Asymmetric nitrogen
81.* Diastereomeric derivatives of 1-alkoxy-2,2-bis(trifluoromethyl)aziridines. Structure and absolute configuration

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The ^{1}H NMR spectra of *O*-derivatives of 1-hydroxy-2,2-bis(trifluoromethyl)aziridine containing such substituents as EtO_2CCH_2, (*R/S*)-$RO_2CCH(Me)$ (R = Me, Pr^i, or Bu^t), (*R/S*)-$H_2NC(O)CH(Me)$, and (*R*)-$H_2NC(O)CH(Me)$ were analyzed. Both of the diastereomerically pure amides of the latter type were isolated. The validity of the ^{1}H NMR criteria, which were suggested for the determination of absolute configurations of diastereomers of *N*-alkoxyaziridines, was confirmed by X-ray diffraction study of the (*R,R*)-amide.

Key words: 1-alkoxy-2,2-bis(trifluoromethyl)aziridines, esters, amides, diastereomers; optical activity; absolute configuration; ^{1}H NMR spectra; X-ray diffraction study.

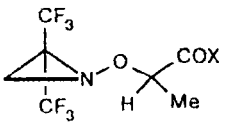
Previously, thermally and chemically stable compounds with an asymmetric nitrogen atom have been synthesized, namely, derivatives of 1-hydroxy-2,2-bis(trifluoromethyl)aziridine,[2—7] 1-hydroxy-2-methyl-2-trifluoromethylaziridine,[5] and 1-hydroxy-3-methyl-2,2-bis(trifluoromethyl)aziridine[8] and nonsubstituted 1-hydroxy-2,2-bis(trifluoromethyl)aziridine (**1**).[9,10] However, the absolute configurations of the N atom in optically active aziridine **1** and in its enantiomerically and diastereomerically pure *O*-derivatives[10] have not been established. The determined inversion barriers of the N atom ($\Delta G^{\neq}$) were found to be 27—30 kcal mol^{-1} (see Refs. 5, 6, and 10—13).

O-Carboxymethyl and *O*-(1-carboxy-1-methyl)ethyl derivatives of aziridine **1** were resolved into antipodes, which were converted into esters and acid chlorides, and then into various amides with retention of the configuration of the N atom.[11—13]

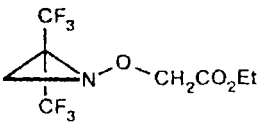
For two diastereomeric α-phenylethylamides of *O*-aziridinoglycolic acid, the absolute configuration of the chiral N atom was determined by X-ray diffraction analysis. Therefore, the absolute configurations of the initial aziridinoglycolic acids were also established. The absolute configurations of *O*-aziridino-2-hydroxybutyric acids were determined based on the chiroptical characteristics.[13]

Previously, the NMR criteria have been developed for the determination of the stereochemistry of these compounds.[8] However, simple methods for establishing the absolute configuration of the N atom are unavailable. Recently, we have solved this problem for diastereomeric derivatives of 1-hydroxyaziridine-2,2-dicarboxylic acids by ^{1}H NMR spectroscopy.[1] This work is devoted to the studies of their 2,2-bistrifluoromethyl analogs.

Esters of *O*-aziridinolactic acid **2a—c** and model ester **3** were prepared by reactions of the corresponding eters of hexafluoroacetone oxime with CH_2N_2 followed by photolysis of the intermediate triazolines.[6]



2a—d



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X = MeO (**a**), Pr^{i}O (**b**), Bu^{t}O (**c**), NH_2 (**d**)

* For Part 80, see Ref. 1.

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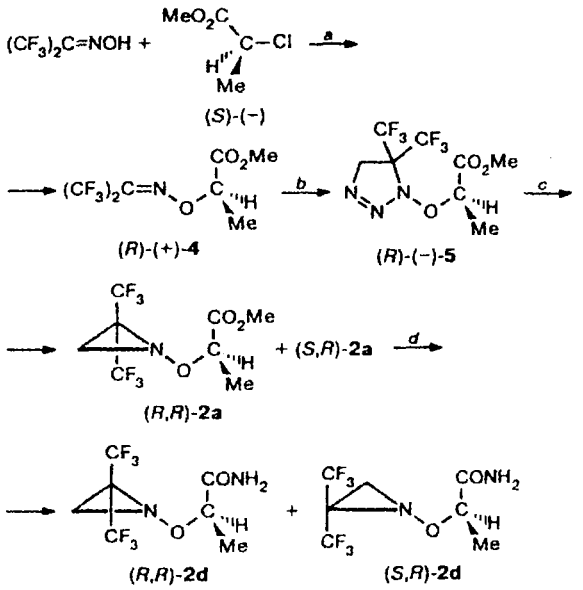
Amide **2d** was prepared by ammonolysis of ester **2a**.[6]

Optically active diastereomers **2a** and **2d** were synthesized according to Scheme 1.

Scheme 1



Reagents: *a*. K_2CO_3, MeCN; *b*. CH_2N_2, Et_2O; *c*. CF_3CO_2H, $-N_2$; *d*. 1) NH_3/MeOH, 2) crystallization.

Alkylation of hexafluoroacetone oxime with methyl (*S*)-(−)-2-chloropropionate[14] (prepared from methyl (*S*)-(−)-lactate[15]) gave ester (*R*)-(+)-**4**, as in the case of an analogous reaction reported previously.[1] The formation of product (*R*)-(+)-**4** was accompanied by inversion of the configuration of the C(2) atom. Under the action of CH_2N_2, the latter compound was transformed into triazoline (*R*)-(−)-**5** and its acid-catalyzed decomposition gave a mixture of diastereomers (*R,R*)- and (*S,R*)-**2a**. Ammonolysis of this mixture followed by fractional crystallization afforded diastereomerically pure (according to the ^1H NMR data) amides (*R,R*)-(−)-**2d** and (*S,R*)-(+)-**2d**.

An unambiguous assignment of the signals for the protons of the ring in the ^1H NMR spectra of aziridines **2a—d** and **3** was made[6—8,12] based on the values of the stereospecific long-range spin-spin coupling constants $^4J_{H_a,CF_3\text{-}B}$ (2.6—3.0 Hz) > $^4J_{H_a,CF_3\text{-}A}$ (≈ 1 Hz) as well as taking into account the change in the chemical shift induced by the aromatic solvent (ASIS effect, $\Delta\delta = \delta(CCl_4) - \delta(C_6D_6)$), which is substantially larger for the H_a proton than for the H_b proton ($\Delta\delta$ 0.06—0.18).

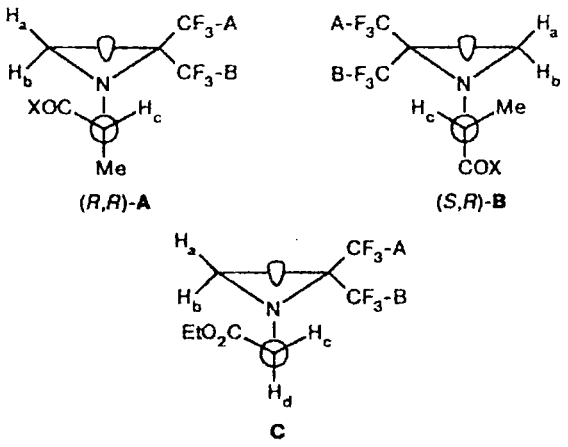
The diastereomers of aziridines **2a—d** are readily divided into two series (~2 : 1) according to the equilibrium ratio resulting from the inversion epimerization and the parameters of the ^1H NMR spectra (Table 1). These series differ substantially in the chemical shifts of the protons of the Me group ($\Delta\delta$ 0.10—0.13) and of the H_b protons ($\Delta\delta$ 0.14—0.16) (the chemical shifts of the H_a and H_c protons are virtually identical). It should be noted that the chemical shifts of the H_a, H_b, and H_c protons in the spectra of esters **2a,b** and model compound **3** have similar values.

As in the case of dimethyl aziridine-2,2-dicarboxylates,[1] these regularities can be explained by the preferred populations of the conformations, namely, **A** and **B** (for the major and minor diastereomers, respectively) for aziridines **2a—d** and **C** for aziridine **3**. In these conformations, nonbonded interactions between the substituents and the lone electron pairs of the N and O atoms are minimized. It is evident that conformation **A** is thermodynamically favorable because the conformational energy of the CO_2Me group is smaller than

Table 1. Equilibrium ratio and selected parameters of the ^1H NMR spectra (δ) of the diastereomers of aziridines **2a—d** and **3** (CCl_4 and CD_3OD were used as the solvent for **2a—c** and **2d**, respectively)

Compound	X	Configuration	Equilibrium concentration (%)	δMeC	$\Delta\delta$MeC	δH_a	δH_b	$\Delta\delta H_b$ (H_aH_b)	$\delta H_c(H_d)$
2a	MeO	*RR/SS*	63	1.26	0.12	2.53	2.98	0.15	4.46
		SR/RS	37	1.38	—	2.53	2.83	—	4.46
2b	PrⁱO	*RR/SS*	66	1.24	0.12	2.49	2.95	0.16	4.35
		SR/RS	34	1.36	—	2.44	2.79	—	4.35
2c	BuᵗO	*RR/SS*	66	1.21	0.10	2.48	2.93	0.16	4.24
		SR/RS	34	1.31	—	2.43	2.77	—	4.24
2d	NH_2	*RR/SS*	68	1.22	0.12	2.69	3.15	0.14	4.28
		SR/RS	32	1.34	—	2.73	3.01	—	4.27
(−)-**2d**	NH_2	*RR*	—	1.17 (d)[a]	0.13	2.69 (dq)[b]	3.14 (dq)[c]	0.14	4.24 (q)
(+)-**2d**		*SR*	—	1.30 (d)[a]	—	2.73 (dq)[d]	3.00 (dq)[e]	—	4.26 (q)
3	—	—	—	—	—	2.54	2.96	(0.42)	4.37 (4.25)

[a] ^3J = 7.0 Hz. [b] ^2J = −5; $^4J_{H_a,CF_3\text{-}B}$ = 2.8 Hz. [c] $^4J_{H_b,CF_3\text{-}A}$ = 1.1 Hz. [d] ^2J = −5.2; $^4J_{H_a,CF_3\text{-}B}$ = 2.7 Hz. [e] $^4J_{H_b,CF_3\text{-}A}$ = 1.0 Hz.



that of the Me substituent (1.27 and 1.70 kcal mol^{-1}, respectively[16]).

The above-considered regularities of the changes in the parameters of the ^{1}H NMR spectra (see Table 1) in relation to the configuration of the diastereomers can be explained based on the above-mentioned models. The major diagnostic difference between diastereomers **A** and **B** is the downfield shift of the signal of the methyl protons of diastereomer **B**. This shift corresponds to the arrangement of the Me group in diastereomer **B** in the vicinity of the plane of the aziridine ring, which is the deshielding zone of aziridine.[17]

It thus follows that the diastereomers of alkoxyaziridines **2a—d** with the relatively shielded MeC group have conformation **A**, while the diastereomers with the deshielded MeC group have conformation **B**. The validity of the above-considered ^{1}H NMR criteria was unambiguously confirmed by X-ray diffraction analysis. The *R* configuration of the N atom (Figs. 1 and 2, Tables 2—5) was established for high-melting (−)-diastereomer **2d** (the major diastereomer in the equilibrium mixture),

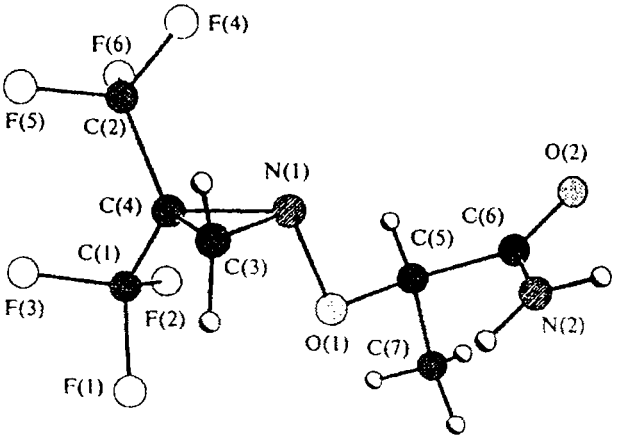


Fig. 1. Molecular structure of aziridine (*R,R*)-(−)-**2d**.

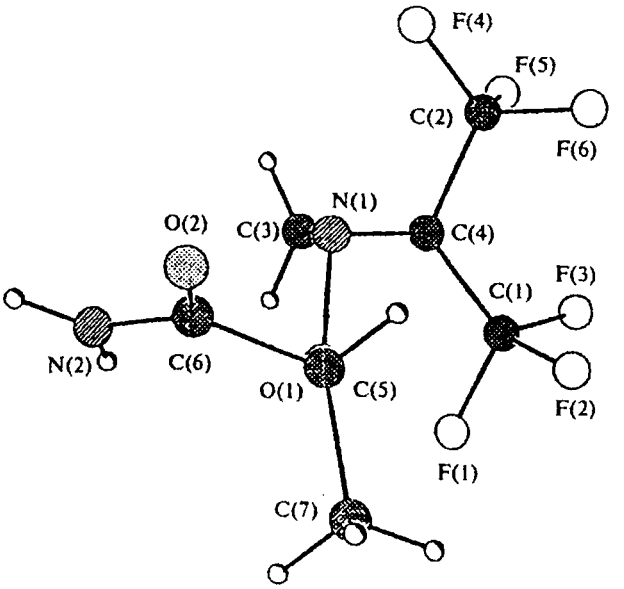


Fig. 2. Projection of the molecule of aziridine (*R,R*)-**2d** along the C(5)—O(1) axis.

Table 2. Coordinates of nonhydrogen atoms (×10^4) and isotropic thermal parameters (U_{eq}×10^3) in the molecule of (*R,R*)-(−)-**2d**

Atom	*x*	*y*	*z*	U_{eq}/Å
F(1)	1788(11)	4111(23)	3890(9)	5.4(3)
F(2)	1691(12)	117(26)	4337(9)	6.0(3)
F(3)	−224(10)	2541(27)	4079(8)	5.3(3)
F(4)	−1422(8)	−1422(1)	956(7)	6.6(6)
F(5)	−2328(7)	1032(19)	1978(7)	7.0(6)
F(6)	−1048(8)	−2307(21)	2809(8)	7.1(7)
O(1)	2883(10)	1016(22)	2487(8)	3.8(4)
O(2)	4471(13)	−4059(32)	1194(10)	4.7(3)
N(1)	1335(13)	410(30)	1722(10)	2.9(3)
N(2)	4066(14)	355(33)	712(11)	3.6(3)
C(1)	890(17)	1944(37)	3607(14)	3.4(4)
C(2)	−1150(17)	−382(33)	2005(13)	3.7(4)
C(3)	501(18)	2815(41)	1385(14)	3.6(4)
C(4)	297(15)	1231(0)	2365(12)	1.9(3)
C(5)	3794(20)	−1275(44)	2560(17)	3.3(4)
C(6)	4119(17)	−1714(40)	1402(14)	3.0(4)
C(7)	5292(22)	−870(48)	3588(16)	5.4(5)

Table 3. Bond lengths (*d*) in the molecule of (*R,R*)-(−)-**2d**

Bond	*d*/Å	Bond	*d*/Å
F(1)—C(1)	1.355(21)	N(1)—C(3)	1.431(24)
F(2)—C(1)	1.317(20)	N(1)—C(4)	1.477(21)
F(3)—C(1)	1.368(21)	N(2)—C(6)	1.321(25)
F(4)—C(2)	1.295(18)	C(1)—C(4)	1.433(20)
F(5)—C(2)	1.303(18)	C(2)—C(4)	1.513(19)
F(6)—C(2)	1.345(19)	C(3)—C(4)	1.476(23)
O(1)—N(1)	1.457(13)	C(5)—C(6)	1.517(28)
O(1)—C(5)	1.425(24)	C(5)—C(7)	1.529(23)
O(2)—C(6)	1.280(26)		

Table 4. Bond angles (ω) in the molecule of (*R,R*)-(−)-**2d**

Angle	ω/deg	Angle	ω/deg
N(1)—O(1)—C(5)	108.1(12)	F(4)—C(2)—C(4)	111.2(11)
O(1)—N(1)—C(4)	107.6(8)	N(1)—C(3)—C(4)	61.1(9)
O(1)—N(1)—C(3)	109.1(12)	C(2)—C(4)—C(3)	114.2(9)
C(3)—N(1)—C(4)	60.9(9)	C(1)—C(4)—C(3)	124.2(11)
F(2)—C(1)—F(3)	103.2(13)	C(1)—C(4)—C(2)	115.4(13)
F(1)—C(1)—F(3)	102.1(14)	N(1)—C(4)—C(2)	58.0(8)
F(1)—C(1)—F(2)	103.9(13)	N(1)—C(4)—C(3)	112.2(8)
F(3)—C(1)—C(4)	113.0(13)	N(1)—C(4)—C(1)	120.3(9)
F(2)—C(1)—C(4)	115.8(14)	O(1)—C(5)—C(7)	107.8(16)
F(1)—C(1)—C(4)	117.0(13)	O(1)—C(5)—C(6)	111.1(16)
F(5)—C(2)—F(6)	106.1(12)	C(6)—C(5)—C(7)	109.5(16)
F(4)—C(2)—F(6)	109.1(13)	N(2)—C(6)—C(5)	117.7(17)
F(4)—C(2)—F(5)	107.9(11)	O(2)—C(6)—C(5)	116.8(17)
F(6)—C(2)—C(4)	110.3(11)	O(2)—C(6)—N(2)	125.4(16)
F(5)—C(2)—C(4)	111.9(12)		

Table 5. Selected torsion angles (τ) in the molecule of (*R,R*)-(−)-**2d**

Angle	τ/deg
N(1)—O(1)—C(5)—C(6)	73.6(17)
N(1)—O(1)—C(5)—C(7)	−166.4(14)
C(5)—O(1)—N(1)—C(4)	130.1(13)
C(5)—O(1)—C(5)—C(3)	−165.3(14)
O(1)—N(1)—C(4)—C(1)	−11.3(16)
O(1)—N(1)—C(4)—C(2)	−152.1(11)
O(1)—N(1)—C(4)—C(3)	102.4(13)
O(1)—N(1)—C(3)—C(4)	−100.1(11)
C(3)—N(1)—C(4)—C(1)	−113.7(15)
C(3)—N(1)—C(4)—C(2)	105.5(14)
N(1)—C(3)—C(4)—C(1)	−102.0(13)
N(1)—C(3)—C(4)—C(2)	107.2(15)
O(1)—C(5)—C(6)—N(2)	24.5(23)
O(1)—C(5)—C(6)—O(2)	−157.7(15)
C(7)—C(5)—C(6)—N(2)	−94.5(20)
C(7)—C(5)—C(6)—O(2)	83.4(21)

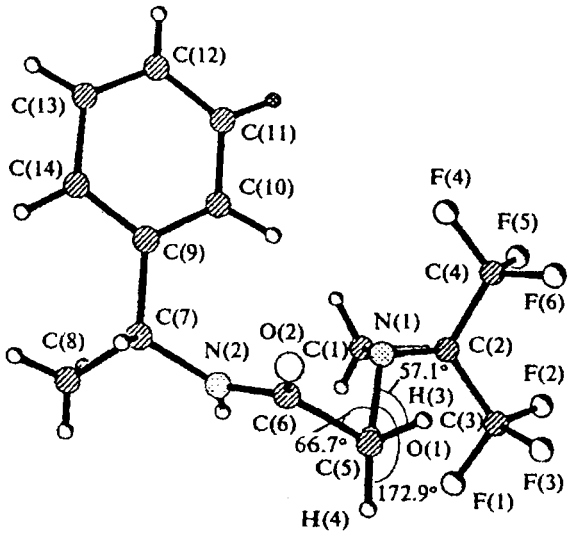


Fig. 3. Projection of the molecule of (*S,S*)-(−)-1-(*N*-α-phenylethylcarbamoylmethoxy)-2,2-bis(trifluoromethyl)aziridine[13] along the CH_2—O axis (see Table 6).

which contains the relatively more shielded MeC group (see Table 1) and the asymmetric carbon atom with the known *R* configuration. In addition, analogous regularities have been observed previously for esters and amides of 1-alkoxyaziridine-2,2-dicarboxylic acids that contain analogous 1-alkoxy substituents.[1]

The conformation of aziridine (*R,R*)-(−)-**2d** observed in the crystal (see Fig. 2) is close to form **A**, as in the case of the 2,2-dicarbamoyl analog.[1] Analogously, in the case of the (*S,S*)-(−)-diastereomer of α-phenylethylamide, which corresponds to ester **3**, the conformation in the crystal is close to form **C** (Fig. 3, Table 6; for the

Table 6. Atomic coordinates in the molecule of (*S,S*)-(−)-1-(*N*-α-phenylethylcarbamoylmethoxy)-2,2-bis(trifluoromethyl)aziridine[13]

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
F(1)	0.6165	−0.0303	1.1556	C(4)	0.6293	−0.1641	0.8251	H(3)	0.4444	0.0753	0.8074
F(2)	0.7545	−0.0972	1.0542	C(5)	0.3936	0.0662	0.8833	H(4)	0.3875	0.1255	0.9332
F(3)	0.6795	0.0226	0.9619	C(6)	0.2785	0.0397	0.8228	H(5)	0.2419	−0.0317	0.9914
F(4)	0.5519	−0.2097	0.7531	C(7)	0.1041	−0.0483	0.8521	H(6)	0.0658	−0.0016	0.7930
F(5)	0.7049	−0.2260	0.8688	C(8)	0.0258	−0.0593	0.9796	H(7)	0.0633	−0.1171	1.0397
F(6)	0.6801	−0.1060	0.7382	C(9)	0.1113	−0.1371	0.7681	H(8)	0.0216	−0.0063	1.0113
O(1)	0.4366	0.0039	0.9853	C(10)	0.2133	−0.1788	0.7362	H(9)	−0.0496	−0.0713	0.9477
O(2)	0.2506	0.0707	0.7077	C(11)	0.2195	−0.2587	0.6562	H(10)	0.2874	−0.1506	0.7550
N(1)	0.4603	−0.0804	0.9129	C(12)	0.1226	−0.2979	0.6077	H(11)	0.2835	−0.2996	0.6839
N(2)	0.2148	−0.0155	0.9002	C(13)	0.0211	−0.2579	0.6349	H(12)	0.1278	−0.3545	0.5607
C(1)	0.4751	−0.1538	1.0171	C(14)	0.0129	−0.1758	0.7156	H(13)	−0.0524	−0.2807	0.6074
C(2)	0.5769	−0.1142	0.9471	H(1)	0.4618	−0.1428	1.1043	H(14)	−0.0578	−0.1537	0.7513
C(3)	0.6565	−0.0534	1.0314	H(2)	0.4455	−0.2160	0.9905				

structural data see Ref. 13, but the atomic coordinates are lacking).

The major geometric parameters of aziridine (*R,R*)-(−)-**2d** are similar to those reported previously for two 1-alkoxy-2,2-bis(trifluoromethyl)aziridines.[13] Strong nonbonded interactions between the substituents are manifested in the elongation of the C(4)—C(1) bond compared to the C(4)—C(2) bond and in the increase in the N(1)—C(4)—C(1) and C(3)—C(4)—C(1) bond angles compared to the N(1)—C(4)—C(2) and C(3)—C(4)—C(2) bond angles, respectively (see Tables 3 and 4).

Experimental

The ^{1}H NMR spectra were recorded on Tesla BS-487C (80 MHz) and Varian HA-100 (100 MHz) spectrometers with HMDS as the internal standard. The optical rotation was measured on a Perkin—Elmer 111 polarimeter.

Methyl (*S*)-(−)-lactate was prepared from (*S*)-(−)-lactic acid by treating with an ethereal solution of CH_2N_2 at 0 °C; the yield was 60%, b.p. 65—70 °C (70 Torr), $[\alpha]_D^{15}$ −10.1° (neat) (*cf.* Ref. 15).

Methyl (*S*)-(−)-2-chloropropionate. A solution of (*S*)-(−)-methyl lactate (25.8 g, 0.25 mol) and $SOCl_2$ (33.3 g, 0.23 mol) in anhydrous ether (50 mL) was kept at 20 °C for 16 h and then concentrated. The residue was heated at 80—100 °C for 0.5 h and distilled. The yield was 21.4 g (72%), b.p. 64—67 °C (55 Torr), n_D^{20} 1.4189, $[\alpha]_D^{20}$ −26° (pure) (*cf.* Ref. 14).

Methyl *O*-(hexafluoroisopropylideneamino)-(*R*)-(+)-lactate, (*R*)-4. Finely dispersed K_2CO_3 (6.9 g, 50 mmol) and then methyl (*S*)-(−)-2-chloropropionate (6.1 g, 50 mmol) were added with cooling (0—5 °C) and stirring to a solution of hexafluoroacetone oxime (9.1 g, 50 mmol) in MeCN (30 mL). The reaction mixture was stirred for 10 h and then kept at 20 °C for 10 h. The precipitate was separated and washed with MeCN. The filtrate was concentrated *in vacuo*, and the residue was distilled. The product was obtained in a yield of 7.8 g (64%), b.p. 64—65 °C (42 Torr), n_D^{20} 1.3435 (*cf.* the racemate, Ref. 6), $[\alpha]_D^{20}$ +3.9° (*c* 5.7, $CHCl_3$).

Methyl *O*-[5,5-bis(trifluoromethyl)-Δ^2-1,2,3-triazolino]-(*R*)-(−)-lactate, (*R*)-5. The ester of oxime (*R*)-4 (8.1 g, 30 mmol) was added to a twofold excess of CH_2N_2 in ether (15 mL). The reaction mixture was kept at 29 °C for 4 days. After the removal of the solvent, the residue was chromatographed on a column with silica gel (L100/250, $CHCl_3$ as the eluent). The product was obtained in a yield of 4 g (43.3%), n_D^{20} 1.3885 (*cf.* the racemate, Ref. 6), $[\alpha]_D^{20}$ −18.4° (*c* 9.3, $CHCl_3$).

Methyl (*R,R*/*S,R*)-*O*-[2,2-bis(trifluoromethyl)aziridino]-lactate, (*S,R*/*R,R*)-2a. CF_3COOH (2 mL) was added to a solution of triazoline (R)-5 (1.5 g, 11 mmol) in anhydrous CH_2Cl_2 (15 mL). The reaction mixture was kept at 20 °C for 1 h. The mixture was concentrated *in vacuo*, and the residue was distilled. The product was obtained in a yield of 2.9 g (~100%) (a mixture of diastereomers, see Table 1), b.p. 78 °C (35 Torr), n_D^{20} 1.3669 (*cf.* the racemate, Ref. 6), $[\alpha]_D^{20}$ −29.9° (*c* 9, $CHCl_3$).

(*R,R*)-(−)- and (*S,R*)-(+)-[2,2-Bis(trifluoromethyl)-aziridino]lactamides, (*R,R*)-2d and (*S,R*)-2d. A solution of a mixture (2.4 g, 7 mmol) of diastereomers (*S,R*/*R,R*)-**2a** and NH_3 (1 g, 6 mmol) in anhydrous MeOH (5 mL) was kept at 20 °C for 1 month. The reaction mixture was concentrated *in vacuo* to obtain a mixture of diastereomers (*S,R*/*R,R*)-**2d** in a yield of 1.7 g (91.4%), m.p. 79—81 °C (for the racemate, m.p. 68—70 °C, *cf.* Ref. 6). The product was dissolved in benzene (100 mL), and the solution was concentrated to 10 mL over 1 week. The crystals that precipitated were separated and recrystallized from MeOH until the melting point became constant. Diastereomerically pure product (*R,R*)-(−)-**2d** was obtained in a yield of 0.7 g (41.2%), m.p. 111 °C (for the diastereomerically pure racemate, m.p. 101 °C, *cf.* Ref. 6), $[\alpha]_D^{20}$ −69.4° (*c* 2.8, $CHCl_3$). After concentration of the mother liquor, the residue (1 g) was recrystallized from CCl_4 (control by the ^{1}H NMR spectra). Diastereomerically pure product (*S,R*)-(+)-**2d** was obtained in a yield of 0.2 g (11.7%), m.p. 55—56 °C, $[\alpha]_D^{20}$ +31.8° (*c* 1.5, $CHCl_3$).

X-ray diffraction study of aziridine (*R,R*)-(−)-2d was carried out on an automated Nonius CAD-4 diffractometer (Mo-Kα radiation, graphite monochromator, θ/2θ scanning technique, θ_{max} = 23°). A total of 949 independent reflections were measured of which 382 reflections with $I > 1.5\sigma(I)$ were used for solving the structure. The colorless crystals of (*R,R*)-(−)-**2d** belong to the monoclinic system, at 20 °C a = 9.321(3) Å, b = 5.076(8) Å, c = 11.838(4) Å, β = 109.50(3)°, V = 528 Å^3, d_{calc} = 1.673 g cm^{-3}, Z = 2, $F(000)$ = 268, $C_7H_8N_2O_2F_6$, M = 266.1, space group $P2_1$.

The structure was solved by the direct method using the MULTAN-80 program and refined isotropically by the full-matrix least-squares method using the SHELX-76 program. The positions of the hydrogen atoms were calculated geometrically and refined using the riding model. The refinement was converged to R = 6.4%, GOF = 1.25. The molecular geometry and crystal packing were calculated using the PARST program.

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