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Concise asymmetric synthesis of a model compound, (4*S*,5*S*,6*S*)-6-(2,2-dimethoxy)ethyl-4,5-epoxy-6-hydroxy-2-cyclohexenone, for the cyclohexenone core of scyphostatin

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Abstract—The optically pure cyclohexenone core of scyphostatin (**1**) has been synthesized from cyclohexadiene acetal **5**. The crucial aspects of our synthesis include the intramolecular bromoetherification of **5**, the SeO_2 oxidation of **7**, and the enone formation of **13** to **4** in the final step. © 2002 Elsevier Science Ltd. All rights reserved.

Scyphostatin (**1**), isolated from *Dasyscyphus mollissimus* SANK-13892 in 1997, possesses potent inhibitory activity against a neutral sphingomyelinase (N-SMase).[1] Its promising biological profile, still now the most powerful among the few known inhibitors of the enzyme, makes it a lead compound for the treatment of inflammation and autoimmune diseases, because N-SMase promotes the transformation of sphingomyelin to ceramide which plays an important role in these disease pathways.[2] Its structure consists of the highly functionalized (oxygenated) cyclohexenone unit and a side chain. Although its attractive structure in addition to its biological profile makes it a very attractive synthetic target, only five reports concerning the synthetic studies of scyphostatin analogues have been published so far.[3] Gurjar and Hotha synthesized the dihydroxylated cyclohexenone **2**,[3a] and Katoh and Izuhara prepared the benzyl analogue **3a** and more recently, the potential precursor **3b**.[3b–d] They were prepared in the optically active form from natural products, **2** from glucose and **3a**,**b** from quinic acid. Their methodologies still require many reaction steps. Although quite recently, Runcie and Taylor reported other analogues **3c–f** prepared in a concise way, they were prepared in racemic forms.[3e] Therefore, a concise method for obtaining the cyclohexenone unit of **1** in an enantioselective manner is strongly desired.

We present here our concise asymmetric synthesis of (4*S*,5*S*,6*S*) - 6 - (2,2 - dimethoxy)ethyl - 4,5 - epoxy - 6-hydroxy-2-cyclohexenone **4**, a model compound for the cyclohexenone core of **1** (Fig. 1).

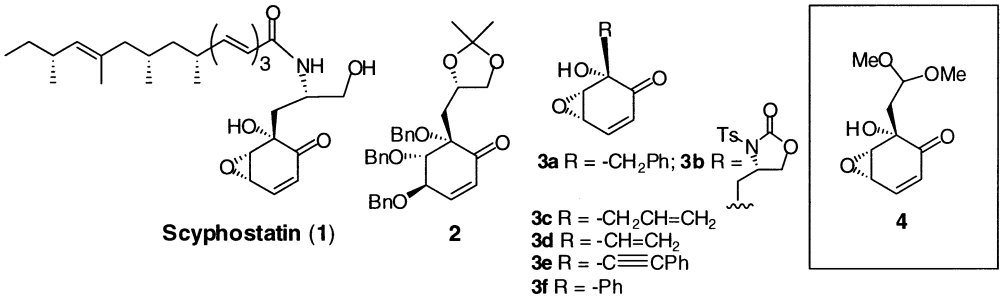

Figure 1.

Keywords: asymmetric synthesis; model compound of cyclohexenone core of scyphostatin; cyclohexadiene acetal; chiral hydrobenzoin.
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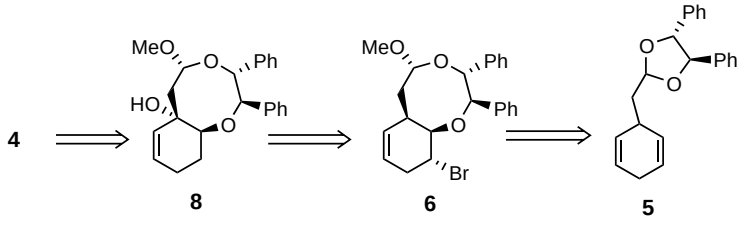
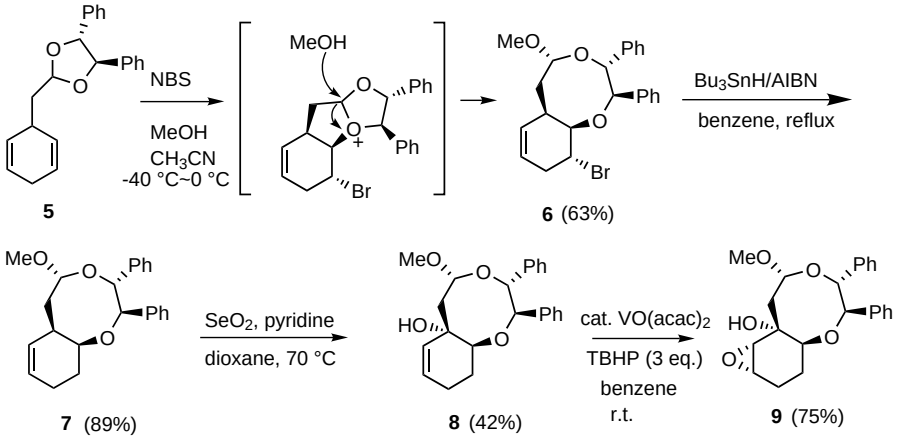
Our synthetic strategy is shown in Scheme 1. Since the selective intramolecular bromoetherification of ene acetals have been achieved by us,[4] the same reaction of cyclohexadiene acetal **5** would selectively proceed to give the cyclohexene acetal **6**. The conformation of the cyclohexene ring of **6** is fixed by the eight-membered acetal. If the SeO_2 oxidation would stereoselectively proceed to give **8** with an α-*tert*-alcohol after reduction of the bromo atom of **6**, the epoxidation of the double bond of **8** would then stereoselectively occur to give the α-epoxide, and the further transformations would afford **4**, the cyclohexenone core of **1**.

According to the synthetic plan in Scheme 1, the intramolecular bromoetherification of the cyclohexadiene acetal **5**, prepared from cyclohexa-2,5-dienylethanal diethylacetal[5] and (*R*,*R*)-hydrobenzoin,[6] in the presence of MeOH was accomplished to stereoselectively give the bromo ene acetal **6** in 63% yield. The stereochemistry of **6** was determined by an NOE experiment and the X-ray analysis of **7** obtained by the radical reduction of **6**. The *trans*-relationship between the bromo atom and ether oxygen atom in **6** was determined by a ^1H NMR spectrum showing a large coupling constant (9.0 Hz) between Ha and Hb and the mechanistic consideration[7] (Fig. 2). The SeO_2 oxidation of **7** gave the hydroxylated compound **8** as a single isomer in 42% yield (20% of **7** was recovered. The yield based on the consumed **7** is 52.4%.). The stereochemistry of **8** was determined as follows. Epoxidation of **8** with vanadium(IV) oxide acetylacetonate ($VO(acac)_2$) and *tert*-butylhydroperoxide (TBHP)[8] gave the *cis*-epoxy alcohol **9** as a single isomer (Scheme 2). The stereochemistry of **9** was determined by an NOE experiment. Namely, the relation between the epoxide and the *tert*-alcohol must be *cis* from the many examples of the stereoselective Sharpless epoxidation.[8] The observation of the presence of NOE



Scheme 1.



Scheme 2.

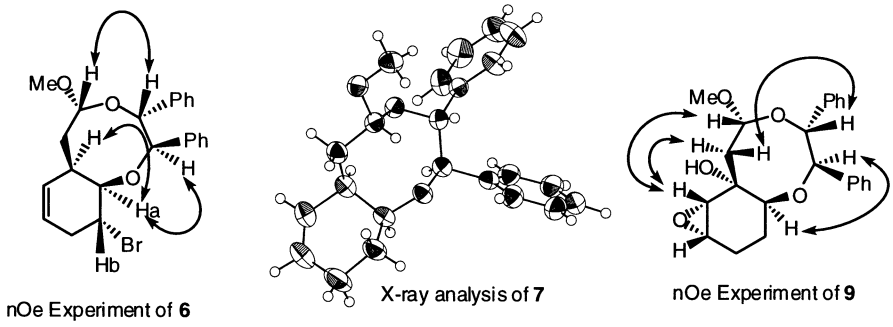
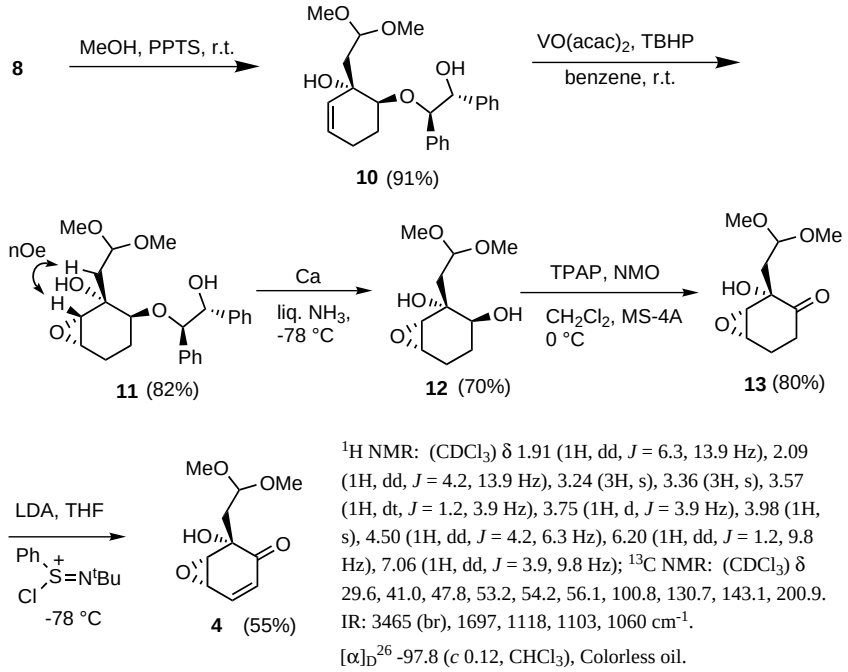


Figure 2.



^{1}H NMR: ($CDCl_3$) δ 1.91 (1H, dd, J = 6.3, 13.9 Hz), 2.09 (1H, dd, J = 4.2, 13.9 Hz), 3.24 (3H, s), 3.36 (3H, s), 3.57 (1H, dt, J = 1.2, 3.9 Hz), 3.75 (1H, d, J = 3.9 Hz), 3.98 (1H, s), 4.50 (1H, dd, J = 4.2, 6.3 Hz), 6.20 (1H, dd, J = 1.2, 9.8 Hz), 7.06 (1H, dd, J = 3.9, 9.8 Hz); ^{13}C NMR: ($CDCl_3$) δ 29.6, 41.0, 47.8, 53.2, 54.2, 56.1, 100.8, 130.7, 143.1, 200.9. IR: 3465 (br), 1697, 1118, 1103, 1060 cm^{-1}.
$[\alpha]_D^{26}$ -97.8 (c 0.12, $CHCl_3$), Colorless oil.

Scheme 3.

between the hydrogen atom on the acetal carbon and the hydrogen atom on the oxirane ring proved the stereochemistry of the epoxy ring to be α (Fig. 2), and the results revealed the stereochemistry of **8**. As we expected from the conformation of **7**, the stereochemistry of the *tert*-alcohol of **8** was α.

Although opening of the acetal ring of **9** by cat. PPTS in MeOH gave a complex mixture and the Birch reduction of **9** showed fruitless results, compound **8** afforded the dimethyl acetal **10** under the same acidic methanolysis. The epoxidation of **10** with $VO(acac)_2$ and TBHP gave the epoxy alcohol **11** as a single isomer, whose stereochemistry was determined by the presence of an NOE between the hydrogen atom on the epoxide and the hydrogen atom of the side chain. The Birch reduction of **11** with Ca metal in liq. NH_3 afforded the dihydroxy epoxy acetal **12**. The oxidation of the secondary alcohol of **12** with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO) afforded the epoxy ketone **13**.[9] The LDA treatment of **13** and the reaction with *N*-*tert*-butylphenylsulfinimidoyl chloride gave the enone **4** in 55% yield[10] (Scheme 3).

The characteristic points of our synthesis are that the acetal works not only as a chiral auxiliary for the discrimination of two olefins and the protective group of alcohol unit but also as the template for the stereoselective SeO_2 oxidation. Every reaction proceeds in a stereoselective manner. We are now studying the total synthesis of scyphostatin.

Acknowledgements

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