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Regiochemical control of the ring opening of 1,2-epoxides by means of chelating processes. Part 15: Regioselectivity of the opening reactions with MeOH of remote *O*-substituted regio- and diastereoisomeric pyranosidic epoxides under condensed- and gas-phase operating conditions

Paolo Crotti,[a,*] Gabriele Renzi,[b,*] Lucilla Favero,[a] Graziella Roselli,[b] Valeria Di Bussolo[a] and Micaela Caselli[a]

[a]*Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy*
[b]*Dipartimento di Scienze Chimiche, Università di Camerino, Via S.Agostino 1, 62032 Camerino, Italy*

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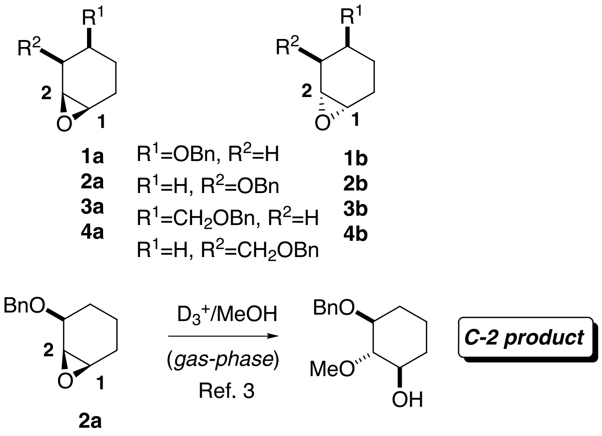
Abstract—The regiochemical behavior of pairs of regio- and diastereoisomeric epoxides derived from the 3,4,5,6-tetrahydro-2*H*-pyrane system, bearing an acetal group as the remote functionality, was determined in the acid methanolysis in the condensed phase (cd-phase) and in the reaction with MeOH in the gas-phase using a gaseous acid (D_3^+), as the promoting agent. With only one exception, the results obtained in the opening process of these epoxides indicate the incursion in the gas-phase of D^+-mediated chelated bidentate species able to modify the regiochemical result found in the methanolysis in the cd-phase. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

The regiochemical outcome of remote OBn-substituted cycloaliphatic oxiranes, such as epoxides **1**–**4a**,**b**, can be controlled, in the condensed phase (cd-phase) and in the presence of a *cis* relationship between the oxirane and the –OBn functionality (epoxides **1**–**4a**) by the use of standard opening reaction conditions or chelating conditions,[1] to give nice regioalternating processes, in some cases.[2] In the cd-phase, the proton did not give evidence of possessing a chelating ability in any of the opening reactions of epoxides examined.[2,3] The situation is different when gas-phase operating conditions are used. It was recently demonstrated that the use of gaseous reaction conditions are particularly effective in promoting, in the reaction of *cis* epoxides **1**–**4a** with MeOH, the intrinsic chelating ability of the proton with regioselectivity levels similar to the ones obtained in the cd-phase under chelating conditions.[3] By means of this procedure, it was possible, in the case of epoxide **2a**, to obtain the corresponding regioisomeric *C-2 product*,[4] never obtained in the cd-phase under any conditions (Scheme 1).[2c,3]

In order to verify the potential of the gas-phase operating procedures and the associated chelating ability of a proton, we have extended our examination, in the reaction with MeOH, to epoxides *cis* **5** and **7** and *trans* **6** and **8**,[2b,c] which are structurally related to the previously studied epoxides **1**–**2a**,**b**, but in which the remote heterofunctionality, due to the insertion of the endocyclic oxygen close to the exocyclic –OBn group, is now a typical acetal group. The pairs of diastereoisomeric epoxides **5**–**8** are regioisomers, differing



Scheme 1.

Keywords: epoxides; regioselectivity; gas phase reactions; chelation.

* Corresponding authors. Tel.: +39-50-44074; fax: +39-50-43321; e-mail: crotti@farm.unipi.it; gabriele.renzi@unicam.it

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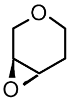
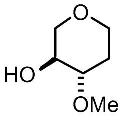
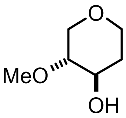
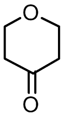
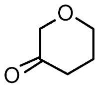
Table 1. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of epoxide **9**

Gas phase							
System composition (Torr)[a]			Product distribution[b]				
 **9**			 **18**	 **19**	 **28**	 **27**	
Epoxide	Bulk gas	MeOH	*G* %	*G* %	*G* %	*G* %	Total abs. yield (%)[c]
(0.53)	D_2 (100)	(1.69)	(0.44) 23	(0.09) 5	(0.82) 43	(0.54) 28	63
(0.61)	D_2 (760)	(1.84)	(0.40) 28	(0.11) 9	(0.52) 37	(0.38) 27	47
(0.59)	D_2 (760)	(1.81)[d]	(0.19) **35**	(0.07) **13**	(0.15) **28**	(0.13) **24**	18
Condensed phase							
0.2N H_2SO_4/MeOH[e]			**74**	**26**			
10 M $LiClO_4$/MeOH[f]			**98**	**2**			
5 M $LiClO_4$/MeCN/MeOH (10 equiv.)[e]			**95**	**5**			

[a] O_2: 4 Torr, radiation dose 1.5×10^4 Gy (dose rate 1×10^4 Gy h^{-1}).

[b] *G* values expressed as the number of molecules produced per 100 eV absorbed energy.

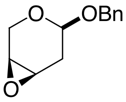
[c] Total absolute yields (%) estimated from the percentage ratio of the combined *G*(M) values of products and the literature *G*(GA^+) values.[13]

[d] 3 Torr of NMe_3 added to the gaseous mixture.

[e] Ref. 5.

[f] This work.

only in the relative position of the acetal group with respect to the oxirane moiety. While, on one hand, the presence of the exocyclic −OBn group is of fundamental importance for the incursion of chelating processes in the *cis* distereoisomers, as previously observed,[2d] the presence of the endocyclic oxygen could also make the *trans* diastereoisomers, commonly not sensitive to different operating conditions (standard or chelating), susceptible to chelating processes and, as a consequence, to regioalternating procedures.[2b,c] For a better insight into the importance of the endocyclic oxygen in determining the regiochemical outcome of the ring opening process of these oxirane systems, the reaction in the gas-phase was carried out also on the simplest reference oxirane **9**,[5] which is devoid of the exocyclic OBn group. Epoxides **9** (Table 1) and **5**–**8** were previously examined by the present authors in opening reactions in the cd-phase with various nucleophiles both under standard and chelating conditions, but, in the case of **5**–**8**, with the exclusion of MeOH.[2b,c,5–7] As a consequence, a preliminary examination of the regiochemical behavior of epoxides **5**–**8** also in the reaction with MeOH in the cd-phase, under different conditions, appeared to be necessary to rationalize the behavior of the same epoxides in the gas-phase.



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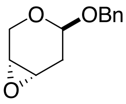

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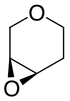

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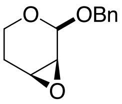

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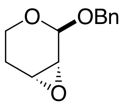

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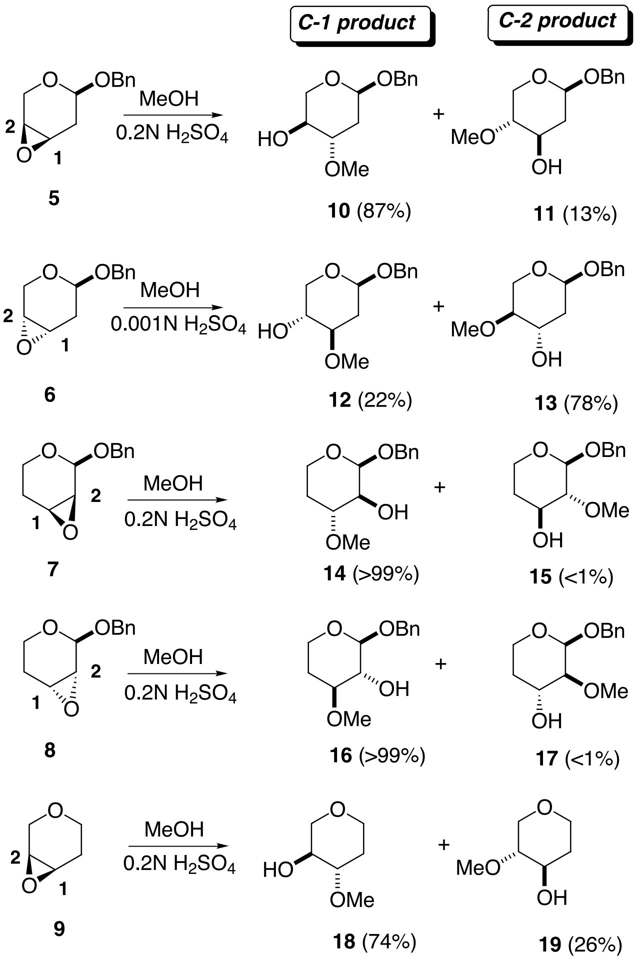
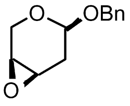
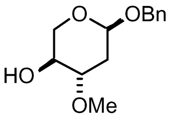
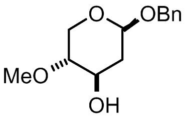
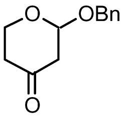
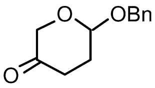
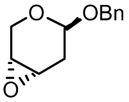
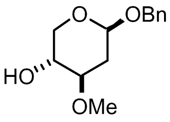
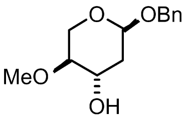
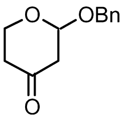
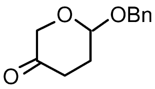


Scheme 2.

Table 2. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of epoxides *cis* **5** and *trans* **6**

Gas phase							
System composition (Torr)[a]			Product distribution[b]				
							
5			**10**	**11**	**25**	**24**	
Epoxide	Bulk gas	MeOH	*G* %	*G* %	*G* %	*G* %	Total abs. yield (%)[c]
(0.62)	D_2 (100)	(1.79)	(0.82) 37	(0.69) 31	(0.43) 19	(0.28) 13	74
(0.58)	D_2 (760)	(1.73)	(0.60) 33	(0.79) 43	(0.25) 14	(0.19) 10	61
(0.57)	D_2 (760)	(1.72)[d]	(0.20) **23**	(0.45) **52**	(0.12) **14**	(0.10) **11**	29
Condensed phase							
	0.2N H_2SO_4/MeOH		**87**	**13**			
	MeONa/MeOH		**94**	**6**			
	10 M $LiClO_4$/MeOH		**22**	**78**			
Gas phase							
System composition (Torr)[a]			Product distribution[b]				
							
6			**12**	**13**	**25**	**24**	
Epoxide	Bulk gas	MeOH	*G* %	*G* %	*G* %	*G* %	Total abs. yield (%)[c]
(0.60)	D_2 (100)	(1.77)	(0.35) 17	(0.90) 45	(0.44) 22	(0.32) 16	67
(0.71)	D_2 (760)	(1.93)	(0.47) 24	(0.76) 40	(0.38) 20	(0.31) 16	64
(0.62)	D_2 (760)	(1.80)[d]	(0.17) **27**	(0.25) **40**	(0.12) **19**	(0.09) **14**	21
Condensed phase							
	0.001N H_2SO_4/MeOH		**22**	**78**			
	MeONa/MeOH		**20**	**80**			
	10 M $LiClO_4$/MeOH		**98**	**2**			

[a] O_2: 4 Torr, radiation dose 1.5×10^4 Gy (dose rate 1×10^4 Gy h^{-1}).

[b] *G* values expressed as the number of molecules produced per 100 eV absorbed energy.

[c] Total absolute yields (%) estimated from the percentage ratio of the combined *G*(M) values of products and the literature *G*(GA^+) values.[13]

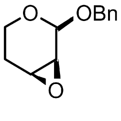
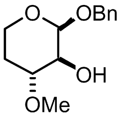
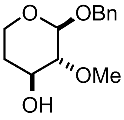
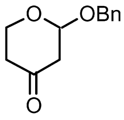
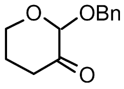
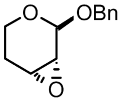
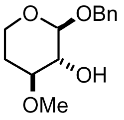
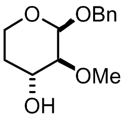
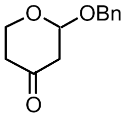
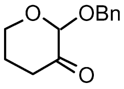
[d] 3 Torr of NMe_3 added to the gaseous mixture.

2. Results

Epoxides **5**–**9** were prepared as previously described.[2b,c,5] The reference compounds, the pairs of regioisomeric hydroxy ethers (HEs, *C-1* and *C-2 products*)[4] from each epoxide (HEs **10** and **11** from **5**, **12** and **13** from **6**, **14** and **15** from **7**, **16** and **17** from **8**) were prepared as follows. The direct acid methanolysis (0.2N H_2SO_4/MeOH) of epoxides **5** and **6**[8] afforded corresponding mixtures of HEs **10** (*C-product*) and **11** (*C-2 product*) (87:13 from **5**) and HEs **12** (*C-1 product*) and **13** (*C-2 product*) (22:78 from **6**) which were separated by preparative TLC. The same reaction carried out on the regioisomeric epoxides *cis* **7** and *trans* **8** afforded only the corresponding *C-1 product* (HEs **14** and **16** from **7** and **8**, respectively) (Scheme 2 and Tables 2 and 3).

The methanolysis reactions in the cd-phase of epoxides **5**–**8** were repeated under chelating conditions (10N $LiClO_4$/MeOH) to give the results shown in Tables 2 and 3. Whereas epoxides **7** and **8** turned out to be completely insensitive to different operating conditions, showing a complete C-1 regioselectivity as under standard conditions, epoxides **5** and **6** showed an interesting inversion of regioselectivity and the corresponding *C-2* (HE **11**, from **5**) and *C-1 products* (HE **12**, from **6**) were the ring-opened products largely (in the case of HE **11**) or exclusively present (in the case of HE **12**) in the corresponding crude reaction product (Table 2). From all these results (Tables 2 and 3), it appeared that the *C-2 products* from both epoxides **7** and **8** (HEs **15** and **17** from **7** and **8**, respectively), because not present in the methanolysis reaction of the corresponding epoxides, had to be prepared by alternative unequivocal synthetic procedures (Scheme 3). The alkaline hydrolysis of *cis* and *trans* epoxides **7** and **8** afforded the *trans* diols **20** and **22**, respectively, as the only reaction product (see Section 4). Monomethylation of diols **20** and **22** by means of

Table 3. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of epoxides *cis* **7** and *trans* **8**

Gas phase							
System composition (Torr)[a]			Product distribution[b]				
 **7**			 **14**	 **15**	 **25**	 **26**	
Epoxide	Bulk gas	MeOH	*G* %	*G* %	*G* %	*G* %	Total abs. yield (%)[c]
(0.58)	D_2 (100)	(1.72)	(0.76) 38	(0.59) 29	(0.41) 20	(0.25) 12	67
(0.51)	D_2 (760)	(1.58)	(0.50) 35	(0.57) 40	(0.22) 15	(0.15) 10	48
(0.61)	D_2 (760)	(1.81)[d]	(0.14) **25**	(0.30) **53**	(0.08) **14**	(0.05) **9**	19
Condensed phase							
	0.2N H_2SO_4/MeOH		>**99**	<**1**			
	MeONa/MeOH		>**99**	<**1**			
	10 M $LiClO_4$/MeOH		>**99**	<**1**			
Gas phase							
System composition (Torr)[a]			Product distribution[b]				
 **8**			 **16**	 **17**	 **25**	 **26**	
Epoxide	Bulk gas	MeOH	*G* %	*G* %	*G* %	*G* %	Total abs. yield (%)[c]
(0.64)	D_2 (100)	(1.84)	(1.24) 59	(0.10) 5	(0.46) 22	(0.30) 14	70
(0.53)	D_2 (760)	(1.60)	(0.93) 66	(0.06) 4	(0.25) 18	(0.17) 12	47
(0.53)	D_2 (760)	(1.62)[d]	(0.46) **73**	(0.01) **2**	(0.10) **16**	(0.06) **9**	21
Condensed phase							
	0.2N H_2SO_4/MeOH		>**99**	<**1**			
	MeONa/MeOH		>**99**	<**1**			
	10 M $LiClO_4$/MeOH		>**99**	<**1**			

[a] O_2: 4 Torr, radiation dose 1.5×10^4 Gy (dose rate 1×10^4 Gy h^{-1}).
[b] *G* values expressed as the number of molecules produced per 100 eV absorbed energy.
[c] Total absolute yields (%) estimated from the percentage ratio of the combined *G*(M) values of products and the literature *G*(GA^+) values.[13]
[d] 3 Torr of NMe_3 added to the gaseous mixture.

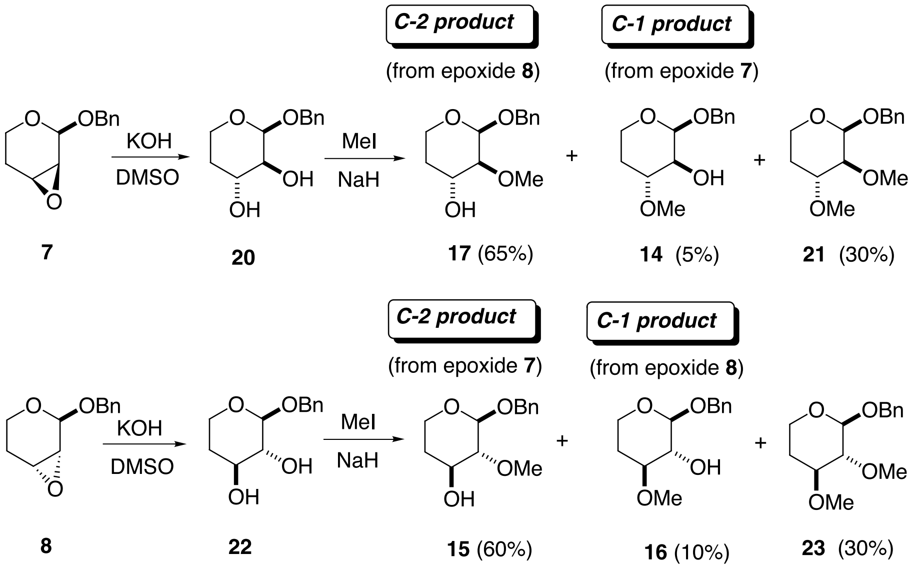
the MeI/NaH protocol (1 equiv.) afforded the corresponding crude reaction products consisting of a 65:5:30 mixture of HEs **17** and **14**, and dimethoxy derivative **21** from **20**, and of a 60:10:30 mixture of HEs **15** and **16**, and dimethoxy derivative **23** from **22** (^{1}H NMR), from which HEs **17** and **15** were separated pure by preparative TLC.

As for epoxide **9**, the corresponding reference compounds, the HEs **18** and **19**, were prepared as previously described (Scheme 2).[5]

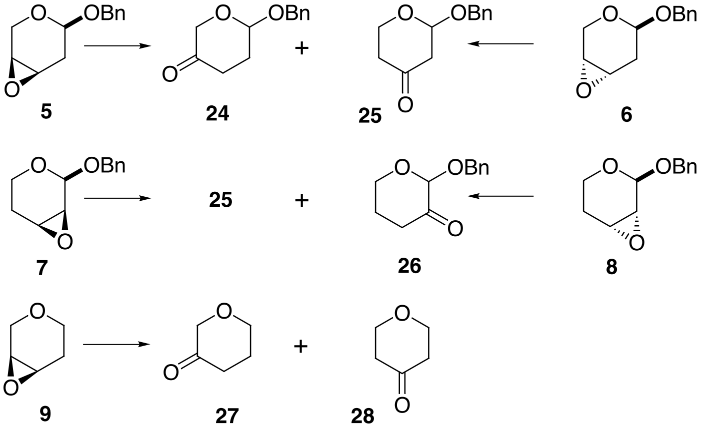
Ketones **24–28** were also prepared as possible reference non-addition products, whose formation could be particularly favored in the reactions carried out under gas-phase operating conditions. In fact, in these conditions, as a consequence of the low amount of the nucleophilic molecules (MeOH) present in the reaction mixture, the rearrangement pathway of the intermediate protonated epoxide (**34a** in Scheme 6, vide infra) to carbonyl compounds could be significant (ketones **24** and **25** from epoxides **5** and **6**, ketones **25** and **26** from epoxides **7** and **8**, and ketones **27** and **28** from epoxide **9**) (Scheme 4).

Hydroboration–oxidation of olefin **29**[2b] afforded a crude reaction product reasonably consisting of an uninvestigated mixture of regio- and stereoisomeric alcohols of types **30** and **31**, which were oxidized by PCC to give an almost 1:1 mixture of the corresponding ketones **24** and **25**, which were separated by preparative TLC. The $LiAlH_4$ reduction of epoxides **8** and **9** afforded, in an almost exclusive way, alcohols **32** and **33**, respectively,[2c,5] which were oxidized (PCC) to pure ketones **26**[9a] and **27**.[9b] Ketone **28** is commercially available (Scheme 5).

Epoxides **5–9** were subjected to opening reactions with MeOH in the cd-phase under standard (acid methanolysis by 0.2N H_2SO_4/MeOH)[8] and chelating conditions (10 M $LiClO_4$ in MeOH)[6] and in the gas-phase under the catalysis



Scheme 3.



Scheme 4.

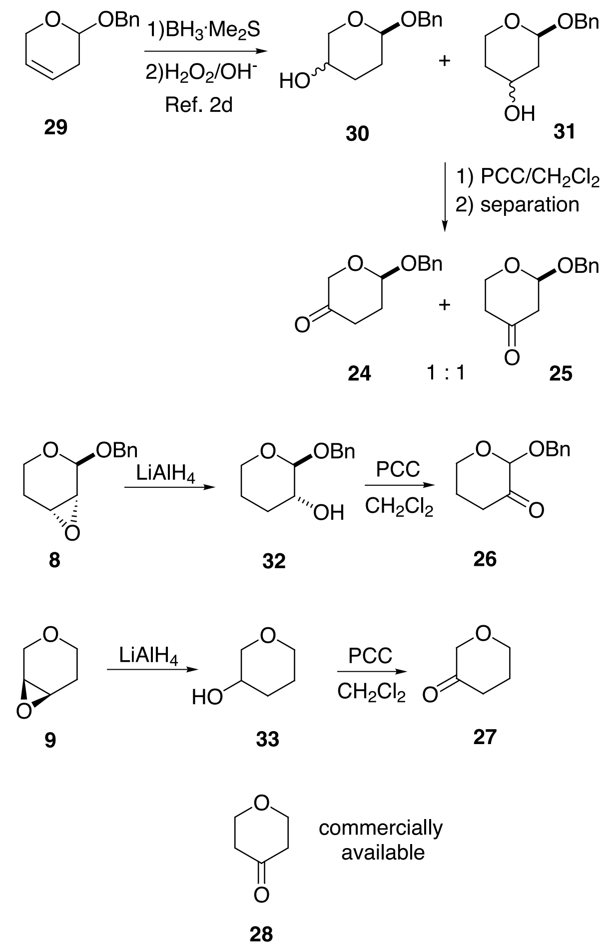
of a gaseous Brönsted acid $[GA^+ = D_3^+]$ obtained by γ-radiolysis of the corresponding neutral bulk gas precursor $(G = D_2)$ (Scheme 6).[10] The primary ionic product from γ-radiolysis of D_2 is D_2^+, which rapidly reacts with D_2 to give D_3^+ and a D atom. The D_3^+ ion is stable in pure D_2, while the D atom can be efficiently trapped by O_2, appropriately added to the reaction mixture, to give the stable DO_2 species.[11] In this way, it is possible to exclude the incursion of radical processes under our protocol. The results obtained are shown in Tables 1–3. In the gas-phase, the bulk gas pressure was varied, and different operating conditions were used: low- (100 Torr) and high-pressure bulk gas (760 Torr). In this last case, the opening reactions were repeated also in the presence of NMe_3 (3 Torr). Low-pressure bulk gas conditions correspond to long-lived excited-ion conditions, because of the reduced collapse of the ionic species with the molecules of the bulk gas, while the use of a high pressure and the contemporary presence of NMe_3 correspond to a low ion lifetime.[12] The sharp yield decrease when NMe_3 is introduced demonstrates the ionic origin of the reaction products, independently ensured by the presence of O_2, an effective radical scavenger (see above).

^1H NMR and GC–MS examination of the crude reaction mixtures from the cd- and gas-phase methanolysis reactions of epoxides **5–9** indicated the presence of addition products, the corresponding HEs **10–19** and non-addition products, the corresponding ketones **24–28** (Tables 1–3).

As a different product distribution is obtained in D_2 as a function of the experimental conditions (low or high bulk gas pressure) and the presence or absence of NMe_3, the reactions carried out in the gas-phase in conditions of low ion lifetime, that is under high pressure and in the presence of NMe_3 (see above), appear to be more similar to the cd-phase operating conditions and, as a consequence, more appropriate for an effective comparison between the results obtained in the cd- and gas-phase (Tables 1–3, results in bold), as previously stated.[3]

3. Discussion

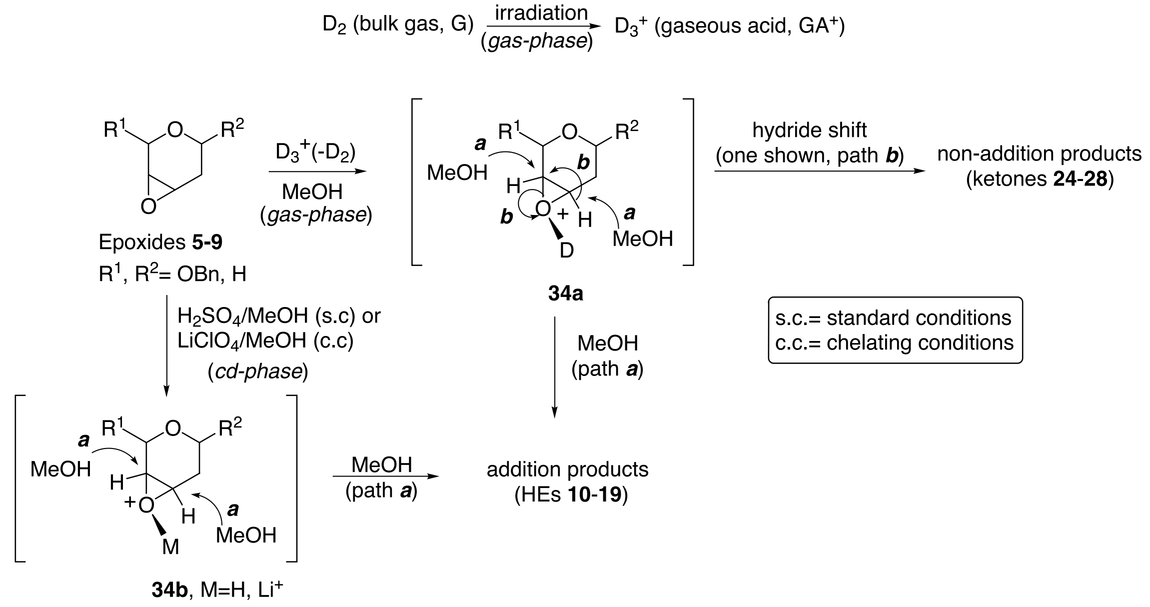
The behavior of epoxide **9** in methanolysis reactions in the cd-phase[5,6] shows an almost complete regioselectivity (up to 98%) towards the *C-1 product*, the 'chelation product'



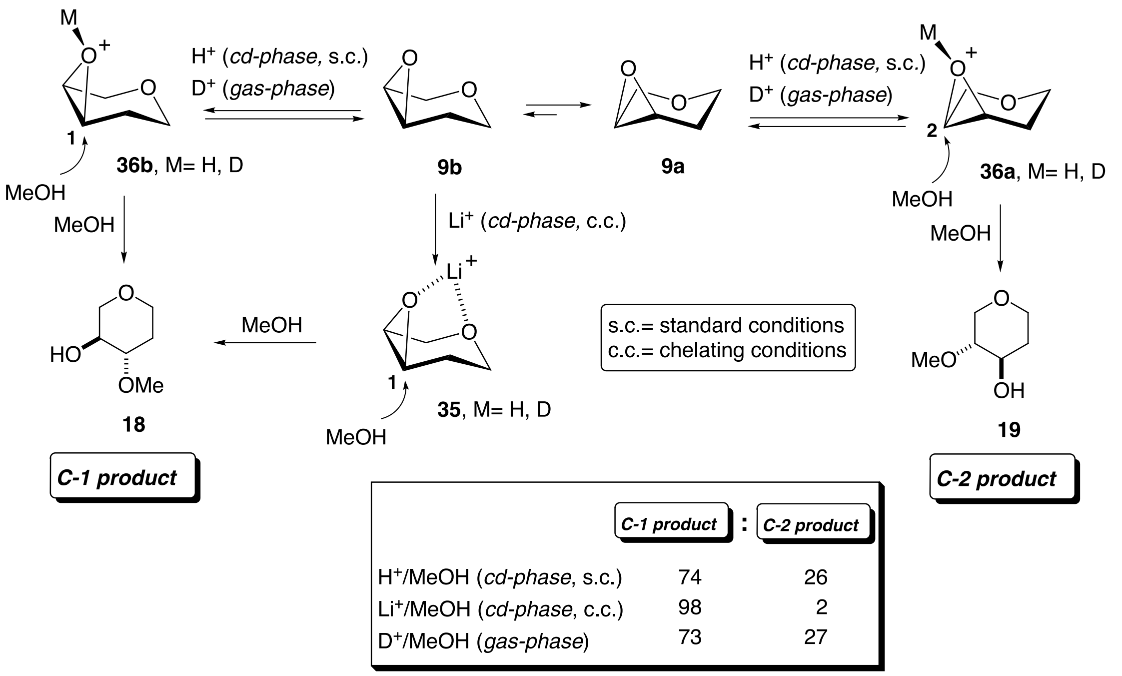
Scheme 5.

(HE **18**, Table 1) in the methanolysis carried out in the presence of $LiClO_4$ (Table 1), confirming the extraordinary ability of Li^+ to chelate between the heterofunctionalities present in **9**, the endocyclic and the oxirane oxygens, as shown in structure **35** (Scheme 7).[14] Under standard conditions, the observed high C-1 regioselectivity (74%) is driven by the electron-withdrawing inductive effect of the endocyclic oxygen, which forces epoxide **9** to react through the less stable conformation **9b**, and the corresponding protonated structure **36b**, in order to allow, in accordance with Fürst–Plattner rule,[15] *trans* diaxial attack of the nucleophile on the less electronically unfavored C(1) oxirane carbon. The same regioselectivity result (70%) is also obtained in the gas-phase (D^+/MeOH), indicating that the proton is not able to chelate in this system (Scheme 7 and Table 1), in any, cd- or gas-phase, conditions.

The regioselectivity observed in the cd-phase with epoxides *cis* **5** and *trans* **6** indicates that these epoxides are sensitive to the variation of the reaction operating conditions. In fact, under standard conditions (0.2 and 0.001N $MeOH/H_2SO_4$ for **5** and **6**, respectively)[8] a C-1 (87%) and a C-2 selectivity (78%) is observed with **5** and **6**, respectively, which corresponds to a non-chelated process through the more stable conformations **5a** in the case of **5** and **6a** in the case of **6**, as previously discussed,[2b] with *trans* diaxial nucleophilic attack on the C(1) and C(2) oxirane carbons of the corresponding protonated structure **37a** (from **5a**) and **39a** (from **6a**), respectively (Schemes 8 and 9). The use of $LiClO_4$, as the promoting agent, has a great influence on the regiochemical outcome in the methanolysis of both epoxides **5** and **6**: in **5** and **6** an inversion of regioselectivity with respect to standard conditions is observed and in the case of **6** an almost complete C-1 selectivity is obtained (Table 2).[16] These results may be easily rationalized by admitting the incursion in these chelating conditions of chelated bidentate species such as **38** ($M{=}Li^+$) (from **5**) and **40** ($M{=}Li^+$) (from **6**) (Schemes 8 and 9) which are attacked by the MeOH at the C(2) and C(1) oxirane carbon, respectively, in accordance with the Fürst–Plattner rule.[15,17] Under gas-phase operating conditions, the regioselectivity observed with epoxides **5** and **6** (Table 2) gives evidence of the incursion of the chelating ability of the proton in these conditions, even if with reasonable differences: with respect to standard conditions, while on one hand a nice C-2



Scheme 6.

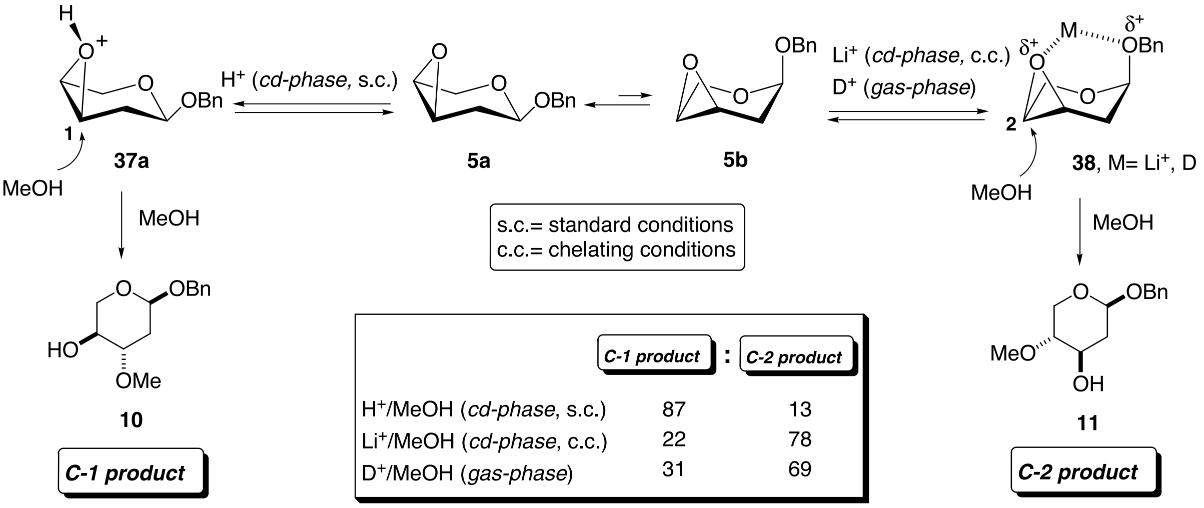


	C-1 product	C-2 product
H^+/MeOH (*cd-phase*, s.c.)	74	26
Li^+/MeOH (*cd-phase*, c.c.)	98	2
D^+/MeOH (*gas-phase*)	73	27

Scheme 7.

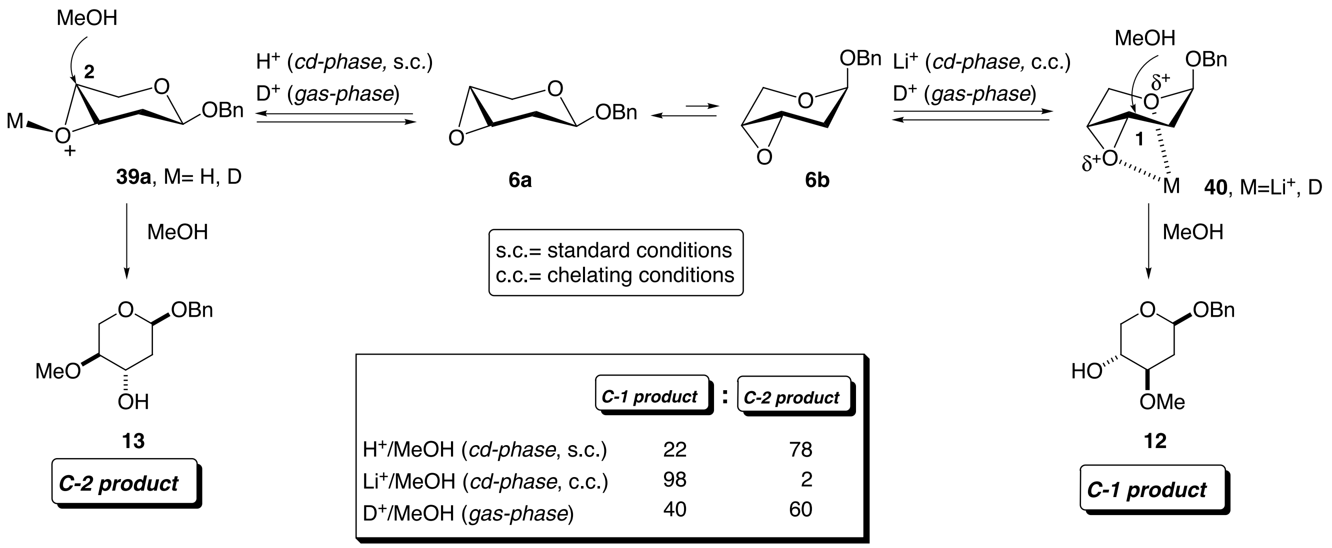
selectivity is observed in the case of **5**, only a slight decrease of the *C-2*/*C-1 product* ratio (from 78/22 to 60/40, Scheme 9) is observed in the case of **6**. These results may be rationalized by reasonably admitting the incursion of chelated structures **38** (M=D, Scheme 8) from **5** and **40** (M=D, Scheme 9) from **6**. The partially disappointing result obtained with epoxide **6** is to be correlated with the poor ability of the proton to act as a chelating agent between the oxirane and endocyclic oxygens, as previously observed in the case of epoxide **9** (see above). On the contrary, the regiochemical result obtained with epoxide **5** would indicate that the chelation of the proton between the oxygens of the oxirane and the exocyclic OBn group (as shown in **38**, Scheme 8) appears to be particularly favored.

Decidedly less interesting results are obtained in the methanolysis in the cd-phase with epoxides **7** and **8**, which turned out to be completely insensitive to the variation of the reaction conditions (standard or chelating).[2c] In fact in these epoxides, due to the closeness of the oxirane ring to the acetal functionality, the regioselectivity appears to be driven by the inductive electron-withdrawing effect of the heterofunctionality. As a consequence, under standard conditions, epoxides **7** and **8** react in that conformation (less stable conformation **7b** and **8b**[2c] and the corresponding protonated structure **41b** and **45**, Schemes 10 and 11) which allows nucleophilic attack by the MeOH on the corresponding C(1) oxirane carbon furthest from the acetal group and related unfavorable inductive effect, giving the complete C-1 selectivity constantly observed in these conditions (Tables 2 and 3). On passing to chelating conditions, no variation of the regioselectivity is observed in the case of epoxide **8**, simply



	C-1 product	C-2 product
H^+/MeOH (*cd-phase*, s.c.)	87	13
Li^+/MeOH (*cd-phase*, c.c.)	22	78
D^+/MeOH (*gas-phase*)	31	69

Scheme 8.



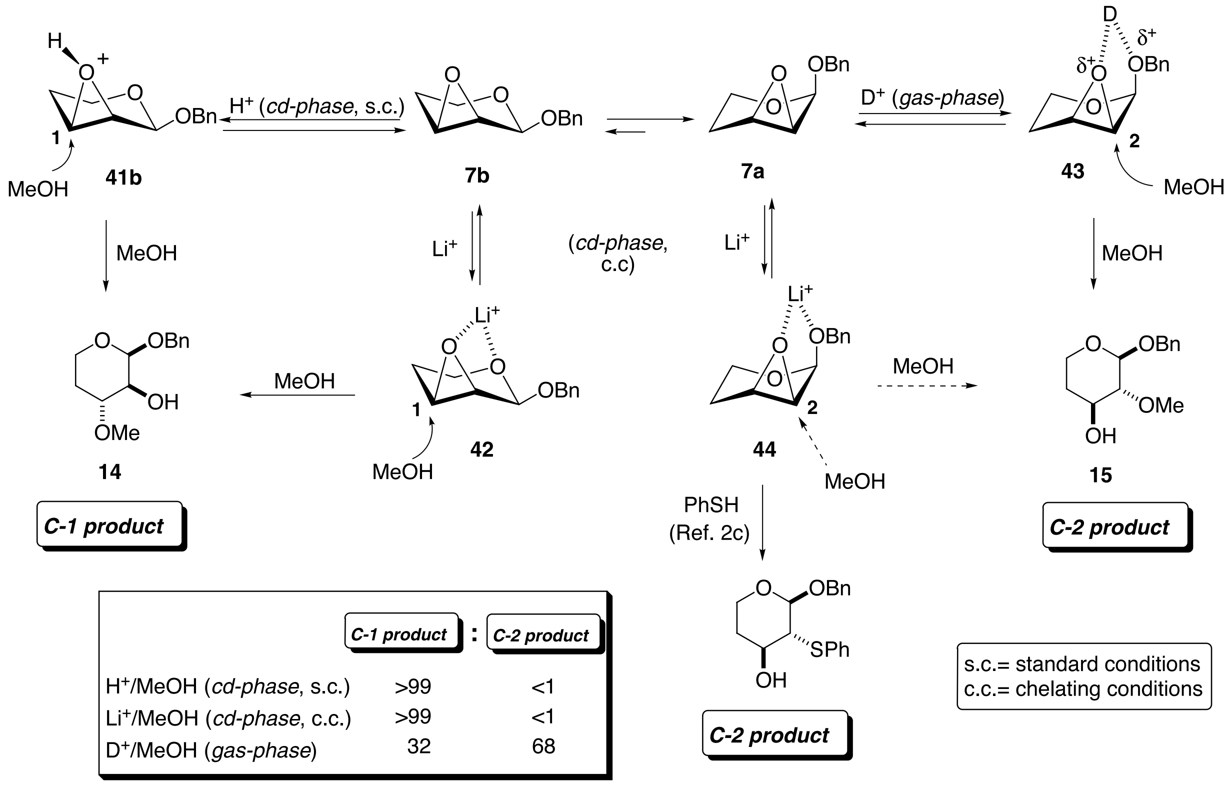
s.c.= standard conditions
c.c.= chelating conditions

	C-1 product	C-2 product
H^+/MeOH (*cd-phase*, s.c.)	22	78
Li^+/MeOH (*cd-phase*, c.c.)	98	2
D^+/MeOH (*gas-phase*)	40	60

Scheme 9.

because the only chelation process possible in this system (chelated structure **46**) occurs in conformation **8b** which is also reactive under standard conditions (protonated structure **45**, see above) (Scheme 11). A similar situation is present also in the case of epoxide **7**: chelation can occur, as shown in **42**, in conformation **7b** which is also reactive under standard conditions (protonated structure **41b**, see above) (Scheme 10). Actually in the case of **7**, an important difference is present with respect to **8**, but evidently not influential on the final regioselective result. In **7**, in fact, there is also the possibility of a chelation process through conformation **7a** as shown in **44**, which would afford, by nucleophilic *trans* diaxial attack of MeOH on the C(2) oxirane carbon, a C-2 selectivity actually not observed. Evidently, as previously admitted,[2c] MeOH is too weak nucleophile to attack the electronically unfavored C(2) oxirane carbon of **44** (Scheme 10).[18]

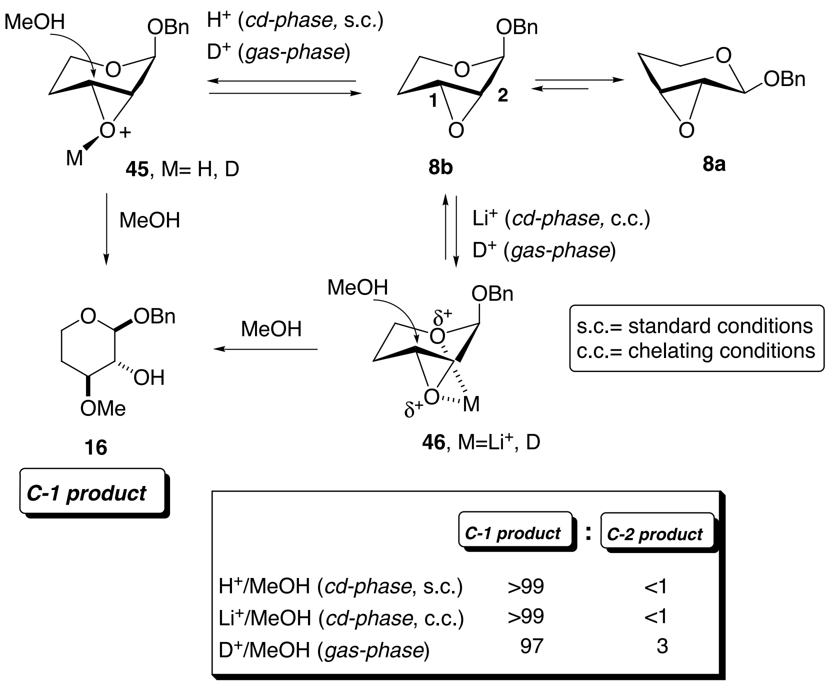
The use of gas-phase operating conditions, while uneffective, as expected, in the case of *trans* epoxide **8**, to modify the result of complete C-1 regioselectivity observed in the cd-phase (no chelation process can occur, but the one depicted in **46**, M=D, Scheme 11, see discussion above), really makes the difference in the case of the *cis* epoxide **7**:



	C-1 product	C-2 product
H^+/MeOH (*cd-phase*, s.c.)	>99	<1
Li^+/MeOH (*cd-phase*, c.c.)	>99	<1
D^+/MeOH (*gas-phase*)	32	68

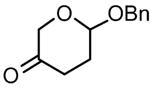
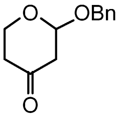
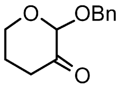
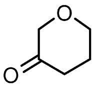
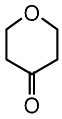
s.c.= standard conditions
c.c.= chelating conditions

Scheme 10.



Scheme 11.

Table 4. Heats of formation (kcal mol^{-1}) for ketones **24**–**28**

				
24 -102.761	**25** -105.050	**26** -101.541	**27** -89.957	**28** -91.370

Data obtained by semiempirical calculation AM1 (HYPERCHEM).

Table 5. ^{1}H NMR and IR data for HEs **10**–**17** and diols **20** and **22**

HE	^{1}H NMR δ			IR (CCl$_4$) (OH stretching), cm^{-1}		
	H$_a$ (J, Hz)[a]	H$_b$ (Jor $W_{1/2}$, Hz)[b]	H$_c$ (J or $W_{1/2}$, Hz)[c]	1,2 OH···O[d]	1,2 OH···O[e]	1,3 OH···O[f]
10	4.88 (3.1, 2.3)[g]	[h]	[h]	3605[i]		
11	4.83 (3.2)[j]	3.79 ($W_{1/2}$=11.4)[k]	3.12 ($W_{1/2}$=4.6)[k]	3601[l]		3537[i]
12	4.47 (8.3, 2.4)[g]	3.57 (8.7, 4.8)[m]	[h]	3605[i]		
13	4.87 (3.6, 1.2)[g]	3.91 (11.3, 8.6, 5.1)[n]	3.09 (10.5, 8.6, 5.0)[n]	3605[i]		
14	5.00 (3.0)[o]	[h]	3.67 (11.7, 5.5, 2.5)[n]	3601[p]	3582[i]	
15	4.43 (5.6)[o]	3.64 (8.7, 7.0, 4.4)[n]	2.96 (7.0, 5.6)[g]	3597[i]		3539[i]
16	4.26 (7.3)[o]	[h]	3.25 (10.8, 8.8, 4.9)[n]	3603[i]		
17	4.97 (3.4)[o]	3.96 (11.7, 9.4, 5.2)[n]	3.02 (9.4, 3.4)[g]	3601[i]		
20	4.98 (3.8)[o]	3.40 (9.2, 3.8)[g]	[h]	3599[i]	3574[i]	
22	4.31 (6.9)[o]	3.34 (8.2, 6.9)[g]	3.67 (11.5, 8.2, 5.1)[n]	3605[i]		3539[l]

[a] C*H*OBn.

[b] C*H*OH.

[c] C*H*OMe, in the case of HEs **10**–**17**; C*H*OH in the case of diols **20** and **22** (see Schemes 1, 2, and 12).

[d] *Trans* 1,2-diequatorial interaction.

[e] *Cis* 1,2-equatorial–axial interaction.

[f] *Cis* 1,3-diaxial interaction.

[g] Doublet of doublets.

[h] The signal overlaps with other signals.

[i] Strong band.

[j] Unresolved triplet.

[k] Multiplet.

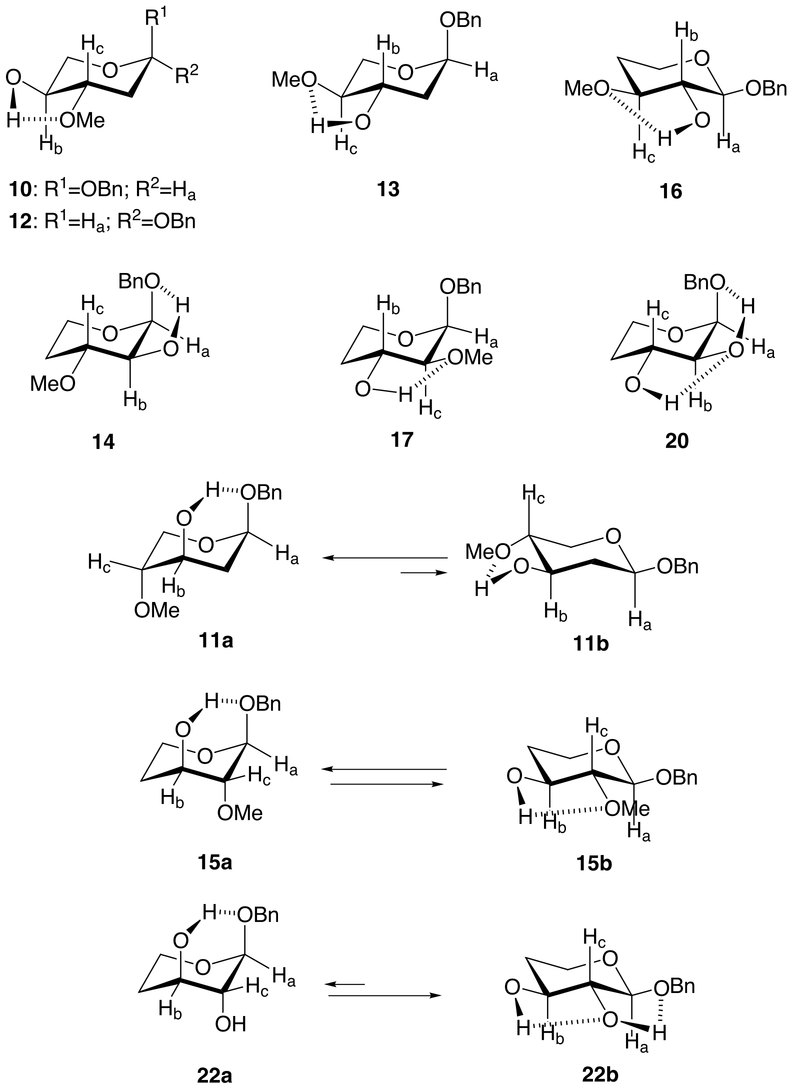
[l] Weak band.

[m] Triplet of doublets.

[n] Doublet of doublets of doublets.

[o] Doublet.

[p] Shoulder.



Scheme 12.

in these conditions, a 2.1:1 ratio is obtained between regioisomeric *C-2* and *C-1 products* (Table 3). This result may reasonably be explained by the necessary incursion of the chelated bidentate species **43** in which the epoxide adopts its more stable conformation **7a**: subsequent nucleophilic attack on C(2) oxirane carbon of **43** leads to the regioselectivity observed. However, it would be difficult to explain why the same result is not observed under chelating conditions in the cd-phase, through the corresponding chelated species **44**, without invoking some other factors such as a synergic effect due to an increased nucleophilicity of MeOH in the gas-phase,[19] which makes the weak nucleophile MeOH able to attack the electronically unfavorable C(2) oxirane carbon of **43** (Scheme 10), as only stronger nucleophiles (PhSH, NHEt$_2$, and N_3^-) are able to do on the corresponding chelated species **44** in the related opening reaction under chelating conditions in the cd-phase (Scheme 10).[2c]

As expected, non-addition products, the corresponding ketones **24–28**, completely absent in the opening reactions carried out in the cd-phase, were constantly obtained under gas-phase operating conditions (about 9–28%). The relative amounts of the components of the pairs of regioisomeric ketones **24–29** from each epoxide (Tables 1–3 and Scheme 4) appear to reflect the corresponding calculated relative stability shown in Table 4.[3]

4. Structures and configurations

The structure and relative configuration of HEs **10–17** obtained as regioisomeric pairs (*C-1* and *C-2 products*) in the above-mentioned opening reactions of epoxides **5–8** with MeOH was unequivocally determined by simple considerations based on (i) their method of synthesis and configuration of the starting epoxide, (ii) the anti stereoselectivity commonly observed in the opening reactions of typically cycloaliphatic epoxides under the conditions used,[2] (iii) an examination of their ^{1}H NMR spectra (coupling constants and/or half-band-width ($W_{1/2}$)) of the signal of the protons α to OBn, OH and OMe groups (H$_a$, H$_b$ and H$_c$, respectively, Table 5),[2,20a] and the use of appropriate double resonance experiments, and finally (iv) by examination of their IR spectra in dilute CCl_4 in the 3μ range (OH stretching band, Table 5).[2,20b] Keeping in mind that OH and OMe groups are necessarily in a 1,2-*trans* relationship in all the HEs **10–17**, the presence of a strong intramolecular 1,3 OH···O hydrogen bond in **11** (conformer **11a**) and **15** (conformer **15a**) (ν 3537 and 3539 cm^{-1}, respectively) and of a strong equatorial-axial 1,2 OH···O interaction in **14** (ν 3582 cm^{-1}) (Table 5), possible only when a *cis* 1,3- and 1,2-relationship between the two interacting groups (–OH and OBn) is, respectively, present,[20b] confirms the structure of HEs **11**, **14** and **15** (Scheme 12).[21]

The presence of a sole, intense *trans* diequatorial 1,2 OH···O interaction (ν 3601–3605 cm^{-1})[20b] in HEs **10**, **12**, **13**, **16**, and **17**, indicates for these compounds the preference for a conformation having more substituents in the equatorial position. As a consequence, the axial (in **12** and **16**) or equatorial nature (in **10**, **13**, and **17**) of the H_a proton makes the determination of the exact structures of HEs **10**, **12**, **13**, **16** and **17** possible (Table 5). The structure and relative configuration of diols **20** and **22**, derived from epoxides **7** and **8**, respectively (Scheme 3), was reasonably assigned on the basis of the regiochemical behavior previously observed in the ring-opening reactions of the same epoxides with other common nucleophiles under basic conditions ($NHEt_2$/EtOH, PhSH/NEt_3, $AlMe_3$),[2c] and on the reasonable assumption that epoxides **7** and **8** should have a similar regiochemical behavior also in a fairly similar reaction like alkaline hydrolysis (KOH/DMSO). However, the structure of **20** and **22** were confirmed by the presence in **22** of a weak 1,3–OH···O hydrogen bond (ν 3539 cm^{-1}) possible only if the interacting OH and OBn groups are in a *cis* relationship, as shown in the corresponding conformer **22a** (Scheme 12), and by the presence in **20** of an equatorial–axial 1,2–OH···O interaction (ν 3574 cm^{-1}) possible only if the central OH group is in a *cis* relationship with the OBn group, as shown in Scheme 12 (Table 5).[20b]

5. Conclusion

In conclusion, we have verified that in the gas-phase operating conditions, without the complicating interference of the solvent and counterion effects, it is possible to observe the incursion of intramolecular chelating processes mediated by the proton (actually D^+)[10] in opening reactions with MeOH in the presence of a gaseous acid ($GA^+=D_3^+$) of a series of pyranosidic epoxides bearing a remote acetal functionality.[22] The regiochemical behavior towards the chelation product is in all cases similar or decidedly superior to that obtained in the cd-phase when the opening reactions were carried out in the presence of a metal salt such as $LiClO_4$, indicating that the proton, which turns out to be scarcely or not at all effective in the cd-phase as a chelating agent, possesses chelating properties in the gas-phase even superior to those of Li^+ in the cd-phase. This is well-demonstrated by the fact that the *cis* epoxide **7** afforded in the gas-phase a high relative amount of HE **15** (the chelation product, Scheme 10) which was *completely absent* in the corresponding methanolysis reactions carried out with **7** under any conditions in the cd-phase.

6. Experimental

6.1. General

^1H and ^{13}C NMR spectra were determined with a Bruker AC 200 spectrometer on $CDCl_3$ solution using tetramethylsilane as the internal standard. IR spectra for comparison between compounds were taken with a Mattson 3000 FTIR spectrophotometer. All reactions were followed by TLC on Alugram SIL G/UV_{254} silica gel sheets (Machery–Nagel) with detection by UV. Preparative TLC were performed on 2.0 or 0.5-mm Macherey–Nagel DC-Fertigplatten UV_{254} silica gel plates. Silica gel 60 (Machery–Nagel 230–400 mesh) was used for flash chromatography. THF was distilled from sodium/benzophenone ketyl under a nitrogen atmosphere immediately prior to use. Epoxides **5–9**[2b,c,5] olefin **29**,[2b] alcohols **32**,[2b] **33**,[5] HEs **18** and **19**,[5] were prepared as previously described. Ketone **28** is commercially available (Aldrich).

6.1.1. Hydroboration–oxidation of olefin 29. Following a previously described procedure,[2b] a solution of olefin **29** (0.25 g, 1.31 mmol) in anhydrous THF (3.0 mL) was treated at 0°C with 10 M $BH_3 \cdot Me_2S$ (0.18 mL) in anhydrous THF (2.0 mL) and the reaction mixture was stirred at rt for 18 h. Aqueous 2N NaOH (0.56 mL) was carefully added, then the reaction mixture was cooled at 0°C and treated with 36% H_2O_2 (0.56 mL). After 1 h refluxing under stirring, dilution with water, extraction with ether and evaporation of the washed (water) ether extracts afforded a crude liquid product (0.23 g) which was filtered through a short silica gel column. Elution with an 8:2 petroleum ether/AcOEt afforded an oily product (0.14 g) consisting of a mixture of alcohols of type **30** and **31** (^1H NMR).[2b]

6.1.2. Synthesis of ketones 24 and 25. A solution of the mixture of alcohols **30** and **31** (0.10 g, 0.48 mmol) in CH_2Cl_2 (3.0 mL) was added at 0°C to a mixture of PCC (0.155 g, 0.72 mmol), AcONa (0.044 g, 0.54 mmol) and molecular sieves (0.41 g) in CH_2Cl_2 (5.0 mL) and the resulting reaction mixture was stirred 4 h at rt. Et_2O was added and the mixture was stirred overnight at the same temperature. Evaporation of the washed (water) and filtered (celite) organic solution afforded a liquid product (0.080 g) mostly consisting of an almost 1:1 mixture of ketones **24** and **25** which was subjected to preparative TLC (a 7:3 hexane/AcOEt mixture was used as the eluant). Extraction of the two most intense bands (the faster moving band contained **24**) afforded pure ketones **24** (0.025 g, 25% yield) and **25** (0.030 g, 30% yield).

2-(*Benzyloxy*)-3,4,5,6-*tetrahydro*-2*H*-*pyran*-5-*one* (**24**), a colorless liquid (Found: C, 69.54; H, 7.12. $C_{12}H_{14}O_3$ requires: C, 69.89; H, 6.84): IR ν 1724 cm^{-1} (CO); ^1H NMR δ 7.25–7.46 (m, 5H), 5.09 (t, 1H, J=4.2 Hz), 4.80 (d, 1H J=12.0 Hz), 4.59 (d, 1H J=12.0 Hz), 4.22 (d, 1H J=16.9 Hz), 3.95 (d, 1H J=16.9 Hz), 2.39–2.70 (m, 2H), 2.20–2.37 (m, 1H), 1.98–2.14 (m, 1H). ^{13}C NMR δ 209.21, 137.97, 129.07, 128.44, 95.89, 70.02, 67.88, 34.30, 28.72. MS (m/z) 65, 77, 85, 91, 104, 206 (M^+).

2-(*Benzyloxy*)-3,4,5,6-*tetrahydro*-2*H*-*pyran*-4-*one* (**25**), a colorless liquid (Found: C, 69.71; H, 7.06. $C_{12}H_{14}O_3$

requires: C, 69.89; H, 6.84): IR ν 1728 cm^{-1} (CO); ^{1}H NMR δ 7.14–7.37 (m, 5H), 5.14 (dd, 1H, J=3.9, 2.8 Hz), 4.70 (d, 1H J=12.1 Hz), 4.46 (d, 1H J=12.1 Hz), 4.09 (td, 1H, J=11.1, 3.9 Hz), 3.89 (ddd, 1H, J=11.1, 6.8, 3.2 Hz), 2.27–2.69 (m, 4H). ^{13}C NMR δ 205.12, 137.65, 129.02, 128.41, 98.68, 69.54, 59.72, 47.77, 42.14. MS (*m*/*z*) 65, 71, 91, 99, 133, 206 (M$^+$).

6.1.3. Synthesis of ketones 26 and 27. Proceeding as above described for the preparation of ketones **24** and **25**, a solution of alcohol **32** (0.065 g, 0.31 mmol) in CH_2Cl_2 (2 mL) was added at 0°C to a mixture of PCC (0.101 g, 0.47 mmol), AcONa (0.284 g, 0.35 mmol), and molecular sieves (0.27 g) in CH_2Cl_2 (4 mL) and the resulting reaction mixture was stirred 4 h at rt. Usual work-up afforded a liquid product (0.057 g) mostly consisting of ketone **26** which was subjected to preparative TLC (a 7:3 hexane/Et_2O mixture was used as the eluant). Extraction of the most intense band afforded pure *2-(benzyloxy)-3,4,5,6-tetrahydro-2H-pyran-3-one* (**26**) (0.033 g, 52% yield), as a colorless liquid (Found: C, 69.53; H, 6.61. $C_{12}H_{14}O_3$ requires: C, 69.89; H, 6.84): IR ν 1724 cm^{-1} (CO); ^{1}H NMR δ 7.17–7.34 (m, 5H), 4.74 (d, 1H, J=11.7 Hz), 4.64 (s, 1H), 4.51 (d, 1H, J=11.7 Hz), 4.09 (dt, 1H, J=11.3, 3.7 Hz), 3.64 (ddt, 1H, J=11.3, 4.4, 2.1 Hz), 2.73 (ddd, 1H, J=14.8, 11.8, 7.5 Hz), 2.28–2.42 (m, 1H), 1.91–2.20 (m, 2H). ^{13}C NMR δ 203.14, 137.39, 129.07, 128.58, 99.62, 70.10, 59.59, 36.43, 28.12. MS (*m*/*z*) 65, 71, 91, 99, 133, 206 (M$^+$).

Application of the same procedure to alcohol **33** (0.102 g, 1.0 mmol) afforded a crude product (0.075 g) which was subjected to preparative TLC (a 7:3 hexane/Et_2O mixture was used as the eluant). Extraction of the most intense band afforded pure ketone **27** (0.040 g, 40% yield).[9a]

6.1.4. Synthesis of diols 20 and 22. Typical procedure. A solution of *cis* epoxide **7** (0.16 g, 0.78 mmol) in DMSO (2.5 mL) and aqueous 2N KOH (2.5 mL) was stirred for 18 h at 70°C. Dilution with water, extraction with Et_2O and evaporation of the washed (water) ether extracts afforded a crude oily product (0.15 g) which was subjected to preparative TLC (a 6:4 hexane/AcOEt mixture was used as the eluant). Extraction of the most intense band afforded pure *c-2-(benzyloxy)-3,4,5,6-tetrahydro-2H-pyran-r-3,t-4-diol* (**20**) (0.11 g, 63% yield), as a solid, mp 101–103°C (recrystallized from hexane) (Found: C, 64.55; H, 7.01. $C_{12}H_{16}O_4$ requires: C, 64.27; H, 7.19): IR, see Table 5; ^{1}H NMR δ 7.29–7.41 (m, 5H), 4.78 (d, 1H, J=11.6 Hz), 4.48 (d, 1H, J=11.6 Hz), 3.62–3.94 (m, 3H), 1.97 (ddt, 1H, J=12.6, 4.0, 2.0 Hz), 1.69 (tdd, 1H, J=12.6, 11.4, 5.3 Hz), and see Table 5. ^{13}C NMR δ 137.83, 129.00, 128.51, 128.43, 98.79, 75.00, 69.86, 69.30, 59.09, 41.27, 33.09.

Application of the same procedure to *trans* epoxide **8** (0.20 g, 0.97 mmol) afforded a crude oily product (0.17 g) which was subjected to preparative TLC (a 7:3 hexane/Et_2O mixture was used as the eluant). Extraction of the most intense band afforded pure *t-2-(benzyloxy)-3,4,5,6-tetrahydro-2H-pyran-r-3,t-4-diol* (**22**) (0.14 g, 64% yield), as a solid, mp 77–79°C (recrystallized from hexane) (Found: C, 64.39; H, 6.92. $C_{12}H_{16}O_4$ requires: C, 64.27; H, 7.19): IR, see Table 5; ^{1}H NMR δ 7.10–7.35 (m, 5H), 4.90 (d, 1H, J=11.5 Hz), 4.58 (d, 1H, J=11.5 Hz), 4.00 (ddd, 1H, J=11.5, 4.7, 2.7 Hz), 3.47 (td, 1H, J=11.5, 2.7 Hz), 1.96 (dtd, 1H, J=13.3, 5.1, 2.7 Hz), 1.71 (dtd, 1H, J=13.3, 11.5, 4.7 Hz), and see Table 5. ^{13}C NMR δ 137.68, 129.07, 128.73, 128.58, 102.56, 75.65. 71.36, 71.27, 61.69, 32.38.

6.1.5. Methylation of diols 20 and 22. Typical procedure. A solution of diol **22** (0.14 g, 0.62 mmol) in anhydrous THF (4 mL) was added at 0°C to a suspension of NaH (0.15 g of a 60% dispersion in mineral oil, 0.62 mmol) in anhydrous THF (2 mL) and the reaction mixture was stirred at 40°C for 4 h. MeI (0.91 g, 6.30 mmol) was added and the resulting reaction mixture was stirred at 50°C for 18 h. After cooling, dilution with Et_2O and water, and evaporation of the washed (water) organic extracts afforded a crude liquid product (0.136 g) which was subjected to preparative TLC (a 7:3 hexane/AcOEt mixture was used as the eluant). Extraction of the three most intense bands (the fastest- and slowest-moving bands contained **23** and **15**, respectively) afforded pure dimethoxy derivative **23** (0.037 g, 24% yield), HE **16** (0.012 g, 8% yield) and HE **15** (0.050 g, 34% yield).

r-2-(*Benzyloxy*)-*t*-3,*c*-4-*dimethoxy*-3,4,5,6-*tetrahydro*-2*H*-*pyran* (**23**), a colorless liquid (Found: C, 66.32; H, 7.74. $C_{14}H_{20}O_4$ requires: C, 66.65; H, 7.99); ^{1}H NMR δ 7.16–7.36 (m, 5H), 4.83 (d, 1H, J=12.0 Hz), 4.55 (d, 1H, J=12.0 Hz), 4.26 (d, 1H, J=7.0 Hz), 3.91 (ddd, 1H, J=11.8, 4.7, 2.7 Hz), 3.52 (s, 3H), 3.38 (s, 3H), 3.29 (td, 1H, J=11.8, 2.7 Hz), 3.18 (ddd, 1H, J=10.5, 8.2, 5.0 Hz), 2.96 (dd, 1H, J=8.2, 7.0 Hz), 1.96 (ddt, 1H, J=13.2, 5.0, 2.7 Hz), 1.51 (dddd, 1H, J=13.2, 11.8, 10.5, 4.7 Hz). ^{13}C NMR δ 138.20, 128.84, 128.19, 128.11, 103.10, 83.87, 80.10, 71.06, 61.37, 60.83, 57.82, 30.42.

c-2-(*Benzyloxy*)-*t*-3-*methoxy*-*r*-3,4,5,6-*tetrahydro*-2*H*-*pyran*-4-*ol* (**15**), a colorless liquid (Found: C, 65.29; H, 7.37. $C_{13}H_{18}O_4$ requires: C, 65.53; H, 7.61): IR, see Table 5; ^{1}H NMR δ 7.16–7.34 (m, 5H), 4.80 (d, 1H, J=11.8 Hz), 4.51 (d, 1H, J=11.8 Hz), 3.92 (ddd, 1H, J=11.9, 5.3, 4.4 Hz), 3.48 (s, 3H), 3.34–3.48 (m, 2H), 1.86–2.02 (m, 1H), 1.59 (dtd, 1H, J=13.2, 8.5, 4.4 Hz), and see Table 5. ^{13}C NMR δ 137.79, 129.04, 128.44, 101.64, 82.81, 70.91, 69.30, 60.46, 59.88, 31.35. MS (*m*/*z*) 45, 59, 91, 101, 135, 238 (M$^+$).

Application of the same procedure to diol **20** (0.106 g, 0.47 mmol) afforded a crude liquid product (0.13 g) which was subjected to preparative TLC (a 7:3 hexane/Et_2O mixture was used as the eluant). Extraction of the three most intense bands (the fastest- and slowest-moving bands contained **21** and **17**, respectively) afforded pure dimethoxy derivative **21** (0.021 g, 18% yield), HE **14** (0.003 g, 3% yield), and HE **17** (0.042 g, 37% yield).

r-2-(*Benzyloxy*)-*c*-3,*t*-4-*dimethoxy*-3,4,5,6-*tetrahydro*-2*H*-*pyran* (**21**), a colorless liquid (Found: C, 66.54; H, 7.68. $C_{14}H_{20}O_4$ requires: C, 66.65; H, 7.99); ^{1}H NMR δ 7.16–7.36 (m, 5H), 4.92 (d, 1H, J=3.4 Hz), 4.70 (d, 1H, J=12.2 Hz), 4.49 (d, 1H, J=12.2 Hz), 3.70 (ddd, 1H, J=11.8, 5.5, 2.4 Hz), 3.51–3.77 (m, 2H), 3.37 (s, 3H), 3.34 (s, 3H), 3.12 (dd, 1H, J=9.0, 3.4 Hz), 2.00 (ddt, 1H, J=12.6, 4.8, 2.4 Hz), 1.48 (dtd, 1H, J=12.6, 10.8, 5.5 Hz). ^{13}C NMR δ 138.01, 128.89, 128.62, 128.25, 96.26, 82.49, 76.88, 76.94, 69.33, 58.70, 57.77, 30.97.

t-2-(Benzyloxy)-t-3-methoxy-r-3,4,5,6-tetrahydro-2H-pyran-4-ol (**17**), a colorless liquid (Found: C, 65.40; H, 7.82. $C_{13}H_{18}O_4$ requires: C, 65.53; H, 7.61): IR, see Table 5; ^{1}H NMR δ 7.16–7.36 (m, 5H), 4.69 (d, 1H, J=12.2 Hz), 4.47 (d, 1H, J=12.2 Hz), 3.73 (ddd, 1H, J=12.7, 11.7, 2.5 Hz), 3.55 (ddd, 1H, J=11.7, 5.4, 1.6 Hz), 3.27 (s, 3H), 1.90 (dddd, 1H, J=12.7, 5.2, 2.5, 1.6 Hz), 1.63 (tdd, 1H, J=12.7, 11.7, 5.4 Hz), and see Table 5. ^{13}C NMR δ 137.94, 128.96, 128.64, 128.35, 95.17, 83.97, 69.30, 67.30, 58.73, 57.89, 33.14. MS (*m/z*) 45, 59, 91, 101, 135, 238 (M^+).

6.1.6. Acid methanolysis of epoxides 5–8. Typical procedure. A solution of *cis* epoxide **5** (0.052 g, 0.25 mmol) in 0.2N H_2SO_4 in MeOH (2 mL) was stirred 2 h at rt. Dilution with ether and evaporation of the washed (saturated aqueous $NaHCO_3$) organic solution afforded a crude product (0.059 g) consisting of a 13:87 mixture of HEs **11** and **10** (GC), which was subjected to preparative TLC (an 8:2 hexane/AcOEt mixture was used as the eluant). Extraction of the two most intense bands (the faster-moving band contained **11**) afforded pure HEs **11** (0.006 g, 10% yield) and **10** (0.041 g, 69% yield).

c-2-(Benzyloxy)-t-5-methoxy-r-3,4,5,6-tetrahydro-2H-pyran-4-ol (**11**), a colorless liquid (Found: C, 65.21; H, 7.44. $C_{13}H_{18}O_4$ requires: C, 65.53; H, 7.61): IR, see Table 5; ^{1}H NMR δ 7.20–7.36 (m, 5H), 4.72 (d, 1H J=11.8 Hz), 4.44 (d, 1H J=11.8 Hz), 4.04 (dd, 1H, J=12.7, 2.1 Hz), 3.55 (dd, 1H, J=12.7, 3.2 Hz), 3.38 (s, 3H), 2.14 (dt, 1H, J=14.1, 3.5 Hz), 1.75 (ddd, 1H, J=14.1, 4.3, 3.2 Hz), and see Table 5. ^{13}C NMR δ 137.69, 129.09, 128.51, 97.81, 78.49, 70.27, 66.21, 58.39, 57.85, 32.96. MS (*m/z*) 58, 91, 108, 131, 147, 238 (M^+).

c-2-(Benzyloxy)-t-4-methoxy-r-3,4,5,6-tetrahydro-2H-pyran-5-ol (**10**), a colorless liquid (Found: C, 65.78; H, 7.39. $C_{13}H_{18}O_4$ requires: C, 65.53; H, 7.61): IR, see Table 5; ^{1}H NMR δ 7.19–7.33 (m, 5H), 4.64 (d, 1H, J=11.8 Hz), 4.36 (d, 1H, J=11.8 Hz), 3.66–3.74 (m, 1H), 3.41–3.65 (m, 3H), 3.33 (s, 3H), 2.19 (ddd, 1H, J=12.9, 4.4, 2.3 Hz), 1.45 (ddd, 1H, J=12.9, 9.8, 3.1 Hz), and see Table 5. ^{13}C NMR δ 138.17, 129.02, 128.52, 128.35, 97.54, 79.12, 70.51, 69.44, 63.00, 57.11. MS (*m/z*) 91, 99, 122, 131, 147, 238 (M^+).

Application of the same procedure to *cis* epoxide **7** (0.052 g, 0.25 mmol) afforded after 1 h a crude liquid product consisting of practically pure *c-2-(benzyloxy)-t-4-methoxy-r-3,4,5,6-tetrahydro-2H-pyran-3-ol* (**14**) (0.058 g, 97% yield), as a colorless liquid (Found: C, 65.60; H, 7.31. $C_{13}H_{18}O_4$ requires: C, 65.53; H, 7.61): IR, see Table 5; ^{1}H NMR δ 7.27–7.39 (m, 5H), 4.77 (d, 1H, J=11.8 Hz), 4.51 (d, 1H, J=11.8 Hz), 3.78 (td, 1H, J=11.7, 2.4 Hz), 3.10–3.59 (m, 2H), 3.43 (s, 3H), 2.00–2.13 (m, 1H), 1.43–1.64 (m, 1H), and see Table 5. ^{13}C NMR δ 137.91, 129.04, 128.58, 128.44, 98.87, 78.28, 73.31, 70.02, 59.10, 57.40, 30.14. MS (*m/z*) 71, 91, 92, 101, 160, 238 (M^+).

Application of the same procedure to *trans* epoxide **8** (0.052 g, 0.25 mmol) afforded after 1 h a crude liquid product consisting of practically pure *t-2-(benzyloxy)-t-4-methoxy-r-3,4,5,6-tetrahydro-2H-pyran-3-ol* (**16**) (0.058 g, 97% yield), as a colorless liquid (Found: C, 65.59; H, 7.36. $C_{13}H_{18}O_4$ requires: C, 65.53; H, 7.61): IR, see Table 5; ^{1}H NMR δ 7.23–7.43 (m, 5H), 4.91 (d, 1H, J=11.7 Hz), 4.61 (d, 1H, J=11.7 Hz), 4.01 (ddd, 1H, J=12.2, 5.0, 2.0 Hz), 3.43 (s, 3H), 3.47–3.88 (m, 2H), 2.04 (ddt, 1H, J=12.8, 4.9, 2.0 Hz), 1.58 (tdd, 1H, J=12.8, 10.8, 5.0 Hz), and see Table 5. ^{13}C NMR δ 137.72, 128.97, 128.60, 128.40, 102.89, 80.60, 75.03, 71.28, 62.25, 57.53, 30.18. MS (*m/z*) 71, 91, 92, 101, 160, 238 (M^+).

Application of the same procedure to *trans* epoxide **6** (0.052 g, 0.25 mmol) afforded after 1 h a crude liquid product (0.058 g), consisting of a complex mixture also containing products deriving from −OBn/MeOH exchange at the anomeric carbon (GC and ^{1}H NMR). When the same reaction was repeated using a 0.001N H_2SO_4–MeOH solution (3 h, rt), a crude reaction product (0.052 g) was obtained, consisting of a 78:22 mixture of HEs **13** and **12** (GC), which was subjected to preparative TLC (an 8:2 hexane/AcOEt mixture was used as the eluant). Extraction of the two most intense bands (the faster-moving band contained **13**) afforded pure HEs **12** (0.010 g, 17% yield) and **13** (0.037 g, 62% yield).

t-2-(Benzyloxy)-t-4-methoxy-r-3,4,5,6-tetrahydro-2H-pyran-5-ol (**12**), a colorless liquid (Found: C, 65.69; H, 7.48. $C_{13}H_{18}O_4$ requires: C, 65.53; H, 7.61): IR, see Table 5; ^{1}H NMR δ 7.18–7.34 (m, 5H), 4.79 (d, 1H J=11.9 Hz), 4.49 (d, 1H, J=11.9 Hz), 4.00 (dd, 1H, J=11.5, 4.8 Hz), 3.33 (s, 3H), 3.15 (dd, 1H, J=11.5, 8.7 Hz), 3.07–3.20 (m, 1H), 2.24 (ddd, 1H, J=12.9, 4.6, 2.4 Hz), 1.48 (ddd, 1H, J=12.9, 10.3, 8.3 Hz), and see Table 5. ^{13}C NMR δ 138.00, 129.02, 128.52, 128.38, 99.36, 80.62, 70.77, 69.99, 65.46, 56.94, 34.35. MS (*m/z*) 65, 91, 99, 131, 147, 238 (M^+).

t-2-(Benzyloxy)-t-5-methoxy-r-3,4,5,6-tetrahydro-2H-pyran-4-ol (**13**), a colorless liquid (Found: C, 65.82; H, 7.33. $C_{13}H_{18}O_4$ requires: C, 65.53; H, 7.61): IR, see Table 5; ^{1}H NMR δ 7.14–7.36 (m, 5H), 4.61 (d, 1H, J=11.9 Hz), 4.35 (d, 1H, J=11.9 Hz), 3.77 (dd, 1H, J=10.5, 5.0 Hz), 3.42 (unresolved t, 1H, J=10.5 Hz), 3.38 (s, 3H), 2.09 (ddd, 1H, J=13.1, 5.1, 1.2 Hz), 1.59 (ddd, 1H, J=13.1, 11.3, 3.6 Hz), and see Table 5. ^{13}C NMR δ 138.23, 128.99, 128.31, 128.25, 97.28, 81.89, 69.32, 68.43, 60.14, 58.58, 37.39. MS (*m/z*) 74, 91, 113, 131, 147, 238 (M^+).

6.1.7. Alkaline methanolysis (MeONa/MeOH) of epoxides 5–8. General procedure. A solution of the epoxide (0.052 g, 0.25 mmol) and MeONa (0.21 g, 4.0 mmol) in anhydrous MeOH (4.0 mL) was stirred at 80°C for 18 h. Dilution with Et_2O and evaporation of the washed (water) organic solution afforded a crude reaction product which was analyzed by GC to give the results shown in Tables 2 and 3.

6.1.8. Methanolysis of epoxides 5–9 in the presence of $LiClO_4$. General procedure. A solution of the epoxide (0.052 g, 0.25 mmol) in anhydrous MeOH (2 mL), containing $LiClO_4$ (2.13 g, 10 M solution), was stirred at 80°C for the time shown in Tables 2 and 3. Dilution with ether and evaporation of the washed (water) organic solution afforded a crude reaction product which was analyzed by GC to give the results shown in Tables 1–3.

6.2. Reactions in the gas-phase

6.2.1. 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 chemical purity of starting pyranosidic oxirane substrates was verified by analytical gas chromatography on the same columns used for the analysis of their gas-phase products.

6.2.2. Procedure. The gaseous mixtures were prepared by conventional procedures[23] with the use of a greaseless vacuum line. The selected pyranosidic oxirane, the methanol, the thermal radical scavenger O_2, and the trimethylamine were introduced into carefully outgassed 250-mL Pyrex bulbs, each equipped with a break-seal arm. The bulbs were filled with D_2 (100 or 760 Torr), and then allowed to come to room temperature; the fragile ampoules were broken, and the gaseous components were allowed to mix before being subjected to 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). The total absolute yields of the radiolytic products are given as the percentage ratio of their G(M) values, i.e. the number of molecules of product M formed per 100 eV of energy absorbed by the gaseous mixture, in relation to the G value for the formation of the Brönsted acid precursor, $G(D_3^+)=3.11$. 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. The constancy of the G(M) value for a given product M by varying the radiation dose indicates that products arise from a single radiolytic reaction.[13,23]

6.2.3. Product analysis. The radiolytic products were analyzed by injecting measured portions of the homogeneous reaction mixture into a Hewlett–Packard 5890 series II gas chromatograph, equipped with a flame ionization detector. 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 reference compounds on the following columns: (i) a 50 m long, 0.31 mm i.d. Ultra1™ crosslinked methyl silicone fused silica capillary column, operating at temperatures ranging from 80 to 220°C, 5°C min^{-1}; (ii) a 25 m long, 0.32 mm i.d. Carbowax 20™ Ultra performance capillary column, operating at temperatures ranging from 60 to 180°C, 4°C min^{-1}. The identity of the products was further confirmed by GLC–MS, using a Hewlett–Packard 5890A gas chromatograph in line with a HP 5971A quadrupole mass spectrometer. The yields were determined from the areas of the corresponding eluted peaks, using the internal standard method and individual calibration factors to correct for the detector response. The results given in Tables 1–3 are the average of at least three measurements taken on at least two different runs for each point.

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References

1. *Standard reaction conditions*: epoxide opening reactions carried out with the nucleophile (MeOH in the methanolysis) under protic acid catalysis, or without any catalysis in an appropriate solvent (MeOH/H_2SO_4 and MeONa/MeOH, in the case of methanolysis). *Chelating reaction conditions*: epoxide opening reactions carried out with the nucleophile in the presence of a metal salt (MeOH/$LiClO_4$, in the case of methanolysis).
2. (a) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron* **2002**, *58*, 6069–6091, and references therein. (b) Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *J. Org. Chem.* **1994**, *59*, 4131–4137. (c) Calvani, F.; Crotti, P.; Gardelli, C.; Pineschi, M. *Tetrahedron* **1994**, *50*, 12999–13021. (d) Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *J. Org. Chem.* **1990**, *55*, 4265–4272.
3. Crotti, P.; Di Bussolo, V.; Favero, L.; Pineschi, M.; Marianucci, F.; Renzi, G.; Amici, G.; Roselli, G. *Tetrahedron* **2000**, *56*, 7513–7524.
4. The *C-1* and *C-2 product* nomenclature refers to the attacking site of the nucleophile, i.e. at the C(1) or C(2) oxirane carbon of epoxides **1**–**9**, in accordance with the numbering scheme shown in Schemes 1 and 2.
5. Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* **1994**, *50*, 1261–1274.
6. In the case of epoxide **9**, the methanolysis in the cd-phase under chelating conditions has been previously conducted with 5 M $LiClO_4$ in MeCN in the presence of MeOH (10 equiv.),[5] that is in conditions slightly different from the ones used in the present paper with epoxides **5**–**8** (10 M $LiClO_4$ in MeOH). As a consequence, for the sake of an appropriate comparison of the results, the methanolysis of **9** under chelating conditions was repeated using the conditions adopted for epoxides **5**–**8**. For the reactions in the cd-phase under standard conditions, the acid solution (0.2N H_2SO_4 in MeOH) presently utilized with epoxides **5**–**8** is the same previously utilized with epoxide **9**.[5]
7. For other studies on the regioselectivity of the opening reactions of oxirane systems structurally related to epoxides **7** and **8**, see: (a) Schulz, M.; Kluge, R.; Liebsch, S.; Lessig, J.; Halik, M.; Gadissa, F. *Tetrahedron* **1996**, *52*, 13151–13166. (b) Carret, G.; Grouiller, A.; Pacheco, H. *Carbohydr. Res.* **1982**, *111*, 59–66. (c) Picq, D.; Anker, D.; Pacheco, H. *Tetrahedron Lett.* **1981**, *22*, 4517–4520.
8. The acid methanolysis of *trans* epoxide **6** conducted with the commonly used 0.2N H_2SO_4/MeOH solution, afforded a complex reaction mixture containing, in addition to HEs **12** and **13**, also large amounts of products, not further investigated, deriving from exchange between the acetalic –OBn group and MeOH, with consequent epimerization at the anomeric C(1)-carbon. On the contrary, the use of a more diluted acid condition (0.001N H_2SO_4/MeOH) afforded a

crude reaction product only containing the addition products, the HEs **12** and **13** (Table 2).

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10. In the gas-phase, D^+ (actually D_3^+) was used instead of H^+ (actually H_3^+) simply for practical reasons (necessary purity of the corresponding bulk gas, D_2 and H_2, respectively). However, in the opening reactions of epoxides **5**–**9** with MeOH, D_3^+ and H_3^+ obviously behave in the same way, except for the hydron transfer kinetic isotopic effect (KIE). However, in the gas-phase D_3^+-protonation of organic molecules is normally a very fast, highly exothermic process and, therefore, the hydron transfer KIE is usually invisibly small. As a consequence, no difference is made in the discussion between D_3^+ and H_3^+.
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14. Structure **35** is the only chelated structure possible from epoxide **9**, with the epoxide forced in the less stable conformation **9b**. In accordance with Fürst–Plattner's rule,[15] nucleophilic attack on **35** can occur only at the C(1) oxirane carbon.
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16. Under chelating conditions, epoxides **5** and **6** gave significative inversion of regioselectivity with respect to standard conditions also with other nucleophiles (Cl^-, N_3^-, Et_2NH).[2b]
17. The regioalternating process obtained with epoxide **6** would also indicate, besides the particular ability of Li^+ to be a bidentate ligand between the oxirane oxygen and the endocyclic oxygen (structure **40**, M=Li^+, Scheme 9), as previously observed also in the case of the reference oxirane **9**, that when a chelating process leads to nucleophilic attack on the electronically more favored oxirane carbon (like the C(1) oxirane carbon of **40**, M=Li^+, Scheme 9, and of the previously examined **35**,[5] Scheme 7), decidedly high regioselectivities are obtained.
18. Stronger nucleophiles than MeOH, such as N_3^-, Et_2NH, and PhSH gave, in the case of epoxide **7** under chelating conditions in the cd-phase, significative amount (23–25%) of *C-2 product*.[2c] On the contrary, epoxide **8** constantly gave, as in the case of the presently examined methanolysis, a complete *C-1* regioselectivity with all the nucleophiles (N_3^-, Et_2NH, PhSH) and conditions (standard and chelating) tried.[2c]
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21. The confirmed structure of HE **11** makes it possible to assign the regioisomeric structure to HE **10**.
22. Obviously, the different regiochemical results obtained on passing from the cd-phase to the gas phase operating conditions could be explained by admitting that the conformational equilibrium inside epoxides **5**–**9**, and therefore the results, could be simply affected by the change from solution to gas phase conditions and not by the incursion of chelating processes mediated by the proton. However, the perfect correspondence of the regioselectivity observed in the reaction with MeOH, both under cd-phase and gas-phase conditions, of the *trans* epoxides **1**–**4b**,[3] in which, for purely structural reasons, no type of chelating process is possible, suggests that any regioselectivity difference observed with epoxides **5**–**9** (as in the case of *cis* epoxides **1**–**4a**) between cd-phase and gas-phase conditions should be reasonably ascribed to the incursion, in these last conditions, of proton-mediated chelating processes, as previously adequately stated.[3]
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