An Improved Synthesis of 3β-Acetoxy-lanost-8-en-24-one (24-Ketolanosteryl Acetate)

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Abstract: The oxidation of a borane intermediate by PFC provides a convenient synthesis of 24-ketolanosteryl acetate.

Keywords: 24-ketolanosteryl acetate, oxidation.

Introduction

The C-24 of lanosterol is a major site of sterol metabolism in plants, fungi, and animals [1,2,3]. As a result of our continuing studies on sterol biosynthesis, we have devised a simplified chemical synthesis of 3β-acetoxy-lanost-8-en-24-one (2, 24-ketolanosteryl acetate), a key intermediate in the synthesis of C-24 alkylated metabolites and potential regulators of sterol biosynthesis.

Results and Discussion

We now report a rapid and convenient chemical synthesis of 2 utilizing commercial lanosterol as a starting material. Previous syntheses have required multiple step procedures resulting in poor yields [4,5,6,7]. In the present study, we have utilized the technique of hydroboration to form an organoborane intermediate. Oxidation of the resulting organoborane by pyridinium fluorochromate (PFC) in refluxing methylene chloride gave the ketone 2 directly, in high yield. PFC is a mild and selective oxi-
dant and has been used in the oxidation of organic compounds [8,9,10].

![Chemical structures](image)

**Scheme 1.** Synthesis of 24-ketolanosteryl acetate.

**Conclusion**

The high yields, anhydrous reaction conditions and easy work-up procedure make this a highly convenient method for the synthesis of 2 and expands the scope and utility of using PFC in organic oxidations.

**Experimental**

**General**

Commercial lanosterol was purified by multiple (4) recrystallizations from acetone/water and after recrystallization was found to be a mixture of lanosterol (61%) and 24,25-dihydrolanosterol (39%) upon GLC analysis. Acetylation of purified commercial lanosterol was accomplished by using acetic anhydride and pyridine, which yielded lanosteryl acetate. Lanosteryl acetate (1) (12.0 g, aprox. 15.6 mmol based on 61% purity) was dissolved in THF (75 mL) and cooled to 2°C in an ice-H₂O bath.
While maintaining a N₂ atmosphere, 10 mL (10 mmol) of a 1M BH₃·THF solution was added over a 10 min period. The reaction was stirred for 1h at 2°C under N₂. Ice was cautiously added to decompose the excess hydride, H₂O was added, and the reaction thoroughly extracted with ether. The extracts were dried over anhydrous MgSO₄, evaporated at reduced pressure, toluene was added and the solvent evaporated at reduced pressure to remove traces of H₂O (azeotrope). The residue was dried in a vacuum desicator over P₂O₅ for 2h and dissolved in methylene chloride (100 mL), PFC (15 g) and molecular sieves (100 mg, type 4Å) were added, and the reaction mixture refluxed for 3h. Saturated aqueous NaCl was added and the mixture was extracted with methylene chloride. The solvent was removed under reduced pressure and the residue subjected to column chromatography. The solvent system used to perform the separation was toluene/hexane, the concentrations and amounts were varied as follows: 1:1 (500 mL), 3:1 (500 mL), and toluene (500 mL). The less polar component eluted first and after removal of the solvent, under reduced pressure, was recrystallized from acetone/water to yield 3.93 g (approx. 84% of the 24,25-dihydrolanosteryl acetate portion of commercial lanosteryl acetate), melting at 118-119°C.[11] Continued elution resulted in the isolation of the more polar component. After evaporation of the solvent, the dried residue was recrystallized from acetone/water (cooling to -15°C) to yield 6.65 g (approx. 88%) of 3β-acetoxy-lanost-8-en-3β-ol-24-one (2). m.p. 136-137°C (lit. 137°C)[5].

Spectral Data

¹H NMR (CDCl₃) [12] 0.682(s, 3H, C-18-CH₃), 0.853-.903(m, 12H, C-14-CH₃, 2 C-4-CH₃, C-18-CH₃), .972(s, 3H, C-19-CH₃), 1.078(d, 3H, C27), 1.106(d, 6H, C-26), 2.050 (s, 3H, acetate), 4.486 (m, 1H, C-3-H).

¹³C NMR (CDCl₃) [12,13] 15.970(C30), 16.729(C18), 18.309(C6), 18.519 & 18.578(C26,C27), 18.696(C21), 19.392(C19), 21.184(C11), 21.525(Acetate), 24.375(C2), 24.427(C28), 26.564(C7), 28.108(C29), 28.292(C16), 30.309(C23), 30.983 & 31.163(C12,C15), 35.468(C1), 36.292(C16), 37.097(C10), 37.682(C22), 38.002(C4), 41.023(C25), 44.692(C13), 50.004(C14), 50.561 & 50.693(C5,C17), 81.110(C3), 134.448 & 134.659(C8,C9), 171.199(Acetate), 215.659(C24).

MS (Electron Impact) 484 (M, 9%), 469 (M-CH₃, 16%), 424 (M-acetic acid, 2%), 409 (M-CH₃-acetic acid, 35%), 394 (M-2CH₃-acetic acid, 2%), 379 (M-3CH₃-acetic acid, 1%), 71 (98%), 43 (acetoxy, 100%).

IR: v_max: 1729 (acetate), 1702 (ketone), 1240, 1025 cm⁻¹.

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