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A Short and Efficient Route to Novel Scyphostatin Analogues

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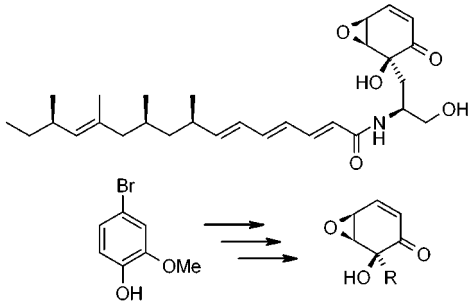
ABSTRACT



Several novel scyphostatin analogues have been prepared in up to 18% yield over five steps from commercially available 4-bromoguaiacol, utilizing an organometallic addition to afford the desired *syn*-hydroxy-epoxides.

Scyphostatin (**1**) was first isolated in 1997 from a mycelial extract of the microorganism *Dasyscyphus mollissimus* SANK-13892 by Ogita et al.[1] It was found to exhibit selective inhibitory activity against the enzyme neutral sphingomyelinase (N-SMase) and to date remains the most potent of the few known inhibitors of this enzyme. It is believed that inhibition of N-SMase may lead to treatments for inflammatory and autoimmune disorders because ceramide, a product of sphingomyelin hydrolysis by N-SMase, plays a key role in these disease pathways.[2]

The structure of scyphostatin (**1**, Figure 1) was determined by extensive spectroscopic and derivatization studies, although the stereochemistry of the side chain methyl groups was not initially assigned. Subsequent degradation studies established the absolute configuration of scyphostatin and revealed the 14′*R*,10′*S*,8′*R* configuration of the side chain.[3] The side chain unit was successfully prepared by total synthesis and its stereochemistry unambiguously confirmed.[4] The highly functionalized epoxycyclohexenone nucleus of scyphostatin is noteworthy from a structural and synthetic viewpoint. Several papers have recently been published

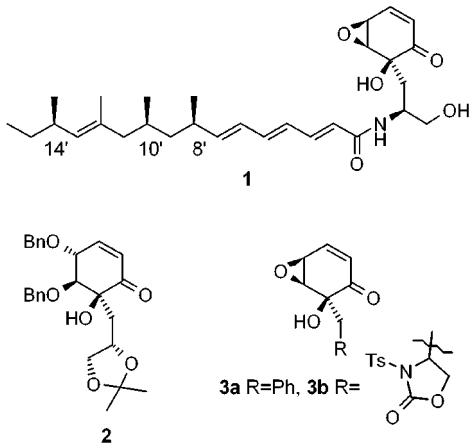


Figure 1. Structure of scyphostatin (**1**) and cyclohexenone analogues **2** and **3**.

(1) Tanaka, M.; Nara, F.; Suzuki-Konagai, K.; Hosoya, T.; Ogita, T. *J. Am. Chem. Soc.* **1997**, *119*, 7871−7872.
(2) Kolesnick, R.; Golde, D. W. *Cell* **1994**, *77*, 325−328. For recent advances, see: Arnez, C.; Thutewohl, M.; Block, O.; Waldmann, H.; Altenbach, H.-J.; Giannis, A. *Chembiochem* **2001**, 141−143.
(3) Saito, S.; Tanaka, N.; Fujimoto, K.; Kogen, H. *Org. Lett.* **2000**, *2*, 505−506.
(4) Hoye, T. R.; Tennakoon, M. A. *Org. Lett.* **2000**, *2*, 1481−1483.

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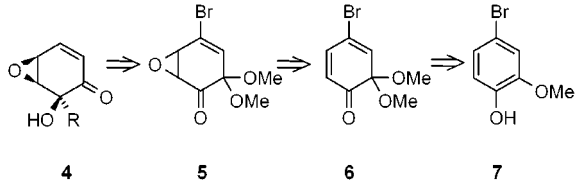
concerning the synthesis of scyphostatin analogues, but as yet, the final target has remained elusive. Gurjar and Hotha[5] reported a preparation of dihydroxylated cyclohexenone **2** starting from glucose, and Katoh and Izuhara[6] used quinic acid to prepare benzyl analogue **3a**. More recently,[7] this pathway was extended to the preparation of the potential scyphostatin precursor **3b**.

As part of our ongoing research into the preparation of epoxycyclohexenone-based natural products,[8] we were particularly interested in a total synthesis of scyphostatin. We envisaged that the highly functionalized nature of the cyclohexenone fragment **4** would provide a suitable challenge to the organometallic methodology developed in our manumycin synthesis[8b] and felt that the unsaturated side chain could be prepared using our recently developed in situ oxidation−Wittig procedure.[9]

In view of the interest in scyphostatin analogues, we first set out to establish an efficient racemic route to cyclohexenone analogues of scyphostatin. This Letter outlines our progress. The approach is shown in retrosynthetic form in Scheme 1.

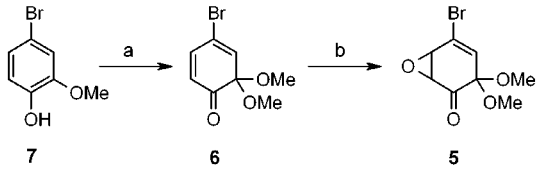
Scheme 1



The key intermediate is bromide **5** which, on the basis of our manumycin studies,[8b] we anticipated would undergo stereoselective epoxide-directed organometallic addition, with subsequent functional group interconversion giving the required target **4**. We intended to prepare **5** by epoxidation of the known[10] bromide **6**, which we felt should be readily available by oxidation of 4-bromoguaiacol (**7**). We chose the bromo-substituted dienone **6** since the corresponding unsubstituted compound is known to undergo facile dimerization by a Diels−Alder pathway.[11]

Starting from commercially available 4-bromoguaiacol (**7**), oxidation using iodosobenzene diacetate in the presence of methanol gave rise to bromocyclohexa-2,4-dienone **6** in excellent yield. The presence of the bromide atom does indeed reduce the propensity for dimerization, although some dimerization is observed on storage. Compound **6** was thus prepared and immediately subjected to epoxidation under conditions developed in our laboratory[12] to give **5** in an excellent 81% yield. Bromo-epoxide **5** could be stored in the freezer under nitrogen for 4−5 weeks without noticeable decomposition (Scheme 2).

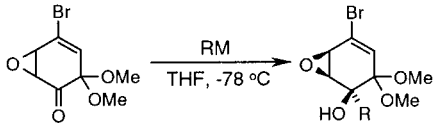
Scheme 2[a]

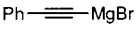


[a] Reagents and conditions: (a) iodosobenzene diacetate, CH_3OH, 0 °C, 90−98%; (b) *tert*-butylhydroperoxide, 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine, 0 °C, 81%.

To demonstrate the generality of our approach, a range of organometallic reagents was employed in the key addition step (Table 1).

Table 1. Organometallic Addition to Epoxyketone **5**



entry	RM	product	yield / %
1		**8a**	54
2		**8b**	54
3		**8c**	74
4	Ph−MgBr	**8d**	51
5	Ph−Li	**8d**	29

The additions proceeded smoothly,[13] giving adducts **8a**−**d** as single diastereomers in modest to good yields,[14] with polar decomposition products making up the material balance. The predicted *syn*-stereochemistry was confirmed for the allyl adduct **8a** by X-ray crystallographic analysis (Figure 2).[15] Elaboration of the allyl side chain could provide access to scyphostatin itself.

With these results in hand, the remaining steps in our proposed route involved reductive debromination of vinyl bromides **8a**−**d** and ketal hydrolysis (Scheme 3).

(5) Gurjar, M. K.; Hotha, S. *Heterocycles* **2000**, *53*, 1885−1889.
(6) Katoh, T.; Izuhara, T. *Tetrahedron Lett.* **2000**, *41*, 7651−7655.
(7) Katoh, T.; Izuhara, T. *Org. Lett.* **2001**, *3*, 1653−1656.
(8) For examples, see: (a) McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1385−1393. (b) Alcaraz, L.; Macdonald, G.; Ragot, J.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1999**, *55*, 3707−3716.
(9) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 3815−3818.
(10) Mitchell, A. S.; Russell, R. A. *Tetrahedron* **1997**, *53*, 4387−4410.
(11) Gao, S.-Y.; Lin, Y.-L.;. Rao, P. D.; Liao, C.-C. *Synlett* **2000**, 421−423 and references therein.
(12) Genski, T.; Macdonald, G.; Wei, X.; Lewis, N.; Taylor, R. J. K. *Synlett* **1999**, 795−797.
(13) When ethyl- and cyclopentylmagnesium bromide were employed, the product (possibly the corresponding secondary alcohol resulting from hydride addition) was exceptionally unstable and decomposed violently upon concentration.
(14) All new compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy and HRMS/microanalysis.
(15) Further confirmation of the *syn*-stereochemistry of the organometallic adducts was obtained by X-ray analysis of **10d**.

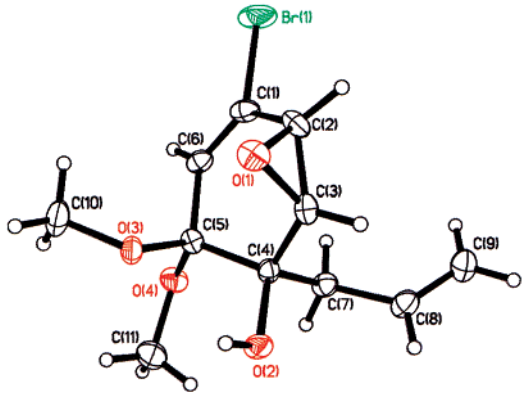
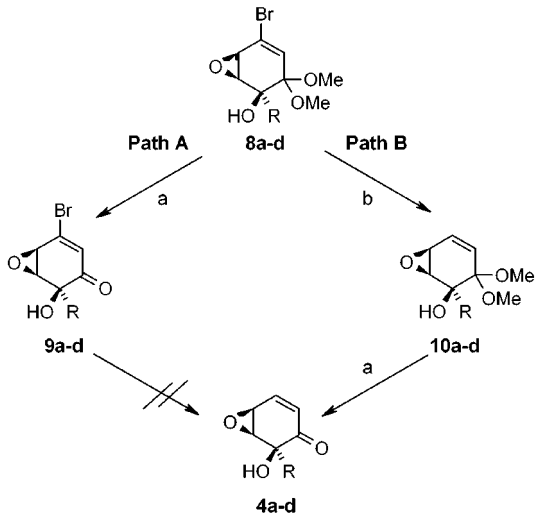


Figure 2. ORTEP drawing of **8a** (50% probability thermal ellipsoids; CCDC 165946).

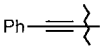
Initial attempts focused on ketal hydrolysis followed by debromination (path A). However, while ketal hydrolysis proceeded smoothly using Montmorillonite K10[16] (typically in yields of 65−70%), the resulting vinyl bromides **9a−d** proved almost completely resistant to reductive debromination, giving very low yields of impure products. Therefore, we turned our attention to initial reduction of vinyl bromides **8a−d** using tributyltin hydride and subsequent ketal hydrolysis (path B). Dilute solutions of compounds **8a−d** in THF at reflux containing catalytic AIBN were subjected to a very slow addition of tributyltin hydride (typically addition over 6 h). This approach, while still unoptimized, proved markedly more successful and the results are summarized in Table 2.

Scheme 3[a]



[a] Reagents and conditions: (a) Montmorillonite K10, CH_2Cl_2, rt; (b) Bu_3SnH, AIBN, THF, reflux.

Table 2. Reduction of Vinyl Bromides **8a−d** Followed by Ketal Hydrolysis

entry	R	product yield %		product yield %	
1		**10a**	62	**4a**	53
2		**10b**	75	**4b**	55
3		**10c**	55	**4c**	40
4		**10d**	67	**4d**	60

As can be seen from Table 2, reduction of vinyl bromides **8a−d** under standard conditions gave rise to adducts **10a−d** in good to excellent yields. Subsequent ketal hydrolysis proceeded smoothly to furnish a range of scyphostatin analogues (**4a−d**) with spectral data in accordance with that of the natural product.[17]

In conclusion, we have developed a novel and extremely concise route toward the highly functionalized cyclohexenone nucleus of scyphostatin (**1**) utilizing organometallic addition reactions as the key step. We have shown our synthesis to be general, producing a range of novel analogues of scyphostatin. We are currently working toward an asymmetric version of our methodology as well as a total synthesis of scyphostatin itself.

Acknowledgment. We thank the University of York for financial support. Miss Phillipa Timmins is gratefully acknowledged for assistance with X-ray crystallography as is Dr. T. A. Dransfield for mass spectrometry services.

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

OL0164132

(16) Gautier, E. C. L.; Graham, A. E.; McKillop, A.; Standen, S. P.; Taylor, R. J. K. *Tetrahedron Lett.* **1997**, *38*, 1881−1884.

(17) ^{13}C NMR data for cyclohexenone nucleus of scyphostatin:[1] δ_C (CD_3OD, 360 MHz) 49.8, 58.7, 78.0, 132.5, 146.6, 201.0. For compound **4a**: δ_C (CD_3OD, 270 MHz) 48.4, 58.0, 78.1, 132.4, 146.7, 199.6.