Asymmetric Synthesis of Novel Structural Mimics of Sulphidoleukotrienes

Timo V. Ovaska,* George H. Voynov, Nicole McNeil, and Joel A. Hokkanen
Department of Chemistry, Connecticut College, 270 Mohegan Avenue, New London, CT 06320, U.S.A.

(Received September 17, 1996)

An asymmetric synthetic route toward a new class of structural mimics of the sulphidoleukotrienes has been developed. The key steps in the overall synthetic sequence include Sharpless asymmetric epoxidation followed by stereo- and regioselective opening of the epoxide ring.

Sulphidoleukotrienes LTC_4, LTD_4, and LTE_4 have recently been implicated in the pathophysiology of asthma and related disorders. This finding has sparked considerable interest in the development of therapeutic agents which would inhibit the biosynthesis of leukotrienes and/or block their actions at the target tissue.[1,2] Herein we wish to report the initial results of our investigation aimed at the development of enantioselective strategies to novel structural mimics of the sulphidoleukotrienes having antagonistic activity. The series of compounds shown in Figure 1 has been obtained on the basis of a putative model for the LTD_4 receptor[3] which suggests that the active site is composed of two adjacent hydrophilic sites capable of binding to similar groups in the substrate, and a hydrophobic site which can accommodate the lipophilic tail of the leukotriene molecule. In general, similar features are shared by most of the leukotriene antagonists developed thus far.[1] It should be noted that the quinolinylmethoxy moiety, which is intended to mimic the lipophilic region of LTD_4 in our proposed series, has also been found to increase the potency of some early leukotriene antagonists.[4] In addition, there have been reports suggesting that this functionality contributes to inhibition of the 5-lipoxygenase (5-LO) enzyme which is directly responsible for the biosynthesis of sulphidoleukotrienes.[5,6] Indeed, compounds possessing dual activity as leukotriene antagonists and 5-LO inhibitors are known.[7]

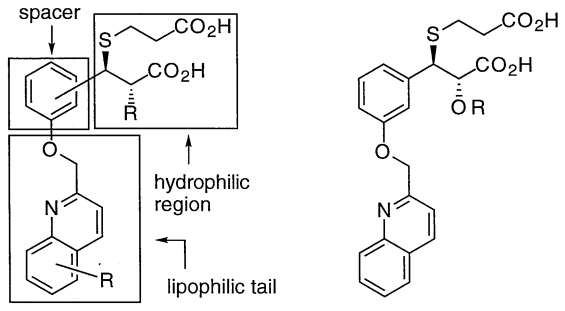
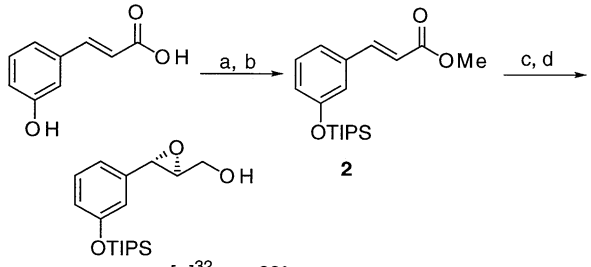


Figure 1.

Our initial goal was to construct the *meta*-substituted derivative **1** having the same absolute stereochemistry as the natural substrate at the two stereogenic centers located in the hydrophilic part of the molecule (Figure 1). In combination with the quinolinylmethoxy moiety, this arrangement of groups represents a new class of potential therapeutic agents aimed at intervening with the leukotriene pathway. As our starting material, we chose the commercially available *m*-hydroxycinnamic acid which was efficiently converted to **2** through esterification and protection of the phenolic OH as its triisopropylsilyl (TIPS) derivative[8] (Scheme 1). Reduction using $LAH/AlCl_3$ and subsequent epoxidation of the allyl alcohol under Sharpless' conditions[9] provided the TIPS protected epoxide **3** in nearly quantitative yield. NMR analysis of the Mosher ester derived from **3** indicated a diastereomeric excess of >98 %.[10]



a) MeOH, cat. H_2SO_4 (90%); b) $(i\text{-}Pr)_3SiOSO_2CF_3$, Et_3N, DCM (94%); c) 1. $LiAlH_4$/ $AlCl_3$/ Et_2O, 2. 2M NaOH (87%); d) TBHP/ (+)-diisopropyl tartrate/ $Ti(O\text{-}i\text{-}Pr)_4$/ CH_2Cl_2 , −30 °C, mol. sieves, 12 h (93\%).

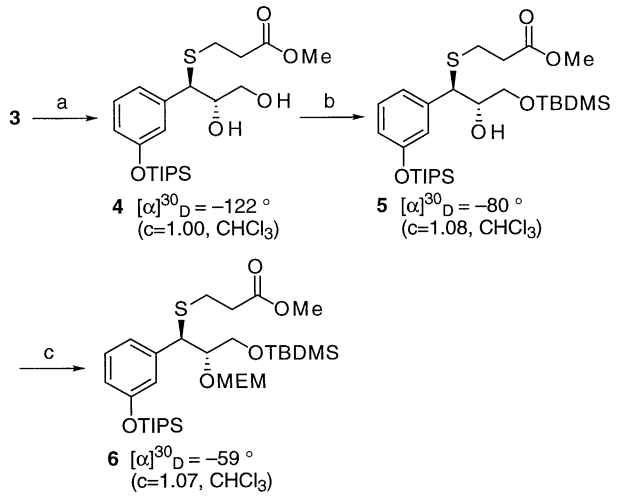
Scheme 1.

Opening of the epoxide ring was effected at room temperature using methyl 3-mercaptopropionate as the nucleophile in a solution of methanol/triethylamine (Scheme 2). Notably, this reaction was found to proceed with complete regio- and stereoselectivity[11,12] to afford diol **4** in high yield. Selective protection of the primary hydroxyl group to give **5** was achieved on treatment with one equiv of *t*-butyldimethylsilyl (TBDMS) chloride in dichloromethane, and subsequent reaction with 2-methoxyethoxymethyl (MEM) chloride furnished the MEM derivative **6**.

Removal of both TBDMS and TIPS groups was readily achieved at room temperature in a single step using an excess of tetrabutylammonium fluoride in THF (Scheme 3). The phenolic hydroxyl group was then derivatized with ω-bromoquinaldine (prepared from quinaldine following the procedure of Brown et al.[13]) in the presence of cesium carbonate in anhydrous DMF. Swern oxidation afforded a relatively unstable aldehyde[14] which was used immediately to give diacid **9** following treatment with silver oxide and subsequent hydrolysis. It should be noted that both the aldehyde oxidation and hydrolysis of the methyl ester were accomplished in an excellent yield in a one-pot reaction, and without affecting the stereochemistry at the α carbon.

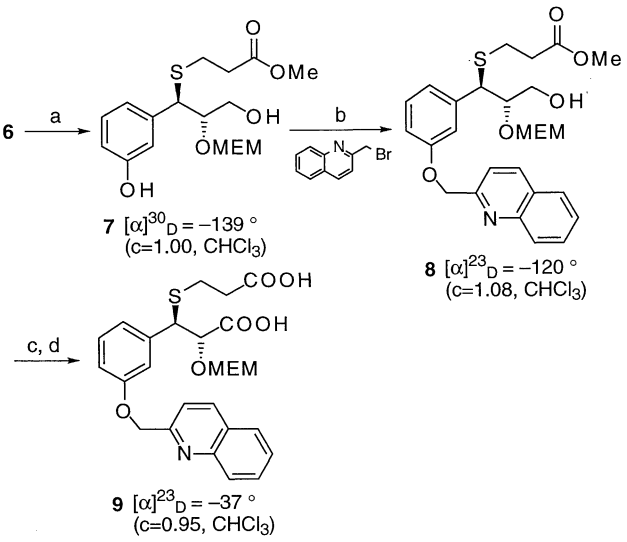
To summarize, an efficient, highly enantioselective synthetic route was developed toward the construction of a new series of potential leukotriene D_4 antagonists. The final MEM derivative produced should be readily deprotected and manipulated further to provide other analogs of **1**. The results of the biological testing of these compounds will be reported in due course.

Copyright © 1997 The Chemical Society of Japan



a) $HS(CH_2)_2COOMe$, Et_3N, MeOH, RT (89%); b) TBDMS-Cl, DMP, Et_3N, DCM, RT (80%); c) MEM-Cl, Hünigs base, DCM, mol. sieves, RT (95%).

Scheme 2.



a) TBAF, THF, RT (78%); b) Cs_2CO_3, DMF (82%); c) oxalyl chloride, DMSO, DCM, –78 °C (87%); d) 1. Ag_2O/NaOH 2. HCl (81%)

Scheme 3.

Financial support for this work from Pfizer, Inc. is gratefully acknowledged.

References and Notes

1 For a recent review on the status of leukotriene research, see: A. Shaw and R. D. Krell, *J. Med. Chem.*, **34**, 1235 (1991). See also "Lipoxygenases and Their Products," ed by S. T. Crooke, A.Wong, Academic Press, Inc., San Diego (1991).

2 R. D. Larsen, E. G. Corley, A. O. King, J. D. Carroll, P. Davis, T. R. Verhoeven, P. J. Reider, M. Labelle, J. Y. Gauthier, Y. B. Xiang, and R. J. Zamboni, *J. Org. Chem.*, **61**, 3398 (1996).

3 R. N. Young, *Adv. Prostaglandin, Thromboxane, Leukotriene Res.*, **19**, 643 (1989).

4 F-C. Huang, R. A. Galermo, Jr., G. B. Poli, K. S. Learn, M. M. Morrisette, W. H. Johnson, Jr., W. P. Dankulich, H. F. Campbell, G. W. Carnathan, and R. G. Vanlnwegen, *J. Med. Chem.*, **34**, 1704 (1991).

5 J. H. Musser, A. F. Kreft, R. H. W. Bender, D. M. Kubrak, R. P. Carlson, J. Chang, J. Hand, and *J. Med. Chem.*, **32**, 1176 (1989).

6 P. J. Gardiner, N. J. Cuthbert, H. P. Francis, M. F. Fitzgerald, A. M. Thompson, T. G. Carpenter, U. P. Patel, B. B. Newton, K. Mohrs, R. Mullerpeddinghaus, and W. A. Taylor, *Eur. J. Pharmacol.*, **258**, 95 (1994).

7 J. D. White, K. M. Yager, and F. Stappenbeck, *J. Org. Chem.*, **58**, 3466 (1993).

8 Satisfactory C and H analyses and/or exact mass spectroscopic molecular weight have been determined for all previously unreported compounds, and their ^1H and ^{13}C NMR spectra are in full accord with the assigned structures.

9 Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765 (1987).

10 The absolute configuration of the epoxide was assigned as (S,S) based on the results obtained by Sharpless et al. (see Ref. 9) employing closely related allylic alcohols and (+)-diisopropyl tartrate.

11 The enantiomeric purity of **4** was assessed through the NMR analysis of the Mosher ester prepared from **5**; no trace of the other diastereomer was detected in neither ^1H NMR nor in the ^{13}C NMR of this compound.

12 For factors controlling the stereo- and regioselectivity of nucleophilic ring opening of 2,3-epoxy alcohols, see e.g. R. M. Hanson, *Chem. Rev.*, **91**, 437 (1991), and references therein.

13 B. R. Brown, D. L. Hammick, and B. H. Thewlis, *J. Chem. Soc.*, **1951**, 1145.

14 All attempts to perform the oxidation with other oxidizing agents, including PCC, PDC, and Collin's reagent, failed to produce appreciable quantities of the desired aldehyde or carboxylic acid.