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m-CPBA/KOH: An Efficient Reagent for Nucleophilic Epoxidation of *gem*-Deactivated Olefins†

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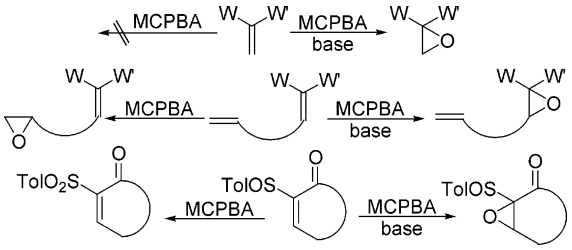


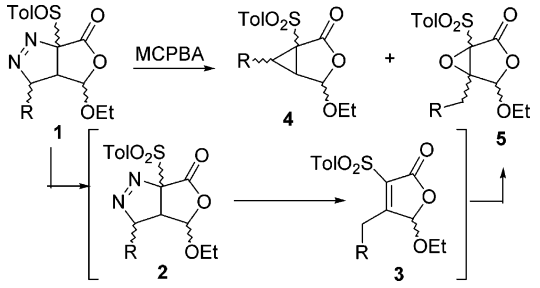
The *m*-chloroperoxybenzoate anion (generated from *m*-CPBA and bases such as K_2CO_3 or KOH) is a highly efficient nucleophilic epoxidating reagent for strongly deactivated olefins containing two electron-withdrawing groups at the same carbon, under mild conditions which affect neither other double bonds nor electrophilic oxidizable centers such as sulfoxides.

Introduction

In the course of our research on 1,3-dipolar reactions of diazoalkanes with activated vinylsulfoxides,[1] we were interested in the synthesis of cyclopropanes by thermal extrusion of nitrogen from pyrazolines. In refluxing toluene, sulfinylpyrazolines **1** evolved into olefins instead of cyclopropanes, but other sulfonylpyrazolines could be transformed into cyclopropanes[2] despite the fact that their corresponding sulfinyl derivatives only evolved into complex mixtures. As these results suggested that sulfonyl derivatives are more appropriate than the sulfinyl derivatives as precursors of the cyclopropanes, we decided to study the pyrolisis of sulfonylpyrazolines **2**, derived from **1**. The oxidation of **1** with *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded mixtures of sulfonyl cyclopropanes **4** and sulfonyl oxiranes **5** (Scheme 1). The formation of **5** can only be explained by assuming the epoxidation of **3** under the reaction conditions, which is completely unexpected because they are strongly deactivated olefins toward electrophilic epoxidation (Scheme 1).

As the oxiranes are essential intermediates and building blocks in organic synthesis,[3] epoxidation has become

SCHEME 1



one of the most significant reactions in the oxy-functionalization of organic molecules. Among the numerous reagents existing for direct epoxidation of double bonds,[4] *m*-CPBA is the one of choice for laboratory-scale experiments in the case of electron-rich olefins because it is very efficient and it can be easily and safely handled in very clean reactions.[5] The usually accepted mechanism for the *m*-CPBA epoxidation involves a concerted elec-

† Dedicated to Prof. Joaquin Plumet on the occasion of his 60th birthday.

(1) García Ruano, J. L.; Fraile, A.; González, G.; Martín, M. R.; Clemente, F. R.; Gordillo, R. *J. Org. Chem.* **2003**, *68*, 6522−6534 and references therein.

(2) García Ruano, J. L.; Alonso de Diego, S. A.; Martín, M. R.; Torrente, E.; Martín Castro, A. M. *Org. Lett.* **2004**, *6*, 4945−4948.

(3) See, for example: (a) Gorzynski Smith, J. *Synthesis* **1984**, 629−655. (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431. (c) Lauret, Ch. *Tetrahedron: Asymmetry* **2001**, *12*, 2359−2383. (d) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625−1642. (e) Antoniotti, S.; Duñach, E. *Synthesis* **2003**, 2753−2762.

(4) See, for example: (a) Rao, A. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Oxford: Pergamon Press: 1991; Vol. 7, p 357. (b) Sawaki, Y. Epoxidation and Hydroxylation. In *The Chemistry Hydroxyl, Ether and Peroxide Groups*; Patai, S., Ed.; John Wiley and Sons; Sussex, UK, 1993; p 587. (c) Hudlicky, M. *Oxidation in Organic Chemistry*; American Chemical Society: Washington, DC, 1990.

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trophilic addition of the oxygen to the double bonds,[6] and therefore, only the electron-rich olefins give satisfactory results. By contrast, the reactivity of alkenes bearing one electron-withdrawing group at the double bond is considerably depressed, though not entirely extinguished if any alkyl or phenyl substituent is also present.[7] In these cases, epoxidation with *m*-CPBA is much more difficult.[8] More strongly deactivated olefins are not able to suffer electrophilic epoxidation, but require nucleophilic reagents, such as HOO^-,[9] *t*-$BuOO^-$,[10] or NaClO[11] for epoxidation. They react according to a mechanism involving the conjugated addition of the reagents followed by the attack of the intermediate carbanion to the oxygen forming the epoxide, the OH^-, *t*-BuO^-, or Cl^- being the leaving groups. On the basis of this evolution, we reasoned that *m*-$ClC_6H_4CO_2O^-$ should be very efficient in these reactions due to the high nucleophilicity of the peroxycarboxylate anion and the stability of the leaving carboxylate ion. Moreover, the use of the *m*-$ClC_6H_4CO_2O^-$ instead HOO^- or *t*-$BuOO^-$ could provide significant advantages due to presumably higher solubility in organic solvents and lower nucleophilicity and basicity of the *m*-$ClC_6H_4CO_2^-$with respect to those of the OH^- and *t*-BuO^-. A thorough scrutiny of the literature revealed some examples where *m*-CPBA has been used for the epoxidation of highly electron-deficient olefins.[12] To explain the epoxidation of antracene-1,4,9,10-tetrone[13] and sulfonyl pyridazinones[14] with *m*-CPBA, the initial addition of the reagent to form a neutral adduct, followed by elimination of *m*-chlorobenzoic acid has been postulated. Different mechanisms have been proposed to explain the *m*-CPBA oxidation of 1,1-disulfonyl ethylenes[15] and alkylidenemalonates,[16] (conjugated addition[15] and 1,3-dipolar cycloaddition[17]) despite their similar structures. Concerning the use of *m*-$ClC_6H_4CO_2O^-$ as an epoxidating reagent we have only found the reaction of the (*Z*)-*p*-tolylsulfonyl styrene with *m*-CPBA in alkaline aqueous dioxan.[18] However the aim of this study was not strictly synthetic but it intented to solve the lack of stereospecificity observed in reactions with HOO^-epoxidations. Although there are several papers describing the nucleophilic character of the epoxidation with *m*-CPBA in alkaline medium,[19] ref 18 is the only one cited in all of them.

Thus, we can conclude that the use of *m*-CPBA/base as an epoxidating reagent has been scarcely investigated and its scope and limitations remain unknown. In this paper, we report the efficiency of the system *m*-CPBA/base in organic solvents for epoxidating strongly deactivated olefins containing two electron-withdrawing groups at the same carbon as well as its use in some chemoselective processes.[20]

Results and Discussion

We first studied the behavior of 2-*p*-tolylsulfonylcyclopent-2-en-1-one (**6**) and 5-ethoxy-3-*p*-tolylsulfonylfuran-2(5*H*)-one (**8**) in their reactions with *m*-CPBA under different conditions (Table 1).

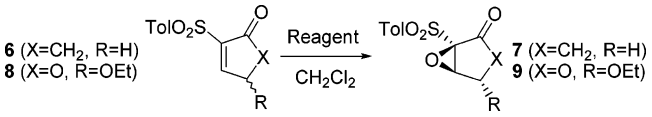
The reactions of sulfonylcyclopentenone **6** with *m*-CPBA are very slow (entries 1−3). Even with an excess of the reagent (2.1 equiv), 4 days were required to achieve a 72:28 mixture of **7**:**6** (entry 3). The addition of K_2CO_3 or KOH to the reaction mixture significantly improved the results (entries 4−8). Reaction times were shorter when [*m*-$ClC_6H_4CO_2O^-$] became higher due to an increase in the amount of the base (compare entries 4 and 5) or its strength (compare entries 6 and 8). Even under sub-stoichiometric amounts of base the improvements are quite significant (entry 4). Almost quantitative yields are obtained under several very mild conditions (entries 5 and 7), which evidences the efficiency of the system *m*-CPBA/base to get the epoxidation of **6**.

A similar study was performed on sulfonylfuranone **8**. Its behavior was similar to that observed for **6** but its reactivity with *m*-CPBA was clearly higher (entries 12 and 13), its conversion being complete after 24 h (entry 13). The addition of bases (entries 14−22) sharply decreased the reaction times but in some cases the yields were also much poorer, presumably due to the low stability of the resulting epoxylactone in the basic medium. The best yields were achieved by shortening the reaction time and decreasing the amount and strength of base as much as possible (entries 13, 14, and 16). It is evident that decomposition of *m*-CPBA in basic medium[21] is not significant under the reaction conditions used in Table 1.

The exclusive formation of the *anti*-epoxide **9** in these reactions must be a consequence of the electrostatic repulsion of the OEt group and the negatively charged peroxycarboxylate ion unstabilizing the *syn* approach.

(5) Fieser; Fieser. *Reagents for Organic Synthesis*; Wiley & Sons: New York, 1967, Vol. I, pp 135−139.
(6) (a) Kim, C.; Traylor, T. G.; Perrin, C. L. *J. Am. Chem. Soc.* **1998**, *120*, 9513−9516 and references therein. (b) Bach, R. D.; Gluskhovtsev, M. N.; Gonzalez, C. *J. Am. Chem. Soc.* **1998**, *120*, 9902−9910.
(7) Swern, D. *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1971; Vol. 2, Chapter V.
(8) See, for example: (a) MacPeek, D. L.; Starcher, P. S.; Phillips, B. *J. Am. Chem. Soc.* **1959**, *81*, 680−683. (b) Valente, V. R.; Wolfhagen, J. L. *J. Org. Chem.* **1966**, *31*, 2509−2512. (c) Glabe, A. R.; Sturgeon, K. L.; Ghizzoni, S. B.; Musker, W. K.; Takahashi, J. N. *J. Org. Chem.* **1996**, *61*, 7212−7216. (d) Moyna, G.; Willams, H. J.; Scott, A. I. *Synth. Commun.* **1996**, *26*, 2235−2239.
(9) (a) Bunton, C. A.; Minkoff, C. J. *J. Chem. Soc.* **1949**, 665−670. (b) Patai, S.; Rappoport, Z. In *The Chemisry of Alkenes*; Patai, S., Ed.; Wiley-Interscience: New York, 1964; Chapter 8, pp 512−517.
(10) (a) Jackson, R. F. W.; Standen, S. P.; Clegg, W. *J. Chem. Soc., Perkin Trans. 1* **1995**, 149−156. (b) Rodríguez, S.; Vidal, A.; Monroig, J. J.; González, F. V. *Tetrahedron Lett.* **2004**, *45*, 5359−5361.
(11) (a) Nishide, K.; Aratama, A.; Kamanaka, T.; Inoue, T.; Node, M. *Tetrahedron* **1994**, *50*, 8337−8346. (b) Reed, A. D.; Hegedus, L. S. *J. Org. Chem.* **1995**, *60*, 3787−3794.
(12) (a) Ross, W. J.; Todd, A.; Clark, B. P.; Morgan, S. E. *Tetrahedron Lett.* **1981**, *22*, 2207−2208. (b) Eğe, S. N.; Adams, A. D.; Gess, E. J.; Ragone, K. S.; Kober, B. J.; Lampert, M. B.; Umrigar, P.; Lankin, D. C.; Griffin, G. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 325−331. (c) Potts, K. T.; Cipullo, M. J.; Ralli, P.; Theodoridis, G. *J. Org. Chem.* **1982**, *47*, 3027−3038.
(13) Chandler, M.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans 1* **1980**, 1007−1012.
(14) Fariña, F.; Martín, M. V.; Romañach, M.; Sánchez, F. *An. Quim., Ser. C* **1988**, *84*, 173−175.
(15) Ogura, K.; Takahashi, S.; Kawamoto, Y.; Suzuki, M.; Fujita, M.; Suzuki, Y.; Sugiyama, Y. *Tetrahedron Lett*. **1993**, *34*, 2649−2652.
(16) De Cock, C. J. C.; De Keyser, J.-L.; Poupaert, J. H.; Dumont, P. *Bull. Soc. Chim. Belg*. **1987**, *96*, 783−786.
(17) (a) Kwart, H.; Hoffman D. M. *J. Org. Chem*. **1966**, *31*, 419−425. (b) Kwart, H.; Starcher, P. S.; Tinsley, S. W. *J. Chem. Soc., Chem. Commun*. **1967**, 335−337.
(18) Curci, R.; DiFuria, F. *Tetrahedron Lett*. **1974**, *15*, 4085−4086.
(19) (a) Curci, R.; DiFuria, F.; Meneghin, M. *Gazz. Chim. Ital*. **1978**, *108*, 123−125. (b) Apeloig, Y.; Karni, M.; Rappoport, Z. *J. Am. Chem. Soc.* **1983**, *105*, 2784−2793. (c) Washington, W.; Houk, K. N. *Org. Lett*. **2002**, *4*, 2661−2664.
(20) Part of this work has been presented at the 21th International Symposium on the Organic Chemistry of Sulfur (ISOCS XXI), Madrid, Spain, July 2004; Poster 18-Tu.

TABLE 1. Reactions of Compounds 6 and 8 with *m*-CPBA under Different Conditions



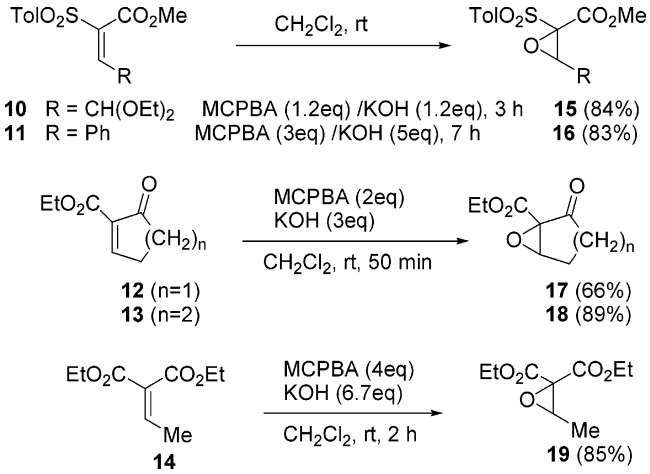
entry	starting material (1 equiv)	reagent (equiv)	*T* (°C)	reaction time	**6**:**7** or **8**:**9** ratio (% yield)
1	6	*m*-CPBA (1.1)	20	1.5 h	100:0
2	6	*m*-CPBA (2.1)	20	4.5 h	85:15
3	6	*m*-CPBA (2.1)	20	96 h	28:72
4	6	*m*-CPBA (1.15)/ K_2CO_3 (0.33)	20	30 min	0:100 (85)
5	6	*m*-CPBA (1.5)/ K_2CO_3 (1.5)	20	5 min	0:100 (90)
6	6	*m*-CPBA (1.15)/ K_2CO_3 (1.15)	−20	40 min	0:100 (82)
7	6	*m*-CPBA (1.5)/ KOH (1.5)	20	5 min	0:100 (94)
8	6	*m*-CPBA (1.15)/ KOH (1.15)	−20	10 min	0:100 (88)
9	6[a]	*t*-BuOOH (2)/ K_2CO_3 (2)	20	15 min	0:100 (51)
10	6[a]	*t*-BuOOH (1.15)/ K_2CO_3 (1.15)	−20	90 min	0:100 (<30)
11	6[a]	*t*-BuOOH (1.15)/ KOH (1.15)	−20	30 min	dec
12	8	*m*-CPBA (1.12)	20	30 min	82:18
13	8	*m*-CPBA (1.12)	20	24 h	0:100 (77)
14	8	*m*-CPBA (1.12)/ K_2CO_3 (0.5)	20	30 min	0:100 (75)
15	8	*m*-CPBA (1.12)/ K_2CO_3 (1.12)	20[b]	5 min	0:100 (55)
16	8	*m*-CPBA (2)/ K_2CO_3 (1)	20	5 min	0:100 (77)
17	8	*m*-CPBA (1.12)/ K_2CO_3 (0.5)	−78	3 h	40:60
18	8	*m*-CPBA (2)/ KOH (1)	20	5 min	0:100 (68)
19	8	*m*-CPBA (1.12)/ KOH (1.12)	20[b]	5 min	0:100 (32)
20	8	*m*-CPBA (1.12)/ KOH (1.12)	−78	5 min	0:100 (52)
21	8	*m*-CPBA (2)/ KOH (1)	−78	3 h	0:100 (57)
22	8	*m*-CPBA (1.12)/ KOH (0.5)	−78	3 h	0:100 (66)
23	8[a]	*t*-BuOOH (2)/ K_2CO_3 (2)	20	1 h	0:100 (<30)
24	8[a]	*t*-BuOOH (1.12)/ KOH (1.12)	−78	40 min	0:100 (<30)[c]

[a] Solvent: THF. [b] The same result was obtained at −20 °C. [c] It is obtained along with other unidentified products.

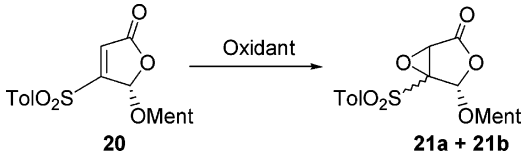
The fact that the same *anti*-epoxide is exclusively formed in the reaction with *m*-CPBA suggests that, also in this case, the epoxidation is the result of a nucleophilic attack of the peroxybenzoate to the double bond, and its low concentration is responsible for their low reactivity. The fact that the reactivity of furanone **8** with *m*-CPBA is higher than that of ketone **6** (compare entries 1−3 with 12−13) could be due to the higher basicity of the lactonic carbonyl, which produces deprotonation of the *m*-CPBA in higher extension than the ketonic carbonyl at **6**. In this sense, the anomalously high reactivity of the sulfonylpyridazinones with *m*-CPBA[14] (24 h, rt, quantitative yield) could also be a consequence of the influence of the nitrogen atoms on the dissociation degree of the *m*-CPBA.

For comparative purposes, we have included in Table 1 the results obtained in the reactions of **6** (entries 9−11) and **8** (entries 23 and 24) with *t*-BuOOH/base, which had been used for nucleophilic epoxidation of other deactivated substrates. The reactivity was lower than that of the systems *m*-CPBA/base and, which is more important,

SCHEME 2



SCHEME 3



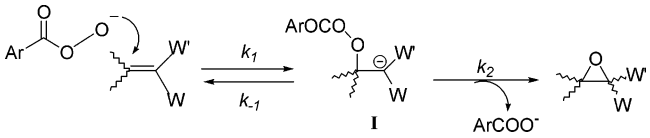
the yields obtained were quite lower, probably due to the larger basicity of the ROO^- compared with RCO_2O^-.

The best results obtained in the epoxidation of other deactivated double bonds (**10**−**14**) are indicated in Scheme 2. The sulfonyl esters **10** and **11** can be efficiently transformed into their epoxides **15** and **16** by treatment with *m*-CPBA/KOH, at rt in 3 and 7 h, respectively. It evidences that the reactivity of these acyclic esters is lower than that of the cyclic ones, such as lactone **8** (Table 1), which is typical for Michael-addition-type reactions. The epoxidation of cyclic ketoesters **12** and **13** as well as acyclic diester **14** were also possible with *m*-CPBA/KOH, affording oxyranes **17**−**19** in good yields. The relative reactivity of compounds **10**−**14** can be easily rationalized based on the electronic density of their double bonds.

We next studied the behavior, under two different conditions (*m*-CPBA and 1:1 *m*-CPBA/KOH), of the following monoactivated olefins: furan-2(5*H*)-one, 5-methoxyfuran-2(5*H*)-one, cyclopent-2-en-1-one, cyclohex-2-en-1-one, and 4-methylphenyl vinyl sulfone. After 24 h at rt, none of these reactions had advanced significantly, which indicated that these olefins are not appropriate substrates for nucleophilic or electrophilic epoxidation with *m*-CPBA. The same behavior was observed for diethyl maleate. Finally, we studied the reactions of *m*-CPBA with 4-phenylsulfonyl 5-menthyloxyfuranone **20** (Scheme 3), whose electronic density at the double bond must be similar than that of **8**. Sulfone **20** remaind unaltered when it was stirred with *m*-CPBA at rt for 24 h. The addition of K_2CO_3 allowed the formation of the epimeric epoxides **21** (Scheme 3), but only 50% of conversion was achieved after 23 h, whereas **8** completely reacted after 0.5 h under similar conditions (entry 14, Table 1). When the amount of K_2CO_3 was increased or KOH was used, the reaction was faster but the appear-

(21) Dryuk, V. G. *Tetrahedron* **1976**, *32,* 2855−2866 and references therein.

SCHEME 4



ance of menthol and other decomposition products was also detected, as happened for **8** (entries 19 and 20, Table 1). The same but even faster decomposition was observed with *t*-BuOOH/K_2CO_3.

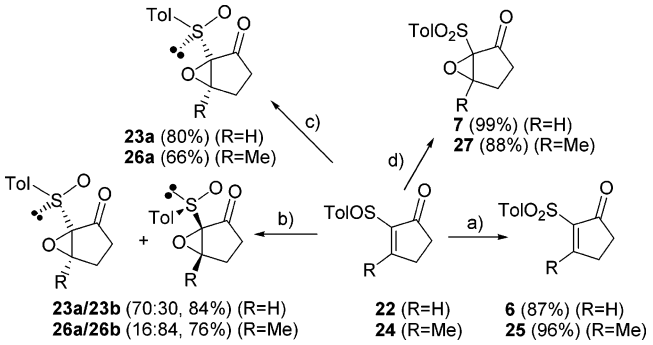
The formation of the mixture of epoxides **21a** and **21b** indicates a lack of stereoselectivity and suggests that the nucleophilic attack must take place onto C-3, which is scarcely sensitive to the steric discrimination of the OR group at C-5. On the basis of these results, it seems that peroxybenzoates are efficient only for epoxidizing olefins bearing two electron-withdrawing groups at the same carbon (i.e., *gem*-disubstituted olefins), which are the best Michael acceptors. The usually accepted mechanism[19b] is that depicted in Scheme 4. The highly stabilized carbanion intermediate **I** quickly evolves into the epoxide in a process where the benzoate acts as a leaving group. If we assume for *gem*-deactivated olefins that the second step is the rate-determining step, the lower reactivity of the best nucleophile ($R-O_2^-$) than that of RCO_3^- can be explained considering that RO^- is a poorer leaving group than $R-CO_2^-$. Reactions of monoactivated or 1,2-deactivated olefins with *m*-CPBA/base systems are not satisfactory enough, probably due to their lower value of k_1, which corresponds to the rate-limiting step.

It is remarkable that the use of substoichiometric amounts of bases is enough to achieve the complete transformation of the substrates into their epoxides. It indicates that $Ar-CO_2^-$ generated in these reactions must be in equilibrium with *m*-CPBA, giving rise to $Ar-CO_3^-$ required for the reaction to proceed until completion. The weak nucleophilic character of $Ar-CO_2^-$ (lower than that of $R-O^-$) makes slower its attack to other functional groups, such as esters, lactones, and even the previously formed epoxides. It would explain why the *m*-CPBA/base systems afford better yields than other reagents, as well as the fact that the use of *m*-CPBA with a catalytic amount of K_2CO_3 offers some advantages with respect to their 1:1 mixtures or *m*-CPBA/KOH, despite the slower reaction rate of the former system.

On the basis of the previously mentioned results, we reasoned that the careful choice of the reaction conditions would allow the highly chemoselective oxidation of electron-rich (with *m*-CPBA) or strongly electron-poor (with *m*-CPBA/base) centers in molecules containing both of them. In order to verify this point, we studied the epoxidation of 2-*p*-tolylsulfinylcyclopent-2-en-1-one (**22**), and its 3-methyl derivative **24**, both of them with the sulfur atom as an electron-rich center and the double bond as an electron-poor one. The best results obtained under different conditions are indicated in Scheme 5.

The exclusive oxidation of the sulfinyl sulfur at **22** and **24** was achieved with *m*-CPBA in 1 h at rt, yielding sulfones **6** and **25**, respectively. Under these conditions, the double bond remained unaltered and the formation of compounds **7** and **27** could only be detected after much longer reaction times. When the oxidation was performed with a 1:≥1 mixture *m*-CPBA/KOH at ≤0 °C, only

SCHEME 5[a]



[a] Key: (a) *m*-CPBA (1.5 equiv), rt, 1 h; (b) *m*-CPBA (2 equiv)/KOH (2.2 equiv), −20 °C (15 min, R = H; 6 h, R = Me); (c) *m*-PCBA (2 equiv)/KOH (2.2 equiv)/$Yb(OTf)_3$ (0 °C, 60 min, R = H; −20 °C, 7 h, R = Me); (d) *m*-CPBA (2.5 equiv)/K_2CO_3 (1.2 equiv), rt, 2.5 h.

sulfinyl epoxides **23** and **26**, both of them as a mixture of diastereoisomers, were formed in high yields (the epoxides **23** and **26** represented in Scheme 5 are those corresponding to the enantiomers formed from the sulfoxide with *R* configuration at the sulfur atom). As expected, the reaction of **24** (6 h) was slower than that of **22** (15 min) (Me group decreases the reactivity of **24** from steric and electronic grounds). Both the ratio of the reagents and the temperature seem to be critical to achieve complete chemoselectivity. A smaller proportion of KOH and temperatures above 0 °C, or the use of K_2CO_3 instead KOH as the base, determined the formation of mixtures of sulfonyl and sulfinyl epoxides (**7** + **23** or **27** + **26**), probably due to the existence of nondissociated *m*-CPBA. It suggests that $Ar-CO_3^-$ is unable to oxidize sulfinylic sulfur under the conditions that we have used.[22] The complete oxidation of **22** and **24** into **7** and **27** could be achieved with *m*-CPBA (2.5 equiv) and K_2CO_3 (1.2 equiv) in 2.5 h (Scheme 5).

The stereoselectivity of the oxidation into epoxysulfoxides was moderate (**23a**:**23b** = 70:30 and **26a**:**26b** = 16:84), and the separation of the diastereoisomers was only possible for the 4-methyl derivatives. The configurational assignment of the epoxides could not be made on the basis of their ^1H NMR spectroscopic data because they only differ in the chemical shift of the proton or methyl group at the oxiranic carbon ($\Delta\delta$ = 0.03 ppm). However, when the reactions were performed with *m*-CPBA (2 equiv)/KOH (2.2 equiv) in the presence of $Yb(OTf)_3$ (1 equiv) they became completely stereoselective and only **23a** and **26a** were isolated in good yields (Scheme 5). It is remarkable that in the presence of the Lewis acid the reaction was slower, which suggests some type of interaction with the reagent ($Ar-CO_3^-$) which decreases its efficiency. Epoxides **23a** (obtained chemically and diastereoisomerically pure in the presence of $Yb(OTf)_3$) and **26b** gave good crystals for X-ray analysis,[23] which made it possible to establish that their relative configurations are those depicted in Scheme 5.

(22) There are some reports suggesting that the oxidation of sulfoxides into sulfones can be performed with the peroxibenzoate anion. See: Curci, M.; Modena, G. *Gazz. Chim. Ital.* **1964**, *94*, 1257−1267.

(23) The authors have deposited atomic coordinates for **23a** and **26b** with the Cambridge Crystallographic Data Centre (Deposit Number 256915 and 258513, respectively).

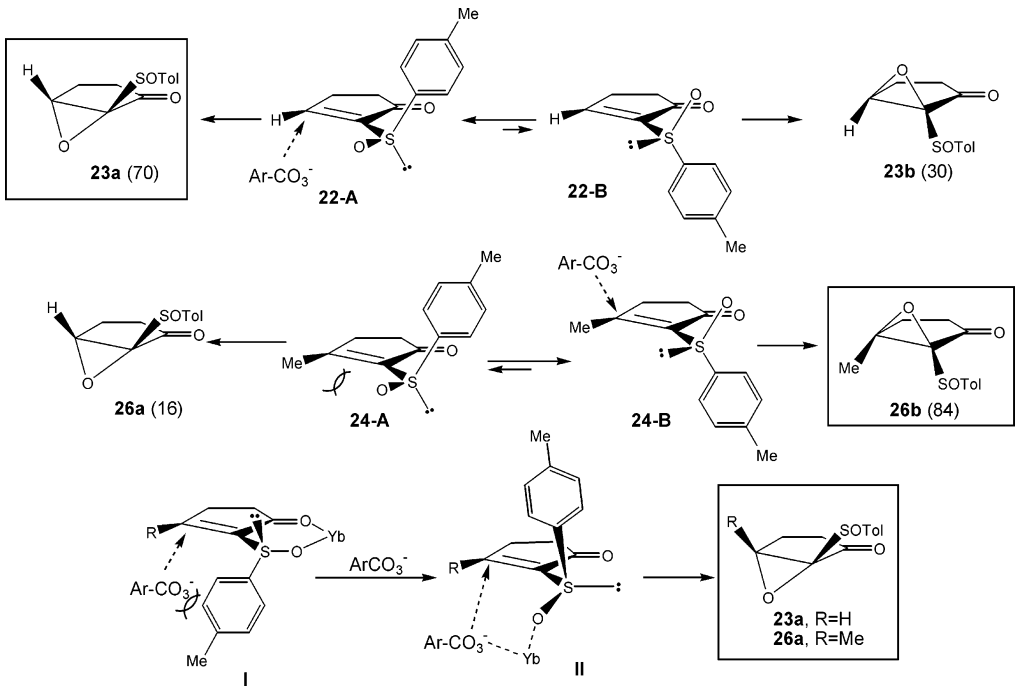
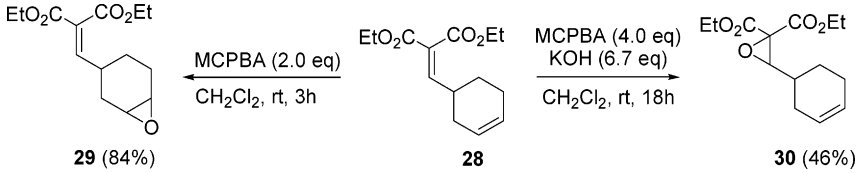


FIGURE 1. Stereochemical model for reactions of **22** and **24** with *m*-CPBA anion.

SCHEME 6



By assuming a steric approach control for the nucleophilic attack, the stereochemical results must be rationalized as follows (see Figure 1).

The equilibrium between the two presumably more stable conformations around the C−S bond, **A** and **B**, must be shifted toward conformer **A** in **22** (thus minimizing the electrostatic repulsion between its oxygen atoms) but toward **B** in **24** (thus avoiding the steric repulsion of the methyl group at C-4 and the sulfinyl oxygen). The major isomer, which would be obtained in the approach of the reagent to the less hindered face of the substrate, must be different for **22** and **24**, which affords **23a** and **26b**, respectively, as the major epoxides (Figure 1). In the presence of $Yb(OTf)_3$, the formation of chelated species such **I** should be expected.[24] In this case the major epoxides should be **23b** and **26b** resulting from the sterically favored attack of $Ar-CO_3^-$. As the only obtained epoxides are **23a** and **26a** it is necessary to assume that the peroxybenzoate must became associated to the metal, distorting the original chelate and giving species such as **II**, with no eclipsing interaction between R and SO groups. The approach of the peroxycarboxylate must take place to the lower face of the double bond, which is that occupied by the oxygen at **II**, yielding **23a** and **26a** as the exclusive products (Figure 1). The association of the peroxybenzoate to the metal would explain the lower reactivity observed in the presence of the $Yb(OTf)_3$.

(24) Similar chelates have been proposed for other ketosulfoxides. See: García Ruano J. L.; Fernández-Ibáñez, M. A.; Maestro, M. C.; Rodríguez-Fernández, M. M. *J. Org. Chem.* **2005**, *70*, 1796−1801.

The last substrate that we have studied is diethyl (cyclohex-3-en-1-ylmethylene)malonate (**28**) (Scheme 6). Its reaction with *m*-CPBA only afforded oxirane **29**, resulting from the attack to the electron-rich double bond. The use of mixtures 1:≥1 *m*-CPBA/KOH led to the exclusive epoxidation of the electron-poor double bond, yielding compound **30**. However, this reaction was too slow and decomposition of **30** was observed when the reaction times were longer than 24 h. Better yield (46%) was obtained by using a large excess of the reagent (*m*-CPBA (4 equiv)/KOH (6.7 equiv)) for 18 h (Scheme 6).

In conclusion, we have reported that the combined use of *m*-CPBA with catalytic or stoichiometric amounts of KOH or K_2CO_3 allows the selective formation of oxiranes only from strongly *gem*-disubstituted olefins by electron-withdrawing groups. This transformation increases the usefulness of the *m*-CPBA as an epoxidizing reagent.

Experimental Section

General Procedure for Oxidation with *m*-CPBA (GP1). To a stirred solution of the corresponding substrate (1.0 equiv) in dry CH_2Cl_2 (13 mL/mmol) was added under argon at room temperature a solution of *m*-CPBA in dry CH_2Cl_2 (13 mL/mmol). After the time indicated in each case, the reaction mixture was washed with a $NaHSO_3$ solution (40%) and then with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The amount of reagents, the reaction time, and the purification method are indicated in each case.

3-Methyl-2-[(4-methylphenyl)sulfonyl]cyclopent-2-en-1-one (25). Compound **25** was obtained following GP1 from

sulfoxide **24**[25,26] (43 mg, 0.18 mmol) and *m*-CPBA (57 mg, 0.28 mmol) after 1 h of reaction. Purification by flash column chromatography (ethyl acetate−hexane, 1:2) gave pure sulfone **25** (44 mg, yield 96%) as a white solid (ethyl ether), which decomposed at temperatures higher than 175 °C: IR (film) 1702; ^{1}H NMR δ 7.92 and 7.31 (AA′BB′ system, 4H), 2.71 (m, 2H), 2.62 (s, 3H), 2.41 (s, 3H), 2.39 (m, 2H); ^{13}C NMR δ 199.9, 184.8, 144.8, 139.5 and 137.5 (C), 129.5 and 128.3 (CH), 34.3 and 33.6 (CH_2), 21.6 and 18.9 (CH_3).

General Procedure for Oxidation with *m*-CPBA/K_2CO_3 (GP2). To a mixture of *m*-CPBA (0.50 mmol) and K_2CO_3 (0.24 mmol) in dry CH_2Cl_2 (6.5 mL), under argon at room temperature, was added a solution of the corresponding substrate (0.2 mmol) in dry CH_2Cl_2 (2.6 mL). After 3 h, the reaction mixture was washed with a $NaHSO_3$ solution (40%) and then with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. It was purified by flash column chromatography (ethyl acetate−hexane, 1:4).

1-[(4-Methylphenyl)sulfonyl]-6-oxabicyclo[3.1.0]hexan-2-one (7). Compound **7** was obtained from sulfinylcyclopentenone **22**[25] following GP2: yield 99%; white solid (hexane); mp 138−139 °C; IR (KBr) 1743; ^{1}H NMR δ 7.96 and 7.38 (AA′BB′ system, 4H), 4.58 (d, J = 1.8 Hz, 1H), 2.45 (s, 3H), 2.42−2.29 (m, 3H), 2.28−2.14 (m, 1H); ^{13}C NMR δ 200.1, 146.0, and 133.9 (C), 129.8 and 129.6 (CH), 70.8 (C), 65.2 (CH), 33.3 (CH_2), 21.8 (CH_3), 21.3 (CH_2).

(1*SR*,4*SR*,5*RS*)-4-Ethoxy-1-[(4-methylphenyl)sulfonyl]-3,6-dioxabicyclo[3.1.0]hexan-2-one (9). Compound **9** was synthesized by GP2 modified as follows: sulfone **8** (37 mg, 0.13 mmol) was oxidized using *m*-CPBA (30 mg, 0.15 mmol) and K_2CO_3 (9 mg, 0.06 mmol). The reaction time was 30 min. Flash column chromatography (ethyl acetate−hexane, 1:6) gave pure epoxide **9** (29 mg, 75%). Compound **9** was also obtained following GP1 from sulfone **8** (38 mg, 0.13 mmol) and *m*-CPBA (31 mg, 0.15 mmol) after 24 h of reaction. The same purification as described above gave pure epoxide **9** (30 mg, yield 77%) as a white solid: mp 152−153 °C; IR (KBr) 1796, 1596, 1158; ^{1}H NMR δ 7.99 and 7.43 (AA′BB′ system, 4H), 5.42 (s, 1H), 4.67 (s, 1H), 3.96 (m, 1H), 3.72 (m, 1H), 2.48 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 163.1, 146.8 and 132.6 (C), 130.0 and 129.8 (CH), 99.0 (CH), 66.7 (CH_2), 65.8 (C), 62.6 (CH), 21.8 and 14.7 (CH_3). Anal. Calcd for $C_{13}H_{14}O_6S$: C, 52.34; H, 4.73; S, 10.75. Found: C, 52.38; H, 4.66; S, 10.99.

5-Methyl-1-[(4-methylphenyl)sulfonyl]-6-oxabicyclo-[3.1.0]hexan-2-one (27). Compound **27** was obtained from sulfinylcyclopentenone **24**[25,26] following GP2: yield 88%; white solid (hexane); mp 115-116 °C; IR (KBr) 1748; ^{1}H NMR δ 7.97 and 7.37 (AA′BB′ system, 4H), 2.45 (s, 3H), 2.35−2.06 (m, 4H), 2.04 (s, 3H); ^{13}C NMR δ 202.0, 145.7 and 135.2 (C), 129.6 and 129.5 (CH), 76.1 and 73.8 (C), 32.4 and 27.9 (CH_2), 21.7 and 16.3 (CH_3). Anal. Calcd for $C_{13}H_{14}O_4S$: C, 58.63; H, 5.30; S, 12.04. Found: C, 58.67; H, 5.34; S, 12.00.

General Procedure for the Epoxidation with *m*-CPBA/KOH (GP3). A mixture of *m*-CPBA and KOH (the amounts of reagents are indicated in each case) in dry CH_2Cl_2 (13 mL/mmol) was stirred under argon at room temperature for 1 h. A solution of alkene (1 equiv) in dry CH_2Cl_2 (13 mL/mmol) was added at room temperature. The reaction was monitored by TLC. The mixture was filtered off, washed with dichloromethane, and concentrated under vacuum. The reaction time and the purification method are indicated in each case.

Methyl (2*SR*,3*RS*)-3-(Diethoxymethyl)-2-[(4-methylphenyl)sulfonyl]oxirane-2-carboxylate (15). Compound **15** was obtained following GP3 from alkene **10**[27] (24 mg, 0.07 mmol), *m*-CPBA (18 mg, 0.09 mmol), and KOH (6 mg, 0.09 mmol) after 3 h of reaction. In this case, the workup is the same as described for GP1. Flash column chromatography (ethyl acetate−hexane, 1:4) gave pure epoxide **15** (21 mg, yield 84%) as a colorless oil: IR (film) 1751; ^{1}H NMR δ 7.78 and 7.36 (AA′BB′ system, 4H), 4.72 (d, J = 2.8 Hz, 1H), 3.92 (d, J = 2.8 Hz, 1H), 3.75 (s, 3H), 3.64 (m, 2H), 3.51 (m, 2H), 2.46 (s, 3H), 1.15 (2t, J = 6.9 Hz, 6H); ^{13}C NMR δ 162.0, 146.2 and 132.6 (C), 129.8, 129.4 and 96.8 (CH), 72.1 (C), 62.4 and 62.0 (CH_2), 61.2 (CH), 53.1, 21.7, and 14.9 (CH_3). Anal. Calcd for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19; S, 8.95. Found: C, 53.43; H, 6.26; S, 8.76.

Methyl 2-[(4-Methylphenyl)sulfonyl]-3-phenyloxirane-2-carboxylate (16). Compound **16** was obtained following GP3 from alkene **11**[28] (50 mg, 0.16 mmol), *m*-CPBA (97 mg, 0.47 mmol), and KOH (52 mg, 0.79 mmol) after 7 h of reaction. Flash column chromatography (ethyl acetate−hexane, 1:5) gave a pure epoxide **16** (44 mg, yield 83%) as a white solid (ethyl ether): mp 94−96 °C; IR (film) 1750; ^{1}H NMR δ 7.83 and 7.40 (AA′BB′ system, 4H), 7.29 (m, 5H), 4.86 (s, 1H), 3.52 (s, 3H), 2.47 (s, 3H); ^{13}C NMR δ 161.7, 146.3, 132.9 and 130.4 (C), 130.0, 129.6, 129.4, 128.6 and 126.1 (CH), 65.8 (C), 62.1 (CH), 53.2 and 21.8 (CH_3).

General Procedure A for the Preparation of Sulfinyl Epoxides (GP4A). A mixture of *m*-CPBA (0.56 mmol) and KOH (0.62 mmol) in dry CH_2Cl_2 (7.3 mL) was stirred under argon at room temperature for 1 h. It was cooled at −20 °C, and a solution of the corresponding sulfoxide (0.28 mmol) in dry CH_2Cl_2 (3.6 mL) was added. After the time indicated in each case, the reaction mixture was washed with $NaHSO_3$ solution (40%) and then with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. It was purified by flash column chromatography (ethyl acetate−hexane, 1:2).

General Procedure B for the Preparation of Sulfinyl Epoxides (GP4B). A solution of the corresponding sulfoxide (0.30 mmol) and $Yb(OTf)_3$ (0.30 mmol) in dry CH_2Cl_2 (3.9 mL) was stirred under argon at room temperature during 1 h. Then, it was added to a mixture of *m*-CPBA (0.6 mmol) and KOH (0.66 mmol) in dry CH_2Cl_2 (7.8 mL), previously stirred at room temperature for 1 h and then cooled at the temperature indicated in each case. After the time indicated in each case, the reaction mixture was washed with a $NaHSO_3$ solution (40%), saturated aqueous $NaHCO_3$, and a saturated solution of NH_4Cl. The organic layer was dried (Na_2SO_4), filtered off, and concentrated under vacuum. It was purified by flash column chromatography (ethyl acetate−hexane, 1:2).

[1*SR*,5*RS*,(S)*RS*]-1-[(4-Methylphenyl)sulfinyl]-6-oxabicyclo[3.1.0]hexan-2-one (23a). This compound was obtained from sulfinylcyclopentenone **22**[25] as a mixture of diastereoisomers (**23a/23b** 70:30) following GP4A after 15 min of reaction (combined yield 84%). Sulfinyl epoxide **23a** was obtained as the sole compound following GP4B from sulfinylcyclopentenone **22** after 1 h of reaction at 0 °C: yield 80%; white solid (ethyl ether/hexane); mp 85−86 °C; IR (KBr) 1737; ^{1}H NMR δ 7.65 and 7.32 (AA′BB′ system, 4H), 4.33 (m, 1H), 2.41 (s, 3H), 2.49−2.30 (m, 2H), 2.21−2.15 (m, 1H), 2.03−1.92 (m, 1H); ^{13}C NMR δ 203.3, 142.9 and 136.3 (C), 130.0 and 125.7 (CH), 74.0 (C), 61.1 (CH), 33.4 and 21.7 (CH_2), 21.5 (CH_3). Anal. Calcd for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12; S, 13.57. Found: C, 60.94; H, 5.16; S, 13.37.

[1*RS*,5*SR*,(S)*RS*]-1-[(4-Methylphenyl)sulfinyl]-6-oxabicyclo[3.1.0]hexan-2-one (23b). This compound was obtained from sulfinylcyclopentenone **22**[25] as a mixture of diastereoisomers (**23a/23b** 70:30) following GP4A after 15 min of reaction (combined yield 84%). It could not be isolated as a pure isomer. The signals were measured from the spectrum of a mixture of **23a** and **23b** in a ratio of 70:30: ^{1}H NMR δ 7.67 and 7.32 (AA′BB′ system, 4H), 4.30 (m, 1H), 2.41 (s, 3H), 2.49-2.30 (m, 2H), 2.21-2.15 (m, 1H), 2.03-1.92 (m, 1H); ^{13}C NMR δ 204.6, 142.6 and 135.3 (C), 129.8 and 125.4 (CH), 75.1 (C), 64.6 (CH), 33.5 and 29.6 (CH_2), 22.0 (CH_3).

(25) Hulce, M.; Mallazo J. P.; Frye, L. L.; Bogan, T. P.; Posner, G. H. *Org. Synth*. **1985**, *64*, 196-206.
(26) Posner, G. H.; Kogan, T. P.; Hulce, M. *Tetrahedron Lett*. **1984**, *25*, 383−386.
(27) García Ruano, J. L.; Fajardo, C.; Martín, M. R. *Tetrahedron*. **2005**, *61*, 4363−4371.
(28) Reedy, G. R.; Gupta, S. V. S. A. K.; Reedy, D. B.; Seenaiah, B. *J. Indian Chem. Soc*. **1992**, *69*, 396−397.

[1*SR*,5*RS*,(S)*RS*]-5-Methyl-1-[(4-methylphenyl)sulfinyl]-6-oxabicyclo[3.1.0]hexan-2-one (26a). This compound was obtained from sulfinylcyclopentenone **24**[25,26] as a mixture of diastereoisomers (**26a/26b** 16:84) following GP4A after 6 h of reaction (combined yield 76%). Isolated yield 13%. Sulfinyl epoxide **26a** was also obtained along with the starting material and sulfone **25** (ratio **24/25/26b** 15:6:79) following GP4B from sulfinylcyclopentenone 24 after 7 h of reaction at −20 °C: yield 66%; white solid (hexane); mp 75−76 °C; IR (film) 1744; ^{1}H NMR (CD_2Cl_2) δ 7.64 and 7.33 (AA′BB′ system, 4H), 2.40 (s, 3H), 2.32−1.95 (m, 4H), 1.87 (s, 3H); ^{13}C NMR (CD_2Cl_2) δ 204.7, 142.7 and 136.6 (C), 130.1 and 125.9 (CH), 74.2 and 73.4 (C), 33.4 and 27.5 (CH_2), 21.7 and 16.5 (CH_3).

[1*RS*,5*SR*,(S)*RS*]-5-Methyl-1-[(4-methylphenyl)sulfinyl]-6-oxabicyclo[3.1.0]hexan-2-one (26b). This compound was obtained from sulfinylcyclopentenone **24** as a mixture of diastereoisomers (**26a/26b** 16:84) following GP4A after 6 h of reaction (combined yield 76%): isolated yield 61%; white solid (ethyl acetate/hexane); mp 74−75 °C; IR (KBr) 1731; ^{1}H NMR (CD_2Cl_2) δ 7.66 and 7.33 (AA′BB′ system, 4H), 2.39 (s, 3H), 2.35-1.96 (m, 4H), 1.84 (s, 3H); ^{13}C NMR (CD_2Cl_2) δ 207.0, 143.1 and 137.7 (C), 130.2 and 126.3 (CH), 77.1 and 76.2 (C), 32.8 and 28.7 (CH_2), 21.8 and 16.3 (CH_3). Anal. Calcd for $C_{13}H_{14}O_3S$: C, 62.38; H, 5.64; S, 12.81. Found: C, 62.45; H, 5.59; S, 12.39.

Diethyl (7-Oxabicyclo[4.1.0]hept-3-ylmethylene)malonates (29). The compounds were obtained following GP1 from diester **28**[29] (66 mg, 0.26 mmol) and *m*-CPBA (108 mg, 0.52 mmol) after 3 h of reaction. By ^{1}H NMR analysis, the obtained residue showed the signals corresponding to diastereoisomeric epoxides **29** (50:50). Flash column chromatography (acetone−hexane 1:12) gave a 50:50 mixture of pure diastereoisomers **29** (59 mg, yield 84%) as a colorless oil: IR (film) 1733; ^{1}H NMR δ 6.70 (d, J = 10.5 Hz, 1H), 6.64 (d, J = 10.5 Hz, 1H), 4.25 (2q, J = 7.1 Hz, 4H), 4.18 (2q, J = 7.1 Hz, 4H), 3.12 (m, 4H), 2.54 (m, 1H), 2.33 (m, 1H), 2.21−1.94 (m, 4H), 1.91−1.44 (m, 4H), 1.43−1.02 (m, 4H), 1.30 (t, J = 7.1 Hz, 6H), 1.26 (t, J = 7.1 Hz, 6H). ^{13}C NMR δ 165.3, 165.2 and 163.9 (C), 151.9 and 151.3 (CH), 128.0 and 127.7 (C), 61.3 and 61.2 (CH2), 51.7 (CH), 51.6 (C), 50.8, 50.3, 33.8 and 31.0 (CH), 30.1, 28.9, 25.8, 24.1, 23.4 and 22.6 (CH_2), 14.1 and 14.0 (CH_3). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.62; H, 7.51.

Diethyl 3-Cyclohex-3-en-1-yloxirane-2,2-dicarboxylates (30). The compounds were obtained following GP3 from diester **28**[29] (103 mg, 0.41 mol), *m*-CPBA (336 mg, 1.6 mmol), and KOH (181 mg, 2.7 mmol) after 18 h of reaction. By ^{1}H NMR analysis, the obtained residue showed the signals corresponding to diastereoisomeric epoxides **30** (50:50) and starting material in a 54:46 ratio. Flash column chromatography (ethyl ether−hexane 1:18) gave a 50:50 mixture of pure diastereoisomers **30** (51 mg, yield 46%) as a colorless oil: IR (film) 1748; ^{1}H NMR δ 5.66 (m, 4H), 4.40−4.22 (m and q, J = 7.1 Hz, 8H), 3.37 (d, J = 8.1 Hz, 1H), 3.34 (d, J = 8.3 Hz, 1H), 2.37−2.23 (m, 2H), 2.20−1.77 (m, 8H), 1.61−1.32 (m, 4H), 1.32 and 1.31 (3t, J = 7.1 Hz, 12H); ^{13}C NMR δ 166.2, 166.1 and 164.9 (C), 127.2, 126.7, 124.9, 124.4, 65.7 and 65.5 (CH), 62.6, 62.1 and 62.0 (CH_2), 60.8 and 60.6 (C), 34.0, and 33.9 (CH), 28.5, 26.4, 25.7, 24.1, 23.7 and 23.5 (CH_2), 14.1, 14.0 and 13.9 (CH_3).

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Supporting Information Available: Experimental procedures and characterization data of all new compounds, as well as the X-ray for compounds **23a** and **26b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) Papadakis, P. E.; Haven, G. *J. Pharm. Sci*. **1956**, *55*, 1016−1018.