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An efficient and stereoselective route to 1-deoxy-5-hydroxy sphingosine analogues

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ABSTRACT

A short and efficient synthesis of 1-deoxy-5-hydroxy sphingolipid is described. The key steps involved are a Jacobsen hydrolytic kinetic resolution (HKR) and Shibasaki's asymmetric Henry reaction.

Sphingolipids are ubiquitous components of cell membranes that play critical roles in many physiological processes including cell recognition, adhesion and signalling.[1] Over the past decade, significant strides have been made in the elucidation of the biological function of sphingolipids. One remarkable finding 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 grows, efforts for the effective preparation of natural and nonnatural sphingolipids have generated much attention.[3]

This family of biomolecules has been shown to play a variety of important roles in the chemistry of cellular membranes as well as in cell growth, differentiation and apoptosis. For instance, the anticancer activity of the parent D-erythro-(2*S*,3*R*)-sphingosine **1** and other sphingolipids has been demonstrated both in vitro and in vivo against colon cancer cell lines. However, it was observed that sphingosine 1-phosphate produced in vivo from sphingosine **1** possessed promitotic and antiapoptotic properties. In order to overcome this problem, Liotta et al.[4] have developed 1-deoxy-5-hydroxysphingosine analogues **2** and **3** with C-2, C-3 amino alcohol stereochemistry of safingol **4**. The primary hydroxyl group of sphingosine has been moved to the C-5 position to maintain similar lipophilicity while further decreasing the opportunity for phosphorylation of hydroxyl substituents (Fig. 1). The resulting 1-deoxy-5-hydroxysphingosine analogue **2** has exhibited excellent activity against colon cancer. Similar aminodiol stereochemistry is also found in the substructure of fungal toxin fumonisin B1 **5**. So far, only one synthesis of **2** has been reported in the literature.[5]

Over the past few years, investigations in our laboratory have demonstrated the utility of nitroaliphatics in the synthesis of pharmacologically important natural products.[6] In this context, we report herein our successful exercise towards the synthesis of 1-deoxy-5-hydroxy sphingolipid **2**.

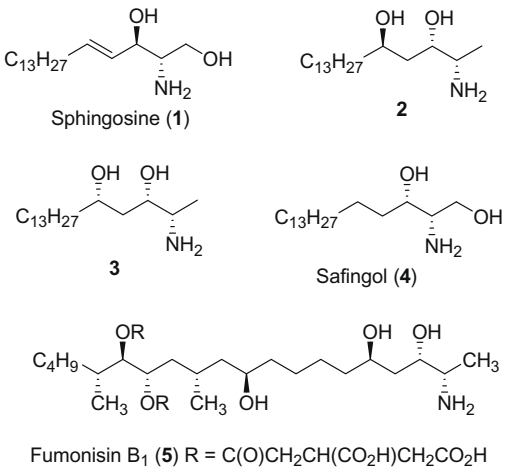

Figure 1. 1-Deoxy-5-hydroxysphingolipid analogues and an aminodiol substructure containing natural products.

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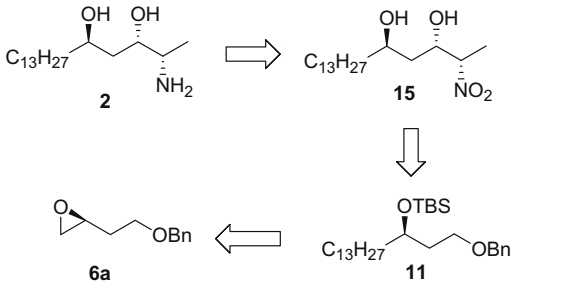
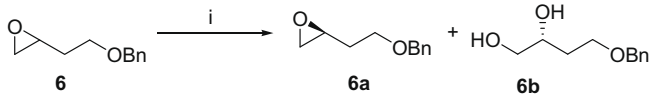
The retrosynthetic analysis envisioned for **2** is depicted in Scheme 1. As indicated in the scheme, the nitro alcohol **15** could serve as the key intermediate, which can be traced back to the protected alcohol **11**, which in turn could be obtained from the epoxide **6a**. We reasoned that the stereochemistry at C-5 could be secured by the regioselective ring opening of the epoxide. For the installation of the stereochemistry of the C-2 and C-3 stereocentres, we relied on Shibasaki's asymmetric Henry reaction.

The synthesis of the 1-deoxy-5-hydroxy sphingolipid analogue (**2**) started from racemic 2-(2-benzyloxyethyl)-oxirane (**6**). Thus, racemic 2-(2-benzyloxyethyl)-oxirane (**6**) was subjected to Jacobsen's HKR[7] using (*S*,*S*)-(salen)Co^{III}·OAc complex to give (*S*)-2-(2-benzyloxyethyl)-oxirane[8] (**6a**) as the optically pure isomer (Scheme 2).

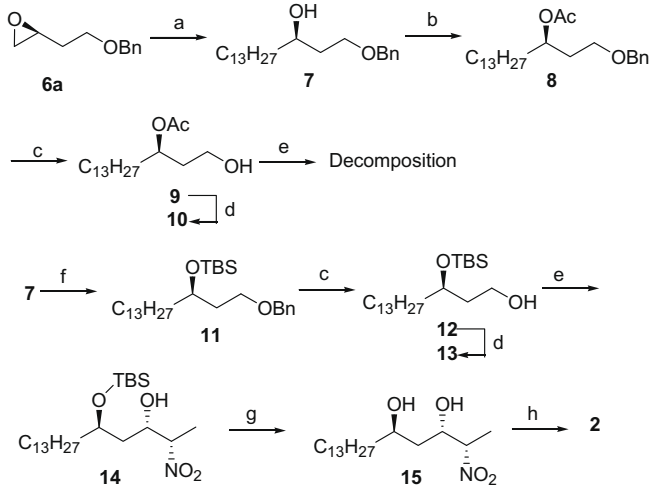
With enantiomerically pure 2-(2-benzyloxyethyl)-oxirane (**6a**) in hand, we then subjected it to Li_2CuCl_4-catalysed[9] regioselective ring opening with dodecyl magnesium bromide to give the corresponding alcohol **7** in 88% yield (Scheme 3). The hydroxyl protection of **7** with acetic anhydride in the presence of pyridine furnished **8** in a quantitative yield. Compound **8** was then subjected to Pd–C-catalysed hydrogenation to afford **9** in 92% yield.



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (i) (*S*,*S*)-(salen)Co^{III}·OAc (0.5 mol %), distd. H_2O (0.55 equiv), 0 °C, 14 h, (44% for **6a**, 46% for **6b**).



Scheme 3. Reagents and conditions: (a) $C_{12}H_{25}MgBr$, Li_2CuCl_4, THF, 0 °C; (b) Ac_2O, pyridine, rt; (c) H_2, Pd–C, ethyl acetate; (d) Dess–Martin periodinane, CH_2Cl_2, 0 °C; (e) nitroethane, La-(*R*)-BINOL, THF, −40 °C: (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (g) 3 N HCl, THF, rt; (h) H_2, Pd–C, EtOH.

Our next aim was to carry out the two-carbon homologation of **9** with the generation of the desired stereocentres by means of Shibasaki's asymmetric Henry reaction.[10] To this end, compound **9** was oxidised to the aldehyde **10** with DMP in 94% yield. Then, the aldehyde **10** was treated with nitroethane in the presence of La-(*R*)-BINOL catalyst at −40 °C, but under these reaction conditions **10** was not stable and slowly decomposed without yielding the nitroaldol product. Therefore, we decided to change the protecting group of the alcohol **7**. Accordingly, treatment of **7** with TBS triflate in the presence of 2,6-lutidine afforded **11** in 95% yield. Removal of the benzyl protecting group in **11** released the terminal hydroxyl group to furnish **12** in 85% yield. Oxidation of **12** with DMP smoothly proceeded to produce the aldehyde **13**. The aldehyde **13** without further purification was subjected to Shibasaki's asymmetric nitroaldol reaction with nitroethane under the influence of La-(*R*)-BINOL catalyst in THF at −40 °C to deliver the nitro alcohol **14** in 68% yield over two steps with a satisfactory diastereomeric ratio (10:1; *syn*:*anti*).[11] Desilylation of **14** with 3 N HCl gave **15** in 73% yield. Finally, reduction of the nitro group in **15** with H_2/Pd–C afforded the target compound **2** in 82% yield, the spectral and physical data of which were identical to those reported.[5]

In conclusion, we have demonstrated a new and flexible synthetic sequence for the preparation of 1-deoxy-5-hydroxy sphingolipid analogues in 29% overall yield from chiral oxirane **6a**. The synthetic route detailed herein is potentially useful for the synthesis of other natural products bearing similar aminodiol substructures. Moreover, this synthetic strategy is perceptibly efficient for tuning the stereochemistry at the C-2, C-3 and C-5 positions to obtain different sphingolipid analogues.

*Spectral data of selected compounds: Compound **6a***: $[\alpha]_D^{20}$ −15.6 (*c* 1.26, $CHCl_3$). IR ($CHCl_3$): ν = 3031, 2860, 1601, 1492, 1255, 1098 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5H), 4.52 (s, 2H), 3.62 (t, 2H, *J* = 7.2 Hz), 3.07–3.01 (m, 1H), 2.79–2.76 (m, 1H), 2.53–2.52 (m, 1H), 1.96–1.86 (m, 1H), 1.82–1.76 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 128.1, 127.8, 127.3, 66.7, 49.8, 46.8, 32.6. MS (ESI): *m*/*z* = 179.0 (M^++1). Compound **7**: $[\alpha]_D^{20}$ +6.2 (*c* 0.8, $CHCl_3$). IR ($CHCl_3$): ν = 3413, 2924, 2853 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 5H), 4.52 (s, 2H), 3.79–3.75 (m, 1H), 3.68–3.63 (m, 2H), 2.92 (br s, 1H), 1.75–1.73 (m, 2H), 1.49–1.42 (m, 2H), 1.25 (br s, 20H), 0.90 (t, 3H, *J* = 5.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.6, 128.1, 127.4, 127.3, 73.0, 71.2, 69.0, 37.1, 36.0, 31.6, 29.4, 29.0, 25.3, 22.4, 13.8. MS (ESI): *m*/*z* = 372.0 (M^++Na); Compound **11**: $[\alpha]_D^{20}$ −7.1 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): ν = 2953, 2926, 2854, 1463 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 5H), 4.46–4.45 (d, 2H, *J* = 3.0 Hz), 3.80–3.78 (m, 1H), 3.50 (t, 2H, *J* = 6.0 Hz), 1.75–1.68 (m, 2H), 1.38–1.36 (m, 2H), 1.22 (br s, 22H), 0.86–0.84 (m, 12H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 128.3, 127.6, 127.5, 72.9, 69.4, 67.2, 37.6, 36.9, 31.9, 29.8, 29.74, 29.72, 29.6, 29.4, 25.9, 25.0, 22.7, 18.1, 14.1, −4.3, −4.5. MS (ESI): *m*/*z* = 485.1 (M^++Na); Compound **12**: $[\alpha]_D^{20}$ −14.6 (*c* 1.2, $CHCl_3$). IR ($CHCl_3$): ν = 3351, 2926, 2855, 1463, 1255 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.82–3.80 (m, 2H), 3.63 (m, 1H), 2.45 (br s, 1H), 1.80–1.65 (m, 1H), 1.43–1.41 (m, 2H), 1.16 (br s, 24H), 0.80–0. 76 (m, 12H), 0.00 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 72.1, 60.3, 37.5, 36.7, 31.9, 29.8, 29.7, 29.67, 29.63, 29.61, 29.4, 25.8, 25.3, 22.7, 17.9, 14.1, −4.4, −4.7. MS (ESI): *m*/*z* = 374.2 (M^++2); Compound **14**: $[\alpha]_D^{20}$ −16.1 (*c* 1.04, $CHCl_3$). IR ($CHCl_3$): ν = 3428, 2926, 2854, 1551 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.43–4.39 (m, 1H), 4.21–4.19 (m, 1H), 3.85–3.81 (m, 1H), 1.55–1.45 (m, 4H), 1.43 (d, 3H, *J* = 6.6 Hz), 1.17 (br s, 22H), 0.80–0.77 (m, 12H), −0.03 (s, 3H), −0.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 87.8,

70.1, 44.7, 37.8, 35.9, 31.9, 29.6, 29.5, 29.3, 25.7, 22.7, 17.9, 15.5, 14.1, 11.1, −3.9, −4.5. MS (ESI): m/z = 446.5 (M^++1); Compound **15**: mp 54–56 °C. $[\alpha]_D^{20}$ −6.7 (*c* 0.9, $CHCl_3$). IR ($CHCl_3$): ν = 3401, 2924, 2853, 1552 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.60–4.57 (m, 1H), 4.30–4.25 (m, 1H), 3.94–3.90 (m, 1H), 3.37 (br s, 2H), 1.69–1.58 (m, 4H), 1.55 (d, 3H, J = 6.3 Hz), 1.25 (br s, 22H), 0.90 (t, 3H, J = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 70.4, 68.7, 37.5, 31.9, 29.6, 29.5, 29.3, 25.6, 22.7, 16.1, 14.1. MS (ESI): m/z = 354.2 (M^++Na); Compound **2**: mp 64–65 °C. $[\alpha]_D^{20}$ +2.9 (*c* 0.8, $CHCl_3$). IR ($CHCl_3$): ν = 3400, 2920, 2848, 1474 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.8 (m, 1H), 3.74 (m, 1H), 3.24 (br s, 4H), 2.81 (m, 1H), 1.6 (m, 1H), 1.45 (m, 3H), 1.25 (br s, 22H), 1.00 (d, 3H, J = 6.2 Hz), 0.87 (t, 3H, J = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 76.5, 70.1, 52.3, 41.2, 35.5, 32.2, 29.82, 29.76, 29.6, 29.5, 25.8, 22.9, 17.4, 14.2. MS (ESI): m/z = 324.4 (M^++Na).

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