The Angular Trifluoromethyl Group. Part 1. Total Synthesis of 13-Trifluoromethyl Estrogens

Jean-Claude Blazejewski, Régine Dorme, and Claude Wakselman*
CNRS-CERCOA, 2 rue Henri Dunant, 94320 Thiais, France

The total synthesis of 18,18,18-trifluoro-17β-estradiol and related steroids is described, following the Torgov route. Some of these compounds show significant biological activity.

The search for steroid agonists and/or antagonists of the natural estrogens, with the aim of separating estrogenicity and antifertility effects, is actively pursued.[1] Among the numerous possible modifications of the steroid nucleus to achieve this goal, the introduction of a trifluoromethyl group seems attractive for several reasons. The trifluoromethyl group is one of the most lipophilic substituents and can increase the solubility of drugs in lipids,[2] thus enhancing their penetrating ability. Since its size is close to that of the methyl group,[3] it does not seriously modify the steric bulk of the steroid, thus ensuring a good fit to the target receptor. Its high electron-attracting properties[4] could alter the reactivity of neighbouring groups, causing a possible modification of the biological activity of the molecule. Moreover, if the trifluoromethyl group is angular, one can expect a high chemical inertness under physiological conditions which may ensure a low level of toxicity. The introduction of a trifluoromethyl group is a more difficult task than that of a single fluorine atom;[5] thus it is not surprising that only a limited number of steroids bearing this group appear in the chemical literature.† The number of angularly substituted ones is even lower.*

In this report we describe the preparation, by a Torgov-type reaction,[6] of the 18,18,18-trifluoro analogues of the estrogens estrone, estradiol, ethynylestradiol (estranol), and also of 19-nortestosterone.[7] Initial attempts to perform the condensation of 2-trifluoromethylcyclopentane-1,3-dione[8] (**2**) with the allyl alcohol (**1**) or its derived isothiouronium salt using standard conditions[9] failed to give useful yields of the secodione (**3**). However, the dione (**2**) is quite reactive and the condensation was achieved in anhydrous benzene at room temperature using a catalytic amount (0.03 mol equiv.) of triethylamine, thus affording the desired crystalline secodione (**3**) in 44% isolated yield along with 34% recovered (**2**).

Cyclisation of the diketone (**3**) with toluene-*p*-sulphonic acid (PTSA) proceeded smoothly in refluxing benzene to give the pentaene (**4**) in 84% yield. In order to achieve a greater stereospecificity in the hydrogenation of the Δ^{14} double bond, the ketone (**4**) was reduced with sodium borohydride in aqueous ethanol and the resulting alcohol (**5**) (94% yield) was acetylated using standard procedures to give the acetate (**6**) (84%).

Catalytic hydrogenation of the acetate (**6**) to the 14α-tetraene (**7a**) proved troublesome. However, this reduction was best achieved using 5% palladium–alumina as catalyst and 2% pyridine in acetone as solvent[10] to give a 68% yield of the desired 14α-acetate (**7a**). Pre-equilibration of the solvent and the catalyst with hydrogen was essential for the success of the reaction. Thus incomplete pre-equilibration of the catalyst gave, besides the 14α-acetate (**7a**) (28% by n.m.r. spectroscopy) and its 14β-isomer (**7b**) (18%), a mixture of the 8-isoestradiol (**8**) (39%) and the equilenin (**9**) (15%) derivatives which could be isolated by fractional crystallisation. Attempted isolation of the 14β-acetate (**7b**) by t.l.c. failed owing to isomerisation of this compound during the purification process.

The 17β configuration for the acetate (**7a**) could be readily deduced from its ^{1}H n.m.r. spectrum (500 MHz; $CDCl_3$). Thus the signal for 17-H at δ_H 5.02 shows two splittings of 8.5 and 6.9 Hz which could be assigned to couplings with 16-H_α and 16-H_β respectively; this implies the α configuration for 17-H and hence the 17β configuration for the acetate (**7a**);[11] this signal was further split by coupling with the trifluoromethyl group ($J_{H,F}$ 1.5 Hz). The 14α configuration could not be readily deduced due to considerable overlapping, in the range δ_H 1.8—2.9, and broadening of signals by extensive couplings with the fluorine atoms. Nevertheless this configuration follows from that of the correlated estrone derivative (**12**) (*vide infra*).

In order to secure the 'natural' 9α,8β configuration, the $\Delta^{5(10)}$ double bond of the unsaturated acetate (**7a**) was reduced with sodium–liquid ammonia in the presence of aniline.[12] During the reaction the acetoxy group was cleaved leaving the free alcohol (**10**) (74% yield), but the tertiary trifluoromethyl group remains unaffected by these strongly basic conditions, indicating a high chemical inertness as already noted in the introduction.

With the trifluoroestradiol methyl ether (**10**) at hand, a number of derivatives could be obtained for n.m.r. studies and biological testing. Thus the alcohol (**10**) was readily oxidised to the ketone (**12**) in 95% yield using Jones' reagent. The ^{1}H n.m.r. spectrum (500 MHz; C_6D_6) of this ketone could be fully analysed using a combination of SECSY experiment and selected sections of the 2D-*J* spectrum.[13,14] The parameters obtained (Table) were fully consistent with an 8β,9α,14α configuration and were close to those of related systems.[14] A notable feature was the coupling between all but two of the 11 protons of the C and D rings with the trifluoromethyl group. Furthermore the *trans* configuration of the B/C ring fusion was confirmed by the ^{13}C chemical shift of the C-1 carbon atom[15] (δ_C 126.1 p.p.m.).

In our hands, boron tribromide cleavage[16] of the aromatic methyl ethers (**10**) and (**12**) was unsatisfactory. Better yields of cleaner products were realised with the older pyridine hydrochloride fusion method.[12] The free phenols 18,18,18-trifluoro-17β-estradiol (**11**) and 18,18,18-trifluoroestrone (**13**) were thus obtained in 77 and 79% yield respectively.

† Some steroids, ring-substituted by a trifluoromethyl group, have been described: W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, 1961, **15**, 1786; A. Bowers and J. Edwards, U.S.P. 3 151 132/1964; A. F. Pascual and M. E. Wolff, *J. Med. Chem.*, 1971, **14**, 164; G. H. Rasmusson, A. Chen, and G. E. Arth, *J. Org. Chem.*, 1973, **38**, 3670; G. H. Rasmusson, R. D. Brown, and G. E. Arth, *ibid.*, 1975, **40**, 672.

‡ J. H. Fried, U.S.P. 3 409 610/1968; in two patents, T. B. Windholz, A. A. Patchett, and J. Fried (Belg. P. 638 079/1964 and Belg. P. 638 080/1964) have described the synthesis of a large number of 13-alkylgonane derivatives starting from 2-alkylcyclopentane-1,3-diones. The authors claim the reaction can be extended to 2-trifluoromethylcyclopentane-1,3-dione. However, the method of preparation, in a strongly basic medium, described by these authors for this base-sensitive dione casts some doubt on its isolation and on that of the compounds derived therefrom. Moreover, no characteristics of the compounds said to be obtained are given.

Table. ^{1}H N.m.r. data (500 MHz; C_6D_6) for (±)-18,18,18-trifluoro-3-*O*-methylestrone (**12**)

Proton	δ_H	Coupling constants (Hz)
1-H	6.99	$J_{1,2}$ 8.2
2-H	6.79	$J_{2,4}$ 2.6
4-H	6.68	
6-H$_\alpha$	2.65	$J_{6\alpha,6\beta}$?,* $J_{6\alpha,7\alpha}$ 6.5, $J_{6\alpha,7\beta}$ 2.2
6-H$_\beta$	2.65	$J_{6\beta,7\alpha}$ 11.8, $J_{6\beta,7\beta}$ 6.6
7-H$_\alpha$	1.00	$J_{7\alpha,7\beta}$ −12.2, $J_{7\alpha,8\beta}$ 3.0
7-H$_\beta$	1.64	$J_{7\beta,8\beta}$ 3.0
8-H$_\beta$	1.83	$J_{8\beta,9\alpha}$ 11.3, $J_{8\beta,14\alpha}$ 11.3, $J_{8\beta,F}$ 1.4
9-H$_\alpha$	1.93	$J_{9\alpha,11\alpha}$ 4.2, $J_{9\alpha,11\beta}$ 11.6, $J_{9\alpha,F}$ 0.9
11-H$_\alpha$	2.03	$J_{11\alpha,11\beta}$ −13.9, $J_{11\alpha,12\alpha}$ 4.4, $J_{11\alpha,12\beta}$ 2.4, $J_{11\alpha F}$ 2.3
11-H$_\beta$	1.57	$J_{11\beta,12\alpha}$ 14.0, $J_{11\beta,12\beta}$ 4.4, $J_{11\beta,F}$ 2.3
12-H$_\alpha$	1.19	$J_{12\alpha,12\beta}$ −14.2, $J_{12\alpha,F}$ 2.3
12-H$_\beta$	2.48	$J_{12\beta,F}$ <0.5
14-H$_\alpha$	1.07	$J_{14\alpha,15\alpha}$ 6.5, $J_{14\alpha,15\beta}$ 14.0, $J_{14\alpha,F}$ 3.2
15-H$_\alpha$	1.43	$J_{15\alpha,15\beta}$ −12.2, $J_{15\alpha,16\alpha}$ 8.7, $J_{15\alpha,16\beta}$ 1.5, $J_{15\alpha,F}$ 1.6
15-H$_\beta$	1.58	$J_{15\beta,16\alpha}$ 8.5, $J_{15\beta,16\beta}$ 9.4, $J_{15\beta,F}$ 2.1
16-H$_\alpha$	1.79	$J_{16\alpha,16\beta}$ −19.3, $J_{16\alpha,F}$ <0.5
16-H$_\beta$	2.23	$J_{16\beta,F}$ 0.7
OMe	3.42	

* This coupling constant could not be evaluated due to near degeneracy of the two coupled protons. However, a value of −17.3 Hz was obtained from a 500 MHz spectrum run in $CDCl_3$.

Ethynylation of the ketone (**12**) with lithium acetylide-ethylene diamine complex[17] in tetrahydrofuran (THF) stopped half-way, giving the ethynyl derivative (**14**) in 36% isolated yield. However, the reaction is highly stereoselective and a single stereoisomer was isolated with a presumed α configuration for the ethynyl group.

Birch reduction of the trifluoroestradiol methyl ether (**10**) with lithium and ethanol in liquid ammonia[18] gave the enol ether (**15**) which was directly hydrolysed to the 19-nor-testosterone derivative (**16**) with hydrochloric acid in methanol (77% yield).

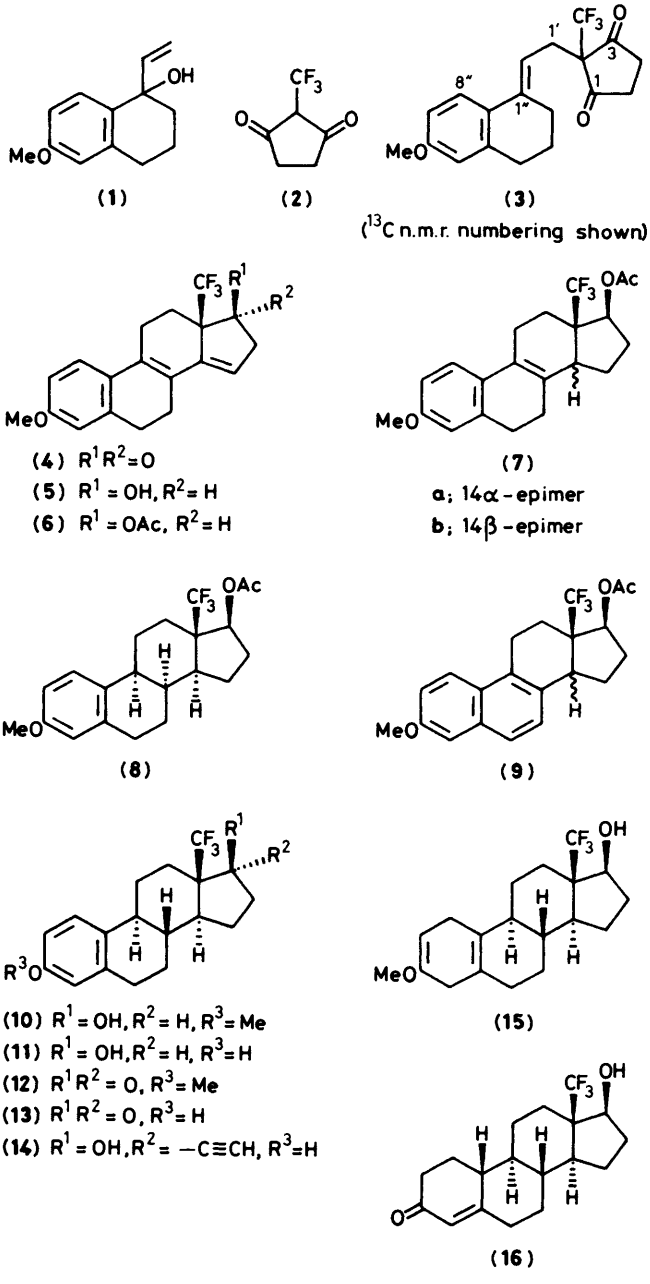
The 10β configuration for compound (**16**) was readily deduced from the ^{1}H n.m.r. spectrum (500 MHz; $CDCl_3$). Thus the signal at δ_H 2.16, which could be assigned to 10-H by a COSY experiment and selective decoupling of 4-H[13] ($J_{4,10}$ 0.6 Hz), shows a large coupling (10.5 Hz) with 9-H (δ_H 0.86) which suggests a *trans* relationship and hence the 10β configuration.

A minor product (*ca.* 10%) which may be the 10α-isomer of the enone (**16**) was also present in the crude mixture (δ_F −58.9 p.p.m.) but could not be isolated.

The estradiol derivatives (**11**) and (**14**) and the 19-nortestosterone derivative (**16**) were tested for biological activity. *In vitro* relative binding affinity (RBA) for the mouse uterine estrogen receptor[19] (RBA = 100 for natural estradiol) were determined for compounds (**11**) and (**14**). The racemic estradiol (**11**) shows an RBA of 47 at 0 °C which decreases to 18 after incubation at 25 °C; this indicates a weak estrogen with potential antiestrogenic activity. In fact in the mouse uterotrophic assay *in vivo*, 18,18,18-trifluoro-17β-estradiol (**11**) shows only 1% of the estrogenic activity of estradiol itself, but has antiestrogenic properties at a total dose of 10 μg per mouse.

The ethynylestradiol (**14**) has about the same *in vitro* agonist activity as compound (**11**) (RBA = 42 at 0 °C) with an increase in binding to the cytosolic receptor at higher temperature (RBA = 57 at 25 °C). *In vivo* (**14**) was only three times less uterotrophic than estradiol but was devoid of antagonist activity.

The 19-nortestosterone derivative (**16**) shows weak androgenic activity with only 10% of the binding activity of testosterone for the androgenic receptor. None of the three compounds shows significant binding to the progesterone or glucocorticoid receptors.



Experimental

M.p.s were determined on a Mettler FP-61 apparatus. I.r. spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. ^{1}H N.m.r. spectra were taken on Bruker WH-90 or Bruker WM-500 spectrometers using tetramethylsilane (TMS) as internal standard. ^{13}C N.m.r. spectra were recorded on a Varian CFT-20 instrument in deuteriochloroform with TMS as internal standard. The spectral width was 5 KHz; pulse width, 9 μs; acquisition time, 0.8 s; pulse delay, 1.5 s. Signal assignments were assisted by signal multiplicities obtained from SFORD spectra. ^{19}F N.m.r. spectra were taken on a Varian EM-360 L spectrometer with $CFCl_3$ as internal reference. Mass spectra were taken on a AEI MS-30 instrument operating at 70 eV. Silica gel refers to silica gel 60, 70—230 mesh (Merck).

2-{2-[3,4-*Dihydro*-6-*methoxy*-1(2H)-*naphthylidene*]*ethyl*}-2-*trifluoromethylcyclopentane*-1,3-*dione* (**3**).—A solution of 1,2,3,4-tetrahydro-6-methoxy-1-vinylnaphthalen-1-ol (**1**) (1.3 g, 6.37 mmol) in dry benzene (10 ml) containing triethylamine (30 μl, 0.2 mmol) was added to a suspension of 2-trifluoromethylcyclopentane-1,3-dione (**2**) (1.0 g, 6.02 mmol) in dry benzene (20 ml). The mixture was stirred for 4 h. Unchanged cyclopentanedione (**2**) (0.34 g, 2.05 mmol) was recovered by filtration and washed with benzene (2 × 10 ml). The residue, after removal of solvents and washings, was chromatographed on silica gel (benzene eluant) to give the *secodione* (**3**) (940 mg, 44%) as an oil which crystallised after a time, m.p. 57—57.5 °C (from hexane) (Found: C, 64.6; H, 5.4. $C_{19}H_{19}F_3O_3$ requires C, 64.8; H, 5.4%); $\nu_{max.}$ (CCl_4) 1 740 (C=O) and 1 600 cm^{-1} (C=C); δ_H (90 MHz; $CDCl_3$) 3.79 (3 H, s, OMe) and 5.50 (1 H, t, *J* 8 Hz, vinylic H); δ_C (20 MHz; $CDCl_3$) 23.2 (C-3″ or -2″), 26.5 (C-2″ or -3″), 28.7 (C-1′, J_{CF} 2 Hz), 30.5 (C-4″), 36.9 (C-4 and C-5), 55.2 (OMe), 61.9 (C-2, J_{CF} 24 Hz), 110.5 (C-7″ or -2′), 112.6 (C-2′ or -7″), 113.3 (C-5″), 121.9 (CF_3, J_{CF} 284 Hz), 125.1 (C-8″), 127.8 (C-8a″), 139.5 (C-4″), 140.4 (C-1″), 159.3 (C-6″), and 206.7 p.p.m. (C-1 and -3); δ_F (56 MHz; $CDCl_3$) −68.7 p.p.m.; *m/z* 352 (M^+, 28%) and 187 (100).

(±)-18,18,18-*Trifluoro*-3-*methoxyestra*-1,3,5(10),8,14-*pentaen*-17-*one* (**4**).—A solution of the secodione (**3**) (940 mg, 2.67 mmol) in dry benzene (30 ml) containing PTSA (10 mg, 0.06 mmol) was held at 70 °C (preheated bath) for 2 h under an inert atmosphere. After having cooled, the solution was concentrated and chromatographed on silica gel (benzene). A deep blue impurity was then removed by sublimation (100 °C; 5 × 10^{-3} mmHg) to give the *ketone* (**4**) (750 mg, 84%), m.p. 110—111 °C (Found: C, 68.3; H, 4.9. $C_{19}H_{17}F_3O_2$ requires C, 68.3; H, 5.1%); $\nu_{max.}$(CCl_4) 1 770 (C=O), and 1 605 and 1 595 cm^{-1} (C=C); δ_H (90 MHz; $CDCl_3$) 2.97 and 3.40 (2 H, J_{AB} 23 Hz, 16-H_2), 3.83 (3 H, s, OMe), and 6.22 (1 H, t, *J* 2.5 Hz, 15-H); δ_C (20 MHz; $CDCl_3$) 23.0 (C-11 or -12), 23.3 (C-12 or -11), 28.3 (C-6 and -7), 43.4 (C-16), 55.2 (OMe), 56.2 (C-13, J_{CF} 25 Hz), 111.3 (C-2), 113.8 (C-4), 121.3 (C-15), 124.4 (C-1), 125.1 (C-8), 125.3 (CF_3, J_{CF} 286 Hz), 128.0 (C-10), 130.8 (C-9), 138.2 (C-5 and -14), 158.6 (C-3), and 208.5 p.p.m. (C-17, J_{CF} 2 Hz); δ_F (56 MHz; $CDCl_3$) −70.2 p.p.m.; *m/z* 334 (M^+, 100%).

(±)-18,18,18-*Trifluoro*-3-*methoxyestra*-1,3,5(10),8,14-*pentaen*-17β-*ol* (**5**).—Sodium borohydride (0.2 g, 5.3 mmol) was added portionwise to a suspension of the ketone (**4**) (710 mg, 2.13 mmol) in 90% ethanol (30 ml) cooled in an ice-bath and under argon. The mixture was stirred for 10 min at 0—5 °C, then for 1 h at room temperature, and cooled again after this period. Acetic acid (200 μl) was added cautiously and the solvent was removed under reduced pressure. The residue was eluted with benzene–ether (4:1) through a short column of silica gel to give the *alcohol* (**5**) (670 mg, 94%), m.p. 133.5—134.5 °C (from benzene) (Found: C, 67.9; H, 5.5. $C_{19}H_{19}F_3O_2$ requires C, 67.85; H, 5.7%); $\nu_{max.}$(CCl_4) 3 620 (OH), and 1 600 and 1 590 cm^{-1} (C=C); δ_H (90 MHz; $CDCl_3$) 2.1 (1 H, s, OH), 3.82 (3 H, s, OMe), 4.36 (1 H, t, *J* 8 Hz, 17-H), and 5.91 (1 H, t, *J* 2.5 Hz, 15-H); δ_C (20 MHz; $CDCl_3$) 23.2 (C-11 or -12), 23.9 (C-12 or -11), 28.5 (C-7), 29.3 (C-6), 39.7 (C-16), 53.4 (C-13, J_{CF} 22 Hz), 55.3 (OMe), 82.2 (C-17), 111.2 (C-2), 113.6 (C-4), 123.9 (C-1), 124.2 (C-15), 125.8 (C-8), 128.6 (CF_3, J_{CF} 288 Hz), 128.6 (C-10), 130.1 (C-9), 138.1 (C-5 and -14), and 158.8 p.p.m. (C-3); δ_F (56 MHz; $CDCl_3$) −67.8 p.p.m. *m/z* 336 (M^+, 40%) and 78 (100).

(±)-18,18,18-*Trifluoro*-3-*methoxyestra*-1,3,5(10),8,14-*pentaen*-17β-*yl Acetate* (**6**).—The alcohol (**5**) (337 mg, 1.00 mmol) was acetylated overnight with acetic anhydride (2 ml) in dry pyridine (5 ml). After dilution with water (25 ml), neutralisation (6M, HCl), and extraction with dichloromethane (3 × 20 ml), the residue was eluted on a short column of silica gel (dichloromethane) to give the acetate (**6**) (319 mg, 84%), m.p. 156—157 °C (from ether) (Found: C, 66.5; H, 5.5. $C_{21}H_{21}F_3O_3$ requires C, 66.7; H, 5.6%); $\nu_{max.}$(CCl_4) 1 750 (acetate), and 1 605 and 1 595 cm^{-1} (C=C); δ_H (90 MHz; $CDCl_3$) 2.11 (3 H, s, OAc), 3.78 (3 H, s, OMe), 5.31 (1 H, t, *J* 8.5 Hz, 17-H), and 5.87 (1 H, t, *J* 2.5 Hz, 15-H); δ_C (20 MHz; $CDCl_3$) 20.9 (CO*Me*), 23.2 (C-11 or -12), 23.8 (C-12 or -11), 28.4 (C-7), 29.5 (C-6), 36.5 (C-16), 53.4 (C-13, J_{CF} 23 Hz), 55.2 (OMe), 80.1 (C-17), 111.1 (C-2), 113.6 (C-4), 123.6 (C-1), 124.2 (C-15), 125.2 (C-8), 127.9 (CF_3, J_{CF} 287 Hz), 128.3 (C-10), 130.4 (C-9), 137.8 (C-14), 138.0 (C-5), 158.7 (C-3), and 170.9 p.p.m. (*C*OMe); δ_F (56 MHz; $CDCl_3$) −69.3 p.p.m.; *m/z* 378 (M^+, 40%) and 318 (100).

Catalytic Hydrogenation of the Acetate (**6**).—(*a*) The acetate (**6**) (522 mg, 1.38 mmol) in a solution of 2% pyridine in acetone (30 ml) was hydrogenated over a slurry of 5% palladium–alumina (150 mg), pre-equilibrated for at least 3 h with hydrogen, at room temperature and atmospheric pressure. After 3 h the catalyst was filtered off through a pad of Celite and thoroughly washed with acetone. After removal of the solvent and washings, the residue was twice recrystallised from ethanol to afford (±)-18,18,18-*trifluoro*-3-*methoxyestra*-1,3,5(10),8-*tetraen*-17β-*yl acetate* (**7a**) (358 mg, 68%), m.p. 173—173.5 °C (Found: C, 66.1; H, 6.2. $C_{21}H_{23}F_3O_3$ requires C, 66.3; H, 6.1%); $\nu_{max.}$(CCl_4) 1 740 (acetate) and 1 600 cm^{-1} (C=C); δ_H (500 MHz; $CDCl_3$) 1.8—2.0 (6 H), 2.08 (3 H, s, OAc), 2.2—2.3 (2 H), 2.33 (1 H, 16-H), 2.54—2.60 (2 H), 2.73 (1 H), 2.87 (1 H, 14-H), 3.77 (3 H, s, OMe), 5.02 (1 H, m, *J* 8.5, 6.9, and 1.5 Hz, 17-H), 6.66—6.71 (2 H), and 7.07 (1 H, d, *J* 7.5 Hz); δ_C (20 MHz; $CDCl_3$) 21.0 (CO*Me*), 23.4 (C-11), 24.2 (C-12 or -15), 24.3 (C-15 or -12), 28.5 (C-7), 29.5 (C-6), 30.2 (C-16), 46.2 (C-14), 51.1 (C-13, J_{CF} 21 Hz), 55.2 (OMe), 79.3 (C-17), 110.8 (C-2), 113.6 (C-4), 122.9 (C-1), 126.3 (C-8, J_{CF} 2 Hz), 127.8 (C-18, J_{CF} 288 Hz), 128.4 (C-10), 128.7 (C-9), 136.9 (C-5), 158.0 (C-3), and 171.0 p.p.m. (*C*OMe); δ_F (56 MHz; $CDCl_3$) −63.3 p.p.m.; *m/z* 380 (M^+, 100%).

(*b*) In another experiment the solvent was pre-equilibrated for only 0.5 h and the hydrogenation was performed overnight. The ^{19}F n.m.r. spectrum of the crude mixture showed the presence of four compounds: (% of the mixture; δ_F/p.p.m.) the (8α)-17-acetate (**8**) (39; −60.0), the pentaene (**9**) (15; −62.8), the (14α)-17-acetate (**7a**) (28; −63.3), and its presumed 14β-isomer (**7b**) (18; −65.2). Pure samples of compounds (**8**) and (**9**) could be isolated by fractional crystallisation from hexane and methanol respectively. (±)-18,18-18-*Trifluoro*-3-*methoxy*-(8αH)-*estra*-1,3,5(10)-*trien*-17β-*yl acetate* (**8**) had m.p. 130—131 °C (from hexane) (Found: C, 65.9; H, 6.7. $C_{21}H_{25}F_3O_3$ requires C, 66.0; H, 6.6%); $\nu_{max.}$(CCl_4) 1 747 cm^{-1} (acetate); δ_H (500 MHz; $CDCl_3$) 1.55—1.65 (2 H), 1.68—1.76 (2 H), 1.76—1.85 (2 H), 1.88 (1 H, 16-H_β), 2.02 (1 H), 2.06 (3 H, s, OAc), 2.1—2.2 (2 H), 2.26 (1 H, 16-H_α), 2.37 (1 H, 12-H_β), 2.64 (1 H, 6-H_β), 2.67 (1 H, 9-H_α), 2.78 (1 H, 6-H_α), 3.76 (3 H, s, OMe), 4.94 (1 H, 17-H_α), 6.61 (1 H, 4-H), 6.71 (1 H, 2-H), and 7.04 (1 H, 1-H); δ_C (20 MHz; $CDCl_3$) 19.3 (C-7, J_{CF} 6 Hz), 21.0 (CO*Me*), 23.6 (C-15), 28.4 (C-16 or -11), 29.0 (C-11 or -16), 31.4 (C-6), 33.5 (C-12), 37.7 (C-8), 40.5 (C-9), 48.9 (C-14), 49.4 (C-13, J_{CF} 22 Hz), 55.2 (OMe), 80.8 (C-17), 112.2 (C-2), 113.4 (C-4), 128.1 (C-18, J_{CF} 287 Hz), 130.1 (C-1), 132.7 (C-10), 138.2 (C-5), 157.5 (C-3), and 171.0 p.p.m. (*C*OMe); δ_F (56 MHz; $CDCl_3$) −60.0 p.p.m.; *m/z* 382 (100%).

(±)-18,18,18-*Trifluoro*-3-*methoxy*-14ξ-*estra*-1,3,5,7,9-*pentaen*-17β-*yl acetate* (**9**) had m.p. 208—209 °C (from methanol) (Found: C, 66.6; H, 5.8. $C_{21}H_{21}F_3O_3$ requires C, 66.7; H, 5.6%); $\nu_{max.}$(CCl_4) 1 748 cm^{-1} (acetate); δ_H (90 MHz; $CDCl_3$) 2.2 (3 H, s, OAc), 4.0 (3 H, s, OMe), 5.3 (1 H, 17-H), 7.1—7.3 (3 H, ArH), 7.7 (1 H, d, *J* 8 Hz, ArH), and 7.9 (1 H, d, *J* 10 Hz, ArH); δ_F (56 MHz; $CDCl_3$) −62.8 p.p.m.; *m/z* 378 (M^+, 100%).

(±)-18,18,18-*Trifluoro*-3-O-*methyl*-17β-*estradiol* (**10**).—A solution of the acetate (**7a**) (110 mg, 0.29 mmol) in dry THF (10 ml) was added to a solution of sodium (0.25 g, 10.8 mg-atom) in liquid ammonia (30 ml) containing aniline (3 ml). The solution was stirred for 30 min, after which excess of solid ammonium chloride was added in portions. The ammonia was evaporated off, the residue was diluted with water (30 ml), and the mixture was extracted with dichloromethane (3 × 20 ml). The extracts were washed successively with 1M-hydrochloric acid and water, dried (Na_2SO_4), and evaporated to give a solid which was recrystallised from methanol to give the *title compound* (73 mg, 74%), m.p. 131—132 °C (Found: C, 67.1; H, 6.9. $C_{19}H_{23}F_3O_2$ requires C, 67.0; H, 6.8%); $\nu_{max.}$(CCl_4) 3 620 cm^{-1} (OH); δ_H (90 MHz; $CDCl_3$) 3.8 (3 H, s, OMe), 3.9 (1 H, 17-H), 6.5—6.8 (2 H, 2- and 3-H), and 7.1 (1 H, d, *J* 8.0 Hz, 1-H); δ_C (20 MHz; $CDCl_3$) 23.7 (C-15), 26.1 (C-7), 27.9 (C-11), 29.5 (C-6), 32.4 (C-12 and -16), 37.8 (C-8, J_{CF} 2 Hz), 43.9 (C-9), 50.6 (C-14), 51.5 (C-13), J_{CF} 19 Hz), 55.2 (OMe), 81.9 (C-17), 111.5 (C-2), 113.9 (C-4), 126.0 (C-1), 129.0 (C-18, J_{CF} 289 Hz), 131.9 (C-10), 137.7 (C-5), and 157.7 p.p.m. (C-3); δ_F (56 MHz; $CDCl_3$) −58.1 p.p.m.; *m/z* 340 (M^+, 100%).

(±)-18,18,18-*Trifluoro*-17β-*estradiol* (**11**).—A mixture of the methyl ether (**10**) (138 mg, 0.41 mmol) and freshly prepared pyridine hydrochloride (750 mg, 6.5 mmol) was held at 210—220 °C for 2 h under argon. After the mixture had cooled, 1M-hydrochloric acid (5 ml) was added. The mixture was cooled in an ice-bath for 1 h, and the deposited crystals were collected by filtration and eluted through a short column of silica gel (15% methanol in benzene). Sublimation (150 °C; 10^{-3} mmHg) of the residue obtained on evaporation of the filtrate gave the *title compound* (102 mg, 77%), m.p. 217.5—218 °C (Found: C, 65.9; H, 6.5. $C_{18}H_{21}F_3O_2$ requires C, 66.25; H, 6.5%); $\nu_{max.}$($CHCl_3$) 3 610 and 3 320 cm^{-1} (OH); δ_H (90 MHz; $CDCl_3$) 4.0 (1 H, 17-H_α), 4.6 (1 H, OH), 6.5—6.7 (2 H, 2- and 4-H), and 7.1 (1 H, d, *J* 8 Hz, 1-H); δ_F (56 MHz; $CDCl_3$) −58.3 p.p.m.; *m/z* 326 (M^+, 100%).

(±)-18,18,18-*Trifluoro*-3-O-*methylestrone* (**12**).—The methyl ether (**10**) (96 mg, 0.28 mmol) was dissolved in acetone (6 ml) and oxidised with Jones' reagent (150 μl; 8M; 1.2 mmol) at 5 °C for 5 min. Excess of reagent was destroyed with methanol (2 ml) and the solution was diluted with water. After work-up (CH_2Cl_2; $MgSO_4$), the *ketone* (**12**) (91 mg, 95%) was isolated, m.p. 145—146 °C (from methanol) (Found: C, 67.4; H, 6.3. $C_{19}H_{21}F_3O_2$ requires C, 67.4; H, 6.2%); $\nu_{max.}$(CCl_4) 1 760 cm^{-1} (CO); δ_H (see Table); δ_C (20 MHz; $CDCl_3$) 21.8 (C-15), 26.1 (C-12), 27.0 (C-7), 27.8 (C-11), 29.3 (C-6), 38.0 (C-8 and -16), 44.0 (C-9), 52.0 (C-14), 55.0 (C-13, J_{CF} 21 Hz), 55.2 (OMe), 111.7 (C-2), 114.0 (C-4), 126.1 (C-1), 126.4 (C-18, J_{CF} 288 Hz), 131.4 (C-10), 137.5 (C-5), 157.9 (C-3), and 211.4 p.p.m. (C-17); δ_F (56 MHz; $CDCl_3$) −60.2 p.p.m.; *m/z* 338 (M^+, 100%).

(±)-18,18,18-*Trifluoroestrone* (**13**).—A mixture of the ketone (**12**) (460 mg, 1.36 mmol) and pyridine hydrochloride (2.5 g, 22 mmol) was held at 210—220 °C for 2 h under argon. After being cooled, the mixture was diluted with ether (50 ml), washed with 1M-hydrochloric acid, and dried ($MgSO_4$). The residue obtained on evaporation was eluted on a column of silica gel (5% ether–dichloromethane) to give the starting material (**12**) (35 mg, 8% recovery) and the *trifluoroestrone* (**13**) (350 mg, 79%), which after sublimation (120 °C; 10^{-3} mmHg) had m.p. 188—188.5 °C (Found: C, 66.5; H, 6.2. $C_{18}H_{19}F_3O_2$ requires C, 66.7; H, 5.9%); $\nu_{max.}$($CHCl_3$) 3 610 (OH) and 1 755 cm^{-1} (CO); δ_H (90 MHz; $CDCl_3$) 6.5—6.7 (2 H, 2- and 4-H) and 7.1 (1 H, d, *J* 8 Hz, 1-H); δ_F (56 MHz; $CDCl_3$) −59.8 p.p.m.; *m/z* 324 (M^+, 100%).

(±)-17α-*Ethynyl*-18,18,18-*trifluoro*-17β-*estradiol* (**14**).—To a solution of the trifluoroestrone (**13**) (350 mg, 1.08 mmol) in dry THF (20 ml) under argon was added lithium acetylide–ethylene diamine complex (1 g, 10.8 mmol). The mixture was stirred for 18 h, poured on crushed ice, extracted with ether (3 × 20 ml), washed successively with 2M-sulphuric acid and water, and dried ($MgSO_4$). The crude material obtained on evaporation (368 mg) was eluted on a column of silica gel (5% ether–dichloromethane) to give recovered starting material (**13**) (198 mg, 57%) and the ethynylestradiol (**14**) (136 mg, 36%), m.p. 153—154 °C (from acetone–hexane) (Found: C, 68.6; H, 6.2. $C_{20}H_{21}F_3O_2$ requires C, 68.6; H, 6.0%); $\nu_{max.}$($CHCl_3$) 3 610 (OH) and 3 320 cm^{-1} (≡C–H); δ_H (90 MHz; $CDCl_3$) 2.74 (1 H, s, acetylenic H), 6.5—6.7 (2 H, 2- and 4-H), and 7.1 (1 H, d, *J* 8 Hz, 1-H); δ_F (56 MHz; $CDCl_3$) −54.0 p.p.m.; *m/z* 350 (M^+, 36%) and 149 (100).

(±)-18,18,18-*Trifluoro*-19-*nortestosterone* (**16**).—Lithium (100 mg, 14.4 mg-atom) was added in small pieces to a solution of the methyl ether (**10**) (100 mg, 0.295 mmol) in a mixture of anhydrous ether (10 ml) and ammonia (10 ml) at −60 °C. After complete dissolution of the metal (*ca.* 5 min), absolute ethanol (1.5 ml) was added *via* a syringe through a septum. The ammonia was allowed to evaporate off, and the residue was diluted with ether (10 ml) and water (10 ml). After extraction, drying (Na_2SO_4), and work-up the crude enol ether (**15**), which had δ_H (90 MHz; $CDCl_3$) 3.5 (3 H, s, OMe), 3.9 (1 H, 14-H_α), and 4.6 (1 H, t, *J* 2.5 Hz, 2-H); δ_F (56 MHz; $CDCl_3$) −58.3 p.p.m., was used, without further purification, in the next step.

Thus to a solution of compound (**15**) in methanol (5 ml) kept at 60 °C was added 3M-hydrochloric acid (3 ml) and the mixture was stirred for 15 min. After cooling of the mixture, dilution with water (10 ml), and extraction with ether, the organic layers were washed successively with dil. aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). The crude material obtained on work-up (97 mg) was further purified by t.l.c. (SiO_2; 5% ether–dichloromethane) to give the *title enone* (**16**) (80 mg, 77%) which had m.p. 168—169 °C (from ether–hexane) (Found: C, 65.6; H, 7.0. $C_{18}H_{23}F_3O_2$ requires C, 65.8; H, 7.1%); $\nu_{max.}$(CCl_4) 1 670 cm^{-1} (CO); δ_H (500 MHz; $CDCl_3$) 0.89 (1 H, 9-H_α), 1.02 (1 H, 7-H_α), 1.23 (1 H, 12-H_α), 1.33 (1 H, 14-H_α), 1.43 (1 H, 11-H_β), 1.53 (1 H, 1-H_α), 1.66 (1 H, 15-H_β), 1.7—1.8 (2 H, 15- and 16-H_α), 1.82 (1 H, 8-H_β), 1.90 (1 H, 11-H_α), 1.93 (1 H, 7-H_β), 2.16 (1 H, 10-H_β), 2.2—2.3 (3 H, 1-, 2-, and 16-H_β), 2.32 (1 H, 6-H_β), 2.41 (1 H, 2-H_α), 2.51 (1 H, 6-H_α), 2.55 (1 H, 12-H_β), 3.92 (1 H, 17-H_α), and 5.85 (1 H, 4-H); δ_C (20 MHz; $CDCl_3$) 23.7 (C-15), 25.9 (C-11), 26.6 (C-1), 31.0 (C-16), 32.1 (C-7 and -12), 35.1 (C-6), 36.5 (C-2), 39.4 (C-8), 42.2 (C-10), 49.2 (C-9), 49.9 (C-14), 50.7 (C-13, J_{CF} 21 Hz), 81.5 (C-17), 124.8 (C-4), 128.2 (C-18, J_{CF} 288 Hz), 166.0 (C-5), and 199.9 p.p.m. (C-3); δ_F (56 MHz; $CDCl_3$) −58.3 p.p.m.; *m/z* 328 (M^+, 100%).

Acknowledgements

We thank Mr. R. Bucourt for fruitful discussions, Mr. L. Nedelec and Mrs. M. M. Bouton from Roussel-Uclaf for the biological assays, and Mr. D. Davoust for performing the 500 MHz n.m.r. experiments.

References

1 P. D. Klimstra and F. B. Colton, in 'Contraception: The Chemical Control of Fertility,' ed. D. Lednicer, M. Dekker, New York, 1969, p. 69; 'Hormone Antagonists,' ed. M. K. Agarwal, Walter de Gruyter, New York, 1982.
2 R. Filler, in 'Organofluorine Chemicals and their Industrial Applications,' ed. R. E. Banks, Ellis Horwood Ltd., London, 1979, p. 124.
3 A. Yokozeki and S. H. Bauer, *Top. Curr. Chem.*, 1975, **53**, 71.
4 L. M. Yagupol'skii, A. Ya. Il'chenko, and N. V. Kondratenko, *Russ. Chem. Rev.* (*Engl. Transl.*), 1974, **43**, 32.

5 J. Fried and N. A. Abraham in 'Organic Reactions in Steroid Chemistry,' eds. J. Fried and J. A. Edwards, Van Nostrand-Reinhold, New York, 1972, vol. 1, p. 423.
6 I. V. Torgov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1982, **31**, 271.
7 For a preliminary communication on part of this work, see J. C. Blazejewski, R. Dorme, and C. Wakselman, *J. Chem. Soc., Chem. Commun.*, 1983, 1050.
8 J. C. Blazejewski, R. Dorme, and C. Wakselman, submitted for publication in *Synthesis*.
9 C. H. Kuo, D. Taub, and N. L. Wendler, *J. Org. Chem.*, 1968, **33**, 3127.
10 D. Hainaut and R. Bucourt, *Bull. Soc. Chim. Fr.*, 1978, 119.
11 C. H. Robinson, C. Erman, and D. P. Hollis, *Steroids*, 1965, **6**, 509.
12 G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 1963, 5072.
13 A. G. J. Sedee, G. M. J. Beijersbergen van Henegouwen, W. Guijt, and C. A. G. Haasnoot, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1755.
14 D. Leibfritz, E. Haupt, M. Feugel, W. E. Hull, and W. D. Weber, *Liebigs Ann. Chem.*, 1982, 1971; L. D. Hall and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1980, **102**, 5703.
15 T. Terasawa, Y. Yoshimura, and K. Tori, *J. Chem. Soc., Perkin Trans. 1*, 1983, 903.
16 K. Ponsold and H. Wagner, *Z. Chem.*, 1977, **17**, 61.
17 H. Laurent and R. Wiechert in 'Organic Reactions in Steroid Chemistry,' eds. J. Fried and J. A. Edwards, Van Nostrand-Reinhold, New York, 1972, vol. 2, p. 53.
18 H. L. Dryden, Jr., ref. 17, vol. 1, p. 1.
19 J. P. Raynaud, M. M. Bouton, D. Gallet-Bourquin, D. Philibert, C. Tournemine, and G. Azadian-Boulanger, *Mol. Pharmacol.*, 1973, **9**, 520; J. P. Raynaud and T. Ojasoo in 'Steroid Hormones Receptors Structure and Function,' eds. H. Eriksson and J. A. Gustafsson, Elsevier, 1983, p. 141.

Received 1*st July* 1985; *Paper* 5/1102