

Olefin epoxidation of α - β unsaturated esters. Comparison of reactivity of some simple esters and enantiomerically pure diesters of TADDOL and BINOL: a computational study.

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Abstract

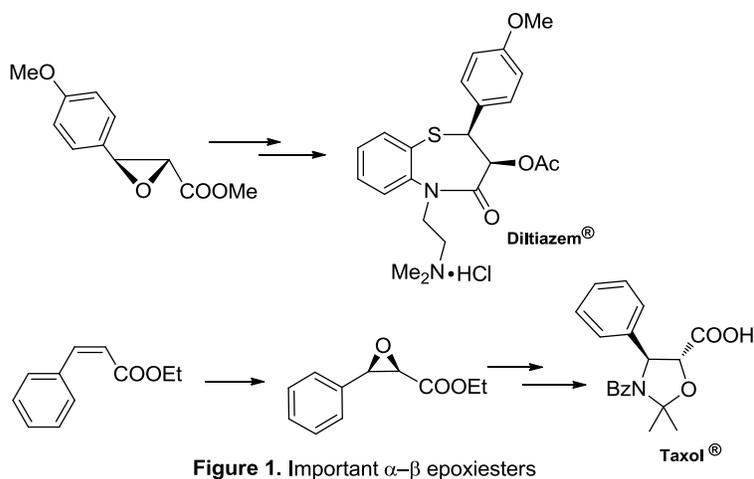
Epoxidation reaction has been the subject of numerous investigations and a number of useful methodologies have been studied. The electrophilic reagents commonly used, react preferentially with electron-rich olefins. For this reason, electron-deficient olefins such as α , β -unsaturated esters react very slowly and with low yields. Besides, optically active epoxides are highly versatile intermediates that can be converted into a wide variety of enantiomerically enriched molecules. Our group has previously reported the synthesis of enantiomerically pure α - β unsaturated diesters of TADDOL and BINOL.¹ As a part of the studies, we decided to analyze the stereoselective di-epoxidation of diacrylate derivatives with C_2 -symmetry. First, we studied simple substrates with the intention to extend the results to more complex molecules. Thus, several epoxidation methods were tested on α - β -unsaturated esters with the aim to improve the previously reported data. Among all the experimental conditions used, *m*CPBA reagent was the best one, giving the glycidic esters derivatives with very good yields and short reaction time compared with reported methods.² Due to the fact that the reaction conditions were unsuccessful with the C_2 -diacrylate systems, we decided to study the reactivity of these substrates applying Density Functional Theories (DFT) calculations. The reactivity of *m*CPBA, in olefins epoxidation reactions, can be rationalized by frontier orbital interactions.³ We evaluated the coefficients and shape of HOMO OMs of a series of simple esters and diesters derivatives from TADDOL and BINOL. We achieved interesting results concerning the reactivity of these compounds.

Keywords. Olefin epoxidation; *m*CPBA; epoxidation reactivity; frontier orbital interaction, DFT.

Introduction

Epoxides are an important class of functional groups that are widely employed in organic synthesis. These compounds are important synthetic intermediates in medicinal chemistry as well as versatile building blocks in biologically active compounds and natural products synthesis. Many natural products possess epoxide units as essential structural moieties for their biological activities.⁴

The α - β -epoxy esters moiety are important intermediates for the synthesis of complex molecules. For example, methyl (2*R*,3*S*)-4-methoxyglycidate is a key intermediate in the synthesis of Diltiazem® hydrochloride, one of the most potent calcium antagonist that has been used for the last twenty years for the treatment of angina and hypertension. The asymmetric epoxidation of cis-ethyl cinnamate, produces ethyl (2*R*,3*R*)-3-phenylglycidate, a starting material for the synthesis of Taxol® side chain, which is a mitotic inhibitor used in cancer chemotherapy (Figure 1).⁵



Epoxidation of olefins is typically performed with organic peracids (such as *m*-CPBA and magnesium monoperoxyphthalate) or a combination of transition metal catalyst and a co-oxidant (such as H_2O_2 , *t*-BuOOH, PhIO, NaOCl, and even oxygen). It has been a great challenge to devise a generally applicable and environmentally benign epoxidation method that operates under mild neutral conditions.⁶ In 1909, Prilezhaev was the first to use peroxy-carboxylic acids to oxidize isolated double bonds to the corresponding oxiranes. This transformation is referred to as the *Prilezhaev reaction* (Figure 2). The general features of the *Prilezhaev reaction* are: 1) the reaction is stereospecific, since the stereochemistry of the alkene substrate is retained in the epoxide product and a *syn* addition of the oxygen to the double bond is observed in all cases; 2) the reaction rates increases if the substituents on the alkene are electron-donating and electron-withdrawing substituent on the peroxyacid; 3) most widely used peroxyacid is *m*CPBA which is a relatively stable solid with good solubility in most organic solvents. Epoxidation with *m*CPBA is usually carried out under ambient temperature and a mild basic work-up ensures the removal of the benzoic acid by-product from the epoxide product. The observed stereospecificity supports the assumption that the epoxidation of alkenes by peroxyacids is a concerted process. The reaction take place at the terminal oxygen atom of the peroxyacid, and the $\pi(\text{C}=\text{C})$ HOMO of the olefin approaches the $\sigma^*(\text{O}-\text{O})$ LUMO at an angle of 180° (butterfly transition structure).⁷

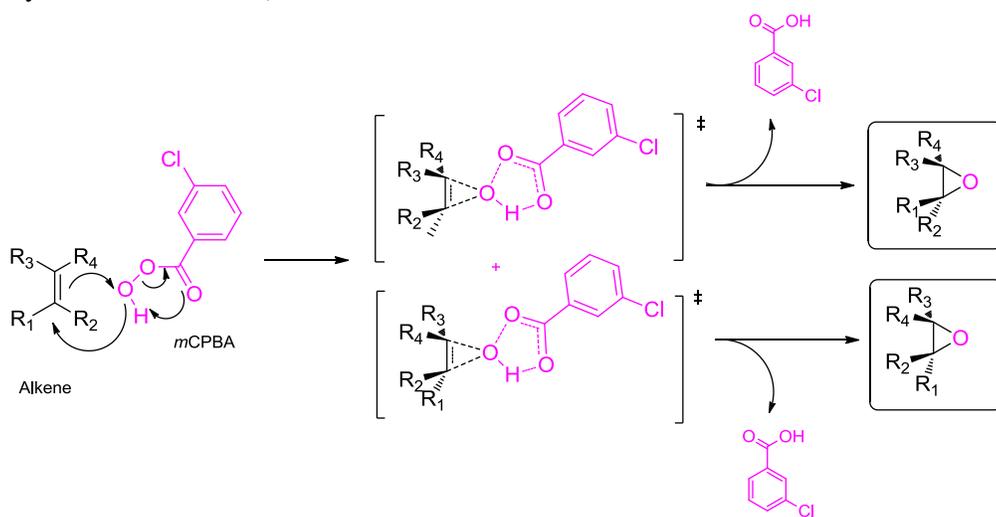
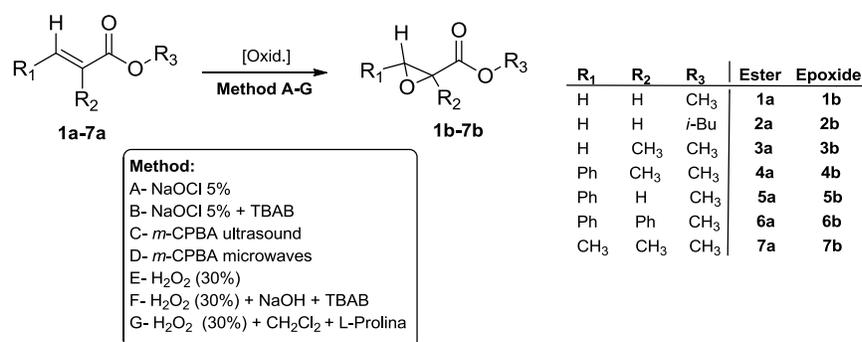


Figure 2. *Prilezhaev reaction* mechanism with *m*CPBA

As noted, the electrophilic reagents used in this reaction are preferably combined with electron rich olefins. So, α,β -unsaturated esters react very slowly and with low yields. Moreover, to our knowledge, there is no diepoxidation of α,β -unsaturated diesters reported in the literature. Thus, we decided to study the methodology of epoxidation of esters and in the first place, we studied simple substrates with the intention to extend the results to more complex molecules. Several epoxidation methods were tested on α,β -unsaturated esters with the aim to improve previously reported data.⁸ Due to the fact that the diepoxidation reactions were unsuccessful with TADDOL and BINOL acrylate diesters, (C_2 - systems), we study the reactivity of these substrates applying DFT calculations in order to justify these unpleasant results.

Results and Discussions

As can be observed from Scheme 1, different conditions were tested: a) NaOCl 5% with and without TBAB (Methods A and B); b) *m*CPBA, assisted by ultrasound or microwaves (Methods C and D) and c) H_2O_2 , L-proline, with or without TBAB, (Methods E to G).



Scheme 1. General synthetic route of epoxides

The reaction conditions for the microwave and ultrasound methods (C and D) were optimized for ester **4a**. As can be seen from Table 1, the relation substrate *vs* oxidant was established as 1:2 in both cases.

Metod	Condition	Relation Subs/Oxid.	Time	Yield % ^a
C	<i>m</i> CPBA + CH_2Cl_2	1:1.3	8 hs	61
	<i>m</i> CPBA + CH_2Cl_2	1:2	6 hs	63
	<i>m</i> CPBA + CH_2Cl_2 + $NaHCO_3$	1:2	8 hs	53
D	37°C 50W	1:1.3	4.25 hs	63
	37°C 50W	1:2	5 hs	52
	37°C 200W	1:2	40 min	83
	85°C 200W	1:2	15 min	96

^a Isolated Yield

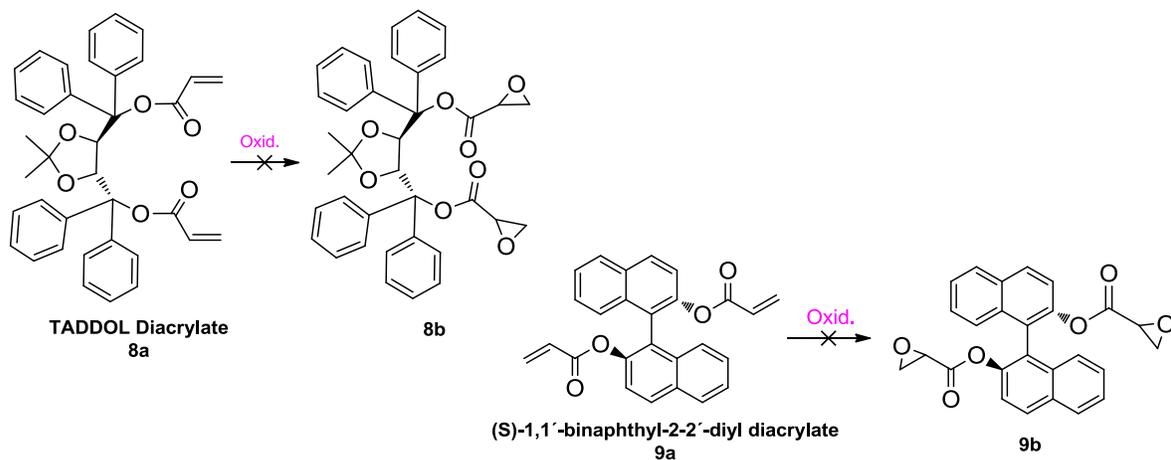
Among all the methods used, *m*CPBA allowed the epoxidation of α,β -unsaturated esters to derivatives of glycidic esters in short reaction times and good yields (60-95%) compared with traditional methods. On the other hand, Methods A and B, gave positive reaction with the simplest or less substituted substrates while H_2O_2 (Methods E to G) gave no satisfactory results in any case (Table 2).

Table 2

Ester	R ₁	R ₂	R ₃	Method	Time	Yield% ^a
1a	H	H	CH ₃	A	3.5 hs	32
				B	3.5 hs	3.5
				C	7 hs	-
				D	20 min	72
2a	H	H	<i>i</i> -Bu	A	3.5 hs	12
				B	3.5 hs	29
				C	7 hs	40
				D	10 min	80
3a	H	CH ₃	CH ₃	A	3.5 hs	-
				B	10 hs	-
				C	12 hs	57
				D	20 min	50
4a	Ph	CH ₃	CH ₃	A	3.5 hs	-
				B	10 hs	-
				C	6 hs	63
				D	15 min	96
5a	Ph	H	CH ₃	A	3.5 hs	-
				B	10 hs	-
				C	5 hs	58
				D	15 min	80
6a	Ph	Ph	CH ₃	A	3.5 hs	-
				B	10 hs	-
				C	5 hs	56
				D	15 min	58
7a	CH ₃	CH ₃	CH ₃	A	5.5 hs	51
				B	4.5 hs	56
				C	18 hs	53
				D	20 min	55

^a Isolated Yield

Taking into account that TADDOL⁹ and BINOL¹⁰ derivatives have proven to be excellent chiral auxiliars in assymmetric reactions, we decided study the epoxidation reaction of the corresponding acrylate diesters (**8a**) and (**9a**) previously reported.¹ Unfortunately, we were unable to obtain the corresponding products (Scheme 2).



Scheme 2

These observations prompted us to study the epoxidation process, using density functional theory (DFT) calculations, considering that the reactivity of *m*CPBA, in olefins epoxidation reactions, can be rationalized by frontier orbital interactions,³ we theoretically study the neutral perbenzoic acid, the α,β -unsaturated esters and the corresponding TADDOL and BINOL derivatives. The calculations were performed with the B3LYP¹¹ DFT¹² functional and the 6-31G* basis set, which is known to be an appropriate methodology for the theoretical study of this reactive system.^{3,13}

Taking into account that the reaction take place as a concerted process when the $\sigma^*(\text{O-O})$ LUMO of the peroxyacid approaches to the $\pi(\text{C=C})$ HOMO of the α,β -unsaturated esters, we calculate the corresponding MOs of the compounds involved in this process.

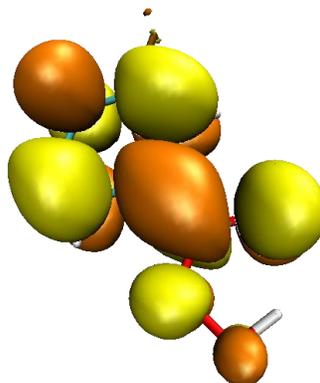


Figure 3. LUMO MO (orange and yellow) for *m*CPBA

As can be seen from Figure 3, the LUMO MO of the neutral *m*CPBA have σ -symmetry at O-O bond. Then, we choose two α,β -unsaturated methyl esters as representatives, **4a** that have a phenyl moiety attached directly to the C=C bond, and **7a** that is an alkyl derivative. The first give the product **4b** almost quantitatively and the second give **7b** in lower yield (Table 2). As expected, both have π -symmetry at C=C bond (shown in Figure 4). Besides, both have a high orbital coefficient at the $\pi(\text{C=C})$ MO that can be inferred from the size of the lobes after doing the Kohn-Sham orbital analysis.

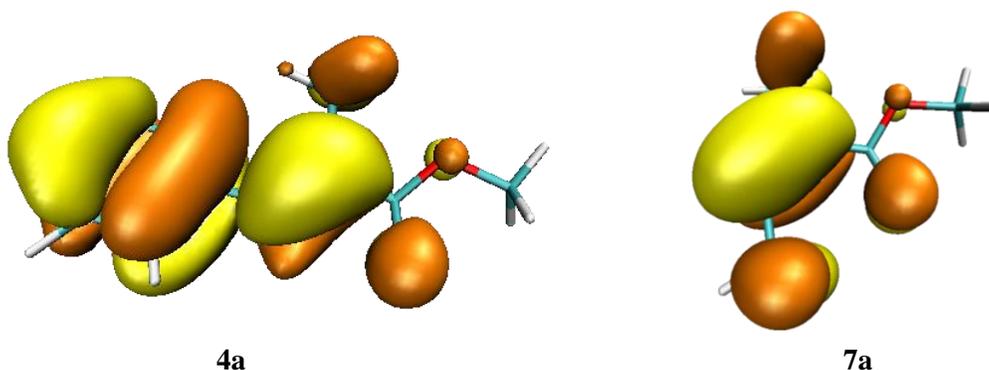


Figure 4. HOMO MOs (orange and yellow) for α,β -unsaturated esters **4a** and **7a**

On the other hand, the DFT calculations showed significant differences for the corresponding TADDOL and BINOL acrylate diesters which are no reactive in the studied conditions. In these species, the HOMO OMs are located mainly on the aromatic π -systems (Figure 5). Besides, when comparing the C=C

reactive bond of the α,β -unsaturated methyl esters with that of the corresponding TADDOL and BINOL derivatives, the main change observed is that, in the both last compounds, the orbital coefficient is close to zero over this π -system, and as a consequence, no orbital lobes are observed (shown with a red oval in Figure 5).

Considering that the epoxidation reactivity is strongly affected by the HOMO-LUMO interaction, in orbital interaction terms, the lack of reactivity of TADDOL and BINOL derivatives could be attributed to the smaller (or zero) orbital coefficients at the $\pi(\text{C}=\text{C})$ HOMO MOs.¹⁴

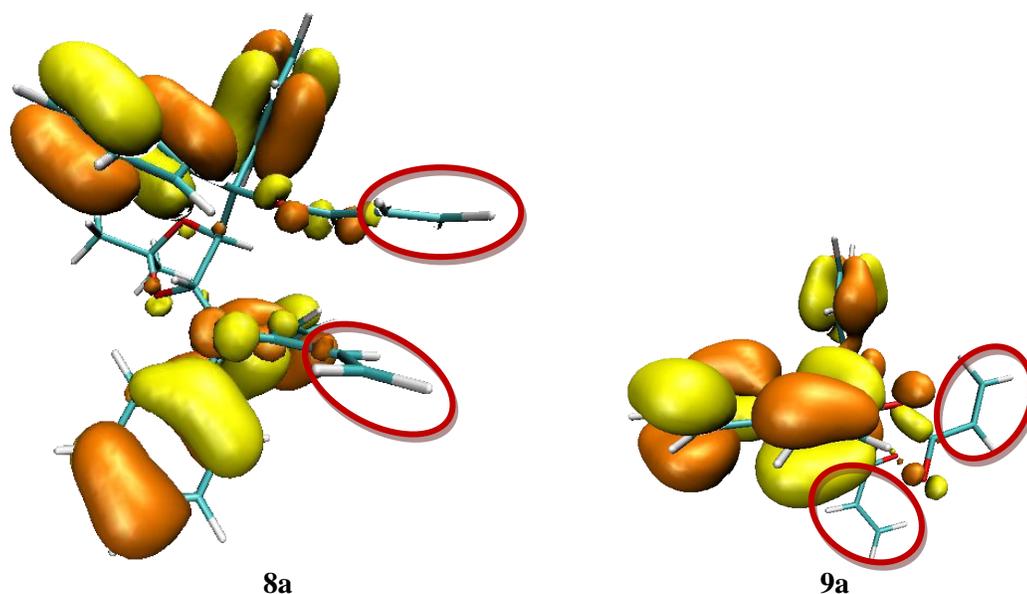


Figure 5. HOMO MOs (orange and yellow) for TADDOL (**8a**) and BINOL (**9a**) derivatives

Conclusions

Based on the results presented here, we can conclude that for all the α,β -unsaturated esters studied in this work, the best yields were obtained with *m*CPBA in the presence of microwaves or ultrasound (Methods C and D). As can be seen in Table 2, in the case of esters **1a**, **2a**, **4a** y **5a**, the yields are good to excellent (72% to 96 %). It is important to note that **2b**, **4b** and **6b** derivatives, as far to our knowledge, are not reported in the literature. Besides, the conditions reactions employed in these studies are of low environmental impact. In all cases, the products were purely obtained after the *work-up* and no further purification was needed. On the other hand, DFT calculations have shown to be a successful approach for studying the epoxidation of α,β -unsaturated esters as well as to explain the lack of reactivity of TADDOL and BINOL derivatives in term of frontier orbital interactions.

Experimental Section

General methods

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. *m*CPBA commercial material (purity 85%) is washed with a phosphate buffer of pH 7.5 and dried under reduced pressure to furnish reagent with purity >99%. NaOCl was titrated with sodium

thiosulfate to determine the amount of active chlorine. Thin layer chromatography was performed on Merck precoated silica gel 60 F254 plates and visualization was accomplished with UV light and/or 5% ethanol solution of phosphomolibdic acid. NMR spectra were recorded on a Bruker ARX 300 Multinuclear instrument, using CDCl₃ as solvent. Compounds described in the literature were characterized by comparison of their ¹H- and ¹³C-NMR spectra to the previously reported data. Ultrasonic reaction were performed in NDI ULTRASONIC 104X apparatus (Output power: 190W, Frequency: 48 khz, 30°C +/- 1°). Microwave reactions were carried out in a microwave CEM Discover® at 200W, 85°C.

Method A¹⁵

To a solution of 5% NaOCl (1.1 mmol) at 0°C, 1.1 mmol of ester was added with vigorous stirring. After standing 30 min. at 0°C, the reaction mixture was placed in water-bath (20°C) and stirred for additional 3 hs. The mixture was then extracted with CH₂Cl₂ (5 x 5 ml). The combined organic extracts were dried over anhydrous MgSO₄. The solvent was evaporated under vacuum.

Method B¹⁶

To a solution of 5% NaOCl (1.1 mmol) and TBAB (0.009 mmol) in 2 ml of CH₂Cl₂ at 0°C, 1 mmol of ester was added with vigorous stirring. After standing 30 min. at 0°C, the reaction mixture was placed in water-bath (20°C) and stirred for additional 3 hs. The mixture was then extracted with CH₂Cl₂ (5 x 5 ml). The combined organic extracts were dried over anhydrous MgSO₄. The solvent was evaporated under vacuum.

Method C¹⁷

2 mmol of *m*CPBA was dissolved in 1 ml of CH₂Cl₂. To this solution, 1 mmol of ester in 2 ml of CH₂Cl₂ was added, and the mixture was placed in an ultrasonic bath. The reaction progress was monitored by TLC plates of silica gel 60. The crude reaction was filtered through a Buchner funnel with glass wool containing celite in order to retain impurities. The organic layer was then extracted with 10% bisulfite solution (2 x 8ml) and saturated sodium bicarbonate (2 x 8ml). The aqueous layer was further extracted with CH₂Cl₂ (3 x 8ml). The combined organic extracts were dried over MgSO₄ and the CH₂Cl₂ removed under vacuum.

Method D

2 mmol of *m*CPBA was dissolved in 1 ml of CH₂Cl₂ in a microwave vessel and then 1 mmol of ester was added and mixed carefully with a small rod. The mixture was irradiated in the microwave oven at 200W for the times reported in Table 1. The microwave was programmed to give a maximum internal temperature to 85 °C. The reaction progress was monitored by TLC plates of silica gel 60. The crude reaction was filtered through a Buchner funnel with glass wool containing celite in order to retain impurities. The organic layer was then extracted with 10% bisulfite solution (2 x 8ml) and saturated sodium bicarbonate (2 x 8ml). The aqueous layer was further extracted with CH₂Cl₂ (3 x 8ml). The combined organic extracts were dried over MgSO₄ and the CH₂Cl₂ removed under vacuum.

Methyl oxirane-2-carboxylate (1b)

The best yield was obtained with method D (72%) in 20 min of reaction time. Yellow Oil. ¹H - NMR (300 MHz, CDCl₃): δ 3.79 (3H, s), 3.45 (2H, s), 2.98 (1H, s); ¹³C - NMR (75.4 MHz, CDCl₃): δ 51.95, 46.77, 45.81, 169.41.

Isobutyl oxirane-2-carboxylate (2b)

The best yield was obtained with method D (80%) in 10 min of reaction time. Yellow Oil. ^1H - NMR (300 MHz, CDCl_3): δ 0.85 (3H, d), 1.87 (1H, m), 2.85 (2H, m), 3.33 (CH, t), 3.85 (2H, d); ^{13}C - NMR (75.4 MHz, CDCl_3): δ 18.81, 27.54, 46.08, 47.15, 71.34, 169.15.

Methyl-2-methyloxirane-2-carboxylate (3b)

The best yield was obtained with method C (57%) in 12 hs of reaction time. Yellow Oil. ^1H - NMR (300 MHz, CDCl_3): δ 1.51 (3H, s), 2.70 (1H, d, 4.4 Hz), 3.04 (1H, d, 4.4 Hz), 3.69 (3H, s); ^{13}C - RMN (75.4 MHz, CDCl_3): δ 17.42, 53.72, 53.00, 52.60, 171.19.

Methyl-2-methyl-3-phenyloxirane-2-carboxylate (4b)

The best yield was obtained with method D (96%) in 15 min of reaction time. Yellow Oil. ^1H - NMR (300 MHz, CDCl_3): δ 1.15 (3H, s), 3.64 (1H,s), 4.18 (3H,s), 6.97-7.87 (H-Ar, m); ^{13}C - NMR (75.4 MHz, CDCl_3): δ 12.66, 52.70, 59.87, 62.49, 126.81, 128.36, 133.84, 171.26.

Methyl 3-phenyloxirane-2-carboxylate (5b)

The best yield was obtained with method D (80%) in 15 min of reaction time. Yellow Oil. ^1H - NMR (300 MHz, CDCl_3): δ 3.35 (1H, d), 3.61 (3H, s), 3.94 (1H, d), 7.12-7.27 (HAr, m); ^{13}C - NMR (75.4 MHz, CDCl_3): δ 52.45, 56.63, 57.96, 125.82, 128.63, 128.96, 130.31, 168.71.

Methyl 2,3-diphenyloxirane-2-carboxylate (6b)

The best yield was obtained with method D (58%) in 15 min of reaction time. Yellow Oil. ^1H - NMR (300 MHz, CDCl_3): δ 3.74 (3H, s), 4.52 (1H, s), 6.81-8.12 (H-Ar, m); ^{13}C - NMR (75.4 MHz, CDCl_3): δ 12.78, 52.68, 59.83, 62.36, 126.67, 128.33, 129.73, 130.34, 133.79, 134.46, 135.09, 171.25.

Methyl 2,3-dimethyloxirane-2-carboxylate (7b)

The best yield was obtained with method D (55%) in 20 min of reaction time. Yellow Oil. ^1H - NMR (300 MHz, CDCl_3): δ 1.26 (3H, s), 1.45 (3H, d, 4.2Hz), 3.23, 3.67 (3H,s); ^{13}C - NMR (75.4 MHz, CDCl_3): δ 13.22, 13.38, 52.67, 57.44, 58.09, 172.38

Computational Procedure

The calculations were performed with Gaussian09.¹⁸ The initial conformational analysis of selected compounds was performed with the semiempirical AM1 method. The geometry of the most stable conformers thus obtained was used as starting point for the B3LYP studies of the corresponding esters and peroxide at the 6-31G* level. Figures were built with the VMD program using an isosurface of 0.02.

Acknowledgments

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