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ORIGINAL PAPER

Oxidation of steroidal diols and triols with air/NaH

Agnieszka Wojtkielewicz · Jadwiga Maj · Lech Szczepaniak · Jacek W. Morzycki

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Abstract The unusual air oxidation of steroidal triols and diols in the presence of sodium hydride in THF is described. The initial oxidation product, ketone or aldehyde, frequently undergoes further transformations in the reaction medium. The course of the reaction depends on the stereochemistry of the substrate. For example, oxidation of (20*R*)-20-hydroxymethyl-6*β*-methoxy-3α,5α-cyclopregnane-16*β*,17α-diol with air/NaH afforded 6*β*-methoxy-23,24,25,26,27-pentanor-3α,5α-cyclofurostane-16α,17α-diol in 60% yield whereas similar reaction of (20*R*)-20-hydroxymethyl-6*β*-methoxy-3α,5α-cyclopregnane-16α,17α-diol gave 6*β*-methoxy-D-homo-16a-oxa-3α,5α-cycloandrostan-16-one in 30% yield. The objective of this preliminary study was to select alcohols susceptible to air/NaH oxidation and to establish the effect of conditions on the course of the reaction.

Keywords Oxidation · Autoxidation · Alkoxides · Sodium hydride · Steroids

Introduction

A few years ago we attempted a standard Williamson etherification of a steroidal triol with an alkyl halide. The sodium alkoxide salt was prepared using sodium hydride [1]. Selective alkylation of the alkoxide at the primary hydroxyl group was expected. However, treatment of a THF solution of the triol with NaH at reflux surprisingly afforded the product of oxidation of the secondary hydroxyl group. Because the reaction was carried out under an argon atmosphere we came to the conclusion that dehydrogenation of the secondary alcohol promoted by NaH occurred during the reaction. However, further study described herein proved that the reaction consisted, in fact, of air oxidation of a polyalkoxide ion formed by treatment of the triol with NaH. Similar purported oxidation of benzyl alcohols to the corresponding ketones with sodium hydride was recently reported by Wang et al. [2]. However, the authors have apparently overlooked the role of oxygen from air in the process. Skeptical readers commented on the likelihood that the oxidation reactions actually consisted of autoxidation brought about by adventitious introduction of air [3, 4]. Indeed, even if attempts are made to maintain an inert atmosphere, it is difficult to avoid drawing some air into the reaction mixture during the long reaction time. The precedents of aerobic oxidation of benzyl alcohols, e.g. *p*-nitrobenzyl alcohol, promoted by sodium hydride are described in the literature [5] but there are no examples of autoxidation of non-activated alcohols.

Results and discussion

The reaction of triol **1** [6] with NaH as a promoter in THF under reflux afforded lactol **2** in 60% yield after 48 h (Scheme 1, Table 1). An analogous reaction carried out in dioxane afforded only 10% of product **2**, and reactions in other solvents (DMF, toluene, diethyl ether) proved much less efficient. A brief comparison was also made between different hydrides of the main groups showing that the most efficient and regioselective are sodium hydride and

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A. Wojtkielewicz · J. Maj · L. Szczepaniak · J. W. Morzycki (✉)
Institute of Chemistry, University of Białystok, Piłsudskiego 11/4, 15-443 Bialystok, Poland
e-mail: morzycki@uwb.edu.pl

Scheme 1

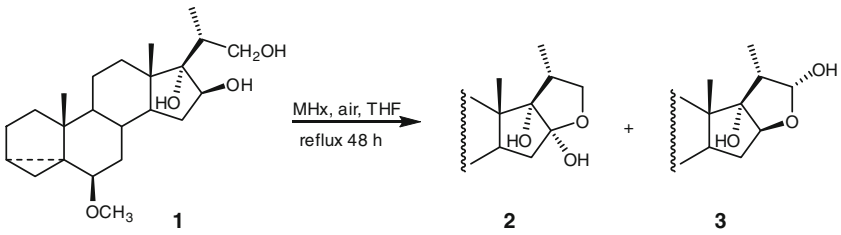
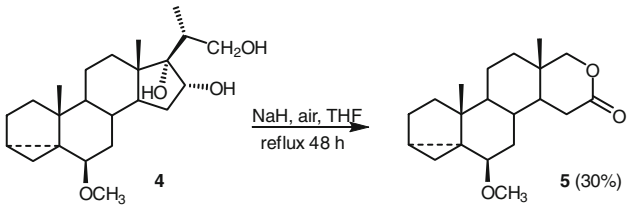


Table 1 Air oxidation of triol **1** promoted by metal hydrides of the main groups

MHx	Lactol **2** (%)	Lactol **3** (%)
NaH	60	–
KH	70	–
LiH	20	10



Scheme 2

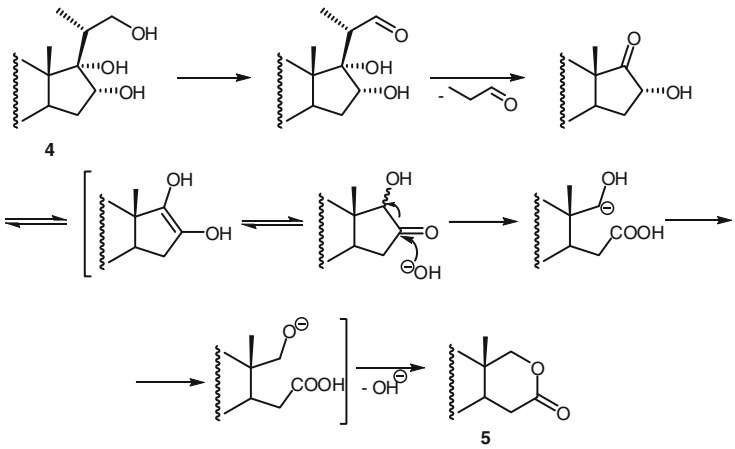
potassium hydride. Lithium hydride promoted autoxidation at both secondary and primary positions, whereas calcium hydride did not promote reaction. It was also shown that, under similar conditions, non-hydride deprotonating agents were either much less efficient than NaH in catalyzing autoxidation (e.g. sodium methoxide and potassium hexamethyldisilazane) or were completely inactive (e.g. potassium *tert*-butoxide).

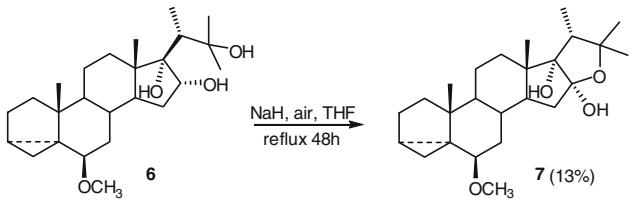
The reaction proved to be very sensitive to small changes of the starting triol structure. A similar reaction of the isomeric triol **4** [7] with sodium hydride unexpectedly afforded lactone **5** in 30% yield (Scheme 2).

A tentative mechanism of formation of this unusual product is shown in Scheme 3. It is most likely that the first step of the reaction consisted of autoxidation of the primary hydroxyl group to the aldehyde. In the case of an α-oriented hydroxyl group at C16 (as in triol **4**) the hemiacetal cannot be formed for steric reasons. Therefore the intermediate aldehyde may undergo further transformation under basic conditions. A retro-aldol reaction led to the splitting of this compound into two fragments—the steroidal hydroxyketone and propionaldehyde (confirmed by GC analysis). Such transformation of a similar 17α-hydroxy-22-aldehyde to the corresponding 17-ketone in a basic medium has previously been reported [8]. The transposition of the 17-ketone into the 16-ketone via a common enediol form was followed by a nucleophilic opening of the strained ring D and lactonization. The nucleophile could be either the hydroxyl ion, which is formed in the final lactonization step, or a hydride ion. However, in the latter case an additional autoxidation step would be required.

Steric hindrance in the side chain partially suppressed autoxidation. The triol **6** with additional methyl groups at C22 (Scheme 4) reacted with sodium hydride much more slowly under standard conditions [9]. The reaction took place at the secondary hydroxyl group affording lactol **7** in 13% yield. However, the reaction was accelerated (34%) by bubbling oxygen into the flask during the reaction

Scheme 3





Scheme 4

Table 2 Air oxidation of the hindered triol **6** promoted by sodium hydride. Effect of oxygen on the course of the reaction

Reaction conditions	Lactol **7** (%)	Recovered **6** (%)
NaH, air, THF, reflux, 48 h	13	63
NaH, O_2, THF, reflux, 48 h	34	57
NaH, THF sat. with O_2, reflux, 48 h	26	64
NaH, N_2, THF, reflux in a sealed ampoule, 48 h	5	90
NaH, hydroquinone (0.2 eq), Ar, THF, reflux, 48 h	2	92

(Table 2). The yield of lactol **7** was also increased (to 26%), when the reaction mixture was first saturated with oxygen at room temperature and then heated at reflux for 48 h. On the other hand, when the concentration of oxygen in the reaction mixture was reduced (reactions in a sealed ampoule under nitrogen or in the presence of 0.2 eq hydroquinone), yields of lactol **7** were considerably lower.

Participation of the neighboring hydroxyl group in air oxidation reactions at C16 is clear from the following experiments (Scheme 5). When a substrate devoid of a hydroxyl group at C17 (i.e. diol **8** [10]) was submitted to reaction with sodium hydride, only very slow oxidation at C16 to lactol **9** (4%) occurred. The product yield could not be improved by saturation of the reaction mixture with oxygen or any other changes of the reaction conditions (e.g. addition of 1 eq. ethanol, vide infra). The lack of a hydroxyl group in the side chain (diol **10** [11]) completely suppressed autoxidation. However, in this case the reactivity could be restored by addition of one equivalent of ethanol. The reaction afforded a complex mixture of products: ketones **11** and **12** were accompanied by lactone **13**, D-seco-acid **14**, and epoxide **15**. It is most likely that the initial reaction product, the 16-ketone **11**, isomerized to the more thermodynamically stable 17-ketone **12** in the basic medium (isomerization of **11** into **12** in the presence of NaH was proved in a separate experiment). Compounds **13** and **14** were also formed from ketone **11**, presumably by ring D cleavage in a manner similar to that described earlier for formation of lactone **5**. The configuration of epoxide **15**, a product of an intramolecular nucleophilic substitution of diol **10**, was not definitely established. Similar products were also obtained by NaH-promoted air oxidation of **10** carried out in the absence of ethanol but under an oxygen atmosphere. However, in this case the product yields proved to be much lower (Table 3).

The mechanism of the described autoxidation reactions is unclear. We hypothesize that the alkoxide ion is oxidized by triplet oxygen via a complex radical mechanism (Scheme 6). It is likely that NaOOH and THF hydroperoxide are formed during the reaction and play a role in the process. However, such peroxides are rapidly reduced by

Scheme 5

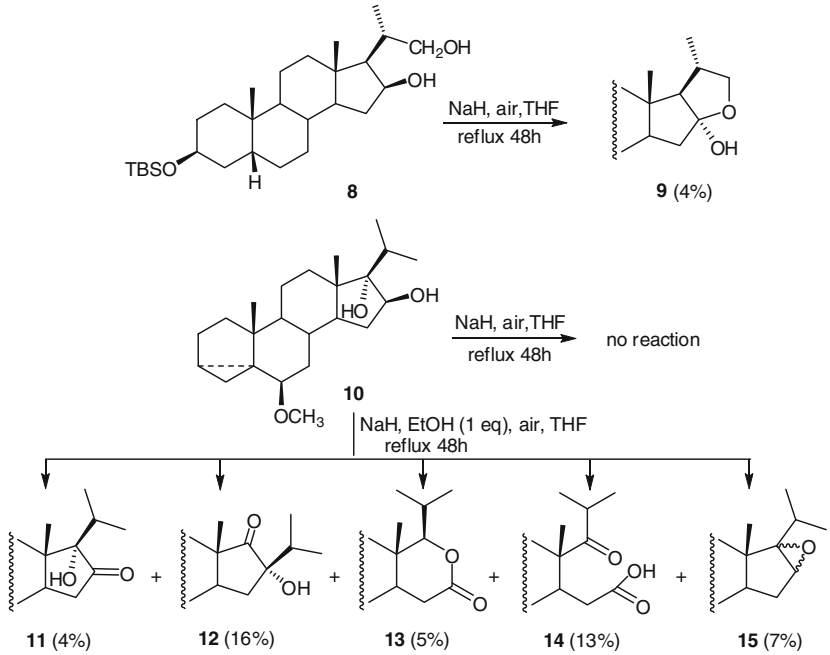
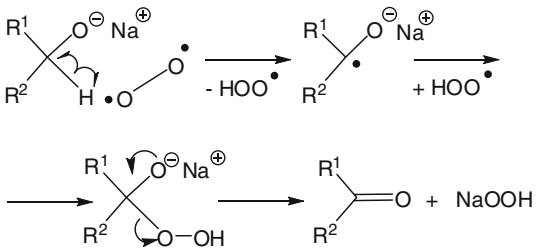


Table 3 Oxidation of diol **10** with air/NaH. Effect of ethanol on the course of the reaction

Reaction conditions	Compound (product yield)				
	11	**12**	**13**	**14**	**15**
NaH, air, THF, reflux, 48 h	–	–	–	–	–
NaH, O_2, THF, reflux, 48 h	–	2%	–	2%	8%
NaH, ethanol (1 eq), air/O_2, THF, reflux, 48 h	4%	16%	5%	13%	7%



Scheme 6

excess NaH. The reaction is clearly accelerated by the presence of other alkoxide ions in the immediate proximity of the reaction center. These additional alkoxide ions increase the electron density on the reacting alkoxide rendering its oxidation to a carbonyl group easier.

So far, only examples of such autoxidation of the most reactive benzyl alcohols, benzoins [12], and polyols are known. However, the last example demonstrates that an external source of alkoxide may also activate autoxidation promoted by NaH. In this way the range of alcohols susceptible to such reactions may be widened.

Conclusions

Previous studies have shown that alkoxides derived from benzyl alcohols are susceptible to aerobic oxidation. Now we have demonstrated that some diols and triols also undergo autoxidation when treated with sodium hydride. It should be stressed that on the basis of our results it cannot be conclusively ruled out that autoxidation is accompanied by a side reaction, namely NaH-promoted dehydrogenation of the starting alcohol (β-hydride elimination), leading to the same products as suggested in previous reports [1, 2]. This conclusion may be drawn from the observation that even under strictly anaerobic conditions some oxidation usually occurred. Further study of the mechanism of the autoxidation reaction, its scope and limitation, the role and importance of neighboring hydroxyl groups, steric requirements, etc., is in progress in our laboratory. An important conclusion from this study is that sodium hydride should be used for deprotonation of alcohols with caution, because the reagent may promote some undesired oxidative side reactions, especially if there is more than one hydroxyl group present in the molecule.

Experimental

Melting points were determined on a Kofler apparatus of the Boetius type. NMR spectra were recorded in $CDCl_3$ solutions with Bruker Avance II (400 MHz) or Bruker AC 200 F (200 MHz) spectrometers using the residual solvent as internal standard (only selected signals in the ^{1}H NMR spectra are reported). Infrared spectra were recorded on a Nicolet series II Magna-IR 550 FT-IR spectrometer in anhydrous chloroform solutions. Mass spectra were obtained with AMD-604 (EI, 70 eV) or LCT (ESI-TOF) spectrometers.

The reaction products were isolated by column chromatography performed on 70–230 mesh silica gel (J.T. Baker). Yields refer to chromatographically purified products unless otherwise stated. Sodium hydride was purchased from Riedel–de Haën, as a 60% dispersion in mineral oil. Anhydrous THF was distilled from sodium-benzophenone. Triols **1**, **4**, **6** and diols **8**, **10** used as substrates for oxidation reactions were synthesized by known methods [6–10].

General procedure for oxidation with air/NaH

Sodium hydride (5 eq, 1.3 mmol, 52 mg of 60% dispersion in mineral oil) was suspended in 2 cm^3 pentane under argon atmosphere. After brief stirring the supernatant solvent was removed and 5 cm^3 dry THF was added. To the cooled suspension of NaH, a solution of alcohol (0.26 mmol, 1 eq) in 10 cm^3 dry THF was added and the reaction mixture was heated under reflux for 48 h. After cooling, the reaction was quenched by addition of water. The reaction mixture was neutralized with dilute hydrochloric acid (5%) and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel.

6β-Methoxy-23,24,25,26,27-pentanor-3α,5α-cyclofurostane-16α,17α-diol (**2**, $C_{23}H_{36}O_4$)

The title compound was obtained in 60% yield by autoxidation of triol **1** [6] in the presence of NaH in accordance with the general procedure (purification by column chromatography, elution with hexane–ethyl acetate 8.8:1.2). IR ($CHCl_3$): $\bar{\nu}$ = 3,604, 3,415, 1,722 (small), 1,456, 1,383, 1,144, 1,006 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.15 (m, 1H, 22-H), 3.67 (m, 1H, 22-H), 3.33 (s, 3H, CH_3O), 3.31 (s, 1H, HO), 2.78 (m, 1H, 6α-H), 2.46

(m, 1H, 20β-H), 1.91–1.65 (m, 8H), 1.56–1.50 (m, 3H), 1.47–1.33 (m, 3H), 1.13 (m, 1H), 1.04 (s, 3H, 19-H), 0.95 (s, 3H, 18-H), 0.92 (d, $J = 7.1$ Hz, 3H, 21-H), 0.90–0.83 (m, 2H), 0.67 (m, 1H, 4-H), 0.45 (m, 1H, 4-H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 112.8$ (C), 89.3 (C), 82.1 (CH), 76.7 (CH_2), 56.6 (CH_3), 52.0 (CH), 47.5 (CH), 45.8 (C), 43.5 (C), 39.8 (CH_2), 35.1 (C), 34.0 (CH), 33.3 (CH_2), 31.8 (CH_2), 30.2 (CH), 24.9 (CH_2), 21.3 (CH), 19.3 (CH_3), 16.5 (CH_3), 13.3 (CH_3), 13.1 (CH_2) ppm; MS (70 eV): $m/z = 376$ (M^+, 20%), 361 (33%), 344 (23%), 321 (80%), 214 (55%).

6β-Methoxy-23,24,25,26,27-pentanor-3α,5α-cyclofurostane-17α,22α-diol (**3**, $C_{23}H_{36}O_4$)

The title compound was obtained in 10% yield by autoxidation of triol **1** [6] in the presence of LiH instead of NaH (purification by column chromatography, elution with hexane–ethyl acetate 8.8:1.2). IR ($CHCl_3$): $\bar{\nu} = 3{,}602$, 3,399, 1,728 (small), 1,456, 1,382, 1,081 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.46$ (d, $J = 4.4$ Hz, 1H, 22β-H), 4.30 (t, $J = 7.6$ Hz, 1H, 16α-H), 3.34 (s, 3H, CH_3O), 2.79 (m, 1H, 6α-H), 2.42 (dq, $J = 4.4$ Hz, $J = 7.2$ Hz, 1H, 20β-H), 2.11 (m, 1H, 15-H), 1.96–1.86 (m, 3H), 1.77–1.63 (m, 4H), 1.56–1.30 (m, 8H), 1.16 (m, 1H), 1.05 (s, 3H, 19-H), 1.00 (d, $J = 7.2$ Hz, 3H, 21-H), 0.90 (s, 3H, 18-H), 0.85 (m, 1H), 0.67 (m, 1H, 4-H), 0.46 (dd, $J = 5.2$ Hz, $J = 8.0$ Hz, 1H, 4-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 104.5$ (CH), 91.5 (CH), 89.4 (C), 82.1 (CH), 56.6 (CH_3), 52.7 (CH), 47.6 (CH), 44.5 (C), 43.4 (C), 40.6 (CH), 35.2 (CH_2), 35.1 (C), 33.3 (CH_2), 32.1 (CH_2), 30.9 (CH_2), 30.1 (CH), 24.9 (CH_2), 22.3 (CH_2), 21.3 (CH), 19.3 (CH_3), 17.4 (CH_3), 13.1 (CH_2), 8.2 (CH_3) ppm; MS (ESI): $m/z = 399.3$ ($M + Na^+$, 100%).

6β-Methoxy-homo-16a-oxa-3α,5α-cycloandrostan-16-one (**5**, $C_{20}H_{30}O_3$)

The title compound was obtained in 30% yield by autoxidation of triol **4** [7] in the presence of NaH in accordance with the general procedure (purification by column chromatography, elution with hexane–ethyl acetate 8:2). IR ($CHCl_3$): $\bar{\nu} = 1{,}720$, 1,474, 1,382, 1,244, 1,192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.98$ (d, $J = 10.7$ Hz, 1H, 17-H), 3.89 (d, $J = 10.7$ Hz, 1H, 17-H), 3.33 (s, 3H, CH_3O), 2.82 (m, 1H, 6α-H), 2.77 (dd, $J = 6.1$ Hz, $J = 18.7$ Hz, 1H, 15-H), 2.19 (dd, $J = 12.8$ Hz, $J = 18.7$ Hz, 1H, 15-H), 1.95 (dt, $J = 13.2$ Hz, $J = 3.1$ Hz, 1H, 7-H), 1.76 (m, 1H), 1.64 (dq, $J = 3.0$ Hz, $J = 10.9$ Hz, 1H), 1.61–1.49 (m, 4H), 1.46–1.37 (m, 2H), 1.10 (m, 1H), 1.05 (s, 3H, 19-H), 1.03 (s, 3H, 18-H), 0.95–0.88 (m, 4H), 0.68 (m, 1H, 4-H), 0.49 (dd, $J = 5.1$ Hz, $J = 8.0$ Hz, 1H, 4-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.0$ (C), 81.6 (CH), 81.2 (CH_2), 56.6 (CH_3), 47.0 (CH), 44.3 (CH), 43.5 (C), 34.8 (C, CH_2), 33.22 (CH_2), 33.16 (CH_2), 32.5 (C), 31.9 (CH_2), 24.8 (CH_2), 21.7 (CH), 21.1 (CH_2), 19.3 (CH_3), 15.2 (CH_3), 13.1 (CH_2) ppm; MS (70 eV): $m/z = 318$ (M^+, 21%), 303 (47%), 286 (42%), 263 (100%).

6β-Methoxy-22-methyl-24,25,26,27-tetranor-3α,5α-cyclofurostane-16α,17α-diol (**7**, $C_{25}H_{40}O_4$)

The title compound was obtained in 13% yield by autoxidation of triol **6** [8] in the presence of NaH in accordance with the general procedure (purification by column chromatography, elution with hexane–ethyl acetate 8.5:1.5). The yield of product **7** was increased to 34% by bubbling of oxygen through the reaction mixture. IR ($CHCl_3$): $\bar{\nu} = 3{,}411$, 1,727 (small), 1,494, 1,452, 1,384, 1,164, 947 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.68$ (s, 1H, HO), 3.30 (s, 3H, CH_3O), 2.89 (s, 1H, HO), 2.76 (t, $J = 2.8$ Hz, 1H, 6α-H), 2.26 (q, $J = 7.3$ Hz, 1H, 20β-H), 1.92–1.67 (m, 8H), 1.55–1.49 (m, 3H), 1.45–1.32 (m, 2H), 1.24 (s, 3H, CH_3-22), 1.22 (s, 3H, CH_3-22), 1.13 (m, 1H), 1.03 (s, 3H, 19-H), 0.94 (s, 3H, 18-H), 0.90–0.83 (m, 2H), 0.86 (d, $J = 7.3$ Hz, 3H, 21-H), 0.65 (m, 1H, 4-H), 0.43 (dd, $J = 8.0$, 5.1 Hz, 1H, 4-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 111.8$ (C), 90.8 (C), 89.1 (C), 82.1 (CH), 56.5 (CH_3), 51.9 (CH), 47.5 (CH), 46.1 (C), 44.4 (CH), 43.4 (C), 41.0 (CH_2), 35.13 (CH_2), 35.06 (C), 33.2 (CH_2), 32.2 (CH_2), 30.0 (CH), 28.6 (CH_3), 24.9 (CH_2), 24.8 (CH_3), 22.2 (CH_2), 21.3 (CH), 19.3 (CH_3), 17.8 (CH_3), 13.1 (CH_2), 10.4 (CH_3) ppm; MS (ESI): $m/z = 427.3$ ($M + Na^+$, 100%); HRMS ($C_{25}H_{40}O_4Na$): calcd. 427.2824, found 427.2831.

3β-tert-Butyldimethylsilyloxy-23,24,25,26,27-pentanorfurostan-16α-ol (**9**, $C_{28}H_{50}O_3Si$)

The title compound was obtained in 4% yield by autoxidation of diol **8** [9] in the presence of NaH in accordance with the general procedure (purification by column chromatography, elution with hexane–ethyl acetate 9.2:0.8). IR ($CHCl_3$): $\bar{\nu} = 3{,}586$, 3,397, 1,717 (small), 1,463, 1,381, 1,257, 1,092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.91$ (t, $J = 7.5$ Hz, 1H, 22-H), 3.55 (m, 1H, 3α-H), 3.49 (dd, $J = 8.3$ Hz, $J = 11.0$ Hz, 1H, 22-H), 2.12 (m, 1H, 20β-H), 1.94 (dd, $J = 12.2$ Hz, $J = 6.2$ Hz, 1H, 15-H), 1.70–1.22 (m, 17H), 1.10–1.02 (m, 2H), 1.00 (s, 3H, 19-H), 0.99 (d, $J = 6.5$ Hz, 3H, 21-H), 0.89 (s, 9H, $(CH_3)_3CSi$), 0.82 (s, 3H, 18-H), 0.82–0.73 (m, 2H), 0.06 (s, 6H, $(CH_3)_2Si$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 116.7$ (C), 73.8 (CH_2), 72.1 (CH), 68.5 (CH), 54.1 (CH), 49.7 (CH), 44.9 (CH), 41.8 (C), 40.6 (CH_2), 38.6 (CH_2), 37.1 (CH_2), 36.5 (CH), 35.6 (C), 34.9 (CH), 33.4 (CH_2), 32.3 (CH_2), 31.9 (CH_2), 28.6 (CH_2), 25.9 ($3CH_3$), 20.7 (CH_3), 20.5 (CH_2), 18.3 (C), 15.5 (CH_3), −4.6 (CH_3) ppm; MS (ESI): $m/z = 485.3$ ($M + Na^+$, 100%).

Compounds **15** (7%), **12** (16%), **11** (4%), **13** (5%), and **14** (13%) were obtained by autoxidation of diol **10** [10] in the presence of NaH in accordance with the general

procedure but with an additional one equivalent of ethanol. The products were separated by silica gel column chromatography.

17-Isopropyl-6β-methoxy-16ξ,17ξ-oxido-3α,5α-cycloandrostane (**15**, $C_{23}H_{36}O_2$)
Eluted with *n*-hexane–ethyl acetate 9.5:0.5. IR ($CHCl_3$): $\bar{\nu}$ = 1,471, 1,380, 1,089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.34 (s, 3H, CH_3O), 3.28 (s, 1H, 16-H), 2.79 (m, 1H, 6α-H), 2.33 (septet, J = 6.8 Hz, 1H, 20-H), 1.86–1.81 (m, 3H), 1.79–1.69 (m, 2H), 1.55–1.36 (m, 5H), 1.32–1.24 (m, 2H), 1.19–1.10 (m, 2H), 1.04 (s, 3H, 19-H), 1.02 (d, J = 6.8 Hz, 3H, isopropyl CH_3), 0.91–0.85 (m, 2H), 0.89 (s, 3H, 18-H), 0.81 (d, J = 6.8 Hz, 3H, isopropyl CH_3), 0.67 (m, 1H, 4-H), 0.45 (dd, J = 5.1 Hz, J = 8.0 Hz, 1H, 4-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.3 (CH), 73.9 (C), 59.5 (CH), 56.6 (CH_3), 48.3 (CH), 45.3 (CH), 43.4 (C), 42.9 (C), 35.1 (C), 35.0 (CH_2), 33.5 (CH_2), 33.2 (CH_2), 28.9 (CH), 27.3 (CH_2), 24.9 (CH_2), 24.2 (CH), 22.4 (CH_2), 21.3 (CH), 19.5 (CH_3), 19.2 (CH_3), 19.1 (CH_3), 16.5 (CH_3), 13.1 (CH_2) ppm; MS (ESI): m/z = 711.6 (2M + Na^+), 367.3 (M + Na^+, 100%).

16α-Hydroxy-16β-isopropyl-6β-methoxy-3α,5α-cycloandrostan-17-one (**12**, $C_{23}H_{36}O_3$)
Eluted with hexane–ethyl acetate 9.1:0.9. IR ($CHCl_3$): $\bar{\nu}$ = 3,566, 1,736, 1,468, 1,455, 1,375, 1,093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.38 (s, 3H, CH_3O), 2.84 (m, 1H, 6α-H), 1.98 (m, 1H, 8-H), 1.96 (m, 1H, 20-H), 1.88 (m, 1H), 1.86–1.83 (m, 2H), 1.82–1.68 (m, 1H), 1.64–1.46 (m, 6H), 1.38 (m, 1H), 1.23 (m, 2H), 1.06 (s, 3H, 19-H), 1.00 (d, J = 6.8 Hz, 3H, isopropyl CH_3), 0.97 (s, 3H, 18-H), 0.95–0.85 (m, 3H), 0.90 (d, J = 6.8 Hz, 3H, isopropyl CH_3), 0.69 (m, 1H, 4-H), 0.46 (dd, J = 5.2 Hz, J = 8.0 Hz, 1H, 4-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 221.3 (C), 82.0 (CH), 81.9 (C), 56.7 (CH_3), 48.4 (C), 48.2 (CH), 46.9 (CH), 43.6 (C), 42.9 (C), 35.0 (C), 34.9 (CH), 33.3 (CH_2), 32.6 (CH_2), 32.3 (CH_2), 29.5 (CH), 24.9 (CH_2), 21.8 (CH_2), 21.2 (CH), 19.2 (CH_3), 17.8 (CH_3), 16.2 (CH_3), 13.7 (CH_3), 13.2 (CH_2) ppm; MS (ESI): m/z = 383.2 (M + Na^+, 100%).

17α-Hydroxy-16β-isopropyl-6β-methoxy-3α,5α-cycloandrostan-16-one (**11**, $C_{23}H_{36}O_3$)
Eluted with *n*-hexane–ethyl acetate 9.1:0.9. IR ($CHCl_3$): $\bar{\nu}$ = 1,736, 1,470, 1,384, 1,090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.35 (s, 3H, CH_3O), 2.81 (m, 1H, 6α-H), 2.34 (dd, J = 7.2 Hz, J = 17.9 Hz, 1H, 15-H) 2.08 (m, 2H, 15-H, 20-H), 1.96–1.70 (m, 7H), 1.66 (s, 1H, OH), 1.54 (m, 1H), 1.30–1.26 (m, 2H), 1.20 (d, J = 6.8 Hz, 3H, isopropyl CH_3), 1.06 (s, 3H, 19-H), 0.98 (d, J = 6.8 Hz, 3H, isopropyl CH_3), 0.93–0.84 (m, 4H), 0.92 (s, 3H, 18-H), 0.69 (m, 1H, 4-H), 0.48 (dd, J = 5.2 Hz, J = 8.1 Hz, 1H, 4-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 217.8 (C), 82.8 (C), 82.1 (CH), 56.7 (CH_3), 47.4 (CH), 46.5 (C), 45.2 (CH), 43.5 (C), 47.8 (CH_2), 35.5 (CH_2), 35.0 (C), 33.1 (CH_2), 31.3 (CH_2), 30.8 (CH), 29.6 (CH), 24.9 (CH_2), 21.8 (CH_2), 21.3 (CH), 19.2 (CH_3), 18.6 (CH_3), 17.3 (CH_3), 14.2 (CH_3), 13.2 (CH_2) ppm; MS (ESI): m/z = 743.6 (2 M + Na^+), 383.3 (M + Na^+, 100%).

6β-Methoxy-homo-16a-oxa-3α,5α-cycloandrostan-16-one (**13**, $C_{23}H_{36}O_3$)
Eluted with hexane–ethyl acetate 7.5:2.5. IR ($CHCl_3$): $\bar{\nu}$ = 1,713, 1,469, 1,382, 1,240, 1,088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.90 (d, J = 3.5 Hz, 1H, 17α-H), 3.32 (s, 3H, CH_3O), 2.81 (m, 1H, 6α-H), 2.73 (dd, J = 5.9 Hz, J = 18.7 Hz, 1H, 15-H), 2.15 (m, 2H, 15-H, 20-H), 1.97 (ddd, J = 13.2 Hz, J = 2.7 Hz, J = 2.3 Hz, 1H, 7-H), 1.73–1.64 (m, 2H), 1.60–1.55 (m, 4H), 1.50–1.42 (m, 3H), 1.10 (s, 3H, 18-H), 1.09 (d, J = 6.0 Hz, 3H, isopropyl CH_3), 1.03 (s, 3H, 19-H), 0.98 (d, J = 6.8 Hz, 3H, isopropyl CH_3), 0.95–0.87 (m, 4H), 0.68 (m, 1H, 4-H), 0.49 (dd, J = 5.2 Hz, J = 8.0 Hz, 1H, 4-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6 (C), 93.6 (CH), 81.7 (CH), 56.6 (CH_3), 46.9 (CH), 43.6 (C), 38.8 (CH), 36.0 (C), 34.9 (C), 33.5 (CH_2), 33.3 (CH_2), 33.2 (CH), 31.9 (CH_2), 29.0 (CH), 24.9 (CH_2), 23.7 (CH_3), 21.5 (CH), 21.4 (CH_2), 19.5 (CH_3), 19.3 (CH_3), 18.3 (CH_3), 13.1 (CH_2) ppm; MS (ESI): m/z = 743.6 (2M + Na^+), 383.3 (M + Na^+, 100%).

17-Isopropyl-6β-methoxy-17-oxo-3α,5α-cyclo-16,17-secoandrostan-16-oic acid (**14**, $C_{23}H_{36}O_4$)
Eluted with hexane–ethyl acetate 7:3. IR ($CHCl_3$): $\bar{\nu}$ = 3,100 (broad), 1,712, 1,696, 1,469, 1,384, 1,089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.6 (broad s, 1H, COOH), 3.35 (s, 3H, CH_3O), 3.20 (septet, J = 6.6 Hz, 1H, isopropyl CH), 2.85 (m, 1H, 6α-H), 2.14 (m, 2H, 15-H), 2.08–2.02 (m, 1H), 1.80–1.70 (m, 3H), 1.59–1.55 (m, 3H), 1.53–1.40 (m, 3H), 1.18 (s, 3H, 18-H), 1.07 (d, J = 6.6 Hz, 3H, isopropyl CH_3), 1.06 (d, J = 6.6 Hz, 3H), 1.02 (s, 3H, 19-H), 0.95–0.89 (m, 4H), 0.67 (m, 1H, 4-H), 0.49 (dd, J = 5.1 Hz, J = 8.1 Hz, 1H, 4-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 222.6 (C), 175.9 (C), 81.8 (CH), 56.6 (CH_3), 53.4 (C), 46.9 (CH), 43.5 (C), 42.0 (CH), 38.1 (CH_2), 35.1 (CH_2), 34.6 (C), 34.3 (CH_2), 33.16 (CH_2), 34.1 (CH), 33.9 (CH), 33.5 (CH_2), 24.8 (CH_2), 21.33 (CH_2), 21.28 (CH), 20.6 (CH_3), 20.0 (CH_3), 19.2 (CH_3), 14.5 (CH_3), 13.2 (CH_2) ppm; MS (ESI): m/z = 399.2 (M + Na^+, 100%).

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