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Aerobic Catalytic Epoxidation of Unfunctionalized Olefins Using a New (Salen)manganese (III) Complex Bearing a Sesquiterpene Salicylaldehyde Derivative

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Abstract: A chiral (salen) manganese (III) complex **1** bearing a sesquiterpene salicylaldehyde and (*R,R*)-1,2-cyclohexanediamine moieties has been prepared. This complex catalyses the epoxidation of unfunctionalized olefins with iodosylbenzene and molecular oxygen/pivalaldehyde as terminal oxidants. In all cases the chemical yield was high although the enantiomeric excess obtained were low. Copyright © 1996 Elsevier Science Ltd

Epoxides are versatile and important intermediates in organic synthesis because they easily undergo stereospecific ring-opening to form bifunctional compounds. The preparation of homochiral epoxides is of special interest for the synthesis of biologically active compounds.[1] The Sharpless epoxidation of allylic alcohols is the most practicable method for the preparation of homochiral epoxide alcohols.[2] However the enantioselective catalytic oxidations of unfunctionalized alkenes remained a long challenge yet. Designer catalysts based on biomimetic antecedents is an area of great current interest in synthetic organic chemistry, being metalloporphyrins[3] and chiral (salen)manganese(III) complexes[4] the most promising and practical catalysts.

Several kinds of these latter complexes having chiral salicylaldehyde and ethylenediamine moieties were recently found to be efficient catalysts for epoxidation of olefins by Jacobsen[5] and Katsuki[6] especially. With these (salen) manganese complexes as catalysts, moderate to high enantioselectivities has been realised in the epoxidation of several kinds of olefins depending of the substitution degree of the double bond. Several terminal oxidants have been used (iodosylbenzene,[7] sodium hypochlorite,[8] hydrogen peroxide,[9] periodates,[10]) including the combined use of molecular oxygen[11] and an aliphatic aldehyde. The selective oxidation of organic substrates with molecular oxygen is a challenging goal in synthetic organic chemistry.

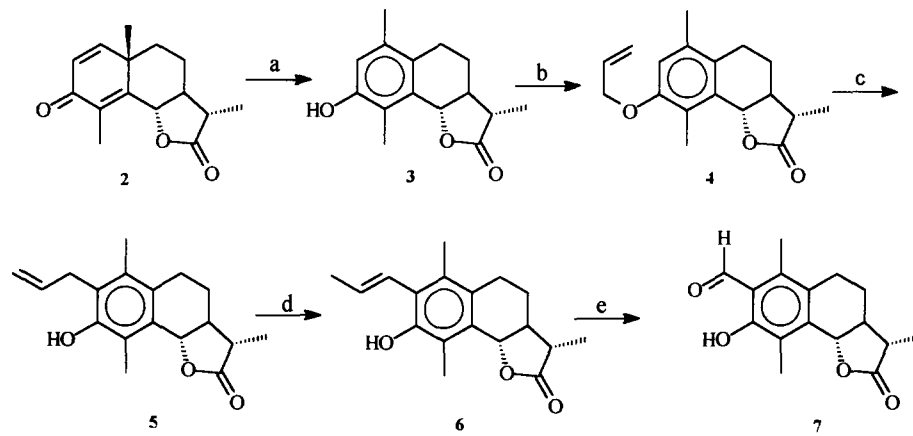
Both challenges, the enantioselective epoxidation of unfunctionalized olefins and the development of new catalytic processes using molecular oxygen as oxidant has led us to explore the utility of a new (salen)manganese (III) complex **1** bearing a chiral sesquiterpene salicylaldehyde moiety as catalyst in the epoxidation of olefins.

Santonin **2**, a sesquiterpene lactone that has been used as starting material in the synthesis of several natural sesquiterpenes,[12,13] fits up several conditions that had it also an interesting starting material for the synthesis of chiral salicylaldehydes: a) it is commercially available, b) it has several chiral carbon, c) it is known the easy aromatization of its A ring and therefore the synthesis of a chiral salicylaldehyde derivative could be carried out easily and d) the presence of two additional rings in the sesquiterpene salicylaldehyde derivative could favour the enantioselectivity of the reaction since the known alteration of the enantioselectivity caused by the addition of donor ligands has been attributed to conformational changes of the complex.[14]

RESULTS AND DISCUSSION

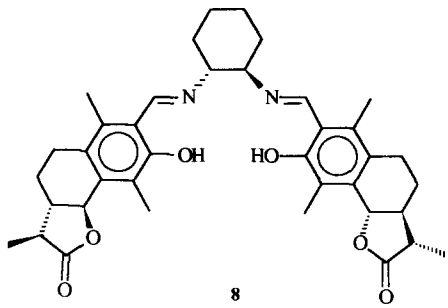
Preparation of the (Salen)manganese (III) Complex

The first step in the preparation of the sesquiterpene salicylaldehyde derivative involved an acid treatment [15] of santonin (**2**), which converted the dienone system in a phenolic aromatic ring giving **3**. The *ortho* formylation of this compound was carried out by indirect form through a Claisen rearrangement of the allyl ether **4**, which was prepared by reaction of **3** with allyl bromide in acetone in basic conditions.[16] Heating of **4** at 200 °C in tetraline arised a Claisen rearrangement to produce the *ortho* allyl phenol **5**, which by a $RhCl_3$ mediated isomerization[17] of the double bond to conjugated position to aromatic ring gave **6.** Finally a double bond oxidation with $OsO_4/NaIO_4$ gave the salicylaldehyde derivative **7**.[18]



a: Formic acid, reflux; b: CH_2=$CHCH_2Br$, K_2CO_3 acetone, reflux;
c: Tetraline, 200°C d: $RhCl_3$ ethanol, room temperature; e: $OsO_4/NaIO_4$

Treatment of **7** with (*R,R*)-1,2-cyclohexanediamine in methanol at reflux gave by crystallisation, after to reduce the volume to the half, several crops of the salen derivative **8**. This compound was dissolved in hot methanol and treated with $Mn(OAc)_3$, after a modification of a previously reported procedure,[19] and by interchange of the anion with $NaClO_4$ gave by crystallisation greenish manganese (III) complex **1**.



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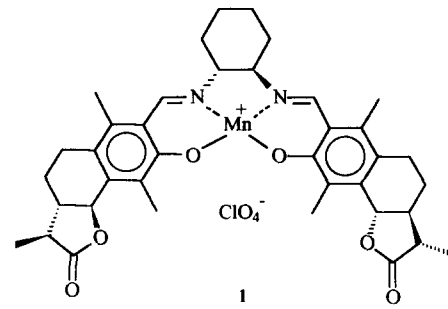

1

Catalytic Epoxidation of Unfunctionalized Olefins

The epoxidations catalysed by **1** were first examined by taking the epoxidation of dihydronaphthalene as a model reaction. Several of the usually employed terminal oxidants were screened: iodosylbenzene, sodium and tetra-*n*-butylammonium periodate in acetonitrile and dichloromethane, sodium hypochlorite in dichloromethane and molecular oxygen/pivalaldehyde in fluorobenzene. In all cases the reaction was carried out in presence of *N*-methylimidazole as a donor ligand, because it is known that the addition of this kind of ligand improves the chemical yields of epoxides and influences on the enantioselectivity.[14] The results are summarized in Table 1. The chemical yields were good either with iodosylbenzene (entry 1), sodium periodate/tetra-*n*-butylammonium bromide (entry 3) and oxygen/pivalaldehyde (entry 6). However the enantioselectivity observed was low (25% e.e. in the case of iodosylbenzene and between 5-10% e.e. in the other cases.)

Table 1. Epoxidation of 1,2-Dihydronaphthalene Catalysed by (Salen)Mn(III) Complex 1.[a]

Entry	Oxidant	Mmol Oxi..	Solvent	Time (h)	Yield[b,c](%)
1	PhIO	2	Acetonitrile[f]	2	95
2	$NaIO_4$[d]	5	Acetonitrile	8	68
3	$NaIO_4/Bu_4NBr$[d]	6	Dichloromethane	7	75
4	Bu_4NIO_4[d]	6	Acetonitrile[g]	24	57
5	NaClO[e]	5	Acetonitrile	24	46
6	O_2/pivalaldehyde	2	Fluorobenzene	4	90

a) All reactions were carried out in the presence of *N*-methylimidazole as a donor ligand.

b) Yields refer to isolated and chromatographically pure compounds (on neutral alumine). The epoxide was identified by its spectroscopic properties.

c) 25% e.e. in entry 1 and between 5-10% in the other entries. The determination of % e.e. was carried out by ^1H NMR analysis in $CDCl_3$ using $Eu(hfc)_3$ as a chiral shift reagent.

d) Pietiäinen's procedure, ref. 10

e) The reaction was carried out with aqueous sodium hypochlorite (0.67 M),after Jacobsen's procedure, ref.8

f) Exchange of solvent from acetonitrile to dichloromethane gave similar results, but the reaction was slower (3 h).

g) Exchange of solvent from acetonitrile to dichloromethane gave identical results.

In view of this results we decided to complete the study of this epoxidation with several olefins using as terminal oxidants iodosylbenzene and oxygen/pivalaldehyde. The first because the e.e. obtained was bigger and the latter because to the importance of the utilization of molecular oxygen in synthetic organic chemistry. As shown in Table 2, with iodosylbenzene as terminal oxidant, complex **1** catalysed the epoxidation of di- and tri-substituted alquenes giving the corresponding epoxides with good yield. However the epoxidation of *cis*-stilbene (entry 3) gave mixtures of *cis*- and *trans*-epoxides, suggesting the intervention of radical species in the course of the reaction. Unfortunately the enantioselectivity observed was low, between 5-10% e.e. in all cases (1,2-dihydronaphthalene 25% e.e.).

Table 2. Epoxidation of Unfunctionalizated Olefins Catalysed by (Salen)Mn(III) Complex 1 Using Iodosylbenzene as terminal Oxidant.[a]

Entry	Olefin	Time (h)	Yield[b,c](%)
1	1,2-Dihydronaphthalene	2	95
2	Indene	3	82
3	*cis*-stilbene	1	85[d]
4	*trans*-stilbene	5	85
5	*trans*-β-methylstyrene	8	80
6	triphenylethylene	24	94

a) All reactions were carried out in acetonitrile in the presence of *N*-methylimidazole as a donor ligand.

b) Yields refer to isolated and chromatographically pure compounds. Column chromatography was carried out on neutral alumine in entries 1,2 and 5. The epoxides were identified by their spectroscopic properties.

c) 25% e.e. in entry 1 and between 5-10% in other entries. The determination of % e.e. was carried out by ^{1}H NMR analysis in $CDCl_3$ using $Eu(hfc)_3$ as a chiral shift reagent.

d) The product is a mixture of *cis*- and *trans*-epoxides in a ratio of 1:1

When the reaction was carried out using molecular oxygen /pivalaldehyde as terminal oxidant, the complex **1** catalysed the epoxidation of di- and tri-substituted alquenes giving the corresponding epoxides with very good yields (Table 3). However changes in the reaction times were observed, especially in the epoxidation of *cis*-stilbene and triphenylethylene. The first reacted in 1 hr using iodosylbenzene whilst required 24 hr using molecular oxygen/pivalaldehyde. The second reacted in 24 hr using iodosylbenzene and in 4 hr only with oxygen. These dramatic changes in the reaction times can be attributed to the different mechanism involved in the epoxidation: Through a Mn(V)=O species in the case of iodosylbenzene, as postulated in other cases[7] and through an acylperoxo-Mn complex[20] in the case of molecular oxygen/pivalaldehyde.

In conclusion, the complex **1** catalyses the epoxidation of unfunctionalized di- and tri-substituted olefins with iodosylbenzene and molecular oxygen/pivalaldehyde as terminal oxidants. In this latter case the reaction elapsed very cleanly and with very good yields, although the e.e. observed were low.

Table 3. Epoxidation of Unfunctionalizated Olefins Catalysed by (Salen)Mn(III) Complex 1 Using Molecular Oxygen and Pivalaldehyde as Terminal Oxidant.[a]

Entry	Olefin	Time (h)	Yield[b,c](%)
1	1,2-Dihydronaphthalene	5	90
2	Indene	3	91
3	*cis*-stilbene	24	89[d]
4	*trans*-stilbene	5	78
5	*trans*-β-methylstyrene	4	91
6	triphenylethylene	4	99

a) All reactions were carried out in fluorobenzene in the presence of *N*-methylimidazole as a donor ligand.

b) Yields refer to isolated and chromatographically pure compounds. Column chromatography was carried out on neutral alumine in entries 1,2 and 5. The epoxides were identified by their spectroscopic properties.

c) 5-10% e.e.in all entries. The determination of % e.e. was carried out by ^1H NMR analysis in $CDCl_3$ using $Eu(hfc)_3$ as a chiral shift reagent.

d) The product is a mixture of *cis*- and *trans*-epoxides in a ratio 1:2

EXPERIMENTAL

Melting points were determined in capillary tubes with a Büchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 281 spectrometer, as liquid films for oils and in KBr disk for solids. NMR spectra were run on a Brucker AC-200 instrument (200.1 MHz for ^1H and 50.3 MHz for ^{13}C) or a Varian Unity 400 (399.95 MHz for ^1H and 100.58 MHz for ^{13}C) in $CDCl_3$ solutions. The carbon type (methyl, methylene, methine, or quaternary) was determined by DEPT experiments. Mass spectra were recorded at 70 eV. Optical rotations were determined on a Polartronic D (Schmidt and Haensch) polarimeter as solutions in $CHCl_3$. Flash chromatography was carried out on SDS Chromagel 60 silica gel. Enantiomeric excess for the resulting epoxides were determined by ^1H NMR spectroscopy using chiral shift reagent, tris[3-(heptafluoropropyl hydroxymethylene - (+) camphoratoleuropium(III), Eu(hfc)3

Preparation of compound 3

A solution of santonin (**2**) (10 g, 40 mmol) in 98% formic acid (80 mL) was heated under reflux for 8 h. After this time, water (20 mL) was added to the reaction mixture, of the which on standing at refrigerator a crystalline solid was deposited, compound **3** (3.665 g, 37%) with the following physical and spectroscopic features: m.p. 175-176°C; $[\alpha]_D^{24}$ -108.8°; MS *m/e* 246 (35, M^+), 231 (2), 202 (5), 187 (21), 173 (100); IR ν_{max} 3500-3200, 1730, 1600 cm^{-1};^1H NMR δ, 6.67 s, 5.59 d, J = 6.6 Hz, 2.28 s, 2.18 s, 1.39 d, J = 7.5 Hz; ^{13}C NMR, 19.5, 14.5 and 11.4 (CH_3), 24.1 and 23.9 (CH_2), 117.9, 75.8, 41.8 and 40.4 (CH) and 181.5, 153.3, 134.5, 130.8, 127.6 and 123.5 (C).

Preparation of compound 4

A solution of compound **3** (0.675 g, 2.74 mmol), allyl bromide (0.665 g, 5.48 mmol), anhydrous potassium carbonate (0.760 g, 5.48 mmol) in acetone (20 mL) was heated under reflux for 8 h with stirring. After this time the reaction mixture was poured into water and extracted with ether. The combined organic layer was washed with 2N ammonium hydroxide and brine, and dried over Na_2SO_4. Filtration and solvent removal gave compound **4** (0.734 g, 93.5 %): m.p. 52-54°C; $[\alpha]_D^{24}$ -114.5°; MS *m/e* 286 (20, M^+), 245 (6), 213 (21), 199 (32), 171 (100); IR ν_{max} 1745, 1580 cm^{-1}; ^1H NMR δ 6.71 s, 6.05 m, 5.61 d, J = 6.5 Hz, 5.40 d, J = 17.0 Hz, 5.25 d, J = 10.4 Hz, 4.50 d, J = 4.8 Hz, 2.29 s, 2.21 s, 1.37 d, J = 7.2 Hz; ^{13}C NMR, 19.9, 14.5 and 11.6 (CH_3), 116.9, 23.6, 23.6 and 69.3 (CH_2), 133.6, 114.8, 75.7, 41.8 and 40.5 (CH) and 179.6, 154.8, 133.9, 130.7, 128.1 and 126.0 (C).

Preparation of compound 5.

A solution of compound **4** (0.296 g, 1.022 mmol) in tetraline was heated at 200°C under argon for 8 h. After removal of tetraline by heating (60 °C) in vacuo, chromatography eluting with hexane-ethyl acetate gave compound **5** (0.178 g, 61%): m.p. 108-110°C; $[\alpha]_D^{24}$ -96°; MS *m/e* 286 (60, M^+), 242 (10), 227 (34), 213 (100), 172 (20); IR ν_{max} 3550-3300, 1745, 1635 cm^{-1}; ^1H NMR δ , 5.94 m, 5.60 d, J = 6.4 Hz, 5.06 d, J = 10.0 Hz, 4.99 d, J = 17.2 Hz, 3.47 d, J = 5.8 Hz, 2.28 s, 2.14 s, 1.37 d, J = 7.4 Hz; ^{13}C NMR, 15.1, 14.4 and 11.9 (CH_3), 115.5, 31.3, 24.5 and 23.8 (CH_2), 135.5, 76.2, 41.6 and 40.6 (CH) and 179.5, 150.8, 132.9, 128.8, 128.4, 125.0 and 122.3 (C).

Preparation of compound 6.

A solution of compound **5** (94 mg, 0.30 mmol) dissolved in absolute ethanol (18 mL) was treated with $Rh\ Cl_3.\ 3H_2O$ (29 mg, 0.108 mmol) at room temperature for 7 h under an atmosphere of argon. Removal of solvent in vacuo and chromatography on silica gel eluting with hexane-ethyl acetate 7:3 gave compound **6** (73 mg, 78%): m.p. 157-158°C; $[\alpha]_D^{24}$ -148°; MS *m/e* 286 (52, M^+), 242 (13), 227 (47), 213 (100), 198 (21), 173 (16); IR ν_{max} 3500-3300, 1740 cm^{-1}; ^1H NMR δ 6.30 d, J = 16.2 Hz, 5.90 dq, J = 16.2 and 6.4 Hz, 5.60 d, J = 6.2 Hz, 2.29 s, 2.09 s, 1.96 d, J = 6.4 Hz, 1.37 d, J = 7.2 Hz; ^{13}C NMR, 18.3, 15.6, 13.8 and 11.3 (CH_3), 23.5 and 23.1 (CH_2), 132.9, 125.4, 75.4, 41.1 and 40.0 (CH) and 179.6, 149.0, 131.6, 129.2, 126.9, 124.7 and 122.2 (C).

Preparation of compound 7.

To a mixture of dioxane (1 mL), water (0.3 mL), compound **6** (68 mg, 0.23 mmol) and osmium tetroxide (1.3 mg , 0.005 mmol) at room temperature was added sodium metaperiodate (111 mg, 0.5 mmol) in portions over a period of 30 min. Then the slurry was stirred for an additional 5 h. After this time the reaction mixture was poured into water and extracted with ether. The combined organic layers was washed with brine and dried over Na_2SO_4. Filtration, solvent removal and flash chromatography yielded compound **7** (50 mg 77%), m.p. 233-234°C; $[\alpha]_D^{24}$ -186°; MS *m/e* 274 (35, M^+), 259 (2), 229 (2), 215 (5), 201 (100), 173 (19); IR ν_{max} 3500, 1760, 1630 cm^{-1}; ^1H NMR δ 2.16 s,10.43 s, 5.58 d, J = 6.2 Hz, 2.47 s, 2.30 s, 1.38 d, J = 7.2 Hz. ^{13}C NMR 14.4, 13.1 and 11.0 (CH_3), 23.6 and 23.4 (CH_2), 195.9, 75.1, 41.3 and 40.5 (CH) and 179.0, 159.2, 138.8, 137.1, 126.6, 126.3 and 118.0 (C).

Preparation of compound 8.

To a solution of compound **7** (196 mg, 0.7 mmol) in methanol (100 mL) was added (*R,R*)-1,2-cyclohexanediamine (41 mg, 0.35 mmol) and the resulting mixture was heated under reflux for 1 h. After this time the reaction mixture was concentrated in vacuo to reduce the volume to the half. On standing in the refrigerator several crops of solid were deposited, compound **8** (0.136 mg, 60%).m.p. 257-258°C; $[\alpha]_D^{24}$ -470°; MS *m/e* 626 (83, M^+), 259 (2), 582 (13), 553 (13), 353 (100), 273 (29); 200 (12); HRMS *m/e* 626.3347, $C_{38}H_{46}O_6N_2$ required 626.3356; IR ν_{max} 3600-3300, 1760, 1615 cm^{-1}; ^1H NMR δ , 8.71 s, 5.54 d, J = 6.2 Hz, 2.30 s, 2.26 s, 1.35 d, J = 7.3 Hz; ^{13}C NMR, 14.3, 13.1 and 11.2 (CH_3), 33.1, 24.1, 23.8 and 23.5 (CH_2), 162.8, 75.5, 72.8, 41.3 and 40.1 (CH) and 179.3, 158.1, 133.9, 137.7, 125.1, 124.7 and 116.2 (C).

Preparation of complex 1.

To a solution of compound **8** (387.7 mg, 0.61 mmol) in hot methanol (300 mL) was added $Mn(OAc)_3.2H_2O$ (16.5 mg, 0.614 mmol) and the resulting mixture was heated under reflux for 30 minutes. After this time the reaction mixture was concentrated in vacuo to reduce the volume to the half and then was heated around 60 °C and $NaClO_4$. H_2O (170 mg, 1.21 mmol) was added in portions. On standing at room temperature, several crops of solid were deposited, filtered and air-dried. Complex **1** (397 mg, 81%): Anal. Calcd. for $C_{38}H_{46}N_2O_6Mn.3H_2O$ (ClO_4): C 54.64, H 6.27, N 3.35, Found: C 54.81, H 5.99, H 3.37. IR ν_{max} 3500-3300, 1760, 1610,1535, 1400, 1305, 1285, 1100, 950, 920, 835, 705, 665, 585, 525 cm^{-1}

Typical experimental procedure for epoxidation with iodosylbenzene.

Iodosylbenzene (0.22 mmol) was added to a solution of olefin (0.11 mmol), complex **1** (2.6 μmol) and N-methylimidazole (0.055 mmol) in acetonitrile (1 mL) at room temperature. After stirring for the indicated time in table 2, the mixture was concentrated in vacuo and the epoxide was purified by flash column chromatography on silica gel or neutral alumine.

Typical experimental procedure for epoxidation with molecular oxygen/pivalaldehyde.

A solution of olefin (0.11 mmol) and pivalaldehyde (0.33 mmol) in fluorobenzene (0.2 mL) was added to a stirred mixture of catalyst (6.5 μmol) and N-methylimidazol (0.055 mmol) in fluorobenzene (0.2 mL). The mixture was stirred at room temperature under a molecular oxygen ballon for the indicate time in table 3. The epoxide was purified by flash column chromatography on silicagel or neutral alumnine.

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