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# A new type of steroids with a cyclobutane fragment in the AB-ring moiety

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ABSTRACT

The synthesis of a 5,10-seco steroid containing two double bonds in a AB-macrocycle as well as the preparation of a steroidal skeleton with a cyclobutane fragment is described. The structures of these compounds are different from those of natural steroids, but they are very similar with respect to conformation of the carbon skeleton.



## 1. Introduction

The development of new compounds to improve the selectivity and to minimize side effects of steroidal drugs has been a challenge for a long time [1]. For many years, the main direction of steroid research focused on the search for compounds with a normal tetracyclic skeleton, which differed mainly by their functional groups. At the same time, a number of pharmacologically active substances belonging to non-vitamin D seco steroids were found [2–6]. During the last few years, we were interested in preparing steroids with unusual carbon skeletons, in particular, those having no internal $C_5$–$C_{10}$– or $C_{13}$–$C_{14}$–bonds [7–10]. Radical oxidation of 5α- and 14α-alcohols and Grob fragmentation of 14β-hydroxy-17β-tosylates were explored till now. Oxidative cleavage of $\Delta^{5(10)}$-olefins in the 19-norsteroid series offers an additional synthetic route to such compounds, and we have used this approach for the synthesis of new 5,10-seco steroids. Especially the preparation of derivatives having two double bonds in a ten membered macrocycle seemed interesting, since inspection of molecular models showed common features in their main conformation with that of normal steroids. In addition, the obtained *trans*,*trans*-cyclodeca-1,6-dienes were supposed to be interesting not only as final compounds for bioassays, but also as intermediates for re-cyclization to steroids with unusual cyclic parts. A typical example of such a strategy is the synthesis of 1-hydroxy cholesterols via 5,10-seco steroids [11]. In the present work, the synthesis of a

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5,10-seco steroid containing $\Delta^{1(10)}$- and $\Delta^{5(6)}$-double bonds in the AB ring, and its photochemical transformation to a new non-olefinic product containing a cyclobutane fragment in the cyclic part of the molecule, is described.

## 2. Experimental

Melting points were taken on a Boetius micro-melting point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were taken on a Bruker AC-200 (200 MHz for $^1$H, 50 MHz for $^{13}$C) spectrometer in $CDCl_3$ using TMS as an internal standard and chemical shifts are given in $\delta$ (ppm). For compounds **6** and **7** 1D and 2D NMR spectra were recorded on an AVANCE-500 (Bruker Biospin) spectrometer operating at 500 MHz for $^1$H and 125 MHz for $^{13}$C. Assignment of $^1$H and $^{13}$C resonances were done by the combined use of 1D and 2D experiments, including COSY, HSQC, HMBC, TOCSY, and NOESY methods. All experiments were carried out using standard pulse sequences supplied with the spectrometer. The exact mass measurements were carried out on a Finnigan MAT 95 mass spectrometer, operating in the 70 eV-EI mode. Chemicals were purchased from Aldrich and Fluka chemical companies and were used as received. 7α-Methyl-19-norandrost-5(10)-en-17-on-3α-ol was supplied by Organon. Reactions were monitored by TLC using aluminium or plastic sheets, silica gel 60 $F_{254}$ precoated (Merck Art. 5715). Column chromatography was carried out on Kieselgel 60 (Merck Art. 7734).

### 2.1. *3α,17β-Diacetoxy-7α-methyl-19-norandrosta-5,10-diol (3)*

A mixture of 3α,17β-diacetoxy-7α-methyl-19-norandrost-5(10)-ene **1** (prepared from 7α-methyl-19-norandrost-5(10)-en-17-on-3α-ol according to procedures described in [12] and [13], mp 98–100 °C (EtOH)) (400 mg, 0.98 mmol), $NaHCO_3$ (400 mg, 4.76 mmol), $CHCl_3$ (8 ml), and MeOH (4 ml) was ozonized at −50 °C. When the starting material had disappeared, $Me_2S$ (1 ml) was added and the mixture was allowed to warm to room temperature. The solvents were evaporated in vacuo, the residue was dissolved in EtOH (5 ml) and $CaCl_2$ (185 mg, 1.7 mmol) and $NaBH_4$ (129 mg, 3.4 mmol) were added to the reaction mixture. After stirring for 5 min at room temperature, the mixture was neutralized with AcOH. The precipitate was filtered off, the filtrate was evaporated, and the residue was chromatographed on $SiO_2$ (toluene–EtOAc) to give diol **3** (185 mg, 42%). Mp 90–95 °C (hexane–EtOAc). $^1$H NMR $\delta$: 0.85 (s, 3H, 18-Me), 1.10 (d, 3H, *J* 7 Hz, 7-Me), 2.04 (s, 6H, OAc), 3.73 (dd, 1H, *J* 11.3, 7.6 Hz, $C_{10}$–H), 4.30 (m, 1H, $C_5$–H), 4.57 (m, 1H, $C_{17}$–H), 5.00 (m, 1H, $C_3$–H). $^{13}$C NMR $\delta$: 12.2, 21.2, 21.3, 24.0, 25.0, 26.7, 26.9, 28.0, 29.9, 32.3, 34.5, 37.2, 37.5, 41.0, 42.7, 43.2, 46.9, 67.6, 71.5, 76.4, 82.4, 170.2, 171.4.

### 2.2. *3α,17β-Diacetoxy-5,10-bis-[(1H-imidazol-1-ylthiocarbonyl)oxy]-7α-methyl-5,10-secoandrostane (4)*

A mixture of **3** (1.6 g, 3.9 mmol), 1,1′-thiocarbonyldiimidazole (1.39 g, 7.8 mmol), and pyridine was kept at ambient temperature for 120 h. Then it was diluted with water and extracted with $CHCl_3$ and EtOAc. The combined extracts were dried and the solvents were evaporated. The residue was chromatographed on $SiO_2$ (cyclohexane–EtOAc = 1:1) to give **4** (1.03 g, 42%) as an oil. $^1$H NMR $\delta$: 0.80 (s, 3H, 18-Me), 1.22 (d, 3H, *J* 7.0 Hz, 7-Me), 2.03 (s, 3H, OAc), 2.07 (s, 3H, OAc), 4.56 (dd, 1H, 9.2, 8.2 Hz, $C_{17}$–H), 5.05 (m, 1H, $C_3$–H), 5.68 (dd, 1H, *J* 11.4, 7.8 Hz, $C_{10}$–H), 6.14 (m, 1H, $C_5$–H), 7.04 (s, 1H, Im), 7.10 (s, 1H, Im), 7.59 (d, 1H, *J* 1.2 Hz, Im), 7.65 (d, 1H, *J* 1.2 Hz, Im), 8.31 (s, 1H, Im), 8.36 (s, 1H, Im). $^{13}$C NMR $\delta$: 12.1, 21.1, 21.2, 23.5, 24.9, 25.0, 26.6, 26.9, 27.7, 28.2, 29.3, 29.7, 30.2, 34.3, 36.7, 40.4, 43.2, 44.5, 46.7, 69.7, 80.4, 81.8, 87.3, 117.9, 130.97, 131.04, 131.2, 136.5, 136.6, 136.8, 169.9, 171.1, 183.0, 183.8.

### 2.3. *3α,17β-Diacetoxy-5,10-bis-[(methoxythiocarbonyl)oxy]-7α-methyl-5,10-secoandrostane (5)*

To a solution of **4** (300 mg, 0.48 mmol) in MeOH (6 ml), 5% KOH in MeOH (0.2 ml) was added. The mixture was stirred at room temperature for 30 min, and then neutralized with AcOH. The solvents were removed in vacuo, and the residue was chromatographed on $SiO_2$ (cyclohexane–EtOAc = 4:1, 2:1) to give compound **5** (150 mg, 57%) as an oil. $^1$H NMR $\delta$: 0.82 (s, 3H, 18-Me), 1.08 (d, 3H, *J* 6.9 Hz, 7-Me), 2.04 (s, 3H, OAc), 2.06 (s, 3H, OAc), 4.02 (s, 3H, OMe), 4.07 (s, 3H, OMe), 4.52 (dd, 1H, *J* 9.2, 7.4 Hz, $C_{17}$–H), 4.92–5.08 (m, 1H, $C_3$–H), 5.38 (dd, 1H, *J* 11.3, 7.7 Hz, $C_{10}$–H), 5.75–5.91 (m, 1H, $C_5$–H).

### 2.4. *3α,17β-Diacetoxy-7α-methyl-5,10-secoandrosta-1(10)(E),5(E)-diene (6)*

A solution of **5** (150 mg, 0.27 mmol) in toluene (2 ml) was heated under reflux for 1.5 h. Then the solvent was evaporated in vacuo, and the residue was chromatographed on $SiO_2$ (cyclohexane–EtOAc = 15:1) to give **6** (75 mg, 50%). Mp 82–85° C (hexane–EtOAc). For $^1$H and $^{13}$C NMR data see Table 1. HRMS Calc. for $C_{23}H_{34}O_4Na$ $(M+Na)^+$ 397.2355. Found: 397.2375.

### 2.5. *Irradiation of (6)*

A solution of **6** (100 mg, 0.27 mmol) in MeOH (12 ml) in a quartz cuvet was irradiated with a low-pressure Hg lamp. The reaction progress was monitored periodically by taking NMR spectra of the reaction mixture. After the starting material had disappeared, the solvent was evaporated under reduced pressure and the residue was chromatographed on $SiO_2$ (cyclohexane–EtOAc = 15:1) to give **7** (66 mg, 66%) as an oil. For $^1$H and $^{13}$C NMR data see Table 1. HRMS Calc. for $C_{23}H_{34}O_4$ $(M^+)$ 374.2457; Found: 374.2454; Calc. for $C_{21}H_{30}O_2$ ($[M\text{-}HOAc]^+$) 314.2246; Found: 314.2244. EIMS *m/z*: 374 ($M^{+\bullet}$, 32), 314 ($[M\text{-}HOAc]^{+\bullet}$, 100), 254 ($[M\text{-}2*2HOAc]^{+\bullet}$, 23), 239 (29), 163 (36), 161 (31), 133 (37), 93 (29).

## 3. Results and discussion

Olefin **1** seemed to be an appropriate compound for the preparation of various 5,10-seco steroids *via* ozonolysis of the $\Delta^{5(10)}$-double bond (Scheme 1). This compound can be obtained from 3α-hydroxytibolone, a major metabolite of the marketed drug tibolone, from which it can be prepared by a stereoselective reduction [12]. Conversion of 3α-hydroxytibolone into **1** can

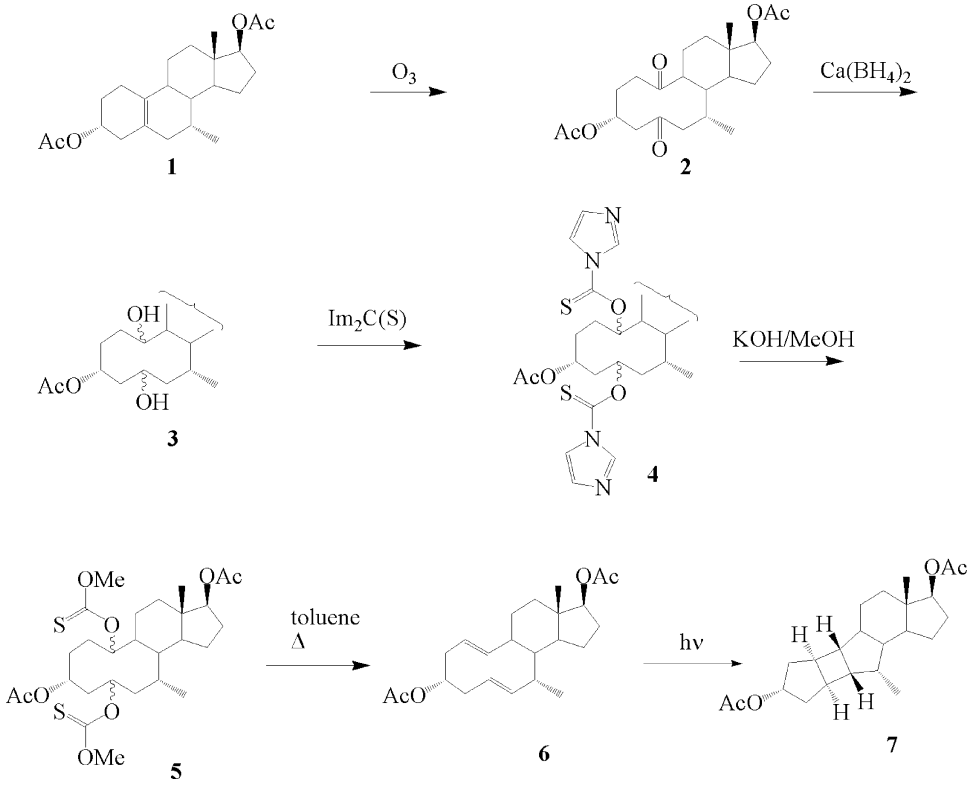
**Table 1 – $^{13}C$ and $^{1}H$ NMR data for compounds 6 and 7 in $CDCl_3$ (500 MHz)**

| Position | 6 | | | 7 | | |
|---|---|---|---|---|---|---|
| | σ, C | σ, H-α | σ, H-β | σ, C | σ, H-α | σ, H-β |
| 1 | 126.37 | 5.23 | – | 40.15 | 2.25 | – |
| 2 | 38.64 | 2.60 | 2.45 | 37.52 | 1.60 | 2.0 |
| 3 | 68.87 | – | 4.97 | 76.36 | – | 5.40 |
| 4 | 38.18 | 2.69 | 2.55 | 34.64 | 1.58 | 1.91 |
| 5 | 122.72 | 5.20 | – | 33.91 | 2.64 | – |
| 6 | 143.84 | – | 5.47 | 46.04 | – | 2.26 |
| 7 | 36.11 | – | 2.34 | 34.25 | – | 2.15 |
| 8 | 41.53 | – | 1.40 | 48.47 | – | 1.24 |
| 9 | 42.90 | 2.21 | – | 49.71 | 1.26 | – |
| 10 | 141.11 | – | 4.98 | 47.90 | – | 1.68 |
| 11 | 29.34 | 1.4 | 1.33 | 25.86 | 1.78 | 1.14 |
| 12 | 36.23 | 1.17 | 1.65 | 36.77 | 1.06 | 1.68 |
| 13 | 42.81 | – | – | 43.59 | – | – |
| 14 | 45.86 | – | 1.34 | 45.83 | 1.24 | – |
| 15 | 23.42 | 1.68 | 1.32 | 23.39 | 1.70 | 1.35 |
| 16 | 26.87 | 2.16 | 1.48 | 27.59 | 2.17 | 1.48 |
| 17 | 82.96 | 4.64 | – | 82.56 | 4.62 | – |
| 18 | 11.82 | – | 0.84 | 12.16 | – | 0.74 |
| 7-Me | 10.83 | 1.14 | – | 12.16 | 0.86 | – |
| 3-OAc (CO) | 171.19 | | | 171.10 | | |
| 3-OAc (Me) | 21.16 | | 2.03 | 21.3 | | |
| 17-OAc (CO) | 170.45 | | | 171.2 | | |
| 17-OAc (Me) | 21.36 | | 2.09 | 21.1 | | |

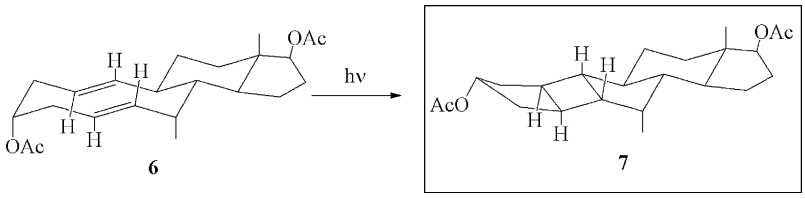
be accomplished by treatment with silver carbonate [13] followed by acetylation of the resulting diol.

Our first attempts to ozonolyze olefin **1** proved to be of little practical value. Ozonolysis of $\Delta^{5(10)}$-olefin did not lead to the corresponding 5,10-diketone, but this was an unstable compound and it reacted further to A-nor-B-homo- and A-homo-B-nor-derivatives due to intramolecular aldol condensation. This process took place prior to all other reactions that have been studied, except for the reduction of **2** with $Ca(BH_4)_2$.

After this reduction, a mixture of all four alcohols **3** was formed, but attempts to separate the isomers, as alcohols or as esters, were unsuccessful. The best way to utilize the mix-




**Scheme 1**




**Scheme 2**

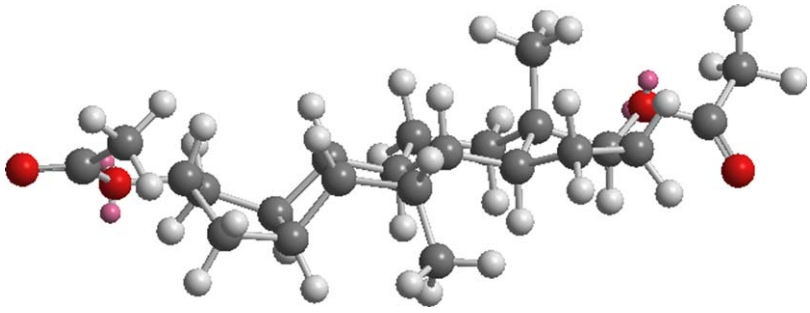


**Fig. 1 – Model for 7 from the MM2 force field energy minimization.**

ture of **3** for the preparation of other 5,10-seco steroids proved to be the *syn*-elimination of the corresponding thioesters. From the reaction of the mixture of **3** with an excess of 1,1′-thiocarbonyldiimidazole one bisthioimidazolide **4** could be isolated. The stereochemistry of this compound at C-5 and C-10 could not be established and attempts to carry out pyrolysis gave poor results. However, the desired olefinic product **6** could be obtained via pyrolysis of the corresponding methoxythiocarbonyloxy derivative. The latter was prepared by basic transesterification of **4**. This reaction was accompanied by partial hydrolysis of the acetoxy groups at C-3 and C-17, but the diacetate **5** could be obtained in a reasonable 57% yield. Pyrolysis of **5** in refluxing toluene then gave the desired *trans*, *trans*-cyclodeca-1,6-diene **6** in a reasonable 50% yield.

Most informative in the NMR spectra of **6** was a string of $^{3}J$ coupled protons, starting with the 7-methyl substituent at $\delta$ 1.14. This allowed the location of H-7 ($\delta$ 2.33, multiplet), the protons at C-6 ($\delta$ 5.47, dd, $J$ 16.4 and 2.5 Hz) and C-5 ($\delta$ 5.20 multiplet). The second double bond gave rise to signals at $\delta$ 4.98 (multiplet) and 5.22 (multiplet) corresponding with the protons at C-10 and C-1, respectively. Despite the overlapping the resonances of protons at C-10 and C-3, $^{3}J$(H-10–H-9) = 10 Hz and $^{3}J$(H-10–H-1) = 15.3 Hz could be determined using decoupling procedures. The large coupling constants (more than 15 Hz) between the protons of both C–C double bonds clearly indicate that these have a trans-relationship. Strong nOe's were observed between the protons H-10 and protons H-11β and H-2β. Similarly, strong nOe's were seen between the proton at C-6 and the protons C-4β and C-8. This is highly suggestive for a ten-membered ring adopting a regular and rather rigid crown-like conformation (Scheme 2) [14,15] and similar to the conformation of the AB-rings in normal steroids. In addition, the proximity of the two double bonds, which are lying parallel and close to each other, allows a successful [2 + 2] photochemical cycloaddition. An example of such a reaction is the photochemical transformation of allohedicaryol into a sesquiterpene with a bourbonane system [16]. Indeed, irradiation of **6** in MeOH solution with a low-pressure Hg lamp led to the formation of a new non-olefinic product **7** containing a cyclobutane fragment in the cyclic part of the molecule.

Analysis of the long-range correlation HMBC spectrum of **7** proved to be particularly important for the distinction of C-8, C-9, and C-14, because their protons give strongly overlapping resonances in the $^{1}$H NMR spectrum. In this case an assignment was made taking into account the cross-peaks of C-14 to H-18 and H-15, of C-8 to 7-Me, of C-9 to H-12. A distinction of the methylene groups at C-2 and C-4 in the proton and carbon spectra was made on the basis of HMBC correlations from H-2β to C-10 and from H-4β to C-6. A determination of the α- and β-faced protons of the steroidal skeleton was done by analysis of NOESY spectra, assuming that the β-orientation of 18-Me and 17-OAc and the α-orientation of 7-Me and 3-OAc had not changed in the course of the reactions. NOESY correlation from 7-Me to H-1 and H-5 confirms their α-orientation, while correlation from H-3 to H-6 and H-10 supports the β-orientation of the last two protons and the $^{3}$E conformation of the five membered ring A, because only in this conformation the distances H-3–H-6 and H-3–H-10 are small enough to allow interaction. The same geometry of the molecule was obtained from the MM2 force field energy minimization (Fig. 1).

In conclusion, the present study has resulted in the preparation of new types of steroids which may expand the number of pharmacologically active compounds.

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