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β-Selective Epoxidation of Cholesterol Derivatives with Molecular Oxygen and Aldehyde Catalyzed by Manganese(II) Complex

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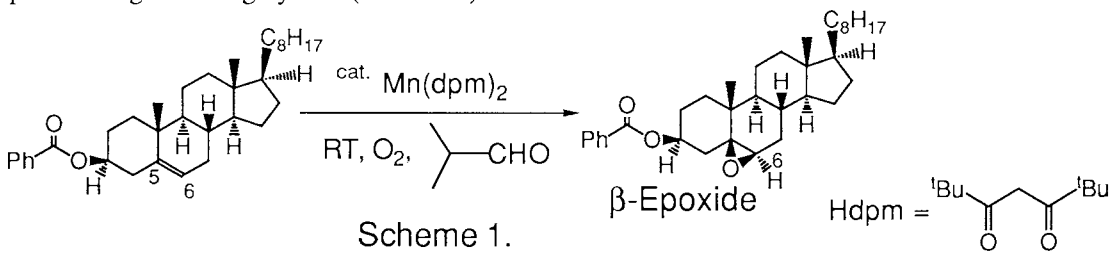
In the presence of a catalytic amount of bis(dipivaloylmethanato)-manganese(II) (= $Mn(dpm)_2$), various cholesterol derivatives are smoothly converted into the corresponding β-epoxides in good to high yields with combined use of molecular oxygen and isobutyraldehyde. These stereoselectivities are the reversal of the cases using peracid such as *m*CPBA.

In our previous communications, efficient methods for the epoxidation of olefins catalyzed by oxovanadium(IV) complexes,[1] nickel(II) complexes,[2-5] or iron(III) complexes[6] with combined use of molecular oxygen and primary alcohols or aldehydes have been reported. It was also shown that propene was monooxygenated into propylene oxide with molecular oxygen in the coexistence of aldehyde, such as *trans*-crotonaldehyde, and a peracid generated from aldehyde by autoxidation manner was proposed as the reactive intermediate in their systems.[7] *cis*-Olefin was converted into a mixture of *cis*- and *trans*-epoxides according to the present procedure, while *cis*-epoxide was specifically obtained when *m*CPBA (*m*-chloroperbenzoic acid) was employed as an oxidant.[8] Therefore, it is suggested that the active oxidant in the present epoxidation[3-5] is not a simple carboxylic peracid directly generated from aldehyde in autoxidation manner.

In this communication, we would like to report that the epoxidation of various cholesterol derivatives with combined use of molecular oxygen and isobutyraldehyde by using a catalytic amount of bis(dipivaloylmethanato)manganese(II) (= $Mn(dpm)_2$) stereoselectively affords the corresponding 5,6 β-epoxide as a major product in good to high yields (Scheme 1).



Scheme 1.

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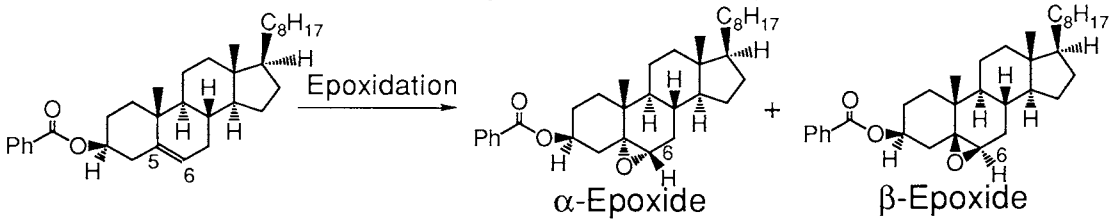
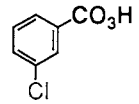
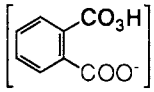
In the first place, stereochemistries of the epoxidation of 5,6-double bond in cholesteryl benzoate were examined with molecular oxygen and isobutyraldehyde using several metal complexes coordinated with 1,3-diketones as catalysts (see Table 1). It was found that epoxidation catalyzed by metal complexes, such as nickel(II), iron(III), palladium(II), ruthenium(III), cobalt(II), or manganese(II) complexes coordinated with 1,3-diketones (acetylacetone), afforded the *hindered* 5,6 β-epoxide as a major isomer (Entries 1-6). In the case of employing $Mn(dpm)_2$ as a catalyst, stereoselectivity of 5,6 β-epoxide was improved up to 82% (Entry 7). On the contrary, it was reported that by using peracids, such as *m*CPBA or MMPP (magnesium monoperphthalate hexahydrate),[10] cholesteryl benzoate was converted into the corresponding mixture of 5,6 α- and 5,6 β-epoxides in the ratio of 71 to 29 (*m*CPBA, Entry 8),[12] and 85 to 15 (MMPP, Entry 9),[10] respectively. It is interesting to point out that the *less hindered* 5,6 α-epoxide was obtained as a major product when a peracid was used as an oxidant. These remarkable reverse stereoselectivities in the epoxidation of cholesteryl bezoate obviously indicate that the active oxidant of the present metal complex catalyzed epoxidation is not a simple carboxylic peracid generated from an aldehyde with autoxidation manner, but an oxygenated metal complex is tentatively considered as the reactive intermediate of the present epoxidation. The above consideration is also supported by several observations described in references.[8, 9, 11]

Table 1. Stereoselective Epoxidation Using Varoius Metal Complexes



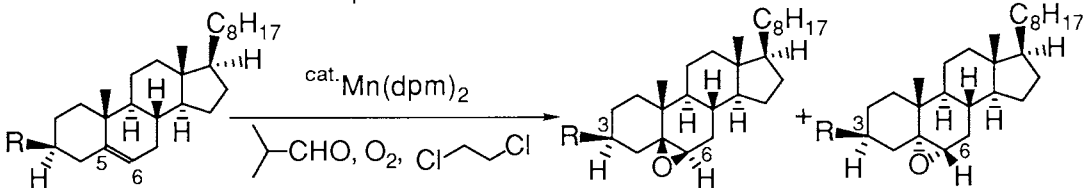
Entry	Epoxidation reagent	α-Epoxide : β-Epoxide[c]
1[a]	cat. $Ni(dmp)_2$, O_2, ⟩—CHO	31 : 69
2[a]	cat. $Fe(acac)_3$	33 : 67
3[a]	cat. $Pd(acac)_2$	30 : 70
4[a]	cat. $Ru(acac)_3$	24 : 76
5[a]	cat. $Co(acac)_2$	23 : 77
6[a]	cat. $Mn(acac)_2$	20 : **80**
7[a]	cat. $Mn(dpm)_2$	18 : **82**
8[b]	 (*m*CPBA)	**71** : 29
9[b]	 (MMPP)	**85** : 15

a) Reaction Conditions: Cholesteryl benzoate 245 mg (0.5 mmol), isobutyraldehyde (2.0 mmol), catalyst (0.0047 mmol, 0.94 mol%) in 1,2-dichloroethane (5.0 ml), RT, 1.0 atm O_2, 2.0 h. b) Ref. 10.
c) Determined by HPLC analysis.

Manganese(II) complexes catalyzed epoxidation with combined use of molecular oxygen and an aldehyde, such as isobutyraldehyde, is particularly effective and convenient in the transformation of various cholesterol derivatives into the corresponding 5,6 β-epoxides (see Table 2). Stereochemistries of the products

were identified by chemical shift of C-6 proton in ^{1}H NMR,[12, 13] and the ratios of 5,6 α- and 5,6 β-epoxides were obtained by integrations of the C-6 protons ($H_{6\alpha}$ and $H_{6\beta}$) in ^{1}H NMR or HPLC analysis. The cholesteryl esters, such as benzoate and acetate, were rapidly converted into the corresponding 5,6 β-epoxides in high yields (93% and 83%, respectively) and with good β-stereoselectivities (82% and 81%, Entires 1 and 2). Even the cholesteryl aliphatic-esters with longer alkyl chains, such as *n*-caproate and *n*-caprate, were also oxygenated smoothly (complete in 2-4 h) into the 5,6 β-epoxide in high yields (85% and 89%) and with good β-stereoselectivities (82% and 81%, Entries 3 and 4). Ethyl carbonate and formate of cholesterol were also monooxygenated into the β-epoxides as a major isomer (Entries 5 and 6). Cholesterol, without any protection on hydroxyl group at the 3 position, was converted into the β-epoxide in high yield (Entry 7). It is interesting to note that, in the presence of $Mn(dpm)_2$ catalyst, the epoxidation of the *hindered* β-side of steroids proceeded predominantly, which provides an efficient and convenient method for the preparation of 5,6 β-epoxides of various cholesterol derivatives.

Table 2. Stereoselective Epoxidation of Various Steroids[a)]



Entry	R	Yield/%[b)]	Ratio of β-epoxide:α-epoxide	
			NMR[c)]	HPLC[d)]
1	PhCOO	93	82 : 18	82 : 18
2	CH_3COO	83	81 : 19	
3	$CH_3(CH_2)_4COO$	85	82 : 18	
4	$CH_3(CH_2)_8COO$	89	81 : 19	
5	EtOCOO	79	76 : 24	
6	HCOO	77	77 : 23	
7	HO	85	82 : 18	

a) Reaction conditions; Cholesteryl derivative (0.5 mmol), isobutyraldehyde (2.0 mmol), $Mn(dpm)_2$ (3.0 mg, 0.0047 mmol, 0.94 mol%) in 1,2-dichloroethane (5.0 ml), RT, 1.0 atm O_2, 2.0 h. b) Isolated yields. c) Determined by ^{1}H NMR($H_{6\alpha}$: $H_{6\beta}$, see Ref. 13). d) Determined by HPLC analysis (Hexane : AcOEt).

A typical procedure is described for the epoxidation of cholesteryl benzoate (Entry 1 in Table 2): A mixture of cholesteryl benzoate (245 mg, 0.5 mmol), isobutyraldehyde (2.0 mmol), and $Mn(dpm)_2$ (3.0 mg, 0.0047 mmol, 0.94 mol%) in 1,2-dichloroethane (5.0 ml) was stirred at room temperature under an atmospheric pressure of oxygen for 2.0 h. After the reaction, the mixture was diluted with ethyl acetate and washed with aqueous $NaHCO_3$(10%) and brine. Purification by TLC (Hexane : AcOEt) afforded the corresponding 5,6-epoxide as white crystals (253 mg, 93% yield).[13]

It is noted that, in the presence of bis(dipivaloylmethanato)manganese(II) ($Mn(dpm)_2$), various cholesterol derivatives were smoothly monooxygenated into the corresponding 5,6 β-epoxide in good yields and with good selectivities by combined use of molecular oxygen and isobutyraldehyde at room temperature .

References

1) T. Takai, T. Yamada, and T. Mukaiyama, *Chem. Lett.*, **1990**, 1657; S. Inoki, T. Takai, T. Yamada, and T. Mukaiyama, *ibid.*, **1991**, 941.

2) T. Mukaiyama, T. Takai, T. Yamada, and O. Rhode, *Chem. Lett.*, **1990**, 1661.

3) T. Yamada, T. Takai, O. Rhode, and T. Mukaiyama, *Chem. Lett.*, **1991**, 1.

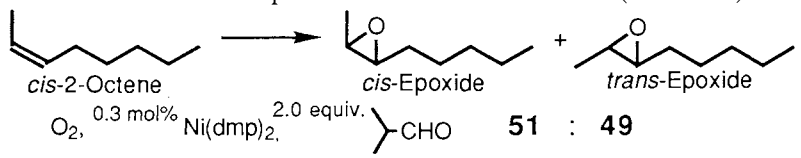
4) T. Yamada, T. Takai, O. Rhode, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **64**, 2109 (1991).

5) T. Takai, T. Yamada, O. Rhode, and T. Mukaiyama, *Chem. Lett.*, **1991**, 281.

6) T. Takai, E. Hata, T. Yamada, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **64**, 2513 (1991).

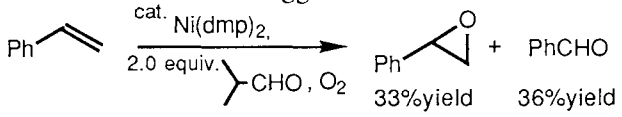
7) Y. Maeda, M. Ai, and S. Suzuki, *Kogyo Kagaku Zasshi*, **73**, 99 (1970).

8) In the presence of a catalytic amount of $Ni(dmp)_2$ (bis[1,3-di(*p*-methoxyphenyl)-1,3-propanedionato]nickel(II)), *cis*-2-octene was oxidized with molecular oxygen and isobutyraldehyde into the corresponding mixture of *cis*- and *trans*-epoxides in the ratio of 51 to 49 (Scheme 2).[4)]



Scheme 2.

9) According to the present epoxidation method, styrene was converted into styrene oxide and benzaldehyde in 33% and 36% yield, respectively (Scheme 3), while styrene oxide is obtained selectively by using a peracid, such as *m*CPBA, as an oxidant. This result also suggests that the reactive intermediate is not simple peracid.



Scheme 3.

10) P. Brougham, M. S. Cooper, D. A. Cummerson, H. Heaney, and N. Thompson, *Synthesis*, **1987**, 1015.

11) Similar β-selection in the epoxidation of cholesterol derivatives was reported to give 5,6 β-epoxysteroid derivative in 80% selectivity by using molybdenum(V) chloride as a catalyst and *t*-butylhydroperoxide as an oxidant. G. A. Tolstikov, U. M. Dzhemilev, and V. P. Yur'ev, *J. Org. Chem. U. S. S. R.*, **8**, 2253 (1972). Recently it was also reported that aerobic epoxidation of cholesterol derivatives catalyzed by ruthenium(II) tetramesitylporphyrin gave β-epoxides selectively, see Ref. 12.

12) J. -C. Marchon and R. Ramasseul, *Synthesis*, **1989**, 389.

13) Chemical shifts in ^1H NMR of 5,6-epoxide (**1**α,β-**7**α,β in Table 2) were assigned as follows: **1**α,β; δ=2.90(d, J=4.3 Hz, $H_{6\beta}$(α-epoxide)), 3.10(d, J=2.1 Hz, $H_{6\alpha}$(β-epoxide)), 5.00(m, $H_3(\beta)$), 5.20(m, $H_3(\alpha)$): **2**α,β; δ=2.90(d, J=4.3 Hz, $H_{6\beta}$), 3.10(d, J=2.1 Hz, $H_{6\alpha}$), 4.80(m, $H_3(\beta)$), 4.95(m, $H_3(\alpha)$): **3**α,β; δ=2.90(d, J=4.3 Hz, $H_{6\beta}$), 3.10(d, J=2.1 Hz, $H_{6\alpha}$), 4.80(m, $H_3(\beta)$), 4.95(m, $H_3(\alpha)$): **4**α,β; δ=2.90(d, J=4.3 Hz, $H_{6\beta}$), 3.10(d, J=2.1 Hz, $H_{6\alpha}$), 4.80(m, $H_3(\beta)$), 4.95(m, $H_3(\alpha)$): **5**α,β; δ=2.90(d, J=4.3 Hz, $H_{6\beta}$), 3.10(d, J=2.1 Hz, $H_{6\alpha}$), 4.60(m, $H_3(\beta)$), 4.85(m, $H_3(\alpha)$): **6**α,β; δ=2.90(d, J=4.3 Hz, $H_{6\beta}$), 3.10(d, J=2.1 Hz, $H_{6\alpha}$), 4.90(m, $H_3(\beta)$), 5.10(m, $H_3(\alpha)$): **7**α,β; δ=2.90(d, J=4.3 Hz, $H_{6\beta}$), 3.10(d, J=2.1 Hz, $H_{6\alpha}$), 3.70(m, $H_3(\beta)$), 3.90(m, $H_3(\alpha)$).

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