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Short and Efficient Route to the Fully Functionalized Polar Core of Scyphostatin

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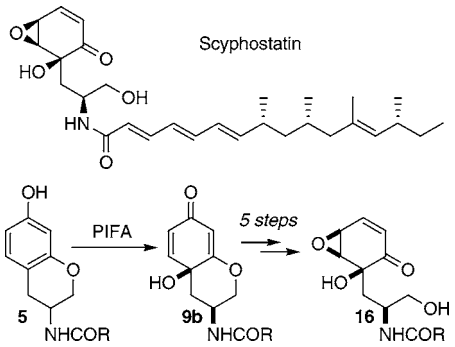
ABSTRACT



Diastereoselective oxidative dearomatization of benzopyran 5 to the corresponding *p*-quinol 9b allows a fast, efficient, and versatile entry to scyphostatin's polar epoxycyclohexenone moiety as demonstrated by the preparation of its palmitoyl analogue 16 (R = $(CH_2)_{14}CH_3$).

Neutral sphingomyelinase (N-SMase) has emerged as a promising pharmacological target for the treatment of inflammation and immunological and neurological disorders.[1] Among the many low molecular weight N-SMase inhibitors of natural[2] or synthetic origin[3] known to date, scyphostatin (**1**, Scheme 1) stands out as the most potent and specific one. This natural product was isolated in 1997 by Ogita and co-workers from a culture broth of *Dasyscyphus mollisimus* SANK-13892 and features a novel, aminopropanol-substituted, epoxycyclohexenone polar core and a polyunsaturated fatty acid moiety.[4] Inhibitory activity was mainly attributed to the polar moiety of the molecule, while the fatty side chain was blamed for its short half-life in the solid state, even when stored at −20 °C. Interestingly and in order to elucidate the

(1) Waschologwski, V.; Giannis, A. *Drug News Perspect.* **2001**, *14*, 581−590.

(2) (a) Uchida, R.; Tomoda, H.; Dong, Y.; Omura, S. *J. Antibiot.* **1999**, *52*, 572−574. (b) Tanaka, M.; Nara, F.; Yamasato, Y.; Masuda-Inoue, S.; Doi-Yoshioka, H.; Kumakura, S.; Enokita, R.; Ogita, T. *J. Antibiot.* **1999**, *52*, 670−673. (c) Tanaka, M.; Nara, F.; Yamasato, Y.; Ono, Y.; Ogita, T. *J. Antibiot.* **1999**, *52*, 827−830. (d) Arenz, C.; Thutewohl, M.; Block, O.; Waldmann, H.; Altenbach, H.-J.; Giannis, A. *ChemBioChem* **2001**, *2*, 141−143. (e) Uchida, R.; Tomoda, H.; Arai, M.; Omura, S. *J. Antibiot.* **2001**, *54*, 882−889.

(3) (a) Hakogi, T.; Monden, Y.; Iwama, S.; Katsumura, S. *Org. Lett.* **2000**, *2*, 2627−2630. (b) Arenz, C.; Giannis, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1440−1442. (c) Arenz, C.; Gartner, M.; Waschologwski, V.; Giannis, A. *Bioorg. Med. Chem.* **2001**, *9*, 2901−2904. (d) Arenz, C.; Giannis, A. *Eur. J. Org. Chem.* **2001**, 137−140. (e) Yokomatsu, T.; Takechi, H.; Akiyama, T.; Shibuya, S.; Kominato, T.; Soeda, S.; Shimeno, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1277−1280. (f) Hakogi, T.; Monden, Y.; Taichi, M.; Iwama, S.; Fujii, S.; Ikeda, K.; Katsumura, S. *J. Org. Chem.* **2002**, *67*, 4839−4846. (g) Lindsey, C. C.; Gomez-Diaz, C.; Villalba, J. M.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 4559−4565. (h) Pitsinos, E. N.; Waschologwski, V.; Karaliota, S.; Rigou, C.; Couladouros, E. A.; Giannis, A. *ChemBioChem* **2003**, *4*, 1223−1225. (i) Yokomatsu, T.; Murano, T.; Akiyama, T.; Koizumi, J.; Shibuya, S.; Tsuji, Y.; Soeda, S.; Shimeno, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 229−236. (j) Taguchi, M.; Sugimoto, K.; Goda, K.-i.; Akama, T.; Yamamoto, K.; Suzuki, T.; Tomishima, Y.; Nishiguchi, M.; Arai, K.; Takahashi, K.; Kobori, T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1963−1966. (k) Taguchi, M.; Goda, K.-i.; Sugimoto, K.; Akama, T.; Yamamoto, K.; Suzuki, T.; Tomishima, Y.; Nishiguchi, M.; Arai, K.; Takahashi, K.; Kobori, T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3681−3684. (l) Deigner, H.-P. (Biofrontera Pharmaceuticals GmbH). U.S. Patent US6790992B2, 2004.

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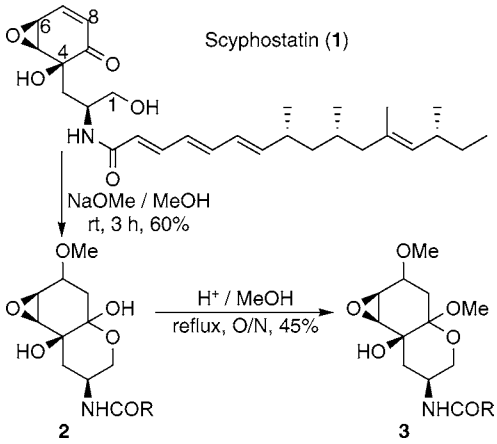
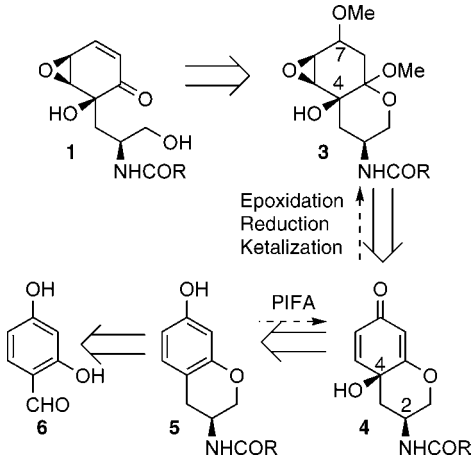
Scheme 1. Transformation of Scyphostatin (**1**) to Ketal **3** by Ogita and Co-workers



Scheme 2. Retrosynthetic Plan for Scyphostatin's Polar Core[a]



[a] PIFA = [bis(trifluoroacetoxy)iodo]benzene.

absolute stereochemistry of the hydrophilic head moiety, Ogita and co-workers have succeeded in converting scyphostatin to hemiketal **2** and ketal **3**.[4a]

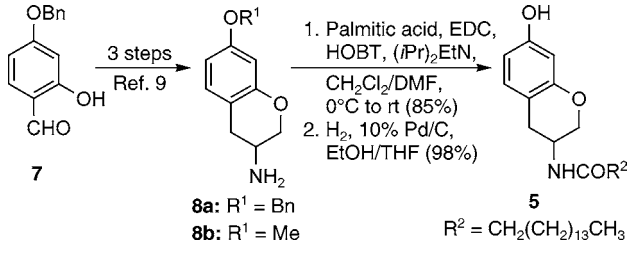
In light of its significant biological activity and structural novelty, it is not surprising that scyphostatin, and in particular its polar moiety,[5] has attracted considerable attention either as a target for synthetic studies[6] or as a prototype for the design of novel N-SMase inhibitors.[3b−d,h] Recently, an elegant total synthesis of (+)-scyphostatin has been disclosed by Katoh and co-workers.[6k] However, more than 20 synthetic steps were required to establish the fully functionalized core starting from D-arabinose. This prompted us to disclose herein an alternative, shorter approach to the fully functionalized polar core of scyphostatin.

Key to the conception of our retrosynthetic plan was the realization that the transformations of scyphostatin to hemiketal **2** and ketal **3** are in principle reversible. Thus, ketal **3** (Scheme 2) could serve as an advanced key intermediate. The introduction of additional oxygenation at C7 led us to envision *p*-quinol **4** as a suitable precursor.[7] We anticipated that the two double bonds present in **4**, by merit of their different conjugation, would exhibit different reactivity, thus allowing regioselective epoxidation. Concerning the stereoselectivity of this transformation, we planned to exploit the directing effect of the tertiary hydroxyl group at C4. This left us with the challenge of controlling the stereochemistry of **4**, hopefully by diastereoselective oxidative dearomatization[8] of benzopyran **5**. Such benzopyranes can be easily prepared from 2,4-dihydroxybenzaldehyde (**6**).[9]

Thus, the required aminobenzopyrane **8a** (R^1 = Bn, Scheme 3) was easily prepared, in analogy with the known aminobenzopyrane **8b** (R^1 = Me),[9] in three steps and 61% overall yield from 4-benzyloxy-2-hydroxy-benzaldehyde (**7**).[10] To explore the feasibility of our strategy, we chose palmitic acid as a surrogate for the fatty side chain of scyphostatin and decided to utilize racemic aminobenzopyrane **8a**.[11] Hence, coupling of amine **8a** with palmitic acid and subsequent hydrogenolysis of the benzyl protective group furnished phenol **5** in 83% yield.

Attempted oxidation of this substrate, employing [bis(trifluoroacetoxy)iodo]benzene (PIFA) in wet acetonitrile,[12] was disappointing in that an almost equimolar, yet at least separable, mixture of diastereomeric quinols **9a** and **9b** was formed in 43% combined yield. The relative stereochemistry of the two isomers was initially assigned on the basis of the comparative analysis of their ^{1}H NMR and NOESY spectra.[13] Not satisfied with the observed lack of diastereoselectivity,

Scheme 3. Preparation of Phenol **5**

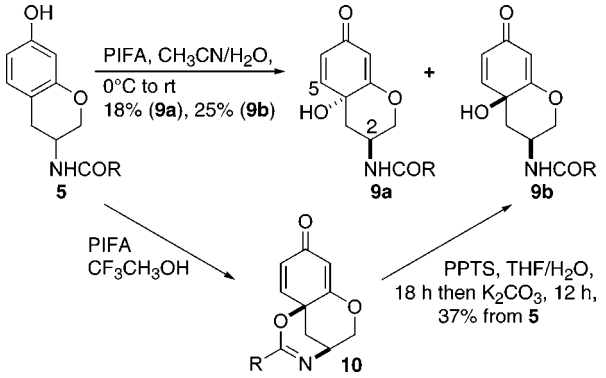


(4) (a) Tanaka, M.; Nara, F.; Suzuki-Konagai, K.; Hosoya, T.; Ogita, T. *J. Am. Chem. Soc.* **1997**, *119*, 7871−7872. (b) Nara, F.; Tanaka, M.; Hosoya, T.; Suzuki-Konagai, K.; Ogita, T. *J. Antibiot.* **1999**, *52*, 525−530. (c) Nara, F.; Tanaka, M.; Masuda-Inoue, S.; Yamasato, Y.; Doi-Yoshioka, H.; Suzuki-Konagai, K.; Kumakura, S.; Ogita, T. *J. Antibiot.* **1999**, *52*, 531−535. (d) Saito, S.; Tanaka, N.; Fujimoto, K.; Kogen, H. *Org. Lett.* **2000**, *2*, 505−506.

(5) For syntheses of the scyphostatin side chain, see: (a) Hoye, T. R.; Tennakoon, M. A. *Org. Lett.* **2000**, *2*, 1481−1483. (b) McAllister, G. D.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 2551−2554. (c) Tan, Z.; Negishi, E.-i. *Angew. Chem., Int. Ed.* **2004**, *43*, 2911−2914.

(6) (a) Izuhara, T.; Katoh, T. *Tetrahedron Lett.* **2000**, *41*, 7651−7656. (b) Gurjar, M. K.; Hotha, S. *Heterocycles* **2000**, *53*, 1885−1889. (c) Izuhara, T.; Katoh, T. *Org. Lett.* **2001**, *3*, 1653−1656. (d) Runcie, K. A.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 3237−3239. (e) Izuhara, T.; Yokota, W.; Inoue, M.; Katoh, T. *Heterocycles* **2002**, *56*, 553−560. (f) Takagi, R.; Miyanaga, W.; Tamura, Y.; Ohkata, K. *Chem. Commun.* **2002**, 2096−2097. (g) Fujioka, H.; Kotoku, N.; Sawama, Y.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **2002**, *43*, 4825−4828. (h) Eipert, M.; Maichle-Mossmer, C.; Maier, M. E. *Tetrahedron* **2003**, *59*, 7949−7960. (i) Murray, L. M.; O'Brien, P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 1943−1946. (j) Kenworthy, M. N.; McAllister, G. D.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 6661−6664. (k) Inoue, M.; Yokota, W.; Murugesh, M. G.; Izuhara, T.; Katoh, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 4207−4209.

Scheme 4. Diastereoselective Oxidative Dearomatization[a]

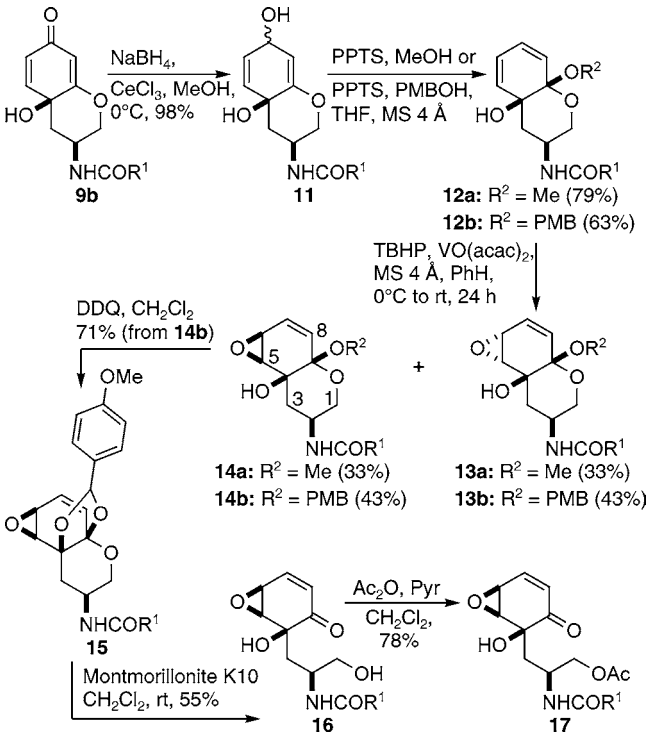


[a] R = $CH_2(CH_2)_{13}CH_3$.

we decided to investigate the use of 2,2,2-trifluoroethanol, a polar but not nucleophilic solvent,[12] and were rewarded by formation of **10**. Treatment with pyridinium *p*-toluenesulfonate (PPTS) in wet THF at ambient temperature for 18 h followed by addition of powdered K_2CO_3 achieved the hydrolysis of the oxazine ring of **10** to furnish quinol **9b** in 37% overall yield. Thus, a diastereoselective route to this key intermediate was secured, and at the same time our initial assignment of the relative stereochemistry at C4 was confirmed.

To our dismay, however, all attempts to introduce the epoxide ring at this stage were met with complete failure, making the question of the regio- and diastereoselectivity of this transformation irrelevant. Thus, we were forced to reconsider the timing of the planned transformations toward **3**. The issue of epoxide introduction was postponed, and we proceeded to reduce, employing Luche conditions, the keto functionality of **9b**.[14] Diol **11** (Scheme 5) was obtained in excellent yield as a 2:1 mixture of diastereomers, provided any acid treatment was avoided during its preparation and purification. The observed low diastereoselectivity was of

Scheme 5. Final Synthetic Steps to the Fully Functionalized Polar Core of Scyphostatin[a]



[a] R^1 = $CH_2(CH_2)_{13}CH_3$.

no consequence, since subsequent ketal formation was accompanied by dehydration. Thus, treatment of the mixture of diastereomers of diol **11** with PPTS in anhydrous methanol furnished ketal **12a** in 79% yield and as a sole diastereomer.

To achieve stereo- and regioselective epoxidation of diene **12a**, we resorted to the use of *tert*-butylhydroperoxide (TBHP) in the presence of catalytic amount of vanadyl acetylacetonate, a reagent combination known to be best suited for such transformations.[15a] Nonetheless, in our case, although the regioselectivity was excellent, the observed stereoselectivity was disappointingly low, and epoxides **13a** and **14a** were obtained in 1:1 ratio and in 66% combined yield.[15b,16] Even more alarming, however, was our failure to achieve final deprotection of epoxide **14a** or **13a** toward our target. A variety of ketal deprotection conditions were tested, but invariably epoxide ring opening was observed prior to ketal hydrolysis, if any.[17]

In an attempt to circumvent this obstacle, we decided to retrace our steps and replace methanol with 4-methoxy-

(7) (a) In the course of our work, the potential utility of *p*-quinol derivatives for the construction of scyphostatin's polar core has been postulated; see ref 6h and: Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383−1429. (b) For other quinol-based approaches to scyphostatin's core, see refs 3h and 6f.

(8) (a) Rama Rao, A. V.; Gurjar, M. K.; Sharma, P. A. *Tetrahedron Lett.* **1991**, *32*, 6613−6616. (b) McKillop, A.; McLaren, L.; Watson, R. J.; Taylor, R. J. K.; Lewis, N. *Tetrahedron Lett.* **1993**, *34*, 5519−5522. (c) Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649−1650. (d) Mejorado, L. H.; Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2004**, *6*, 1535−1538.

(9) Boyé, S.; Pfei, B.; Renard, P.; Rettori, M.-C.; Guillaumet, G.; Viaud, M.-C. *Bioorg. Med. Chem.* **1999**, *7*, 335−341 and refs therein.

(10) Mendelson, W. L.; Holmes, M.; Dougherty, J. *Synth. Comm.* **1996**, *26*, 593−601.

(11) Closely related aminobenzopyranes have been successfully resolved: Hammarberg, E.; Nordvall, G.; Leideborg, R.; Nylöf, M.; Hanson, S.; Johansson, L.; Thorberg, S.-O.; Tolf, B.-R.; Jerning, E.; Svantesson, G. T.; Mohell, N.; Ahlgren, C.; Westlind-Danielsson, A.; Csöregh, I.; Johansson, R. *J. Med. Chem.* **2000**, *43*, 2837−2850.

(12) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435−438.

(13) The following cross-peaks appear in the NOESY spectra: **12a** H-2, H-3eq; **12b** H-5, H-3eq and H-2, H-3ax. Furthermore, the amide proton signal of **12b** appears downfield (7.02 ppm) compared with that of **12a** (5.90 ppm), indicative of an intramolecular hydrogen bond.

(14) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678−11688.

(15) (a) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63−71. (b) For other examples where this methodology gave poor diastereoselectivity, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370 and references therein.

(16) The indicated relative stereochemistry was assigned to epoxide **14a** on the basis of analysis of its NOESY spectrum; cross-peak H-8, H-1ax indicated that the NHCOR moiety is axial, while cross-peaks H-5, H-3eq and H-5, H-3ax are in accordance with the indicated relative stereochemistry of the oxirane ring.

(17) For example, treatment with montmorillonite K 10 led solely to epoxide ring opening, while treatment with acidic (oxalic acid) silica led to concomitant epoxide ring opening and ketal hydrolysis.

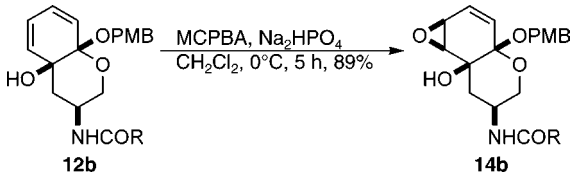
benzyl alcohol (PMBOH) as the nucleophile at the ketalization step. Thus, treatment of the mixture of diastereomers of diol **11** in dry THF with PPTS in the presence of 5 equiv of PMBOH and powdered activated 4 Å molecular sieves formed ketal **12b** in 63% yield as a single diastereomer. Subsequent epoxidation, in analogy to diene **12a**, furnished epoxides **13b** and **14b** as a 1:1 mixture of diastereomers and in 86% combined yield.[18] The formation of acetal **15**, upon treatment of ketal **14b** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), allowed assignment of the relative stereochemistry of ketal **12b** and paved the way for the final deprotection step. Thus, further treatment of acetal **15** with montmorillonite K 10[6d] afforded in 55% yield the targeted, fully functionalized, unprotected palmitoyl analogue of scyphostatin **16**. All NMR data for **16** and its acetyl derivative **17** were in accordance with the corresponding data reported in the literature for the polar core of scyphostatin[4a] and its acetyl derivative.[6k]

Having established the viability of our approach toward the fully functionalized polar core of scyphostatin, we turned our attention to the problematic epoxidation step. Models indicated that the rigid cis-fused bicyclic frame of **12b** and the differential steric requirements it imposes on the two double bonds present might allow its regio- and diastereoselective conversion to the desired epoxide **14b** by employing an organic peracid. Indeed, upon treatment of **12b** with a slight excess of *m*-chloroperbenzoic acid (*m*-CPBA; 1.2 equiv) in the presence of Na_2HPO_4 at 0 °C, fast and exclusive formation of epoxide **14b** was accomplished (Scheme 6).[19]

(18) The indicated relative stereochemistry was assigned to epoxide **14b** on the basis of analysis of its NOESY spectrum and its successful conversion to compounds **16** and **17**. Cross-peak H-8, H-1ax indicated that the NHCOR moiety is axial, while cross-peaks H-5, H-3eq; H-5, H-3ax; and H-6, H-3ax are in accordance with the indicated relative stereochemistry of the oxirane ring.

(19) This experiment was performed while the manuscript was being evaluated. Nonetheless, the authors wish to acknowledge and thank both referees for suggesting it, among their other kind and useful remarks.

Scheme 6. Diastereoselective Epoxidation of Compound **12b**[a]



12b **14b**

[a] R = $CH_2(CH_2)_{13}CH_3$.

In conclusion, the presented synthetic route to scyphostatin's polar core provides a short and efficient entry to scyphostatin analogues. Furthermore, it is flexible, since it not only has the potential for producing analogues bearing various fatty acid side chains but in addition is amenable to the preparation of any desired enantiomer or diastereomer. The preparation of additional analogues of scyphostatin bearing various fatty acid side chains and the evaluation of their biological activities are currently in progress, and our results will be reported in due course.

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Supporting Information Available: Spectral data and experimental procedures for compounds **5**, **9**, and **11**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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