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β-Selective epoxidation of Δ^5-steroids by O_2 using surface functionalised silica supported cobalt catalysts

Samuel M. Silvestre [a], Jorge A.R. Salvador [a,*], James H. Clark [b,1]

[a] *Laboratório de Química Farmacêutica, Faculdade de Farmácia, Universidade de Coimbra, 3000-295 Coimbra, Portugal*
[b] *Chemistry Department, Clean Technology Centre, University of York, York YO10 5DD, UK*

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Abstract

A general catalytic and relatively environment friendly method for β-epoxidation of Δ^5-steroids has been developed, which uses silica supported cobalt as catalysts and molecular oxygen as the oxidant. The reactions are regio- and stereoselective.

A whole range of Δ^5-steroids, with different functional groups such as hydroxyl, carbonyl or acetyl, as well as different side chains, were conveniently converted to the corresponding biologically interesting 5β,6β-epoxides with high degree of stereoselectivity and high yields.

Keywords: Δ^5-Steroids; Oxygen; Cobalt; Heterogeneous catalysts; 5β,6β-Epoxides

1. Introduction

The synthesis of 5β,6β-epoxides is a useful reaction since this group is present in many biologically active steroids [1]. More importantly, the 5β,6β-epoxy functionality is found in a number of naturally occurring steroids with antitumor activities, for example, jaborosalactone A [1], withaferin A [2] and withanolide D [3]. Moreover, the geometry imposed by the 5β,6β-epoxide on rings A and B of a steroid is quite different from that of a 5α,6α-epoxide. The β-oriented angular methyl group at C-10 normally dominates the epoxidation of Δ^5-steroids by peracids such as MCPBA [4], or by dioxiranes [5], leading invariably to the predominant formation of the α-epoxide [6]. Epoxidation of the 3α-halo-Δ^5-steroids afforded epimeric mixtures of epoxides in which the β-epimer predominated [7]. Mixtures of 5α,6α- and of the 5β,6β-epoxides were obtained by treatment with hydrogen peroxide in the presence of iron(II), iron(III), and titanium(III) ions [8] or alkyl hydroperoxides catalysed by molybdenum compounds [9]. Chandrasekaran and co-workers [10] and more recently a number of other groups [11–14] including ourselves [15] have shown that these epoxides can be obtained from Δ^5-steroids using biphasic systems involving potassium permanganate and metal salts. Potassium permanganate can be used catalytically for this epoxidation [16]. Recently, the β-epoxidation of Δ^5-steroids using ketones as catalysts and oxone as the terminal oxidant was reported [17].

The use of molecular oxygen or air as the oxidant in the presence of metalloporphyrin catalyst is of greater industrial interest [18,19]. The major drawback of these methods is the synthesis of the catalyst, which is not always easy. Similar results have been reported using Mn(II) [20], Ni(II) [21], Fe(III) [22], Ru(II) [23] and Co(II) [24] complexes as catalysts, but a difficult separation step is needed to remove the catalyst which cannot easily be reused.

Hence, there is a need for an efficient, safe and cost effective procedure for selectively effecting the 5β,6β-epoxidation of Δ^5-steroids and especially in which the separation stages of the reaction are simple and enable catalyst recycling. The heterogenisation of inorganic reagents and catalysts useful in organic reactions is a very important area [25] and led us to recently report the use of $Co(OAc)_2{\cdot}4H_2O$ as catalyst in heterogeneous forms for the allylic oxidation of unsaturated steroids [26].

Here, we report the use of some of these heterogeneous catalysts (Fig. 1) for the 5β,6β-epoxidation of

* Corresponding author. Tel.: +351 239 859900; fax: +351 239 827126.
E-mail address: salvador@ci.uc.pt (J.A.R. Salvador).
[1] Co-corresponding author.

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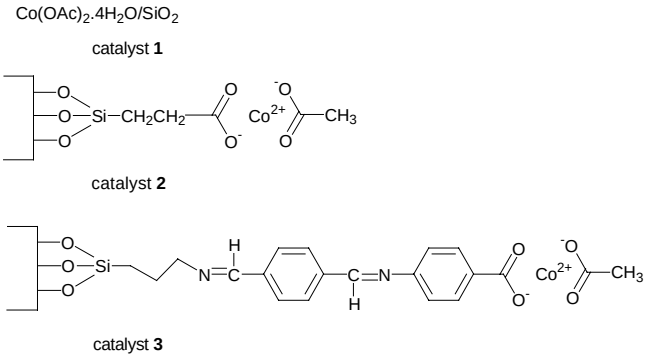


Fig. 1. $Co(OAc)_2{\cdot}4H_2O/SiO_2$.

Δ^5-steroids under Mukaiyama reaction conditions, according to Scheme 1.

2. Experimental

The steroids used as substrates were commercially available from Sigma and Aldrich. Reaction solvents were distilled before use, according to standard procedures. Kieselgel $60HF_{254}$/Kieselgel 60G was used for TLC analysis. Melting points were determined with a Reichert microscope apparatus and were uncorrected. IR spectra were performed in a JASCO FT/IR-420 spectrophotometer. ^1H and ^{13}C NMR were recorded on a Bruker AMX 300, in $CDCl_3$ solution with Me_4Si as internal standard.

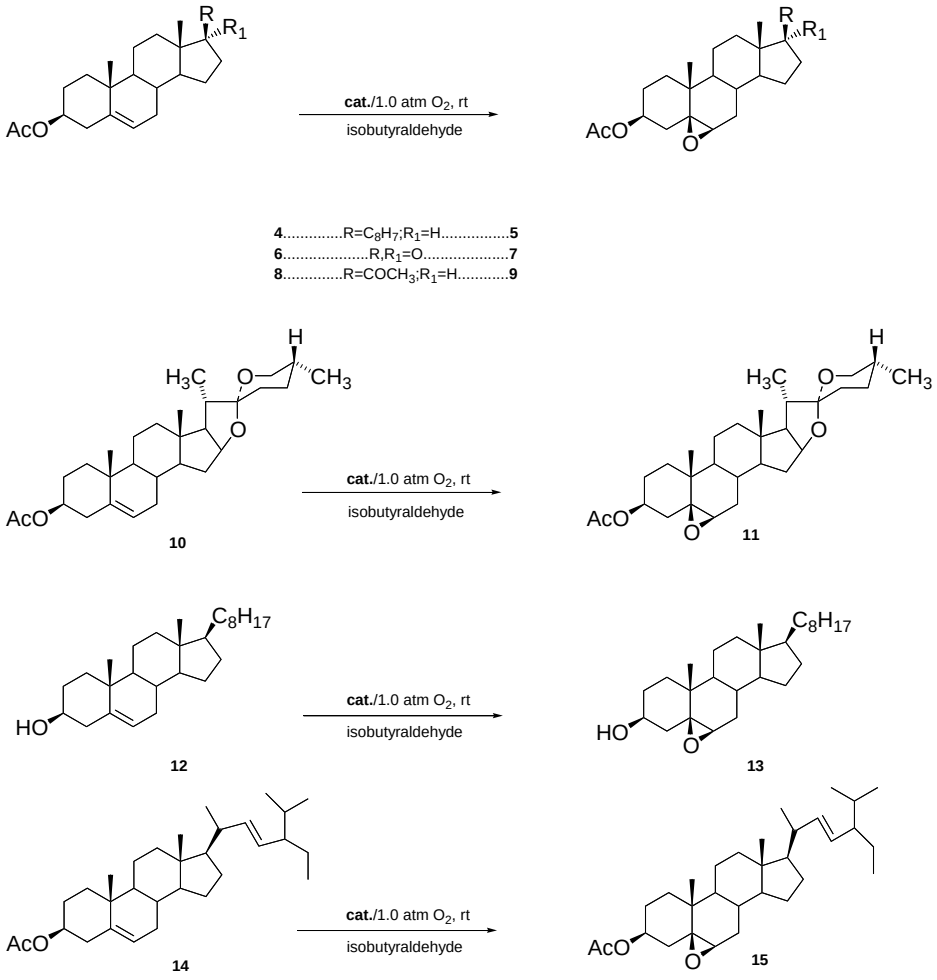
2.1. Catalysts preparation

To prepare catalyst **1**, SiO_2 (Kiesel Gel 60, 0.2–0.5 mm, 35–70 mesh) was added to $Co(AcO)_2{\cdot}4H_2O$ (0.747 g, 3 mmol), dissolved in an excess of water and the resulting slurry was evaporated in a rotary evaporator and dried under reduced pressure at 90 °C overnight.

Catalyst **2** was prepared as previously reported [27], but with a loading of 1 mmol g^{-1}. Catalyst **3** was prepared as previously reported by Chisem et al. [28].

2.2. General procedure for β-selective epoxidation of Δ^5-steroids catalysed by silica supported cobalt catalysts

In a typical reaction, to a solution of the substrate (e.g. cholest-5-en-3β-yl acetate **4**, 107.16 mg/0.25 mmol)



Scheme 1.

in 1,2-dichloroethane (4 ml) under oxygen atmosphere (1 atm), isobutyraldehyde (0.1 ml) and catalyst (e.g. catalyst **1**, 15 mg) were added. After 7 h under magnetic stirring at room temperature, the reaction was complete (t.l.c. control). The catalyst was removed by filtration and the solvent was evaporated in vacuo; then, dichloromethane was added and this organic phase was washed with an aq. saturated solution of $NaHCO_3$, water, dried and evaporated to dryness. The residue was crystallized from methanol to give **5**. m.p. 110–112 °C (MeOH); Ref. [29], 111–112 °C; IR: 1038, 1240, 1365, 1468, 1730, 2935 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.63 (s, 3H, 18-H_3), 1.00 (s, 3H, 19-H_3), 3.07 (m, 1H, 6α-H), 4.76 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 62.51 (C^5), 63.56 (C^6), 71.30 (C^3), 170.51 ($CH_3\underline{C}O$).

7. m.p. 188–190 °C (MeOH); Ref. [30], 188–190 °C; IR: 1030, 1230, 1360, 1470, 1715, 1735, 2950 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.84 (s, 3H, 18-H_3), 1.03 (s, 3H, 19-H_3), 3.14 (m, 1H, 6α-H), 4.77 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 62.56 (C^5), 63.15 (C^6), 71.12 (C^3), 170.49 ($CH_3\underline{C}O$), 220.57 (C^{17}).

9. m.p. 129–131 °C (MeOH); Ref. [31], 132–136 °C; IR: 1040, 1230, 1340, 1435, 1685, 1735, 2930 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.59 (s, 3H, 18-H_3), 1.01 (s, 3H, 19-H_3), 3.09 (m, 1H, 6α-H), 4.77 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 62.34 (C^5), 63.55 (C^6), 71.13 (C^3), 170.41 ($CH_3\underline{C}O$), 209.13 (C^{20}).

11. m.p. 189–192 °C (MeOH); Ref. [10], 187–190 °C; IR: 1041, 1258, 1361, 1446, 1729, 2946 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.74 (s, 3H, 18-H_3), 1.02 (s, 3H, 19-H_3), 3.08 (m, 1H, 6α-H), 4.76 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 62.45 (C^5), 63.37 (C^6), 66.83 (C^{26}), 71.24 (C^3), 80.63 (C^{16}), 109.22 (C^{22}), 170.45 ($CH_3\underline{C}O$).

13. m.p. 131–132 °C (MeOH); Ref. [32], 130–132 °C; IR: 1034, 1215, 1458, 2933, 3343 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.65 (s, 3H, 18-H_3), 1.05 (s, 3H, 19-H_3), 3.11 (m, 1H, 6α-H), 5.03 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 62.54 (C^6), 63.54 (C^5), 71.90 (C^3).

15. m.p. 138–140 °C (MeOH); Ref. [33], 139–140 °C; IR: 1040, 1251, 1366, 1457, 1727, 2934, 3033 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.66 (s, 3H, 18-H_3), 0.72–0.90 (m, 9H, 26-H_3, 27-H_3 and 29-H_3), 1.01 (s, 3H, 19-H_3), 3.09 (m, 1H, 6α-H), 4.76 (m, 1H, 3α-H), 5.1 (t, J = 6 Hz, 2H, 22-H and 23-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 62.49 (C^5), 63.56 (C ^{6}), 71.31 (C^3), 170.55 ($CH_3\underline{C}O$).

3. Results and discussion

In spite of the great number of papers reporting new applications of Mukaiyama's oxidation reactions to a great variety of organic substrates (alkenes, aldehydes, silyl enol ethers, silyl ketene acetals, ketones, lactams and alkanes) in the presence of aldehydes or acetals, with various transition-metal complexes as catalytic systems (Mukaiyama's conditions), only a few reports have been dedicated to the study of the epoxidation of unsaturated steroids under these reaction conditions [20–24].

Although the majority of papers in the literature describe homogeneous catalytic systems for this reaction, Mastrorilli et al. [24,34] reported the the use of polymerizable β-ketoesterate complexes such as $Fe(AAEMA)_3$ and $Co(AAEMA)_2$ as catalytic centres ($AAEMA^-$ = deprotonated form of 2-(acetoacetoxy)ethyl methacrylate), as potential hybrid epoxidation catalysts with a view to laying the foundations for effecting the reactions under heterogeneous conditions.

Despite the good yields and selectivities reported with a cobalt catalyst in homogeneous conditions in a previous communication [20], the catalyst cannot be easily recovered and reused, which encouraged us to use heterogeneous forms of cobalt catalysts, **1**, **2** and **3**, Fig. 1, for the epoxidation reaction of Δ^5-steroids.

Using Δ^5-steroids **4**, **6**, **8**, **10**, **12** and **14** as substrates, the hindered 5β,6β-epoxide products **5**, **7**, **9**, **11**, **13** and **15** were obtained in very high isolated yields and selectivities (Scheme 1, Tables 1–3).

A preliminary control experiment showed that the catalyst is not required for efficient epoxidation of the steroid substrate **6**, but the absence of the catalyst makes the reaction occur slowly with significant lost of diastereoselectivity (ratio of isomers β:α 65:35) corroborating with previous findings [18].

Table 1
Stereoselective epoxidation of Δ^5-steroids with catalyst **1**

Entry	Substrate/mmol	Catalyst/mmol	Solvent	Time (h)	Product	Ratio of isomers (β:α)[a]	Isolated yield (%)[b]
1	**4**/0.25	**1**/0.006	1,2-Dichloroethane	7	**5**	80:20	90
2	**6**/0.25	**1**/0.0045	1,2-Dichloroethane	6	**7**	80:20	90
3	**6**/0.25	**1**/0.0045	Dichloromethane	8	**7**	84:16	91
4	**6**/0.25	**1**/0.0045	Acetonitrile	20	**7**	72:28	90
5	**6**/0.25	**1**/0.0045	Ethyl acetate	48	**7**[c]	77:23	86
6	**8**/0.25	**1**/0.0045	1,2-Dichloroethane	6	**9**	74:26	90
7	**10**/0.25	**1**/0.0045	1,2-Dichloroethane	7	**11**	76:24	81
8	**14**/0.25	**1**/0.0045	1,2-Dichloroethane	5	**15**	75:25	89

[a] The ratio of β:α-epoxides was determined by ^1H NMR spectroscopy by integration of the 6-H signals in crude samples.
[b] Traces of starting material and a by product are visible in TLC plates but not detectable in ^1H NMR spectrum (300 MHz) of the crude product.
[c] Approximately 20% of 7-keto-Δ^5-steroid was obtained as a by product.

Table 2
Stereoselective epoxidation of Δ^5-steroids with catalyst **2**

Entry	Substrate/mmol	Catalyst/mmol	Solvent	Time (h)	Product	Ratio of isomers (β:α)[a]	Isolated yield (%)[b]
1	**4**/0.25	**2**/0.006	1,2-Dichloroethane	6	**5**	78:22	89
2	**4**/0.25	**2**/0.006	Dichloromethane	7	**5**	84:16	90
3	**4**/0.50	**2**/0.015	Dichloromethane	6	**5**	79:21	91
4	**4**/0.50	**2**/(Recycled, 0.012)	Dichloromethane	7	**5**	76:24	90
5	**6**/0.25	**2**/0.005	1,2-Dichloroethane	5	**7**	78:22	91
6	**8**/0.25	**2**/0.006	1,2-Dichloroethane	6	**9**	75:25	84
7	**10**/0.25	**2**/0.006	1,2-Dichloroethane	10	**11**	74:26	91
8	**12**/0.25	**2**/0.006	Dichloromethane	4	**13**	76:24	80
9	**14**/0.25	**2**/0.005	Dichloromethane	10	**15**	82:18	85

[a] The ratio of β:α-epoxides was determined by ^{1}H NMR spectroscopy by integration of the 6-H signals in crude samples.
[b] Traces of starting material and a by product are visible in TLC plates but not detectable in ^{1}H NMR spectrum (300 MHz) of the crude product.

A whole range of Δ^5-steroids, with different functional groups such as hydroxyl, carbonyl or acetyl, as well as different side chains, including diosgenine acetate, were conveniently converted to the corresponding biologically interesting 5β,6β-epoxides with high degree of stereoselectivity and high yields.

The epoxidation reaction was performed with different types of solvents (Table 1), but in general reactions with halogenated solvents dichloromethane and 1,2-dichloroethane provided better yields and selectivities. Using substrate **6**, catalyst **1** and ethyl acetate as the solvent, the reaction's time increased as well as the amount of by-product resulting from the allylic oxidation reaction (approximately 20% of 7-keto-Δ^5-steroid derivative), as determined by ^{1}H NMR (Table 1, entry 5).

While the product yields of the epoxidation reaction are very similar under homogeneous and heterogeneous conditions, the easier recovery of the catalyst makes the latter more environment friendly. Furthermore, heterogeneous catalysts **2** and **3** can be reused with only a small reduction in the product yields under similar experimental conditions (90% for recycled catalyst **2**, Table 2, entry 4 and 89% for recycled catalyst **3**, Table 3, entry 4) without significant lost of stereoselectivity.

These results suggest the formation of a reactive silica supported cobalt species which would preferentially attack the steroid substrate on the β-face, in a process similar to the β-stereoselective epoxidation catalysed by manganese-, iron- and ruthenium-porphyrin species [35].

To test for leaching, catalysts **2** and **3** were filtered after 30 min under reaction conditions in the absence of substrate, and the filtrate was allowed to react further. This filtration was performed at reaction temperature. We found for both catalysts that after filtration, the filtrate reacted slowly, with significant lost of diastereoselectivity (*ratio* of isomers β:α 66:34, for substrate **6**), similar to the reaction performed in absence of the catalysts.

The free 3-OH group of Δ^5-steroids is not compatible with some metal-based oxidants in the epoxidation reactions [10–15]. However, it is interesting to note that a Δ^5-steroid with a free 3-OH group (cholesterol **12**) were directly converted to their 5β,6β-epoxide with high selectivity (β:α 76:24, Table 2, entry 8) and yield, 80%.

Interestingly, this methodology is also regioselective in that the oxidation of stigmasteryl acetate **14**, led to the formation of the corresponding 5β,6β-epoxide, *ratio* of isomers 82:18, in high yield (85% catalyst **2**, Table 2 entry 9, or 90% catalyst **3**, Table 3, entry 9) where the trisubstituted double bond has reacted in preference to the disubstituted double bond in the side chain.

Table 3
Stereoselective epoxidation of Δ^5-steroids with catalyst **3**

Entry	Substrate/mmol	Catalyst/mmol	Solvent	Time (h)	Product	Ratio of isomers (β:α)[a]	Isolated yield (%)[b]
1	**4**/0.25	**3**/0.006	1,2-Dichloroethane	8	**5**	78:22	89
2	**4**/0.25	**3**/0.006	Dichloromethane	8	**5**	80:20	91
3	**4**/0.50	**3**/0.012	Dichloromethane	6	**5**	79:21	91
4	**4**/0.50	**3**/(Recycled, 0.011)	Dichloromethane	6	**5**	79:21	89
5	**6**/0.25	**3**/0.006	1,2-Dichloroethane	5	**7**	81:19	89
6	**8**/0.25	**3**/0.006	1,2-Dichloroethane	8	**9**	78:22	88
7	**10**/0.25	**3**/0.006	1,2-Dichloroethane	10	**11**	74:26	91
8	**12**/0.25	**3**/0.006	Dichloromethane	5	**13**	75:25	90
9	**14**/0.25	**3**/0.006	Dichloromethane	8	**15**	82:18	90

[a] The ratio of β:α-epoxides was determined by ^{1}H NMR spectroscopy by integration of the 6-H signals in crude samples.
[b] Traces of starting material and a by product are visible in TLC plates but not detectable in ^{1}H NMR spectrum (300 MHz) of the crude product.

4. Conclusions

In conclusion, a relatively environment friendly method for β-epoxidation of Δ^5-steroids has been developed, which uses silica supported cobalt as catalysts and molecular oxygen as the oxidant. A whole range of Δ^5-steroids were conveniently converted to the corresponding biologically interesting 5β,6β-epoxides with high degree of stereoselectivity and high yields. The supported Co(II) catalysts used are easily recoverable and reusable.

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