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ASYMMETRICAL NONBRIDGEHEAD NITROGEN—XXIII

CHIRAL 3,3-BIS(TRIFLUOROMETHYL)DIAZIRIDINES[1]

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Abstract—By means of the reaction of *O*-tosyloxime **1a** with propargyl amine, esters of glycine and (*S*)-α-alanine, β-acetoxyethyl amine and β-dimethylaminoethyl amine functionally substituted 3,3-*bis*(trifluoromethyl)diaziridines **2a–g** have been obtained. In the reactions with more bulky amines, (*S*)-phenylalanine Et ester, (*R, S*)-α-phenylethyl amine and *t*-butyl amine, **1a** acts as a tosylating reagent. The ester group in diaziridine **2e** is readily saponified by alcoholic alkali, whereas diaziridine **2c** is rearranged in these conditions with ring-expansion. Complete asymmetric transformation has been found to take place on the formation of the solid phase of diastereomers **2d** and **2j**, and a closed cycle of diastereomeric transformations has been accomplished. Diaziridine **2g** with chiral centres only at the nitrogen atoms has been obtained with the optical purity of 85.5% by resolution via salt **5c** with d-(+)-camphor-3-carboxylic acid. The absolute configuration of (+)-**2g** and its quaternary salt, (+)-**2h**, has been determined from CD spectra. Optically active (−)-**2h** salt (optical purity 2.0%) has been also obtained by asymmetric synthesis on the basis of 1-10-camphorsulphonyl oxime **1b**. From the kinetics of **2g, h** racemization and **2d, e, i, j, k** epimerization the energy parameters of the inversion of N atoms in 3,3-*bis*(trifluoromethyl)diaziridines have been determined.

Configuration stability of N atoms in 3,3-*bis*(trifluoromethyl)diaziridines is sufficient for the separation of optical isomers ($\Delta G^{\neq} \simeq 25$ kcal/mole).[2] By means of asymmetric synthesis, based on hexafluoroacetoxime 1-10-0-camphorsulphonate, optically active 1-ethyl and 1-iso-propyl derivatives containing only the nitrogen chiral centre were previously obtained, but their enantiomeric purity was not determined. It can be assumed not to be very high since the optical yield of this reaction, e.g. for (+)-(1*R*, 2*R*)-1,3,3-trimethyldiaziridine, amounts to only 9.9%.[3,4] Complete separation of enantiomeric diaziridines was accomplished in the presence of a functional group suitable for the insertion of an asymmetric substituent.[5] Consequently, having extended the reaction described in Ref. 6 to cover the functionally substituted amines (Scheme 1) we studied the synthesis of diaziridines **2a–g** and the possibility of separating their optical isomers.

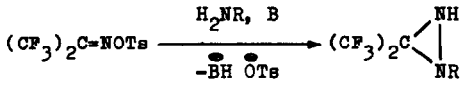
O-Tosyloxime **1a** is stable to Beckmann rearrangement,[6] and diaziridines **2a, c, e–g** are obtained in good yield (Table 1). Reaction (1) is carried out in DMF (synthesis of **2a** without a solvent) in the presence of Et_3N. Diaziridine **2g** is synthesized with *t*-BuONa or NaOH used as a base (B) to prevent the concurrent bonding of TsOH with the high-basicity Me_2N group. In the latter case, the yield of **2g** is substantially increased when the reaction is provided in a heterophase system (CH_2Cl_2/H_2O). The relatively low yield of **2b, d** (Table 1) can be explained by the intermolecular condensation of the initial methyl esters of amino acids. For the corresponding ethyl esters such condensation is hindered,[7] and, therefore, the yield of the products, **2c, e** increases.

O-Tosyloxime **1a** in the reactions with (*S*)-phenyl alanine ethyl ester, (*R, S*)-α-phenylethyl amine and *t*-butyl amine acts as a tosylating reagent (Scheme 2).

Thus, with an increase in the volume of the *R* substituent in amines, steric interaction with CF_3 groups becomes the deciding factor in the reaction with **1a**, and the nucleophilic attack is directed at the *S* atom of the sulphonyl group, whereas the less bulky amines attack the most electrophilic carbon atom of the C=N bond in **1a** with the formation of intermediate aminal and then the diaziridine ring.[3,6]

The presence of electronegative CF_3 groups ensures a high thermal and chemical stability of diaziridines **2a–g**: these compounds are stable to heating up to 200°, to the action of organic acids and dry HCl in inert solvent. Diaziridine **2g**, when treated with MeI in ether or MeCN, yields stable quaternary salt **2h** (Scheme 3).

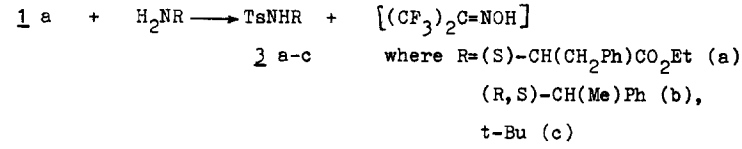
Nonfluorinated analogue of **2g**, 1 - (β - dimethyl-



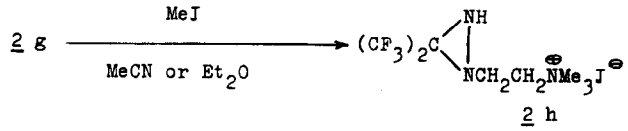
1 a 2 a-g

where R= $CH_2C{\equiv}CH$ (a)
CH_2CO_2Me (b)
CH_2CO_2Et (c)
(S)-$CH(Me)CO_2Me$ (d)
(S)-$CH(Me)CO_2Et$ (e)
CH_2CH_2OCOMe (f)
$CH_2CH_2NMe_2$ (g)

Scheme 1.



Scheme 2.



Scheme 3.

Table 1. Characteristics of synthesized compounds

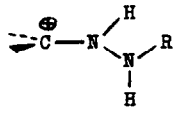
Compound	Yield %	B.p.(mm) or m.p.°C	n_D^{20}	IR, ν, cm^{-1} CO	IR, ν, cm^{-1} NH	Analysis, % found / calcd. C	H	N
2 a	65.0	50 (66)	1.3553	2150 (C≡C)	3260	-	-	12.70 12.84
2 b	30.4	81-82 (20)	1.3642	1725	3225	28.71 28.58	2.47 2.40	11.14 11.11
2 c	85.2	77-78 (12)	1.3677	1720	3225	31.58 31.59	3.11 3.03	10.45 10.53
2 d	30.01	66-68 (14) 50-51	-	1740	3245	31.59 31.59	3.08 3.03	10.69 10.53
2 e	69.1 100 [a]	78-80 (14)	1.3671	1730	3245	34.32 34.27	3.79 3.60	9.98 9.99
2 f	66.2	81-82 (16)	1.3674	1710	3225	-	-	10.63 10.53
2 g	52.2 [b] 68.0 [c]	81-82 (55) 29-30	-	-	3170	33.51 33.47	4.49 4.41	16.53 16.73
2 h	81.0 89.6 [d] 35.0 [e]	154-155 (dec.) 150-152 (dec.) 153-155 (dec.)	-	-	3195	24.43 24.44	3.50 3.59	10.67 10.69
2 i	83.0 100 [f]	223 (dec.)	-	1590	3150	24.69 24.83	1.87 1.74	9.63 9.64
2 j	74.8	86-86.5	-	1705	3270	28.76 28.59	2.56 2.40	11.24 11.11

Table 1. (*Contd*).

2 k	96.5	64-65	-	1680	3175 3335 3430	28.76 28.70	2.99 2.81	16.69 16.73
3 a	26.8	77-78	-	1715	3270	62.33 62.23	6.03 6.09	4.11 4.03
3 b	62.7	81-82.5	-	-	3250	65.54 65.43	6.30 6.22	4.95 5.09
3 c	82.6[g]	113-114[g]	-	-	3270	-	-	-
4	58.9	110-111	-	1745	3235	27.24 27.29	1.19 0.91	12.80 12.72
5 a	88.1[h] 37.6	161.5-162.5 (dec.) 162-163 (dec.)	-	1730	3160	42.07 42.15	5.79 5.83	8.60 8.67
5 b	58.2	139-140 (dec.)	-	1725 1738	3260	49.27 49.27	3.99 4.13	6.86 6.89
5 c	100 27.4[i]	54-57 67-69	-	1745	3140	48.73 48.32	5.94 6.08	9.43 9.39

(a) By reaction of **2j** with $MeCHN_2$; (b) method A; (c) method B; (d) by reaction of (+)-**2g** with MeI; (e) according to Scheme 9; (f) from **2j** by reaction with KOH; (g) cf. Ref. 16; (h) after 2 recrystallizations from MeCOEt; (i) after 3 recrystallizations from benzene-*n*-hexane mixture.

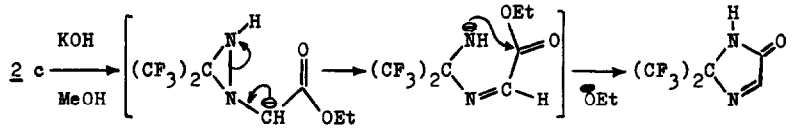
aminoethyl) - 3,3 - dimethyldiaziridine is readily hydrolyzed in acid medium,[2] whereas **2g** in these conditions is absolutely stable because CF_3 groups destabilize carbocation (A) through which the acid hydrolysis of 3,3-dialkyldiaziridines is actualized (see p. 146 in Ref. 8).



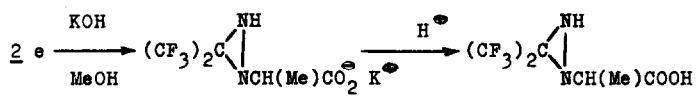
A

The seemingly insignificant structural differences of **2c** and **2e** diaziridines result in their radically different behaviour in the conditions of alkaline hydrolysis. Under the action of alcoholic alkali, **2c** is rearranged with ring expansion (Scheme 4), which seems to be caused by the deprotonation of the N substituent methylene group under the action of OH^- followed by the opening of the diaziridine ring and the nucleophilic attack of the azaanion upon the ester group with the formation of the imidazolone. For nonfluorinated diaziridines the ring was also observed to open by cleavage of the N–N bond with a simultaneous detachment of the proton from the N substituent α-carbon atom, but under acid and not base catalysis (see p. 149 in Ref. 8).

In the same conditions **2e** is easily saponified by alcoholic alkali with the formation of salt **2i** (Scheme 5). It can be assumed that the α-Me group, for electronic or steric reasons, prevents the detachment of the methine proton. Alkaline hydrolysis, as well as ammonolysis, of **2e** (Scheme 6) is not complicated by side reactions.

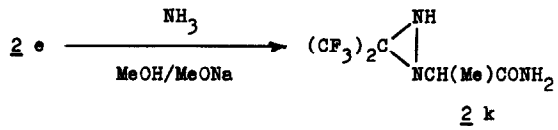


Scheme 4.



2 i **2 j**

Scheme 5.



Scheme 6.

Stereochemical lability of nitrogen chiral centres in **2d, e, i–k** makes these diaziridines a suitable model to study the thermodynamically controlled transformations (Scheme 7).

In the case of Me ester **2d** and acid **2j** complete asymmetric transformation was found to take place dur-

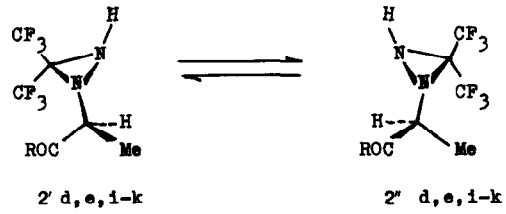
Table 2. Optically active diastereomeric and enantiomeric 3,3-*bis*(trifluoromethyl)diaziridines

Compound	Solvent (conc., vol.%)	Diastereomeric [a] (optical) purity	$[\alpha]_D^{20}$ deg.	$[\alpha]_{546}^{20}$ deg.
2d (E.M.[b])	CCl_4 (2.5)	45.8	-19.4	-23.4
	$CHCl_3$ (2.4)	43.8	-24.8	-29.3
	Me_2CO (2.9)	36.8	-18.6	-22.0
	MeCN (2.5)	33.5	-18.7	-22.1
2'd	CCl_4 (2.5)	100	-27.8	-32.9
	$CHCl_3$ (2.4)	100	-30.6	-36.2
	Me_2CO (2.9)	100	-37.9	-45.2
	MeCN (2.5)	100	-35.3	-42.1
2'' d[c]	CCl_4 (2.5)	100	-12.3	-15.4
	$CHCl_3$ (2.4)	100	-20.3	-23.9
	Me_2CO (2.9)	100	- 7.7	- 8.9
	MeCN (2.5)	100	-10.3	-12.0
2e (E.M.)	CCl_4 (2.2)	46.2	-23.7	-27.6
2'e	CCl_4 (2.2)	100	-33.8	-38.8
2'' e	CCl_4 (2.2)	100	-15.0	-17.9
2g	$n\text{-}C_6H_{14}$ (3.1)	(85.5)	+41.3	+49.2
2 h	MeOH (1.1)	(81.7)[d]	+34.9	+110.8(366nm)
2 h	MeOH (2.4)	(2.0)[e]	- 0.8	- 4.3 (366nm)
2 i	H_2O (2.8)	61.5[f]	-11.4	-12.3
2 i (E.M.)	H_2O (2.9)	29.9	- 2.2	- 2.4
2'i	H_2O (2.9)	100	-21.5	-25.6
2'' i	H_2O (2.9)	100	+ 6.0	+ 7.5
2 j (E.M.)	MeOH (3.7)	33.3	+11.8	-13.5
2'j	MeOH (3.7)	100	-26.5	-31.1
2'' j	MeOH (3.7)	100	- 4.5	- 4.7
2 k	Me_2CO (2.5)	54.4[g]	+ 7.9	+ 9.6
2 k (E.M.)	Me_2CO (2.5)	41.0	+ 2.8	+ 3.3
5 a	MeOH (2.8)	-	-16.9[h]	-21.0
5 b	MeOH (2.2)	-	-16.9[i]	-61.3
5 c	MeOH (2.7)	85.5[j]	+60.8	+72.3

(a) For **2d, e, i–k**, **5c** "P" corresponds to the content of 2' and 5' epimer. Determined by the NMR method; (b) Equilibrium mixture; (c) specific rotation of **2d, e, i, j** diastereomer has been found from formula:

$$[\alpha]_{2''} = \frac{[\alpha]_{equil.} - [\alpha]_{2'} \cdot P/100}{1 - P/100};$$

(d) obtained from (+)-**2g** with p = 81.7%; (e) product of asymmetric synthesis (Scheme 9); (f) isolated from reaction 5; (g) isolated from reaction 6; (h) after 3 recrystaltizations from MeCOEt; (i) after several recrystallization from MeCN; (j) after 2 recrystallizations from benzene-hexane mixture.



Scheme 7.

ing the formation of solid phase.[9] With the crystallization of the melt or with the removal of the solvent from solution containing a **2'd, j/2''d, j** equilibrium mixture (Table 2) only one diastereomer, **2'd, j** is formed. The absolute configuration of nitrogen atoms in the diastereomerically pure **2d, j** diaziridines obtained has not been established and is given tentatively.

Diastereomer **2'j** has also been obtained by complete vacuum sublimation from the **2j** melt (Table 2). Complete transformation of a **2'd, 2''d–2'j, 2'** equilibrium mixture into **2'd, j** indicates that the formation of solid phase (crystallization) is accompanied with inversional epimerization, the energy barrier of which for these compound in solution is not high (Table 4). The reverse process, **2'd, j → 2'd, 2''d–2'j, 2''dj**, can be observed polarimetrically or by means of the NMR method (Fig. 1). Thus, as in the case of *O* - (*α* - polyfluoroalkylbenzyl) - methylchlorophosphonates,[10] a closed cycle of diastereomeric transformations (Scheme 8) has been accomplished.

In the solid state it has proved impossible to obtain **2''d,j** or a **2'd, 2''d–2'j, 2''j** mixture. With low-temperature crystallization of **2'j** from $CHCl_3$, however, the mother solution is enriched with **2''j** diastereomer up to the ratio of **2'j/2''j** = 24/76 (equilibrium ratio in $CHCl_3$ is 44/56). The existence of **2d, j** in crystalline state only in the **2'd, j** form can be explained by a greater energy gain of the crystal lattice of one diastereomer as compared with the other or with a mixture of them. A smaller difference in solvation energies in solutions of diaziridines **2d, e, i–k** results in only a partial predominance of one of the epimers (Table 2), with the **2''d, j** epimer predominating for **2d, j**, i.e. the one with a higher energy of the crystal lattice. By treating **2'j** cooled to −70° with KOH methanol solution or $MeCHN_2$/ether solution it is possible to obtain diastereomerically pure diaziridines **2'i** and **2'e**, respectively (Scheme 8, Table 2) and, therefore,

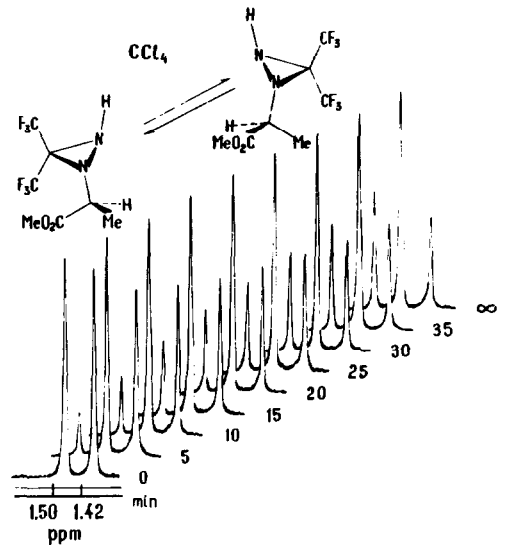
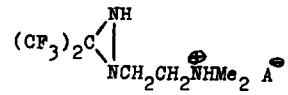


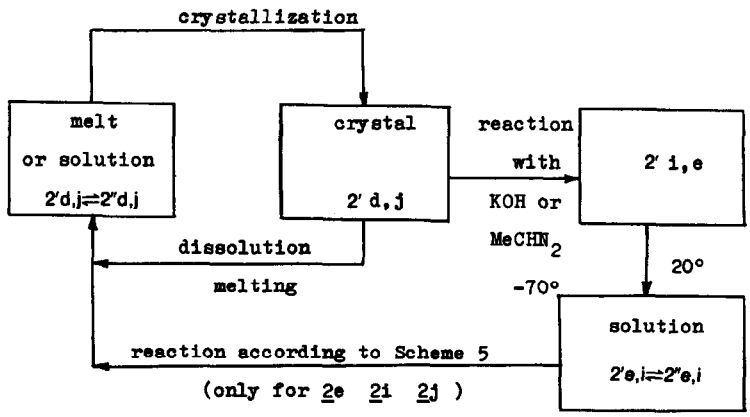
Fig. 1. Kinetics of inversive epimerization of diastereomer **2d** in CCl_4 at 25.5°C observed from the PMR spectra of MeCH group. Predominance of diastereomer **2''d** is noticeable in the equilibrium mixture.

confirm the *a priori* assignment of signals in the NMR spectra of equilibrium **2'e, i/2''e, i** mixtures, i.e. the predominance of **2''e, i** in these mixtures. No assumptions have been made concerning the absolute configuration at N in the compounds when interpreting NMR spectrum. An increase in **2''d** content with an increase in solvent polarity (Table 2) indicates a higher dipole moment of **2''** as compared with **2'**.

To obtain enantiomeric 3,3-*bis*(trifluoromethyl)diaziridines with a high degree of optical purity the most simple method appeared to be that of separating the **2g** racemic amine via diastereomeric **5a–d** salts with optically active acids: 1-10-camphorsulphonic acid (a), (*R, R*)-dibenzoyltartaric (b), d-camphor-3-carboxylic (c), and (*R, R*)-tartaric (d) acids.



5 a-d



Scheme 8.

Table 3. Parameters of NMR spectra for 3,3-*bis*(trifluoromethyl)diaziridines)

Compound	Solvent	δ [a], ppm (60 and 80 MHz ^1H; 56.45 MHz ^{19}F)						J, Hz	
		CH_3	CH_2	CH	NH	a-CF_3 [b]	b-CF_3	F-F	Other
2 a	CCl_4	-	3.35m	2.25t	3.14	-4.4q	-14.7q	7.9	5.7($CH_2C{\equiv}CH$), 1.3(b-CF_3-CH_2)
2 b	CCl_4	3.61	3.32d 3.58d	-	3.60	-4.6q	-14.2q	7.9	16.5 (H_A-H_B)
2 c	CCl_4	1.17t	3.34d 3.54d 4.05q	-	3.80	-4.7q	-14.2q	7.9	17.1 (H_A-H_B)
2'd	CCl_4	1.42d 3.75	-	3.36q	3.52	-4.6q	-14.1q	8.5	6.5 (CH_3-CH)
2''d	CCl_4	1.50d 3.72	-	3.39q	3.22	-4.2q	-13.6q	8.3	6.8 (CH_3-CH)
2'e	CCl_4	1.35d 1.21t	4.14	3.32q	3.45	-5.0q	-14.0q	8.2	6.4 (CH_3-CH), 7.0 (CH_3-CH_2)
2''e	CCl_4	1.42d	4.12	3.37q	3.12	-4.6q	-13.7q	8.2	6.6 (CH_3-CH), 7.0 (CH_3-CH_2)
2 f	CCl_4	1.95	4.20m 2.90m	-	3.25	-4.4q	-14.4q	8.6	-

2 g	C_6H_6	1.88	2.85–2.03m	–	2.98	–4.3q	–13.9q	8.2	–
2 h	CD_3OD	3.33	3.96–2.83m	–	–	–4.0q	–13.3q	8.2	–
2'i	D_2O[c]	1.71d	–	3.63q	–	–5.0q	–13.9q	8.5	7.0 (CH_3-CH)
2" i	D_2O	1.77d	–	3.53q	–	–5.1q	–14.3q	7.8	7.0 (CH_3-CH)
2'j	CD_3OD	1.33d	–	3.34q	–	–3.6q	–12.3q	8.1	7.0 (CH_3-CH)
2" j	CD_3OD	1.41d	–	3.21q	–	–3.4q	–12.0q	7.7	6.8 (CH_3-CH)
2'k	$(CD_3)_2CO$	1.37d	–	3.12q	2.87	4.30q	–13.0q	7.5	6.6 (CH_3-CH)
2" k	$(CD_3)_2CO$	1.30d	–	3.12q	2.87 4.85	–4.26q	–12.6q	7.8	6.8 (CH_3-CH)
5'c[d]	C_6H_6	2.00	2.96–2.12m	–	–	–4.43q	–13.10q	7.9	–
5" c	C_6H_6	2.03	2.96–2.12m	–	–	–4.62q	–12.96q	7.9	–

(a) d—doublet; q—quartet; m—multiplet; t—triplet; (b) Assignment of the signals of CF_3 groups (a-CF_3 *cis* to NH) was made in accordance with the data from Refs. 6, 17, 18 and by the broadening of the low-field quartet that does not disappear under the conditions of fast proton exchange; (c) from ext. HMDS; (d) the chemical shifts of diaziridine cation are given. The spectrum of d-camphor-3-carboxilate anion coincides for both diastereomers (Fig. 2): (δ, ppm, J, Hz) 0.51, 0.58, 0.73 (8, 9, 10-Me), 1.82–0.79 (multiplet), 3.28 (doublet, J = 5).

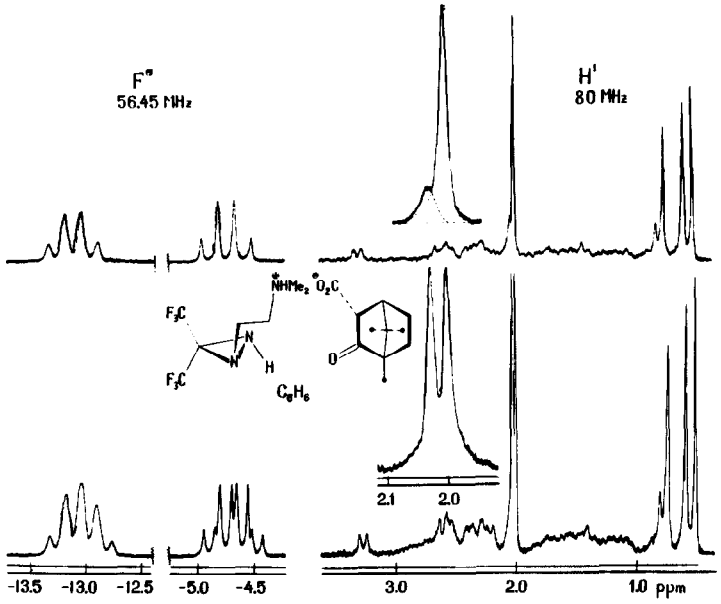


Fig. 2. NMR spectrum of diastereomeric salt **5c**: racemate (below) and after two recrystallizations (above). Optical purity has been determined by integrating the signals of $\underline{Me_2}N$ group at 2.00 and 2.03 ppm.

Salts **5a–c** are crystalline compounds (Tables 1 and 2). Because of the low configuration stability of 3,3-*bis*(trifluoromethyl)diaziridines[2] (Table 4), these salts were recrystallized at a temperature not higher than 0°; the optical rotations and NMR spectra were measured, as in the case of **2d, e, i–k**, immediately after the dissolution of the sample. The isolation of **2g** amine from **5a–c** salts was also conducted in controlled conditions at $t < 0°$. It was thus possible to attain a high diastereomeric purity of **5c** salt (Table 2, Fig. 2), whereas many times repeated recrystallization of **5a, b** salts did not result in any noticeable enrichment.

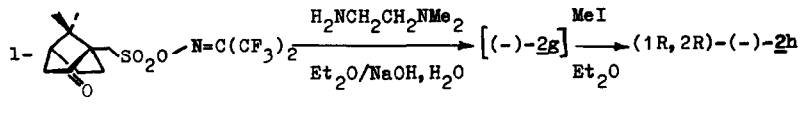
The diastereomeric purity (85.5%) of **5c** salt and, therefore the enantiomeric purity of **2g** amine has been determined by integrating the PMR signals of the Me_2N^+ group (Fig. 2, Tables 2 and 3). Previously the optical purity of enantiomeric diaziridines was determined from the PMR spectra of either a mixture of diastereomers obtained by the reaction with (*R*)- or (*S*)-α-phenylethylisocyanate[2–4] or of a directly enriched mixture of antipodes with chiral shift-reagent added.[5,11] It was also reported that the signals of 1,2,3,3-tetramethyldiaziridine in $CDCl_3$ in the presence of an equimolar quantity of (*R, R*)-dibenzoyltartaric acid are separated in the PMR spectra.[12] Diaziridine **2g** does not react with (*R*)-α-phenylethylisocyanate (ether, 0°), and in the NMR spectra, when a shift-reagent is added (**2g**/Eu(tfc)$_3$ = 8.3 mole, CCl_4), the signals of enantiomers are not separated. Separation of the signals of **5c** diastereomers in benzene (Fig. 2, Table 3) seems to be caused by a high magnetic anizotropy of benzene and its assisting the "chiral anion–chiral cation" association, whereas in dissociating solvents (e.g. CD_3OD) this interaction is averaged out.

By means of Scheme 3 optically active quaternary (+)-**2h** salt (Tables 1 and 2) has been obtained from (+)-**2g** with MeI in ether. The reaction is accomplished in mild conditions (−5°) and without the involvement of chiral centers, so the optical purity and the absolute configuration of N atoms can be regarded as unchanging in this case.

In the circular dichroism (CD) spectrum of (+)-**2g** in n-hexane a positive Cotton effect (CE) is observed (Fig. 3). This seems to be the result of the superposition of the effects caused by optically active transitions of the tertiary $-NMe_2$ group[13,14] and the N-N-diaziridine chromophore proper.[2,4] From the comparison of $\Delta\epsilon$ values for both chromophores in hexane (for NMe_2 $\Delta\epsilon \simeq 0.2$,[14] for N–N in diaziridine $\Delta\epsilon \simeq 4.5$, as recalculated for 100% optical purity[2,4]) it follows that the greatest contribution to the observed CE of (+)-**2g** is made by the N–N chromophore, hence the absolute configuration of N atoms in (+)-**2g** can be inferred as 1*S*, 2*S*.[4] The (+)-**2h** diaziridine with the same absolute configuration of N atoms gives in MeOH a short-wave CE with the opposite sign (Fig. 4). The above configuration assignment is confirmed by the fact that in the case of (1*S*, 2*S*) - 1 - methyl - 3,3 - pentamethylenediaziridine[4] the replacement of heptane by MeOH also results in the reversal of the CE sign (Fig. 3).

Optically active quaternary (−)-**2h** salt has also been obtained by asymmetric synthesis in accordance with Scheme 9, and in this case it is possible to estimate the optical yield of the reaction (Table 2).

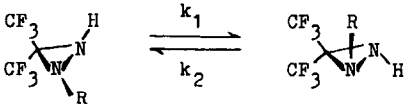
From the comparison of the optical purity of the products of asymmetric synthesis based on 1 - 10 - camphorsulphonylketoximes—(1*R*, 2*R*) - (+) - trimethyl-



1 b

Scheme 9.

Table 4. Energy parameters of the inversion of N atoms in 3,3-*bis*(trifluoromethyl)diaziridines at 25.5°



Compound	Solvent	$k_{obs.} \cdot 10^4$ sec.$^{-1}$	$\tau_{1/2}$ min.	$k_1 \cdot 10^4$ sec.$^{-1}$	$k_2 \cdot 10^4$ sec.$^{-1}$	$\Delta G_1^{\neq}$ kcal/mole	$\Delta G_2^{\neq}$ kcal/mole	Method
2 d	CCl_4	4.1 ± 0.3	28.18	2.2 ± 0.2	1.9 ± 0.1	22.48	22.56	PMR [a]
2 d	Me_2CO	1.74 ± 0.01	66.40	1.112 ± 0.006	0.628 ± 0.004	22.38	23.22	Plm. [b]
2 e	CCl_4	4.35 ± 0.08	26.56	2.34 ± 0,04	2.01 ± 0.04	22.44	22.53	Plm.
2 g	C_6H_6	1.46 ± 0.03	79.13	0.73 ± 0.02	0.73 ± 0.02	23.13	23.13	Plm.
2 h	MeOH	0.245 ± 0.006	471.56	0.123 ± 0.003	0.126 ± 0.003	24.17	24.17	Plm.
2 i	H_2O	2.15 ± 0.02	53.74	1.65 ± 0.02	0.500 ± 0.005	22.64	23.35	Plm.
2 j	CD_3OD	4.9 ± 0.3	23.58	3.3 ± 0.2	1.6 ± 0.1	22.23	22.66	PMR
2 k	Me_2CO	2.96 ± 0.09	39.03	1.74 ± 0.05	1.22 ± 0.04	22.61	22.83	Plm.

(a) From the intensity of the signals of MeCH groups (see, e.g. Fig. 1); (b) Polarimetrically at $\lambda = 546$ nm.

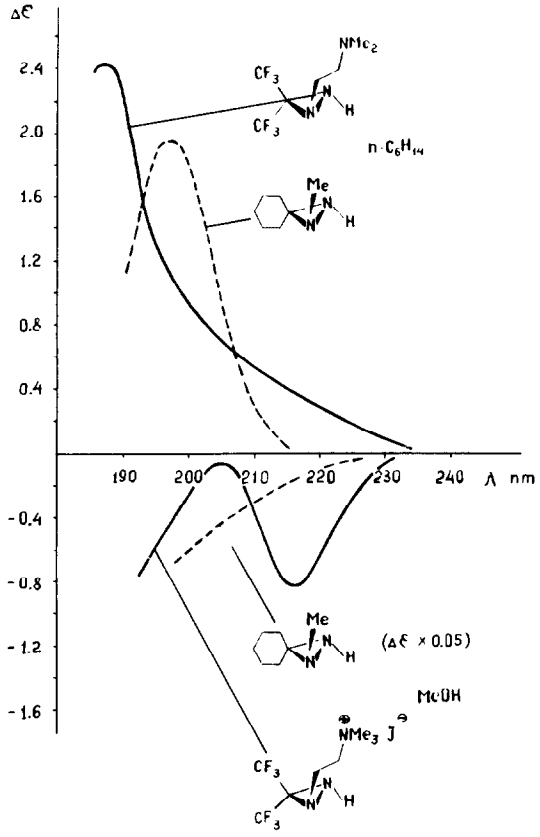


Fig. 3. CD spectra of enantiomeric 3,3-*bis*(trifluoromethyl)diaziridines **2g** and **2h** (———) and (1*S*,2*S*)-1-methyl-3,3-pentamethylene diaziridine (— — —).

diaziridine—9.9%[3,4] (1*R*,2*R*)-(−)-**2h**—2.0% and (1*R*,2*R*)-(+)-dimethyl ester of 1 - methyldiaziridine - 3,3 - dicarboxylic acid—0.2%[a]—it follows that enantioselectivity of the reaction decreases with an increase in electronegativity of substituents at the carbon of the azomethine bond, whereas the same 1*R*,2*R* absolute configuration of N atoms in diaziridines is indicative of the common geometry of the reactions transition state independently of the nature of substituents at the C=N bond.

EXPERIMENTAL

NMR spectra have been obtained on JNM-C-60HL spectrometers (^{1}H, 60 MHz, int. standard HMDSO; ^{19}F, 56.45 MHz, ext. standard CF_3COOH) and BS-487C (^{1}H, 80 MHz); IR spectra—on a UR-20 spectrophotometer (in a molecular layer for liquid samples and in pellets with KBr for solid samples); CD spectra—on a Dichrographe-III Jobin Ivon dichrograph. Optical rotation has been measured with polarimeters Perkin-Elmer-141 and Polamat A.

Hexafluoroacetone O-*tosyloxime* (**1a**). 37.6 g (0.57 mole) of ClNO was passed through a solution of 100.0 g (0.51 mole) of $(CF_3)_2CHCOOH$ in 400 ml of dry pyridine with cooling (−5 to −10°) and stirring. The stirring was conducted for 2 hr at 20° and 1 hr at 80° (until cessation of gas evolution). The reaction mixture was cooled down to −10 to −5°, and 97.2 g (0.51 mole) of TsCl was added in small portion with stirring. After the mixture had been stirred for 2 hr and left overnight at 20°, it was poured into 2 l of cold 10% HCl. The precipitate was filtered off, washed with water and dried in vacuum over P_2O_5. After recrystallization from heptane, 139.6 g (81.7%) of **1a** with m.p. 89–90° was obtained [lit.[6] m.p. 88–90°]. The one-stage method of synthesis makes it possible to double the yield of **1a** (in terms of $(CF_3)_2CHCO_2H$) as compared with the two-stage method.[6,15]

Hexafluoroacetone 1-10-0-*camphorsulphonyloxime* (**1b**) was obtained according to Ref. 3 with yield of 90.5%, m.p. 89–90° (from MeOH), $[\alpha]^{20}_{546} = -30.2°$, $[\alpha]^{20}_{D} = -25.9°$ (c 3.5 MeOH) [lit.[3] m.p. 89–90°, $[\alpha]^{20}_{546} = -26.9°$ (c 5.2 MeOH)].

1 - *Propargyl* - 3,3 - *bis*(*trifluoromethyl*)*diaziridine* (**2a**). A mixture of 8.38 g (0.025 mole) of **1a**, 1.38 g (0.025 mole) of propargyl amine and 2.63 g (0.026 mole) of Et_3N was stirred for 1 hr at 0°. The solidified mass was treated with 10 ml of cold water. The organic layer was separated, dried over $MgSO_4$ and distilled twice in vacuum (66 mm). 3.51 g of **2a** (Table 1) was obtained.

1 - *Carbmethoxymethyl*-, 1 - *carbethoxymethyl*-, 1 - (S) - α - *carbmethoxyethyl*-, 1 - (S) - α - *carbethoxyethyl*- *and* 1 - β - *acetoxyethyl* - 3,3 - bis(*trifluoromethyl*)*diaziridines* (**2b–f**) were obtained by means of the following common procedure. To a mixture of 8.38 g (0.025 mole) of **1a** and 0.025 mole amine hydrochloride in 30 ml of dry DMF (distilled over P_2O_5) 5.17 g (0.051 mole) of Et_3N was added dropwise with stirring and cooling, the stirring continued for 4 hr. After being left at rest during 24 hr at 0° the reaction mixture was poured into 150 ml of cold water, the product was extracted with ether (3 × 20 ml), the etherial soln was diluted with an equal volume of pentane, washed with water (2 × 30 ml) and dried over $MgSO_4$. After the removal of the solvent the product was distilled twice in vacuum (Tables 1 and 2).

1 - β - *Dimethylaminoethyl* - 3,3 - bis(*trifluoromethyl*)*diaziridine* (**2g**). *Method A.* To a mixture of 4.40 g (0.05 mole) of β-dimethylaminoethyl amine and 4.90 g (0.051 mole) of *t*-BuONa in 30 ml of dry DMF a soln of 16.73 g (0.05 mole) of **1a** in 50 ml dry DMF was added dropwise with stirring and cooling (−8°), the stirring was continued for 1 hr. After being left at rest for the night at 0° the reaction mixture was poured into 250 ml of water with ice, the product was extracted with ether (5 × 30 ml) and dried over $MgSO_4$. After the removal of the ether the residue was distilled twice in vacuum (20 mm). 6.29 g of **2g** (Tables 1 and 2) has been obtained.

Method B. To a mixture of 5.28 g (0.060 mole) of β-dimethyleminoethyl amine and 3.2 g (0.08 mole) of NaOH in 35 ml of water a soln of 20.40 g (0.061 mole) of **1a** in 70 ml of CH_2Cl_2 was added dropwise with stirring and cooling (−5 to −10°), the stirring was continued for 1 hr at −5° and for 3 hr at 20°. The organic layer was separated and dried over $MgSO_4$. After the removal of the solvent the residue was distilled in vacuum. 10.23 g of **2g** (Table 1) has been obtained.

1 - β - *Trimethylammonioethyl* - 3,3 - bis(*trifluoromethyl*)*diaziridine iodide* (**2h**). A soln of 1.50 g (6 mmole) of **2g** and 1.28 g (9 mmole) of MeI in 5 ml of dry MeCN was kept at 20° for 24 hr. After the removal of the solvent the precipitate was recrystallized from i-PrOH. 1.95 g of **2h** (Table 1) has been obtained.

Potassium salt of 1 - (S) - α - *carboxyethyl* - 3,3 - bis(*trifluoromethyl*)*diaziridine* (**2i**). To a soln of 1.68 g (0.030 mole) of KOH in 20 ml of absolute MeOH a soln of 8.69 g (0.031 mole) of **2e** in 10 ml of absolute MeOH was added dropwise with cooling (0 to 5°) and stirring. The mixture was left at rest for 1 hr, the precipitate was filtered off and washed with dry ether. 7.23 g of **2i** (Tables 1 and 2) has been obtained.

1 - (S) - α - *Carboxyethyl* - 3,3 - bis(*trifluoromethyl*)*diaziridine* (**2'j**). To a soln of 5.80 g (0.02 mole) of **2i** in 30 ml of water 5 ml of conc. HCl was added dropwise with cooling (5 to 10°) and stirring. The precipitated crystals were filtered off and dried over P_2O_5. After sublimation in vacuum (0.5 mm) 3.65 g of **2'j** (Tables 1 and 2) has been obtained.

1 - (S) - α - *carboxyethyl* - 3,3 - bis(*trifluoromethyl*)*diaziridine amide* (**2k**). To 10 ml of absolute MeOH saturated with ammonia and with traces of MeONa 2.80 g (0.01 mole) of **2e** was added. The mixture was left at rest for 10 days at 20°, the solvent was then removed and the residue sublimated in vacuum (0.5 mm). 2.42 g of **2k** (Tables 1 and 2) has been obtained.

[a]Calculated from formula $P_x \simeq \{[\alpha]_x/[\alpha]\} \cdot p$, where $[\alpha]_x = +0.24°$ ($\lambda = 365$ nm) is the specific rotation of the product of asymmetric synthesis in $CHCl_3$,[3] $[\alpha] = +127.9°$ ($\lambda = 365$ nm) is the specific rotation of a pre-assigned sample in $CHCl_3$ with a known optical purity, p = 98%.[5]

Diastereomerically pure ester (2'e). To a soln of 0.8 mmole of $MeCHN_2$ in 1.5 ml of CCl_4, cooled to −78°, 0.0982 g (0.39 mmole) of 2'j was added. The solvent was concentrated by evaporation in vacuum at a temperature not higher than 0°. The residue (0.108 g of 2'e, Table 1) was dissolved in CCl_4 with cooling, and the solution obtained was analyzed polarimetrically (Table 2) and by the NMR method (Table 3).

Diastereomerically pure salt 2'i. To a soln of 0.074 g (1.3 mmole) of KOH in 1 ml of absolute MeOH 0.400 g (1.6 mmole) of 2'j was added with cooling (−70°) and stirring. The precipitate formed was filtered off, washed with dry ether and dried in vacuum. 0.376 g of diastereomerically pure 2'i salt (Tables 1 and 2) has been obtained. Diastereomeric purity was monitored by means of the NMR method.

Reaction of **1a** *with ethyl ester of* (S)-α-*phenyl alanine.* To a mixture of 5.84 g (0.0174 mole) of **1a** and 3.89 g (0.017 mole) of amino acid ester hydrochloride in 20 ml of dry DMFA 3.44 g (0.034 mole) of Et_3N was added dropwise with cooling (0 to 5°) and stirring. The stirring was continued for 4 hr at 20°. After being kept at 20° for 4 hr the reaction mixture was poured into 100 ml of cold water, the product was extracted with CH_2Cl_2 (2 × 20 ml) and dried over $MgSO_4$. The solvent was concentrated by evaporation in vacuum, and the residue was twice recrystallized from hexane. 1.62 g of N-tosyl-(*S*)-α-phenyl alanine ethyl ester **3a** (Table 1) has been obtained with $[\alpha]_D^{20} = +5.5°$ (c 2.2 MeOH). PMR spectrum (80 MHz, CCl_4, δ ppm): 0.95 ($MeCH_2$, t), J_{MeCH_2} 7.0 Hz, 2.29 (MeC), 2.89 (CH_2Ph, d), J_{CH_2CH} 6.5 Hz, 3.79 ($MeCH_2$, q), 3.98 (CH, doublet of triplets), J_{CHNH} 9.0 Hz, 5.65 (NH, d), 7.01 (Ph), 7.04 and 7.49 (C_6H_4Me), J = 8 Hz.

Reaction of **1a** *with* (R, S)-α-*phenylethyl amine.* To a stirred soln of 6.71 g (0.02 mole) of **1a** in 30 ml of dry DMFA 4.85 g (0.04 mole) of (*R, S*)-α-phenylethyl amine was added at 0°, and the stirring was continued for 2 hr. After being left at rest for the night at 0° the reaction mixture was poured into 100 ml of cold water, the product was extracted with CH_2Cl_2 (2 × 20 ml) and dried over $CaCl_2$. After the removal of the solvent the residue was recrystallized from *i*-PrOH–pentane (2:3) mixture, 3.45 g of *N*-α-phenylethyl *p*-toluenesulphonamide **3b** (Table 1) has been obtained. PMR spectrum (60 MHz, $CDCl_3$, δ ppm): 1.30 (MeCH), J_{MeCH} 7.1 Hz, 2.30 (MeC), 4.40 (CH), J_{CHNH} 7.1 Hz, 5.57 (NH), 7.20 (Ph), 7.20 and 7.67 (C_6H_4Me), J = 8 Hz.

Reaction of **1a** *with* t-*butyl amine.* A mixture of 6.71 g (0.02 mole) of **1a** and 5.85 g (0.08 mole) of *t*-$BuNH_2$ in a sealed tube was shaken at regular intervals for 10 hr at 20° and for 1 hr at 100° and then treated with 50 ml of cold water. The solid residue was separated and dried in vacuum. After three recrystallizations from heptane 3.75 g of N-*t*-butyl *p*-toluenesulphonamide **3c** (Table 1) has been obtained. PMR spectrum (60 MHz, CCl_4, δ ppm): 1.10 (Me_3C), 2.30 (MeC), 5.0 (NH), 7.0 and 7.46 (C_6H_4Me), J = 8 Hz.

2,2 - Bis(*trifluoromethyl*) - 4 - *hydroxyimidazole* - 1,3 (**4**). To a soln of 1.18 g (0.021 mole) of KOH in 20 ml of absolute MeOH 5.83 g (0.022 mole) of **2c** was added dropwise with stirring. After the reaction mixture had been kept at rest for 3 hr at 20°, 12 g of Dowex 50W × 12 (in H^+ form) was added to it, and the mixture was stirred during 12 hr. The cationite was separated, concentrated by evaporation in vacuum, and the residue was sublimated in vacuum (14 mm) at 80–100°. 3.09 g of **4** (Table 1) has been obtained. NMR spectrum (CD_3COCD_3, δ ppm): 8.43 (CH), 10.30 (NH⇌OH) (^1H, 80 MHz); −1.65 (CF_3), (^{19}F).

Resolution of racemic **2g**

Via 1-10-*camphorsulphonate.* A solution of 0.527 g (2.1 mmole) of (±)-**2g** and 0.465 g (2.0 mmole) of 1-(−)-10-camphorsulphonic acid in 3 ml of *iso*-PrOH was kept for 24 hr at 0°. The precipitated crystals were separated and dried in vacuum over P_2O_5. 0.852 g of **5a** salt (Tables 1 and 2). This was three times recrystallized from methylethyl ketone, with the salt being dissolved at 5 to 10° and the solution kept at 0 to 5°. After each recrystallization the melting point and the specific rotation of the salt did not undergo any substantial changes. 0.364 g of **5a** (Tables 1 and 2) has been obtained.

To a suspension of 0.3 g (0.62 mmole) of **5a** in 3 ml of ether a solution of 0.561 g (0.01 mole) of KOH in 1 ml of H_2O was added dropwise with cooling (−5 to −10°) and stirring. The ethereal layer was promptly separated and dried over solid KOH at −15 to −10°. After the removal of the ether 0.131 g (83.9%) of **2g** has been obtained. It has no optical activity when its 3.4% (vol.) solution in hexane is investigated, the length of cuvette 1 dm.

Via (R, R)-(−)-*dibenzoyl tartrate.* A soln of 0.260 g (1.4 mmole) of (±)-**2g** and 0.352 g (0.98 mmole) of (*R, R*)-(−)-dibenzoyltartaric acid in 3 ml of MeOH was kept for 10 hr at 0°. Methanol was concentrated by evaporation in vacuum, and the only residue dissolved in 5 ml of absolute EtOH. After the mixture had been kept for 2 days at 0° the precipitated crystals were separated. 0.348 g of **5b** salt (Tables 1 and 2) has been obtained. Its melting point and specific rotation after subsequent recrystallizations from EtOH and MeCN remained practically unchanged.

Diaziridine **2g** isolated in accordance with the preceding procedure from **5b** is optically inactive.

Via d-(+)-camphor-3-carboxylate. To a soln of 5.09 g (0.0203 mole) of (±)-**2g** in 15 ml of dry ether a soln of 3.68 g (0.020 mole) of d-(+)-camphor-3-carboxylic acid in 15 ml of dry ether was added dropwise with stirring. After the removal of the ether 8.77 g of **5c** salt (Tables 1 and 2) was obtained. This was dissolved at 10° in 20 ml of benzene. 100 ml of hexane was added to the solution, which was left for 24 hr at −5°. The precipitated crystals [3.84 g, m.p. 59–65°, $[\alpha]_D^{20} = +56.34°$ (c 3.4 MeOH), diastereomeric purity 76.5% (PMR)] were separated and recrystallized for a second time from the benzene (20 ml)–hexane (80 ml) mixture. 2.40 g of **5c** salt (Tables 1 and 2) has been obtained.

Optically active **2g** was isolated from the **5c** salt, as in the case of **5a** under the conditions excluding the possibility of racemization. From 1.788 g (4 mmole) of **5c** 0.853 g (83.2%) of (+)-**2g** (Table 2) has been obtained.

Reaction of (+)-**2g** *with methyl iodide.* To soln of 0.178 g (0.709 mmole) of (+)-**2g**, $[\alpha]_D^{20} = +38.45°$ (c 1.4 hexane) and optical purity 81.7%, in 3 ml of dry ether a soln of 0.120 g (0.845 mmole) of MeI in 2 ml of dry ether was added dropwise with stirring and cooling (−5°). The mixture was left for the night at −5 to −7°, and the precipitated crystals were filtered off, washed with dry ether and dried in vacuum. 0.250 g of (+)-**2h** (Tables 1 and 2) had been obtained.

Asymmetric synthesis of (−)-**2h**. To a soln of 0.41 g (0.0046 mole) of β-dimethylaminoethyl amine and 0.40 g (0.01 mole) of NaOH in 3 ml of water a soln of 1.82 g (0.0046 mole) of **1b** in 3 ml of ether was added dropwise with stirring and cooling (−20 to −26°), and the stirring was continued for 1 hr at −5 to −10°. The ethereal layer was promptly separated and dried over solid KOH at −10 to −15°. The dried solution was cooled to −30 to −38°, and a solution of 0.88 g (0.0062 mole) of MeI in 1 ml of dry ether was added to it with stirring. The mixture was left for the night at −7°. The precipitated crystals were filtered off, washed with dry ether and dried in vacuum. 0.63 g of (−)-**2h** (Tables 1 and 2) has been obtained.

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