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Synthesis of carba analogs of 6-*O*-(benzyl)-D-allal- and -D-galactal-derived allyl epoxides and evaluation of the regio- and stereoselective behavior in nucleophilic addition reactions

Valeria Di Bussolo [a,*], Ileana Frau [a], Lorenzo Checchia [a], Lucilla Favero [a], Mauro Pineschi [a], Gloria Uccello-Barretta [b], Federica Balzano [b], Graziella Roselli [c], Gabriele Renzi [c], Paolo Crotti [a,*]

[a] *Dipartimento di Scienze Farmaceutiche, Università di Pisa, Via Bonanno 33, I-56126 Pisa, Italy*
[b] *Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 33, I-56126 Pisa, Italy*
[c] *Scuola di Scienze e Tecnologie-Sezione Chimica, Università di Camerino, Via S. Agostino 1, I-62032 Camerino, Italy*

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This work is dedicated to the memory of Professor David Y. Gin, outstanding scientist and dear friend

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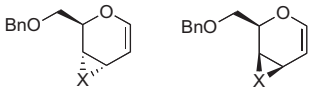
ABSTRACT

The new racemic diastereoisomeric epoxides **6α** and **6β**, the carba analogs of the corresponding D-galactal- and D-allal-derived allyl epoxides have been synthesized and their regio- and stereoselective behavior examined in addition reactions with model *O*-, *C*-, *N*-, and *S*-nucleophiles. The results have indicated that epoxide **6β** has a pronounced tendency toward *anti*-1,2-addition, whereas epoxide **6α** shows interesting levels of *syn*- and/or *anti*-1,4-addition processes. A chiral recognition process found with epoxide **6β**, turned out to be consistently reduced in epoxide **6α**. All the results have been rationalized on the basis of conformational, steric, and stereoelectronic effects.

1. Introduction

The structural resemblance to the parent sugars makes carbasugars attractive compounds for acting as carbohydrate mimetics with a possible recognition by enzymes or other biological systems in place of the related 'true' sugars. For this reason, carba analogs with similar or even improved biological properties and/or with increased stability toward endogenous degradation, compared with those of the parent carbohydrate structures, have been prepared with interesting biological properties, in particular as enzymatic inhibitors.[1]

Epoxides **1α** and **1β** and related *N*-nosyl aziridines **2α** and **2β** were found to be excellent glycosyl donors, particularly in glycosylation of *O*-nucleophiles, as alcohols, where corresponding alkyl *O*-glycosides, having the same configuration as the starting epoxide or aziridine, were obtained in a completely stereoselective way by means of a new, uncatalyzed, completely stereoselective, directly substrate-dependent glycosylation process.[2,3]



1α **2α** X = O X = N-Ns **1β** **2β**

The versatility and the efficiency of the new glycosylation process made its application in a reiterative version possible on epoxide **1β** for the synthesis of 2,3-unsaturated-1,6-di- **3** and trisaccharides **4**.[4] Subsequently, disaccharide **3** was dihydroxylated to the corresponding fully-OH substituted disaccharide **5** by a completely stereofacial selective process (Scheme 1).[5]

On the basis of these results, we thought it interesting to examine the regio- and stereoselective behavior in nucleophilic addition reactions of the new diastereoisomeric allyl epoxides **6α** and **6β**, the carba analogs of glycal-derived epoxides **1α** and **1β**,

* Corresponding authors. Tel.: +390502219690; fax: +390502219660; e-mail addresses: valeriadb@farm.unipi.it (V. Di Bussolo), crotti@farm.unipi.it, paolo.crotti@farm.unipi.it (P. Crotti).

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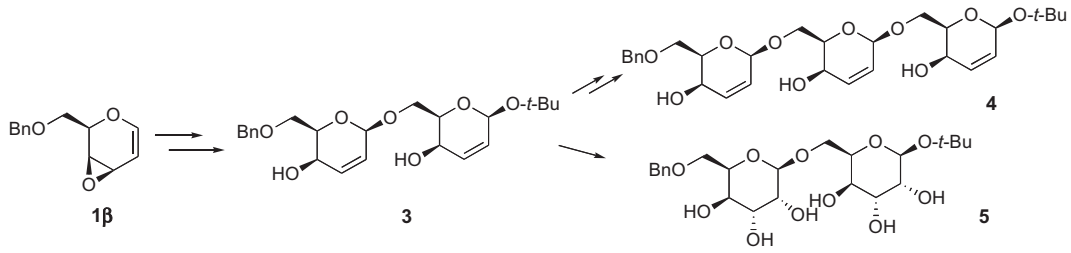
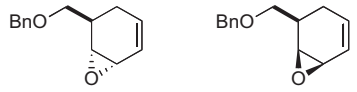


Scheme 1. 2,3-Unsaturated-1,6-di- and trisaccharides from epoxide **1β**.

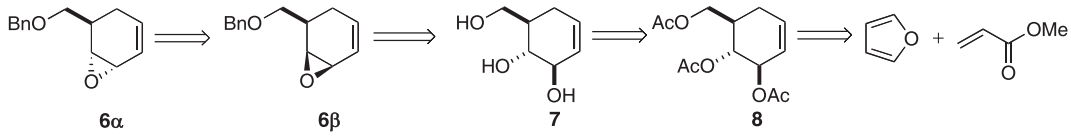
with a view toward their subsequent use in the synthesis of carba oligosaccharides, analogs of **3**–**5**.



2. Results and discussion

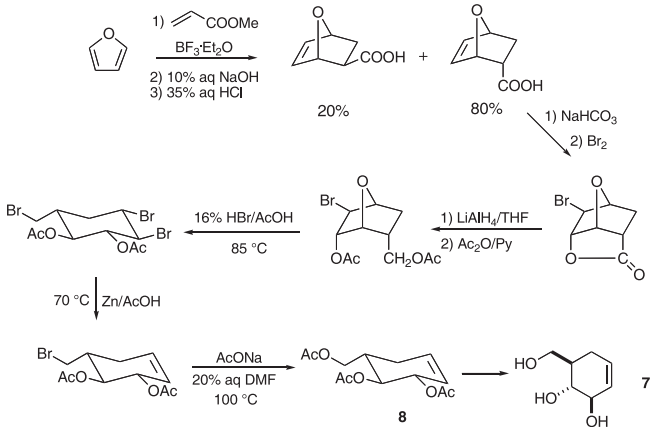
2.1. Synthesis of epoxides 6α and 6β

For the synthesis of racemic epoxide **6β**,[6] the known racemic *c*-3-hydroxymethyl-5-cyclohexen-*r*-1,*t*-2-diol **7**,[7a] obtained by saponification (catalytic MeONa in MeOH) of the corresponding triacetate **8**,[7] was considered an appropriate precursor. Subsequently, epoxide **6β** could be the precursor of the diastereoisomeric carbaepoxide **6α** (Scheme 2).



Scheme 2. Retrosynthetic analysis for epoxides **6α** and **6β**.

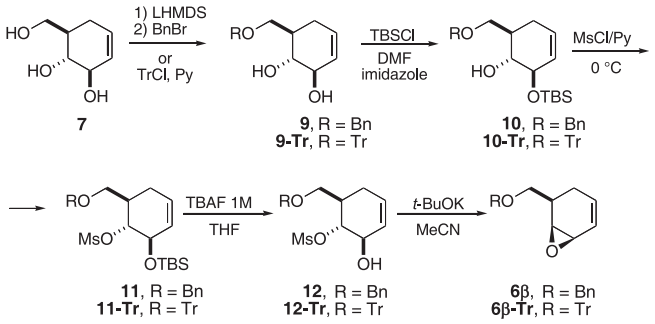
Following the pioneering procedure described by Ogawa,[8a,b] triacetate **8** was prepared starting from Diels–Alder reaction between furane and methyl acrylate,[8c] as shown in Scheme 3.



Scheme 3. Ogawa's synthesis of triol **7**.

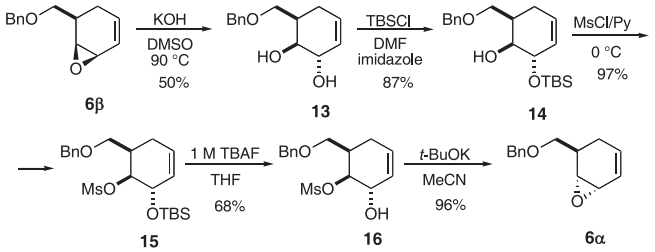
The regioselective benzylation of the primary alcoholic functionality of triol **7** by means of BnBr in the presence of hindered LHMDS as the base, afforded the monobenzyl derivative **9**, which was subjected to the usual protection/deprotection protocol, as shown in Scheme 4. Following this protocol, monobenzyl derivative **9** was selectively protected at the secondary allyl hydroxyl group by means of the bulky TBSCl, affording the corresponding *O*-TBS derivative **10**. Mesylation (MsCl/Py) of the residual secondary hydroxyl group of **10** yielded mesylate **11**. Deprotection of mesylate **11** by the TBAF/THF protocol provided *trans* hydroxy mesylate **12**, which on treatment under alkaline conditions (*t*-BuOK), yielded the desired *cis* epoxide **6β** through a completely regio- and stereoselective process (66% overall yield starting from *trans* diol **9**, four steps).

Because of some difficulties initially encountered in the monobenzylation, triol **7** was initially protected at the primary hydroxyl functionality as corresponding *O*-trityl ether **9-Tr**. Application to **9-Tr** of the same protocol previously described for the monobenzyl ether **9** led, through the formation of the corresponding *O*-trityl derivatives **10**–**12-Tr**, to the synthesis of epoxide **6β-Tr** (Scheme 4). Whilst useful for some nucleophilic addition reactions under alkaline conditions, the *O*-trityl protecting group present in epoxide **6β-Tr** turned out, unfortunately, not to be stable even under the mild acid conditions necessary for epoxide ring opening. As a consequence, we decided to go back to the *O*-benzyl protection, which was finally realized, as described above (Scheme 4).



Scheme 4. Synthesis of *O*-benzyl- and *O*-trityl-protected epoxide **6β** and **6β-Tr**.

The synthesis of diastereoisomeric epoxide **6α** starts from *trans* diol **13**, which is reasonable to expect may be prepared by acid or alkaline hydrolysis of epoxide **6β**. Actually, application of the well-known KOH/DMSO/90 °C protocol[9] to epoxide **6β** led to desired *trans* diol **13**, which was unexpectedly obtained in an unsatisfactory low yield (50%). *trans* Diol **13** was subjected to the usual protocol: regioselective protection of the allyl hydroxyl group to give the corresponding *O*-TBS derivative **14**, which was transformed (MsCl/Py) into mesylate **15**, and subsequently deprotected (TBAF/THF) with the formation of *trans* hydroxy mesylate **16**. Base-catalyzed (*t*-BuOK/MeCN) cyclization of **16** afforded epoxide **6α**, which was obtained with 27% overall yield (five steps, Scheme 5).



Scheme 5. Synthesis of epoxide **6α**.

The unsatisfactory overall yield obtained in the synthesis of epoxide **6α**, mostly due to the low yield (50%) observed in the first step prompted us to check other opening reaction conditions of epoxide **6β** in order to obtain *trans* diol **13**, or a corresponding synthetically useful derivative, with a decidedly better yield. Unfortunately, other opening procedures initially taken into consideration were unsatisfactory too (Scheme 6); (a) the acid hydrolysis of epoxide **6β** (0.01 N TsOH in THF/H_2O) turned out not to be regioselective, and the desired *trans* diol **13** was accompanied by a substantial amount of the corresponding 1,4-addition products (30% in a mixture of *cis* and *trans* diastereoisomers **17**), (b) the use of commercially available $Me_3SiO^-K^+$, a KOH synthetic equivalent, was completely ineffective, whereas (c) the use of the AcONa/H_2O/DMF (100 °C) or tetrabutylammonium acetate (TBAAc, room temperature) led to the desired *trans* diol **13**, still with an unsatisfactory yield for such a simple transformation (65–70%) (Scheme 6).[10]

At this point, we thought that the use, under acid conditions, of a nucleophile weaker than H_2O in order to minimize the formation of regioisomers might represent the solution of the problem. A first attempt based on the acetolysis of epoxide **6β** by means of 0.2 N TsOH in AcOH led, once again, to a non-regioselective result, affording a 77:23 mixture of *trans*-1,2-hydroxy acetate **18** and *trans*-1,4-hydroxy acetate **19** (Table 1 and Scheme 7). However, when the same reaction was repeated by means of an AcOH solution in CH_2Cl_2, in the presence of 0.01 N TsOH, in such a way as to have a 1:3 epoxide/AcOH ratio, a complete 1,2-regio- and *anti* stereoselectivity was observed, with the exclusive and quantitative formation of *trans*-hydroxy acetate **18** (99% yield),[11] sufficiently pure to be directly transformed (MsCl/Py) into the corresponding *trans* mesyloxy acetate **20**, the ultimate precursor of epoxide **6α**. Actually, the treatment of **20** under basic conditions (*t*-BuOK/MeCN) resulted in the alkaline hydrolysis of the acetate group, followed by intramolecular S_N2-type reaction of the intermediate alcoholate on the vicinal carbon, with the formation of the desired epoxide **6α** (Scheme 7).

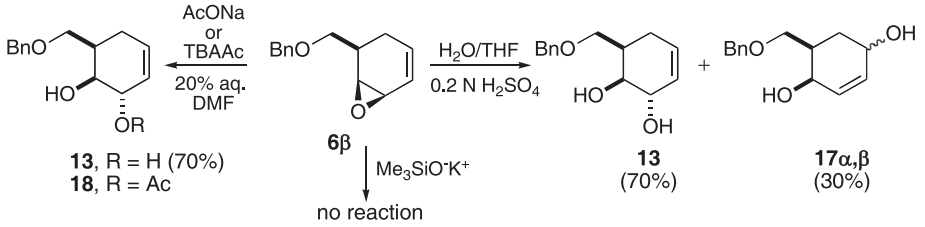
In this way, starting from diastereoisomeric epoxide **6β**, epoxide **6α** was obtained with a good overall yield (62%) through a reduced (three steps) synthetic sequence. Epoxides **6α**, **6β**, and **6β-Tr** turned out to be sufficiently stable, and could be stored for a long time at −15 °C.

2.2. Nucleophilic addition reaction to epoxides 6α and 6β

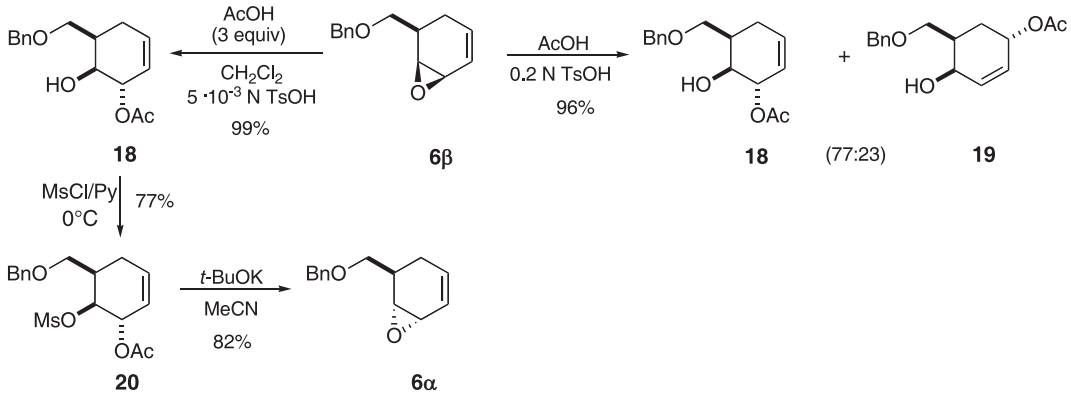
Simple *O*-, *N*-, *S*-, and *C*-nucleophiles were taken as appropriate models in order to check the regio- and stereoselective behavior of diastereoisomeric epoxides **6α** and **6β** in nucleophilic addition reactions. In all cases, the addition products obtained were generically indicated as *anti*-1,2-addition products (*trans*-1,2-derivatives) and/or *syn*- and *anti*-1,4-addition products (*cis*- and *trans*-1,4-derivatives), and for the sake of convenience an arbitrary nomenclature and numbering was used, as shown in Scheme 8. *Protocol A* (nucleophile as the solvent) and/or *protocol B* (nucleophile, 3–6 equiv, in a non-nucleophilic solvent) reaction conditions were used, depending on the type of the nucleophile.

2.2.1. O-Nucleophiles. The regio- and stereoselective behavior of epoxides **6α** and **6β** with *O*-nucleophiles was examined by means of simple and synthetically significant MeOH and AcOH, used under different reaction conditions (acid or basic conditions with different epoxide/nucleophile ratio). The results obtained are collected in Tables 1 and 2.

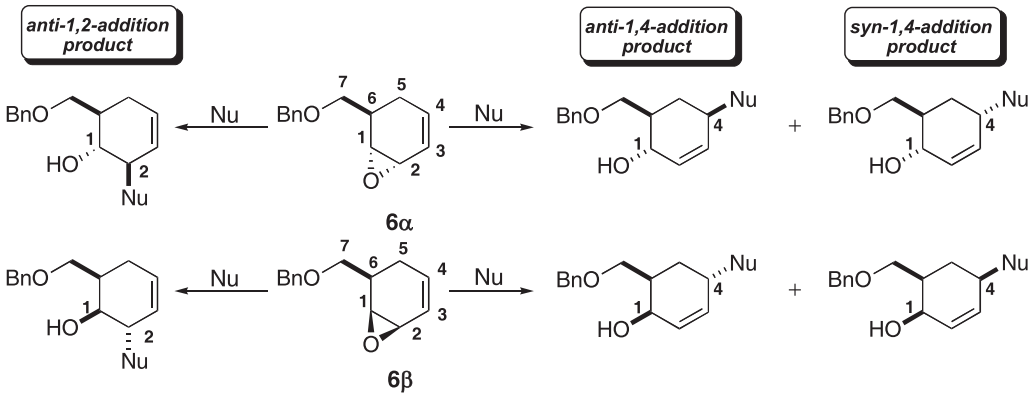
The methanolysis of epoxide **6β** carried out under alkaline conditions (MeONa/MeOH, *protocol A*) is completely 1,2-regioselective and *anti* stereoselective, with the exclusive obtainment of *trans* methoxy alcohol **21** (entry 1, Table 1 and Scheme 9).



Scheme 6. Synthesis of *trans* diol **13** from epoxide **6β**.

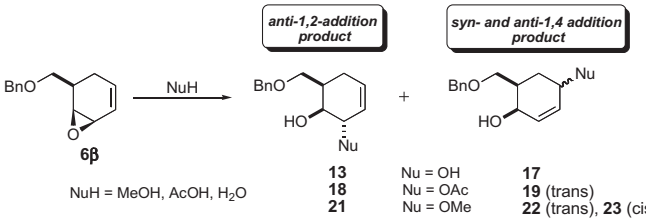


Scheme 7. Acetolysis of epoxide **6β**.



Scheme 8. *anti*-1,2- and *syn*- and *anti*-1,4-addition products from epoxides **6α** and **6β**.

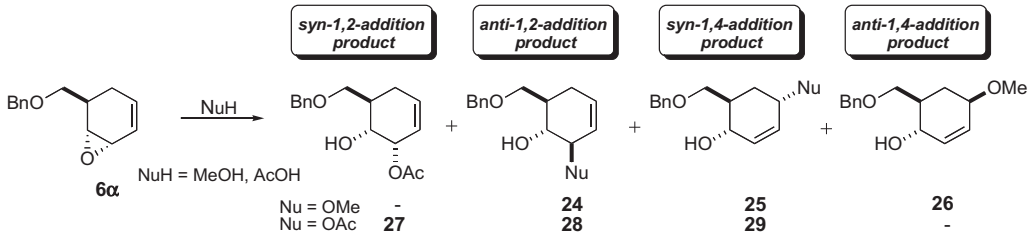
Table 1
Regio- and stereoselectivity of solvolysis reactions of epoxide **6β** with *O*-nucleophiles



Entry	Reagents	*T* (°C)	*anti*-1,2-Addition product	*syn*- and *anti*-1,4-Addition product
1	2 N MeONa/MeOH	80	>99	<1
2	MeOH/0.2 N H_2SO_4	rt	80	20 (*trans* **22**/*cis* **23**=2:1)
3	MeOH/$LiClO_4$	90	77	23[a]
4	MeOH/$Cu(OTf)_2$	rt	75	25[a]
5	D_3^+/MeOH in D_2 (gas-phase)	rt	<1	>99 (*trans* **22**/*cis* **23**=4:1)
6	MeOH/CH_2Cl_2/0.01 N TsOH[b]	rt	>99	>1
7	AcOH/0.2 N TsOH	rt	77	23 (*trans* **19**)
8	AcOH/CH_2Cl_2/0.01 N TsOH[c]	rt	>99	<1
9	AcONa/DMF/H_2O	90	>99[d]	<1
10	TBAAc/DMF	90	>99[d]	<1
11	2 N aq KOH/DMSO	90	>99	<1
12	H_2O/THF/0.01 N TsOH	rt	70	30[a]

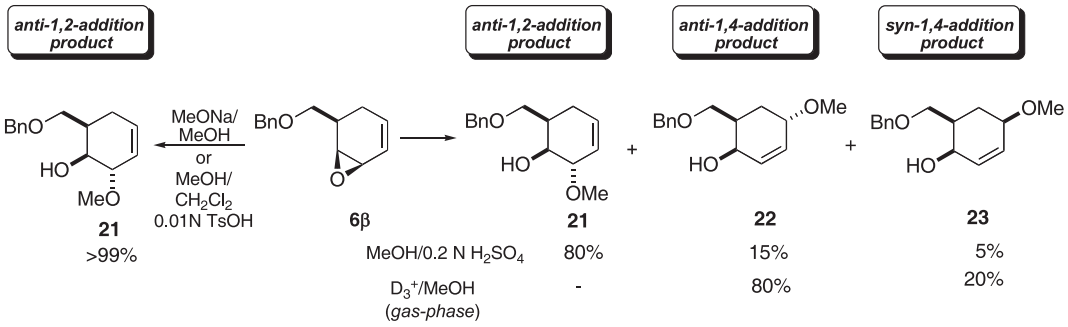
[a] *syn*/*anti* Ratio not determined.
[b] Epoxide/MeOH ratio 1:6.
[c] Epoxide/AcOH ratio 1:3.
[d] *trans* Diol **13**.

Table 2
Regio- and stereoselectivity of solvolysis reactions of epoxide **6α** with *O*-nucleophiles



Entry	Reagents	*T* (°C)	*syn*-1,2-Addition product	*anti*-1,2-Addition product	*syn*-1,4-Addition product	*anti*-1,4-Addition product
1	2 N MeONa/MeOH	80	—	>99	<1	<1
2	MeOH/0.2 N H_2SO_4	rt	—	32	44	24
3	D_3^+/MeOH in D_2 (gas-phase)	rt	—	—	76	24
4	MeOH/CH_2Cl_2/0.01 N TsOH[a]	rt	—	43	47	10
5	AcOH/0.2 N TsOH	rt	28	56	16	—
6	AcOH/CH_2Cl_2/5×10^{-3} N TsOH[b]	rt	30	38	32	—

[a] Epoxide/MeOH ratio 1:6.
[b] Epoxide/AcOH ratio 1:3.



Scheme 9. Methanolysis of epoxide **6β** under alkaline and acidic conditions.

When the methanolysis reaction is carried out under acid conditions ($MeOH/H_2SO_4$ 0.2 N, *protocol A*), the reaction is not regioselective, and leads to an 80:20 mixture of the corresponding 1,2- and 1,4-addition products. Inside this mixture, while the 1,2-addition process is completely *anti* stereoselective and leads to the *trans* methoxy alcohol **21**, the 1,4-addition process is not stereoselective, leading to a 1:2 mixture of the corresponding *syn* (the *cis*-1,4-methoxy alcohol **23**) and *anti*-1,4-addition product (the *trans*-1,4-methoxy alcohol **22**) (entry 2, Table 1 and Scheme 9).

Considering that the 1,4-addition of an appropriate *O*-nucleophile to epoxide **6β** is necessary for the synthesis of 'carba' oligosaccharides, the present results obtained in the methanolysis were not encouraging, seeing the low amount of 1,4-regioselectivity obtained in these reactions. For this reason, we tried to increase the desired 1,4-regioselectivity by carrying out the same reactions under different reaction conditions (Scheme 9).

In view of our continuing interest in the regio- and stereoselectivity of the opening reactions of epoxides under gas-phase reaction conditions, we thought it interesting to repeat the methanolysis reactions of epoxide **6β** also in the gas-phase.[12] Following the typical protocol,[13] the methanolysis of epoxide **6β** in the gas-phase turned out to be completely 1,4-regioselective, with the exclusive formation of a 4:1 mixture of the corresponding *anti*- (*trans*-1,4-methoxy alcohol **22**) and *syn*-1,4-addition product (*cis*-1,4-methoxy alcohol **23**).[14]

On the basis of this result, we repeated the acid methanolysis of epoxide **6β** in the condensed-phase, trying to adopt reaction conditions similar to the gas-phase by using a 0.01 N $TsOH/CH_2Cl_2$ solution containing a drastically reduced amount of methanol, in such a way that the epoxide/MeOH ratio was 1:6. Unfortunately, also in these conditions (*protocol B*), the methanolysis of epoxide **6β** turned out to be completely 1,2-regioselective with the exclusive formation of the corresponding *anti*-1,2-addition product, the *trans*-1,2-methoxy alcohol **21** (Scheme 9 and Table 1).

The completely or highly 1,2-regioselective behavior found in the methanolysis of epoxide **6β** was also found in the corresponding acetolysis reaction (see Scheme 7 and Table 1). Under *protocol A* reaction conditions (0.2 N TsOH in AcOH), a 77:23 mixture of the corresponding *anti*-1,2-addition product (*trans*-1,2-hydroxy acetate **18**) and *anti*-1,4-addition product (*trans* 1,4-hydroxy acetate **19**) was obtained, whereas under *protocol B* reaction conditions (CH_2Cl_2 as the solvent, epoxide/AcOH/TsOH=1:3:0.05), the reaction was completely 1,2-regioselective and the *trans*-hydroxy acetate **18** turned out to be the only reaction product.[15]

The methanolysis of the diastereoisomeric carba-epoxide **6α** indicated that the behavior of this epoxide is similar to that of epoxide **6β**, but significant and synthetically useful differences are present (Table 2).

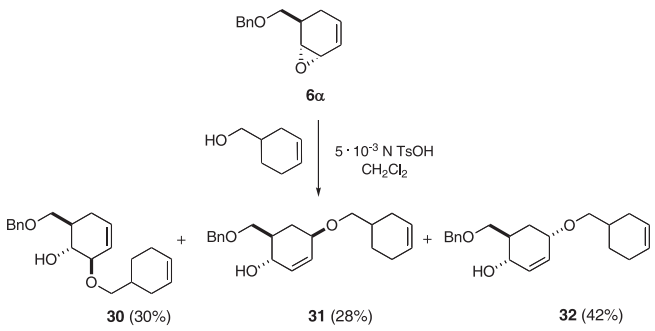
As with **6β**, the alkaline methanolysis (MeONa/MeOH) of epoxide **6α** is completely 1,2-regio- and *anti* stereoselective and the acid methanolysis ($MeOH/0.2\ N\ H_2SO_4$) is not regioselective, leading to a mixture of the corresponding *anti*-1,2-addition product (*trans* 1,2-methoxy alcohol **24**, 32%) and 1,4-addition products (a 2:1 mixture of *syn*- and *anti*-1,4-addition products, the *cis*- **25**, and *trans*-1,4-methoxy alcohol **26**), but the significant difference is that the 1,4-addition is now the main addition process (68%). Also in this case, the application of *protocol B* reaction conditions determines a slight decrease in the overall 1,4-regioselectivity (57%), which is accompanied by an increase in the *syn*-1,4-/*anti*-1,4-addition product stereoselectivity (from 2:1 to 4.7:1, entry 4, Table 2). Analogously to observations with epoxide **6β**, the methanolysis of epoxide **6α** under gas-phase-operating conditions led to a completely 1,4-regioselective result, but now the reaction was largely *syn* stereoselective and the *syn*-1,4-addition product (the *cis*-1,4-methoxy alcohol **25**) was the main reaction product (76%).

Decidedly different is the behavior of epoxide **6α** in acetolysis. Actually, under these conditions a substantial amount of *syn*-1,2-addition product, the *cis*-1,2-acetoxy alcohol **27**, was obtained, to the point that an almost 1:1:1 mixture of **27**, *trans*-1,2-acetoxy alcohol **28**, and *cis*-1,4-acetoxy alcohol **29** was obtained under *protocol B* reaction conditions. Corresponding *syn*-1,2-addition products were never observed in the opening reactions of epoxide **6β** with *O*-nucleophiles (Tables 1 and 2).

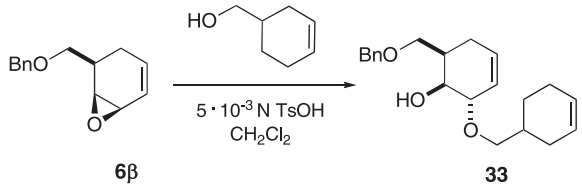
The sufficiently satisfactory 1,4-regioselective result observed in the methanolysis, under *protocol B* reaction conditions, indicated epoxide **6α** as a potentially useful candidate for the construction of O-linked carba oligosaccharides. This possibility was checked by examining the addition reaction of epoxide **6α** to 3-cyclohexene-1-methanol, taken as a simplified model of a carba-monosaccharide with a free primary alcoholic functionality ($-CH_2OH$). The addition reaction was carried out in CH_2Cl_2 in the presence of TsOH (0.005 N) with a 1:3 epoxide/nucleophile ratio. After two days stirring at room temperature, the crude reaction mixture showed the presence of three addition products, the corresponding *anti*-1,2-addition product **30** and the regioisomeric *anti*- **31** and *syn*-1,4-addition product **32** in a 30:28:42 ratio. Separation of this mixture by preparative TLC afforded the *syn*-1,4-addition product **32** pure, whereas the remaining *anti*-1,2- **30** and *anti*-1,4-addition product **31** were still obtained in a mixture. The structure of the obtained pure addition product **32** corresponds to that of a simplified α-O-linked-1,6-carba-disaccharide, as desired (Scheme 10).

As a control, the same reaction was repeated also on the diastereoisomeric epoxide **6β**. As expected a complete 1,2-regio- and *anti* stereoselectivity was obtained and the corresponding *anti*-1,2-addition product **33** was the only reaction product (Scheme 11).

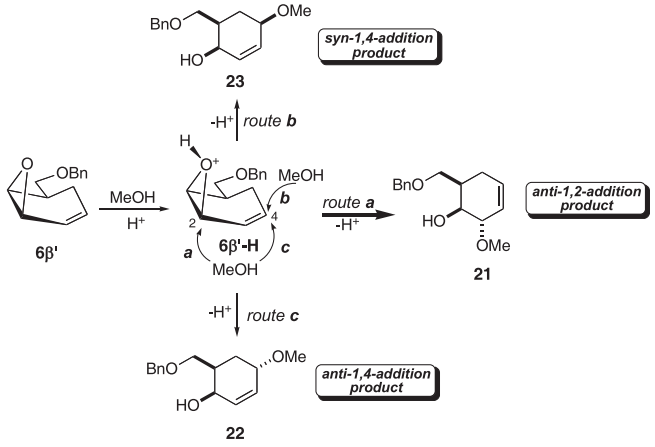
As indicated by a theoretical study carried out on corresponding simplified, 6-CH_2OMe-substituted models (see Supplementary data) and confirmed by ^1H NMR conformational analysis, epoxides **6α** and **6β** exist almost exclusively (96% in the case of **6α** and >99% in the case of **6β**) as the corresponding conformer **6α′** and **6β′** with the side chain axial and equatorial, respectively (Schemes 12 and 13).[16]



Scheme 10. Addition of 3-cyclohexene-1-methanol to epoxide **6α**.



Scheme 11. Addition of 3-cyclohexene-1-methanol to epoxide **6β**.

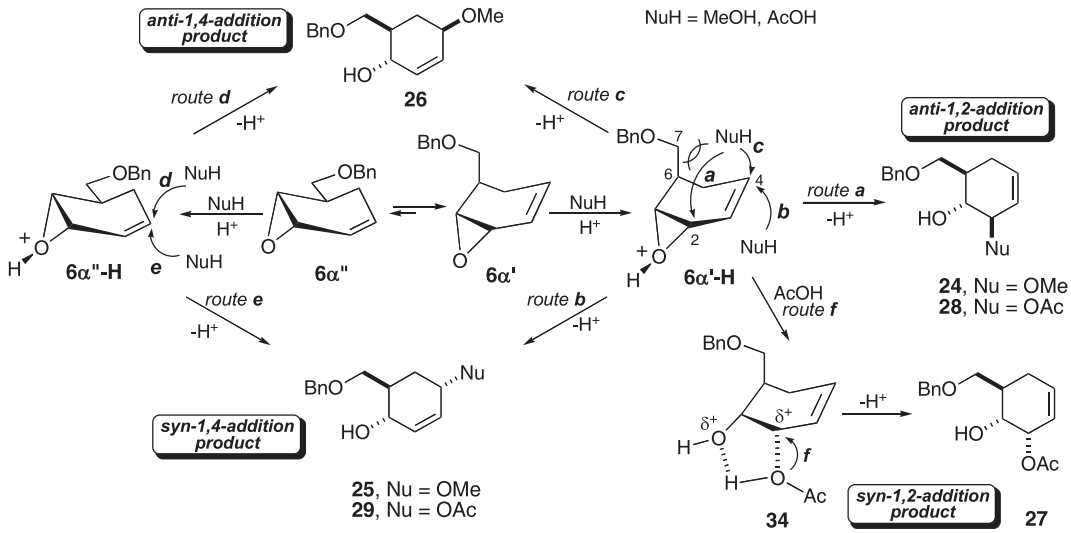


Scheme 12. Methanolysis of epoxide **6β**.

Considering that stereoelectronic factors associated with the opening processes of three-membered rings make *trans* diaxial opening of a cycloaliphatic oxirane the favored opening process, the conformational population inside **6α** and **6β** is responsible, in our opinion, for the opposite regioselective behavior found for these epoxides in methanolysis reactions. Actually, in epoxide **6β**, nucleophilic attack on the C(2) allyl oxirane carbon, from the **α**-side, of the only existing protonated conformer **6β′-H** (*route a*) corresponds to the requirement for a *trans* diaxial opening process, and does not show any particular steric hindrance. Accordingly, the *anti*-1,2-addition process is correctly the main opening process with this epoxide (Scheme 12 and Table 1), whereas the 1,4-addition process (*routes b* and *c*) is decidedly less important.

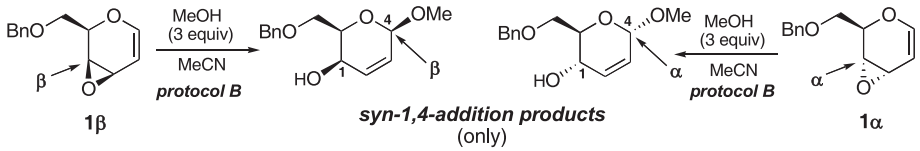
In diastereoisomeric epoxide **6α**, the corresponding *trans* diaxial opening of the oxirane ring can only occur by nucleophilic attack from the **β**-side of the largely existing corresponding protonated conformer **6α′-H**, but in this case the attack is subjected to an unfavorable 1,3-diaxial interaction (torsional strain) with the C(6)–C(7) bond of the axial side chain (*route a*, Scheme 13). As a consequence, *anti*-1,2-addition process is sufficiently slowed down to make the 1,4-addition process [*routes b* and *c* from more stable protonated conformer **6α′-H** and *routes d* and *e* from less stable protonated conformer **6α″-H**] competitive to the point of becoming the main addition process. Inside the 1,4-addition pathway, in agreement with the experimental results, the *syn*-1,4-addition process (*routes b* and *e*), which is not subjected to any particular strain (*route b*) or corresponds to a pseudoaxial attack (*route e*), prevails over the alternative *anti*-1,4-addition process (*routes c* and *d*) for which a 1,3-diaxial interaction with the axial side chain is present (*route c*) or it corresponds to a less favored pseudoequatorial attack (*route d*) (Scheme 13). In this framework, considering that the 1,2-addition process with retention of configuration is favored by the axial opening of the oxirane ring and formation of a discrete (not free) allyl carbocationic species (possible only in protonated conformer **6α′-H**),[17a] the slowing steric effect of the side chain toward nucleophilic attack from the **β** face of **6α′-H**, could be responsible of the formation of a substantial amount (27%) of the corresponding *syn*-1,2-addition product (*cis* derivative **27**) with the less nucleophilic AcOH. Evidently, in these conditions, a *syn*-1,2-addition process, which necessarily develops entirely on the less hindered **α** face, can become competitive (*route f*, Scheme 13).[17b]

A comparison of the regio- and stereoselective behavior of epoxides **6α** and **6β** with the corresponding glycal-derived epoxides



Scheme 13. Methanolysis of epoxide **6α**.

1α and **1β** in their reactions with MeOH[2] appears particularly interesting. Glycal-derived epoxides **1α** and **1β** react with MeOH under practically neutral reaction conditions at room temperature, in the absence of any catalyst, affording only corresponding 1,4-addition products, as an almost 1:1 *syn*-/*anti*-1,4-addition product mixture, under *protocol A*, and only the corresponding *syn*-1,4-addition product, under *protocol B* (Scheme 14).[2,18] On the contrary, with the present epoxides **6α** and **6β**, decidedly alkaline (MeONa/MeOH) or acidic conditions (MeOH/H_2SO_4 or TsOH) are necessary for the opening process to occur, and the reactions are completely (basic conditions) or consistently (acid conditions, particularly with epoxide **6β**) 1,2-regio- and *anti* stereoselective (Tables 1 and 2).



Scheme 14. Methanolysis of epoxides **1α** and **1β**, under *protocol B* reaction conditions.

We think that the decidedly different, almost opposite, regio- and stereoselective behavior observed in the methanolysis of epoxides **1a** and **1b** with respect to epoxides **6a** and **6b** can be attributed to the presence in epoxides **1a** and **1b** of the endocyclic oxygen, which facilitates by conjugation the development of a partial positive charge on C(4) during the opening process. In association with the hypothesized epoxide/nucleophile coordination (hydrogen bond),[2] this makes the attack of the poorly nucleophilic MeOH more favorable only at the more electrophilic C(4) carbon, further from the partially negative oxirane oxygen.[2]

It is interesting to note that a regioselective behavior very similar to that observed with glycal-derived epoxides **1α** and **1β** in the condensed-phase (complete 1,4-regioselectivity) is obtained in the acid methanolysis of epoxides **6α** and **6β** in the gas-phase. Evidently, under these particular reaction conditions, characterized by the absence of any solvent and acid counterion, the developing of a partially positive charge on the C(4) carbon atom, then attacked by the nucleophile by a S_N2' process, is particularly favored.[19]

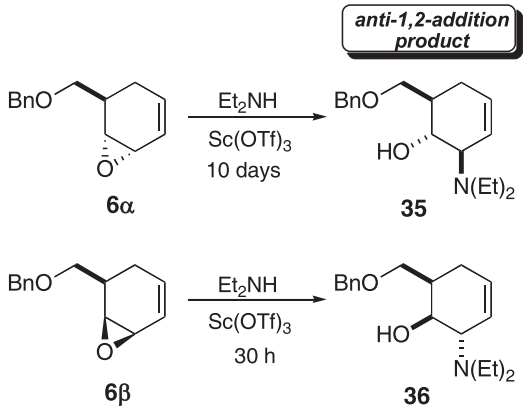
2.2.2. N-Nucleophiles. As examples of *N*-nucleophiles, diethylamine and an azide ion (from NaN_3 and $TMSN_3$) were considered in their reactions with epoxides **6α** and **6β**.

Epoxides **6α** and **6β** did not react with diethylamine under *protocol A*; even after several days, the starting epoxides were recovered completely unreacted. However, if the reactions were repeated in the same conditions but in the presence of a Lewis acid (LA), such as $Sc(OTf)_3$ (0.1–0.2 equiv) completely 1,2-regio- and *anti* stereoselective reactions were observed, with the exclusive formation of *trans*-1,2-*N*,*N*-diethylamino alcohols **35**, from **6α**, and **36**, from **6β** (*anti*-1,2-addition products). Even if the regio- and stereoselectivity observed is the same, the corresponding reactivity is decidedly different: epoxide **6β** completely reacts in 30 h, whereas for the complete conversion of epoxide **6α**, extremely long reaction times (10 days) were necessary. The previously discussed stereoelectronic factors associated with the *trans* diaxial opening of the oxirane ring of epoxide **6α**, absent in epoxide **6β**, could be responsible for the different reactivity observed (Scheme 15).

The azidolysis of epoxides **6α** and **6β**, carried out with NaN_3 (5 equiv)/NH_4Cl in MeOH/H_2O turned out not to be regioselective, but completely *anti* stereoselective. Actually, 8:2 and 55:45 mixtures of the corresponding *anti*-1,2-addition products (*trans*-1,2-azido alcohols **37** and **40**) and *anti*-1,4-addition products (*trans*-1,4-azido alcohols **38** and **41**) were obtained from **6α** and **6β**, respectively (Scheme 16). The larger amount of the corresponding 1,4-addition products found for epoxide **6α** (45%) is the consequence of the previously stated reduced reactivity at the C(2) oxirane carbon for this epoxide.

$TMSN_3$ (3 equiv) in MeCN reacts with epoxides **6α** and **6β** only in the presence of a Lewis acid [$Sc(OTf)_3$, (0.15 equiv)]. In these conditions, epoxide **6β** leads to a complex reaction mixture mostly consisting of *trans*-1,2-azido alcohol **40** (*anti*-1,2-addition product), as the only addition product, whereas epoxide **6α**, in accordance with its lower reactivity, leads only to a non-addition product, the unsaturated ketone **39** (Scheme 16).[20]

2.2.3. S-Nucleophiles. PhSH was used as typical *S*-nucleophile and no substantial differences were observed in the behavior of either



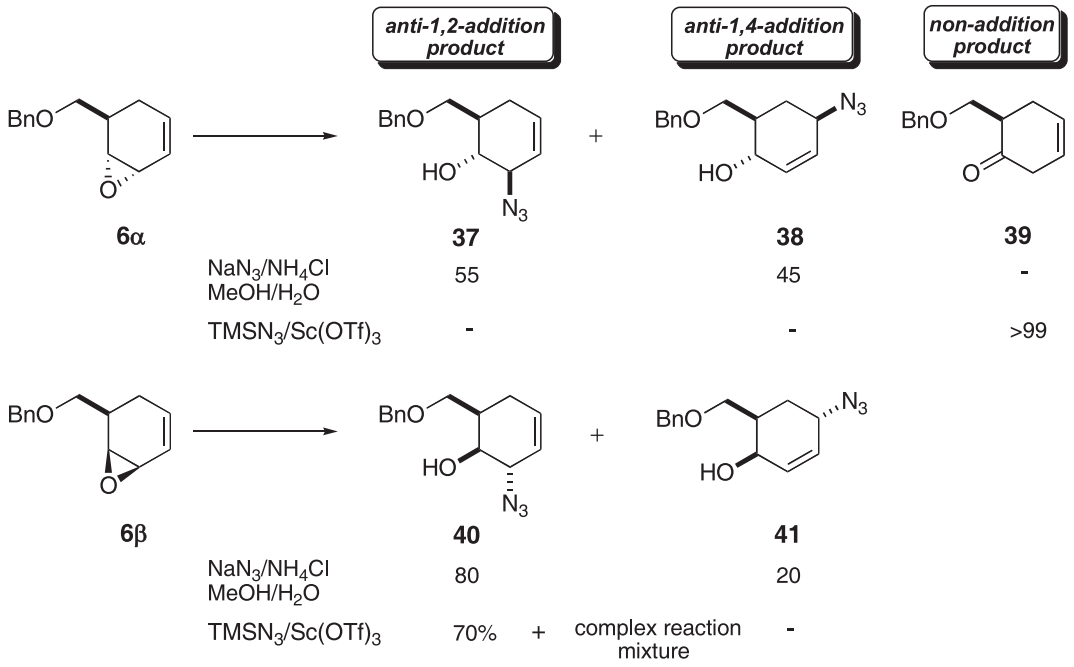
Scheme 15. Aminolysis of epoxides **6α** and **6β** with diethylamine.

epoxides. Actually, the reactions of epoxides **6α** and **6β** with $PhSH/NEt_3$ (*protocol B*) are completely 1,2-regio- and *anti* stereoselective, with the exclusive formation of the corresponding *anti*-1,2-addition product, *trans*-1,2-phenylthio alcohol **42** and **43** from **6α** and **6β**, respectively (Scheme 17). Due to the high nucleophilicity of PhSH, both reactions are very fast (30 min) and do not need the presence of any Lewis acid catalyst to occur.

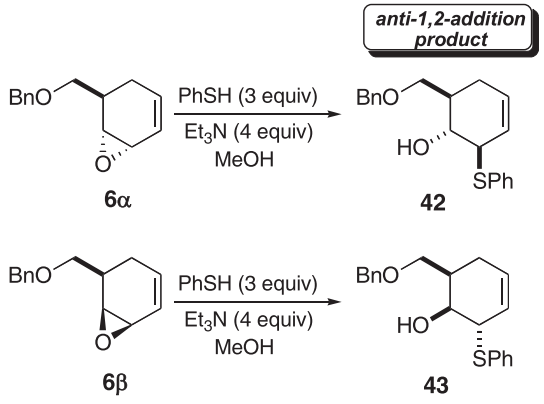
2.2.4. C-Nucleophiles. As the addition of organocopper reagents to allylic epoxides is an important method for regio- and stereoselective carbon–carbon bond formation,[21] the behavior of epoxides **6α** and **6β** with some methyl-based organocopper reagents was examined (Tables 3 and 4 and Fig. 1).

The addition reaction of Me_2CuLi to epoxide **6β** is not regioselective, but completely *anti* stereoselective, and leads to a 57:43 mixture of the corresponding *anti*-1,2-addition product (*trans*-1,2-methyl alcohol **45**) and *anti*-1,4-addition product (*trans*-1,4-methyl alcohol **46**) (entry 1, Table 3). On the contrary, the corresponding reaction of epoxide **6α** turned out to be neither regio- nor stereoselective, affording a mixture of *anti*-1,2-addition product (*trans*-1,2-methyl alcohol **47**, 26%), *anti*-1,4-addition product (*trans*-1,4-methyl alcohol **48**, 23%), and the *syn*-1,4-addition product (*cis*-1,4-methyl alcohol **49**, 25%), accompanied by a non-addition product, ketone **39** (26%) (entry 1, Table 4).

The complete *anti* stereoselectivity observed in the addition of Me_2CuLi to epoxide **6β** is in agreement with the typical behavior of cuprates with allyl oxirane systems.[21] In this framework, the initial



Scheme 16. Azidolysis of epoxides **6α** and **6β** by the NaN_3/NH_4Cl and $TMSN_3/Sc(OTf)_3$ protocol.

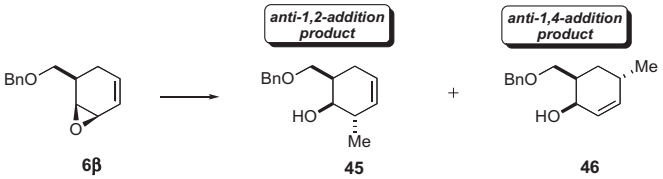


Scheme 17. Addition reaction of PhSH to epoxides **6α** and **6β**.

formation of a π complex, from the opposite side of the oxirane ring, as **50** is reasonably followed by an oxidative addition to the allylic system to give the *anti* γ-Cu(III) intermediate **51**, which can directly undergo reductive elimination to *anti*-1,4-addition product **46** (Scheme 18). A competitive isomerization of **51**, through a Cu(III) π-allyl system as **52**, to the regioisomeric *anti*-α-Cu(III) intermediate **53** and subsequent reductive elimination, could be responsible of the formation of the *anti*-1,2-addition product **45**. A comparison of the present result with the one obtained by Marino in the addition of Me_2CuLi to 1,3-cyclohexadiene monoepoxide, where an almost 1:1 mixture of the corresponding *anti*-1,2- and *anti*-1,4-addition product was obtained,[22] would indicate that the $-CH_2OBn$ side chain, present in epoxide **6β**, has a modest influence on the addition process.

In epoxide **6α**, the formation of a π complex as **54** in an *anti* fashion to the oxirane ring and subsequent oxidative addition to *anti*-γ-Cu(III) intermediate **55** (*route a*, X=Me, Scheme 19), which can lead to both *anti*-1,4- **48** (by reductive elimination) and *anti*-1,2-addition product **47** (through corresponding π-allyl system and *anti*-α-Cu(III) intermediate **56**) suffers from the presence of the axial side chain (steric hindrance). As a consequence, a corresponding, not similarly hindered, *syn*-1,4-addition process (*route b*) leading to the *syn* γ-Cu(III) intermediate **58**, through π complex **57**, becomes highly competitive and a substantial amount of the *syn*-1,4-addition product (*cis*-1,4-methyl alcohol **49**, 25%) is obtained, after the reductive elimination step (Scheme 19).[23]

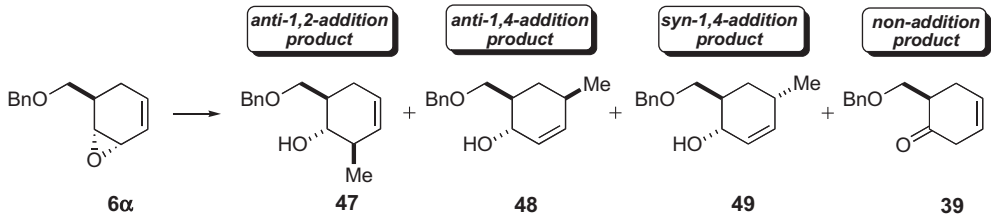
Table 3
Ring opening reaction of epoxide **6β** with methyl-based organocopper reagents



Entry	Reagents	*T* (°C)	*anti*-1,2-Addition product	*anti*-1,4-Addition product
1	Me_2CuLi	−15	57	43
2	MeMgBr/CuCN	−40	7	93
3	Me_2Zn (0.6 equiv)/$Cu(OTf)_2$/(*R*,*R*,*R*)-**44**[a]	−78		>99 (79% ee)
4	Me_2Zn (1.5 equiv)/$Cu(OTf)_2$/(*R*,*R*,*R*)-**44**[b]	−78	28 (98% ee)	72 (45% ee)

[a] At 26% conversion, unreacted epoxide 24% ee.
[b] Conversion (100%).

Table 4
Ring opening reaction of epoxide **6α** with methyl-based organocopper reagents



Entry	Reagents	T (°C)	**47**	**48**	**49**	**39**
1	Me_2CuLi	−15	26	23	25	26
2	MeMgBr/CuCN	−40	10	90	—	—
3	Me_2Zn (1.5 equiv)/$Cu(OTf)_2$/(*R*,*R*,*R*)-**44**[a]	−78→−50	—	>99 (24% ee)	—	—
4	Me_2Zn (1.5 equiv)/$Cu(OTf)_2$/(*R*,*R*,*R*)-**44**[b]	−78→rt	—	86 (16% ee)	—	—

[a] Conversion (40%). Under the same reaction conditions and 71% conversion, compound **48** showed 16% ee.
[b] Conversion (100%): a non-addition by-product was also present (14%).

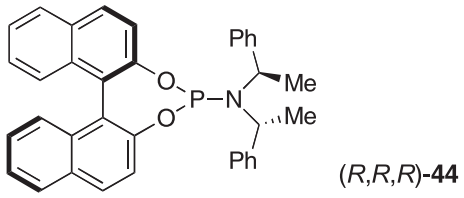
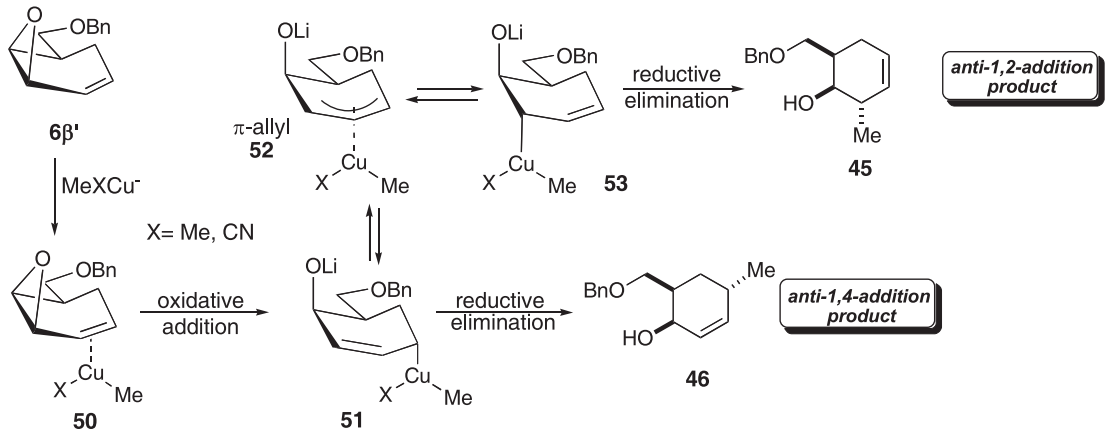


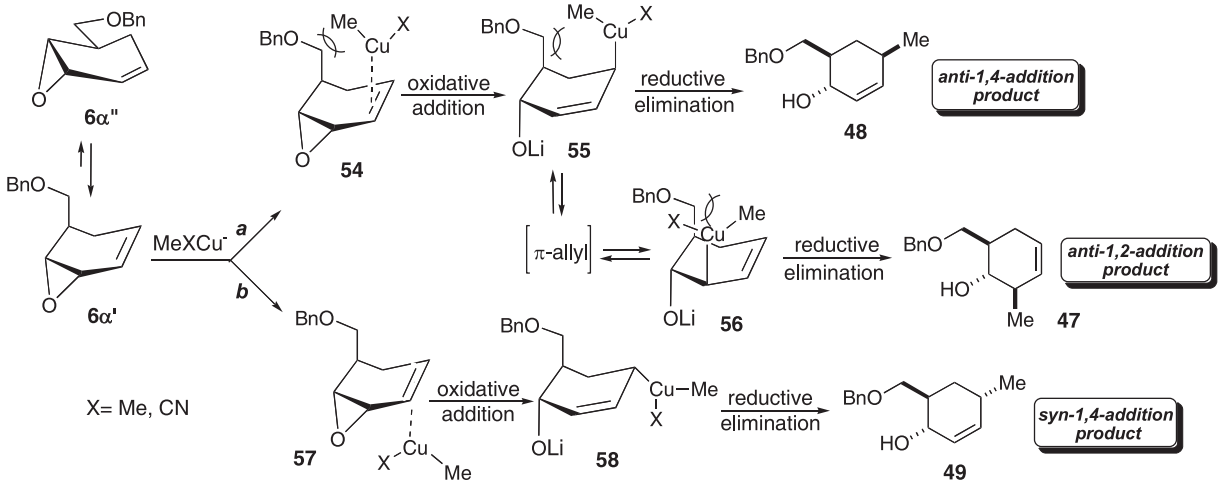
Fig. 1. Chiral ligand (*R*,*R*,*R*)-**44** used in $Me_2Zn/Cu(OTf)_2$ nucleophilic addition protocol.

The formation of ketone **39** in this reaction is a further demonstration of the reduced tendency of epoxide **6α** to addition reactions, to the point that also an LA-catalyzed isomerization process becomes competitive. In this case, the reagent (e.g., $Me_2CuLi{\cdot}LiI$) behaves as the LA catalyst, too (Scheme 20).

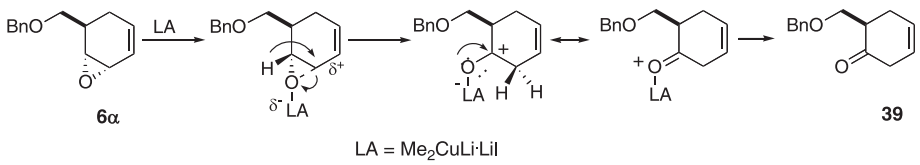
Even if modest as regards the regio- and/or stereoselectivity, the addition reaction of Me_2CuLi to epoxides **6α** and **6β** is synthetically useful, because it turned out to be the only protocol available for



Scheme 18. Formation of *anti*-1,2- and *anti*-1,4-addition product from epoxide **6β**.



Scheme 19. Formation of *anti*-1,2-, *anti*-1,4-, and *syn*-1,4-addition product from epoxide **6α**.



Scheme 20. Formation of ketone **39**.

a substantial formation of the corresponding *anti*-1,2-addition products from both epoxides and the corresponding *syn*-1,4-addition product from epoxide **6α** (Tables 3 and 4).

As for the regio- and stereoselectivity, decidedly better results were obtained in the addition reactions of MeMgBr to epoxides **6α** and **6β** in the presence of catalytic amounts of CuCN. Actually, with this reagent, only mixtures of the corresponding *anti*-1,2-addition products and *anti*-1,4-addition products were obtained from both epoxides, with the corresponding *anti*-1,4-addition product, the *trans*-1,4-methyl alcohol **48** (90%), from epoxide **6α**, and **46** (93%), from epoxide **6β**, as the main reaction products (entry 2, Tables 3 and 4). With regard to this, it is widely accepted that the electron-withdrawing nature of −CN group destabilizes the initially formed *anti*-γ-Cu(III) intermediates **51** (from epoxide **6β**) and **55** (from epoxide **6α**) accelerating the reductive elimination step from these intermediates with a subsequent marked increase of the 1,4-regioselectivity, as experimentally found (X=CN, Schemes 18 and 19).[24]

A complete or highly regioselective formation of *anti*-1,4-addition products **46** and **48** was obtained, under kinetic resolution conditions, in the addition reactions of Me_2Zn to allyl oxiranes **6β** and **6α**, respectively, in the presence of a catalytic amount of copper complex with chiral phosphoramidite **44** (entry 3, Tables 3 and 4).[25] Even if apparently similar, these reactions have shown significant differences between the two epoxides **6α** and **6β**, which are particularly interesting. With epoxide **6α**, the complete 1,4-regioselectivity and *anti* stereoselectivity initially obtained at −78 °C (40% conversion), with the exclusive formation of *trans*-1,4-methyl alcohol **48** (*anti*-1,4-addition product), is maintained also when the reaction temperature is allowed to rise to room temperature in order to have a complete conversion of the starting epoxide into **48** (entries 3 and 4, Table 4). Epoxide **6β** turned out to be more reactive than **6α**, and a complete 1,4-regioselectivity and *anti* stereoselectivity, with the exclusive formation of *trans*-1,4-methyl alcohol **46** (*anti*-1,4-addition product), with a consistent 79% ee, was observed at low temperature (−78 °C) and in the presence of a low amount of Me_2Zn (0.6 equiv) (entry 3, Table 3). When the amount of organometallic reagent was increased (1.5 equiv) and the reaction temperature was maintained at −78 °C, there was a loss of regioselectivity. Actually, under these conditions, the *anti*-1,4-addition product (*trans*-1,4-methyl alcohol **46**) was now obtained with a reduced enantiomeric excess (45% ee), accompanied by the corresponding *anti*-1,2-addition product (*trans*-1,2-methyl alcohol **45**) in an almost 3:1 ratio (entry 4, Table 3). Interestingly, *trans*-1,2-methyl alcohol **45** was obtained in a low yield (28%), but with a high enantiomeric excess (98% ee). These data clearly indicate chiral recognition of the chiral catalyst complex by the enantiomers of epoxide **6β**. However, this recognition is inferior to that previously observed by us, under the same reaction conditions, for the enantiomers of 1,3-cyclohexadiene monoepoxide.[25] In that case the increased regiodivergency (*anti*-1,4-/*anti*-1,2-addition product=60:40) and enantiomeric excess found (97% and 64% ee for the corresponding *anti*-1,2- and *anti*-1,4-addition product, respectively) indicated the complementary reactions of the enantiomers of the starting allyl epoxide.

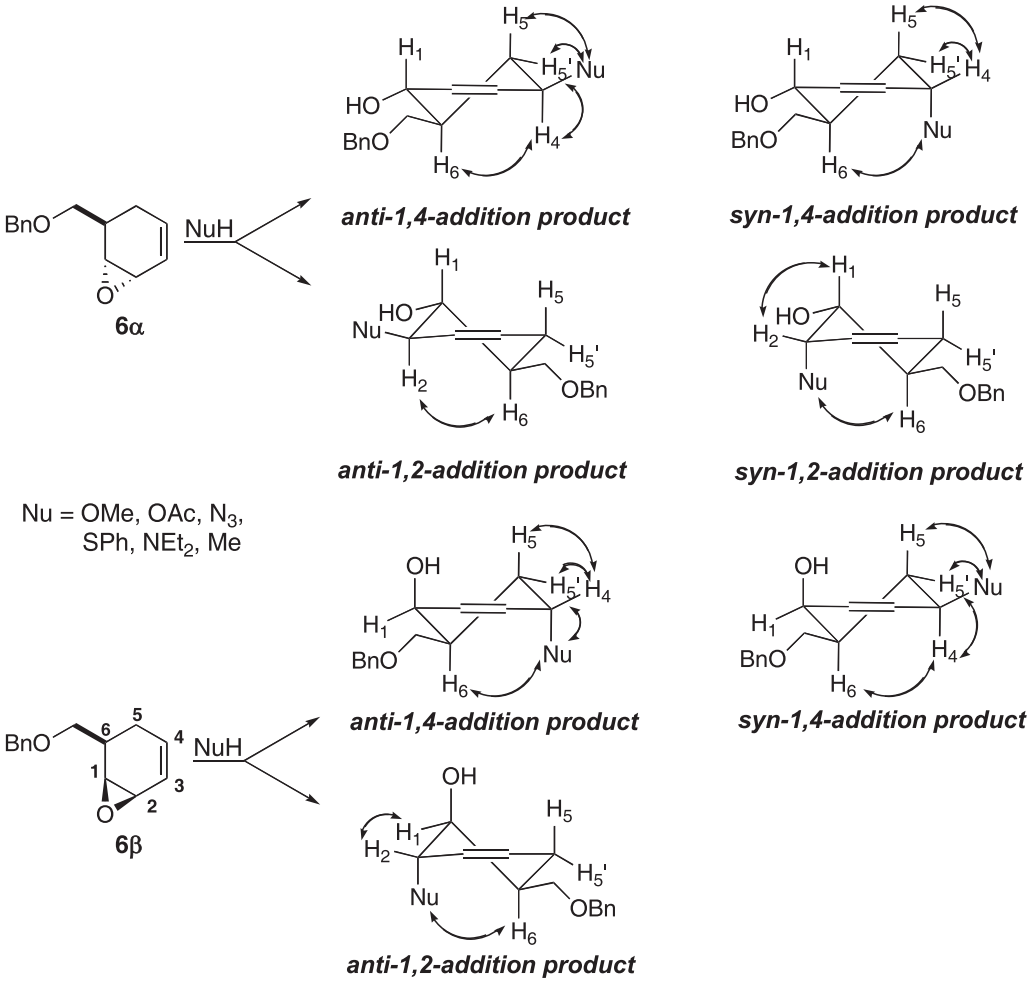
A corresponding chiral recognition is consistently reduced in the case of epoxide **6α**, where at 40% conversion, the only addition product, the corresponding *anti*-1,4-addition product (*trans*-1,4-methyl alcohol **48**), showed a low enantiomeric excess (24% ee, entry 3, Table 4). Even forcing the reaction to completion, by operating at room temperature and in the presence of an excess of Me_2Zn, the result did not change and the *trans*-1,4-methyl alcohol **48** obtained in these conditions showed a lower enantiomeric excess (16% ee), and was accompanied by a certain amount (14%) of a non-addition by-product, not further examined (entry 4, Table 4). Evidently, the approaching and the subsequent coordination of the chiral copper catalyst to the double bond of epoxide **6α**, which would normally proceed from the opposite side of the oxirane ring is sterically hindered by the presence of the axial benzyloxymethyl moiety on C(6) (see intermediates **54** and **55**, X=phosphoramidite, Scheme 19), with a subsequent detrimental effect on the chiral recognition process.

3. Structures and configurations

The regioisomeric 1,2- and 1,4-addition product structure of the products obtained in the opening reactions of epoxides **6α** and **6β** has been simply determined by means of ^1H NMR COSY and NOESY experiments. An appropriate NMR conformational analysis has indicated that all the obtained 1,2- and 1,4-addition products from epoxide **6α** and **6β** preferentially exist as the corresponding conformer with the side chain equatorial, respectively. In particular, axial arrangement of H(6) proton was established on the basis of the dipolar interaction detected between H(6) and only one of adjacent methylene protons, H(5′). Relative arrangement of protons H(1) and H(6) of products from epoxide **6α** was assessed both on the basis of coupling constants pattern for H(1) and its dipolar interaction with proton H(5). In the case of products from epoxide **6β**, H(1) and H(6) were, respectively, in equatorial and axial arrangement as shown by coupling constants values and detection of inter-NOE H(1)—H(6). On this basis, considering that the configuration at C(1) necessarily corresponds to that of the starting epoxide, the relative configuration at the remaining C(2) or C(4) carbons in each 1,2- and 1,4-addition product, respectively, has been firmly established on the basis of dipolar interactions involving protons H(2), H(1), and H(6) in 1,2-addition products and protons H(4), H(5), H(5′), and H(6) in 1,4-addition products and by examination of the coupling constants associated to these protons. When Nu=Me, OMe, also NOE between the protons of these groups and H(6), H(5), and H(5′) have been considered (Scheme 21).

4. Conclusions

In nucleophilic addition reactions with *O*-, *N*-, and *S*-nucleophiles, under basic and/or acid conditions, epoxides **6α** and **6β** show a regioselectivity favoring 1,2- rather than 1,4-addition process. The only significant exception is offered by epoxide **6α** with *O*-nucleophiles under *protocol B* reaction conditions and in the acid azidolysis, where consistent amounts of corresponding 1,4-addition products are obtained. These results make epoxide **6α** a potentially useful candidate for the construction of O-and N-linked carba oligosaccharides. With methyl-based *C*-nucleophiles (Me_2CuLi and MeMgBr/catalytic CuCN), the regioselectivity is generally shifted toward 1,4-addition processes by both epoxides **6α** and **6β**. In the addition reactions of Me_2Zn, under kinetic resolution conditions in



Scheme 21. NOE in *anti*- and *syn*-1,2- and -1,4-addition products from epoxides **6α** and **6β**.

the presence of a catalytic amount of a copper complex with chiral phosphoramidite **44**, a complementary reaction of the enantiomers of the starting allyl epoxide was observed with epoxide **6β**. Under the same conditions, a corresponding chiral recognition is completely absent in the case of epoxide **6α**. The presence of the axial $-CH_2OBn$ side chain in the more stable conformer **6a**′ of epoxide **6α**, besides having, in general, a slowing effect toward nucleophilic attack, is, in our opinion, responsible, in this epoxide, for the competitive formation of 1,4-addition products, *syn*-1,2-addition product (*O*-nucleophiles) and, in some cases, of non-addition products (*N*- and *C*-nucleophiles) and for the absence of chiral recognition by the chiral $Cu(OTf)_2$/(*R*,*R*,*R*)-phosphoramidite **44** complex in addition reactions of Me_2Zn.

5. Experimental

5.1. General

All reactions requiring anhydrous conditions were performed in a flame-dried modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper or rubber septa under a positive pressure of argon. Anhydrous benzene, toluene, Et_2O, and THF were obtained by distillation from sodium/benzophenone. Flash column chromatography was performed employing 230–400 mesh silica gel (Macherey–Nagel). Analytical TLC was performed on Alugram SIL G/UV_{254} silica gel sheets (Macherey–Nagel) with detection by 0.5% phosphomolybdic acid solution in 95% EtOH. Routine ^1H and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively. ^1H NMR COSY and NOESY experiments were performed on a spectrometer operating at 600 MHz. The enantiomeric excesses for alcohols **45**, **46**, and **48** and epoxide **6β** were determined by HPLC Daicel Chiracel OD-H column. Triacetate **8** and triol **7** were prepared as previously described.[7]

5.2. Addition reaction of MeOH and AcOH (*O*-nucleophiles) to epoxides 6β and 6α

*5.2.1. Reaction of epoxide **6β** with 0.2 N H_2SO_4/MeOH (protocol A). Typical procedure.* Epoxide **6β** (0.080 g, 0.37 mmol) was added to a 0.2 N H_2SO_4/MeOH (1.5 mL) and the resulting reaction mixture was stirred 24 h at room temperature. After dilution with CH_2Cl_2, solid $NaHCO_3$ was added. Evaporation of the filtered organic solution afforded a crude product (0.087 g, 95% yield) consisting of *trans*- 1,2-methoxy alcohol **21** (80%) and a 1:2 mixture of *cis*- and *trans*-1,4-methoxy alcohol **23** and **22** (20%) (^1H NMR), which was subjected to preparative TLC, using an 8:2 hexane/AcOEt mixture as the eluant. Extraction of the most intense bands afforded *trans*-1,2-methoxy alcohol **21** (*anti*-1,2-addition product, 0.045 g, 49% yield) and 1:2 mixture of 1,4-methoxy alcohols **23** and **22** (0.014 g). This mixture was subjected to preparative TLC, using a 9:1 CH_2Cl_2/*i*-Pr_2O mixture as the eluant. Extraction of the two most intense bands afforded *cis*-1,4-methoxy alcohol **23** (*syn*-1,4-addition product, 0.003 g, 3% yield) and *trans*-1,4-methoxy alcohol **22** (*anti*-1,4-addition product, 0.009 g, 9% yield).

5.2.1.1. (1R,4S*,6R*)-6-(Benzyloxymethyl)-4-methoxy-2-cyclohexen-1-ol (**22**).* A liquid, R_f=0.06 (9:1 CH_2Cl_2/*i*-Pr_2O); FTIR (neat) ν 3445, 1449, 1095 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40–7.28 (m, 5H, Ph), 6.07–5.94 (m, 2H, CH=CH), 4.55 (d, 1H, *J*=12.0 Hz, CH_aH_bPh), 4.53 (d, 1H, *J*=12.0 Hz, CH$_a$$H_b$Ph), 4.36–4.27 (m, 1H, C*H*OH), 3.76–3.68 (m, 1H, C*H*OMe), 3.66–3.56 (m, 2H, CH_2OBn), 3.35 (s, 3H, OMe), 2.43 (d, 1H, *J*=4.6 Hz, OH), 2.41–2.23 (m, 1H, C(6)H), 1.88–1.73 (m, 1H, C(5)H_aH_b), 1.72–1.62 (m, 1H, C(5)H_aH_b). ^{13}C NMR ($CDCl_3$) δ 138.2, 132.3, 128.9, 128.7, 127.9, 127.8, 77.4, 73.4, 72.6, 71.9, 56.6, 34.8. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.14; H, 7.76. MS (*m*/*z*) 77, 79, 91, 109, 124, 157 (M^+).

5.2.1.2. (1R,4R*,6R*)-6-(Benzyloxymethyl)-4-methoxy-2-cyclohexen-1-ol (**23**).* A liquid, R_f=0.04 (9:1 CH_2Cl_2/*i*-Pr_2O); FTIR (neat) ν 3431, 1452, 1097 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40–7.28 (m, 5H, Ph), 5.60–5.87 (m, 2H, CH=CH), 5.54 (s, 2H, CH_2Ph), 4.27–4.16 (m, 1H, C*H*OH), 3.80 (dd, 1H, *J*=10.0, 5.8 Hz, C*H*OMe), 3.67 (dd, 1H, *J*=9.2, 5.8 Hz, CH_aH_bOBn), 3.51 (dd, 1H, *J*=9.2, 5.8 Hz, CH$_a$$H_b$OBn), 3.38 (s, 3H, OMe), 1.96–1.87 (m, 2H, C(6)H and C(5)H_aH_b), 1.51–1.42 (m, 1H, C(5)H$_a$$H_b$). ^{13}C NMR ($CDCl_3$) δ 138.4, 132.6, 130.1, 128.7, 127.9, 76.1, 73.5, 72.0, 64.8, 56.0, 37.8, 29.9 (1 aromatic signal overlapped). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.24; H, 7.89. MS (*m*/*z*) 77, 79, 91, 109, 121, 157 (M^+).

*5.2.2. Reaction of epoxide **6β** with 0.01 N TsOH in MeOH/CH_2Cl_2 (protocol B). Typical procedure.* Epoxide **6β** (0.025 g, 0.116 mmol) was added to a CH_2Cl_2 solution (1.2 mL) containing MeOH (0.030 mL, 0.696 mmol, 6.0 equiv), TsOH·H_2O (0.002 g, 0.012 mmol, 0.1 equiv) (epoxide/TsOH/MeOH=1:0.1:6) and the resulting mixture was stirred 24 h at room temperature. Dilution with CH_2Cl_2 and evaporation of the washed (saturated aqueous $NaHCO_3$ and saturated aqueous NaCl) afforded a crude product consisting of *trans* 1,2-methoxy alcohol **21** (0.026 g, 90% yield), practically pure.

*5.2.3. Reaction of epoxide **6β** with 0.01 N TsOH in AcOH/CH_2Cl_2 (protocol B). Typical procedure.* Epoxide **6β** (0.150 g, 0.694 mmol) was dissolved in a CH_2Cl_2 solution (6.8 mL) containing AcOH (0.12 mL, 2.08 mmol, 3.0 equiv) and TsOH·H_2O (0.006 g, 0.034 mmol, 0.05 equiv) (epoxide/TsOH/AcOH=1:0.05:3) and the reaction mixture was stirred for 6 h at room temperature, adding two portions of TsOH·H_2O: after 1.5 h (0.005 g, 0.027 mmol) and 3.5 h (0.003 g, 0.016 mmol). The reaction mixture was diluted with CH_2Cl_2 and solid $NaHCO_3$ was added. Evaporation of the filtered organic solution afforded a crude product consisting of (1*S**,2*S**,6*R**)-2-(*acetoxy*)-6-(*benzyloxymethyl*)-3-*cyclohexen*-1-*ol* (**18**) (0.199 g, 99% yield), practically pure as a liquid, which was used in the next step without any further purification: R_f=0.12 (8:2 hexane/AcOEt); FTIR (neat) ν 3481, 1735, 1368, 1230, 1170, 1089, 972, 935 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40–7.28 (m, 5H, Ph), 6.04–5.94 (m, 1H), 5.73–5.62 (m, 1H), 5.18–5.09 (m, 1H), 4.58–4.47 (m, 2H, CH_2Ph), 4.06–3.97 (m, 1H), 3.72–3.06 (m, 2H), 2.34–2.08 (m, 3H), 2.06 (s, 3H, MeC=O). ^{13}C NMR ($CDCl_3$) δ 170.7, 137.9, 132.4, 128.7, 128.1, 127.9, 122.7, 73.8, 72.7, 70.9, 70.7, 35.1, 24.8, 21.4. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.34; H, 7.19.

*5.2.4. Reaction of epoxide **6α** with 0.2 N H_2SO_4/MeOH (protocol A).* Proceeding as previously described for the corresponding reaction of epoxide **6β**, the reaction of epoxide **6α** (0.040 g, 0.185 mmol) with 0.2 N H_2SO_4/MeOH (1.0 mL) afforded a crude reaction product (0.040 g, 87% yield) consisting of a 32:44:24 mixture of methoxy alcohols **24**, **25**, and **26** (^1H NMR), which was subjected to preparative TLC (an 8:2 hexane/AcOEt mixture was used as the eluant). Extraction of the more intense bands afforded *trans*-1,2-methoxy alcohol **24** (*anti*-1,2-addition product) (0.007 g, 15% yield), *cis*-1,4-methoxy alcohol **25** (*syn*-1,4-addition product) (0.011 g, 24% yield), and *trans*-1,4-methoxy alcohol **26** (*anti*-1,4-addition product) (0.004 g, 9% yield).

5.2.4.1. (1S,4S*,6R*)-6-(Benzyloxymethyl)-4-methoxy-2-cyclohexen-1-ol (**25**).* A liquid, R_f=0.13 (8:2 hexane/AcOEt); FTIR (neat) ν 3460, 1447, 1370, 1097 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40–7.28 (m, 5H, Ph), 5.93–5.81 (m, 2H, CH=CH), 4.58 (d, 1H, *J*=12.0 Hz, CH_aH_bPh), 4.53 (d, 1H, *J*=12.0 Hz, CH$_a$$H_b$Ph), 4.09 (d, 1H, *J*=8.8 Hz, C*H*OH), 3.70–3.65 (m, 1H, C*H*OMe), 3.64–3.58 (m, 1H, CH_aH_bOBn), 3.48 (dt, 1H, *J*=8.8, 2.6 Hz, CH$_a$$H_b$OBn), 3.36 (s, 3H, OMe), 2.21–2.03 (m, 1H, C(6)H), 1.86–1.74 (m, 1H, C(5)H_aH_b), 1.42–1.27 (m, 1H, C(5)H$_a$$H_b$). ^{13}C NMR ($CDCl_3$) δ 138.0, 134.9, 128.7, 127.9, 127.8, 126.3, 75.1, 73.7, 72.1, 71.8, 56.7, 37.1, 28.3. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.64; H, 7.59. MS (*m*/*z*) 77, 79, 91, 109, 124, 157 (M^+).

5.2.4.2. (1S,4R*,6R*)-6-(Benzyloxymethyl)-4-methoxy-2-cyclohexen-1-ol (**26**).* A liquid, R_f=0.15 (8:2 hexane/AcOEt); FTIR (neat) ν 3458, 1445, 1370, 1098 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40–7.28 (m, 5H, Ph), 5.81 (dd, 1H, *J*=10.3, 1.4 Hz, CH=C(3)*H*), 5.70–5.77 (m, 1H, C(2)*H*=CH), 4.53 (s, 2H, CH_2Ph), 4.25–4.16 (m, 1H, C*H*OH), 4.00–3.89 (m, 1H, C*H*OMe), 3.62 (dd, 1H, *J*=8.9, 4.4 Hz, CH_aH_bOBn), 3.53 (t, 1H, *J*=8.9 Hz, CH$_a$$H_b$OBn), 3.35 (s, 3H, OMe), 2.05–1.85 (m, 2H, C(6)H and C(5)H_aH_b), 1.23–1.15 (m, 1H, C(5)H$_a$$H_b$). ^{13}C NMR ($CDCl_3$) δ 137.8, 132.3, 129.7, 128.7, 128.1, 127.9, 75.9, 75.2, 73.8, 72.1, 55.8, 41.7, 30.2. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.84; H, 7.88. MS (*m*/*z*) 77, 79, 91, 109, 121, 157 (M^+).

*5.2.5. Reaction of epoxide **6α** with 0.005 N TsOH in AcOH/CH_2Cl_2 (protocol B).* Proceeding as previously described for the corresponding reaction of epoxide **6β**, the treatment of epoxide **6α** (0.072 g, 0.333 mmol) with a CH_2Cl_2 solution (3.2 mL) containing AcOH (0.06 mL, 0.999 mmol, 3.0 equiv) and TsOH·H_2O (0.003 g, 0.017 mmol, 0.05 equiv) (epoxide/TsOH/AcOH=1:0.05:3) for 18 h at room temperature (two additional portions of TsOH·H_2O (0.001 g, 0.004 mmol) were added after 3 h and 14 h) afforded a crude reaction product (0.075 g, 81% yield) consisting of a 38:30:32 mixture of *trans*-1,2-hydroxy acetate **28** (*anti*-1,2-addition product), *cis*-1,2-hydroxy acetate **27** (*syn*-1,2-addition product), and *cis*-1,4-hydroxy acetate **29** (*syn*-1,4-addition product) (^1H NMR), which was subjected to preparative TLC (a 9:1 CH_2Cl_2/(*i*-$Pr)_2O$) mixture was used as the eluant. Extraction of the three most intense bands (the faster moving band contained **29** and the slower moving band contained **27**) afforded pure *cis*-1,2-hydroxy acetate **27** (0.008 g, 8% yield), *trans*-1,2-hydroxy acetate **28** (0.018 g, 20% yield), and *cis*-1,4-hydroxy acetate **29** (0.014 g, 15% yield).

5.2.5.1. (1R,2S*,6R*)-6-(Benzyloxymethyl)-2-acetoxy-3-cyclohexen-1-ol (**27**).* R_f=0.13 (9:1 CH_2Cl_2/(*i*-$Pr)_2O$); FTIR (neat) ν 3489, 1730, 1367, 1234, 1170, 1091 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.39–7.28 (m, 5H, Ph), 5.98–5.87 (m, 1H), 5.82–5.73 (m, 1H), 5.31 (t, 1H, *J*=4.5 Hz), 4.55 (s, 2H, CH_2Ph), 3.90–3.81 (m, 1H), 3.66–3.59 (m, 2H), 2.37–2.18 (m, 2H), 2.09 (s, 3H, MeC=O), 2.08–2.06 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 171.3, 138.1, 132.7, 128.9, 127.8, 123.4, 122.7, 73.9, 72.7, 71.6, 69.0, 35.6, 28.8. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.94; H, 7.01.

5.2.5.2. (1R, 2R*,6R*)-6-(Benzyloxymethyl)-2-acetoxy-3-cyclohexen-1-ol (**28**).* R_f=0.16 (9:1 CH_2Cl_2/(*i*-$Pr)_2O$); FTIR (neat) ν 3475, 1732, 1370, 1235, 1171, 1090 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.39–7.28 (m, 5H, Ph), 5.82–5.72 (m, 1H), 5.54–5.45 (m, 1H), 5.38–5.29 (m, 1H), 4.56 (s, 2H, CH_2Ph), 3.81 (dd, 1H, *J*=10.6, 7.9 Hz), 3.71–3.56 (m, 3H), 2.26–2.14 (m, 2H), 2.12 (s, 3H, MeC=O), 2.08–1.92 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 171.8, 137.9, 129.2, 128.7, 128.0, 127.7, 125.3, 77.4, 77.0, 73.7, 72.9, 29.8, 28.0. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.83; H, 6.97.

5.2.5.3. (1S,4S*,6R*)-6-(Benzyloxymethyl)-4-acetoxy-2-cyclohexen-1-ol (**29**).* R_f=0.19 (9:1 CH_2Cl_2/(*i*-Pr)$_2$O); FTIR (neat) ν 3485, 1732, 1368, 1229, 1170, 1092 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.39–7.28 (m, 5H, Ph), 5.94 (dd, 1H, *J*=10.1, 1.8 Hz), 5.85–5.77 (m, 1H), 5.22–5.15 (m, 1H), 4.57 (s, 2H, C*H*$_2$Ph), 4.13 (d, 1H, *J*=10.1 Hz), 3.64 (dd, 1H, *J*=9.0, 4.4 Hz), 3.52–3.49 (m, 1H), 3.48 (t, 1H, *J*=9.0 Hz), 2.24–2.06 (m, 1H), 2.04 (s, 3H, MeC=O), 1.79–1.57 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 171.1, 137.7, 136.4, 128.7, 128.1, 127.9, 124.7, 75.1, 73.8, 71.9, 65.8, 37.2, 29.9, 29.0. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.79; H, 6.88.

5.3. Addition reactions of *C*-nucleophiles to epoxides 6β and 6α

*5.3.1. Reaction of epoxide **6β** with Me_2CuLi. Typical procedure.* A solution of CuI (0.055 g, 0.291 mmol, 3.0 equiv) in anhydrous Et_2O (2.6 mL) was treated, under argon at −15 °C, with 1.6 M MeLi (0.42 mL, 0.677 mmol, 6.0 equiv). After few minutes, a solution of epoxide **6β** (0.021 g, 0.046 mmol) in anhydrous Et_2O (0.3 mL) was added and the resulting reaction mixture was stirred at 0 °C for 1.5 h. Dilution with Et_2O and evaporation of the washed (10% aqueous NH_4Cl and saturated aqueous NaCl) organic solution afforded a crude reaction product (0.021 g, 94% yield) consisting of a 57:43 mixture of *trans*-1,2-methyl alcohol **45** and *trans*- 1,4-methyl alcohol **46** (^1H NMR, entry 1, Table 3), which was subjected to preparative TLC (an 8:2 hexane/AcOEt mixture was used as the eluant). Extraction of the more intense bands yielded *trans*-1,2-methyl alcohol **45** (*anti*-1,2-addition product, 0.009 g, 40% yield) and *trans*- 1,4-methyl alcohol **46** (*anti*-1,4-addition product, 0.006 g, 27% yield).

5.3.1.1. (1R,2S*,6R*)-6-(Benzyloxymethyl)-2-methyl-3-cyclohexen-1-ol (**45**).* A liquid, R_f=0.21 (8:2 hexane/AcOEt); FTIR (neat) ν 3390, 1350, 1225, 1089 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40–7.28 (m, 5H, Ph), 5.67–5.56 (m, 1H), 5.55–5.46 (m, 1H), 4.53 (s, 2H, C*H*$_2$Ph), 3.79–3.64 (m, 2H), 3.59 (dd, 1H, *J*=9.1, 4.0 Hz), 3.01 (br s, 1H), 2.17–2.31 (m, 1H), 2.16–1.99 (m, 3H), 1.04 (d, 3H, *J*=7.2 Hz, Me). ^{13}C NMR ($CDCl_3$) δ 138.1, 130.4, 128.7, 127.9, 127.8, 124.8, 74.5, 73.7, 73.4, 37.2, 35.1, 25.6, 19.2. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.69; H, 8.29.

5.3.1.2. (1R,4S*,6R*)-6-(Benzyloxymethyl)-4-methyl-2-cyclohexen-1-ol (**46**).* A liquid, R_f=0.18 (8:2 hexane/AcOEt); FTIR (neat) ν 3398, 1347, 1221, 1084 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40–7.28 (m, 5H, Ph), 5.81–5.67 (m, 2H, CH=CH), 4.53 (s, 2H, C*H*$_2$Ph), 4.27 (br s, 1H, C*H*OH), 3.69 (dd, 1H, *J*=9.1, 3.0 Hz, C*H*$_a$H$_b$OBn), 3.52 (dd, 1H, *J*=9.1, 5.0 Hz, CH$_a$*H*$_b$OBn), 2.48–2.34 (m, 1H, C*H*Me), 2.33–2.12 (m, 2H, C(6)H and C(5)*H*$_a$H$_b$), 1.83–1.68 (m, 1H, C(5)H$_a$*H*$_b$), 0.98 (d, 3H, *J*=7.2 Hz, Me). ^{13}C NMR ($CDCl_3$) δ 138.3, 135.9, 128.6, 127.8, 73.5, 72.0, 66.1, 35.7, 28.8, 28.6, 20.4 (two aromatic signals overlapped). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.91; H, 8.46.

*5.3.2. Reaction of epoxide **6β** with Me_2Zn/Cu(OTf)$_2$/(R,R,R)-phosphoramidite **44** under kinetic resolution conditions.* (*R*,*R*,*R*)-Phosphoramidite **44** (0.004 g, 0.007 mmol, 0.03 equiv) was added, at room temperature, to a solution of Cu(OTf)$_2$ (0.6 mg, 0.0035 mmol, 0.015 equiv) in anhydrous toluene (0.4 mL) and the resulting reaction mixture was stirred 20 min at the same temperature, then cooled at −78 °C and treated with a solution of epoxide **6β** (0.050 g, 0.231 mmol) in anhydrous toluene (0.4 mL) and subsequently with 2.0 M Me_2Zn in toluene (0.069 mL, 0.139 mmol, 0.6 equiv). After 35 min, HPLC analysis showed 26% conversion. The reaction mixture was diluted with Et_2O: evaporation of the washed (10% aqueous NH_4Cl and saturated aqueous NaCl) organic solution afforded a crude reaction product (0.050 g) consisting of a mixture of *trans*-1,4-methyl alcohol **46**, as the only addition product (entry 3, Table 3), and starting, unreacted, epoxide **6β** (^1H NMR). *trans*-1,4-Methyl alcohol **46** showed 79% ee, whereas the starting epoxide **6β** showed 24% ee (determined on the crude reaction mixture). The crude reaction product was subjected to preparative TLC with an 8:2 hexane/AcOEt mixture as the eluant. Extraction of the most intense band afforded pure *trans*-1,4-methyl alcohol **46** (0.006 g, 11% yield), [α]D^{25} +26.9 (*c* 0.3, $CHCl_3$).

*5.3.3. Reaction of epoxide **6β** with Me_2Zn/Cu(OTf)$_2$/(R,R,R)-phosphoramidite **44**.* (*R*,*R*,*R*)-Phosphoramidite **44** (0.004 g, 0.006 mmol, 0.03 equiv) was added to a solution of Cu(OTf)$_2$ (0.0012 g, 0.004 mmol, 0.015 equiv) in anhydrous toluene (0.8 mL) and the reaction mixture was stirred 20 min at room temperature, then cooled at −78 °C and treated in succession with a solution of epoxide **6β** (0.050 g, 0.231 mmol) in anhydrous toluene (0.4 mL) and 2.0 M Me_2Zn in toluene (0.175 mL, 0.35 mmol, 1.5 equiv). After 1 h stirring at the same temperature, dilution with Et_2O and evaporation of the washed (10% aqueous NH_4Cl and saturated aqueous NaCl) organic solution afforded a crude reaction product (0.050 g, 93% yield) consisting of a 28:72 mixture of *trans*- 1,2-methyl alcohol **45** (*anti*-1,2-addition product) and *trans*- 1,4-methyl alcohol **46** (*anti*-1,4-addition product) (^1H NMR, entry 4, Table 3). *trans*-1,2-Methyl alcohol **45** showed 98% ee (determined on the crude reaction mixture), whereas *trans*-1,4-methyl alcohol **46** showed 45% ee (determined on the crude reaction mixture). The crude reaction mixture was subjected to preparative TLC with an 8:2 hexane/AcOEt mixture, as the eluant. Extraction of the two most intense bands (the faster moving band contained **45**) afforded pure (+)-*trans*-1,2-methyl alcohol **45** (0.008 g, 15% yield), [α]D^{25} +86.4 (*c* 0.36, $CHCl_3$), and *trans*- 1,4-methyl alcohol **46** (0.028 g, 52% yield).

5.4. Reactions in the gas-phase

5.4.1. Materials. Oxygen and trimethylamine were high-purity gases from Matheson Gas Products Inc., deuterium (99.98%) was purchased from Aldrich and all were used without further purification. The purity of starting epoxides **6α** and **6β** was checked by analytical gas chromatography on the same columns employed for the analysis of their gas phase products.

5.4.2. Procedure. The gaseous mixtures were prepared by introducing fragile ampoules, containing weighed amounts of selected epoxide (0.0076–0.0080 mmol) and methanol (0.0231–0.0237 mmol), into 250-mL Pyrex bulbs, equipped with a break-seal arm, and connected to a greaseless vacuum line. Following the introduction of the gaseous components (deuterium, oxygen, and trimethylamine) at the desired partial pressures into the carefully evacuated and outgassed vessels, the latter were then allowed to come to room temperature, the fragile ampoules broken, and the gaseous components allowed to mix before being subjected to the irradiation. The gaseous mixtures were submitted to irradiation at a constant temperature (37.5 °C) in a ^{60}Co 220 Gammacell from Nuclear Canada Ltd. (dose: 1.5×10^4 Gy; dose rate: 1×10^4 Gy h^{-1}, determined with a Fricke dosimeter). Control experiments, carried out at doses ranging from 1×10^4 to 1×10^5 Gy, showed that the relative yields of products are largely independent of the dose. In order to verify the 'stability' of the reactions products, the methoxy alcohols **21**–**26** were placed with the gaseous members (D_2, O_2, and NMe_3) into Pyrex bulbs and irradiated at the same experimental conditions adopted for epoxides **6α** and **6β** (37.5 °C—dose: 1.5×10^4 Gy). In all the cases the methoxy alcohols were recovered unchanged and no trace of isomerization products was found.

5.4.3. Product analysis. The analysis of the products was performed by injecting measured portions of the homogeneous reaction mixture into a Hewlett–Packard 5890 series II gas chromatograph, equipped with a flame ionization detection unit. In order to prevent

selective loss of the reaction products by adsorption on the glass of the reaction bulb (and to obtain reproducible and meaningful reaction yields), the analysis was repeated after careful washing of the bulb walls with anhydrous ether. Satisfactory agreement between the results of the gaseous mixture and the ether solution analysis was found in all runs. The products were identified by comparison of their retention volumes with those of authentic standard compounds on the following columns: (i) a 30 m long, 0.25 mm i.d. HP5MS™ fused silica capillary column, operating at temperatures ranging from 100 to 210 °C, 5 °C min^{-1}; (ii) a 30 m long, 0.32 mm i.d. Supelcowax 10™ fused silica capillary column, operating at 190 °C. The identity of the products was further confirmed by GLC/MS, using a Hewlett–Packard 5890A gas chromatograph in line with an HP 5971A quadrupole mass spectrometer. The yields of the products were measured, using the internal standard method and individual calibration factors to correct for the detector response. The results given in Tables 1 and 2 (see also Table 1, Supplementary data) are the average of at least three measurements taken on at least two different runs for each point.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.04.036.

References and notes

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5. Unpublished results from our laboratory.
6. Epoxides **6α** and **6β** were prepared as corresponding racemic mixtures, considering that it was not necessary to have them as pure enantiomers for these preliminary studies on their reactivity.
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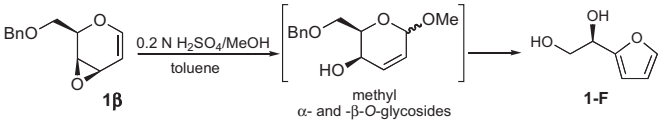
10. Evidently, the corresponding allyl *trans*-hydroxy acetate **18**, the primary reaction product, is hydrolyzed in the reaction mixture to *trans* diol **13**.
11. It is interesting to note that when the same opening protocol is applied to the corresponding hydrolysis (H_2O, 3 equiv, in THF) and methanolysis reaction (MeOH, 3 equiv, in CH_2Cl_2) in the presence of TsOH, the reactions are not regioselective, affording a 7:3 (hydrolysis) and 8:2 mixture (methanolysis) of the corresponding *anti*-1,2-addition product and 1,4-addition products (vide infra and see Table 1).
12. Obviously, the opening reactions of epoxides carried out in the gas-phase have no synthetic valence. They can only give information about the intrinsic reactivity of epoxides unperturbed by the effects of solvation and ion-pairing which affect, to a variable extent, the corresponding processes carried out in solution. Accordingly, this information can often be useful for the rationalization of the regio- and stereoselective behavior of the same epoxides in opening reactions carried out in the condensed phase. See, as an example: Crotti, P.; Di Bussolo, V.; Macchia, F.; Favero, L.; Pineschi, M.; Lucarelli, L.; Roselli, G.; Renzi, G. *J. Phys. Org. Chem.* **2005**, *18*, 321–328 and references therein.
13. The methanolysis of epoxide **6β** in the gas-phase was carried out in a D_2 atmosphere containing epoxide **6β** and only a small excess of MeOH (3 equiv) in the presence of Me_3N. The irradiation of the reaction mixture with a ^{60}Co 220 Gammacell generates the gaseous Brönsted acid D_3^+, the necessary gaseous catalyst of the reaction. The crude reaction product was examined by GC/MS (see Experimental section).
14. The stereoselectivity toward *trans*-1,4-methoxy alcohol **22** is similar to that found in the small amount (20%) of 1,4-addition products obtained from the corresponding reaction carried out in the condensed phase (0.2 N H_2SO_4/MeOH).
15. (a) These results would indicate that in epoxide **6β**, the C(2) oxirane carbon is largely the more reactive center of the allyl system, to the point that in the presence of a low amount of *O*-nucleophile, it becomes the only reactive one. (b) The result obtained by AcOH/TsOH under *protocol B* reaction conditions (entry 8, Table 1) turned out to be particularly useful for the synthesis of epoxide **6α** (see Scheme 7).
16. The 96:4 **6α'** ⇌ **6α''** equilibrium given for epoxide **6α** is the average of the values obtained by means of MP2 and B3LYP calculations when $CHCl_3$ is considered as the solvent (Supporting data). This value is in accordance with the corresponding result obtained by ^1H NMR conformational analysis. A similar result was previously obtained by a theoretical conformational analysis carried out on the corresponding 6-methyl substituted epoxides, see: Crotti, P.; Di Bussolo, V.; Pomelli, C. S.; Favero, L. *Theor. Chem. Account* **2009**, *122*, 245–256.
17. (a) The possibility that a corresponding *syn*-1,2-addition process of epoxide **6α** can occur by an equatorial opening of the oxirane ring through the less stable conformer **6α''-H** cannot reasonably be ruled out (Scheme 13). However, it was demonstrated that, in nucleophilic opening reactions, the 'axial cleavage' of 1,2-epoxycyclohexanes is easier than the corresponding 'equatorial cleavage' and favours the *syn* stereoselectivity of the addition process. See: Battistini, C.; Crotti, P.; Damiani, D.; Macchia, F. *J. Org. Chem.* **1979**, *44*, 1643–1647 and references therein. (b) As previously demonstrated in the case of 2-aryl-oxiranes, we think that the *syn*-1,2-addition process leading to *cis*-2-acetoxy alcohol **27** derives from a nucleophile-separated ion–dipole pair, such as **34**, followed by nucleophilic pseudoequatorial attack on the partially developed C(2) carbocation with retention of configuration (Scheme 13). See Ref. 12 and Crotti, P.; Dell'Omodarme, G.; Ferretti, M.; Macchia, F. *J. Am. Chem. Soc.* **1987**, *109*, 1463–1469.
18. No corresponding anti-1,2-addition products were ever observed in any case under these conditions. Under acid conditions (0.2 N H_2SO_4/MeOH/toluene), epoxides **1α** and **1β** lead to mixtures of the corresponding methyl α- and β-*O*-glycosides,[2] which are rapidly transformed into the furane derivative **1-F** (unpublished results from our laboratory; for the sake of simplicity, only epoxide **1β** is shown). For the formation of **1-F**, see: Zamojski, A.; Chmielewski, M.; Konowal, A. *Tetrahedron* **1970**, *26*, 183–189.



19. The 1,4-regioselectivity (S_N2' process) observed in the acid methanolysis of epoxides **6α** and **6β** under gas-phase operating conditions is in accordance with the slightly preferred S_N2' pathway, previously observed in the gas-phase-acid-induced methanolysis of allyl alcohols. See: Renzi, G.; Lombardozzi, A.; Dezi, E.; Pizzabiocca, A.; Speranza, M. *Chem. Eur. J.* **1996**, *2*, 316–322.
20. The formation of ketone **39** is due to the presence of $Sc(OTf)_3$. Actually, even after long reaction times (3 days) in the presence of $TMSN_3$, epoxide **6α** could be recovered completely unreacted. Only when $Sc(OTf)_3$ was added, was a fast formation of ketone **39** observed.
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23. Actually, epoxide **6α** can react also by means of the less stable conformer **6α''**. However, in the discussion, the attention was directed toward the more stable conformer **6α'** because only in this conformer a more favorable axial opening of the oxirane ring can occur (see Ref. 17a).
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