Pergamon

Tetrahedron Letters, Vol. 37, No. 44, pp. 7909-7912, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01793-5

A Radical Prototype To Steroids: Synthesis of d,l-5α-D-Homoandrostane-4α-Methyl-3,17a-Dione

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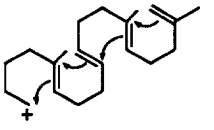
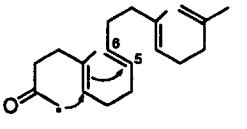
Abstract: An intramolecular radical methodology is described as an approach to D-homoandrostanes. The angular C-8 cyano group in tetracycle **7** derived from radical cyclization of polyene **6** serves as a latent functional group for elaboration to the C-8 βH in *d,l*-homoandrostane **11**.

For over a quarter of a century chemists have tried to simulate the enzymatic conversion of squalene to terpenoids with varying degrees of success. Toward these ends the sequential cationic cyclization of polyenes, elegantly pioneered by Johnson,[1] most closely parallels the enzymatic synthesis of steroids from squalene oxide.

As suggested by the Stork and Eschenmoser hypothesis[2] carbocation **i** undergoes sequential cyclizations through chair-like transition states to yield an all *trans*-tetracyclic system. In the analogous electrophilic radical cyclization of **ii**, a definite preference for the 5-exo trig mode in the second cyclization step would be expected over the desired 6-endo trig mode. Thus a radical approach to steroids using polyenes such as **ii** is not feasible.



i



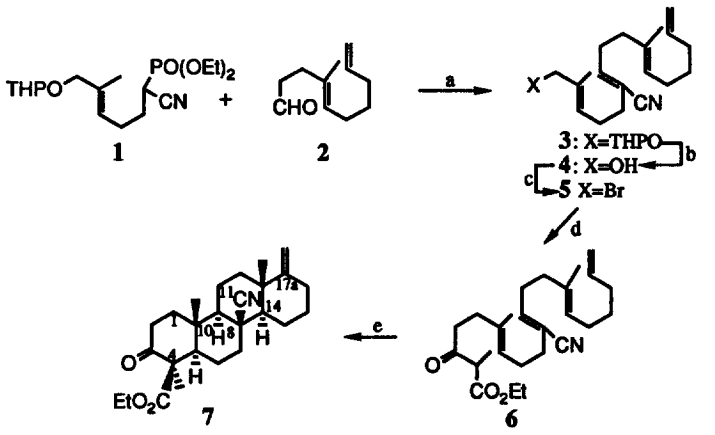
ii

Theoretically the control of the second cyclization step to favor the 6-endo trig mode should be realized by modification of the pro C-8 angular position (steroid numbering) in **ii**. We have demonstrated that the incorporation of a pro C-8 angular methyl[3] or cyano[4] group effectively favors the

6-endo trig closure and that the incorporation of an α,β-unsaturated cyano moiety in the polyene increases yields of polycycle products. As a test case, we were interested in determining if this type of radical strategy could be extended to steroid synthesis. Herein we wish to communicate the first radical prototype in the construction of an intact steroid nucleus and the total synthesis of *d,l*-homoandrostanedione **11**. The synthesis of polyene **6** and the stereoselective generation of tetracycle **7**, containing seven chiral centers, from sequential radical cyclization of **6** is detailed in Scheme I.

Reaction of the potassium salt of cyano phosphonate **1**[4] with aldehyde **2**,[3] using the conditions developed by Takayanagi,[5] gave an 89:11 mixture of the 2E,6Z,10E-triene **3** and the corresponding 2E,6E,10E isomer in 90% yield. Although the mixture could be enriched in **3** after chromatography, it was found that an easier separation could be achieved at the allylic alcohol stage. Thus subsequent cleavage of the protecting group in **3** with MeOH in the presence of an acid afforded alcohol **4** (91%) which upon reaction with CBr_4[6] and Ph_3P gave bromide **5** (76%).

Scheme I



[a] $KN(SiMe_3)_2$, -78 °C, then **2**, -78 °C 4h->rt, overnight; [b] MeOH, *p*-TsOH·H_2O; [c] CBr_4 Ph_3P, CH_2Cl_2, rt, 1h; [d] $LiCH_2C(O)CMe(Na)CO_2Et$, 0 °C, THF, 1.5h; then aq. HCl; [e] $Mn(OAc)_3{\cdot}2H_2O$, $Cu(OAc)_2{\cdot}H_2O$, HOAc, Ar.

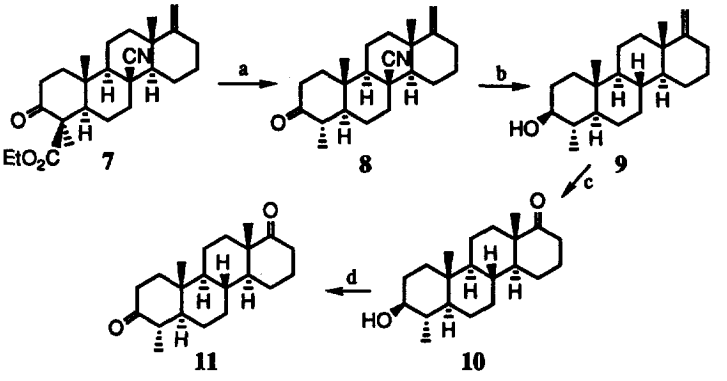
Alkylation of the dianion of ethyl 2-methylacetoacetate (inverse addition) with **5** gave tetraene **6** in 84% yield, after chromatography. Sequential oxidative free-radical cyclization[7-9] of **6**, as a 0.1M solution in deaerated HOAc, with a 2:1 molar ratio of $Mn(OAc)_3{\cdot}2H_2O$ and $Cu(OAc)_2{\cdot}H_2O$ gave stereoselectively tetracycle **7**[10] (mp 185-186 °C; 38-45%).

In our radical approach to steroids, it was anticipated at the beginning that the angular cyano group in **7** would serve as a latent functionality to introduce the crucial C-8 βH present in the steroid

nucleus. Thus this new approach to steroids would hinge on this key transformation. Decarboethoxylation of **7** gave the cyano ketone **8** (mp 234-236 °C) in 65% yield. Reaction of **8** with excess Li[11] in NH_3 afforded alcohol **9** (mp 187-188 °C; 91%), after chromatography. The excellent yield of **9**[12] substantiates the use of the CN group for the introduction of the crucial C-8 βH. Alcohol **9** was converted to *d,l*-**11** by two standard reactions. Thus ozonolysis of **9** and subsequent reduction of the resulting ozonide with Me_2S gave ketone **10** (mp 206.4-207 °C, 84%) which upon oxidation with Jones reagent yielded *d,l*-**11** (mp 214-216 °C; 95%).

The stereochemistry shown in **10** and **11** is consistent with the following observations. The angular methyl groups in *d,l*-**10** (C-18 Me, δ 1.08; C-19 Me, δ 0.82) have comparable chemical shifts to that of the known angular methyl shifts (C-18 Me, δ 1.10; C-19 Me, δ 0.81) observed in 5α-D-homoandrostane-3β-hydroxy-17a-one.[13] Similarly the angular methyl groups in *d,l*-**11** (C-18 Me, δ 1.11; C-19 Me, δ 1.07) are comparable to the angular methyl shifts (C-18 Me, δ 1.14; C-19 Me, δ 1.04) observed for 5α-D-homoandrostane-3,17a-dione.[14] The ^{13}C chemical shifts of the angular methyl groups in **11** are also identical to those reported for 5α-D-homoandrostane-3,17a-dione.[15]

Scheme II



[a] LiCl, wet DMSO, Δ; [b] excess Li, NH_3, - 33 °C 4.5h; then EtOH; [c] O_3, CH_2Cl_2, MeOH, -78 °C; then Me_2S, -78 °C -> rt, overnight; [d] Jones oxidation, 0 °C, acetone.

In summary this study illustrates a highly stereoselective radical approach to homosteroids. The application of this methodology to the synthesis of natural steroids should be highly plausible.

Acknowledgement: We are indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and two of us (Z. C. and Y. Z.) would like to thank the Burroughs Wellcome Foundation for a research fellowship.

REFERENCES AND NOTES

1. (a) Johnson, W. S. *Tetrahedron* **1991**, 41, pp xi. For reviews see: (a) Sutherland, J. K., "Polyene Cyclizations", in Comprehensive Organic Synthesis, **1991**, *3*, 341, ed. Trost, B. B., Pergamon Press; (b) Taylor, S. K. *Org. Prep. Proc. Int.* **1992**, *24*, 245.
2. Stork, G.; Eschenmoser A. *J. Am. Chem. Soc.* **1955**, *77* 5068.
3. Zoretic, P. A.; Weng, Y.; Caspar, M. L.; Davis, D. G. *Tetrahedron Lett.* **1991**, *32*, 4819.
4. Zoretic, P. A.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 1751.
5. Takayanagi, H. *Tetrahedron Lett.* **1994**, *35*, 1581.
6. Hagashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749; and references within.
7. Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759.
8. For recent radical reviews see: (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (d) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (e) Melikyan, G. G. *Synthesis* **1993**, 833.
9. For recent studies of radical strategies toward steroid ring construction see: (a) Batsanov, A.; Chen, L.; Gill, G. B.; Pattenden, G. *J. Chem. Soc., Perkin Trans I*, **1996**, 45; (b) Takahashi, T.; Katouda, W.; Sakamoto, Y.; Tomida, S.; Yamada, H. *Tetrahedron Lett.* **1995**, *36*, 2273.
10. For **7**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.58 (s, 1H), 4.53 (s, 1H), 4.16 (m, 2H), 3.01 (6 line ddd, 1H, H_{2ax}, J = 6.6, 14.8 Hz), 2.26-2.45 (m, 4H, H_{2eq}, H_{7eq}, H_{17}, H_{6ax}), 2.17 (ddd, partially overlapped, H_{1eq}, J = ~2.4, ~6.6, ~13.4 Hz), and 2.12 (br dd, partially overlapped, H_{17}, J = 4.1, 13.9 Hz)[2H], 1.90-1.98 (m, 2H, H_{16eq}, H_{6eq}), 1.65-1.84 (m, 5H, H_{12eq}, H_{11eq}, H_{11ax}, H_{15eq}, H_{15ax}), 1.55 (m, 1H, H_{12ax}, superimposed on H_2O peak), 1.35 (s, 3H, C-4 Me), 1.30 (s, C-13 Me), 1.28 (s, C-10 Me) and 1.28 (t, $\underline{CH_3}CH_2O$, J = 7.2 Hz) and 1.24 (dd, H_{5ax}, J = ~2.4, 12.5 Hz) and 1.23-1.31 (m, H_{1ax}, H_{16ax})[12H], 1.07-1.13 (m, 2H, H_{7ax}, H_{14ax}), 0.91 (distorted dd, 1H, H_{9ax}, J = ~1.8, ~11.3 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz, 77.00) δ 207.83 (C3), 173.20 (ester CO), 157.78 (C17a), 123.57 (CN), 104.00 (exo CH_2), 61.33 (CH_2O), 57.66 (C9), 57.24 (C4), 56.95 (C5), 54.97 (C14), 40.25 (C13), 39.94 (C1), 39.63 (C10), 38.67 (C7), 37.96 (C8), 37.44 (C12), 36.39 (C2), 32.17 (C17), 27.65 (C16), 21.76 (C15), 21.19 (C6), 20.71 (C-4 Me), 19.80 (C11), 19.74 (C-13 Me), 13.93 ($\underline{CH_3}CH_2$), 12.59 (C-10 Me).
11. For metal / NH_3 reduction of a tertiary nitrile see: Arapakos, *J. Am. Chem. Soc.* **1967**, *89*, 6794.
12. All new compounds gave satisfactory micro analyses and spectral data.
13. Contreras, L. E.; Evans, J. M.; de Marcano, D.; Marquez, L. ; Molina, M.; Tempestini, L. *J. Org. Chem.* **1974**, *39*, 1550.
14. de Marcano, D.; Evans, J. M.; Kohout, L.; Ludovic, I.; Narvaez, M.; Salas, O.; Vallejos, C. A. *J. Org. Chem.* **1977**, *42*, 1221.
15. Marcano, D.; Rojas, A.; Mendez, B.; de Mendez,J. *Org. Magn. Reson.* **1981**, *16*, 205.

(*Received in USA* 17 *June* 1996; *revised* 30 *August* 1996; *accepted* 9 *September* 1996)