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Selective ring-opening carbonylation of epoxy-steroids☆

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Abstract

Ring-opening alkoxycarbonylation of epoxy-steroids has been carried out with a $Co_2(CO)_8$/3-hydroxypyridine catalytic system. High chemo- and regioselectivities were obtained under the reaction conditions applied. Structural analysis of the products proved their high stereochemical purity in each case, accompanied by inversion of the original configuration. No carbonylation took place for sterically hindered steranic epoxides.

Keywords: Epoxy-steroid; Cobalt; Homogeneous catalysis; Alkoxycarbonylation; Asymmetric ring-opening

1. Introduction

Stereospecific nucleophilic substitution reactions of chiral carbon atoms represent a challenging, fast developing area of asymmetric catalysis. Such transformations have already been applied in successful desymmetrization of *meso*-substrates, kinetic resolution of racemic compounds and stereospecific reactions of enantiopure compounds ([1] and references therein).

The development of asymmetric ring-opening (ARO) reactions of epoxides has advanced rapidly since the discovery of Jacobsen's metal–salen catalyst complexes. Applied successfully in asymmetric epoxidation, these catalysts have proven to be efficient in ring-opening reactions as well ([1] and references therein). Available either by classical methods [2] or by transition metal-catalyzed oxidation [3,4], epoxides are valuable sources leading to a wide range of products, such as β-amino alcohols [5], β-hydroxy esters [6], α-aryloxy alcohols [7], β-hydroxy mercaptans [8], and diols [9].

As far as ring-opening carbonylation is concerned, some authors found that alkynyl oxiranes can be carbomethoxylated in presence of palladium catalysts to yield axially chiral 5-hydroxy-penta-2,3-dienoates [10,11]. Also, a tridentate ligand-containing (P,P,N)-$Co(CO)_4$ catalyst together with $BF_3{\cdot}Et_2O$ was tested with good results in transformation of simple and functionalized epoxides to β-lactones [12]. It was Drent who reported first selective catalytic carbonylation of epoxides using $Co_2(CO)_8$ as catalyst with 3-hydroxypyridine as co-catalyst [13]. Based on this report and their own previous results, Jacobsen's team transformed a series of terminal, enantiomerically pure epoxides regio- and enantioselectively into β-hydroxy esters [6]. Considering the reaction above as a starting point, we investigated its application to non-terminal steroidal epoxides (Fig. 1) as rather complex molecules of obvious biological importance. Our goal was also to screen the optimal reaction conditions, catalyst composition, and substrate-selectivity interdependence, as well as the influence of the nucleophilic reagent. The new compounds prepared were then to be isolated and fully characterized, especially from the point of view of stereochemistry.

2. Experimental

Tetrahydrofuran (THF) was dried over sodium and distilled under argon in presence of benzophenone prior to use. Anhydrous alcohols and solvents were purchased from Sigma-Aldrich. The starting steroids were received from the Chemical Works of Gedeon Richter Ltd. Crude $Co_2(CO)_8$ was prepared at our site by a well-known method [14]. After recrystallization from dichloromethane and pentane its purity was checked by IR spectroscopy [15]. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Unity 300

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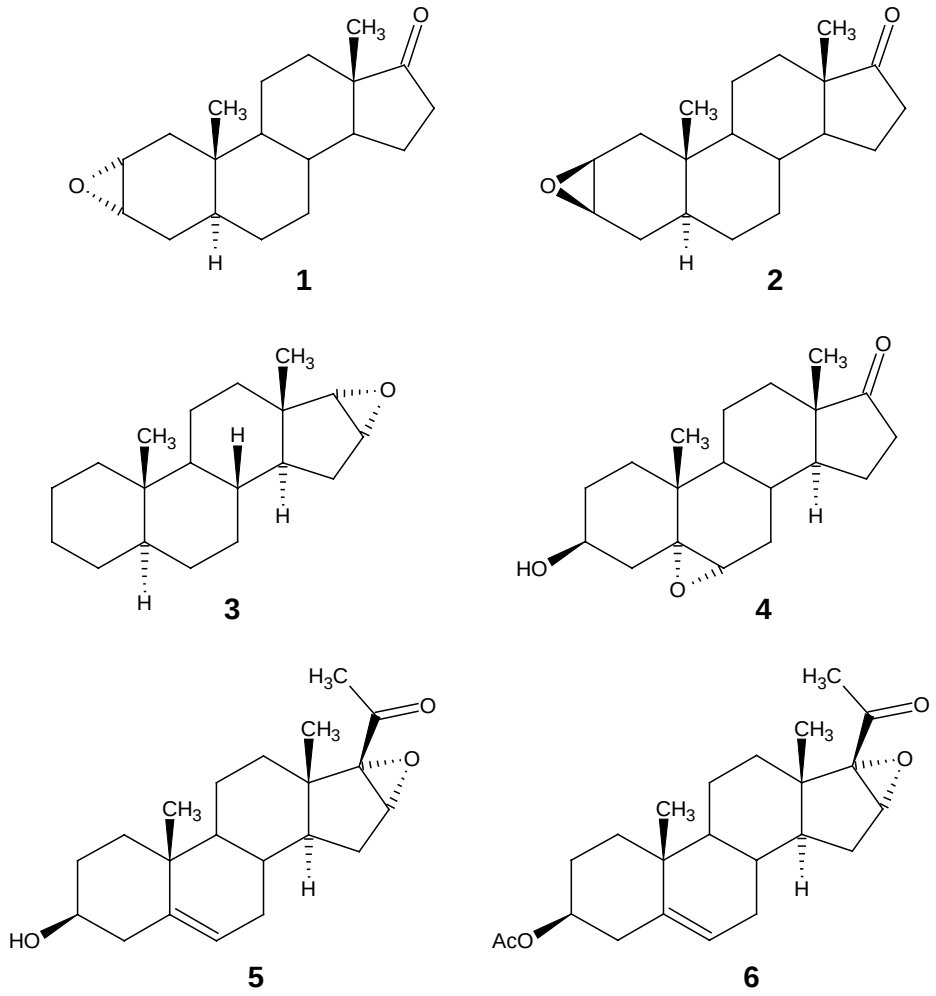

Fig. 1. Structures of the starting steroids.

spectrometer (Palo Alto, CA, USA) at 300 and 75.5 MHz, respectively. Proton chemical shifts were referenced to residual C*H*Cl$_3$ ($\delta = 7.24$), and ^{13}C NMR chemical shifts were referenced to the solvent *C*DCl$_3$ ($\delta = 77.0$). ^{1}H and ^{13}C assignments were based on DEPT, COSY, CYCLENOE, and NOESY experiments. GLC analyses were performed on a Hewlett-Packard 5917 gas chromatograph fitted with a 10 m HP-1 column. GC–MS measurements were run on a Hewlett Packard 5971A GC-MSD with a 25 m HP-1 column. TLC analyses were performed on silica gel TLC-cards with fluorescent indicator at 254 nm (0.2 mm, Fluka), the chromatograms were developed in an iodine chamber. FT-IR spectra were obtained with Avatar 330 Thermo Nicolet spectrophotometer in KBr pellets. All manipulations were performed under argon using standard inert techniques.

2.1. Preparation procedure

In a typical procedure a solution of 1.5 mL of THF and 20 mmol (1.1 mL) ethanol was transferred under argon into a 20 mL stainless steel autoclave containing the epoxy-steroid **1** (1 mmol, 288 mg), $Co_2(CO)_8$ (0.05 mmol, 17.4 mg), and 0.3 mmol (19.2 mg) 3-hydroxypyridine. The autoclave was pressurized to 100 atm with CO, placed into an oil bath, heated to 75 °C, and stirred magnetically for 72 h at this temperature. The reaction was followed by GLC and TLC. Chromatography on neutral alumina with ethyl acetate/hexane (1:1), ethyl acetate/hexane (3:1), and ethyl acetate yielded the desired compound, ethyl ester **7b** (307 mg, 85%) which was then characterized by GC–MS and various NMR techniques.

2.2. Characterization of the products

2.2.1. Methyl 3α-hydroxy-17-keto-5α-androstan-2β-carboxylate (*7a*)

White powder (isolated yield: 132 mg, 38%), mp = 112 °C; $[\alpha]_D = 58$ ($c = 1$ in chloroform); TLC: R_f = 0.38 [ethyl acetate/hexane (2:3) as eluting solvent]; ^{1}H NMR (δ, CDCl$_3$): 0.65 (s, 3H, C$^{19}H_3$), 0.80 (s, 3H,

$C^{18}H_3$), 0.68−2.43 (m, 20H, ring protons), 2.62 (m, 1H, C^2H), 3.63 (s, 3H, –OCH_3), 4.38 (m, 1H, C^3H); ^{13}C NMR (δ, $CDCl_3$): 11.87, 13.77, 20.20, 21.67, 27.75, 30.66, 31.47, 33.31, 34.74, 35.13, 35.77, 36.45, 39.05, 44.64, 47.75, 51.33, 51.47, 54.6, 65.89, 175.13, 221.35; MS (*m*/*z*/relative intensity): 348/64 [M^+], 330/23, 271/25, 218/63, 147/40, 105/100; IR (KBr, ν [cm^{-1}]): 1736 (C=O).

2.2.2. Ethyl 3α-hydroxy-17-keto-5α-androstan-2β-carboxylate (**7b**)

White powder (isolated yield: 307 mg, 85%), mp = 119 °C; $[\alpha]_D = 60$ ($c = 1$ in chloroform); TLC: $R_f = 0.42$ [ethyl acetate/hexane (2:3) as eluting solvent]; ^{1}H NMR (δ, $CDCl_3$): 0.68 (s, 3H, $C^{19}H_3$), 0.89 (s, 3H, $C^{18}H_3$), 0.94–2.15 (m, 20H, ring protons), 1.24 (t, $J = 7$ Hz, 3H, –OCH$_2$CH_3), 2.6 (m, 1H, C^2H), 4.14 (q, $J = 7$ Hz, 2H, –OCH_2CH$_3$), 4.42 (m, 1H, C^3H); ^{13}C NMR (δ, $CDCl_3$): 12.06, 13.8, 14.1, 20.16, 21.68, 27.75, 30.66, 31.48, 33.36, 34.75, 35.14, 35.77, 36.5, 39.06, 44.83, 47.72, 51.36, 54.61, 60.34, 65.99, 174.58, 221.27; MS (*m*/*z*/relative intensity): 362/26 [M^+], 344/30, 270/12, 218/33, 147/30, 105/100; IR (KBr, ν [cm^{-1}]): 1701, 1733 (C=O).

2.2.3. Isopropyl 3α-hydroxy-17-keto-5α-androstan-2β-carboxylate (**7c**)

White powder (isolated yield: 330 mg, 88%), mp = 183–187 °C; $[\alpha]_D = 62$ ($c = 1$ in chloroform); TLC: $R_f = 0.47$ [ethyl acetate/hexane (2:3) as eluting solvent]; ^{1}H NMR (δ, $CDCl_3$): 0.69 (s, 3H, $C^{19}H_3$), 0.82 (s, 3H, $C^{18}H_3$), 1.20 (d, $J = 6.1$ Hz, 3H, –CH(CH_3)$_2$), 1.24 (d, $J = 6.1$ Hz, 3H, –CH(CH_3)$_2$), 0.91–2.45 (m, 20H, ring protons), 2.58 (m, 1H, $J_1 = 8.7$ Hz, $J_2 = 2.7$ Hz, C^2H), 4.39 (q, 1H, $J = 2.7$ Hz, C^3H), 5.0 (septet, 1H, $J = 6.1$ Hz, –COCH(CH$_3$)$_2$); ^{13}C NMR (δ, $CDCl_3$): 12.19, 13.81, 20.11, 21.65, 21.68, 21.75, 27.75, 30.67, 31.49, 33.34, 34.75, 35.1, 35.78, 36.53, 39.04, 45.03, 47.76, 51.36, 54.61, 66.03, 67.70, 174.04, 221.34; MS (*m*/*z*/relative intensity): 376/32 [M^+], 358/18, 333/21, 315/100, 218/33, 147/30, 105/10; IR (KBr, ν [cm^{-1}]): 1722 (C=O).

2.2.4. Ethyl 2β-hydroxy-17-keto-5α-androstan-3α-carboxylate (**10b**)

White powder (isolated yield: 288 mg, 80%), mp = 122–125 °C; $[\alpha]_D = 115$ ($c = 1$ in chloroform); TLC: $R_f = 0.54$ [ethyl acetate/hexane (2:3) as eluting solvent]; ^{1}H NMR (δ, $CDCl_3$): 0.83 (s, 3H, $C^{18}H_3$), 0.99 (s, 3H, $C^{19}H_3$), 0.94–2.47 (m, 20H, ring protons), 1.24 (t, $J = 7$ Hz, 3H, –OCH$_2$CH_3), 2.6 (m, 1H, C^2H), 4.14 (q, $J = 7$ Hz, 2H, –OCH_2CH$_3$), 4.42 (m, 1H, C^3H); ^{13}C NMR (δ, $CDCl_3$): 13.8, 14.18, 14.62, 20.09, 21.66, 26.0, 27.94, 30.55, 31.48, 34.36, 35.72, 35.76, 42.33, 42.52, 46.66, 47.78, 51.31, 55.18, 60.35, 67.91, 173.78, 221.27; MS (*m*/*z*/relative intensity): 362/2 [M^+], 345/5, 270/10, 231/20, 213/10, 147/18, 121/25, 107/65, 79/75, 67/80, 55/100; IR (KBr, ν [cm^{-1}]): 1726, 1734 (C=O).

2.2.5. Isopropyl 2β-hydroxy-17-keto-5α-androstan-3α-carboxylate (**10c**)

White powder (isolated yield: 315 mg, 84%), mp = 174 °C; $[\alpha]_D = 112$ ($c = 1$ in chloroform); TLC: $R_f = 0.6$ [ethyl acetate/hexane (2:3) as eluting solvent]; ^{1}H NMR (δ, $CDCl_3$): 0.67 (m, 1H,), 0.82 (s, 3H, $C^{18}H_3$), 1.01 (s, 3H, $C^{19}H_3$), 0.78–2.44 (m, ring protons), 1.19 (d, $J = 6.1$ Hz, 3H, –CH(CH_3)$_2$), 1.22 (d, $J = 6.1$ Hz, 3H, –CH(CH_3)$_2$), 2.65 (m, 1H, C^3H), 4.39 (q, 1H, $J = 3.1$ Hz, C^2H), 5.0 (septet, 1H, $J = 6.1$ Hz); ^{13}C NMR (δ, $CDCl_3$): 13.8, 14.64, 20.09, 21.66, 21.71, 21.79, 26.05, 27.99, 30.61, 31.48, 34.38, 35.72, 35.77, 43.34, 42.54, 46.76, 47.78, 51.29, 55.26, 67.54, 67.94, 173.25, 221.25; MS (*m*/*z*/relative intensity): 376/1 [M^+], 335/3, 316/8, 231/12, 213/10, 173/11, 149/15, 121/22, 107/34, 93/48, 67/70, 55/100; IR (KBr, ν [cm^{-1}]): 1722, 1736 (C=O).

2.2.6. Methyl 17α-hydroxyandrostane-16α-carboxylate (**13a**)

White powder (isolated yield: 94 mg, 28%), mp = 109 °C; $[\alpha]_D < 1$ ($c = 1$ in chloroform); TLC: $R_f = 0.45$ [ethyl acetate/hexane (1:4) as eluting solvent]; ^{1}H NMR (δ, $CDCl_3$): 0.66 (s, 3H, $C^{18}H_3$), 0.76 (s, 3H, $C^{19}H_3$), 0.6–1.88 (m, 22H, ring protons), 2.01 (m, 1H, $C^{15}H$), 2.68 (m, 1H, $C^{16}H$), 3.68 (s, 3H, –OCH_3), 3.98 (d, 1H, $J = 1.4$ Hz, $C^{17}H$); ^{13}C NMR (δ, $CDCl_3$): 12.18, 16.84, 20.07, 22.13, 26.71, 28.88, 28.96, 29.25, 31.74, 32.31, 35.29, 36.23, 38.67, 45.08, 46.89, 49.64, 51.83, 52.57, 54.25, 82.8, 175.43; MS (*m*/*z*/relative intensity): 334/6 [M^+], 306/32, 288/19, 274/34, 256/25, 233/100, 217/48, 149/53, 109/54, 95/51; IR (KBr, ν [cm^{-1}]): 1736 (C=O).

2.2.7. Ethyl 17α-hydroxyandrostane-16α-carboxylate (**13b**)

White powder (isolated yield: 285 mg, 82%), mp = 113–115 °C; $[\alpha]_D < 1$ ($c = 1$ in chloroform); TLC: $R_f = 0.46$ [ethyl acetate/hexane (1:4) as eluting solvent]; ^{1}H NMR (δ, $CDCl_3$): 0.66 (s, 3H, $C^{18}H_3$), 0.76 (s, 3H, $C^{19}H_3$), 0.66–1.75 (m, 22H, ring protons), 1.21 (t, 3H, $J = 7.1$ Hz, –OCH$_2$CH_3), 2.01 (m, 1H, $C^{15}H$), 2.67 (dt, 1H, $J_1 = 8.7$ Hz, $J_2 = 1.5$ Hz, $C^{16}H$), 3.98 (d, 1H, $J = 1.5$ Hz, $C^{17}H$), 4.13 (q, 2H, $J = 7.1$ Hz, –OCH_2CH$_3$); ^{13}C NMR (δ, $CDCl_3$): 12.18, 14.22, 16.82, 20.09, 22.13, 26.72, 28.89, 28.96, 29.25, 31.76, 35.28, 35.30, 36.27, 38.67, 45.06, 46.88, 49.63, 52.79, 54.20, 60.54, 82.78, 174.98; MS (*m*/*z*/relative intensity): 348/1 [M^+], 274/16, 256/35, 233/100, 217/31, 149/21, 109/14, 95/11; IR (KBr, ν [cm^{-1}]): 1729 (C=O).

2.2.8. Isopropyl 17α-hydroxyandrostane-16α-carboxylate (**13c**)

White powder (isolated yield: 304 mg, 84%), mp = 77–83 °C; $[\alpha]_D < 1$ ($c = 1$ in chloroform); TLC: $R_f = 0.46$ [ethyl acetate/hexane (1:4) as eluting solvent]; ^{1}H NMR (δ, $CDCl_3$): 0.66 (s, 3H, $C^{18}H_3$), 0.77 (s, 3H, $C^{19}H_3$), 0.66–1.7 (m, 22H, ring protons), 1.2 (d, 6H, $J = 6.4$ Hz,

–CH(CH_3)$_2$), 2.01 (m, 1H, C^{15}H), 2.66 (dt, $J_1 = 8.5$ Hz, $J_2 = 1.4$ Hz, 1H, C^{16}H), 3.98 (d, $J = 1.4$ Hz, 1H, C^{17}H), 5.00 (septet, 1H, $J = 6.4$ Hz, –OCH(CH$_3$)$_2$); ^{13}C NMR (δ, $CDCl_3$): 12.18, 16.77, 20.09, 21.76, 22.13, 26.72, 28.89, 28.97, 29.22, 31.74, 32.31, 35.28, 35.31, 36.29, 38.67, 45.05, 46.89, 49.61, 53.01 54.22, 67.69, 82.78, 174.45; MS (*m*/*z*/relative intensity): 362/1 [M^+], 334/4, 301/10, 274/14, 256/14, 233/100, 217/33, 149/20, 109/20, 95/13; IR (KBr, ν [cm^{-1}]): 1724 (C=O).

*2.2.9. 2 (or 3)-Hydroxy-3 (or 2)-methyoxy-17-ketoandrostane (**9a**)*

MS (*m*/*z*/relative intensity): 320/5, 270/5, 230/12, 215/5, 108/22, 97/90, 84/100, 67/50, 55/66.

*2.2.10. 2 (or 3)-Hydroxy-3 (or 2)-ethyoxy-17-ketoandrostane (**9b**)*

MS (*m*/*z*/relative intensity): 334/25, 270/8, 218/100, 190/80, 161/92, 147/50, 105/100, 91/85, 55/50.

*2.2.11. 2 (or 3)-Hydroxy-3 (or 2)-isopropyloxy-17-ketoandrostane (**9c**)*

MS (*m*/*z*/relative intensity): 348/6, 326/8, 281/14, 270/16, 231/18, 214/5, 161/10, 107/60, 91/45, 55/100.

*2.2.12. 16 (or 17)-Methyoxy-17 (or 16)-hydroxyandrostane (**14a**)*

MS (*m*/*z*/relative intensity): 306/60, 274/32, 259/28, 243/55, 217/100, 189/50, 149/48, 109/85, 95/82, 67/80, 55/72.

*2.2.13. 16 (or 17)-Ethyoxy-17 (or 16)-hydroxyandrostane (**14b**)*

MS (*m*/*z*/relative intensity): 320/44, 305/3, 274/20, 259/24, 243/80, 231/75, 217/100, 203/64, 189/65, 149/35, 109/26, 55/16.

*2.2.14. 16 (or 17)-Isopropyloxy-17 (or 16)-hydroxyandrostane (**14c**)*

MS (*m*/*z*/relative intensity): 334/5, 306/40, 274/45, 256/30, 233/100, 217/32, 149/14, 109/5, 55/4.

3. Results and discussion

*3.1. Alkoxycarbonylation of 2α,3α- and 2β,3β-epoxy-5α-androstan-17-ones (**1** and **2**)*

Screening for the optimal reaction conditions, catalyst composition, and influence of nucleophilic reagent was carried out using epoxide **1** as a model substrate. The progress of the reaction (Fig. 2) was monitored by GC, GC–MS, and TLC.

The conditions described by Jacobsen for simple oxiranes with methanol resulted in only moderate conversion and low yield (Table 1). As side-reactions, water elimination from the substrate and direct nucleophilic attack of the alcohol on the substrate were detected, this latter resulting in ether **9a–c** formation which were identified by GC–MS analysis of the reaction mixture. Compound **9a** was further characterized also by ^{1}H NMR from chromatographically enriched samples in mixture with **7a**.

Both reaction time and temperature were increased to reach an almost complete conversion (Table 1); however, hydroxy ester yield remained still unsatisfactory. In EtOH better results were obtained. While further temperature increase shifts the product composition towards undesired side-reactions, higher pressure proved to be beneficial. Since product yields were only moderate, we changed the co-catalyst/Co molar ratio, which was determinant for our reaction.

The effect of nucleophilic reagent was studied as well (Table 2). At similar conversions the chemo- and regioselectivity increased with an increasing bulkiness of the alcohol. The main side-reaction, ether formation, is facilitated especially in the case of methanol.

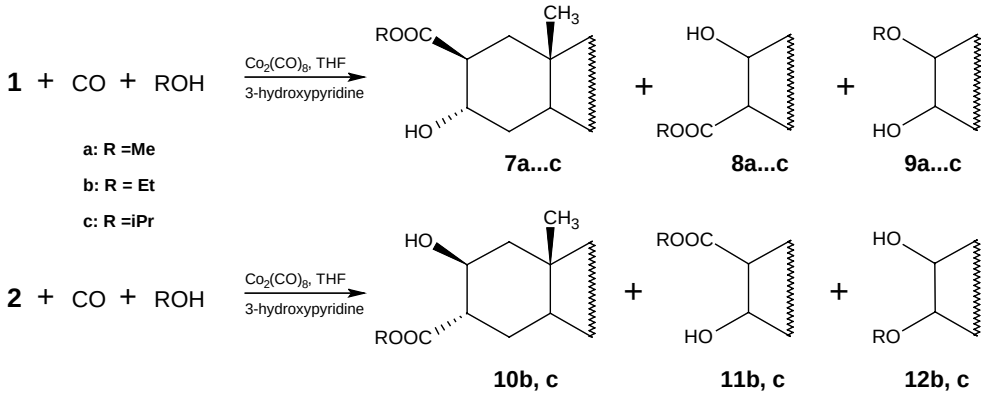

Fig. 2. Alkoxycarbonylation of 2,3-epoxy-steroids.

Table 1
Determination of the optimal reaction conditions in alkoxycarbonylation of **1**[a]

Run	Alcohol	Base/Co ratio(mol/mol)	Reaction time(h)	Reaction temperature (°C)	P_{CO} (atm)	Conversion[b] (%)	Yield[c] (%)
1	MeOH	2	9	65	45	51	24
2	MeOH	2	72	75	45	97	27
3	EtOH	2	9	75	45	77	20
4	EtOH	2	72	75	45	90	43
5	EtOH	2	144	75	45	93	46
6	EtOH	2	72	105	45	74	24
7	EtOH	2	72	75	100	95	49
8	EtOH	6	72	75	100	95	91

[a] General conditions: 1 mmol substrate **1**; 0.05 mmol $Co_2(CO)_8$ catalyst; 3-hydroxypyridine; 1 mL THF; 20 mmol alcohol; CO atmosphere.
[b] [(1 mmol unreacted **1**/1 mmol starting **1**)] × 100.
[c] [mmol (**7b** + **8b**)/mmol **1**] × 100 based on GC.

It should be mentioned that a control experiment was carried out during which a pure sample of **7c** was reacted under the standard reaction conditions in order to check its stability. After 72 h the hydroxy ester was recovered unchanged, as verified by GC–MS and ^{1}H NMR.

3.1.1. Structure elucidation

The structure and configuration of the new molecules were determined from their ^{1}H NMR spectra (for all spectra referred to see *Supporting information*). Detailed measurements have been carried out on pure samples of **7c** and **10c**.

There are two distinct one-proton signals in the spectrum of **7c** at 4.46 and 2.58 ppm, corresponding to the protons of –OH- and –COOR-substituted methylene groups, respectively. To decide between the two possible regioisomers (3-hydroxy, 2-carboxylate, or 2-hydroxy, 3-carboxylate), one has to identify unambiguously the coupling partners and the magnitude of the relevant scalar couplings. This was possible by routine two-dimensional (2D) (COSY 90-45 spectra) and one-dimensional (1D) ^{1}H techniques. Good use was made of the large diaxial vicinal couplings which gave sufficiently strong cross peaks. Based on these spectra, we could identify isopropyl 3-hydroxy-17-ketoandrostan-2-carboxylate as the main product. The minor amount of isomeric β-hydroxy ester **8c** was identified on the base of the ^{1}H spectrum of a sample containing esters **7c** and **8c**, chromatographically enriched in the latter. Two signal pairs with similar fine structure at 4.46 and 4.38 ppm and at 2.96 and 2.58 ppm indicate the presence of two possible regioisomers.

Concerning the α or β position of the substituents on the A ring, the fine structures of the ^{1}H signals gave important clues. The small coupling values observed for both signals exclude the existence of diaxial relations between the protons involved. Assuming the usual chair conformation for the A ring, this predicts C^2H^α and C^3H^β position for the protons, i.e. 2β and 3α positions for the –COOR and –OH substituents, respectively [16,17]. These configurations were confirmed further by steady-state 1D NOE difference and 2D transient NOE (NOESY) experiments [17].

The same measurements have been carried out for **10c** when the product was found to be isopropyl 2β-hydroxy-5α-androstan-17-one-3α-carboxylate. Comparison of the ^{1}H NMR spectra of **7c** and **10c** revealed a low-frequency (upfield) shift of the $C^{19}H_3$ protons for **7c**, indicating the spatial proximity of –COOR and the angular methyl group as an other evidence for the configuration deduced.

As obvious from the various NMR measurements, the stereochemistry of the starting materials **1** and **2** has not been preserved, as the configuration of the carbon atoms bearing –COOR substituents has changed. This seems to be in agreement with those observed by other authors for simple, non-terminal epoxides, where inversion of configuration occurs at the supposed site of attack [18,19].

Table 2
Alkoxycarbonylation of epoxy-steroids **1**, **2**, and **3** with different alcohols[a]

Product	Conversion[b] (%)	Chemoselectivity[c] (%)	Regioselectivity[d] (%)
7a	99	70	93
7b	98	91	95
7c	96	95	97
10b	98	90	96
10c	98	96	97
13a	96	68	99
13b	98	89	99
13b	96	91	99

[a] General conditions: 1 mmol steroid **1**, **2**, or **3**; 0.3 mmol 3-hydroxypyridine; 0.05 mmol $Co_2(CO)_8$; 1.5 mL THF; 20 mmol alcohol; 100 atm CO; 75 °C.
[b] [(1 mmol unreacted **1**, **2**, or **3**/1 mmol starting **1**, **2**, or **3**) × 100], based on GC.
[c] [(mmol esters/mmol products) × 100], based on GC.
[d] [(mmol major ester/mmol major + minor esters) × 100], based on GC.

3.2. Alkoxycarbonylation of 16α,17α-epoxy-5α-androstane (3)

Likewise the 2,3-epoxy-derivatives discussed above, unhindered 16,17-epoxide **3** underwent efficient alkoxycarbonylation in the Co-catalyzed process (Fig. 3). The conditions of the reaction were analogous to the former,

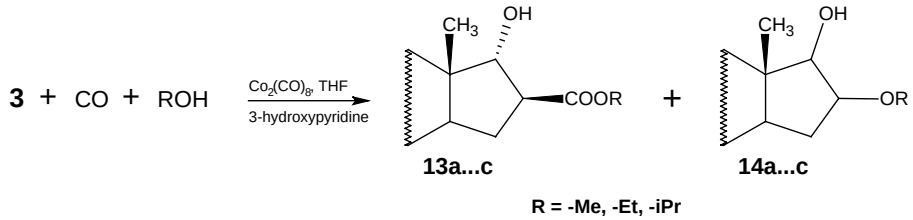

Fig. 3. Alkoxycarbonylation of 16α,17α-epoxy-steroids.

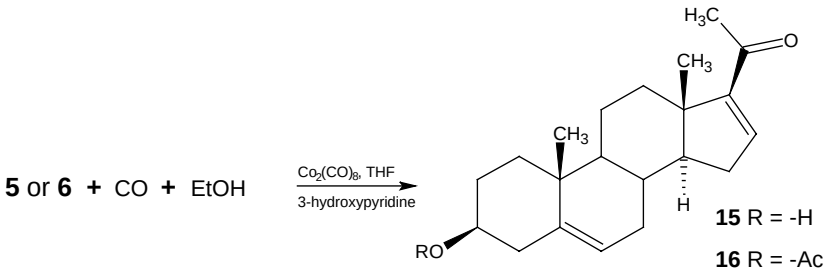

Fig. 4. Alkoxycarbonylation of 16α,17α-epoxy-17-substituted epoxy-pregnenes.

and high chemo- and regioselectivities were observed in the main product **13a** (Table 2, lines 4–6). The same tendencies were observed also when the alcohol was varied. The high regioselectivities are attributed to the steric effect of the angular $C^{18}H_3$ methyl group [20,21]. Losses in chemoselectivity are due again to ether (**14a**–**c**) formation.

3.2.1. Structure elucidation

The relevant NMR spectra (see *Supporting information*) were obtained on a chromatographically purified sample of **13c**. In the ^{1}H NMR spectrum there is only one signal at 3.98 ppm (doublet with a small coupling value of 1.4 Hz) and with an integral value of one proton and an other one-proton signal at much lower frequency (2.66 ppm). This latter has, however, double-triplet fine structure, indicating almost identically strong (∼8–9 Hz) couplings to two other protons and a small one (1.4 Hz) to the signal at 3.98 ppm. Based on their chemical shift values, we can safely assume that these are the C^{17}H and C^{16}H ring protons attached to carbon atoms bearing –OH and –COOR groups, respectively. Since the signal at 3.98 ppm shows only a small coupling, the isopropyl 16-hydroxyandrostane-17-carboxylate regioisomer can be excluded, the main structure being isopropyl 17-hydroxyandrostane-16-carboxylate.

Concerning the α or β position of the substituents on the conformationally more flexible D ring, the answer is less obvious (in comparison with the A ring), since the ring conformation is always perturbed by the substituents themselves. Nevertheless, fine structures of the ^{1}H signals give again important clues. The very small coupling [22] (1.4 Hz) between C^{17}H and C^{16}H (although smaller than the typical three-bond equatorial–axial couplings obtained from the generalized Karplus equation [23] and experimental data [24]) suggests 16α,17β or 17α,16β arrangement for them. 1D NOE measurements indicate that C^{17}H is β, therefore, C^{16}H must be α, so the original configuration of the C^{16} carbon atom involved was not preserved during the reaction (like in the 2,3-epoxy cases).

3.3. Alkoxycarbonylation of sterically hindered epoxy-steroids

Pregnenolones with sterically hindered 16,17-epoxides (**5** and **6**) were subjected to alkoxycarbonylation in presence of EtOH under the same conditions. No ester could be detected by GC–MS analyses. TLC screening of the mixture showed one dominant product, which remained the same if reacting the substrate with MeOH. The ^{1}H NMR spectrum of the product revealed the formation of a pregnadiene as a result of a reductive elimination reaction (Fig. 4). The 5,6-double bond was left intact under the conditions applied.

The other sterically hindered substrate **4** was reacted with ethanol for as long as 96 h. As TLC analyses showed, a rather complex reaction mixture was formed. The GC–MS and ^{1}H NMR spectra of the components showed that no carbonylation took place, and only unsaturated steroids were detectable. This is in agreement with our former results obtained in carbonylation of sterically hindered unsaturated steroids [21].

4. Conclusion

Homogeneous catalytic ring-opening alkoxycarbonylation of various epoxy-steroids has been carried out successfully in presence of $Co_2(CO)_8$/3-hydroxypyridine as catalyst precursor. The reactions took place in a highly chemo- and regioselective manner with unhindered 2,3- and 16,17-epoxides.

Conversion and selectivity depended on the suitable choice of the conditions and the Co/base ratio, as well as the bulkiness of the nucleophilic reagent. Even more important is the accessibility and position of the epoxide moiety. No carbonylation took place with 5,6- and 16,17-epoxides where a C–O bond belongs to a tertiary carbon atom.

The resulting steroidal β-hydroxy esters were obtained as isomerically pure compounds. The new compounds were isolated and characterized in pure form. Both 2α,3α- and 2β,3β-epoxy-5α-androstan-17-one and 16α,17α-epoxy-androstane underwent alkoxycarbonylation with configuration inversion at the carbon atoms bearing the –COOR moiety.

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