Pergamon

Tetrahedron Letters 39 (1998) 9355–9356

TETRAHEDRON LETTERS

Simple, Stereocontrolled Syntheses of 24(*S*),25-Epoxy-22(*R*)-hydroxycholesterol, 22(*R*),24(*S*)-Dihydroxycholesterol and Diastereomers, New Ligands for Binding and Activation of LXRs

E. J. Corey* and Michael J. Grogan

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Received 29 September 1998; accepted 8 October 1998

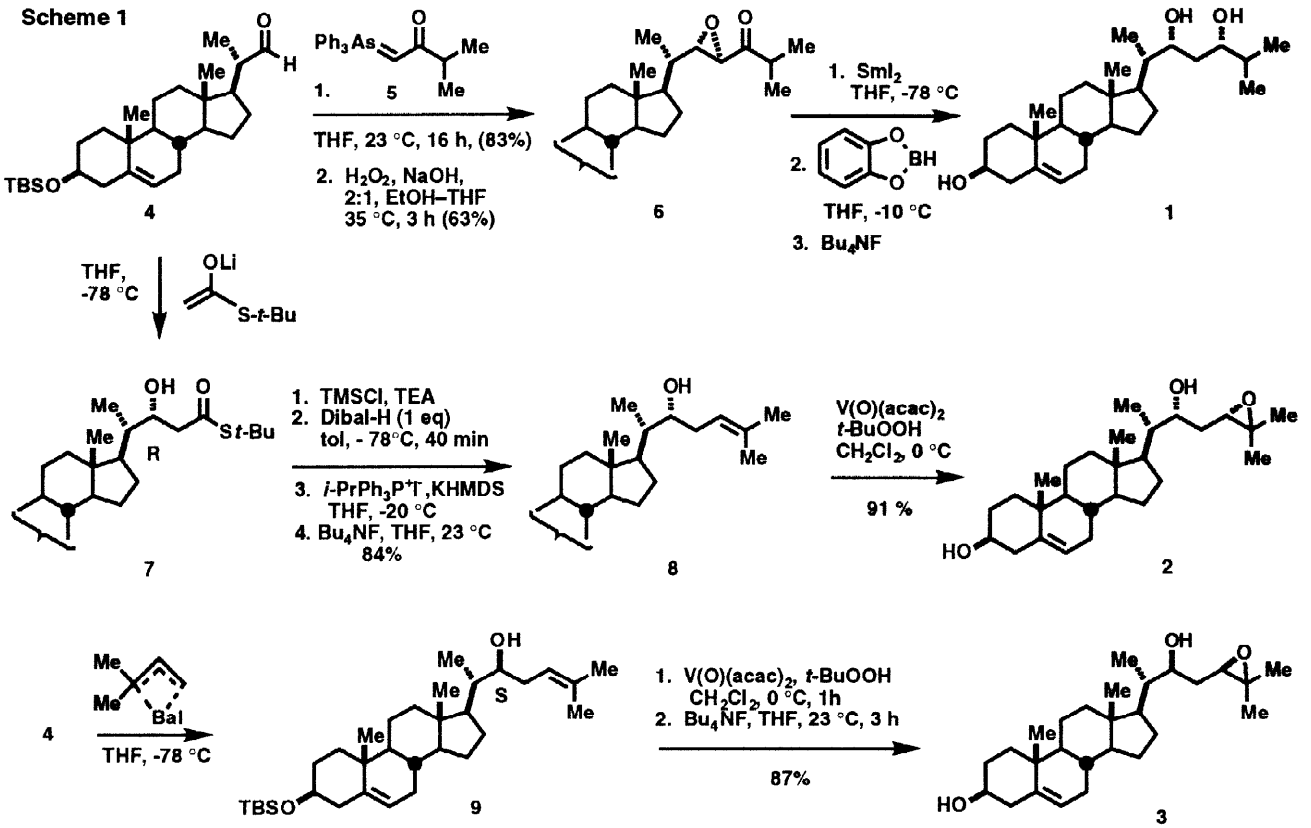
Abstract: *Described herein are stereocontrolled syntheses of a series of sidechain oxygenated cholesterols for the study of binding and activation of nuclear receptors of the LXR family.*

The orphan nuclear receptor LXRα and LXRβ are activated by the naturally occurring sterols 22(*R*)-hydroxycholesterol (22(*R*)-HCH), 24(*S*)-hydroxycholesterol (24(*S*)-HCH), and 24(*S*),25-epoxycholesterol (24(*S*),25-ECH).[1,2] Hydroxylation of cholesterol to 22(*R*)-HCH marks the rate-limiting step of steroid hormone biosynthesis. The flux of 24(*S*)-HCH, cerebrosterol, produced in the brain is important to cholesterol homeostasis.[3] 24(*S*),25-ECH[4] is formed during normal cholesterol biosynthesis from squalene 2,3(*S*), 22(*S*),23-dioxide via 24(*S*),25-oxidolanosterol.[5,6] Since the LXRs are important sensors for cholesterol metabolism, we have undertaken the study of other natural or designed tight-binding ligands. Based upon our model for ligand binding to LXRs, we have prepared the oxysterols **1**, **2** and **3** for studies of binding to and activation of LXRs.[7]

Since 22(*R*)- and 24(*S*)-hydroxycholesterols both bind well to and activate LXR, the synthesis and evaluation of 22(*R*),24(*S*)-dihydroxycholesterol (**1**) was of great interest. The synthetic route to **1** is summarized in Scheme **1**. Arsonium ylide **5** and 3β-*tert*-butyldimethylsilyloxy-bisnor-5-cholenaldehyde (**4**) afforded an *E*-α,β-enone which was epoxidized diastereoselectively (> 10 : 1) to give **6**.[8] C_α-O reductive cleavage of **6** followed by carbonyl reduction[9] and desilylation provided **1**. Similarly, 24(*S*),25-epoxy-22(*R*)-hydroxycholesterol (**2**) was of interest as a bidentate sidechain coordinator to LXR; its synthesis is also summarized in Scheme 1. Addition of the lithium enolate of S-*tert*-butyl thioacetate gave a mixture of aldol products which was separated by silica chromatography to give the (*R*)-β-hydroxy ester **7**. This was converted to homoallylic alcohol **8** by (1) TMS ether formation, (2) reduction of thio ester to aldehyde, (3) Wittig coupling and (4) bis-desilylation. Diastereoselective hydroxyl-directed epoxidation[10] of **8** produced the 22(*R*)-hydroxy derivative of 24(*S*),25-epoxycholesterol (**2**). Finally, the synthesis of **3** was accomplished by the sequence: (1) prenylbarium addition[11] to **4** to form **9** with 7 : 1 diastereoselectivity[12] (2) hydroxyl-directed epoxidation[10] and (3) desilylation. The structure of **3** was confirmed by single crystal X-ray diffraction analysis.[13]

The synthetic routes outlined in Scheme 1 allow ready access to the key oxysterols **1** - **3**. The binding and functional analyses of these compounds with LXR receptors are discussed elsewhere,[7] but in summary, **1**, **2** and **3** each bind to the ligand binding domain of LXRα and LXRβ with K_d values of *ca.* 1 μM. Remarkably, although they bound well, none of these sidechain oxygenated sterols were capable of functional activation of LXRs in the whole cell assay.[14]

PII: S0040-4039(98)02182-0



References and Notes

1. Janowski, B. A.; Willy, P. J.; Devi, T. R.; Falck, J. R.; Mangelsdorf, D. J. *Nature* **1996**, *383*, 728.
2. Lehmann, J. M.; Kliewer, S. A.; Moore, L. B.; Smith-Oliver, T. A.; Oliver, B. B.; Su, J.-L.; Sundseth, S. S.; Winegar, D. A.; Blanchard, D. E.; Spencer, T. A.; Willson, T. M. *J. Biol. Chem.* **1997**, *272*, 3137.
3. Lutjohann, D.; Breuer, O.; Ahlborg, G.; Nennesmo, I.; Siden, A.; Diczfalusy, U.; Bjorkhem, I. *Proc. Natl. Acad. Sci.* **1996**, *93*, 9799.
4. Corey, E. J.; Grogan, M. J. *Tetrahedron Letters* **1998**, *39*, 9351
5. Corey, E. J.; Gross, S. K. *J. Am. Chem. Soc.* **1967**, *89*, 4561.
6. Spencer, T. A. *Acc. Chem. Res.* **1994**, *27*, 83.
7. Janowski, B. A.; Grogan, M. J.; Jones, S. A.; Kliewer, S. A.; Corey, E. J.; Mangelsdorf, D. J. *Proc. Natl. Acad. Sci. USA* submitted.
8. Zhou, W.-S.; Jiang, B.; Pan, X.-F. *Tetrahedron* **1990**, *46*, 3173.
9. Evans, D. A.; Hoveyda, A. H. *J .Org. Chem.* **1990**, *55*, 5190.
10. Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690.
11. Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130.
12. Anh, N. T.; Eisenstein, O. *Nov. J. Chim.* **1977**, *1*, 61; Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Letters* **1968**, 2199.
13. X-ray data for 2 (epoxyalcohol **3**) • *n*-heptane: $C_{61}H_{102}O_6$; triclinic; P1 a = 8.260(3) Å; b = 13.215(6) Å; c = 13.576(6) Å; α = 82.73(2)°; β = 77.19(2)°; γ = 89.115(18)°; Z = 3; $R_1[I>2\sigma(I)]$ = 0.0459.

14. This work was supported by a grant from the National Institutes of Health and a predoctoral fellowship for MJG from Eli Lily and Co.