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The synthesis of functionalized 13,14-seco-steroids via Grob fragmentation

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Abstract

A synthetic methodology for the synthesis of 13,14-seco-steroids with substituents at C-14 and C-17 is described. The approach involves Grob fragmentation of 14β-hydroxy-17β-tosylates, hydroboration–oxidation of the intermediate $\Delta^{13(17)}$-olefin, and hydride reduction of the 14-ketone. An unambiguous structural assignment of (13*R*,14*S*,17*S*)-14,17-diacetoxy-3-methoxy-7α-methyl-13,14-secoestra-1,3,5(10)-triene was determined by X-ray analysis.

Keywords: Grob fragmentation; X-ray analysis; Secosteroids; Nine membered ring

1. Introduction

Our recent studies focused on the synthesis of 13,14-seco-steroids [1–3] as new analogues of human steroids, which posses a more flexible CD-ring in comparison with normal tetracyclic steroid skeletons.

A small number of C-13–C-14-seco-steroids have been isolated from natural sources [4–7], but the configuration at C-13 has not been well established. Synthetically useful routes to such compounds have been hardly investigated. There are only a few examples of 13,14-seco-steroid syntheses, which date back to the beginning of the 1960s. One of the described approaches deals with the radical oxidation of 14α-hydroxy steroids [8,9]; the other one describes the Grob fragmentation of 14β-hydroxy-17α-tosylates [10–12]. It was shown that Grob fragmentation of 14β-hydroxy-17α-tosylates gave the expected $\Delta^{13(17)}$-14-ketones [11,12]. In the case of 14α-hydroxy-17β-tosylates a similar reaction proceeded with the formation of 14α,17α-epoxide [10]. The reaction pattern of 14β-hydroxy-17β-tosylates has never been investigated, and also, no attention has been paid to the creation of steroidal hormone functionality in the resulting nine membered ring or to the stereochemistry at C-13 after cleavage of the C-13–C-14 bond.

The present paper describes a 13,14-seco-steroid synthesis by Grob fragmentation of 14β-hydroxy-17β-tosylates and further transformations, which lead to functionalized 13,14 seco-steroids. An X-ray analysis was performed to confirm the structure of the final compound.

2. Experimental

The detailed description of experimental details is given in our previous article [2]. Crystal data and numerical details of the structure determination are given in Table 1. 17,17-(Ethylenedioxy)-3-methoxy-7α - methylestra - 1,3,5(10),15-tetraene was supplied by Organon.

2.1. 3-Methoxy-7α-methylestra-1,3,5(10),15-tetraen-17-one (2)

Compound **2** was prepared from **1** according to the procedure of Segaloff and Gabbard [13] in 92% yield. mp 193–195 °C (EtOAc) (Lit. [13] 191–194 °C). ^{1}H NMR δ: 0.96 (d, $J = 7$ Hz, 3H, 7-Me), 1.11 (s, 3H, 18-H), 3.78 (s,

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Table 1
Crystal data and structure refinement for (13*R*,14*S*,17*S*)-14,17-diacetoxy-3-methoxy-7α-methyl-13,14-secoestra-1,3,5(10)-triene (**12**)

Empirical formula	$C_{24}H_{34}O_5$
Formula weight	402.51
Temperature (K)	293(2)
Wavelength (Å)	0.71069
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	$a = 9.498(3)$ Å, $\alpha = 90^\circ$ $b = 11.530(3)$ Å, $\beta = 90^\circ$ $c = 21.025(5)$ Å, $\gamma = 90^\circ$
Volume (Å^3)	2302.3(10)
Z	4
Density (calculated) (mg/m^3)	1.161
Absorption coefficient (mm^{-1})	0.080
F (0 0 0)	872
Theta range for data collection (°)	1.94–27.56
Index ranges	$0 \le h \le 12$, $0 \le k \le 15$, $-1 \le l \le 27$
Reflections collected	3265
Independent reflections	3142 [R(int) = 0.0113]
Completeness to theta = 27.56°	100.0%
Absorption correction	None
Refinement method	Full-matrix least-squares on F
Data/restraints/parameters	3142/0/267
Goodness-of-fit on F^2	1.024
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0409$, $wR_2 = 0.1051$
R indices (all data)	$R_1 = 0.0595$, $wR_2 = 0.1252$
Absolute structure parameter	2.0(16)
Largest difference (peak and hole) (eÅ^{-3})	0.134 and −0.147

3H, OMe), 6.10 (m, C_{16}-H), 6.64 (d, $J = 2.4$ Hz, 1H, 4-H), 6.74 (dd, 1H, $J = 8.5$, 2.7 Hz, 2-H), 7.23 (d, 1H, $J = 8.5$ Hz, 1-H), 7.60 (d, 1H, $J = 6$ Hz, 15-H). ^{13}C NMR δ: 12.9, 21.1, 25.9, 27.2, 29.5, 37.8, 38.0, 51.7, 53.0, 55.1, 111.8, 114.6, 126.5, 130.8, 132.2, 136.2, 157.8, 212.9.

2.2. 3-Methoxy-7α-methylestra-1,3,5(10),14-tetraen-17-one (*3*)

Et_3N (58.3 ml) and SiO_2 (235 g, dried at 120 °C for 20 h) were added to a solution of enone **2** (3.6 g, 12.2 mmol) in EtOAc (725 ml). The reaction mixture was kept at 75 °C for 20 h. The silica gel was filtered, washed with EtOAc, and the solvent was evaporated. The residue was chromatographed on silica gel (hexane–EtOAc = 10:1) to give the deconjugated enone **3** (2.50 g, 69%). mp 138–140 °C (EtOAc) (Lit. [14] 142–144 °C). IR (cm^{-1}): 1770, 1630, 1520, 1290, 1280, 1260, 1060. ^{1}H NMR δ: 0.98 (d, $J = 7$ Hz, 3H, C_7-Me), 1.15 (s, 3H, 18-H), 3.78 (s, 3H, OMe), 5.62 (br.s, 1H, 15-H), 6.64 (d, $J = 2.4$ Hz, 1H, 4-H), 6.74 (dd, 1H, $J = 8.5$, 2.7 Hz, 2-H), 7.24 (d, 1H, $J = 8.8$ Hz, 1-H). ^{13}C NMR δ: 13.3, 20.9, 26.8, 26.9, 32.2, 37.4, 38.7, 41.4, 42.3, 50.9, 55.1, 111.8, 114.1, 114.8, 127.0, 130.9, 136.4, 150.1, 157.7, 221.7.

2.3. 17β-Hydroxy-3-methoxy-7α-methylestra-1,3,5(10)14-tetraene (*4*)

$LiAlH_4$ (0.64 g, 17 mmol) was added to a solution of ketone **3** (2.50 g, 8.44 mmol) in THF (50 ml). After 15 min water (0.6 ml) was added, followed by a 15%-solution of NaOH (0.6 ml) and again water (1.8 ml). The residue was filtered, the solvent was evaporated, and the residue was chromatographed on silica gel (hexane–EtOAc = 5:1) to give the alcohol **4** (2.11 g, 85%). mp 163–165 °C (EtOH) (Lit. [14] 162–165 °C). IR (cm^{-1}): 1630, 1520, 1465, 1325, 1265, 1250, 1045, 820. ^{1}H NMR δ: 0.90 (d, $J = 7$ Hz, 3H, 7-Me), 0.99 (s, 3H, 18-H), 3.10 (dd, $J = 17$, 6 Hz, 1H, 6-H), 3.78 (s, 3H, OMe), 4.06 (dd, 1H, $J = 9$, 8 Hz, 17-H), 5.16 (m, 1H, 15-H), 6.62 (d, $J = 2.4$ Hz, 1H, 4-H), 6.74 (dd, 1H, $J = 8.5$, 2.7 Hz, 2-H), 7.22 (d, 1H, $J = 8.5$ Hz, 1-H). ^{13}C NMR δ: 13.2, 16.0, 26.9, 27.8, 37.0, 38.1, 38.4, 39.0, 42.5, 47.1, 55.1, 83.5, 111.7, 114.6, 115.4, 127.2, 131.3, 136.6, 149.7, 157.6. HRMS Calc. for $C_{20}H_{27}O_2$ (M + H) 299.2005; Found 299.2012.

2.4. 17β-Hydroxy-3-methoxy-14β,15β-epoxy-7α-methylestra-1,3,5(10)-triene (*5*)

A solution of homoallylic alcohol **4** (2.60 g, 8.72 mmol) and 70% MCPBA (4.29 g, 17.4 mmol) in CHCl3 (50 ml) was kept at room temperature for 40 min. The reaction mixture was washed with 10% NH_4OH, then with water, and the organic layer was dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (hexane–EtOAc = 4:1) to give the epoxide **5** (1.59 g, 58%). mp 179–180 °C (EtOH). IR (cm^{-1}): 1615, 1510, 1475, 1240, 1170, 1100, 1030. ^{1}H NMR δ: 0.82 (d, $J = 6.7$ Hz, 3H, 7-Me), 1.14 (s, 3H, 18-H), 3.05 (dd, $J = 16$, 5 Hz, 1H, 6-H),

3.78 (s, 3H, OMe), 3.83 (s, 1H, 17-H), 6.62 (d, $J = 2.7$ Hz, 1H, 4-H), 6.74 (dd, 1H, $J = 8.5$, 2.7 Hz, 2-H), 7.20 (d, 1H, $J = 8.9$ Hz, 1-H). ^{13}C NMR δ: 13.6, 14.3, 24.0, 27.5, 34.5, 36.1, 37.2, 39.6, 39.9, 46.5, 55.1, 61.8, 74.0, 77.0, 112.0, 114.7, 127.1, 131.0, 136.5, 157.8. HRMS Calc. for $C_{20}H_{27}O_3$ (M + H) 315.1954; Found 315.1936.

2.5. 14β,17β-Dihydroxy-3-methoxy-7α-methylestra-1,3,5 (10)-triene (6)

A mixture of epoxide **5** (700 mg, 2.23 mmol) and $LiAlH_4$ (510 mg, 13.4 mmol) in ether (60 ml) was refluxed for 8 h. Then, water (0.5 ml), 15% NaOH (0.5 ml) and again water (1.5 ml) were added. The precipitate was filtered off, and the filtrate was evaporated. The residue was chromatographed on SiO_2 (petroleum ether–EtOAc = 2:1) to give the diol **6** (644 mg, 92%). mp 200–204 °C (EtOH). IR (cm^{-1}): 1630, 1515, 1465, 1445, 1250, 1090. ^{1}H NMR δ: 0.92 (d, 3H, J = 7 Hz, 7-Me), 1.10 (s, 3H, 18-H), 3.64–3.86 (m, 1H, 17-H), 3.78 (s, 3H, OMe), 6.56–7.26 (m, 3H, arom. H). ^{13}C NMR δ: 13.4, 14.5, 24.7, 27.8, 31.2, 33.0, 33.6, 34.0, 40.6, 46.7, 50.2, 55.1, 81.8, 85.1, 111.9, 114.3, 127.4, 131.2, 136.5, 157.4.

2.6. 14β-Hydroxy-17β-toluenesulfonyloxy-3-methoxy-7α -methylestra-1,3,5(10),14-triene (7)

A mixture of diol **6** (400 mg, 1.27 mmol), TsCl (400 mg, 2.10 mmol), and pyridine (3 ml) was kept at 30 °C for 5 h. Then, it was diluted with water and extracted with EtOAc and $CHCl_3$. The combined extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on SiO_2 (toluene–EtOAc = 10:l) to give the tosylate **7** (429 mg, 72%). mp 137–140 °C (hexane). IR (cm^{-1}): 1615, 1510, 1480, 1370, 1240, 1180, 900. ^{1}H NMR δ: 0.87 (d, 3H, J = 1 Hz, 7-Me), 0.95 (s, 3H, 18-H), 2.45 (s, 3H, OTs), 3.76 (s, 3H, OMe), 4.52 (d, 1H, $J = 6.5$ Hz, 17-H), 6.60 (d, 1H, $J = 2.7$ Hz, 4-H), 6.70 (dd, 1H, $J = 8.5$, 2.7 Hz, 2-H), 7.16 (d, 1H, $J = 8.5$ Hz, OTs), 7.34 (m, 2H, OTs and arom. H), 7.80 (d, 1H, $J = 8.2$ Hz, OTs). ^{13}C NMR δ: 13.7, 14.5, 21.7, 24.7, 27.7, 29.3, 33.0, 33.9, 34.2, 40.7, 46.7, 50.8, 55.1, 83.8, 91.6, 112.0, 114.4, 127.4, 127.8, 129.8, 130.9, 134.2, 136.7, 144.7, 157.6.

2.7. Grob fragmentation of (7)

A mixture of DMSO (5 ml) and NaH (80%, 288 mg, 9.6 mmol) was stirred under argon at 40 °C for 1 h [15]. Then a solution of tosylate **7** (290 mg, 0.64 mmol) in DMSO (3 ml) was added, and the mixture was kept at 40 °C for 1 h. It was subsequently diluted with brine and extracted with EtOAc. The extract was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on SiO_2 (petroleum ether–EtOAc = 10:1) to give 3-methoxy-7α-methyl-13,14-secoestra-1,3,5(10),13(17)*E*-tetraen-14-one (**8**) (100 mg, 52%). mp 103–105 °C (EtOH). IR (cm^{-1}): 1710, 1620, 1510, 1465, 1325, 1245. ^{1}H NMR δ: 0.95 (d, 3H, $J = 7$ Hz, 7-Me), 1.87 (s, 3H, 18-H), 3.78 (s, 3H, OMe), 5.44 (m, 1H, 17-H), 6.50–7.30 (m, 3H, arom. H). ^{13}C NMR δ: 16.8, 18.6, 21.6, 29.1, 34.6, 38.4, 39.6, 40.6, 41.8, 55.0, 59.8, 112.4, 112.9, 122.6, 129.4, 131.5, 137.8, 138.1, 156.9, 217.7. HRMS Calc. for $C_{20}H_{27}O_2$ (M + H) 299.2005; Found: 299.2010.

2.8. (14S)-14-Hydroxy-3-methoxy-7α-methyl-13,14-secoestra-1,3,5(10),13(17)(E)-tetraene (9)

$LiAlH_4$ (51.7 mg, 1.36 mmol) was added to a solution of ketone **8** (50 mg, 0.17 mmol) in Et_2O (2 ml). The reaction mixture was stirred for 20 min at RT, and then, water (0.05 ml), NaOH solution (15%, 0.05 ml) and again water (0.15 ml) were added. The precipitate was filtered off, and the filtrate was evaporated. The residue was chromatographed on SiO_2 (hexane–EtOAc = 8:1) to give alcohol **9** (44 mg, 87%) as an oil. IR (cm^{-1}): 1620, 1510, 1450, 1270, 1255, 1045. ^{1}H NMR δ: 1.10 (d, $J = 7$ Hz, 3H, 7-Me), 1.62 (s, 3H, 18-H), 3.74 (s, 3H, OMe), 4.04 (m, 1H, 14-H), 5.40 (m, 1H, 17-H), 6.54 (d, 1H, $J = 2$ Hz, 1-H), 6.70 (dd, 1H, $J = 8$, 2 Hz, 2-H), 7.02 (d, 1H, $J = 8$ Hz, 4-H). ^{13}C NMR δ: 17.5, 19.5, 24.3, 27.5, 35.2, 36.0, 36.4, 37.2, 40.6, 44.5, 55.2, 70.9, 112.4, 112.9, 127.9, 130.5, 133.2, 133.7, 138.8, 157.0. HRMS Calc. for $C_{20}H_{29}O_2$ (M + H) 301.2162; Found: 301.2158.

2.9. (13R,14S,17S)-14,17-Dihydroxy-3-methoxy-7α-methyl-13,14-secoestra-1,3,5(10)-triene (10)

A mixture of **9** (330 mg, 1.1 mmol) and BH_3·THF (1 M, 15 ml) was stirred for 1.5 h at ambient temperature. Then, it was cooled to 0 °C, and H_2O (1 ml), NaOH (2 M, 0.5 ml), and H_2O_2 (30%, 0.5 ml) were added consecutively. The reaction mixture was stirred for 30 min, diluted with water, and extracted with $CHCl_3$ and EtOAc. The extracts were dried (Na_2SO_4), and evaporated, and the residue was chromatographed on SiO_2 (hexane–EtOAc = 1:1) to give diol **10** (200 mg, 57%). mp 103–107 °C (EtOH). IR (cm^{-1}): 1620, 1510, 1470, 1275, 1050, 800. ^{1}H NMR and ^{13}C (see Fig. 1). HRMS Calc. for $C_{20}H_{31}O_3$ (M + H) 319.2267; Found 319.2274.

2.10. Acetylation of the diol (10)

Ac_2O (0.1 ml) was added to a solution of diol **10** (47 mg, 0.147 mmol) in pyridine (0.2 ml). The reaction mixture was stirred at RT for 4 h and diluted with water. This mixture was extracted with $CHCl_3$ and EtOAc, and the extracts were dried (Na_2SO_4). The solvents were evaporated, and the residue was chromatographed on SiO_2 (hexane–EtOAc = 7:1) to give: (a) (13*R*,14*S*,17*S*)-14,17-diacetoxy-3-methoxy-7α-methyl-13,14-secoestra-1,3,5(10)-

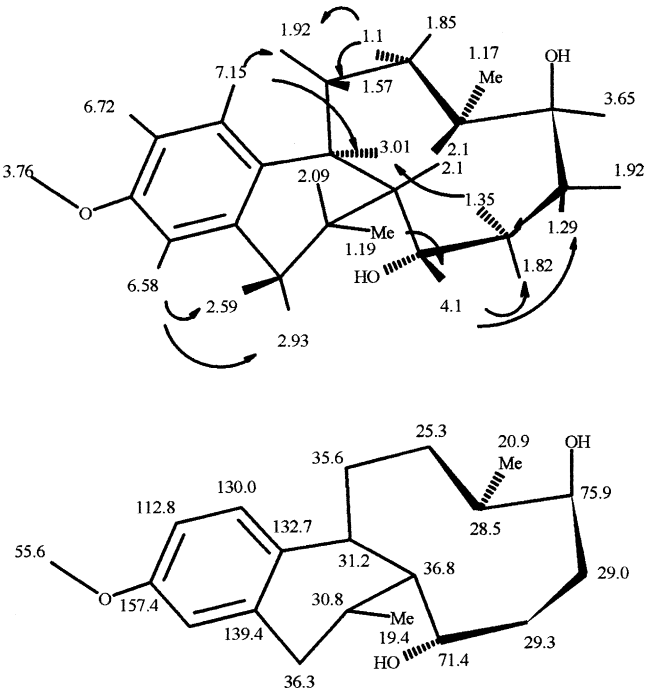
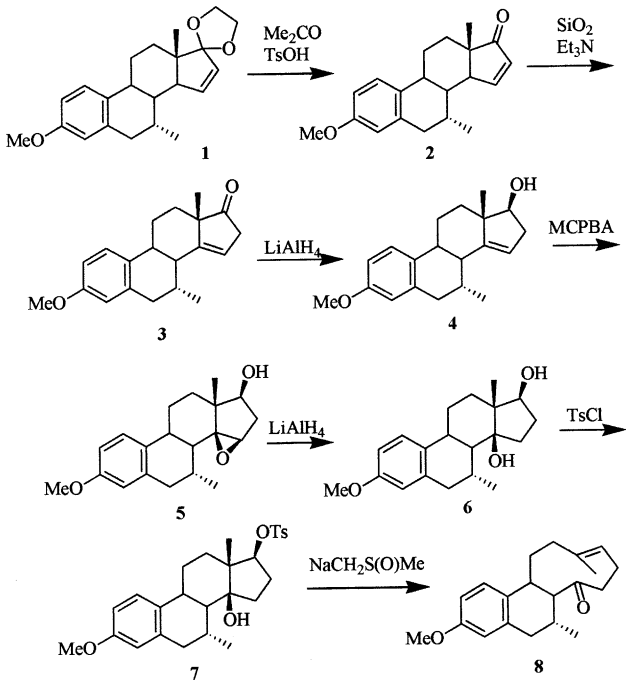


Fig. 1. ^{1}H and ^{13}C assignment for compound **10**.



Scheme 1.

triene (**12**) (17 mg, 28%). mp 120–124 °C (EtOH). IR (cm^{-1}): 1745, 1620, 1510, 1470, 1380, 1250, 1025. ^{1}H NMR δ: 0.98 (d, $J = 7$ Hz, 18-H or 7-Me), 1.02 (d, $J = 7$ Hz, 18-H or 7-Me), 1.65 (s, 3H, OAc), 2.05 (s, 3H, OAc), 3.71 (s, 3H, OMe), 4.85 (m, 1H, 14- or 17-H), 5.30 (m, 1H, 17- or 14-H), 6.50 (d, 1H, $J = 2$ Hz, 4-H), 6.70 (dd, 1H, $J = 8$, 2 Hz, 2-H), 7.10 (d, 1H, $J = 8$ Hz, 1-H). ^{13}C NMR δ: 18.8, 20.2, 21.0, 21.7, 24.4, 24.8, 26.3, 28.0, 29.2, 32.1, 35.1, 35.3, 35.7, 55.1, 72.7, 77.4, 112.0, 112.3, 129.4, 132.3, 138.2, 156.9, 170.5, 170.7; (b) (13*R*,14*S* 17*S*)-14-hydroxy-17-acetoxy-3-methoxy-7α-methyl-13,14-secoestra-1,3,5(10)-triene (**11**) (16.8 mg, 32%). mp 110–114 °C (EtOH). IR (cm^{-1}): 1740, 1620, 1510, 1470, 1380, 1255, 1050, 750. ^{1}H NMR δ: 1.05 (d, $J = 7$ Hz, 18-H or 7-Me), 1.75 (d, $J = 7$ Hz, 18-H or 7-Me), 2.05 (s, 3H, OAc), 3.76 (s, 3H, OMe), 4.10 (m, 1H, 14-H), 4.40 (m, 1H, 17-H), 6.51 (d, 1H, $J = 2$ Hz, 4-H), 6.70 (dd, 1H, $J = 8$, 2 Hz, 2-H), 7.12 (d, 1H, $J = 8$ Hz, 1-H). ^{13}C NMR δ: 19.0, 20.3, 21.1, 25.1, 26.2, 28.2, 28.7, 29.5, 29.7, 30.9, 35.2, 35.9, 36.5, 55.1, 70.8, 77.7, 112.4, 112.9, 129.5, 132.2, 139.0, 157.0, 170.9.

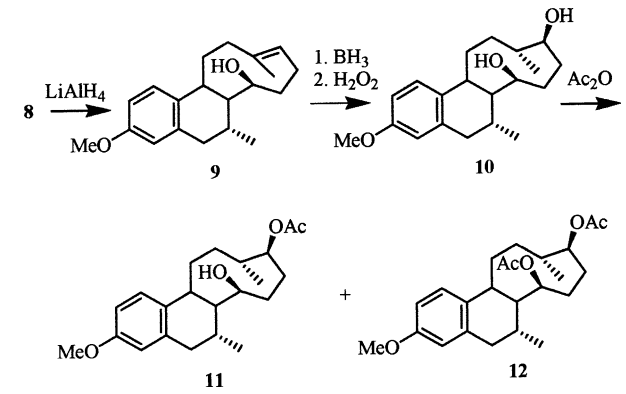
3. Results and discussion

Enone **2** proved to be a good starting material for the preparation of the desired hydroxy tosylate which could then be subjected to Grob fragmentation. The α,β-unsaturated ketone **2** [13] was obtained by removal of the ketal protecting group (Scheme 1), and deconjugation of the enone system in **2** was achieved by treatment with Et_3N and SiO_2 [16]. Reduction of the β,γ-unsaturated ketone **3** [14] with $LiAlH_4$ did not affect the Δ^{14}-double bond and led smoothly to the homoallylic alcohol **4** [14]. Its epoxidation proceeded with formation of the 14β,15β-epoxide **5** as the main product. The hydride reduction of **5** afforded diol **6**, which was transformed into tosylate **7**. Finally, the Grob fragmentation [17,18] of **7** gave the desired seco-steroid **8** in a reasonable 52% yield. It can thus be concluded that the 14β-hydroxy-17β-tosylate also undergoes a Grob fragmentation reaction, although its conformation is not optimal for such a fragmentation.

According to the NMR data, the obtained sample seemed to contain about 15% of another steroid, which at first was presumed to be the (*Z*)-isomer of the olefin **8**. However, careful study of the NMR spectra led us to the conclusion that this compound could be an (*E*)-cyclononene derivative as well. From the (*E*)-cyclononene compound β-caryophyllene, it is known that four conformations are possible [19]. It is likely that another conformer of compound **8** was seen as a distinct species at normal temperature in the ^{1}H and ^{13}C NMR spectra.

The hydride reduction of **8** proceeded smoothly with formation of only one isomer **9** using $NaBH_4$, $Ca(BH_4)_2$, or $LiAlH_4$ (Scheme 2). To our surprise, the hydroboration–oxidation [20] of **9** also led to only one product **10**. Molecular models showed that indeed the double bond in **9** was oriented in such a way that borane attack from the inner side of the nine-membered ring was not possible. The preparation of compounds without a substituent at C-14 can be performed using the approaches described by us earlier [3].

The NMR spectra of **10** (Fig. 1) were markedly different from the normal 7α-methyl steroids [21]. Due to a flip of ring



Scheme 2.

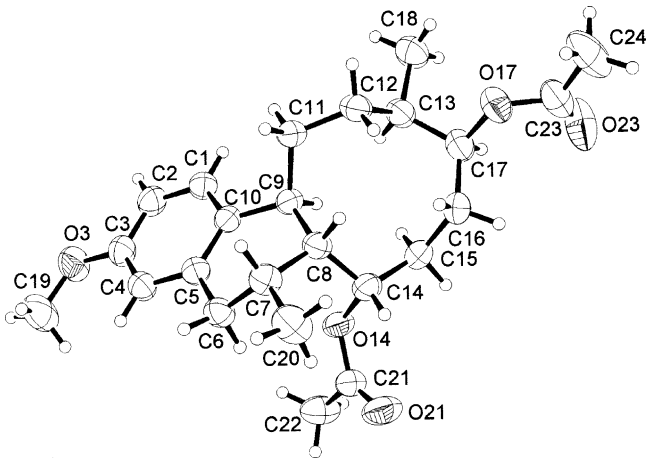


Fig. 2. ORTEP view of (13*R*,14*S*,17*S*)-14,17-diacetoxy-3-methoxy-7α-methyl-13,14-secoestra-1,3,5(10)-triene (**12**).

B, the 7α-methyl group and the C-8 and C-9 protons were more or less equatorial, which resulted in a $J \sim 0$ Hz between the two protons, although they were trans. The C-9–C-11 bond and the C-8–C-14 bond were axial, sticking up and down, respectively, and the angle between H-8 and H-14 is approximately 90° ($J \sim 0$ Hz). This minimized the steric interaction between the 7-methyl group and C-14/C-15. The protons at C-9, C-13, and C-16 were on the inside of the 9-membered ring (NOE contacts). An unambiguous assignment of the configuration at C-13, C-14, and C-17 for compounds **16**–**19** could not be done based on NMR data only. This problem was solved with the synthesis of diacetate **19**, which produced a crystal suitable for X-ray analysis (Fig. 2 and Table 1).

In conclusion, the synthesis of compounds possessing a substituted C-13–C-14 seco-steroidal skeleton was accomplished using a Grob fragmentation reaction of a 14β-hydroxy-17β-tosylated steroid.

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