Transformation of steroidal cyclohexadienyl anion without fragmentation: unexpected synthesis of methylenesteroid

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In contrast with androsta-1,4-diene-3α/β,17β-diol, its 3-*O*-methyl ether is transformed upon C(3)-deprotonation into the corresponding 3-methylene steroid with migration of the *O*-methyl group on the steroid skeleton (by the scheme of Wittig rearrangement) rather than eliminating the 19-methyl group.

Key words: androsta-1,4-diene-3α/β,17β-diol, *O*-methylation; cyclohexadienyl anion, rearrangement; divinyl carbinol, etherification; methoxycyclohexadienyl anion, rearrangement; Wittig rearrangement.

We have recently reported that androsta-1,4-diene-3α/β,17β-diol (**1a**) prepared from readily available androsta-1,4-diene-3,17-dione by the hydride reduction is smoothly transformed into estradiol (**3**) on treatment with Bu^nLi under drastic conditions (50—100 °C)[1]. The mechanism of this transformation includes C(3)-deprotonation (with simultaneous deprotonation at the O(3) and O(17) atoms) with formation of cyclohexadienyl anion (**2a**), which is thermally cleaved at the C(10)—C(19) bond with expulsion of the $C(19)H_3$ anion and aromatization of the ring A[2]. However, when a similar transformation of the 3-*O*-methyl ether of diol **1a** (**1b**) into the 3-methyl ether of estradiol **3** (**4**) was attempted, we found that the thermal transformation of the intermediate methoxycyclohexadienyl anion (**2b**) proceeded in a different way with the formation of a new C—C-bond.

The starting methyl ether **1b** was prepared by an unconventional method, *viz*, by the interaction of diol **1a** with methanol in the presence of anhydrous $MgSO_4$ (Scheme 1). Under these mild conditions unstable diol **1a** was smoothly and selectively transformed in an acceptable yield of 75% into 3-ether **1b**; the latter was formed as a mixture of 3α- and 3β-epimers with the ratio of the epimers (1 : 1.2, respectively) different from that of starting diol **1a**. The method is based on an earlier observation of simple etherification of a steroid dienylcarbinol under similar conditions[3]. The mechanism of the etherification probably includes the formation of an intermediate cyclohexadienyl cation (in which the positive charge is delocalized over the ring A) from diol **1a** followed by stabilization of the cation by the reaction with methanol at C(3). The weak acidity of $MgSO_4$ is sufficient for the elimination of the doubly allylic 3-hydroxy group which is very easily dehydrated with the dienol-benzene rearrangement[4,5]. According to the calculation (semiempirical PM3 method) the cation formed has the maximum of the positive charge density at the sterically non-hindered C(3) position. These two factors are sufficient for the regio- (but not stereo-) selectivity of the reaction.

The C(3)-deprotonation of ether **1b** occurs upon the action of the Bu^nLi—TMEDA complex as follows from the appearance of the red color characteristic of the anions similar to anion **2b**. Pyrolysis of the anion at 75 °C is accompanied by the fading of the red component of the color; however, even traces of the expected ether **4** were not formed. Instead, 3-methylenesteroid **5** (35%, not optimized) contaminated with estrane dimethylsteroid **6**, as well as testosterone **7** (14%), were isolated. The structure of methylenesteroid **5** was clearly confirmed by the ^1H NMR spectrum, in which the positions and multiplicity of signals of five vinyl protons practically coincided with those published for the corresponding 17-keto analog[6]. Another confirmation of the structure followed from the total transformation of the acid-labile 3-methylenesteroid **5** into dimethylsteroid **6** during chromatography on silica gel by rearrangement similar to the dienol-benzene rearrangement[5].

A common explanation based on the difference of expected properties of cyclohexadienyl anions **2a** and **2b** is possible for the formation of products **5**—**7** (and the absence of ether **4**). Because of the lack of a negatively charged alkoxide substituent at C(3) in **2b** this anion should be more stable and the presence of a methoxy group allows a second way of its stabilization, *viz*, Wittig rearrangement[7] with O→C-migration of the methyl group. According to the calculation (PM3 method) the negative charge density at C(3) (−0.331) in anion **2b** is high enough for the rearrangement to occur. The protonation of the formed alkoxide **8** during aqueous work-up leads to the doubly allylic tertiary carbinol **9**, even more

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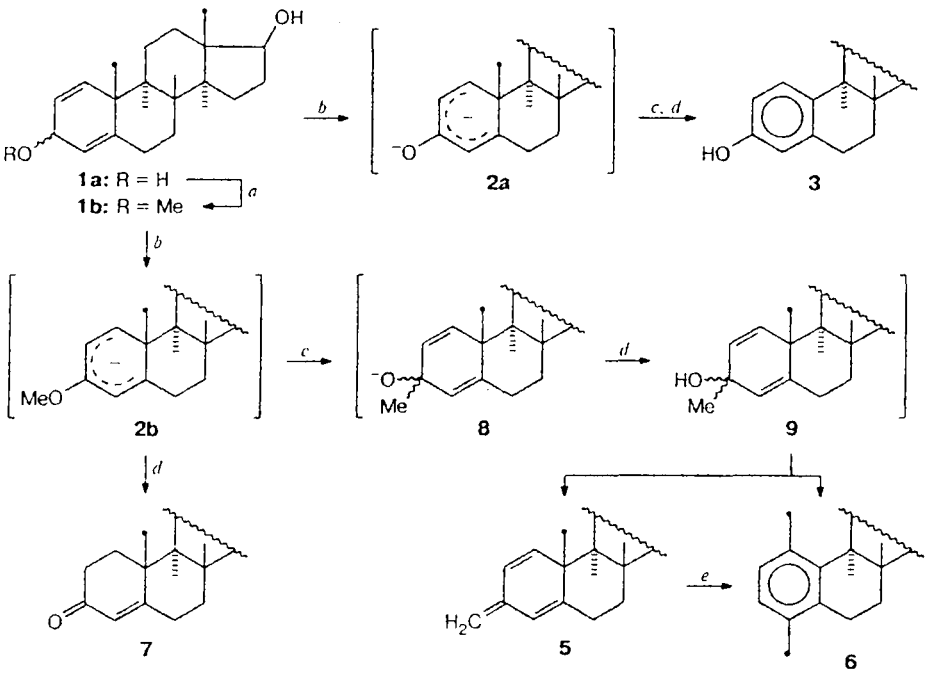
Scheme 1



Reagents and conditions: *a*, MeOH, $MgSO_4$, 22 °C; *b*, Bu^nLi, 22 °C; *c*, 60—75 °C; *d*, H_2O; *e*, SiO_2.

prone to dehydration than its secondary analog **1a**. Due to the presence of a methyl group the dehydration of carbinol **9** occurs without rearrangement and leads to methylenesteroid **5**.[5] Aromatic steroid **6** could arise as a result of both dehydration with rearrangement and subsequent rearrangement of methylenesteroid **5**. The side formation of testosterone **7** is possible *via* the protonation at C(1) of the remaining anion **2b** followed by hydrolysis of the arisen methylvinyl ether during work-up. Earlier[1] we have observed a similar formation of testosterone **7** from anion **2a** after its incomplete pyrolysis.

The two presented transformations, selective synthesis of diunsaturated ether **1b** and its transformation into methylenesteroid **5**, are not only of mechanistic but also of practical interest for the preparation of organic compounds with similar functional groups. A methylenesteroid structurally very similar to **5** was proposed as a second-generation antitumor agent.[8]

Experimental

^1H NMR spectra were recorded with a Bruker WM-250 (250.13 MHz) spectrometer. Analytical TLC was performed on Kieselgel 60 (Merck) using the developing systems indicated below. Column chromatography was performed on Al_2O_3, activity II, pH 9—10 of water extract. A solution of Bu^nLi in hexane (1.6 *M*) and TMEDA (Fluka) were used. The latter was dried by distillation from KOH.

3α/β-Methoxyandrosta-1,4-diene-17β-ol (1b). To a solution of diol **1a**[1] (48.6 mg, 0.169 mmol) (a mixture of 3-epimers, ratio α : β = 1 : 2.3) in anhydrous methanol (0.6 mL) and ether (4 mL) finely ground anhydrous $MgSO_4$ (0.6 g, 5 mmol) was added and the white suspension was stirred for 24 h at 22 °C until the starting diol was consumed (TLC monitoring). The reaction mixture was filtered, the solid residue on the filter was washed with ether and the filtrate was concentrated to dryness. The residue was subjected to column chromatography on Al_2O_3 (3.6 g, hexane—EtOAc, 4 : 1) to give a mixture of 3-epimers of methyl ether **1b** (38 mg, 75%), the ratio α : β = 1 : 1.2 (according to ^1H NMR spectrum), colorless oil, R_f 0.51 (3β-epimer) and 0.57 (EtOAc—hexane, 2 : 3, developed twice). ^1H NMR spectrum ($CDCl_3$), δ: 0.78 (s, 3 H, C(18)H_3); 1.06 (s, 1.64 H, C(19)H_3 in 3β-epimer); 1.12 (s, 1.36 H, C(19)H_3 in 3α-epimer); 3.22 (s, 1.36 H, OMe in 3α-epimer); 3.27 (s, 1.64 H, OMe in 3β-epimer); 3.61 (t, 1 H, H(17), J = 8.5 Hz); 4.35 (br.s, 1 H, H(3)); 5.44 (br.s, 1 H, H(4)); 5.70 (m, 1 H, H(2)); and 6.06 (d, 1 H, H(1), J = 10.5 Hz). The compound is unstable in $CDCl_3$, and can be stored in toluene solution at −20 °C.

3-Methyleneandrosta-1,4-dien-17β-ol (5) and 1,4-dimethylestra-1,3,5(10)-trien-17β-ol (6). To a stirred solution of ether **1b** (150 mg, 0.50 mmol) in TMEDA (620 mL, 4.1 mmol) 1.6 *M* Bu^nLi (5.1 mmol, 3.2 mL) was added at 22 °C under argon. During 4 h at the same temperature the solution became intensely reddish-brown. The mixture was stirred for 1.5 h at 60—75 °C, cooled, and diluted with ether and then with a phosphate buffer (pH 6). The two-layer light-yellow mixture was carefully acidified to pH 3 with 2 *M* HCl (to remove TMEDA) and extracted with EtOAc, and the extract was washed with water until the pH of the washings became neutral, dried with anhydrous Na_2SO_4, and concentrated to dryness. The residue (160 mg, yellow oil) was subjected to column chromatography on Al_2O_3 (6 g, EtOAc—hexane, 20→80%) to give methylenesteroid **5** (50 mg, 35%) (contains 25% of steroid **6** as follows from the NMR spectrum), R_f 0.62 (EtOAc—hexane,

2 : 3, developed twice), and testosterone **7** (20 mg, 14%), R_f 0.20 (the same conditions) identical with an authentic sample by TLC and ^{1}H NMR data. Steroid **5**: light-yellow oil (lit. data[5]: oil). ^{1}H NMR data ($CDCl_3$), δ: 0.79 (s, 3 H, C(18)H_3); 1.16 (s, 3 H, C(19)H_3); 3.62 (t, 1 H, H(17), J = 8.3 Hz); 4.70 and 4.74 (both s, both 1 H, C(3)=CH_2); 5.92 (d, 1 H, H(1), J = 9.6 Hz); 5.95 (s, 1 H, H(4)); and 6.16 (d, 1 H, H(2), J = 9.6 Hz). On attempted purification of methylenesteroid **5** by preparative TLC on silica gel it was completely transformed into aromatic steroid **6** (see Ref. 5), colorless oil. ^{1}H NMR spectrum ($CDCl_3$), δ: 0.83 (s, 3 H, C(18)H_3); 2.20 (s, 3 H, 4-Me); 2.34 (s, 3 H, 1-Me); 3.80 (t, 1 H, H(17), J = 7.7 Hz); and 6.92 (s, 2 H, H(2) + H(3)) (*cf.* with a spectrum in Ref. 9).

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