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Synthesis of an orthogonally protected D-(+)-erythro-sphingosine

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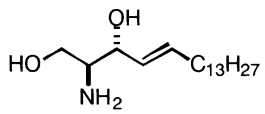
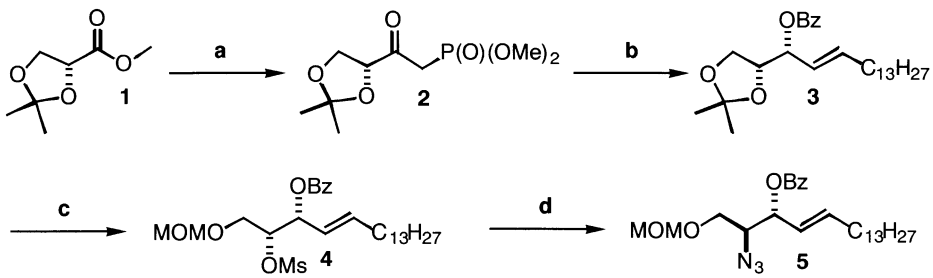
Abstract—The synthesis presented provides rapid access to an orthogonally protected D-(+)-*erythro*-sphingosine: 1-methoxymethyl, 2-azido, 3-benzoyl. After selective deprotection the resulting sphingosine derivative is suitable for coupling to a wide variety of saccharides or other molecules at either the 1- or 3-position. © 2001 Elsevier Science Ltd. All rights reserved.

Glycosphingolipids are involved in many essential biological processes such as cellular recognition and cell growth.[1–4] They inhibit protein kinase C and are ligands for numerous receptor proteins (lectins, toxins and antibodies). Glycosphingolipids consist of a carbohydrate attached to a sphingosine lipid through a glycosidic bond. While the saccharide varies from system to system the most common lipid moiety is D-(+)-*erythro*-sphingosine, with a 2*S*,3*R*,*E* olefin configuration (Scheme 1). We sought to develop a synthetic route generating ample amounts of orthogonally protected D-(+)-*erythro*-sphingosine suitable for coupling to carbohydrates. In order to enhance coupling yields we desired an azide group at the 2-position of sphingosine instead of an amine or amide as NH protons in many cases dramatically lower coupling yields.[5] Over 65 syntheses of sphingosine have been reported previously and the advantages and disadvantages of each have recently been reviewed.[6–8] However, most of these syntheses do not proceed via an azide and do not produce a differentially protected sphingosine. Scheme 2 represents our overall synthetic sequence which, although different from those previously reported, combines advantageous elements of former studies.



Scheme 1. Sphingosine.

Sphingosine consists of a polar head portion connected to a long-chain alkane by an *E* olefin. Following the precedent of Yamanoi et al. the polar head portion was synthesized from D-mannitol in multigram quantities and then coupled to tetradecyl aldehyde via a Horner–Wadsworth–Emmons (HWE) reaction.[9] D-Mannitol was protected as the 1,2,5,6 diacetonide,[10] which was then in one-pot oxidatively cleaved and esterified producing the commercially available **1**.[11] Compound **1** was treated with the lithium anion of dimethyl methyl phosphonate generating the HWE reagent **2**.[9] Com-



Scheme 2. (a) $LiCH_2PO(OMe)_2$, THF, −77°C; (b) (i) tetradecyl aldehyde, CH_3CN, K_2CO_3, (ii) L-Selectride®, THF, −100°C, (iii) BzCl, pyr., 62% yield from **1**; (c) (i) H^+/H_2O, (ii) TBSCl, pyr., (iii) MsCl, pyr., (iv) HF·pyr., THF, (v) MOMCl, pyr., 69% yield from **3**; (d) LiN_3, DMF, 15-crown-5, 90°C, 90% yield.

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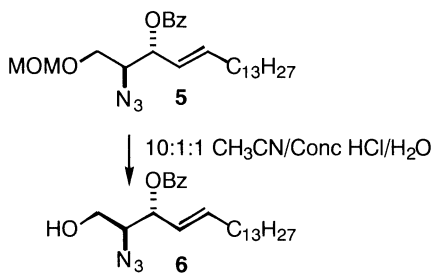
pound **2** was then coupled to commercially available tetradecyl aldehyde giving exclusively the *trans* isomer.[9] The main advantage of the HWE procedure is the exclusive formation of the *trans* isomer. The ketone was then reduced with L-Selectride® (11:1, *syn*:*anti*),[9] followed by protection of the 3-OH as the benzoyl ester to give **3** (62% over four steps from **1**). We observed no loss in selectivity or yield with the omission of labor intensive chromatographic separation after each step, and thus only compound **3** was purified.

Protection of the 3-OH as the benzoyl ester was essential for orthogonal protection and also proved important during subsequent steps. Removal of the acetonide with aqueous acid from material containing the unprotected 3-OH yielded an appreciable amount of a side product, most likely via an allylic transposition. Previous synthetic routes in general did not protect the 3-OH but removed the acetonide with aqueous acid and then protected the 1,3-OH groups as a benzyl acetal in approximately 45% yield for the two steps.[9] Subsequent mesylation of the benzyl acetal, displacement of the mesylate with azide, and removal of the acetal also proceeded in low yield.[9,12] Due to these low yielding reactions we chose an alternative route to an orthogonally protected azide.

The acetonide was then removed from compound **3** by aqueous acid and the 1° alcohol was protected selectively as the TBS ether.[13] The 2° alcohol was then activated for S_N2 displacement as the mesylate and the protecting group on the 1° alcohol was exchanged from a TBS group to a MOM group thereby providing **4** in 69% yield over five steps.[14] The circular route was necessitated by the requirements for high 1° versus 2° alcohol selectivity of the initial protecting group and a sterically small protecting group at the 1° alcohol for subsequent $^{-}N_3$ displacement. The robust OTBS group sterically blocked the C-2 OMs preventing any $^{-}N_3$ displacement at the site later in the synthesis. The extra steps were offset by very high yields and omission of chromatographic separation. As in the earlier portions of the synthesis all the intermediates were thoroughly characterized but we obtained higher yields when only one final purification step was performed on **4**. The final azido displacement goes smoothly in 90% yield producing compound **5**.[15] To verify the structure and to demonstrate selective deprotection, compound **5** was quantitatively deprotected at C1 to known compound **6** which is the most commonly used sphingosine derivatives for carbohydrate coupling reactions (Scheme 3).[13]



Scheme 3. Selective deprotection at C1.

In summary, we have demonstrated the synthesis of a protected D-(+)-*erythro*-sphingosine in 39% overall yield from commercially available **1** with three chromatographic steps. The synthesis provides rapid access to an orthogonally protected precursor suitable for coupling to a wide variety of saccharides or other molecules at either the 1- or 3-positions. The route is rapid, high yielding and results in pure material without the need for numerous purification steps.

Acknowledgements

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14. All compounds described have been fully characterized by ^1H and ^{13}C NMR spectroscopy, and microanalysis. Procedure and characterization data for compound **4**: To a solution of **3** (2.36 g, 5.30 mmol) in CH_3CN (40 mL) was added 6N HCl (10 mL). The reaction was followed by TLC (hexanes:EtOAc 5:1) until the complete consumption of **3**, about 2 h. The solution was then poured into an EtOAc/H_2O partition and the organic layer removed. The organic portion was further washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was then dried by a single azeotropic distillation with toluene and dissolved in $CHCl_3$ (20 mL). To the solution was added TBSCl (1.00 g, 6.90 mmol) and pyridine (1.00 g, 12.70 mmol). After 4 h the solution was diluted with $CHCl_3$ (100 mL) and washed twice with brine, dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in $CHCl_3$ (20 mL). Pyridine (1.00 g, 12.70 mmol) and MsCl (1.80 g, 15.70 mmol) were then added. The solution was stirred at

room temperature for 12 h then diluted with $CHCl_3$ (100 mL), washed one time with 5% HCl, twice with brine, dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in THF (25 mL) and HF·pyridine was added (5 mL). After 1 h the reaction was neutralized with 2N NaOH, and diluted with EtOAc. The mixture was extracted once with brine, dried and concentrated. The resulting syrup was dried by a single azeotropic distillation with toluene and used without further purification. The crude syrup was dissolved in $CHCl_3$ (10 mL) to which was then added pyridine (1.00 mL, 12.70 mmol) and MOMCl (1.00 g, 12.70 mmol). The solution was stirred for 12 h then diluted with 100 mL $CHCl_3$ and washed once with 5% HCl and once with brine, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to column chromatography on silica gel (hexanes:EtOAc 3:1) to give **4** (1.92 g, 69% in five steps); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, $J=7.0$ Hz, 2H), 7.51 (t, $J=7.4$ Hz, 1H), 7.43 (t, $J=7.7$ Hz, 2H), 6.00 (dt, $J=15.4$, 6.7 Hz, 1H), 5.74 (t, $J=7.4$ Hz, 1H), 5.51 (dd, $J=15.4$, 7.6 Hz, 1H), 5.00 (td, $J=6.6$, 3.3 Hz, 1H), 4.66 (s, 2H), 3.85 (dd, $J=11.4$, 3.3 Hz, 1H), 3.76 (dd, $J=11.4$, 6.4 Hz, 1H), 3.37 (s, 3H), 3.01 (s, 3H), 2.05 (broad q, $J=7.1$ Hz, 2H), 1.50–1.16 (m, 22H), 0.91 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.22, 138.89, 138.42, 133.25, 129.78, 128.47, 122.71, 96.64, 81.38, 73.11, 66.44, 55.51, 38.81, 32.33, 31.92, 29.64, 29.39, 29.15, 28.60, 22.68, 14.11. Anal. calcd for $C_{28}H_{46}O_7S$: C, 63.85; H, 8.80. Found: C, 63.79; H, 8.71%.

15. Procedure and characterization data for compound **5**: To a solution of **4** (0.100 g, 0.190 mmol) in DMF (25 mL) was added 15-crown-5 (0.140 g, 0.630 mmol) and LiN_3 (0.031 g, 0.630 mmol). The mixture was stirred at 90°C for 1 day, cooled and diluted with Et_2O (100 mL). The mixture was washed once with 5% HCl and once brine, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to column chromatography on silica gel (hexanes:EtOAc 7:1) to give **5** (0.081 g, 90%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, $J=7.0$ Hz, 2H), 7.51 (t, $J=7.4$ Hz, 1H), 7.43 (t, $J=7.7$ Hz, 2H), 5.94 (dt, $J=13.5$, 6.6 Hz, 1H), 5.66–5.54 (m, 2H), 4.66 (s, 2H), 3.95 (dt, $J=7.4$, 4.3 Hz, 1H), 3.67 (dd, $J=10.5$, 4.7 Hz, 1H), 3.59 (dd, $J=10.4$, 7.6 Hz, 1H), 3.37 (s, 3H), 2.05 (broad q, $J=7.1$ Hz, 2H), 1.50–1.16 (m, 22H), 0.91 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.22, 138.77, 133.21, 129.76, 128.44, 122.94, 96.72, 74.82, 66.88, 64.09, 55.51, 32.34, 31.90, 29.64, 29.57, 29.41, 29.34, 29.12, 28.68, 22.68, 14.12. Anal. calcd for $C_{27}H_{43}N_3O_4$: C, 68.47; H, 9.15; N, 8.87. Found: C, 68.45; H, 9.21; N, 8.84%.