Pergamon

Tetrahedron Letters 41 (2000) 7651–7655

TETRAHEDRON LETTERS

Enantiocontrolled synthesis of (4*S*,5*S*,6*S*)-6-benzyl-4,5-epoxy-6-hydroxy-2-cyclohexen-1-one, a model compound for the epoxycyclohexenone moiety of scyphostatin

Takashi Izuhara† and Tadashi Katoh*

Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229-0012, Japan

Received 22 June 2000; revised 26 July 2000; accepted 28 July 2000

Abstract

An efficient synthesis of (4*S*,5*S*,6*S*)-6-benzyl-4,5-epoxy-6-hydroxy-2-cyclohexen-1-one (**2**) representing a model compound for the cyclohexenone moiety of scyphostatin (**1**) was accomplished; the method features masking of the enone system in **10** in the form of the bromo ether **13** (**10**→**11**→**12**→**13**), aldol coupling of **13** with benzaldehyde to construct the requisite asymmetric quaternary carbon center at the C-6 position (**13**→**14**), and epoxide ring formation (**21**→**2**) as the key steps. The key intermediate **10** was prepared from commercially available (−)-quinic acid (**3**).

Keywords: scyphostatin; antibiotics; aldol reactions; enantiocontrol; cyclohexenones; epoxycyclohexenones.

Scyphostatin (**1**), isolated from the culture broth of *Dasyscyphus mollissimus* SANK-13892 by the Sankyo research group in 1997, has been shown to be a powerful and specific inhibitor of neutral sphingomyelinase (N-SMase).[1–4] The use of N-SMase inhibitors can regulate the level of ceramide, the product of sphingomyelin hydrolysis by N-SMase, in a wide variety of cells.[5] Therefore, **1** is anticipated to be a promising agent for the treatment of ceramide-mediated pathogenic states such as inflammation and immunological and neurological disorders.[2,3,5] The gross 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.[1,6–8] Its remarkable biological properties as well as its unique structural features make **1** an exceptionally intriguing and timely target for total synthesis (Fig. 1).

* Corresponding author. Fax: +81-427-49-7631; e-mail: takatoh@alles.or.jp

† Graduate student from Department of Electronic Chemistry, Tokyo Institute of Technology, Yokohama 226-8502, Japan.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01312-5

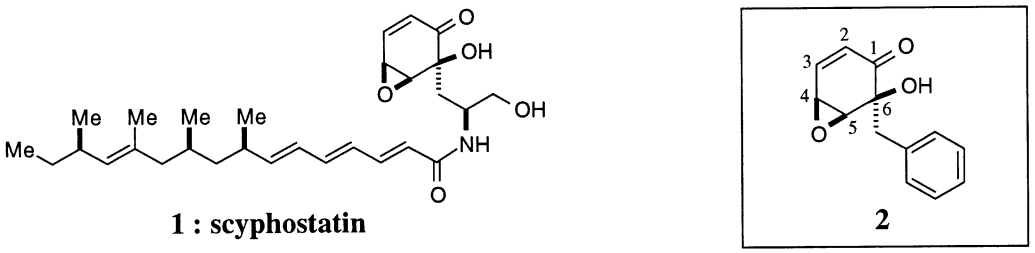
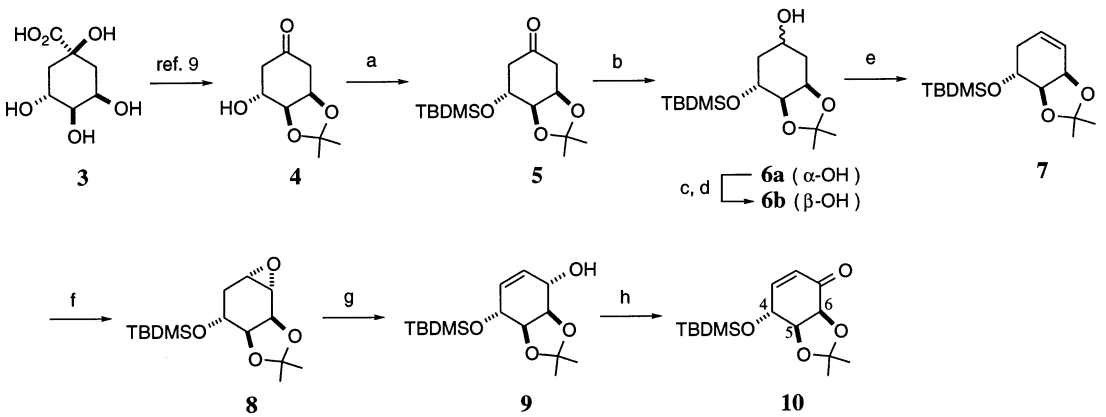


Figure 1. Structures of scyphostatin (**1**) and the model compound (**2**) for the cyclohexenone moiety of **1**

We embarked on a project directed at the total synthesis of **1** and its congeners with the aim of exploring the structure–activity relationships. In this communication, we wish to report an efficient and facile method for the synthesis of (4*S*,5*S*,6*S*)-6-benzyl-4,5-epoxy-6-hydroxy-2-cyclohexen-1-one (**2**) which represents a model compound for the cyclohexenone moiety of **1**. To the best of our knowledge, this is the first approach toward the highly functionalized cyclohexenone moiety of **1**. The method for the synthesis of **2** involves the masking of the highly reactive enone system in **10** in the form of the bromo ether **13** (**10**→**11**→**12**→**13**), the aldol coupling of **13** with benzaldehyde to construct the requisite asymmetric quaternary carbon center at the C-6 position (**13**→**14**), and the sequential epoxide ring formation (**19**→**20**→**21**→**2**) as the key steps.

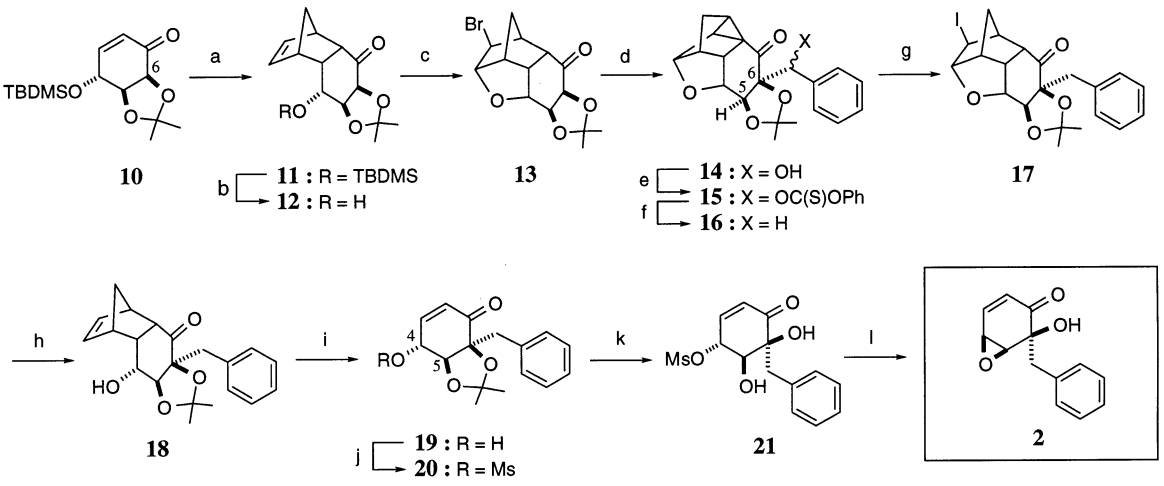
At first, we pursued the synthesis of the key intermediate **10** possessing the requisite enone system and three contiguous oxygen functionalities with correct stereochemistries at the C-4, C-5, and C-6 positions (2-cyclohexen-1-one numbering) (Scheme 1). The starting material **4** was prepared from commercially available (−)-quinic acid (**3**) in three steps according to the reported procedure.[9] After protection of the hydroxy group in **4** as its *tert*-butyldimethylsilyl (TBDMS) ether (98%), the carbonyl group in the resulting TBDMS ether **5** was reduced with sodium borohydride to provide the alcohols **6a** (53%) and **6b** (44%) as an epimeric mixture, which could be separated by column chromatography on silica gel. Dehydration of **6b** by treatment with diethyl azodicarboxylate (DEAD) and triphenylphosphine occurred regioselectively to afford the



Scheme 1. Synthesis of the key intermediate **10** (a) TBDMSCl, imidazole, DMF, rt, 98%; (b) $NaBH_4$, THF–H_2O, rt, 53% for **6a**, 44% for **6b**; (c) DEAD, Ph_3P, benzoic acid, THF, rt, 98%; (d) KOH, MeOH, rt, 100%; (e) DEAD, Ph_3P, THF, rt, 67%; (f) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt, 92%; (g) Se_2Ph_2, $NaBH_4$, EtOH, 0°C→reflux; H_2O_2, THF, 0°C→reflux, 78%; (h) Dess–Martin periodinane, CH_2Cl_2, rt, 95%

desired olefin **7** in 67% yield.[10] In this reaction, the other regioisomeric olefin was not obtained at all. On the contrary, treatment of the epimeric alcohol **6a** under the same conditions gave none of the desired dehydration product **7**, and resulted in complete recovery of the starting material **6a**.[11] Therefore, **6a** was converted to **6b** (98%, two steps) by using the Mitsunobu inversion procedure.[12] To forward the synthesis, the olefin **7** was treated with 3-chloroperoxybenzoic acid (*m*CPBA) to furnish the epoxide **8**[13] (92%) as a single stereoisomer, which was then transformed to the allylic alcohol **9** (78%) by employing the Sharpless protocol.[14] Finally, oxidation of **9** by the use of Dess–Martin periodinane[15] provided the key intermediate **10**[16] in 95% yield.

Having obtained the key intermediate **10**, our next efforts were devoted to the crucial aldol coupling of **10** with benzaldehyde. We envisaged that the introduction of the benzyl group at the C-6 position in **10** would occur exclusively from the less hindered α-face of the enolate generated from **10** under the influence of the β-oriented *O*-isopropylidenedioxy moiety. However, initial attempts to achieve aldol coupling of **10** with benzaldehyde were quite fruitless because the enone olefin moiety involved in **10** was extremely susceptible to nucleophilic attack of the enolate generated from **10** itself.[17] Consequently, we decided to mask the highly reactive enone system of **10** in the form of the bromo ether **13** during the aldol coupling. Toward this end, as shown in Scheme 2, **10** was converted to **13** in 63% overall yield via a three-step sequence involving Diels–Alder reaction with cyclopentadiene in the presence of diethylaluminum chloride,[18] deprotection of the TBDMS group in the *endo*-adduct **11**, and bromo etherification of the resulting alcohol **12** with *N*-bromosuccinimide (NBS).[19] We were delighted to find that the crucial coupling of **13** with benzaldehyde under standard conditions [$LiN(TMS)_2$ (2.5 equiv.), THF, −78°C] proceeded smoothly with concomitant formation of a cyclopropane ring, affording a remarkable yield (98%) of the coupling product **14** as an almost inseparable mixture of the epimeric alcohols (ca. 6:1 by 500 MHz ^1H NMR). Removal of the hydroxy group in **14** was



Scheme 2. Synthesis of the model compound **2** (a) Cyclopentadiene, Et_2AlCl, CH_2Cl_2, −78→0°C, 98%; (b) TBAF, THF, 0°C, 75%; (c) NBS, CH_2Cl_2, 0°C, 86%; (d) $LiN(TMS)_2$, THF, −78°C; benzaldehyde, −78°C, 98%; (e) phenyl chlorothionoformate, DMAP, MeCN, rt, 92%; (f) *n*-Bu_3SnH, AIBN, toluene, 110°C, 79%; (g) TMSI, CCl_4, −10°C, 89%; (h) Zn, AcOH, MeOH, 60°C, 91%; (i) Ph_2O, reflux, 93%; (j) MsCl, pyridine, DMAP, CH_2Cl_2, 0°C→rt, 89%; (k) TFA, H_2O, 0°C, 85%; (l) 0.2 M NaOH, Et_2O, 0°C, 90%

effected by using Robins' modification[20] of the Barton method. Thus, treatment of **14** with phenyl thionochloroformate in acetonitrile in the presence of 4-dimethylaminopyridine (DMAP) provided the corresponding phenoxythionocarbonyl ester **15** (92%), which was then allowed to react with tri-*n*-butyltinhydride and a catalytic amount of 2,2-azobisisobutyronitrile (AIBN) in toluene at 110°C, furnishing the desired deoxygenated product **16**[21,22] in 79% yield.

Having introduced the requisite benzyl substituent with the correct stereochemistry at the C-6 position, we then focused our attention on regeneration of the cyclohexenone olefin moiety. After regioselective cleavage of the cyclopropane ring in **16** by reaction with iodotrimethylsilane (TMSI)[23] (89%), the resulting γ-iodo ketone **17** was effectively converted to the requisite cyclohexenone **19** by applying the conditions of Ogasawara.[19] Thus, **17** was treated with zinc powder in methanol containing acetic acid to give the *endo*-alcohol **18** (91%), which was then subjected to a retro-Diels–Alder reaction[19] by thermolysis at reflux in diphenyl ether, providing **19** in 93% yield. The final phase remaining to complete the synthesis of **2** was the critical epoxide ring formation utilizing the two oxygen functionalities present at the C-4 and C-5 positions in **19**. Mesylation of the hydroxy group in **19** under the standard conditions followed by acid hydrolysis of the acetonide moiety in the mesylate **20** afforded the corresponding diol **21** in 76% yield for the two steps. Finally, brief exposure of **21** to aqueous sodium hydroxide in ether at 0°C led to the formation of the target model compound **2**[24] in 90% yield.

In summary, we have succeeded in developing a facile synthetic pathway to (4*S*,5*S*,6*S*)-6-benzyl-4,5-epoxy-6-hydroxy-2-cyclohexen-1-one (**2**) which is the first entry to the highly functionalized cyclohexenone moiety of scyphostatin (**1**). The explored synthetic method features the masking of the highly reactive enone system in **10** in the form of the bromo ether **13**, the aldol coupling of **13** with benzaldehyde to construct the requisite asymmetric quaternary carbon center at the C-6 position, and the final epoxide ring formation as the key steps. Based on this strategy, work on the total synthesis of **1** is in progress and will be reported shortly.

Acknowledgements

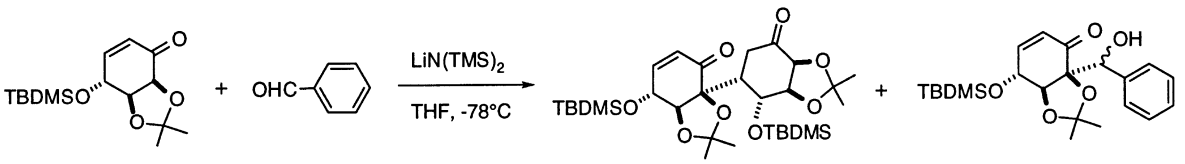
We are grateful to Drs. H. Kogen and T. Ogita, Sankyo Co., Ltd., for many valuable suggestions and encouragement.

References

1. Tanaka, M.; Nara, F.; Suzuki-Konagai, K.; Hosoya, T.; Ogita, T. *J. Am. Chem. Soc.* **1997**, *119*, 7871–7872.
2. Nara, F.; Tanaka, M.; Hosoya, T.; Suzuki-Konagai, K.; Ogita, T. *J. Antibiot.* **1999**, *52*, 525–530.
3. Nara, F.; Tanaka, M.; Masuda-Inoue, S.; Yamamoto, Y.; Doi-Yoshioka, H.; Suzuki-Konagai, K.; Kumakura, S.; Ogita, T. *J. Antibiot.* **1999**, *52*, 531–535.
4. It is reported that scyphostatin (**1**) exhibits N-SMase and acidic SMase (A-SMase) with IC_{50} values of 1.0 and 49.3 μM, respectively.[1–3] This natural product is the most potent of the few known small molecule inhibitors for N-SMase.
5. Ceramide, the primary sphingomyelin catabolite, 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. 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*, 1532–1568.
6. This initial structure elucidation[1] only determined the relative and absolute stereochemistry of the cyclohexenone moiety in **1**. Quite recently, the Sankyo group elucidated and reported the relative and absolute configurations of

the three stereocenters within the C-20 unsaturated fatty acid moiety by chemical degradation of **1** followed by extensive chemical correlation to the known chiral compounds.[7] Subsequently, Hoye et al. disclosed the enantioselective synthesis of the C-20 unsaturated fatty acid moiety, leading to alternative proof of its stereostructure including absolute configuration.[8]

7. Saito, S.; Tanaka, N.; Fujimoto, K.; Kogen, H. *Org. Lett.* **2000**, *2*, 505–506.
8. Hoye, T. R.; Tennakoon, M. A. *Org. Lett.* **2000**, *2*, 1481–1483.
9. Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443–6458 and references cited therein.
10. The NOESY experiment of **6b** supported that the cyclohexane ring adopts a boat-form which places the hydroxy group in an axial position; this conformation would facilitate E2 elimination leading to the formation of **7**.
11. The NOESY experiment of **6a** indicated that the cyclohexane ring takes a boat-form and the hydroxy group is equatorial orientation; this conformation may preclude any possibility of E2 elimination.
12. Mitsunobu, O. *Synthesis* **1981**, 1–28.
13. The stereochemistry of the newly produced epoxide ring in **8** was determined by an NOE experiment.
14. Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1973**, *38*, 2697–2699.
15. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
16. Compound **10**: Colorless prisms; mp 55–56°C; $[\alpha]_D^{20}$ −84.7° (*c* 1.02, $CHCl_3$); IR (KBr): 3545, 3368, 2990, 2934, 2859, 1696, 1464, 1383, 1252, 1167, 1076, 1005, 891, 839, 779, 727, 669, 517 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.14 (3H, s), 0.17 (3H, s), 0.92 (9H, s), 1.40 (3H, s), 1.43 (3H, s), 4.39–4.42 (1H, m), 4.44 (1H, d, J=5.9 Hz), 4.52–4.55 (1H, m), 6.08 (1H, d, J=10.3 Hz), 6.76 (1H, ddd, J=0.9, 3.8, 10.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 194.53, 148.47, 127.87, 110.17, 79.64, 74.36, 67.07, 27.43, 25.88, 25.70 (three carbons), 18.08, −4.73, −4.74; EIMS *m*/*z*: 298 (M^+), 283 [$(M-Me)^+$].
17. Reaction of the enolate of **10**, generated by treatment with $LiN(TMS)_2$, with benzaldehyde in THF at −78°C resulted in the predominant formation of the dimerized product **i** (46%) along with a small amount of the desired coupling product **ii** (12%).



10 **i** **ii**

18. It is noteworthy that this Diels–Alder reaction proceeded smoothly in a completely diastereofacial- and *endo*-selective manner to give the corresponding adduct **11** as a single isomer in almost quantitative yield (98%).
19. Ogasawara, K. *J. Synth. Org. Chem. Jpn.* **1999**, 57, 957–968 and references cited therein.
20. Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059–4065.
21. Compound **16**: Colorless prisms; mp 103–104.5°C; $[\alpha]_D^{20}$ −69.6° (*c* 0.97, $CHCl_3$); IR (KBr): 2986, 2934, 1711, 1494, 1454, 1381, 1296, 1238, 1167, 1062, 939, 877, 831, 767, 702, 513 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.91 (3H, s), 1.36 (3H, s), 1.67 (1H, d, J=1.4, 6.4 Hz), 1.79 (1H, d, J=11.0 Hz), 1.85 (1H, d, J=11.0 Hz), 2.33 (1H, d, J=6.4 Hz), 2.46 (1H, s), 2.90 (1H, t, J=2.3 Hz), 2.99 (1H, d, J=13.8 Hz), 3.22 (1H, d, J=13.8 Hz), 4.38 (1H, d, J=3.0 Hz), 4.53 (1H, t, J=2.8 Hz), 4.57 (1H, t, J=2.3 Hz), 7.20–7.35 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.48, 135.20, 131.90 (two carbons), 127.88 (two carbons), 126.96, 109.22, 85.73, 83.20, 78.54, 76.83, 46.16, 43.29, 41.20, 31.91, 31.85, 30.30, 28.12, 26.32, 20.55; EIMS *m*/*z*: 338 (M^+), 280 [$(M-Me_2CO)^+$], 247 [$(M-PhCH_2)^+$].
22. At this stage, the stereochemistry at the newly formed C-6 position of the aldol coupling product **14** was confirmed by NOE experiment of **16**; thus, NOE interactions between the signals due to the benzylic methylene protons and the C-5 proton were observed.
23. Miller, R. D.; Mckean, D. R. *J. Org. Chem.* **1981**, *46*, 2412–2414.
24. Compound **2**: Colorless caramel; $[\alpha]_D^{20}$ +45.6° (*c* 0.80, $CHCl_3$); IR (neat): 3481, 3030, 2920, 1690, 1495, 1454, 1379, 1254, 1238, 1196, 1146, 1094, 958, 860, 843, 750, 704, 627, 579, 544, 503 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.93 (1H, d, J=13.6 Hz), 3.01 (1H, d, J=13.6 Hz), 3.60 (1H, dt, J=1.6, 3.9 Hz), 3.65 (1H, s), 3.77 (1H, d, J=3.9 Hz), 6.16 (1H, dd, J=1.6, 9.9 Hz), 7.09–7.15 (3H, m), 7.22–7.32 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.48, 145.14, 133.55, 130.31 (two carbons), 130.15, 128.37 (two carbons), 127.33, 77.66, 56.01, 47.94, 44.37; EIMS *m*/*z*: 216 (M^+), 199 [$(M-OH)^+$].