Highly Position and Enantioselective Catalytic Epoxidation of Poly-olefins Mediated by a Chiral Mn Complex, Including a One-step Conversion of Squalene to the (*S*)-2,3-Epoxide, Precursor of Natural Steroids and Terpenoids

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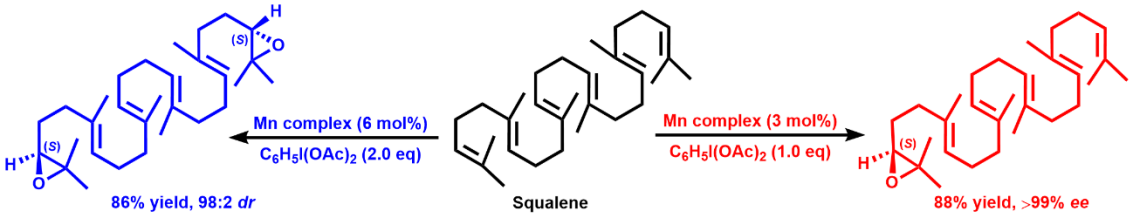
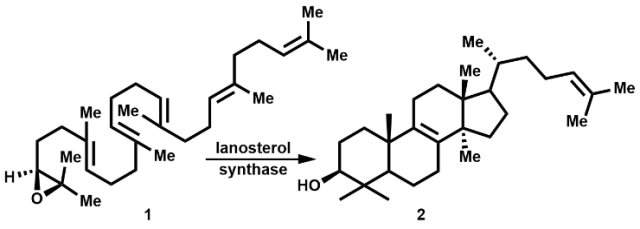
KEYWORDS: Enantioselective epoxidation, Chiral Mn catalyst, 2,3-(S)-Oxidosqualene, Chiral Mn(V)-oxo intermediate.



ABSTRACT: Reported herein is the synthesis of a novel chiral dicarboxylic ligand for Mn(II) and the application of the Mn complex to the highly **enantio**- and position-selective epoxidation of C=C under mild conditions, even with poly-olefinic substrates. A stereo-mechanistic basis for asymmetric induction is suggested.

(*S*)-2,3-Oxidosqualene (**1**) is the immediate precursor of lanosterol (**2**) (Scheme 1), the predecessor of cholesterol and thus the whole steroid family.[1] It also gives rise to countless naturally occurring polycyclic triterpenes. The formation **1** from squalene is mediated by flavin adenosine dinucleotide (FAD) epoxidases, as exemplified by the human SQLE whose structure is now known.[2]

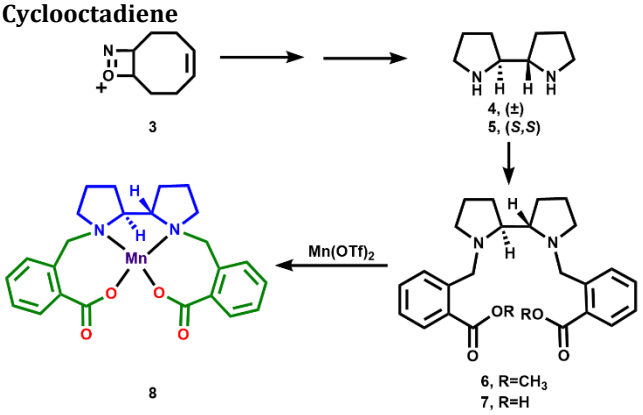
Scheme 1. Biosynthesis of Lanosterol from 2,3-(*S*)-Oxidosqualene



Most of the molecular details of the enzymatic cyclizations involving **1** are fairly clear, e.g. in the biosynthesis of lanosterol and cholesterol.[3] However, the strictly chemical enantioselective epoxidation of squalene to **1** and also the one-step conversion of **1** to **2** have long remained as outstanding unsolved synthetic problems. Reported herein is a solution to the epoxidation challenge by the use of a designed chiral manganese complex as a catalyst.[4a,b] Previous research in our laboratory using the chiral engineered "Noe-Lin" catalyst enabled the position- and enantioselective 2,3-dihydroxylation of geranyl or farnesyl esters.[4c,d,e]

The work described herein on the enantioselective conversion of squalene to (*S*)-2,3-oxido squalene (**1**) was facilitated by the recently developed efficient conversion of 1,5-cyclooctadiene to (±)-2,2-bispyrrolidine **4** (via the cationic 1,2-oxazetium intermediate **3**)[5] which by the known resolution with tartaric acid[6] gave the *S,S*-enantiomer **5**[7] (Scheme 2), and also the *R,R*-enantiomer.

Scheme 2. Synthesis of Manganese Complex 8 from 1,5-Cyclooctadiene

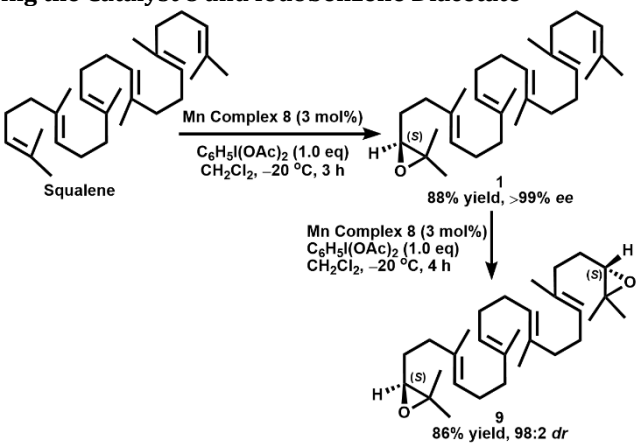


We selected the chiral *S,S*-dicarboxylato ligand **7** (Scheme 2) for epoxidation studies for a number of reasons. First we were mindful of the fact that *N,N'*-ethylenediamine tetraacetate complexes of manganese(II) undergo decarboxylation upon oxidation of Mn to higher valence states.[8] Second, the complex of 2 equiv. of picolinic acid with Mn(II) is an excellent catalyst for the H_2O_2-promoted epoxidation of olefins.[9]

Finally, the dicarboxylato ligand **7** could be accessed in two simple steps from the chiral bis-pyrrolidine **5**, as detailed in the Supporting Information (SI) and as follows: (1) reaction of **5** with 2.3 equiv. of methyl-*o*-bromomethylbenzoate and 2.2 equiv. of potassium carbonate in THF at 23 °C for 12 h to give **6** (70%) and (2) saponification of **6** with 4 equiv. of LiOH in THF at 50 °C for 2 h to give **7** (90%).

The diacid **7** was converted to the Mn(II) complex **8** by reaction in CH_3CN solution with 1 equiv. of manganese(II) triflate and 2 equiv. of $NaHCO_3$ at 23 °C for 16 h followed by filtration and removal of solvent. It was obtained as a brown powder (which thus far has resisted crystallization). The composition was confirmed by high resolution mass spectrometry and infrared spectroscopy (carbonyl absorption 1650 cm^{-1}).[10] The chiral Mn(II) complex is a highly effective epoxidation catalyst at 3 mol% in CH_2Cl_2 as solvent using one equiv. of either iodosobenzene diacetate (IBA)[10] or tetra-*n*-butylammonium bromate[10] at –20 °C. These two oxidants are equally effective for the epoxidation reactions reported herein. We were gratified that squalene was converted to **1** in 3 h in 88% yield and 99.9:0.1 *S*/*R*-enantiomeric ratio as determined by chiral HPLC analysis using a Daicel ChiralPak IB column.[10] During the epoxidation the reaction mixture is dark red brown, the color of the active oxidant which we consider is probably a Mn(V)-oxo species. The same Mn(V)-oxo species is formed rapidly by the action of ozone on a CH_2Cl_2 solution of **8** at –20 °C or below. After removal of any excess ozone this species reacts at –20 °C with one equiv. of squalene to form (*S*)-2,3-oxidosqualene (**1**) in 90% yield and 99.8:0.2 *S*/*R* selectivity, implicating it as a likely reaction intermediate. So far, we have not been able to obtain crystals of this Mn(V)-oxo complex for X-ray structural analysis. Methylene chloride was found to be the optimum solvent not only for epoxidation of squalene but also for the other epoxidation reactions described below. The commonly used epoxidation solvent acetonitrile led to slower reaction and poorer results.

Scheme 3. Enantio- and Position Selective Catalytic Epoxidation of Squalene and (*S*)-2,3-oxidosqualene using the Catalyst 8 and Iodobenzene Diacetate

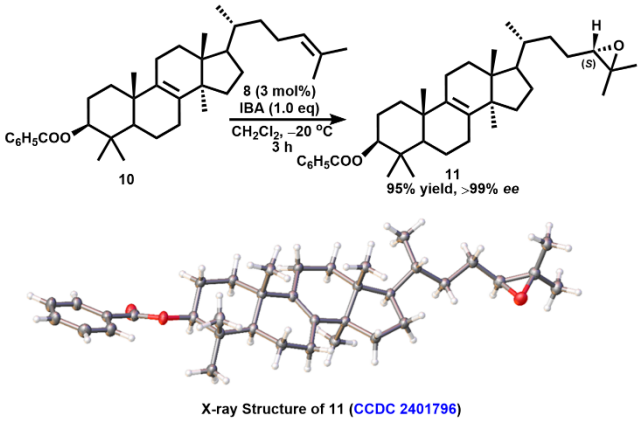


Catalytic epoxidation of the chiral epoxide **1** with the chiral Mn complex **8** (3 mol%, –20 °C, in CH_2Cl_2, 4 h) produced the 2,3-*S*, 22,23-*S*-diepoxide of squalene (**9**) with *dr* of 98:2 and isolated yield of 86%,[10] as shown in Scheme 3. Squalene was also directly converted to **9** in a single step just by the use of catalyst **8** and 2 equiv. of iodosobenzene diacetate (86% yield). The diepoxide **9** is an important natural product since it gives rise to the 24,25-(*S*)-epoxide of lanosterol (**11**) and 24,25-epoxy cholesterol in vivo which activate the "oxysterol" pathway for nuclear hormone receptor-mediated degradation of cholesterol and its regulation.[11]

Squalene diepoxide **9** and its cyclization product 24,25-epoxy lanosterol have been of special interest not only for in vivo cholesterol regulation but also for anti-fungal and anti-cancer studies.[2]

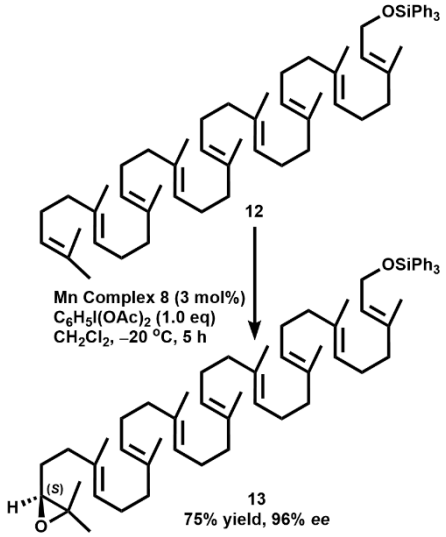
We also have applied the epoxidation catalyst **8** (3 mol%) to the diastereoselective epoxidation of lanosterol benzoate (**10**) to the 24,25-(*S*)-epoxide (**11**) which after 3 h at –20 °C in CH_2Cl_2 was obtained in 95% yield and >99% *ee* using 1 equiv. of iodosobenzene diacetate (see Scheme 4). The experimental X-ray crystal structure of **11** is shown in Scheme **4**.

Scheme 4. Diastereoselective Epoxidation of Lanosterol Benzoate



Highly position and enantioselective epoxidation could even be demonstrated with all *E*-nonaprenol triphenylsilyl

Scheme 5. Position- and Enantioselective Epoxidation of a Solanesol Silyl Ether



ether (**12**) which was oxidized with iodosobenzene diacetate (1 equiv.), catalyst **8** (3 mol%) in CH_2Cl_2 at –20 °C for 5

h to give selectively the (*S*)-2,3-epoxide **13** with 96% *ee* in 75% yield (Scheme 5), a case of remarkable selectivity for one of nine similar C=C subunits.

Eight additional examples of catalytic enantioselective epoxidation, using the chiral manganese complex **8** (3 mol%) iodosobenzene diacetate (1 equiv.) in CH_2Cl_2 at –20 °C for 3-5 h, are summarized in Figure 1. There was no reaction with dimethyl fumarate, in accord with electrophilic rather than radical character of the oxidant.

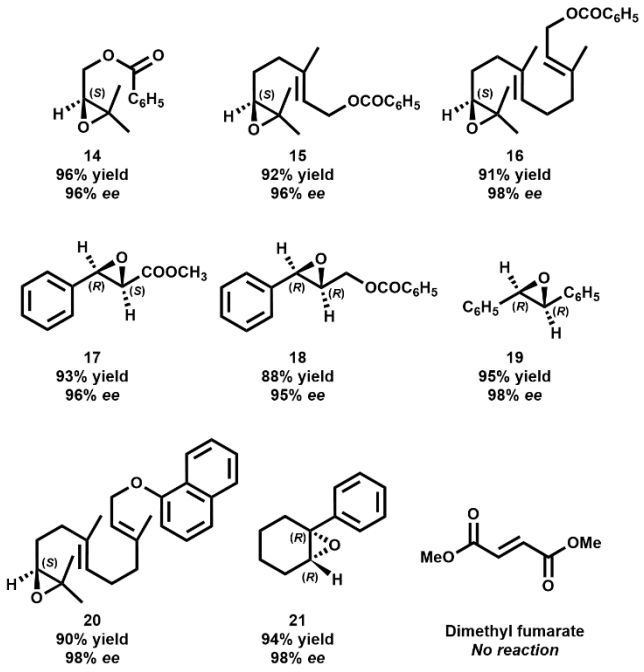


Figure 1. Major epoxidation products derived from catalyst 8 using iodosobenzene diacetate at –20 °C in 3-5 h (see SI)

Synthetic chemistry has also been enriched by several contributions of multiple research groups around the world which demonstrate the value of other chiral manganese oxidation catalysts.[12]

The results described above for the highly enantio-and position selective epoxidation suggest that the Mn(II) complex **8** will be a useful addition to the arsenal synthetic chemistry. They also underscore the importance of establishing the stereo-mechanistic basis for the unusually high synthetic selectivity. The fact that the strong oxidizing agents iodobenzene diacetate, tetra-*n*-butylammonium bromate and ozone are more efficient than H_2O_2 favors oxo-Mn(V) over oxo-Mn(IV) as the effective oxidant.

Although further research is required to establish the precise pathway for the enantioselective epoxidations described above, there is one working hypothesis which is especially interesting because it explains simply and clearly the observed absolute stereochemical course of all the enantioselective epoxidations described herein. It is based upon the cationic Mn(V)-oxo species **22** as the effective

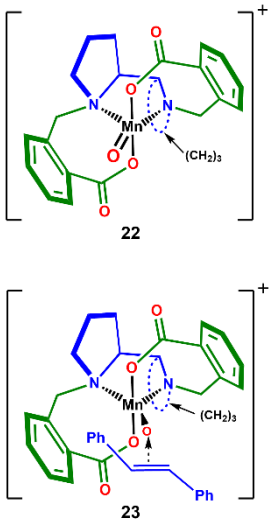


Figure 2. Possible structures of the Mn(V)-oxo cationic intermediate (22) and of the pre-transition state assembly (23)

oxidant (see Figure 2). Complex **22** is essentially a C_2-symmetric trigonal bipyramide with the electrophilic oxygen residing between the two carboxylate ligands in a cleft formed by the two benzenoid rings. Assuming the oxygen attached to Mn has oxene-like reactivity and adds concertedly to the π-bond, that cleft clearly favours attachment of O at the *si* face of squalene to form the (*S*)-2,3-oxidosqualene (see **23**). Obviously, the experimental determination of the 3-D structure of the oxo Mn species is an essential next step, and the subject of ongoing studies. Predictions arising from this conjecture are now being tested.

In summary, the research outlined above has resulted in the discovery of a highly effective catalyst for the enatioselective epoxidation of a wide range of unsaturated molecules, including the key biomolecule (*S*)-2,3-oxidosqualene.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.
Experimental procedures and characterization data for novel reactions and products including copies of ^1H and ^{13}C -NMR spectra data X-ray crystallographic data for compound **11** (PDF).

Accession Codes

CCDC **2401796** contains the supplementary crystallographic data for this paper. The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

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