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PREPARATIVE SEPARATIONS AND RACEMIZATIONS OF ENANTIOMERIC DIAZIRIDINES

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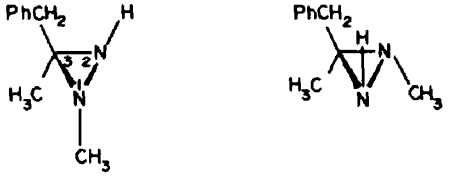
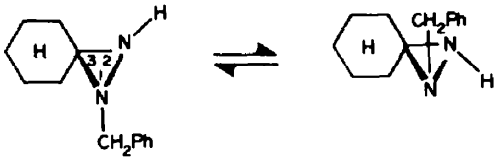
Abstract—Preparative separations or enrichments of enantiomers of diaziridines **1**, **2**, and **5** were achieved by liquid chromatography on triacetylcellulose, (+)-**1** and (+)-**2** being isolated almost pure (Table 1). Enantiomeric purities were determined by ^{1}H NMR in the presence of the optically active auxiliary compound (+)-Eu(hfbc)$_3$. The barriers to nitrogen inversion in **1** and **4** were determined and its lower limit in the nitrogen unsubstituted diaziridine **3** was estimated.

Chiral diaziridines[2] have been the subject of investigations in the recent years, largely because of the interesting display of steric and electronic effects upon nitrogen inversion barriers. trans-Diaziridine if suitably substituted exhibits stable diastereoisomers[3] or enantiomers,[4,5] e.g. (1*R*, 2*R*)- and (1*S*, 2*S*)-**4**, which aroused more interest since their interconversion by two consecutive nitrogen inversions[3] starts from two isoenergetic ground states in contrast to diastereomeric diaziridines the interconversion of which is more complicated.[3]

	R	X	
(1*R*, 2*R*)-**1**	H	CH_2CH_2Ph	(1*S*, 2*S*)-**1**
(1*R*, 2*R*)-**3**	Ph	H	(1*S*, 2*S*)-**3**
(1*R*, 2*R*)-**4**	H	CH_2Ph	(1*S*, 2*S*)-**4**
(1*R*, 2*R*)-**6**	Ph	CH_3	(1*S*, 2*S*)-**6**



(1*R*, 2*R*, 3*S*)-**2** (1*S*, 2*S*, 3*R*)-**2**



(1*R*, 2*R*)-**5** (1*S*, 2*S*)-**5**

Scheme 1.

The classical resolution of chiral compounds via formation of diastereomeric salts has been carried out on diaziridines bearing functional groups in only two cases.[6,7] Therefore, we tried liquid chromatography on an optically active sorbent, microcrystalline triacetylcellulose.[8] The successful application[4,5] of this obviously more universal method stimulated our interest for further enantiomers of diaziridines needed for the study of chiroptical properties as well as substituent and medium effects upon the barrier to nitrogen inversion.

Preparative separations of enantiomeric diaziridines by liquid chromatography on triacetylcellulose

An almost complete preparative separation of enantiomers has been achieved for diaziridine (±)-**1** (Table 1) as can be seen from the analytical chromatogram (Fig. 1) showing very small overlap of the peaks of the enantiomers.

In diaziridines (±)-**5** and (±)-**2** slight enrichment and nearly complete separation of enantiomers were obtained, respect. (Table 1) by using the recycling procedure[4,5] combined with fractionating the eluate. Surprisingly, 3,3-dibenzyldiaziridine (**3**) showed no separation of enantiomers by liquid chromatography on triacetylcellulose. In this connection it is interesting to note that 1,2-bis(2-phenylethyl)-diaziridine,[9] possessing two phenyl groups also, showed deviations from the chromatographic behaviour of other diaziridines[4] by strong tailing of peaks and reduced separation. Preliminary experiment on 3,3-dibenzyl-1-methyldiaziridine (**6**) showed only marginal resolution of enantiomers.

^{1}H NMR in the presence of the optically active auxiliary compound (+)-tris(3-heptafluorobutyryl-D-camphorato) europium(III), (+)-Eu(hfbc)$_3$, served for the determination of enantiomeric purities P (Table 1). Enantiotopic[10] groups in diaziridines become diastereotopic by association to (+) Eu(hfbc)$_3$ and display unequal ^{1}H NMR shifts,[11] e.g. the 3-CH_3^c groups of (+)- and (−)-**1** (Fig. 2). From the relative intensities of such signals the enan-

Table 1. Separations by liquid chromatography and properties of enantiomeric diaziridines

Predominant enantiomer	Number of passages	Eluates used	δ	b (Hz)	S	r	Solvent Temp.	P (%)	$(\alpha)_{365}$ Temp.
(+)-1	2	first fractions of eluate	2.70	2.5	3-CH_3	0.2	$CDCl_3$ 26°C	92 ± 3	+285 ± 5° 22°C
(−)-1	2	last fractions of eluate	2.80	2.3				90 ± 3	−280 ± 5° 22°C
(+)-1	2	first fractions of eluate	2.83	2.7	3-CH_3	0.2	$CDCl_3$ 26°C	96 ± 3	+297 ± 4° 27°C
(−)-1	2	last fractions of eluate	2.86	2.5				89 ± 3	−277 ± 5° 27°C
(+)-5	6	early eluates and firs fractions of final eluate							+21 ± 1° 22°C
(−)-5	6	last fractions of final eluate							−24 ± 1° 22°C
(+)-2	6	early eluates and first fractions of final eluate	20.3	18.8	N-H	0.48	CCl_4 26°C	98 ± 2	+72 ± 4° 26°C
(−)-2	6	last fractions of final eluate	15.3	17.3	N-H	0.48	CCl_4 26°C	76 ± 3	−54 ± 2° 26°C

δ and b: ^{1}H NMR shift and linewidth for a signal of the predominant enantiomer in the presence of (+)-Eu(hfbc)$_3$

S: Signals chosen

r: Numbers of equivalents of (+)-Eu(hfbc)$_3$

P: Enantiomeric purity, determined from ^{1}H NMR intensities of the above signals.

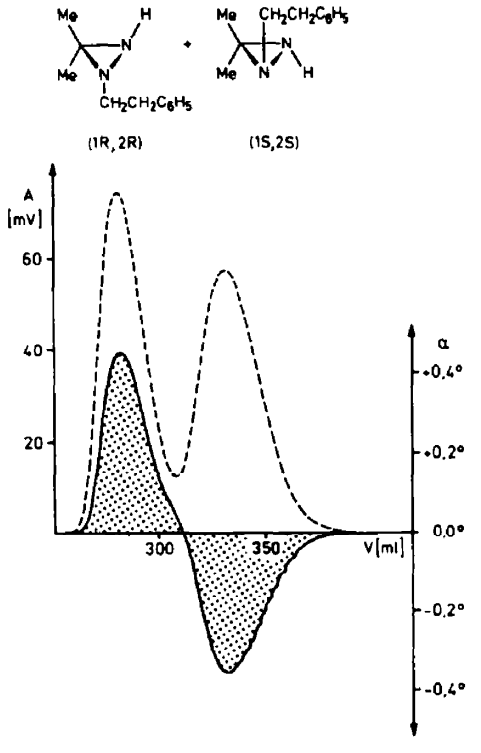


Fig. 1. Analytical chromatogram of (±)-1 after passage through two columns of triacetylcellulose. α: Rotation angle (—) at 365 nm. A: Absorbance (---) at 257 nm. V: Volume of eluate; injection at V = 0.

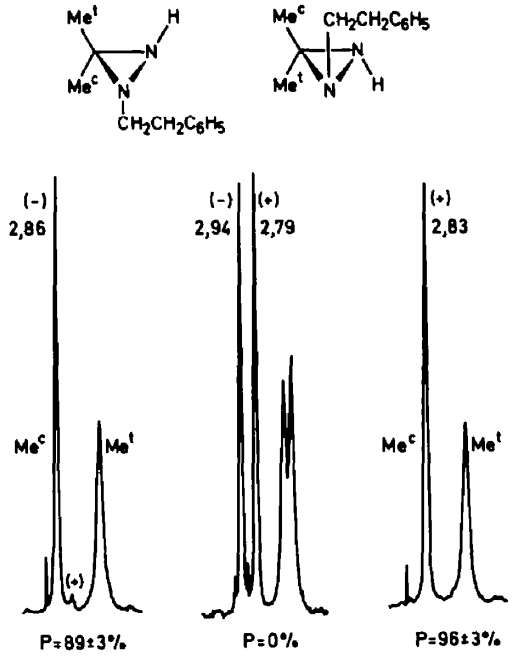


Fig. 2. 90 MHz ^{1}H PFT NMR of Me groups of (−)-1 (left), (±)-1 (centre), and (+)-1 (right) in the presence of (+)-Eu(hfbc)$_3$. Numbers are δ-values. Spectral width 1200 Hz; 42° pulses; 50 scans.

tiomeric purities were obtained by cutting and weighing of the corresponding spectra.

Barriers to nitrogen inversion

For the interconversion of the enantiomers of *trans*-diaziridine two mechanisms have been proposed (i)

simultaneous double nitrogen inversion and (ii) consecutive nitrogen inversions via a *cis* intermediate.[3,4] Lone pair interaction is probably decisive in favouring the monoplanar transition state of inversion at one nitrogen atom in the diaziridine ring. This is understandable since the dihedral angle between the lone pairs in this case amounts to about 25°[12] which corresponds to less conjugative destabilization than in the ecliptical conformation of the biplanar transition state of a hypothetical synchronous inversion. Additionally, the consecutive mechanism is preferred energetically as estimated by *ab initio* calculations, using a 4-31 G basis set,[13] which show that the monoplanar transition state is more stable by 122.6 kJ/mol than the biplanar one. Furthermore, the difference in total energies of the monoplanar transition state (E = − 148.69925 a.u.) and the pyramidal ground state of *trans*-diaziridine (E = − 148.74266 a.u., obtained by Pople *et al.*[14] with the same basis) is equal to 113.8 kJ/mol, which is in reasonable accord with our experimental findings[4] (Table 2). The mechanism of consecutive inversions requires[3] a statistical factor of 0.5 in the calculation of $\Delta G^{\neq}$ for one *trans* → *cis* inversion. Therefore, this factor has been applied throughout. In order to obtain a "true" inversion barrier for each particular N atom and make possible strict comparison with known $\Delta G^{\neq}$ values for substituted diaziridines, we synthesized compound **3** not substituted at either nitrogen. However, the separation of enantiomers was not accomplished. The methylene protons of **3** are diastereotopic as demonstrated by the appearance of an AB quartet. This is compatible only with the *trans* configuration of the molecule. The shift difference $\Delta\nu$ decreases with increasing temperature. This is accompanied by broadening of the signals, though the coalescence temperature in diphenyl ether cannot be attained even at 192°. The highest temperature of measurement and the rate constant k at this temperature permitted to calculate[15] the lower limit of $\Delta G^{\neq}$, which has to be greater than 98 kJ/mol (Table 2). A proton catalysed exchange reaction seems to take place in $C_2D_2Cl_4$. The ^{1}H NMR spectrum of **3** at 67° in this solvent showed a singlet revealing an averaging of the methylene shifts which was obviously due to the presence of trace amounts of acid or water which catalysed N–H exchange. In this case two processes, namely inversion and proton exchange, must be considered. However, unequal chemical shifts of the methylene protons were observed in the spectra of **3** in benzene-d_6 (25°), toluene-d_8 (25° and 108°), $CDCl_3$ (25°), CD_3CD_2OD (82.5°), and CD_3OD (45°). The same phenomenon was observed when the inversion rate of 2,2,3,3-tetramethylaziridine was measured.[16]

The comparison of barriers to inversion shows that replacement of a benzyl group by phenylethyl does not generate a significant change ($\Delta G^{\neq}$ values for **1** and **4**, Table 2). The slight decrease of the barrier of **4** in *n*-propanol compared to benzene. (Table 2) indicates that N–H proton dissociation and recombination cannot be excluded as a possible interconversion mechanism for N–H containing diaziridines.

EXPERIMENTAL

M.ps were determined on a Büchi SMP 20 instrument and are not corrected. ^{1}H NMR spectra were recorded on Varian T-60 (CW mode, 60 MHz) and Bruker WH-90 (PFT mode, 8K data points, 90 MHz) spectrometers in $CDCl_3$, unless indicated otherwise. Abbreviations employed: s, singlet; d, doublet; m, multiplet. ^{13}C NMR spectra were recorded in the PFT mode at 22.63 MHz on a Bruker WH-90 spectrometer with 8K data points, ^{15}N NMR spectra on a Bruker WH-90 spectrometer (PFT mode, 9.12 MHz) and UV spectra on the Beckman Acta M VI spectrometer. Specific rotations were measured by means of a Perkin–Elmer 241 electronic polarimeter, CD spectra on a JASCO J-40 A instrument at 22°, and Dichrographe Mark III, Jobin Yvon at 20°, respect. A low and high resolution mass spectra were

Table 2. Barriers to nitrogen inversions in diaziridines **1**, **3**, and **4**

	Method	Solvent	T (°C)	10^5 k (sec^{-1})	$\Delta G^{\neq}$ (kJ/mol)
1 (+)	polarim., 365 nm	benzene	70.1 ± 0.2[a]	4.05[a]	111.3 ± 0.1[b]
1 (−)	polarim., 365 nm	benzene	70.0 ± 0.1[a]	4.01[a]	111.3 ± 0.1[b]
4 (−)	polarim., 365 nm	benzene	70.1 ± 0.1[a]	3.32[a]	111.8 ± 0.2[b] 4)
4 (+)	polarim., 365 nm	n-propanol	70.1 ± 0.1[a]	5.65[a]	110.3 ± 0.1[b]
(±)-**2**	^{1}H NMR signal spliting	$D_5C_6CD_3$	>108[c]	<8.7·10[15][d]	>80[d]
(±)-**2**	^{1}H NMR signal spliting	$H_5C_6OC_6H_5$	>192[c]	<8.1·10[15][e]	>98[e]

a) For two consecutive nitrogen inversions, interconverting the *trans*-diaziridine into the enantiomeric *trans*-diaziridine via a *cis*-intermediate[3]

b) Corrected for a single nitrogen inversion, converting the *trans*-diaziridine into a *cis*-intermediate[3]

c) Highest temperature of measurement

d) Calculated for the coalescence of the AB absorption (^2J = 14.1 Hz, $\Delta\delta$ = 0.10) of the diastereotopic methylene protons

e) Calculated for the coalescence of the AB absorption (^2J = 14.2 Hz, $\Delta\delta$ = 0.12) of the diastereotopic methylene protons

obtained with Varian MAT-CH5 and Varian MAT-311A spectrometers, respect., operating at 70 eV by direct insertion probes. The fractionations under reduced pressure were carried out on a Spaltrohr column (Fischer, Labor- und Verfahrenstechnik, Bonn-Bad Godesberg). The separation of enantiomers was performed by liquid chromatography (glass columns of 2.5 × 30 cm) on swollen microcrystalline triacetylcellulose (particle size 0.032–0.056 mm) and ethanol/H_2O (96:4) as an eluent. The chromatographic equipment has been described earlier.[4] (+)-tris (3-heptafluorobutyryl-D-camphorato) europium(III), (+)-Eu(hfbc)$_3$, was available from Regis Chemical Co., Morton Grove. Ill., U.S.A.

Racemizations monitored by polarimetry. The thermal racemizations of (+)-**1** (P = 92 ± 3%), (−)-**1** (P = 90 ± 3%) and (+)-**4** (P = 90 ± 3%) respect., were monitored by polarimetry at 365 nm at 70.1 ± 0.2° during a period of two-half lives $t_{0.5}$. The reaction was performed by setting a 0.025 M solution of enriched (+)-**1**, (−)-**1**, and (+)-**4** respect., into the 5 cm cell of Perkin–Elmer 141 polarimeter and measuring the rotation angle vs time. The final angle of rotation was zero. The temp. of the thermostated cell was read at its inlet and outlet. The racemizations were of first order. The evaluation of the rate constants and $\Delta G^{\neq}$-values was carried out with the program[17] KIN 3 using the least square procedure. The calculations were performed on the Siemens TR 440 computer.

(±)-1-(2-*Phenylethyl*)-3, 3-*diethyladiaziridine* (**1**) prepared as reported[18] and fractionated under reduced pressure. The main fraction, b.p. 66–67° (0.005 Torr) was purified by chromatography on triacetylcellulose with EtOH/H_2O (96:4) as an eluent. ^{1}H NMR ($CDCl_3$, 26°, 0.087 M): δ = 1.24 (C–Me, s), 1.39 (C–Me, s), 2.03 (N–H, s), 2.6–3.1 (CH_2CH_2, m), 7.2–7.3 (phenyl ring, m). UV (n-hexane): λ_{max} = 267 nm (ϵ = 128 l mol^{-1} cm^{-1}), 264 (shoulder, 144), 259 (195), 253 (162), 248 (shoulder, 116), 214 (3618). (MS molecular ion: Calc.: 176.1313. Found: 176.1313. $C_{11}H_{16}N_2$ Requires: C, 74.96; H, 9.15; N, 15.89. Found: C, 74.86; H, 9.07; N, 15.97%).

(+)- *and* (−)-1-(2-*Phenylethyl*)-3,3-*dimethyldiaziridine* (**1**), obtained from 100 mg of (±)-**1** which were conducted through two columns at a flow rate of 130 ml/hr. Altogether two column passages took place. The first fractions of the eluate contained 30 mg of (+)-**1**, m.p. = 37.5–38°, $(\alpha)^{27}_{365}$ = + 297 ± 4°, $(\alpha)^{27}_{436}$ = + 180 ± 2°, and $(\alpha)^{27}_{546}$ = + 102 ± 2° (0.461 g/100 ml CCl_4), P = 96 ± 3%. The last fractions of the eluate contained 43 mg of (−)-**1**, m.p. 37–38°, $(\alpha)^{27}_{365}$ = − 227 ± 5°, $(\alpha)^{27}_{436}$ = − 170 ± 2°, and $(\alpha)^{27}_{546}$ = − 96 ± 2°, (0.419 g/100 ml CCl_4), P = 89 ± 3%. The (+)-**1** and (−)-**1** with enantiomeric purities P = 92 ± 3% and P = 90 ± 3%, respect. were obtained analogously from 100 mg of (±)-**1**. The first fractions of the eluate contained 28 mg of (+)-**1**, m.p. = 36–37°, $(\alpha)^{22}_{365}$ = + 285 ± 5°, $(\alpha)^{22}_{436}$ = + 170 ± 4° and $(\alpha)^{22}_{546}$ = + 98 ± 4°, (0.385 g/100 ml CCl_4). The last fractions of the eluate contained 37 mg of (−)-**1**, m.p. = 36–37°, $(\alpha)^{22}_{365}$ = − 280 ± 3°, $(\alpha)^{22}_{436}$ = − 172 ± 6°, and $(\alpha)^{22}_{546}$ = − 108 ± 6° (0.344 g/100 ml CCl_4).

(±)-trans-3-*Benzyl*-1,3-*dimethyldiaziridine* (**2**) prepared as reported.[19,20] ^{1}H NMR (CCl_4, 33°, 0.19 M δ = 1.28 (C–CH_3, s), 2.04 (N–H, s, broad), 2.48 (N–CH_3, s), 2.74 and 2.94 (CH_AH_B, ^3J = 13.3 Hz), 7.3 (C_6H_5, m). ^{13}C NMR (28°, 1.14 M): δ = 15.0 (3–CH_3), 40.6 (1–CH_3), 47.7 (CH_2), 59.8 (C^3, diaziridine), 126.9 (C^4, phenyl), 128.5 (C^3, phenyl), 129.7 (C^2, phenyl), 137 (C^1, phenyl). (MS molecular ion: Calc.: 126.1157. Found: 126.1159).

(+)- *and* (−)-*trans*-3-*Benzyl*-1,3-*dimethyldiaziridine* (**2**) obtained from 100 mg of (±)-**2** through two columns at a flow rate of 130 ml/h. Altogether five column passages by applying the recycling procedure took place. Three early eluates and the first fractions of the final eluate contained 18 mg of (+)-**2**, $(\alpha)^{26}_{365}$ = + 72 ± 4° (0.267 g/100 ml CCl_4), P = 98 ± 2%. The last fractions of the final eluate contained 25 mg of (−)-**2**, $(\alpha)^{26}_{365}$ = − 54 ± 2 (0.405 g/100 ml CCl_4), P = 76 ± 3%. CD (acetonitrile, 22°): λ_{max} = 267.1 ($\Delta\epsilon$ = − 0.029 l cm^{-1} mol^{-1}), 260.5 (− 0.030), 253.9 (− 0.021), 248.1 (− 0.012). λ_{max} = 266.9 nm ($\Delta\epsilon$ = + 0.029 l cm^{-1} mol^{-1}), 260.2 (+ 0.031), 253.9 (+ 0.024), 249.9 (+ 0.014).

3,3-*Dibenzyldiaziridine* (**3**) obtained from 1,3-diphenyl acetone, liquid ammonia, and t-butylhypochlorite according to the procedure given for 3-benzyl-3-methyldiaziridine.[19] The isolation procedure was modified as follows: After removing the excess of ammonia by boiling off and filtration, the mother liquor was evaporated under reduced pressure. The raw product was purified by repeated columns chromatography on silica gel with acetone/chloroform (1:5) as an eluent. Two fold recrystallization from acetone yielded colourless crystals, m.p. 95–95.5°. ^{1}H NMR (25°, 0.065 M): δ = 2.86 and 3.04 (CH_AH_B, ^3J = 13.7 Hz), 1.7 (NH, s, broad), 7.1–7.6 (C_6H_5, m). ^{1}H NMR (d_8-toluene, 25°, 0.18 M): δ = 2.20 and 2.48 (CH_AH_B, ^2J = 14.0 Hz), 1.3 (NH, s, broad), 6.9 (C_6H_5, s). ^{1}H NMR (CD_3OD, 25°, 0.07 M): δ = 2.78 and 2.80 (CH_AH_B, satellites not visible), 7.2–7.4 (C_6H_5, m). ^{13}C NMR (27°, 1 M): δ = 42.2 (CH_2), 57.7 (C^3, diaziridine), 127.0 (C^4, phenyl), 128.4 (C^3, phenyl) 122.9 (C^2, phenyl), 135.8 (C^1, phenyl). MS: *m/z* = 225 (12%), 224 (66, $M^{+\cdot}$), 206 (12), 182 (7), 180 (15), 179 (11), 133 (59), 132 (19), 130 (14), 118 (22), 117 (16), 116 (12), 106 (14), 93 (12), 92 (18), 91 (100), 90 (8), 89 (8), 77 (9), 65 (24). $C_{15}H_{16}N_2$ requires: C, 80.32; H, 7.19; N, 12.49%. (Found: C, 80.29; H, 7.09; N, 12.49).

(+)-1-*Benzyl*-3,3-*dimethyldiaziridine* (**4**) obtained as reported.[4]

(±)-1-*Benzyl*-3,3-*cyclohexylidenediaziridine* (**5**) prepared from cyclohexanone, benzylamine, and hydroxylamine-O-sulfonic acid, according to the general procedure given in the literature.[21] The raw product was purified by fractionation under reduced pressure. The main fraction, b.p. 114–115°/0.016 Torr, yielded an oil which crystallized from n-pentane at − 30°: Colourless crystals, m.p. 34–35° (lit.[22] 34–35°). ^{1}H NMR (26°. O.079 M): δ = 1.3–2.0 (cyclohexylidene, m) 3.75 (CH_2, s), 7.2–7.5 (phenyl, m). ^{13}C NMR (27°, 1 M): δ = 39.0 (C^6, cyclohexylidene), 28.3, 25.5, 25.0, 24.9 (four other cyclohexylidene carbons), 56.7 (CH_2), 61.7 (C^3, diaziridine), 126.9 (C^4, phenyl), 128.3 (C^3, and C^2, phenyl), 139.2 (C^1, phenyl). ^{15}N NMR (CH_3OH, 7 M): δ = − 286.3 (N–H, s), and − 287.7 (N-benzyl, s), relative to external NO_3^-. (MS, molecular ion: Calc.: 202.1470. Found: 202.1473. $C_{13}H_{18}N_2$ requires: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.05; H, 8.69; N, 13.62%).

(+)- *and* (−)-1-*Benzyl*-3,3-*cyclohexylidenediaziridine* (**5**) obtained from 120 mg of (±)-**5** through two columns at a flow rate of 140 ml/hr. Altogether six column passages by applying the recycling procedure took place. Five early eluates and the first fractions of the final eluate contained 45 mg of (+)-**5**, $(\alpha)^{22}_{365}$ = + 21 ± 1° (0.945 g/100 ml of benzene). The last fractions of the final eluate contained 25 mg of (−)-**5**, $(\alpha)^{22}_{365}$ = − 24 ± 1° (1.183 g/100 ml of benzene). The ^{1}H NMR spectra of (+)- and (−)-**5** were in complete agreement with the one of (±)-**5** respectively.

3,3-*Dibenzyl*-1-*methyldiaziridine* (**6**) synthesized from 1,3-diphenylacetone, methylamine, and hydroxylamine-O-sulfonic acid in methanol as a solvent, according to the general procedure given in the literature.[19,21] The isolation procedure was modified as follows: After filtration, the mother liquor was evaporated under reduced pressure, and the raw product purified by column chromatography on silica gel with acetone/chloroform (1:5) as an eluent. The oily product was purified by high pressure liquid chromatography on Lichrosorb RP-8 (particle sizes 0.01 mm) with MeOH/water (3:2) as an eluent at a flow rate of 130 ml/hr. A steel column (Knauer, Berlin) of 1.5 cm internal diameter and 25 cm length was used. The final purification was achieved by chromatography on triacetylcellulose with EtOH/water (96:4) as an eluent. ^{1}H NMR (C_6D_6, 26°, 0.048 M): σ = 2.25, $^4J_{CHNH} \approx 0$, and 2.78, $^4J_{CHNH} \approx 0$, (CH_AH_B, ^3J = 13.9 Hz), 2.58, $^4J_{CHNH}$ = 1.2 Hz, and 2.72, $^4J_{CHNH} \approx 0.5$ Hz (CH_AH_B, ^3J = 14.7 Hz), 1.8 (NH, s, broad), 7.0–7.4 (C_6H_5, m). ^{13}C NMR (27°, 0.66 M): δ = 34.3 and 43.4 (CH_2^c and CH_2^t, respectively), 40.7 (N–CH_3), 62.6 (C^3, diaziridine), 126.5 and 126. 7 (C^4, phenyl), 128.3 and 128.4 (C^3, phenyl), 129.7 and 129.9 (C^2, phenyl), 136.3 and 136.7 (C^1, phenyl). MS: *m/z* = 239 (7%), 238 (35, $M^{+\cdot}$), 180 (13), 179 (8), 165 (8), 152 (16), 151 (10), 147 (33), 146 (6), 132 (12), 131 (23), 130 (14), 95 (29), 92 (22), 91 (100), 90 (8), 89 (12), 65 (26), 58 (26). (Found: C, 80.64; H, 7.70; N, 11.97%. $C_{16}H_{18}N_2$ requires: C, 80.63; H, 7.62; N, 11.75%).

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