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Efficient and versatile synthesis of (2*S*,3*R*)-sphingosine and its 2-azido-3-*O*-benzylsphingosine analogue

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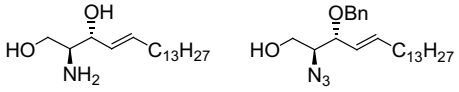
Abstract—The title compounds (**1**, **2**) were synthesized from (2*R*,3*S*)-2-*O*-benzyl-3,4-*O*-(3′-pentylidene)-2,3,4-trihydroxybutanal (**5**). Installation of the *E*-double bond and aliphatic chain into the sphingosine base was effected by a sequence of Horner–Wadsworth–Emmons olefination of **5**, conversion to allylic acetate **8**, and copper-mediated Grignard coupling. The method is versatile, allowing a broad variety of aliphatic chains to be introduced in the organocuprate coupling step.

Sphingolipids are structural components of eukaryotic cell membranes, are the key contributors to the stability of 'lipid raft' microdomains, and are a source of lipid messengers that regulate a wide variety of biological processes ranging from inflammation to cell proliferation and apoptosis.[1] Sphingoid bases, which form the backbone of sphingolipids, are aliphatic 2-amino-1,3-diols. The most prevalent base is (2*S*,3*R*)-2-amino-4*E*-1,3-octadecenediol, known as D-*erythro*-sphingosine (**1**).

Facile synthetic routes to sphingosine and its analogues are needed. Indeed, a great deal of effort has been devoted toward the synthesis of **1** and its derivatives for use in biological and pharmacological studies.[2] Many synthetic efforts have utilized starting materials derived from the chiral pool, in particular, carbohydrate, serine, and tartaric acid precursors,[3] whereas other syntheses have employed asymmetric induction, including Sharpless asymmetric epoxidation, asymmetric aldol, and other stereoselective reactions, to achieve high diastereoselectivity.[4] When chiral substrates are used as the starting materials, the characteristic *trans* double bond of sphingosine is often generated by Wittig reaction[4e] or Julia olefination.[5] When an *E*,*Z* mixture is obtained, photoisomerization has been used to convert the *Z* unsaturation to the desired *E* configuration.[4e]

In this communication, we describe an efficient method for the preparation of **1** and its 2-azido-3-*O*-benzyl analogue **2**, which has been used as a glycosyl acceptor in glycosphingolipid synthesis.[6,7] We recently reported the utility of D-threose synthon **4**, which is derived from D-tartaric acid (**3**),[8] as a convenient synthon of a phosphonate of phytosphingosine.[9] The Horner–Wadsworth–Emmons (HWE) reaction, followed by coupling of an allylic acetate with dodecylorganocuprate to introduce the 4,5-*trans* double bond and the long chain, completed the synthesis of **1** in nine steps from **4**.



1 **2**

Scheme 1 illustrates the synthesis of sphingosine **1** from pentylidene-protected D-threitol derivative **4**.[9] The advantage of pentylidene acetal **4** is that it is less acid sensitive and thus more stable than the corresponding isopropylidene acetal. Alcohol **4** was oxidized with PCC to afford aldehyde **5**, which was used directly in the next step without further purification. After the *trans* double bond was formed with diisopropyl (ethoxycarbonylmethyl)phosphonate in the presence of lithium bromide and triethylamine, the resulting ester **6**[10] was converted via alcohol **7**[11] to allylic acetate **8**.[12]

In our initial attempt to install the aliphatic chain, allylic alcohol **7** was activated by mesylation and then subjected to copper-mediated Grignard reaction. Unfortunately, the coupling reaction with mesylate **12**[13] was

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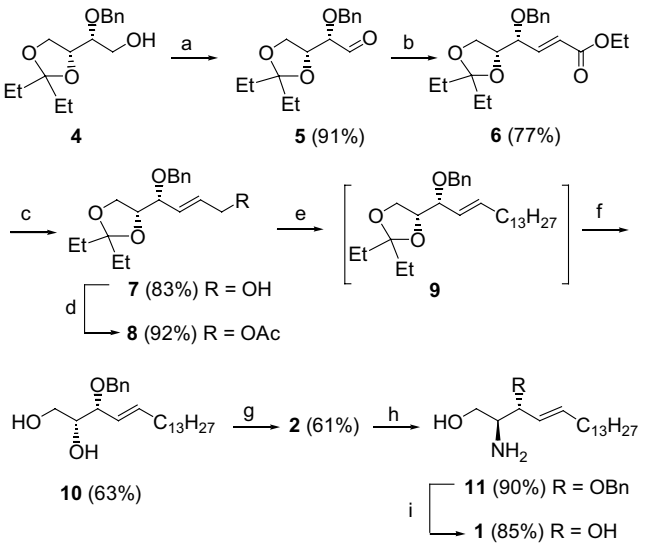

Scheme 1. Synthesis of (2*S*,3*R*)-sphingosine (**1**) and intermediate **2**. Reagents and conditions: (a) PCC, NaOAc, CH_2Cl_2, MS; (b) (*i*-PrO)$_2$P(O)CH_2CO_2Et, NEt_3, LiBr, THF, rt; (c) DIBAL-H, −78 °C, CH_2Cl_2; (d) AcCl, *i*-Pr_2NEt, CH_2Cl_2, −40 °C–rt; (e) $C_{12}H_{25}MgBr$, Li_2CuCl_4, Et_2O, −78 °C–rt; (f) 5% H_2SO_4, MeOH; (g) (i) PPh_3, DIAD, CH_2Cl_2, 0 °C, (ii) $TMSN_3$, 0 °C–rt, (iii) TBAF, THF; (h) PPh_3, THF/H_2O 9:1; and (i) Na, NH_3, THF, −78 °C, 30 min.

not regioselective, giving a 1:2 mixture of the desired coupling product **9** (via α attack) and product **13** (via γ attack).[14] Therefore, allylic alcohol **7** was converted to acetate derivative **8** by treatment with acetyl chloride in the presence of *i*-Pr_2NEt. Coupling of acetate **8** with freshly prepared $C_{12}H_{25}MgBr$ in the presence of catalytic Li_2CuCl_4 in Et_2O at −78 °C was regioselective, affording intermediate **9** exclusively.

Deprotection of acetal **9** with 5% H_2SO_4 in methanol provided diol **10** (65% yield for the two steps).[15] The secondary hydroxy group of **10** was converted to an azido group in a one-pot reaction,[16] which was accomplished by adding diol **10** to a mixture of diisopropyl azodicarboxylate (DIAD) and Ph_3P at 0 °C. After 3 h, $TMSN_3$ was added to give the azide substitution product with concomitant transfer of the silyl group to the primary hydroxyl group. Hydrolysis of the silyl ether and purification by column chromatography provided azidosphingosine derivative **2** in 61% yield.[17] Although Birch reduction would reduce the azido group and cleave the *O*-benzyl group of **2** in one-pot, it was reported that the yield is low for this conversion.[18] Therefore, the azide was first reduced to an amino group by the Staudinger reaction (PPh_3, THF/H_2O (9:1))[19] to afford α-amino alcohol **11** in high yield,[20] and then the benzyl group was removed by Birch reduction (−78 °C, 30 min) to give sphingosine **1** in 85% yield. The structure of **1** was confirmed by the identity of its physical data (^1H and ^{13}C NMR, $[\alpha]_D^{25}$, mp)[21] with those reported in the literature.[3,4]

In summary, a facile synthesis of sphingosine (**1**) via aldehyde **5** in eight steps in 17% overall yield has been described. 2-Azido-3-*O*-benzylsphingosine **2** was also prepared (six steps from **5**, 23% overall yield). The advantage of the method described here lies in its versatility, since many (2*S*,3*R*)-sphingosine derivatives can be readily prepared with the desired 4*E* stereochemistry. In addition, if the enantiomer of **4** is prepared from L-tartaric acid, this method would provide a convenient route to the enantiomer of **1**.

Acknowledgements

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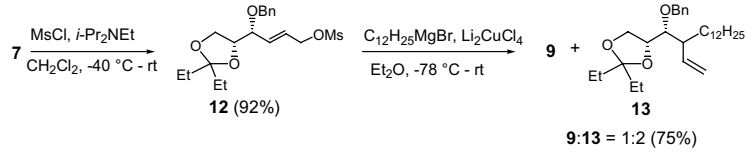
10. Data for (−)-**6**: R_f 0.72 (EtOAc/hexane 1:3); $[\alpha]_D^{25}$ −11.0 (*c* 2.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.84–0.92 (m, 6H), 1.32 (t, 3H, *J* = 6.8 Hz), 1.58–1.66 (m, 4H), 3.68 (t, 1H, *J* = 7.6 Hz), 3.98 (t, 1H, *J* = 6.8 Hz), 4.13 (m, 1H), 4.22 (m, 3H), 4.52 (d, 1H, *J* = 12.0 Hz), 4.70 (d, 1H, *J* = 12.0 Hz), 6.10 (d, 1H, *J* = 16.0 Hz), 6.85 (dd, 1H, *J* = 6.0, 7.6 Hz), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 8.1, 8.2, 14.2, 28.9, 29.4, 60.6, 65.9, 71.5, 77.2, 79.0, 83.1, 113.8, 124.4, 127.8, 128.4, 137.7, 143.4, 165.8.
11. Reduction of ester **6** to allylic alcohol **7** with DIBAL-H was carried out at −78 °C because it was found that the acetal was reduced to release the primary hydroxy group when the temperature was raised to 0 °C. Data for ((−)-**7**): R_f 0.21 (EtOAc/hexane 1:3); $[\alpha]_D^{25}$ −18.6 (*c* 2.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.84–0.92 (m, 6H), 1.70–1.86 (m, 4H), 3.77 (t, 1H, *J* = 8.0 Hz), 3.92 (m, 4H), 4.28 (m, 1H), 4.48 (d, 1H, *J* = 12.4 Hz), 4.70 (d, 1H, *J* = 12.0 Hz), 5.73 (m, 2H), 7.20 (m, 1H), 7.25–7.47 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 8.4, 8.5, 29.6, 30.1, 62.5, 66.5, 70.6, 78.7, 80.9, 113.6, 126.7, 134.8, 139.2.
12. Data for (−)-**8**: R_f 0.64 (EtOAc/hexane 1:3); $[\alpha]_D^{25}$ −13.5 (*c* 4.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.84–0.91 (m, 6H), 1.60–1.65 (m, 4H), 2.07 (s, 3H), 3.65 (t, 1H, *J* = 8.0 Hz), 3.92 (m, 2H), 4.20 (dd, 1H, *J* = 6.8, 13.6 Hz), 4.48 (d, 1H, *J* = 12.4 Hz), 4.59 (m, 1H), 4.70 (d, 1H, *J* = 12.4 Hz), 5.66 (dd, 1H, *J* = 7.2, 15.6 Hz), 5.85 (dt, 1H, *J* = 5.6, 15.6 Hz), 7.25–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 8.0, 8.2, 20.9, 29.1, 29.6, 63.9, 66.2, 70.6, 77.8, 79.7, 113.4, 127.6, 128.0, 128.4, 129.4, 129.9, 138.1, 170.7.
13. Data for (−)-**12**: R_f 0.70 (hexane/EtOAc 3:1); $[\alpha]_D^{25}$ −16.4 (*c* 1.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.84–0.92 (m, 6H), 1.70–1.86 (m, 4H), 3.77 (t, 1H, *J* = 8.0 Hz), 3.92 (m, 4H), 4.28 (m, 1H), 4.48 (d, 1H, *J* = 12.4 Hz), 4.70 (d, 1H, *J* = 12.0 Hz), 5.73 (m, 2H), 7.20(m, 1H), 7.25–7.47 (m, 4H); ^{13}C NMR ($CDCl_3$) (8.4, 8.5, 29.6, 30.1, 62.5, 66.5, 70.6, 78.7, 80.9, 113.6, 126.7, 134.8, 139.2.
14. Copper-mediated Grignard reaction of allylic mesylate **12** gave a mixture of **9** and **13**:



15. Preparation of (−)-**10**. To a solution of acetate **8** (1.74 g, 5.0 mmol) and Li_2CuCl_4 (0.1 mmol, 1 mL of a 0.1 M solution) in 50 mL of Et_2O at −78 °C was quickly added freshly prepared $C_{12}H_{25}MgBr$ (15 mmol) in 50 mL of Et_2O. The solution was stirred at −78 °C for 3 h, then warmed to room temperature and stirred overnight. After the reaction was quenched with water, the organic phase was separated, the aqueous phase was extracted with Et_2O (3 × 20 mL), the organic layer was dried (Na_2SO_4), and the solvent was removed. To the residue was added 100 mL of MeOH, followed by 10 mL of 5% aqueous H_2SO_4. The mixture was stirred overnight, 5 g of K_2CO_3 was added, the mixture was filtered, and the filtrate was removed. Column chromatography (hexane/EtOAc 2:1) gave 1.23 g of **10** (63% for two steps) as a colorless oil; R_f 0.15 (hexane/EtOAc 3:1); $[\alpha]_D^{25}$ −23.7 (*c* 4.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 6.8 Hz), 1.25–1.41 (m, 22H), 2.10 (m, 2H), 3.54 (m, 1H), 3.65 (m, 2H), 3.77 (m, 1H), 4.30 (d, 1H, *J* = 11.6 Hz), 4.60 (d, 1H, *J* = 11.6 Hz), 5.38 (m, 1H), 5.76 (m, 1H), 7.27–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) 14.2, 19.5, 29.0, 29.3, 29.5, 29.8, 29.9, 30.0, 30.1, 31.9, 32.3, 63.3, 70.0, 74.1, 81.1, 126.3, 127.9, 128.0, 128.6, 138.0, 138.2. MS (ESI) *m*/*z* 408.3 (MNH_4^+).
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17. Data for (−)-**2**: R_f 0.51 (hexane/EtOAc 3:1); $[\alpha]_D^{25}$ −55.2 (*c* 1.34, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 6.8 Hz), 1.25–1.41 (m, 22H), 2.10 (m, 2H), 3.50 (m, 1H), 3.71 (m, 2H), 3.90 (m, 1H), 4.34 (d, 1H, *J* = 11.6 Hz), 4.62 (d, 1H, *J* = 11.6 Hz), 5.48 (m, 1H), 5.80 (m, 1H), 7.27–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) 14.1, 22.7, 28.9, 29.2, 29.3, 29.6, 31.9, 32.4, 62.7, 66.0, 70.1, 80.7, 126.3, 127.7, 128.5, 137.8, 138.4. MS (ESI) *m*/*z* 433.4 (MNH_4^+).[18]
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20. Data for (−)-**11**: R_f 0.38 ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{25}$ −35.3 (*c* 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 6.8 Hz), 1.25–1.41 (m, 22H), 2.10 (m, 2H), 3.10 (m, 4H), 3.71 (m, 3H), 4.31 (d, 1H, *J* = 12.0 Hz), 4.65 (d, 1H, *J* = 12.0 Hz), 5.38 (m, 1H), 5.76 (m, 1H), 7.27–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) 14.1, 22.7, 29.2, 29.3, 29.5, 29.8, 32.8, 32.9, 55.9, 63.0, 70.1, 74.1, 81.2, 126.6, 127.7, 127.8, 128.4, 138.1. MS (ESI) *m*/*z* 390.3 (MH^+).
21. Data for (−)-**1**: R_f 0.35 ($CHCl_3$/MeOH/NH_4OH 135:25:4); mp 81.0–82.3 °C [lit.[4b] mp 72–75 °C, lit.[4c] mp 76–77 °C, lit.[4e] mp 80.7–82.1 °C]; $[\alpha]_D^{25}$ −2.9 (*c* 1.0, $CHCl_3$) [lit.[3a] $[\alpha]_D^{22}$ −2.5°(*c* 6, $CHCl_3$), lit.[4b] $[\alpha]_D^{21}$ −1.3° (*c* 3.5, $CHCl_3$), lit.[4e] $[\alpha]_D^{25}$ −2.7 (*c* 1.2, $CHCl_3$), lit.[4f] $[\alpha]_D^{20}$ −1.4 (*c* 0.42, $CHCl_3$), lit.[4g] $[\alpha]_D^{20}$ −1.6 (*c* 1.0, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J* = 7.0 Hz), 1.23 (m, 20H), 1.35 (m, 2H), 2.02 (q, 2H, *J* = 7.0 Hz), 2.64 (br s, 4H), 2.84 (q, 1H, *J* = 5.2 Hz), 3.64 (m, 2H), 4.04 (t, 1H, *J* = 6.0 Hz), 5.44 (dd, 1H, *J* = 15.4, 7.2 Hz), 5.71 (dt, 1H, *J* = 15.4, 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 29.2, 29.3, 29.4, 29.5, 29.62, 29.65, 29.68, 31.9, 32.4, 56.2, 63.7, 75.1, 129.1, 134.7. MS (ESI) *m*/*z* 300.3 (MH^+).