Microwave-induced selective deacetylation and stereospecific acyl migration of steroid acetates on alumina

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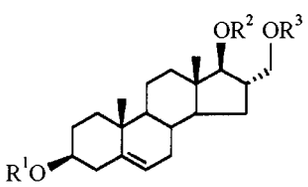
A simple high-yielding method for the deprotection of acetylated steroid stereoisomers is described, which occurs under mild conditions on an alumina surface in response to microwave irradiation.

The protection of hydroxy groups by acetylation is a common procedure and numerous methods are known both for acetylation and for the deprotection sequence.[1] We earlier observed a deacetylation reaction proceeding with high stereospecificity on alkaline alumina at room temperature.[2] The isomers of 16-acetoxymethylandrost-5-ene-3β,17-diyl 3,17-diacetate **1a**, **2a**, **3a**, **4a** underwent selective deacetylation at the 16-function when kept on an alumina column under usual conditions of chromatography.



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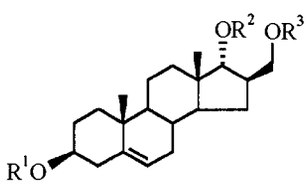

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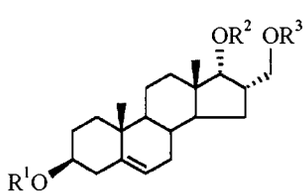
	R^1	R^2	R^3
a	Ac	Ac	Ac
b	Ac	Ac	H
c	Ac	H	H
d	H	Ac	H



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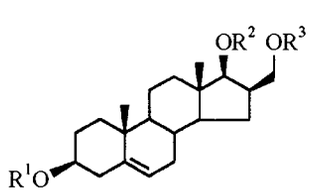

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	R^1	R^2	R^3
a	Ac	Ac	Ac
b	Ac	Ac	H
c	Ac	H	Ac
d	Ac	H	H

When kept for 6–7 days on alkaline alumina, 16α-acetoxymethylandrost-5-ene-3β,17β-diyl 3,17-diacetate **1a** lost its primary acetoxy group, while the secondary acetoxy groups remained intact to give 16α-hydroxymethylandrost-5-ene-3β,17β-diyl 3,17-diacetate **1b**. Under similar conditions, 16β-acetoxymethylandrost-5-ene-3β,17α-diyl 3,17-diacetate **2a**, again containing the 16,17 functional groups in the *trans* orientation, resulted in 16β-hydroxymethylandrost-5-ene-3β,17α-diyl 3,17-diacetate **2b**.

Under similar conditions, 16α-acetoxymethylandrost-5-ene-3β,17α-diyl 3,17-diacetate **3a**, containing the 16,17 functional groups in the *cis* orientation with respect to one another, underwent deacetylation to give 16α-hydroxymethylandrost-5-ene-3β,17α-diyl 3,17-diacetate **3b**. However, compound **3b** transformed further on the alkaline alumina to furnish 16α-acetoxymethyl-17α-hydroxyandrost-5-en-3β-yl 3-acetate **3c** by acyl migration, followed by cleavage of the newly formed primary acetoxy group to give 16α-hydroxymethyl-17β-hydroxyandrost-5-en-3β-yl 3-acetate **3d**.

16β-Acetoxymethylandrost-5-ene-3β,17β-diyl 3,17-diacetate **4a**, again containing the 16,17 functional groups in the *cis* orientation, behaved similarly to **3a** and gave **4b** on alkaline alumina. Compound **4b** proved to be unstable under the applied experimental conditions and underwent acyl migration to afford **4c**. Further deacetylation of **4c** at the primary acetoxy function resulted in **4d**.

Since all the above reactions are sluggish, we have developed appropriate conditions to increase the rate of deacetylation. We report here a facile and simple procedure to effect the deacetylation of a variety of acetylated steroid stereoisomers **1a**, **2a**, **3a**, **4a** on alkaline alumina under solvent-free conditions, reactions which can be further accelerated safely by using an unmodified common household microwave oven.

We set out to obtain answers to the following questions: (1) How do the deacetylation processes of the four isomers **1a**, **2a**, **3a**, **4a** differ? (2) How is the deacetylation process influenced by the steric position of the acetoxy groups? (3) What are the differences in the rates of the deacetylation and the acyl migration of the two *cis* isomers?

Results and discussion

Examination of the deacetylation processes of the four isomers **1a**, **2a**, **3a**, **4a** revealed that the deesterification rates differ. Fig. 1 depicts the rates of alumina-mediated cleavage of the starting materials.

The compounds containing a 16β-acetoxymethyl group, **2a** and **4a**, undergo a relatively slow reaction. The deacetylation of the compounds bearing a 16α-acetoxymethyl function, **1a**

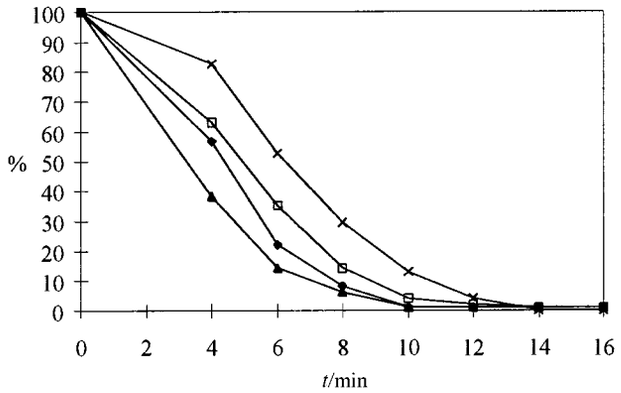


Fig. 1 Decreases in quantity of triacetate isomers **1a** (◆), **2a** (□), **3a** (▲), **4a** (×) as a function of time

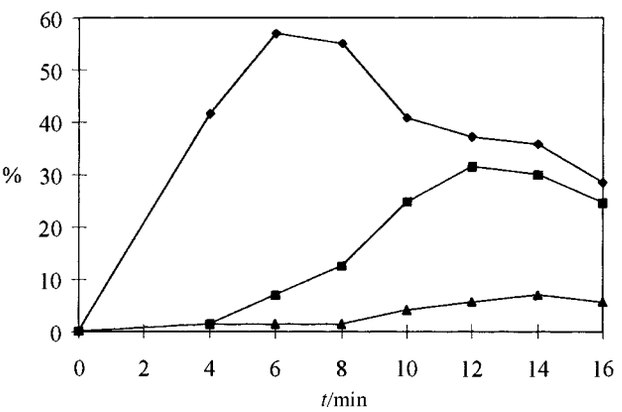


Fig. 2 Deacetylation process of **1a**; 3,17-diacetate **1b** (◆), 3-acetate **1c** (▲), 17-acetate **1d** (■)

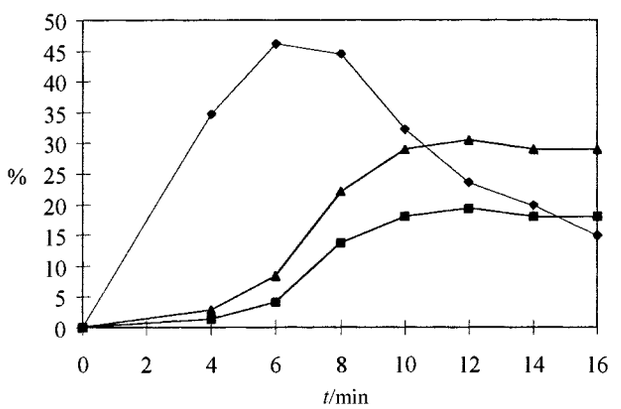


Fig. 3 Deacetylation process of **2a**; 3,17-diacetate **2b** (◆), 3-acetate **2c** (▲), 17-acetate **2d** (■)

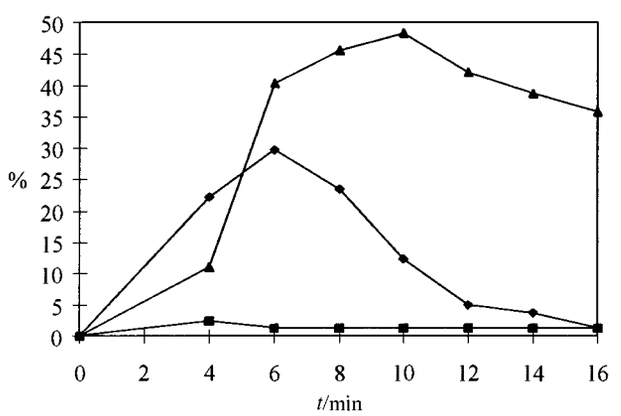


Fig. 4 Deacetylation process of **3a**; 3,16-diacetate **3b** (◆), 3,17-diacetate **3c** (■), 3-acetate **3d** (▲)

and **3a**, is faster. It seems that the *pseudo-axial* 16α group, on the opposite side to the C-18 methyl function, enhances the adsorption on the surface of alumina, and the deacetylation process is therefore faster than in the case of the *pseudo-equatorial* 16β group.

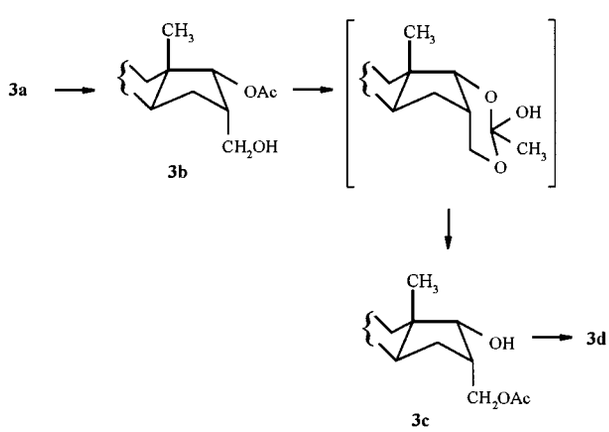
Compound **1a** and its 16β,17α isomer **2a**, containing the 16,17 functional groups in the *trans* orientation, first lost the primary acetoxy group, the secondary acetoxy groups remaining intact to give the 3,17-diacetates **1b** (61%) and **2b** (49%), respectively, after irradiation with 90 W power for 6 min. The temperature of the sample in this case was 75 °C. (After 8, 10, 12, 14 and 16 min, the temperature of the samples was 93, 105, 109, 112, 120 and 127 °C, respectively.) This result is in agreement with the picture of selective deacetylation on alkaline alumina at room temperature, as observed earlier.[2] At higher temperature, the secondary acetoxy groups too are sensitive, as found by Varma *et al*. for cholesteryl 3-acetate.[3]

The two *trans* 3,17-diacetate isomers **1b** and **2b** differ in behaviour. Since the 17-acetoxy group in the 3β,17β-diacetate **1b** is sterically hindered by the 18-methyl group, the 3-acetoxy group reacts much faster, resulting in a product mixture consisting of 28% **1d** and 6% **1c** after 16 min (Fig. 2).

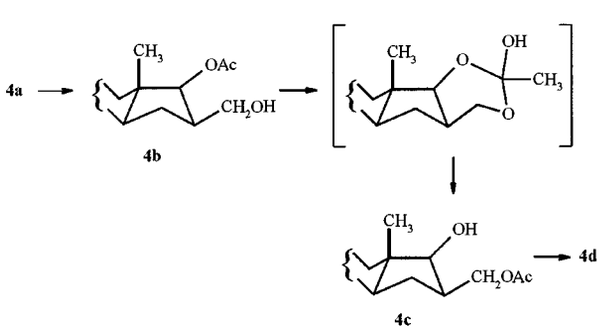
The other *trans* isomer, the 3β,17α-diacetate **2b**, primarily lost its sterically unhindered 17α-acetyl group, giving **2d** and **2c** in quantities of 17% and 28%, respectively, after the same time (Fig. 3).

Under similar conditions, the 16α,17α isomer **3a** and the 16β,17β isomer **4a**, containing the 16,17 functional groups in the *cis* orientation, underwent deacetylation to give 16-hydroxymethylandrost-5-ene-3β,17-diyl 3,17-diacetates **3b** and **4b**. However, compounds **3b** and **4b** transformed further on the alkaline alumina to yield 16-hydroxymethyl-17-hydroxyandrost-5-ene-3β-yl 3-acetate **3c** and **4c**. These are formed by acyl migration through cyclic *ortho*-esters, followed by cleavage of the newly formed primary acetoxy group to give 3β-monoacetates **3d** and **4d**, respectively (Schemes 1 and 2).

Fig. 4 shows that the deacetylation and acyl migration of **3a** are very fast: after 6 min, the concentration of 3,17-diacetate



Scheme 1



Scheme 2

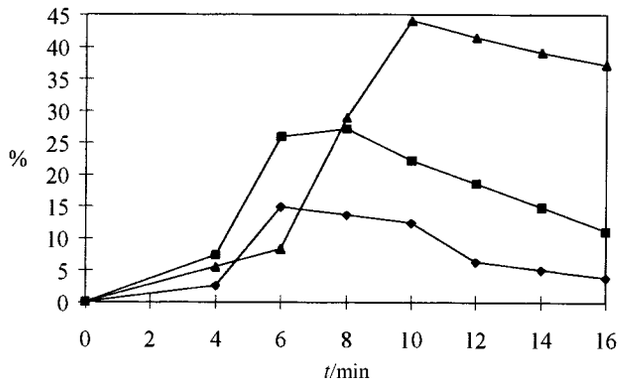


Fig. 5 Deacetylation process of **4a**; 3,16-diacetate **4b** (◆), 3,17-diacetate **4c** (■), 3-acetate **4d** (▲)

3b is lower than that of **4b** (Fig. 5). The reason for the fast deesterification process is again the α functional group on the D ring, with a more favourable surface adsorption as compared to that of the 16β,17β isomer **4a**.

Experimental

In the deacetylation reactions, alkaline alumina (pH 8–9) of activity I–II, standardized according to Brockmann (Aldrich Chemical Co. Ltd.) was used. Alkaline alumina (5 g) was added to a solution of triacetate **1a**, **2a**, **3a**, **4a** (0.2 mmol) dissolved in the minimum amount of dichloromethane (5 cm^3) at room temperature, and the solvent was evaporated *in vacuo* at ambient temperature. The dried material was placed in a Pyrex tube and irradiated for 4–16 min at 90 W inside a MAXIDIGEST-350 microwave oven. All reaction mixtures were monitored with a TESTO-901 thermometer within 15 s of irradiation. The products were added to chloroform (25 cm^3), the alumina was filtered off and washed with methanol (2 × 25 cm^3). The solution was evaporated to dryness and the residue was dissolved in chloroform in a volumetric flask (10 cm^3).

The reaction mixture was subjected to quantitative analysis by thin-layer chromatography. From the solution of the sample, 5 μL was transferred with a take-up apparatus (Linamat IV; Camag) as a strip to the thin layer (Kieselgel 60 F_{254} HPTLC plate) and developed in a horizontal developing chamber (Camag) with chloroform–methanol (98 : 2). A densitometer (CD 60; Camag) with solutions calibrated at 200 nm was used for the quantitative analysis.

The starting materials and their various acetylated derivatives were prepared earlier in our laboratory; the syntheses of **1a**, **1c**, **2a**, **2c**, **4a**, **4b**, **4c**, and **4d** were described in ref. 4; those of **3a**, **3b**, and **3d** in ref. 5; and those of **1b**, **2b**, and **3c** in ref. 2.

Mp's were determined on a Kofler block and are uncorrected. Specific rotations were measured with a POLAMAT-A polarimeter for solutions in chloroform (*c* 1) and are given in units of 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded with a Varian VXR-500 instrument. Chemical shifts are reported in ppm units, and coupling constants (*J*) in Hz. Mass spectra were obtained on a VARIAN MAT 311A spectrometer.

Preparation of 16α-hydroxymethylandrost-5-ene-3β,17β-diyl 17-acetate 1d and 16α-hydroxymethylandrost-5-ene-3β,17α-diyl 17-acetate 2d

General procedure. Alkaline alumina (25 g) was added to a solution of triacetate **1a** or **2a** (446.5 mg, 1 mmol) dissolved in the minimum amount of dichloromethane (3–5 cm^3) at room temperature and the solvent was evaporated *in vacuo*. The air-dried material, in a small beaker, was placed in an alumina bath inside the microwave oven. Upon completion of the reaction (90 W, 16 min, followed by TLC examination) the product was extracted into chloroform (5 × 20 cm^3). After evaporation the residue was dissolved in chloroform–light petroleum (1 : 3) and chromatographed on an alumina column (length 25 cm; diameter 2.0 cm; alumina 50 g). Chloroform–light petroleum (1 : 3) first eluted **1d**. Continued elution with chloroform–light petroleum (1 : 1) resulted in **1d** (54 mg; 15%), mp 202–203 °C, $[a]_D^{20}$ −73 (*c* 1 chloroform) (Found: C, 72.7; H, 9.2. $C_{22}H_{34}O_4$ requires C, 72.8; H, 9.4%); δ_H(500 MHz, $CDCl_3$, Me_4Si) 0.84 (3H, s, 18-CH_3), 0.93 (1H, m), 0.98 (3H, s, 19-CH_3), 1.02–1.22 (3H, m), 1.35–1.60 (7H, m), 1.69 (1H, m), 1.81 (2H, m), 1.96 (1H, m), 2.05 (3H, s, CH_3-CO), 2.10–2.31 (3H, m), 3.50 (1H, m, 3-H), 3.57 (2H, m, CH_2-OH), 4.54 (1H, d, *J* 7.3, 17-H), 5.33 (1H, d, *J* 4.4, 6-H); δ_C(125 MHz, APT, $CDCl_3$, Me_4Si) 12.8 (18-C), 19.4 (19-C), 20.4, 21.2 (*C*H_3-CO), 28.1, 31.4, 31.6 (2C), 36.6, 36.7, 37.2, 42.2, 43.8, 44.2, 49.9, 50.0, 65.5 (*C*H_2-OH), 71.6 (3-C), 84.9 (17-C), 121.1 (6-C), 140.9 (5-C), 173.2 (CH_3*C*O); *m/z* (EI) 362 ($M^{\cdot+}$, 100%), 344 (55), 287 (67), 269 (43), 191 (70), 107 (42), 105 (43), 43 (68). **2d**: (94 mg; 26%), mp 144–146 °C, $[a]_D^{20}$ −102 (*c* 1 chloroform) (Found C, 72.5; H, 9.5. $C_{22}H_{34}O_4$ requires C, 72.8; H, 9.4%); δ_H(500 MHz, $CDCl_3$, Me_4Si) 0.82 (3H, s, 18-CH_3), 0.86–1.02 (3H, m), 1.03 (3H, s, 19-CH_3), 1.09 (1H, m), 1.36–1.72 (7H, m), 1.81–2.06 (5H, m), 2.06 (3H, s, CH_3-CO), 2.19–2.35 (2H, m), 3.53 (1H, m, 3-H), 3.63 (2H, m, CH_2-OH), 4.49 (1H, d, *J* 1.7, 17-H), 5.36 (1H, d, *J* 4.3, 6-H); δ_C(125 MHz, APT, $CDCl_3$, Me_4Si) 17.3 (18-C), 19.4 (19-C), 20.3, 21.4 (*C*H_3-CO), 29.7, 31.6 (2C), 32.0 (2C), 36.7, 37.2, 42.2, 44.1, 49.7, 50.5, 50.8, 66.2 (*C*H_2-OH), 71.7 (3-C), 84.8 (17-C), 121.3 (6-C), 140.8 (5-C), 172.2 (CH_3*C*O); *m/z* (EI) 362 ($M^{\cdot+}$, 95%), 302 (100), 287 (55), 269 (57), 191 (74).

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