ORGANIC LETTERS

2005
Vol. 7, No. 15
3155−3157

1-Deoxy-5-hydroxysphingolipids as New Anticancer Principles: An Efficient Procedure for Stereoselective Syntheses of 2-Amino-3,5-diols

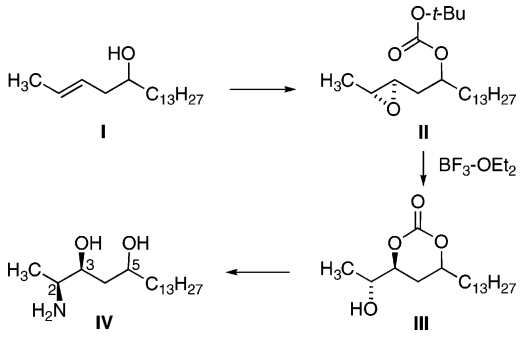
John M. Wiseman, Frank E. McDonald,* and Dennis C. Liotta

Department of Chemistry, Emory University, Atlanta, Georgia 30322

fmcdona@emory.edu

Received April 15, 2005

ABSTRACT



Enantioselective preparation of the linear homoallylic alcohol I allows efficient formation of the 2-amino-3,5-diol moiety present in several biologically active compounds, including 1-deoxy-5-hydroxysphingosine analogue IV, which has exhibited excellent biological activity against colon cancer. The conversion of I into IV involves a sequence of enantioselective epoxidation of the *O-tert*-butoxycarbonyl derivative of I, followed by regioselective and stereospecific oxacyclization of II to introduce differentiated oxygens in III.

Sphingolipids are a diverse family of biomolecules that have been shown to play a variety of important roles in the chemistry of cellular membranes, as well as cell growth, differentiation, and apoptosis.[1] Thus sphingolipids have been identified as a potentially new class of anticancer principles. For instance, the parent D-*erythro*-(2*S*,3*R*)-sphingosine (**1**) (Figure 1) has been shown to affect multiple signaling pathways, including but not limited to potent inhibition of protein kinase C dependent pathways for cell proliferation,[2] as well as activation of caspase pathways for apoptosis.[3] The anticancer activity of sphingosine and other sphingolipids has been demonstrated both in cell culture and in vivo, particularly against colon cancer cell lines.[4] However, in vivo phosphorylation of the primary alcohol of sphingosine to sphingosine 1-phosphate (S1P) is problematic, as S1P has exhibited promitotic and antiapoptotic activity.[5] Safingol (2*S*,3*S*-sphinganine (**2**)) has been explored as an anticancer lead, as this compound is less reactive with sphingosine kinase despite the primary hydroxyl group, perhaps as a result of the different C2,C3-amino alcohol stereochemistry.[6] The laboratories of Liotta and Merrill have developed a class of

(1) Merrill, A. H., Jr.; Sandhoff, K. Sphingolipids: Metabolism and Cell Signaling. In *Biochemistry of Lipids, Lipoprotein, and Membranes*; Vance, D. E., Vance, J. E., Eds.; Elsevier: New York, 2002; pp 373−407.

(2) (a) Hannun, Y. A.; Loomis, C. R.; Merrill, A. H., Jr.; Bell, R. M. *J. Biol. Chem.* **1986**, *261*, 12604. (b) Smith, E. R.; Merrill, A. H.; Obeid, L, M.; Hannun, Y. A. *Methods Enzymol.* **2000**, *312*, 361.

(3) (a) Obeid, L. M.; Linardic, C. M.; Karolak, L. A.; Hannun, Y. A. *Science* **1993**, *259*, 1769. (b) Jan, M. S.; Liu, H. S.; Lin, Y. S. *Biochem. Biophys. Res. Commun.* **1999**, *264*, 724.

(4) Symolon, H.; Schmelz, E. M.; Dillehay, D. L.; Merrill, A. H., Jr. *J. Nutr.* **2004**, *134*, 1157.

(5) Spiegel, S.; Milstein, S. *J. Biol. Chem.* **2002**, *277*, 25851.

(6) (a) Buehrer, B. M.; Bell, R. M. *J. Biol. Chem.* **1992**, *267*, 3154. (b) Kedderis, L. B.; Bozigian, H. P.; Kleeman, J. M.; Hall, R. L.; Palmer, T. E.; Harrison, S. D. *Fundam. Appl. Toxicol.* **1995**, *25*, 201. (c) Schwartz, G. K.; Ward, D.; Saltz, L.; Casper, E. S.; Speiss, T.; Mullen, E. *Clin. Cancer Res.* **1997**, *3*, 343.

10.1021/ol050829o CCC: $30.25
Published on Web 06/22/2005

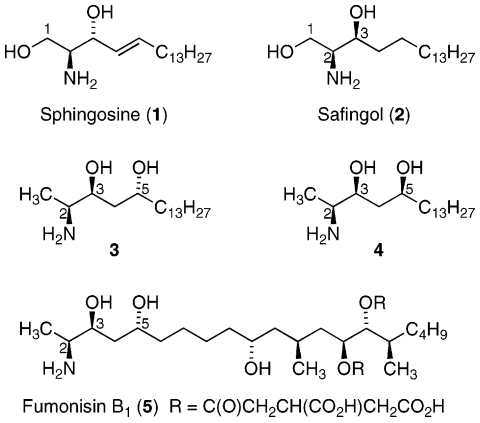


Figure 1. Representative aminodiol natural products and 1-deoxy-5-hydroxysphingolipid analogues.

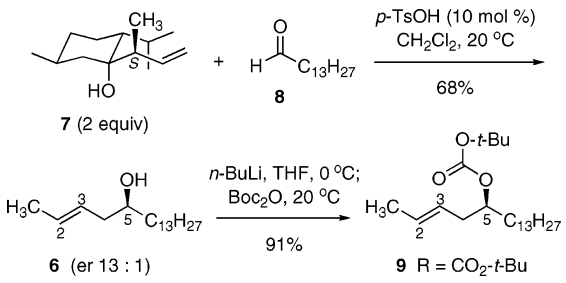
1-deoxy-5-hydroxysphingosine analogues **3** and **4**,[7] with the C2,C3-amino alcohol stereochemistry of safingol but with the primary hydroxyl group of sphingosine moved to the C5-position to maintain similar lipophilicity while further decreasing opportunity for phosphorylation of hydroxyl substituents. Interestingly, the 2-amino-3,5-diol of compound **3** is structurally identical to a substructure of the fungal toxin fumonisin B_1 (**5**).[8]

The aminodiol substructures of 1-deoxy-5-hydroxysphinganine analogues **3** and **4**, as well as fumonisins structurally related to **5**, have been previously prepared from L-alanine via α-aminoketone[7] or α-aminoaldehyde[9] synthetic intermediates. Unfortunately such α-aminocarbonyl compounds are notoriously prone to epimerization of the chiral center.[10] This was a serious impediment to reproducible gram-scale production of **3** and **4** via the cross-aldol reaction of tetradecanal with the kinetic enolate derived from an α-aminomethyl ketone arising from L-alanine.[7] Thus, we were encouraged to explore a substantially different synthetic protocol in which the possibility of epimerization of chiral centers would be unlikely or impossible.

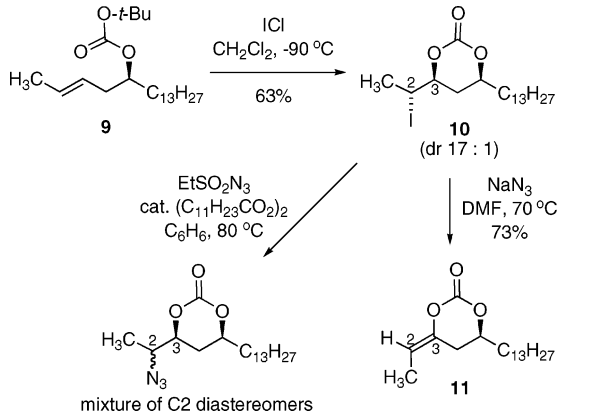
We envisioned that the enantioselective preparation of the linear homoallylic alcohol **6** (Scheme 1) might provide a simple starting point for the preparation of **3** and **4**, and the chiral hydroxyl group of **6** would offer opportunity for regio- and stereoselective introduction of the required functional groups onto the alkene carbons. Compound **6** was easily prepared by application of enantioselective crotyl transfer methodology pioneered by Nokami.[11] Acid-catalyzed reaction of the branched crotyl-menthol reagent **7** with tetradecanal (**8**) provided only the *trans* alkene **6** with high enantioselectivity for the chiral alcohol.[12] As each enantiomer of **7** can be prepared in two steps from the corresponding enantiomer of menthol, both **6** and its enantiomer were easily synthesized by this method.

The original plan was to convert the *tert*-butyl carbonate derivative of **9** into the iodocarbonate **10** (Scheme 2), which proceeded with good yield and high stereoselectivity for the 1,3-*syn* cyclic carbonate.[13] We had anticipated that **10** would then undergo azide substitution of the secondary iodide with inversion of configuration at C2, which would have given the three heteroatom substituents at C2, C3, and C5 with all-*syn* stereochemistry corresponding to target compound **4**. Unfortunately attempted substitution of **10** with azide nucleophiles[14] under a variety of conditions gave the elimination product **11** and only traces of the azidocarbonate **15** (successfully prepared later, as shown in Scheme 3). Although azide substitution could be achieved from **11** by

Scheme 1. Enantioselective Synthesis of Linear Homoallylic Alcohol **6**



Scheme 2. Formation of Iodocarbonate **10** and Attempted Azide Substitutions



(7) Menaldino, D. S.; Bushnev, A.; Sun, A.; Liotta, D. C.; Symolon, H.; Desai, K.; Dillehay, D. L.; Peng, Q.; Wang, E.; Allegood, J.; Trotman-Pruett, S.; Sullards, M. C.; Merrill, A. H., Jr. *Pharmacol. Res.* **2003**, *47*, 373.

(8) (a) Merrill, A. H. Jr.; Liotta, D. C.; Riley, R. T. *Trends Cell Biol.* **1996**, *6*, 218. (b) Desai, K.; Sullards, M. C.; Allegood, J.; Wang, E.; Schmelz, E. M.; Hartl, M.; Humpf, H.-U.; Liotta, D. C.; Peng, Q.; Merrill, A. H., Jr. *Biochim. Biophys. Acta* **2002**, *1585*, 188.

(9) (a) Shi, Y.; Peng, L. F.; Kishi, Y. *J. Org. Chem.* **1997**, *62*, 5666. (b) Gurjar, M. K.; Rajendran, V.; Rao, B. V. *Tetrahedron Lett.* **1998**, *39*, 3803.

(10) Myers, A. G.; Kung, D. W.; Zhong, B. *J. Am. Chem. Soc.* **2000**, *122*, 3236.

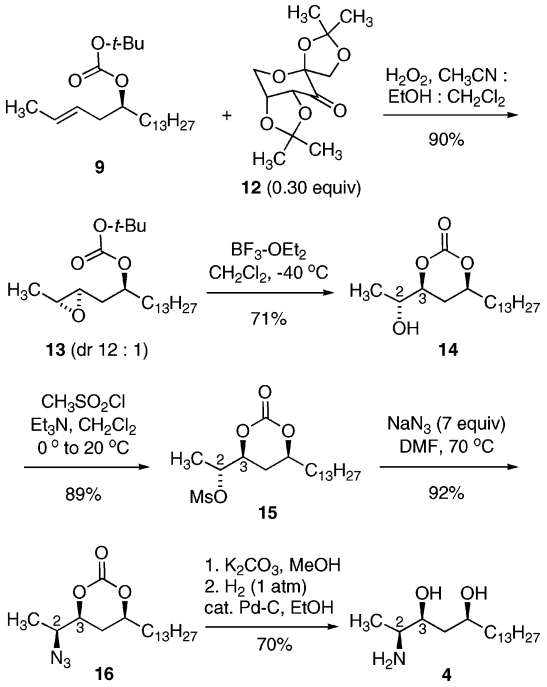
(11) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168.

(12) Determined by Mosher ester analysis (Supporting Information).

(13) (a) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013. (b) Duan, J. J. W.; Smith, A. B. *J. Org. Chem.* **1993**, *58*, 3703.

(14) (a) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465. (b) Davies, S. G.; Ichihara, O. *Tetrahedron Lett.* **1999**, *40*, 9313.

Scheme 3. Stereoselective Synthesis of **4**

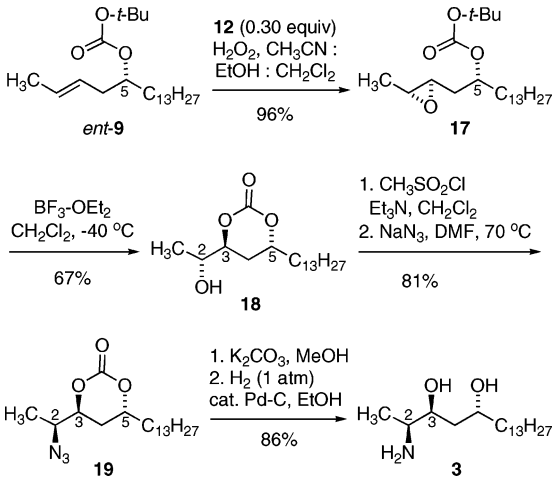


radical substitution conditions,[15] the mixture of azide diastereomers obtained was considered impractical for efficient large-scale synthesis.

However, a solution favoring substitution over elimination was found merely by changing the leaving group at C2. Specifically, Shi enantioselective epoxidation of **9** catalyzed by ketone **12** with hydrogen peroxide as the stoichiometric oxidant[16,17] was followed by Lewis acid promoted intramolecular oxacyclization[18] of the epoxycarbonate **13** (Scheme 3), to provide the cyclic carbonate **14** bearing the secondary alcohol at C2 and 1,3-*syn* relationship of the C3 and C5 oxygen substituents.[19] The derived C2-mesylate **15** then underwent efficient substitution with sodium azide to provide azidocarbonate **16** as a single isomer, and the elimination side product **11** was not observed. The target aminodiol **4** was prepared on gram-scale by basic methanolysis of the cyclic carbonate of **16**, followed by catalytic hydrogenation of the azide.

We also conducted the same series of transformations from the enantiomer of **9**, beginning with Shi epoxidation, which afforded **17** (Scheme 4), the diastereomer of **13**. With

Scheme 4. Stereoselective Synthesis of **3**



samples of both diastereomers **13** and **17** in hand, which exhibit differentiable ^{1}H and ^{13}C NMR characteristics, we could unambiguously verify stereochemical and constitutional purity of these intermediates. Lewis acid oxacyclization of the epoxycarbonate **17** provided the cyclic carbonate **18** with 1,3-*anti* relationship of the C3 and C5 oxygen substituents.[19] The remaining steps of mesylate activation, azide substitution to **19**, carbonate methanolysis, and azide hydrogenation occurred uneventfully to provide the aminodiol diastereomer **3**.

In conclusion, we have demonstrated a new synthetic sequence that is robust and highly stereo- and regioselective for the preparation of 2-amino-3,5-diol substructures, applied herein to the efficient synthesis of 1-deoxy-5-hydroxy-sphingolipid analogues. The dichotomy of substitution versus elimination for a secondary electrophilic substrate bearing mesylate **15** versus iodide **10** was unexpected and may merit further study. We note that this synthetic procedure is potentially useful for other natural product types bearing similar aminodiol substructures, including fumonisins.

Acknowledgment. We thank the National Institutes of Health (CA-87525) for support of this research. We also acknowledge use of shared instrumentation provided by grants from the National Institutes of Health, National Science Foundation, and the Georgia Research Alliance (NMR spectroscopy, mass spectrometry), as well as the University Research Committee of Emory University (polarimeter).

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

OL050829O

(15) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717.

(16) (a) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213. (b) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.

(17) The use of Oxone as the stoichiometric oxidant provided epoxycarbonate **13** with higher stereoselectivity (dr 19:1), but then two or three recycles with additional Shi chiral ketone catalyst **12** were generally required for complete conversion of substrates **9** and *ent*-**9**.

(18) (a) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodriguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515. (b) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586.

(19) In preparations of each diastereomer **14** and **18**, trace amounts of the other diastereomer were isolated (arising from the minor enantiomers generated in either the crotyl transfer or epoxidation step) and were separated by silica gel chromatography, so that cyclization of each epoxy carbonate **13** and **17** afforded the major cyclic carbonates **14** and **18** respectively, in enantio- and diastereomerically pure form.