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Efficient Synthesis of D-*erythro*-Sphingosine and D-*erythro*-Azidosphingosine from D-*ribo*-Phytosphingosine via a Cyclic Sulfate Intermediate

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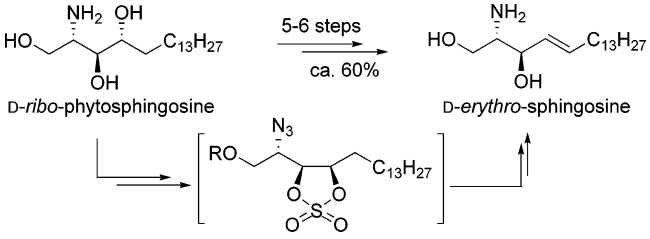

The synthesis of naturally occurring D-*erythro*-sphingosine and synthetically useful D-*erythro*-2-azidosphingosine from commercially available D-*ribo*-phytosphingosine is described. An important feature of this synthesis is the selective transformation of the 3,4-vicinal diol of phytosphingosine into the characteristic *E*-allylic alcohol of sphingosine via a cyclic sulfate intermediate.

Sphingolipids are important structural and functional components of the plasma membranes of essentially all eukaryotic cells. They play critical roles in many physiological processes including cell recognition, adhesion, and signaling.[1] Over the past decade, significant strides have been made in the elucidation of biological function of sphingolipids. One of the remarkable findings is the identification of sphingolipid metabolites as second messengers, which provides the basis for the emerging concept of sphingolipid metabolites as therapeutics with clinical potential.[2]

While the interest in investigating the biological functions of sphingolipids grew, efforts for the effective preparation of natural and nonnatural sphingolipids have generated much attention.[3] One of the keys to their successful preparation is the acquirement of appropriate sphingoid bases, the principal backbone of sphingolipids. Sphingoid bases are long-chain aliphatic compounds typically possessing a 2-amino-1,3-diol functionality. The most common naturally occurring sphingoid bases of animal and plant tissues are D-*erythro*-sphingosine (**1**, Figure 1) and D-ribo-phytosphingosine (**2**), respectively.[4] They are currently commercially available. While D-*ribo*-phytosphingosine is readily obtainable on an industrial scale from a yeast fermentation process,[5] D-*erythro*-sphingosine is available only by chemical synthesis or laborious animal tissue extraction.

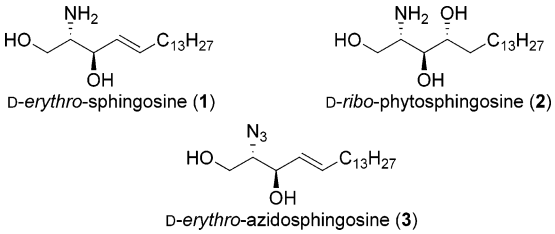

FIGURE 1. Chemical structures of compounds **1**−**3**.

To meet the growing demand for D-*erythro*-sphingosine, a number of synthetic methodologies have been reported.[3,6] Many syntheses start from various chiral pools such as carbohydrates and amino acids, whereas other syntheses have employed asymmetric induction such as Sharpless asymmetric epoxidation and asymmetric aldol to install the absolute stereochemistry of sphingosine. In addition, van Boom and co-workers recently reported the efficient preparation of sphingosine **1** from another sphingoid base, phytosphingosine **2**, by employing the regiospecific reduction of a *Z*-enol triflate intermediate[7] or the TMSI/DBN promoted selective eliminative epoxide opening of oxirane intermediate[8] as key steps. Their syntheses have several advantages over other syntheses in that minimal protecting group manipulations and purification steps are required, thereby allowing the multigram synthesis of **1**. However, their first approach, via a *Z*-enol triflate intermediate, is hampered by the use of rather expensive reagents and low-temperature manipulation. Their second approach, via an oxirane intermediate, suffers from an unwanted ditosylate as a side product.

Herein, we wish to report a new concise and efficient synthetic route to sphingosine **1** and synthetically useful

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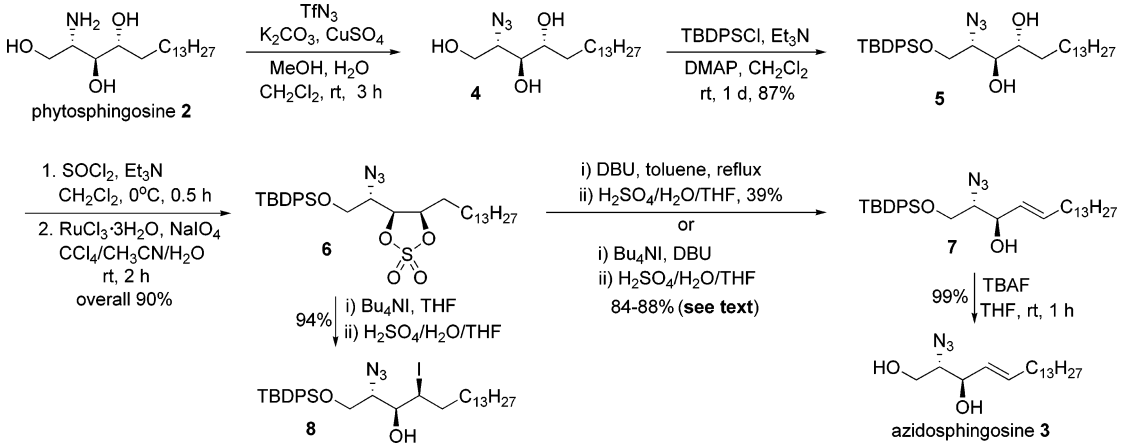
SCHEME 1. Synthesis of Azidosphingosine 3



2-azidosphingosine **3**[7,9] from inexpensive phytosphingosine **2**. Our strategy is based on the use of a cyclic sulfate[10] for the regio- and stereoselective transformation of the C-4 hydroxyl group of phytosphingosine into the characteristic 4,5-trans double bond of sphingosine. One of the advantages of the cyclic sulfate in this approach is that it eliminates the need for selective activation of only one vicinal hydroxyl group.

Our approach commenced with the protection of the amino function and primary hydroxyl group of phytosphingosine. The azide was chosen as an amino protecting group. Thus, the known azido-phytosphingosine **4** was prepared without column chromatographic purification in high yield (90−99%) according to the published procedure.[7,9a,11] The primary alcohol was protected selectively as its silyl ether **5** (87%). Conversion of 3,4-vicinal diol **5** to its cyclic sulfite with thionyl chloride in the presence of triethylamine followed by oxidation with $RuCl_3/NaIO_4$[12] provided cyclic sulfate **6**[13] in high yield (90%) (Scheme 1).

With multigram quantities of cyclic sulfate **6** in hand, we explored the possibility of a base-mediated direct transformation of cyclic sulfate into allylic alcohol by the regioselective abstraction of a β-hydrogen. A limited number of applications of this transformation have been made by us and others to install the cis double bond in the carbocyclic ring system.[14] However, to our knowledge, the scope of the elimination reaction of cyclic sulfate in an acyclic system has not been explored.[15] To our delight, we found that the elimination reaction of cyclic sulfate **6** was feasible even in an inactivated acyclic system. The reaction of cyclic sulfate **6** with DBU in refluxing toluene[14] led, after hydrolysis of the resulting sulfate ester intermediate with aqueous sulfuric acid, to the formation of the desired allylic alcohol **7** with the trans selectivity. No cis olefin was detected in the crude ^{1}H NMR spectra. Unfortunately, however, the chemical yield was too low (39%) to utilize this condition on a preparative scale. The reason for this unsatisfactory yield was partially due to the nucleophilic substitution of cyclic sulfate with DBU.[16] We were unable to fully characterize the DBU adduct and could not prevent the formation of this byproduct by modification of the solvent, reaction temperature and stoichiometry. The employment of other so-called nonnucleophilic bases, such as LHMDS and *t*-BuOK, did not improve the yield.

To utilize the facile nucleophilic substitution of cyclic sulfate in this transformation, we decided to employ the ring opening of cyclic sulfate by the iodide and subsequent dehydrohalogenation reaction. A similar strategy was employed previously by Shing[17] for the transformation of a cyclic sulfate into an allylic alcohol in a carbocyclic ring system. To accomplish this, we first needed to examine the regioselectivity of nucleophilic ring opening of cyclic sulfate by the iodide. We found that the treatment of cyclic sulfate **6** with Bu_4NI in THF followed by acidic hydrolysis of the intermediate *O*-sulfate provided the iodo alcohol **8** as the only identifiable regioisomer in 94% yield (Scheme 1). The regiochemistry of **8** was determined by the ^{1}H NMR chemical shifts and splitting patterns of the protons at C-3 and C-4. Although more systematic studies are needed to elucidate the origin of this excellent regioselectivity, one possible reason may be due to the steric and electronic interactions between the neighboring substituents and nucleophile.

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(12) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538−7539.

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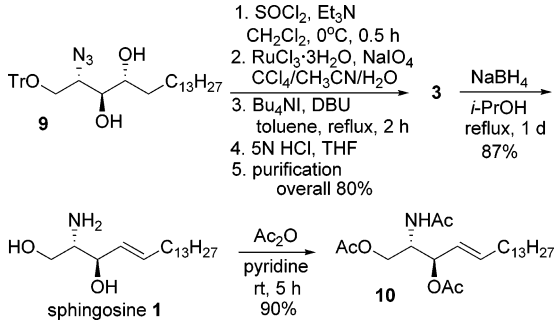
SCHEME 2. Synthesis of D-*erythro*-Sphingosine (1)



Pleased with this result, we studied the direct one-pot ring opening/ dehydrohalogenation sequence. After the nucleophilic ring opening reaction in THF was completed as judged by TLC analysis, DBU was added and the reaction temperature was raised to reflux. This treatment followed by acidic hydrolysis successfully furnished the desired *E*-allylic alcohol **7** as the only isomer in much higher yield (84%) compared to that of the direct elimination reaction of the cyclic sulfate (39%). When the solvent of one-pot process was replaced with toluene, the yield of **7** was slightly improved to 88%. Alternatively and more conveniently, **7** could be obtained in similar yield (87%) by simultaneous addition of both Bu_4NI and DBU to a toluene solution of cyclic sulfate **6** and refluxing for 2 h. At this stage, it is of interest to note that diol **5** could be converted to allylic alcohol **7** even without column chromatographic purification of cyclic sulfate intermediate **6** in similar overall yield (80%) (Scheme 1).

With a facile route to the large-scale preparation of the desired compound **7**, efforts were next directed toward the deprotection steps. The silyl group was removed by treatment with Bu_4NF in THF, affording the known 2-azidosphingosine **3** in 99% yield. The analytical and spectroscopic data of **3** were in good agreement with literature data.[7,9]

Alternatively, when the known diol **9**,[9a,18] containing an acid-labile trityl ether protecting group, was employed as a 1,2-amino-alcohol protected phytosphingosine, the application of the above sequence also successfully afforded 2-azidosphingosine **3** in high overall yield (Scheme 2). The diol **9** was converted to a cyclic sulfate, which was submitted directly to one-pot ring opening/dehydrohalogenation conditions (Bu_4NI and DBU in refluxing toluene) without column chromatography. Exposure of the resulting reaction mixture to HCl/THF resulted in simultaneous hydrolysis of the sulfate ester intermediate and removal of the trityl protecting group to give the 2-azidosphingosine **3** in 80% overall yield.

A final reduction of the azide to an amino group was achieved by treatment of **3** with $NaBH_4$ in refluxing 2-propanol[19] to give D-*erythro*-sphingosine (**1**) as waxy solid in 87% isolated yield (Scheme 2). Other literature conditions,[6c,20] such as Staudinger reaction, $LiAlH_4$, and Zn/NH_4Cl, gave several products and modest isolated yield in our hands. The analytical and spectroscopic data of both the synthetic **1** and its triacetate derivative **10**[21] were identical to those reported.[6,8,22]

In conclusion, these studies provide a practical preparative route to D-*erythro*-sphingosine (**1**) from the low cost phytosphingosine **2** in high overall yield (ca 60%). An important feature of this synthesis is the selective transformation of the 3,4-vicinal diol of phytosphingosine into the characteristic *E*-allylic alcohol of sphingosine via a cyclic sulfate. The treatment of cyclic sulfate **6** with Bu_4NI/ DBU led to the exclusive formation of trans olefin in high yield. This transformation is complementary to the eliminative epoxide opening. Further studies will be forthcoming which will elucidate the scope and limitations of the elimination reaction of cyclic sulfate in an acyclic system.

Experimental Section

(2*S*,4*S*,5*R*)-[2-Azido-2-(2,2-dioxo-5-tetradecyl-2λ^6-[1,3,2]dioxathiolan-4-yl)ethoxy]-*tert*-butyldiphenylsilane (6). To a solution of diol **5** (1.10 g, 1.88 mmol) in CH_2Cl_2 (10 mL) were added triethylamine (786 μL, 5.64 mmol) and thionyl chloride (160 μL, 2.26 mmol) at 0 °C. After 30 min, this reaction mixture was poured into brine and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. This crude cyclic sulfite was dried in vacuo for 3 h and dissolved in $CCl_4/CH_3CN/H_2O$ (12 mL, 1:1:1). To the resulting solution were added $RuCl_3 \cdot 3H_2O$ (19 mg, 0.09 mmol) and $NaIO_4$ (1.21 g, 5.64 mmol). After this reaction mixture was stirred at room temperature for 2 h, it was diluted with EtOAc and washed with saturated $NaHSO_3$ solution. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to give cyclic sulfate **6** (1.09 g, 90%) as a colorless oil: $[\alpha]^{25}_D$ +53.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, J = 6.6 Hz, 3H), 1.11 (s, 9H), 1.29 (s, 22H), 1.47−1.63 (m, 2H), 1.71−1.80 (m, 1H), 1.88−2.00 (m 1H), 3.70 (ddd, J = 2.4, 5.1, 9.9 Hz, 1H), 3.91 (dd, J = 5.1, 11.4 Hz, 1H), 4.05 (dd, J = 2.4, 11.4 Hz, 1H), 4.91−5.03 (m, 2H), 7.41−7.51 (m, 6H), 7.68−7.72 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 19.1, 22.6, 25.1, 26.6, 28.0, 28.9, 29.2, 29.3, 29.4, 29.5, 29.59, 29.61, 29.63, 31.9, 59.1, 63.5, 79.8, 86.4, 127.90, 127.92, 130.1, 131.9, 132.1, 135.47, 135.50; IR ($CHCl_3$) υ_{max} 2108, 1392 (cm^{-1}); HRMS (FAB) calcd for $C_{34}H_{52}O_5N_3SiS$ 642.3397 ($[M-H]^-$), found 642.3378.

(2*S*,3*R*)-(*E*)-2-Azido-1-(*tert*-butyldiphenylsilyoxy)octadec-4-en-3-ol (7). To a solution of cyclic sulfate **6** (534 mg, 0.83 mmol) in toluene (8 mL) were added Bu_4NI (336 mg, 0.91 mmol) and DBU (187 μL, 1.25 mmol). This reaction mixture was heated to reflux for 2 h. The reaction was cooled to room temperature, and to it were added concentrated H_2SO_4 (14 μL), H_2O (17 μL), and THF (217 μL). The mixture was stirred for 1 h at room temperature and then diluted with EtOAc. It was washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give **7** (408 mg, 87%) as a colorless oil: $[\alpha]^{25}_D$ +2.54 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J = 6.9 Hz, 3H), 1.08 (s, 9H), 1.26 (s, 20H), 1.31−1.33 (m, 2H), 1.98−2.05 (m, 2H), 3.51 (td, J = 1.2, 5.1 Hz, 1H), 3.77 (dd, J = 4.5, 11.1 Hz, 1H), 3.82 (dd, J = 6.6, 11.1 Hz, 1H), 4.23 (app. t, J = 6.0 Hz, 1H), 5.43 (tdd, J = 1.2, 6.9, 15.3 Hz, 1H), 5.74 (dtd, J = 0.9, 7.8, 15.3 Hz, 1H), 7.37−7.48 (m, 6H), 7.67−7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 19.0, 22.6, 26.7, 28.9, 29.1, 29.3, 29.4, 29.5, 29.6, 31.9, 32.2,

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(21) Owing to the reported instability of **1**, it was also characterized as the triacetate derivative **10**.

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64.1, 66.9, 72.7, 127.75, 127.84, 129.8, 132.7, 135.2, 135.5; IR ($CHCl_3$) υ_{max} 3420, 2101, 1642 (cm^{-1}); HRMS (FAB) calcd for $C_{34}H_{52}O_2N_3Si$ 562.3829 ($[M-H]^-$), found 562.3838.

(2*S*,3*S*,4*S*)-2-Azido-1-(*tert*-butyldiphenylsilyloxy)-4-iodooctadecan-3-ol (8). To a solution of cyclic sulfate **6** (104 mg, 0.16 mmol) in THF (3 mL) was added Bu_4NI (65.0 mg, 0.176 mmol). This reaction mixture was heated for 1 h at 40 °C. The reaction was cooled to room temperature, and to it were added concentrated H_2SO_4 (14 μL), H_2O (17 μL), and THF (212 μL). The mixture was stirred for 1 h at room temperature and then diluted with EtOAc. It was washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give iodo alcohol **8** (104 mg, 94%) as a colorless oil: $[\alpha]^{25}_D$ +7.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.9 Hz, 3H), 1.09 (s, 9H), 1.26 (s, 22H), 1.72−1.82 (m, 1H), 1.86 (d, J = 9.6 Hz, 1H), 2.01−2.13 (m, 1H), 2.55 (dt, J = 1.5, 9.3 Hz, 1H), 3.45 (ddd, J = 3.3, 6.3, 9.6 Hz, 1H), 3.93 (dd, J = 6.0, 11.1 Hz, 1H), 4.06 (dd, J = 3.3, 11.1 Hz, 1H), 4.53 (ddd, J = 1.5, 6.0, 9.0 Hz, 1H), 7.38−7.49 (m, 6H), 7.68−7.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 19.1, 22.7, 26.7, 28.7, 29.3, 29.4, 29.5, 29.59, 29.63, 29.7, 31.9, 38.0, 46.3, 64.3, 68.1, 72.0, 127.83, 127.85, 129.92, 129.94, 132.66, 132.70, 135.6; IR ($CHCl_3$) υ_{max} 3449, 2926, 2854, 2101, 1113 (cm^{-1}); HRMS (CI) calcd for $C_{34}H_{55}N_3IO_2Si$ 692.3108 ($[M+H]^+$), found 692.3108.

(2*S*,3*R*)-(*E*)-2-Azidooctadec-4-ene-1,3-diol (3). From **7**: To a solution of **7** (138 mg, 0.24 mmol) in THF (1.2 mL) was added TBAF (480 μL, 0.48 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 1 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, concentrated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 3:1) to give azidosphingosine **3** (80 mg, 99%) as a colorless oil: $[\alpha]^{25}_D$ −37.3 (*c* 0.7, $CHCl_3$).

From **9**: Following the same procedure as for **6**, the crude cyclic sulfate was obtained from diol **9** (856 mg, 1.46 mmol). To a solution of crude cyclic sulfate in toluene (15 mL) were added Bu_4NI (595 mg, 1.61 mmol) and DBU (296 μL, 1.98 mmol). This reaction mixture was heated to reflux for 2 h. After the reaction mixture was cooled to room temperature, 5.0 N HCl (7 mL) and toluene (5 mL) were added. The resulting mixture was stirred for 2 h at room temperature and then diluted with EtOAc. It was washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 4:1) to give azidosphingosine **3** (381 mg, 80% from **9**) as a colorless oil: $[\alpha]^{24}_D$ −37.7 (*c* 1.0, $CHCl_3$) (Optical rotation values of azidosphingosine **3** range from −29.1 to −34.1. See: refs 7, 9b−f, and 19); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H), 1.26 (s, 20H), 1.36−1.41 (m, 2H), 2.04−2.10 (m, 2H), 3.51 (dd, J = 5.7, 10.2 Hz, 1H), 3.76 (dd, J = 5.7, 11.7 Hz, 1H), 3.81 (dd, J = 4.8, 11.7 Hz, 1H), 4.25 (app. t, J = 6.3 Hz, 1H), 5.54 (tdd, J = 1.2, 7.5, 15.3 Hz, 1H), 5.82 (dtd, J = 0.6, 7.8, 14.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.6, 28.9, 29.2, 29.3, 29.4, 29.55, 29.59, 29.61, 31.9, 32.3, 62.3, 66.7, 73.4, 128.0, 135.8; IR ($CHCl_3$) υ_{max} 3382, 2101, 1642 (cm^{-1}); HRMS (FAB) calcd for $C_{18}H_{34}O_2N_3$ 324.2651 ($[M - H]^-$), found 324.2661.

(2*S*,3*R*)-(*E*)-2-Aminooctadec-4-ene-1,4-diol (D-*erythro*-sphingosine) (1). To a solution of azidosphingosine **3** (98 mg, 0.30 mmol) in 2-propanol (3 mL) was added $NaBH_4$ (68 mg, 1.8 mmol). This reaction mixture was heated to reflux for 24 h and cooled to room temperature. Acetone (1 mL) was added to destroy unreacted $NaBH_4$, and the resulting mixture was stirred for 10 min and concentrated. It was diluted with Et_2O and centrifuged (1000 rpm) for 10 min twice. The supernatant was concentrated and purified by silica gel column chromatography ($CHCl_3$/ MeOH/NH_4OH, 135:25:4) to give a white solid. The obtained solid was dissolved in $CHCl_3$ and passed through a pad of Celite to remove residual silica gel. The filtrate was concentrated to give sphingosine **1** (77 mg, 87%) as a white waxy solid: R_f = 0.15 ($CHCl_3$/MeOH/NH_4OH, 135:25:4); (mp 76−77 °C (lit.[6d] mp 72−75 °C, lit.[6e] mp 73−75 °C, lit.[9b] mp 75−80 °C, lit.[22a] mp 79−82 °C); $[\alpha]^{24}_D$ −3.0 (*c* 1.0, $CHCl_3$) (Optical rotation values of sphingosine **1** range from −1.4 to −2.9. See: refs 6−8 and 22a); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H), 1.25 (s, 20H), 1.37 (m, 2H), 2.05 (q, J = 6.6 Hz, 2H), 2.34 (br s, 4H), 2.88 (br s, 1H), 3.66 (br s, 2H), 4.06 (br s, 1H), 5.47 (dd, J = 6.9, 15.3 Hz, 1H), 5.76 (td, J = 6.6, 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 29.2, 29.25, 29.34, 29.5, 29.7, 31.9, 32.3, 56.2, 63.7, 75.1, 129.0, 134.7; IR ($CHCl_3$) υ_{max} 3240, 2919, 2851, 1467, 1032, 970 (cm^{-1}); HRMS (FAB) calcd for $C_{18}H_{38}O_2N$ 300.2903 ($[M + H]^+$), found 300.2907. Compound **1** was also characterized as the triacetate derivative **10** (see Supporting Information).

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Supporting Information Available: Experimental procedures for the synthesis of **5**, **9**, and **10**; copies of ^1H NMR and ^{13}C NMR spectra of compounds **1**, **3**, **5**, **6**, **7**, **8**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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