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Regiochemical control of the ring opening of aziridines by means of chelating processes. Part 3: Regioselectivity of the opening reactions with methanol of remote *O*-substituted regio- and diastereoisomeric activated aziridines under condensed- and gas-phase operating conditions

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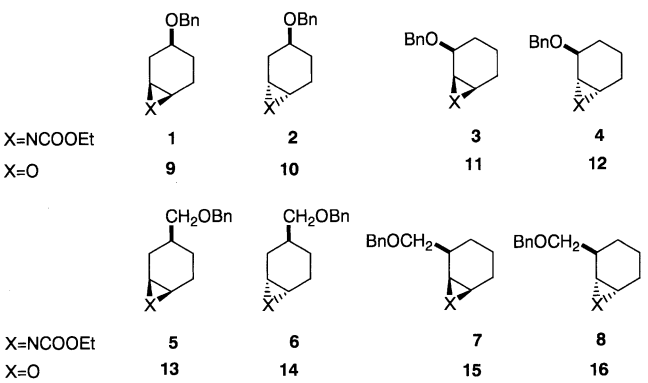
Abstract—The regiochemical behavior of the pairs of diastereoisomeric activated aziridines **1**–**8** deriving from the cyclohexane system, bearing a remote *O*-functionality, was determined in the acid methanolysis in the condensed phase (cd-phase) and in the reaction with MeOH in the gas-phase using a gaseous acid (D_3^+) as the promoting agent. The results obtained in the opening process of the *cis* diastereoisomers indicate the constant incursion in the gas phase of D^+(corresponding to H^+)-mediated chelated bidentate species able to modify the regiochemical result found in the methanolysis in the cd-phase.

1. Introduction

In recent years, from the seminal work of Sharpless,[1] it has been demonstrated that the presence of heterofunctionality (–OBn) close to the oxirane ring,[2] and the use of appropriate opening reaction conditions, are able in the condensed phase (cd-phase) to influence the regiochemical outcome of opening of typical aliphatic and cycloaliphatic oxiranes.[2a–f] Commonly, the regioselectivity observed under protic acid-catalyzed opening conditions (so-called standard conditions) could be inverted or, in some cases, decidedly reinforced when the same reactions were repeated in the presence of a metal salt, as the promoting agent, in a polar aprotic solvent (so-called chelating conditions).[3] By the use of standard or chelating conditions, nice regio-alternating processes were obtained in some cases. The incursion of intermediate chelated bidentate species was considered to be responsible for the different regioselectivity found under chelating conditions with respect to standard conditions.[1,2] Appropriate comparison of the regiochemical outcome observed in the methanolysis reaction conducted in the cd-phase under standard and chelating conditions gave clear evidence that the proton is not a species able to chelate between the oxygens of the oxirane and the remote functionality (–OBn) as a metal (such as Li^+) does.[2a–f] When the opening reactions with MeOH under acid conditions were repeated under gas-phase operating conditions, a different behavior and, consequently, a different result was found.[4] Under these conditions, in fact, a regioselectivity practically corresponding, or even superior, to the one observed under chelating conditions in the cd-phase was constantly found, indicating that in the gas-phase, the proton is a chelating agent as Li^+ is in the cd-phase.[4]

We were encouraged by these results which disclosed, for the first time, the chelating ability of the proton in opening reactions of epoxides, and as we are interested in the chemistry (particularly the reactivity and regioselectivity in



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

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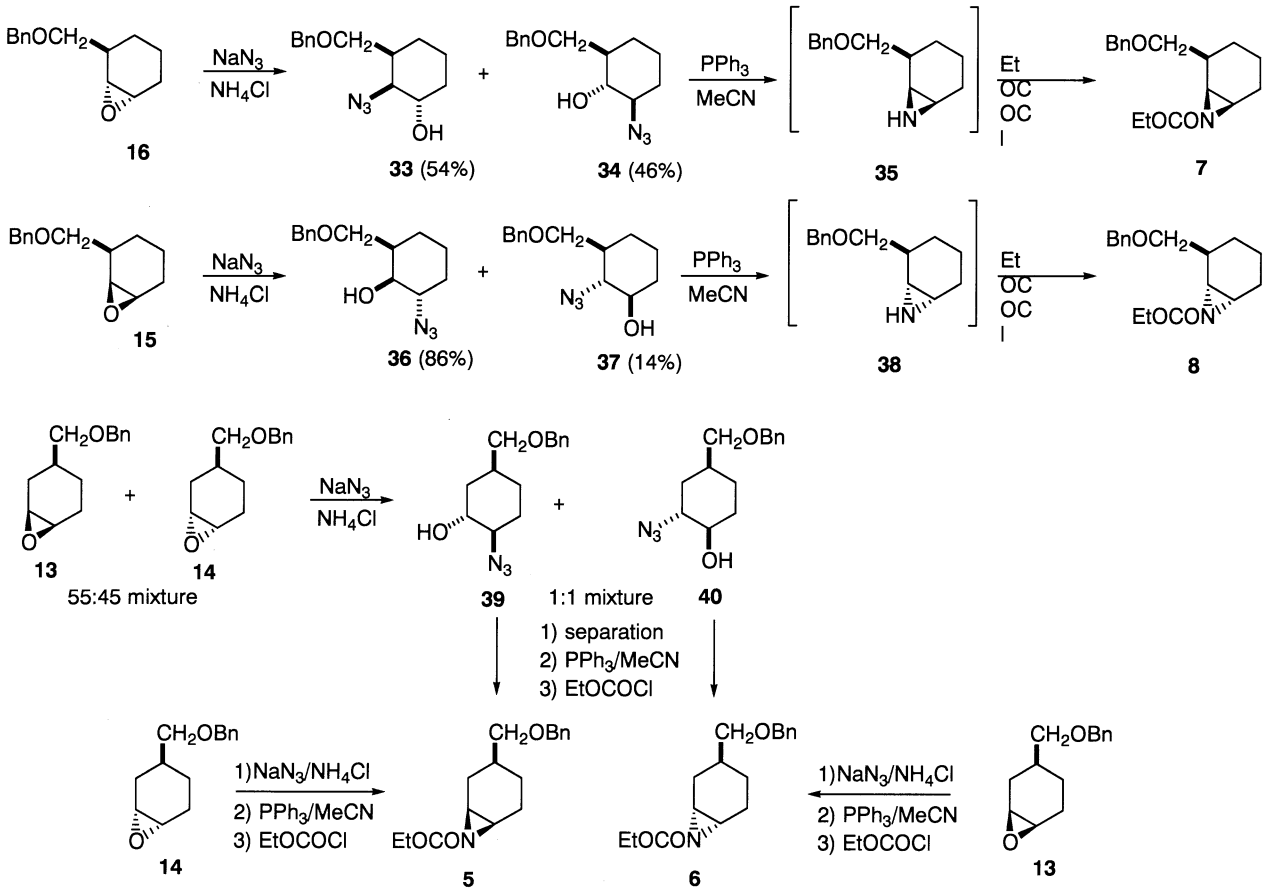
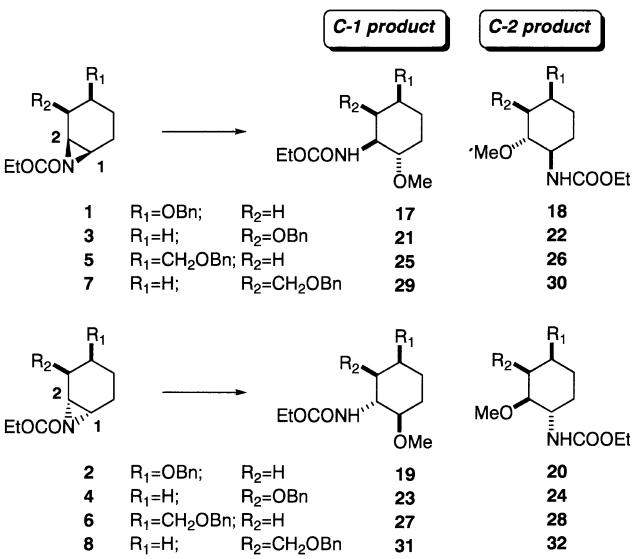


Scheme 1.

opening reactions) of other small-size heterocycles such as aziridines, we have now examined the regiochemical behavior of activated aziridines **1**–**8**, structurally related to the previously studied epoxides **9**–**16**, in the methanolysis reaction both in the cd- and gas-phase.[5,6]

2. Results

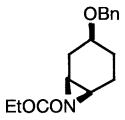
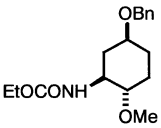
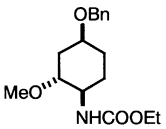
The pairs of diastereoisomeric aziridines *cis* **1** and **3** and *trans* **2** and **4** were prepared, as previously described, starting from the corresponding epoxides *trans* **10** and **12** and *cis* **9** and **11**, respectively.[6a,b] Following the same procedure, the reaction of *trans* epoxide **16** with the NaN_3/NH_4Cl protocol afforded a 54:46 mixture of azido-alcohols **33** and **34**[2c] which was treated with PPh_3 in MeCN at 80°C[6a] to afford the unactivated *cis* aziridine **35**, which was not separated but directly transformed into the corresponding *N*-ethoxycarbonyl derivative, the activated *cis* aziridine **7** (Scheme 1). The same procedure applied to *cis* epoxide **15** yielded an 86:14 mixture of azido alcohols **36** and **37**[2c] which were transformed into *trans* aziridine **8**. The 55:45 mixture of epoxides *cis* **13** and *trans* **14** derived from the *m*-CPBA oxidation of the corresponding olefin[2b] was utilized for the preparation of aziridines *cis* **5** and *trans* **6**. Acid azidolysis of the mixture of **13** and **14** afforded a reaction product consisting of an almost 1:1 mixture of azido alcohols **39** (from *trans* epoxide **14**) and **40** (from *cis* epoxide **13**)[7] which were separated by TLC. Independent reaction of **39** and **40** with PPh_3 afforded, after treatment with EtOCOCl of the corresponding intermediate N-unsubstituted aziridines, the activated aziridines **5** and **6**, respectively. The relative configuration of both aziridines **5** and **6** and thus of the respective starting azido alcohols **39** and **40**, was unambiguously confirmed by synthesizing aziridines **5** and **6** stereoselectively, starting from pure samples of epoxide *trans* **14** and *cis* **13**, respectively, prepared as previously described (Scheme 1).[2b]



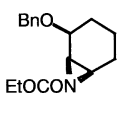
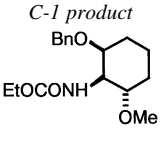
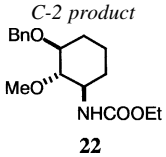
Scheme 2.

Table 1. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of *cis* aziridines **1** and **3**

Gas phase

System composition (Torr)[a]			Product distribution[b]				
			C-1 product		*C-2 product*		
							
1			**17**		**18**		
Aziridine	Bulk gas	MeOH	*G*	%	*G*	%	Total abs. yield%[c]
(0.54)	D_2 (100)	(1.68)	(2.17)	93	(0.15)	7	77
(0.63)	D_2 (760)	(1.84)	(1.94)	95	(0.10)	5	68
(0.57)	D_2 (760)	(1.73)[d]	(0.87)	**98**	(0.02)	**2**	30
Condensed phase[e]							
	$MeOH/H^+$[f]			**68**		**32**	
	$MeOH/LiClO_4$[g]			>**99**		<**1**	

Gas phase

System composition (Torr)[a]			Product distribution[b]				
			C-1 product		*C-2 product*		
							
3			**21**		**22**		
Aziridine	Bulk gas	MeOH	*G*	%	*G*	%	Total abs. yield%[c]
(0.61)	D_2 (100)	(1.79)	(0.54)	23	(1.86)	77	80
(0.53)	D_2 (760)	(1.69)	(0.49)	22	(1.79)	78	76
(0.66)	D_2 (760)	(1.81)[d]	(0.11)	**12**	(0.82)	**88**	31
Condensed phase							
	$MeOH/H^+$[f]			>**99**		<**1**	
	$MeOH/LiClO_4$[g]			**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 $G(D_3^+)$ values.[10]
[d] 3 Torr of NMe_3 added to the gaseous mixture.[12]
[e] Ref. 6a.
[f] Standard conditions.
[g] Chelating conditions.

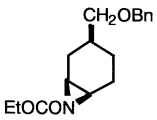
The reference compounds for the ring opening reactions with MeOH of aziridines **1**–**8**, the methoxy urethanes (MUs) **17**–**32** (Scheme 2), were prepared as follows. The direct acid methanolysis ($MeOH/H_2SO_4$) of aziridines **3**–**7** afforded as almost the only reaction product the corresponding MUs **21** (*C-1 product* from **3**), **23** (*C-1 product* from **4**), **26** (*C-2 product* from **5**), **27** (*C-1 product* from **6**), and **29** (*C-1 product* from **7**).[8] The same reaction carried out on aziridine *cis* **1** and *trans* **2** and **8** afforded both the respective regioisomeric MUs, the *C-1* and *C-2 products* **17** and **18** (ratio 68:32, from **1**)[6a] **19** and **20** (ratio 67:33, from **2**)[6a] and **31** and **32** (ratio 59:41, from **8**) which were separated by preparative TLC (Tables 1–4). The missing regioisomeric *C-2 product* from *cis* aziridine **3**, the MU **22**, was prepared starting from *trans* epoxide **12** (Scheme 3). Azidolysis of **12** afforded an 83:17 mixture of regioisomeric azido alcohols **41** and **42**,[2d] from which **41** was separated pure by preparative TLC. O-Methylation of **41** by means of the MeI/NaH protocol afforded the methoxy derivative **43** which was reduced ($LiAlH_4$) to the amine **44**. Protection of **44** with EtOCOCl afforded the desired MU **22**. Starting from epoxides *cis* **11** and **13** and *trans* **16**, a similar procedure was utilized for the preparation of MUs **24** (from epoxide **11**) and **30** (from epoxide **16**), the missing *C-2 products* from aziridines *trans* **4** and *cis* **7**, respectively, and to confirm (from epoxide **13**) the structure of the only product, the MU **27**, obtained in the acid methanolysis of *trans* aziridine **6**. Accordingly, the azidolysis of epoxides **11**, **13** and **16** afforded azido alcohols **45** (from **11**),[2d] **40** (from **13**) and **34** (separated from a 46:54 mixture with regioisomer **33**, from **16**),[2c] which were subjected to the methylation–reduction–protection sequence to afford the desired MUs **24** (from **45**–**47**), **27** (from **40**, **48**, **49**) and **30** (from **34**, **50**, **51**), respectively (Scheme 3).[9]

Aziridines **1**–**8** were subjected to opening reactions with MeOH in the cd-phase under standard (acid methanolysis by

Table 2. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of *cis* aziridines **5** and **7**

Gas phase

System composition (Torr)[a] | Product distribution[b]



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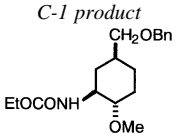

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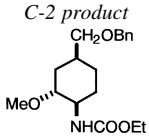

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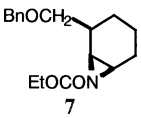
Aziridine	Bulk gas	MeOH	*C-1 product* *G*	*C-1 product* %	*C-2 product* *G*	*C-2 product* %	Total abs. yield%[c]
(0.67)	D_2 (100)	(1.91)	(0.59)	27	(1.63)	73	74
(0.53)	D_2 (760)	(1.74)	(0.54)	29	(1.32)	71	62
(0.60)	D_2 (760)	(1.79)[d]	(0.31)	**36**	(0.56)	**64**	29
Condensed phase							
	$MeOH/H^{+}$[e]			**3**		**97**	
	$MeOH/LiClO_4$[f]			**20**		**80**	

Gas phase

System composition (Torr)[a] | Product distribution[b]



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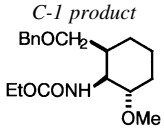

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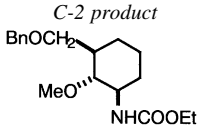


30

Aziridine	Bulk gas	MeOH	*C-1 product* *G*	*C-1 product* %	*C-2 product* *G*	*C-2 product* %	Total abs. yield%[c]
(0.58)	D_2 (100)	(1.82)	(1.78)	97	(0.05)	3	61
(0.64)	D_2 (760)	(1.88)	(1.41)	96	(0.06)	4	49
(0.55)	D_2 (760)	(1.70)[d]	(0.52)	**96**	(0.02)	**4**	18
Condensed phase							
	$MeOH/H^{+}$[e]			**98**		**2**	
	$MeOH/LiClO_4$[f]			**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 $G(D_3^+)$ values.[10]
[d] 3 Torr of NMe_3 added to the gaseous mixture.[12]
[e] Standard conditions.
[f] Chelating conditions.

0.2N H_2SO_4 in MeOH) and chelating conditions (10 M $LiClO_4$ in MeOH) and in the gas-phase under the catalysis of a gaseous Brönsted acid $[GA^+=D_3^+]$ obtained by γ-radiolysis of the corresponding neutral bulk gas precursor ($G=D_2$) (Scheme 4).[5] The results obtained are presented in Tables 1–4.[6] 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.[11] 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.[12]

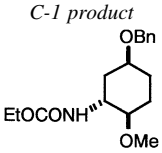
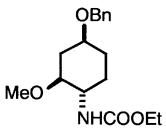
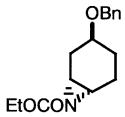
^{1}H NMR and GC–MS examination of the crude reaction mixtures from the cd- and gas-phase methanolysis reactions of activated aziridines **1**–**8** indicated only the presence of the addition products, the corresponding MUs **17**–**32** (Tables 1–4).[13]

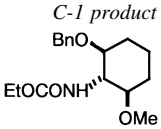
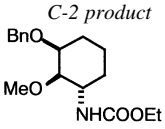
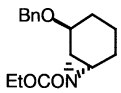
As a different product distribution is obtained in D_2 as a function of the experimental conditions (low or high bulk gas pressure) and the presence or absence of NMe_3, the reactions carried out in the gas-phase in conditions of low ion lifetime, that is under high pressure and in the presence of NMe_3 (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 1–4, bolded results), as previously stated.[14]

3. Discussion

For strictly structural reasons, *trans* aziridines **2**, **4**, **6** and **8** are not able to lead to any type of chelated bidentate intramolecular species mediated by a metal or proton. Consequently, the regiochemical behavior of **2**, **4**, **6** and **8** in the cd-phase appears to be mostly driven by the

Table 3. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of *trans* aziridines **2** and **4**

Gas phase System composition (Torr)[a]			Product distribution[b]				
			C-1 product  **19**		*C-2 product*  **20**		
 **2**							
Aziridine	Bulk gas	MeOH	*G*	%	*G*	%	Total abs. yield%[c]
(0.65)	D_2 (100)	(1.91)	(1.08)	68	(0.51)	32	53
(0.57)	D_2 (760)	(1.82)	(0.92)	68	(0.43)	32	45
(0.54)	D_2 (760)	(1.69)[d]	(0.41)	**72**	(0.16)	**28**	19
Condensed phase[e]							
	$MeOH/H^{+}$[f]			**67**		**33**	
	$MeOH/LiClO_4$[g]			**52**		**48**	

Gas phase System composition (Torr)[a]			Product distribution[b]				
			C-1 product  **23**		*C-2 product*  **24**		
 **4**							
Aziridine	Bulk gas	MeOH	*G*	%	*G*	%	Total abs. yield%[c]
(0.53)	D_2 (100)	(1.68)	(1.41)	96	(0.06)	4	49
(0.60)	D_2 (760)	(1.78)	(1.17)	95	(0.06)	5	41
(0.58)	D_2 (760)	(1.76)[d]	(0.52)	**96**	(0.02)	**4**	18
Condensed phase							
	$MeOH/H^{+}$[f]			**>99**		**<1**	
	$MeOH/LiClO_4$[g]			**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 $G(D_3^+)$ values.[10]
[d] 3 Torr of NMe_3 added to the gaseous mixture.[12]
[e] Ref. 6a.
[f] Standard conditions.
[g] Chelating conditions.

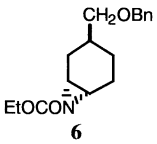
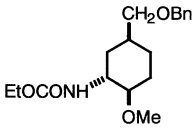
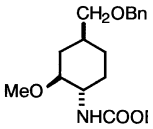
electron-withdrawing inductive effect of the corresponding *O*-functionality and by related conformational effects, in a very close analogy with the behavior observed with the corresponding epoxides **10**, **12**, **14** and **16** (Tables 3 and 4).[2a–d]

The regioselectivity observed in the gas-phase with *trans* aziridines **2**, **4**, **6**, and **8** is practically identical to that obtained in the cd-phase, both under standard and chelating conditions (Tables 3 and 4). This observation makes it reasonable to admit that the chemical behavior of *trans* aziridines **2**, **4**, **6** and **8** and, by a reasonable extension, also of the diastereoisomeric *cis* aziridines **1**, **3**, **5**, and **7**, is governed in the gas-phase by the same factors (*trans*-diaxial ring opening[15] and electronic effect of the substituent) as in the cd-phase, and can consequently be rationalized by means of the same considerations previously applied to the results obtained in the ring-opening reactions in the cd-phase of aziridines and epoxides.[2a–e,4,6] It means that all the differences in regioselectivity found in the gas-phase with respect to the corresponding results obtained in the cd-phase under standard conditions will reasonably be ascribed to the incursion of chelated bidentate species, as admitted in the cd-phase when comparing the different regiochemical results obtained on passing from standard to chelating conditions.[2a–e,4]

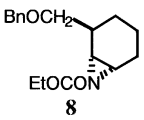
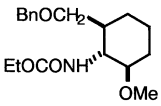
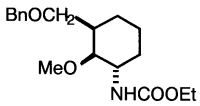
The *cis* aziridine **1** has previously been studied in methanolysis reactions in the cd-phase and an almost complete regioselectivity towards the *C-1 product*, the 'chelation product' (MU **17**, Table 1), was obtained in the methanolysis carried out in the presence of $LiClO_4$, confirming the extraordinary ability of Li^+ to chelate between the heterofunctionalities, present in a molecule, such as the homoallylic –OBn group and the aziridine nitrogen of **1**, as shown in structure **53** (M=Li^+, Scheme 5).[6,16] With **1**, an unexpectedly high level of the same *C-1 product* (68%, Table 1) was obtained also when the methanolysis reaction was conducted in the presence of a protonic catalysis ($MeOH/H_2SO_4$). This result was

Table 4. Distribution of products in the gas-phase acid-induced ring-opening with MeOH and in the methanolysis (condensed phase) of *trans* aziridines **6** and **8**

Gas phase

System composition (Torr)[a]			Product distribution[b]				
			C-1 product		*C-2 product*		
 **6**			 **27**		 **28**		
Aziridine	Bulk gas	MeOH	*G*	%	*G*	%	Total abs. yield%[c]
(0.62)	D_2 (100)	(1.81)	(2.22)	95	(0.12)	5	78
(0.59)	D_2 (760)	(1.73)	(1.80)	94	(0.11)	6	64
(0.67)	D_2 (760)	(1.92)[d]	(0.64)	**97**	(0.02)	**3**	22
Condensed phase							
	$MeOH/H^{+}$[e]			**96**		**4**	
	$MeOH/LiClO_4$[f]			**98**		**2**	

Gas phase

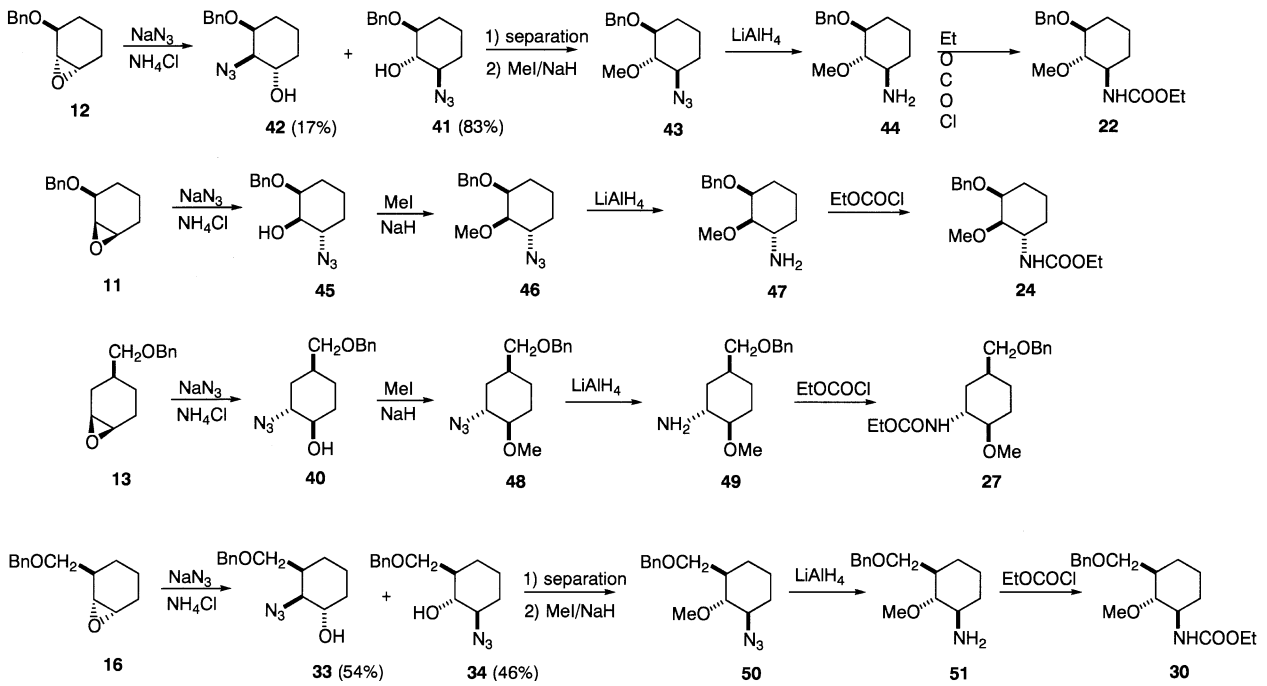
System composition (Torr)[a]			Product distribution[b]				
			C-1 product		*C-2 product*		
 **8**			 **31**		 **32**		
Aziridine	Bulk gas	MeOH	*G*	%	*G*	%	Total abs. yield%[c]
(0.51)	D_2 (100)	(1.64)	(0.78)	48	(0.84)	52	54
(0.64)	D_2 (760)	(1.70)	(0.74)	52	(0.67)	48	47
(0.63)	D_2 (760)	(1.73)[d]	(0.28)	**52**	(0.26)	**48**	18
Condensed phase							
	$MeOH/H^{+}$[e]			**59**		**41**	
	$MeOH/LiClO_4$[f]			**51**		**49**	

[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 $G(D_3^+)$ values.[10]
[d] 3 Torr of NMe_3 added to the gaseous mixture.[12]
[e] Standard conditions.
[f] Chelating conditions.

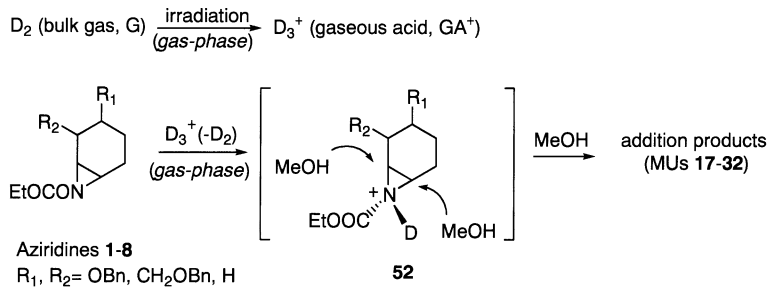
rationalized by admitting that in the case of aziridine **1**, the proton was able in the cd-phase to give sufficient amounts of the chelated bidentate species **53** (M=H) similar to the one admitted for the corresponding Li^+-promoted reaction.[17]

The *cis* aziridine **1** in the reaction with MeOH, in the presence of D_3^+ as the gaseous acid (GA^+), shows a C-1 selectivity (98%) far superior to the one observed in the cd-phase under proton catalysis, and practically identical to that observed in the corresponding metal salt-promoted reaction. This result confirms that the gas-phase conditions (absence of the solvent and related solvating effects, absence of counterion) are particularly indicated in order to exalt the intrinsic ability of the proton, which is not always in a condition to be operative or so clearly evident, in chelating between heterofunctionalities appropriately disposed (structure **53**, M=D, Scheme 5).[5b]

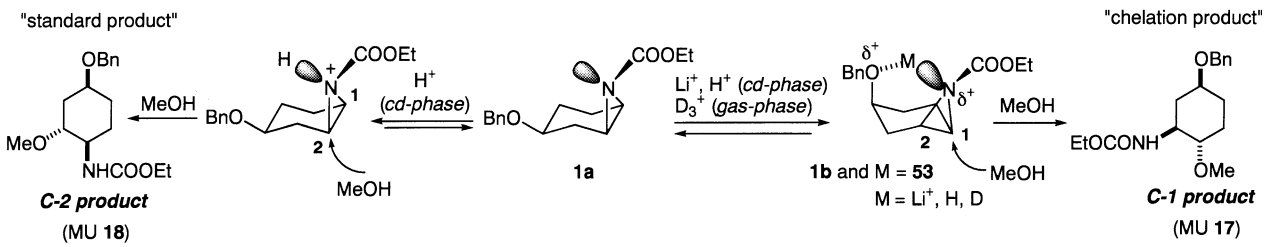
The *cis* aziridine **3** shows in the methanolysis carried out in the cd-phase a regiochemical behavior decidedly different from the one observed with the regioisomeric *cis* aziridine **1**. In fact, a C-1 selectivity, corresponding in this case to a non-chelated process through the more stable conformer **3a**, is constantly observed, both under standard (H^+/MeOH) and chelating opening conditions (Li^+/MeOH). This means that with aziridine **3**, no chelating structures of type **54** (H or Li^+ instead of D, Scheme 6) seem to intervene at all or, if they intervene, their reactivity is strongly diminished by the electron-withdrawing effect of the nearby benzyloxy group.[2d] However, it is a fact that when the opening reaction with MeOH is repeated in the gas-phase, an almost complete inversion of regioselectivity is obtained and MU **22** (the *C-2 product*, the 'chelating product' in this case) is obtained as the main component by far of the reaction mixture (88%).[18] It is reasonable to admit that the inversion of regioselectivity observed is due to an effective incursion of the proton-mediated chelated bidentate intermediate species **55** in which the aziridine necessarily adopts the less stable conformation **3b**.[5b] *trans* Diaxial attack by the



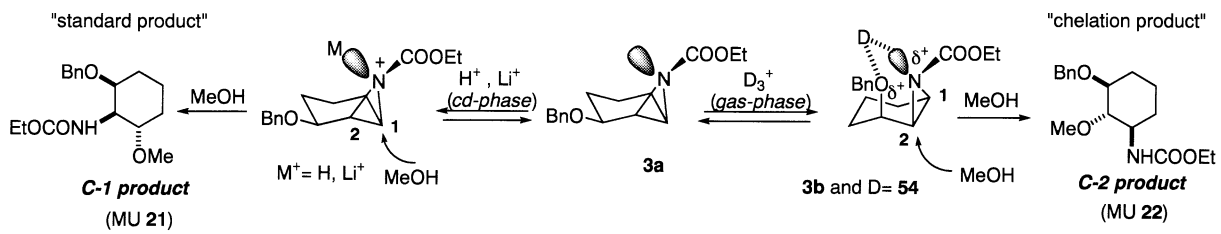
Scheme 3.



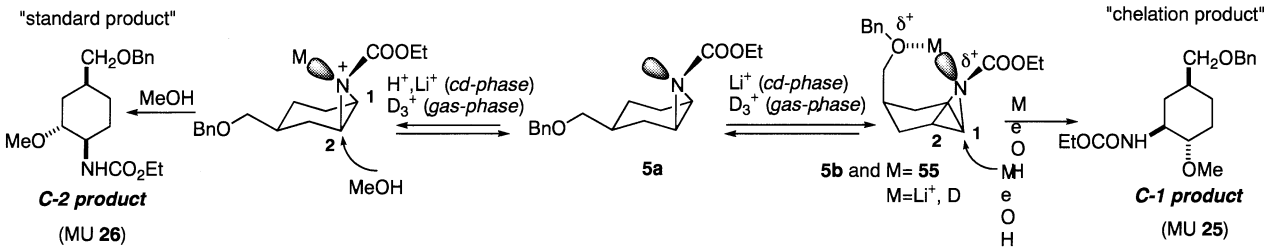
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

nucleophile (MeOH) occurs at the C(2) aziridine carbon to give the result observed (Scheme 6).[15]

The methanolysis of *cis* aziridine **5** in the cd-phase under standard conditions is almost completely C-2 regioselective showing a preferred reactivity of the aziridine in its more stable conformer **5a** with the $-CH_2OBn$ substituent equatorial, thus excluding any possible incursion of the chelated species **55** (M=H, Scheme 7), mediated by the proton. Application of chelating conditions in the cd-phase allows the obtainment of a significative amount of *C-1 product* (20%) whose presence can be justified only by the intermediate incursion of the chelated bidentate species **55** (M=Li^+, Scheme 7), in which the $-CH_2OBn$ group is kept in an axial relationship to the oxirane ring. *trans* Diaxial attack of the nucleophile on the C(1) aziridine carbon of **55** (M=Li^+) affords the chelation product, the MU **25** (Scheme 7 and Table 2). Application of gas-phase conditions leads to a C-1 regioselectivity (36%) superior to that observed with Li^+ in the cd-phase, indicating also in this system the incursion of the chelating ability of the proton (see intermediate species **55**, M=D, Scheme 7), completely absent in the cd-phase.

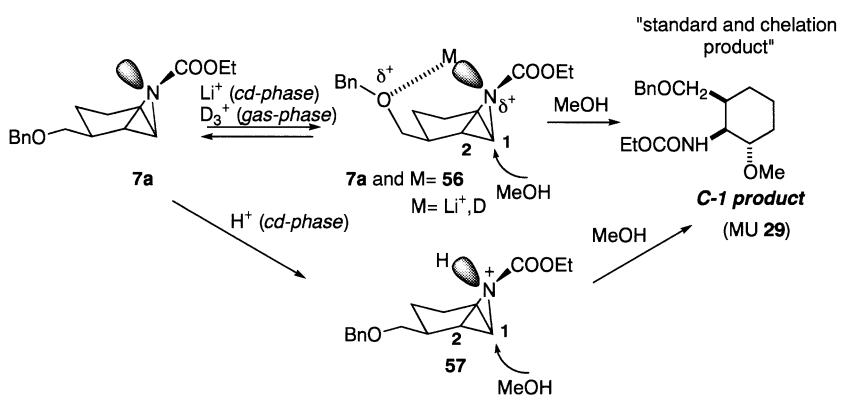
The regiochemical behavior of the *cis* aziridine **7** is decidedly different from the one observed with the previously examined *cis* aziridines **1**, **3** and **5**. Unique among the systems studied so far, the chelation process in **7** can already occur in the more stable conformation **7a** (as shown in **56**, Scheme 8), that is, in that conformation in which aziridine **7** reacts in the cd-phase under standard-non-chelating conditions (through protonated aziridine **57**) affording an almost complete C-1 selectivity with the obtainment of MU **29**, as practically the only reaction product. As a consequence, no difference in regioselectivity may be observed when chelating, in the cd-phase, or gas-phase operating conditions are utilized. In these conditions, in fact, a chelation process is reasonably involved through the intermediate chelated structure **56** (M=Li^+, and D, respectively, Scheme 8), leading to the *C-1 product*, but because of the almost complete C-1 regioselectivity observed under standard conditions (through **57**), no direct evidence of their incursion may be obtained (Scheme 8).

4. Structures and configurations

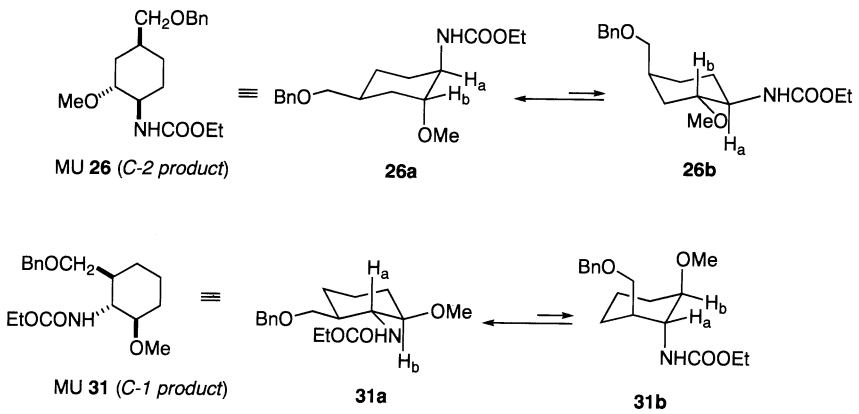
The relative configurations of the *cis* (**5** and **7**) and *trans* aziridines (**6** and **8**) are unequivocally demonstrated, as in the case of the known aziridines **1**–**4**,[6] on the basis of their stereospecific method of synthesis from the known *trans* **14** and **16** and *cis* epoxides **13** and **15**, respectively,[2b,c,6] as shown in Scheme 1.

The *trans* relationship between the –NHCOOEt and the –OMe groups in both the *C-1* and the *C-2 products* from either the *cis* (**1**, **3**, **5**, and **7**) or the *trans* aziridines (**2**, **4**, **6** and **8**) can be assumed on the basis of the usual *anti* stereoselectivity commonly observed in the ring opening of these systems.[6] On the other hand, the *cis* and *trans* relationship between the –OBn or the $-CH_2OBn$ and the –NHCOOEt groups in all the ring opening products must necessarily be the same as in the starting aziridines and a regioisomeric relationship must be necessarily present between the *C-1* and *C-2 products* obtained from each aziridine.

On this basis, the structure and relative configuration of MUs **21**, **23**, and **29** (*C-1 products* from aziridines **3**, **4** and **7**, respectively) is firmly established by the fact that they are



Scheme 8.



Scheme 9.

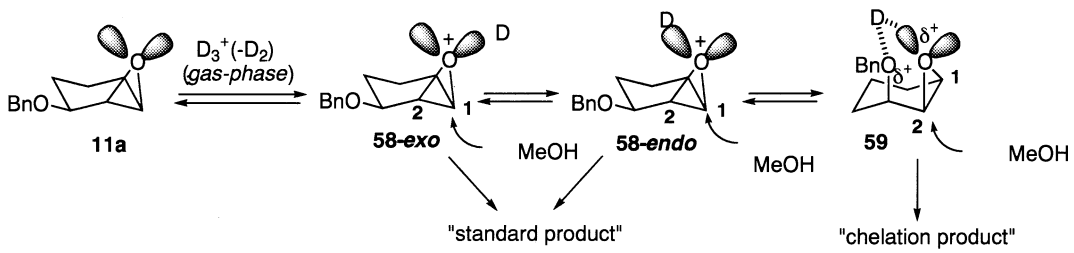
different from the corresponding regioisomeric *C-2 products* (MUs **22**, **24** and **30**, respectively, Scheme 2) appropriately prepared by independent, unequivocal synthetic pathways starting from known epoxides **12**, **11**, and **16**, respectively (Scheme 3).[2c,d] The structure of the only regioisomer (MU **27**, Table 4 and Scheme 2) obtained from aziridine **6** was directly confirmed by preparing it through a corresponding stereo- and regioselective synthesis, starting from known epoxide **13** (Scheme 3).[2b] The structure of MUs **17**–**20** (Scheme 2) have been previously demonstrated.[6a]

The regiochemical assignment inside the pair of *C-1* and *C-2 products* (MUs **31** and **32**) from *trans* aziridine **8** and for the only regioisomer (MU **26**) recovered from the opening reactions of *cis* aziridine **5** (Scheme 2 and Tables 2 and 4) was carried out by means both of the $W_{1/2}$ value[6,20] of the signals of the proton α to decoupled –NHCOOEt (proton H_a) and OMe groups (proton H_b, resolved only in the case of **31**) in the ^{1}H NMR spectra of these compounds and by simple conformational considerations. The relatively small $W_{1/2}$ value (10.0 Hz) of the signal of proton H_a in the only recovered MU from *cis* aziridine **5**[9] is consistent with an equatorial proton and, as a consequence, with a *C-2 product* structure (MU **26**, Scheme 2) which should exist in the reasonably more stable conformation **26a** with the $-CH_2OBn$ group equatorial (Scheme 9).[21]

The relatively large $W_{1/2}$ value of the signals of the protons H_a and H_b ($W_{1/2}$=20.0 and 24.0 Hz, respectively) observed for one regioisomer from aziridine **8** are consistent with axial protons and, as a consequence, with a *C-1 product* structure (MU **31**, Scheme 2) which should reasonably exist in the consistently more favored triequatorial conformation **31a** (Scheme 9). Established the *C-1 product* structure of MU **31**, a *C-2 product* structure is necessarily given to regiosomeric MU **32** (Scheme 2).[22]

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^+)[5b] in opening reactions with MeOH in the presence of a gaseous acid (GA^+=D_3^+) of a series of cyclohexane-derived aziridines bearing a remote heterofunctionality in an appropriate *cis* relationship to the aziridine nitrogen. In fact, all the *cis* aziridines examined (**1**, **3**, **5** and **7**) showed a regiochemical behavior towards the chelation product, 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. To our knowledge, this is the first example showing the chelating ability of the proton in opening reactions of aziridines in the gas-phase. As in the case of the corresponding epoxide **11**, the *cis* aziridine **3** afforded in the gas-phase a high relative amount of MU **22** (the chelation product, Scheme 6) which was completely absent in the corresponding methanolysis reactions carried out with **3** in the cd-phase. Comparison of the regiochemical results obtained in the gas-phase with *cis* aziridines **1**, **3**, and **5** and corresponding *cis* epoxides **9**, **11**, and **13** shows that the amount of chelation product is constantly higher with aziridines than with epoxides (98, 88, and 36% with aziridines **1**, **3**, and **5**, and 37, 46, and 33% with corresponding epoxides **9**, **11**, and **13**, respectively)[4] inferring that the chelating ability of the proton in these conditions is decidedly higher in the case of the nitrogen-derived heterocycles. Probably, the reasonably preferred *exo*-disposition of the *N*-substituent (–COOEt) in **1**, **3**, and **5**



Scheme 10.

makes the remaining nitrogen lone pair suitably disposed for bridging with the remote heterofunctionality through the proton (Schemes 5–7). In the epoxides (**9**, **11**, and **13**), competitive *exo*- vs. *endo*-protonation of the oxirane oxygen in the gas-phase (protonated epoxide **58**-*exo* and **58**-*endo*, as shown for simplicity in Scheme 10 only for epoxide **11**) leads to a reasonable reduced amount, in the reaction medium, of the intermediate chelated structure (**59** in the case of **11**, Scheme 10) with respect to that from the corresponding aziridine (chelated structure **54** from aziridine **3** corresponding to epoxide **11**, Scheme 6) and thus to a reduction of the chelation product in the final reaction mixture, as observed.

6. Experimental

6.1. General

^{1}H 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. Aziridines **1**–**4**[6] and azido alcohols **33**, **34**, **36**, **37**, **41**, **42** and **45**[2c,d] were prepared from the corresponding epoxides **9**–**12**[2a,d] and **15**–**16**,[2c] as previously described.

6.1.1. Synthesis of azido alcohols 39 and 40. A solution of the 55:45 mixture (2.20 g, 10.10 mmol) of epoxides *cis* **13** and *trans* **14**[2b] in an 8:1 MeOH/H_2O mixture (45 mL) was treated with NaN_3 (1.95 g, 30.0 mmol) and NH_4Cl (0.696 g, 31.0 mmol) and the reaction mixture was stirred at 80°C for 18 h. Dilution with ether and evaporation of the washed (saturated aqueous $NaHCO_3$ and water) organic solution afforded a crude product (2.18 g) consisting of an almost 1:1 mixture of azido alcohols **39** and **40** which was subjected to preparative TLC (a 65:35:15 hexane/CH_2Cl_2/$(i\text{-}Pr)_2O$ mixture was used as the eluant). Extraction of the two most intense bands (the faster moving band contained **40**) afforded pure azido alcohols **40** (0.83 g, 31% yield) and **39** (0.74, 28% yield).

t-5-(Benzyloxymethyl)-t-2-azido-r-1-cyclohexanol (***39***). A liquid (Found: C, 64.01; H, 7.21; N, 16.34. $C_{14}H_{19}N_3O_2$ requires: C, 64.35; H, 7.33; N, 16.08): ^{1}H NMR δ 7.01–7.36 (m, 5H), 4.39 (s, 2H), 3.56 (dt, 1H, J=7.2, 3.6 Hz), 3.20–3.36 (m, 3H), 1.99–2.21 (m, 1H), 1.67–1.98 (m, 2H), 1.40–1.66 (m, 4H). ^{13}C NMR δ 138.92, 128.96, 128.19, 128.13, 73.62, 73.64, 69.50, 64.99, 33.66, 32.85, 25.29, 25.03.

c-4-(Benzyloxymethyl)-t-2-azido-r-1-cyclohexanol (***40***). A liquid (Found: C, 64.11; H, 7.58; N, 15.72. $C_{14}H_{19}N_3O_2$ requires: C, 64.35; H, 7.33; N, 16.08): ^{1}H NMR δ 7.20–7.42 (m, 5H), 4.50 (s, 2H), 3.40–3.60 (m, 2H), 3.37 (d, 2H, J=6.9 Hz), 1.70–2.17 (m, 3H), 1.38–1.69 (m, 4H). ^{13}C NMR δ 138.73, 128.89, 128.11, 128.05, 73.44, 73.01, 71.54, 62.84, 32.93, 30.01, 28.57, 24.38.

The same reaction repeated under the same experimental conditions with pure epoxides **13** and **14**,[2b] afforded a crude product consisting of practically pure azido alcohols **40** and **39**, respectively, which were purified by preparative TLC.

6.1.2. Methylation of azido alcohols 34, 40, 41, and 45. *Typical procedure*. A solution of azido alcohol **41**[2d] (0.317 g, 1.28 mmol), in anhydrous THF (5 mL), was added at 0°C to a suspension of NaH (0.102 g of a 60% dispersion in mineral oil, 2.56 mmol) in anhydrous THF (7 mL) and the reaction mixture was slowly warmed to 40°C. After 2 h stirring at the same temperature, MeI (0.89 g, 6.30 mmol) was added and the resulting reaction mixture was stirred at 50°C for 18 h. After cooling, dilution with ether and water, treatment with 10% aqueous NaOH and evaporation of the washed (water) organic extracts afforded a crude liquid product (0.32 g) which was subjected to flash chromatography (a 9:1 hexane/AcOEt mixture was used as the eluant) to give pure *c-3-benzyloxy-t-2-methoxy-r-1-azidocyclohexane* (***43***) (0.28 g, 84% yield), as a liquid (Found: C, 64.72; H, 7.68; N, 15.83. $C_{14}H_{19}N_3O_2$ requires: C, 64.35; H, 7.33; N, 16.08): ^{1}H NMR δ 7.03–7.44 (m, 5H), 4.66 (s, 2H), 3.69 (s, 3H), 3.13–3.41 (m, 2H), 3.02 (t, 1H, J=9.1 Hz), 1.94–2.13 (m, 1H), 1.80–1.94 (m, 1H), 1.67–1.72 (m, 1H), 1.05–1.35 (m, 3H). ^{13}C NMR δ 139.37, 128.99, 128.22, 88.92, 82.16, 72.86, 64.69, 61.66, 30.97, 30.89, 21.34 (1×Ph signal unresolved).

Application of the same procedure to azido alcohol **45**[2d] (0.39 g, 1.58 mmol) afforded a crude product (0.338 g) which was subjected to preparative TLC (a 9.5:0.5 hexane/AcOEt mixture was used as the eluant). Extraction of the most intense band afforded pure *t-3-benzyloxy-t-2-methoxy-r-1-azidocyclohexane* (***46***) (0.131 g, 32% yield), as a liquid (Found: C, 64.13; H, 7.42; N, 16.47. $C_{14}H_{19}N_3O_2$ requires: C, 64.35; H, 7.33; N, 16.08): ^{1}H NMR δ 7.22–7.44 (m, 5H), 4.63 (s, 2H), 3.84–3.94 (m, 1H), 3.82 (ddd, 1H, J=10.6, 9.3, 4.7 Hz), 3.42 (s, 3H), 3.06 (dd, 1H, J=9.3, 2.7 Hz), 1.92–2.02 (m, 2H), 1.36–1.79 (m, 2H), 1.14–1.36 (m, 2H). ^{13}C NMR δ 139.27, 128.87, 128.13, 128.05, 85.21, 73.31, 71.64, 60.95, 57.86, 30.46, 28.06, 18.99.

Application of the same procedure to azido alcohol **40** (0.342 g, 1.31 mmol) afforded a crude reaction product (0.38 g) which was subjected to flash chromatography (a 9.5:0.5 hexane/AcOEt mixture was used as the eluant) to give pure *t-5-benzyloxy-t-2-methoxy-r-1-azidocyclohexane* (***48***) (0.30 g, 83% yield), as a liquid (Found: 64.72; H, 7.88; N, 15.01. $C_{15}H_{21}N_3O_2$ requires: C, 64.43; H, 7.69; N, 15.26): ^{1}H NMR δ 7.23–7.39 (m, 5H), 4.50 (s, 2H), 3.68 (q, 1H, J=5.1 Hz), 3.37 (s, 3H), 3.32 (d, 1H, J=6.7 Hz), 3.16–3.27 (m, 1H), 1.91–2.09 (m, 1H), 1.55–1.83 (m, 4H), 1.33–1.55 (m, 2H). ^{13}C NMR δ 139.11, 128.97, 128.13, 79.36, 74.36, 73.58, 60.30, 57.15, 32.78, 30.07, 24.95, 24.18.

Application of the same procedure to azido alcohol **34** (0.212 g, 0.81 mmol)[2c] afforded a crude reaction product consisting of *c-3-(benzyloxymethyl)-t-2-methoxy-r-1-azidocyclohexane* (***50***), practically pure as a liquid (0.21 g 94% yield) (Found: C, 64.66; H, 8.00; N, 14.98. $C_{15}H_{21}N_3O_2$

requires: C, 64.43; H, 7.69; N, 15.26): ^{1}H NMR δ 7.20–7.42 (m, 5H), 4.51 (s, 2H), 3.61 (dd, 1H, J=8.9, 4.9 Hz), 3.46–3.55 (m, 1H), 3.52 (s, 3H), 3.27 (ddd, 1H, J=11.3, 9.6, 4.4 Hz), 3.00 (t, 1H, J=9.6 Hz), 1.90–2.03 (m, 1H), 1.50–1.87 (m, 4H), 1.18–1.44 (m, 2H). ^{13}C NMR δ 139.09, 128.93, 128.12, 84.66, 73.71, 71.14, 66.70, 60.78, 44.55, 31.52, 30.28, 28.75, 24.00 (1×Ph signal unresolved).

6.1.3. Synthesis of methoxy amines 44, 47, 49 and 51. *Typical procedure*. A solution of methoxy azide **43** (0.28 g, 1.07 mmol) in anhydrous Et_2O (9 mL) was treated at 0°C with $LiAlH_4$ (0.161 g, 4.28 mmol) and the reaction mixture was stirred at room temperature for 3 h. Dilution with ether, treatment with 10% aqueous NaOH, and evaporation of the filtered (Celite) organic solution afforded a crude liquid product consisting of *c-3-benzyloxy-t-2-methoxy-r-1-aminocyclohexane (**44**)* (0.243 g, 97% yield), practically pure as a liquid (Found: C, 71.65; H, 9.28; N, 5.69. $C_{14}H_{21}NO_2$ requires: C, 71.46; H, 8.99; N, 5.95): ^{1}H NMR δ 7.10–7.36 (m, 5H), 4.60 and 4.53 (ABdd, 2H, J=11.8 Hz), 3.60 (s, 3H), 3.25 (ddd, 1H, J=10.5, 9.2, 4.8 Hz), 2.74 (t, 1H, J=9.2 Hz), 2.54 (td, 1H, J=9.2, 4.2 Hz), 1.98–2.08 (m, 1H), 1.56–1.77 (m, 2H), 1.00–1.32 (m, 3H). ^{13}C NMR δ 139.58, 128.95, 128.20, 128.06, 91.01, 82.60, 72.35, 61.90, 54.88, 33.60, 31.23, 21.90.

Application of the same procedure to methoxy azide **46** (0.131 g, 0.50 mmol) afforded a crude liquid product consisting of *t-3-benzyloxy-t-2-methoxy-r-1-aminocyclohexane (**47**)* (0.092 g, 78% yield), practically pure as a liquid (Found: C, 71.78; H, 9.17; N, 5.68. $C_{14}H_{21}NO_2$ requires: C, 71.46; H, 8.99; N, 5.95): ^{1}H NMR δ 7.14–7.32 (m, 5H), 4.58 and 4.47 (ABdd, 2H, J=12.4 Hz), 3.84–3.87 (m, 1H), 3.25 (s, 3H), 3.08 (ddd, 1H, J=10.9, 9.7, 4.3 Hz), 2.70 (dd, 1H, J=9.7, 2.7 Hz), 1.68–2.03 (m, 2H), 1.43–1.68 (m, 1H), 1.27–1.43 (m, 1H), 0.96–1.24 (m, 2H). ^{13}C NMR δ 139.47, 128.81, 128.18, 127.95, 88.24, 71.87, 71.23, 57.23, 50.06, 33.81, 28.43, 19.28.

Application of the same procedure to methoxy azide **48** (0.15 g, 0.54 mmol) afforded a crude liquid product consisting of *t-5-(benzyloxymethyl)-t-2-methoxy-r-1-aminocyclohexane (**49**)* (0.11 g, 82% yield), practically pure as a liquid (Found: C, 72.00; H, 9.53; N, 5.94. $C_{15}H_{23}NO_2$ requires: C, 72.25; H, 9.30; N, 5.62): ^{1}H NMR δ 7.19–7.40 (m, 5H), 4.49 (s, 2H), 3.38 (d, 2H, J=8.7 Hz), 3.35 (s, 3H), 2.76–2.93 (m, 2H), 1.95–2.11 (m, 1H), 1.58–1.95 (m, 3H), 1.31–1.58 (m, 3H). ^{13}C NMR δ 139.09, 128.90, 128.09, 84.62, 73.57, 73.40, 56.85, 50.38, 34.33, 33.00, 25.26, 24.48 (1×Ph signal unresolved).

Application of the same procedure to methoxy azide **50** (0.208 g, 0.76 mmol) afforded a crude liquid product consisting of *c-3-(benzyloxymethyl)-t-2-methoxy-r-1-aminocyclohexane (**51**)* (0.174 g, 92% yield), practically pure as a liquid (Found: C, 72.55; H, 9.07; N, 5.95. $C_{15}H_{23}NO_2$ requires: C, 72.25; H, 9.30; N, 5.62): ^{1}H NMR δ 7.18–7.40 (m, 5H), 4.50 (s, 2H), 3.50–3.60 (m, 2H), 3.47 (s, 3H), 2.79 (t, 1H, J=9.6 Hz), 2.66 (ddd, 1H, J=10.4, 9.6, 3.8 Hz), 1.77–1.91 (m, 2H), 1.50–1.77 (m, 2H), 1.02–1.46 (m, 3H). ^{13}C NMR δ 139.13, 128.76, 127.90, 87.61, 73.52, 71.78, 60.20, 56.08, 43.77, 34.33, 30.17, 29.54, 24.37 (1×Ph signal unresolved).

6.1.4. Synthesis of MUs 22, 24, 27, and 30. *Typical procedure*. A solution of amine **44** (0.243 g, 1.03 mmol), in anhydrous Et_2O (10 mL) containing NEt_3 (0.174 g, 1.6 mmol) was treated at 0°C with ClCOOEt (0.17 g, 1.60 mmol) and the reaction mixture was stirred at the same temperature for 2 h. Dilution with ether and evaporation of the washed (10% aqueous Na_2CO_3 and water) organic solution afforded a crude solid product (0.288 g) mostly consisting of MU **22** which was recrystallized from hexane to give pure *c-3-benzyloxy-t-2-methoxy-r-1-(ethoxycarbonylamino)cyclohexane (**22**)* (0.16 g, 51% yield), as a solid, mp 86.5–88.5°C (Found: C, 66.31; H, 8.03; N, 4.77. $C_{17}H_{25}NO_4$ requires: C, 66.43; H, 8.20; N, 4.56): ^{1}H NMR δ 7.20–7.44 (m, 5H), 5.37–5.50 (m, 1H), 4.65 and 4.57 (ABdd, 2H, J=11.7 Hz), 4.11 (q, 2H, J=7.1 Hz), 3.62–3.80 (m, 1H, $W_{1/2}$=20.0 Hz, H_a), 3.48–3.57 (m, 1H), 3.48 (s, 3H), 3.13 (t, 1H, J=6.2 Hz, H_b), 1.79–1.93 (m, 2H), 1.24–1.75 (m, 4H), 1.24 (t, 3H, J=7.1 Hz). ^{13}C NMR δ 156.85, 139.01, 128.96, 128.12, 82.96, 79.20, 72.13, 61.15, 59.56, 51.22, 29.44, 28.26, 18.59, 15.21 (1×Ph signal unresolved). MS (*m*/*z*) 91, 112, 140, 169, 201, 307 (M^+).

The same procedure repeated on amine **47** (0.092 g, 0.39 mmol) afforded a crude product (0.12 g) consisting of MU **24** which was recrystallized from hexane to give pure *t-3-benzyloxy-t-2-methoxy-r-1-(ethoxycarbonylamino)-cyclohexane (**24**)* (0.080 g, 67% yield), as a solid, mp 73–78°C (Found: C, 66.66; H, 7.95; N, 4.80. $C_{17}H_{25}NO_4$ requires: C, 66.43; H, 8.20; N, 4.56): ^{1}H NMR δ 7.14–7.49 (m, 5H), 4.62–4.82 (m, 1H), 4.65 and 4.58 (ABdd, 2H, J=12.3 Hz), 4.10 (q, 2H, J=7.1 Hz), 3.78–3.96 (m, 2H), 3.37 (s, 3H), 3.18 (dd, 1H, J=9.6, 2.7 Hz, H_b), 2.03–2.23 (m, 1H), 1.86–2.03 (m, 1H), 1.57–1.83 (m, 2H), 1.24–1.52 (m, 2H), 1.24 (t, 3H, J=7.1 Hz). ^{13}C NMR δ 156.03, 139.40, 128.83, 128.11, 127.97, 83.00, 73.31, 71.33, 61.22, 57.70, 50.68, 30.50, 28.00, 19.42, 15.20. MS (*m*/*z*) 91, 110, 140, 169, 184, 307 (M^+).

The same procedure repeated on amine **49** (0.11 g, 0.44 mmol) afforded a crude reaction product (0.135 g, 96% yield) consisting of *t-5-(benzyloxymethyl)-t-2-methoxy-r-1-(ethoxycarbonylamino)cyclohexane (**27**)*, practically pure, as a liquid (Found: C, 67.59; H, 8.72; N, 4.11. $C_{18}H_{27}NO_4$ requires: C, 67.26; H, 8.47; N, 4.36): ^{1}H NMR δ 7.20–7.38 (m, 5H), 4.78 (bd, 1H, J=7.5 Hz), 4.49 (s, 2H), 4.11 (q, 2H, J=7.1 Hz), 3.82–3.95 (m, 1H, $W_{1/2}$=10.0 Hz, H_a), 3.36 (s, 3H), 3.22–3.34 (m, 3H), 1.29–1.90 (m, 7H), 1.24 (t, 3H, J=7.1 Hz). ^{13}C NMR δ 156.58, 139.02, 128.92, 128.11, 77.95, 75.40, 73.61, 61.34, 56.92. 48.66, 33.13, 30.21, 24.96, 23.86, 15.15 (1×Ph signal unresolved). MS (*m*/*z*) 91, 124, 155, 168, 200, 321 (M^+).

The same procedure repeated on amine **51** (0.109 g, 0.41 mmol) afforded a crude solid reaction product (0.132 g) mostly consisting of MU **30** which was recrystallized from hexane to give pure *c-3-(benzyloxymethyl)-t-2-methoxy-r-1-(ethoxycarbonylamino)cyclohexane (**30**)* (0.064 g, 49% yield), as a solid, mp 57–58°C (Found: C, 67.61; H, 8.71; N, 4.12. $C_{18}H_{27}NO_4$ requires: C, 67.26; H, 8.47; N, 4.36): ^{1}H NMR δ 7.22–7.38 (m, 5H), 4.60–4.77 (m, 1H), 4.50 (s, 2H), 4.12 (q, 2H, J=7.1 Hz), 3.45–3.61 (m, 3H), 3.36 (s, 3H), 2.98 (t, 1H, J=10.0 Hz, H_b),

1.96–2.12 (m, 1H), 1.59–1.91 (m, 3H), 1.07–1.43 (m, 3H), 1.24 (t, 3H, J=7.1 Hz). ^{13}C NMR δ 156.88, 139.18, 128.87, 128.06, 83.19, 73.69, 71.64, 61.21, 58.15, 54.94, 43.25, 33.14, 29.07, 24.30, 15.24 (1×Ph signal unresolved). MS (*m/z*) 91, 111, 126, 184, 230, 321 (M^+).

6.1.5. Synthesis of activated aziridines 5–8. *Typical procedure*. A solution of azido alcohol **40** (0.75 g, 2.87 mmol) in MeCN (3 mL) was treated with PPh_3 (0.753 g, 2.87 mmol) and the resulting reaction mixture was stirred at room temperature until evolution of N_2 was observed (about 30 min), and then refluxed overnight. After cooling, the solvent was removed (rotary evaporator) and the residue was repeatedly extracted with petroleum ether. Evaporation of the organic extracts afforded an oily residue which was dissolved in anhydrous ether (30 mL) and treated at 0°C with ClCOOEt (0.488 g, 4.50 mmol) in the presence of NEt_3 (0.45 g, 4.50 mmol). The resulting reaction mixture was stirred at the same temperature for 2 h, and then diluted with ether. Evaporation of the washed (10% aqueous Na_2CO_3) organic solution afforded a crude liquid product which was subjected to flash chromatography (an 85:15 hexane/AcOEt mixture was used as the eluant) to give pure *(1α,3β,6α)-3-(benzyloxymethyl)-7-(ethoxycarbonyl)-7-azabicyclo[4.1.0]heptane* (***6***) (0.54 g, 65% yield), as a liquid (Found: C, 70.81; H, 8.28; N, 5.02. $C_{17}H_{23}NO_3$ requires: C, 70.56; H, 8.01; N, 4.84): ^{1}H NMR δ 7.20–7.41 (m, 5H), 4.48 (s, 2H), 4.13 (q, 2H, J=7.1 Hz), 3.30 (dd, 1H, J=11.6, 6.3 Hz), 3.24 (dd, 1H, J=11.6, 6.3 Hz), 2.59–2.74 (m, 2H), 1.26–1.94 (m, 2H), 1.71–1.94 (m, 2H), 1.50–1.71 (m, 1H), 1.41 (ddd, 1H, J=13.9, 10.5, 3.2 Hz), 1.27 (t, 3H, J=7.1 Hz), 1.00 (dtd, 1H, J=12.7, 11.3, 6.7 Hz). ^{13}C NMR δ 164.67, 139.20, 128.89, 128.08, 128.02, 75.38, 73.44, 62.81, 38.59, 36.94, 31.05, 28.25, 25.02, 23.02, 14.92.

Application of the same procedure to azido alcohol **39** (0.742 g, 2.84 mmol) afforded a crude product which was subjected to flash chromatography (an 85:15 hexane/AcOEt mixture was used as the eluant) to give pure *(1β,3β,6β)-3-(benzyloxymethyl)-7-(ethoxycarbonyl)-7-azabicyclo-[4.1.0]heptane* (***5***) (0.509 g, 62% yield), as a liquid (Found: C, 70.33; H, 7.85; N, 5.13. $C_{17}H_{23}NO_3$ requires: C, 70.56; H, 8.01; N, 4.84): ^{1}H NMR δ 7.14–7.30 (m, 5H), 4.40 (s, 2H), 4.05 (q, 2H, J=7.1 Hz), 3.14 (d, 2H, J=6.1 Hz), 2.54–2.63 (m, 2H), 2.00–2.16 (m, 2H), 1.36–1.68 (m, 4H), 1.19 (t, 3H, J=7.1 Hz), 1.05 (qd, J=12.4, 4.1 Hz). ^{13}C NMR δ 164.65, 139.06, 128.90, 128.05, 128.00, 75.76, 73.60, 62.80, 38.60, 36.40, 34.18, 27.48, 24.73, 22.34, 14.92.

Application of the same procedure to the 54:46 mixture of azido alcohols **33** and **34** (1.93 g, 7.39 mmol)[2c] afforded a crude product which was subjected to flash chromatography (an 85:15 hexane/AcOEt mixture was used as the eluant) to give pure *(1β,2β,6β)-2-(benzyloxymethyl)-7-(ethoxycarbonyl)-7-azabicyclo[4.1.0]heptane* (***7***) (1.40 g, 65% yield), as a liquid (Found: C, 70.72; H, 8.34; N, 4.61. $C_{17}H_{23}NO_3$ requires: C, 70.56; H, 8.01; N, 4.84): ^{1}H NMR δ 7.21–7.43 (m, 5H), 4.63 and 4.51 (ABdd, 2H, J=11.8 Hz), 4.12 (qd, 2H, J=7.2, 0.7 Hz), 3.63 (dd, 1H, J=8.9, 7.7 Hz), 3.47 (dd, 1H, J=8.9, 6.5 Hz), 2.68–2.83 (m, 2H), 2.03–2.23 (m, 1H), 1.68–2.00 (m, 2H), 1.31–1.62 (m, 2H), 1.04–1.31 (m, 1H), 1.24 (t, 3H, J=7.2 Hz). ^{13}C NMR δ 164.71, 139.18, 128.82, 128.12, 127.98, 73.89, 62.72, 40.16, 37.51, 35.28, 23.82, 22.63, 20.41, 14.87 (1×CH signal unresolved).

Application of the same procedure to the 86:14 mixture of azido alcohols **36** and **37** (0.90 g, 3.45 mmol)[2c] afforded a crude product which was subjected to flash chromatography (a 9:1 hexane/AcOEt mixture was used as the eluant) to give pure *(1α,2β,6α)-2-(benzyloxymethyl)-7-(ethoxycarbonyl)-7-azabicyclo[4.1.0]heptane* (***8***) (0.694 g, 70% yield), as a liquid (Found: C, 70.82; H, 8.30; N, 4.58. $C_{17}H_{23}NO_3$ requires: C, 70.56; H, 8.01; N, 4.83): ^{1}H NMR δ 7.22–7.41 (m, 5H), 4.60 and 4.52 (ABdd, 2H, J=12.0 Hz), 4.14 (q, 2H, J=7.1 Hz), 3.53 (dd, 1H, J=9.4, 6.0 Hz), 3.46 (dd, 1H, J=9.4, 7.0 Hz), 2.64–2.71 (m, 1H), 2.60 (unresolved dd, 1H, J=6.3 Hz), 2.03–2.23 (m, 1H), 2.00–2.13 (m, 1H), 1.34–1.84 (m, 4H), 1.08–0.86 (m, 1H), 1.27 (t, 3H, J=7.1 Hz). ^{13}C NMR δ 164.71, 139.01, 128.90, 128.09, 73.66, 73.45, 62.83, 39.58, 38.37, 35.16, 25.11, 24.65, 18.10, 14.92 (1×Ph signal unresolved).

6.1.6. Acid methanolysis of aziridines 3–8 with 0.2N H_2SO_4 in MeOH. *Typical procedure*. A solution of the aziridine **3** (0.050 g, 0.18 mmol) in 0.2N H_2SO_4 in MeOH (1 mL) was stirred at room temperature for 2 h. Dilution with ether and evaporation of the washed (saturated aqueous $NaHCO_3$ and water) organic solution afforded a crude reaction product (0.040 g) consisting of MU **21** which was recrystallized from hexane to give pure *c-2-benzyloxy-t-6-methoxy-r-1-(ethoxycarbonylamino)cyclohexane* (***21***) (0.025 g, 45% yield), as a solid, mp 73.5–76.5°C (Found: C, 66.71; H, 8.48; N, 4.32. $C_{17}H_{25}NO_4$ requires: C, 66.43; H, 8.20; N, 4.56): ^{1}H NMR δ 7.08–7.52 (m, 5H), 4.90–5.15 (m, 1H), 4.57 and 4.38 (ABdd, 2H, J=11.6 Hz), 4.10 (q, 2H, J=7.1 Hz), 3.80–3.90 (m, 1H, $W_{1/2}$=10.0 Hz, C*H*OBn), 3.60–3.78 (m, 1H, $W_{1/2}$=18.0 Hz, H_a), 3.28–3.45 (m, 1H), 3.34 (s, 3H), 1.81–2.14 (m, 2H), 1.17–1.70 (m, 4H), 1.24 (t, 3H, J=7.1 Hz). ^{13}C NMR δ 157.18, 139.07, 128.95, 128.16, 78.96, 77.34, 71.33, 61.26, 57.09, 56.53, 29.29, 27.87, 18.87, 15.20 (1×Ph signal unresolved). MS (*m/z*) 91, 112, 141, 201, 307 (M^+).

The same reaction carried out on aziridines **1** and **2** afforded MUs **17** and **18** (from **1**) and **19** and **20** (from **2**) (Scheme 2 and Tables 1 and 3), as previously described.[6a] **17**: MS (*m/z*) 91, 101, 112, 123, 201, 307 (M^+); **18**: MS (*m/z*) 91, 112, 128, 155, 218, 307 (M^+); **19**: MS (*m/z*) 91, 112, 128, 169, 201, 307 (M^+); **20**: MS (*m/z*) 91, 101, 112, 169, 201, 307 (M^+).

The same reaction carried out on aziridine **4** (0.10 g, 0.36 mmol) afforded a crude solid product (0.108 g) consisting of MU **23** which was recrystallized from hexane to give pure *t-2-benzyloxy-t-6-methoxy-r-1-(ethoxycarbonylamino)cyclohexane* (***23***) (0.062 g, 56% yield), as a solid, mp 87–89°C (Found: C, 66.09; H, 7.95; N, 4.95. $C_{17}H_{25}NO_4$ requires: C, 66.43; H, 8.20; N, 4.56): ^{1}H NMR δ 7.19–7.49 (m, 5H), 4.62–4.78 (m, 1H), 4.65 and 4.48 (ABdd, 2H, J=11.7 Hz), 4.12 (qd, 2H, J=7.2, 0.7 Hz), 3.42–3.54 (m, 1H), 3.36 (s, 3H), 3.17–3.42 (m, 2H), 2.03–2.23 (m, 2H), 1.69–1.86 (m, 1H), 1.09–1.41 (m, 3H), 1.25 (t, 3H, J=7.2 Hz). ^{13}C NMR δ 157.17, 139.30, 128.84, 128.21, 128.03, 80.44, 78.55, 71.78, 61.30, 61.12, 57.43,

31.12, 30.40, 20.35, 15.24. MS (*m/z*) 91, 112, 140, 201, 307 (M^+).

The same reaction carried out on aziridine **5** (0.050 g, 0.173 mmol) afforded a crude product (0.056 g) mostly consisting of MU **26** which was subjected to preparative TLC (an 8:2 hexane/AcOEt mixture was used as the eluant). Extraction of the most intense band afforded pure *c-4-(benzyloxymethyl)-t-2-methoxy-r-1-(ethoxycarbonylamino)cyclohexane* (***26***) (0.038 g, 68% yield), as a liquid (Found: C, 67.59; H, 8.24; N, 4.55. $C_{18}H_{27}NO_4$ requires: C, 67.26; H, 8.47; N, 4.36): ^{1}H NMR δ 7.20–7.38 (m, 5H), 4.71–4.87 (m, 1H), 4.49 (s, 2H), 4.11 (q, 2H, J=7.1 Hz), 3.73–3.89 (m, 1H), 3.36 (s, 3H), 3.32–3.42 (m, 1H, $W_{1/2}$=11.0 Hz, H_a), 3.29 (d, 1H, J=6.3 Hz), 1.04–2.09 (m, 7H), 1.24 (t, 3H, J=7.1 Hz). ^{13}C NMR δ 156.59, 139.15, 128.90, 128.06, 75.29, 73.47, 61.35, 56.99, 48.99, 32.16, 29.30, 25.77, 24.59, 15.18 (1×Ph and 1×CH signals unresolved). MS (*m/z*) 91, 98, 111, 142, 232, 321 (M^+).

The same reaction carried out on aziridine **6** (0.050 g, 0.173 mmol) afforded a crude product (0.052 g, 94% yield) mostly consisting of MUs **27** which was subjected to preparative TLC (an 8:2 mixture of petroleum ether and AcOEt was used as the eluant). Extraction of the most intense band afforded pure MU **27** (0.033 g, 60% yield). Evidence of the presence of regioisomer **28** (Scheme 2 and Table 4) in the crude reaction mixture was obtained by GC–MS analysis.[9] **28**: MS (*m/z*) 91, 111, 168, 198, 232, 321 (M^+).

The same reaction carried out on aziridine **7** (0.050 g, 0.173 mmol) afforded a crude product (0.052 g, 93% yield) consisting of *c-2-(benzyloxymethyl)-t-6-methoxy-r-1-(ethoxycarbonylamino)cyclohexane* (***29***) (94% yield) practically pure, as a liquid (Found: C, 67.57; H, 8.28; N, 4.72. $C_{18}H_{27}NO_4$ requires: C, 67.26; H, 8.47; N, 4.36): ^{1}H NMR δ 7.21–7.38 (m, 5H), 5.07–5.19 (m, 1H), 4.47 (s, 2H), 4.10 (q, 2H, J=7.1 Hz), 3.90–4.01 (m, 1H, $W_{1/2}$=9.0 Hz, H_a), 3.31–3.55 (m, 3H), 3.38 (s, 3H), 2.14–2.34 (m, 1H), 1.38–1.79 (m, 5H), 1.16–1.35 (m, 1H), 1.24 (t, 3H, J=7.1 Hz). ^{13}C NMR δ 156.97, 138.95, 128.87, 128.09, 77.61, 73.74, 73.17, 61.27, 56.97, 51.57, 35.39, 25.75, 24.62, 19.92, 15.15 (1×Ph signal unresolved). MS (*m/z*) 91, 111, 124, 198, 215, 321 (M^+).

The same reaction carried out on aziridine **8** (0.10 g, 0.35 mmol) afforded a crude product (0.11 g) consisting of a 59:41 mixture of MUs **31** and **32** which was subjected to preparative TLC (an 8:2 mixture of petroleum ether and AcOEt was used as the eluant). Extraction of the two most intense bands (the faster moving band contained **32**) afforded pure MUs **31** (0.040 g, 36% yield) and **32** (0.030 g, 27% yield).

t-6-(Benzyloxymethyl)-t-2-methoxy-r-1-(ethoxycarbonylamino)cyclohexane (***31***). A solid, mp 84–86°C (recrystallized from hexane) (Found: C, 67.59; H, 8.72; N, 4.55. $C_{18}H_{27}NO_4$ requires: C, 67.26; H, 8.47; N, 4.36): ^{1}H NMR δ 7.20–7.38 (m, 5H), 4.50–4.64 (m, 1H), 4.50 and 4.43 (ABdd, 2H, J=12.0 Hz), 4.10 (q, 2H, J=7.1 Hz), 3.57 (dd, 1H, J=9.2, 3.6 Hz), 3.38 (dd, 1H, J=9.2, 6.8 Hz), 3.34 (s, 3H), 3.26 (t, 1H, J=10.0 Hz, $W_{1/2}$=20.0 Hz, H_a), 2.94–3.14 (m, 1H, $W_{1/2}$=24.0 Hz, H_b), 2.06–2.21 (m, 1H), 1.58–2.01 (m, 3H), 1.06–1.39 (m, 3H), 1.22 (t, 3H, J=7.1 Hz). ^{13}C NMR δ 157.39, 139.13, 128.86, 128.14, 128.03, 82.73, 73.80, 72.91, 61.23, 57.10, 57.24, 43.33, 30.61, 29.67, 23.40, 15.19. MS (*m/z*) 91, 111, 126, 215, 230, 321 (M^+).

t-3-(Benzyloxymethyl)-t-2-methoxy-r-1-(ethoxycarbonylamino)cyclohexane (***32***). A liquid (Found: C, 67.62; H, 8.67; N, 4.64. $C_{18}H_{27}NO_4$ requires: C, 67.26; H, 8.47; N, 4.36): ^{1}H NMR δ 7.22–7.41 (m, 5H), 4.72–4.83 (m, 1H), 4.50 (s, 2H), 4.10 (q, 2H, J=7.1 Hz), 3.85–3.98 (m, 1H, $W_{1/2}$=9.7 Hz, H_a), 3.52 (dd, 1H, J=9.0, 7.0 Hz), 3.30–3.42 (m, 2H), 3.38 (s, 3H), 1.17–2.04 (m, 7H), 1.24 (t, 3H, J=7.1 Hz). ^{13}C NMR δ 156.61, 139.11, 128.92, 128.22, 128.11, 78.96, 73.79, 71.77, 61.37, 58.14, 47.68, 37.46, 26.83, 24.09, 20.36, 15.17. MS (*m/z*) 91, 111, 126, 168, 184, 321 (M^+).

6.1.7. Methanolysis of aziridines 3–8 in the presence of $LiClO_4$. *Typical procedure*. A solution of aziridine **3** (0.069 g, 0.25 mmol) in anhydrous MeOH (2 mL) containing $LiClO_4$ (2.13 g, 10 M solution) was stirred at 80°C for 24 h. Dilution with ether and evaporation of the washed (water) organic solution afforded a crude reaction product (0.072 g), which was analyzed by ^{1}H NMR and GC–MS.

The same reaction carried out on aziridine **5** afforded a crude reaction product (0.070 g) consisting of an 8:2 mixture of MUs **26** and **25** (Table 2 and Scheme 2) which was subjected to preparative TLC (an 8:2 mixture of hexane and AcOEt was used as the eluant). Extraction of the most intense band afforded MU **26** (0.030 g), whereas, also by extracting other bands, it was not possible to isolate MU **25**. However, clear evidence of the presence of regioisomer **25** in the crude reaction mixture was obtained by ^{1}H NMR and GC–MS examination of the reaction product.[9] **25**: ^{1}H NMR δ 4.84–4.99 (m, 1H), 4.46 (s, 2H), 3.41–3.59 (m, 1H, $W_{1/2}$=20.0 Hz, H_a), 3.32 (s, 3H), 2.92 (td, 1H, J=11.5, 4.5 Hz, $W_{1/2}$=25.5 Hz, H_b). MS (*m/z*) 91, 124, 155, 168, 232, 321 (M^+).

6.2. Reactions in the gas-phase

6.2.1. Materials. Deuterium, oxygen, and trimethylamine were high-purity gases from Matheson Gas Products Inc. and were used without further purification. The aziridines were repeatedly purified by preparative gas chromatography on a 5 m×4 mm (i.d.) stainless steel column packed with 5% FFAP on 80–100 mesh Chromosorb G-AW-DMCS at 160°C. Their final purity exceeds 99.96%. The purity of starting aziridines, with special regard to the absence of their substituted derivatives, was checked by analytical gas chromatography on the same columns employed for the analysis of the products from radiolytic experiments.

6.2.2. Procedure. The samples were prepared by introducing fragile ampoules, containing weighed amounts of selected aziridine and methanol, 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. Irradiations of the mixtures were carried out at 37.5°C in a ^{60}Co 220 Gammacell from Nuclear Canada Ltd. The total dose received by the samples was 1.5×10^4 Gy, at a dose rate of 1×10^4 Gy h^{-1}, as measured with a Fricke dosimeter. Control irradiations, 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.

6.2.3. 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 50 m long, 0.31 mm i.d. Ultra1™ crosslinked methyl silicone fused silica capillary column, operating at temperatures ranging from 100 to 250°C, 4°C min^{-1}; (ii) a 30 m long, 0.32 mm i.d. Supelcowax 10™ fused silica capillary column, operating at temperatures ranging from 50 to 230°C, 5°C min^{-1}. The identity of the products was further confirmed by GC–MS, using a Model 5971A Hewlett–Packard quadrupole 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 1–4 are the average of at least three measurements taken on at least two different runs for each point.

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3. *Standard reaction conditions:* epoxide opening reactions carried out with the nucleophile (MeOH in the methanolysis) under protic acid catalysis (MeOH/H_2SO_4), or without any catalysis in an appropriate solvent (MeONa/MeOH). *Chelating reaction conditions:* epoxide opening reactions carried with the nucleophile in the presence of a metal salt (MeOH/$LiClO_4$, in the methanolysis).
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5. (a) Methanolysis was chosen because it is an intrinsically simple reaction which has the unique advantage of offering a clear indication of the regioselectivity of the opening process and of being easily conducted both in the cd-phase (standard, H^+/MeOH, or chelating conditions, MeOH/$LiClO_4$) and in the gas-phase (D_3^+, MeOH) (Tables 1–4), making a direct comparison possible between all these conditions and in particular a direct comparison of the behavior of the proton under different operating conditions. (b) In the gas-phase, D^+ (actually D_3^+) was used instead of H^+ simply for practical reasons (necessary purity of the corresponding bulk gas, D_2 and H_2, respectively). However, in the opening reactions of aziridines **1**–**8** with MeOH, the behavior of D^+ is to be considered completely identical to that of H^+, to the point that no difference is made in the discussion between them.
6. Aziridines **1**–**4** were previously examined by the authors in opening reactions in the cd-phase with different nucleophiles (including MeOH only in the case of **1** and **2**), both under standard and chelating conditions: (a) Crotti, P.; Favero, L.; Gardelli, C.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1995**, *60*, 2514–2525, (aziridines **1** and **2**). (b) Crotti, P.; Di Bussolo, V.; Favero, L.; Pineschi, M. *Tetrahedron* **1997**, *53*, 1417–1438, (aziridines **3** and **4**).
7. The regiochemistry of azido alcohols **39** and **40**, derived from epoxides **14** and **13**, respectively (Scheme 1), 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 acid conditions (HCl/$CHCl_3$, MeOH/H_2SO_4),[2b] and on the reasonable assumption that epoxides **13** and **14** should have a similar regiochemical behavior also in a fairly similar reaction like acid azidolysis.
8. 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) aziridine carbon of aziridines **1**–**8**, in accordance with the numbering scheme shown in Schemes 5–8.
9. As it was present in insufficient amounts in the methanolysis of the corresponding *trans* aziridine **6** (Table 4), MU **28** (*C-2 product*) was not separated, nor was an alternative synthesis carried out. Although present in sufficient amounts (20%) in

the methanolysis of *cis* aziridine **5** carried out in the presence of $LiClO_4$ (Table 2), we were not able to separate pure the MU **25** (*C-1 product*) from the crude reaction mixture. However, clear evidences of the presence of MUs **28** and **25** in the opening reactions of the corresponding aziridines *trans* **6** and *cis* **5**, respectively, both in the cd- and gas-phase, was obtained by GC–MS and ^1H NMR examination of the corresponding crude opening reaction product (see Experimental).

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12. NMe_3 is a powerful positive-ion scavenger, as demonstrated by its high proton affinity (225.1 kcal/mol). When present in the gaseous mixture, NMe_3 is able to intercept ionic gaseous acids (e.g. D_3^+), generated from radiolysis of D_2, to yield closed-shell very stable ionic products (e.g. $NDMe_3^+$). Thus, the effect of the presence of NMe_3 in the irradiated mixture is twofold: first, it decreases the steady-state concentration of the ionic intermediates (e.g. **52**, Scheme 4) by intercepting their immediate precursor D_3^+, second, it reduces the lifetime of the charged intermediates (e.g. **52**, Scheme 4) and, hence, the extent of conversion to their addition derivatives. In both cases, the addition of NMe_3 to the gaseous mixture causes a strong decrease in the product yield, thus demonstrating the ionic origin of the neutral products.
13. Unlike observations for the reaction with MeOH, under acid conditions, of epoxides **9**–**16** in the gas-phase,[4] no traces of non-addition products were found in the corresponding reactions of aziridines **1**–**8**.
14. The similarity between low ion lifetime conditions in the gas-phase and the common acid methanolysis conditions in the cd-phase, previously admitted for the acid ring-opening reaction of oxiranes,[4] can now reasonably be extended to the corresponding reactions of aziridines. In fact, in the cd-phase, the intermediate protonated aziridine **52** (Scheme 4), as the corresponding protonated epoxide, rapidly undergoes nucleophilic addition by the surrounding nucleophilic solvent (MeOH) to afford the corresponding opening products, a situation which actually corresponds to low ion lifetime conditions in the gas-phase.
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16. Other nucleophiles (Cl^-, N_3^-, $NHEt_2$, PhSH) gave in opening reactions of *cis* aziridine **1** in the cd-phase a similar or a regioalternating result on passing from standard to chelating reaction conditions.[6a]
17. In order for the chelation to take place, aziridine **1** adopts the conformation **1b**, which, on the basis of the *trans*-diaxial ring opening of small heterocycles (the Fürst–Plattner rule)[15] can be nucleophilically attacked only at the C(1) aziridine carbon giving the result observed (Scheme 5).
18. In order to justify the high C-2 regioselectivity so far observed, it is impossible to exclude also a synergic effect due to an increased nucleophilicity of MeOH in the gas-phase,[19] which makes MeOH itself able to attack the electronically unfavorable C(2) aziridine carbon of **54** (Scheme 6), as only the strongly nucleophilic PhSH is able to do in the related opening reaction of the corresponding epoxide **11** under chelating conditions in the cd-phase, with attack of PhSH on the C(2) oxirane carbon of intermediate chelated structure **59** (Li^+ instead of D, Scheme 10).[2d]
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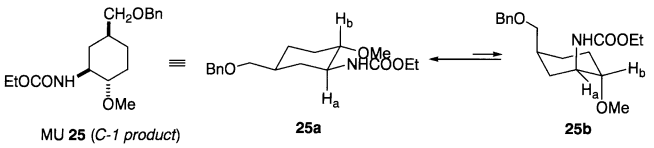
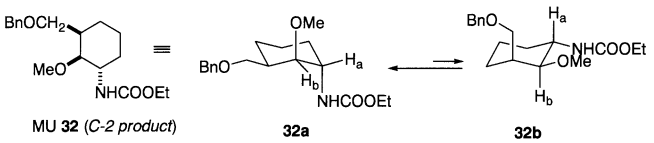
21. The regioisomeric MU **25** was not separated.[9] However, accurate ^1H NMR examination of the crude mixture (containing both MUs **26** and **25**, Table 2) obtained from the reaction of *cis* aziridine **5** with MeOH/$LiClO_4$, showed for **25** relatively large $W_{1/2}$ values of the signal of the corresponding protons H_a ($W_{1/2}$=20.0 Hz) and H_b ($W_{1/2}$=25.5 Hz). These values are consistent with axial protons (both H_a and H_b) and, as a consequence, with a *C-1 product* structure for MU **25** which should exist in the largely more stable triequatorial conformation **25a**.



MU **25** (*C-1 product*) **25a** **25b**

22. As a confirmation of the regiochemical assignment to MU **31**, the signal of proton H_a in the regioisomeric MU **32** (Scheme 2) shows a relatively small $W_{1/2}$ value (9.7 Hz) consistent with an equatorial proton, and, as a consequence, with a *C-2 product* structure for MU **32** which should reasonably exist in the more stable conformation **32a**, with the large $-CH_2OBn$ group equatorial.



MU **32** (*C-2 product*) **32a** **32b**