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# The preparation of simplified scyphostatin analogues using a tethered aminohydroxylation (TA) strategy

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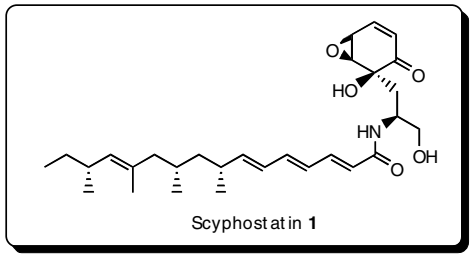
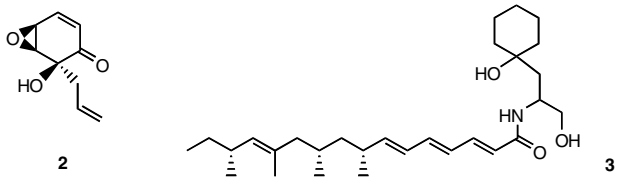
**Abstract**—The first tethered aminohydroxylation reaction employing a tertiary alcohol is reported as part of a route to prepare analogues of the naturally occurring sphingomyelinase inhibitor, scyphostatin. The tethered aminohydroxylation of 1-allylcyclohexanol produces the β-amino alcohol product, in protected form, with the required regiochemistry. Two approaches to the installation of the lipophilic side chain are described and the successful route used to prepare five novel scyphostatin analogues, one containing the natural lower side chain.


Scyphostatin (**1**) was isolated in 1997 by Ogita and co-workers from a mycelial extract of *Dasyscyphus mollissimus* SANK-13892 and its gross structure determined by extensive spectroscopic and derivatisation studies.[1] Unambiguous assignment of the stereochemistry of the side-chain methyl groups, together with the total synthesis of the side-chain acid, was published by Hoye and Tennakoon[2] in 2000, and an improved synthesis was recently published by our group.[3] Scyphostatin was found to have potent inhibitory activity of neutral sphingomyelinase (N-SMase), and was also found to possess a good level of acidic sphingomyelinase (A-SMase) inhibition. It has been proposed that this activity could assist in the therapy of inflammation and autoimmune diseases.[1]




The unusual enzyme inhibitory properties of scyphostatin, together with its challenging structure, have generated considerable interest from synthetic and medicinal chemists. Initial synthetic approaches to the total synthesis of this natural product concentrated on the construction of the highly functionalised epoxy-cyclohexenone core. Thus, wide-ranging approaches have been employed to set up the absolute and relative chemistry of the epoxy-enone system; these include 'chiral-pool' approaches by the groups led by Gurjar [4a] and Katoh,[4b,c] an intramolecular bromo-etherification approach by Fujioka et al.[4d] and an oxidative approach by Ohkata and co-workers.[4e] Our efforts in this area have led to two syntheses of the allyl-substituted core **2**, via an organometallic route[5a] and a chiral pool approach commencing from (−)-quinic acid.[5b] In addition to synthetic approaches to the natural product, Giannis and co-workers have pioneered efforts to synthesise novel scyphostatin analogues in search of selective inhibitors of N-SMase.[6] A range of compounds were prepared and several were found to exhibit selective irreversible inhibition of N-SMase. However, selective, reversible inhibitors of N-SMase are still required.

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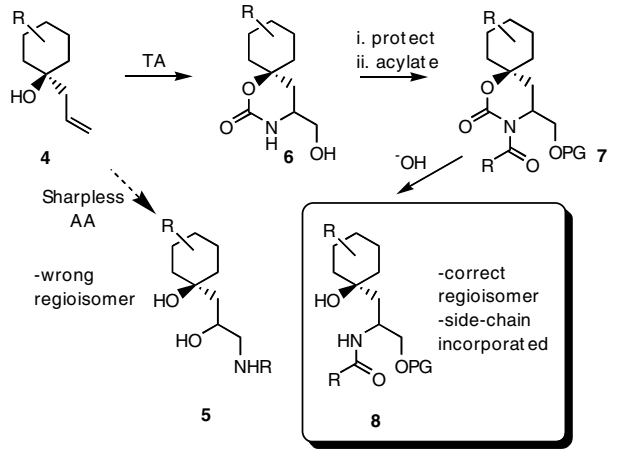
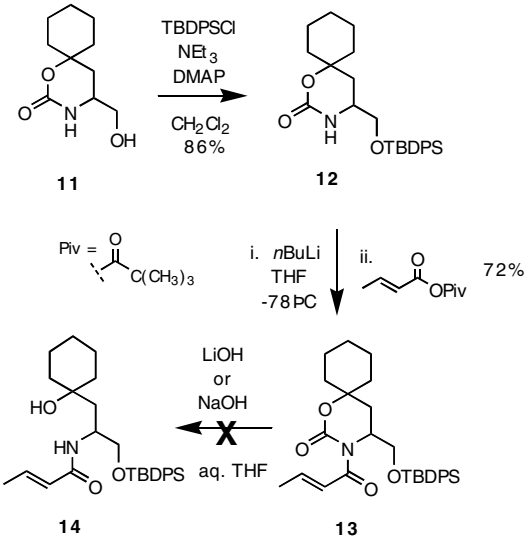
In this paper we report the development of methodology to access lower side-chain analogues of scyphostatin, including **3**, which possesses the complete scyphostatin lower side chain. This methodology should aid on-going structure–activity studies, and could provide an end-game strategy for scyphostatin itself. Our aim (Scheme 1) was to use the Sharpless asymmetric aminohydroxylation (AA)[7] to deliver the required β-amino alcohol directly from an allyl-substituted cyclohexanol **4**. Unfortunately, AA reactions on terminal mono-substituted alkenes have been found[8] to deliver the terminal amino group, in this case presumably giving product **5** (Scheme 1). Recently, an alternative regio-controlled tethered aminohydroxylation reaction (TA) of allylic and homo-allylic alcohols has been developed by Donohoe et al.[9] by employing an internally-disposed carbamate. In this way the nitrogen source is delivered in an intramolecular manner, providing the required regioselectivity. We, therefore, considered using the TA methodology on **4** as is shown in Scheme 1, providing the cyclic carbamate **6**. Protection of the primary alcohol and installation of the unsaturated amide would deliver *N*-acyl carbamate **7**. We then hoped to use the electron-withdrawing nature of the *N*-acyl group to cleave the cyclic carbamate under mild, basic conditions[10] to produce the required system **8**. In this paper we report the eventual success of a modified version of this strategy, installing the β-amino alcohol functionality and hydrophobic side chain, starting from the parent allylic cyclohexanol system **4**, R = H. We then describe the utilisation of this model system to prepare several novel scyphostatin analogues.



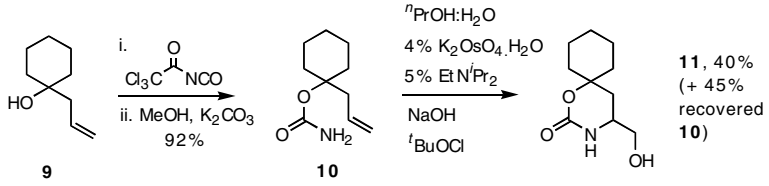

**Scheme 1.** Synthetic plan.

Initial studies aimed at establishing the feasibility of this approach are shown in Scheme 2. The known homo-allylic alcohol **9**,[11] which was prepared in quantative yield from cyclohexanone, was treated with trichloroacetyl isocyanate. The carbamate **10** was then obtained by methanolysis of the intermediate trichloroacetylcarbamate in excellent overall yield. Treatment of **10** under the standard TA conditions[9] led to formation of cyclic carbamate **11** in 40% yield, with recovery of 45% of the starting material. This level of conversion is comparable to many examples reported by Donohoe et al.[9] It should be noted that this is the first report of the TA reaction employing a tertiary alcohol, further expanding the range of substrates for this process.

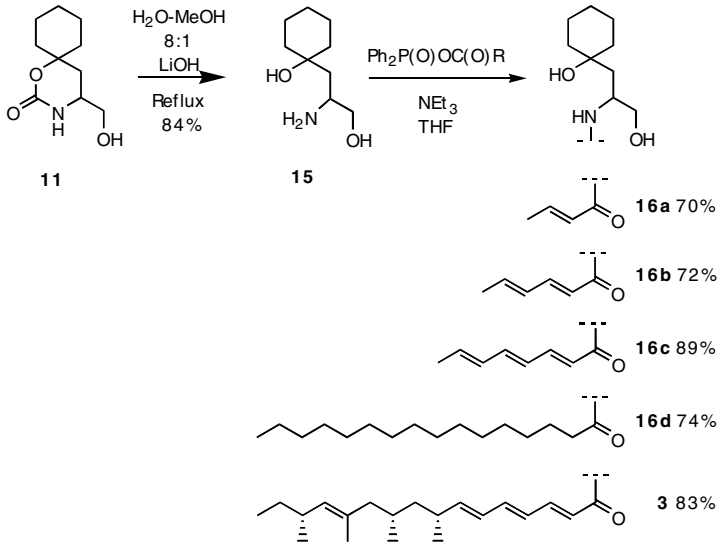
On acquiring cyclic carbamate **11**, we examined the possibility of installing the unsaturated amide side chain and subsequent cleavage of the *N*-acyl carbamate (Scheme 3). Protection of the primary alcohol was performed with TBDPSCl delivering the silyl ether **12** in good yield. Deprotonation of the nitrogen with *n*-butyllithium at −78 °C in THF, followed by treatment with the mixed pivaloyl anhydride of crotonic acid gave the *N*-acyl carbamate **13** in good yield. We had hoped at this point to be able to cleave the cyclic carbamate employing mild basic conditions. To this end, the *N*-acyl carbamate was treated with LiOH or NaOH in THF at 0 °C,[10a] but disappointingly conversion into amide **14** was not observed, and by-products owing to silyl group cleavage were identified after extended reaction times.




**Scheme 3.** Attempted carbamate cleavage.




**Scheme 2.** Tethered aminohydroxylation (TA) reaction.




**Scheme 4.** Synthesis of novel scyphostatin analogues.

Due to the failure of our first approach described in Scheme 3, we investigated an alternative strategy for the transformation of cyclic carbamate **11** into scyphostatin analogues. To this end, the direct hydrolysis of the cyclic carbamate **11** was explored. We eventually found that this could be achieved by heating **11** in aqueous methanol with LiOH,[12] delivering aminodiol **15** in 84% yield. Direct amide formation from aminodiol **15** was then carried out using the diphenylphosphinic chloride—derived anhydrides of various acids to give the analogues **16a**–**d** and **3** in good yield, with no protection needed during the procedure. In this sequence, we used commercially available crotonic acid, sorbic acid and palmitic acid, along with octatrienoic acid[13] and the natural scyphostatin side chain recently synthesised by our group.[3] In this way, a wide variety of side-chain structural analogues are available, from mono-unsaturated **16a** to the more complex **16d** and **3**.[14] It should be noted that compound **3** is the first scyphostatin analogue known, which possesses the complete southern hemisphere functionality, that is, the aminodiol unit acylated with the enantiomerically pure, natural lipophilic acid. These analogues will be useful in future biological tests to understand further the effect of structure on inhibitory activity (Scheme 4).

In conclusion, we have applied the TA reaction of a homo-allylic tertiary alcohol **9** to the synthesis of a model system of the core of scyphostatin (**1**). In this way we were able to obtain the correct β-amino alcohol regiochemistry for the natural compound. We then used this system to investigate a strategy for incorporation of the unsaturated amide side chain into a late-stage synthetic intermediate. Also, using our model system, we synthesised five novel scyphostatin analogues **16a**–**d** and **3**, which could give insights into the mode of action of scyphostatin in future biological tests. We are currently extending this methodology to evaluate its use as an end-game strategy for the synthesis of scyphostatin itself.

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14. Example characterisation **16b**, white powder ($Et_2O$), mp 120–122 °C. $\nu_{max}$ (film)/$cm^{-1}$ 3365, 3285 (OH and NH), 2924, 2853 (CH), 1655, 1625, 1600 (amide and conjugated alkenes). $\delta_H$ (400 MHz, $CD_3OD$) 7.10 (1H, dd, *J* 10.5, 15.5), 6.22 (1H, m), 6.12 (1H, dq, *J* 15.5, 6.5), 5.90 (1H, d, *J* 15.5), 4.16 (1H, m), 3.51 (2H, d, *J* 9), 1.84 (3H, d, *J* 6.5), 1.73–1.24 (12H, m). $\delta_C$ (100 MHz; $CD_3OD$) 168.7, 142.2, 138.7, 131.1, 123.0, 71.8, 66.3, 1C signal under $CD_3OD$, 44.5, 39.3, 37.8, 26.9, 23.3, 23.2, 18.6. (Found: $MH^+$, 268.1905. $C_{15}H_{25}NO_3$ requires $MH^+$, 268.1913).