

A practical synthesis of D-erythro-sphingosine using a cross-metathesis approach†

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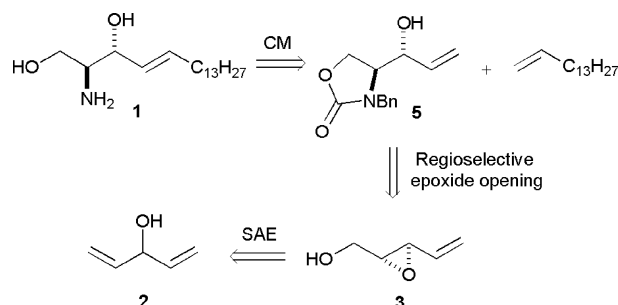
Received 9th March 2004, Accepted 26th March 2004

First published as an Advance Article on the web 20th April 2004

Starting from a vinyl epoxide, a short and practical synthesis of D-erythro-sphingosine is described. The key transformations are a regioselective opening of the vinyl epoxide and an E-selective cross-metathesis, affording the target molecule in 5 steps and 51% overall yield.

Introduction

Sphingolipids are constituents of cell membranes in all eukaryotic cells and the recent discovery of their biologically active metabolites *e.g.* sphingosine, ceramide and lysosphingolipids has generated interest in the physiological role of these molecules. D-erythro-Sphingosine (**1**, Scheme 1) and related compounds have been shown to inhibit protein kinase C, which affects cell regulation and signal transduction, and exhibits antitumor promoter activities in various mammalian cells. In addition, these compounds may function as modulators of cell function and possibly also as secondary messengers.^{1–3} Due to the biological importance of **1** and its derivatives many synthetic routes to enantiopure sphingolipids have been described in the literature. Most of these utilize starting materials from the chiral pool *e.g.* L-serine or carbohydrates,^{4–8} while asymmetric routes are more rare.^{9–12}



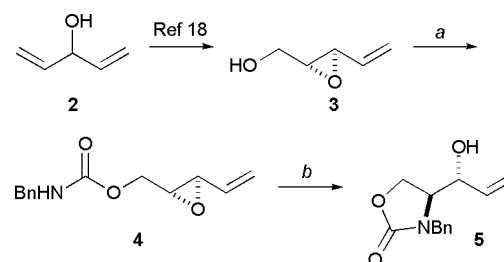
Scheme 1 Retrosynthetic analysis of D-erythro-sphingosine.

We became interested in assembling **1** by using a cross-metathesis reaction to introduce the required *E*-olefin moiety (Scheme 1). Such a strategy would be convenient compared to alternatives using more traditional C–C double bond forming reactions, since the required catalyst is commercially available and the metathesis usually proceeds with a low amount of byproduct formation.^{13,14} The polar head group **5** should be available from epoxide **3**, which, in turn, is readily prepared from divinylcarbinol (**2**). The realization of this strategy yields a practical synthesis of **1** that is outlined below.

Results and discussion

Synthesis of oxazolidinone 5

The synthesis of oxazolidinone **5** starts from commercially available **2** (Scheme 2). Sharpless epoxidation of **2** followed



Scheme 2 Synthesis of oxazolidinone **5**. Reagents and conditions: *a.* BnNCO, Et₃N, Et₂O, 60 °C, 98%; *b.* NaHMDS, THF, –15 °C, 88%.

by base-induced Payne rearrangement gave **3** in high yield and excellent enantiomeric purity (>99% ee¹⁵), as described previously.^{16–18} It was expected that intermolecular reaction of **3** with various nitrogen nucleophiles would, due to electronic influences, result in a preferential ring-opening at the allylic position.¹⁹ To circumvent this the C-2 amino functionality was introduced through a two-step procedure. Alkyl isocyanates have previously been used as nitrogen nucleophiles to give regioselective attack at the C-2 position of epoxy alcohols.^{20,21} Consequently, when epoxy alcohol **3** was treated with benzyl isocyanate and Et₃N in a sealed tube benzyl carbamate **4** was obtained in excellent yield. The subsequent intramolecular ring-opening of **4** using NaH proceeded sluggishly and gave a poor yield of oxazolidinone **5**.^{20,21} Gratifyingly, when using NaHMDS in THF at low temperature instead, **5** was obtained in 88% yield.²²

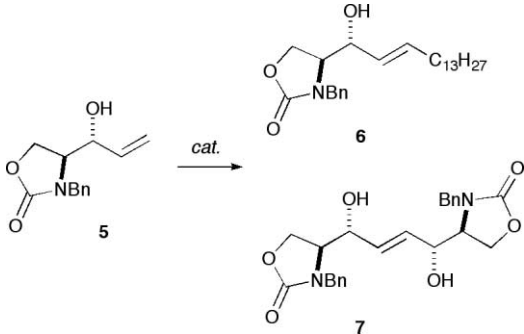
Cross-metathesis and completion

Due to the lipid chain and the hydrophilic head group, compound **1** exhibits surfactant-like properties such as low solubility in organic solvents at low temperature, and problems with flash chromatography due to aggregation of the material on the silica gel column.¹² The late introduction of the aliphatic chain by a cross-metathesis reaction overcomes many of these problems and has advantages over several of the existing strategies of **1** where the lipid chain is introduced at an early stage of the synthetic route.

Compound **6** was synthesized by coupling allylic alcohol **5** with 1-pentadecene using Ru-catalysts A–C (Fig. 1 and Table 1).

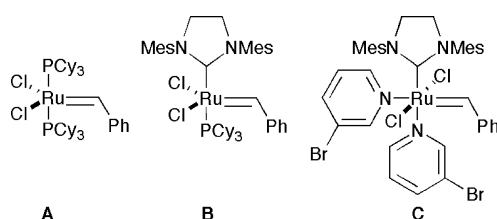
The initial coupling attempts under standard conditions¹⁴ using catalyst **A** or **B** resulted in no reaction or required prolonged reaction times, giving **6** in moderate yield and *E* : *Z* selectivity (Table 1, entries 1–3). When using toluene²³ as solvent homodimer **7** precipitated as a white solid and thereby shifted the equilibrium toward **7** (entry 4). This could be resolved by addition of Ti(O^{*i*}Pr)₄ to the reaction mixture and **6** was isolated in 52% yield (78% based on recovered starting material) with 16 : 1 *E* : *Z* selectivity (entry 7). The *E* : *Z* isomers

† Electronic supplementary information (ESI) available: spectroscopic data for compounds **1** and **4–8**. See <http://www.rsc.org/suppdata/ob/b4/b403568b/>

Table 1 Cross-metathesis


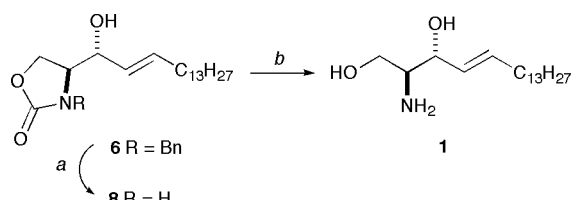
Entry	Catalyst (mol%)	Conditions ^a	Product (Yield % ^b)	<i>E</i> : <i>Z</i>
1	A (5)	40 °C, 43 h	No reaction	N.A.
2	B (5)	rt, 3 d	6 (35)	14 : 1
3	B (5)	40 °C, 24 h	6 (49)	5 : 1
4 ^c	B (10)	50 °C, 1.5 h	6 (7)	12 : 1
			7 (57)	<i>E</i>
5 ^d	A (5)	40 °C, 40 h	6 (7)	N.A.
6 ^d	B (10)	40 °C, 22 h	6 (30)	N.A.
7 ^d	B (10)	40 °C, 45 min	6 (52)	16 : 1
8	C (10)	rt, 48 h	6 (53)	13 : 1
9	C (10)	40 °C, 1.5 h	6 (59)	17 : 1

^a 2 equiv. 1-pentadecene in CH₂Cl₂. ^b Isolated yield. ^c 2 equiv. of 1-pentadecene in PhMe. ^d 2 equiv. Ti(O^{*i*}Pr)₄ was added prior to the catalyst.

**Fig. 1** Ru-catalysts used in the cross-metathesis reaction.

were easily separated by flash chromatography. The need for Ti(O^{*i*}Pr)₄ could be explained by the heteroatom density in **5**, as Ru catalyst **B** can form inactive chelates with Lewis-basic sites in the substrate.²³ The presence of Ti(O^{*i*}Pr)₄ decreases the amount of Ru-substrate chelates and increases the amount of desired product.^{24–26} When employing Grubbs' phosphine-free 3-bromopyridine catalyst **C**²⁷ (Fig. 1) the yield and *E* : *Z* selectivity were increased to 59% (82% based on recovered starting material) and 17 : 1 respectively (Table 1, entry 9). Catalyst **C** was easily made from the commercially available **B** and has shown increased reactivity in various cross-metathesis reactions.^{28–30}

Removal of the benzyl group in **6** with sodium in liquid ammonia gave oxazolidinone **8** which was then hydrolyzed with KOH to afford *D*-erythro-sphingosine (**1**) in quantitative yield over two steps (Scheme 3). Analytical data of **1** were in good agreement with literature data.^{4–12}

**Scheme 3** Deprotection of **1**. Reagents and conditions: a. 1 M KOH, H₂O : EtOH 1 : 1, 100 °C, 100%; b. Na, NH₃(l), –78 °C, 100%.

Conclusions

In conclusion, an efficient and practical route for the synthesis of *D*-erythro-sphingosine (**1**), based on a cross-metathesis

approach, has been developed. The required stereochemistry was introduced *via* a regioselective epoxide opening while the aliphatic chain of **1** was introduced with a highly *E*-selective cross-metathesis in the presence of Grubbs' phosphine free catalyst **C**. Two quantitative deprotection steps completed the synthetic route, furnishing **1** in 51% yield over five steps. The strategy is flexible and would permit the synthesis of sphingolipids with different aliphatic chains by using other olefins in the cross-metathesis reaction.

Experimental

For general experimental procedures see ref 12.

((2*R*,3*R*)-3-Vinyloxiran-2-yl)methyl benzylcarbamate (**4**)

To a solution of ((2*R*,3*R*)-3-vinyloxiran-2-yl)methanol¹⁸ (509 mg, 5.08 mmol) in Et₂O (20 cm³) was added freshly distilled Et₃N (1.42 cm³, 10.16 mmol) followed by BnNCO (0.94 cm³, 7.62 mmol). The resultant mixture was heated to 60 °C in a sealed tube for 17 h, cooled to rt and quenched with sat. NH₄Cl (15 cm³). The phases were separated and the aqueous layer was extracted twice with CH₂Cl₂. The combined organic phases were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography (CH₂Cl₂ → CH₂Cl₂ + 1% MeOH) of the residue gave **4** (1.161 g, 98%) as a low melting white solid: δ_H(400 (MHz; CDCl₃) 3.14 (1 H, m), 3.29 (1 H, d, *J* 6.6), 4.01 (1 H, dd, *J* 12.2 and 6.0), 4.39 (2 H, d, *J* 6.0), 4.46 (1 H, dd, *J* 12.2 and 3.1), 5.08 (1 H, br s), 5.31–5.34 (1 H, m), 5.63–5.48 (2 H, m) and 7.26–7.37 (5 H, m); δ_C(100 (MHz; CDCl₃) 45.2, 56.4, 57.5, 64.8, 120.3, 127.6, 127.7, 128.8, 134.5, 138.4 and 156.1; [α]_D²⁰ +26.2 (*c* 0.39 in CHCl₃/CHCl₃) [lit.²¹ [α]_D²⁰ +25.7 (*c* 0.39 in CHCl₃)].

(*S*)-3-Benzyl-4-((*R*)-1-hydroxyallyl)oxazolidin-2-one (**5**)

To a stirred solution of urethane **4** (1.022 g, 4.38 mmol) in THF (50 cm³) at –15 °C was added dropwise NaHMDS (6.57 cm³, 6.57 mmol, 1 M in THF). The resultant mixture was slowly allowed to reach 0 °C (5 h) and then quenched by addition of sat. NH₄Cl (20 cm³). The phases were separated and the aqueous layer was extracted twice with Et₂O, dried over MgSO₄

and then concentrated *in vacuo*. Flash chromatography (pentane : EtOAc 3 : 2) of the residue gave **5** (899 mg, 88%) as a colorless oil. $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3216, 1745, 1265 and 739; $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3)$ 2.20 (1 H, d, J 3.5), 3.70 (1 H, ddd, J 9.2, 6.2 and 2.6), 4.15 (1 H, t, J 8.8), 4.25 (1 H, dd, J 8.8 and 6.3), 4.36 (1 H, A-part of ABq, J 15.2), 4.37 (1 H, s), 4.73 (1 H, B-part of ABq, J 15.2), 5.28 (1 H, dd, J 10.6 and 1.3), 5.41 (1 H, dd, J 17.2 and 1.3), 5.66 (1 H, ddd, J 17.2, 10.6 and 4.9) and 7.32–7.37 (5 H, m); $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3)$ 46.8, 58.4, 62.4, 69.2, 118.2, 128.2, 128.3, 129.2, 134.6, 136.3 and 159.3; $[\alpha]_{\text{D}}^{20} +4.7$ (c 1.04 in CHCl_3); m/z (FAB+) 234.1134 ($M + H$) $\text{C}_{13}\text{H}_{16}\text{NO}_3$ requires 234.1130).

(S)-3-Benzyl-4-((R,E)-1-hydroxyhexadec-2-enyl)oxazolidin-2-one (**6**)

Typical cross-metathesis protocol. To a solution of allylic alcohol **5** (34.8 mg, 0.15 mmol) in CH_2Cl_2 (1.0 cm^3) was added 1-pentadecene (43.6 mm^3 , 0.30 mmol). To the resultant mixture at reflux was added catalyst **C**²⁸ (13.2 mg, 0.015 mmol) in CH_2Cl_2 (0.5 cm^3) and the resultant mixture was stirred at reflux for 1.5 h and then cooled to rt. The solvent was evaporated to give a brown residue with 17.4 : 1 *E* : *Z* selectivity (crude NMR). Flash chromatography (pentane : EtOAc 4 : 1) of the residue gave isomerically pure **6** (36.5 mg, 59%) as a white solid and recovered **5** (8 mg, 23%).

Typical cross-metathesis protocol using $\text{Ti}(\text{O}^i\text{Pr})_4$. To a solution of allylic alcohol **5** (827 mg, 3.55 mmol) in CH_2Cl_2 (20 cm^3) was added $\text{Ti}(\text{O}^i\text{Pr})_4$ (2.10 cm^3 , 7.09 mmol) and the resultant mixture was refluxed for 30 min. To the mixture was then added 1-pentadecene (1.040 cm^3 , 7.09 mmol) and catalyst **B** (301 mg, 0.35 mmol) in CH_2Cl_2 (10 cm^3) and the resultant mixture was refluxed for 45 min and then cooled to rt. The solvent volume was reduced to approx. 4 cm^3 and the resultant mixture was subjected to flash chromatography (pentane : EtOAc 4 : 1) to give **6** (*E* : *Z* 16 : 1) as a white solid and recovered **5** (280 mg, 34%). The *E* : *Z*-isomers were separated with a second flash chromatography (pentane : EtOAc 4 : 1) to give isomerically pure **6** (761 mg, 52%): mp 54–56 °C (lit.³¹ mp 56–57 °C); $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3)$ 0.88 (3 H, t, J 6.9), 1.27 (22 H, m), 2.01 (2 H, q, J 7.3), 2.06 (1 H, s), 3.66 (1 H, ddd, J 9.1, 6.2 and 2.9), 4.17 (1 H, t, J 8.8), 4.25 (1 H, dd, J 8.8 and 6.3), 4.28 (1 H, s), 4.33 (1 H, A-part of ABq, J 15.2), 4.74 (1 H, B-part of ABq, J 15.2), 5.27 (1 H, dd, J 15.5 and 6.1), 5.79 (1 H, ddt, J 15.4, 6.9 and 1.2) and 7.31–7.36 (5 H, m); $\delta_{\text{C}}(125 \text{ MHz}; \text{CDCl}_3)$ 14.3, 22.8, 29.1, 29.3, 29.5, 29.6, 29.71, 29.78, 29.80, 29.81, 32.1, 32.5, 46.8, 58.7, 62.8, 69.7, 69.8, 126.22, 126.24, 128.2, 128.3, 129.1, 135.65, 135.68, 135.72, 136.4 and 159.3; $[\alpha]_{\text{D}}^{20} -12.5$ (c 1.07 in CHCl_3) [lit.³¹ $[\alpha]_{\text{D}}^{20} -11.8$ (c 1.07 in CHCl_3); m/z (FAB+) 416.3174 ($M + H$) $\text{C}_{26}\text{H}_{42}\text{NO}_3$ requires 416.3165).

Homodimer (**7**)

To a solution of allylic alcohol **5** (29.0 mg, 0.12 mmol) in toluene (1 cm^3) was added 1-pentadecene (36.4 mm^3 , 0.25 mmol) and catalyst **B** (10.6 mg, 0.012 mmol) in toluene (0.5 cm^3) and the resultant mixture was heated to 50 °C for 1.5 h and then cooled to rt. The white precipitate was filtered off and washed with toluene to give **7** (15.6 mg, 57%). Flash chromatography (pentane : EtOAc 4 : 1) of the residue gave **6** (3.6 mg, 7%, *E* : *Z* 12 : 1) as a white solid and recovered **5** (8 mg, 28%): mp 158.9–159.9 °C (dec); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3056, 1712, 1267 and 739; $\delta_{\text{H}}(500 \text{ MHz}; d_6\text{-acetone})$ –3.76 (1 H, m), 4.16 (2 H, m), 4.24 (1 H, A-part ABq, J 15.4), 4.58 (2 H, m), 4.74 (1 H, B-part of ABq, J 15.4), 5.82 (1 H, d, J 1.3) and 7.28–7.36 (5 H, m); $\delta_{\text{C}}(125 \text{ MHz}; d_6\text{-acetone})$ 46.4, 58.5, 62.8, 68.67, 68.76, 128.4, 128.9, 129.5, 131.2, 137.8 and 159.2; $[\alpha]_{\text{D}}^{20} -51.8$ (c 0.83 in acetone); m/z (FAB+) 439.1877 ($M + H$) $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_6$ requires 439.1864).

(S)-4-((R,E)-1-Hydroxyhexadec-2-enyl)oxazolidin-2-one (**8**)

To a solution of Na (excess) in freshly distilled NH_3 (45 cm^3) at –78 °C was cannulated oxazolidinone **6** (558 mg, 1.34 mmol) in Et_2O (10 cm^3). The resultant blue solution was stirred at –78 °C for 4 h and then carefully quenched with sat. NH_4Cl . The NH_3 was then slowly evaporated under a stream of N_2 . The phases were separated and the aqueous layer was extracted three times with EtOAc, dried over MgSO_4 and concentrated *in vacuo* to give **8** (437 mg, 100%) as a white solid: mp 71–72 °C (lit.³² 73–74 °C); $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3)$ 0.81 (3 H, t, J 6.8), 1.20–1.37 (22 H, m), 2.04 (2 H, q, J 7.0), 2.92 (1 H, br s), 3.86 (1 H, m), 4.12 (1 H, m), 4.33 (1 H, dd, J 8.8 and 5.2), 4.39 (1 H, t, J 8.8), 5.37 (1 H, ddt, J 15.4, 6.8 and 1.2), 5.83 (1 H, ddt, 15.4, 6.8 and 0.8) and 6.11 (1 H, s); $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3)$ 14.2, 22.8, 29.1, 29.4, 29.5, 29.6, 29.74, 29.79, 29.81, 32.1, 32.5, 56.4, 66.4, 73.3, 126.3, 126.6, 136.6 and 160.5; $[\alpha]_{\text{D}}^{20} -1.3$ (c 1.75 in CHCl_3) [lit.³² $[\alpha]_{\text{D}}^{20} -0.8$ (c 2.0 in CHCl_3)].

D-erythro-Sphingosine (**1**)

Oxazolidinone **8** (425.8 mg, 1.31 mmol) in 1 M KOH (20 cm^3 , H_2O : EtOH 1 : 1) was heated to reflux for 2.5 h, cooled to rt and then 2 M NaOH (10 cm^3) was added. The mixture was extracted with EtOAc (3 × 20 cm^3) and the combined organic layers were dried over MgSO_4 and concentrated *in vacuo* giving **1** (390.1 mg, 100%) as a white solid: mp 72–75 °C (lit.⁷ mp 70 °C, lit.¹² mp 73–75 °C); $\delta_{\text{H}}(500 \text{ MHz}; \text{CDCl}_3)$ 0.87 (3 H, t, J 6.9), 1.25–1.38 (22 H, m), 2.05 (2 H, q, J 7.0), 2.27 (4 H, br s), 2.85 (1 H, m), 3.63 (1 H, dd, J 10.9 and 5.8), 3.67 (1 H, dd, J 10.9 and 4.6), 4.04 (1 H, t, J 6.3), 5.47 (1 H, dd, J 15.4 and 7.2) and 5.75 (1 H, dt, J 15.4 and 6.7); $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3)$ 14.3, 22.8, 29.3, 29.4, 29.5, 29.6, 29.76, 29.80, 29.82, 32.1, 32.5, 56.3, 64.2, 75.8, 129.4 and 134.9; $[\alpha]_{\text{D}}^{20} -1.6$ (c 1.0, CHCl_3) [lit.⁷ $[\alpha]_{\text{D}}^{20} -1.2$ (c 1.74 in CHCl_3), lit.⁸ $[\alpha]_{\text{D}}^{20} -1.5$ (c 0.52, CHCl_3)].

Acknowledgements

This work was supported financially by AstraZeneca, Södertälje, and the Swedish Research Council.

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