A Highly β-Stereoselective Catalytic Epoxidation of Δ5-Unsaturated Steroids with a Novel Ruthenium(II) Complex under Aerobic Conditions

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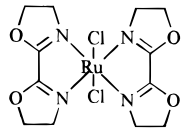
Catalytic β-stereoselective epoxidation of Δ5-unsaturated steroid derivatives has been effected by a novel ruthenium(II) bioxazoline complex under aerobic conditions. The reactions are regio- and stereoselective. The reaction conditions provide the corresponding 5β,6β-epoxides with high degree of stereoselectivity (88−96%) in very good yields, while oxidation of steroid derivatives with peracids leads to 5α,6α-epoxides as the major products. The overall conformation of the steroid nucleus is nearly planar in the cholesteryl ester, while it is bent at the junction between the rings A and B in the 5β,6β-epoxide. This change from pseudo-trans- to cis-stereochemistry of the A−B ring junction provides more room for the catalyst to approach from the β-face of the steroidal skeleton.

There has been considerable interest in recent years in the synthesis of 5β,6β-epoxides of Δ5-unsaturated steroids[1−3] particularly since this functionality is present in a number of biologically active steroids.[4] Moreover, epoxides are extremely useful for further elaboration since their facile ring opening allows the introduction of various substituents in a stereospecific manner. Due to the presence of the C(10)-angular methyl group on the β-face of the steroid skeleton, epoxidations of Δ5-unsaturated steroids with peracids[5] or dioxiranes[6] invariably yield the 5α,6α-epoxides as the major products. Synthesis of β-epoxides of Δ5-unsaturated steroids has been accomplished via the formation of halohydrins in two or three steps in moderate yields.[7] Earlier attempts to effect stereoselective β-epoxidation involved the introduction of a bulky 3α-halo substituent that would block the entry of the reagent from the α-face.[8] Miura[9] reported epoxidation of cholesteryl acetate by iodosobenzene in the presence of chromium, manganese, or iron tetramesitylporphyrin with a high degree of selectivity (70−90%) but in very poor yields (15−25%). Under very high dilution, β-epoxidation of steroids has been achieved with chromyl acetate in moderate yields, but this procedure is complicated by the formation of side products.[10] Reports are available on the successful β-epoxidation of steroids using ruthenium tetramesitylporphyrin catalyst. The major drawbacks of this methodology are that the synthesis of the catalyst is not always easy and the reactions generally required a few days for reasonable conversion for most of the steroids studied.[11] Reagent systems involving $KMnO_4$−$CuSO_4$[12a] and modification thereof[12b] have been shown to provide 5β,6β-epoxides in good yields and with good selectivity.

The homogeneous transition metal-catalyzed epoxidation of alkenes[13] and the use of oxoruthenium complexes as catalysts for oxidations of organic substrates[14] have been the subject of intense study in recent years. With regard to aerobic oxidation catalyzed by transition metal complexes, several reactions involving the combined use of molecular oxygen with reducing agents have been reviewed.[15] Since ruthenium porphyrin complexes are not that easily accessible, it was of interest to use the ruthenium(II) bioxazoline complex **1**, which has a square



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planar structure around the ruthenium core analogous to ruthenium porphyrin systems.[11] Recently we have shown that this ruthenium(II) complex **1** is an efficient catalyst for epoxidation of alkenes with a high degree of selectivity.[16] Therefore we decided to explore the efficiency of this catalyst for stereoselective epoxidation of Δ5-unsaturated steroids and our successful results of this investigation are presented in this paper.

(1) (a) Salvador, J. A. R.; Sáemelo, M. L.; Campos Neves, A. S. *Tetrahedron. Lett.* **1996**, *37*, 687. (b) Hanson, J. R.; Hitchcock, P. B.; Liman, M. D.; Nagaratnam, S.; Manickavasagar, R. *J. Chem. Res., Synop.* **1995**, 220.

(2) Galagovsky, L. R.; Gros, E. G. *J. Chem. Res., Synop.* **1993**, 137.

(3) Marchon, J. C.; Ramasseul, R. *J. Chem. Res., Synop.* **1992**, 104.

(4) (a) Glotter, E.; Kirson, I.; Lavie, D.; Abraham, A. *Bio-organic chemistry*; Van Tamelen, E. E., Ed.; Academic Press: New York, 1979; Vol. 2, p 57. (b) Tschesche, R.; Schwang, H. H.; Legler, G. *Tetrahedron* **1966**, 22, 1121.

(5) Kirk, D. N.; Hartshon, M. P. *Steroid Reaction Mechanism*; Elsevier: London, 1968; Chapter 3, p 70.

(6) Bovicelli, P.; Lupattelli, P.; Mincione, E. *J. Org. Chem.* **1992**, *57*, 2182.

(7) Matthews, G. J.; Hassner, A. *The Organic Reactions in Steroid Chemistry;* Fried, J., Edwards, J. A., Eds.; Van Nostrand: New York, 1972; Vol. 2, p 2.

(8) Shiota, M.; Ogihara, T.; Watanabe, Y. *Bull. Chem. Soc. Jpn.* **1964**, *34*, 40. (b) Hanson, J. R.; Truneh, A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2001.

(9) Muto, T.; Umehara, J.: Masumori, H.; Miura, T.; Kimura, M. *Chem. Pharm. Bull.* **1985**, *33*, 4749.

(10) Galagovsky, L. R.; Eurton, G.; Gros, E. G. Z. *Naturforsch.* **1989**, *14b*, 806.

(11) Marchon, J. C.; Ramasseul, R. *Synthesis* **1989**, 389.

(12) (a) Syamala, M. S.; Das, J.; Baskaran, S.; Chandrasekaran, S. *J. Org. Chem.* **1992**, *57*, 1928. (b) Salvador, J. A. R.; Sae Melo, M. L.; Campor Neves, A. S. *Tetrahedron Lett.* **1996**, *37*, 687.

(13) Jorgensen, K. A. *Chem. Rev.* **1989**, *89*, 431.

(14) Griffith, W. P. *Chem. Soc. Rev.* **1992**, *21*, 179.

(15) Mukaiyama, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 17.

(16) Kesavan, V.; Chandrasekaran, S. *J. Chem. Soc., Perkin Trans 1* **1997**, 3115.

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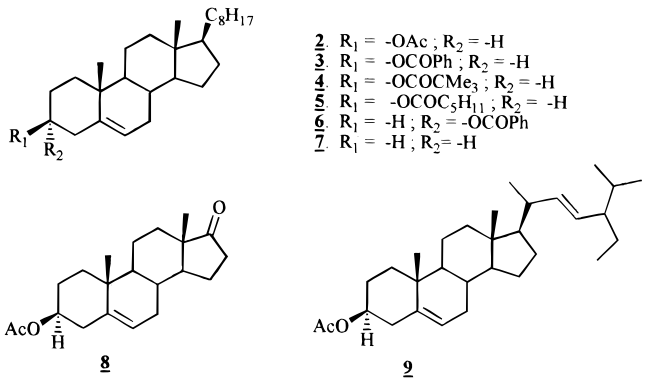
Table 1. Epoxidation of Δ^5-unsaturated Steroid Derivatives with 1

entry	substrate	reactn time (h)	β:α	yield (%)
1	**2**	4	88:12	90
2	**3**	6	88:12	85
3	**4**	8	90:10	92
4	**5**	8	90:10	95
5	**6**	8	95:5	91
6	**7**	6	94:6	95
7	**8**	5	96:4	96
8	**9**	6	92:8	88

Chart 1



4,4′,5,5′-tetrahydro-2,2′-bioxazole was treated with *trans*-tetrakis(acetonitrile)dichlororuthenium(II)[17] to give rise to $RuCl_2(biox)_2$ (**1**).[18] A number of unsaturated steroids were subjected to homogeneous oxidation in the presence of 2.5 mol % of the catalyst **1**, 1.5 equiv of isobutyraldehyde, and 1.3 equiv of sodium hydrogen carbonate under aerobic conditions at room temperature (25 °C, 4−8 h). The results are summarized in Table 1.

The nature of the 3β-ester has only a marginal effect on the rate of the reaction but has no effect on the stereoselectivity of the reaction. Thus cholesteryl acetate (**2**), cholesteryl benzoate (**3**), cholesteryl pivalate (**4**) and cholesteryl caproate (**5**) formed the corresponding 5β,6β-epoxides in very good yields (see Chart 1). The stereochemistry of the substituent at C-3 does not have any profound effect on the stereoselectivity of epoxidation. Thus, 3α-cholesteryl benzoate (**6**) also gave 5β,6β-epoxide with a slightly increased selectivity. Even when there is no substituent at C-3, the stereoselectivity of epoxidation is very high. This has been demonstrated in the reaction of 5-cholestene (**7**), where the β-epoxide is the only product that can be isolated in high yield. The present methodology of catalytic epoxidation with ruthenium catalyst **1** is compatible with functional groups such as carbonyl group in the steroid molecule. Epoxidation of keto steroid **8** under similar conditions afforded the corresponding β-epoxide in 96% yield (96% selectivity). Interestingly this methodology is also regioselective in that the oxidation of stigmasteryl acetate (**9**) led to the formation of the corresponding 5β,6β-epoxide in high yield where the trisubstituted double bond has reacted in preference to the disubstituted double bond in the side chain.

Steric hindrance of the β-face by the axial methyl groups at C-10 and C-13 is generally advanced as an explanation for β-stereoselective epoxidation of cholesterol.[7] Tavares *et al.*[19] in their study of oxidation with ruthenium porphyrin systems have invoked specific steric effects to explain β-stereoselectivity. They postulate interactions between the substrate and the catalyst in which the metal−oxo bond approaches the olefin in the perpendicular geometry required for reaction. (Figure 1). It has also been pointed out that the overall conformation of the steroid nucleus is nearly planar in the cholesteryl ester, while it is bent at the junction between the rings A and B in the 5β,6β-epoxide. This change from pseudo-trans- to cis-stereochemistry of the A−B ring junction bends the steroid and opens up more room for the approach of the ruthenium complex from the β-face. We believe that this explanation holds good in the case of epoxidation with ruthenium bioxazoline catalyst **1** resulting in high β-stereoselectivity.

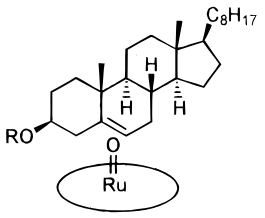


Figure 1.

In summary, we have been able to demonstrate that the usually difficult β-epoxidation of Δ^5-unsaturated steroids can be conveniently carried out in high yields and in a short period of time with easily accessible ruthenium bioxazoline **1** catalyst under aerobic conditions.

Experimental Section

All the reactions were carried out under oxygen atmosphere. Dicholoromethane was kept over phosphorus pentoxide, distilled, and stored over molecular sieves (4 Å). TLC was performed on 0.25 mm precoated silica plates (60F-254); the plates were initially examined under UV light, and spots were then visualized with iodine and 10% solution of phosphomolybdic acid in ethanol. Cholesteryl pivalate[11] and epicholesterol[20] were prepared according to the literature procedure. The melting points reported are uncorrected. IR spectral frequencies are reported in wavenumbers (cm^{-1}). ^1H NMR spectra were run using $SiMe_4$ as internal standard; spectra were measured at 90 and 300 MHz.

Synthesis of Complex 1. *trans*-Tetrakis(acetonitrile)-dichlororuthenium(II)[17a] (0.336 g, 1 mmol) was refluxed with 4,4′,5,5′-tetrahydro-2,2′-bioxazole[17b] (0.308 g, 2.2 mmol) for 6 h in ethanol (10 mL). The solvent was removed under reduced pressure to give a red colored solid. The solid was recrystallized from EtOH/Et_2O (1:3) and stored in a desiccator: mp 280 °C; yield 0.380 g, 82%; IR (thin film) 2950, 1610 cm^{-1}; ^1H NMR (90 MHz, D_2O) δ 3.4 (m, 8H), 3.8 (m, 8H); ^{13}C NMR (22.5 MHz, D_2O) δ 53.61, 68.87, 155.26. Anal. Calcd for $C_{12}H_{16}Cl_2N_4O_4Ru$: C, 31.86; H, 3.56; N, 12.38. Found: C, 31.81; H, 3.48; N, 12.40.

Typical Experimental Procedure for Epoxidation: Epoxidation of Cholesteryl Pivalate (4). Ruthenium complex **1** (0.011 g, 2.5 mol %) was added to cholesteryl pivalate[11] (**4**) (0.470 g, 1 mmol) dissolved in dichloromethane (4 mL). To this homogeneous solution, $NaHCO_3$ (0.126 g, 1.5 equiv) and isobutyraldehyde (0.108 g, 0.136 mL, 1.5 equiv) were added successively. The mixture was stirred under an

(17) (a) Johnson, B. F. G.; Lewis, J.; Ryder, I. E. *J. Chem. Soc., Dalton. Trans.* **1977**, 719. (b) Hendry, W. *J. Am. Chem. Soc.* **1938**, *60*, 2152.

(18) Onishi, M.; Isagawa, K. *Inorg. Chim. Acta* **1991**, *179*, 155.

(19) Tavares, M.; Ramasseul, R.; Marchon, J. C.; Bachet, B.; Brassy, C.; Mornon, J. P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1321.

(20) Houminer, Y. *J. Org. Chem.* **1975**, *40*, 1361.

atmosphere of oxygen at 25 °C, and the reaction was monitored by TLC. Once the reaction was over (8 h), the reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite and silica gel. Removal of solvent yielded the crude product which was purified by flash chromatography over silica gel. (elution with 3:97 EtOAc/petroleum ether). Total yield: 0.448 g, 92%.

3*β*-(Pivaloyloxy)-5*β*,6*β*-epoxy-5*β*-cholestane: 0.403 g; mp 156−157 °C (lit[11] mp 157−158 °C); IR (KBr) 1724 cm^{-1}; ^1H NMR δ 0.64 (s, 3H), 0.87 (d, 6H), 0.89 (d, 3H), 1.01 (s, 3H), 1.26 (s, 9H), 3.08 (d, 1H, J = 2.1 Hz), 4.50 (m, 1H).

3*β*-(Pivaloyloxy)-5α,6α-epoxy-5α-cholestane: 0.044 g; mp 170−172 °C; IR (KBr) 1726 cm^{-1}; ^1H NMR δ 0.64 (s, 3H), 0.87 (d, 6H), 0.89 (d, 3H), 1.01 (s, 3H), 1.26 (s, 9H), 2.93 (d, 1H, J = 3.8 Hz), 4.60 (m, 1H); ^{13}C NMR: δ 11.8 (C-18), 17.1 (C-19), 51.0 (C-9), 56.8 (C-14, 17), 62.5 (C-5), 63.6 (C-6), 75.7 (C-3), 177.9 (CO_2); MS m/z 486 (M^+). Anal. Calcd for $C_{32}H_{54}O_3$: m/z C, 78.95; H, 11.18. Found: C, 79.04; H, 11.51.

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Supporting Information Available: ^1H NMR data for the 5α,6α- and 5*β*,6*β*-epoxides of substartes **2**, **3**, and **5**−**9** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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