Highly Enantioselective Synthesis of Glycidic Amides Using Camphor-Derived Sulfonium Salts. Mechanism and Applications in Synthesis.

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Supporting Information

General Methods	S2
General procedure for the synthesis of the sulfonium salts	S2
Synthesis of (2 <i>R</i> ,3 <i>S</i>)-2,3-Epoxy-Amides	S9
Ring-Opening of the (2 <i>R</i> ,3 <i>S</i>)-(2,3)-Epoxy-Amides	S14
Further Transformations of the Ring-Opened Epoxy-Amides	S16
Total synthesis of SK&F 104353	S17
Cross-over experiments	S22
X-ray data	S25
Computational information	S30
References	S35

General methods

Flash chromatography was performed on silica gel (Merck Kiesegel 60 F₂₅₄ 230-400 mesh). TLC was performed on aluminium backed silica plates (60 F₂₅₄) which were developed using standard visualizing agents: UV fluorescence (254 and 366 nm), molybdic acid / Δ , anisaldehyde / Δ , permanganate / Δ . Melting points were determined on a Khöfler hot stage. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. Only selected absorbances ($\nu_{\max}$) were reported. ^1H NMR spectra were recorded at 250, 270 or 400 MHz on Bruker AC-250, Delta GX/270 or Delta GX/400 instruments, respectively. Chemical shifts (δ_{H}) are quoted in parts per million (ppm), referenced to TMS. ^{13}C NMR spectra were recorded at either 68 or 100 MHz on Delta GX/270 or Delta GX/400 instruments, respectively. Chemical shifts (δ_{C}) are quoted in parts per million (ppm), referenced to the appropriate residual solvent. Low resolution mass spectra (m/z) were recorded on a Micromass Analytical Autospec spectrometer with only molecular ions (M^+), and major peaks being reported and intensities quoted as percentages of the base peak. High-resolution mass spectra were recorded on a Micromass Analytical Autospec spectrometer. Microanalyses were performed using a Carlo Erba EA1108. Ee values were determined by chiral HPLC on a Chiralcel OD, ODH or OJ column. All chemicals were purchased from Aldrich, Fluka or Lancaster, and used as delivered. Solvents were purified by passing through a solvent column prior to use.¹

General procedure for the synthesis of the sulfonium salts

The sulfonium salts were prepared by stirring either sulfide **2** or **3** (1 eq.) with the corresponding α -bromo acetamide (1 eq.), in the minimum amount of acetone necessary to dissolve the reactants, at r.t. for 24 h. In order to exchange the bromide counter ion for tetraphenylborate, perchlorate or tetrafluoroborate (when needed), one equivalent of NaBPh₄, NaClO₄ or NaBF₄ respectively, was added to the reaction mixture. The sulfonium salt was obtained as a mixture of two diastereomers (ratio of diastereomers is specified for each case). Purification of the crude product was carried out as specified for each case.

(R)-[2-(Diethylamino)-2-oxoethyl][(2R,3S,4R)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium bromide (1a)

Diastereomeric ratio: 11:1. After purification by recrystallization from MeOH, the title compound was obtained as a white solid (as a single diastereomer); eluent DCM/MeOH. 10:1, $R_f = 0.52$; m.p. 162-164 °C (Et₂O); $[\alpha]_D^{21} +68.3$ (c 0.91 in MeOH); ¹H NMR (270 MHz, CDCl₃) δ 0.87 (3H, s, CH₃), 0.98 (3H, s, CH₃), 1.14 (3H, t, $J = 7.3$ Hz, CH₂CH₃), 1.17 (3H, s, CH₃), 1.29 (3H, t, $J = 7.3$ Hz, CH₂CH₃), 1.41 (1H, m, H-5 / H-6), 1.58 (1H, m, H-5 / H-6), 1.82-2.06 (2H, m, 2 $\times$ H-5 / H-6), 2.05 (1H, d, $J = 4.8$ Hz, H-1), 3.13 (3H, s, SCH₃), 3.38 (2H, m, CH₂CH₃), 3.51 (1H, m, CHHCH₃), 3.60 (1H, m, CHHCH₃), 4.34 (1H, dd, $J = 7.4$ and 6.9 Hz, H-3), 4.58 (1H, d, $J = 7.4$ Hz, OH), 5.17 (1H, d, $J = 15.6$ Hz, SCHH), 5.32 (1H, d, $J = 6.9$ Hz, H-2), 5.52 (1H, d, $J = 15.6$ Hz, SCHH); ¹³C NMR (68 MHz, CDCl₃) δ 11.3, 12.9, 14.6, 20.9, 21.2, 23.5, 27.5, 28.0, 32.2, 40.9, 43.3, 47.8, 48.0, 49.3, 50.5, 63.2, 162.5; IR $\nu_{\max}/\text{cm}^{-1}$ 3148, 2968, 2917, 1634, 1459, 1077, 813; MS m/z (EI) 314 ([M-Br]⁺, 11), 300 (32), 282 (58), 194 (100), 183 (60), 167 (22), 148 (38), 135 (95), 116 (70); Anal. Calc'd for C₁₇H₃₂BrNO₂S: C, 51.77; H, 8.18; N, 3.55. Found: C, 51.79; H, 8.27; N, 3.51.

(*R*)-[2-(Diethylamino)-2-oxoethyl][(2*R*,3*S*,4*R*)-3-methoxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium bromide (1b)²

Diastereomeric ratio: 10:1. After purification by recrystallization from hexane/acetone, the title compound was obtained as a white solid (as a single diastereomer); mp 105-106 °C, $[\alpha]_D +111.2$ (c 0.17, dichloromethane); IR (film) 3055, 1422, 1266, 896, 738, 704 cm⁻¹; δ_H (250 MHz, CDCl₃) 6.52 (d, J_{AB} 15.9, 1H), 5.50 (d, J 7.6, 1H), 4.12 (d, J_{AB} 15.9, 1H), 3.76 (d, J 7.6, 1H), 3.65 (m., 1H), 3.53 (s, 3H), 3.51 (m., 1H), 3.34 (m., 2H), 3.23 (s, 3H), 2.02 (d, J 4.3, 1H), 2.00-1.80 (m, 1H), 1.60-1.10 (m, 3H), 1.28 (t, J 7.3, 3H), 1.17 (t, J 7.3, 3H), 1.17 (s, 3H), 1.06 (s, 3H), 0.87 (s, 3H); δ_C (63 MHz, CDCl₃) 162.2, 88.4, 61.4, 59.6, 51.4, 48.0, 47.7, 47.4, 43.0, 41.0, 32.1, 27.4, 23.2, 21.0, 20.5, 14.3, 12.3, 11.7; MS (EI) m/z 281 (84), 167 (50), 115 (100), 100 (62), 86 (51), 72 (60), 58 (64); MS (CI) m/z 328 (76), 194 (62), 135 (72), 116 (100); Anal. calcd for C₁₈H₃₄NO₂BrS: C, 52.93; H, 8.39; N, 3.43. Found: C, 52.86; H, 8.41; N, 3.39; HRMS calcd for C₁₈H₃₄NO₂S⁺ 328.2310, found 328.2311.

(*R*)-(2-Amino-2-oxoethyl][(2*R*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium bromide (3a)

Diastereomeric ratio: 3:1. After purification by column chromatography (eluent DCM/MeOH 10:1), the title compound was obtained as a white solid (as a single diastereomer); eluent DCM/MeOH. 10:1, $R_f = 0.24$; m.p. 112-114 °C (MeOH); $[\alpha]_D^{21} +22.40$ (c 0.87 in MeOH); ^1H NMR (270 MHz, CDCl_3) δ 0.86 (3H, s, CH_3), 0.97 (3H, s, CH_3), 1.10-1.28 (1H, m, H-5 / H-6), 1.20 (3H, s, CH_3), 1.43-1.64 (2H, m, $2 \times$ H-5 / H-6), 1.78-2.01 (1H, m, H-5 / H-6), 2.00 (1H, d, $J = 4.1$ Hz, H-1), 3.19 (3H, s, SCH_3), 3.48 (1H, s, OH), 4.48 (1H, d, $J = 7.8$ Hz, H-3), 4.75 (1H, d, $J = 15.9$ Hz, $\text{S}(\text{CH}_3)\text{CHH}$), 5.22 (1H, d, $J = 15.9$ Hz, $\text{S}(\text{CH}_3)\text{CHH}$), 5.45 (1H, d, $J = 7.8$ Hz, H-2), 6.94 (1H, br s, NHH), 8.18 (1H, br s, NHH); ^{13}C NMR (68 MHz, CDCl_3) δ 11.7, 20.9, 21.3, 22.8, 28.2, 29.4, 31.1, 31.4, 32.0, 47.8, 50.2, 64.1, 164.7; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3308, 3156, 2960, 2896, 1678, 1603, 1393, 1069; MS m/z (FAB) 258 ($[\text{M}-\text{Br}]^+$, 58), 186 (100); Anal. Calc'd for $\text{C}_{13}\text{H}_{24}\text{BrNO}_2\text{S}$: C, 46.15; H, 7.15; N, 4.14. Found: C, 46.02; H, 7.14; N, 4.22.

(*R*)-[2-(Benzylamino)-2-oxoethyl](2*R*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium bromide (4a)

Diastereomeric ratio: 5:1. After purification by column chromatography (DCM/MeOH 10:1), the title compound was obtained as a white solid (as a single diastereomer, 46% yield); eluent DCM/MeOH. 10:1, $R_f = 0.38$; m.p. 190-191 °C (MeOH); $[\alpha]_D^{25} +44.12$ (c 0.72 in MeOH); ^1H NMR (400 MHz, CDCl_3) δ 0.82 (3H, s, CH_3), 0.83-0.92 (2H, m, $2 \times$ H-5 / H-6), 0.93 (3H, s, CH_3), 1.14 (3H, s, CH_3), 1.44-1.49 (1H, m, H-5 / H-6), 1.79-1.85 (1H, m, H-5 / H-6), 1.87 (1H, d, $J = 4.9$ Hz, H-1), 3.08 (3H, s, SCH_3), 3.67 (1H, d, $J = 7.3$ Hz, OH), 3.90 (1H, t, $J = 7.3$ Hz, H-3), 4.28 (1H, dd, $J = 14.3$ and 5.4 Hz, NCHHPh), 4.56 (1H, dd, $J = 14.3$ and 6.8 Hz, NCHHPh), 4.58 (1H, d, $J = 14.1$ Hz, SCHH), 4.66 (1H, d, $J = 14.1$ Hz, SCHH), 5.84 (1H, d, $J = 7.3$ Hz, H-2), 7.22-7.46 (5H, m, Ph), 9.48 (1H, dt, $J = 6.8$ and 5.4 Hz, NH); ^{13}C NMR (100 MHz, CDCl_3) δ 14.8, 18.1, 20.1, 20.2, 29.9, 35.5, 43.0, 49.0, 49.5, 51.1, 55.4, 63.8, 85.4, 126.8, 128.8, 128.8, 135.9, 175.2; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3191, 3050, 2972, 2877, 1673, 1564, 1224, 1079, 697; MS m/z (FAB) 348 ($[\text{M}-\text{Br}]^+$, 62), 186 (82), 168 (56), 91 (100); Anal. Calc'd for $\text{C}_{20}\text{H}_{30}\text{BrNO}_2\text{S}$: C, 56.07; H, 7.06; N, 3.27. Found: C, 55.90; H, 7.00; N, 3.44.

(*R*)-[2-(Diallylamino)-2-oxoethyl][(2*R*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium bromide (6a)

Diastereomeric ratio: 3:1. After purification by column chromatography (eluent DCM/MeOH 20:1) the title compound was obtained as a white solid (as a single diastereomer); eluent DCM/MeOH 10:1, $R_f = 0.5$; m.p. 143-144 °C (DCM); $[\alpha]_D^{22} +86.80$ (c 0.59 in MeOH); ^1H NMR (270 MHz, CDCl_3) δ 0.88 (3H, s, CH_3), 0.98 (3H, s, CH_3), 0.80-1.05 (1H, m, H-5 / H-6), 1.22 (3H, s, CH_3), 1.20-1.40 (1H, m, H-5 / H-6), 1.50-1.65 (1H, m, H-5 / H-6), 1.85-2.00 (1H, m, H-5 / H-6), 2.04 (1H, d, $J = 4.3$ Hz, H-1), 3.05 (3H, s, SCH_3), 3.80-4.15 (2H, m, $2 \times \text{CONCHHCH}=\text{CH}_2$), 4.25-4.50 (3H, m, $2 \times \text{CONCHHCH}=\text{CH}_2$ and H-3), 4.95 (1H, d, $J = 15.9$ Hz, SCHHCON), 5.10-5.33 (5H, m, $2 \times \text{CH}_2\text{CH}=\text{CH}_2$, and OH), 5.76 (1H, d, $J = 15.9$ Hz, SCHHCON), 5.60-6.05 (3H, m, $2 \times \text{CH}_2\text{CH}=\text{CH}_2$ and H-2); ^{13}C NMR (68 MHz, CDCl_3) δ 11.2, 20.9, 21.2, 23.9, 28.2, 32.2, 44.8, 47.9, 48.1, 48.7, 49.9, 50.2, 50.5, 63.9, 117.9, 118.8, 131.6, 132.6, 163.9; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3308, 3156, 2961, 2897, 1678, 1603, 1393, 1069; MS m/z (FAB) 338 (M^+ , 70), 186 (100); Anal. Calc'd for $\text{C}_{19}\text{H}_{32}\text{BrNO}_2\text{S}$: C, 54.54; H, 7.71; N, 3.35. Found: C, 54.80; H, 7.68; N, 3.44.

(R)-[2-(Diallylamino)-2-oxoethyl][(2R,3S,4R)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium perchlorate (6a)

Diastereomeric ratio: 3:1. After purification by column chromatography (eluent DCM/MeOH 10:1) the title compound was obtained as a white solid (as a single diastereomer); eluent DCM/MeOH 10:1, $R_f = 0.55$; m.p. 138-140 °C (DCM); $[\alpha]_D^{22} +93.41$ (c 1.17 in DCM); ^1H NMR (400 MHz, CDCl_3) δ 0.88 (3H, s, CH_3), 0.97 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.13-1.28 (1H, m, H-5 / H-6), 1.30-1.45 (1H, m, H-5 / H-6), 1.47-1.62 (1H, m, H-5 / H-6), 1.86-1.96 (1H, m, H-5 / H-6), 2.09 (1H, d, $J = 4.5$ Hz, H-1), 2.99 (3H, s, SCH_3), 3.94-4.10 (4H, m, $2 \times \text{CONCH}_2$), 4.15 (1H, d, $J = 6.4$ Hz, H-2), 4.31 (1H, t, $J = 6.4$ Hz, H-3), 4.73 (1H, d, $J = 17.2$ Hz, SCHHCON), 5.11 (1H, d, $J = 17.2$ Hz, SCHHCON), 5.20-5.30 (5H, m, $2 \times \text{CH}_2\text{CH}=\text{CH}_2$ and OH), 5.69-5.90 (2H, m, $2 \times \text{CH}_2\text{CH}=\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 10.9, 20.8, 21.2, 24.4, 28.0, 32.0, 47.8, 48.1, 48.5, 49.8, 50.0, 50.5, 63.0, 78.4, 118.2, 119.1, 131.6, 132.1, 163.3; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3457, 3016, 2971, 2947,

1738, 1638, 1366, 1229, 922; MS m/z (FAB) 338 (M^+ , 78), 186 (100); Anal. Calc'd for $C_{19}H_{32}ClNO_6S$: C, 52.10, H, 7.36, N, 3.20. Found: C, 52.34, H, 7.03, N, 3.45.

(*R*)-[2-(Diallylamino)-2-oxoethyl][(2*R*,3*S*,4*R*)-3-methoxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium perchlorate (6b)

Diastereomeric ratio: 16:1. After purification by column chromatography (eluent DCM/MeOH 20:1) the title compound was obtained as a white solid (as a single diastereomer); eluent DCM/MeOH 20:1, R_f = 0.24; m.p. 111 °C (DCM); $[\alpha]_D^{22}$ +71.76 (c 0.93 in MeOH); 1H NMR (270 MHz, $CDCl_3$) δ 0.85 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.18 (3H, s, CH_3), 0.98-1.15 (1H, m, H-5 / H-6), 1.20-1.36 (1H, m, H-5 / H-6), 1.40-1.65 (1H, m, H-5 / H-6), 1.78-1.95 (1H, m, H-5 / H-6), 2.01 (1H, d, J = 4.9 Hz, H-1), 2.97 (3H, s, SCH_3), 3.45 (3H, s, OCH_3), 3.68-4.08 (2H, m, $2 \times CHHCH=CH_2$), 3.76 (1H, d, J = 7.6 Hz, H-3), 4.20-4.42 (2H, m, $2 \times CHHCH=CH_2$), 4.35 (1H, d, J = 16.2 Hz, $SCHHCON$), 4.45 (1H, d, J = 7.6 Hz, H-2), 5.10-5.34 (4H, m, $2 \times CH_2CH=CH_2$), 5.25 (1H, d, J = 16.2 Hz, $SCHHCON$), 5.60-5.95 (2H, m, $2 \times CH_2CH=CH_2$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 11.2, 20.8, 21.3, 24.7, 28.0, 32.1, 47.9, 48.1, 49.7, 49.9, 50.1, 51.7, 61.8, 69.3, 88.4, 117.7, 119.3, 131.5, 132.1, 163.7; IR ν_{max}/cm^{-1} 3022, 2955, 1437, 1644, 1026, 1081, 926; MS m/z (FAB) 352 ($[M-ClO_4]^+$, 100), 186 (29), 167 (18), 135 (28); Anal. Calc'd for $C_{20}H_{34}ClNO_6S$: C, 53.14; H, 7.58; N, 3.10. Found: C, 53.01; H, 7.39; N, 3.11.

(*R*)-{2-[bis(4-Methoxybenzyl)amino]-2-oxoethyl}[(2*R*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium perchlorate (7a)

Diastereomeric ratio: 100:1. Purified by filtering the crude product through a sinter funnel and washing the residue several times with acetone. The filtrate was then concentrated *in vacuo* to give

the title compound as a white solid (as a single diastereomer); eluent DCM/MeOH 10:1, $R_f = 0.50$; m.p. 87-88 °C (acetone); $[\alpha]_D^{22} +54.84$ (c 0.83 in MeOH); ^1H NMR (400 MHz, CDCl_3) δ 0.86 (3H, s, CH_3), 0.92 (3H, s, CH_3), 1.05-1.15 (1H, m, H-5 / H-6), 1.21 (3H, s, CH_3), 1.26-1.37 (1H, m, H-5 / H-6), 1.41-1.60 (1H, m, H-5 / H-6), 1.80-1.93 (1H, m, H-5 / H-6), 1.98 (1H, d, $J = 4.4$ Hz, H-1), 2.99 (3H, s, SCH_3), 3.48 (1H, t, $J = 6.1$ Hz, H-3), 3.79 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.14 (1H, d, $J = 6.1$ Hz, H-2), 4.40-4.60 (4H, m, $2 \times \text{CONCH}_2$), 4.46 (1H, d, $J = 6.1$ Hz, OH), 4.86 (1H, d, $J = 16.1$ Hz, SCHHCON), 5.09 (1H, d, $J = 16.1$ Hz, SCHHCON), 6.86 (2H, d, $J = 8.1$ Hz, $2 \times \text{H}_m\text{-ArOCH}_3$), 6.89 (2H, d, $J = 8.1$ Hz, $2 \times \text{H}_m\text{-ArOCH}_3$), 7.09 (2H, d, $J = 8.1$ Hz, $2 \times \text{H}_o\text{-ArOCH}_3$), 7.11 (2H, d, $J = 8.1$ Hz, $2 \times \text{H}_o\text{-ArOCH}_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 11.9, 20.9, 21.1, 21.8, 24.7, 28.8, 31.9, 47.8, 48.2, 48.9, 50.0, 50.0, 55.2, 55.2, 62.8, 78.3, 114.2, 114.4, 127.7, 127.9, 129.2, 129.2, 129.8, 129.9, 163.7; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3320, 2933, 1639, 1611, 1512, 1246, 1072, 811; MS m/z (FAB) 499 ($[\text{M-ClO}_4]^+$, 12), 121 (100); Anal. Calc'd for $\text{C}_{29}\text{H}_{40}\text{ClNO}_8\text{S}$: C, 58.23, H, 6.74, N, 2.34. Found: C, 58.04, H, 6.36, N, 2.41.

(R)-{2-[Allyl(4-methoxybenzyl)amino]-2-oxoethyl}[(2R,3S,4R)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium perchlorate (8a)

Diastereomeric ratio: 15:1. After purification by column chromatography (eluent DCM) the title compound was obtained as a white solid (as a single diastereomer); eluent DCM, $R_f = 0.20$; m.p. 78-79 °C (DCM); $[\alpha]_D^{22} +54.25$ (c 0.94 in MeOH); ^1H NMR (400 MHz, MeOH-D_4) major rotamer δ 0.89 (3H, s, CH_3), 0.84-1.00 (1H, m, H-5 / H-6), 0.97 (3H, s, CH_3), 1.08-1.20 (1H, m, H-5 / H-6), 1.26 (3H, s, CH_3), 1.50-1.65 (1H, m, H-5 / H-6), 1.88-2.01 (1H, m, H-5 / H-6), 2.25 (1H, d, $J = 4.3$ Hz, H-1), 3.05 (3H, s, SCH_3), 3.76 (3H, s, OCH_3), 3.85-4.15 (2H, m, $\text{CONCH}_2\text{CH}=\text{CH}_2$), 3.95 (1H, d, $J = 7.8$ Hz, H-2), 4.03 (1H, d, $J = 7.8$ Hz, H-3), 4.45-4.48 (2H, m, $\text{CONCH}_2\text{ArOCH}_3$), 5.10-5.30 (2H, m, $\text{CONCH}_2\text{CH}=\text{CH}_2$), 5.70-5.90 (1H, m, $\text{CONCH}_2\text{CH}=\text{CH}_2$), 6.88 (2H, d, $J = 8.8$ Hz, $2 \times \text{H}_o\text{-ArOCH}_3$), 7.21 (2H, d, $J = 8.8$ Hz, $2 \times \text{H}_m\text{-ArOCH}_3$); ^{13}C NMR (100 MHz, CDCl_3) (mixture of 2 rotamers) δ 10.8, 20.9, 21.4, 24.7, 27.9, 32.1, 33.3, 38.1, 39.6, 43.4, 47.9, 48.0, 48.3, 49.7, 50.2, 50.9, 54.7, 62.7, 78.8, 114.6, 114.7, 118.0, 129.3, 130.0, 130.1, 131.2, 132.1, 132.4, 162.8, 163.7; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3441, 3051, 2936, 1635, 1611, 1513, 1445, 1246, 1071, 924; MS m/z (CI) 400 ($[\text{M-ClO}_4\text{-H}_2\text{O}]^+$, 4), 386 (12), 266 (24), 153 (64), 146 (86), 135 (58), 121 (100) 109 (78); Anal. Calc'd for $\text{C}_{24}\text{H}_{36}\text{ClNO}_7\text{S}$: C, 55.64, H, 7.00, N, 2.70. Found: C, 55.29, H, 7.15, N, 2.65.

(R)-[2-(2,5-Dihydro-pyrrol-1-yl)-2-oxoethyl][(2R,3S,4R)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium bromide (10a)

Diastereomeric ratio: 8:1. After purification by recrystallisation from MeOH, the title compound was obtained as a white solid (as a single diastereomer); eluent EtOAc/P.E. 1:1, $R_f = 0.24$; m.p. 183-185 °C (MeOH); $[\alpha]_D^{22} +83.52$ (c 0.71 in MeOH); ^1H NMR (400 MHz, MeOH- d_4) δ 0.91 (3H, s, CH₃), 0.97 (3H, s, CH₃), 1.11-1.32 (2H, m, 2 $\times$ H-5 / H-6), 1.26 (3H, s, CH₃), 1.62 (1H, td, $J = 12.2$ and 3.9 Hz, H-5 / H-6), 1.99 (1H, m, H-5 / H-6), 2.25 (1H, d, $J = 4.8$ Hz, H-1), 3.04 (3H, s, CH₃), 4.01 (1H, d, $J = 6.9$ Hz, H-3), 4.03 (1H, d, $J = 6.9$ Hz, H-2), 4.24 (4H, m, 2 $\times$ CONCH₂), 5.91 (2H, m, CONCH₂CH=CH); ^{13}C NMR (100 MHz, MeOH) δ 10.1, 19.8, 20.3, 22.6, 27.8, 31.7, 50.3, 53.2, 53.5, 78.2, 78.2, 100.0, 124.7, 125.2, 161.8; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3173, 2869, 1654, 1622, 1453, 1074, 1001, 681; MS m/z (FAB) 310 ($[\text{M}-\text{HBr}]^+$, 59), 158 (100), 109 (12); HRMS: found 310.1841, C₁₇H₂₈BrNO₂S requires 310.1847.

(R)-[2-(2,5-Dihydro-pyrrol-1-yl)-2-oxoethyl][(1S,2R,3S,4R)-3-methoxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methylsulfonium bromide (10b)

Diastereomeric ratio: 3:2. After purification by column chromatography (eluent DCM/MeOH 10:1), the title compound was obtained as a pale brown solid (as a single diastereomer); eluent DCM/MeOH. 9:1, $R_f = 0.34$; m.p. 81-83 °C (DCM); $[\alpha]_D^{22} +71.51$ (c 0.88 in MeOH); ^1H NMR (400 MHz, CDCl₃) major diastereomer (10b): δ 0.87 (3H, s, CH₃), 1.06 (3H, s, CH₃), 1.17 (3H, s, CH₃), 1.08-1.35 (2H, m, 2 $\times$ H-5 / H-6), 1.57 (1H, m, H-5 / H-6), 1.90 (1H, m, H-5 / H-6), 2.02 (1H, d, $J = 4.1$ Hz, H-1), 3.26 (3H, s, SCH₃), 3.52 (3H, s, OCH₃), 3.72 (1H, d, $J = 7.9$ Hz, H-3), 4.05 (1H, d, $J = 16.2$ Hz, SCHH), 4.19-4.47 (3H, m, 3 $\times$ CONCHH), 4.90 (1H, m, CONCHH), 5.49 (1H, d, $J = 7.9$ Hz, H-2), 5.83 (2H, m, CH=CH), 6.58 (1H, d, $J = 16.2$ Hz, SCHH); minor diastereomer: δ 0.85 (3H, s, CH₃), 1.06 (3H, s, CH₃), 1.17 (3H, s, CH₃), 1.08-1.35 (2H, m, 2 $\times$ H-5 / H-6), 1.57 (1H, m, H-5 / H-6), 1.90 (1H, m, H-5 / H-6), 2.02 (1H, d, $J = 4.2$ Hz, H-1), 3.28 (3H, s,

SCH₃), 3.51 (3H, s, OCH₃), 3.65 (1H, d, J = 8.0 Hz, H-3), 4.24 (1H, d, J = 16.1 Hz, SCHH), 4.19-4.47 (3H, m, 3 × CONCHH), 4.85 (1H, m, CONCHH), 5.32 (1H, d, J = 8.0 Hz, H-2), 5.85 (2H, m, CH=CH), 6.31 (1H, d, J = 16.1 Hz, SCHH); ¹³C NMR (100 MHz, CDCl₃) major diastereomer (10b) δ 11.2, 20.0, 20.1, 22.2, 27.3, 31.8, 46.8, 47.6, 47.9, 51.0, 53.8, 54.1, 59.9, 61.8, 88.7, 125.1, 126.1, 161.8; IR ν_{max} /cm⁻¹ 3406, 2955, 2903, 2871, 1649, 1619, 1445, 1102, 1084, 676; MS m/z (FAB) 324 ([M-Br]⁺, 100), 167 (13), 158 (52), 135 (23), 109 (12); Anal. Calc'd for C₁₈H₃₀BrNO₂S: C, 53.46, H, 7.48, N, 3.46. Found: C, 53.84, H, 7.40, N, 3.20.

Synthesis of (2R,3S)-2,3-Epoxy-Amides

General Procedure for the Synthesis of (2R,3S)-2,3-Epoxy-Amides (table 2, entry 1³, entries 2-9⁴ entries 10-11⁵)

Powdered KOH (35.0 mg, 0.62 mmol) was added to a solution of the chiral sulfonium salt (0.24 mmol) and the corresponding aldehyde (0.24 mmol) in anhydrous ethanol (5 mL), at -50 °C (unless otherwise specified), under N₂. The reaction mixture was stirred at this temperature for 48 h (aromatic and heteroaromatic aldehydes) or 72 h (aliphatic aldehydes). After removal of the solvent under reduced pressure, the residue was purified by column chromatography using the conditions specified below, to give the pure *trans* epoxide. When necessary, a minimum amount of anhydrous MeOH was added to the reaction mixture in order to dissolve the sulfonium salt.

Table 2. Asymmetric synthesis of (2R,3S)-2,3-epoxy-amides using camphor-derived sulfonium salt **1b** and a variety of aldehydes.

Entry	R	% Yield of 5	% ee ^a
1	Ph	93	97
2	p-MeOC ₆ H ₄	90	97
3	p-ClC ₆ H ₄	87	99
4	p-MeC ₆ H ₄	88	98
5	p-FC ₆ H ₄	85	96
6	p-CF ₃ C ₆ H ₄	89	96
7	p-NO ₂ C ₆ H ₄	85	92
8	3-pyridyl	87	95
9 ^b	dodecyl	84	63
10 ^c	i-propyl	79	10
11 ^c	t-butyl	87	93

^a The enantiomeric excess has been determined by chiral HPLC and the absolute configuration of the product in entries 1 and 3 have been determined by comparison of HPLC elution orders and α_D values with the literature respectively (see supporting information for further details). All others are given by analogy (except for entry 10 where absolute configuration was not determined). ^b Epoxidation was carried out at -30 °C. ^c Epoxidation was carried out at -20 °C.

(2*R*,3*S*)-*N,N*-Diallyl-3-(4-chlorophenyl)-2-oxiranecarboxamide (table 3, entries 2-6)

The reaction was carried out at r.t. for 4 h. Purification by column chromatography (eluent EtOAc/Hex 1:5) gave the title compound as a white solid (98%); eluent EtOAc/Hex 1:5, $R_f = 0.22$; m.p. 61 °C (EtOAc); $[\alpha]_D^{22} -93.75$ (c 0.56 in DCM); ^1H NMR (400 MHz, CDCl_3) δ 3.54 (1H, d, $J = 1.5$ Hz, ArCH(O)CH), 3.93-4.10 (4H, m, $2 \times \text{CH}_2\text{CH}=\text{CH}_2$), 4.06 (1H, d, $J = 1.5$ Hz, ArCH(O)CH), 5.13-5.23 (4H, m, $2 \times \text{CH}_2\text{CH}=\text{CH}_2$), 5.73-5.82 (2H, m, $2 \times \text{CH}_2\text{CH}=\text{CH}_2$), 7.23 (2H, d, $J = 8.4$ Hz, $2 \times \text{H}_o\text{-pClPh}$), 7.33 (2H, $J = 8.4$ Hz, $2 \times \text{H}_m\text{-pClPh}$); ^{13}C NMR (100 MHz, CDCl_3) δ 48.6, 48.7, 57.3, 57.3, 117.4, 118.3, 127.1, 128.9, 132.5, 132.7, 134.2, 134.7, 166.5; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3065, 2990, 1654, 1599, 1479, 1233, 915, 843; MS m/z (EI) 277 (M^+ , 6), 249 (7), 136 (13), 125 (44), 89 (31), 84 (100); Anal. Calc'd for $\text{C}_{15}\text{H}_{16}\text{ClNO}_2$: C, 64.87, H, 5.81, N, 5.04. Found: C, 64.73, H, 5.90, N, 4.77; Enantiomeric excess (90%) was determined by HPLC (Chiracel[®] OD column, UV-VIS detector); mobile phase: 10% *i*-PrOH, 90% hexane; flow rate (mL/min): 1; first enantiomer: 10.0 min (minor) and second enantiomer 11.8 min (major).

(2*R*,3*S*)-*N,N*-bis(4-Methoxybenzyl)-3-phenyl-2-oxiranecarboxamide (table 3, entries 7-8)

Purification by column chromatography (eluent EtOAc/Hex 1:3) gave the title compound as a white solid (61%); eluent EtOAc/Hex 1:3, $R_f = 0.26$; m.p. 79-81 °C (EtOAc); $[\alpha]_D^{22} -39.54$ (c 2.16 in DCM); ^1H NMR (400 MHz, CDCl_3) δ 3.67 (1H, d, $J = 6.9$ Hz, ArCH(O)CH), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.11 (1H, d, $J = 6.9$ Hz, ArCH(O)CH), 4.46 (2H, s, $\text{CH}_2\text{PhOCH}_3$), 4.57 (2H, s, $\text{CH}_2\text{PhOCH}_3$), 6.83 (2H, d, $J = 8.8$ Hz, $2 \times \text{H}_o\text{-ArOCH}_3$), 6.87 (2H, d, $J = 8.8$ Hz, $2 \times \text{H}_o\text{-ArOCH}_3$), 7.05 (2H, d, $J = 8.8$ Hz, $2 \times \text{H}_m\text{-ArOCH}_3$), 7.15-7.40 (7H, m, $2 \times \text{H}_m\text{-ArOCH}_3$ and Ph); ^{13}C NMR (100 MHz, CDCl_3) δ 48.1, 48.7, 55.4, 55.6, 57.7, 58.1, 114.2, 114.5, 125.7, 128.0, 128.6, 128.7, 128.8, 130.0, 130.2, 136.1, 159.3, 159.4, 167.0; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3037, 2915, 2838, 1649, 1612, 1510, 1465, 1240, 1024, 804; MS m/z (EI) 403 (M^+ , 6), 387 (7), 282(40), 162 (47), 136 (38), 121 (100), 91 (22), 77 (17); Anal. Calc'd for $\text{C}_{25}\text{H}_{25}\text{NO}_4$: C, 74.42, H, 6.25, N, 3.47. Found: C, 74.52, H, 6.52,

N, 3.67; Enantiomeric excess (97%) was determined by HPLC (Chiracel[®] OD column, UV-VIS detector); mobile phase: 10% *i*-PrOH, 90% hexane; flow rate (mL/min): 1; first enantiomer: 44.2 min (major) and second enantiomer 56.2 min (minor).

(2*R*,3*S*)-*N*-Allyl-*N*-(4-methoxybenzyl)-3-phenyl-2-oxiranecarboxamide (table 3, entry 9)

Purification by column chromatography (eluent EtOAc/P.E. 1:4) gave the title compound as a colourless oil (55%); eluent EtOAc/P.E. 1:4, $R_f = 0.25$; $[\alpha]_D^{22} -62.24$ (c 0.49 in DCM); ¹H NMR (400 MHz, CDCl₃) major rotamer: δ 3.61 (1H, d, $J = 1.9$ Hz, ArCH(O)CH), 3.81 (3H, s, OCH₃), 4.04-4.16 (2H, m, CH₂CH=CH₂), 4.11 (1H, d, $J = 1.9$ Hz, ArCH(O)CH), 4.51-4.65 (2H, m, CH₂ArOCH₃), 5.10-5.29 (2H, m, CH₂CH=CH₂), 5.66-5.89 (1H, m, CH₂CH=CH₂), 6.87 (2H, d, $J = 8.8$ Hz, $2 \times H_o$ -ArOCH₃), 7.23 (2H, d, $J = 8.8$ Hz, $2 \times H_m$ -ArOCH₃), 7.18-7.42 (5H, m, Ph), minor rotamer: δ 3.65 (1H, d, $J = 1.9$ Hz, ArCH(O)CH), 3.79 (3H, s, OCH₃), 4.07 (1H, d, $J = 1.9$ Hz, ArCH(O)CH), 3.84-4.00 (2H, m, CH₂CH=CH₂), 4.51-4.65 (2H, m, CH₂ArOCH₃), 5.10-5.29 (2H, m, CH₂CH=CH₂), 5.66-5.89 (1H, m, CH₂CH=CH₂), 6.83 (2H, d, $J = 8.8$ Hz, $2 \times H_o$ -ArOCH₃), 7.08 (2H, d, $J = 8.8$ Hz, $2 \times H_m$ -ArOCH₃), 7.18-7.42 (5H, m, Ph); ¹³C NMR (100 MHz, CDCl₃) (mixture of 2 rotamers) δ 49.1, 49.5, 56.8, 56.8, 58.7, 59.3, 69.3, 69.6, 70.4, 70.7, 115.4, 115.4, 115.9, 116.2, 118.2, 119.1, 128.0, 128.4, 129.2, 129.5, 131.0, 131.9, 159.5, 160.8, 164.5; IR ν_{max}/cm^{-1} 3042, 2933, 2837, 1655, 1611, 1510, 1468, 1222, 1174, 753; MS m/z (EI) 323 (M⁺, 17), 282 (11), 176 (38), 121 (100), 91 (21), 77 (14); HRMS: found 323.1521, C₂₀H₂₁NO₃ requires 323.1521; Enantiomeric excess (92%) was determined by HPLC (Chiracel[®] OD column, UV-VIS detector); mobile phase: 10% *i*-PrOH, 90% hexane; flow rate (mL/min): 1; first enantiomer: 22.7 min (major) and second enantiomer 26.8 min (minor).

1-[(2*R*,3*S*)-3-Phenyloxiranyl]carbonyl]-2,5-dihydropyrrole (table 3, entries 11 and 13)

Purification by column chromatography (eluent EtOAc/P.E. 1:4) gave the title compound as a white solid (74%); eluent EtOAc/P.E. 2:1, $R_f = 0.28$; m.p. 72-75 °C (EtOAc); $[\alpha]_D^{22} -82.52$ (c 0.71 in DCM); ¹H NMR (400 MHz, CDCl₃) δ 3.56 (1H, d, $J = 1.8$ Hz, ArCH(O)CH), 4.15 (1H, d, $J = 1.8$

Hz, ArCH(O)CH), 4.26-4.43 (3H, m, 3 × CONCHHCH=CH), 4.51 (1H, m, CONCHHCH=CH), 5.82 (1H, m, CH=CH), 5.90 (1H, m, CH=CH), 7.30-7.47 (5H, m, Ph); ¹³C NMR (100 MHz, CDCl₃) δ 52.8, 53.7, 57.5, 57.5, 124.7, 125.7, 125.7, 128.7, 128.7, 136.2, 165.0; IR ν_{max}/cm⁻¹ 3021, 2891, 2854, 1652, 1621, 1453, 1398, 896, 749, 670; MS *m/z* (EI) 215 (M⁺, 27), 158 (12), 131 (15), 120 (28), 105 (22), 96 (38), 91 (84), 84 (47), 68 (72), 54 (100); HRMS: found 215.0946, C₁₃H₁₃NO₂ requires 215.0941; Enantiomeric excess (90%) was determined by HPLC (Chiracel[®] OJ column, UV-VIS detector); mobile phase: 5% *i*-PrOH, 95% hexane; flow rate (mL/min): 1; first enantiomer: 44.9 min (major) and second enantiomer 53.6 min (minor).

1-[(2*R*,3*S*)-3-(4-Chloro-phenyl)oxiranyl]carbonyl]-2,5-dihydropyrrole (table 3, entry 12)

Purification by column chromatography (eluent EtOAc/P.E. 1:4) gave the title compound as a white solid (82%); eluent EtOAc/P.E. 1:4, *R_f* = 0.19; m.p. 54-55 °C (EtOAc); [α]_D²⁵ -45.88 (*c* 0.90 in DCM); ¹H NMR (400 MHz, CDCl₃) δ 3.51 (1H, d, *J* = 1.9 Hz, ArCH(O)CH), 4.13 (1H, d, *J* = 1.9 Hz, ArCH(O)CH), 4.31-4.42 (3H, m, 3 × CONCHHCH=CH), 4.52 (1H, m, CONCHHCH=CH), 5.82 (1H, m, CH=CH), 5.90 (1H, m, CH=CH), 7.26 (2H, d, *J* = 8.5, 2 × H_{*o*}-pClPh), 7.38 (2H, d, *J* = 8.5, 2 × H_{*m*}-pClPh); ¹³C NMR (100 MHz, CDCl₃) δ 50.9, 57.2, 58.8, 60.7, 121.3, 121.4, 128.0, 128.8, 135.0, 135.3, 167.2; IR ν_{max}/cm⁻¹ 3028, 2888, 1662, 1589, 791, 645; MS *m/z* (EI) 249 (M⁺, 4), 215 (14), 158 (9), 120 (32), 112 (16), 96 (28), 91 (72), 68 (65), 54 (100); Anal. Calc'd for C₁₃H₁₂ClNO₂: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.52, H, 4.61, N, 5.87; Enantiomeric excess (85%) was determined by HPLC (Chiracel[®] OD column, UV-VIS detector); mobile phase: 10% *i*-PrOH, 90% hexane; flow rate (mL/min): 1; first enantiomer: 26.7 min (major) and second enantiomer 32.0 min (minor).

1-[(2*R*,3*S*)-3-phenyloxiranyl]carbonyl]-pyrrole (17)⁶

A solution of **16** (table 3, entries 11 and 13) (0.10 g, 0.47 mmol) in dry 1,4-dioxane (5 mL), was treated with DDQ (0.13 g, 0.56 mmol) and the resulting mixture stirred for 8 h at 85 °C. After cooling to r.t., the reaction mixture was concentrated under reduced pressure, followed by addition of brine (10 mL) and DCM (10 mL) to the residue. A solution 0.1 M of NaHCO₃ (5 mL) was added

to this mixture and the aqueous layer was extracted with DCM (2×10 mL). The combined extracts were washed with brine (10mL), dried (MgSO_4) and concentrated *in vacuo*. Purification by column chromatography (eluent EtOAc/P.E. 1:9) gave the title compound as a white solid (77.1 mg, 78%); ^1H NMR (400 MHz, CDCl_3) δ 4.01 (1H, d, $J = 1.9$ Hz, $\text{ArCH}(\text{O})\text{CH}$), 4.20 (1H, d, $J = 1.9$ Hz, $\text{ArCH}(\text{O})\text{CH}$), 6.33-6.36 (2H, m, $2 \times \text{H}_\alpha$ -pyrrole), 7.32-7.42 (7H, m, $2 \times \text{H}_\beta$ -pyrrole and Ph); ^{13}C NMR (100 MHz, CDCl_3) δ 57.3, 58.8, 114.1, 119.0, 125.7, 128.8, 129.2, 134.4, 164.3.

General procedure for addition of organolithium reagents to epoxy-amides (Scheme 3)⁵.

To a solution of epoxy-amide (0.25 mmol) in THF (0.75 mL) at -78°C was treated dropwise with appropriate organolithium reagents (1.5 equivalents). The reaction mixture was stirred at this temperature for 30 minutes. Water (0.5 mL) and ether were added (0.5mL). The organic layer was separated and the aqueous layer re-extracted with ether (3x 2mL). The combined organic layers were dried over MgSO_4 , concentrated, and the residue purified by flash chromatography with a mixture of light petroleum ether and ethyl acetate (12/1 to 8/1) as the eluant to give the pure epoxy-ketone.

Ring-Opening of the (2R,3S)-(2,3)-Epoxy-Amides

General procedure for the epoxide ring-opening reaction (Schemes 3,⁵ 4 and 5)

A solution of the Lewis acid (specified in each case) (3.40 mmol) in dry THF (5 mL) was added to a solution of the epoxy-amide (2.12 mmol) and thiophenol (0.58 g, 5.30 mmol), in dry THF (15 mL), at -78°C under N_2 . This solution was stirred overnight and, during that time, the temperature was allowed to warm to r.t. After this, a 0.1 M solution of HCl (2 mL) was added. The reaction mixture was diluted with ether (20 mL) followed by the addition of water (20 mL) after which the organic phase was separated. The aqueous phase was extracted with ether (2×20 mL), and the combined organic phases were dried (MgSO_4) and concentrated *in vacuo*. Purification of the crude residue was performed by column chromatography using the conditions specified in each case.

(2S,3R)-N,N-Diallyl-2-hydroxy-3-(4-chlorophenyl)-3-(phenylsulfanyl)propanamide (13)

13

$\text{Yb}(\text{OTf})_3$ was used as the Lewis acid. Purification by column chromatography (eluent Hex/EtOAc 5:1) gave the title compound as a colourless oil (65%); eluent Hex/EtOAc 5:1, $R_f = 0.20$; $[\alpha]_D^{25} - 34.53$ (c 0.98 in DCM); ^1H NMR (270 MHz, CDCl_3) δ 3.68 (2H, m, $2 \times \text{CONCHHCH}=\text{CH}$), 3.81

(1H, dd, $J = 16.1$ and 4.9 Hz, CONCHHCH=CH), 4.13 (1H, dd, $J = 15.2$ and 5.8 Hz, CONCHHCH=CH), 4.34 (1H, d, $J = 4.4$ Hz, CHSPh), 4.68 (1H, d, $J = 4.4$ Hz, CHCHOH), 5.14 (4H, m, $2 \times \text{CH}=\text{CH}_2$), 5.68 (2H, m, $2 \times \text{CH}=\text{CH}_2$), 7.28 (2H, d, $J = 2.4$ Hz, $2 \times \text{H}_m\text{-}p\text{ClPh}$), 7.29 (2H, d, $J = 2.4$ Hz, $2 \times \text{H}_o\text{-}p\text{ClPh}$), 7.24-7.51 (5H, m, Ph); ^{13}C NMR (68MHz, CDCl_3) δ 43.2, 48.3, 60.2, 94.5, 121.6, 124.4, 125.3, 128.3, 128.8, 129.7, 130.9, 131.4, 131.9, 132.8, 133.2, 141.1, 165.4; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3372, 3040, 2982, 1647, 1608, 1210; MS m/z (EI) 369 ($[\text{M}-\text{H}_2\text{O}]^+$, 10), 336 (8), 199 (18), 136 (26), 125 (58), 84 (100); Anal. Calc'd for $\text{C}_{21}\text{H}_{22}\text{ClNO}_2\text{S}$: C, 65.02; H, 5.72; N, 3.61. Found: C, 65.08; H, 5.54; N, 3.70.

(2*S*,3*R*)-3-(phenyl)-2-hydroxy-*N*-(4-methoxybenzyl)-*N*-[2-(4-methoxyphenyl)ethyl]-3-(phenylsulfanyl)propanamide (15)

Freshly distilled $\text{Ti}(\text{O}i\text{-Pr})_4$ was used as the Lewis acid. Purification by column chromatography (eluent EtOAc/P.E. 2:3) gave the title compound as a colourless oil (71%); eluent EtOAc/P.E. 2:3, $R_f = 0.48$; $[\alpha]_D^{25} -12.35$ (c 0.85 in DCM); ^1H NMR (400 MHz, CDCl_3) δ 3.72 (1H, d, $J = 8.8$ Hz, SCHCHOH), 3.83 (6H, s, $2 \times \text{OCH}_3$), 3.85 (1H, d, $J = 14.4$ Hz, CONCHH), 4.03 (1H, d, $J = 16.6$ Hz, CONCHH), 4.34 (1H, d, $J = 16.6$ Hz, CONCHH), 4.39 (1H, d, $J = 4.4$ Hz, OH), 4.83 (1H, dd, $J = 8.8$ and 4.4 Hz, CHCHOH), 4.98 (1H, d, $J = 14.4$ Hz, CONCHH), 6.82 (2H, d, $J = 8.8$ Hz, $2 \times \text{H}_o\text{-PhOCH}_3$), 6.88 (2H, d, $J = 8.9$ Hz, $2 \times \text{H}_o\text{-PhOCH}_3$), 7.00 (2H, d, $J = 8.8$ Hz, $2 \times \text{H}_m\text{-PhOCH}_3$), 7.09 (2H, d, $J = 8.9$ Hz, $2 \times \text{H}_m\text{-PhOCH}_3$), 7.12-7.34 (10H, m, SPh and Ph); ^{13}C NMR (100 MHz, CDCl_3) δ 47.8, 48.4, 55.3, 55.4, 58.0, 70.4, 113.9, 114.5, 127.9, 128.0, 128.0, 128.0, 128.1, 128.3, 128.4, 128.9, 129.2, 132.7, 135.1, 137.3, 159.3, 159.5, 171.9; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3387, 3042, 2989, 1645, 1615, 1502, 1305, 890; MS m/z (EI) 513 (M^+ , 2), 495 ($[\text{M}-\text{H}_2\text{O}]^+$, 16), 165 (48), 199 (22), 121 (100), 91 (10); Anal. Calc'd for $\text{C}_{31}\text{H}_{31}\text{NO}_4\text{S}$: C, 72.49; H, 6.08; N, 2.73. Found: C, 72.62; H, 6.18; N, 2.78.

(2*S*,3*R*)-1-Oxo-3-phenyl-3-(phenylsulfanyl)-1-(pyrrol-1-yl)-2-propanol (18)

18

Yb(OTf)₃ was used as the Lewis acid. Purification by column chromatography (eluent EtOAc/Hex 1:6) gave the title compound as a colourless oil (68%); eluent EtOAc/P.E. 1:4, R_f = 0.26; $[\alpha]_D^{22}$ –51.12 (*c* 0.80 in DCM); ¹H NMR (400 MHz, CDCl₃) δ 3.24 (1H, d, J = 8.5 Hz, CHSPh), 4.57 (1H, d, J = 3.3 Hz, OH), 5.12 (1H, dd, J = 8.5 and 3.3 Hz, CHCHOH), 6.32 (2H, dd, J = 3.0 and 2.1 Hz, 2 $\times$ H $_{\alpha}$ -pyrrole), 7.14-7.49 (12H, m, Ph, SPh and 2 $\times$ H $_{\beta}$ -pyrrole); ¹³C NMR (100 MHz, CDCl₃) δ 58.3, 72.5, 114.3, 114.4, 119.1, 119.2, 128.2, 128.6, 128.8, 129.3, 133.2, 134.4, 135.7, 141.0, 170.8; IR $\nu_{\max}$ /cm⁻¹ 3466, 2856, 2898, 1708, 1583, 1469, 1323, 1074, 914, 863; MS m/z (EI) 323 (M⁺, 7), 306 (8), 239 (9), 199 (100), 165 (12), 109 (19), 91 (62); HRMS: found 323.0980, C₁₉H₁₇NO₂S requires 323.0978; Anal. Calc'd for C₁₉H₁₇NO₂S: C, 70.56, H, 5.30, N, 4.33. Found: C, 70.01, H, 5.49, N, 4.16.

Further Transformations of the Ring-Opened Epoxy-Amides

(2*S*,3*R*)-2-Hydroxy-3-phenyl-3-(phenylsulfanyl)propanoic acid (19)

19

A solution of **18** (40.0 mg, 0.12 mmol) in DME (0.5 mL) was treated with a 2M solution of NaOH (2 mL) at r.t. The resulting mixture was stirred for 16 h. After this time, water (2 mL) and ether (2 mL) were added and the phases separated. The pH of the aqueous phase was adjusted to 2 with a 0.1 M solution of HCl. After extraction of the aqueous phase with ether (3 $\times$ 5 mL), the organic layers were combined, dried (MgSO₄) and concentrated *in vacuo* to give the title compound as a white solid (23.0 mg, 70%); eluent DCM/MeOH. 1:1, R_f = 0.71; m.p. 164-168 °C (MeOH/DCM); $[\alpha]_D^{22}$ –29.22 (*c* 0.41 in MeOH); ¹H NMR (400 MHz, MeOH-*d*₄) δ 4.37 (1H, d, J = 4.6 Hz, CHSPh), 4.82 (1H, d, J = 4.6 Hz, CHCHOH), 7.15-7.28 (6H, m, Ph and SPh), 7.37-7.50 (4H, m, Ph and SPh); ¹³C NMR (100 MHz, MeOH-*d*₄) δ 51.2, 82.2, 125.1, 126.4, 126.8, 128.0, 128.8, 128.9, 138.1, 140.2, 177.0; IR $\nu_{\max}$ /cm⁻¹ 3396, 2919, 2850, 1732, 1438, 1099, 695.

Total synthesis of SK&F 104353 (Scheme 7, Route A,⁵ Route B compounds below)

We were able to prepare this molecule by two complementary routes, both of which involved the sulfur ylide methodology discussed above as the key step (Scheme 7).

Scheme 7 Two approaches to the total synthesis of SK&F 104353.

Reagents and conditions. (a) t-BuNH₂, toluene, 110 °C, 93%; (b) (i) LDA, Ph(CH₂)₇Br, THF, -78 °C to 60 °C, (ii) HCl, 85%; (c) **22**, KOH, MeOH, -30 °C, 24 h, 77%, (d) (i) PhLi, THF, -78 °C, 84%, (ii) m-CPBA, CH₂Cl₂, Δ, 68%, (e) HS-(CH₂)₂-CO₂Me, Yb(OTf)₃, CH₂Cl₂, -78 °C to r.t., 64%, (f) NaOH, MeOH, H₂O, r.t., 16 h, 81%, (g) **22**, KOH, EtOH, -50 °C, 48 h, 62%; (h) DDQ, dioxane, 85 °C, 8 h, 81%; (i) HS-(CH₂)₂-CO₂Me, Yb(OTf)₃, CH₂Cl₂, -78 °C to r.t., 58%; (j) NaOH, DME, H₂O, r.t., 16 h, 85%

Our original synthesis was carried out in six steps from the commercially available o-methyl benzaldehyde. The starting aldehyde was alkylated in the benzylic position, following a two step procedure reported by Forth and co-workers to provide compound **22**. Diastereomerically pure sulfonium salt **1b** was reacted with the sterically hindered aldehyde **22** in the presence of KOH at

-30 °C to yield the corresponding glycidic amide **23** in 90% ee. The epoxy-amide was converted into the epoxy-ester via a two step sequence involving the addition of phenyl lithium followed by a Baeyer-Villiger oxidation, and this was followed by regioselective ring-opening of the epoxy-ester with the desired thiol. Subsequent hydrolysis gave the target molecule **20** in 21% overall yield.

2-Methyl-*N*-[(2-methylphenyl)methylidene]-2-propanamine (**21**)⁷

21

A stirred solution of *o*-tolylaldehyde (8.10 g, 0.06 mol), *t*-butylamine (10.20 g, 0.14 mol) and 50 mL of dry toluene was heated at reflux for 5 h. The reaction mixture was cooled to r.t. and concentrated *in vacuo*. Purification by vacuum distillation (70-73°C, 0.6 mmHg) gave the title compound as a colourless oil (10.81 g, 93%); ¹H NMR (400 MHz, CDCl₃) δ 1.30 (9H, s, *t*-Bu), 2.46 (3H, s, CH₃), 7.25-7.11 (3H, m, H-3, H-4 and H-5), 7.86-7.83 (1H, m, H-6), 8.56 (1H, s, CHN); ¹³C NMR (100 MHz, CDCl₃) δ 19.2, 29.8, 57.5, 126.4, 127.1, 129.6, 130.5, 135.1, 137.1, 153.7.

2-(8-Phenylloctyl)benzaldehyde (**22**)⁷

22

A stirred solution of **21** (1.12 g, 6.40 mmol), and 2,2,6,6-tetramethylpiperidine (90.0 mg, 0.64 mmol) in dry THF (10 mL) was cooled to -5 °C. To this mixture was added *n*-BuLi (1.6 M, 4.00 mL, 6.42 mmol) over 60 min *via* a syringe pump (the temperature was maintained below 0 °C). The mixture was stirred for 30 min and 7-phenyl-heptyl chloride (1.12 g, 5.30 mmol) in dry THF (5 mL) was quickly added. The reaction mixture was heated for 2 h at 55 °C, cooled to 40 °C and then quenched by the slow addition of a 0.1 M solution of HCl. Hydrolysis was completed by heating the mixture at 55 °C for 2.5 h. The mixture was cooled to r.t. and the phases were separated. The aqueous phase was extracted with hexane (20 mL) and the combined organic extracts were washed with water (20 mL). The extracts were dried (MgSO₄) and concentrated *in vacuo*. The resulting slurry was purified by column chromatography (eluent EtOAc/P.E. 1:15) to give the title compound as a pale yellow oil (1.60 g, 85%); ¹H NMR (400 MHz, CDCl₃) δ 1.30 (8H, m, Ph(CH₂)₂(CH₂)₄(CH₂)₂), 1.58 (4H, m, PhCH₂CH₂(CH₂)₄CH₂CH₂), 2.58 (2H, t, *J* = 7.7 Hz, PhCH₂(CH₂)₇), 2.98 (2H, t, *J* = 7.7 Hz, Ph(CH₂)₇CH₂), 7.13-7.33 (2H, m, H-4 and H-5), 7.45 (1H,

m, H-3), 7.80 (1H, dd, $J = 7.9$ and 1.2 Hz, H-6), 10.25 (1H, s CHO); ^{13}C NMR (100 MHz, CDCl_3) δ 29.2, 29.3, 29.4, 29.5, 31.4, 32.3, 32.4, 35.9, 125.5, 126.3, 128.2, 128.3, 130.9, 131.3, 133.6, 133.7, 142.8, 145.7, 192.2.

1-((2*R*,3*S*)-3-[2-(8-Phenyl)octyl]phenyl]oxiranyl)carbonyl-2,5-dihydropyrrole (24)

24

Powdered KOH (35.0 mg, 0.62 mmol) was added to a solution of **22** (73.0 mg, 0.24 mmol) and the chiral sulfonium salt **10b** (0.10 g, 0.24 mmol) in dry methanol (5 mL), at -50 °C under N_2 . The reaction mixture was stirred at this temperature for 48 h. After removal of the solvent under reduced pressure, the crude mixture was directly purified by column chromatography (eluent EtOAc/P.E. 1:2) to give the pure *trans* epoxide as a colourless oil (59.9 mg, 62%); eluent EtOAc/P.E. 1:2, $R_f = 0.30$; $[\alpha]_D^{22} -21.5$ (c 0.80 in CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.30 (8H, m, $\text{Ph}(\text{CH}_2)_2(\text{CH}_2)_4(\text{CH}_2)_2$), 1.59 (4H, m, $\text{PhCH}_2\text{CH}_2(\text{CH}_2)_4\text{CH}_2\text{CH}_2$), 2.58 (2H, t, $J = 7.3$ Hz, $\text{Ph}(\text{CH}_2)_7\text{CH}_2$), 2.73 (2H, m, $\text{PhCH}_2(\text{CH}_2)_7$), 3.46 (1H, d, $J = 1.8$ Hz, $\text{ArCH}(\text{O})\text{CH}$), 4.32 (1H, d, $J = 1.8$ Hz, $\text{ArCH}(\text{O})\text{CH}$), 4.30-4.41 (3H, m, $3 \times \text{CONCHHCH}=\text{CH}$), 4.49 (1H, m, $\text{CONCHHCH}=\text{CH}$), 5.79 (1H, m, $\text{CH}=\text{CH}$), 5.89 (1H, m, $\text{CH}=\text{CH}$), 7.14-7.37 (9H, m, Ph and $4 \times \text{H-Ar}$); ^{13}C NMR (100 MHz, CDCl_3) δ 29.3, 29.4, 29.5, 31.6, 31.6, 31.7, 32.8, 36.0, 52.9, 53.7, 55.7, 57.4, 124.6, 124.7, 126.3, 126.7, 126.8, 128.2, 128.3, 128.4, 129.0, 134.2, 141.8, 143.1, 165.3; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3025, 2925, 2853, 1660, 1623, 1452, 1390, 749, 698, 671; MS m/z (EI) 404 (M^+ , 14), 386 (67), 376 (17), 347 (22), 319 (32), 198 (18), 131 (28), 11 (57), 91 (100), 68 (49); HRMS: found 404.2545, $\text{C}_{27}\text{H}_{33}\text{NO}_2$ requires 404.2565; Enantiomeric excess (81%) was determined by HPLC (Chiracel[®] OD column, UV-VIS detector); mobile phase: 10% *i*-PrOH, 90% hexane; flow rate (mL/min.): 1; first enantiomer: 20.7 min (minor) and second enantiomer 27.4 min (major).

1-((2*R*,3*S*)-3-[2-(8-Phenyl)octyl]phenyl]oxiranyl)carbonyl-pyrrole (25)

25

A solution of **24** (0.10 g, 0.25 mmol) in dry 1,4-dioxane (5 mL), was treated with DDQ (67.6 mg, 0.30 mmol) for 8 h at 85 °C. After cooling to r.t., the reaction mixture was concentrated under reduced pressure followed by the addition of brine (10 mL) and DCM (10 mL) to the residue. A 0.1 M solution of NaHCO_3 (5 mL) was added to this mixture and the aqueous layer was extracted with

DCM (2×10 mL). The combined extracts were washed with brine (10mL), dried (MgSO_4) and concentrated *in vacuo*. Purification by column chromatography (eluent EtOAc/P.E. 1:9) provided the title compound as a colourless oil (79.3 mg, 81%); eluent EtOAc/P.E. 1:9, $R_f = 0.42$; $[\alpha]_D^{22} -12.2$ (c 0.62 in CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.24 (8H, m, $\text{Ph}(\text{CH}_2)_2(\text{CH}_2)_4(\text{CH}_2)_2$), 1.55 (4H, m, $\text{PhCH}_2\text{CH}_2(\text{CH}_2)_4\text{CH}_2\text{CH}_2$), 2.55 (2H, t, $J = 8.0$ Hz, $\text{Ph}(\text{CH}_2)_7\text{CH}_2$), 2.68 (2H, m, $\text{PhCH}_2(\text{CH}_2)_7$), 3.93 (1H, d, $J = 1.8$ Hz, $\text{ArCH}(\text{O})\text{CH}$), 4.38 (1H, d, $J = 1.8$ Hz, $\text{ArCH}(\text{O})\text{CH}$), 6.34 (2H, m, $2 \times \text{H}_\alpha$ -Pyrrole), 7.13-7.49 (11H, m, Ph, $4 \times \text{H-Ar}$ and $2 \times \text{H}_\beta$ -Pyrrole); ^{13}C NMR (100 MHz, CDCl_3) δ 29.2, 29.3, 29.5, 31.1, 31.2, 32.4, 36.0, 56.9, 57.0, 67.2, 114.2, 119.1, 124.3, 125.6, 126.9, 128.3, 128.4, 128.8, 129.8, 132.4, 136.5, 137.9, 141.7, 143.4, 176.8; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3025, 2926, 2854, 1721, 1469, 1349, 1281, 723, 698; MS m/z (EI) 402 ($[\text{M}+\text{H}]^+$, 8), 373 (11), 344 (20), 317 (6), 212 (8), 168 (7), 145 (8), 131 (34), 117 (29), 105 (43), 91 (100); HRMS: found 401.2354, $\text{C}_{27}\text{H}_{31}\text{NO}_2$ requires 401.2344.

3-[(1R,2R)-2-Hydroxy-3-oxo-1-[2-(8-phenyloctyl)phenyl]-3-(pyrrol-yl)propyl]sulfanyl}propionic acid methyl ester (26)

26

To a solution of **25** (23.2 mg, 0.06 mmol) and 3-mercaptopropionate (53.7 mg, 0.48 mmol), in dry THF (2 mL), cooled at -78°C , was added $\text{Yb}(\text{OTf})_3$ (53.6 mg, 0.085 mmol). The resulting solution was stirred overnight and during that time the temperature was allowed to warm to r.t. After this, a 0.1 M solution of HCl (0.5 mL) was added. The reaction mixture was diluted with ether (5 mL) and water (5 mL) and the organic phase was separated. The aqueous phase was extracted with ether (2×5 mL), and the combined organic phases were dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent EtOAc/P.E. 1:4) to give the title compound as a colourless oil (17.7 mg, 58%); eluent EtOAc/P.E. 1:4, $R_f = 0.25$; $[\alpha]_D^{22} -38.8$ (c 0.88 in CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.15-1.38 (8H, m, $\text{Ph}(\text{CH}_2)_2(\text{CH}_2)_4(\text{CH}_2)_2$), 1.46 (2H, m, $\text{Ph}(\text{CH}_2)_6\text{CH}_2\text{CH}_2$), 1.61 (2H, m, $\text{PhCH}_2\text{CH}_2(\text{CH}_2)_6$), 2.28 (2H, m, $\text{Ph}(\text{CH}_2)_7\text{CH}_2$), 2.51 (2H, t, $J = 7.2$ Hz, $\text{SCH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 2.63 (2H, t, $J = 7.7$ Hz, $\text{PhCH}_2\text{CH}_2(\text{CH}_2)_4\text{CH}_2\text{CH}_2$), 2.74 (2H, t, $J = 7.2$ Hz, $\text{SCH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 3.19 (1H, d, $J = 8.5$ Hz, CHCHOH), 3.64 (3H, s, CO_2CH_3), 4.66 (1H, d, $J = 1.9$ Hz, OH), 5.16 (1H, dd, $J = 8.5$ and 1.9 Hz, CHCHOH), 6.32 (2H, m, $2 \times \text{H}_\alpha$ -pyrrole), 7.08-7.69 (11H, m, Ph, $4 \times \text{H-Ar}$ and $2 \times \text{H}_\beta$ -pyrrole); ^{13}C NMR (100 MHz, CDCl_3) δ 27.8, 29.3, 29.3, 29.4, 29.4, 29.5, 31.6, 31.6, 32.0, 34.4, 36.0, 51.8, 72.9, 114.3, 119.3, 125.6, 126.3, 128.2, 128.3, 128.3, 128.4, 128.4, 129.6, 130.0, 134.1, 141.0, 142.9, 169.7, 172.8; IR $\nu_{\text{max}}/\text{cm}^{-1}$ 3466,

3025, 2925, 2853, 1714, 1469, 1322, 1074, 732, 698; MS m/z (CI) 522 ($[M+H]^+$, 13), 504 ($[M-H_2O]^+$, 10), 442 (8), 430 (23), 402 (82), 279 (12), 207 (13), 175 (9), 162 (10), 121 (11), 89 (61), 85 (100); Anal. Calc'd for $C_{31}H_{39}NO_4S$: C, 71.37, H, 7.53, N, 2.68. Found: C, 71.58, H, 7.71, N, 2.33.

(2*R*,3*R*)-3-(2-Carboxyethylsulfanyl)-2-hydroxy-3-[2-(8-phenyloctyl)phenyl]-propionic acid (SK&F 104353) (20**)²**

20

A solution of **26** (51.0 mg, 0.09 mmol) in MeOH (0.5 mL) was treated with a 2.5 M solution of NaOH (0.5 mL) at r.t. The resulting mixture was stirred for 16 h. After this time, water (1 mL) and ether (1 mL) were added and the phases separated. The pH of the aqueous phase was adjusted to 2 with a 0.1 M solution of HCl. After extraction of the aqueous phase with ether (3×2 mL), the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a colourless oil (34.5 mg, 77%); 1H NMR (400 MHz, $CDCl_3$) δ 1.34 (8H, m, $Ph(CH_2)_2(CH_2)_4(CH_2)_2$), 1.60 (4H, m, $PhCH_2CH_2(CH_2)_4CH_2CH_2$), 2.58-2.84 (8H, m, $SCH_2CH_2CO_2H$ and $PhCH_2(CH_2)_6CH_2$), 4.58 (1H, d, $J = 4.7$ Hz, $CHCHOH$), 4.64 (1H, d, $J = 4.7$ Hz, $CHCHOH$), 7.18-7.30 (8H, m, Ph and Ar), 7.58 (1H, d, $J = 7.3$ Hz, H-2 / H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 29.4, 29.5, 29.5, 29.7, 31.2, 31.5, 32.7, 34.2, 36.0, 73.1, 125.6, 126.3, 128.0, 128.3, 128.4, 128.6, 129.8, 134.5, 141.1, 142.9, 175.7, 177.4. ($1 \times Csp^3$ is not observed).

Cross-Over Experiments

N,N-Diethyl α -methythioethanamide.

To a three necked flask cooled under nitrogen in a water/ice bath and fitted with a reflux condenser, dropping funnel and a water gas trap and was placed thionyl chloride (3.35 mL, 45.9 mmol) and to this was added dropwise and with rapid stirring methylthioacetic acid (4.0 mL, 45.9 mmol). The reaction vessel was then left to stir for a further 90 min during which time evolution of HCl and SO₂ occurred and the mixture gradually turned pea green. The reaction mixture was diluted by the addition of ether (40 mL) and cooled to -10 °C. Diethylamine (10.1 mL, 91.8 mmol) in ether (40 mL) was added to the acid chloride over a period of approx. 15min where upon a white precipitate of amine hydrochloride formed. The reaction vessel was stirred for a further hour at -10 °C before being worked up by the addition of ice cold water (40mL) to dissolve the precipitated amine hydrochloride. The organic layer was separated off and washed successively with HCl (3% v/v aq, 1H NMR 3 x 10 mL), dil. K₂CO₃ (3x10 mL) and then brine (2x10 mL) until neutral. The combined extracts were then dried (MgSO₄) and concentrated *in vacuo* to yield a pale yellow oil. The product was then purified by distillation using Kugelrohr apparatus to furnish a clear oil (5.724g, 77%), bp 90 °C, 0.1mmHg [bp lit.,⁸ 59-62 °C (0.1mmHg)]; R_f 0.43 (DCM); ¹H NMR (250MHz; CDCl₃) δ 1.10 (3H, t, *J* 7.0, N(CH₂CH₃)₂); 1.18 (3H, t, *J* 7.0, N(CH₂CH₃)₂), 2.15 (3H, s, SCH₃), 3.34 (4H, 2q, *J* 7.0, N(CH₂CH₃)₂), 3.24 (2H, s, CH₂); ¹³C NMR (63MHz; CDCl₃) δ 12.9, 14.3, 15.7, 35.0, 40.2, 42.5, 168.2.

N,N-diethyl-1-hydroxyphenyl-2-methylthiopropionamide.

To a mixture of LiCl (0.80 g, 18.6 mmol) and diisopropylamine (0.98 mL, 6.97 mmol) in THF (10 mL) under nitrogen was added *n*BuLi (5.4 mL, 1.2 M, 6.53 mmol) and the reaction stirred for 1 h. After this time the reaction vessel was cooled to -78 °C and a solution of α -methylthio-*N,N*-diethylamide in THF (10 mL) added dropwise over a period of approx. 30 min, then stirred for 1 h. Finally benzaldehyde (0.39 mL, 3.7 mmol) was added dropwise at -78 °C and the reaction vessel stirred overnight at room temperature. Ethanolic HCl (2M, 10 mL) was then added with rapid

stirring and then the combined organics were washed with satd. NaHCO_3 (2x10mL) followed by brine (2x10 mL), dried (MgSO_4) and reduced *in vacuo* to yield an orange oil. (1:4 *syn:anti* ratio by crude ^1H NMR). This was then purified by flash column chromatography, eluent (2/3 EtOAc/hexane) and the two diastereoisomers separated to yield an initial fraction (132.0 mg, 16%, *syn*) and a lower fraction (527.8 mg, 65%, *anti*) (overall yield 81%); Found: C, 62.93; H, 7.92; N, 5.13; $\text{C}_{14}\text{H}_{21}\text{SO}_2\text{N}$ requires C, 62.89; H, 7.91; N 5.24; ν_{max} (thin film) cm^{-1} 3396 (OH), 2975 and 2933 (CH), 1634 (CO); $m/z(\text{CI})$ 268 (M^+ , 100%), 250 (5), 220 (13), 162 (14) **Syn** : mp 87-89 °C (hexane); R_f 0.48 (2/3 EtOAc/hexane); ^1H NMR (250MHz; CDCl_3) δ 1.00 (6H, 2t, J 7.0, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 2.15 (3H, s, SCH₃), 2.95-3.50 (4H, m, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.40 (1H, d, J 6.5, CH), 4.05 (1H, s, OH), 5.15 (1H, d, J 6.5, CH), 7.20-7.45 (5H, m, aryl-H); ^{13}C NMR (63MHz; CDCl_3) δ 12.9, 13.1, 14.5, 40.7, 42.2, 50.6, 72.3, 126.9, 127.8, 128.1, 140.7, 169.0; **Anti** : mp 70-72 °C (hexane); R_f 0.55 (2/3 EtOAc/hexane); ^1H NMR (250MHz; CDCl_3) δ 0.95 (3H, t, J 7.0, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.05 (3H, t, J 7.0, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 2.10 (3H, s, SCH₃), 2.95-3.50 (4H, m, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.45 (1H, d, J 6.5, CH), 5.00 (1H, d, J 6.5, CH), 7.15-7.35 (5H, m, aryl-H); ^{13}C NMR (63MHz; CDCl_3) δ 13.0, 13.7, 14.2, 40.7, 42.2, 48.8, 75.6, 126.6, 127.8, 128.3, 141.7, 169.9.

N, N diethyl-1 hydroxyphenyl-amyl dimethyl sulfonium tetrafluoroborate (27 and 28).

N, *N*-diethyl-1-hydroxyphenyl--methylthio-propionamide (1.03 g, 3.85 mmol) and trimethyloxonium tetrafluoroborate (0.57 g, 3.85 mmol) were stirred overnight in DCM (8 mL) at room temperature. A white precipitate formed which was filtered off and washed with 95/5 hexane/DCM to yield a creamy white powder (1.30 g, 91%), Found: C, 47.94; H, 6.47; N, 3.69 $\text{C}_{15}\text{H}_{24}\text{SO}_2\text{NBF}_4$ requires C, 47.80; H, 6.55; N 3.79; ν_{max} (thin film) cm^{-1} 3398 (OH), 2923 and 2854 (CH), 1637 (CO); $m/z(\text{FAB})$ 282 (M^+-BF_4 , 100%), 220 (11), 176 (12); **anti** : mp 123-125 °C; ^1H NMR (250MHz; $\text{d}^6\text{-DMSO}$) δ 1.00 (3H, t J 7.0, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.05 (3H, t J 7.0, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 2.80 (3H, s, $\text{S}(\text{CH}_3)_2$), 2.83 (3H, s, $\text{S}(\text{CH}_3)_2$), 2.90-3.50 (4H, m, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 5.20 (2H, m, 2xCH), 6.60 (1H, bs, OH), 7.35-7.50 (5H, m, aryl H); ^{13}C NMR (63MHz; $\text{d}^6\text{-DMSO}$) δ 12.9, 14.5, 23.9, 24.1, 62.6, 71.1, 127.6, 129.0, 129.4, 139.5, 163.2; **Syn**: mp 133-135 °C; ^1H NMR (250MHz; $\text{d}^6\text{-DMSO}$) δ 0.45 (3H, t, J 7.0, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 0.90 (3H, t, J 7.0, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 2.95 (3H, s, $\text{S}(\text{CH}_3)_2$), 3.00 (3H, s, $\text{S}(\text{CH}_3)_2$), 2.75-3.30 (4H, m, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 5.00 (2H, 2d, J

10.6, 2xCH), 6.95 (1H, bs, OH), 7.35-7.50 (5H, m, aryl-H); ^{13}C NMR (63MHz; $\text{d}^6\text{-DMSO}$) δ 12.9, 13.8, 23.2, 25.4, 60.1, 73.4, 127.3, 129.2, 129.6, 140.3, 163.2.

General Procedure for cross-over reactions in dichloromethane.

To a solution of sulfonium salt **31** (0.10 g, 0.27 mmol) and *p*-nitrobenzaldehyde (0.12 g, 0.81 mmol) in dichloromethane (6 mL) was added sodium hydroxide (16.3 mg, 0.41 mmol) and a few drops of water. The mixture was stirred for 48 hrs. and after dilution with dichloromethane, the reaction mixture was washed with water, dried (MgSO_4) and concentrated *in vacuo*. The crude reaction mixture was analysed by ^1H NMR to determine the ratios of epoxides produced. The crude product was then purified by flash column chromatography, eluent (1/1 ethyl acetate/petrol) to give solely *trans-N,N*-diethyl-3-(*p*-nitrophenyl)-2-oxiranecarboxamide as a creamy yellow solid. Literature data as described in reference 5.

X-Ray Crystallographic Data

General directions

Crystallographic data for compound **6b** are presented in Tables 1-x. A single crystal of the compound was coated in perfluoropolyether oil and mounted on a glass fibre. X-ray measurements were made using a Bruker SMART CCD area-detector diffractometer with Mo-K α radiation ($\lambda = 0.71073$ Å). Intensities were integrated⁹ from several series of exposures, each exposure covering 0.3° in ω or ϕ . Absorption corrections were applied, based on multiple and symmetry-equivalent measurements.¹⁰ The structure was solved by direct methods and refined by least squares on weighted F^2 values for all reflections (see Table 1).¹¹ All non-hydrogen atoms were assigned anisotropic displacement parameters and refined without positional constraints. All hydrogen atoms were constrained to ideal geometries and refined with fixed isotropic displacement parameters. Refinement proceeded smoothly to give the residuals shown in Table 1. Complex neutral-atom scattering factors were used.¹²

Sulfonium salt **6b**:

Table 1. Crystal data and structure refinement for **6b**

Identification code	sh1a	
Empirical formula	C20 H34 Cl N O6 S	
Formula weight	451.99	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.6504(9) Å b = 13.3702(18) Å c = 11.4418(19) Å	$\alpha = 90^\circ$ $\beta = 98.291(12)^\circ$ $\gamma = 90^\circ$
Volume	1158.1(3) Å ³	
Z	2	
Density (calculated)	1.296 Mg/m ³	
Absorption coefficient	0.289 mm ⁻¹	
F(000)	484	
Crystal size	0.2 x 0.2 x 0.2 mm	
θ range for data collection	1.80 to 27.48°	
Index ranges	-9<= h <=9, -16<= k <=17, -13<= l <=14	
Reflections collected	6051	
Independent reflections	4106 [$R_{\text{int}} = 0.0254$]	
Completeness to $\theta = 27.48^\circ$	96.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.940 and 0.845	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4106 / 1 / 269	
Goodness-of-fit on F^2	S = 1.041	
R indices [for 3598 reflections with $I > 2\sigma(I)$]	$R_1 = 0.0348$, $wR_2 = 0.0810$	
R indices (for all 4106 data)	$R_1 = 0.0446$, $wR_2 = 0.0856$	
Weighting scheme	$w_1 = \sigma^2(F_o^2) + (aP)^2 + (bP)$, where $P = [\max(F_o^2, 0) + 2F_c^2]/3$ a = 0.0444, b = 0.0439	
Absolute structure (Flack) parameter	0.00(5)	
Extinction coefficient	0.0094(16)	
Largest diff. peak and hole	0.211 and -0.216 eÅ ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å² $\times 10^3$) for **6b**. U(eq) is defined as one third of the trace of the orthogonalised U_{ij} tensor.

	x	y	z	U(eq)
C(1)	4673(3)	4623(2)	6836(2)	27(1)
C(2)	5618(3)	4130(2)	8001(2)	29(1)
C(3)	4590(3)	3128(2)	8035(2)	30(1)
C(4)	5135(4)	2519(2)	6999(2)	35(1)
C(5)	4117(4)	3013(2)	5882(3)	34(1)
C(6)	3161(3)	3890(2)	6395(2)	28(1)
C(7)	2645(3)	3433(2)	7543(2)	29(1)
C(8)	7089(4)	4749(2)	9854(3)	52(1)
C(9)	4894(4)	2602(2)	9218(3)	41(1)
C(10)	1386(4)	2535(2)	7297(3)	41(1)
C(11)	1758(3)	4165(2)	8307(3)	35(1)
C(12)	3115(3)	6279(2)	5626(3)	35(1)
C(13)	6099(3)	6510(2)	7261(3)	32(1)
C(14)	5778(3)	7625(2)	7358(2)	29(1)
C(15)	6780(4)	9326(2)	7206(2)	33(1)
C(16)	7231(4)	9777(2)	8403(3)	40(1)
C(17)	8451(5)	10441(2)	8678(4)	63(1)
C(18)	8884(3)	7890(2)	7045(2)	34(1)
C(19)	10039(4)	7592(2)	8160(3)	40(1)
C(20)	9574(4)	7518(2)	9201(3)	43(1)
N(1)	7111(3)	8239(2)	7189(2)	28(1)
O(1)	4334(2)	7920(1)	7566(2)	38(1)
O(2)	5551(2)	4780(1)	8982(2)	34(1)
S(1)	3980(1)	5899(1)	7099(1)	28(1)
Cl(1)	1600(1)	9937(1)	5101(1)	32(1)
O(3)	3267(2)	10405(2)	5506(2)	45(1)
O(4)	1851(3)	8896(2)	4925(2)	63(1)
O(5)	857(3)	10387(2)	3996(2)	53(1)
O(6)	409(2)	10084(2)	5940(2)	48(1)

Table 3. Bond lengths [Å] and angles [°] for **6b**

C(1)-C(6)	1.544(3)
C(1)-C(2)	1.567(4)
C(1)-S(1)	1.824(2)
C(1)-H(1)	1.0000
C(2)-O(2)	1.427(3)
C(2)-C(3)	1.557(3)
C(2)-H(2)	1.0000
C(3)-C(9)	1.513(4)
C(3)-C(4)	1.544(4)
C(3)-C(7)	1.567(4)
C(4)-C(5)	1.546(4)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.542(4)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.550(4)
C(6)-H(6)	1.0000
C(7)-C(11)	1.533(4)
C(7)-C(10)	1.540(4)
C(8)-O(2)	1.429(3)
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-S(1)	1.793(3)
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-C(14)	1.517(3)
C(13)-S(1)	1.802(2)
C(13)-H(13A)	0.9900

C(13)-H(13B)	0.9900
C(14)-O(1)	1.228(3)
C(14)-N(1)	1.344(3)
C(15)-N(1)	1.476(3)
C(15)-C(16)	1.491(4)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-C(17)	1.294(4)
C(16)-H(16)	0.9500
C(17)-H(17A)	0.9500
C(17)-H(17B)	0.9500
C(18)-N(1)	1.466(3)
C(18)-C(19)	1.498(4)
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-C(20)	1.294(4)
C(19)-H(19)	0.9500
C(20)-H(20A)	0.9500
C(20)-H(20B)	0.9500
Cl(1)-O(4)	1.423(2)
Cl(1)-O(6)	1.4291(19)
Cl(1)-O(3)	1.4360(19)
Cl(1)-O(5)	1.441(2)
C(6)-C(1)-C(2)	104.07(19)
C(6)-C(1)-S(1)	115.20(16)
C(2)-C(1)-S(1)	111.23(17)
C(6)-C(1)-H(1)	108.7
C(2)-C(1)-H(1)	108.7
S(1)-C(1)-H(1)	108.7
O(2)-C(2)-C(3)	115.4(2)
O(2)-C(2)-C(1)	110.43(19)
C(3)-C(2)-C(1)	102.1(2)
O(2)-C(2)-H(2)	109.5
C(3)-C(2)-H(2)	109.5
C(1)-C(2)-H(2)	109.5
C(9)-C(3)-C(4)	114.7(2)
C(9)-C(3)-C(2)	114.1(2)
C(4)-C(3)-C(2)	104.0(2)
C(9)-C(3)-C(7)	117.3(2)
C(4)-C(3)-C(7)	102.1(2)
C(2)-C(3)-C(7)	102.92(19)
C(3)-C(4)-C(5)	104.4(2)
C(3)-C(4)-H(4A)	110.9
C(5)-C(4)-H(4A)	110.9
C(3)-C(4)-H(4B)	110.9
C(5)-C(4)-H(4B)	110.9
H(4A)-C(4)-H(4B)	108.9
C(6)-C(5)-C(4)	102.7(2)
C(6)-C(5)-H(5A)	111.2
C(4)-C(5)-H(5A)	111.2
C(6)-C(5)-H(5B)	111.2
C(4)-C(5)-H(5B)	111.2
H(5A)-C(5)-H(5B)	109.1
C(5)-C(6)-C(1)	103.47(19)
C(5)-C(6)-C(7)	102.5(2)
C(1)-C(6)-C(7)	104.1(2)
C(5)-C(6)-H(6)	115.1
C(1)-C(6)-H(6)	115.1
C(7)-C(6)-H(6)	115.1
C(11)-C(7)-C(10)	106.6(2)
C(11)-C(7)-C(6)	114.8(2)
C(10)-C(7)-C(6)	112.4(2)
C(11)-C(7)-C(3)	115.9(2)
C(10)-C(7)-C(3)	113.5(2)
C(6)-C(7)-C(3)	93.57(19)
O(2)-C(8)-H(8A)	109.5
O(2)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
O(2)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(3)-C(9)-H(9A)	109.5
C(3)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(3)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(7)-C(10)-H(10A)	109.5
C(7)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(7)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5

C(7)-C(11)-H(11A)	109.5
C(7)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(7)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
S(1)-C(12)-H(12A)	109.5
S(1)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
S(1)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(14)-C(13)-S(1)	107.51(17)
C(14)-C(13)-H(13A)	110.2
S(1)-C(13)-H(13A)	110.2
C(14)-C(13)-H(13B)	110.2
S(1)-C(13)-H(13B)	110.2
H(13A)-C(13)-H(13B)	108.5
O(1)-C(14)-N(1)	123.6(2)
O(1)-C(14)-C(13)	119.3(2)
N(1)-C(14)-C(13)	117.1(2)
N(1)-C(15)-C(16)	113.2(2)
N(1)-C(15)-H(15A)	108.9
C(16)-C(15)-H(15A)	108.9
N(1)-C(15)-H(15B)	108.9
C(16)-C(15)-H(15B)	108.9
H(15A)-C(15)-H(15B)	107.8
C(17)-C(16)-C(15)	124.4(3)
C(17)-C(16)-H(16)	117.8
C(15)-C(16)-H(16)	117.8
C(16)-C(17)-H(17A)	120.0
C(16)-C(17)-H(17B)	120.0
H(17A)-C(17)-H(17B)	120.0
N(1)-C(18)-C(19)	115.5(2)
N(1)-C(18)-H(18A)	108.4
C(19)-C(18)-H(18A)	108.4
N(1)-C(18)-H(18B)	108.4
C(19)-C(18)-H(18B)	108.4
H(18A)-C(18)-H(18B)	107.5
C(20)-C(19)-C(18)	126.7(3)
C(20)-C(19)-H(19)	116.6
C(18)-C(19)-H(19)	116.6
C(19)-C(20)-H(20A)	120.0
C(19)-C(20)-H(20B)	120.0
H(20A)-C(20)-H(20B)	120.0
C(14)-N(1)-C(18)	123.8(2)
C(14)-N(1)-C(15)	117.6(2)
C(18)-N(1)-C(15)	118.5(2)
C(2)-O(2)-C(8)	114.4(2)
C(12)-S(1)-C(13)	99.93(13)
C(12)-S(1)-C(1)	100.76(13)
C(13)-S(1)-C(1)	99.38(11)
O(4)-Cl(1)-O(6)	110.01(14)
O(4)-Cl(1)-O(3)	109.91(13)
O(6)-Cl(1)-O(3)	110.27(13)
O(4)-Cl(1)-O(5)	109.15(15)
O(6)-Cl(1)-O(5)	108.80(13)
O(3)-Cl(1)-O(5)	108.67(13)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **6b** (the anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	25(1)	22(1)	35(2)	-2(1)	9(1)	-2(1)
C(2)	28(1)	26(1)	32(2)	-3(1)	6(1)	2(1)
C(3)	32(1)	24(1)	33(2)	0(1)	5(1)	0(1)
C(4)	40(2)	26(1)	40(2)	-3(1)	5(1)	1(1)
C(5)	43(2)	27(1)	34(2)	-7(1)	6(1)	-3(1)
C(6)	28(1)	23(1)	32(2)	-1(1)	4(1)	-4(1)
C(7)	29(1)	27(1)	31(2)	3(1)	3(1)	-4(1)
C(8)	51(2)	49(2)	51(2)	-14(2)	-13(1)	5(1)
C(9)	48(2)	35(2)	39(2)	8(1)	3(1)	3(1)
C(10)	41(2)	34(2)	49(2)	4(1)	8(1)	-14(1)
C(11)	33(1)	37(2)	37(2)	7(1)	13(1)	0(1)
C(12)	32(1)	27(1)	45(2)	5(1)	2(1)	-3(1)
C(13)	24(1)	26(1)	48(2)	-7(1)	8(1)	-6(1)
C(14)	30(1)	26(1)	30(2)	-2(1)	4(1)	-1(1)

C(15)	39(1)	25(1)	36(2)	6(1)	4(1)	-3(1)
C(16)	49(2)	26(2)	45(2)	0(1)	7(1)	4(1)
C(17)	73(2)	35(2)	76(3)	-10(2)	-6(2)	-3(2)
C(18)	32(1)	33(2)	41(2)	-2(1)	15(1)	-8(1)
C(19)	28(1)	33(2)	60(2)	-7(1)	6(1)	2(1)
C(20)	38(2)	40(2)	47(2)	1(2)	-1(1)	10(1)
N(1)	28(1)	25(1)	31(1)	1(1)	4(1)	-2(1)
O(1)	31(1)	31(1)	54(1)	-3(1)	12(1)	0(1)
O(2)	35(1)	31(1)	35(1)	-7(1)	0(1)	3(1)
S(1)	24(1)	22(1)	38(1)	-1(1)	10(1)	-2(1)
Cl(1)	25(1)	30(1)	42(1)	1(1)	10(1)	-3(1)
O(3)	28(1)	54(1)	54(1)	-7(1)	8(1)	-11(1)
O(4)	58(1)	34(1)	99(2)	-12(1)	16(1)	2(1)
O(5)	43(1)	73(2)	42(1)	18(1)	2(1)	-13(1)
O(6)	41(1)	53(1)	54(1)	5(1)	24(1)	-3(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **6b**

	x	y	z	U(eq)
H(1)	5517	4641	6246	32
H(2)	6877	3987	7920	34
H(4A)	4795	1808	7053	42
H(4B)	6426	2559	6994	42
H(5A)	4935	3255	5349	41
H(5B)	3263	2541	5446	41
H(6)	2160	4186	5845	33
H(8A)	7191	4085	10222	78
H(8B)	6991	5257	10459	78
H(8C)	8139	4882	9479	78
H(9A)	4195	1986	9175	61
H(9B)	4535	3042	9825	61
H(9C)	6150	2438	9419	61
H(10A)	1140	2253	8047	62
H(10B)	1938	2024	6857	62
H(10C)	278	2756	6829	62
H(11A)	636	4394	7866	52
H(11B)	2536	4740	8511	52
H(11C)	1536	3827	9031	52
H(12A)	2886	7000	5614	52
H(12B)	2011	5920	5365	52
H(12C)	3975	6124	5095	52
H(13A)	6856	6266	7979	38
H(13B)	6699	6369	6568	38
H(15A)	5517	9452	6916	40
H(15B)	7485	9659	6658	40
H(16)	6579	9563	9004	48
H(17A)	9128	10672	8099	75
H(17B)	8669	10698	9460	75
H(18A)	9486	8429	6662	41
H(18B)	8764	7310	6502	41
H(19)	11235	7442	8098	48
H(20A)	8392	7660	9311	51
H(20B)	10415	7322	9854	51

Computational details

Computations have been carried out using the Jaguar 4.0 pseudospectral program package. All species have been fully geometry optimized, and the Cartesian coordinates are supplied below. In the case of transition states, the “loose” geometry convergence parameters within Jaguar (which correspond to rms gradients below 0.0015 hartree/au) have been used. Test calculations using the standard convergence criteria led to insignificant changes in structure, but were much more time consuming. Previous computational investigations of reactivity and selectivity in sulfur ylide reactions (see ref. 52 and 56) indicate that such reactions can be properly described using B3LYP method. Accordingly, geometry optimization was carried out using the well established B3LYP hybrid density functional as implemented in Jaguar. The standard split valence polarized 6-31G* basis set was used for optimization. The covalent radius of the sulfur atom was set to 1.7 Å for optimization and single point calculations of ring closure TSs. Because of the importance of solvent effects, the optimization was carried out using the polarizable continuum-Poisson method as incorporated in Jaguar. The results are not expected to depend strongly on the parameters used for the continuum solvent, so we have used a single set of parameters, *i.e.* a dielectric constant of 24.3, and a solvent probe radius of 2.27055 Å, which are suitable for ethanol, the solvent used in these reactions. All given energies are obtained after corresponding single point calculations at the B3LYP/6-311+G**(ethanol) level using the fine grid and high accuracy parameters within Jaguar. Frequency calculations for large molecules of the type studied here, especially if solvation effects need to be taken into account, are of prohibitive computational expense and have not been performed, so that we cannot be absolutely certain that the optimized structures have the desired character as minima or transition states, and cannot either include zero-point energy or thermal corrections. However, given the low symmetry of the molecules, it is extremely unlikely that the optimized structures correspond to anything else than minima or transition states. Zero-point energy corrections are expected to be fairly small and to be near identical for isomeric pathways leading to *cis* and *trans* aziridine so that their neglect should be of little consequence.

There are usually several local minima or saddle points corresponding to each intermediate or transition state. This is due to the possibility of multiple conformations of substituents. We have made a systematic attempt to locate all possible local minima and saddle points, with the data presented referring to the lowest energy form unless mentioned otherwise.

Energies and Geometries

All geometries have been optimized at the B3LYP/6-31G* level of theory including a continuum description of ethanol solvent (EtOH). Energies are given in a.u., geometries as Cartesian coordinates in Å.

Me₂SCHCONMe₂

E(B3LYP 6-31G*) = -764.56269
 E(B3LYP 6-311+G**) = -764.70281
 E(B3LYP 6-31G*(EtOH)) =
 -764.58734
 E(B3LYP 6-311+G**(EtOH)) =
 -764.73034

S	-2.04032	.34792	-.48556
C	-2.69319	1.86454	.32284
C	-1.38333	-.66384	.70847
C	-1.90501	-1.99766	.77637
O	-2.80391	-2.43010	.00611
N	-1.37588	-2.83815	1.74550
C	-1.87747	-4.19847	1.87887
C	-.33088	-2.41118	2.66483
C	-.64554	1.12291	-1.39147
H	-3.01059	2.56980	-.45163
H	-1.92387	2.30988	.95963
H	-3.55250	1.55781	.92360
H	-.63504	-.25152	1.37232
H	-1.08194	-4.93719	1.70644
H	-2.29293	-4.37345	2.88116
H	-2.66290	-4.34712	1.13937
H	-.07072	-3.24810	3.31747
H	-.65795	-1.57645	3.29923
H	.57823	-2.10169	2.13278
H	-.14054	.32456	-1.94020
H	.04498	1.59369	-.68630
H	-1.04629	1.86395	-2.09021

PhCHO

E(B3LYP 6-31G*) = -345.570618
 E(B3LYP 6-311+G**) =
 -345.66856
 E(B3LYP 6-31G*(EtOH)) =
 -345.584112
 E(B3LYP 6-311+G**(EtOH)) =
 -345.68089

C	-1.08581	.81759	.00000
C	-.37228	-.39047	.00000
C	1.03396	-.37928	.00000
C	1.71500	.83450	.00000
C	.99757	2.03971	.00000
C	-.40111	2.03278	.00000
H	-2.17419	.79593	.00000
H	1.57287	-1.32300	.00000
H	2.80212	.84927	.00000
H	1.53230	2.98645	.00000
H	-.95246	2.96924	.00000
C	-1.12085	-1.65847	.00000
O	-.61007	-2.77087	.00000
H	-2.22444	-1.55153	.00000

Syn addition TS

E(B3LYP 6-31G*) = -1110.12471
 E(B3LYP 6-311+G**) =
 -1110.35786
 E(B3LYP 6-31G*(EtOH)) =
 -1110.15742
 E(B3LYP 6-311+G**(EtOH)) =
 -1110.39454

S	1.37314	1.09962	-.81296
C	.04603	1.46599	.37793
C	1.72880	-.62239	-.41363
C	2.45726	-1.24979	-1.52799
O	3.11683	-.52136	-2.30688
N	2.50269	-2.61327	-1.61953
C	1.63546	-3.52575	-.87962
C	3.30318	-3.23170	-2.67217
C	.41760	1.10909	-2.37151
C	3.01883	-.27804	1.07117
O	2.59664	.73173	1.73318
H	3.86815	-.12730	.37084
H	-.23534	2.51477	.25043
H	.49260	1.29832	1.35809
H	-.81037	.80913	.20355
H	.84323	-1.10271	-.00626
H	.75617	-3.80862	-1.47552
H	2.19815	-4.43383	-.64143
H	1.30717	-3.08786	.06109
H	3.91787	-4.03278	-2.24544
H	3.94689	-2.47568	-3.11836
H	2.66128	-3.66374	-3.45248
H	1.09996	.79004	-3.15945
H	.09533	2.14005	-2.54685
H	-.44271	.43980	-2.29829
C	3.39986	-4.06174	3.12926
C	4.28855	-3.73133	2.10228
C	4.15257	-2.51639	1.42389
C	3.12955	-1.62086	1.76186
C	2.25414	-1.95255	2.80499
C	2.38124	-3.16695	3.47992
H	3.50614	-5.00416	3.66204
H	5.09389	-4.41329	1.83787
H	4.85619	-2.25218	.63650
H	1.48555	-1.23772	3.08696
H	1.69522	-3.41391	4.28756

Anti addition TS

E(B3LYP 6-31G*) = -1110.12290
 E(B3LYP 6-311+G**) =
 -1110.35450
 E(B3LYP 6-31G*(EtOH)) =
 -1110.15577
 E(B3LYP 6-311+G**(EtOH)) =

-1110.39209

S	1.27561	.97219	-.80102
C	.47122	1.32002	.80198
C	2.03734	-.59995	-.41598
C	2.61452	-1.20192	-1.63977
O	2.77252	-.51003	-2.66971
N	3.04891	-2.49601	-1.56584
C	2.86560	-3.38487	-.41901
C	3.69900	-3.11023	-2.71981
C	-.18900	.64227	-1.84848
C	3.41743	-.32121	.95086
O	2.86690	-.51979	2.08754
C	4.07196	1.03605	.68965
C	4.84789	1.28479	-.45332
C	5.51740	2.50042	-.60853
C	5.42444	3.48741	.37997
C	4.65759	3.24739	1.52328
C	3.99124	2.02844	1.67473
H	.18803	2.37454	.81664
H	1.20557	1.08868	1.57813
H	-.40768	.68082	.92083
H	1.34962	-1.21475	.15917
H	2.08866	-4.13312	-.62822
H	3.80485	-3.91356	-.21825
H	2.59292	-2.83477	.48048
H	4.72570	-3.40300	-2.46441
H	3.72015	-2.39461	-3.53994
H	3.15053	-4.00845	-3.03116
H	.18749	.36657	-2.83443
H	-.76676	1.56943	-1.90989
H	-.78759	-1.6258	-1.41467
H	4.06568	-1.12028	.53023
H	4.93364	.52219	-1.22380
H	6.12041	2.67720	-1.49669
H	5.95498	4.42991	.26323
H	4.59138	4.00202	2.30462
H	3.42490	1.81204	2.57563

Cisoid betaine syn

E(B3LYP 6-31G*) = -1110.07850
 E(B3LYP 6-311+G**) =
 -1110.35926
 E(B3LYP 6-31G*(EtOH)) =
 -1110.16394
 E(B3LYP 6-311+G**(EtOH)) =
 -1110.40157

S	1.04488	.86992	-.37006
C	-.39662	.82051	.74799
C	1.71857	-.86381	-.26233
C	2.39460	-1.21905	-1.57184
O	2.93287	-.29813	-2.21273
N	2.49353	-2.52061	-1.94606
C	1.87880	-3.66892	-1.28170

C	3.32211	-2.86739	-3.10233
C	.13672	.91003	-1.96442
C	2.75830	-.67440	.95304
O	2.21190	.19870	1.81479
H	3.68275	-.30491	.44402
H	-.79010	1.83931	.81136
H	.00760	.49230	1.70336
H	-1.15687	.13758	.36052
H	.88425	-1.49609	.04282
H	1.25077	-4.21116	-1.99881
H	2.65677	-4.34709	-.91333
H	1.26535	-3.36678	-.43608
H	4.09939	-3.57915	-2.79972
H	3.78561	-1.96410	-3.49409
H	2.70588	-3.33153	-3.88171
H	.87629	.93808	-2.76347
H	-.44756	1.83503	-1.95978
H	-.52570	.04713	-2.07100
C	3.80183	-4.49501	2.75371
C	2.61122	-3.84553	3.10129
C	2.27952	-2.62676	2.50751
C	3.12074	-2.04151	1.55191
C	4.31432	-2.69352	1.21750
C	4.65487	-3.91398	1.81134
H	4.06811	-5.43863	3.22518
H	1.95035	-4.28418	3.84642
H	1.37795	-2.09498	2.80060
H	4.99406	-2.23258	.50200
H	5.59212	-4.40134	1.55018

Cisoid betaine anti

E(B3LYP 6-31G*) =
-1110.12454
E(B3LYP 6-311+G**) =
-1110.35533
E(B3LYP 6-31G*(EtOH)) =
-1110.16133
E(B3LYP 6-311+G**(EtOH)) =
-1110.39825

S	1.03534	.86714	-.342022
C	-.36928	.68074	.812180
C	1.87093	-.79759	-.238064
C	2.48014	-1.17379	-1.575198
O	2.76216	-.28208	-2.389903
N	2.76697	-2.48670	-1.796900
C	2.49427	-3.59787	-.886208
C	3.47915	-2.86655	-3.016766
C	.06090	.80404	-1.896690
C	2.88925	-.57201	.995534
O	2.29159	.27968	1.842770
C	4.30027	-.13693	.541677
C	5.26610	-1.06769	.133736
C	6.56472	-.66374	-.188982
C	6.92039	.68578	-.101286
C	5.96873	1.62175	.316169
C	4.67397	1.20820	.639655
H	-.90525	1.63410	.825977
H	.08848	.46359	1.774444
H	-1.02629	-.12563	.475761
H	1.08679	-1.47911	.096641
H	1.87144	-4.34692	-1.390957
H	3.43472	-4.07792	-.587051
H	1.97937	-3.26776	.014205

H	4.45631	-3.29692	-2.764875
H	3.62043	-1.98323	-3.636231
H	2.89893	-3.61514	-3.569507
H	.74541	.94893	-2.729715
H	-.65266	1.63143	-1.838850
H	-.47419	-.14427	-1.991764
H	3.01929	-1.61271	1.386069
H	5.01072	-2.12556	.092002
H	7.30328	-1.40282	-.492854
H	7.93373	1.00181	-.340125
H	6.24171	2.67173	.405101
H	3.93776	1.91491	1.009430

Torsional Rotation TS *syn*

E(B3LYP 6-31G*) = -1110.09637
E(B3LYP 6-311+G**) =
-1110.34682
E(B3LYP 6-31G*(EtOH)) =
-1110.15498
E(B3LYP 6-311+G**(EtOH)) =
-1110.39536

S	1.18473	.93564	-.57609
C	-.03494	1.02320	.78170
C	1.67655	-.83966	-.45708
C	2.36402	-1.18466	-1.76377
O	2.77711	-.26209	-2.49172
N	2.51522	-2.49409	-2.06858
C	2.05584	-3.60806	-1.23563
C	3.18421	-2.87550	-3.31029
C	.05568	1.08349	-2.00630
C	2.55226	-1.05196	.95923
O	1.99112	-2.01066	1.66481
H	2.50574	-.02125	1.41803
H	-.29583	2.07580	.91781
H	.43566	.63694	1.68638
H	-.91868	.43081	.53182
H	.75657	-1.39952	-.28369
H	1.18377	-4.09316	-1.69522
H	2.86052	-4.34800	-1.16326
H	1.81876	-3.27536	-.22221
H	4.11740	-3.40670	-3.08723
H	3.40634	-1.98012	-3.88804
H	2.53431	-3.53845	-3.89412
H	.66771	1.01888	-2.90505
H	-.42120	2.06485	-1.93386
H	-.69416	.28848	-1.97907
C	6.82256	-1.61801	.25506
C	6.00642	-2.69769	.60621
C	4.63740	-2.50330	.80775
C	4.05733	-1.24138	.64373
C	4.88422	-.16520	.29730
C	6.25650	-.34756	.10498
H	7.89211	-1.76108	.11552
H	6.44024	-3.68701	.74098
H	3.99530	-3.31865	1.12585
H	4.45662	.83206	.20223
H	6.88689	.50244	-1.14871

Torsional Rotation TS *anti*

E(B3LYP 6-31G*) = -1110.11489
E(B3LYP 6-311+G**) =
-1110.349328

E(B3LYP 6-31G*(EtOH)) =
-1110.15638
E(B3LYP 6-311+G**(EtOH)) =
-1110.39462

S	.21303	.531868	-.38472
C	-.92828	-.062525	.90811
C	1.57735	-.694968	-.22010
C	2.43767	-.539420	-1.45999
O	2.35991	.509802	-2.12885
N	3.30125	-1.540129	-1.75650
C	3.44318	-2.784322	-.99398
C	4.16274	-1.431453	-2.93313
C	-.71455	.006340	-1.86941
C	2.48789	-.589424	1.20544
O	2.31683	-1.690768	1.90291
C	2.23016	.734969	1.96385
C	2.54272	1.990205	1.42127
C	2.39845	3.152138	2.18463
C	1.94036	3.073341	3.50475
C	1.62789	1.826158	4.05360
C	1.77701	.668125	3.28551
H	-1.81668	.572394	.86785
H	-.42827	.052716	1.87017
H	-1.18939	-1.108432	.73033
H	1.09646	-1.670551	-.14196
H	2.99444	-3.622779	-1.54365
H	4.51126	-2.994252	-.86441
H	2.99481	-2.702244	-.00024
H	5.21642	-1.434629	-2.62805
H	3.93964	-.505086	-3.45971
H	3.99013	-2.284559	-3.60066
H	-.10121	.261600	-2.73333
H	-1.64802	.576040	-1.88407
H	-.91551	-1.067119	-1.82748
H	3.50967	-.450596	.76268
H	2.91780	2.057361	.40083
H	2.65308	4.118677	1.75487
H	1.83915	3.976267	4.10285
H	1.28220	1.754532	5.08317
H	1.57859	-.318097	3.69487

Transoid betaine syn

E(B3LYP 6-31G*) = -1110.06576
E(B3LYP 6-311+G**) =
-1110.34523
E(B3LYP 6-31G*(EtOH)) =
-1110.15625
E(B3LYP 6-311+G**(EtOH)) =
-1110.39685

S	.15539	-.12781	-.41412
C	1.93957	.04171	-.05654
C	-.42993	1.62397	-.17067
C	-1.78834	1.68438	-.85988
O	-2.39249	.61247	-1.05397
N	-2.29404	2.88700	-1.21910
C	-1.60432	4.17174	-1.07554
C	-3.59706	2.95139	-1.87973
C	.24840	-.37929	-2.22262
C	-.41941	2.04514	1.42288
O	-.20975	3.34933	1.50884
H	.40821	1.40527	1.83642
H	2.40238	-.92428	-.27461

H	2.05654	.27299	1.00319
H	2.37932	.82877	-.67420
H	.33091	2.25878	-.63004
H	-1.18137	4.48982	-2.03865
H	-2.33658	4.92337	-.75934
H	-.84322	4.10151	-.29438
H	-4.29506	3.53731	-1.26989
H	-3.98693	1.94406	-2.01314
H	-3.49346	3.43989	-2.85650
H	-.77317	-.49262	-2.58205
H	.81922	-1.29688	-2.38928
H	.74418	.47361	-2.69329
C	-3.96021	.76803	3.62723
C	-3.87537	2.05723	3.09020
C	-2.74769	2.43918	2.36126
C	-1.69357	1.54407	2.14206
C	-1.78675	.25784	2.68726
C	-2.90999	-.13207	3.42431
H	-4.82903	.47371	4.21224
H	-4.68135	2.76964	3.25650
H	-2.64404	3.45069	1.98073
H	-.95978	-.44059	2.56166
H	-2.95782	-1.13036	3.85462

Transoid betaine anti

E(B3LYP 6-31G*) = -1110.11317
E(B3LYP 6-311+G**) =
-1110.34704
E(B3LYP 6-31G*(EtOH)) =
-1110.15618
E(B3LYP 6-311+G**(EtOH)) =
-1110.39622

S	0.02295	0.00024	0.00455
C	1.84734	0.01631	-0.03812
C	-0.38934	1.83563	0.00345
C	-1.76172	1.93118	-0.66429
O	-2.57114	1.01319	-0.43201
N	-2.04547	2.97369	-1.47494
C	-1.16978	4.13139	-1.67744
C	-3.34650	3.03376	-2.14248
C	-0.31272	-0.62520	-1.68089
C	-0.52151	2.44994	1.48957
O	-0.79085	3.74305	1.32736
C	0.72700	2.16526	2.34703
C	0.73413	1.17001	3.33260
C	1.84835	0.98725	4.16108
C	2.97282	1.80171	4.00884
C	2.97353	2.80460	3.02999
C	1.85563	2.98726	2.21598
H	2.17676	-1.02405	-0.10047
H	2.19690	0.46334	0.89205
H	2.20196	0.58653	-0.90029
H	0.42220	2.33631	-0.52811
H	-0.57548	4.02435	-2.59456
H	-1.79859	5.02214	-1.77803
H	-0.54255	4.26532	-0.79696
H	-3.95327	3.84621	-1.72321
H	-3.86674	2.08757	-2.00470
H	-3.20174	3.22488	-3.21206
H	-1.39514	-0.65959	-1.79841
H	0.10956	-1.63245	-1.73602
H	0.14774	0.02765	-2.42628
H	-1.34249	1.83299	1.94211

H	-0.15042	0.54951	3.47145
H	1.83015	0.22148	4.93377
H	3.83640	1.66952	4.65689
H	3.84035	3.45269	2.91632
H	1.82502	3.79215	1.48653

Ring closure TS syn

E(B3LYP 6-31G*) = -1110.09921
E(B3LYP 6-311+G**) =
-1110.34216
E(B3LYP 6-31G*(EtOH)) =
-1110.14661
E(B3LYP 6-311+G**(EtOH)) =
-1110.38170

S	-1.1233	-.29231	-.19714
C	1.68674	-.22620	.10357
C	-.60079	1.83417	.09785
C	-1.86465	1.93878	-.74609
O	-2.77249	1.11474	-.56730
N	-1.90671	2.86558	-1.74055
C	-.97606	3.98551	-1.88826
C	-3.07493	2.89770	-2.62175
C	-.16213	-.51736	-2.00822
C	-.70695	2.21980	1.55876
O	-.95643	3.52022	1.21337
H	.28224	2.04748	2.04023
H	2.13543	-1.19014	-.15096
H	1.82983	-.03263	1.16938
H	2.15216	.57219	-.48184
H	.31336	2.22403	-.34195
H	-.30181	3.83044	-2.74031
H	-1.55278	4.90016	-2.06935
H	-.41345	4.12205	-.96728
H	-3.79511	3.65799	-2.29035
H	-3.56144	1.92328	-2.61577
H	-2.75183	3.14370	-3.63880
H	-1.21504	-4.9275	-2.29714
H	.26143	-1.49237	-2.26463
H	.38823	.28202	-2.51176
C	-3.60311	.43381	4.25755
C	-3.93951	1.56267	3.50319
C	-3.01431	2.11414	2.61376
C	-1.74577	1.54558	2.45626
C	-1.41384	.42012	3.22264
C	-2.33502	-.13749	4.11463
H	-4.31754	.01117	4.96077
H	-4.91977	2.02121	3.61890
H	-3.25331	3.00568	2.04344
H	-.41455	-.00810	3.14926
H	-2.05812	-1.00493	4.71019

Ring closure TS anti

E(B3LYP 6-31G*) = -1110.11932
E(B3LYP 6-311+G**) =
-1110.34896
E(B3LYP 6-31G*(EtOH)) =
-1110.15045
E(B3LYP 6-311+G**(EtOH)) =
-1110.38663

S	-.025448	-.22604	-.07950
C	1.789624	-.23077	-.27190

C	-.426535	1.91783	.15390
C	-1.785326	1.99383	-.53121
O	-2.682497	1.22877	-.14407
N	-1.946846	2.83574	-1.58324
C	-1.024678	3.91923	-1.93004
C	-3.228061	2.84321	-2.29086
C	-.553724	-.70026	-1.76356
C	-.487851	2.32275	1.60499
O	-.768237	3.61766	1.24716
C	.777362	2.11849	2.43365
C	.891577	1.05592	3.33995
C	2.039836	.90711	4.12498
C	3.085452	1.82855	4.01554
C	2.975638	2.89737	3.11861
C	1.827616	3.04045	2.33717
H	2.121618	-1.24928	-.48941
H	2.216792	.09731	.67784
H	2.098580	.44649	-1.07320
H	.442881	2.30406	-.36964
H	-.453655	3.68299	-2.83678
H	-1.607058	4.82844	-2.11814
H	-.357340	4.11964	-1.09452
H	-3.864456	3.66666	-1.93974
H	-3.743348	1.89966	-2.11678
H	-3.046828	2.97412	-3.36271
H	-1.643694	-.65035	-1.77550
H	-.229524	-1.72633	-1.95972
H	-.133757	-.02066	-2.51004
H	-1.316455	1.78304	2.10663
H	.067331	.35168	3.44674
H	2.110124	.08411	4.83288
H	3.973734	1.72367	4.63448
H	3.779574	3.62653	3.04012
H	1.712148	3.88467	1.66335

Cis aziridine

E(B3LYP 6-31G*) = -632.13112
E(B3LYP 6-311+G**) =
-632.33417
E(B3LYP 6-31G*(EtOH)) =
-632.17864
E(B3LYP 6-311+G**(EtOH)) =
-632.35522

C	-.50344	.28700	-.36565
C	.94356	.11480	-.09773
O	.28312	1.33824	.25108
H	-1.17267	-.21619	.33389
C	1.96743	.05207	-1.21679
O	1.93931	-.94891	-1.94365
N	2.88457	1.04296	-1.35020
C	3.86654	.95657	-2.43052
C	3.11773	2.11780	-.38626
H	1.21486	-.51356	.75464
H	4.84138	.63332	-2.04170
H	3.98317	1.94160	-2.89514
H	3.52254	.23699	-3.17207
H	4.14119	2.04186	.00230
H	2.42012	2.05952	.44573
H	3.00447	3.09373	-.87363
C	-2.34852	1.02962	-4.18047
C	-2.85930	.05769	-3.31573
C	-2.24771	-.17048	-2.08084
C	-1.11399	.56215	-1.70047

C	-.61235	1.54200	-2.56913
C	-1.22537	1.77220	-3.80185
H	-2.82711	1.21306	-5.13962
H	-3.73905	-.51610	-3.59747
H	-2.65529	-.91890	-1.40374
H	.24677	2.13545	-2.27116
H	-.82884	2.53704	-4.46562

***Trans* aziridine**

E(B3LYP 6-31G*) = -632.16219
 E(B3LYP 6-311+G**) =
 -632.33702
 E(B3LYP 6-31G*(EtOH)) =
 -632.18128
 E(B3LYP 6-311+G**(EtOH)) =
 -632.35804

C	-.52360	.06714	-.22050
C	.94298	-.02247	-.04967
O	.23114	1.12819	.42065
C	-1.49909	-.68447	.62150
C	-1.33233	-.80135	2.00934
C	-2.26016	-1.51125	2.77253
C	-3.36520	-2.11147	2.15913
C	-3.53911	-1.99431	.77764
C	-2.61236	-1.28032	.01341
C	1.84470	.07195	-1.26854
O	1.83011	-.89359	-2.04536
N	2.61966	1.16647	-1.45595
C	3.42138	1.27145	-2.67467
C	2.82606	2.23688	-.48087
H	-.88348	.33213	-1.21525
H	1.32470	-.68224	.73232
H	-.48579	-.32062	2.49284
H	-2.12385	-1.59225	3.84831
H	-4.08848	-2.66190	2.75618
H	-4.39952	-2.45172	.29512
H	-2.75593	-1.18149	-1.06074
H	4.48508	1.11792	-2.45121
H	3.29414	2.26922	-3.10991
H	3.09211	.51523	-3.38591
H	3.90157	2.35270	-.29996
H	2.33599	2.01033	.46294
H	2.43416	3.18687	-.86488

SMe₂

E(B3LYP 6-31G*) = -478.00653
 E(B3LYP 6-311+G**) =
 -478.06656
 E(B3LYP 6-31G*(EtOH)) =
 -478.01940
 E(B3LYP 6-311+G**(EtOH)) =
 -478.07196

S	.00000	0.00000	-.57673
C	.00000	1.42428	.57101
H	.00000	2.32736	-.04750
H	-.89609	1.42623	1.19831
H	.89609	1.42623	1.19831
C	.00000	-1.42428	.57101
H	.00000	-2.32736	-.04750
H	.89609	-1.42623	1.19831
H	-.89609	-1.42623	1.19831

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