Synthesis of D/L-erythro-Sphingosine Using a Tethered Aminohydroxylation Reaction as the Key Step

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Abstract: A diastereoselective synthesis of racemic D/L-erythro-sphingosine is described. The approach involves employing tethered aminohydroxylation (TA) to introduce the 2-amino and 3-hydroxy functions with required stereochemistry.

Key words: sphingolipids, sphingosine, ceramide, amino alcohols, diastereoselectivity

In 1881, when Johann Thudichum first described a compound that would later be fully characterized as sphingosine, he named it after the Greek mythological character, the Sphinx, “in commemoration of the many enigmas which it has presented to the inquirer”.1 Sphingolipids have emerged over the last decades as a family of key signaling molecules, which include sphingosine and ceramide.2 These compounds, together with glycerophospholipids and cholesterol, are building blocks3 that play essential roles as structural cell membrane components4 and participate in higher order physiological processes including inflammation5 and vasculogenesis.6 Recent studies demonstrated the involvement of sphingolipids in many of the most common human diseases, including infection by microorganisms,7 diabetes,8 a range of cancers,9 Alzheimer’s,10 and many others.11

Structurally, the prevalent backbone in sphingolipids is sphingosine which, when bearing a long-chain fatty acid into the amino function, is called ceramide (Figure 1). There are four sphingosine stereoisomers with a wide range of biological activities.12,13 The D-erythro-isomer is the most common metabolite and has been widely studied. Since, sphingosine and its derivatives are only available in limited amounts from natural sources, there is growing interest in developing efficient methods for their synthesis. There are many reported methods for synthesizing sphingosine,14 which can be classified into four categories: (i) first, carbohydrates are used as the source of chirality; (ii) second, the Sharpless asymmetric epoxidation is used to generate the stereogenic centers; (iii) the third relies on the aldol reaction with a chiral auxiliary and finally (iv) the amino acid serine is used as the source of chirality.

Here, we wish to enrich this diverse range of strategies for sphingosine synthesis. In this paper, we report an efficient method for the synthesis of racemic D/L-erythro-sphingosine employing an aminohydroxylation reaction as the key step. Unfortunately, this reaction is not compatible with the use of cinchona alkaloid-derived chiral ligands, which therefore precludes an enantioselective version. Our choice of starting material was dictated by the type of reaction that we planned to employ to generate the asymmetric centers. The chiral aminohydroxyl functions were introduced in the last step by an aminohydroxylation of diene 3, which has the appropriate E,Z-configuration in the aminohydroxylation reaction. This diene can be prepared by reduction of 4, which in turn can be obtained from aldehydes 5 through a Wittig reaction (Scheme 1).

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Figure 1 The prevalent backbone in sphingolipids
The Sharpless asymmetric aminohydroxylation\textsuperscript{16} (AA) and tethered aminohydroxylation\textsuperscript{17} (TA) allows the catalytic and diastereoselective synthesis of amino alcohols. However, in AA the drawbacks of regioselectivity persist during the oxidation of unsymmetrical alkenes. This inconvenience can be avoided through the use of TA. At this point of the synthesis, we were interested in extending the convenience can be avoided through the use of TA. At this point of the synthesis, we were interested in extending the use of TA methodology\textsuperscript{18} as a general strategy in order to amino-alchols.

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In conclusion, D/L-erythro-sphingosine (1) has been synthesized in eight steps and 33\% overall yield from alcohol 7 using a tethered aminohydroxylation (TA) as key step. This approach allowed the introduction of the 2-amino and 3-hydroxy groups with complete regio- and stereoselectivity.

Scheme 2 Synthesis of sphingosine 1

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1H NMR (400 MHz, CDCl₃): δ = 6.10 (s, 1 H), 5.83 (dd, J = 15.4, 6.8, 0.8 Hz, 1 H), 5.37 (dd, J = 15.4, 6.8, 1.2 Hz, 1 H), 4.39 (dd, J = 8.8, 8.5 Hz, 1 H), 4.33 (dd, J = 8.8, 5.2 Hz, 1 H), 4.12 (m, 1 H), 3.86 (m, 1 H), 2.92 (br s, 1 H), 2.04 (q, J = 7.0 Hz, 2 H), 1.37–1.2 (m, 22 H), 0.81 (t, J = 6.8 Hz, 3 H).

13C NMR (100 MHz, CDCl₃): δ = 106.5, 136.6, 126.6, 73.3, 66.4, 56.4, 32.5, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 29.1, 22.8, 14.2.

HRMS (FAB+): m/z [M + H]+ calcd for C₁₈H₃₇NO₂: 326.2695; found: 326.2699.

Anal. Calcd for C₁₈H₃₇NO₂: C, 72.19; H, 12.41; N, 4.70.

Oxazolidinone 10 (100 mg, 0.30 mmol) in 1 M KOH (H₂O–EtOH, 1:1; 5 mL) was heated to reflux for 2.5 h, then cooled to r.t. and aq HCl (2 M, 2.5 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried over MgSO₄ and concentrated under vacuum to give 1.

Yield: 89 mg (100%); white solid.¹⁰

1H NMR (400 MHz, CDCl₃): δ = 5.76 (dt, J = 15.4, 6.7 Hz, 1 H), 5.47 (dd, J = 15.4, 7 Hz, 1 H), 4.11 (m, 1 H), 3.70 (dd, J = 11, 3 Hz, 1 H), 3.65 (dd, J = 11, 5.8 Hz, 1 H), 2.92 (m, 1 H), 2.05 (dt, J = 6.7, 7.3 Hz, 2 H), 1.37 (m, 2 H), 1.20–1.40 (m, 20 H), 0.88 (t, J = 6.9 Hz, 3 H).

13C NMR (100 MHz, CDCl₃): δ = 134.7, 128.8, 74.7, 63.3, 56.3, 32.5, 31.9, 29.7–29.2, 22.7, 14.1.

HRMS (FAB+): m/z [M + H]+ calcd for C₁₉H₃₅NO₃: 326.2693; found: 326.2693.

Anal. Calcd for C₁₉H₃₅NO₃: C, 70.11; H, 10.80; N, 4.32. Found: C, 70.19; H, 10.84; N, 4.30.

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