Pergamon

Tetrahedron Letters, Vol. 35, No. 46, pp. 8587-8590, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

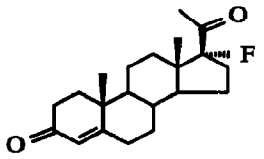
0040-4039(94)01877-4

A FACILE CONSTRUCTION OF THE 17α-FLUOROPROGESTERONE SIDE CHAIN

Günter Neef*, Gerhard Ast, Günter Michl, Wolfgang Schwede, and Harry Vierhufe
Research Laboratories of Schering AG,
D-13342 Berlin,
Germany

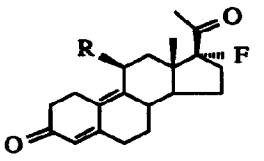
Summary: The ambident functionality of a 21-hydroxy-20-methoxy-17(20)-unsaturated pregnane side chain is used for a new access to 17α-fluoroprogesterone derivatives by reaction with diethylaminosulfur trifluoride.

The regio- and stereoselective introduction of fluorine into biologically active molecules has often proven to be a valuable strategy in enhancing or modifying drug activity[1]. The replacement of C-H or C-OH linkages by a carbon-fluorine bond is of particular interest when metabolism is known to attack the respective sites. Therefore, the steroid nucleus which forms the basic skeleton of numerous valuable drugs has served as a primary target for fluorination at metabolically relevant positions[2].
The increasing number of mild and selective fluorination agents[3] has considerably facilitated fluorine introduction, the stereoselective substitution of tertiary positions, however, often remains a tedious task.
The continued interest in progesterone agonists and antagonists led us to look for a convenient and versatile access to 17α-fluoroprogesterone derivatives of type II.



I

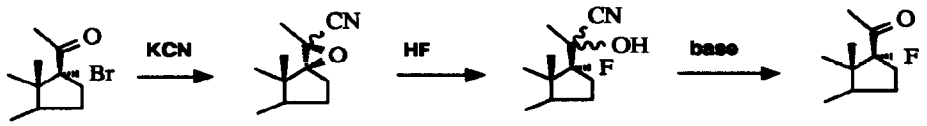
17α-Fluoroprogesterone



II

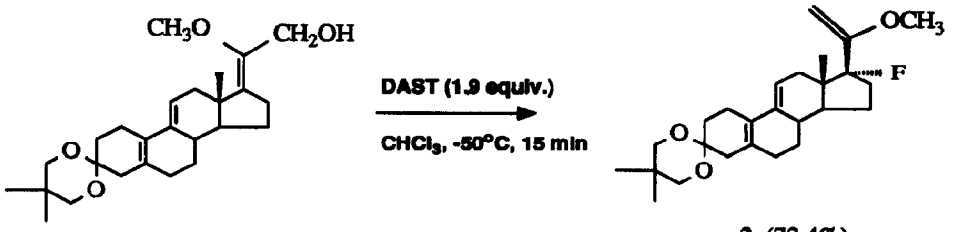
R = H, alkyl, aryl

17α-Fluoroprogesterone I is a known compound first reported by Deghenghi[4] and synthesized from 17α-bromoprogesterone via the route outlined below[5].



The conceptually elegant procedure suffers from requiring the bromo-acetyl derivative as a starting material. In order to achieve the synthesis of type II compounds we had to envisage an approach making use of a 17-ketosteroid precursor.

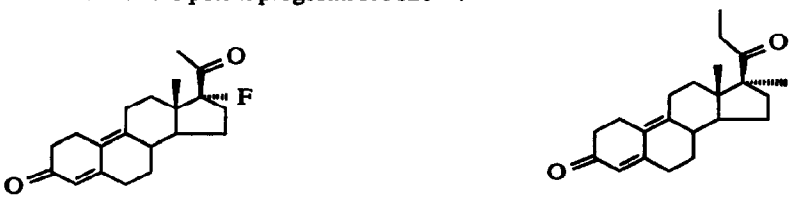
The solution turned out to be surprisingly simple: On treatment with diethylaminosulfur trifluoride (DAST) under standard conditions[6] the allylic alcohol moiety of steroid intermediate 1 exclusively reacted by a formal S_N2' process[7] to give the 17α-fluoro substituted rearranged enol ether 2.



1 2 (72.4%)

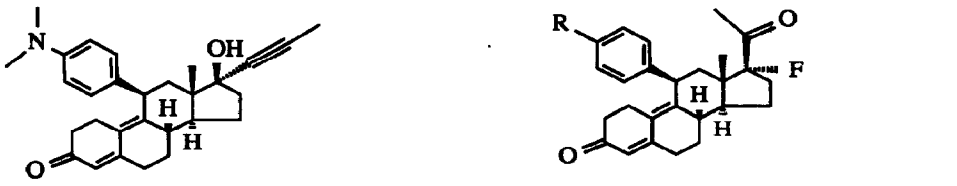
Since compounds of type 1 are easily obtained from the corresponding 17-keto precursors[8] by a three-step procedure reported previously[9], a large variety of 17α-fluoroprogesterone derivatives in the 19-nor series became conveniently accessible.

Acid hydrolysis of enol ether 2 cleanly resulted in the formation of dienone 3 which shares a number of structural features with the potent progestin R 5020[10].



3 R 5020

As an even more interesting aspect, the above fluorination process offered the possibility of combining 11ß-aryl substitution with a 17α-fluoro-17ß-acetyl side chain as exemplified by compounds 4a,b. The discovery of RU 486 as the first progesterone antagonist[11] made such a combination appear a rewarding synthetic objective.

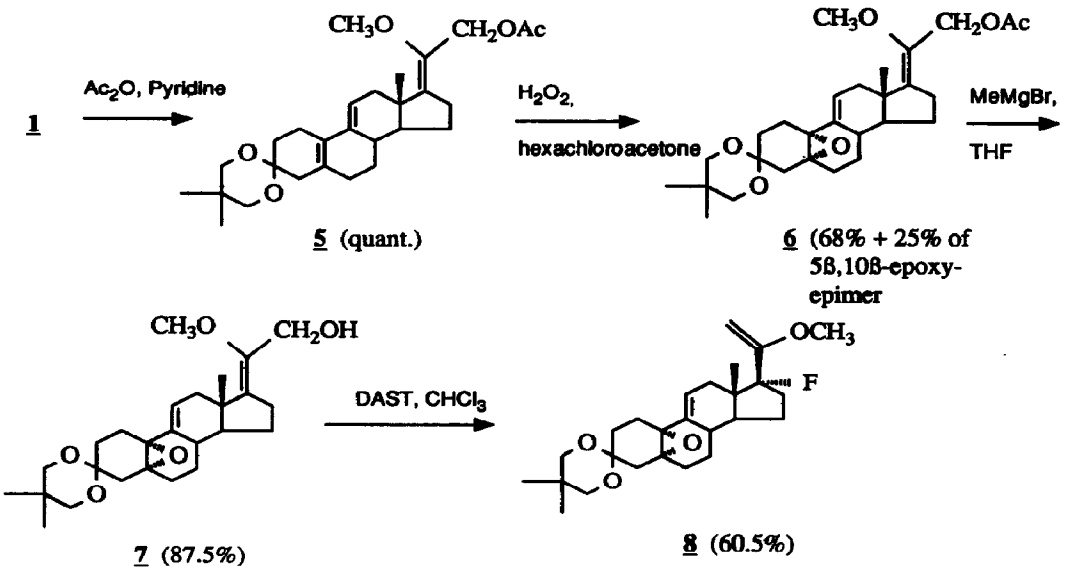


RU 486 4a,b

a R = $N(CH_3)_2$

b R = acetyl

Epoxide **8** required as the central intermediate for the synthesis of type **4** compounds was easily prepared from diene-ketal **1** by acetylation and subsequent epoxidation[12]. Interestingly, simple esterification of the allylic alcohol function was found sufficient to prevent the electron-rich enol ether moiety from being oxidized. As anticipated, no epoxidation procedure was found for the unprotected alcohol **1** to react with preferential formation of a 5α,10α-epoxide. The unusual saponification of epoxyacetate **6** with methylmagnesium bromide (1,2m in THF, 3 equiv., 0°C, 15 min) turned out to be the method of choice since standard procedures (K_2CO_3, methanol) led to concomitant S_N2-type opening of the epoxide moiety.



Although the fluorination of epoxide **7** proceeded slightly less efficient than the parent process with diene-ketal **1**, the 17α-fluoro derivative **8** was obtained with a 60% yield, allowing for the facile completion of the scheme to form the target compounds **4a,b** according to the reported methodology (Cu(I)-catalyzed Grignard reaction, acid-catalyzed deprotection)[13].

The newly synthesized compounds **3**, **4a** and **4b** exhibited very strong affinity for the progesterone receptor. Biological activity data will be reported elsewhere.

References and notes:

1.a) Resnati, G. *Tetrahedron* **1993**, *49*, 9385. b) Welch, J.T. *Tetrahedron* **1987**, *43*, 3123.

2.Fried, J. and Edwards, J.A., eds. *Organic Reactions in Steroid Chemistry*, Vol. I, p. 432, Von Nostrand/Reinhold, New York **1972**.

3.Wilkinson, J.A.; *Chem.Rev.* **1992**, *92*, 505.

4.Deghenghi, R. and Gaudry, R. *Can.J.Chem.* **1961**, *39*, 1553.

5.Herzog, H.L.; Gentles, M.J.; Marshal, H.M.; Hershberg, E.B. *J.Am.Chem.Soc.* **1960**, *82*, 3691.

6.Middleton, W.J. *J.Org.Chem.* **1975**, *40*, 574.

7.Tellier, F.; Sauvetre, R. *Tetrahedron Lett.* **1993**, *33*, 3643.

8.Teutsch, G. and Belanger, A. *Tetrahedron Lett.* **1979**, 2051.

9.Neef, G.; Eder, U.; Seeger, A.; Wiechert, R. *Chem.Ber.* **1980**, *113*, 3086.

10.Raynaud, J.P. and Ojasoo, T. *J.Gyn.Obst.Biol.Rep.* **1983**, *12*, 679.

11.Teutsch, G. in *The Antiprogestin RU 486 and Human Fertility Control*, Baulieu, E.E. and Segal, S.J., eds., Plenum Press, New York **1985**, pp 27 - 47.

12. Roussel-Uclaf: Europ. Patent Application EP 0 005 100, **1979**, inventors: Cousterousse, G. and Teutsch, G.; *Chem.Abstr.* **1980**, *93*, 186 675x.

13. a) Belanger, A.; Philibert, D.; Teutsch, G. *Steroids* **1981**, *37*, 361. b) Neef, G.; Cleve, G.; Ottow, E.; Seeger, A.; Wiechert, R. *J.Org.Chem.* **1987**, *52*, 4143.

14. Physical data for key intermediates and products: **2**, m.p. 154-155°C (from hexane/diisopropyl ether); $[\alpha]_D$ +105.9 (CH_2Cl_2, c = 0.515); ^{1}H-nmr ($CDCl_3$, 300 MHz): δ = 0.62 ppm (s,3H,H-18); 0.88 (s,3H,ketal-CH_3); 1.06 (s,3H,ketal-CH_3); 3.38 - 3.70 (m,4H,ketal-CH_2); 3.56 (s,3H,OCH_3); 4.15 (d,*J* 2 Hz,1H,H-21); 4.33 (d,*J* 2 Hz,1H,H-21); 5.56 (m,1H,H-11). **3**, m.p. 178-179°C (from ethyl acetate/diisopropyl ether); $[\alpha]_D$ -135.8° ($CHCl_3$, c = 0,52); ^{1}H-nmr ($CDCl_3$, 300 MHz): δ = 0.82 ppm (s,3H,H-18); 2.22 (d,*J* 5 Hz,3H,H-21); 5.70 (s,1H,H-4). **4a**, oil ; $[\alpha]_D$ +305.6 ($CHCl_3$, c = 0.515); ^{1}H-nmr ($CDCl_3$, 300 MHz): δ = 0.39 ppm (s,3H,H-18); 2.26 (d,*J* 5 Hz,3H,H-21); 2.92 (s,6H,N-CH_3); 4.39 (d,*J* 6 Hz,1H,H-11); 5.78 (s,1H,H-4); 6.64 (d,*J* 9 Hz,2H,arom.H); 6.99 (d,*J* 9 Hz,2H,arom.H). **4b**, oil; $[\alpha]_D$ +288° ($CHCl_3$, c = 0.52); ^{1}H-nmr ($CDCl_3$, 300 MHz): δ = 0.33 ppm (s,3H,H-18); 2.26 (d,*J* 5 Hz,3H,H-21); 2.58 (s,3H,$COCH_3$); 4.51 (d,*J* 7 Hz,1H,H-11); 5.81 (s,1H,H-4); 7.28 (d,*J* 9 Hz,2H,arom.H); 7.88 (d,*J* 9 Hz,2H,arom.H). **6**, m.p. 130-131°C (from diisopropyl ether); $[\alpha]_D$ +16.2° ($CHCl_3$, c = 0.5); ^{1}H-nmr ($CDCl_3$, 300 MHz): δ = 0.87 ppm (s,3H,H-18); 0.88 (s,3H,ketal-CH_3); 1.06 (s,3H,ketal-CH_3); 2.10 (s,3H,OAc); 3.35 - 3.65 (m,4H,ketal-CH_2); 3.52 (s,3H,OCH_3); 4.63 (ABq,J = 12 and 18 Hz,2H,H-21); 6.04 (m,1H,H-11). **8**, m.p. 174-176°C (from ethyl acetate/diisopropyl ether); $[\alpha]_D$ 0° ($CHCl_3$, c = 0.5); ^{1}H-nmr ($CDCl_3$, 300 MHz): δ = 0.62 ppm (s,3H,H-18); 0.87 (s,3H,ketal-CH_3); 1.06 (s,3H,ketal-CH_3); 3.45 - 3.65 (m,4H,ketal-CH_2); 3.57 (s,3H,OCH_3); 4.16 (d,*J* 2 Hz,1H,H-21); 4.33 (d,*J* 2 Hz,1H,H-21); 6.04 (m,1H,H-11).

(*Received in Germany* 13 *September* 1994; *accepted* 20 *September* 1994)