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Short asymmetric syntheses of sphinganine [(2*S*,3*R*)-2-aminooctadecane-1,3-diol] and its C(2)-epimer

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Dedicated to Professor Stephen F. Martin in recognition of his significant contributions to organic chemistry.

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ABSTRACT

A short asymmetric synthesis of sphinganine [(2*S*,3*R*)-2-aminooctadecane-1,3-diol] and its C(2)-epimer is reported. The synthesis of sphinganine employs diastereoselective aminohydroxylation of *tert*-butyl 2-octadecenoate [conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, then *in situ* enolate oxidation with (+)-camphorsulfonyloxaziridine (CSO)] and a stereospecific rearrangement of the resultant *anti*-α-hydroxy-β-amino ester into the corresponding *anti*-α-amino-β-hydroxy ester. Final hydrogenolysis and ester reduction completes the synthesis of the sphingoid base target. The synthesis of the C(2)-epimer follows a similar route, incorporating a diastereoselective reduction protocol to transform the *anti*-α-hydroxy-β-amino ester into its *syn*-α-hydroxy-β-amino ester counterpart.

Sphinganine—(2*S*,3*R*)-2-aminooctadecane-1,3-diol (Fig. 1)—is one of the three main sphingoid bases that form the backbones of the sphingolipids, which are essential components of eukaryotic cells [1]. Sphingoid bases and their derivatives have been shown to elicit growth inhibition and provoke apoptosis in a number of tumor cells [1,2], and for example the non-natural, C(3)-epimer of sphinganine—safingol, or (2*S*,3*S*)-2-aminooctadecane-1,3-diol (Fig. 1)—was evaluated in a Phase I clinical trial, in combination with cisplatin, for the treatment of advanced solid tumors [3]. The culmination of the interest in these compounds renders methods for their production of continued interest to the research community [4,5], and of particular interest are those methods which have the potential to enable the synthesis of all of the possible stereoisomers of 2-aminooctadecane-1,3-diol [6]. Herein we report a short and concise asymmetric synthesis of sphinganine and its C(2)-epimer reliant on the diastereoselective aminohydroxylation of *tert*-butyl 2-octadecenoate with enantiopure lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide in conjunction with the oxidant (+)-camphorsulfonyloxaziridine (CSO). The *anti*-α-hydroxy-β-amino ester product of this reaction can be readily transformed into the corresponding *syn*-α-hydroxy-β-amino ester by effecting epimerization of the α-stereocentre through an oxidation and diastereoselective reduction reaction sequence. The stereospecific conversion of these epimeric α-hydroxy-β-amino esters to their α-amino-β-hydroxy ester counterparts is then followed by ester reduction and hydrogenolysis to give the targets. The ready availability of *N*-benzyl-*N*-(α-methylbenzyl)amine in either enantiomerically pure form renders this approach equally applicable to the preparation of the remaining two stereoisomeric forms.

The requisite epimeric α-hydroxy-β-amino esters **2** and **4**, the substrates for the proposed stereospecific rearrangement to the corresponding epimeric α-amino-β-hydroxy esters, were prepared using established methodology [7–11]. α,β-Unsaturated *tert*-butyl ester **1** was prepared in 71% yield from hexadecanal, via a modified Wadsworth-Emmons olefination [7]. Diastereoselective aminohydroxylation of **1** was achieved upon conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide followed by *in situ* enolate oxidation with (+)-camphorsulfonyloxaziridine (CSO) [8], which gave *anti*-α-hydroxy-β-amino ester **2** in 64% yield as a single compound (>95:5 dr). The absolute (2*S*,3*S*,α*S*)-configuration of **2** was confidently assigned by reference to the well-established outcome of this aminohydroxylation procedure when applied to achiral α,β-unsaturated esters [8]. Oxidation of **2** under Swern conditions gave complete conversion to ketone **3**, which was reduced diastereoselectively using $NaBH_4$ in MeOH at −20 °C [9,11] to give *syn*-α-hydroxy-β-amino ester **4** in 96:4 dr [12], and upon

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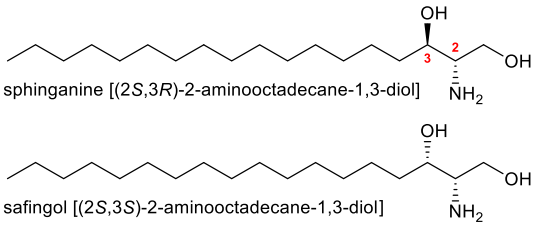
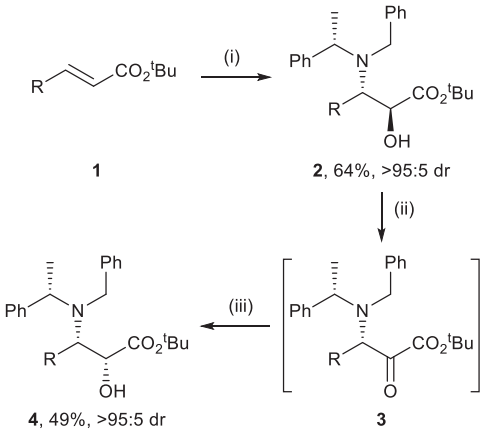


Fig. 1. Structures of sphinganine and safingol.

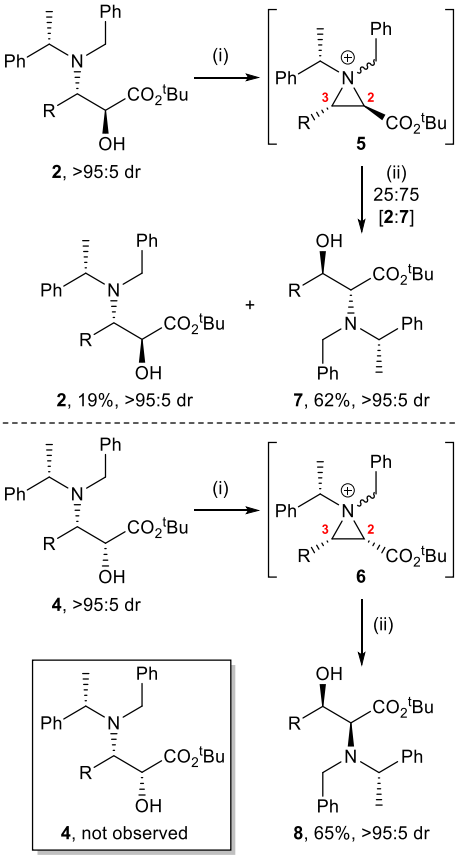
chromatography **4** was isolated in 49% yield (from **2**) as a single compound (Scheme 1).

Treatment of *syn*-α-hydroxy-β-amino ester **4** with Tf_2O in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) followed by addition of H_2O [10,11] resulted in formation of a single product **8** which was isolated in 65% yield, and whose connectivity was established unambiguously by $^1H–^{13}C$ HMBC NMR spectroscopic analysis. The relative *syn*-configuration within **8** was then assigned given the known stereochemical outcome of this transformation as applied to *syn*-α-hydroxy-β-amino esters [11], and can be rationalized by formation of the aziridinium ion intermediate **6** (of unknown stereoisomeric ratio at the nitrogen atom) being followed by hydrolytic ring-opening upon attack of water at the C(3)-position exclusively; this mechanism engenders rearrangement accompanied by inversion of configuration at both C(2) and C(3). In contrast, reaction of *anti*-α-hydroxy-β-amino ester **2** under the same reaction conditions resulted in formation of a 25:75 mixture of *anti*-α-hydroxy-β-amino ester **2** (i.e., the starting material) and *anti*-α-amino-β-hydroxy ester **7**, which were separated and isolated in 19% and 62% yields, respectively. The connectivity within **7** was established unambiguously by $^1H–^{13}C$ HMBC NMR spectroscopic analysis, and the relative configuration was then assigned on the basis of the rearrangement proceeding via the aziridinium ion intermediate **5**. Hydrolytic ring-opening of **5** upon attack of water at C(3) then gives *anti*-α-amino-β-hydroxy ester **7**, although in this case competitive ring-opening upon attack of water at C(2) would rationalize regeneration of the starting material, *anti*-α-hydroxy-β-amino ester **2** [13]. This difference mirrors the behaviour of other pairs of α-hydroxy-β-amino esters, epimeric at the α-position and bearing β-alkyl substituents, that we have investigated within this reaction manifold [10,11] (Scheme 2).

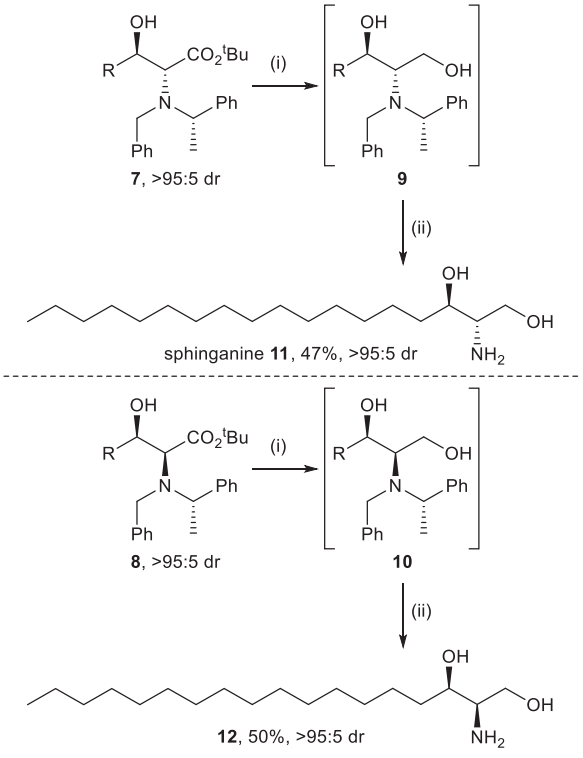
With α-amino-β-hydroxy esters **7** and **8** in hand, elaboration to the targets was pursued. Treatment of **7** with $LiAlH_4$ achieved reduction of the ester moiety to give the corresponding diol **9**, with



Scheme 1. *Reagents and conditions:* (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl) amide, THF, −78 °C, 2 h, then (+)-CSO, −78 °C to rt, 12 h; (ii) DMSO, $(ClCO)_2$, Et_3N, CH_2Cl_2, −78 °C to rt, 1 h; (iii) $NaBH_4$, MeOH, −20 °C, 2 h. R = *n*-$C_{15}H_{31}$.



Scheme 2. *Reagents and conditions:* (i) Tf_2O, DTBMP, CH_2Cl_2, 0 °C to rt; (ii) add H_2O, rt, 16 h. R = *n*-$C_{15}H_{31}$.



Scheme 3. *Reagents and conditions:* (i) $LiAlH_4$, THF, 0 °C to rt, 16 h; (ii) $Pd(OH)_2/C$, H_2, MeOH, rt, 3 days. R = *n*-$C_{15}H_{31}$.

subsequent hydrogenolysis giving sphinganine **11** in 47% isolated yield from **7**. An analogous two-step procedure using **8** as the starting material furnished the C(2)-epimer **12** in 50% yield from **8** (Scheme 3). The specific rotations and ^{1}H and ^{13}C NMR spectroscopic data for these samples of **11** and **12** were in good agreement with previously reported values [5]. Hence, the stereochemical assignments of all the intermediate compounds **2**–**10** (from which **11** and **12** were derived) were also validated.

In conclusion, we have completed a short asymmetric synthesis of sphinganine and its C(2)-epimer. As the source of chirality for this synthesis is *N*-benzyl-*N*-(α-methylbenzyl)amine, which is readily available in either enantiomerically pure form, this synthesis would be equally applicable to the synthesis of the remaining two stereoisomeric forms of 2-aminooctadecane-1,3-diol (i.e., *ent*-**11** and *ent*-**12**), and readily adaptable for the preparation of analogues of varying chain length.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152743.

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