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Regiochemical Control of the Ring Opening of 1,2-Epoxides by Means of Chelating Processes.11. Ring Opening Reactions of Aliphatic Mono- and Difunctionalized cis and trans 2,3- and 3,4-Epoxy Esters[1]

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Abstract : The regiochemical outcome of the ring opening of 1,2-epoxides through chelation processes assisted by metal ions, was verified in the azidolysis of simple aliphatic cis and trans 2,3- and 3,4-epoxy esters and in the corresponding derivatives bearing an ether functionality (OBn) in an allylic relationship to the oxirane ring. The results indicate that the behavior of these epoxides is influenced both by the opening conditions (standard or metal-assisted) and the promoting metal salt [$LiClO_4$ or $Mg(ClO_4)_2$].

β- and γ-Amino-acids (non-α-amino-acids) containing a hydroxyl functionality have been the object of a growing interest in recent years because of their intrinsic biological properties[2] and because they have been found in nature as part of more complex biologically active molecules (see the side chain of taxol,[3] for example), and in low molecular weight peptides such as amastatin, bestatin, and pepstatin.[4]

If a simple elaboration of the primary addition products (the hydroxy azido ester) is applied, the azidolysis of aliphatic 2,3- and 3,4- epoxy esters constitutes a simple procedure for the synthesis of β- and γ-amino acids containing the 1,2-amino alcoholic residue. However, the validity of this procedure lies in its rigid stereo- and regiochemical control of the oxirane ring opening process, which only makes it possible to obtain simple products with a well-defined structure, to be efficaciously utilized in organic synthesis.

Studies carried out in our laboratories[1,5] on some opening reactions (particularly azidolysis) of functionalized 1,2-epoxides derived from various aliphatic and cycloaliphatic systems have indicated that, while the stereochemistry of the opening process is constantly anti, the regiochemical outcome can be favorably influenced by the operating conditions (standard, non-chelating, or chelating conditions), and in some cases complete regioselectivity and an interesting regioalternating process have been obtained.[6]

As part of a program aimed at examining, and if possible, controlling the regiochemical and stereochemical outcome of the ring opening reactions of differently functionalized 1,2-epoxides, we decided to examine the chemical behavior of typical aliphatic 2,3- and 3,4-epoxy esters in an opening reaction such as azidolysis which was exclusively taken into consideration for these studies, both in view of its operative simplicity and its intrinsic synthetic interest (see above).

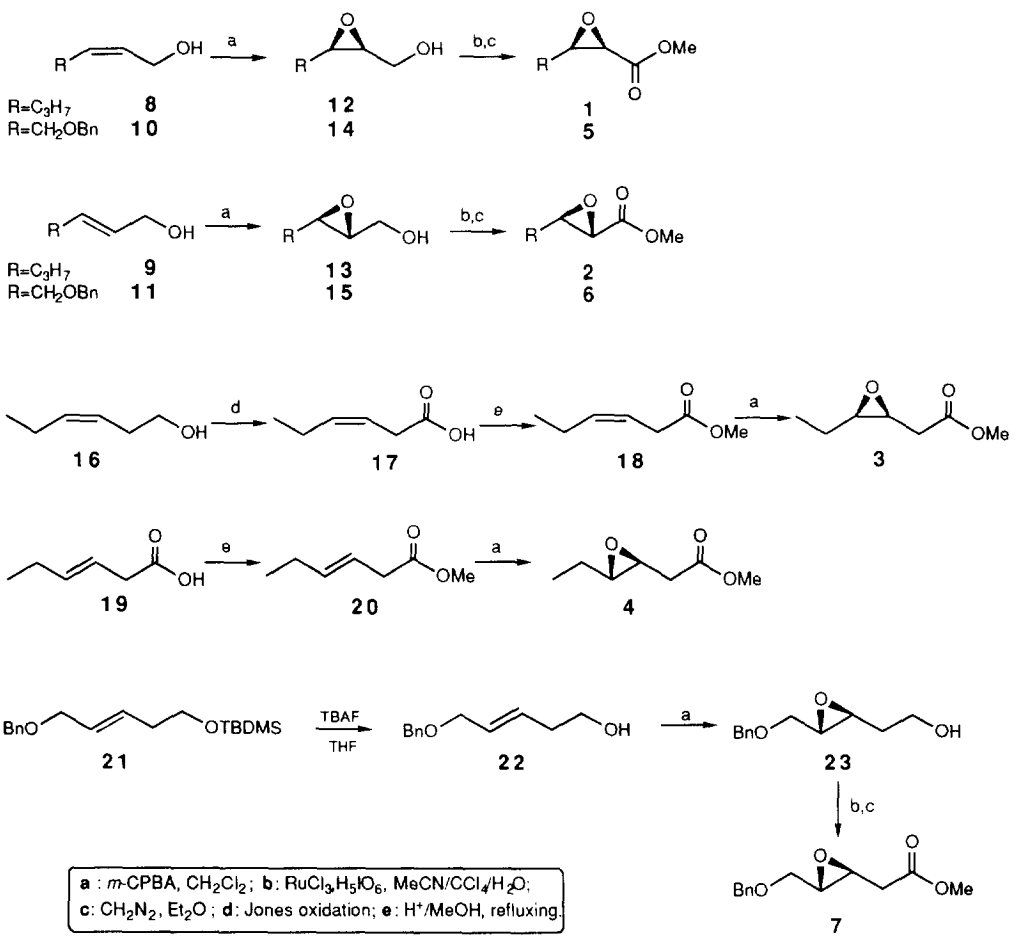
As a consequence, the diastereoisomeric allylic cis **1** and trans **2** and homoallylic cis **3** and trans **4** epoxy esters were synthesized and studied. Moreover, in view of our interest in evaluating how the competitive effect of two heterofunctionalities simultaneously present in a 1,2-epoxide system might affect the regioselectivity of the oxirane ring opening process,[1] and how our operating procedures (chelating and not chelating)[1,5,6] might give a satisfactory degree of regiocontrol in complex systems, the difunctionalized diastereoisomeric cis **5** and trans **6** epoxy esters and the trans homologue **7**, containing an ether functionality (OBn), were prepared and

studied, too. While the OBn functionality is always in an allylic relationship to the oxirane ring in epoxides **5-6** and **7**, the methoxycarbonyl group is allylic in **5-6** and homoallylic in **7**.

Mono- and difunctionalized epoxides such as **1-2** and **5-7**, respectively, have attracted the attention of other researchers in recent times, and interesting results have been obtained. For example, Sharpless found a noteworthy C-3 selectivity in some nucleophilic additions to 2,3-epoxy acids and amides when the opening reactions were carried out in the presence of $Ti(O\text{-}i\text{-}Pr)_4$;[7] on the other hand, Saito and Moriwake found that the use of an HN_3-amine system made a selective C-2 opening in 2,3-epoxy esters.[8] We now wish to report the results obtained in the azidolysis of these epoxy ester systems making use both of typically standard and metal-assisted opening procedures.[5]

Cis **1** and trans **2** epoxides were obtained by *m*-CPBA oxidation of the corresponding commercially available unsaturated alcohols **8** and **9** to the epoxy alcohols **12** and **13**, respectively (Scheme 1). $RuCl_3$-H_5IO_6 oxidation of **12** and **13**, and subsequent methylation (CH_2N_2) of the unpurified corresponding epoxy

Scheme 1



acids afforded the desired epoxy esters **1** and **2**. The same reaction sequence was used for the synthesis of the difunctionalized cis **5** and trans **6** and **7** epoxides, starting from the corresponding unsaturated alcohols **10**, **11**, and **22**, respectively. Alcohol **22** was obtained from the previously prepared *O*-TBDMS derivative **21**,[1] by its reaction with tetrabutylammonium fluoride (TBAF) in THF. Cis **3** and trans **4** epoxides were simply obtained from the corresponding β,γ-unsaturated cis **17** and trans **19** acids, as shown in Scheme 1.

All the epoxides prepared were subjected to the azidolysis opening reactions carried out both under standard (non-chelating) conditions (NH_4Cl-NaN_3 in an 8:1 MeOH-H_2O mixture, 80°C), and chelating conditions which imply the use of the couple NaN_3-simple metal salt [$LiClO_4$ or $Mg(ClO_4)_2$] in a non-protic solvent (MeCN).[1,5,6] The results obtained are shown in Tables 1 and 2. The opening products are simply named *C-2* and *C-3 product* in the case of products from epoxides **1**-**2** and **5**-**6**, and *C-3* and *C-4 product* in the case of products from epoxides **3**-**4** and **7**, depending on the site of the nucleophile attack, in accordance with the numbering shown in Scheme 2. The exact structure and regiochemistry of the opening products were unambiguously assigned, on the basis of the usually complete anti stereoselectivity observed in the opening reactions of typical aliphatic 1,2-epoxides,[1,5b] by an examination of their ^1H NMR spectra and by appropriate double resonance experiments carried out on the corresponding acetates, using the well-separated and easily distinguishable proton α to the acetyl group (Scheme 2).

First of all, let us examine the results obtained with the allylic substituted cis **1** and trans **2** epoxy esters. Under standard conditions, both epoxides **1** and **2** lead to mixtures of the corresponding opening products in which the *C-3 product* prevails consistently (from **1**), or slightly (from **2**) in accordance with a preferential attack of the nucleophile on the C(3) oxirane carbon which is less negatively influenced by the inductive electron-withdrawing effect of the methoxycarbonyl substituent group (entries 1 and 4, Table 1).[9] In these reactions, some amounts of C-2 product (named *C-2 retention product*) derived from an oxirane ring opening through a syn process are also present (5% from the cis epoxide **1** and 26% from the trans epoxide **2**). Considering the complete anti stereoselectivity commonly observed in the opening reactions of aliphatic epoxides,[1,5b] this result is somewhat surprising. However, this behavior could be easily explained by admitting a nucleophilic participation of the adjacent methoxycarbonyl group,[11] as shown in Scheme 3 for trans **2** epoxide. Following this rationale, under standard conditions (H^+), the protonated epoxide **42** can lead to two intimate ion-dipole pairs **43** and/or **44** with the weakening of the oxirane C(2)-O or C(3)-O bond, respectively. The nucleophilic attack on **43** (*route a*) and/or **44** must necessarily occur from the back of the breaking oxirane bond to give the corresponding adducts (*C-2 product* from **43** and *C-3 product* from **44**) with complete inversion of configuration. However, ion-dipole **43** could be attacked by the favorably disposed allylic -COOMe group (the internal nucleophile) (*route b*) to give an oxonium species such as **45**. The subsequent nucleophilic attack on **45** by N_3^- must necessarily occur from the back of the oxonium bridge to yield an addition product (*C-2 retention product*) which is actually formed by a retention process (double inversion). Analogous considerations can be used to explain the similar results from the cis epoxide **1** under the same conditions. In this case, the amount of the corresponding *C-2 retention product* is lower, as a consequence of the steric hindrance between the aliphatic chain and the cis -COOMe group which makes the formation of the corresponding oxonium species **46** less favored (Scheme 3). However, when the same reactions were carried out under chelating conditions, (M^+ in Scheme 3), the *C-3 product* was the only reaction product from both epoxides cis **1** and trans **2** (entries 2, 3, 5 and 6, Table 1). In this case, the

Table 1. Regioselectivity of the Azidolysis of the Monofunctionalized cis 1 and trans 2 and Difunctionalized cis 5 and trans 6 2,3-Epoxy Esters.

entry	epoxide	reagents[a]	solvent	*C-2 product*	*C-3 product*	*C-2 retention product*	yield %
1	**1**	NaN_3-NH_4Cl	MeOH-H_2O	15	80	5	75
2	**1**	NaN_3-$LiClO_4$ 5M	MeCN	<1	>99	-	70
3	**1**	NaN_3-$Mg(ClO_4)_2$ 2.5 M	MeCN	<1	>99	-	90
4	**2**	NaN_3-NH_4Cl	MeOH-H_2O	26	48	26	80
5	**2**	NaN_3-$LiClO_4$ 5M	MeCN	<1	>99	-	83
6	**2**	NaN_3-$Mg(ClO_4)_2$ 2.5 M	MeCN	<1	>99	-	90
7	**5**	NaN_3-NH_4Cl	MeOH-H_2O	35	45	20	85
8	**5**	NaN_3-$LiClO_4$ 5M	MeCN	<1	>99	-	80
9	**5**	NaN_3-$Mg(ClO_4)_2$ 2.5 M	MeCN	<1	>99	-	89
10	**6**	NaN_3-NH_4Cl	MeOH-H_2O	48	14	38	82
11	**6**	NaN_3-$LiClO_4$ 5M	MeCN	complex	mixture	-	
12	**6**	NaN_3-$Mg(ClO_4)_2$ 2.5 M	MeCN	27	73	-	90

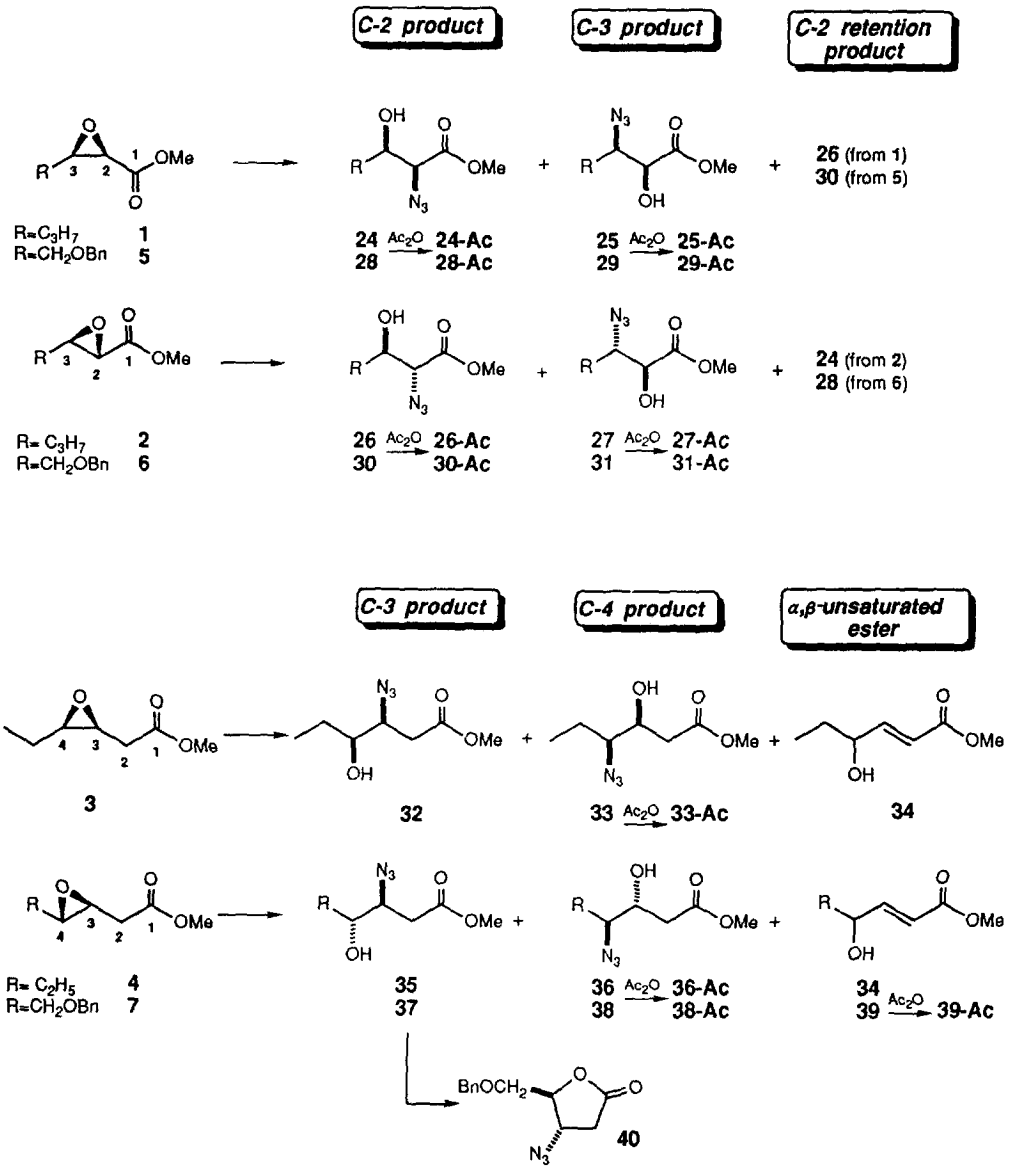
[a] All the reactions were carried out at 80°C for 18 h.

Table 2. Regioselectivity of the Azidolysis of Monofuntionalized cis 3 and trans 4 and Difunctionalized trans 7 3,4-Epoxy Esters.

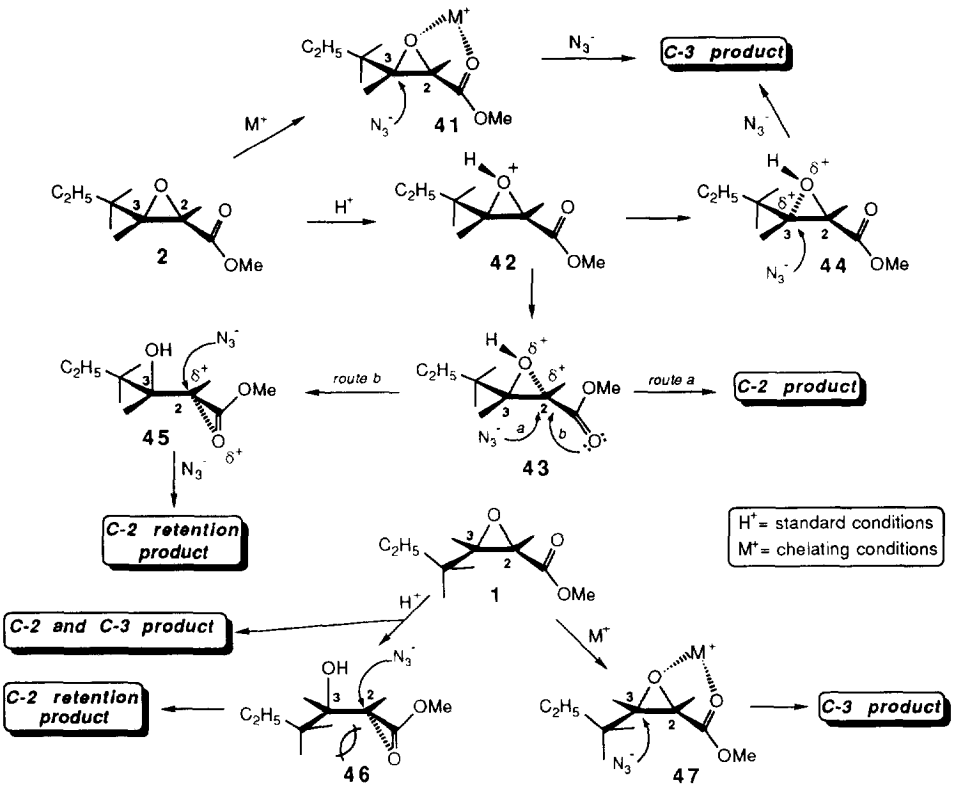
entry	epoxide	reagents[a]	solvent	*C-3 product*	*C-4 product*	α,β-unsatd ester[b]	yield %
1	**3**	NaN_3-NH_4Cl	MeOH-H_2O	-	88	12	70
2	**3**	NaN_3-$LiClO_4$ 5M	MeCN	-	10	90	82
3	**3**	NaN_3-NH_4ClO_4-$LiClO_4$ 5M	MeCN	-	>99	<1	80
4	**3**	NaN_3-$Mg(ClO_4)_2$ 2.5 M	MeCN	-	>99	<1	85
5	**4**	NaN_3-NH_4Cl	MeOH-H_2O	-	88	12	70
6	**4**	NaN_3-$LiClO_4$ 5M	MeCN	-	11	89	70
7	**4**	NaN_3-NH_4ClO_4-$LiClO_4$ 5M	MeCN	-	>99	<1	80
8	**4**	NaN_3-$Mg(ClO_4)_2$ 2.5 M	MeCN	-	>99	<1	86
9	**7**	NaN_3-NH_4Cl	MeOH-H_2O	-	65	35	90
10	**7**	NaN_3-$LiClO_4$ 5M	MeCN	-	11	89	70
11	**7**	NaN_3-NH_4ClO_4-$LiClO_4$ 5 M	MeCN	-	>99	<1	85
12	**7**	NaN_3-$Mg(ClO_4)_2$ 2.5 M	MeCN	45[c]	55		80

[a] All the reactions were carried out at 80°C for 18 h. [b] Unsaturated ester **34** and **39** from epoxides **3**-**4** and **7**, respectively (Scheme 2).[c] The regioisomer was obtained as the corresponding γ-lactone **40** (Scheme 2).

Scheme 2


C-2 product
C-3 product
C-2 retention product
R=C3H7 1
R=CH2OBn 5
24 Ac2O 24-Ac
28 28-Ac
25 Ac2O 25-Ac
29 29-Ac
26 (from 1)
30 (from 5)
R= C3H7 2
R=CH2OBn 6
26 Ac2O 26-Ac
30 30-Ac
27 Ac2O 27-Ac
31 31-Ac
24 (from 2)
28 (from 6)
C-3 product
C-4 product
α,β-unsaturated ester
3
32
33 Ac2O 33-Ac
34
R= C2H5 4
R=CH2OBn 7
35
37
36 Ac2O 36-Ac
38 38-Ac
34 Ac2O 39-Ac
40

Scheme 3



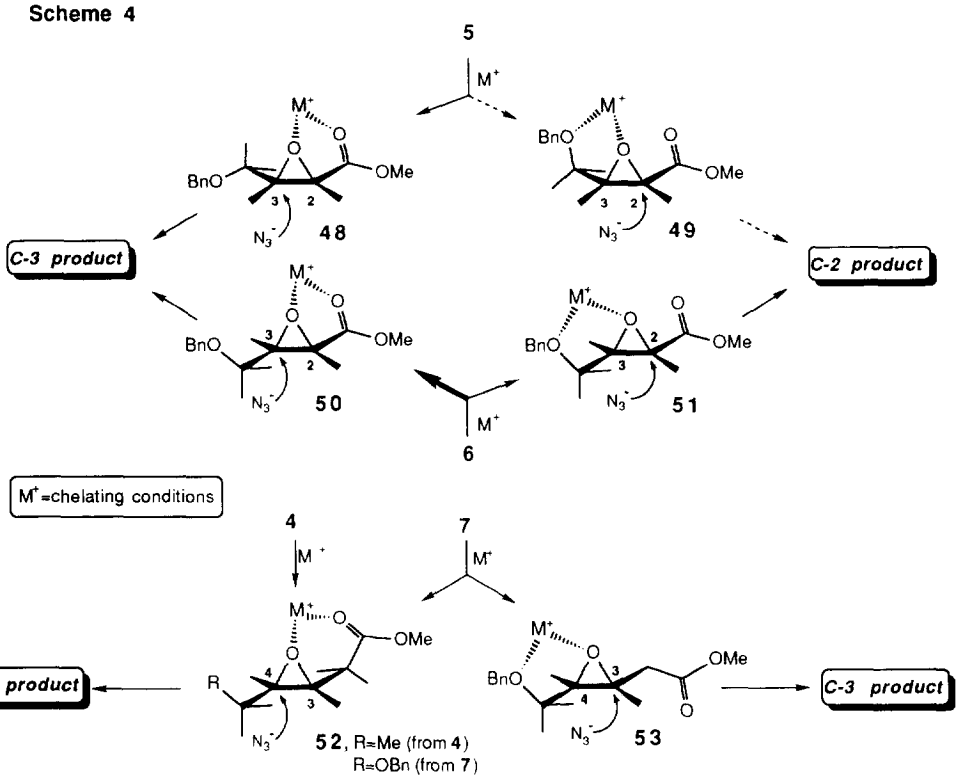
reasonable intermediacy of the chelated bidentate species **41** from **2** and **47** from **1**, favors the formation of *C-3 product*, as a consequence of all the stereoelectronic factors associated with the reactivity of these chelated species,[1,5,6,12] Furthermore, it makes the carbonyl oxygen of the -COOMe group so engaged with the metal in the formation of the chelated species, that it cannot simultaneously behave as the participating neighboring group.

The opening reactions of the homoallylic cis **3** and trans **4** epoxy esters are completely C-4 selective, both under standard and chelating conditions (entries 1-8, Table 2), indicating that the behavior of these epoxides is strongly dominated by the inductive electron-withdrawing effect of the -COOMe substituent.[9] However, in this case, some amounts of the unsaturated ester **34** were formed, as a consequence of the basicity of the reaction medium.[13] Only when an equivalent amount of NH_4ClO_4 was added to the reaction mixture (entries 3 and 7, Table 2),[1] or when the more acidic $Mg(ClO_4)_2$ was used instead of $LiClO_4$ (entries 4 and 8, Table 2), were the reactions completely *C-4 product*-selective, the unsaturated ester **34** being no longer present in the reaction product.[14]

The behaviour of the difunctionalized cis **5** and trans **6** epoxides with two allylic heterofunctionalities, is very similar to that observed with the corresponding monofunctionalized epoxy esters cis **1** and trans **2** (Table 1). Also in this case, under standard conditions, mixtures of *C-2* and *C-3 product* are obtained together with consistent amounts of the corresponding *C-2 retention product* derived from a syn addition process (20% from

5, and 38% from 6, entries 7 and 10, Table 1) (see above). When the same reactions were repeated under chelating conditions, a complete (in the case of the epoxide cis 5) or an increased (in the case of the epoxide trans 6) C-3 selectivity was observed, while the *C-2 retention product* was no longer present in the crude reaction mixtures (entries 8,9 and 12, Table 1). The results obtained with epoxides 5 and 6 are consistent with the rationalization previously formulated for the corresponding monofunctionalized epoxides 1 and 2 (Scheme 3): in particular, the complete or increased C-3 selectivity observed under chelating conditions points to an exclusive or preferential formation of the chelated species **48** (from cis 5) and **50** (from trans 6), respectively, which involves the oxirane oxygen and the -COOMe group, rather than **49** (from cis 5) and **51** (from trans 6) which involves the oxirane oxygen and the OBn group, then attacked by the nucleophile (N_3^-), as shown in Scheme 4.

Scheme 4



Comparing the results obtained from the monofunctionalized epoxides 1 and 2 and difunctionalized 5 and 6 (Table 1), it appears that the simultaneous presence of the ether functionality (OBn) in epoxides 5 and 6 is not able to substantially modify the chemical behaviour of the 2,3-epoxy ester framework of epoxides 1,2,5, and 6. In order to verify the extent of the above observed preference, under chelating operating conditions, of the metal for coordination with the -COOMe group rather than with the OBn group, we examined the trans epoxide 7, too, in which the latter group is closer than the former one to the oxirane ring. That is, we wanted to see if, in this case, a chelated bidentate structure such as **53**, involving the allylic OBn functionality, could substantially intervene in the opening reaction process under chelating opening conditions,

in competition with the chelated structure **52** (R=OBn), involving the homoallylic -COOMe group, to determine the corresponding regiochemical result, as shown in Scheme 4. The results obtained under standard opening conditions indicate that epoxide **7** behaves like the corresponding monofunctionalized trans epoxy ester **5**, showing a complete C-4 selectivity and the presence, in the reaction mixture, of the α,β-unsaturated ester **39** (Scheme 2 and entry 9, Table 2).[13] Considering the inductive electron-withdrawing effect of the allylic OBn group, as clearly demonstrated by previous results obtained with allylic OBn-substituted epoxides,[5b] and comparing this effect with that of the more distant homoallylic -COOMe group, the result of a complete C-4 selectivity is decidedly surprising, seeing that a mixture of *C-3* and *C-4 product* might more reasonably have been expected. As for the metal-promoted opening reactions, while the use of $LiClO_4$ as the metal salt does not substantially modify the behavior of the epoxide already observed under standard conditions (complete C-4 selectivity and presence of ester **39**, except when NH_4ClO_4 is added to the reaction mixture, entries 10 and 11, Table 2),[14] the use of $Mg(ClO_4)_2$ appears to be considerably more interesting. In this case, not only is the unsaturated ester **39** absent, but also a consistent modification of the regiochemical outcome is observed: both the regioisomers, the *C-3 product* (45%, obtained as the corresponding γ-lactone **40**) and the *C-4 product* (55%) are obtained in substantial amounts (Scheme 2, and entry 12, Table 2). A comparison of the results obtained under the same chelating operating conditions with epoxide **7** (entries 10-12, Table 2) and the corresponding results obtained with the monofunctionalized trans **4** epoxy ester (entries 6-8, Table 2), indicates that, while the $LiClO_4$ appears to be totally indifferent, $Mg(ClO_4)_2$ turns out to be favorably sensitive to the structural differences present in the two epoxides. In fact, whereas $LiClO_4$ leads to *C-4 product* in both epoxides **4** and **7**, as a consequence of the exclusive formation of an intermediate chelated bidentate structure such as **52**, $Mg(ClO_4)_2$ is able, in the case of **7**, to give a consistent amount of *C-3 product*, which indicates the likely intermediacy in the opening process of the alternative chelated bidentate species **53**, the only one which can lead to *C-3 product* (Scheme 4).[1,5,6,12] In this way, the *C-3 product* from epoxide **7**, which is not easily accessible by common oxirane opening procedures, may be effectively obtained, thus making $Mg(ClO_4)_2$ a very interesting and useful promoting agent (metal salt) for the opening reactions of difunctionalized 1,2-epoxides, as previously observed in other simple aliphatic oxirane systems.[1]

Experimental

IR spectra were taken with a Mattson 3000 FTIR spectrometer. ^1H NMR spectra were determined in $CDCl_3$ with a Bruker AC 200 spectrometer. GC analyses of mixtures of azido alcohols (column 140°C) were performed on a Perkin-Elmer 8420 apparatus (FI detector) with a 30 m x 0.25 mm (i.d.) x 0.25 μm DB-WAX fused silica capillary column. The order of increasing retention times was **25<27<26<24** and **34<36<33.** In all cases, the injector and detector temperature was 250°C and a 2 ml/min nitrogen flow rate was employed. Preparative TLC were performed on a 0.5-mm Macherey-Nagel DC-Fertigplatten UV_{254} silica gel plates. Procedure for the acetylation reaction: a solution of the product (0.050 g) in anhydrous pyridine (2.0 ml) was treated with Ac_2O (1.0 ml) and the resulting reaction mixture was left 20 h at r.t. Toluene (10 ml) was added and the resulting solution was carefully evaporated to dryness under reduced pressure (rotating evaporator: this procedure was commonly repeated several times) to give a crude reaction product consisting of the corresponding acetylated derivative. Alcohol **13**[5b] and ether **21**[1] were prepared as previously described.

cis-3-Hexenoic acid (17). A stirred solution of the alcohol **16** (5.0 g, 50.0 mmol) in freshly distilled ($KMnO_4$) acetone (80 ml) was treated at r.t. with 8 M CrO_3 (Jones reagent) (28 ml). The reaction mixture was diluted with ether and extracted with saturated aqueous $NaHCO_3$. Acidification (H_2SO_4 10%) of the alkaline extracts, extraction with ether and evaporation of the washed (saturated aqueous NaCl) ether extracts afforded a crude liquid (4.85 g) consisting of **17** practically pure: IR ν 1714 cm^{-1}; ^1H NMR δ 5.44-5.68 (m, 2H, olefinic protons), 3.13 (d, 2H, J=6.4 Hz, CH_2CO), 1.99-2.14 (m, 2H), 0.98 (t, 3H, J=7.4 Hz, CH_3). Anal.Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. A purified (TLC) analytical sample gave: C, 63.25; H, 8.71.

Methyl cis-3-hexenoate (18). A solution of the acid **17** (4.85 g, 42.6 mmol) in anhydrous MeOH (60 ml) was treated with 98% H_2SO_4 (0.2 ml) and the reaction mixture was refluxed for 18h. After cooling, evaporation of the washed (saturated aqueous $NaHCO_3$) organic solution afforded a crude liquid which was distilled to give pure ester **18**, as a liquid, b.p. 63°C (20 mmHg); IR ν 1741 cm^{-1}; ^1H NMR δ 5.45-5.62 (m, 2H, olefinic protons), 3.69 (s, 3H, OCH_3), 3.09 (d, 2H, J=5.7 Hz, CH_2CO), 1.99-2.13 (m, 2H), 0.98 (t, 3H, J=7.6 Hz, CH_3). Anal.Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.52; H, 9.18.

Methyl trans-3-hexenoate (20). Proceeding as above described for **17**, the reaction of the commercially available acid **19** (5.8 g, 51.0 mmol) in anhydrous MeOH (80 ml) containing 98% H_2SO_4 (0.2 ml) afforded a crude liquid (5.4 g) which was distilled to give pure ester **20**, as a liquid, b.p. 63°C (20 mmHg); IR ν 1742 cm^{-1}; ^1H NMR δ 5.54-5.59 (m, 2H, olefinic protons), 3.69 (s, 3H, OCH_3), 3.03 (d, 2H, J=5.8 Hz, CH_2CO), 1.92-2.11 (m, 2H), 0.99 (t, 3H, J=7.4 Hz, CH_3). Anal.Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.29; H, 9.38.

trans-5-Benzyloxy-3-penten-1-ol (22). A solution of the trans olefin **21**[1] (3.0 g, 9.8 mmol) in anhydrous THF (20 ml) was treated at r.t. with 1M tetrabutylammonium fluoride (TBAF) in THF (20 ml) and the resulting reaction mixture was left at the same temperature for 18 h. Dilution with ether, and evaporation of the washed (saturated aqueous NaCl) organic solution afforded a crude liquid (1.45 g) consisting of alcohol **22**, practically pure, which was utilized in the next step without any further purification: ^1H NMR δ 7.22-7.32 (m, 5H, aromatic protons), 5.55-5.70 (m, 2H, olefinic protons), 4.47 (s, 2H, CH_2Ph), 3.96 (dd, 2H, J=3.5 and 1.0 Hz, CH_2OBn), 3.61 (t, 2H, J=6.3 Hz, CH_2OH), 2.24-2.32 (m, 2H). Anal.Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. A purified (TLC) analytical sample gave: C, 75.17; H, 8.54.

Synthesis of Epoxides 3,4, 12 and 23. General procedure. A solution of the corresponding olefin (**18**, **20**, **8**, or **22**) (15.0 mmol) in CH_2Cl_2 (120 ml) was treated at 0°C with 55% *m*-CPBA (5.15 g, 16.4 mmol) and the resulting reaction mixture was stirred at 0-5°C until the olefin was completely reacted (TLC). 5% Aqueous $Na_2S_2O_3$ (20 ml) was added and the reaction mixture was stirred for 20 min. Dilution with CH_2Cl_2 (200 ml) and evaporation of the washed (saturated aqueous $NaHCO_3$, 5% aqueous NaOH, and water) organic solution afforded a crude reaction product consisting of the corresponding epoxide, practically pure.

Methyl cis-3,4-epoxyhexanoate (3), (1.95 g), a liquid: IR ν 1741 cm^{-1}; ^1H NMR δ 3.66 (s, 3H, OCH_3), 3.26 (ddd, 1H, J=6.3 and 4.2 Hz, oxirane proton), 2.89 (ddd, 1H, J=6.4 and 4.2 Hz, oxirane proton), 2.52 (dd, 2H, J=6.5 and 4.8 Hz, CH_2CO), 1.39-1.52 (m, 2H), 0.98 (t, 3H, J=7.5 Hz, CH_3). Anal.Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. A purified (TLC) analytical sample gave: C, 58.27; H, 8.11.

Methyl trans-3,4-epoxyhexanoate (4), (1.80 g), a liquid: IR ν 1741 cm^{-1}; ^1H NMR δ 3.66 (s, 3H, OCH_3), 2.98 (dt, 1H, J=5.9 and 2.2 Hz, oxirane proton), 2.68 (dt, 1H, J=5.5 and 2.2 Hz, oxirane proton), 2.50 (dd, 2H, J=5.9 and 1.8 Hz, CH_2CO), 1.35-1.79 (m, 2H), 0.93 (t, 3H, J=7.5 Hz, CH_3). Anal.Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. A purified (TLC) analytical sample gave: C, 58.06; H, 8.44.

cis-2,3-Epoxy-1-hexanol (12), (1.65 g), a liquid: ^{1}H NMR δ 3.77 (dd, 1H, *J*=12.2 and 4.0 Hz, one proton of CH_2O), 3.57 (dd, 1H. *J*=12.2 and 6.9 Hz, one proton of CH_2O), 3.08 (ddd, 1H, *J*=6.9 and 4.0 Hz, α oxirane proton), 2.93-3.01 (m, 1H, β oxirane proton), 1.38-1.52 (m, 4H), 0.90 (t, 3H, *J*=6.8 Hz, CH_3). Anal.Calcd for $C_7H_{12}O_2$: C, 62.04; H, 10.41. A purified (TLC) analytical sample gave: C, 62.25; H, 10.22.

trans-5-(Benzyloxy)-3,4-epoxy-1-pentanol (23), (3.10 g), a liquid: ^{1}H NMR δ 7.18-7.28 (m, 5H, aromatic protons), 4.53 and 4.44 (ABdd, 2H, *J*=11.9 Hz, C*H*$_2$Ph), 3.61-3.72 (m, 2H), 3.40-3.46 (m, 2H), 2.91-3.01 (m, 2H, oxirane protons), 1.82-1.98 (m, 2H). Anal.Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. A purified (TLC) analytical sample gave: C, 69.33; H, 7.51.

Synthesis of Epoxides 1, 2, 5-7. The following procedure is typical. A solution of epoxy alcohol **12** (1.15 g, 10.5 mmol) in a 1:1:1.5 mixture of CCl_4, CH_3CN, and water (70 ml) was treated with H_5IO_6 (6.0 g, 26.2 mmol) and $RuCl_3$ (0.042 g, 0.21 mmol), and the reaction mixture was stirred at r.t. for 3h. Dilution with ether and evaporation of the washed (saturated aqueous NaCl) ether extracts afforded a crude liquid which was dissolved in anhydrous ether and treated at 0°C with excess of a solution of CH_2N_2 in ether. Evaporation of the organic solvent yielded **methyl cis-2,3-epoxyhexanoate (1)** (0.60 g), practically pure, as a liquid: IR ν 1741 cm^{-1} ; ^{1}H NMR δ 3.85 (s, 3H, OCH_3), 3.60 (d, 1H, *J*=4.5 Hz, α oxirane proton), 3.18-3.27 (m, 1H, β oxirane proton), 1.38-1.81 (m, 4H), 1.00 (t, 3H, *J*=7.0 Hz, CH_3). Anal.Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. A purified (TLC) analytical sample gave: C, 58.24; H, 8.15.

Methyl trans-2,3-epoxyhexanoate (2) (0.75 g), a liquid: IR ν 1741 cm^{-1}; ^{1}H NMR δ 3.72 (s, 3H, OCH_3), 3.17 (d, 1H, *J*=1.9 Hz, α oxirane proton), 3.05-3.15 (m, 1H, β oxirane proton), 1.39-1.65 (m, 4H), 0.92 (t, 3H, *J*=7.4 Hz, CH_3). Anal.Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. A purified (TLC) analytical sample gave: C, 58.52; H, 8.61.

Methyl cis-4-(benzyloxy)-2,3-epoxybutanoate (5). The crude reaction product (2.20 g) obtained from **14** was purified by flash chromatography. Elution with a 92:8 mixture of hexane and AcOEt afforded pure **5** (1.23 g), as a liquid: IR ν 1753 cm^{-1}; ^{1}H NMR δ 7.28-7.38 (m, 5H, aromatic protons), 4.53 and 4.62 (ABdd, 2H, *J*=11.7 Hz, C*H*$_2$Ph), 3.75 (dd, 2H, *J*=5.8 and 0.9 Hz, C*H*$_2$OBn), 3.76 (s, 3H, OCH_3), 3.60 (d, 1H, *J*=4.4 Hz, α oxirane proton), 3.46 (dt, 1H, *J*=5.8 Hz, β oxirane proton). Anal.Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.50; H, 6.09.

Methyl trans-4-(benzyloxy)-2,3-epoxybutanoate (6). The crude reaction product (2.16 g) obtained from **15** was purified by flash chromatography. Elution with a 70:30 mixture hexane and AcOEt afforded pure **6** (1.40 g), as a liquid: IR ν 1752 cm^{-1}; ^{1}H NMR δ 7.19-7.30 (m, 5H, aromatic protons), 4.50 (s, 2H, C*H*$_2$Ph), 3.71 (s, 3H, OCH_3), 3.38-3.74 (m, 4H, oxirane protons and C*H*$_2$OBn). Anal.Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.59; H, 6.27.

Methyl trans-5-(benzyloxy)-3,4-epoxy-pentanoate (7). The crude reaction product (1.98 g) obtained from **23** was purified by flash chromatography. Elution with a 70:30 mixture of hexane and AcOEt afforded pure **7** (1.1 g), as a liquid: IR ν 1739 cm^{-1}; ^{1}H NMR δ 7.35-7.40 (m, 5H, aromatic protons), 4.64 and 4.56 (ABdd, 2H, *J*=10.3 Hz, C*H*$_2$Ph), 3.78 (dd, 1H, *J*=11.6 and 3.3 Hz, one proton of C*H*$_2$OBn), 3.74 (s, 3H, OCH_3), 3.53 (dd, 1H, *J*=11.6 and 5.4 Hz, one proton of C*H*$_2$OBn), 3.25 (ddd, 1H, *J*=5.7 and 2.3 Hz, oxirane proton), 3.03 (ddd, 1H, *J*=5.4, 3.3 and 2.3 Hz, oxirane proton), 2.64 (d, 2H, *J*=5.7 Hz, CH_2CO). Anal.Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.20; H, 6.99.

Azidolysis of Epoxides 1-7 with NaN_3-NH_4Cl (Standard Conditions). General Procedure. A solution of the epoxide (1.0 mmol) in an 8:1 MeOH/H_2O mixture (9.0 ml) was treated with NaN_3 (0.30 g, 4.6 mmol) and NH_4Cl (0.108 g, 2.0 mmol) and the reaction mixture was stirred at 80°C for 18 h. Dilution with ether and evaporation of the washed (water) organic solution afforded a crude reaction product which was analyzed before and after acetylation by GC and/or ^1H NMR to give the results shown in Tables 1 and 2.

Due to TLC separation problems, regioisomers **24** and **26** and their acetyl derivatives (**24-Ac** and **26-Ac**, respectively) derived from cis **1** (together with **25**) and trans epoxide **2** (together with **27**, Scheme 2), respectively, were not obtained pure. However, their presence in the crude acetylated opening reaction product was firmly established by GC and ^1H NMR evidence: **24-Ac**: ^1H NMR δ 5.20 (ddd, 1H, *J*=8.0 and 4.3 Hz, C*H*OAc), 4.16 (d, 1H, *J*=4.3 Hz, CHN_3), 3.74 (s, 3H, OCH_3), 2.02 (s, 3H, $COCH_3$); **26-Ac**: ^1H NMR δ 5.28 (ddd, 1H, *J*=5.8 and 2.9 Hz, C*H*OAc), 3.71 (s, 3H, OCH_3), 3.68 (d, 1H, *J*=2.9 Hz, CHN_3), 1.99 (s, 3H, $COCH_3$). For **25-Ac** and **27-Ac**, obtained pure in the metal-salt promoted azidolysis of epoxides **1** and **2**, respectively, see below the complete ^1H NMR data.

The crude reaction product (0.130 g) from the cis epoxide **3** was subjected to preparative TLC (a 65:35 mixture of hexane and ether was used as the eluant). Extraction of the most intense band afforded pure **methyl syn-4-azido-3-hydroxyhexanoate** (**33**) (0.075 g), a liquid: IR ν 1739 cm^{-1}; ^1H NMR δ 4.02 (ddd, 1H, *J*=7.7 and 3.8 Hz), 3.66 (s, 3H), 3.09 (ddd, 1H, *J*=7.7, 6.1 and 3.8 Hz), 2.61 (dd, 1H, *J*=16.4 and 8.8 Hz), 2.44 (dd, 1H, *J*=16.4 and 3.8 Hz), 1.66-1.77 (m, 2H), 0.98 (t, 3H, *J*=7.5 Hz). Anal.Calcd for $C_7H_{13}N_3O_3$: C, 44.91; H, 7.00; N, 22.45. Found: C, 45.20; H, 7.23; N, 22.21. **33-Ac**, a liquid: ^1H NMR δ 5.26 (ddd, 1H, *J*=6.7 and 3.4 Hz, C*H*OAc), 3.62 (s, 3H, OCH_3), 3.25 (ddd, 1H, *J*=7.2 and 3.4 Hz, CHN_3), 2.65 (d, 2H, *J*=6.6 Hz, CH_2CO), 2.02 (s, 3H, $COCH_3$), 1.41-1.61 (m, 2H), 0.98 (t, 3H, *J*=7.5 Hz, CH_3). Anal.Calcd for $C_9H_{15}N_3O_4$: C, 47.16; H, 6.60; N, 18.33. Found: C, 47.01; H, 6.29; N, 18.20.

The crude reaction product (0.130 g) obtained from trans epoxide **4** was subjected to preparative TLC (a 65:35 mixture of hexane and ether was used as the eluant). Extraction of the most intense band afforded pure **methyl anti-4-azido-3-hydroxyhexanoate** (**36**) (0.080 g), a liquid: IR ν 2108 and 1739 cm^{-1}; ^1H NMR δ 3.91-3.96 (m, 1H), 3.65 (s, 3H), 3.22-3.32 (m, 1H), 2.51 (dd, 2H, *J*=6.8 and 5.5 Hz), 1.64-1.79 (m, 2H), 0.97 (t, 3H, *J*=7.4 Hz). Anal.Calcd for $C_7H_{13}N_3O_3$: C, 44.91; H, 7.00; N, 22.45. Found: C, 45.16; H, 6.76; N, 22.12. **36-Ac**, a liquid: ^1H NMR δ 5.20 (ddd, 1H, *J*=8.5 and 4.2 Hz, C*H*OAc), 3.63 (s, 3H, OCH_3), 3.50 (ddd, 1H, *J*=9.1 and 4.2 Hz, CHN_3), 2.66 (dd, 1H, *J*=16.1 and 8.5 Hz, one proton of CH_2CO), 2.51 (dd, 1H, *J*=16.1 and 4.2 Hz, one proton of CH_2CO), 2.01 (s, 3H, $COCH_3$), 1.55-1.72 (m, 2H), 0.97 (t, 3H, *J*=7.3 Hz, CH_3). Anal.Calcd for $C_9H_{15}N_3O_4$: C, 47.16; H, 6.60; N, 18.33. Found: C, 47.31; H, 6.89; N, 18.45.

The crude acetylated reaction product (0.197 g) from the cis epoxide **5** was subjected to preparative TLC (a 85:15 mixture of petroleum ether and ether containing 0.4% of isopropyl alcohol was used as the eluant). Extraction of the three most intense bands afforded pure **28-Ac** (0.050 g), **29-Ac** (0.060 g), and **30-Ac** (0.010 g).

Methyl syn-3-acetoxy-2-azido-4-(benzyloxy)butanoate (28-Ac), a liquid: IR ν 2116 and 1751 cm^{-1}; ^1H NMR δ 7.26-7.36 (m, 5H, aromatic protons), 5.49 (dt, 1H, *J*=6.5 and 3.0 Hz, C*H*OAc), 4.56 (s, 2H, CH_2Ph), 4.15 (d, 1H, *J*=3.0 Hz, CHN_3), 3.78 (s, 3H, OCH_3), 3.64 (d, 2H, *J*=6.5 Hz, CH_2OBn), 2.07 (s, 3H, $COCH_3$). Anal.Calcd for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found: C, 54.92; H, 5.41; N, 13.81.

Methyl syn-2-acetoxy-3-azido-4-(benzyloxy)butanoate (29-Ac), a liquid: IR ν 2112 and 1751 cm^{-1}; ^1H NMR δ 7.19-7.28 (m, 5H, aromatic protons), 5.22 (d, 1H, J=3.3 Hz, C*H*OAc), 4.54 and 4.44 (ABdd, 2H, J=12.0 Hz, CH_2Ph), 4.00 (dt, 1H, J=6.5 and 3.3 Hz, CHN_3), 3.70 (s, 3H, OCH_3), 3.57 (dt, 2H, J=6.5 and 1.2 Hz, CH_2OBn), 2.05 (s, 3H, $COCH_3$). Anal.Calcd for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found: C, 54.79; H, 5.32; N, 13.44.

The crude acetylated reaction product (0.192 g) from the trans epoxide **6** was subjected to preparative TLC (a 80:20 mixture of petroleum ether and diisopropyl ether containing 0.2% of MeOH was used as the eluant). Extraction of the slower moving band afforded **methyl anti-3-acetoxy-2-azido-4-(benzyloxy)-butanoate (30-Ac)** (0.054 g), a liquid: IR ν 2114 and 1751 cm^{-1}; ^1H NMR δ 7.25-7.43 (m, 5H, aromatic protons), 5.41 (dt, 1H, J=5.7 and 4.9 Hz, C*H*OAc), 4.56 and 4.46 (ABdd, 2H, J=11.8 Hz, CH_2Ph), 4.37 (d, 1H, J=4.9 Hz, CHN_3), 3.70 (s, 3H, OCH_3), 3.66 (d, 2H, J=5.7 Hz, CH_2OBn), 2.09 (s, 3H, $COCH_3$). Anal.Calcd for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found: C, 54.69; H, 5.64; N, 13.54. The faster moving band contained a mixture of **28-Ac** and **31-Ac** (^1H NMR).

Azidolysis of Epoxides 1-7 with $LiClO_4/NaN_3$ or $Mg(ClO_4)_2/NaN_3$ in CH_3CN (Chelating Conditions). General Procedure. A solution of the epoxide (0.5 mmol) in CH_3CN (1.0 ml) was treated with anhydrous $LiClO_4$ (0.532 g, 5.0 mmol) or $Mg(ClO_4)_2$ (0.557 g, 2.5 mmol) and NaN_3 (0.049 g, 0.75 mmol) and the resulting reaction mixture was stirred at 80°C for 18h. After cooling, dilution with water, extraction with ether, and evaporation of the washed (water) ether extracts afforded a mixture of the corresponding azido alcohols which was analyzed, before and after acetylation, by GC and ^1H NMR to give the results shown in Tables 1 and 2. In the case of the $LiClO_4$-promoted azidolysis of epoxides cis **3** and trans **4** and **7**, NH_4ClO_4 (0.088 g, 0.75 mmol) was added in order to neutralize the basicity of the reaction mixture.

The acetylated crude reaction product (0.084 g) obtained in the $Mg(ClO_4)_2$-promoted azidolysis of the cis epoxide **1** afforded **methyl syn-2-acetoxy-3-azidohexanoate (25-Ac)**, practically pure as a liquid: IR ν 2100 and 1740 cm^{-1}; ^1H NMR δ 5.06 (d, 1H, J=3.4 Hz, C*H*OAc), 3.72 (s, 3H, OCH_3), 3.65-3.72 (m, 1H, CHN_3), 2.13 (s, 3H, $COCH_3$), 1.25-1.71 (m, 4H), 0.90 (t, 3H, J=7.3 Hz, CH_3). Anal. Calcd for $C_9H_{15}N_3O_4$: C, 47.16; H, 6.60; N, 18.33. A purified (TLC) analytical sample gave: C, 47.42; H, 6.79; N, 18.21.

The crude acetylated reaction product (0.070 g) obtained from the $LiClO_4$-promoted azidolysis of the trans epoxide **2** afforded **methyl anti-2-acetoxy-3-azidohexanoate (27-Ac)**, practically pure as a liquid: IR ν 2100 and 1740 cm^{-1}; ^1H NMR δ 5.12 (d, 1H, J=3.5 Hz, C*H*OAc), 3.71 (s, 3H, OCH_3), 3.63 (dt, 1H, J=10.0 and 3.5 Hz, CHN_3), 2.11 (s, 3H, $COCH_3$), 1.25-1.63 (m, 4H), 0.89 (t, 3H, J=7.3 Hz, CH_3). Anal.Calcd for $C_9H_{15}N_3O_4$: C, 47.16; H, 6.60; N, 18.33. A purified (TLC) analytical sample gave: C, 47.21; H, 6.68; N, 18.61.

The crude reaction product (0.065 g) obtained from the $LiClO_4$-promoted azidolysis of the trans epoxide **4** was purified by semipreparative TLC (a 65:35 mixture of hexane and ether was used as the eluant). Extraction of the most intense band afforded **methyl trans-4-hydroxy-2-hexenoate (34)** (0.030 g), as a liquid, IR ν 1711 cm^{-1}; ^1H NMR δ 6.95 (dd, 1H, J=15.7 and 4.9 Hz, α olefinic proton), 6.04 (dd, 1H, J=15.7 and 1.7 Hz, β olefinic proton), 4.26 (ddd, 1H, J=6.7, 5.0 and 1.7 Hz, C*H*OH), 3.75 (s, 3H, OCH_3), 1.54-1.75 (m, 2H), 0.97 (t, 3H, J=7.5 Hz, CH_3). Anal.Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.49; H, 8.55.

The crude acetylated reaction product (0.106 g) obtained from the $Mg(ClO_4)_2$-promoted azidolysis of the trans epoxide **6** was purified by preparative TLC (a 99:1 mixture of benzene and ether was used as the eluant). Extraction of the two most intense bands (the faster moving band contained **31-Ac**) afforded pure **30-Ac** (0.015 g) and **methyl anti-2-acetoxy-3-azido-4-(benzyloxy)butanoate (31-Ac)** (0.048 g), a liquid: IR ν 2110 and 1749 cm^{-1}; ^1H NMR δ 7.19-7.29 (m, 5H, aromatic protons), 5.19 (d, 1H, J=3.6 Hz, C*H*OAc), 4.49 (s, 2H, CH_2Ph), 3.97 (dt, 1H, J=6.2 and 3.6 Hz, CHN_3), 3.64 (d, 2H, J=6.2 Hz, CH_2OBn), 3.65 (s, 3H, OCH_3), 2.10 (s, 3H, $COCH_3$). Anal.Calcd for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found: C, 54.51; H, 5.87; N, 13.42.

The crude acetylated reaction product (0.10 g) obtained from the $LiClO_4$-NH_4ClO_4-promoted azidolysis of the trans epoxide **7** afforded **methyl anti-3-acetoxy-4-azido-5-(benzyloxy)-pentanoate (38-Ac)**, practically pure as a liquid: IR ν 2104 and 1745 cm^{-1}; ^1H NMR δ 7.19-7.28 (m, 5H, aromatic protons), 5.25 (ddd, 1H, J=6.9 and 5.2 Hz, C*H*OAc), 4.48 (s, 2H, CH_2Ph), 3.86 (ddd, 1H, J=6.9 and 4.5 Hz, CHN_3), 3.54 (dd, 1H, J=10.1 and 4.5 Hz, one proton of CH_2OBn), 3.45 (dd, 1H, J=10.1 and 6.9 Hz, one proton of CH_2OBn), 2.62 (d, 1H, J=7.2 Hz, one proton of CH_2CO), 2.61 (d, 1H, J=5.2 Hz, one proton of CH_2CO), 1.97 (s, 3H, $COCH_3$). Anal.Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. A purified (TLC) analytical sample gave: C, 59.32; H, 6.39; N, 13.98.

The crude acetylated reaction product (0.103 g) obtained from the $Mg(ClO_4)_2$-promoted azidolysis of the trans epoxide **7** was subjected to preparative TLC (a 70:30 mixture of petroleum ether and ether containing 0.4% of isopropyl alcohol was used as the eluant). Extraction of the two most intense bands (the slower moving band contained **40**) afforded pure **38-Ac** (0.040 g) and **trans 4-azido-5-(benzyloxy)-4,5-dihydro-2(3*H*)-furanone (40)** (0.035 g), as a liquid: IR ν 2104 and 1784 cm^{-1}; ^1H NMR δ 7.19-7.30 (m, 5H, aromatic protons), 4.53 and 4.42 (ABdd, 2H, J=11.8 Hz, CH_2Ph), 4.39 (dt, 1H, J=5.9 and 2.8 Hz, CHO), 4.29 (ddd, 1H, J=7.7, 5.9 and 3.4 Hz, CHN_3), 3.63 (d, 2H, J=2.8 Hz, CH_2OBn), 2.93 (dd, 1H, J=18.0 and 7.7 Hz, one proton of CH_2CO), 2.44 (dd, 1H, J=18.0 and 3.4 Hz, one proton of CH_2CO). Anal.Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.36; H, 5.41; N, 16.75.

The crude acetylated reaction product (0.130 g) obtained from the $LiClO_4$-promoted azidolysis of the trans epoxide **7** was subjected to preparative TLC (a 70:30 mixture of petroleum ether and ether was used as the eluant). Extraction of the most intense band afforded pure **methyl trans-4-acetoxy-5-(benzyloxy)-2-pentenoate (39-Ac)** (0.065 g), as a liquid: IR ν 1739 cm^{-1}; ^1H NMR δ 7.19-7.32 (m, 5H, aromatic protons), 6.83 (dd, 1H, J=15.7 and 4.9 Hz, α olefinic proton), 5.90 (dd, 1H, J=15.7 and 1.5 Hz, β olefinic proton), 5.54 (ddd, 1H, J=4.9 and 1.5 Hz, C*H*OAc), 4.53 and 4.43 (ABdd, 2H, J=12.2 Hz, CH_2Ph), 3.53 (d, 2H, J=5.3 Hz, CH_2OBn). Anal.Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found: C, 59.32; H, 6.39; N, 13.98. Anal.Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.61; H, 6.28.

References and Notes

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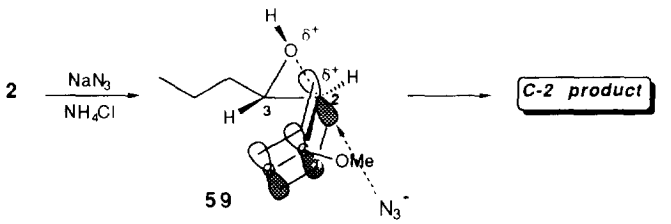
9. It has to be noted that in the opening reactions of epoxides **1** and **2**, as well as in the analogous difunctionalized epoxides **5** and **6**, consistent amounts of *C-2 products* are obtained in spite of the strong unfavorable inductive electron-withdrawing effect of the allylic -COOMe group. This can reasonably be attributed to an acyl activation process which, as shown in structure **59** derived from



trans epoxide **2**, favors substitution at the C(2) oxirane carbon.[7,10] In the case of the homoallylic epoxy esters **3** and **4**, such assistance from the methoxycarbonyl group is no longer possible, and *C-3 products* are consequently not obtained.
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14. The complete *C-4 product* selectivity obtained in the azidolysis of cis **3** and trans **4** 3,4-epoxy esters under metal salt-promoted conditions (entries 3,4,7, and 8, Table 2) might be of a certain interest in organic synthesis, considering that the azidolysis of the corresponding 3,4-epoxy-1-alkanols or their ether derivatives are not selective, leading to mixtures of both the regioisomers.[1]

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