Asymmetric sulfur ylide based enantioselective synthesis of D-*erythro*-sphingosine†

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An asymmetric sulfur ylide reaction was employed to prepare an epoxide intermediate in a convergent manner. This epoxide was efficiently transformed into D-*erythro*-sphingosine.

Sphingolipids, named by Johann Ludwig Wilhelm Thudichum[1] in 1884 after the Greek Sphinx due to their enigmatic function, have emerged over the last several decades as a family of key signalling molecules, and include sphingosine **1**, ceramide **2**, and sphingosine-1-phosphate **3** (Fig. 1).[2] Data indicate that these lipids regulate fundamental and diverse cell processes such as differentiation, migration, and apoptosis.[3,4] Moreover, on the organismal level, sphingolipids play roles in higher order physiological processes including inflammation[5] and vasculogenesis.[6] Recent studies implicate sphingolipid involvement in many of the most common human diseases including diabetes,[7] cancers,[8] infection by microorganisms,[9] Alzheimer's disease,[10] heart disease and an array of neurological syndromes.[11]

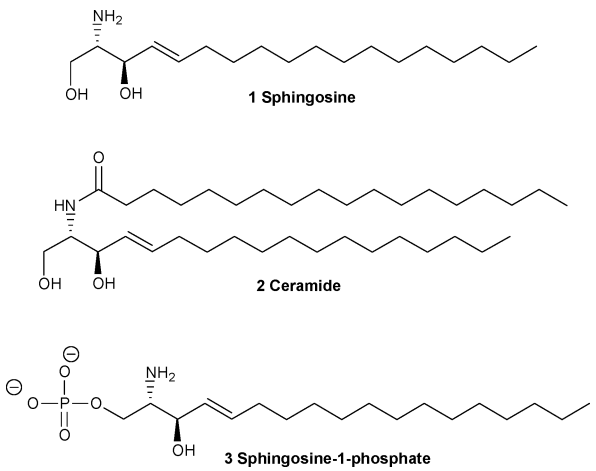
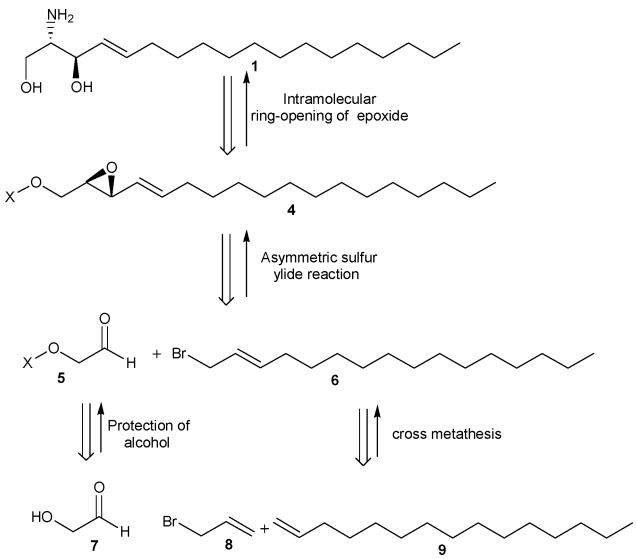


Fig. 1 Naturally occurring sphingolipids.

The basic structure of a sphingolipid consists of a long-chain sphingoid base backbone linked to a fatty acid *via* an amide bond with the 2-amino group and to a polar head group at the C-1 position *via* an ester bond. There are four sphingosine stereoisomers with a wide range of biological activities.[12,13] The isomer D-*erythro* is the most common metabolite and has been meticulously studied. We have recently reported efficient glycosylation protocols of this compound and analogues in order to obtain glycosphingolipids.[14] Since, pure sphingosine and its derivatives are available in a limited amount from natural sources, many methods for their synthesis have been developed by using amino acids, carbohydrates and other building blocks as the starting materials.[15,16] However, most of the methods require multistep reactions that result in low total yields. The key to cost-effective and efficient synthesis is the choice of a proper starting material that requires minimal protection-deprotection steps.

In the present study, we report a convenient and concise route for the synthesis of D-*erythro*-sphingosine **1**. Based on the retrosynthetic analysis depicted in Scheme 1, compound **1** can be generated from the corresponding epoxide **4** *via* an intramolecular ring-opening to introduce the amino functionality at C-2. The selectivity of the intermolecular opening is controlled by the double bond and affords the 3-amino derivative. For synthesising epoxide **4** we envisaged an asymmetric reaction between a chiral sulfur ylide obtained from bromide **6** and aldehyde **5**, which can incorporate the nucleophile (X) for epoxide opening in its structure.



Scheme 1 Retrosynthetic analysis of D-*erythro*-sphingosine.

The aldehyde **5** is readily prepared from the alcohol **7**. Lipophilic chain fragment **6** should be available from allyl bromide (**8**) and alkene **9** by means of cross-metathesis (CM) in order to introduce the required *E*-olefin moiety.

As shown in Scheme 2, the synthesis started with the protection of hydroxyaldehyde **7** as a carbamate, since it is appropriate for opening the epoxide in a subsequent step. Thus, aldehyde **10** for

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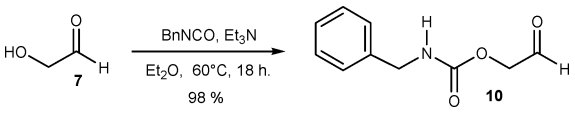
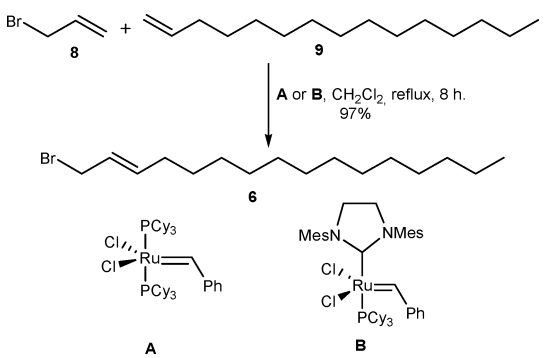


Scheme 2 Protection of alcohol **7**.

asymmetric sulfur ylide reaction was obtained in excellent yield by reaction of hydroxyaldehyde **7** and benzyl isocyanate (1.5 equiv) in the presence of Et_3N, employing Et_2O as the solvent.

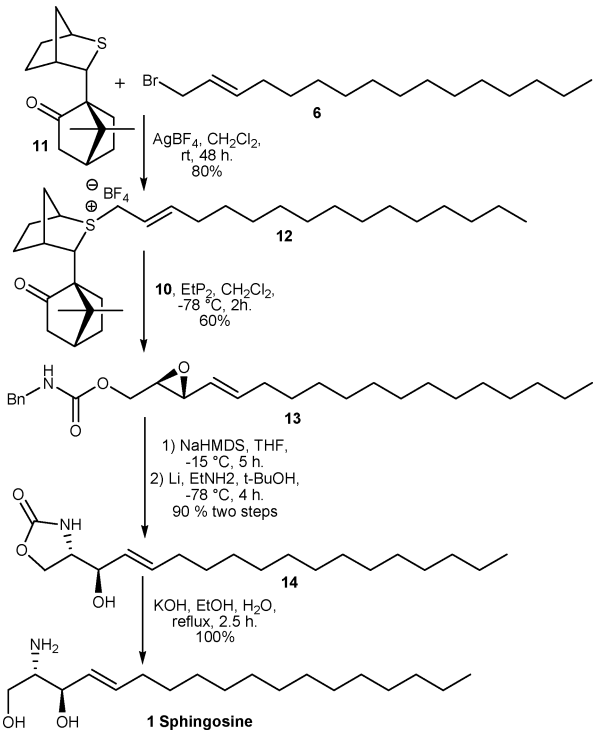
The high *E*-selectivity and the functional tolerance are attractive features of cross-metathesis olefination in the synthesis of natural products.[17] In a recent synthesis of the sphingosines and phytosphingosines, CM has been used as a carbon chain elongation strategy.[18] Therefore, we reasoned that a cross metathesis reaction of allyl bromide **8** and alkene **9** in presence of Grubbs'[19] catalyst will provide the intermediate **6**[20] with the correct configuration. Substrate **8** was stirred with 4 equiv of olefin **9** and 0.02 equiv of second generation Grubbs' catalyst (**B**) in CH_2Cl_2 for 8 h at reflux. The reaction proceeded smoothly, and the desired coupling product **6** was obtained in 97% yield with an *E* : *Z* selectivity of 52 : 1. The homocoupling product of **8** was not observed by ^1H NMR. In this case the use of $Ti(O^iPr)_4$ or other additive was not necessary to obtain excellent results. A decrease in the selectivity (*E* : *Z* 11 : 1) and the yield (78%) was observed when the first generation Grubbs' catalyst (**A**) was employed under similar conditions (Scheme 3).



Scheme 3 Synthesis of **6** by cross-metathesis.

The key step is the synthesis of the epoxide **13** with control of the configuration of the stereogenic centers at C-2 and C-3 by using the stoichiometric sulfur ylide reaction, which is of particular interest because of the valuable synthetic intermediates that have been generated using this reaction.[21] The sequence developed to prepare epoxide **13** is summarized in Scheme 4. Sulfide **11**[22] was selected as chiral auxiliary in order to prepare the corresponding chiral sulfur ylide.[21] Reaction of sulfide **11** (1 equiv) with allyl bromide **6** (1.2 equiv) in CH_2Cl_2 and in the presence of $AgBF_4$ (4 equiv) afforded the required sulfonium salt **12** in 80% yield.[23] Subsequent treatment of the salt **12** with EtP_2 base (1.1 equiv) and the aldehyde **10** (1.1 equiv) furnished the desired epoxide **13** in 60% yield. Crucial to the success of the reaction were conditions that favoured the formation of stabilized ylide **15** (Fig. 2), namely employing the EtP_2 base at −78 °C in CH_2Cl_2.

To complete the synthesis (Scheme 4),[24] epoxide **13** was converted to oxazolidinone **14** with complete regio- and stereoselectivity first by treatment with NaHMDS (1.5 equiv) at −15 °C in THF.[25] Then, removal of the benzyl group employing Li (excess) and $EtNH_2$/*t*-BuOH at −78 °C gave **14** in 90% yield over two steps.[18d,26] Finally, alkaline hydrolysis of oxazolidinone **14** with KOH at reflux for 2.5 h furnished D-*erythro*-sphingosine **1** in quantitative yield. Synthetic **1** gave mp 72–74 °C (lit[18d] mp 72–75 °C), $[\alpha]_D$ −1.6 (*c* 0.9 in $CHCl_3$) (lit[18d] $[\alpha]_D$ −1.6) (*c*1 in $CHCl_3$)). 400 MHz ^1H and 125 MHz ^{13}C NMR spectroscopic data were consistent with data reported for the synthetic product. The match of optical rotation values indicate that the formation of the epoxide **13** was completely stereoselective.



Scheme 4 Synthesis of D-*erythro*-sphingosine.

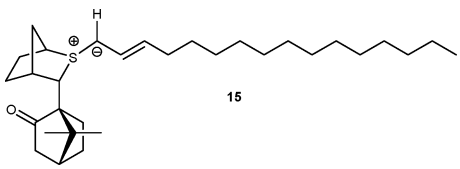


Fig. 2 Ylide intermediate.

In summary, D-*erythro*-sphingosine has been obtained in 42% overall isolated yield and high enantioselectivity by using an asymmetric sulfur ylide reaction between the sulfonium salt **12** and the aldehyde **10** as the key step.

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