Pergamon

Tetrahedron Letters, Vol. 35, No. 46, pp. 8599-8600, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01885-5

SYNTHESIS OF 14,17α-ETHANO-BRIDGED EQUILENIN DERIVATIVES

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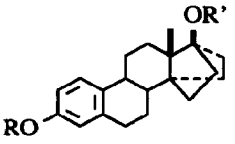
Summary. Oxidation of 3,17β-diacetyloxy-14,17α-ethanoestra-1,3,5(10)-triene (**2**) by ceric ammonium nitrate furnished the equilenin derivative **3**. This intermediate was subsequently converted into epimeric C(11)-alcohols **7** and **9**, the C(11)-methylene derivative **11**, and olefin **13**.

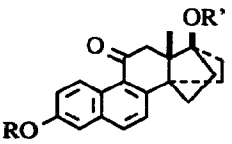
Ceric ammonium nitrate ($(NH_4)_2Ce(NO_3)_6$, CAN) has been utilized for several oxidative transformations[1] in the steroid field with synthetically gratifying regio- and stereocontrol. Estrone acetate may thus be converted into the corresponding 9α,11β-diol-11-nitrate ester in a single operational step.[2] Since the benzylic 9α-hydroxyl group in this compound is readily replaced by a hydrogen atom through the action of triethylsilane in the presence of boron trifluoride etherate, this sequence constitutes an elegant non-enzymatic method for the production of C(11)-substituted estra-1,3,5(10)-triene derivatives.[2b] A recent report on the remarkable biological activity for the 11-nitrate ester of 3,11β-dihydroxy-7α-methylestra-1,3,5(10)-trien-17-one and closely related compounds,[2b] which were prepared by this very two-step procedure, contributes substantially to the importance of CAN-mediated functionalization reactions of steroids.

During the course of a study on the derivatization of 14,17α-ethano-bridged steroids currently pursued in these laboratories,[3] we have uncovered a novel oxidation reaction[4] of a doubly protected derivative of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol[5] by CAN, which will be described in this communication.

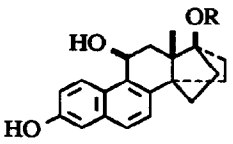
A first series of experiments conducted with the methyl ether **1** gave only discouraging results under a variety of conditions. Deactivation of the steroid skeleton by introducing a second acetate protecting group, **2**, had a beneficial effect. When a solution of **2** in aqueous acetic acid (90%) containing 9.5-10 molar equivalents of CAN was stirred at room temperature for 90 minutes, formation of a discrete major product was observed. Aqueous work-up and chromatography on silica gel (dichloromethane/ethyl acetate, 9:1, gradient elution) afforded this new compound in 61% yield.



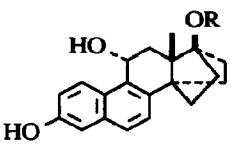
1 R=Me, R'=Ac
2 R=Ac, R'=Ac



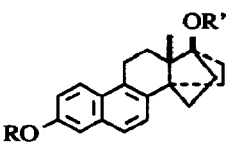
3 R=Ac, R'=Ac
4 R=H, R'=H
5 R=Me, R'=Ac



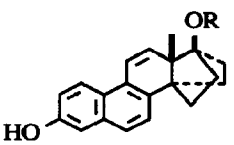
6 R=Ac
7 R=H



8 R=Ac
9 R=H



10 R=Ac, R'=Ac
11 R=H, R'=H



12 R=Ac
13 R=H

According to spectral and analytical evidence, the structure of this steroid has to be formulated as **3**, in which five consecutive carbon atoms have changed their oxidation state.

In an attempt to develop fundamental chemistry for this interesting intermediate, protective group manipulations were among the first transformations to be explored. Twofold base-promoted acetate cleavage (MeOH, 3%KOH, 22°C, 4h; 96%) provided dihydroxy ketone **4**. A two-step sequence including selective deprotection at C-3 (MeOH, K_2CO_3, 22°C, 30 min; 93%) followed by O-methylation (acetone, Me_2SO_4, K_2CO_3, reflux, 2h; 82%) furnished methyl ether **5**, which had escaped preparation in useful quantities by direct oxidation of **1**.

A second set of reactions focused on reductions of the C(11)-carbonyl group of **3** in order to arrive at potentially bioactive derivatives. Epimeric alcohols **6** and **8** were formed in a ratio of 1:9 upon treatment of intermediate **3** with the Luche reagent[6] ($NaBH_4$, $CeCl_3 \cdot 7H_2O$) in methanol solution at -20°C for 1h and subsequent cleavage of the phenolic acetate group. After separation by chromatography on silica gel (dichloromethane/acetone, 4:1, gradient elution), which led to **6** and **8** in 8% and 85% yield, respectively, trihydroxy steroids **7** and **9** were made available almost quantitatively by conventional saponification. Replacement of the C(11)-carbonyl group by two hydrogen atoms (CH_2Cl_2, Et_3SiH, $BF_3 \cdot OEt_2$, reflux, 24h; 80%), **3**→**10**, and saponification (MeOH, 3%KOH, 22°C, 4h; 92%), **10**→**11**, proceeded along an established route.[7] The final target, hexaene **13**,[8] was realized by dehydration (DMSO, 130°C, 24h; 59%),[9] **6/8**→**12**, and saponification of acetate **12**.[10]

References and Notes

1. Ho, T.-L. In *Organic Syntheses By Oxidation With Metal Compounds*; Mijs, W. J., De Jonge, C. R. H. I., Eds.; Plenum Press: New York, 1986; Chapter 11.
2. (a) Sykes, P. J.; Rutherford, F. J.; Laing, S. B.; Phillipps, G. H.; Turnbull, J. P. *Tetrahedron Lett.* **1971**, 3393. (b) Peters, R. H.; Crowe, D. F.; Avery, M. A.; Chong, W. K. M.; Tanabe, M. *J. Med. Chem.* **1989**, *32*, 2306. (c) Rzheznikov, V. M. *Zh. Org. Khim.* **1989**, *25*, 1568.
3. Neef, G.; Michl, G. *Tetrahedron Lett.* **1991**, *32*, 5071.
4. Cambie, R. C.; Carlisle, V. F.; Le Quesne, C. J.; Manning, T. D. R. *J. Chem. Soc. (C)* **1969**, 1234.
5. Bull, J. R.; Thomson, R. I. *J. Chem. Soc. Perkin Trans. 1* **1990**, 241.
6. Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
7. Fry, J. L.; Orfanopoulos, M.; Adlington, M. G.; Dittman, W. R.; Silverman, S. B. *J. Org. Chem.* **1978**, *43*, 374.
8. For a recent total synthesis of related equilenin-type steroids, consult: Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1544.
9. Traynelis, V. J.; Hergenrother, W. L.; Livingston, J. R.; Valicenti, J. A. *J. Org. Chem.* **1962**, *27*, 2377.
10. Physical data for selected steroids are as follows. **3**: mp 169-170 °C (acetone/hexane); $[\alpha]_D^{22}$ -48.2° (c 0.51, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.43 (d, J= 9.5 Hz, 1H), 7.96 (d, J= 8.5 Hz, 1H), 7.57 (d, J= 2.5 Hz, 1H), 7.37 (dd, J= 9.5 Hz, J= 2.5 Hz, 1H), 7.33 (d, J= 8.5 Hz, 1H), 3.03 (d, J= 18.0 Hz, 1H), 2.63 (d, J= 18.0 Hz, 1H), 2.36 (s, 3H), 2.08 (s, 3H), 1.01 (s, 3H); IR (KBr) 2960, 2980, 1763, 1740, 1665, 1603, 1508, 1470, 1368, 1250, 1233, 1202, 1110, 1087, 1045, 1012, 950, 900, 832 cm^{-1}. **4**: mp 266-268 °C (acetone/dichloromethane); $[\alpha]_D^{22}$ -38.4° (c 0.51, CH_3OH). **5**: mp 205-206 °C (acetone/hexane); $[\alpha]_D^{22}$ -53.6° (c 0.50, $CHCl_3$). **10**: mp 131-133 °C (acetone/hexane); $[\alpha]_D^{22}$ +17.6° (c 0.52, $CHCl_3$). **11**: mp 243-245 °C (acetone/hexane); $[\alpha]_D^{22}$ +31.6° (c 0.50, CH_3OH). **12**: mp 247-249 °C (acetone/hexane); $[\alpha]_D^{22}$ -40.2° (c 0.52, C_5H_5N).

(*Received in Germany* 23 *March* 1994; *accepted* 21 *September* 1994)