Highly β-Selective Epoxidation of Δ^5-Unsaturated Steroids Catalyzed by Ketones

Dan Yang* and Guan-Sheng Jiao[a]

Abstract: A general catalytic and environmentally friendly method for β-epoxidation of Δ^5-unsaturated steroids has been developed, which uses ketones as the catalysts and Oxone as the terminal oxidant. A whole range of Δ^5-unsaturated steroids, which bear different functional groups such as hydroxyl, carbonyl, acetyl, or ketal, as well as different side chains, were conveniently converted to the corresponding synthetically and biologically interesting 5β,5β-epoxides with excellent β-selectivities and high yields.

Keywords: β-selectivity · dioxiranes · epoxidations · ketones · steroids

Introduction

Steroid epoxides are an important class of oxysterols (oxygenated derivatives of cholesterol), which regulate cell proliferation and cholesterol homeostasis.[1] They are versatile intermediates for steroid synthesis and useful probes for biochemical studies of enzymes. For example, α- and β-epoxides of cholesterol are autoxidation products of cholesterol in vivo,[2] and both are cytotoxic and mutagenic.[3] These isomeric α- and β-epoxides are hydrolyzed by cholesterol 5,6-epoxide hydrolase to cholestane-3β,5α,6β-triol,[4] which has potent hypocholesterolemic activity. On the other hand, both epoxides inhibit cholesterol 7α-hydroxylase,[5] which catalyzes the rate-determining step of bile acid synthesis. As 5α,6α-epoxides are readily available through the epoxidation of Δ^5-unsaturated steroids with peracids,[6] there have been extensive studies on the biological actions of these epoxides and their derivatives.[7] In contrast, much less is known about the 5β,6β-epoxides and their derivatives, because they are difficult to obtain with high selectivity. More importantly, the 5β,6β-epoxy functionality is found in a number of naturally occurring steroids with antitumor activities, for example, jaborosalactone A,[8a] withaferin A,[8b] and withanolide D.[8c] Thus it is of significant importance to develop efficient methods for the synthesis of 5β,6β-epoxides of steroids. Up to now, the use of metal-based oxidants has met with some success.[9] However, a truly general catalytic and environmentally friendly method for the β-epoxidation of Δ^5-unsaturated steroids remains an elusive target.[10] Here we report a highly β-selective epoxidation of Δ^5-unsaturated steroids catalyzed by ketones.

[a] Dr. D. Yang, G.-S. Jiao
Department of Chemistry, The University of Hong Kong
Pokfulam Road, Hong Kong (China)
Fax: (+852) 2859-2159
E-mail: yangdan@hku.hk

Results and Discussion

Common organic oxidants such as 3-chloroperoxybenzoic acid (*m*CPBA)[6c] generally give α-epoxides as the major products for epoxidation of 3β-substituted Δ^5-steroids and show poor selectivities for epoxidation of 3α-substituted Δ^5-steroids other than *epi*-cholesterol.[11] This is because peracid epoxidation follows a concerted pathway via spiro transition states[12] (α- and β-TS (TS = transition state), see Scheme 1). In the β-TS there are steric interactions between the peracid and the C10 angular methyl group during epoxidation of 3β-substituted Δ^5-steroids, while similar steric hindrance occurs in both the β- and the α-TS during epoxidation of 3α-substituted Δ^5-steroids. Dioxiranes[13] are new-generation reagents for epoxidation under mild and neutral conditions. Unfortunately, poor selectivities were reported in the epoxidation of 3β-substituted Δ^5-steroids by both isolated[14a] and in situ-generated[14b,c] dioxiranes. While dioxiranes also epoxidize olefins via a spiro TS,[12c, 15] their steric environment is different from that of peracids. To minimize steric interactions, dioxiranes prefer to approach the C5=C6 double bond of Δ^5-steroids from the less-substituted side, that is, away from the C10 angular methyl group and the C-ring of steroids (Scheme 1). Therefore, it is the potential steric interactions between the α-substituents of dioxiranes and the 3α- and 4β-substituents of steroids that determine the facial selectivity of epoxidation.[16] We reasoned that high β-selectivity could be achieved by increasing the steric size of either the α-

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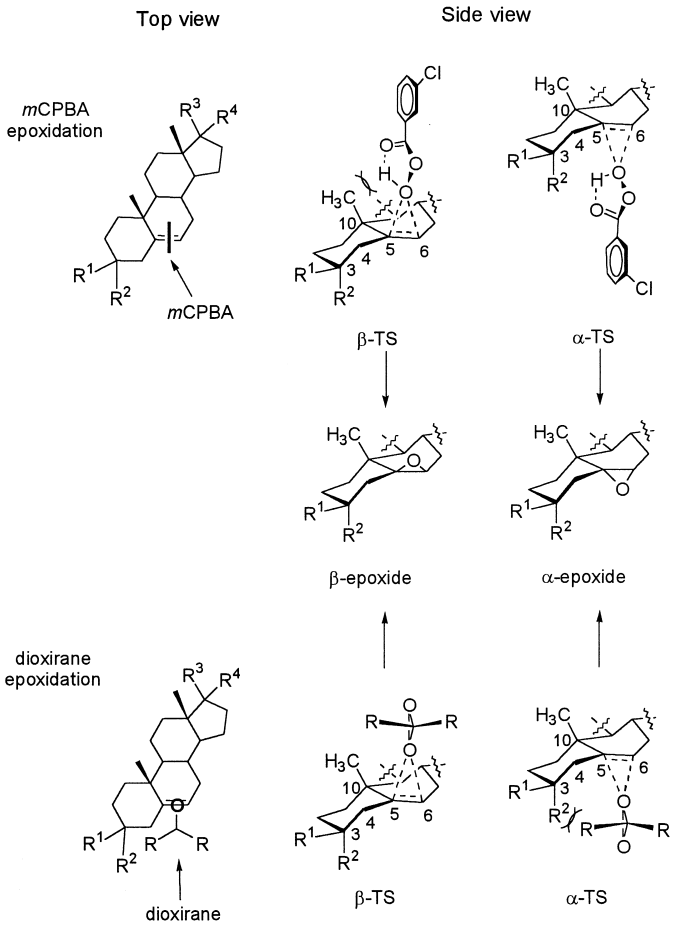
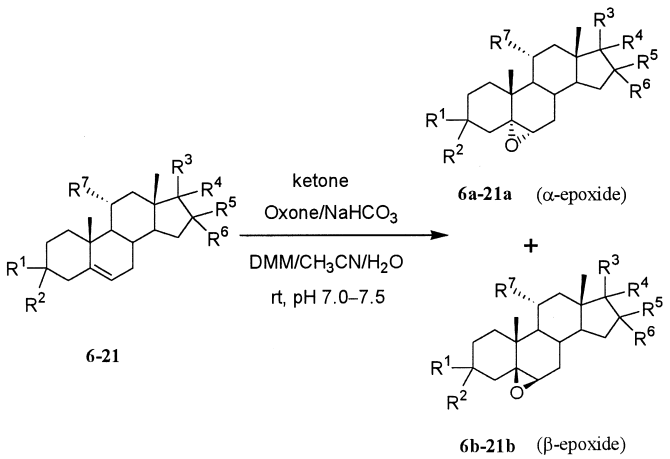


Scheme 1. Top and side views of the attack of *m*CPBA and dioxirane on the Δ^5-steroid with α and β transition states and products. Areas of steric hindrance are indicated.



Scheme 2. Reactions of steroids **6**–**21** that lead to α- and β-epoxides.

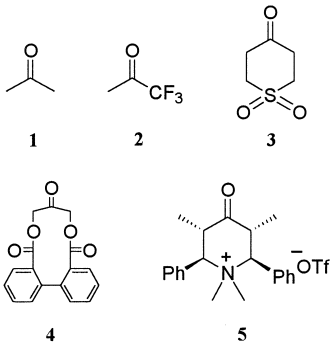
Table 1. Stereoselective epoxidation of 3β-substituted Δ^5-steroids by dioxiranes generated in situ.[a]

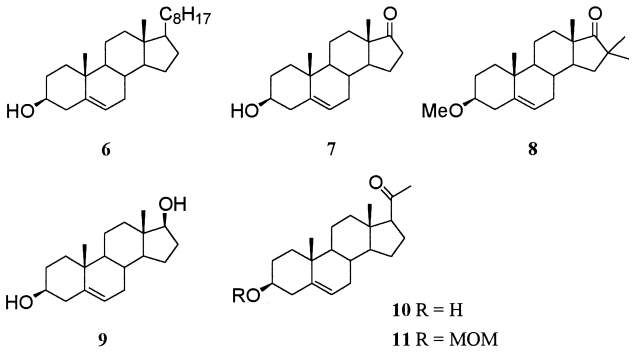
	Ketone catalyst	Substrate	Catalyst loading [equiv]	Reaction time[h][b]	Yield [%][c]	β/α-Epoxide ratio[d,e]
1	**2**[f]	**6**	20	1.5	91	1/1.1 (1/4.0)
2	**3**	**6**	0.05	1.5	93	1.1/1
3	**4**	**6**	0.1	3	92	1/1.1
4	**5**	**6**	0.3	16	82	15.1/1
5	**5**	**7**	0.2	9	91	10.4/1 (1/3.9)
6	**5**	**8**	0.2	20	88	9.0/1 (1/3.1)
7	**5**	**9**	0.2	16	85	8.8/1 (1/3.1)
8	**5**	**10**	0.2	9	93	11.6/1 (1/4.3)
9[g]	**5**	**10**	0.2	12	89	11.4/1
10	**5**	**11**	0.2	20	83	8.5/1 (1/3.7)

[a] Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.3 mmol of substrate, indicated amount of ketone, 1.5 mmol of Oxone, 4.65 mmol of $NaHCO_3$, 9 mL of dimethoxymethane (DMM), 3 mL of CH_3CN, and 6 mL of aqueous $Na_2\cdot$EDTA solution (4×10^{-4} M). [b] Time for complete epoxidation as shown by thin-layer chromatography. [c] Isolated yield. [d] The ratio of β/α-epoxides was determined by ^{1}H NMR spectroscopy (500 or 300 MHz). [e] The value in parentheses was the ratio of β/α-epoxides obtained with *m*CPBA as the oxidant. [f] The epoxidation reaction was carried out at 0–1 °C. [g] On a 10 mmol scale.

substituents of dioxiranes or the 3α- substituents of Δ^5-steroids. Our experimental results confirmed this conjecture.

We first examined four efficient ketone catalysts **2**–**5**[17] for the in situ epoxidation of cholesterol **6**. A modified homogeneous solvent system (dimethoxymethane (DMM)/CH_3CN/H_2O, 3:1:2) was used to increase the solubility of steroid substrates (Scheme 2). The results are summarized in Table 1.[18] While ketones **2**–**4** exhibited poor β-selectivities (β/α epoxide ratio ca. 1:1; entries 1–3), similar to the results reported in the literature,[14b] ketone **5**, with the most bulky α-substituent, gave the best β-selectivity (β/α epoxide ratio 15.1:1; entry 4). A variety of 3β-substituted Δ^5-steroids **7**–**11** were then subjected to in situ epoxidation conditions with 20–30 mol% of ketone **5**.[19] The results revealed that ketone **5** generally gave high β-selectivities (β/α epoxide ratio





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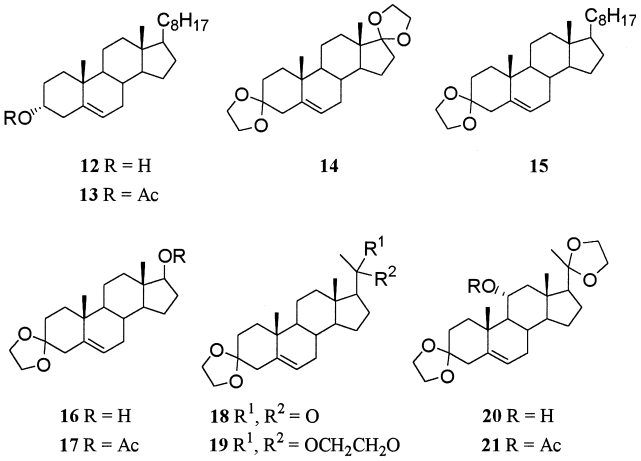
> 8.5:1) and high yields (entries 4–10). It is interesting to note that Δ^5-steroids with a free C3–OH group were directly converted to their 5β,6β-epoxides with high selectivities and yields (entries 4, 5, and 7–9).[20] Meanwhile, a wide range of other functional groups, such as methoxyl, methoxymethyl ether (MOM), and carbonyl, were well tolerated under the mild and neutral reaction conditions (room temperature, pH 7–7.5).

Epoxidation reactions of 3α-substituted Δ^5-steroids **12**–**21** were also carried out with ketone catalysts **1**–**5** (Table 2). For *epi*-cholesterol **12** with a 3α-OH group, the epoxidation reactions catalyzed by ketones **2** and **5** gave much higher β-selectivities than those catalyzed by ketones **1**, **3**, and **4** (entries 1–5), because ketones **2** and **5** have larger α-substituents.[21] For substrates in which the 3α-substituents are larger than the OH group (**13**–**21**), the in situ epoxidation catalyzed by ketones **1**–**5** produced almost exclusively a single 5β,6β-isomer,[22] while *m*CPBA gave approximately a 1:1 ratio of β/α-epoxides for epoxidation of all substrates except **13**. The epoxidation reactions catalyzed by ketone **3** were highly efficient as only 5 mol% of the catalyst was needed, even on a preparative scale.[23] These results clearly demonstrate the power of the ketone-catalyzed epoxidation method. In addition, the easy access of the ketone catalysts, especially acetone (**1**), makes the present method very practical and useful for preparation of 5β,6-epoxides.



12 R = H
13 R = Ac
14
15
16 R = H
17 R = Ac
18 R^1, R^2 = O
19 R^1, R^2 = OCH_2CH_2O
20 R = H
21 R = Ac

Table 2. Stereoselective epoxidation of 3α-substituted Δ^5-steroids by dioxiranes generated in situ.[a]

	Ketone	Substrate	Catalyst loading [equiv]	Reaction time [h][b]	Yield [%][c]	β/α-Epoxide ratio[d,e]
1	**1**	**12**	20	5	90	3:1 (1:9.5)
2	**2**[f]	**12**	20	2	90	19:1
3	**3**	**12**	0.05	2	93	5:1
4	**4**	**12**	0.1	3.5	91	4:1
5	**5**	**12**	0.2	8	92	90:1
6	**3**	**13**	0.05	4	82	72:1 (2:1)
7	**5**	**13**	0.3	18	84[g]	> 99:1
8	**1**	**14**	20	5	94	> 99:1[h] (1:1)
9	**2**[f]	**14**	20	1	86	> 99:1
10	**3**	**14**	0.05	2	94	96:1
11	**4**	**14**	0.1	1.5	93	49:1
12	**5**	**14**	0.3	12	84	> 99:1
13	**1**	**15**	20	6	93	> 99:1 (1:1)
14	**3**	**15**	0.05	3.5	95	> 99:1
15	**5**	**15**	0.3	18	86[i]	> 99:1
16	**3**	**16**	0.05	2	88	79:1 (1:1)
17	**5**	**16**	0.2	10	83	86:1
18	**1**	**17**	20	3.5	93	> 99:1 (1:1)
19	**3**	**17**	0.05	3	95	91:1
20	**5**	**17**	0.2	12	82	> 99:1
21	**3**	**18**	0.05	1	91	84:1 (1:1)
22	**5**	**18**	0.2	15	81	66:1
23	**1**	**19**	20	6	92	> 99:1 (1:1)
24	**3**	**19**	0.05	3.5	96	92:1[j]
25	**5**	**19**	0.2	12	84	61:1
26	**1**	**20**	20	5	91	43:1 (1:1)
27	**3**	**20**	0.05	2	92	51:1
28	**5**	**20**	0.2	9	91	50:1
29	**3**	**21**	0.05	2	92	85:1 (1:1)
30	**5**	**21**	0.3	12	82	62:1

[a] Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.3 mmol of substrate, indicated amount of ketone, 1.5 mmol of Oxone, 4.65 mmol of $NaHCO_3$, 9 mL of DMM, 3 mL of CH_3CN, and 6 mL of aqueous $Na_2 \cdot EDTA$ solution (4×10^{-4} M). [b] Time for complete epoxidation as shown by thin-layer chromatography. [c] Isolated yield unless otherwise noted. [d] The ratio of β/α-epoxides was determined by ^1H NMR spectroscopy (500 or 300 MHz). [e] The value in parentheses was the ratio of β/α-epoxides obtained with *m*CPBA as the oxidant. [f] The epoxidation reaction was carried out at 0–1 °C. [g] Based on recovered starting material (82% conversion). [h] In another run, the ratio of β/α-epoxides was > 99:1 with acetone and water (3:1) as solvents. [i] Based on recovered starting material (61% conversion). [j] On a 10 mmol scale, the ratio of β/α-epoxides was > 99:1.

Conclusion

In summary, by proper steric tuning of either ketone catalysts or Δ^5-steroids, we have developed a general catalytic and environmentally friendly method for the highly β-selective epoxidation of Δ^5-unsaturated steroids. With this method in hand, a library of 5β,6β-epoxides and their derivatives[24] can be readily constructed and then screened for potential ligands that would bind to orphan nuclear receptors.[25] This is crucial to the elucidation of the biological functions of these receptors, as well as for drug discovery.

Experimental Section

General techniques: The ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as internal standard at ambient temperature on a Bruker Avance DPX 300 or 500 Fourier transform spectrometer. Infrared absorption spectra were recorded as a solution of the epoxide in CH_2Cl_2 on a Bio-Rad FTS 165 Fourier transform spectrophotometer. Mass spectra were recorded with a Finnigan MAT 95 mass spectrometer for both low- and high-resolution mass spectra.

General procedure for epoxidation of Δ^5-unsaturated steroids with the dioxiranes generated from ketones: Aqueous $Na_2 \cdot EDTA$ solution (6 mL, 4×10^{-4} M) was added to a solution of steroid (0.3 mmol) and an indicated amount of ketone in DMM (9 mL) and CH_3CN (3 mL) at room temperature. A mixture of Oxone (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) was added to this mixture in portions over the reaction period. The reaction mixture was poured into water and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. A crude residue was obtained by removal of the solvent under reduced pressure. The ratio of β/α-epoxides was then determined by ^1H NMR spectroscopic analysis of

this residue.[18] Pure products were obtained after flash column chromatography on silica gel.

Compounds 8a and 8b (as a mixture in a ratio of 1:9): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.48-3.37$ (m, 1/10 H; C3-H), 3.34 (s, 3 H; OCH_3), 3.30–3.20 (m, 9/10 H; C3-H), 3.11 (d, $J = 2.4$ Hz, 9/10 H; C6-H), 2.95 (d, $J = 4.4$ Hz, 1/10 H; C6-H), 1.18 (s, 27/10 H; C19-H_3), 1.17 (s, 3/10 H; C19-H_3), 1.08 (s, 9/10 H), 1.02 (s, 27/5 H), 0.87 (s, 27/10 H; C18-H_3), 0.85 (s, 3/10 H; C18-H_3); ^{13}C NMR of **8b** (75.5 MHz, $CDCl_3$): $\delta = 225.00$ (C17), 77.70, 63.15, 63.04, 55.71, 51.37, 48.52, 48.01, 45.15, 38.63, 37.82, 36.75, 35.54, 32.30, 31.66, 28.93, 27.27, 27.02, 25.95, 21.08, 17.13, 14.08; IR (CH_2Cl_2): $\tilde{\nu} = 1730$ cm^{-1} (C=O); EIMS (20 eV): *m/z* (%): 346 (100) $[M]^+$, 314 (15), 123 (31), 108 (22); HR-MS (EI, 20 eV) calcd for $C_{22}H_{34}O_3$ $[M]^+$: 346.2508; found 346.2508; elemental analysis calcd (%) for $C_{22}H_{34}O_3$: C 76.26, H 9.89; found: C 76.14, H 9.90.

Compounds 11a and 11b (as a mixture in a ratio of 1:8.5): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.73-4.64$ (m, 2 H; OCH_2O), 3.83–3.74 (m, 2/19 H; C3-H), 3.65–3.55 (m, 17/19 H; C3-H), 3.36 (s, 51/19 H; OCH_3), 3.35 (s, 9/19 H; OCH_3), 3.08 (d, $J = 2.3$ Hz, 17/19 H; C6-H), 2.91 (d, $J = 4.3$ Hz, 2/19 H; C6-H), 2.13 (s, 9/19 H; $COCH_3$), 2.11 (s, 51/19 H; $COCH_3$), 1.06 (s, 9/19 H; C19-H_3), 1.00 (s, 51/19 H; C19-H_3), 0.60 (s, 51/19 H; C18-H_3), 0.56 (s, 9/19 H; C18-H_3); ^{13}C NMR of **11b** (75.5 MHz, $CDCl_3$): $\delta = 209.35$ (C20), 94.67, 74.18, 63.67, 63.44, 62.82, 56.33, 55.26, 51.08, 43.88, 39.43, 38.84, 37.07, 35.16, 32.48, 31.45, 29.74, 28.13, 24.35, 22.77, 21.94, 17.07, 13.11; IR (CH_2Cl_2): $\tilde{\nu} = 1700$ cm^{-1} (C=O); EIMS (20 eV): *m/z* (%): 376 (100) $[M]^+$, 314 (90), 133 (36), 95 (33); HR-MS (EI, 20 eV) calcd for $C_{23}H_{36}O_4$ $[M]^+$: 376.2614; found 376.2617; elemental analysis calcd (%) for $C_{23}H_{36}O_4$: C 73.37, H 9.64; found C 73.11, H 9.68.

Epoxides **6a** and **6b**[26] (as a mixture in a ratio of 1:15.1), **7a** and **7b**[27] (as a mixture in a ratio of 1:10.4), **9a** and **9b**[28] (as a mixture in a ratio of 1:8.8), **10a** and **10b**[27] (as a mixture in a ratio of 1:11.6), **12a**,[29] **12b**,[30] **13b**,[30] **14b**,[31] **15b**,[32] **16b**,[33] **17b**,[18] **18b**,[34] **19b**,[18] **20b**,[35] and **21b**[36] have spectroscopic data which are identical with those reported in literature.

General procedure for epoxidation of Δ^5-unsaturated steroids with *m*CPBA: Sodium bicarbonate (0.4 mmol) and *m*CPBA (0.2 mmol) were added to a solution of substrate (0.1 mmol) in CH_2Cl_2 (3 mL). The resulting mixture was stirred at room temperature for 2 h and quenched with a solution of saturated aqueous $Na_2S_2O_3$. The reaction mixture was diluted with ethyl acetate and washed with a solution of saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and filtered through a pad of silica gel. The product analysis was performed as above.

Acknowledgements

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