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A simple and low cost synthesis of D-*erythro*-sphingosine and D-*erythro*-azidosphingosine from D-*ribo*-phytosphingosine: glycosphingolipid precursors

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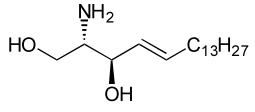
Abstract—D-*erythro*-Sphingosine (**1**) and D-*erythro*-2-azidosphingosine (**2**) are both prepared from commercially available and cheap D-*ribo*-phytosphingosine (**3**) in a yield of 58% and 70%, respectively. A key transformation in the synthesis of D-*erythro*-sphingosine (**1**) is the palladium catalyzed regiospecific reduction of the *Z*-enol triflate **9**. A crucial step in the synthesis of azidosphingosine **2** comprises a regio- and stereoselective in situ *trans*-elimination of the 4-*O*-triflate of azidophytosphingosine **13**.

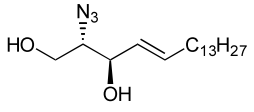
Glycosphingolipids (GLS) are common elements of plasma membranes[1] and important factors in various biological processes, including cellular recognition events and several signal transduction pathways.[2] Many natural GLS are characterized by the presence of D-*erythro*-sphingosine [(2*S*,3*R*,4*E*)-2-amino-3-hydroxyoctadec-4-en-1-ol], the primary hydroxyl group of which is glycosylated while the amino function is acylated by a fatty acid (ceramide unit). At present, GLS are gaining interest for cosmetic and therapeutic applications.[3,4] Unfortunately, GLS are not readily available from natural sources in a homogeneous form. In order to meet the growing demand for GLS, many different methods, starting with the first racemic one in 1954,[5] have been devised[6,7] for the chemical synthesis of (2*S*,3*R*,4*E*)-sphingosine (**1**) in sufficient amounts and high chiral purity. It is also well recognized[8] that the use of 2-azidosphingosine **2** (see Fig. 1) is in several aspects superior to sphingosine **1** in the synthesis of GLS.

We here report a convenient and concise route for the synthesis of sphingosine **1** as well as 2-azidosphingosine **2** from commercially available and cheap[9] phytosphingosine **3**.

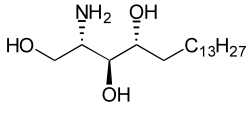
It was envisaged that both target compounds **1** and **2** could in principle be prepared from phytosphingosine (**3**) taking into account the following literature precedents dealing with the introduction of the requisite *E*-alkene moiety. Shiozaki et al. showed[10] that the properly protected 4-ketone derivative **4** (Scheme 1), obtained from D-tartaric acid, could be transformed with a high degree of stereoselectivity into sphingosine (**1**). A key event in this approach is the regiospecific and stereoselective transformation of **4** into the corresponding *Z*-enol triflate followed by a palladium assisted regiospecific reduction. On the other hand, Schmidt et al. reported[11] that the properly protected 2-azido-4-nitrophenylsulfonate derivative **5** (Scheme 1), prepared from D-galactose, could be converted into azidosphin-



1 (D-*erythro*-sphingosine)



2 (D-*erythro*-azidosphingosine)



3 (D-*ribo*-phytosphingosine)

Figure 1.

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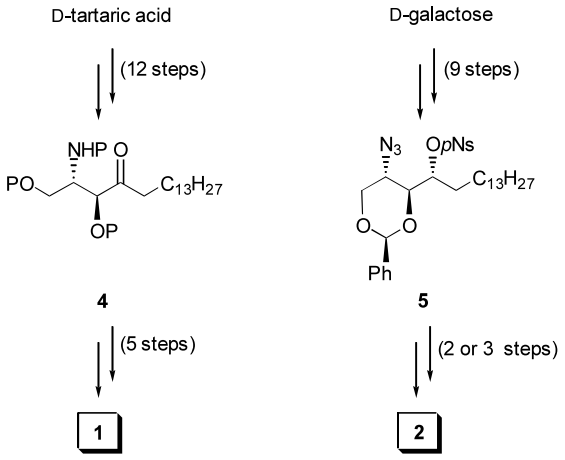
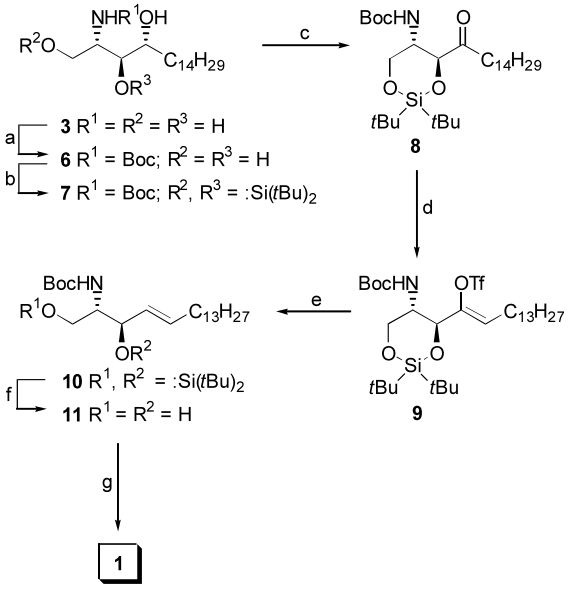


Scheme 1.

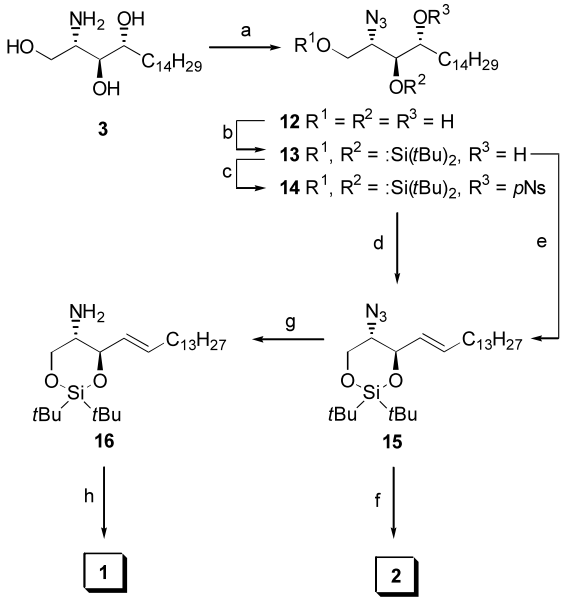
gosine **2** either via a regio- and stereoselective *trans*-elimination or a regio- and stereoselective *cis*-elimination of the corresponding 4-phenylselenoxide.[12]

Consequently, we first examined whether the enol triflate methodology could be readily adopted to the synthesis of sphingosine (**1**) starting from phytosphingosine (**3**). The synthetic route we followed is depicted in Scheme 2 and commences with the protection of the amino function of phytosphingosine (**3**). Thus, treatment of sphingoide **3** with di-*tert*-butyl dicarbonate gave the *N*-Boc protected derivative **6**. Attempts to mask the 1,3-diol in **6** with the benzylidene group led to an inseparable mixture of products. However, regioselective protection of **6** was readily accomplished by silylation with di-*tert*-butylsilyl ditriflate[13] to afford the 2-*N*-Boc-1,3-di-*tert*-butyl silylene derivative **7**. Oxidation of the 4-hydroxyl group in **7** with acetic anhydride in dimethyl sulfoxide[14] provided ketone **8** in a yield of 88% over the three steps. Treatment of **8** with potassium bis(trimethylsilyl)amide followed by sulfonylation of the in situ formed enolate with *N*-phenyl trifluoromethanesulfonimide furnished *E*-enol triflate **9** in a yield of 89%. Ensuing stereospecific reductive elimination of the enol triflate function with formic acid/triethylamine under the agency of $Pd(OAc)_2(PPh_3)_2$[15] led to the exclusive isolation of **10** ($J_{4,5}=15.4$ Hz) in a yield of 81% based on the 4-ketone derivative **8**. Unmasking of **10** proceeded uneventfully by the following two-step procedure. Thus, desilyation of **10** with tetrabutylammonium fluoride in the presence of acetic acid afforded diol **11** in near quantitative yield. Acidolysis of the *N*-Boc protecting group in **11** with trifluoroacetic acid furnished target compound **1**, analytical data of which are in full accord with those reported[16] for the same compound.

At this stage, attention was focused on the synthesis of 2-azidosphingosine (**2**) from phytosphingosine (**3**) following the Schmidt[11] procedure for the introduction of the 4,5 *E*-double bond. In the first step **3** was subjected, as outlined in Scheme 3, to Wong's[17] diazo transfer to furnish the azido derivative **12**. Regioselective protection of the 1,3-diol in **12** with the di-*tert*-butyl silylene protective group afforded alcohol **13** in a yield of 93% over the two steps. Surprisingly, nitrophenylsulfonylation of **13** under standard conditions[11] led to an intractable mixture of products. In contrast, nosylation



Scheme 2. [18] (a) Boc_2O, TEA, THF, rt, 30 min, 92%; (b) $(^tBu)_2Si(OTf)_2$, DMF, pyridine, −40°C, 30 min, 97%; (c) DMSO, Ac_2O, rt, 16 h, 99%; (d) KHMDS, phenylbistrifluoromethanesulfonimide, THF/toluene, −68°C→−20°C, 3 h, 89%; (e) $Pd(OAc)_2$(triphenylphosphine)$_2$, HCO_2H, TEA, DMF, 60°C, 4 h, 91%; (f) TBAF, AcOH, THF, 0°C, 1 h, quantitative; (g) TFA, DCM, 0°C, 15 min, 81%.



Scheme 3. [18] (a) N_3Tf, K_2CO_3, $CuSO_4$, DCM, MeOH, H_2O, rt, 16 h, 93%; (b) $(^tBu)_2Si(OTf)_2$, DMF, pyridine, −40°C, 30 min, quantitative; (c) AgOTf, *p*NsCl, pyridine, rt, 1 h, 96%; (d) DBU, toluene, 80°C, 96 h, 38%; (e) Tf_2O, DCE/pyridine, 0°C, 15 min; 77%; (f) TBAF, AcOH, THF, 0°C, 2 h, 99%; (g) Me_3P, H_2O, THF, 0→55°C, 16 h, 84%; (g) as (f), 98%.

with the mixed anhydride, prepared in situ from silver triflate and 4-nitrophenylsulfonyl chloride, gave the nitrophenylsulfonyl derivative **14** in a yield of 96%. Subjection of **14** ($R^3 = p$Ns) to elimination using 1,8-diazabicyclo[5.4.0]undec-7-ene as a base led to the isolation of the *E*-olefin **15** in a comparable unsatisfactory yield (38%) as reported[11] earlier starting from the differently protected nitrophenylsulfonyl derivative **5** (see Scheme 1). It turned out that a twofold increase in yield of the crucial elimination step could be attained by the following one-pot two-step procedure. Thus, triflation of **13** with triflic anhydride in the presence of pyridine gave after work-up and purification, the *E*-olefin **15** ($J_{4,5} = 15.4$ Hz), instead of expected triflated **13** ($R^3 =$ Tf), in a gratifying yield of 77%. Interestingly, triflation of **13** in the absence of base led to the isolation of a mixture of the *E*- and *Z*-olefins **15**. Ensuing deblocking of the di-*tert*-butyl silylene protecting group in **15** afforded 2-azidosphingosine (**2**) in an overall yield of 70% over the four steps. At this stage, it is also worthwhile mentioning that 2-azidosphingosine could be readily transformed in two high yielding steps (i.e. Staudinger reduction followed by desilylation; see Scheme 3 steps g and h, respectively) into sphingosine (**1**).

The results presented in this paper clearly show that D-*ribo*-phytosphingosine (**3**) can be transformed into D-*erythro*-sphingosine (**1**) and its 2-azido analog **2** in an overall yield of 58% and 70%, respectively. It was also established that sphingosine (**1**) can be prepared in the same overall yield (58%) following the azido route, which invokes a one-pot procedure, instead of a more costly two-step process (cf. conversion of **8**→**10**), in generating the requisite *E*-olefin function. It may therefore be concluded that the azido route not only presents an economic route to sphingosine (**1**) but also to 2-azidosphingosine (**2**), which is a valuable starting compound in the synthesis of GLS. The application of the azido route in a large-scale synthesis of several GLS is currently under investigation.

Acknowledgements

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9. Phytosphingosine [(2*S*,3*S*,4*R*)-2-amino-1,3,4-octadecanetriol] is now readily available from a yeast fermentation process. For information, contact; Cosmoferm B.V., Wateringseweg 1, PO Box 386, 2600 AJ Delft, The Netherlands, Fax: +31(15)2794120; e-mail: info@cosmoferm.com.
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18. All compounds were fully characterized by ^{1}H, ^{13}C NMR and MS. Relevant data of the key compounds, **8**: $[\alpha]_D^{20}$ 4.1 (*c* 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, CH_3), 1.03 (s, 9H, ^{t}Bu), 1.07 (s, 9H, ^{t}Bu), 1.25 (br. s, 2H, CH_2), 1.39 (s, 9H, ^{t}Bu Boc), 1.55 (m, 2H, CH_2), 2.73 (m, 2H, CH_2-5), 3.75 (dd, 1H, H-1ax, $J_{1ax,1eq} = 9.5$ Hz, $J_{1ax,2} = 10.2$ Hz), 3.93 (m, 1H, H-2, $J_{1eq,2} = 4.4$ Hz, $J_{1ax,2} = 10.2$ Hz, $J_{2,3} = 9.5$ Hz, $J_{2,NH} = 8.8$ Hz), 4.13 (d, 1H, H-3, $J_{2,3} = 9.5$ Hz), 4.14 (dd, 1H, H-1eq, $J_{1ax,1eq} = 9.5$ Hz, $J_{1eq,2} = 4.4$ Hz), 4.43 (br. d, 1H, NH, $J_{2,NH} = 8.0$ Hz). ^{13}C{^{1}H} NMR (50.1 MHz, $CDCl_3$): δ 14.0 (CH_3), 20.1 (Cq ^{t}Bu), 22.6, 25.5 (CH_2), 27.0, 27.3, 28.1 (3×^{t}Bu), 29.1, 29.6, 30.9, 31.9, 36.8 (CH_2), 49.8 (C-2), 67.4 (C-1), 79.9 (Cq Boc), 82.8 (C-3), 154.9 (C=O Boc), 210.6 (C-4). ES (ESI): $m/z = 578.7$ $[M+Na]^+$. **10**: $[\alpha]_D^{20}$ 23.4 (*c* 1.64,

$CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, CH_3), 1.01 (s, 9H, ^{t}Bu), 1.03 (s, 9H, ^{t}Bu), 1.25 (br. s, 24H, 12×CH_2), 1.41 (s, 9H, ^{t}Bu Boc), 2.02 (m, 2H, CH_2-6), 3.69–4.17 (m, 5H, H_2-1, H-2, H-3, NH), 5.48 (dd, 1H, H-4, $J_{4,5}$=15.4 Hz, $J_{3,4}$=6.6 Hz), 5.71 (dt, 1H, H-5, $J_{4,5}$=15.4 Hz, $J_{5,6a}$=$J_{5,6b}$=6.6 Hz). $^{13}C\{^1H\}$ NMR (50.1 MHz, $CDCl_3$): δ 14.0 (CH_3), 20.0 (Cq ^{t}Bu), 22.6 (CH_2), 27.1, 27.4, 28.3 (3×^{t}Bu), 29.1, 29.3, 29.6, 31.9, 32.2 (CH_2), 52.2 (C-2), 67.2 (C-1), 79.0 (C-3), 79.6 (Cq Boc), 129.5 (C-5), 133.8 (C-4), 155.0 (C=O Boc). ES (ESI): m/z= 540.6 $[M+H]^+$, 562.3 $[M+Na]^+$, 578.8 $[M+K]^+$. **12**: mp 97–98°C. $[\alpha]_D^{20}$ 15.1 (*c* 1.00, $CHCl_3$). IR: 2120 (broad azido peak). ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, CH_3), 1.25 (s, H, CH_2), 1.56 (br. s, 4H, CH_2), 3.68 (m, 1H, H-2,), 3.80 (m, 2H, H-3, H-4), 3.87 (dd, 1H, H-1a, $J_{1a,1b}$=11.7 Hz, $J_{1a,2}$=4.4 Hz), 4.01 (dd, 1H, H-1b, $J_{1a,1b}$=11.7 Hz, $J_{1b,2}$=5.9 Hz). ES (ESI): m/z=366.5 $[M+Na]^+$, 709.6 $[2M+Na]^+$. **14**: $[\alpha]_D^{20}$ 67.6 (*c* 1.40, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, CH_3), 0.96 (s, 9H, ^{t}Bu), 0.97 (s, 9H, ^{t}Bu), 1.26 (s, 22H, 11×CH_2), 1.54 (m, 2H, CH_2), 1.90 (dd, 2H, CH_2), 3.51 (dt, 1H, H-2, $J_{1eq,2}$=5.1 Hz, $J_{1ax,2}$=$J_{2,3}$=10.2 Hz), 3.88 (dd, 1H, H-1ax, $J_{1ax,1eq}$=10.9 Hz, $J_{1ax,2}$=10.2 Hz), 4.09 (dd, 1H, H-3, $J_{3,4}$=2.2 Hz, $J_{2,3}$=10.2 Hz), 4.23 (dd, 1H, H-1eq, $J_{1ax,1eq}$=10.9 Hz, $J_{1eq,2}$=5.1 Hz), 4.92 (dt, 1H, H-4), 8.12–8.42 (m, 4H, CH_{arm} Ns). $^{13}C\{^1H\}$ NMR (50.1 MHz, $CDCl_3$): δ 14.0 (CH_3), 20.1 (Cq ^{t}Bu), 22.5, 24.9 (CH_2), 26.7, 27.2 (2×^{t}Bu), 27.7, 29.0, 29.3, 29.6, 31.8 (CH_2), 57.9 (C-2), 66.1 (C-1), 77.0 (C-3), 85.1 (C-4), 124.3, 129.0 (CH_{arm} Ns), 142.9, 150.5 (Cq Ns). ES (ESI): m/z=691.4 $[M+Na]^+$. **15**: $[\alpha]_D^{20}$ 6.0 (*c* 1.55, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, CH_3), 1.01 (s, 9H, ^{t}Bu), 1.04 (s, 9H, ^{t}Bu), 1.26 (s, 22H, 11×CH_2), 2.09 (m, 2H, CH_2), 3.30 (m, 1H, H-2, $J_{1eq,2}$=4.4 Hz, $J_{1ax,2}$=11.0 Hz, $J_{2,3}$= 9.5 Hz), 3.81 (t, 1H, H-1ax, $J_{1ax,1eq}$=11.0 Hz, $J_{1ax,2}$=11.1 Hz), 4.10–4.28 (m, 2H, H-1eq, H-3, $J_{1ax,1eq}$=11.0 Hz, $J_{1eq,2}$=4.4 Hz, $J_{2,3}$=9.5 Hz, $J_{3,4}$=5.9 Hz), 5.51 (dd, 1H, H-4, $J_{3,4}$=6.6 Hz, $J_{4,5}$=15.4 Hz), 5.87 (ddd, 1H, H-5, $J_{5,6a}$=6.6 Hz, $J_{5,6b}$=6.5 Hz, $J_{4,5}$=15.4 Hz). $^{13}C\{^1H\}$ NMR (50.1 MHz, $CDCl_3$): δ 14.1 (CH_3), 20.0 (Cq ^{t}Bu), 22.7 (CH_2), 27.0, 27.4 (2×^{t}Bu), 28.9, 29.4, 29.7, 31.9, 32.3 (CH_2), 62.5 (C-2), 66.4 (C-1), 78.1 (C-3), 129.1 (C-5), 134.7 (C-4). ES (ESI): m/z=488.5 $[M+Na]^+$, 931.8 $[2M+H]^+$, 954.0 $[2M+Na]^+$. **1**: mp: 70°C. $[\alpha]_D^{20}$ −1.2 (*c* 1.74, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, CH_3), 1.26 (br. s, 22H, 11×CH_2), 2.05 (q, 2H, CH_2-6), 2.28 (br. s, 3H, OH/NH_2/H_2O), 2.86 (br. s, 1H, H-2), 3.66 (br. s, 2H, H_2-1), 4.05 (br. s, 1H, H-3), 5.46, (dd, 1H, H-4, $J_{4,5}$=15.4 Hz, $J_{3,4}$=6.6 Hz), 5.73 (dt, 1H, H-5, $J_{4,5}$=15.4 Hz, $J_{5,6a}$=$J_{5,6b}$ 6.6 Hz). $^{13}C\{^1H\}$ NMR (50.1 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.6, 29.3, 29.6, 31.8, 32.3 (CH_2), 56.2 (C-2), 63.1 (C-1), 74.5 (C-3), 129.1 (C-5), 134.4 (C-4). ES (ESI): m/z=300.5 $[M+H]^+$. **2**: $[\alpha]_D^{20}$ −29.8 (*c* 1.04, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, CH_3), 1.26 (s, 22H, 11×CH_2), 2.07 (m, 2H, CH_2), 2.21 (s, 2H, 2×OH), 3.50 (dd, 1H, H-2, $J_{1eq,2}$=$J_{2,3}$=5.1 Hz, $J_{1ax,2}$=11.0 Hz), 3.78 (d, 1H, H-2), 4.25 (t, 1H, H-3, $J_{2,3}$=5.9 Hz, $J_{3,4}$=6.6 Hz), 5.54 (dd, 1H, H-4, $J_{3,4}$=6.6 Hz, $J_{4,5}$=15.4 Hz), 5.82 (dt, 1H, H-5, $J_{5,6a}$=6.6 Hz, $J_{5,6b}$=6.5 Hz, $J_{4,5}$=15.4 Hz). $^{13}C\{^1H\}$ NMR (50.1 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.6, 28.9, 29.6, 31.8, 32.2 (CH_2), 62.4 (C-1), 66.7 (C-2), 73.5 (C-3), 128.0 (C-5), 135.9 (C-4). ES (ESI): m/z=348.1 $[M+Na]^+$, 673.6 $[2M+Na]^+$.