Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Asymmetric Sulfur Ylide Based Enantioselective Synthesis of D-*erythro*-sphingosine.

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General methods

All reactions were conducted under a dried argon stream. Solvents (CH_2Cl_2 99.9%, toluene 99.9%) were purchased in capped Pure Solv System-4® bottles and used without further purification and stored under argon. Yields refer to the chromatographically and spectroscopically (^1H and ^{13}C) homogeneous materials, unless otherwise stated. All glassware utilized was flame-dried before use. Reactions were monitored by TLC carried out on 0.25 mm E. Merck silica gel plates. Developed TLC plates were visualized under a short-wave UV lamp and by heating plates that were dipped in ethanol/H_2SO_4 (15:1) and basic solution of permanganate potassium. Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and employed a solvent polarity correlated with TLC mobility. Melting points, determined with Reichert apparatus, are uncorrected. Optical rotations were measured at 598 nm on a Jasco DIP-370 digital polarimeter using a 100 mm cell. NMR experiments were conducted on a Varian 400 MHz instrument using $CDCl_3$ (99.9% D) as the solvent, with chemical shifts (δ) reference to internal standards $CDCl_3$ (7.26 ppm ^1H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm)

Chemical shifts are relative to the deuterated solvent peak and are in parts per million (ppm).

Experimental Procedures

(*E*)-1-bromohexadec-2-ene (6). Allyl bromide (**8**) (240 mg, 2 mmol) was dissolved in 40 mL of dry CH_2Cl_2 and then pentadec-1-ene **9** (1.68 g, 8 mmol) and Grubs catalyst **B** (8 mg, 2%) were added at room temperature. After the addition was completed, the reaction mixture was kept boiling for 8 h under argon atmosphere and then cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using hexane-AcOEt (98:2) as the eluent to give 590 mg of pure 1-bromohexadec-2-ene (**6**) (97 %) as colourless oil and with *E*:*Z* selectivity of 52:1. TLC (Hexane) R_f 0.60; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (1H, dt, *J*=14.8, 7.6 Hz), 5.68 (1H, dt, *J*=14.8, 7.2 Hz), 3.96 (2H, d, *J*=7.6 Hz), 2.03 (2H, q, *J*=7.2, Hz), 1.34-1.20 (22H, m), 0.86 (3H, t, *J*=6.9 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 137, 126.3, 34, 32.3, 32.1, 29.8, 29.6, 29.5, 29.3, 29, 22.9, 14.3. Anal. Calcd. for $C_{16}H_{31}Br$: C, 63.36; H, 10.30. Found: C, 63.34; H, 10.31.

Formylmethyl benzylcarbamate (10). To a solution of 2-hydroxyacetaldehyde **7** (184 mg, 3.06 mmol) in 20 mL of dry Et_2O freshly distilled Et_3N (10.16 mmol) and BnNCO (647 mg, 4.8 mmol) were added. The resulting mixture was heated to 60 °C in a sealed tube for 17 h, cooled to room temperature and quenched with saturate NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using hexane-AcOEt (85:15) as the eluent to give 580 mg of pure formylmethyl benzylcarbamate (**10**) (98 %) as an oil. TLC (Hexane-AcOEt 80:20) R_f 0.70; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (1H, t, *J*=0.7 Hz), 7.35-7.21 (5H, m), 5.08 (1H, br s), 4.89 (2H, d, *J*=0.7 Hz) 4.4 (2H, d, *J*=5.5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 194.2, 153.6, 136.9, 128.5, 124.4, 121.6, 69.5, 45.2. Anal. Calcd. For $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.15; H, 5.75; N, 7.26.

Sulfonium salt 12. To a rapidly stirred solution of chiral sulfide **11** (500 mg, 2.0 mmol) and (*E*)-1-bromohexadec-2-ene (909 mg, 3.0 mmol) in 2 mL dichloromethane was added silver tetrafluoroborate (778 mg, 4.0 mmol) in the dark under an argon atmosphere at room temperature. The reaction was stirred for 48 h and 10 mL of CH_2Cl_2 was added. Silver bromide precipitate was filtered and the filtrate was concentrated in *vacuo*. The residual brown oil was recrystallized from CH_2Cl_2 and Et_2O to give sulfonium salt **12** as a white precipitate which was used directly into the next step.

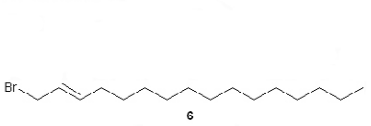
((2*R*,3*R*)-3-((*E*)-pentadec-1-enyl)oxiran-2-yl)methyl benzylcarbamate (13). To a stirred solution of sulfonium salt **12** (465 mg, 0.83 mmol) in 5 mL of CH_2Cl_2 *N,N,N′,N′′*-tetramethyl-N′′-[tris(dimethylamino)phos-phoralidene]phosphoric triamide ethylimine (415 mg, 1.22 mmol) was added at −78 °C under argon. After 30 min, a mixture of 20 mL of CH_2Cl_2 and formylmethyl benzylcarbamate **10** (240 mg, 1.25 mmol) was added to the solution. The reaction mixture was stirred for 2 h and then was warmed up to room temperature and a saturated NaCl solution (10 mL) was added. The phases were separated and the aqueous layer was extracted with AcOEt (2 x 10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using hexane-AcOEt (85:15) as the eluent to give 192 mg of pure epoxide **13** (60 %). Compound **11** (180 mg, 87% was also recovered). TLC (Hexane-AcOEt 70:30) R_f 0.60; $[\alpha]_D$ +15.0 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (5H, m), 5.73 (1H, dt, *J*=14.8, 6.5 Hz), 5.10 (1H, dd, *J*=14.8, 9.1 Hz), 5.01 (1H, br s), 4.47 (1H, dd, *J*=12.2, 3.1 Hz), 4.39 (2H, d, *J*=6), 4.05 (1H, dd, *J*=12.2, 6.3 Hz), 3.30 (1H, dd, J=9.1, 2.4), 3.15 (1H, ddd, *J*=6.3, 3.1, 2.4 Hz), 2.03 (2H, q, *J*=6.5 Hz), 1.37-1.20 (22H, m), 0.81 (3H, t, *J*=6.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 156.0, 138.4, 134.6, 128.8, 127.7, 127.6, 120.3, 64.9, 57.6, 56.5, 45.2, 32.5, 32.1, 29.8, 29.6, 29.5, 29.4, 29.3, 22.8, 14.3. Anal. Calcd. for $C_{26}H_{41}NO_3$: C, 75.14; H, 9.94; N, 3.37. Found: C, 75.12; H, 9.95, N, 3.36.

(*S*)-4-((*R*,*E*)-1-hydroxyhexadec-2-enyl)oxazolidin-2-one (14). To a stirred solution of epoxide **13** (220 mg, 0.57 mmol) in 5 mL of THF at −15 °C was added dropwise NaHMDS (0.57 mmol, 1 M in THF). The resulting mixture was slowly allowed to reach 0 °C (5 h)

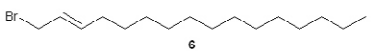
and then quenched by addition of a saturate solution of NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with AcOEt (2 x 10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used directly into next step. Thus, to a stirred mixture of Li (excess) and freshly $EtNH_2$ (15 mL) under argon at −78 °C was added a solution of first residue in dry 2 mL of Et_2O *via* syringe. The reaction mixture was stirred at −78 °C for 4 h and then carefully quenched with saturate $NHCl_4$. The phases were separated and the aqueous layer was extracted with AcOEt (2 X 10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using hexane-AcOEt-MeOH (85:10:5) as the eluent to give 154 mg of pure oxazolidinone **14** (82 %). TLC (Hexane-AcOEt-MeOH 60:30:10) R_f 0.70; m.p. 71-73 °C; $[\alpha]_D$ −1.3 (*c* 1.75 in $CHCl_3$); ^{1}H NMR (400, MHz, $CDCl_3$): δ 5.82 (1H, dtd, *J*=15.4, 6.8, 0.8 Hz), 5.46 (1H, br s), 5.37 (1H, ddt, *J*=15.4, 6.8, 1.2 Hz), 4.41 (1H, dd, *J*=8.8, 8.5 Hz), 4.31 (1H, dd, *J*=8.8, 4.9 Hz), 4.06 (1H, dd, *J*=6.8, 5.2 Hz), 3.82 (1H, ddd *J*=8.5, 5.2, 4.9 Hz), 2.18 (1H, br s), 2.04 (2H, q, *J*=7.0 Hz), 1.37-1.2 (22H, m), 0.81 (3H, t, *J*=6.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 160.5, 136.6, 126.6, 73.3, 66.4, 56.4, 32.5, 32.1, 29.81, 29.79, 29.74, 29.6, 29.5, 29.4, 29.1, 22.8, 14.2. Anal. Calcd. For $C_{19}H_{35}NO_3$: C, 70.11; H, 10.84; N, 4.30. Found: C, 70.19; H, 10.80; N, 4.32.

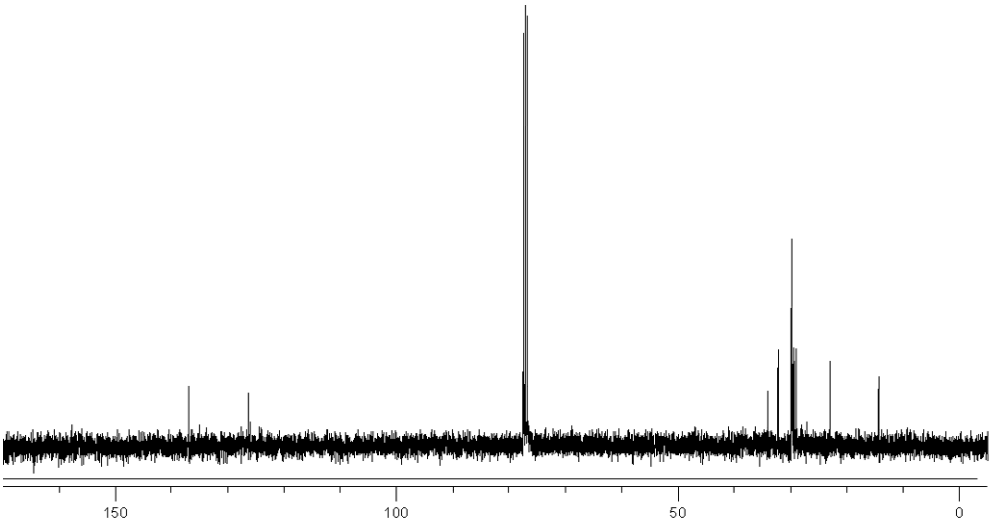
D-*erythro*-sphingosine (1). The mixture of oxazolidinone **14** (32.5 mg, 0.1 mmol) and 1 M KOH (2 mL, H_2O:EtOH 1:1) was heated to reflux for 2.5 h, cooled to room temperature and then 2 M HCl (10 mL) was added. The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo* giving 30 mg of pure D-*erythro*-sphingosine (**1**) (100 %). TLC (Hexane-AcOEt-MeOH 60:30:10) R_f 0.70; m.p. 72–74 °C; $[\alpha]_D$ −1.6 (*c* 1 in $CHCl_3$); ^{1}H NMR (400, MHz, $CDCl_3$): δ 5.76 (dtd, 1H, *J*=15.4, 6.7, 1.2 Hz), 5.47 (ddt, 1H, *J*=15.4, 7.2, 1.6 Hz), 4.04 (dd, 1H, *J*=7.2, 6 Hz), 3.70 (dd, 1H, *J*=10.8, 4.8 Hz), 3.61 (dd, 1H, *J*=10.8, 6 Hz), 2.88 (ddd, 1H, 6, 6, 4.8), 2.05 (td, 2H, *J*=7.6, 6.7 Hz), 1.74 (4H, br s), 1.37 (m, 2H), 1.20–1.40 (m, 20H), 0.88 (t, 3H, *J*=6.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 135.1, 129.4, 75.8, 64.5, 56.3, 32.5, 32.1, 29.9, 29.8, 29.6, 29.5, 29.4, 29.3, 22.9, 14.3. Anal. Calcd. For $C_{18}H_{37}NO_2$: C, 72.19; H, 12.45; N, 4.68. Found: C, 72.21; H, 12.41; N, 4.70.

^{1}H NMR of 6



^{13}C NMR of 6





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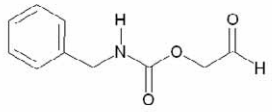

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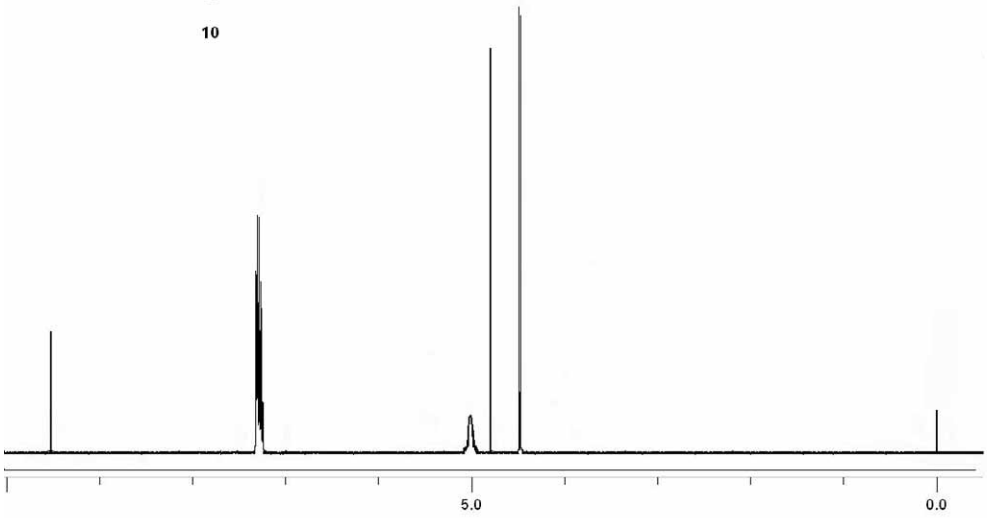

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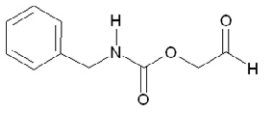

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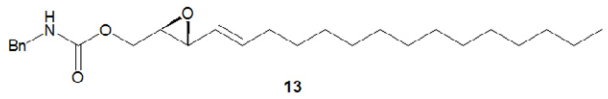
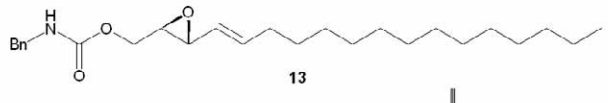


13

^{13}C NMR of 13



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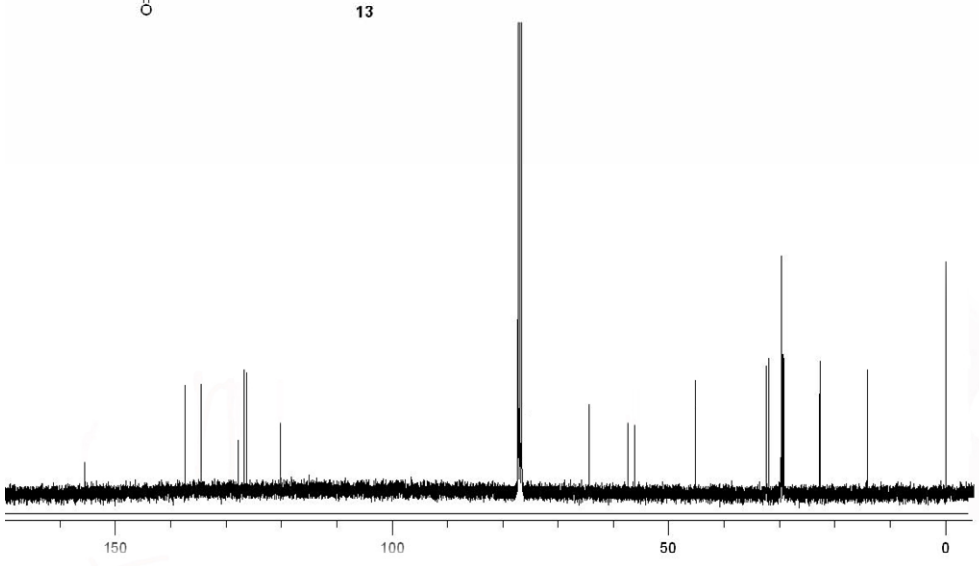

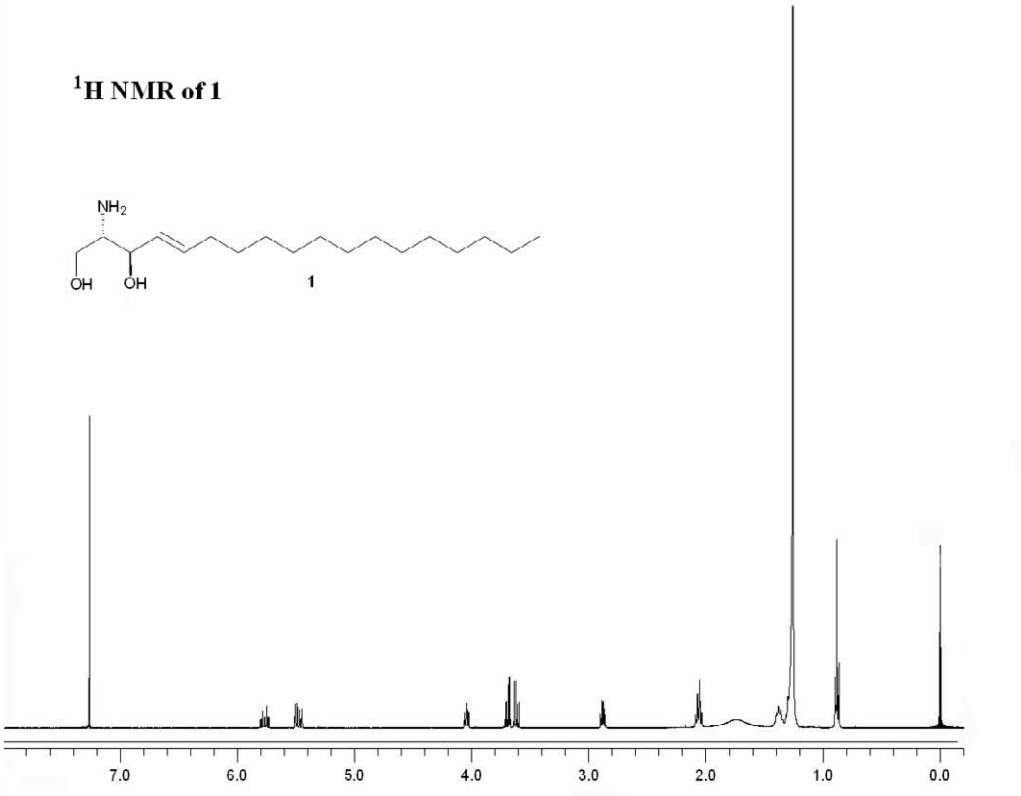
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5.0
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2.0
1.0
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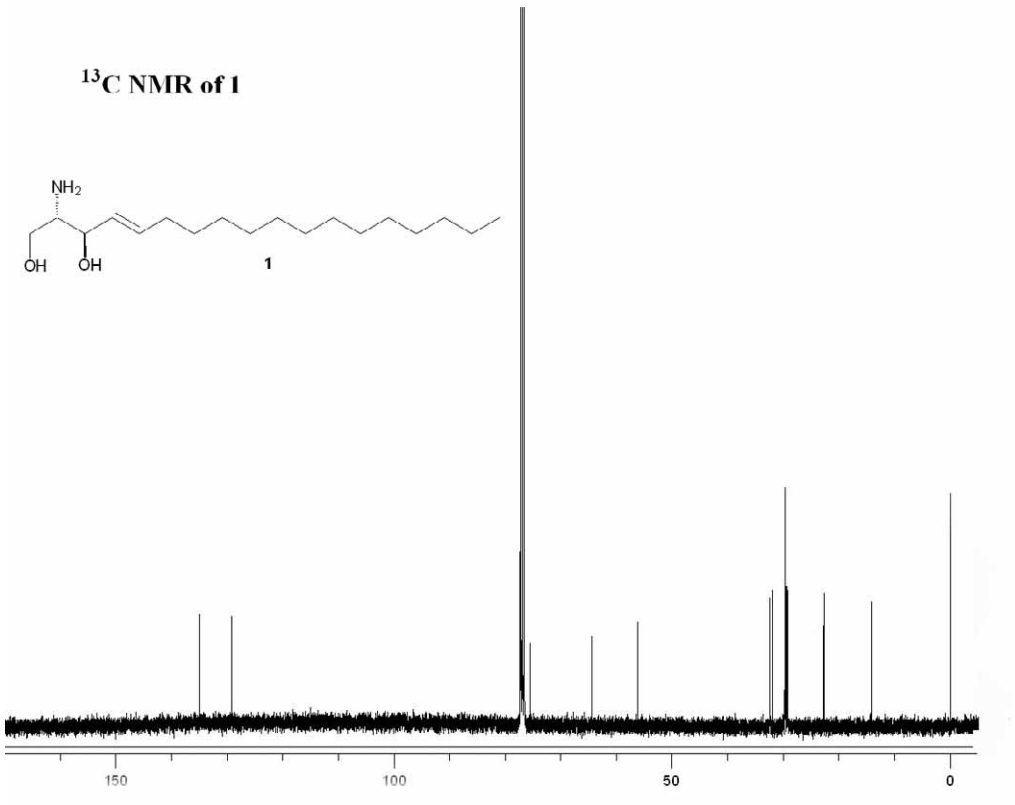
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