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# Studies toward the Total Synthesis of Scyphostatin: First Entry to the Highly Functionalized Cyclohexenone Segment

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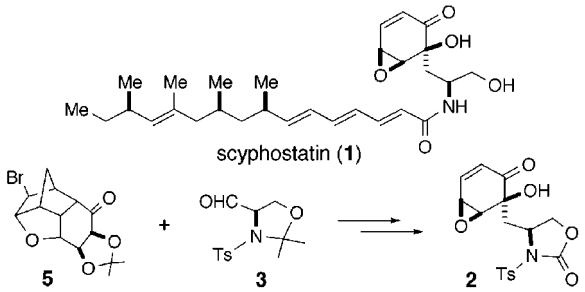
## ABSTRACT




**The cyclohexenone segment 2 of scyphostatin (1), a potent inhibitor of neutral sphingomyelinase, was synthesized in an enantioselective manner starting from the bromo ether 5 and D-serinal derivative 3. The synthetic method features a coupling reaction of 5 with 3 to construct the asymmetric quaternary carbon center and a stereospecific epoxide ring formation as the key steps.**

Scyphostatin (**1**, Figure 1), isolated from the culture broth of *Dasyscyphus mollissimus* SANK-13892 by Ogita et al. at the Sankyo research group in 1997, is a powerful and specific inhibitor of neutral sphingomyelinase (N-SMase).[1−3] This natural product is the most potent of the few known small molecule inhibitors of N-SMase.[4] Ceramide, the product of sphingomyelin hydrolysis by N-SMase, has been recognized to be a lipid second messenger in cell membranes and plays key roles in the regulation of cell proliferation, differentiation, and apoptosis. Since the use of N-SMase inhibitors can regulate the level of ceramide in a wide variety of cells, **1** is anticipated to be a promising agent for the treatment of ceramide-mediated pathogenic states such as inflammation and immunological and neurological disorders.[5]

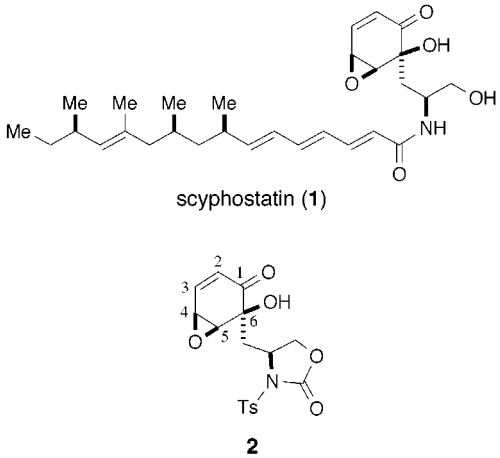



**Figure 1.** Structures of scyphostatin (**1**) and the cyclohexenone segment **2**.

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(1) Tanaka, M.; Nara, F.; Suzuki-Konagai, K.; Hosoya, T.; Ogita, T. *J. Am. Chem. Soc.* **1997**, *119*, 7871.

(2) Nara, F.; Tanaka, M.; Hosoya, T.; Suzuki-Konagai, K.; Ogita, T. *J. Antibiot.* **1999**, *52*, 525.

(3) Nara, F.; Tanaka, M.; Masuda-Inoue, S.; Yamamoto, Y.; Doi-Yoshioka, H.; Suzuki-Konagai, K.; Kumakura, S.; Ogita, T. *J. Antibiot.* **1999**, *52*, 531.

(4) It is reported that **1** exhibits N-SMase and acidic SMase (A-SMase) with $IC_{50}$ values of 1.0 and 49.3 $\mu$M, respectively.

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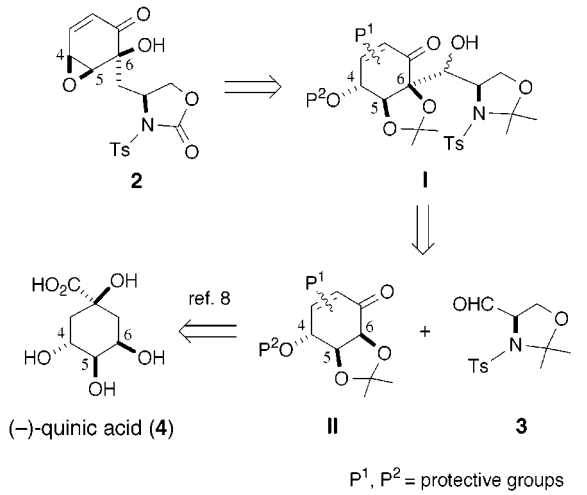
The structure of **1** was revealed by extensive spectroscopic studies to have a novel, highly oxygenated cyclohexane ring incorporated with a C-20 unsaturated fatty acid substituted amino propanol side chain.[1] This initial structure elucidation only determined the relative and absolute stereochemistry of the cyclohexenone moiety in **1**. Recently, Kogen et al. at the Sankyo research group elucidated and reported the relative and absolute configurations of the three stereocenters within the C-20 unsaturated fatty acid moiety.[6] Subsequently, Hoye et al. disclosed an enantioselective synthesis of the C-20 unsaturated fatty acid moiety, leading to alternative proof of its stereostructure including the absolute configuration.[7] Its remarkable biological properties as well as its unique structural features make **1** an exceptionally intriguing and timely target for total synthesis.

In the course of our ongoing project directed toward the total synthesis of **1**, we have recently developed a synthetic pathway to (4*S*,5*S*,6*S*)-6-benzyl-4,5-epoxy-6-hydroxy-2-cyclohexen-1-one, which represents a model compound for the cyclohexenone segment **2**.[8] In this communication, we present an efficient and facile method for the synthesis of **2** possessing the N,O-protected amino propanol side chain with the requisite asymmetric carbon center. To the best of our knowledge, this is the first entry to the highly and densely functionalized cyclohexenone moiety of **1**. Quite recently, a synthetic study toward this type of cyclohexenone system was reported by Gurjar et al.[9]

The retrosynthetic plan for **2** was designed as outlined in Scheme 1, which is based upon our preliminary studies.[8] The

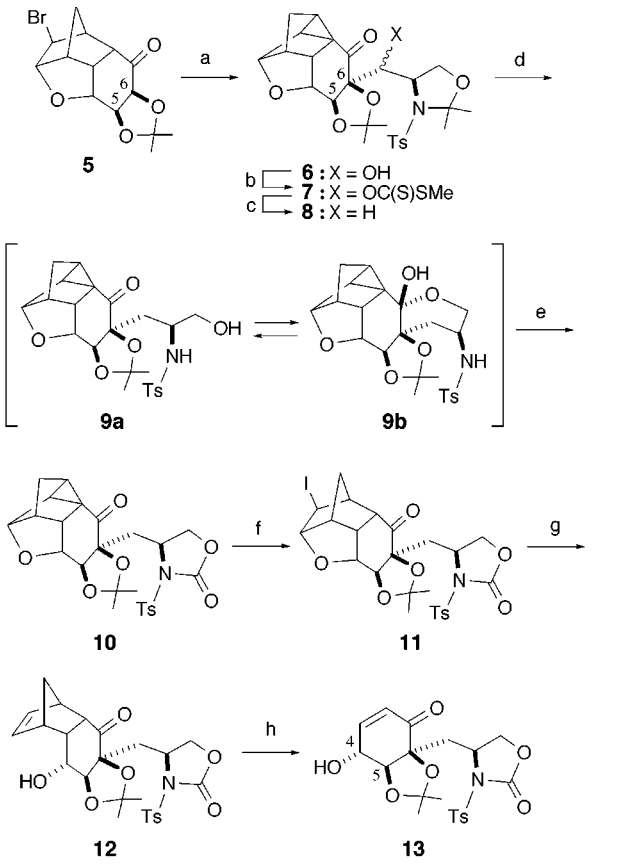
**Scheme 1.** Retrosynthetic Plan for the Cyclohexenone Segment **2**




key feature in this plan is an aldol-type coupling of the olefin-masked enone **II** with D-serinal derivative **3**,[10] where we believed that **3** would access exclusively from the less hindered α-face of the enolate generated from **II** under the influence of the *β*-oriented *O*-isopropylidene moiety, leading to construction of the desired asymmetric quaternary carbon center at C-6. The coupling product **I** would be converted into **2** by sequential functional group manipulation and deprotection or vice versa; the sequence involves regeneration of the cyclohexenone olefin moiety and stereospecific epoxide ring formation as the pivotal steps. The olefin-masked enone **II** bearing three contiguous oxygen functionalities with correct stereochemistries at C-4, C-5, and C-6 has been already prepared starting with commercially available (−)-quinic acid (**4**) in our previous work.[8]

As shown in Scheme 2, the synthesis commenced with the crucial coupling reaction of the bromo ether **5**,[8] a

**Scheme 2.** Synthesis of the Key Intermediate **13**[a]




[a] Reagents and conditions: (a) $LiN(TMS)_2$, THF, −78 °C; (*R*)-*N*-(*p*-toluenesulfonyl)-*N*,*O*-isopropylidene serinal (**3**), −78 °C, 95%; (b) $NaN(TMS)_2$, THF, −78 °C; $CS_2$, −78 → −50 °C; MeI, −78 → −50 °C, 88%; (c) *n*-$Bu_3SnH$, $Et_3B$, toluene, rt, 95%; (d) 1.0 M HCl, THF, 55 °C; (e) $Cl_3COCOCl$, pyridine, THF, rt, 67% (two steps); (f) TMSI, $CCl_4$−$CH_2Cl_2$, −20 °C, 74%; (g) Zn, AcOH, MeOH, 60 °C, 95%; (h) $Ph_2O$, 230 °C, 59%.

synthetic equivalent of the olefin-masked enone **II**, with D-serinal derivative **3**[10] [(*R*)-*N*-(*p*-toluenesulfonyl)-*N*,*O*-

(5) For a recent excellent review on the catabolites of sphingolipids as novel therapeutic targets, see: Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532.

(6) Saito, S.; Tanaka, N.; Fujimoto, K.; Kogen, H. *Org. Lett.* **2000**, *2*, 505.

(7) Hoye, T. R.; Tennakoon, M. A. *Org. Lett.* **2000**, *2*, 1481.

(8) Izuhara, T.; Katoh, T. *Tetrahedron Lett.* **2000**, *41*, 7651.

(9) Gurjar, M. K.; Hotha, S. *Heterocycles* **2000**, *53*, 1885.

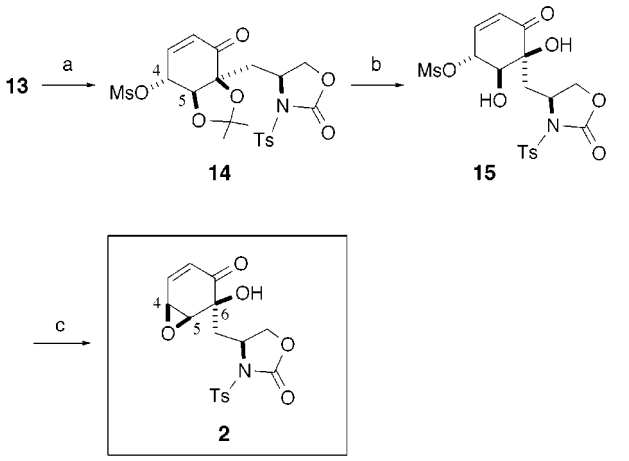
isopropylidene serinal]. The enolate anion generated in situ by treatment of **5** with lithium bis(trimethylsilyl)amide [LiN(TMS)$_2$] (2.2 equiv) in THF at −78 °C was allowed to react with **3**, providing an excellent yield (95%) of the coupling product **6** as a hardly separable mixture of the epimeric alcohols (ca. 9:1 by 500 MHz $^1$H NMR). In this reaction, intramoleculer cyclopropane ring formation occurs prior to the coupling reaction with **3**. Removal of the sterically hindered hydroxy group in **6** was best achieved by applying the Barton procedure[11] with some improvements in the reaction conditions. Thus, reaction of **6** with sodium bis(trimethylsilyl)amide [NaN(TMS)$_2$] followed by carbon disulfide and iodomethane gave the corresponding methyl xanthate **7** in 88% yield, which was then treated with tri-*n*-butyltinhydride and triethylborane[12] in toluene at ambient temperature, providing the desired deoxygenated product **8** in 95% yield.

To differentiate the two isopropylidene protecting groups in **8**, it was converted to the corresponding cyclic carbamate **10**. Thus, treatment of **8** with aqueous hydrogen chloride in THF at 55 °C furnished an equilibrium mixture of the Ts-protected $\beta$-amino alcohol **9a** and the cyclic hemiacetal **9b** (ca. 1:1); this mixture was then allowed to react with phosgene dimer (trichloromethyl chloroformate) in the presence of pyridine in THF, affording the desired cyclic carbamate **10** in 67% yield for the two steps.

With the key intermediate **10** possessing the requisite *N*,*O*-protected amino propanol side chain with correct stereochemistry in hand, our next efforts were devoted to regeneration of the cyclohexenone olefin moiety. Toward this end, regioselective cleavage of the cyclopropane ring in **10** by reaction with iodotrimethylsilane (TMSI) provided the $\gamma$-iodo ketone **11** (74%), which was further treated with zinc powder in methanol containing acetic acid to furnish the *endo*-alcohol **12** in 95% yield. Retro-Diels−Alder reaction of **12** proceeded effectively by thermolysis at 230 °C in diphenyl ether,[13] leading to the formation of the cyclohexenone **13** in 59% yield.

The final route that led to completion of the synthesis of the targeted cyclohexenone segment **2** is summarized in Scheme 3, which involves the critical epoxide ring formation utilizing the two oxygen functionalities present at C-4 and C-5 in **13**. After mesylation of the hydroxy group in **13** under conventional conditions (83%), the resulting mesylate **14** was then subjected to acid hydrolysis of the isopropylidene moiety by reaction with aqueous trifluoroacetic acid at 0 °C, affording the corresponding diol **15** in quantitative yield. Finally, exposure of **15** to aqueous sodium hydroxide in dichloromethane at 0 °C for 30 min led to the formation of

**Scheme 3.** Synthesis of the Cyclohexenone Segment **2**[a]




[a] Reagents and conditions: (a) MsCl, DMAP, pyridine, 0 °C → rt, 83%; (b) TFA, $H_2O$, 0 °C, 100%; (c) 0.1 M NaOH, $CH_2Cl_2$, 0 °C, 75%.

**2** in 75% yield. The stereostructure of **2** was unambiguously confirmed by single X-ray crystal structure analysis as depicted in Figure 2.

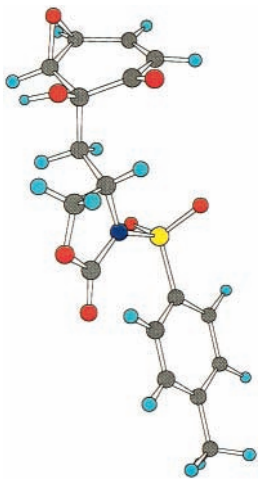


**Figure 2.** Chem 3D representation of **2** from the X-ray coordinates.

In summary, we have succeeded in developing a facile synthetic pathway to the cyclohexenone segment **2**, which is the first entry to the highly and densely functionalized cyclohexenone moiety of **1**. The explored synthetic method features an aldol-type coupling of the bromo ether **5** with D-serinal derivative **3** to construct the requisite asymmetric quaternary carbon center at C-6 and the final epoxide ring formation as the key steps. Further investigation toward the total synthesis of **1** and analogues is now in progress and will be reported in due course.

**Acknowledgment.** We are grateful to Drs. H. Kogen and T. Ogita, Sankyo Co., Ltd., for many useful suggestions and

(10) (a) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051. (b) Uchida, H.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 113.

(11) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(12) (a) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403. (b) Yorimitsu, K.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604 and references therein.

(13) Ogasawara, K. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 957 and references therein.

encouragement. We kindly thank Mr. Y. Ijuin, Sagami Chemical Research Center, for the X-ray crystallographic analysis of **2**.

**Supporting Information Available:** Experimental procedure and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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