EFFICIENT ENTRY TO THE STEROIDAL 14 α -METHYL-8-ENE SYSTEM

Sonoko ARAKI, Sanae EGUCHI, and Masuo MORISAKI*

Kyoritsu College of Pharmacy, Shibakoen, Minatoku, Tokyo 105, Japan

Treatment of 14 α ,15 α -epoxy-5 α -cholestan-3 β -ol trimethylacetate (**1b**) with boron trifluoride etherate in benzene gave the 8-en-15 α -ol (**2b**) in 75% yield, which was then transformed, by oxidation, methylation and deoxygenation, into 14 α -methyl-5 α -cholest-8-en-3 β -ol (**7**). 24,25-Dihydrolanosterol (**8**) was also prepared by these procedures.

KEYWORDS 14 α -methyl steroid; boron trifluoride etherate; dihydrolanosterol; 14 α -methyl-5 α -cholest-8-en-3 β -ol; antimycotic agent; hypocholesterolemic agent; ergosterol biosynthesis

In a continuing study of the acid-catalyzed reaction of steroidal epoxide,¹⁾ we have found that 14 α ,15 α -epoxycholestan-3 β -ol benzoate (**1a**) was converted in a good yield into the 8-en-15 α -ol (**2a**) on brief treatment with boron trifluoride etherate in benzene. This alcohol (**2a**) is considered to be a promising synthetic precursor for 14 α -methyl-8-ene steroids, which are key intermediates of cholesterol (in mammals) and ergosterol (in fungi) biosynthesis. Definite identification of these sterols accumulated during inhibition of sterol biosynthesis, has a key role in the development of antimycotic and/or hypocholesterolemic agent.²⁾ However, the sole method for preparing 14 α -methyl-8-ene steroids had been that of Woodward reported three decades ago.³⁾ The present paper describes facile and efficient preparation of these biologically and practically important sterols.

The pivaloyl ester (**3a**)⁴⁾ mp 167–168°C of 5 α -cholest-14-en-3 β -ol⁵⁾ was oxidized with *m*-chloroperbenzoic acid to give the 14 α ,15 α -epoxide (**1b**) mp 171–173°C, δ 0.85 (13-Me) and 3.30 ppm (15-H), in 82% yield. The stereochemistry of the epoxide was deduced to be the α -configuration from spectroscopic comparison with the corresponding benzoate (**1a**) mp 162–165°C, δ 0.86 (13-Me) and 3.32 ppm (15-H) which was distinguished from the 14 β ,15 β -epoxide benzoate, mp 109–110°C, δ 1.06 (13-Me) and 3.33 ppm (15-H) prepared by bromohydrination (*N*-bromosuccinimide/H₂O) of the 14-olefin benzoate followed by K₂CO₃ treatment

When this α -epoxide pivaloyl ester (**1b**) was treated with three equiv. of boron trifluoride etherate in benzene at ambient temperature for 1 h, the 8-en-15 α -ol (**2b**), δ 0.91 (13-Me) and 4.1 ppm (15-H), was obtained in 75% yield. The sole by-product during this reaction was the 8,14- and/or 7,14-diene (ca. 5% yield), while the 14 β -H-15-ketone (**4a**), which may be an expected compound on Lewis acid-catalyzed reaction with the 14 α ,15 α -epoxide (**1b**), was not detected at all.⁶⁾ Oxidation of the alcohol (**2b**) with pyridinium chlorochromate in dichloromethane afforded the β , γ -unsaturated ketone (**5**) in 73% yield.^{7,8)} The stereochemistry at C-14 of this ketone (and hence the alcohol **2b**) was assigned to 14 β -H from a strongly negative Cotton effect (θ -20500 at 304 nm)⁹⁾ Methylation of the 15-ketone (**5**) with methyl iodide/potassium *tert*-butoxide in *tert*-butanol yielded the 14 α -methyl compound (**6a**), mp 144-146°C, θ +250 at 320 nm, δ 0.78 (13-Me), 0.87 (25-Me₂), 0.97 (10- and 20-Me) and 1.09 ppm (14-Me), in 73% yield. The stereoselective 14 α -methylation¹⁰⁾ was definitely concluded by analogous transformations of the 4,4-dimethyl series producing natural 24,25-dihydrolanosterol (*vide infra*). Huang-Minlon reduction (80% hydrazine hydrate/diethylene glycol at 160°C followed by KOH at 200°C) of **6a** gave 14 α -methylcholest-8-en-3 β -ol (**7**), mp 115-116°C, *m/z* 400 (*M*⁺), δ 0.71 (13-Me), 0.88 (14-Me) and 0.95 ppm (10-Me), ¹³C NMR : 133.6 and 134.8 ppm (C-8,9), in 52% yield with the recovered 3 β -hydroxy-15-one (**6b**, 35%).

With the method of introduction of 14 α -methyl-8-ene system established, we have now applied this method to prepare a natural 14 α -methyl-8-ene sterol. Thus, 4,4-dimethylcholest-7-en-3 β -ol¹¹⁾ was isomerized into the 14-olefin, mp 129-131°C, by treatment with hydrochloric acid in chloroform at -20°C in 72% yield.¹¹⁾ The corresponding pivaloyl ester (**3b**) was successively transformed, in the same manner as described above, to the 14 α ,15 α -epoxide (80%) mp 234-236°C, the 8-en-15 α -ol (77%), mp 149-151°C, 8-en-15-one (83%), the 14 α -methyl compound (85%), and finally 24,25-dihydrolanosterol (**8**) mp 148°C, identical with the natural sample.¹²⁾

REFERENCES AND NOTES

- 1) S. Eguchi, S. Yamaguchi, M. Furuya and M. Morisaki, *Chem. Pharm. Bull.*, **36**, 2813 (1988).
- 2) D. Berg and M. Plempel (ed.) "Sterol Biosynthesis Inhibitors," Ellis Horwood Ltd., Chichester England, 1988.
- 3) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *J. Chem. Soc.*, **1957**, 1131.
- 4) The pivaloyl protecting group was selected for its inertness to boron trifluoride etherate and also to potassium *tert*-butoxide used in later stages.
- 5) J. W. Cornforth, I. Y. Gore and G. Popjak, *Biochem. J.*, **65**, 94 (1957).
- 6) Authentic 14 β -H-15-ketone (**4b**) was prepared from the 14-olefin *t*-butyldimethylsilyl ether by hydroboration-oxidation to give the 14 α -H-15 α -OH and the 14 β -H-15 β -OH (20 : 1), PCC oxidation of the latter alcohol, and acidic treatment to deprotect the TBDMS group (N. Fujita and T. Fujita, unpublished).
- 7) It is noteworthy that the epimeric 14 α -H-15 α -ol prepared by hydroboration-oxidation of the 8,14-diene (R. E. Dolle, S. J. Schmidt and L. I. Kruse, *J. Chem. Soc., Chem. Commun.*, **1988**, 19) was resistant to oxidation to the 15-ketone under the same conditions.
- 8) This ketone (**5**) was converted to hypocholesterolemic 15-oxocholest-8(14)-en-3 β -ol (G. J. Schroeffer, Jr., D. Monger, A. S. Taylor, J. S. Chamberlain, E. J. Parish, A. Kisic and A. A. Kandutsch, *Biochem. Biophys. Res. Commun.*, **78**, 1227, (1977)), by treatment with 5% KOH-methanol at reflux.
- 9) A. R. Van Horn and C. Djerassi, *J. Am. Chem. Soc.*, **89**, 651 (1967).
- 10) For stereoselectivity of 14-methylation of various 15-ketone derivatives see K. Bischofberger, J. R. Bull and J. Floor, *J. Chem. Soc., Perkin Trans. I*, **1987**, 1377; G. Aranda, M. Fétizon and N. Tayeb, *Tetrahedron*, **41**, 5661 (1985).
- 11) Acid-catalyzed isomerization of Δ^7 - to Δ^{14} -olefin will be reported elsewhere.
- 12) We are grateful to Prof. Y. Sato and Dr. Y. Sonoda of this college for the gift of natural 24,25-dihydrolanosterol.

(Received April 19, 1990)