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

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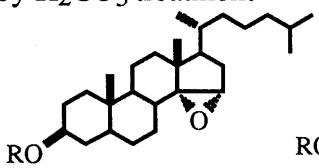
Treatment of 14α,15α-epoxy-5α-cholestan-3β-ol trimethylacetate (**1b**) with boron trifluoride etherate in benzene gave the 8-en-15α-ol (**2b**) in 75% yield, which was then transformed, by oxidation, methylation and deoxygenation, into 14α-methyl-5α-cholest-8-en-3β-ol (**7**). 24,25-Dihydrolanosterol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

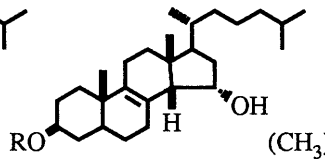
KEYWORDS 14α-methyl steroid; boron trifluoride etherate; dihydrolanosterol; 14α-methyl-5α-cholest-8-en-3β-ol; antimycotic agent; hypocholesterolemic agent; ergosterol biosynthesis

In a continuing study of the acid-catalyzed reaction of steroidal epoxide,[1] we have found that 14α,15α-epoxycholestan-3β-ol benzoate (**1a**) was converted in a good yield into the 8-en-15α-ol (**2a**) on brief treatment with boron trifluoride etherate in benzene. This alcohol (**2a**) is considered to be a promising synthetic precursor for 14α-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 preparating 14α-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.

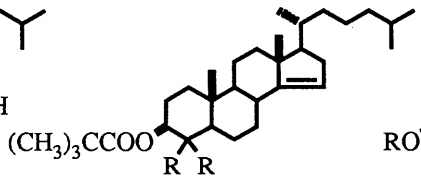
The pivaloyl ester (**3a**)[4] mp 167-168°C of 5α-cholest-14-en-3β-ol[5] was oxidized with *m*-chloroperbenzoic acid to give the 14α,15α-epoxide (**1b**) mp 171-173°C, δ 0.85 (13-Me) and 3.30 ppm (15-H), in 82% yield. The stereochemistry of the epoxide was deduced to be the α-configuration from spectroscopic 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 14β,15β-epoxide benzoate, mp 109-110°C, δ 1.06 (13-Me) and 3.33 ppm (15-H) prepared by bromohydrination (*N*-bromosuccinimide/H_2O) of the 14-olefin benzoate followed by K_2CO_3 treatment



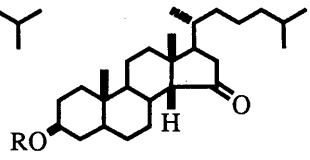
1a: R=COC_6H_5
1b: R=$COC(CH_3)_3$



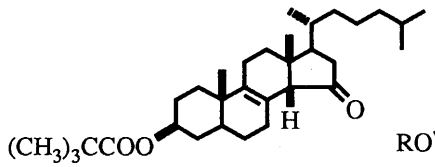
2a: R=COC_6H_5
2b: R=$COC(CH_3)_3$



3a: R=H
3b: R=CH_3



4a: R=$COC(CH_3)_3$
4b: R=H



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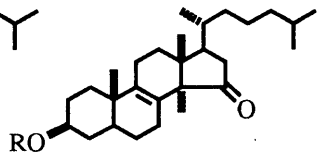
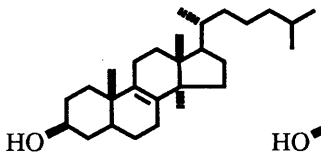


6a: R=$COC(CH_3)_3$
6b: R=H



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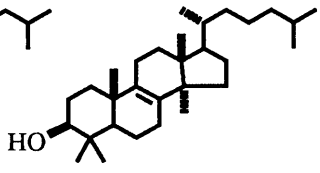

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When this α-epoxide pivaloyl ester (**1b**) was treated with three equiv. of boron trifluoride etherate in benzene at ambient temperature for 1 h, the 8-en-15α-ol (**2b**), δ 0.91 (13-Me) and 4.1 ppm (15-H), was obtained in 75% yield. The sole by-product during this reaction was the 8,14- and/or 7,14-diene (ca. 5% yield), while the 14β-H-15-ketone (**4a**), which may be an expected compound on Lewis acid-catalyzed reaction with the 14α,15α-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 14β-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 14α-methyl compound (**6a**), mp 144-146°C, θ +250 at 320 nm, δ 0.78 (13-Me), 0.87 (25-Me_2), 0.97 (10- and 20-Me) and 1.09 ppm (14-Me), in 73% yield. The stereoselective 14α-methylation[10] 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 14α-methylcholest-8-en-3β-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), ^{13}C NMR : 133.6 and 134.8 ppm (C-8,9), in 52% yield with the recovered 3β-hydroxy-15-one (**6b**, 35%).

With the method of introduction of 14α-methyl-8-ene system established, we have now applied this method to prepare a natural 14α-methyl-8-ene sterol. Thus, 4,4-dimethylcholest-7-en-3β-ol[11] 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 14α,15α-epoxide (80%) mp 234-236°C, the 8-en-15α-ol (77%), mp 149-151°C, 8-en-15-one (83%), the 14α-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 14β-H-15-ketone (**4b**) was prepared from the 14-olefin t-butyldimethylsilyl ether by hydroboration-oxidation to give the 14α-H-15α-OH and the 14β-H-15β-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 14α-H-15α-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-3β-ol (G. J. Schroepfer, 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.

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