A Highly Efficient and Versatile Synthesis of D- and L-*erythro*-Sphinganine

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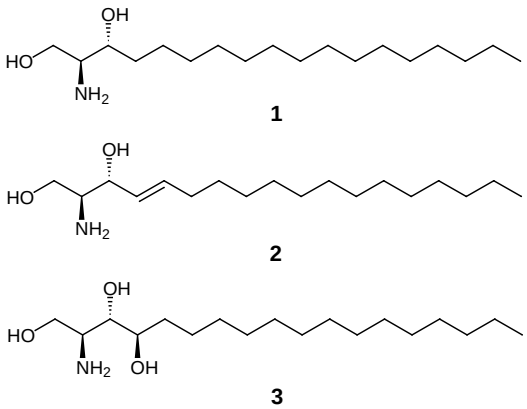
Abstract: An expedient convergent synthesis of naturally occurring C_{18}-*erythro*-sphinganine (dihydrosphingosine, **1**) is presented. Chiral protected 2-amino-1,3,4-butanetriol **6** is readily transformed into oxazolinyl oxirane building block **9**, which is alkylated by a copper mediated S_N2 type nucleophilic substitution with tetradecylmagnesium chloride. This method promises to be suited for large-scale syntheses and for rapid access to sphinganine analogues modified in the backbone.

Key words: amino alcohols, coupling, natural products, sphingolipids, stereoselective synthesis

Sphingolipids, such as ceramides, cerebrosides and gangliosides, are essential components of the cell membrane and play unique and critical roles in physiological processes like cell recognition, signal transduction and apoptosis.[1–3] Common to this diverse group of natural products is a sphingoid base scaffold with a long aliphatic chain and a polar 2-aminoalkanol head group. The most abundant sphingoid bases in nature are sphingosine (**2**), phytosphingosine (**3**), and their shared biosynthetic precursor C_{18}-D-*erythro*-sphinganine (dihydrosphingosine, **1**) (Figure).[4]

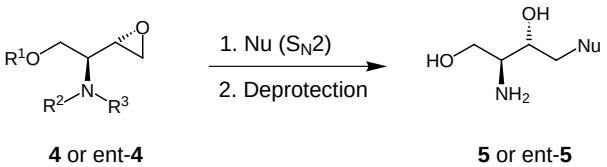


Figure

Members of the sphinganine family have been found to be inhibitors of protein kinase C, hence mediating a variety of cellular responses.[5,6] To date more than 60 sphingoid bases from natural and synthetic sources are known that are often endowed with miscellaneous biological properties.[7] Many methods have thus been developed for sphinganine synthesis, which involve e.g. addition of nucleophilic reagents to amino aldehydes or amino esters,[8–13] hydrogenation of sphingosine derivatives,[14] chain elongation of carbohydrate precursors,[15] or substitution of a reactive oxygen species with azide on a preformed sphinganine skeleton.[16–18]

In the course of our synthetic studies towards sphingolipid metabolites,[14,19,20] we were motivated to establish a practical synthesis of sphinganine making use of the chiral building blocks[21] **6** and *ent*-**6** that are inexpensive industrial intermediates. The enantiopure protected 2-aminobutane-1,3,4-triols **6** and *ent*-**6** are available in bulk quantities by a (large scale) binaphthol titanium-catalyzed asymmetric aminolysis of the corresponding *meso*-epoxide.[21] Compound **6** has been used in the synthesis of nelfinavir[22,23] and is now commercially available in both enantiomeric forms.[24]

Since the biological activity of sphingoid bases can vary substantially with structural modifications of the alkyl side chain, the protocol should allow for the synthesis of both sphinganine and sphinganine analogs modified in the tail. For this purpose, a highly convergent route is desirable, setting the configuration of the polar head group at an early stage. Attachment of functionally diverse tail groups by means of a compatible method would then allow the synthesis of a wide array of derivatives and analogues. Ultimately, no further manipulation of the side chain would be required. These prerequisites are ideally matched by nucleophilic ring opening of an appropriate oxirane building block **4** with a carbanion equivalent (Scheme 1). The versatile building blocks **6** and *ent*-**6** could be readily transformed into functionalized oxiranes **9** or *ent*-**9**, which would be well suitable for the synthesis of D- and L-*erythro*-sphinganine **1** and their analogs.



4 or ent-**4** **5** or ent-**5**

Scheme 1

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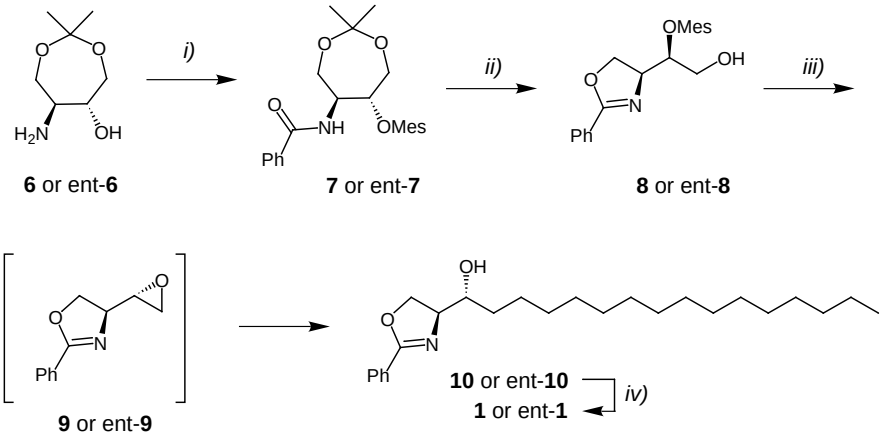

Scheme 2 *Reactions and conditions: i)* a: 1 equiv PhCOCl, 2.5 equiv 10 % aq. $NaHCO_3$–DCM, r.t., 2 h; b: 1.2 equiv MesCl, 1.5 equiv TEA, DCM, 8 °C, 1 h, 92 %; *ii)* 3 equiv $BF_3{\cdot}OEt_2$, DCM, 20 °C, 1 d, 63 %; *iii)* a: 1 equiv *t*-BuOK, THF, 0 °C, 4 h; b: 2 equiv $ClMgC_{14}H_{29}$, 10 mol% CuCN, THF, –78 °C to 0 °C, 2 h, 85 % (over two steps); *iv)* 2 M HCl, THF, 0 °C to r.t., 5 h, then aq. NaOH, MeOH, 80 °C, 1 h, 88 %.

The synthesis of the desired oxazolinyl oxirane **9** is straightforward (Scheme 2). Amino alcohol **6** was benzoylated using benzoyl chloride in biphasic dichloromethane (DCM)/aqueous $NaHCO_3$. The dried amide solution was carried on without purification to the mesylate **7** by treatment with triethylamine and mesyl chloride in DCM (88% yield from **6**). Subsequent boron trifluoride mediated diol deprotection of **7** with concomitant intramolecular cyclization gave oxazoline **8**. A full differentiation of the two primary hydroxyl groups was achieved by the condensation of the amide and its vicinal hydroxyl group, yielding the favored five-membered heterocycle.[22] β-Hydroxymesylate **8** was then converted into the corresponding epoxide **9** by means of potassium *tert*-butoxide in THF at 0 °C. S_N2 displacement proceeded with complete inversion of the asymmetric center at C-3 and provided the desired *erythro* configuration. The rather unstable epoxide **9** was then directly subjected to a nucleophilic ring-opening with a Gilman cuprate, in situ formed from commercially available tetradecylmagnesium chloride and CuCN (10 mol%) at –78 °C in THF.[20] Copper(I) assisted ring openings of functionalized oxiranes have previously been reported to proceed highly regiospecifically.[20,25,26] In fact, the protected C_{18}-D-*erythro*-sphinganine **10** was obtained in high yield (85% from **8**) and without any side reactions.[27] The regioisomer could not be detected by means of LC/MS and NMR spectroscopy.

Acid hydrolysis of oxazolines such as **10** are known to proceed via the *O*-benzoyl compound, which in this case may be used as the precursor for the synthesis of *N*-acyl sphinganines (dihydroceramides).[28] Subsequent base hydrolysis provides the liberated sphingoid base **1** in 88% yield (from **10**).[28,29] The identity of the obtained D-*erythro*-sphinganine was unambiguously confirmed by comparison with the known spectral[30] and physical data {mp 75–76 °C; Lit: 74–76 °C (petroleum ether);[31] α_D^{22}: +5.2 (c = 0.50, $CHCl_3$–ethanol = 9:1), Lit: α_D^{21}: +5.0 (*c* = 0.40, $CHCl_3$–ethanol = 9:1)[9]}, as well as conversion of **1** into the known triacetyl sphinganine.[13,17] In analogy, the enantiomeric L-*erythro*-sphinganine is readily accessible from *ent*-**6**.

In conclusion, optically pure D- and L-*erythro*-sphinganine can be prepared from precursors **6** and *ent*-**6**, which are industrial intermediates. The efficient synthetic route was accomplished without any expensive reagents or complex procedures. In addition, no chromatographic purification is required for any of the intermediates. According to its convergent nature, this approach is ideally suited for accessing sphinganine analogs modified in the backbone. Syntheses of novel sphinganine derivatives using this protocol are in progress and will be reported in due course.

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(27) **Experimental. Compound 10**. To a cooled (0 °C) solution of **7** (1.2 g, 3.5 mmol) in DCM (50 mL) was slowly added $BF_3{\cdot}OEt_2$ (1.3 mL, 10.5 mmol) and the mixture was stirred at r.t. until TLC analysis showed complete consumption of **7** (ca. 1 d). After quenching the reaction with 4-methylmorpholine (2 mL, 1.5 M aqueous solution) at 0 °C and diluting the mixture with DCM (50 mL), the organic phase was separated, washed with brine, dried over Na_2SO_4 and concentrated. Crystallization of the residue from ethanol–hexane gave **8** as colorless crystals (0.76 g, 63%).[22] Mesylate **8** (0.76 g, 2,2 mmol) was dissolved in THF (10 mL) and treated with *t*-BuOK (245 mg, 2.4 mmol) in THF (10 mL) at 0 °C. After the solution was stirred at 0 °C for 4 h, it was washed with 10% sodium phosphate buffer (pH 7.0) and extracted with DCM. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. To a cooled (–78 °C) solution of the crude epoxide **9** in THF (10 mL) were added CuCN (20 mg, 10 mol%) and $ClMgC_{14}H_{29}$ (4.5 mL, 1.0 M solution in THF) at –78 °C. The solution was stirred for 15 min at –78 °C and was then slowly warmed to 0 °C over the period of 2 h. After quenching with sat. NH_4Cl, the solution was extracted with DCM, dried over Na_2SO_4 and concentrated under reduced pressure. Crystallization of the residue from DCM–hexane gave protected sphinganine **10** (725 mg, 85%, over two steps) as colorless solid. mp 95–97 °C, Anal. calcd. for $C_{25}H_{41}NO_2$: C, 77.47; H, 10.66; N, 3.61. Found: C, 77.51; H, 10.62; N, 3.59. α_D^{25}: −2.3 (*c* = 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.7 Hz), 1.25 (18 H, m), 1.49 (2 H, m), 1.68 (1 H, m), 3.92 (1 H, m), 4.15–4.24 (1 H, dd, *J* = 8.8, 9.9 Hz), 4.28 (1 H, dd, *J* = 8.6, 4.6 Hz), 4.46 (2 H, d, *J* = 8.6 Hz), 7.29–7.47 (3 H, m), 7.81–7.92 (2 H, m); IR (KBr): 3153, 1648, 1192 cm^{-1}. MS/MS (ESI, 100 eV): *m/z* = 388, 370, 266, 164, 122.
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