Substrate-Induced Diastereoselectivity in the Dimethyldioxirane Epoxidation of Simple Alkenes and Dienes

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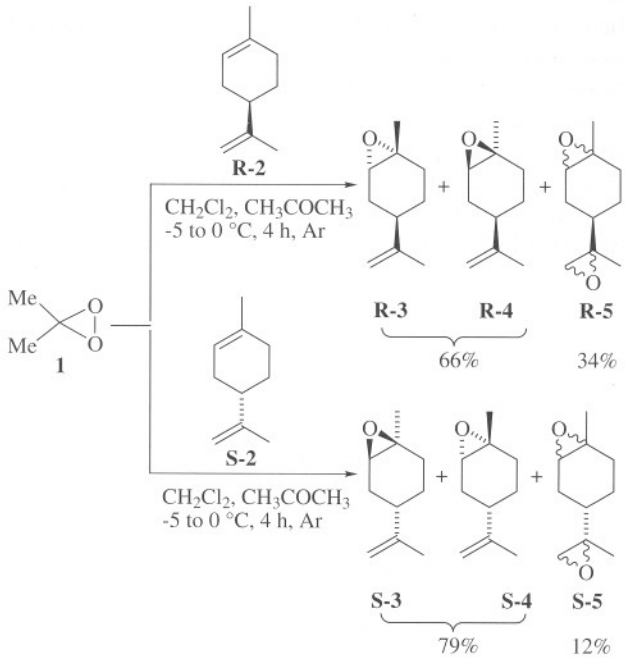
Abstract: Various alkenes and dienes, such as (*R*)- or (*S*)-limonene **2**, 2-carene **6**, 3-carene **8**, (*R*)-α-pinene **10**, (*S*)-α-pinene **12**, and *endo*-dicyclopentadiene **14** were transformed into the corresponding mono- and bis-epoxides by epoxidation with dimethyldioxirane (as an acetone solution). The selectivity observed in these epoxidations is explained by the assumption of hydrogen bonding between bridge protons and the dioxirane.

Key words: dimethyldioxirane, epoxidation, diasteroselectivity, regioselectivity

Dimethyldioxirane (DMD, in situ or isolated as solution) has been established[1] as a widely-used oxidant, due to the convenience of its isolation[2] from cheap, commercially available starting materials, its efficiency, and its performance under strictly neutral conditions. Its reaction mode includes epoxidation[3] of alkenes, oxygen insertion[4] into σ-bonds, and heteroatom oxidation.[5] Alkene epoxidation has found numerous applications[6] in the total syntheses of natural products. However, there are only few impressive results of regio- and diastereoselective epoxidations with DMD, i.e. the regioselective epoxidation[7] of a disubstituted double bond over a trisubstituted enol ether moiety, and the exclusive epoxidation[8] at the endocyclic double bonds of pentafulvenes.

We thought that this powerful oxidant might be more regio- and diastereoselective than initially assumed. A more systematic investigation of simple strained alkenes could lead to interesting observations concerning transition states of the epoxidation mechanism. Herein, we report the DMD epoxidations of simple bicyclic alkenes and dienes yielding often regio- and diastereoselectively the corresponding mono- and bis-epoxides.

Epoxidation of (*R*)-(+)-limonene **R-2** with dimethyldioxirane at –5 °C yields a 65:35 mixture of mono-epoxides **R-3**, **R-4** (66% yield at 90% conversion) and bis-epoxide **R-5** (34% yield at 90% conversion) (Scheme 1). The mixture of epoxides **R-3**, **R-4** was separated from **R-5** by column chromatography; addition of another equivalent of dimethyldioxirane led to the isolation of bis-epoxide **R-5**. The corresponding 8,9-epoxide was not detected in the crude reaction mixture, a fact that indicates the electrophilic character of dimethyldioxirane and its preference for the more electron-rich double bond of the molecule. Although the diastereoselectivity was poor [ratio **R-3**/**R-4** = 1:8], it is better than many other oxidation protocols involving oxidants such as mCPBA[9] or PhIO,[10] H_2O_2[11] and various Fe-porphyrins. The diastereoselectivity was influenced by the co-solvent used in the epoxidation (Table 1). When acetonitrile or methanol, were used as co-solvents (entries 4, 6) the conversion was quantitative but the diastereoselectivity was low, while in the case of methanol the formation of bis-epoxide was negligible (~ 1%). In contrast, when dichloromethane was used (entries 1, 3), the conversion was smaller, the diastereoselectivity better, and bis-epoxide **R-5** was formed in larger amounts. The best diastereoselectivity was observed in the case of petroleum ether (entry 5), where also the lowest conversion was obtained.



Scheme 1

It seems that the diastereoselectivity increases with the electric dipole moment of the solvent; except in the case of methanol where an extra hydrogen bonding of the solvent with dimethyldioxirane prior to addition could occur.

The variation of temperature seems to have an effect only in the conversion (entries 7, 8), even if in the case of petroleum ether the regioselectivity decreases slightly.

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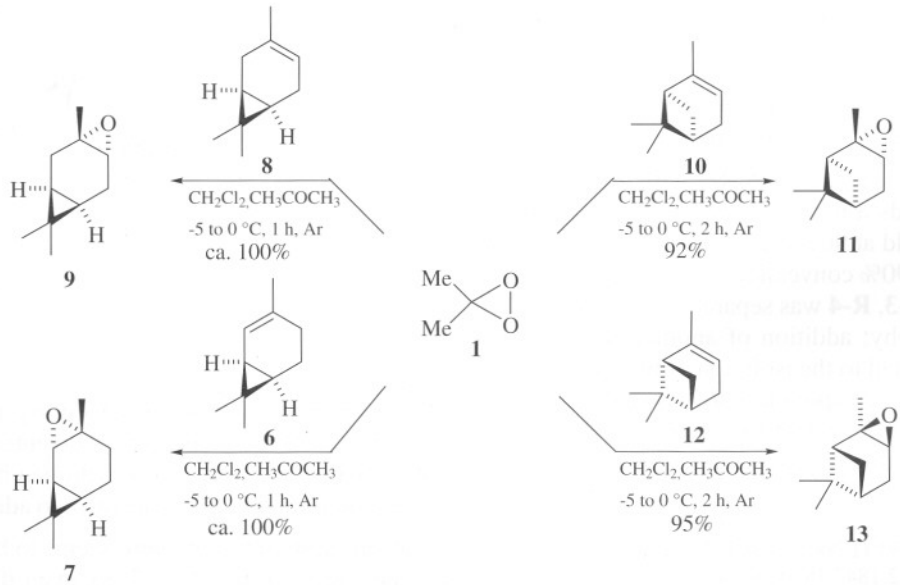
Table 1 Epoxidation of (*R*)-(+)-Limonene **R-2** with Dimethyldioxirane

Entry	DMD (equiv)	Temp (°C)	Time (min)	Solvents	Conversion (%)	Yield (%)			Ratio
						R-3	**R-4**	**R-5**	**R-3–R-4**
1	2	–5	240	CH_3COCH_3–CH_2Cl_2, 6:1	87	49	27	24	1.8:1
2	1	0	60	CH_3COCH_3	84	48	32	20	1.5:1
3	1	0	60	CH_3COCH_3–CH_2Cl_2, 1:9	74	56	26	18	2.2:1
4	1	0	60	CH_3COCH_3–CH_3CN, 1:9	99	44	38	18	1.2:1
5	1	0	60	CH_3COCH_3–C_6H_{14}, 1:9	71	68	26	6	2.6:1
6	1	0	60	CH_3COCH_3–CH_3OH, 1:9	100	58	41	1	1.4:1
7	1	–78	60	CH_3COCH_3–C_6H_{14}, 1:9	48	55	25	20	2.2:1
8	1	–78	60	CH_3COCH_3–CH_3OH, 1:9	100	55	37	8	1.5:1

Similarly, epoxidation of (*S*)-(–)-limonene **S-2** with dimethyldioxirane at –5 °C yields a 55:45 mixture of monoepoxides **S-3**, **S-4** (79% yield at 90% conversion) and bis-epoxide **S-5** (12% yield at 90% conversion) (Scheme 1). The mixture of epoxides **S-3**, **S-4** was separated from **S-5** by column chromatography; treatment of the mixture **S-3**, **S-4** with another equivalent of dimethyldioxirane led to the quantitative formation of bis-epoxide **S-5**. Again, the corresponding 8,9-epoxide was not detected. Although the diastereoselectivity is smaller than for the corresponding *R*-limonene, in both cases the *anti*-epoxide is preferably formed. That means that the dioxirane attacks the trisubstituted double bond from the same side with the proton of the 4-position.

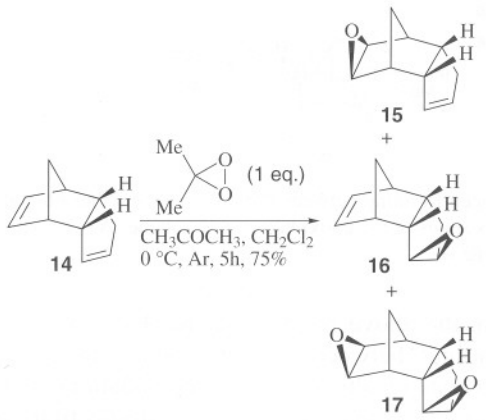
Dimethyldioxirane epoxidation of 2-carene **6** or 3-carene **8** or (1*R*)-(+)-α-pinene **10** or (1*S*)-(–)-α-pinene **12** at –5 °C yields[12] the corresponding *anti*-epoxides **7**, **9**, **11**, and **13** in ca. 100%, ca. 100%, 92% and 95%, respectively (Scheme 2). The other possible *syn*-epoxides were not detected. Elucidation of structures of **7**, **9**, **11**, **13** came from extended NMR studies where the oxiranyl methyl group showed a ROESY effect with the signals of the cyclopropyl methyl or the *gem*-dimethyl groups, a fact that provided convincing evidence that all the methyl groups are on



Scheme 2

the same side, while the oxiranyl moiety resides on the opposite side. This indicates that the dimethyldioxirane approaches the double bond *anti* to the *gem*-dimethyl group or *syn* to the cyclopropyl (bridge) protons.

When *endo*-dicyclopentadiene **14** was treated with dimethyldioxirane (1 equiv) at 0 °C, epoxides **15**, **16** and bis-epoxide **17** were produced[13] in 39:41:20 ratio respectively (Scheme 3). When excess of *endo*-dicyclopentadiene **14** was employed, then a mixture (49:51) of epoxides **15**, **16** were produced. With excess of dimethyldioxirane, bis-epoxide **17** was quantitatively produced. Treatment of mono epoxide **15** or **16** with a new equivalent of dimethyldioxirane yields quantitatively bis-epoxide **17**. These epoxides are single diastereomers, and were separated by column chromatography, which permitted their structure elucidation.



Scheme 3

The regioselectivity of this reaction, was influenced by the co-solvent used for the epoxidation (Table 2). When acetonitrile or methanol was used as co-solvents (entries 4, 6), the conversion was nearly quantitative and the ratio of **15** to **16** was 0.7 and 1.1 respectively. In contrast, when pure acetone or petroleum ether were used (entries 2, 5), the conversion is smaller while the ratio becomes 1.2 and 1.4, respectively.

It is generally accepted that DMD epoxidation proceeds mainly via a spiro transition state. Solvent effects observed in the DMD epoxidation of allylic alcohols,[14] interpreted as a mix of several factors including electrostatic,[15] substituent size,[14] association[14] of dioxirane with the adjacent hydroxy functionality in the transition state through hydrogen bonding, and dipole-dipole interactions.[14] Nevertheless, in the examples reported here, the substrates have no polar substituents but still solvent effects are observed. We anticipate, that in all cases examined, a hydrogen bonding is formed[16] between the incoming dioxirane and the suitable bridge protons leading to an improved regio- and diastereoselectivity. Thus, in the limonene series, a hydrogen bonding between the proton of the C-4 position and the dioxirane could be developed in the transition state (Figure), leading to favored *syn*-addition (towards C-4 proton). On the other hand, the mono-epoxidation (4 possible isomers) of *endo*-dicyclopentadiene could occur either at the 4,5- or the 8,9-double bond. Hydrogen bonding of the dioxirane with the protons at C-2, C-6 favors the formation of epoxide **16**, while the hydrogen bonding with the C-10 proton favors epoxide **15**.

Table 2 Epoxidation of *endo*-Dicyclopentadiene **14** with Dimethyldioxirane

Entry	DMD (equiv)	Temp (°C)	Time (h)	Solvents	Conversions (%)	Yield (%)			Ratio
						15	**16**	**17**	**15–16**
1	1	–10	18	CH_3COCH_3–CH_2Cl_2, 2:1	73	39	41	20	0.9:1
2	1	0	2	CH_3COCH_3	80	55	45	0	1.2:1
3	1	0	2	CH_3COCH_3–CH_2Cl_2, 1:9	71	48	52	0	0.9:1
4	1	0	2	CH_3COCH_3–CH_3CN, 1:9	97	53	47	0	1.1:1
5	1	0	2	CH_3COCH_3–C_6H_{14}, 1:9	77	59	41	0	1.4:1
6	1	0	2	CH_3COCH_3–CH_3OH, 1:9	97	43	57	0	0.7:1
7	2.5	0	14	CH_3COCH_3–CH_2Cl_2, 6:1	100	0	0	100	
8	0.4	0	18	CH_3COCH_3–CH_2Cl_2, 4:1	74	49	51	0	1:1

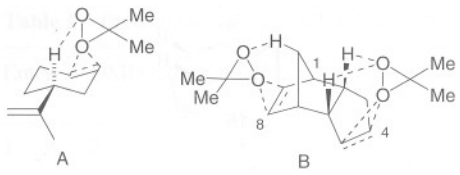


Figure Hydrogen Bonding between the dioxirane and the substrate in the transitions states of the epoxidation of limonene (A) and endo-dicyclopentadiene (B)

In conclusion, the above results indicate that a possible hydrogen bonding[16] between dioxirane and a suitable proton of the substrate results in selective epoxidations. Further research on the extension of this useful selectivity is currently under way in our laboratory.

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(12) **Representative Experimental Procedure. Synthesis of 7**: A 0.062 M solution of dimethyldioxirane in acetone (32 mL; 2 mmol) was added into a cooled (–5 °C) solution of 2-carene (0.16 mL; 1 mmol) in dry CH_2Cl_2 (5 mL) under Ar atmosphere. The resulting solution was stirred at –5 °C for 1 h. The solvents were removed under reduced pressure to give epoxide **7** (150 mg; ca. 100% yield) as a colorless oil. IR (neat): = 2735 cm^{-1}, 1430, 1350, 1300, 1260, 1230, 1190, 1160, 1140, 1115, 1085, 1065, 1020, 965, 950, 880, 850, 790, 765, 710, 680. ^1H NMR (250 MHz, $CDCl_3$): = 0.59–0.66 (m, 1 H), 1.03 (brs, 4 H), 1.04 (s, 3 H), 1.22 (s, 3 H), 1.45–1.57 (m, 1 H), 1.61–1.66 (m, 2 H), 1.80–1.94 (m, 1 H), 2.98 (d, J = 1.5 Hz, 1 H). ^{13}C NMR (63 MHz, $CDCl_3$): = 16.4 (d), 20.7 (t), 21.0 (d), 21.8 (d)23.7 (d), 27.1 (t), 28.1 (d), 57.9 (d), 58.2 (s).

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