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ASYMMETRIC NITROGEN–LXXI. ASYMMETRIC SYNTHESIS AND LACTONIZATION OF 1-β-HYDROXYALKYLAZIRIDINE-2-CARBOXYLIC ESTERS INTO 4-OXA-1-AZABICYCLO[4.1.0]HEPTAN-5-ONES

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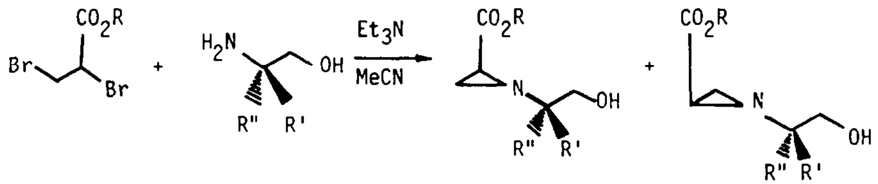
Abstract. Epimeric mixtures of 1-β-hydroxyalkylaziridine-2-carboxylic esters were prepared by the Gabriel-Cromwell reaction, followed by their separation by liquid chromatography with subsequent lactonization of each epimer in the presence of base to give pure enantiomers and diastereomers of lactones differing as to the aziridine (C-2) carbon configuration. According to PMR spectroscopy data, twisted boat is the most preferred six-membered cycle configuration in 4-oxa-1-azabicyclo[4.1.0]-heptane-5-ones in solution. The absolute configurations of carbon atoms in chiral lactones were determined by CD-spectroscopy. Epimers of 1-β-hydroxyalkylaziridine-2-carboxylic esters sharing the same carbon configuration (α-substituent at nitrogen) but differing in C-2 configuration undergo lactonization at different rate. A rational explanation of this phenomenon is provided.

Earlier, new heterobicycles - 4-oxa-1-azabicyclo[4.1.0]heptane-5-ones (OAH) have been derived from 1-β-hydroxyalkylaziridine-2-carboxylic esters (HAE)[2,3]. Here, we describe the preparation of optically active HAE and OAH and examine the stereochemistry of lactonization on the basis of the absolute configuration found for the compounds in study. The two variants of HAE synthesis involved the control of the chiral centre in the α-position of amino alcohol (1a,b; 2a,b) and in the α,β-dibromoacrilate ester group (3a,b; 4a,b).

The closely located chiral centres (initial and nascent) provide a higher stereoselectivity of synthesis from amino alcohols, especially in the case of the sterically hindered (S)-valinol. According to analytical HPLC data, the diastereomer ratio (1a)/(1b) = 1.4 and (2a)/(2b) = 0.32, whereas for the l-mentyl and l-bornyl esters, where the chiral cantres are

a) For communication 70 see ref. [1].

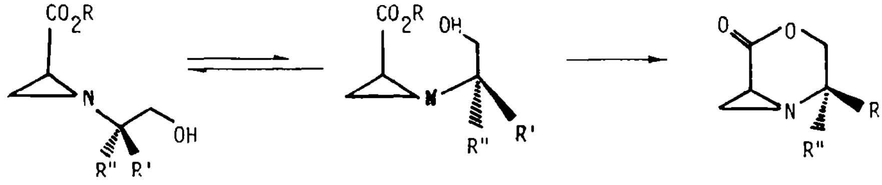


(1S,2S) (1R,2R)

(αR) - (1a) R = Me, R' = Et, R" = H (1b)
(αS) - (2b) R = Me, R' = H, R" = Pr-i (2a)
(3b) R = 1-Menthyl, R' = R" = Me (3a)
(4) R = 1-Bornyl, R' = R" = Me (4a)

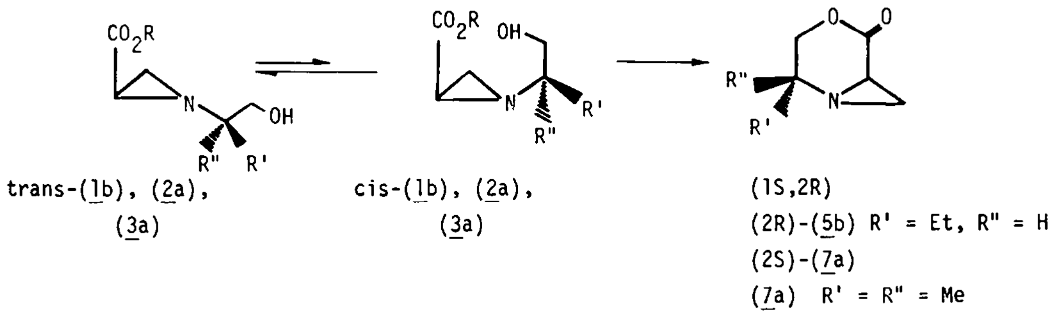
sterically detached from the newly formed ones, the diastereomer ratio (3a)/(3b) ~ (4a/(4b) 1.2. Differences in intramolecular distances between the chiral centres in HAE diastereomers seem to exert a decisive influence on their relative rate of lactonization. For example, (1a) and (1b), (2a) and (2b) with an α-carbon chiral centre in the N-substituent show considerable differences in the rate of lactonization in the presence of 1,8-diazabicyclo[5.4.0]-undec-5-ene (DBU): following 3 hours the conversion of HAE was 90% for (1b) and (2b) and less than 5% for their isomers (1a) and (2a). Under the same conditions, the diastereomers (3a) and (3b), (4a) and (4b) with sterically remote chiral centres undergo lactonization practically at the same rate. Mixtures of diastereomers 1a,b, 2a,b and 3a,b were resolved by preparative liquid chromatography.

Pure OAH diastereomers (5a), (6a) and (5b), (6b) as well as enantiomers (7a) and (7b) were obtained from individual HAE diastereomers (1a)-(3a) and (1b)-(3b).



trans-(1a), (2b), (3b) cis-(1a), (2b), (3b)

(1R,6S)
(2R)-(5a) R' = Et, R" = H
(2S)-(6b) R' = H, R" = i-Pr
(7b) R' = R" = Me



It was also found that Cs_2CO_3 in the presence of dicyclohexyl-18-crown-6 was a more effective catalyst for HAE lactonization than Et_3N [2] and DBU. CD and PMR spectra of AOH (5a,b)-(7a,b) were employed in order to assign their absolute configuration. The spectra CD show absorption bands of opposite sign at 226 and 200 nm (Fig.1, Table 1). The former can be

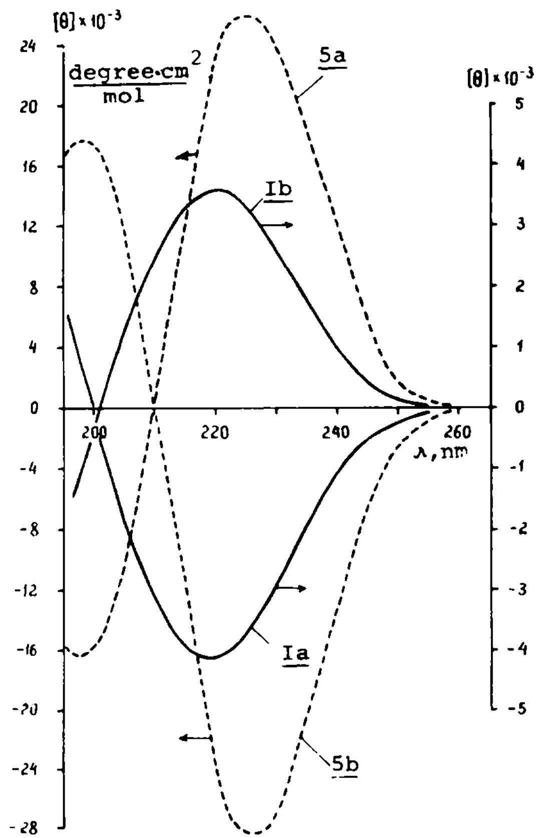


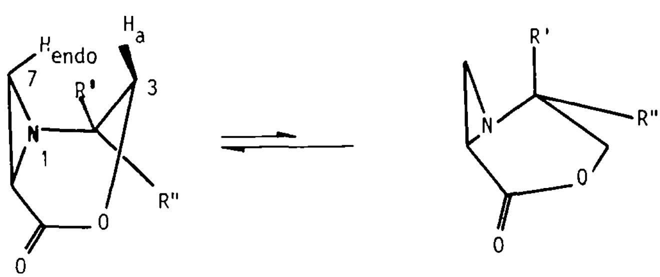
Fig.1. CD spectra of 1-α-ethyl-β-hydroxyethylaziridine-2-carboxylic ester (1a,b) and 2-ethyl-4-oxa-1-azabicyclo[4.1.0]heptane-5-one (5a,b) diastereomers.

Table 1. Optically pure isomers of 1-β-hydroxyethylaziridine-2-carboxylic esters 1a,b-3a,b and 4-oxa-1-azabicyclo[4.1.0]heptane-5-ones 5a,b-7a,b

Compounds	Optical rotation $[\alpha]_D^{20}$, degrees (C, vol.% EtOH)	CD spectra in MeOH, λ_{max}, nm($[\theta]_{max}$, degree·cm^2/mole)
1a	-73.8 (4.3)	220 (-4080)
1b	+88.6 (0.9)	220 (+3600)
2a	+90.6 (7.8)	220 (+5900)
2b	-89.8 (3.0)	220 (-5500)
3a	+2.8 (3.9)	-
3b	-210.8 (1.6)	-
5a	+7.5 (0.6)	226 (+25900), 198 (-16300)
5b	-12.7 (1.2)	226 (-28400), 198 (+17600)
6a	-8.0 (1.4)	226 (-42800), 199 (+23200)
6b	+2.2 (3.3)	226 (+36400), 199 (-27200)
7a	-99.2 (1.0)	226 (-44100), 199 (+21400)
7b	+100.0 (0.7)	226 (+44120), 199 (-21400)

ascribed to the $n_O - \pi^*_{CO}$ transition of the δ-lactone chromophore, for which the sector rule is known, to apply[4,5], relating the absolute configuration with the sign of Cotton effect. However, for this rule to be applicable to OAH, one has to determine the most populate conformation for the lactone cycle, since in the two possible cycle conformations, that of twisted boat (A) and semi-chair (B), the principal perturbing fragment (the N^1-C^2 bond) falls within sectors with opposite sign (Fig.2).

Earlier, lactone cycle conformation has been established for (A) by X-ray analysis of 2,2-bis-hydroxymethyl-substituted OAH. The same conformation has been confirmed for OAH (5a) and (6a) in solution by means of NOESY two-dimensional PMR spectra[6]. The nondiagonal cross-peaks observed due to the nuclear Overhauser effect suggest a close spatial location of the 3-H_a and endo-7-H protons. In fact, as judged by Dreiding's molecular models, the distance between the above protons in OAH in the (A) conformation amounts to ca. 1.5 Å.



(A) (B)

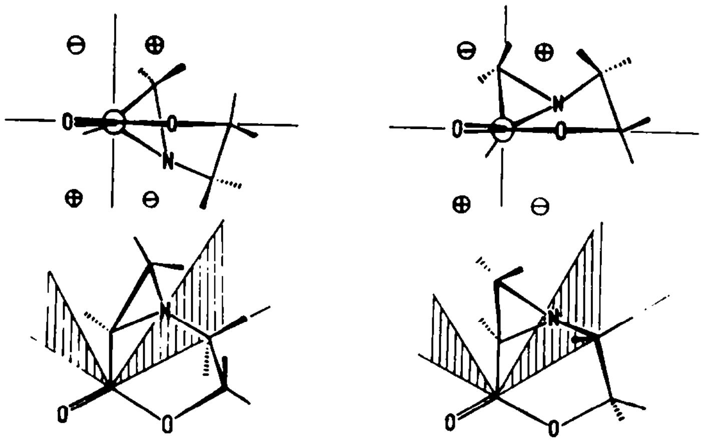


Fig.2. Application of the sector rule to the lactone chromophore of (1S,6R-4-oxa-1--azabicyclo[4.1.0]heptane-5-one in the semi-boat (left) and semi-chair conformation.

The reason of the shift in conformational equilibrium in favour of the OAH (A) can be possibly explained, as in the case of 1-aza- and 1,5-diazabicyclo[3.1.0]hexanes, by the tendency to minimize the destabilizing interaction between the n-orbital of the N atom and the occupied π-orbital shared by adjacent CR'R" group[7].

Hence, the positive longwave Cotton effect in the CD spectra of (5a), (6b), (7b) corresponds, according to the sector rule (Fig.2), to the absolute conformation (1R,6S), wherease the negative effect in the (5b), (6b), (7a) spectra is attributable to (1S,6R). This assignment is supported by the ^3J coupling constants values observed in the PMR spectra (Table 2) indicating that the 2-H proton in OAH (1H,2R,6S)-(5a) and (1S,2S,6R)-(6a) has an axial orientation, while in their isomers (1S,2R,5R)-(5b) and (1R,2S,6S)-(6b) it is oriented equatorially.

Herefrom one can deduce the absolute conformation of the initial HAE: (1S,2S)-(1a), (2b), (3b) and (1R,2R)-(1b), (2a), (3a). It should be emphasized that, as in the case of other diastereomeric derivatives of aziridine-2-carboxylic ester[8], (1S,2S,αR)-(1a) amd (1R, 2R,αS) (2a) are characterized by a greater difference in the chemical shifts of protons in the aziridine cycle H_A and H_B ($\Delta\nu_{AB}$), as compared to their isomers (1R,2R,αS)-(1b) and (1S, 2S,αS)-(2b) (Table 3), despite the fact that these compounds are lacking such a magnetic anisotropic group as MeO_2C in the α-position of the N-substituent[8].

Knowledge of the absolute configuration of HAE (1a,b), (2a,b) allows to explain the higher lactonization rate of the diastereomers (1b) and (2b), in comparison with (1a) and (2a). The most favourable conformation, in terms of the N-C_α bond for three-membered heterocycles containing an asymmetric N-substituent of the CHRR' type is the conformation in which the aziridine cycle is shielded by the least bulky α-substituent, viz. the H atom[9]. Such conformations (C,D) in cis-HAE (1b) and (2b) have closely spaced reacting groups OH and MeO_2C,

Table 2. PMR spectral parameters at 400 MHz for 4-oxa-1-azabicyclo[4.1.0]heptane-5-ones 5a,b; 6a,b[a]

Compound	δ, ppm				J, Hz								Other
	2-H	3-H	6-H	7-H	2a3a	2a3e	2e3a	2e3e	3a3e	6,exo-7	6,endo-7	exo-7 endo-7	
5a	3.23(a)	3.94(a) 4.11(e)	2.80	2.10(exo) 2.41(endo)	12.5	4.6	-	-	-126	6.4	2.9	0.7	1.09(Me), ^3J = 7.5 1.44 and 1.54(CH$_2$Me) ^3J = 13.9, ^3J = 7.6
5b	2.89(e)	4.29(a) 4.12(e)	2.70	2.26(exo) 2.45(endo)	-	-	3.4	2.0	-127	6.4	3.2	0.7	1.08(Me), ^3J = 7.5 1.60 and 1.75(CH$_2$Me) ^2J = 13.2, ^3J = 7.3
6a	3.04(a)	4.06(a) 4.20(e)	2.78	2.15(exo) 2.45(endo)	12.5	4.6	-	-	-127	6.4	2.9	0.7	1.00 and 1.14(Me$_2$C) ^3J = 6.8 1.71(CHMe$_2$), ^3J = 7.5
6b	2.50(e)	4.19(a) 4.22(e)	2.62	2.21(exo) 2.28(endo)	-	-	3.6	2.4	-127	6.6	3.2	0.6	0.98 and 1.07(Me$_2$C) ^3J = 6.8 1.82(CHMe$_2$), ^3J = 7.6

a) The PMR spectral parameters for AOH 7a,b are given in [2].

Table 3. PMR spectral parameters[a)] of 1-β-hydroxyethyl-aziridine-2-carboxylic esters 1a,b-7a,b

Compound[b)]	δ, ppm; J, Hz									
	Me	CH_2	CH	H_A	H_B	H_C	$^3J_{AB}$	$^3J_{AC}$	$^3J_{BC}$	$\Delta\nu_{AB}$
1	2	3	4	5	6	7	8	9	10	11
1a	0.95(MeC) ^3J = 7.5	1.66(Et), ^2J = 13.4, ^3J = 5.4	1.43	2.30	1.72	2.21	6.6	3.2	0.6	232
		1.67(Et), ^3J = 8.3								
	3.75(MeO)	3.65(CH_2O), ^2J = 11.7 ^3J = 4.9								
		3.70(CH_2O), ^3J = 3.4								
1b	0.94(MeC)	1.57(Et), ^2J = 11.7 ^3J = 5.4	1.45	2.17	1.84	2.22	6.6	3.2	0.6	132
	^3J = 7.5	1.69(Et), ^3J = 8.3								
	3.75(MeO)	3.65(CH_2O), ^2J = 11.7 ^3J = 3.7								
		3.70(CH_2O), ^3J = 5.6								
2a	0.98, 1.03 (Me_2C), ^3J = 6.8	3.72(CH_2O), ^2J = 12.0, ^3J = 5.0	1.29(CHN) 2.01($CHMe_2$)	2.30	1.75	2.27	6.6	3.4	1.0	220
	3.75(MeO)	3.74(CH_2O), ^3J = 3.5								

Table 3. (continued)

1	2	3	4	5	6	7	8	9	10	11
2b	0.98, 0.99 (Me$_2$C), ^3J = 6.8 3.75(MeO)	3.71(CH$_2$O), ^3J = 11.7 ^3J = 3.7 3.76(CH$_2$O), ^3J = 6.1	1.35(CHN) 1.98(CHMe$_2$)	2.17	1.87	2.21	6.6	3.4	1.0	120
3a[c)]	0.89, 0.91 (Me$_2$C)	3.38(CH$_2$O)	-	2.31	1.84	1.98	6.0	2.8	1.0	42
3b[c)]	0.89, 0.91 (Me$_2$C)	3.37(CH$_2$)	-	2.29	1.87	2.02	6.3	3.0	1.4	38
4a,b[d)]	0.82, 0.87 (Me$_2$C)	3.40(CH$_2$O)	-	2.33	1.87	2.00	6.0	2.9	1.3	-

Notes:

a) At 400 MHz for 1a,b; 2a,b and at 90 MHz for remaining compounds.

b) δOH(br.s.): 1a, 1b; 2a, 2b; 3a, 3b; 4a,b are the following: 3.27, 2.18, 2.80, 2.53, 2.80, 2.78, 2.40.

c) Spectrum of the menthyl group: 0.87, 0.89, 0.91 (Me), 0.97-1.75 (9H, M), 4.71 (OCH, M).

d) *Measured for a mixture of epimers whose signals coincide with respect to the chemical shifts.*
Spectrum of bornyl group: 0.86 (Me), 1.00-1.78 (7H, M), 4.82-5.04 (OCH, M).

Table 4. Characteristics of 1-β-hydroxyalkylaziridine-2-carboxylic esters 1a,b; 2a,b; 4a,b[a)] and 4-oxa-1-azabicyclo[4.1.0]heptane-5-ones 5a,b-7a,b

Compound	Yield, %	R_f	ν, cm^{-1} CH_{cycle}	C=O	OH	Found,% N	Empirical formula	Calculated,% N
1a	85	0.42	3060	1740	3370	7.73	$C_8H_{15}NO_3$	8.09
1b		0.31				7.78		
2a	89	0.59	3060	1740	3400	7.46	$C_9H_{17}NO_3$	7.48
2b		0.40				7.59		
4a	87	0.85	3070	1740	3390	*	$C_{17}H_{29}NO_3$	4.75
4b		0.85				*		
5a	74	0.48	3070	1740	-	9.82	$C_7H_{11}NO_2$	9.92
5b	68	0.52				9.94		
6a	77	0.66	3070	1740	-	9.40	$C_8H_{13}NO_2$	9.03
6b	81	0.56				9.08		
7a[b)]	71	0.57						
7b[b)]	64	0.57						

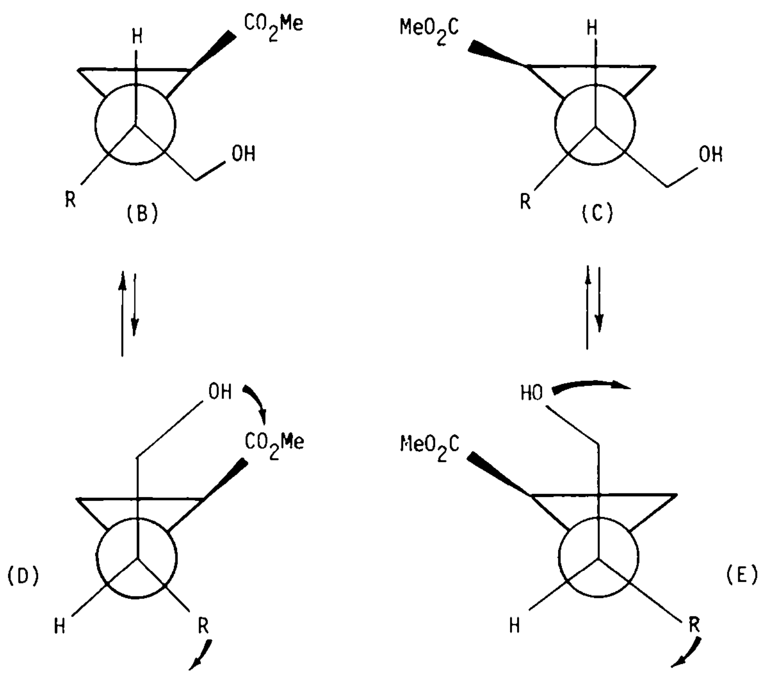
* Satisfactory elemental analysis data could not be obtained.

a) Caracteristics of epimeric mixture of HAE 3a,b are reported in [3].

b) The other parameters of OAH 7a,b are identical to those of racemate [2].

whereas in the cis-HAE (1a) and (2a) they are located far apart. If conformations (D,E) with the closest arrangement of the reacting groups are populated, the steric interaction of the α-alkyl group R with the aziridine cycle will contribute to a still closer location of the OH and MeO_2C groups in (D) and to their further detachment in (E).

cis-2b* cis-2a*



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* In the case of 1b and 1a the structures represent mirror antipodes.

Conformers (B-E) have been explored only for the cis-HAE, because lactonization of the trans-invertomers is sterically unfeasible. It is known, though, that the trans-form is predominantly populated in most 1,2-disubstituted aziridines[10]. Therefore, the conversions of HAE into OAH belong to reactions involving nitrogen inversion as one of the stages. Earlier, it has been demonstrated for this type of reaction (isomerization of 1,2-divinyl-aziridines into azepines) that this stage is the limiting one because of the low inversion barrier of the N atom[11]. In view of inversion barrier data available for N-alkylaziridines (∿ 18 kcal/mole[12]), it can be presumed that inversion cannot be the limiting stage for conversion of HAE into OAH.

EXPERIMENTAL

PMR spectra were measured on a Bruker-WM-400 and Bruker WH-90 spectrometer (400 and

90 MHz) in $CDCl_3$ relative to TMS (internal standard). Two-dimensional NOESY NMR spectra were recorded at 400 MHz, optical rotation angles were measured on a Perkin Elmer-141 polarimeter, CD spectra with a JASCO J-500 A spectropolarimeter fitted with a DP-500 N processor. IR spectra were recorded on a Specord IR-75 and Perkin Elmer 580 B spectrophotometer.

HAE synthesis and lactonization were monitored by GLC using a Chrom-5 chromatograph (column dimensions 3.5 x 1200 mm, phase SE-30, Chromosorb WAW as carrier (100-120 mesh). Analysis of mixtures of diastereomers for 3a,b and 4a,b was conducted on a Du Pont 830 Prep chromatographer (Zorbax Sil column 4.6 x 250 mm, ether-hexane and dioxane-hexane used as eluent).

Preparative separation of mixtures was carried out with a Zorbax Sil column (21.1 x 250 mm). R_f values were measured by TLC on Merck UV_{254} plates with ethyl acetate used as eluent.

General Synthetic Procedure for the Preparation of 1-β-Hydroxyalkylaziridine-2-carboxylic Esters 1a,b-4-a,b. A mixture of amino alcohol (5 mM) and Et_3N (11 mM, 1.54 ml) was added dropwise to a solution of 1,2-dibromopropionic acid ester (5 mM) in absolute MeCN (50 ml) at 0^oC with stirring. The stirring was continued for 1 hr at 60^oC. After removal of solvent *in vacuo* the products were extracted from the solid residue with absolute ether and chromatographed on a Silica gel (40-100 μ) column (2 x 4 cm). The ether was evaporated under vacuum and the residue was purified by HPLC.

General Procedure for Lactonization of 1-β-Hydroxyalkylaziridine-2-carboxylic Esters 1a,b-4a,b. Cs_2CO_3 (1.4 g) and dicyclohexano-18-crown-6 (0.15 g) were added to a solution of hydroxyester epimer (1 mM) in absolute MeCN (5 ml) with substituent stirring for 3.5 hrs (60 hrs in the case of 3a,b) at 20^oC. The solvent was evaporated *in vacuo* and the residue was purified as described in the preceding procedure.

The rate of lactonization for HAE epimers 1a,b-4a,b was compared by assessing the extent of conversion into MeCN ($2\cdot10^{-4}$ mole/l) in the presence of equimolar amounts of DBU. The extent of conversion was measured by GLC and HPLC (for 3a,c, 4a,b). All characteristics of 1-β-hydroxyalkylaziridine-2-carboxylic esters and 4-oxa-1-azabicyclo[4.1.0]heptane-5-ones are given in Table 4.

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