STRUCTURES AND SYNTHESIS OF 4a-HOMO-7,19-DINORSTEROIDS, X-RAY CRYSTALLOGRAPHY AND NMR SPECTROSCOPY+

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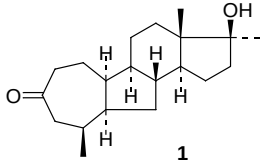
X-Ray diffraction revealed the absolute configuration of 4aβ-methyl-4a-homo-7,19-dinor-5α,10α-androstane-3,17-dione. Detailed NMR analysis suggested that the 5α configuration existed in the starting material, 3β-acetoxy-4a-methylidene-4a-homo-7,19-dinor-5α-androst-9-en-17-one, and related compounds. Thus 5-methyl-5β-estr-9-ene derivatives with a leaving group in position 6β were found to react with nucleophiles to form rearranged 4a-homo-7,19-dinorandrostane derivatives with a 5α configuration.

Key words: Steroids; Antiandrogens; Solvolysis; Rearrangements; NMR Spectroscopy, ^{1}H, ^{13}C; X-Ray diffraction; Absolute configuration; Conformation analysis.

Antiandrogens comprise a series of compounds which bind to androgen receptors without affecting their conformation; the receptor complex does not bind to DNA and thus no biological response is elicited. In the rational design of antiandrogens, new compounds are sought which bind to the receptor but do not force it to expose its DNA-binding domain[2]. One approach involved the synthesis of analogues (*e.g.*, 4,5-seco analogues[3]) which were flexible upon receptor binding and did not elicit a change of its conformation. Many other synthetic steroids have been tested for antiandrogenic activity but none has been found among the 5β-steroids[4]. As a rule, 5β-steroids exert reduced binding to steroid binding protein[5] suggesting that the absolute configuration is important. Of 4a-homo-7,19-dinorandrostane derivatives, compounds **1** and **2** were found to exert anti-

+ Part CDV in the series On Steroids; Part CDIV see ref.[1]

androgenic activity *in vivo*[6]. Since compound **1** had previously been ascribed a 5β configuration[6], a reinvestigation of its structure became necessary. Here we present new X-ray diffraction and NMR results which suggest that a 5α configuration is present in 4a-homo-7,19-dinorandrostane derivatives formed by nucleophilic reaction of 5-methyl-5β-estr-9-ene derivatives with a 6β leaving group. These findings are important in relation to the ring contraction/expansion synthetic methodology, as well as to the biological activities of antiandrogens.



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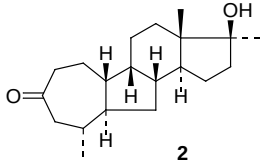
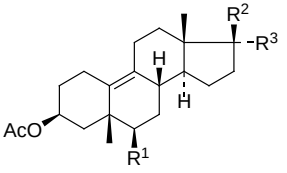


2

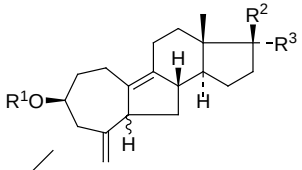
Synthesis of these compounds was based on the experience[7] that this type of skeleton was formed on treatment of 5,6-dihalosteroids with silver salts. Later[8] it was shown that such compounds were more easily accessible by solvolysis of Westphalen type steroids. Thus as shown in Scheme 1, compounds **3** and **4** on treatment with silver salts yielded products which were previously identified as **5b** and **6b**, respectively, with a 5β-H configuration. Reduction of compounds **3**, **4** and **7** with lithium aluminum hydride also gave products of rearrangement formulated previously as **8b** and **9b**. They were accompanied by 3,4-seco derivatives, tentatively given the formula **10b** and **11b**, respectively, as the low stability of the dienes did not allow for detailed NMR characterization. In particular, the doubly allylic 5-position was susceptible to reaction with peroxides in solvents. Moreover, the 7-membered A ring is predisposed to transannular reactions[9]: diene **9** was easily converted to the 3β,10β-epoxy derivative **12** by the action of 3-chloroperoxy-benzoic acid, which was suggested earlier to have a 5β configuration (*i.e.* compound **12b**). The structure determinations of these unstable compounds have been mainly based on chemical experiments and relatively simple ^{1}H NMR measurements.

The reaction mechanism leading to the above dienes was previously interpreted in terms of a concerted process in which a carbenium ion, formed at the carbon C6, was saturated by migration of the antiperiplanar C10–C5 bond. This argument was used to support the 5β configuration of all products, as the C-5 configuration was believed[8] to have been inverted in the process.

In addition, compound **9** was converted to a mixture of diketones **13** and **14** by hydrogenation and oxidation. X-Ray diffraction data for single crystals of one of the diketones, compound **13**, are described below. They confirm the 4a-homo-7,19-dinorandrostane skeleton and the expected the 9α,10α configuration. However, the C-5 configuration is now found to be



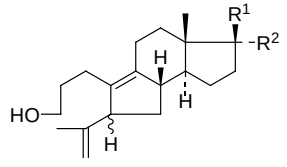
(i) or (ii)



	R^1	R^2	R^3
3	Cl	$OOCC(CH_3)_3$	H
4	Cl	=O	
7	OSO_2CH_3	$-OCH_2CH_2O-$	

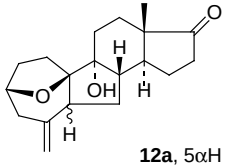
		R^1	R^2	R^3
5a	5αH	Ac	$OOCC(CH_3)_3$	H
5b	5βH	Ac	$OOCC(CH_3)_3$	H
6a	5αH	Ac	=O	
6b	5βH	Ac	=O	
8a	5αH	H	OH	H
8b	5βH	H	OH	H
9a	5αH	H	=O	
9b	5βH	H	=O	

(ii)



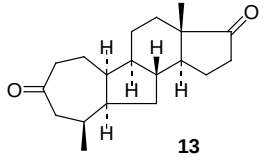
		R^1	R^2
10a	5αH	OH	H
10b	5βH	OH	H
11a	5αH	=O	
11b	5βH	=O	

(iii)

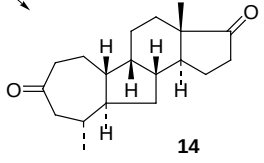


12a, 5αH
12b, 5βH

(iv), (v)



13



14

(i) CH_3COOAg; (ii) $LiAlH_4$; (iii) MCPBA; (iv) H_2, Pt; (v) $CrCO_3$, CH_3COOH

SCHEME 1

5α, thereby casting doubt on the original assignment of the configuration at carbon C-5 of the starting diene **9**. The results are in agreement with a previous X-ray diffraction structural analysis of another product[10] obtained from the diene **9**, *viz*. the saturated diketone **14**.

The question at what stage the 5α configuration was introduced into the molecule, has been investigated by high-field 1D and 2D ^{1}H and ^{13}C NMR spectroscopy of compounds **6a**, **11a**, **12a**, **13** and **14** which were prepared anew immediately before NMR measurements.

NMR Analysis

A general strategy used for a complete structural assignment of ^{1}H and ^{13}C NMR spectra of compounds **6a**, **11a**, **12a**, **13** and **14** was as follows. Starting from the unambiguously assigned signals in 1D proton NMR spectrum, it was possible to deduce proton-proton coupling patterns from ^{1}H,^{1}H 2D-COSY spectra and complete the structural assignment of protons in the whole molecule. The multiplicity of signals and most coupling constants *J*(H,H) could be determined from the expanded parts of resolution-enhanced 1D spectra (except those of strongly coupled spin systems or heavily overlapping regions). If necessary selective proton decoupling was used to confirm the *J* values or eliminate fine splitting and/or line broadening due to long-range couplings (especially on allylic protons). The 2D-*J*-resolved ^{1}H NMR spectrum was helpful in the recognition of some overlapping proton multiplets in compound **13**. Stereochemical assignment of geminal alicyclic protons was derived from characteristic values of vicinal couplings or difference 1D-NOE experiments. The APT carbon-13 NMR spectra were then used to determine chemical shifts and distinguish the multiplicity of individual carbon signals. Structure assignment of CH, CH_2 and CH_3 signals was derived from ^{1}H,^{13}C 2D-HMQC spectra by correlation with the previously assigned proton signals. The remaining quaternary carbons were assigned on the basis of chemical shifts. The ^{1}H and ^{13}C NMR spectra measured after *in situ* TAI-acylation[11,12] of hydroxy derivatives **11a** and **12a** showed characteristic induced shifts in the neighborhood of OH group. ^{1}H and ^{13}C NMR data of compounds **6a**, **11a**, **12a**, **13** and **14** are summarized in Tables I–V. The main structure problem in these compounds was the configuration at carbon C-5 (together with the configurations at C-9 and C-10 in diketones **13** and **14**) which is discussed below.

From inspection of molecular models of compound **6a** it follows that the 5β configuration should lead to a close similarity of torsion angles ϕ(H6α,H5β) ≈ ϕ(H6α,H8β) and ϕ(H6β,H5β) ≈ ϕ(H6β,H8β), due to the approx-

TABLE I
^{13}C and ^{1}H NMR parameters of compound **6a**

Chemical shifts, ppm				Coupling constants, Hz			
Carbon	δ(C)	Proton[a]	δ(H)	H*i*,H*j*	*J*	H*i*,H*j*	*J*
C-1	22.62 t	H-1α	1.79 dddq	1α,1β	14.2	5,6α	9.6
C-2	34.45 t	H-1β	2.48 ddd	1α,2α	2.9	5,6β	5.6
C-3	76.21 d	H-2α	2.05[b]	1α,2β	12.2	6α,6β	13.4
C-4	40.22 t	H-2β	1.37 ddt	1α,5	1.0	6α,8	4.7
C-4a	148.85 s	H-3	4.74 tt	1α,8	1.0	6β,8	8.8
C-4b	114.11 t	H-4α	2.39 dd	1α,11β	1.0	8.14	11.8
C-5	54.47 d	H-4β	2.21 bdd	1β,2α	6.2	11α,11β	14.7
C-6	34.01 t	H-4(en)	4.93 bt	1β,2β	3.3	11α,12α	5.1
C-8	46.04 d	H-4b(ex)	4.97 bd	1β,8	<0.5	11α,11β	2.0
C-9	134.91 s[c]	H-5	3.39 m	2α,2β	12.7	11β,12α	13.0
C-10	138.07 s[c]	H-6α	1.90 ddd	2α,3	4.3	11β,12β	5.4
C-11	21.22 t	H-6β	1.76 ddd	2α,4α	1.5	12α,12β	12.9
C-12	31.84 t	H-8	2.69 m	2β,3	10.2	12α,18	0.8
C-13	48.64 s	H-11α	2.44 ddd	3,4α	3.3	14,15α	5.8
C-14	52.02 d	H-11β	2.07[b]	3,4β	10.3	14,15β	12.5
C-15	22.49 t	H-12α	1.15 bdt	4α,4β	12.4	15α,15β	12.3
C-16	35.76 t	H-12β	1.84 ddd	4α,4b(ex)	0.8	15α,16α	8.8
C-17	220.53 s	H-14	1.36 dt	4β,4b(ex)	1.0	15α,16β	1.1
C-18	13.02 q	H-15α	1.97 ddd	4β,5	≈0	15β,16α	9.4
		H-15β	1.62 tt	4b(en),4b(ex)	1.9	15β,16β	8.9
CH_3**C**OO	170.23 s	H-16α	2.09 dt	4b(en),5	1.0	16β,16β	19.2
CH_3COO	21.38 q	H-16β	2.45 ddd	4b(ex),5	0.6		
		H-18(3H)	0.97 d				
		CH_3COO	2.02 s				

[a] Terms (en) and (ex) express *cis*- and *trans*-relationship between individual H-4b protons and C-5 carbon; [b] signal position was determined from 2D-COSY spectrum; [c] the assignment of signals may be interchanged.

imately symmetrical mutual position of protons H-5β and H-8β in the ring B (see Fig. 1a). Similar relations should also hold for the corresponding vicinal coupling constants; however this is not the case of the experimentally observed *J* values (9.6 and 4.8 Hz for H-6 at δ 1.90; 5.6 and 8.8 Hz for H-6 at δ 1.76). This observation can be rationalized most directly by a 5α configuration with a nearly flat cyclopentane ring B and torsion angles $\phi \approx 0$ and ≈ 120° for the *cis*- and *trans*-oriented protons (see Fig. 1b). To confirm the suggested 5α configuration in compound **6a**, we carried out a series of 1D-NOE difference experiments with selective irradiation of protons H-3 and H-5. Saturation of proton H-3α showed, in addition to trivial NOEs in the neighboring positions (4.4% at H-4α and 4.1% at H-2α), also NOEs at more distant protons H-1α (3.8%) and H-5 (2.0%). Saturation of H-5 allowed us to unambiguously assign the geminal *exo*-methylene protons on C-4b: the observation of a 5.1% NOE at δ 4.93 indicated the H-4b-*endo* proton while the very weak negative NOE of 0.6% at δ 4.97 corresponded to the H-4b-*exo* proton. We have observed further NOEs at H-1α (2.3%), H-4α (1.3%), H-6α (5.4%) and even at H-14 (1.8%). Molecular models show that the distance of H-5α to H-14α can vary between 3–4 Å, depending on the conformation of ring B. The ring flattening indicated by the *J* values (see above) gives a shorter distance of ≈3 Å. All these NOE effects are consistent with the 5α configuration in compound **6a** since the relative distance of the involved atoms would be much larger for the 5β configuration.

In compound **12a**, the second-order pattern of protons on C-1 and C-2 and rather similar chemical shifts of the H-6α and H-1α protons made the investigation of the configuration at C-5 by NOE measurements difficult. However, these problems were circumvented by *in situ* acylation of compound **12a** with TAI. TAI acylation of 9α-OH induced significant downfield shifts of the H-1α and H-5 protons (0.95 and 0.98 ppm), which could be in-

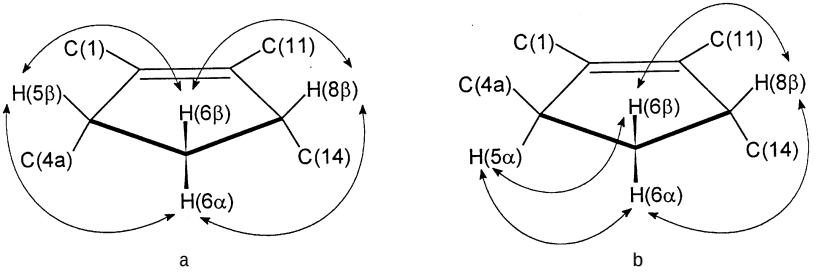


FIG. 1

Schematic conformation formulae of ring B in compounds **6a** and **6b** showing mutual positions of hydrogen atoms: a 5β-H-configuration, b 5α-H-configuration

TABLE II
^{13}C and ^{1}H NMR parameters of compound **12a**

	Chemical shifts, ppm					Coupling constants, Hz			
Carbon	δ(C)	Δδ(C) (+TAI)	Proton[a]	δ(H)	Δδ(H) (+TAI)	H*i*,H*j*	*J*	H*i*,H*j*	*J*
C-1	26.24 t	(–4.46)	H-1α	2.06[b]	(0.95)	1α,1β	13.9	6α,8	3.3
C-2	23.90 t	(–0.34)	H-1β	1.58 ddd	(0.19)	1α,2α	12.0	6β,8	9.3
C-3	69.26 d	(–0.10)	H-2α	1.57 m	(0.05)	1α,2β	7.2	8,14	12.6
C-4	42.07 t	(0.55)	H-2β	1.93[b]	(0.04)	1β,2α	2.2	11α,11β	15.0
C-4a	147.20 s	(–0.39)	H-3	3.97 m	(0.05)	1β,2β	12.0	11α,12α	5.6
C-4b	113.04 t	(2.35)	H-4α	2.66 dp	(0.04)	2α,2β	13.5	11α,12β	2.3
C-5	60.45 d	(–6.72)	H-4β	2.19 ddd	(0.07)	2α,3	1.3	11β,12α	13.2
C-6	31.44 t	(–0.92)	H-4b(en)	4.80 t	(0.20)	2α,4α	2.0	11β,12β	6.4
C-8	49.92 d	(–0.39)	H-4b(x)	4.74 t	(0.13)	2β,3	5.2	12α,12β	13.3
C-9	82.94 s[c]	(13.46)	H-5	2.78 dm	(0.98)	3,4α	2.6	14,15α	5.7
C-10	84.84 s[c]	(–0.16)	H-6α	2.02 ddd	(–0.04)	3,4β	4.0	14,15β	12.3
C-11	30.39 t	(0.83)	H-6β	1.87 ddd	(0.11)	4α,4β	15.3	15α,15β	12.3
C-12	30.00 t	(0.00)	H-8	2.24 ddd	(0.09)	4α, 4b(ex)	2.2	15α,16α	8.9
C-13	47.39 s	(0.00)	H-11α	2.10 ddd	(0.13)	4β,5	1.7	15α,16β	1.1
C-14	48.61 d	(–0.23)	H-11β	1.87 ddd	(0.06)	4b(en), 4b(ex)	1.9	15β,16α	9.6
C-15	23.27 t	(–0.19)	H-12α	1.51 dt	(–0.08)	5,6α	9.8	15β,16β	8.9
C-16	36.14 t	(–0.22)	H-12β	1.72 ddd	(0.07)	5,6β	2.9	16α,16β	19.2
C-17	221.03 s	(–0.96)	H-14	2.08 dt	(–0.31)	6α,6β	14.3		
C-18	12.78 q	(0.25)	H-15α	1.96 dddd	(–0.01)				
			H-15β	1.50 ddt	(0.05)				
			H-16α	2.11 ddd	(–0.04)				
			H-16β	2.47 dd	(0.03)				
			H-18 (3H)	0.99 s	(0.03)				

[a] Terms (en) and (ex) express *cis*- and *trans*-relationship between individual H-4b protons and C-5 carbon; [b] signal position was determined from 2D-COSY spectrum; [c] the assignment of signals may be interchanged.

TABLE III
^{13}C and ^{1}H NMR parameters of compound **11a**

	Chemical shifts, ppm					Coupling constants, Hz			
Carbon	δ(C)	Δδ(C) (+TAI)	Proton[a]	δ(H)	Δδ(H) (+TAI)	H*i*,H*j*	*J*	H*i*,H*j*	*J*
C-1	22.78 t	(–0.24)	H-1	1.89 ddd	(–0.06)	1,1′	16.0	6α,6β	13.2
C-2	30.79 t	(–4.30)	H-1′	2.20 dt	(0.03)	1,2	[b]	6α,8	7.6
C-3	62.87 t	(4.39)	H-2	1.55 m	(0.16)	1,2′	[b]	6β,8	7.9
C-4	19.03 q	(–0.04)	H-2′	1.65 m	(0.18)	1′,2	8.1	8,14	11.6
C-4a	148.10 s	(–0.23)	H-3	3.58 dt	(0.60)	1′,2′	8.2	11α,11β	15.2
C-4b	110.29 t	(0.15)	H-3′	3.61 dt	(0.64)	1′,8	<0.5	11α,12α	5.2
C-5	54.73 d	(–0.04)	H-4	1.61 dd	(0.01)	2,2′	[b]	11α,12β	1.7
C-6	33.48 t	(–0.03)	H-4b(en)	4.68 m	(0.00)	2,3	~6.7	11β,12α	13.1
C-8	45.74 d	(0.03)	H-4b(ex)	4.68 m	(0.00)	2,3′	~6.7	11β,12β	5.6
C-9	134.94 s	(–1.08)	H-5	3.27 m	(–0.02)	2′,3	~6.7	12α,12β	13.1
C-10	138.39 s	(0.89)	H-6α	1.65 ddd	(0.01)	2′,3′	~6.7	12β,18	<0.5
C-11	21.34 t	(0.03)	H-6β	1.89 ddd	(0.01)	3,3′	10.4	14,15α	5.8
C-12	31.56 t	(–0.08)	H-8	2.69 m	(0.00)	4,4b(en)	1.0	14,15β	12.6
C-13	48.52 s	(–0.06)	H-11α	2.52 ddd	(–0.04)	4,4b(ex)	1.2	15α,15β	12.5
C-14	53.71 d	(–0.06)	H-11β	2.08 m	(0.01)	4b(en), 4b(ex)	[b]	15α,16α	8.9
C-15	22.39 t	(–0.01)	H-12α	1.18 dt	(–0,01)	4b(en),5	[b]	15α,16β	1.2
C-16	35.90 t	(–0.04)	H-12β	1.88 ddd	(0.00)	5,6α	9.7	15β,16α	9.5
C-17	220.73 s	(–0.24)	H-14	1.26 ddd	(0.00)	5,6β	2.1	15β,16β	8.9
C-18	12.97 q	(–0.02)	H-15α	1.94 dddd	(0.00)	5.8	2.1	16α,16β	19.3
			H-15β	1.61 tt	(0.01)	5,11β	1.8		
			H-16α	2.09 dt	(0.01)				
			H-16β	2.46 ddd	(0.00)				
			H-18(3H)	0.96 s	(–0.01)				

[a] Terms (en) and (ex) express *cis*- and *trans*-relationship between individual H-4b protons and C-5 carbon; [b] the *J* value could not be determined.

TABLE IV
^{13}C and ^{1}H NMR parameters of compound **13**

Chemical shifts, ppm				Coupling constants, Hz					
Carbon	δ(C)	Proton[a]	δ(H)	H*i*,H*j*	*J*[a]		H*i*,H*j*	*J*[a]	
C-1	21.97 t	H-1α	1.74 m	1α,1β	14.6		8,9	11.0	(166)
C-2	41.07 t	H-1β	1.41[b]	1α,2α	2.2	(84)	8,14	10.8	(168)
C-3	214.15 s	H-2α	2.52 ddd	1α,2β	6.3	(–34)	9,10	4.8	(–45)
C-4	44.81 t	H-2β	2.47 ddd	1α,4α	0.6		9,11α	[c]	(55)
C-4a	30.62 d	H-4α	2.07 ddt	1α,10	3.8	(–67)	9,11β	[c]	(176)
C-4b	22.64 q	H-4β	2.75 dd	1β,2α	11.6	(–158)	11α,11β	[c]	
C-5	52.72 d	H-4a	2.33 dddq	1β,2β	2.8	(84)	11α,12α	4.1	(–55)
C-6	22.16 t	Me4b	0.97 d	1β,10	12.6	(174)	11α,12β	3.6	(65)
C-8	38.71 d	H-5	1.37[b]	2α,2β	16.7		11β,12α	12.3	(–175)
C-9	48.08 d	H-6α	1.41[b]	4α,4β	16.0		11β,12β	2.5	(–55)
C-10	46.89 d	H-6β	1.63[b]	4α,4α	1.3	(90)	12α,12β	13.0	
C-11	24.79 t	H-8	1.84 m	4α,5	1.3		12α,18	0.7	
C-12	31.55 t	H-9	2.40 m	4β,4a	11.6	(–151)	14,15α	5.7	(–35)
C-13	49.27 s	H-10	2.05 dddd	4a,4b	7.0		14,15β	12.8	(–157)
C-14	51.90 d	H-11α	1.43[a]	4a,5	3.6	(–65)	15α,15β	12.3	
C-15	22.54 t	H-11β	1.63[b]	5,6a	[c]	(–13)	15α,16α	9.0	(20)
C-16	35.79 t	H-12α	1.27 dddq	5,6β	[c]	(–135)	15α,16β	1.2	(–101)
C-17	220.33 s	H-12β	1.83 ddd	5,10	5.9	(41)	15β,16α	9.0	(142)
C-18	14.16 q	H-14	1.48 ddd	6α,6β	[c]		15β,16β	8.8	(21)
		H-15α	1.94 dddd	6α,8	8.8	(–132)	16α,16β	19.2	
		H-15β	1.64 ddt	6β,8	10.0	(–10)			
		H-16α	2.10 ddt						
		H-16β	2.46 ddd						
		H-18(3H)	0.87 d						

[a] Torsion angles (in °) found in crystal are given in parentheses; [b] signal position was determined from 2D-COSY spectrum; [c] the *J* value could not be determined.

TABLE V
^{13}C and ^{1}H NMR parameters of compound **14** in $CDCl_3$

Chemical shifts, ppm				Coupling constants, Hz					
Carbon	δ(C)	Proton[a]	δ(H)	H*i*,H*j*	*J*[a]		H*i*,H*j*	*J*[a]	
C-1	24.51 t	H-1α	1.55[b]	1α,1β	13.0		8,9	10.4	(12)
C-2	43.07 t	H-1β	1.84 ddd	1α,2α	≈4.0	(–49)	8,14	11.4	(171)
C-3	213.99 s	H-2α	2.55 dt	1α,2β	11.8	(–165)	9,10	5.6	(–36)
C-4	51.25 t	H-2β	2.38 ddd	1α,10	≈11.8	(–153)	9,11α	11.7	(–176)
C-4a	37.02 d	H-4α	2.55 dd	1β,2α	≈4.0	(68)	9,11β	≈4.4	(–59)
C-4b	22.47 q	H-4β	2.30 dd	1β,2β	4.8	(–47)	11α,11β	[c]	
C-5	51.03 d	H-4a	1.50[b]	1β,10	≈0	(89)	11α,12α	[c]	(40)
C-6	36.93 t	Me4b	1.02 d	2α,2β	16.8		11α,12β	[c]	(158)
C-8	36.77 d	H-5	1.49[b]	4α,4β	12.7		11β12α	[c]	(–76)
C-9	42.32 d	H-6α	1.75 m	4α,4a	10.8	(166)	11β,12β	[c]	(42)
C-10	49.75 d	H-6β	1.46[b]	4β,4a	1.5	(–76)	12α,12β	[c]	
C-11	19.97 t	H-8	2.12[b]	4a,4b	6.2		14,15α	5.3	(–45)
C-12	28.53 t	H-9	2.29 m	4a,5	[c]	(172)	14,15β	12.0	(–169)
C-13	46.75 s	H-10	1.54[b]	5,6α	6.4	(–40)	15α,15β	11.6	
C-14	45.54 d	H-11α	1.34 m	5,6β	≈12.6	(–160)	15α,16α	≈8.6	(21)
C-15	23.53 t	H-11β	1.52[b]	5,10	≈11.8	(175)	15α,16β	1.2	(–99)
C-16	36.33 t	H-12α	1.92 m	6α,6β	12.6		15β,16α	≈9.8	(146)
C-17	221.78 s	H-12β	1.35 m	6α,8	2.3	(–108)	15β16β	8.8	(26)
C-18	18.95 q	H-14	1.62[b]	6β,8	8.5	(12)	16α,16β	19.5	
		H-15α	2.00 m						
		H-15β	1.56[b]						
		H-16α	2.14 dt						
		H-16β	2.47 ddd						
		H-18(3H)	0.95 s						

[a] The *J* values obtained from the spectrum after addition of $Eu[FOD]_3$; torsion angles (in °) found in crystal (ref.[10]) are given in parentheses; [b] signal position was determined from 2D-COSY spectrum; [c] the *J* value could not be determined.

terpreted as a result of the same α configuration of both protons (H-1β was shifted by 0.19 ppm only). Additional evidence indicating the opposite proton configuration at C-5 and C-8 followed from their different vicinal coupling constants with the H-6α (9.8 and 3.3 Hz) and H-6β protons (2.9 and 9.3 Hz); *c.f.* the detailed discussion for compound **6a** and Fig. 1. The final evidence suggesting a 5α configuration was obtained from difference 1D-NOE spectra of the TAC derivative of **12a**: irradiation of H-5 led to an NOE enhancement of 9.4% at *exo*-methylene H-4b-*endo*, 6.1% for the two-proton multiplet of H-6α and H-6β, and finally 2.2% NOE at H-1α. The ^{13}C NMR spectrum of the TAC derivative of **12a** showed a significant downfield shift (13.46 ppm) for the C9-OR carbon, and smaller upfield shifts for C-1 and C-5 (–4.46 and –6.72 ppm) in agreement with literature values[12]. All the data are consistent with the 5α configuration for compound **12a**.

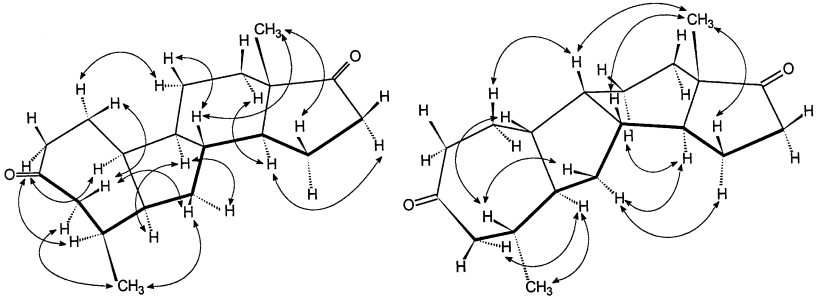
The ^{1}H and ^{13}C NMR data for compound **11a** are summarized in Table III. The opening of ring A in compound **11a** influences the geometry of ring B as indicated by the different *J* values of protons at positions 5, 6 and 8 (see Table III) when compared with compound **6a**. TAI acylation confirmed the presence of the CH_2OH group and enabled the assignment of the protons and carbons of the CH_2–CH_2–CH_2–OH fragment by comparison of the ^{1}H and ^{13}C NMR spectra of the original compound and the TAC derivative. The TAI-induced shifts of other protons and carbons were very small or negligible. Difference 1D-NOE ^{1}H NMR spectra of compound **11a** were used for assignment of the C-5 configuration. On irradiation of the H-8β proton, an H-6β signal was identified at δ 1.89 (2.7% NOE) while no NOE was observed for H-6α at δ 2.02. On saturation of H-5, we observed a 5.0% NOE for the *exo*-methylene protons and an 8.9% NOE at H-6α (δ 1.65); significantly, there was no NOE at H-6β and H-8β. No intensity changes were observed for any other signals, which verifies the 5α configuration for compound **11a**.

The NMR arguments on the configurations at carbon atoms C-5, C-9 and C-10 in diketones **13** and **14** are based mainly on the NOE contacts and vicinal proton coupling constants (when compared with torsion angles of corresponding protons derived from X-ray data of both isomers). It should be noted that energy minimised conformations calculated by molecular mechanics are very close to X-ray structures (torsion angle of protons differ less than 10°). The ^{1}H and ^{13}C NMR data of diketones **13** and **14** are given in Tables IV and V. Although the character of the ^{1}H NMR spectra did not enable determination of some of the relevant coupling constants, the values of all accessible vicinal *J*(H,H) are in good agreement with the ring

annelation and geometry derived by X-ray analysis (see below). The multiplet pattern and *J* values of some overlapping but weakly coupled protons were checked in 2D *J*-resolved spectrum of diketone **13**. For obtaining of a more complete set of coupling constants for diketone **14**, its spectrum after addition of a small amount of lanthanide shift reagent (Eu[FOD]$_3$) was used. The non-trivial NOE contacts (between non-coupled protons) observed in 2D-NOESY spectra are shown in Fig. 2. They confirm stereochemical assignment of geminal protons in both isomers and configuration 5α-H, 9α-H, 10α-H in diketone **13** and configuration 5α-H, 9β-H, 10β-H in diketone **14**. The most of the contacts between protons within a distance <3 Å were detected – the remaining ones could not be assigned unequivocally due to the signal overlap but they are not excluded.

X-Ray Analysis

Compound **13** was characterized in the solid state by X-ray diffraction (Table VI). The absolute configuration was set by the known configurations of C-8, C-9, C-13 and C-14. This determined the relative configurations for C-4aα, C-5α and C-10α. A labelled view of the molecule (see Fig. 3) shows that the ring junctions are *cis, trans, trans* for the A/B, B/C and C/D rings, respectively. All other data, including bond distances, bond angles and torsion angles are included as Supporting Information. Using previously described methods and notation for ring conformation analysis[13,14], the conformations of the rings are as follows. The seven-membered A ring is in a slightly distorted twist-chair conformation with the C_2 axis passing



13 **14**

FIG. 2
Nontrivial NOE contacts observed in 2D-NOESY spectra of diketones **13** and **14**

TABLE VI
X-Ray data collection, data processing and refinement results for compound **13**

Crystal data	
Formula	$C_{19}H_{28}O_2$
F.w.	288.43
F(000)	632
Crystal dimensions, mm	0.30 × 0.40 × 0.47
MoKα radiation λ, Å	0.70930
Temperature, °C	23 ± 1
Space group	orthorhombic, $P2_12_12_1$
Unit cell	
a, Å	11.298(1)
b, Å	11.330(1)
c, Å	12.807(1)
V, Å^3	1 639(2)
Z	4
ρ, g cm^{-3}	1.17
μ, cm^{-1}	0.7
Intensity measurement	
Instrument	Enraf-Nonius CAD4 diffractometer ref.[27]
Scan type	ω–θ
Maximum 2θ, °	50.0
Number of reflections measured	3 210 total, 2 879 unique
Structure solution and refinement	
Solution	direct methods
Refinement	full-matrix least-squares (LSFM program, SDP Package)
Minimization function	$\sum w(\lvert F_o\rvert - \lvert F_c\rvert)^2$
Least-squares weights	$4F_o^2 / \sum^2(F_o^2)$
Anomalous dispersion	all non-hydrogen atoms
Reflections included	2 592 with $F_o^2 > 3.0\ \sigma(F_o^2)$
Parameter refined	190
Unweighted agreement factor	0.042
Weighted agreement factor	0.061
High peak in final difference map, e^{-1} Å^{-3}	0.46(4)
Low peak in final difference map, e^{-1} Å^{-3}	–0.25(4)
Computer software	SDP/VAX (Enraf–Nonius) ref.[28], SHELXS96 ref.[29]

through C-3 and the C5–C10 bond, with ΔC_2(C-3) = 7.5°. The ring B is in a half-chair conformation, with ϕ_{max} = 47.3° and ΔC_2(C-6) = 4.2°. The ring C is in a nearly ideal chair conformation with ΔC_s(C-9–C-11) = 3.9°. The ring D is in an envelope conformation with ΔC_s(C-14) = 8.1° and ϕ_{max} = 45.0°.

EXPERIMENTAL

Compounds

Steroid compounds: 6β-Chloro-5-methyl-17-oxo-19-nor-5β-pregn-9-en-3β-yl acetate[15] (**4**), 4a-methylidene-17-oxo-4a-homo-7,19-dinor-5α-androst-9-en-3β-yl acetate[16] (**6a**), 17,17-ethylenedioxy-5-methyl-19-nor-5β-androst-9-ene-3β,6β-diyl 3-acetate 6-mesylate[10] (**7**), 4a-methylidene-4a-homo-7,19-dinor-5α-androst-9-ene-3β,17β-diol[9] (**8a**), 4-methyl-4-methylidene- 7,19-dinor-3,4-seco-5α-androst-9-ene-3,17β-diol[17] (**10a**), 3-hydroxy-4-methyl-4-methylidene-7,19-dinor-3,4-seco-5α-androst-9-en-17-one[17] (**11**), 3β,10-epoxy-4a-methylidene-4a-homo-7,19-dinor-5α-androstane-3β,17β-diol[9] (**12a**), 4aβ-methyl-4a-homo-7,19-dinor-5α,10α-androstane-3,17-dione[17] (**13**) and 4aα-methyl-4a-homo-7,19-dinor-5α,9β-pregnane-3,17-dione[10] (**14**) were prepared as previously described. A single crystal of the compound **13** was grown slowly from a dilute solution in acetone and heptane.

NMR Spectroscopy

^{1}H and ^{13}C NMR spectra were measured on a Varian UNITY-500 instrument (^{1}H at 500 MHz and ^{13}C at 125.7 MHz) in $CDCl_3$ with TMS as an internal reference. The absolute-value ^{1}H,^{1}H 2D-COSY spectra[18,19] were obtained with spectral width 5 kHz, pulse width 13 μs (90°), relaxation delay 1 s, acquisition time 0.17 s. Four free induction decays (FIDs) were acquired for each of 416 time increments and the data matrix was zero filled to 2 048 × 2 048

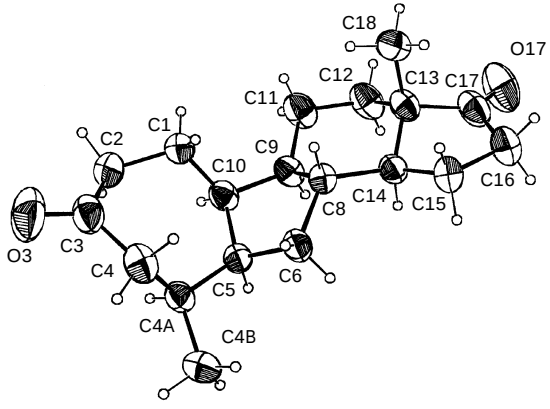


FIG. 3
Perspective view of compound **13** with atom numbering scheme showing absolute configuration of C-5 to be 5α

data points. A sine-bell weighting function was used before Fourier transformation (FT) in both dimensions.

The 2D-*J*-resolved ^{1}H NMR spectrum[20] of compound **13** was recorded at 50 °C using spectral width 2 kHz in F_2 and 50 Hz in F_1 dimension and acquisition time 0.14 s. The 16 FIDs were collected for each of 64 time increments, zero-filled to 2 048 × 256 data matrix and sine-bell-weighed before FT.

Nuclear Overhauser enhancements (NOE) in compounds **6a**, **13a** and **14a** were determined by the difference method using selective irradiation of individual protons during the time period (6 s) before data acqusition. Reference spectra taken under the same conditions but with the irradiation frequency off-resonance, were subtracted to give the difference spectra. The NOE for each signal was quantified using the intensity of the saturated peak in the difference spectra as a reference having its area as 100% and integrating the enhanced peaks relative to this scale.

2D-NOESY spectra[21,22] of compounds **13** and **14** were measured with spectral width 2 400 Hz, 90° pulses (13 μs), mixing time 0.7 s, acquisition time 0.213 s and relaxation delay 3 s. The 16 scans were collected for each of 200 time increments. Data were zero-filled to final data matrix 4 k × 4 k data points and a gaussian apodisation function applied before FT.

Proton decoupled ^{13}C NMR spectra were measured using the "attached proton test" (APT) sequence[23,24] with spectral width 32 kHz, pulse width 6 μs (30°), acquisition time 1 s and relaxation delay 1 s. Zero filling to 64 k data points and exponential function with a line broadening 1 Hz was applied before FT.

The ^{1}H,^{13}C correlated HMQC spectra[25] were acquired with indirect probe in a phase-sensitive mode (hypercomplex method[26]) using BIRD filter (null delay 0.5 s) and ^{13}C GARP decoupling. Relaxation delay was 1.6 s, 90° pulse 19 μs for ^{1}H and 24 μs for ^{13}C, spectral width 4.1 kHz in F_2 (^{1}H) and 20 kHz in F_1 (^{13}C), 32 scans collected for each of 360 increments, data matrix 1 344 × 720 was zero-filled to 2 k × 1 k and apodization with π/2 shifted sinebell was used in both dimensions before FT.

In situ TAI acylation[11,12] of the hydroxy compounds **11a** and **12a** was done by addition of trichloroacetyl isocyanate (small excess) to the $CDCl_3$ solution in the NMR sample tube. The TAC derivatives were characterized by their ^{1}H and ^{13}C NMR spectra.

X-Ray Crystallography

The crystallographic methods employed and data for compound **13** are summarized in Table V. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-128199. Copies of the data can be obtained free of charge on application to CCDC, e-mail: deposit@ccdc.cam.ac.uk.

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