EFFICIENT PREPARATION OF 32-OXYGENATED LANOSTEROL DERIVATIVES

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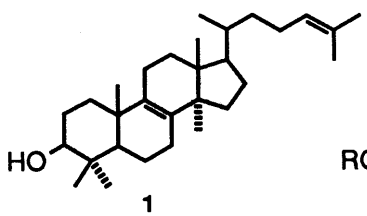
An efficient synthesis of 32-hydroxy- and 32-oxo-lanost-8-en-3β-ol (**2** and **4**) from the 8-ene-15-ketone **7** was described.

KEYWORDS 32-hydroxylanost-8-en-3β-ol; 32-oxo-lanost-8-en-3β-ol; benzyloxymethylation; 14-demethylase; antimycotic agent; hypocholesterolemic agent

One of the key steps in the biosynthesis of cholesterol (in mammals) and ergosterol (in fungi) is the 14-demethylation of lanosterol (**1**). So 14-demethylase is a potential target for the development of hypocholesterolemic and/or antimycotic agents. This reaction is considered to proceed through the intermediacy of 32-hydroxy- and 32-oxo-lanosterol. To elucidate the precise mechanism of this carbon-carbon bond cleavage reaction, adequate samples of these 32-oxygenated lanosterol derivatives are required. These 32-oxygenated compounds should also be useful for preparing sterol-based inhibitors of 14-demethylase.[1] However, no satisfactory method for their chemical preparation has hitherto been reported.[2] Here we describe an efficient synthesis of Δ^8-24,25-dihydro analogs **2** and **4**, based on the recently reported method of 14α-alkylation of the 15-oxo-8-ene system, which in turn was straightforwardly prepared from the 7-ene derivative.[3]

To introduce the 14α-hydroxymethyl group, we first envisaged the hydroxymethylation of an appropriate 8,14-dien-15-ol silyl ether derived from the 8-en-15-one **6** or **7**.[3] When the 15-ketone **6** was treated with LDA/trimethylsilyl chloride, only the 8,15-dienol TMS ether **8** was obtained in a good yield. Similarly treatment of **6** with 2,6-lutidine/triethylsilyl trifluoromethanesulfonate afforded quantitatively the 8,15-dienol TES ether **9** . The 8,15-diene structures but not the expected 8,14-diene counterpart were evident from ^{1}H-NMR, δ 4.5 ppm(16-H) and ^{13}C-NMR, δ 157.3 and 101.9 ppm (C-15 and -16 of **9**, respectively). Reaction of the enol silyl ethers **8** and **9** with methyl lithium followed by methyl iodide or



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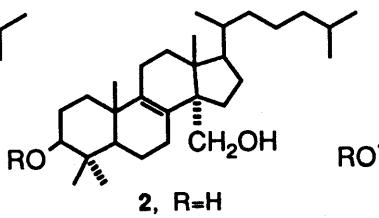
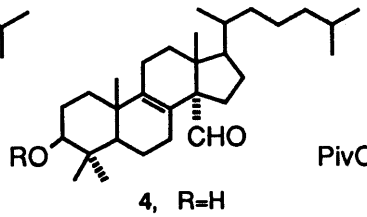
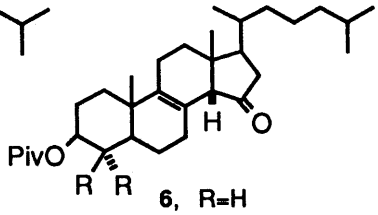


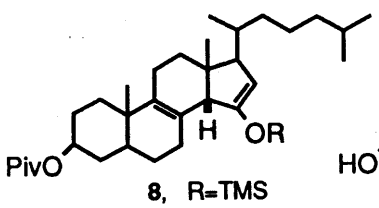
2, R=H
3, R=Ac



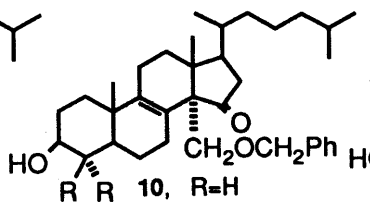
4, R=H
5, R=Ac



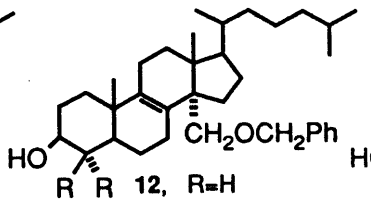
6, R=H
7, R=Me



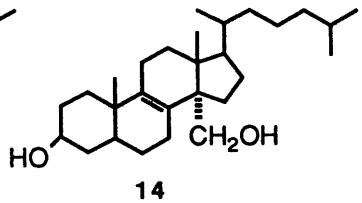
8, R=TMS
9, R=TES



10, R=H
11, R=Me



12, R=H
13, R=Me



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formaldehyde, gave the 16-methyl or 16-hydroxymethyl compounds, respectively. These results are in marked contrast to those of Aranda *et al.*[4] We then turned our attention to benzyloxymethylation of the 15-ketone. When the 15-ketone **6** was treated with NaH/dioxane or LDA/THF followed by benzyloxymethyl chloride,[5] a complex mixture was produced. However, when the latter alkylation was done on the enolate anion formed by t-BuOK/t-BuOH, we obtained, after saponification, the 14α-benzyloxymethyl derivative **10**, ^{1}H-NMR, δ 0.77 (13-Me), 0.93 (10-Me), 3.38 (d, *J*=9 Hz, 32-H), 3.68 (d, *J*=9 Hz, 32-H), 4.38 (d, *J*=12 Hz, benzylic) and 4.45(d, *J*=12 Hz, benzylic), in 60% yield, together with a trace (less than 5%) of the tentatively assigned 14β-isomer. Although the C-14 stereochemistry of **10** was not secured at this stage, it was definitely determined as 14α, based upon the results of analogous reactions of 4,4-dimethyl analog **7**, leading to the known 14α-hydroxymethyl lanostane derivative **2** (*vide infra*). The reaction of **10** with 80% hydrazine hydrate/diethylene glycol followed by the addition of KOH afforded the deoxygenated compound **12**, in 50% yieled: ^{1}H-NMR, δ 0.70 (13-Me), 0.95 (10-Me), 3.31 (d, *J*=8 Hz, 32-H), 3.41 (d, *J*=8 Hz, 32-H), 4.39 (d, *J*=12 Hz, benzylic), 4.53 (d, *J*=12 Hz, benzylic). Catalytic hydrogenation of **12** with 5% Pd-C in ethanol gave 14α-hydroxymethyl-5β-cholest-8-en-3β-ol (**14**), mp 195-197 °C in 75% yield: MS, *m/z* 398 (M-H_2O), 385 (M-H_2O-side chain, base peak), ^{1}H-NMR, δ 0.71 (13-Me), 1.00 (10-Me), 3.20 (d, *J*=11 Hz, 32-H), 3.63 (d, *J*=11 Hz, 32-H).

By analogous procedures as described above, 32-oxygenated lanosterol derivatives, **2** and **4** were then prepared. Thus the 4,4-dimethyl-15-ketone **7** [3] was treated with benzyloxymethyl chloride/t-BuOK/t-BuOH, and the crude alkylation product **11** was then deoxygenated by Huang-Minlon reduction. The resulting 14α-benzyloxymethyl compound **13** (49% yield from **7**), was subjected to hydrogenolysis with H_2/5% Pd-C/EtOH to afford 32-hydroxy-24,25-dihydrolanosterol (**2**, 72%), mp 172-174 °C (ref [2c] mp 173-174 °C). To synthesize 32-oxo derivative **4**, compound **13** was subjected to acetylation and then debenzylation as described above, to yield the 32-hydroxy-3-acetate **3** (72%), mp 130-131 °C, and subsequent oxidation of **3** with pyridinium chlorochromate in dichloromethane provided the aldehyde **5**, mp 147-150 °C in 79% yield. Finally treatment of **5** with 1% KOH-MeOH-benzene gave 32-oxo-24,25-dihydrolanosterol (**4**), mp 178-180 °C (ref [6] mp 177-179 °C).

The present work established an efficient route to synthesize 32-hydroxy- and 32-oxo-lanost-8-en-3β-ol.

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(Received May 13, 1991)