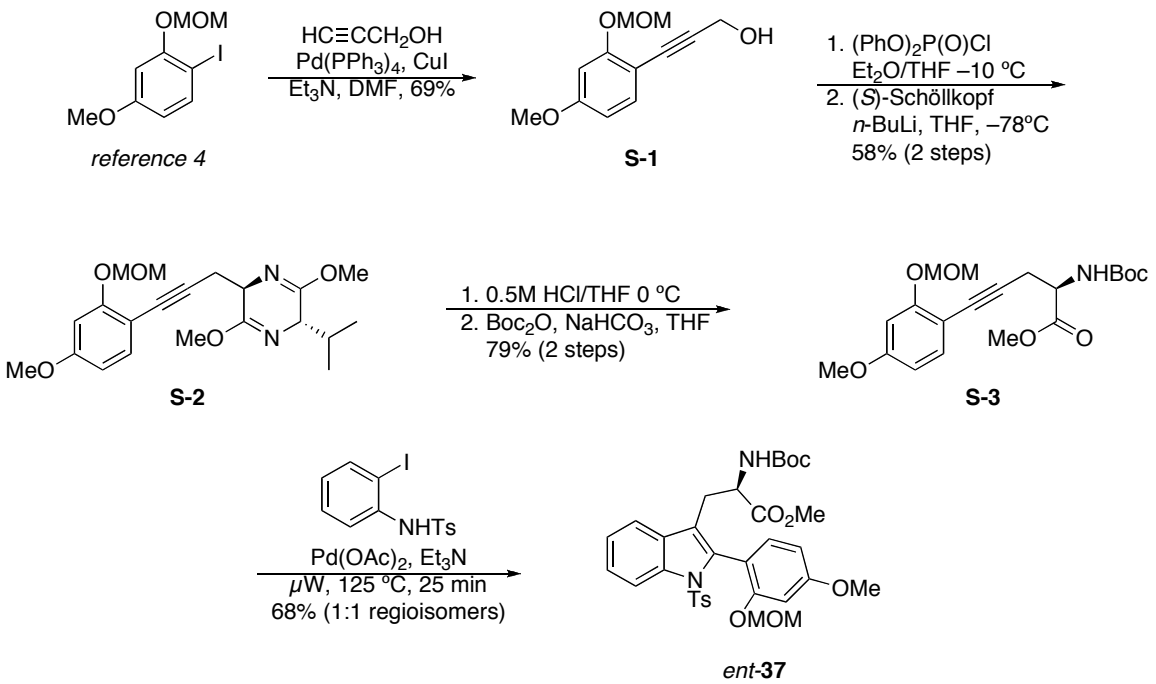
Alternatively, spin diffusion can occur during long mixing times providing incorrect distance information resulting in misleading results. In NOESY spectra of small molecules, spin diffusion is observed as off-diagonal peaks with the same phase as the diagonal peaks; additionally, these peaks tend to disappear with decreasing mixing time.[3] In T-ROESY experiments, spin diffusion peaks are always opposite in phase to the ROE peaks and can be readily identified.[3] The NOESY and T-ROESY data for **41** did not exhibit any of these properties of spin diffusion. Furthermore, the T-ROESY pulse sequence used in this study incorporates modified pulses that remove any artifacts, such as any inherent TOCSY correlations that may be falsely assigned as true ROE correlations.[1] Based on the discussion above, the NOE and ROE correlations observed in the experiments conducted in this study were considered valid, the results of the NOESY and T-ROESY experiments were complementary, and structure **41** was assigned with *SSR* stereochemistry.



35 **36** **37**

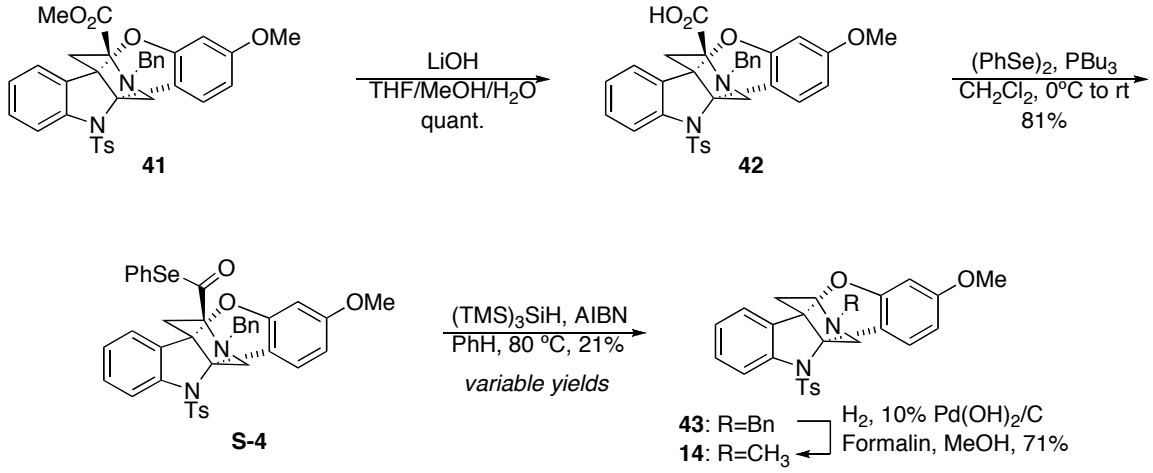
Run	"Pd"	Ligand	Base	Solvent	Time	Result
1	$Pd(PPh_3)_4$	---	Na_2CO_3	DMF:H_2O	7 h	25%
2	Pd_2dba_3	(*o*-tol)$_3$P	"	"	12 h	16% (48% brsm)
3	"	(2-furyl)$_3$P	"	"	19 h	trace
4	"	Cy_3P	"	"	"	trace
5	"	Bu_3P	"	"	"	trace
6	"	DIPHOS	"	"	"	31% (37% brsm)
7	"	"	"	"	0.5 h	trace
8	"	"	K_2CO_3	"	"	31%
9	"	"	Et_3N (no LiCl)	"	"	trace
10	"	"	Na_2CO_3	DME:H_2O	4 h	trace
11	"	"	K_2CO_3	"	"	34%
12	"	"	Cs_2CO_3	"	"	12%
13	"	"	K_3PO_4	"	1 h	32%
14	$Pd(PPh_3)_4$ (50 mol%)		Na_2CO_3	"	"	48% (180 mg scale)
15	$Pd(PPh_3)_4$ (50 mol%)		Na_2CO_3	"	"	41% (992 mg scale)
16	$Pd(PPh_3)_4$ (50 mol%)		Na_2CO_3	"	3 h	53% (5.842 g scale)

Table S1. Optimization of Suzuki coupling to prepare **37**. Reaction with the boronic acid of **36** (prepared by periodate cleavage of the boronate ester) under the optimized condition (run 16) provided **37** in 45% yield.

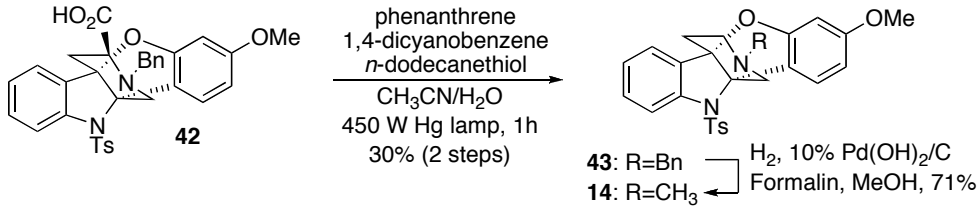


Scheme S1. First generation preparation of *ent*-**37**.

Method 1

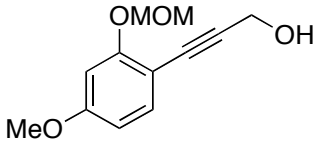


Method 2



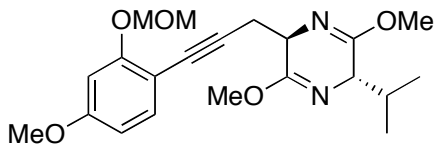
Scheme S2. First and second generation approach to junction compound **14**; either method did not erode the stereointegrity of the product as determined by measurement of the optical rotation of **43**.

Experimental Methods



S-1

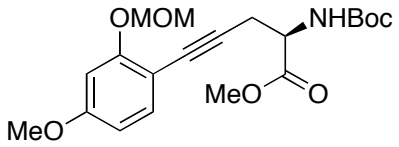
A solution of compound 1-iodo-4-methoxy-2-(methoxymethoxy)benzene[4] (250 mg, 0.850 mmol) in anhydrous, degassed DMF (2.0 mL) was treated with anhydrous, distilled Et_3N (540 µL, 4.60 equiv.), CuI (37 mg, 2.80 equiv.), $Pd(PPh_3)_4$ (125 mg, 0.13 equiv.), and propargyl alcohol (140 µL, 2.80 equiv.). The reaction mixture was heated to 60 ºC in an oil bath for 3h. After cooling to room temperature, the reaction was diluted with EtOAc (20 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was back-extracted with EtOAc (2 x 10 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl (30 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, 30% EtOAc/hexanes) afforded the product as a pale orange oil (130 mg, 189 mg theoretical, 69%): ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.29 (d, 1H, J = 8.5 Hz), 6.72 (d, 1H, J = 2.4 Hz), 6.57 (dd, 1H, J = 2.4, 8.5 Hz), 5.24 (s, 2H), 4.40 (d, 2H, J = 6.0 Hz), 4.19 (t, 1H, J = 6.0 Hz), 3.78 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 161.9, 160.1, 135.1, 107.9, 107.0, 103.2, 95.9, 92.0, 81.2, 56.4, 55.9, 51.3; IR (neat) ν_{max} 3404, 2958, 2836, 2223, 1698, 1607, 1574, 1456, 1393, 1297, 1242, 1218, 1155, 1126, 1077, 1041, 999 cm^{-1}; LRMS (ESI-TOF) m/z 245.0 ([M + Na]$^+$, $C_{12}H_{14}O_4$ requires 245.1).



S-2

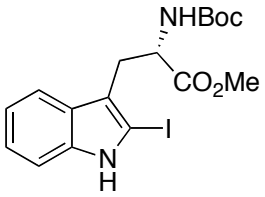
The preparation of **S-1** closely follows the procedure developed by Cook for asymmetric alkylations of silyl acetylides.[5] Compound **S-1** (65 mg, 0.292 mmol) in anhydrous Et_2O (1.0 mL) at –5 ºC was treated with diphenyl chlorophosphate (60 µL, 1.00 equiv.) and KOH (25 mg, 1.50 equiv.) and stirred overnight. The cold reaction suspension was filtered and the eluent was concentrated to an orange-red oil that was azeotropically dried with anhydrous PhH prior to drying under high vacuum for 30 min. At this stage, a solution of the (*S*)-Schöllkopf reagent[6] (80 µL, 1.50 equiv.) in anhydrous THF (1.0 mL) at –78 ºC was treated with *n*-BuLi (0.440 µL, 1.1 M solution in hexanes, 1.65 equiv.) and permitted to age for 10 min. The dried phosphate as a solution in anhydrous THF (0.50 mL) was slowly added to the anionic Schöllkopf solution and stirred at –78 ºC for 1h. The reaction was permitted to warm to room temperature and quenched by the addition of H_2O. The THF was removed by rotary evaporation and the resultant

aqueous layer was extracted with EtOAc (2 x 10 mL). The resultant organic layer was washed with H_2O (20 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, 30% EtOAc/hexanes) provided the product (66 mg, 114 mg theoretical, 58%): $[\alpha]^{25}_D$ –21.0 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.20 (d, 1H, *J* = 8.5 Hz), 6.67 (d, 1H, *J* = 2.4 Hz), 6.48 (dd, 1H, *J* = 2.4, 8.5 Hz), 5.19 (s, 2H), 4.21 (m, 1H), 4.07 (t, 1H, 3.3 Hz), 3.78 (s, 3H), 3.74 (s, 6H), 3.50 (s, 3H), 3.01 (dd, 1H, *J* = 4.5, 16.6 Hz), 2.93 (dd, 1H, *J* = 4.5, 16.6 Hz), 2.30 (m, 1H), 1.06 (d, 3H, *J* = 6.9 Hz), 0.69 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.1, 162.1, 160.5, 159.1, 134.4, 107.3, 106.9, 102.4, 95.2, 88.5, 78.5, 61.0, 56.3, 55.6, 55.0, 52.7, 31.6, 26.6, 19.3, 16.7; IR (neat) ν_{max} 2957, 1698, 1607, 1572, 1505, 1463, 1436, 1308, 1240, 1195, 1154, 1126, 1078, 1005, 924 cm^{-1}; LRMS (ESI-TOF) *m/z* 389.4 ([M + H]$^+$, $C_{21}H_{28}N_2O_5$ requires 389.2). **For *S*-enantiomer:** $[\alpha]^{25}_D$ +19.7 (*c* 1.0, EtOAc).



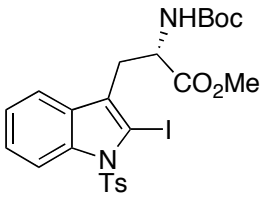
S-3

A solution of **S-2** (66 mg, 0.170 mmol) in THF (4.0 mL) at 0 ºC was treated with 0.5 N HCl (4.0 mL). After 2.5 h, the reaction was quenched by addition of saturated NH_4OH (4.0 mL) and diluted with CH_2Cl_2 (15 mL). The organic phase was washed with H_2O (15 mL), dried over Na_2SO_4, and concentrated. The resultant crude amine was treated with $NaHCO_3$ (48 mg, 3.40 equiv.) and a solution of Boc_2O (128 mg, 3.40 equiv.) in THF (4.0 mL). The reaction was stirred at room temperature overnight. After concentrating the crude reaction mixture by rotary evaporation, flash chromatography (SiO_2, 25% EtOAc/hexanes) provided the product (54 mg, 66 mg theoretical, 82%): $[\alpha]^{25}_D$ –19.7 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.29 (d, 1H, *J* = 8.4 Hz), 6.70 (d, 1H, *J* = 2.4 Hz), 6.51 (dd, 1H, *J* = 2.4, 8.4 Hz), 5.59 (d, 1H, *J* = 8.4 Hz), 5.28 (s, 2H), 4.59 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.55 (s, 3H), 3.04 (dd, 1H, *J* = 4.2, 16.8 Hz), 2.95 (dd, 1H, *J* = 4.2, 16.8 Hz), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.7, 161.0, 159.3, 155.5, 134.0, 107.1, 106.0, 102.1, 95.0, 86.5, 80.3, 56.4, 55.7, 52.7, 52.5, 28.6, 24.2; IR (neat) ν_{max} 3381, 2974, 1749, 1716, 1607, 1571, 1506, 1366, 1217, 1159, 1126, 1078, 998, 924 cm^{-1}; LRMS (ESI-TOF) *m/z* 394.2 ([M + H]$^+$, $C_{20}H_{27}NO_7$ requires 394.2). **For *S*-enantiomer:** $[\alpha]^{25}_D$ +18.3 (*c* 1.0, EtOAc).



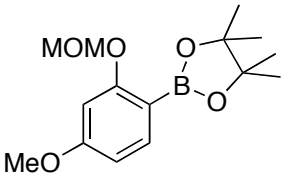
S-5

The crude primary amine **34** (320 mg, 0.930 mmol) provided by the procedure of Vicente[7] was treated with $NaHCO_3$ (117 mg, 1.50 equiv.) and a solution of Boc_2O (297 mg, 1.46 equiv.) in THF (9.3 mL). The reaction was stirred at room temperature overnight. After this time, the reaction mixture was concentrated and purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) to afford the product as a white foam (409 mg, 413 mg theoretical, 99%): $[\alpha]^{25}_D$ +13.0 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.46 (br s, 1H), 7.51 (d, 1H, *J* = 7.6 Hz), 7.26 (d, 1H, *J* = 8.4 Hz), 7.09 (m, 2H), 5.16 (d, 1H, *J* = 8.2 Hz), 4.66 (m, 1H), 3.69 (s, 3H), 3.22 (m, 2H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.7, 155.2, 139.0, 127.9, 122.6, 120.2, 118.2, 116.9, 111.6, 80.0, 79.6, 54.0, 52.7, 30.3, 28.6, 27.6; IR (neat) ν_{max} 3314, 2976, 2954, 2925, 2854, 1693, 1501, 1446, 1364, 1343, 1246, 1215, 1163, 1057, 1011 cm^{-1}; LRMS (ESI-TOF) *m/z* 467.1 ([M + Na]$^+$, $C_{17}H_{21}IN_2O_4$ requires 467.0).



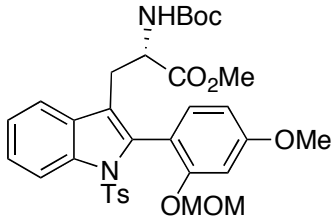
35

A solution of compound **S-5** (1.675 g, 3.770 mmol) in anhydrous CH_2Cl_2 (51 mL) was treated with freshly pulverized (important for reproducibility) NaOH (452 mg, 3.00 equiv.) and *n*-Bu_4NHSO_4 (1.278 g, 1.00 equiv.) and heated to reflux for 10 min. *p*-TsCl (2.156 g, 3.00 equiv.) was added and the reaction was vigorously stirred at reflux for 2 h. The crude reaction mixture was washed with saturated aqueous $NaHCO_3$ (50 mL) and the aqueous phase back-extracted with CH_2Cl_2 (30 mL). The combined organic phases were dried over Na_2SO_4, concentrated, and purified by flash chromatography (SiO_2, 25-35% EtOAc/hexanes gradient elution) to provide the product as a yellow-white foam (1.844 g, 2.256 g theoretical, 82%): $[\alpha]^{25}_D$ –11.9 (*c* 1.0, EtOAc); ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.25 (d, 1H, *J* = 7.8 Hz), 7.77 (d, 2H, *J* = 8.4 Hz), 7.61 (d, 1H, *J* = 7.2 Hz), 7.32 (d, 2H, *J* = 8.4 Hz), 7.27 (m, 2H), 6.20 (d, 1H, *J* = 8.4 Hz), 4.44 (m, 1H), 3.48 (s, 3H), 3.21 (m, 2H), 2.35 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 172.6, 156.0, 146.5, 139.9, 136.3, 131.8, 130.9, 129.2, 128.0, 125.9, 124.6, 120.0, 116.4, 82.7, 79.5, 54.1, 52.5, 31.6, 21.6; IR (neat) ν_{max} 3396, 2976, 2930, 1742, 1714, 1596, 1498, 1441, 1370, 1288, 1249, 1218, 1178, 1105, 1087, 1060, 1020, 965 cm^{-1}; LRMS (ESI-TOF) *m/z* 621.1 ([M + Na]$^+$, $C_{24}H_{27}IN_2O_6S$ requires 621.1).



36

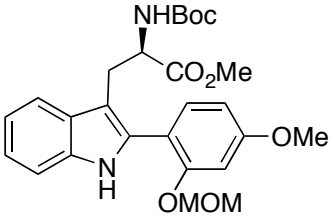
A solution of 1-iodo-4-methoxy-2-(methoxymethoxy)benzene[4] (3.382 g, 11.50 mmol) in anhydrous CH_3CN (46.0 mL, 0.25 M) under Ar was treated sequentially with pinacolborane (2.50 mL, 1.5 equiv), Et_3N (4.80 mL, 3.0 equiv), and $PdCl_2$(dppf) (252 mg, 0.03 equiv). The reaction mixture was heated to 90 °C in a sealed tube and allowed to stir at this temperature for 1 h. After this time, the reaction mixture was cooled to 25 °C and concentrated. Flash chromatography (SiO_2, 15% EtOAc/hexanes) provided the product as a light red, viscous oil that solidified upon standing (3.079 g, 3.383 g theoretical, 91%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.66 (d, 1H, *J* = 7.8 Hz), 6.59 (m, 2H), 5.19 (s, 2H), 3.81 (s, 3H), 3.52 (s, 3H), 1.34 (s, 12H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.7, 163.5, 138.3, 107.3, 102.7, 95.6, 83.3, 56.3, 55.4, 25.0; IR (neat) ν_{max} 2975, 2929, 2837, 1606, 1572, 1508, 1463, 1429, 1397, 1379, 1350, 1321, 1286, 1271, 1250, 1215, 1149, 1086, 1067, 1033, 1004, 964, 922 cm^{-1}; LRMS (ESI-TOF) *m/z* 317.3 ([M + Na]$^+$, $C_{15}H_{23}BO_5$ requires 317.2).



37

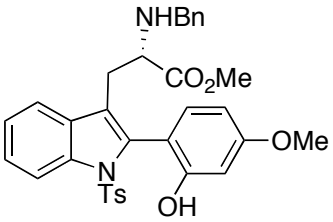
A vessel containing compound **35** (5.842 g, 9.76 mmol) under Ar was treated with **36** (4.06 g, 1.4 equiv), LiCl (998 mg, 2.4 equiv), Na_2CO_3 (4.147 g, 4.0 equiv), and $Pd(PPh_3)_4$ (5.640 g, 0.5 equiv). The solids were dissolved in DME:H_2O (98 mL, 10:1, degassed, 0.1 M) and the vessel sealed. The reaction mixture was heated to 120 °C and allowed to stir vigorously for 3 h. After this time, the reaction mixture was cooled to 25 °C and the dark brown/black crude solution was quenched by pouring into saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 x 75 mL). The combined organic phases were washed with saturated aqueous NaCl (75 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, 5–10% EtOAc/PhMe, gradient elution) afforded the product (light yellow solid) as a 1.3:1.0 mixture of rotamers (3.329 g, 6.235 g theoretical, 53%): $[\alpha]^{25}_D$ –4.7 (*c* 1.0, EtOAc); ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.2 (d, 2H, *J* = 8.4 Hz), 7.68 (d, 1H, *J* = 7.2 Hz), 7.58 (d, 1H, *J* = 7.8 Hz), 7.48 (m, 4H), 7.36 (t, 2H, *J* = 7.8 Hz), 7.28 (m, 6H), 7.13 (d, 1H, *J* = 8.4 Hz), 7.08 (d, 1H, *J* = 8.4 Hz), 6.85 (d, 1H, *J* = 1.8 Hz), 6.84 (d, 1H, *J* = 1.8 Hz), 6.68 (m, 1H), 6.66 (m, 1H), 5.92 (d, 1H, *J* = 7.8 Hz), 5.81 (d, 1H, *J* = 7.8 Hz), 5.16 (m, 2H), 5.11 (m, 2H), 4.36 (m, 1H), 4.28 (m, 1H), 3.88 (s, 6H), 3.50 (s, 3H), 3.41 (s, 9H), 3.05 (dd, 1H, *J* = 6.0, 14.4 Hz), 2.92 (m, 3H), 2.34 (s, 6H), 1.31 (s, 9H), 1.21 (s, 9H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 173.0, 172.93, 162.9, 158.9, 158.5, 156.0, 145.8, 145.7, 137.6, 137.5, 137.22, 137.16, 136.2, 135.9, 134.4, 134.1, 132.1, 131.35, 131.27, 130.52, 130.50, 129.7, 128.0, 127.7, 125.39, 125.36, 124.21, 124.17, 120.5, 120.3, 119.3, 119.2,

115.9, 115.8, 113.8, 113.7, 106.4, 106.3, 102.04, 102.01, 95.69, 95.62, 79.55, 79.47, 72.2, 56.52, 56.46, 55.8, 54.5, 52.25, 52.21, 28.57, 28.54, 28.1, 27.8, 21.5, 19.5; IR (neat) ν_{max} 2973, 2930, 2839, 1739, 1712, 1620, 1596, 1575, 1504, 1449, 1367, 1242, 1175, 1157, 1133 1068, 999, 923 cm^{-1}; LRMS (ESI-TOF) *m/z* 661.3 ([M + Na]$^+$, $C_{33}H_{38}N_2O_9S$ requires 661.2).



S-6

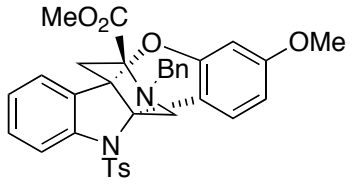
From the above protocol (using the *R*-enantiomer of **35**), the detosylated product was isolated in small quantities (only *R*-enantiomer characterized): $[\alpha]^{25}_{D}$ –25.9 (*c* 1.0, EtOAc); ^{1}H NMR (acetone-d_6, 600 MHz) δ 10.11 (br s, 1H), 7.60 (d, 1H, *J* = 7.8 Hz), 7.36 (d, 1H, *J* = 7.8 Hz), 7.34 (d, 1H, *J* = 7.2 Hz), 7.10 (apparent t, 1H, *J* = 7.2 Hz), 7.05 (apparent t, 1H, *J* = 7.2 Hz), 6.90 (d, 1H, *J* = 2.4 Hz), 6.72 (dd, 1H, *J* = 2.4, 7.8 Hz), 5.68 (d, 1H, *J* = 7.2 Hz), 5.20 (m, 2H), 4.44 (m, 1H), 3.86 (s, 3H), 3.48 (s, 3H), 3.36 (s, 3H), 3.30 (dd, 1H, *J* = 6.0, 14.4 Hz), 3.19 (dd, 1H, *J* = 6.0, 14.4 Hz), 1.31 (s, 9H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 173.5, 162.1, 157.3, 156.0, 137.2, 134.3, 133.4, 129.5, 122.2, 119.7, 119.4, 116.5, 111.9, 108.5, 107.9, 103.6, 96.3, 79.4, 56.5, 55.9, 55.2, 52.1, 28.6, 28.2; IR (neat) ν_{max} 3372, 2976, 1742, 1706, 1614, 1558, 1501, 1462, 1438, 1391, 1370, 1294, 1242, 1218, 1160, 1057, 1011, 995, 923 cm^{-1}; LRMS (ESI-TOF) *m/z* 507.3 ([M + Na]$^+$, $C_{26}H_{32}N_2O_7$ requires 507.2).



39

A flask containing compound **37** (1.509 g, 2.36 mmol) was cooled to 0 °C under Ar and treated with HCl/dioxane (24.0 mL, 4 N, 0.1 M). The reaction mixture was allowed to stir for 1 h. After this time, the reaction mixture was quenched by pouring over ice (ca 25 mL) and adding solid $NaHCO_3$ until the solution was rendered basic. The layers were separated and the aqueous phase extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with saturated aqueous NaCl (15 mL) and dried over Na_2SO_4. The crude amine was concentrated and briefly dried *in vacuo*; **amine intermediate** (compound **38**): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.34 (d, 1H, *J* = 8.4 Hz), 7.72 (apparent t, 1H, *J* = 8.4 Hz), 7.53 (d, 2H, *J* = 8.4 Hz), 7.50 (m, 1H), 7.42 (m, 1H), 7.32 (m, 1H), 7.12 (d,

2H, *J* = 7.8 Hz), 6.98 (d, 1H, *J* = 8.4 Hz), 6.56 (s, 1H), 6.52 (dd, 1H, *J* = 2.4, 8.4 Hz), 3.84 (s, 3H), 3.77 (m, 5H), 3.17 (br m, 1H), 2.41 (br m, 1H), 2.33 (s, 3H). The crude amine was taken up in anhydrous MeOH (24.0 mL. 0.1 M) and treated sequentially with benzaldehyde (1.20 mL, 5.0 equiv) and 3 Å MS (ca 8 g, 5 equiv. w/w) under Ar. The reaction mixture was allowed to stir for 30 min and then treated with $NaCNBH_3$ (1.490 g, 10 equiv). The reaction mixture was allowed to stir for 30 min. After this time, the reaction mixture was filtered over Celite and concentrated. The residue was taken up in EtOAc (25 mL) and quenched by pouring into saturated aqueous $NaHCO_3$ (25 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 x 25 mL). The combined organic phases were washed with saturated aqueous NaCl (15 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, 35–60% EtOAc/hexanes gradient elution containing 1% Et_3N) afforded product (light yellow solid) as a 1.4:1.0 mixture of rotamers (932 mg, 1.38 g theoretical, 67%): ***N*-benzyl product 39**: $[\alpha]^{25}_D$ +11.2 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.24 (d, 1H, *J* = 8.4 Hz), 8.18 (d, 1H, *J* = 8.4 Hz), 7.61 (d, 2H, *J* = 8.4 Hz), 7.52 (d, 2H, *J* 8.4 Hz), 7.45 (d, 1H, *J* 13.8 Hz), 7.42 (d, 1H, *J* = 13.8 Hz), 7.33 (m, 2H), 7.20 (m, 6H), 7.12 (m, 4H), 7.05 (m, 3H), 6.97 (d, 1H, *J* = 8.4 Hz), 6.93 (d, 2H, *J* = 7.2 Hz), 6.52 (m, 3H), 6.46 (dd, 1H, *J* = 2.4, 8.4 Hz), 3.84 (s, 6H), 3.63 (m, 1H), 3.57 (s, 3H), 3.53 (m, 1H), 3.49 (br m, 5H), 3.39 (m, 2H), 2.97 (dd, 1H, *J* = 4.8, 14.4 Hz), 2.93 (m, 1H), 2.80 (m, 1H), 2.63 (dd, 1H, *J* = 9.6, 14.4 Hz), 2.27 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.1, 144.8, 137.3, 136.0, 134.8, 129.5, 129.4, 129.2, 128.8, 128.6, 128.4, 128.2, 127.9, 127.6, 127.2, 125.1, 123.8, 118.5, 116.0, 106.8, 103.7, 102.7, 58.1, 57.5, 55.5, 53.0, 52.9, 52.4, 30.2, 21.7; IR (neat) ν_{max} 2954, 2936, 2848, 1739, 1608, 1572, 1528, 1504, 1449, 1376, 1346, 1294, 1218, 1175, 1160, 1130. 1078, 1038, 1002, 926 cm^{-1}; LRMS (ESI-TOF) *m/z* 585.3 ([M + H]$^+$, $C_{33}H_{32}N_2O_6S$ requires 585.2).

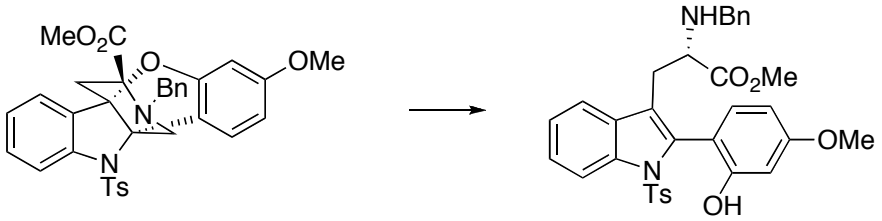


41

A solution of compound **39** (918 mg, 1.57 mmol) in anhydrous $PhCH_3$ (157 mL, 0.01 M) at 25 °C under Ar was treated with 37% aqueous formaldehyde (152 µL, 1.3 equiv), CSA (365 mg, 1.0 equiv), and 3 Å MS (ca 7.0 g, 7.7 equiv. w/w). The reaction mixture was heated to 120 °C in a sealed tube for 2 h. After this time, the reaction mixture was cooled to 25 °C and quenched by pouring into saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with saturated aqueous NaCl (75 mL) and dried over Na_2SO_4. Product was concentrated to provide a white foam that required no purification (881 mg, 937 mg theoretical, 94%): $[\alpha]^{25}_D$ –46.1 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.45 (d, 1H, *J* = 8.4 Hz), 7.39 (d, 1H, *J* = 8.4 Hz), 7.31 (d, 2H, *J* = 7.2 Hz), 7.22

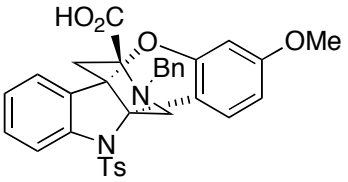
(m, 2H), 7.09 (d, 2H, J = 7.8 Hz), 7.06 (m, 2H), 6.98 (apparent t, 1H, J = 7.2 Hz), 6.89 (d, 2H, J = 7.8 Hz), 6.45 (dd, 1H, J = 2.4, 8.4 Hz), 6.12 (d, 1H, J = 2.4 Hz), 3.87 (d, 1H, J = 12.0 Hz), 3.76 (d, 1H, J = 13.8 Hz), 3.70 (m, 5H), 3.68 (d, 1H, J = 12.0 Hz), 3.50 (m, 1H), 3.35 (s, 3H), 2.82 (dd, 1H, J = 4.8, 14.4 Hz), 2.32 (dd, 1H, J = 4.8, 14.4 Hz), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.6, 161.7, 143.4, 142.8, 137.5, 131.5, 129.4, 129.3, 128.9, 128.5, 128.0, 127.5, 126.7, 124.9, 123.2, 117.9, 114.5, 107.2, 96.3, 93.9, 78.7, 59.2, 57.1, 55.8, 52.3, 51.5, 33.0, 29.9, 21.6; IR (neat) ν_{max} 2925, 2852, 1736, 1705, 1663, 1599, 1497, 1478, 1466, 1444, 1351, 1293, 1239, 1194, 1173, 1157, 1103, 1027, 969 cm^{-1}; LRMS (ESI-TOF) *m/z* 597.3 ([M + H]$^+$, $C_{34}H_{32}N_2O_6S$ requires 597.2). **For *R*-enantiomer:** $[\alpha]^{25}_D$ +46.7 (*c* 1.0, EtOAc).

Condition for Crystallization of 41: crystals of the *(S)*-enantiomer, as white needles, were obtained from flash chromatography (10-20% acetone/hexanes gradient elution containing 5% Et_3N). Melting Point: 199 ^oC.



41 → 39

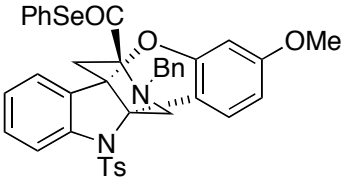
Retro-Mannich protocol: A solution of compound **41** (9.3 mg, 15.59 μmol) in anhydrous $PhCH_3$ (1.60 mL, 0.01 M) under Ar was treated with CSA (3.7 mg, 1.0 equiv). The reaction mixture was heated to 120 °C in a sealed tube for 2 h. After this time, the reaction mixture was cooled to 25 °C and quenched by pouring into saturated aqueous $NaHCO_3$ (5 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 x 5 mL). The combined organic phases were washed with saturated aqueous NaCl (3 mL), dried over Na_2SO_4, and concentrated. The product was recovered as an off-white foam that required no purification (9.1 mg, 9.1 mg theoretical, quantitative), and which matched compound **39** in all respects.



42

A solution of compound **41** (780 mg, 1.31 mmol) in THF:MeOH:H_2O (131 mL, 2:1:1, 0.01 M) was treated with LiOH•H_2O (550.3 mg, 10 equiv). The reaction mixture was allowed to stir for 1.5 h. [Note: If the reaction was not complete after this time, H_2O (25% of the reaction volume) was added and the reaction

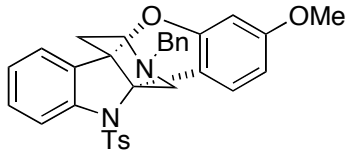
continued to stir for 1 h. This procedure was repeated until TLC analysis (SiO_2, 50% EtOAc–hexanes) showed that the reaction was complete.] After this time, the reaction mixture was quenched by careful addition of aqueous 1 N HCl until the pH of the solution was approximately 6.5. The aqueous solution was saturated with solid NaCl, the phases separated, and the aqueous phase was extracted with EtOAc (2 x 75 mL). The combined organic phases were washed with saturated aqueous NaCl (15 mL), dried over Na_2SO_4, and concentrated. The product was recovered as an off-white foam that required no purification (761 mg, 762 mg theoretical, quantitative): $[\alpha]^{25}_D$ –48.3 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.76 (d, 1H, *J* = 9.0 Hz), 7.39 (m, 3H), 7.32 (m, 3H), 7.25 (m, 5H), 7.06 (t, 1H, *J* = 7.2 Hz), 7.02 (d, 2H, *J* = 8.4 Hz), 6.53 (dd, 1H, *J* = 2.4, 8.4 Hz), 6.33 (d, 1H, *J* = 2.4 Hz), 3.95 (d, 1H, *J* = 13.2 Hz), 3.78 (s, 3H), 3.75 (m, 1H), 3.65 (d, 1H, *J* = 13.8 Hz), 3.57 (d, 1H, *J* = 13.8 Hz), 3.51 (t, 1H, *J* = 6.0 Hz), 2.71 (dd, 1H, *J* = 6.0 Hz), 2.63 (dd, 1H, *J* = 6.0, 14.4 Hz), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.0, 161.4, 144.0, 141.9, 136.9, 135.7, 131.8, 129.7, 129.4, 129.3, 129.2, 128.6, 127.6, 127.2, 125.5, 124.0, 117.2, 113.9, 108.2, 96.4, 93.6, 79.1, 60.6, 58.8, 55.8, 52.9, 21.6; IR (neat) ν_{max} 2925, 2847, 1732, 1623, 1598, 1533, 1498, 1462, 1449, 1350, 1294, 1262, 1234, 1163, 1089, 1026 cm^{-1}; LRMS (ESI-TOF) *m/z* 583.3 ([M + H]$^+$, $C_{33}H_{30}N_2O_6S$ requires 583.2).



S-4

A solution of compound **42** (5.0 mg, 0.0086 mmol) in anhydrous CH_2Cl_2 (450 µL) was treated with diphenyldiselenide (400 µL of a solution of 9.5 mg in 950 µL anhydrous CH_2Cl_2, 0.013 mmol, 1.5 equiv) and cooled in a 0 ºC bath. The reaction mixture was treated with PBu_3 (6.5 µL, 3.0 equiv.), stirred at 0 ºC for 10 min, warmed to room temperature, and stirred overnight. The crude reaction mixture was diluted with EtOAc (5 mL) and washed with H_2O (5 mL). The aqueous layer was back-extracted with EtOAc (5 mL), the combined organic layers were dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, 10-60% EtOAc/hexanes gradient elution) provided the product as a light yellow solid (5.0 mg, 6.2 mg theoretical, 81%); $[\alpha]^{25}_D$ –28.3 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.81 (d, 1H, *J* = 8.4 Hz), 7.47 (d, 2H, *J* = 9.6 Hz), 7.41 (m, 3H), 7.33 (m, 8H), 7.23 (d, 2H, *J* = 7.8 Hz), 7.06 (m, 3H), 6.56 (dd, 1H, *J* = 2.4, 8.4 Hz), 6.39 (d, 1H *J* = 2.4 Hz), 4.07 (d, 1H, *J* = 14.4 Hz), 3.81 (s, 3H), 3.79 (m, 2H), 3.55 (m, 1H), 3.39 (d, 1H, *J* = 14.4 Hz), 2.78 (dd, 1H, *J* = 5.4, 14.4 Hz), 2.57 (dd, 1H, *J* = 9.6, 14.4 Hz), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 209.3, 163.0, 161.6, 143.8, 141.6, 137.11, 137.08, 136.1, 136.0, 131.7, 131.2, 129.8, 129.7, 129.4, 129.3, 129.2, 128.8, 128.7, 127.94, 127.86, 127.6, 127.3, 125.1, 123.7, 118.1, 114.1, 108.1, 96.1, 93.7, 79.2, 67.7, 60.5, 55.8, 50.7, 34.7, 29.9, 21.6; IR (neat) ν_{max} 3066, 2921, 2849, 1712, 1619, 1601, 1496, 1480, 1462,

1443, 1354, 1292, 1240, 1163, 1089, 1030, 962.8/ cm^{-1}; LRMS (ESI-TOF) *m/z* 723.3 ($[M + H]^+$, $C_{39}H_{34}N_2O_5SSe$ requires 723.1).



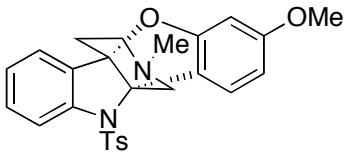
43

A stirred solution of **42** (158 mg, 0.27 mmol) in CH_2Cl_2 (5.4 mL) at ambient temperature was treated with iodobenzene diacetate (192 mg, 0.60 mmol) and iodine (41 mg, 0.16 mmol). The reaction mixture was stirred for 30 min under an argon atmosphere and then treated with $NaCNBH_3$ (170 mg, 2.71 mmol). The reaction mixture was allowed to stir for 30 min and then quenched by the addition of a saturated solution of $Na_2S_2O_3$ (3 mL). The aqueous layer was extracted with EtOAc (2 X 10 mL), and the organic layer was washed with a saturated solution of $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, 10-20% acetone/hexanes gradient elution containing 5% Et_3N) afforded product (93 mg, 146 mg theoretical, 64% yield) as a white solid: $[\alpha]^{25}_D$ –59.1 (*c* 6.6, CH_2Cl_2); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.64 (d, 1H, *J* = 7.8 Hz), 7.52 (d, 1H, *J* = 8.4 Hz), 7.44 (d, 1H, *J* = 7.2 Hz), 7.4 (apparent t, 1H, *J* = 7.2 Hz), 7.32–7.23 (m, 5H), 7.13, (apparent t, 1H, *J* = 7.2 Hz), 6.99 (d, 2H, *J* = 7.8 Hz), 6.90 (d, 2H, *J* = 8.4 Hz), 6.59 (dd, 1H, *J* = 2.4, 8.4 Hz), 6.12 (d, 1H, *J* = 2.4 Hz), 4.19 (dd, 1H *J* = 1.8, 12.0 Hz), 3.79 (s, 3H), 3.61 (d, 1H, *J* = 13.2 Hz), 3.52 (d, 1H, *J* = 13.2 Hz), 2.72 (m, 1H), 2.67 (dd, 1H, *J* = 1.8, 12.0 Hz), 2.45 (d, 1H, *J* = 12.0 Hz), 2.24 (s, 3H), 2.02 (m, 1H), 1.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.4, 161.8, 143.3, 142.9, 138.0, 137.2, 131.4, 129.1, 129.0, 128.7, 128.3, 127.5, 127.2, 126.2, 124.2, 123.5, 117.2, 114.6, 106.7, 96.4, 95.0, 78.6, 61.6, 58.4, 55.5, 48.8, 30.8, 21.3; IR (neat) ν_{max} 2919, 2840, 1734, 1619, 1603, 1496, 1462, 1353, 1294, 1239, 1190, 1169, 1155, 1099, 1027, 1008, 952 cm^{-1}; LRMS (ESI-TOF) *m/z* 539.2 ($[M + H]^+$, $C_{32}H_{30}N_2O_4S$ requires 539.2).

Alternatively from 42: A solution of **42** (351 mg, 0.60 mmol) in degassed MeCN:H_2O (61 mL, 9:1, 0.01 M) in a pyrex flask at 25 °C under Ar was treated with phenanthrene (1.110 g, 97%, 10.0 equiv), 1,4-dicyanobenzene (773 mg, 10.0 equiv), and *n*-dodecanethiol (2.90 mL, 20.0 equiv). The reaction mixture was irradiated with a 450 W medium-pressure Hg lamp for 1 h. After this time, the reaction was diluted with EtOAc (75 mL) and washed with saturated aqueous NaCl (1 x 15 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (SiO_2, 2% EtOAc/$PhCH_3$) afforded the product (**43**, 84 mg, 324 mg theoretical, 30% for two steps) as an off-white solid.

Alternatively from S-4: A solution of **S-4** (5.2 mg, 7.21 μmol) in degassed PhH (800 μL, 0.01 M) at 25 °C under Ar was treated with AIBN (0.6 mg, 0.5 equiv) and $(TMS)_3SiH$ (10 μL, 4.0 equiv). The reaction mixture was heated to 80 °C (oil bath temp) in a sealed tube for 22 h. After this time, the reaction mixture was

cooled to 25 °C and concentrated. Preparative thin layer chromatography (SiO_2, 20 x 20 cm, 10% EtOAc/hexanes) afforded recovered starting material (2.2 mg) and the product (**43**, 0.8 mg, 3.9 mg theoretical, 21%, 36% based on recovered starting material) as a clear film.

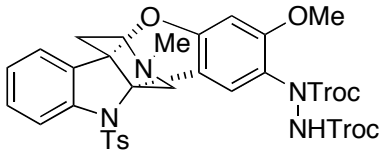


14

Junction Compound

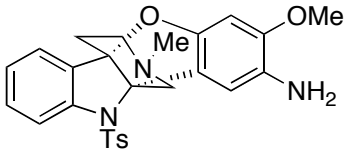
A solution of **43** (25.5 mg, 0.05 mmol) in EtOAc/MeOH (3:1, 4 mL) at ambient temperature was treated with 37% aqueous formaldehyde (50 □L, 0.71 mmol) and $Pd(OH)_2/C$(10.2 mg, 0.4 equiv. w/w). The reaction mixture was placed under an atm of H_2 and allowed to stir for 5 h. After this time, the reaction mixture was filtered over celite and concentrated. Flash chromatography (SiO_2, 10-20% acetone/hexanes gradient elution containing 5% Et_3N) afforded the product (19.0 mg, 21.9 mg theoretical, 87% yield) as a white solid: $[\alpha]^{25}_D$ –88.7 (*c* 8.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (d, 1H, *J* = 8.4 Hz), 7.63 (d, 1H, *J* = 8.2 Hz), 7.46 (d, 1H, *J* = 7.6 Hz), 7.39 (apparent t, 1H, *J* = 7.4 Hz), 7.14 (apparent t, 1H, *J* = 7.4 Hz), 7.03 (d, 2H, *J* = 8.4 Hz), 6.93 (d, 2H, *J* = 8.4 Hz), 6.61 (dd, 1H, *J* = 2.0, 8.4 Hz), 6.12 (d, 1H, *J* = 2.0 Hz), 4.23 (d, 1H, *J* = 11.2 Hz), 3.76 (s, 3H), 2.70 (m, 2H), 2.38 (d, 1H, *J* = 12.2 Hz), 2.32 (s, 3H), 2.25 (s, 3H), 2.00 (m, 1H), 1.80 (m, 1H); LRMS (ESI-TOF) *m/z* 463.3 ($[M + H]^+$, $C_{26}H_{26}N_2O_4S$ requires 463.2).

The following intermediates were prepared accorded to established protocols. The spectroscopic and chromatographic properties for each sample were identical to those of the corresponding known racemic sample.[8] Optical rotation values are reported below.



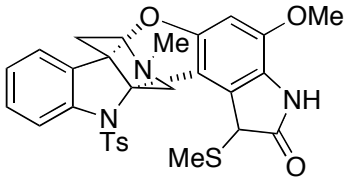
44

$[\alpha]^{25}_D$ –99.3 (*c* 3.4, CH_2Cl_2).



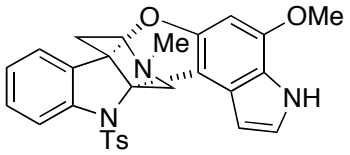
45

$[\alpha]^{25}_D$ –151.1 (*c* 0.7, CH_2Cl_2).



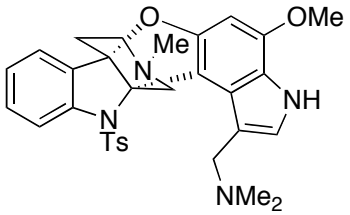
46

$[\alpha]^{25}_{D}$ –273.4 (*c* 0.50, $CHCl_3$).



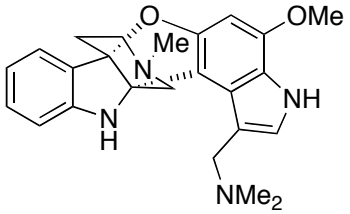
47

$[\alpha]^{25}_{D}$ –121.5 (*c* 0.79, $CHCl_3$).



S-7

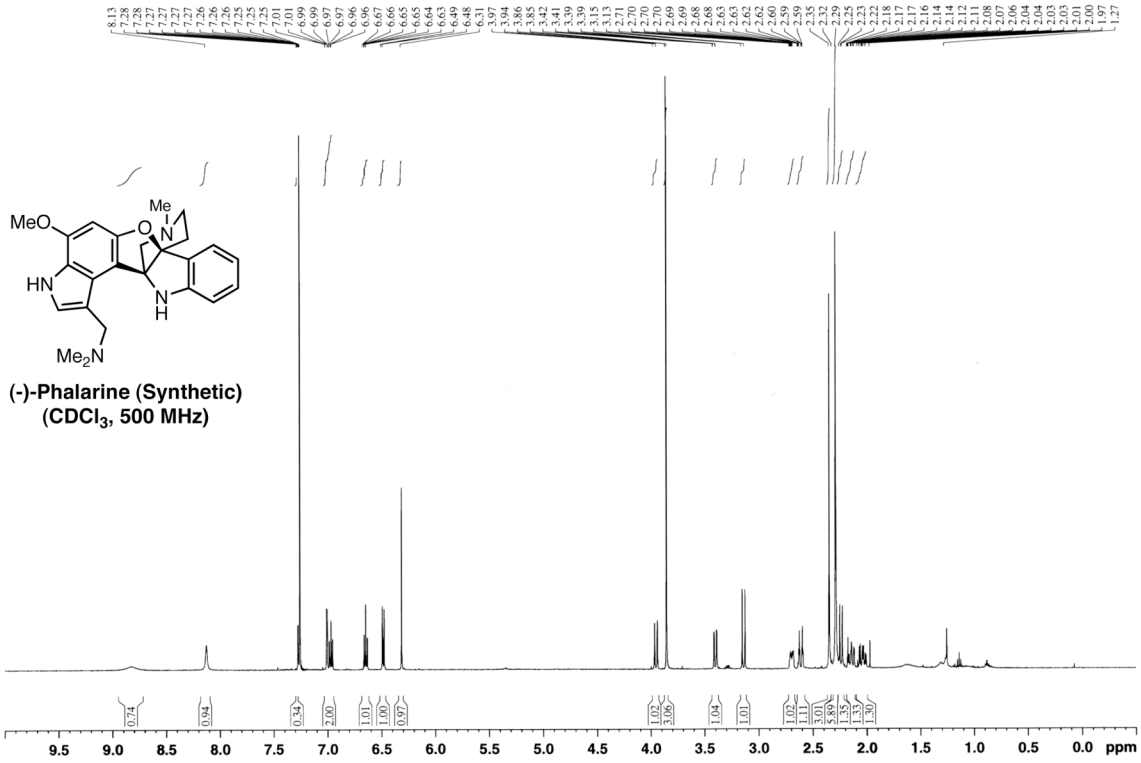
$[\alpha]^{25}_{D}$ –139.2 (*c* 0.77, $CHCl_3$).



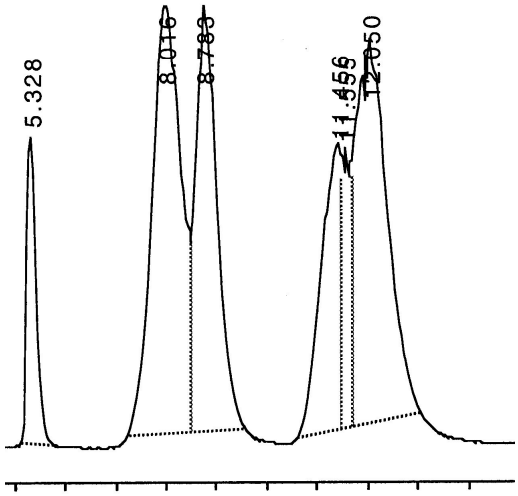
(–)-1 (Phalarine)

Synthetic: $[\alpha]^{25}_{D}$ –84.2 (*c* 0.24, MeOH).

Isolated Natural Product Report: $[\alpha]^{25}_{D}$ –92.0 (*c* 0.0075, MeOH).[9]


MeO
Me
O
N
HN
N
H
Me2N
(-)-Phalarine (Synthetic)
(CDCl3, 500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

Racemic Phalarine



(-)-Phalarine

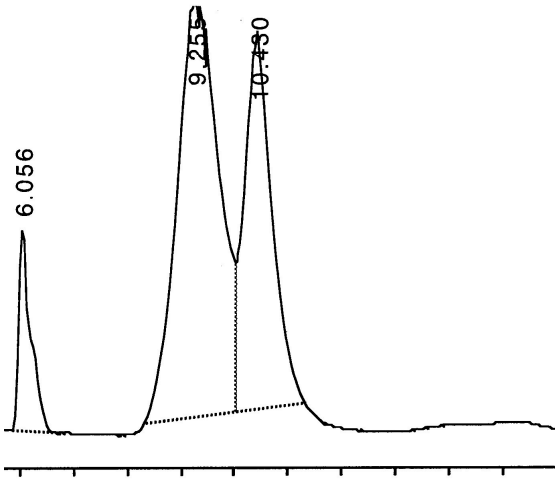


Figure S7. Analytical chiral HPLC of isolated asymmetric Pictet–Spengler reaction products (Chiracel OD-H column, 5% IPA/hexanes isocratic, 0.5 ml/min, λ = 254 nm):

Note: When loaded at high concentrations, the peaks appear to split, as shown. At lower concentrations, single, low-intensity peaks are observed. We propose that the observed peak splitting is a factor of high sample loading in the low-flow assay.

Table 1. Crystal data and structure refinement for Jun.

Identification code	14s10
Empirical formula	$C_{34}H_{32}N_2O_6S$
Formula weight	596.68
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	*a* = 13.841(3) Å alpha = 90°
	b = 11.389(3) Å beta = 94.159(3)°
	c = 18.565(4) Å gamma = 90°
Volume, Z	2919.0(11) $Å^3$, 4
Density (calculated)	1.358 Mg/m^3
Absorption coefficient	0.161 mm^{-1}
F(000)	1256
Crystal size	1.00 x 0.15 x 0.10 mm
Θ range for data collection	1.48 to 30.50°
Limiting indices	$-19 \le h \le 19$, $-16 \le k \le 16$, $-26 \le l \le 26$
Reflections collected	45567
Independent reflections	8888 (R_{int} = 0.0406)
Completeness to Θ = 30.50°	99.7 %
Absorption correction	Empirical
Max. and min. transmission	0.9840 and 0.8553
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8888 / 0 / 388
Goodness-of-fit on F^2	1.022
Final R indices [I>2σ(I)]	R1 = 0.0434, wR2 = 0.1088
R indices (all data)	R1 = 0.0793, wR2 = 0.1321
Largest diff. peak and hole	0.414 and -0.373 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for Jun. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
S	1578(1)	3342(1)	2082(1)	30(1)
N(1)	2378(1)	2384(1)	1843(1)	29(1)
O(1)	1646(1)	3362(1)	2855(1)	40(1)
C(1)	2749(1)	2325(1)	1091(1)	24(1)
O(2)	1746(1)	4393(1)	1690(1)	40(1)
N(2)	4330(1)	2618(1)	579(1)	25(1)
C(2)	2025(1)	2623(1)	475(1)	26(1)
O(3)	1908(1)	618(1)	619(1)	28(1)
C(3)	1788(1)	3660(1)	111(1)	33(1)
O(4)	-178(1)	2722(1)	-1150(1)	46(1)
C(4)	1055(1)	3647(2)	-441(1)	38(1)
O(5)	5442(1)	1531(1)	1771(1)	38(1)
C(5)	557(1)	2609(2)	-624(1)	35(1)
O(6)	5380(1)	-198(1)	1194(1)	37(1)
C(6)	813(1)	1548(2)	-288(1)	32(1)
C(7)	1556(1)	1599(1)	253(1)	27(1)
C(8)	2852(1)	984(1)	975(1)	24(1)
C(9)	2929(1)	486(1)	1724(1)	27(1)
C(10)	3229(1)	-620(2)	1955(1)	34(1)
C(11)	3180(2)	-905(2)	2681(1)	45(1)
C(12)	2835(2)	-91(2)	3151(1)	48(1)
C(13)	2543(1)	1027(2)	2933(1)	41(1)
C(14)	2594(1)	1304(1)	2204(1)	30(1)
C(15)	3716(1)	2975(1)	1149(1)	26(1)
C(16)	4556(1)	1371(1)	589(1)	24(1)
C(17)	3614(1)	670(1)	456(1)	25(1)
C(18)	439(1)	2767(1)	1784(1)	29(1)
C(19)	-62(1)	3225(2)	1178(1)	42(1)
C(20)	-916(1)	2697(2)	918(1)	47(1)
C(21)	-1287(1)	1732(2)	1256(1)	40(1)
C(22)	-783(2)	1310(2)	1872(1)	48(1)
C(23)	79(1)	1815(2)	2142(1)	42(1)
C(24)	-2206(2)	1142(2)	962(2)	60(1)
C(25)	-700(2)	1688(2)	-1371(1)	56(1)
C(26)	5165(1)	939(1)	1259(1)	27(1)
C(27)	5913(2)	-735(2)	1807(1)	49(1)
C(28)	5175(1)	3383(2)	539(1)	31(1)
C(29)	5577(1)	3387(1)	-194(1)	28(1)
C(30)	6571(1)	3457(2)	-253(1)	34(1)
C(31)	6951(1)	3571(2)	-922(1)	41(1)
C(32)	6336(2)	3612(2)	-1539(1)	43(1)
C(33)	5348(2)	3533(2)	-1493(1)	42(1)
C(34)	4968(1)	3418(2)	-824(1)	35(1)

Table 3. Bond lengths [Å] and angles [°] for Jun.

S-O(2)	1.4289(13)	S-O(1)	1.4317(14)
S-N(1)	1.6387(14)	S-C(18)	1.7589(17)
N(1)-C(14)	1.421(2)	N(1)-C(1)	1.5243(19)
C(1)-C(2)	1.502(2)	C(1)-C(15)	1.527(2)
C(1)-C(8)	1.550(2)	N(2)-C(16)	1.4537(19)
N(2)-C(15)	1.4622(19)	N(2)-C(28)	1.4638(19)
C(2)-C(7)	1.384(2)	C(2)-C(3)	1.389(2)
O(3)-C(7)	1.3778(18)	O(3)-C(8)	1.4815(17)
C(3)-C(4)	1.389(2)	O(4)-C(5)	1.364(2)
O(4)-C(25)	1.426(3)	C(4)-C(5)	1.398(3)
O(5)-C(26)	1.2046(19)	C(5)-C(6)	1.394(2)
O(6)-C(26)	1.337(2)	O(6)-C(27)	1.445(2)
C(6)-C(7)	1.385(2)	C(8)-C(9)	1.499(2)
C(8)-C(17)	1.523(2)	C(9)-C(10)	1.384(2)
C(9)-C(14)	1.391(2)	C(10)-C(11)	1.393(3)
C(11)-C(12)	1.382(3)	C(12)-C(13)	1.387(3)
C(13)-C(14)	1.397(2)	C(16)-C(26)	1.533(2)
C(16)-C(17)	1.534(2)	C(18)-C(19)	1.381(2)
C(18)-C(23)	1.383(2)	C(19)-C(20)	1.382(3)
C(20)-C(21)	1.383(3)	C(21)-C(22)	1.381(3)
C(21)-C(24)	1.505(3)	C(22)-C(23)	1.384(3)
C(28)-C(29)	1.507(2)	C(29)-C(30)	1.391(2)
C(29)-C(34)	1.392(2)	C(30)-C(31)	1.391(2)
C(31)-C(32)	1.377(3)	C(32)-C(33)	1.380(3)
C(33)-C(34)	1.389(2)		

O(2)-S-O(1)	119.72(8)	O(2)-S-N(1)	106.39(7)
O(1)-S-N(1)	106.58(8)	O(2)-S-C(18)	109.11(8)
O(1)-S-C(18)	108.23(8)	N(1)-S-C(18)	105.99(7)
C(14)-N(1)-C(1)	108.70(12)	C(14)-N(1)-S	124.90(11)
C(1)-N(1)-S	123.75(10)	C(2)-C(1)-N(1)	115.93(12)
C(2)-C(1)-C(15)	118.49(13)	N(1)-C(1)-C(15)	105.42(12)
C(2)-C(1)-C(8)	100.37(11)	N(1)-C(1)-C(8)	102.13(11)
C(15)-C(1)-C(8)	113.45(12)	C(16)-N(2)-C(15)	113.49(12)
C(16)-N(2)-C(28)	114.21(12)	C(15)-N(2)-C(28)	112.27(12)
C(7)-C(2)-C(3)	118.79(14)	C(7)-C(2)-C(1)	108.05(13)
C(3)-C(2)-C(1)	133.13(14)	C(7)-O(3)-C(8)	105.11(11)
C(4)-C(3)-C(2)	119.01(16)	C(5)-O(4)-C(25)	117.60(15)
C(3)-C(4)-C(5)	120.62(16)	O(4)-C(5)-C(6)	123.74(16)
O(4)-C(5)-C(4)	115.00(15)	C(6)-C(5)-C(4)	121.26(15)
C(26)-O(6)-C(27)	116.28(14)	C(7)-C(6)-C(5)	116.08(15)
O(3)-C(7)-C(2)	113.24(13)	O(3)-C(7)-C(6)	122.71(14)
C(2)-C(7)-C(6)	124.05(14)	O(3)-C(8)-C(9)	107.97(12)
O(3)-C(8)-C(17)	106.27(11)	C(9)-C(8)-C(17)	119.53(13)
O(3)-C(8)-C(1)	104.59(11)	C(9)-C(8)-C(1)	104.24(12)
C(17)-C(8)-C(1)	113.22(12)	C(10)-C(9)-C(14)	121.20(15)
C(10)-C(9)-C(8)	129.14(15)	C(14)-C(9)-C(8)	109.59(13)
C(9)-C(10)-C(11)	118.45(17)	C(12)-C(11)-C(10)	119.91(17)
C(11)-C(12)-C(13)	122.53(18)	C(12)-C(13)-C(14)	117.11(18)
C(9)-C(14)-C(13)	120.78(16)	C(9)-C(14)-N(1)	110.29(14)
C(13)-C(14)-N(1)	128.88(15)	N(2)-C(15)-C(1)	111.52(12)
N(2)-C(16)-C(26)	115.41(12)	N(2)-C(16)-C(17)	109.07(12)
C(26)-C(16)-C(17)	112.02(12)	C(8)-C(17)-C(16)	113.29(12)
C(19)-C(18)-C(23)	120.66(16)	C(19)-C(18)-S	120.09(13)
C(23)-C(18)-S	119.15(13)	C(18)-C(19)-C(20)	119.10(17)

C(19)-C(20)-C(21)	121.61(18)	C(22)-C(21)-C(20)	118.02(17)
C(22)-C(21)-C(24)	120.57(19)	C(20)-C(21)-C(24)	121.4(2)
C(21)-C(22)-C(23)	121.68(18)	C(18)-C(23)-C(22)	118.90(18)
O(5)-C(26)-O(6)	123.59(15)	O(5)-C(26)-C(16)	125.85(15)
O(6)-C(26)-C(16)	110.53(13)	N(2)-C(28)-C(29)	113.32(13)
C(30)-C(29)-C(34)	118.37(15)	C(30)-C(29)-C(28)	120.21(15)
C(34)-C(29)-C(28)	121.22(15)	C(29)-C(30)-C(31)	121.04(17)
C(32)-C(31)-C(30)	119.74(18)	C(31)-C(32)-C(33)	120.07(17)
C(32)-C(33)-C(34)	120.27(18)	C(33)-C(34)-C(29)	120.51(17)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$] for Jun.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
S	29(1)	24(1)	38(1)	-7(1)	10(1)	-2(1)
N(1)	30(1)	26(1)	30(1)	-1(1)	8(1)	3(1)
O(1)	39(1)	44(1)	38(1)	-16(1)	10(1)	-4(1)
C(1)	25(1)	20(1)	28(1)	-2(1)	3(1)	0(1)
O(2)	41(1)	22(1)	60(1)	-4(1)	19(1)	-2(1)
N(2)	26(1)	22(1)	27(1)	-4(1)	4(1)	-3(1)
C(2)	24(1)	23(1)	31(1)	0(1)	2(1)	1(1)
O(3)	24(1)	22(1)	36(1)	2(1)	-4(1)	-2(1)
C(3)	33(1)	24(1)	41(1)	3(1)	4(1)	0(1)
O(4)	40(1)	48(1)	48(1)	10(1)	-13(1)	1(1)
C(4)	38(1)	32(1)	43(1)	11(1)	0(1)	5(1)
O(5)	45(1)	37(1)	29(1)	-6(1)	-7(1)	2(1)
C(5)	29(1)	40(1)	36(1)	6(1)	-2(1)	4(1)
O(6)	39(1)	31(1)	41(1)	-4(1)	-7(1)	8(1)
C(6)	28(1)	30(1)	37(1)	1(1)	-2(1)	-2(1)
C(7)	25(1)	25(1)	32(1)	2(1)	3(1)	1(1)
C(8)	23(1)	18(1)	29(1)	-2(1)	-2(1)	-1(1)
C(9)	25(1)	26(1)	30(1)	1(1)	0(1)	-2(1)
C(10)	36(1)	28(1)	38(1)	4(1)	-1(1)	2(1)
C(11)	52(1)	37(1)	44(1)	14(1)	-3(1)	4(1)
C(12)	55(1)	56(1)	35(1)	15(1)	4(1)	4(1)
C(13)	44(1)	46(1)	32(1)	3(1)	9(1)	3(1)
C(14)	28(1)	30(1)	30(1)	2(1)	4(1)	1(1)
C(15)	27(1)	22(1)	29(1)	-6(1)	4(1)	-1(1)
C(16)	24(1)	25(1)	24(1)	-5(1)	3(1)	0(1)
C(17)	26(1)	22(1)	26(1)	-6(1)	0(1)	0(1)
C(18)	28(1)	25(1)	35(1)	-2(1)	9(1)	2(1)
C(19)	27(1)	44(1)	56(1)	19(1)	9(1)	6(1)
C(20)	26(1)	65(1)	50(1)	15(1)	2(1)	8(1)
C(21)	28(1)	39(1)	52(1)	-9(1)	3(1)	2(1)
C(22)	45(1)	36(1)	61(1)	10(1)	-1(1)	-13(1)
C(23)	42(1)	41(1)	42(1)	10(1)	-2(1)	-10(1)
C(24)	36(1)	59(1)	84(2)	-15(1)	-8(1)	-4(1)
C(25)	41(1)	64(1)	61(1)	10(1)	-19(1)	-10(1)
C(26)	24(1)	30(1)	28(1)	-2(1)	4(1)	-1(1)
C(27)	52(1)	39(1)	54(1)	5(1)	-17(1)	9(1)
C(28)	32(1)	33(1)	28(1)	-4(1)	4(1)	-10(1)
C(29)	32(1)	23(1)	28(1)	0(1)	4(1)	-5(1)
C(30)	33(1)	33(1)	36(1)	-1(1)	3(1)	-5(1)
C(31)	42(1)	35(1)	47(1)	-5(1)	17(1)	-8(1)
C(32)	66(1)	30(1)	34(1)	0(1)	18(1)	-7(1)
C(33)	62(1)	38(1)	28(1)	1(1)	0(1)	-5(1)
C(34)	37(1)	37(1)	31(1)	0(1)	0(1)	-5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for Jun.

	x	y	z	U(eq)
H(3A)	2122	4368	237	39
H(4A)	890	4350	-697	45
H(6A)	497	832	-422	38
H(10A)	3463	-1172	1625	41
H(11A)	3385	-1657	2853	54
H(12A)	2796	-306	3643	58
H(13A)	2318	1580	3265	49
H(15A)	3597	3831	1114	31
H(15B)	4057	2813	1626	31
H(16A)	4947	1220	166	29
H(17A)	3344	814	-45	30
H(17B)	3763	-178	502	30
H(19A)	178	3893	942	51
H(20A)	-1258	3005	498	56
H(22A)	-1034	658	2117	57
H(23A)	417	1511	2565	50
H(24A)	-2465	1556	527	90
H(24B)	-2684	1162	1326	90
H(24C)	-2068	325	840	90
H(25A)	-1211	1891	-1743	85
H(25B)	-991	1343	-954	85
H(25C)	-256	1120	-1567	85
H(27A)	6027	-1565	1703	74
H(27B)	5538	-671	2233	74
H(27C)	6535	-333	1900	74
H(28A)	5688	3123	903	37
H(28B)	4991	4194	663	37
H(30A)	6998	3426	172	41
H(31A)	7632	3621	-954	49
H(32A)	6593	3694	-1998	51
H(33A)	4926	3558	-1919	51
H(34A)	4286	3360	-797	42

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2. In this progression, the intensity of the NOEs should decrease with a decrease in mixing time but all real NOEs should still be visible as artifacts caused by various noises tend to disappear as the mixing time decreases.

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