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Solvolyses of 17-(Tosyloxy)androstanes in Hexafluoroisopropyl Alcohol – An Example for Extreme Reactivity Differences Without the Occurrence of Nonclassical Intermediates[1)]

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Solvolysis in hexafluoroisopropyl alcohol of 17α-(tosyloxy)androstane as well as of the corresponding 18-norsteroid proceeds faster than that of the 17β-isomers by a factor of $> 10^4$ (25 °C), and also considerably faster than that of cyclopentyl or cyclohexyl tosylates. The same 1,2-methyl migration products are observed with *both* epimers. Kinetic comparison with steroids, cyclohexane and cyclopentane derivatives with vicinal methyl groups or hydrogen shows that neither bridging with antiperiplanar C–C bonds, nor hydrogen rearrangements leading to charges at tertiary centers can be responsible for the reactivity differences. Chlorides instead of tosylates show a substantial decrease of the epimeric rate ratios. The epimers are characterized by k_s/k_c ratios differing by a factor of 10^2 to 10^3. Molecular mechanics calculations indicate that the fast reactions of the 17α-isomers are due to steric acceleration; the 17β-epimers react much slower than predicted by the applied force field model, which is in accord with a strong steric hindrance to solvation. Preparations of, e.g., 18-norsteroids and ^{13}C NMR spectra are described.

Solvolyse von 17-(Tosyloxy)androstanen in Hexafluorisopropylalkohol – Ein Beispiel für extreme Reaktivitätsunterschiede ohne Auftreten von nichtklassischen Intermediaten[1)]

Die Solvolyse von 17α-(Tosyloxy)androstan wie die des entsprechenden 18-Norsteroids in Hexafluorisopropylalkohol verläuft um den Faktor $> 10^4$ mal schneller (bei 25 °C) als bei den β-Isomeren sowie auch erheblich schneller als die Solvolyse von Cyclopentyl- oder Cyclohexyltosylat. *Beide* Epimere ergeben die gleichen 1,2-Methylverschiebungs-Produkte. Der Vergleich kinetischer Messungen an Steroid-, Cyclohexan- und Cyclopentan-Derivaten mit vicinalen Methylgruppen oder Wasserstoff zeigt, daß weder eine Verbrückung mit antiperiplanaren C–C-Bindungen noch eine Wasserstoffverschiebung zu tertiären geladenen Zentren für die beobachteten Reaktivitätsdifferenzen verantwortlich ist. Chloride zeigen im Vergleich zu Tosylaten eine erhebliche Erniedrigung des Geschwindigkeitsverhältnisses der Epimeren. Die Epimeren zeichnen sich durch k_s/k_c-Verhältnisse aus, welche einen Bereich von 10^2 bis 10^3 überstreichen. Molekülmechanische Berechnungen zeigen, daß die schnellen Reaktionen der 17α-Isomeren auf sterischen Faktoren beruhen. Die 17β-Epimeren dagegen reagieren wesentlich langsamer als durch das Kraftfeldmodell vorausgesagt; dies stimmt mit einer starken sterischen Hinderung der Solvatation überein. Die Darstellungen z. B. von 18-Norsteroiden sowie ^{13}C-NMR-Spektren werden beschrieben.

In spite of almost countless investigations the either classical (steric) or nonclassical (charge delocalization) origin of large reactivity differences in the solvo-

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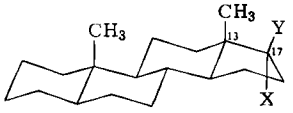
lysis of epimeric esters in saturated alicyclic frameworks remains a highly controversial matter of debate[2,3]. Thus, it has been noted that "... examples of high epimeric ratios in secondary systems when anchimeric assistance is clearly absent ..." are a challenge yet to be met[3g]. We believe to have found such a system, in which the epimeric rate ratio exceeds in fact a recently reported case which was considered to be one of the most dramatic ones[4]. In contrast to the majority of the secondary esters known for their particular reactivity differences our compounds do not contain strained C–C bonds which could lend themselves more easily to charge delocalization.

Results

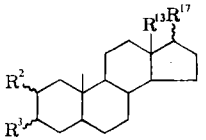


1a: Y = OTs, X = H $k \equiv 1$

1b: X = OTs, Y = H $k = 31.350$

The high reactivity of 17α-(tosyloxy)androstane (**1b**) in hexafluoroisopropyl alcohol (HFIP) as compared to its epimer **1a** rests on a $\Delta H^{\neq}$ difference of ≈ 7 kcal/mol (Table 1), and leads to a much higher epimeric rate ratio than observed, e.g., with the norbornyl tosylates (31350 vs. 1600[3d]). Also, **1b** reacts substantially faster than cyclohexyl (**1c, d**) and cyclopentyl tosylates (**2**–**5**). These findings would agree

Table 1. Solvolysis rates k and activation parameters in HFIP[a]

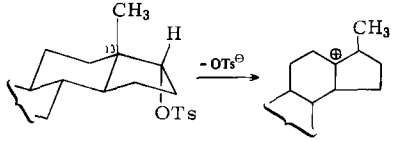


1a-h

	R^2	R^3	R^{13}	R^{17}	k_{rel} (25 °C)	$\Delta H^{\neq}$ kcal/mol	$\Delta S^{\neq}$ cal/deg. · mol	$\Delta G^{\neq}$ kcal/mol
1a	H	H	β-Me	β-OTs	1	21.1	−13	25.16
1b	H	H	β-Me	α-OTs	31350	14.1	−17	19.09
1c	H	β-OTs	β-Me	H	10	18.8	−17	23.85
1d	H	α-OTs	β-Me	H	83	21.6	−3	22.61
1e	H	H	H	β-OTs	0.5	17.3	−27	25.59
1f	H	H	H	α-OTs	12175	16.0	−12	19.64
1g	Me_2	β-OTs	β-Me	H	2510	16.5	−13	20.58
1h	Me_2	α-OTs	β-Me	H	4830	18.6	−5	20.19
2	R = Cyclopentyl				168	15.2	−24	22.10
3	R = *cis*-2-Methylcyclopentyl				3330	13.8	−22	20.41
4	R = *trans*-2-Methylcyclopentyl				376	17.8	−13	21.71
5	R = 2,2,5,5-Tetramethylcyclopentyl				183.5	17.7	−15	22.13

[a] Rates of tosylates (± 1%) relative to $k_{1a} = 2.00 \cdot 10^{-6}$ (s^{-1}) at 25 °C in 97% HFIP. $\Delta H^{\neq}$ (± 1–2 kcal/mol), $\Delta S^{\neq}$ (max. ± 4 cal/deg. · mol) from measurements at 3–5 temperatures with $\Delta T \approx 30$ °C (Table 3).

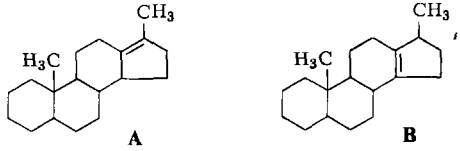
with earlier studies, which concluded from the 1,2-migration of the 13-methyl group observed *only* with 17α-, but not with 17β-isomers that an anti-orientation of leaving group and methyl (≙ **1b**) will lead to a bridged intermediate[5].



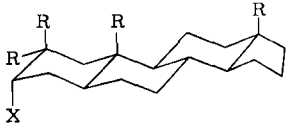
Several experiments were undertaken in order to investigate the contribution of bridging by alkyl groups in *anti*-position to the leaving group:

(1) An S_N2-type solvent assisted mechanism dominates much more with the 17β-tosylate **1a** in comparison to **1b** as evident from the k_s/k_c ratios measured according to the Schleyer-Bentley equation[6] (Table 2). The large difference in steric hindrance at the rear sides of **1a** and **1b** leads to particularly high k_s/k_c differences between the epimers (Table 2). The earlier reported[5] failure to observe the 13-methyl migration in the β-epimer (**1b**) reaction can thus be due entirely to S_N2-type displacement in traditional solvents.

(2) This conclusion is supported by a product study in the weakly nucleophilic solvent HFIP[7], which yielded the *same* amount of the rearranged olefins **A** and **B** from *both* tosylates (**1a, 1b**), as shown by ^{13}C NMR analysis (see Exp. Part).

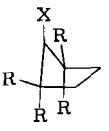


(3) Solvolysis of other tosylates such as **1h** or **5** could also proceed via the development of rather symmetrical bridges and of positive charge at a tertiary center; these tosylates, however, did *not* show such large rate enhancements in comparison to the corresponding epimer **1g** or the parent system **1d**; **5** reacts barely faster than the parent cyclopentyl tosylate (**2**) (Table 1).



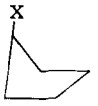
k = 4830

1h (X = OTs, R = Me)



k = 183

5 (X = OTs, R = Me)



k = 168

2 (X = OTs)

(4) Conclusive evidence for the absence of β-methyl bridging as the origin for the high 17α-tosylate (**1b**) reactivity came from the study of the 18-norsteroids **1e, f**. These systems were synthesized in general accordance with literature procedures[8] and showed similar reactivity differences as **1a/1b**, although they lack the 13-methyl group (Table 1).

Table 2. Solvent assistance parameters (k_s/k_c)[a] and leaving group effects[b]

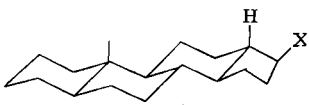
	$k \cdot 10^5$[c]	k_s/k_c[a]	k_{OTs}/k_{Cl}[d]	k_{OTs}/k_{OMs}[e]
1a	0.94	308[f]	2.7	0.85
1b	82.2	2.2[f]	71	–
1c	0.87	44	100	0.65
1d	7.8	28	320	0.96
1g	1.9	0.5	–	–
1h	6.6	0.7	–	–
2	43.1	191	–	–
3	138	38.5	–	–
4	18.3	28.9	–	–
5	0.54	1.7	–	–

[a] From rate comparison to 2-adamantyl tosylates in HFIP and tosylates in 80% ethanol/water (v + v) at 50°C. – [b] From measurements in HFIP at 50°C. – [c] Tosylates in 80% ethanol/water (v + v), 50°C, in s^{-1}. – [d] Rates of RCl see Table 3. – [e] Rates of $ROSO_2Me$ see Table 3. – [f] Comparison with k_s/k_c values obtained for 4-*tert*-butylcyclohexyl tosylates[1] shows that the k_s/k_c difference between axial and equatorial tosylate increases from 140 in 80% ethanol to ≈ 1000 in 50% ethanol.

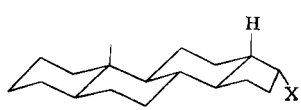
Table 3. Solvolysis rates in 97% HFIP at different temperatures[a]

	X (≡ R^{17})	
1a	OTs	$\cdot 10^6$: 29.2/3.7, 40.1/13.2, 50.0/38.0
1b	OTs	$\cdot 10^3$: 0.0/6.0, 14.6/25.1, 15.0/28.5, 20.3/47.5, 30.3/92.0
1e	OTs	$\cdot 10^6$: 30.0/1.80, 40.0/4.48, 50.0/11.4
1f	OTs	$\cdot 10^3$: 0.0/1.87, 5.0/3.49, 10.0/5.31, 15.0/9.53, 20.0/15.2
1c	OTs	$\cdot 10^5$: 24.9/1.85, 31.0/4.09, 34.5/4.49, 39.5/8.10, 44.9/16.9, 50.2/24.8
1d	OTs	$\cdot 10^4$: 24.9/1.69, 29.2/2.65, 34.5/4.84, 40.7/10.9, 45.0/17.6, 50.0/31.1
1g	OTs	$\cdot 10^3$: 15.0/1.86, 20.0/3.09, 25.0/5.25, 30.0/8.20, 35.0/12.8
1h	OTs	$\cdot 10^4$: 5.0/9.43, 10.0/18.1, 15.0/31.9, 20.0/56.7, 25.0/97.5
2[b]	OTs	$\cdot 10^4$: 25.0/3.51, 40.0/13.9, 50.0/27.0
3	OTs	$\cdot 10^3$: 5.0/1.18, 10.0/1.82, 15.0/2.92
4	OTs	$\cdot 10^4$: 19.7/4.23, 30.4/13.3, 40.2/36.3, 50.0/73.4
5	OTs	$\cdot 10^4$: 30.0/6.14, 40.0/16.4, 50.0/40.4
1a	OMs	$\cdot 10^6$: 30.0/4.46, 40.0/14.2, 50.0/41.2
1h	OMs	$\cdot 10^4$: 20.0/1.71, 30.0/4.23, 40.0/12.4, 50.0/32.2
1g	OMs	$\cdot 10^5$: 30.0/4.87, 40.0/12.7, 50.0/38.2
1b	Cl	$\cdot 10^4$: 10.0/2.61, 20.0/6.18, 30.0/14.3, 40.0/30.5, 50.0/64.5
1a	Cl	$\cdot 10^5$: 50.0/1.31
1h	Cl	$\cdot 10^6$: 50.0/9.73
1g	Cl	$\cdot 10^6$: 50.0/2.48

[a] Temperature in °C/rate constant in ($10^n \cdot s^{-1}$) units. – [b] Measurements by *G. Schmidt*, Dissertation, Universität des Saarlandes 1985.

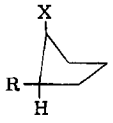


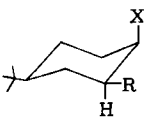
1e (X = OTs), k = 0.5



1f (X = OTs), k = 12175

(5) The migration of hydride in **1f** (instead of methyl in **1b**) would also lead to a tertiary carbocationic center, which could contribute to the high reactivity. This, however, would also hold for similar systems such as **3** or **6**[9], which again do not show any comparable rate enhancements.



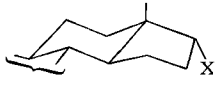


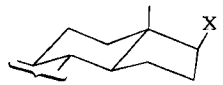
3 (X = OTs, R = Me) **6** (R = Me, X = OTs) **7** (R = H, X = OTs)

k = 3330 k = 805 k = 36

(6) Leaving group effects were studied with the chloro- and tosyloxy-3α/β- and 17α/β-androstane derivatives. The uniformly high k_{OTs}/k_{Cl} ratios for all compounds *except* the 17β-isomer can be due to (a) higher strain for X = Cl in **1a** (X = Cl)[10], (b) to more solvent assistance with the 17β-compounds (cf. the k_s/k_c ratio), which would lower the leaving group differences in comparison to S_N1-type processes; (c) to steric hindrance of solvation[3b], which becomes particularly prominent with the more bulky tosyloxy group in the hindered 17β-position. It should be noted that as a consequence the epimeric k_{1a}/k_{1b} ratio shrinks to 500:1 with X = Cl, from 13143:1 with X = OTs (at 50°C). Methanesulfonates behave, not unexpectedly, similar to the tosylates (Table 2).

(7) Molecular mechanics calculations can be used to predict reactivity differences of steric origin[11]. If cycloalkanone models for simulation of the sp^2-transition state and methylcycloalkanes for the sp^3 ground state model are applied, the calculated strain energy difference ΔSI between sp^3 and sp^2 has been shown to reflect the observed solvolytic activation energy difference ΔG^*, provided some necessary precautions are taken[12]. The following numbers show that the calculated strain relief ΔSI (going from sp^3 to sp^2) is 3.4 kcal/mol larger for the 17α-derivative (**1b**) in comparison to the cyclopentyl system (**5**), in full accord with the corresponding experimental ΔG^* lowering by 3.0 kcal/mol. ΔSI ($sp^3 - sp^2$) for the 17β-isomer (**1a**) would also predict a substantial ΔG^* decrease (by 2.2 kcal/mol), yet we observe an ΔG^* *in*crease by 3.0 kcal/mol in comparison to cyclopentane.



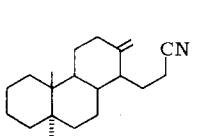


ΔSI(sp^3–sp^2)	−0.42	−3.78	−2.62
ΔG^* (HFIP)	22.10	19.09	25.16

Conclusions

The data assembled in this work demonstrate that unusually fast solvolyses can occur without the contribution of bridged species or simultaneous rearrangement to particularly stable carbocationic centers. It is noticeable that the rate of the

extremely fast reacting epimer is predictable by molecular mechanics, and that the slow isomer is, however, off from the calculation by more than 5 kcal/mol. This clearly points to steric hindrance of solvation as the major source of the reactivity difference, which was advocated for years by *Brown*[3b,f] as possible origin of the lower rates of *endo*-2-norbornyl esters in comparison to the *exo*-isomers.



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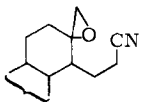

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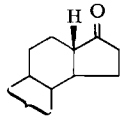

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Experimental Part

NMR measurements and kinetic studies were carried out as described before[1] (^{13}C NMR spectra see Table 4; ^{1}H NMR spectra in $CDCl_3$ at 300 K).

Product analyses were performed similar to earlier procedures[1], except that the steroids could be isolated from the solutions at the rotating evaporator. The olefins obtained from **1a**, **1b** (X = OTs) in HFIP were analyzed by ^{13}C NMR signal area comparison; shifts (in ppm, 10 ± 5% in $CDCl_3$, vs. TMS, ambient temp.): **A** (85 ± 2%) 136.00, 127.82; **B** (15 ± 2%) 138.08, 136.98. The predominance of **A** was furthermore established by a CH_3-singlet at 1.58 ppm; olefinic and substitution product protons were absent (< 2%).

I. *18-Nor-5α,13β-androstan-17-ols* (**1e**, **1f**, X = OH): similar to ref.[8].

a) *13,17-Seco-5α-androst-13(18)-ene-17-carbonitrile* (**8**): 14 g (48 mmol) of 17-(hydroxyimino)-5α-androstane[13] (from 5α-androstan-17-one and hydroxylamine[13]) in 84 ml of absol. benzene, 108 ml of dimethyl sulfoxide, 11 g (53 mmol) of dicyclohexylcarbodiimide, and 2.8 ml of trifluoroacetic acid were reacted for 2 days at 25°C; after the usual work-up[8] and chromatography with benzene/ether (1:1) on silica gel 7.3 g (56%) of product was obtained as viscous oil. – ^{1}H NMR: δ = 4.47 (m, $W_{1/2}$ = 4 Hz, 18-H); 4.76 (m, $W_{1/2}$ = 4 Hz; 18-H); 0.70 (3H, s, CH_3-19).

b) *13,18-Epoxy-13,17-seco-5α-androstane-17-carbonitriles* (**9**) were obtained by treating **8** (7.0 g, 28 mmol) with *m*-chloroperbenzoic acid similar to the literature procedure[8]; chromatography yielded 0.60 g (82%) of the 13-epimeric mixture. – ^{1}H NMR: δ = 2.8–2.2 (m, CH_2-18 and -16); 0.66, 0.62 (2s, CH_3-19 of the epimers).

c) *18-Nor-5α,13β-androstan-17-one* (**10**): Similar to ref.[8] from **9** (3.0 g, 10 mmol) with boron trifluoride; after chromatography 250 mg (10%) of pale yellow crystals are obtained, m.p. (from acetone) 118–120°C. – ^{1}H NMR: δ = 0.78 (s, CH_3-19).

$C_{18}H_{28}O$ (260.4) Calcd. C 83.08 H 10.77 Found C 82.91 H 11.34

d) *18-Nor-5α,13β-androstan-17β-ol* (**1e**, X = OH): 100 mg (0.30 mmol) of **10** were stirred for 2 h first at ice temp., then at room temp. with 20 mg (0.54 mmol) of sodium borohydride in 10 ml of methanol. After addition of 1 ml of acetic acid the solvent was evaporated, the

Table 4. ^{13}C NMR shifts[a]
A. 18-Norsteroids and synthetic precursors

C	[b]	**8**	**9**[c]	**10**	**1f**, X = OH	**1e**, X = OH
1	38.80	38.74	38.54	38.87	38.91	38.97
2	22.29	22.16	22.16	22.16	22.21	22.24
3	26.91	26.78	26.71	26.78	26.83	26.85
4	29.12	28.86	28.79	28.66	28.83	28.97
5	47.19	47.34	46.41	46.93	46.94	46.86
6	29.12	28.86	28.79	29.12	29.09	29.13
7	31.78	31.79	31.72	31.13	31.78	31.81
8	35.03	36.92	34.97	37.50	36.37	36.40
9	55.12	53.75	53.62	55.31	53.89	53.71
10	36.46	36.92	36.53	36.46	36.37	36.40
11	20.47	23.85	22.29	25.61	26.63	26.85
12	34.25	27.49	26.71	24.83	29.10	25.24
13	44.0	150.01	63.25	53.88	49.26	51.27
14	53.49	47.97	45.89	43.03	42.37	42.70
15	23.20	28.86	28.79	22.75	24.93	25.50
16	25.15	14.75	14.82	37.50	32.84	34.15
17	170.68	119.92	120.11	218.06	77.89	74.65
18	17.22	104.77	59.93	—	—	—
19	12.22	12.09	12.15	12.22	12.19	12.22

[a] In ppm from int. TMS, measured in $CDCl_3$ (5–20%) at ambient temperature. – [b] 17-(Hydroxyimino)-5α-androstane. – [c] Only major isomer assigned.

Table 4 B. 2,2-Dimethyl-5α-androstanes

C	3-one	3α-ol	3β-ol	C	3-one	3α-ol	3β-ol
1	55.90	47.66	53.36	12	38.87	38.99	39.06
2	44.52	35.52	39.06	13	40.82	40.94	40.95
3	215.79	74.76	75.65	14	54.34	54.42	54.47
4	41.73	32.22	35.49	15	25.54	25.49	25.48
5	45.82	38.91	46.93	16	20.54	20.51	20.54
6	28.66a	28.42	28.14	17	40.43	40.44	40.49
7	32.17b	35.42	34.97	18	17.61	17.69	17.68
8	35.42	35.52	35.49	19	14.04	15.39	15.40
9	54.53	56.56	56.61	$CH_3\beta$	32.04b	32.22	32.43
10	36.53	38.91	36.92	$CH_3\alpha$	28.40a	28.04	28.14
11	21.45	20.86	21.38				

residue washed with water and recrystallized from methanol. Yield 90%; m.p. 134–137°C. – ^1H NMR: δ = 0.68 (CH_3-19, s), 3.64 (17-H, $W_{1/2}$ = 18 Hz).

$C_{18}H_{30}O$ (262.4) Calcd. C 83.85 H 11.47 Found C 83.04 H 11.45

e) *17β-Tosyloxy-18-nor-5α,13β-androstane* (**1e**): From **1e** (X = OH) with 10% excess tosyl chloride in pyridine as usual[1]; m.p. 102–104°C. – ^1H NMR: δ = 0.63 (CH_3-19, s), 4.80 (17-H, $W_{1/2}$ = 18 Hz).

$C_{25}H_{36}O_3S$ (416.6) Calcd. C 82.44 H 11.45 Found C 81.84 H 11.42

f) *18-Nor-5α,13β-androstan-17α-ol* (**1f**, X = OH): From **1e** by treatment with potassium nitrite/DMSO[14] and water; m.p. 132–135°C. – ^{1}H NMR: δ = 0.71 (CH_3-19, s), 4.11 (17-H, $W_{1/2}$ = 18 Hz).

$C_{18}H_{30}O$ (262.4) Calcd. C 83.04 H 11.47 Found C 83.67 H 11.46

Tosylate: ^{1}H NMR: δ = 0.64 (CH_3-19, s), 4.24 (17-H, $W_{1/2}$ = 10 Hz).

II. *2,2-Dimethyl-5α-androstan-3-ols*

a) *2,2-Dimethyl-5α-androstan-3-one:* A solution of 5.0 g (50 mmol) of metallic potassium in 50 ml *tert*-butyl alcohol was added to a refluxing mixture of 2.0 g (7.0 mmol) of androstan-3-one in 50 ml of benzene and 25 ml of *tert*-butyl alcohol; after adding 15 ml of methyl iodide in 50 ml of benzene the solution was heated to reflux for 1 h and worked up as usual; yield 45% after chromatography and recrystallization (ether/methanol); m.p. 63–64°C. – ^{1}H NMR: δ = 0.62 (CH_3-19, s), 1.08, 0.98, 0.93 (s, other CH_3).

$C_{21}H_{34}O$ (302.5) Calcd. C 83.44 H 11.26 Found C 83.01 H 11.34

b) *2,2-Dimethyl-5α-androstan-3β-ol* was obtained similarly to **1e** (X = OH) (Section Id) in 90% yield; m.p. 104–106°C. – ^{1}H NMR: δ = 0.62 (CH_3-18, s), 0.80, 0.84, 0.90 (other CH_3), 3.27 (3-H, $W_{1/2}$ = 20 Hz).

$C_{21}H_{36}O$ (304.5) Calcd. C 82.89 H 11.84 Found C 82.15 H 11.82

Tosylate: m.p. 100–102°C. – ^{1}H NMR: δ = 0.62 (CH_3-18, s); 0.66, 0.80, 0.89 (other CH_3); 4.22 (3-H, $W_{1/2}$ = 18 Hz).

$C_{28}H_{42}O_3S$ (458.7) Calcd. C 73.36 H 9.17 Found C 73.01 H 9.17

c) *2,2-Dimethyl-5α-androstan-3α-ol* was prepared by reaction of the ketone with lithium tri-*sec*-butylborohydride[15] at −78°C in THF according to standard procedures[15]; yield 90%; m.p. 130–132°C. – ^{1}H NMR: δ = 0.62 (CH_3-18, s); 0.80, 0.89 (other CH_3); 3.37 (3-H, $W_{1/2}$ = 8 Hz).

$C_{21}H_{36}O$ (304.5) Calcd. C 82.89 H 11.84 Found C 82.07 H 11.85

Tosylate: m.p. 84–85°C. – ^{1}H NMR: δ = 0.62 (CH_3-18, s); 0.77, 0.82, 0.71 (other CH_3); 4.36 (3-H, $W_{1/2}$ = 8 Hz).

$C_{28}H_{42}O_3S$ (458.7) Calcd. C 73.36 H 9.17 Found C 72.90 H 9.18

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