WITHDRAWN: See: http://www.mdpi.org/molecules/papers/50800992.pdf

Molecules **2000**, *5*, 114-117

molecules

ISSN 1420-3049
http://www.mdpi.org

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

Edward J. Parish*, Hang Sun, Stephen Kizito and Terrence L. Boos

Department of Chemistry, Auburn University, Auburn, AL, 36849, USA
Tel.: 011.334.844.4043, Fax: 011.334.844.6959, E-mail: parisej@mail.auburn.edu

* Author to whom correspondence should be addressed.

Received: 29 November 1999 / Accepted: 10 January 2000 / Published: 11 February 2000

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

Keywords: 24-ketolanosteryl acetate, oxidation.

WITHDRAWN

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.

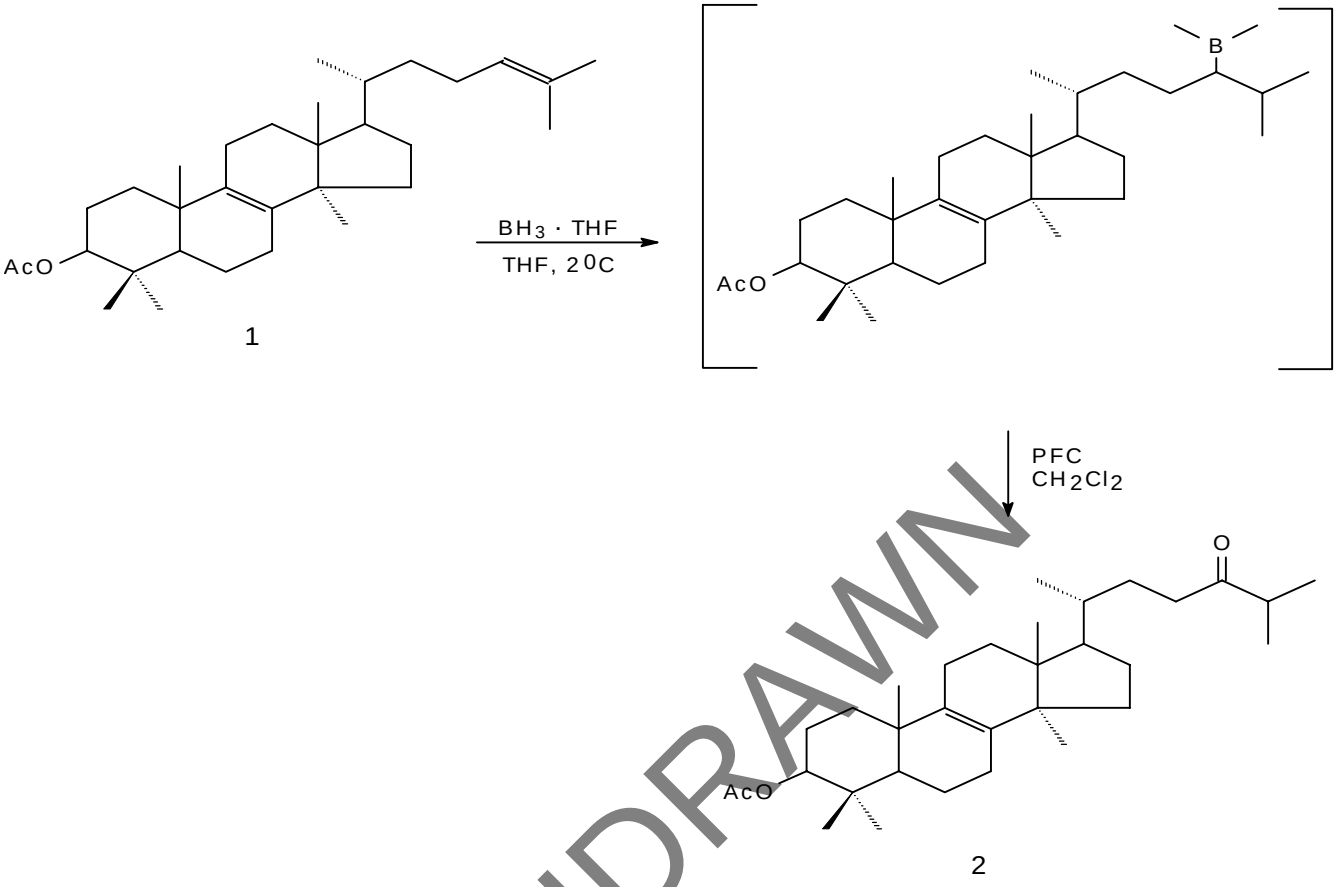
Results and Discussion

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-

© 2000 by MDPI (http://www.mdpi.org). Reproduction is permitted for noncommercial purposes.

WITHDRAWN: See: http://www.mdpi.org/molecules/papers/50800992.pdf

dant and has been used in the oxidation of organic compounds [8,9,10].



Scheme 1. Synthesis of 24-ketolanosteryl acetate.

WITHDRAWN

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-H_2O bath.

WITHDRAWN: See: http://www.mdpi.org/molecules/papers/50800992.pdf

While maintaining a N_2 atmosphere, 10 mL (10 mmol) of a 1M BH_3·THF solution was added over a 10 min period. The reaction was stirred for 1h at 2°C under N_2. Ice was cautiously added to decompose the excess hydride, H_2O was added, and the reaction thoroughly extracted with ether. The extracts were dried over anhydrous $MgSO_4$, evaporated at reduced pressure, toluene was added and the solvent evaporated at reduced pressure to remove traces of H_2O (azeotrope). The residue was dried in a vacuum desicator over P_2O_5 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

^{1}H NMR ($CDCl_3$) [12] 0.682(s, 3H, C-18-CH_3), 0.853-.903(m, 12H, C-14-CH_3, 2 C-4-CH_3, C-18-CH_3), .972(s, 3H, C-19-CH_3), 1.078(d, 3H, C27), 1.106(d, 6H, C-26), 2.050 (s, 3H, acetate), 4.486 (m, 1H, C-3-H).

^{13}C NMR ($CDCl_3$) [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-CH_3, 16%), 424 (M-acetic acid, 2%), 409 (M-CH_3-acetic acid, 35%), 394 (M-2CH_3-acetic acid, 2%), 379 (M-3CH_3-acetic acid, 1%), 71 (98%), 43 (acetoxy, 100%).

IR: ν_{max}: 1729 (acetate), 1702 (ketone), 1240, 1025 cm^{-1}.

References and Notes

1. Nes, W. R.; McKeen, M. L. *Biochemistry of Steroids and Other Isopentenoids*; University Park Press: Baltimore, MD, 1977; pp 346-352.
2. Nes, W. D.; Hanners, P. K.; Parish, E. J. Control of fungal sterol C-24 transalkylation: importance

WITHDRAWN

WITHDRAWN: See: http://www.mdpi.org/molecules/papers/50800992.pdf

to developmental regulation. *Biochem. Biophys. Res. Commun.* **1986**, *139*, 410.
3. Kaneshiro, E. S.; Amit, Z.; Swonger, M. M.; Krieshman, G. P.; Brooks, E. E.; Krershman, M.; Jayasimhulu, K.; Parish, E. J.; Sun, H.; Kizito, S. A.; Beach, D. Pneumocysterol [(24Z)-ehtylidenelanost-8-en-3b-ol], a rare sterol detected in opportunistic pathogen Pneumocystis carinii hominis: structural identity and chemical synthesis. *Proc. Natl. Acad. Sci., USA* **1999**, *96*, 97-102.
4. Barton, D. H. R.; Harrison, D. M.; Moss, G. P. 24-Methylene dihydrolanosterol as a precursor of sterols and titerpenoids. *Chem. Commun.* **1966**, 595.
5. Bloch, K.; Urech, J. The Purification of Lanosterol. *Biochem. Prep.* **1958**, *96*, 32.
6. Briggs, L. H.; Bartley, J. P.; Rutledge, P. S. Degradation of the lanosterol side chain. *J. Chem. Soc., Perkin 1* **1973**, 806-809.
7. Raab, K. H.; De Souza, N.J.; Nes, W. R. The H-migration in the alkylation of sterols at C-24. *Biochem. Biophys. Acta* **1968**, *152*, 742.
8. Bhattarcharjee, M. N.; Chauduri, M. K.; Dasgupta, H. S.; Roy, N.; Khathing, D. Pyridinium fluorochromate; a new and efficient oxidant of organic substrates. *Synthesis* **1982**, 588.
9. Sharma, V.; Sharma, P. K.; Banerji, K. K. Kinetics and Mechanism of the Oxidation of DL-Methionine by Pyridinium Fluorochromate. *J. Chem. Res. (S)* **1996**, 290-291.
10. Parish, E. J.; Sun, H.; Kizito, S. Allylic oxidation of Δ^5-steroids with pyridinium fluorochromate. *J. Chem. Res. (S)* **1996**, 544.
11. Marker, R. E.; Wittle, E. L.; Mixon, L. W. Lanosterol and Agrosterol. *J. Am. Chem. Soc.* **1937**, *59*, 1368.
12. Wilson, W. K.; Sumpter, R. M.; Warren, J. J.; Rogers, P. S.; Raun, B.; Schroepher, G. J. Analysis of unsaturated C27 sterols by nuclear magnetic resonance spectroscopy. *J. Lipid Res.* **1996**, *37*, 1529-1555.
13. Martynow, J.; Paryzek, Z. Epoxidation-Induced Shifts in the Carbon-13 NMR Spectra of Steroids: Lanostane Derivatives. *Magn. Reson. Chem.* **1989**, *27*, 258-262.

Samples Availability: Available from MDPI.

WITHDRAWN

© 2000 by MDPI (http://www.mdpi.org). Reproduction is permitted for noncommercial purposes.