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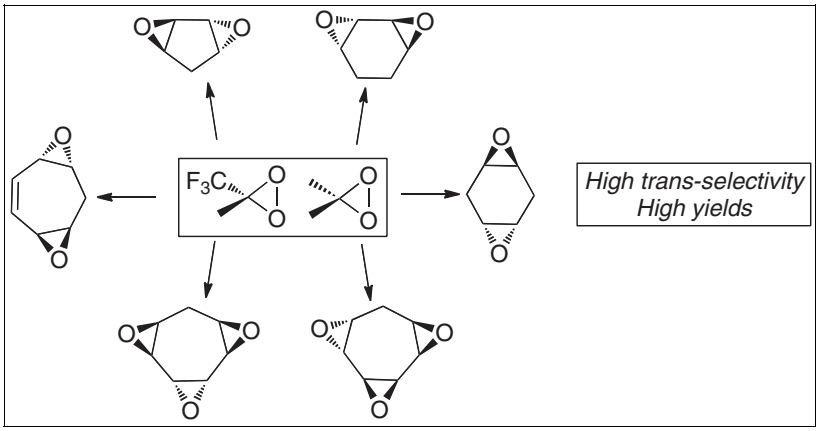

Epoxides are essential building blocks in organic chemistry. The epoxidation of unsubstituted cyclic dienes **2–4** and triene **5** using dimethyldioxirane (**1a**) and its trifluoro analog **1b** methyl(trifluoromethyl)dioxirane has been investigated. The excellent yields obtained (90–98%) are accompanied by outstandingly high diastereoselectivities (90–98%). Interpretation of results based upon the early idea that polar groups can direct the dioxirane attack by dipole–dipole interaction provides a likely rationale, along with a more generalized mechanistic view.

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INTRODUCTION

Many synthetic routes involve epoxides as intermediates, because such compounds are extremely versatile and hence valuable precursors in the manufacture of various synthetically useful products.

During the last decades, we have witnessed an impressive number of studies devoted to the setup of ever-increasingly efficient methods for epoxide synthesis. In such context, we have shown that the three-membered ring peroxides **1**, that is, the dioxiranes (Fig. 1) [1,2], are powerful oxygen-transfer reagents, capable of performing a number of oxidative transformations [3]; the epoxidation of alkenes counts among the most exercised applications of these reagents, mainly because of the generally high product yields and the simplicity of experimental procedures [4,5]. Moreover, the extremely mild reaction conditions normally required (pH close to neutrality and ambient or sub-ambient temperature) make it possible in many cases to isolate even thermally and/or hydrolytically labile epoxides [5c,6].

Concerning the mechanism of alkene epoxidation by dioxiranes, a number of experiments have shown that these cyclic peroxides deliver oxygen to alkenes in a syn stereospecific manner; this and other pertinent observations, coupled with careful theoretical calculations, have pointed to a concerted mechanism, akin to that of alkene epoxidation by peroxyacids [5a,7]. Because of the rigid stereoelectronic requirements for dioxirane-mediated oxidations, peroxides **1** appear rather sensitive to steric and electrostatic influences of the substrate, leading in most cases to outstandingly stereoselective epoxidations.

The epoxidation of small- and medium-ring cyclic dienes and trienes with dioxiranes has not been hitherto investigated, despite the fact that their corresponding epoxides are precursors of drugs [8–10] and can be found in a number of natural bioactive molecules, such as triptolides [11]. In continuation with our interest in the selective epoxidations using dioxiranes [12], we report on the epoxidation of cyclic dienes and trienes **2–5**, conducted with dioxiranes **1a** and **1b** under mild conditions. Results point at the high yields and stereoselectivities achieved as the key features of these relevant transformations.

RESULTS AND DISCUSSION

The results of oxidations of compounds **2–5** by dioxiranes are collected in Table 1. Reactions were routinely carried out by the rapid addition of an aliquot (usually from 5 to 30 mL) of standardized cold solution of 0.1*M*

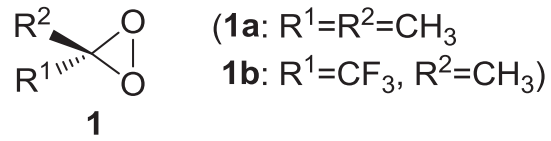


Figure 1. Dioxiranes commonly used in the isolated form (in solution of the parent ketone).

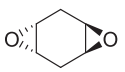
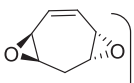
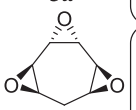
dimethyldioxirane (DDO) (**1a**) in acetone or 0.2*M* trifluorodioxirane (**1b**) in CCl_4 to a stirred solution of the substrate (20–100 mg) in acetone or CCl_4 (5–30 mL) at the conditions given in Table 1; the reaction progress was followed by GC and GC–MS. In most of the cases, pure products (98%+, GC) were simply obtained upon removal of solvent reaction *in vacuo*. The trans-to-cis ratios were estimated by GC and by ^{1}H NMR analysis (± 5%), based on integration of characteristic signals (Table 1).

Inspection of data in Table 1 reveals that the oxidation of cyclopentadiene (**2**) and of 1,3-cyclohexadiene (**3**) (Table 1, entries 1 and 2, respectively) with DDO (**1a**) proceeds smoothly to give the corresponding 1,2;3,4-dioxides (**2a** and **3a**, respectively) in essentially quantitative yields (98%) and with exceptionally high antistereoselectivity (98%). Likewise, the same reactions performed with the more reactive dioxirane **1b** afford the corresponding epoxides within a few minutes without appreciable loss of selectivity (Table 1).

High trans-selectivity (98%) is also achieved in the exhaustive epoxidation of 1,4-cyclohexadiene (**4**) (entry 3, Table 1) by either dioxirane (**1a**,**b**), despite the fact that here the second oxirane ring is introduced in a farther position.

Table 1

Stereoselective epoxidation of cyclic dienes and trienes using dioxiranes **1**.[a]

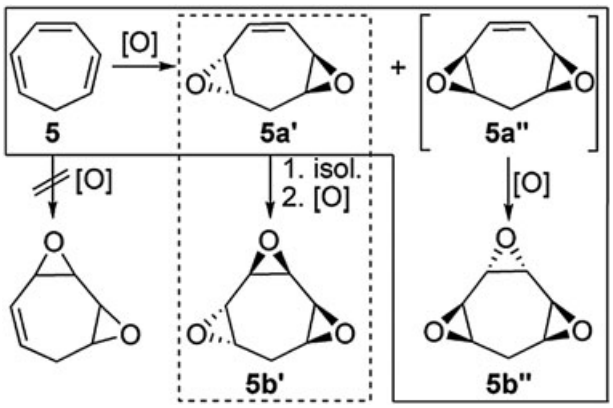
Entry	Substrate	Oxidant (equiv)	Reaction medium	Reaction time (min)	Products	Yield %[b]	Trans/cis %[c]
1	 **2**	**1a** (2.1) **1b** (2.1)	A B	60 2	 **2a**		
2	 **3**	**1a** (2.1) **1b** (2.1)	A B	90 2	 **3a**	98	98
3	 **4**	**1a** (2.1) **1b** (2.1)	A B	90 5	 **4a**		
4	 **5**	**1a** (3.5)	A	180	 **5a'**	90 (86)[d] 10 (8)[d]	90 99
		1b (3.3)	B	10	 **5b"**	93 (89)[d] 7 (7)[d]	93 99
5	 **5a'**	**1b** (1.1)	B	10	 **5b'**	99	—

A: CH_2Cl_2/acetone 1:1; B: CCl_4 (ketone-free solutions of **1b**).
[a]All the reactions were carried out at 0°C.
[b]GC yields (±2%).
[c]Trans to cis ratio, as determined by GC analysis (±2%) as well as by integration (±5%) of characteristic ^{1}H NMR resonances.
[d]Isolated yield.

The oxidation of 1,3,5-cycloheptatriene (**5**) with 3.5 equiv of **1a** (or 3.3 equiv of dioxirane **1b**) affords the *trans*-dioxide **5a′** in 90% yield (or 93%), along with 10% (or 7%) of the *trans*,*trans*-1,2:3,4:5,6-tris-epoxy-cycloheptane (**5b″**) (Table 1, entry 4). It seems reasonable to assume that the latter trioxide **5b″** derives from the rapid overoxidation of the minor *cis*-diastereomer **5a″** also formed (Scheme 1); the latter, in fact, becomes detectable when the epoxidation of **5** is run by stepwise addition of the oxidant [19]. Moreover, we found that isolation and subsequent oxidation of *trans*-dioxide **5a′** with the dioxirane **1b** lead to its *cis*,*trans*-trioxide **5b′** with remarkable yield (entry 5, Table 1; Scheme 1).

In any case, the exhaustive epoxidation of **5** by consecutive dioxirane attack to 1,2–3,4, and then, 5,6 double bonds should actually be discounted on the basis of electronic effect arguments [5a]. In fact, the first 1,2-oxiranyl ring introduced should cause deactivation of the proximal 3,4-double bond by electron-withdrawing effect. In agreement with this view, neither the GC and GC–MS nor the NMR analyses of crude reaction mixtures bring evidence for formation of *cis*-/*trans*-1,2:3,4-bis-epoxides (Scheme 1).

Scheme 1



The high level of diastereoselectivity attained in all the transformations described herein deserves a few comments. Actually, the trans-selectivity observed might find an instructive precedent in our previous reports concerning the trans-stereoselective epoxidation of (homo)allylic methoxycyclopentenes with both dioxiranes [13]. The preferred anti-attack was ascribed to repulsive dipolar interactions between the C–OMe and the dioxirane dipoles, which can act undisturbed in apolar solvents such as CCl_4 [13,14]. On the other hand, we made use of such dipole–dipole interaction arguments in an attempt to explain the highly selective conversion of naphthalene into its *trans*-1,2:3,4-dioxide [15].

A similar scenario seems at play in the epoxidation of cyclic polyenes **2–5** with both dioxiranes. In fact, the first epoxide ring introduced should direct the second dioxirane attack in an antifashion, because of a strong repulsive interaction between the epoxide dipole and the one of the incoming dioxirane. Moreover, such dipole–dipole interaction should act efficaciously on the smaller five- and six-membered ring cyclic polyenes **2–4**, resulting in high trans-stereoselectivity (98%). Instead, the bis-epoxidation of the larger cyclic polyene **5** is met with a drop in diastereoselectivity (trans/cis 90:10, Table 1, entry 4). Perhaps, as the cycle enlarges to seven members, the increased distance between the 1,2 and 5,6 double bonds should bring a relief in the dipolar repulsion. Similar factors may be involved in the selective epoxidation of cyclooctatetraene with **1a** described by Murray and coworkers [16].

We mentioned previously that the minor product *cis*-bisepoxide **5a′** ensuing the epoxidation of **5** is rapidly and quantitatively converted to *cis*,*trans*-trioxide **5b′** under the given conditions, thus escaping detection and isolation. This remarkable diastereoselection could be regarded as another hint of the involvement of dipolar directing effects featuring the oxidative transformations at hand. In fact, in the epoxidation of **5a″**, there is at least one way the dioxirane can approach the substrate double bond so as to experience minimal repulsive effect exerted by the epoxide dipoles [Fig. 2(a)]. On the other hand, at least one of such

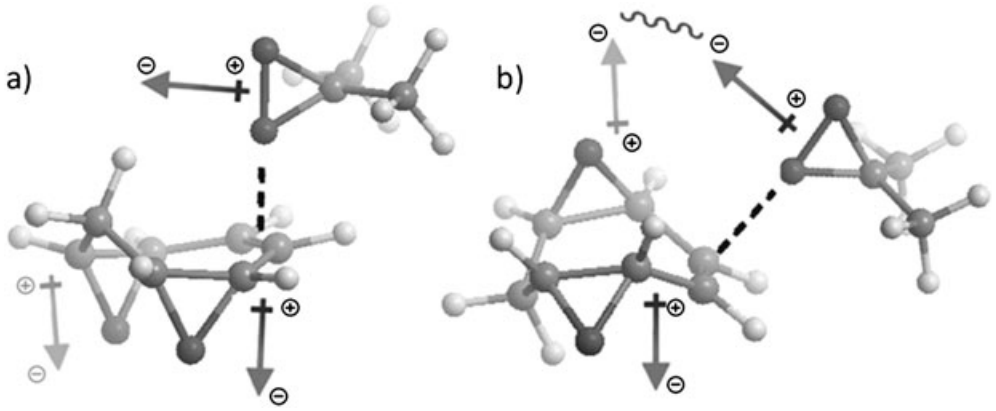


Figure 2. A pictorial representation of dipolar effects arising from interaction of (a) *cis*-dioxide **5a″** and (b) *trans*-dioxide **5a′** with dioxirane **1a**.

unfavorable interactions could be envisaged to occur when the oxidant approaches either side of the *trans*-dioxide **5a′** double bond [Fig. 2(b)].

CONCLUSION

In summary, with the use of dioxiranes **1a** and **1b**, the epoxidation of valuable small- and medium-ring cyclic dienes and trienes can be achieved with excellent yields (up to 98%) and with high trans-selectivity (90–98%) under mild conditions. In all the cases examined, the favored anti-attack following the introduction of the first oxirane ring seems to find a fairly fitting explanation in electrostatic directing effects, already postulated in the dioxirane-mediated epoxidation of naphthalene [15]. Clearly, the results presented herein allow such mechanistic model to gain a more generalized view.

Mechanistic details aside, an improved synthetic route to valuable di- and triepoxides has been described. Compared with traditional and lower yielding methods using peroxyacids [8–10], the use of dioxiranes undeniably offers several advantages including high efficiency and easy work-up.

EXPERIMENTAL

General. Melting points were not corrected. The GC analyses were run using a SPB-1 (0.25-mm film thickness, 30 m × 0.25 mm ID) capillary column in most cases; 1,1,1,2-tetrachloro-2,2-difluoroethane (Freon A112), Sigma-Aldrich Corp. St. Louis, MO, USA was used as inert internal standard; temperature program: 60°C (5 min) to 280 at 3°C/min, gas carrier He (8 mL/min), detector : FID. The GC–MS analyses were performed in EI mode (70 eV). The ^{1}H NMR spectra were recorded on a 500-MHz spectrometer; resonances are referenced to residual isotopic impurity $CHCl_3$ (7.26 ppm) of $CDCl_3$ solvent and/or to TMS. The ^{13}C NMR spectra (125.759 MHz) are referenced to the middle peak of $CDCl_3$ solvent (77.0 ppm). The IR spectra refer to samples as neat or in KBr pellets.

Substrates **2–5** were commercially available; solvents used in oxidations reactions by dioxiranes were purified by standard methods. Commercial 1,1,1-trifluoro-2-propanone (TFP; Sigma-Aldrich, St. Louis, MO) (bp 22°C) was purified by fractional distillation over granular P_2O_5, stored over 5-Å molecular sieves, and routinely redistilled prior to use.

Curox triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (a gift from Peroxid-Chemie GmbH, Munich, Germany) was our source of potassium peroxymonosulfate used in the generation of dioxiranes.

Solutions of 0.3–0.8*M* methyl(trifluoromethyl)dioxirane (**1b**) in TFP or CCl_4 and solutions of 0.08–0.16*M* DDO (**1a**) in acetone were obtained by adopting procedures, equipment, and precautions already reported in detail [1,2].

General procedure for epoxidations with dioxiranes 1a and 1b. To a stirred solution of freshly distilled monomer **2** (100 mg, 1.51 mmol) in the proper reaction solvent (30 mL of CH_2Cl_2 or 2 mL of CCl_4 for reactions with **1a** or **1b**, respectively), containing the Freon A112 internal standard, and kept at 0°C, a solution of DDO (**1a**) in acetone (30 mL, 0.112*M*, 3.36 mmol) or of TFDO (**1b**) in CCl_4 (2.2 mL, 0.32*M*, 0.70 mmol) was added in one portion. The reaction progress was monitored by GC analysis of micro-aliquots periodically withdrawn from the reaction flask. Upon reaction completion, pure (98%+, GC) cyclopentadiene *trans*-1,2:3,4-dioxide (**2a**) was simply obtained by evaporation of the volatile solvents *in vacuo*. Characterization of **2a** by a combination of spectroscopic techniques (^{1}H, ^{13}C NMR, IR, and MS) provides data in agreement with literature [17].

(1α,2β,4β,6α)-Dioxatricyclo[4.1.0.0^{2,4}]heptane (2a) [17]. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (ddd, *J* = 3.0 Hz, 1.5 Hz, 0.8 Hz, 2H), 3.23 (dt, *J* = 3.4 Hz, 1.5 Hz, 2H), 2.05 (m, 2H,); ^{13}C NMR (125 MHz, $CDCl_3$) δ 59.3, 51.3, 31.0; IR (neat): 3046, 2932, 1388, 1294, 1272, 1208, 1032, 1066, 839 cm^{-1}; GC–MS (70 eV) *m/z* (r.i.): 98 (M^+, 2), 97 ($M^+ - H$, 19), 71 (40), 54 (75), 43 (90), 39 (100).

Except for products **5a′** and **5b″**, the isolation of pure (98%+, GC) epoxides **2a–4a** and **5b′** required just removal of solvent upon reaction completion. All products were characterized by ^{1}H, ^{13}C NMR, IR, and MS, and identified upon comparison with spectral data present in the literature.

(1α,2β,4β,7α)-3,8-Dioxatricyclo[5.1.0.0^{2,4}]octane (3a) [8]. Colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.30 (dd, *J* = 3.5 Hz, 1.5, 2H), 3.10 (m, 2H), 1.90 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.1, 50.1, 19.1; IR (neat): 3033, 2975, 1370, 1285, 1261, 1199, 1002, 956 cm^{-1}; GC–MS (70 eV) *m/z* (r.i.): 112 (M^+, 1), 83 (9), 55 (100), 43 (9), 41 (28), 39 (41).

(1α,3β,5β,7α)-4,8-Dioxatricyclo[5.1.0.0^{3,5}]octane (4a) [9]. White powder, mp 184–185°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.04–3.02 (m, 4H), 2.28 (broad s, 4H,); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.0, 25.8; IR (KBr): 2943, 2924, 1420, 1342, 1267, 1135, 1048 cm^{-1}; GC–MS (70 eV) *m/z* (r.i.): 112 (M^+, 1), 83 (17), 69 (6), 55 (100), 43 (10), 41 (53), 39 (45).

(1α,3β,5β,8α)-4,9-Dioxatricyclo[6.1.0.0^{3,5}]non-6-ene (5a′) [18]. Isolated by chromatographic separation (silica gel, hexane/Et_2O 1:1) of the crude reaction mixture of **5** with **1a** (86% yield) or with **1b** (89% yield); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (t, *J* = 1.7 Hz, 2H), 3.32–3.34 (m, 4H), 2.29 (t, *J* = 4.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.4, 53.1, 51.5, 27.7; IR (neat): 2966, 2896, 1620, 1431, 1227, 1143, 1073 cm^{-1}; GC/MS (70 eV) *m/z* (r.i.): 124 (M^+, 1), 123 (1), 95 (19), 81 (45), 68 (100), 41 (42), 39 (49).

(1α,2β,4β,5α,7α,9α)-3,6,10-Trioxatetracyclo[7.1.0.0^{2,4}.0^{5,7}]decane (5b″) [18]. Isolated by chromatographic separation (silica gel, hexane/Et_2O 1:1) of the crude reaction mixture of **5** with **1a** (8% yield) or with **1b** (7% yield); white powder, mp 116°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.33 (d, *J* = 3.8 Hz, 2H), 3.25 (s, 2H), 3.17 (m, 2H), 2.89 (dt, *J* = 14.0 Hz, 5.1 Hz, 1H), 1.00 (dt, *J* = 14.0 Hz, 8.7Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.5, 52.1, 50.8, 32.4; IR (KBr): 2996, 2896, 1342, 1267, 1135; GC–MS (70 eV) *m/z* (r.i.): 139 (1), 81 (36), 68 (100), 55 (55), 39 (85).

(1α,2α,4α,5β,7β,9α)-3,6,10-Trioxatetracyclo[7.1.0.0^{2,4}.0^{5,7}]decane (5b′) [18]. White solid, mp 64°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.39 (t, *J* = 3.6 Hz, 1H), 3.35 (d, *J* = 3.6 Hz, 1H), 3.28 (d, *J* = 4.0 Hz, 1H), 3.23 (ddd, *J* = 6.5 Hz, 4.0 Hz, 1.6 Hz, 1H), 3.16 (td, *J* =3.6 Hz, 0.7 Hz, 1H), 3.02 (m, 1H), 2.75 (dt, *J* = 14.9 Hz, 6.5 Hz, 1H), 1.86 (ddd, *J* = 14.9 Hz, 7.0 Hz, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.8, 53.4, 51.9, 51.3, 51.0, 50.9, 27.9; IR (KBr pellets): 2960, 1453, 1270, 1012; GC/MS (70 eV) *m/z* (r.i.): 139 (1), 123 (2), 111 (22), 83 (23), 81 (64), 71 (48), 68 (59), 55 (90), 53 (79), 39 (100).

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REFERENCES AND NOTES

[1] Murray, R. W.; Singh, M. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R.; Rees, C. W.; Striven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; pp 429–456.

[2] Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. J Org Chem 1988, 53, 3890.

[3] For recent reviews on dioxiranes, see: (a) Adam, W.; Zhao, C.-G.; Kavitha, J. Organic Reactions; Wiley: Hoboken, NJ, 2007; 69, pp 1–346; (b) Curci, R.; D'Accolti, L.; Fusco, C. Acc Chem Res 2006, 39, 1.

[4] (a) Adam, W.; Saha-Moller, C. R.; Zhao, C.-G. Org React 2002, 61, 219; (b) Adam, W.; Saha-Möller, C. R.; Ganeshpure, P. A. Chem Rev 2001, 101, 3499; (c) Shi, Y. In Modern Oxidation Methods; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, 2008; pp 85–115.

[5] (a) Annese, C.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gandolfi, R.; Curci, R. J Am Chem Soc 2008, 130, 1197; (b) D'Accolti, L.; Fusco, C.; Annese, C.; Rella, M. R.; Turteltaub, J. S.; Williard, P. G.; Curci, R. J Org Chem 2004, 69, 8510; (c) Bortolini, O.; Fantin, G.; Fogagnolo, M. Tetrahedron: Asymmetry 2004, 15, 3831; (d) D'Accolti, L.; Fusco, C.; Rella, M. R.; Curci, R. Synth Commun 2003, 33, 3009.

[6] For instance, see: Curci, R.; Detomaso, A.; Lattanzio, M. E.; Carpenter, G. B. J Am Chem Soc 1996, 118, 11089. See also references cited therein.

[7] (a) Bach, R. D. In The Chemistry of Peroxides; Patai, S., Ed.; Wiley: New York, 2006; 1, Chapter 1, pp 85–115 (see references therein); (b) Freccero, M.; Gandolfi, R.; Sarzi-Amade, M. Tetrahedron 1999, 55, 11309.

[8] Aldegunde, M. J.; Castedo, L.; Granja, J. R. Chem Eur J 2009, 15, 4785.

[9] Cavdar, H.; Saracoglu, N. Eur J Org Chem 2008, 27, 4615.

[10] Gruber-Khadjawi, M.; Hönig, H.; Illaszewicz, C. Tetrahedron: Asymmetry 1996, 7, 807.

[11] (a) Yan, R. Y.; Chen, R. Y.; Yu, D. Q. Chinese Chem Lett 2011, 22, 580; (b) Ning, L.; Zhan, J.; Qu, G.; Zhong, L.; Guo, H.; Bi, K.; Guo, D. Tetrahedron 2003, 59, 4209.

[12] Stereoselective epoxidations with dioxiranes Part 2, Part 1: D'Accolti, L.; Fusco, C.; Annese, C. Tetrahedron Lett 2005, 46, 8459.

[13] D'Accolti, L.; Fiorentino, M.; Fusco, C.; Rosa, A. M.; Curci, R. Tetrahedron Lett 1999, 40, 8023.

[14] (a) Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. J Org Chem 1996, 61, 1830; (b) Adam, W.; Smerz, A. K. J Org Chem 1996, 61, 3505; (c) Adam, W.; Smerz, A. K. Bull Soc Chim Belg 1996, 105, 581.

[15] (a) Mello, R.; Ciminale, F.; Fiorentino, M.; Fusco, C.; Prencipe, T.; Curci, R. Tetrahedron Lett 1990, 31, 6097; (b) Curci, R.; Dinoi, A.; Rubino, M. F. Pure Appl Chem 1995, 67, 811.

[16] Murray, R. W.; Singh, M.; Rath, N. P. Tetrahedron 1999, 55, 4539.

[17] Sequin, U.; Farkas, F.; Bur, D.; Zehnder, M. Tetrahedron 1992, 48, 103.

[18] Rücker, C.; McMullen, G.; Krüger, C.; Prinzbach, H. Chem Ber 1982, 115, 2287.

[19] For instance, when cyclotriene **5** is reacted with 2.0 equiv of **1b**, under the usual conditions (Table 1), the composition of products (GC analysis) is as follows: cycloheptatriene 1,2-oxide (5%), *trans*-dioxide **5a′** (81%), and *cis*-dioxide **5a″** (14%) (*trans*/*cis* ratio 85:15). Further addition of dioxirane **1b** (1.3 equiv) to the reaction mixture provides the distribution of products reported in Table 1 (entry 4). In particular, the presence of the *cis*-dioxide 5a″ in the reaction mixture of the first oxidation step could be established based upon the relevant spectral data as follows: GC–MS (70 eV) *m*/*z* (RI): 124 (M^+, 1) ^{13}C NMR ($CDCl_3$, 125 MHz): δ 127.3 (=*C*H), 54.4 (*C*–O), 50.8 (*C*–O), 32.2 (CH_2) [18].