The Selective Protection of the 3-Ketone Functions of Steroids as Heptafluoro-*p*-tolyl Enol Ethers

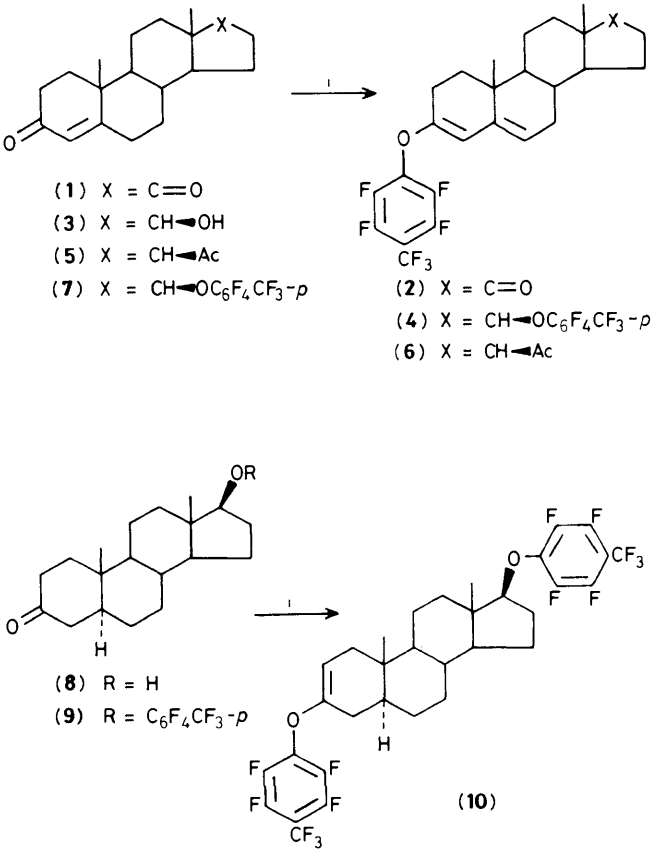
Michael Jarman and Raymond McCague*
Drug Development Section, Cancer Research Campaign Laboratory, Institute of Cancer Research, Clifton Avenue, Sutton, Surrey, SM2 5PX

Conjugated and unconjugated 3-ketone functions in steroids react with octafluorotoluene at above 100 °C in the presence of caesium fluoride to give heptafluoro-*p*-tolyl enol ethers. The related but unusually reactive Wieland–Miescher ketone (**11**) reacted at room temperature in the presence of tetra-n-butylammonium fluoride. Enones were regenerated from their derivatives by acidic hydrolysis. Hydrolysis of the derivative (**10**) of 4,5α-dihydrotestosterone was sluggish but sodium methoxide regenerated the parent steroid. The methods have been applied in a synthesis of deuterium-labelled testosterone.

Our work on inhibitors of oestrogen and androgen biosynthesis for the treatment of steroid-hormone-dependent cancers has led us to require procedures for the assay of steroids in human plasma. We found that steroid derivatives containing hydroxy functions could be derivatised with octafluorotoluene to give heptafluoro-*p*-tolyl enol ethers[1] that are amenable to assay by gas chromatography–mass spectrometry.[2] Our discovery that these derivatives could be cleaved to regenerate the hydroxy compounds[1] enabled us to use heptafluoro-*p*-tolyl as a protecting group; applications have been demonstrated in the synthesis of analogues of the anti-cancer drug tamoxifen.[3,4] The phase-transfer conditions used for the protection of alcohols and phenols caused the derivatisation of the enol function of 4-hydroxyandrost-4-ene-3,17-dione[1] but ketone functions did not react. In order to assay keto steroids that do not contain hydroxy functions it would be necessary to derivatise the ketone functions. We now report that under conditions which promote enolisation of ketones, octafluorotoluene forms enol ether derivatives with steroidal enone functions, and the ketone functions in 4,5α-dihydrotestosterone and the Wieland–Miescher ketone. As an application of our findings, we describe the use of heptafluoro-*p*-tolyl as a protecting group for the enone function in the synthesis of a deuterium-labelled testosterone.†

Results and Discussion

Preparation of Heptafluoro-p-*tolyl Enol Ethers.*—Typically, the keto steroids were heated with octafluorotoluene and caesium fluoride in dimethylformamide (DMF) above 100 °C. The enone functions in androst-4-ene-3,17-dione (**1**) and progesterone (**5**) could be protected, giving the 3,5-dienol ethers (**2**) and (**6**) as the respective sole product (yield 86 and 90%). Thus, in compound (**2**), the i.r. spectrum showed that the 17-keto function was still present, and the ^{13}C n.m.r. spectrum was consistent with an enol ether structure. The 3,5-diene structure was deduced from the ^1H n.m.r. spectrum in which pre-irradiation of either olefinic proton gave a nuclear Overhauser enhancement of the other, and the u.v. spectrum was typical for a *trans*-diene. The reaction conditions also derivatised the alcoholic functions and therefore testosterone (**3**) gave the bis-derivative (**4**) (85%). Unlike the unconjugated ketone functions in (**1**) and (**5**) which were not affected by the derivatisation procedure, that in 4,5α-dihydrotestosterone (**8**) did react and the enol ether bis-derivative (**10**) was obtained (93%) following initial formation of the mono-derivative (**9**) (Scheme 1). The 2-ene structure of compound (**10**) was deduced from its ^1H n.m.r. spectrum in which decoupling of the olefinic proton revealed an adjacent geminally coupled 1-H proton doublet. The considerable reactivity of the 3-keto group in dihydrotestosterone (**8**) has been demonstrated previously by the observation that its reaction with butanoic anhydride similarly gives a bis-ester.[5] In all of these examples, the formation of the preferred regioisomer is attributable to thermodynamic enolate control consistent with findings that methylation under conditions that give equilibration of enolates takes place at C-4 in testosterone[6] and at C-2 in cholestan-3-one.[7]



Scheme 1. *Reagents and conditions:* i, C_7F_8, CsF, Me_2NCHO, 150 °C

† A preliminary report of this part of the work has been published, M. Jarman and R. McCague. *J. Chem. Soc., Chem. Commun.*, 1986, 635.

Table 1. Isolated yields of heptafluoro-*p*-tolyl derivatives of the Wieland–Miescher ketone (**11**)

Conditions	Yield (%) (12)	(13)	(14)	Recovered (11)
C_7F_8, CsF, Me_2NCHO, 85 °C, 2 h	49	9	4	22
C_7F_8, CsF, Me_2NCHO, 20 °C, 20 h	64	4	0	14
C_7F_8, $Bu_4N^+ F^-$, THF, 20 °C, 30 min	10	52	2	21
C_7F_8, $Bu_4N^+ F^-$ ('anhydrous'), THF, 20 °C, 30 min	15	44	3	18

Table 2. Conditions and yields for the cleavage of heptafluoro-*p*-tolyl enol ethers

Derivative	Conditions	Product	Yield (%)
(**2**)	5M-H_2SO_4, THF, 60 °C, 12 h	(**1**)	80
(**4**)	5M-H_2SO_4, THF, 60 °C, 24 h	(**7**)	93
(**6**)	1M-HCl, EtOH, THF, 60 °C, 24 h	(**5**)	95
(**10**)	NaOMe, Me_2NCHO, 60 °C, 1 h	(**8**)	58
(**10**)	HCl (conc.), EtOH, 80 °C, 24 h	(**9**)	28 (42)[a]
(**12**)	HCl (conc.), EtOH, 80 °C, 2 h	(**11**)	60
(**13**)	HCl (conc.), EtOH, 80 °C, 4.5 h	(**11**)	50 (67)[a]

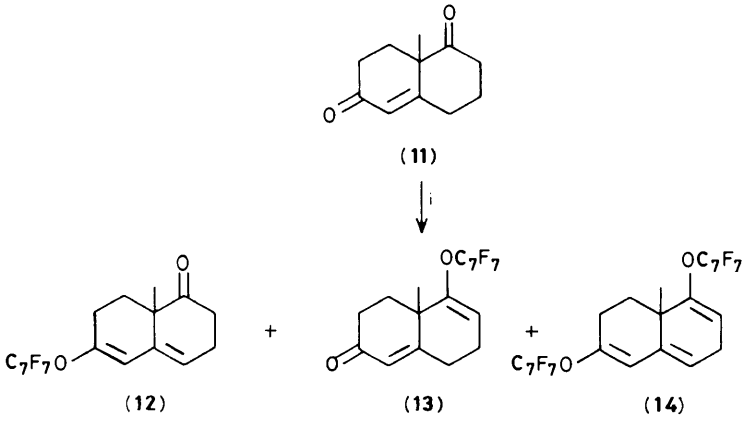
[a] Yield corrected for consumed starting material.

The Wieland–Miescher ketone (**11**) has been examined previously as a model compound in studies aimed at chemoselective dioxolane formation.[8,9] We found that this ketone was exceptionally reactive and was derivatised rapidly under the foregoing conditions, giving not only the expected dienol ether (**12**) as the major product but also the isomeric enol ether (**13**) and the bis-derivative (**14**) (Scheme 2 and Table 1). The products also formed slowly at room temperature. A rapid derivatisation of the dione (**11**) at room temperature could be accomplished by treatment with octafluorotoluene in tetrahydrofuran (THF) in the presence of tetra-n-butylammonium fluoride (TBAF; 1M solution containing <5% water), but the major product was now compound (**13**). Neither derivative (**12**) nor its isomer (**13**) could be established as having arisen as a result of thermodynamic product control since they could not be interconverted using either reaction conditions for derivatisation. The differences in product distribution could be a consequence of differences in the rate of enolate equilibration relative to the rate of reaction with octafluorotoluene. Since kinetic deprotonation of the dione (**11**) gives the enolate that would lead to compound (**13**),[10] isomer (**13**) may have been formed as a result of a rapid reaction of the initially formed enolate with octafluorotoluene, and isomer (**12**) may have formed *via* enolate equilibration.

dehydration at 40 °C/0.1 mmHg/48 h.[11] The high reactivity of the dione (**11**) presumably arises from the inductive electron-withdrawing effect of each ketone function enhancing the acidity of the other so that the ketone functions in (**11**) are not representative of those usually encountered.

Since only *O*-arylated products were obtained in the above reactions, octafluorotoluene reacted as a 'hard' electrophile according to the hard–soft acid–base (HSAB) theory.[12,13] This result is paralleled by observations that perfluorotolyl ethers resist attack by 'soft' nucleophiles,[3,4] and is consistent with fluorine atoms enhancing the 'hardness' of attached carbon atoms. However, another parameter favouring *O*-arylation is that the relatively bulky caesium or tetrabutylammonium counter-cations of the intermediate enolates have poor affinity for the enolate oxygen.

Regeneration of Ketone Functions.—Heptafluoro-*p*-tolyl derivatives of alcohols and phenols are conveniently cleaved with sodium methoxide in DMF to yield the parent hydroxy compounds.[1] These conditions were found suitable only for the regeneration of 4,5α-dihydrotestosterone (**8**) from its bis-derivative (**10**). Enones were unstable to these reaction

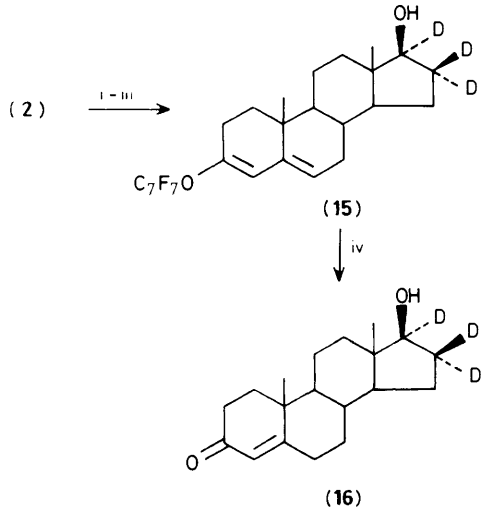


Scheme 2. *Reagents and conditions:* i, see Table 1

The unusually high reactivity of the dione (**11**) was verified by derivatisation of a mixture of (**11**) and androstenedione (**1**), when, with TBAF in THF, both compounds (**12**) and (**13**) were formed but compound (**2**) was not. Indeed, all attempts to derivatise androstenedione or progesterone using TBAF as base were unsuccessful, and only the alcoholic function of dihydrotestosterone was derivatised. It appeared that in these examples hydroxide ions in the TBAF solution consumed the octafluorotoluene. This hydrolysis could not be prevented by using 'anhydrous' TBAF prepared from the trihydrate by conditions but their derivatives behaved as enol ethers in that the enones could be regenerated by acidic hydrolysis. Heptafluoro-*p*-tolyl derivatives of alcohols were unaffected by acid and therefore hydrolysis of the testosterone bis-derivative (**4**) gave the mono-derivative (**7**). The hydrolysis of the enol ether (**10**) to give compound (**9**) was sluggish. Conditions and yields for the deprotection reactions are summarised in Table 2.

Preparation of Deuterium-labelled Testosterone.—An example of the use of the heptafluoro-*p*-tolyl group for the protection of

the enone function in synthesis is the preparation of the deuterium-labelled testosterone (**16**) useful as an internal standard in assays of the natural steroid using gas chromatography–mass spectrometry.[14] If the readily available steroid androst-4-ene-3,17-dione (**1**) is used as the starting material then it is expedient to protect the enone function and thereby both solve the problem of specific reduction of the 17-keto function and avoid the complication of deuterium incorporation at the 2-, 4-, and 6-position. The heptafluoro-*p*-tolyl derivative (**2**) has the enone function suitably protected. Thus, base-catalysed incorporation of deuterium into the derivative (**2**) under phase-transfer conditions,[15] followed by reduction of the 17-keto function with sodium borodeuteride, gave the testosterone derivative (**15**) (Scheme 3) (58% yield) from which the labelled steroid (**16**) was released by acidic hydrolysis (93% yield). The isotopic composition of the labelled testosterone (**16**), determined from the relative abundances of the appropriate molecular ions in the mass spectrum, was 95.0% [$^2H_3$], 4.7 [$^2H_2$], 0.3 [$^2H_1$]. The labelled testosterone (**16**) has been prepared previously, but from 3β-hydroxy-androst-5-en-17-one by a route involving a final enzymatic oxidation step to generate the required 4-en-3-one in the presence of the 17-hydroxy group.[16]



Scheme 3. *Reagents and conditions:* i, D_2O, $(C_7H_{15})_4N^+$ Cl^-, NaOD, PhMe, 60 °C; ii, $NaBD_4$, EtOD, 20 °C; iii, H_2O; iv, H_2SO_4(aq.), THF, 60 °C

In view of the propensity of heptafluoro-*p*-tolyl ether functions to react with methoxide, the group was remarkably resistant to the attack by hydroxide ion under the deuterium-exchange conditions. In addition to being inert to borohydride the perfluorotolyl group in the enol ethers described, in common with that in derivatives from phenols,[1,3,4] was also inert to certain organometallic species. For example derivatives (**4**) and (**10**) were unaffected by methylmagnesium iodide (3M; ether, 35 °C, 3 h) and phenylzinc chloride (0.6M; THF, 60 °C, 3 h). Therefore, it should be possible to use heptafluoro-*p*-tolyl as a protecting group for ketone functions during organometallic-reagent-mediated construction of carbon frameworks.

In conclusion, we have demonstrated that heptafluoro-*p*-tolyl is a versatile protecting group in that in addition to the protection of alcoholic and phenolic functions, certain ketone functions can also be protected selectively.

Experimental

DMF was dried by reflux over calcium hydride under nitrogen for 2 h, then distilled at 10 mmHg onto 3Å molecular sieves. Chromatography refers to column chromatography on silica gel (Merck 15111), with the eluant indicated applied at a positive pressure of 0.6 atm. For details of instrumentation see ref. 1. Ether refers to diethyl ether.

Preparation of Heptafluoro-p-*tolyl Derivatives of Steroids.*—*Derivative of androst-4-ene-3,17-dione*, (**2**). A solution of androst-4-ene-3,17-dione (**1**) (426 mg, 1.5 mmol) and octafluorotoluene (1.3 g, 5.1 mmol) in dry DMF (5 ml) containing powdered caesium fluoride (735 mg, 4.8 mmol) was heated under reflux under nitrogen. After 6 h, the mixture was poured into water (40 ml), the product was extracted with ether (40 ml), and the extract was concentrated. Chromatography of the residue gave, on elution with 1:10 ether–light petroleum (b.p. 40—60 °C), 3-[2,3,5,6-*tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]*androsta*-3,5-*dien*-17-*one* (**2**) (641 mg, 86%) as crystals, m.p. 98—99 °C [from light petroleum , (b.p. 80—100 °C)] (Found: C, 62.5; H, 5.1; F, 26.3. $C_{26}H_{25}F_7O_2$ requires C, 62.2; H, 5.0; F, 26.5%); $\nu_{max.}$ 1 744 cm^{-1} (s, C=O); $\lambda_{max.}$(EtOH) 232 (ε 19 950 dm^3 mol^{-1} cm^{-1}) and 266sh nm (4 500); δ_H (250 MHz; $CDCl_3$) 0.92 (3 H, s, 18-H_3), 1.02 (3 H, s, 19-H_3), 1.0—2.7 (17 H, methylene envelope + 3 × CH), 5.18 (1 H, s, 4-H; intensity enhanced by pre-irradiation at δ 5.29), and 5.29 (1 H, m, 6-H; intensity enhanced by pre-irradiation at 5.18); δ(^{13}C) (63 MHz; $CDCl_3$) 13.7 (q, C-18), 18.8 (q, C-19), 20.6 (t, C-11), 21.9 (t, C-15), 24.4 (t, C-1, -2, or -7), 30.8 (t, C-12), 31.5 (d and t, C-8 + C-1, -2, or -7), 33.6 (t, C-1, -2, or -7), 35.3 (s, C-10), 35.9 (t, C-16), 47.7 (s, C-13), 48.2 (d, C-14), 51.9 (d, C-9), 106.9 (d, C-4), 122.3 (d, C-6), 139.1 (s, C-5), 153.6 (s, C-3), and 220.7 (s, C-17); the carbon atoms of the perfluorotolyl group gave multiplets in the ranges δ 123—130 and δ 136—148; ^{13}C spectrum assignments are by comparison of reported chemical-shift data;[17] *m/z* 502 ($M^{+\cdot}$, 100%), 483 (M^+ − F, 4), 352 (12), and 269 (10).

Derivative of testosterone, (**4**). A solution of testosterone (**3**) (1.04 g, 3.6 mmol) and octafluorotoluene (4.5 g, 19 mmol) in dry DMF (10 ml) containing powdered caesium fluoride (4.5 g, 29 mmol) was heated under reflux under nitrogen for 4 h. Aqueous work-up as above and chromatography gave, on elution with light petroleum (b.p. 40—60 °C), 3,17β-*bis*-[2,3,5,6-*tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]*androsta*-3,5-*diene* (**4**) (2.2 g, 85%) as needles, m.p. 90—92 °C (from ethanol) (Found: C, 54.9; H, 3.7; F, 37.0. $C_{33}H_{26}F_{14}O_2$ requires C, 55.0; H, 3.6; F, 36.9%); δ_H (60 MHz; $CDCl_3$) 1.01 (6 H, s, 2 × Me), 1.0—2.7 (17 H, methylene envelope + 3 × CH), 4.39 (1 H, m, 17-H), and 5.20 (2 H, m, 4- and 6-H); *m/z* 720 ($M^{+\cdot}$, 100%), 701 M^+ − F, 4), 487 (M^+ − OC_7F_7, 24), 340 (20), 135 (26), and 81 (50).

Derivative of progesterone, (**6**). Derivatisation of progesterone (**5**) (591 mg) by the method described above for androst-4-ene-3,17-dione except that reflux was for 2 h and that the eluting solvent during chromatography was 1:5 dichloromethane–light petroleum (b.p. 40—60 °C) gave 3-[2,3,5,6-*tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]*pregna*-3,5-*diene*-20-*one* (**6**) (895 mg, 90%) as crystals, m.p. 114—116 °C [from light petroleum (b.p. 80—100 °C)] (Found: C, 63.45; H, 5.5; F, 25.3. $C_{28}H_{29}F_7O_2$ requires C, 63.4; H, 5.5; F, 25.1%); δ_H (250 MHz; $CDCl_3$) 0.66 (3 H, s, 18-H_3), 0.99 (3 H, s, 19-H_3), 1.0—2.6 (18 H, methylene envelope + 4 × CH), 2.14 (3 H, s, Ac), 5.16 (1 H, s, 4-H), and 5.27 (1 H, m, 6-H); *m/z* 530 ($M^{+\cdot}$, 7%) and 43 (CH_3CO^+, 100).

Derivatives of 4,5α-*dihydrotestosterone*, (**9**) *and* (**10**). (*a*) Derivatisation of 4,5α-dihydrotestosterone (**8**) (427 mg) by the method described above for testosterone except that the reaction mixture was maintained at 100 °C for 20 h instead of at reflux, and that the eluting solvent during chromatography was 1:5 ether–light petroleum (b.p. 40—60 °C), gave 17β-[2,3,5,6-*tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]-5α-*androstan*-3-*one* (**9**) (470 mg, 63%) as needles, m.p. 169—171 °C [from light petroleum (b.p. 80—100 °C)] (Found: C, 61.7; H, 5.8; F, 26.4. $C_{26}H_{29}F_7O_2$ requires C, 61.7; H, 5.8; F, 26.25%); δ_H (250 MHz;

$CDCl_3$) 0.97 (3 H, s, 18-H_3), 1.03 (3 H, s, 19-H_3), 0.7—2.5 (22 H, methylene envelope + 4 × CH), and 4.35 (1 H, t, *J* 7.8 Hz, 17-H); *m/z* 506 ($M^{\cdot+}$, 2%), 491 ($M^+ - CH_3$, 5), and 273 ($M^+ - OC_7F_7$, 100).

(*b*) Derivatisation of 4,5α-dihydrotestosterone (**8**) (2.39 g) by the method described above for testosterone with reflux for 4 h gave 3,17β-*bis*-[2,3,5,6-*tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]-5α-*androst*-2-*ene* (**10**) (5.55 g, 93%), m.p. 132—134 °C [from light petroleum (b.p. 80—100 °C)] (Found: C, 54.9; H, 3.9; F, 36.7. $C_{33}H_{28}F_{14}O_2$ requires C, 54.9; H, 3.9; F, 36.8%); δ_H (250 MHz; $CDCl_3$) 0.82 (3 H, s, 19-H_3), 0.95 (3 H, s, 18-H_3), 0.6—2.3 (20 H, methylene envelope + 4 × CH, containing 1 H, dd, *J* 6.3 and 16.3 Hz which collapsed to a doublet, *J* 16.3 Hz, on irradiation at δ 4.70), 4.38 (1 H, t, *J* 7.9 Hz, 17-H), and 4.70 (1 H, m, 2-H); *m/z* 722 ($M^{\cdot+}$, 2%), 489 ($M^+ - OC_7F_7$, 10), and 81 (100).

Preparation of Heptafluoro-p-*tolyl Derivatives of the Wieland–Miescher Ketone* (**11**).—*Using caesium fluoride*. (*a*) A solution of the enedione (**11**) (612 mg, 3.4 mmol) in dry DMF (7 ml) containing powdered caesium fluoride (1.2 g, 7.9 mmol) and octafluorotoluene (1.5 g, 6.4 mmol) was stirred under nitrogen at 85 °C. After 2 h, the mixture was poured into water (100 ml) and extracted with ether (2 × 50 ml). The combined extracts were washed with water (100 ml), dried with anhydrous sodium sulphate, and concentrated. Chromatography of the residue and (i) elution with light petroleum (b.p. 40—60 °C) gave 8a-*methyl*-3,8-*bis*-[2,3,5,6-*tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]-1,2,6,-8a-*tetrahydronaphthalene* (**14**) (93 mg, 4.4%) as crystals, m.p. 103—104 °C [from light petroleum (b.p. 80—100 °C)] (Found: C, 49.2; H, 2.0; F, 43.3. $C_{25}H_{12}F_{14}O_2$ requires C, 49.2; H, 2.0; F, 43.6%); δ_H (250 MHz; $CDCl_3$) 1.43 (3 H, s, Me), 1.94 (1 H, dt, *J* 6.4 and 12.5 Hz, 1-H), 2.3—3.0 (5 H, m), 4.59 (1 H, m, 7-H), 5.31 (1 H, s, 4-H), and 5.38 (1 H, m, 5-H); *m/z* 610 ($M^{\cdot+}$, 14%), 595 ($M^+ - CH_3$, 27), 377 ($M^+ - OC_7F_7$, 93), and 129 ($M^+ - 2 \times OC_7F_7 - CH_3$, 100).

(ii) Elution with 1:20 ether–light petroleum (b.p. 40—60 °C) gave the air-sensitive 8a-*methyl*-6-[2,3,5,6-*tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]-3,7,8,8a-*tetrahydronaphthalen*-1(2H)-*one* (**12**) (660 mg, 49%) as needles, m.p. 90—92 °C [from cold 1:3 dichloromethane–light petroleum (b.p. 40—60 °C)] (Found: C, 54.8; H, 3.4. $C_{18}H_{13}F_7O_2$ requires C, 54.8; H, 3.3%); δ_H (60 MHz; $CDCl_3$) 1.29 (3 H, s, Me), 1.5—3.0 (8 H, m), 5.38 (3 H, s, 5-H), and 5.55 (1 H, m, 4-H); *m/z* 394 (M^+, 100%).

(iii) Elution with 3:20 ether–light petroleum (b.p. 40—60 °C) gave 4a-*methyl*-5-[2,3,5,6-*tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]-4,4a,7,8-*tetrahydronaphthalen*-2(3H)-*one* (**13**) (123 mg, 9.1%) as crystals, m.p. 73—74 °C [from light petroleum (b.p. 80—100 °C)] (Found: C, 54.8; H, 3.4; F, 33.4. $C_{18}H_{13}F_7O_2$ requires C, 54.8; H, 3.3; F, 33.7%); δ_H (250 MHz; $CDCl_3$) 1.60 (3 H, s, Me), 2.08—2.70 (8 H, m), 4.66 (1 H, br d, *J* 4.9 Hz, 6-H), and 5.88 (1 H, s, 1-H); *m/z* 394 ($M^{\cdot+}$, 100%).

(iv) Elution with 1:1 ether–light petroleum (b.p. 40—60 °C) gave the starting enedione (**11**) (132 mg, 22%).

(*b*) Reaction as above but at 20 °C for 20 h instead of at 110 °C gave derivatives (**12**) (1.52 g, 64%), (**13**) (97 mg, 4%), and unchanged enedione (**11**) (146 mg 13.5%).

Using tetra-n-butylammonium fluoride (*TBAF*). (*a*) A stirred solution of the enedione (**11**) (942 mg, 5.30 mmol) and octafluorotoluene (2.50 g, 10.6 mmol) in THF (10 ml) at 20 °C was treated with a solution of TBAF in THF (1M; <5% water; 10 ml, 10 mmol). After 30 min, work-up as described for the caesium fluoride reaction gave derivatives (**12**) (212 mg, 10%), (**13**) (1.08 g, 52%), and (**14**) (55 mg, 2%), and unchanged enedione (**11**) (202 mg, 21%).

(*b*) On substituting the TBAF solution above with 'anhydrous' TBAF prepared by dehydration of the trihydrate at 40 °C/0.1 mmHg/48 h[13] (weight loss 17.5%, 3.65 mmol) the enedione (**11**) (433.4 mg, 2.43 mmol) gave derivatives (**12**) (146 mg, 15%), (**13**) (420 mg, 44%), and (**14**) (43 mg, 3%), and unchanged enedione (**11**) (76 mg, 18%). Under these conditions androst-4-ene-3,17-dione (**1**) and progesterone (**5**) gave no reaction, and 4,5α-dihydrotestosterone (**8**) gave the derivative (**9**) (t.l.c.).

Regeneration of Ketones from their Derivatives.—The conditions chosen for the cleavage of particular heptafluoro-*p*-tolyl enol ethers (200 mg) are given in Table 2 (text). Either (a) a stirred solution of the enol ether in THF (6 ml) was treated with dil. sulphuric acid (5M; 2 ml), (b) a stirred solution of the enol ether is 1:1 ethanol–THF (10 ml) was treated with dil. hydrochloric acid (1M; 5 ml), (c) a stirred solution of the enol ether in ethanol (6 ml) was treated with conc. hydrochloric acid (1 ml), (d) a stirred solution of the enol ether in dry DMF (1 ml) was treated with sodium methoxide (0.5 g).

Under conditions (a), (b), or (c), the mixtures were heated under reflux for the time indicated in Table 2, and for conditions (d) the mixture was maintained at 60 °C for 1 h. The mixtures were then poured into water (20 ml) and extracted with ether (2 × 15 ml). The combined extracts were washed with water (20 ml), dried with anhydrous sodium sulphate, and concentrated. The products were isolated by chromatography, elution being with 1:2 ether–light petroleum (b.p. 60—80 °C) for androst-4-ene-3,17-dione (**1**), with 1:20 ether–dichloromethane for progesterone (**5**), with 2:5 ether–light petroleum (b.p. 60—80 °C) for compound (**7**), with 1:5 ether–dichloromethane for 4,5α-dihydrotestosterone (**8**), with 1:5 ether–light petroleum (b.p. 60—80 °C) for compound (**9**), or with 1:1 ether–light petroleum (b.p. 60—80 °C) for the Wieland–Miescher ketone (**11**). In each case the compound was identified by comparison of the chromatographic mobility and the ^1H n.m.r. spectrum with those of authentic material. The testosterone derivative (**7**), m.p. 113—115 °C, has been prepared previously.[1] Yields of products are given in Table 2.

Deuterium-labelled Testosterone (**16**).—A solution of the androst-4-ene-3,17-dione derivative (**2**) (413 mg) in toluene (6 ml) containing tetra-n-heptylammonium chloride (200 mg) was stirred with a solution of sodium deuterioxide (1.2 g) in deuterium oxide (11 ml) at 60 °C. After 4 h, the organic layer was concentrated under reduced pressure and the resulting oil was dissolved in ethan[^2H]ol (7 ml). Sodium borodeuteride (170 mg) was added and the mixture was stirred at 20 °C. After 1 h, the mixture was poured into water (40 ml) and the product was extracted with ether (40 ml). The extract was washed with water (2 × 30 ml), dried with anhydrous sodium sulphate, and concentrated. Chromatography of the residue, with 3:7 ether–light petroleum (b.p. 40—60 °C) as eluant, gave 3-[2,3,5,6-*tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*][16,16,17α-$^2H_3$]-*androsta*-3,5-*dien*-17β-*ol* (**15**) as crystals (243 mg, 58%), m.p. 143—144 °C [from light petroleum (b.p. 80—100 °C)]; *m/z* 507 ($M^{\cdot+}$, 100%), 490 ($M^+ - OH$, 6), 352 (6), 339 (12), 274 (8), and 256 (7).

A solution of this perfluorotolyl ether (63 mg) in THF (6 ml) and sulphuric acid (2M; 6 ml) was heated under reflux. After 6.5 h, the mixture was cooled and partitioned between ether (20 ml) and aqueous sodium hydroxide (3M; 20 ml). The ether solution was washed with water (15 ml), dried with sodium sulphate, and concentrated. Chromatography of the residue gave, on elution with 1:4 light petroleum (b.p. 40—60 °C)–ether, [16,16,17α-$^2H_3$] testosterone (**16**) (33.3 mg, 93%) as crystals, m.p. 154—155 °C [from 1:1 light petroleum (b.p. 80—100 °C)–chloroform]; *m/z* 291 ($M^{\cdot+}$, 43%), 249 (35), 206 (15), 150 (18), and 124 (100). Relative intensities in the molecular-ion region were 294 (0.6%), 293 (5), 292 (32), 291 (100), 290 (5), and 289 (0.3).

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