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Enantioselective epoxidation of isoflavones by Jacobsen's Mn(III)salen catalysts and dimethyldioxirane oxygen-atom source

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Abstract

The catalytic enantioselective epoxidation of the isoflavones **1a–f** has been performed by the Mn(III)salen complexes (*R,R*)-**3** and (*S,S*)-**3** as catalysts and dimethyldioxirane as the oxygen-atom source to afford optically active isoflavone epoxides **2a–f**. The absolute configuration of the nonracemic epoxides **2** have been determined by X-ray diffraction analysis. Our present results constitute the first examples of the preparation of optically active isoflavone epoxides.

The Jacobsen's Mn(III)salen complexes have proven to be highly efficient catalysts for the enantioselective epoxidation of simple *cis*-olefins by using various oxygen donors, e.g. NaOCl, H_2O_2, n-Bu_4IO_4 and iodosobenzene.[1] Recently we have demonstrated that a novel combination of such Mn(III)salen complexes and isolated dimethyldioxirane (DMD)[2] may be advantageously utilized for the enantioselective epoxidation of 2,2-dimethyl-2*H*-chromenes.[3] Our results constitute an important contribution on the applicability of DMD for the enantioselective epoxidation. In view of its achiral structure, the convenient and versatile DMD[4] had to be used as an oxygen source in conjunction with a chiral catalyst to obtain optically active oxyfunctionalized products. We report herein the adoption of this protocol for the enantioselective epoxidation of isoflavones, electron-poor substrates, for which no direct catalytic asymmetric oxidation exists so far.

Isoflavones are well-known natural products isolated from various plants.[5] The first representatives of their epoxides were synthesized either by an intramolecular Darzens reaction of α-bromo-o-acyloxyacetophenones[6] or by the Weitz–Scheffer alkaline hydrogen peroxide epoxidation of

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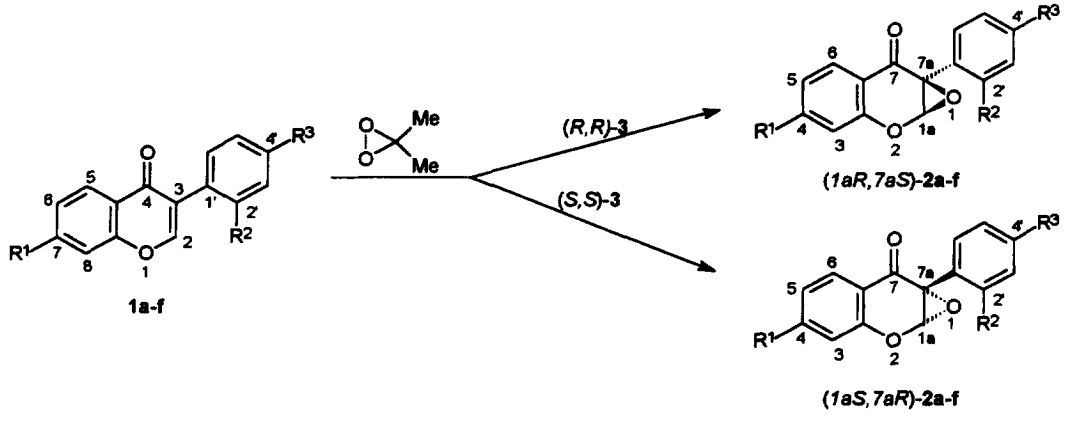
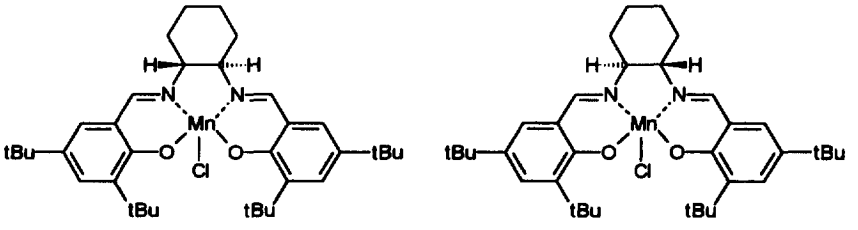
isoflavones.[7] In our own experiments, dimethyldioxirane proved to be a convenient and effective oxidant to provide the epoxides of isoflavones and their glycosides in high yields under neutral conditions.[8] However, it has also turned out that the presence of the chiral sugar auxiliary does not exercise any enantiofacial selectivity during the dimethyldioxirane epoxidation and a 1:1 mixture of the diastereomeric epoxides were obtained in each case.[8b]

The enantioselective epoxidation of the isoflavones **1a–f** has been performed with the complexes (*R,R*)-**3** and (*S,S*)-**3** by using isolated DMD (ca. 0.05–0.1 M acetone solution)[2] as an oxygen source (Scheme 1). The results in Table 1 show that the use of 14–16 mol% catalyst, together with 6–10 equiv. of DMD,[9] provides optically active isoflavone epoxides **2a–f** in moderate yields. The low yields are a consequence of incomplete conversion of the starting material in view of the electron-poor nature of the substrates. The enantioselectivities varied within the range of 20 to 92% e.e., which depended on the substitution pattern of the starting isoflavone (Scheme 1 and Table 1). It is worth emphasizing that substrates with methoxy-substituted aryl groups, as in derivatives **1e** and **1f** are epoxidized in considerably higher enantiofacial selectivity (*cf.* Table 1).





1,2	R^1	R^2	R^3
a	H	H	H
b	MeO	H	H
c	$MeSO_2O$	H	H
d	MeO	H	MeO
e	MeO	MeO	H
f	$MeSO_2O$	MeO	H

Scheme 1.

The structures of the epoxides **2a–f** have been confirmed by microanalysis and NMR spectroscopy. In the ^1H NMR spectra, the disappearance of the singlet signal of the 2-H proton at ca. 7.9 ppm, characteristic of the isoflavone skeleton, and the appearance of a singlet signal at about 5.5 ppm assigned

Table 1
Enantioselective epoxidation of isoflavones **1a–f** by the Mn(III)salen/DMD oxidant[a,b]

Epoxide[c]	DMD (eq)	Catalyst (mol%)	Yield[d] (%)	M.p. (°C)	$[\alpha]_D$[e] (c=1, $CHCl_3$)	e.e. (%)[f] (^{1}H NMR)	e.e. (%)[g] (HPLC)
(*1aR,7aS*)-**2a**	9	14	31	oil	-152.9	54	52
(*1aS,7aR*)-**2a**	9	14	34	oil	+200.0	56	65
(*1aR,7aS*)-**2b**	6	14	27	124-126	-122.4	40	37
(*1aS,7aR*)-**2b**	6	14	36	124-125	+103.3	42	39
(*1aR,7aS*)-**2c**	10	14	22	118-120	-46.7	18	21
(*1aS,7aR*)-**2c**	10	14	27	117-119	+59.8	34	48
(*1aR,7aS*)-**2d**	10	16	39	159-161	-112.2	52	47
(*1aS,7aR*)-**2d**	10	16	29	160-161	+65.4	28	22
(*1aR,7aS*)-**2e**	6	16	31	126-128	-122.2	80	82
(*1aS,7aR*)-**2e**	6	16	32	127-129	+125.7	86	86
(*1aR,7aS*)-**2f**	6	16	25	144-145	-58.0	72	72
(*1aS,7aR*)-**2f**	6	16	23	145-146	+86.7	92	90

[a] Used as 0.05-0.1 M acetone solution. [b] Reaction time is 10 days. [c] All new compounds gave satisfactory microanalysis (C,H) data. [d] Isolated material [e] Measured on a Perkin-Elmer 241 polarimeter.
[f] Determined in $CDCl_3$ solution at room teperature (ca. 20 °C) by using tris[3-(heptafluroro-propylhydroxymethylene)-d-camphorato]europium(III) as optically active NMR shift reagent. [g] Measured by HPLC (Chiralcel OD, 9:1 n-hexane/2-propanol, flow 0.6 ml/min).

to the 1a-H proton of the isoflavone epoxides,[8] establish the presence of the oxirane ring. Characteristic chemical shift values of the C-1a (83–84 ppm) and C-7a (62–64 ppm) atoms in the ^{13}C NMR spectra also corroborate the epoxide structure. The absolute configuration of the nonracemic epoxides **2f** have been determined by X-ray analysis (Fig. 1).

In summary, our results unequivocally demonstrate that the combination of the optically active Jacobsen's Mn(III)salen catalysts and dimethyldioxirane as the oxygen donor may be used successfully for the enantioselective epoxidation of even such electron-poor substrates as the isoflavones. Isoflavones, which necessarily possess a trisubstituted olefinic double bond in conjugation with a carbonyl group, represent substrates with functionality of higher complexity, which have been epoxidized enantioselectively by Mn(III)salen complexes to afford the optically active isoflavone epoxides by the first catalytic process.

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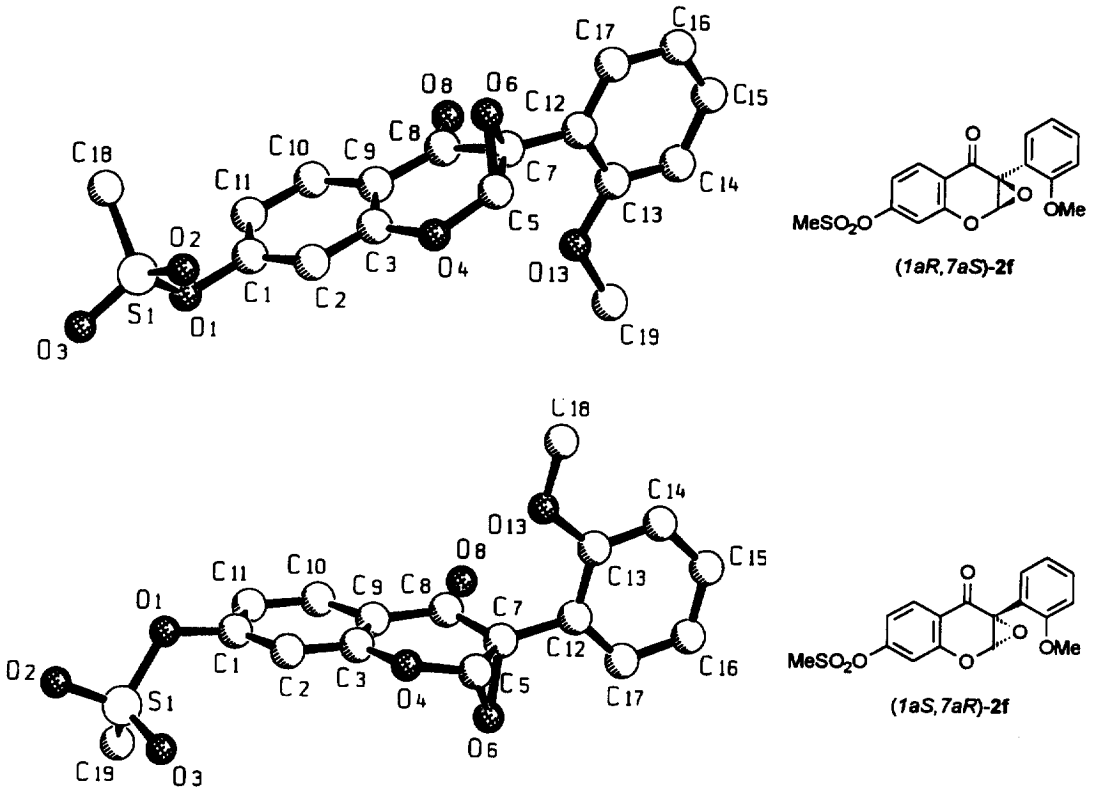

Fig. 1. Molecular structures and stereoformulae with the atom numbering of the derivatives (1a*R*,7a*S*)-**2f** and (1a*S*,7a*R*)-**2f**[10]

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9. Dimethyldioxirane (ca. 0.05–0.1 M acetone solution) was added to a stirred solution of the particular isoflavone **1** (1.0 mmol) and Mn(III)salen complex **3** (14–16 mol%) in anhydrous CH_2Cl_2 (10.0 ml) and the stirring was continued at room temperature (ca. 20°C). The progress of the reaction was monitored by TLC and new batches of DMD were added in 24 h intervals until the conversion of the starting material halted (10 days). The solvent was evaporated (ca. 25°C/15 torr) and the epoxides **2a–f** (Scheme 1 and Table 1) were purified by silica-gel chromatography.
10. (1a*R*,7a*S*)-**2f**: Space group $P2_12_12_1$; a=5.569(1) Å, b=9.905(1) Å, c=29.646 (3) Å. (1a*S*,7a*R*)-**2f**: Space group $P2_12_12_1$; a=5.5799(5) Å, b=9.905(1) Å, c=29.562(3) Å. Determination of the absolute configuration was based on the Flack parameter (SHELXL>93). The X-ray data are deposited in the Cambridge Crystallographic Date Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.