190. Asymmetric Catalysis by Vitamin B_{12}: The Isomerization of Achiral Aziridines to Optically Active Allylic Amines

by **Zhong da Zhang**[1]) and **Rolf Scheffold***

Institut für Organische Chemie, Universität Bern, Freiestrasse 3, CH–3012 Bern

(1.IX.93)

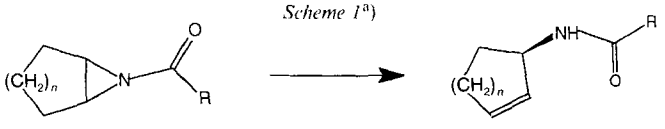
Achiral *N*-acylaziridines are isomerized to optically active *N*-acyl-allylamines in ee's of up to 95% by catalytic amounts of cob(I)alamin in MeOH.

Introduction. – Allylamines and their derivatives are important intermediates in organic synthesis, and many of them show biological activity as antimycotics like naftifine [1], SF 86-327 [2], and 1-aminocycloalk-2-enes [3], as neurotoxins like gabaculine [4], as antibiotics like oryzoxymycin [5], and as compounds with potential antiviral activity like dideoxynucleosides [6] as *e.g.* cytosimine [7], neplanocine [8], and carbovir [9].

The synthesis of primary allylamines has been reviewed in [10]. Recent related work concerns mainly the enantioselective allylic amination of *cis*-alkenes by chiral *N*-sulfinyl-carbamates [11], of alkynes with chiral Zr-derived reagents [12], and of allylic carbonates with chiral Pd complexes [13] and the enantioselective aziridination of olefins catalyzed by chiral transition-metal complexes [14].

As an extension of our previous work on the enantioselective isomerization of epoxides to allylic alcohols [15], we report here on the cob(I)alamin-catalyzed conversion of achiral *N*-acylaziridines **1** to optically active (*R*)-*N*-acyl(cycloalk-2-en-1-yl)amines **2** (*Scheme 1*).

Scheme 1[a])



1a R = *t*-BuO, *n* = 1
b R = *t*-BuO, *n* = 2
d R = Ph, *n* = 1
e R = Ph, *n* = 2
f R = Et, *n* = 2

2a R = *t*-BuO, *n* = 1
b R = *t*-BuO, *n* = 2
d R = Ph, *n* = 1
e R = Ph, *n* = 2
f R = Et, *n* = 2

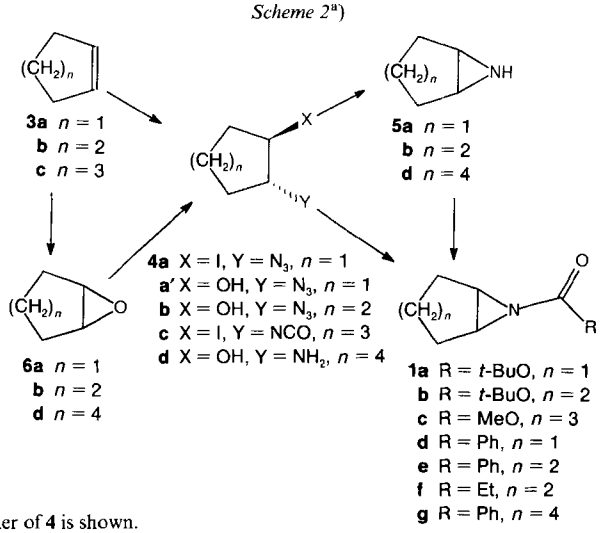
[a]) Only one enantiomer of **2** is shown.

Results and Discussion. – *Starting Materials.* Among the many methods to prepare aziridines and their derivatives [16], the most simple and cheap procedures were chosen. According to *Hassner et al.* [17], IN_3 was added to olefin **3a** affording *trans*-iodoazide **4a**

[1]) Part of the Ph.D. thesis of *Z. da Z.*, University of Bern, 1992; presented in part at the Autumn Meeting of the New Swiss Chemical Society, October 16, 1992, Berne.

(quant.), which, on reduction with $LiAlH_4$, gave **5a** in 70% yield. The alternative method of *Zwanenburg et al.* [18], opening of epoxide **6a** [19] with NaN_3 and cyclization of the *trans*-hydroxyazide **4a'** with PPh_3 was less efficient, because of problems on isolation of the volatile **5a**. However, these methods proved to be versatile in case of the transformation of higher homologues: **6b**→**4b**→**5b** (84% from **6b**). Aziridine **5d** was prepared in *ca.* 11% yield from **6d** by ring opening with ammonia to **4d**, followed by cyclization of the corresponding ammonium hydrogensulfate with NaOH [20]. The procedure of *Hassner et al.* [21] was applied to the conversion of **3c** to **1c** (31%) *via* the *trans*-iodoisocyanate **4c**. The aziridines **5a** and **5b** were acylated with di(*tert*-butyl) dicarbonate ($(Boc)_2O$) to give **1a** (84%) and **1b** (42%), respectively [22], **5a**, **5b**, and **5d** were benzoylated to give **1d** (44%), **1e** (89%), and **1g** (47%), respectively, and **5b** was propanoylated to afford **1f** (73%).

Scheme 2[a])



[a]) Only one enantiomer of **4** is shown.

Cob(I)alamin-Catalyzed Isomerization. If achiral *N*-acylaziridines **1a**,**b**,**d**–**f** were dissolved in MeOH containing a catalytic amount of cob(I)alamin (= Cbl) [23] under Ar, the corresponding (+)-(*R*)-*N*-acyl(cycloalk-2-en-1-yl)amines **2a**,**b**,**d**–**f** were formed on standing at room temperature (*Scheme 1*). The yield and enantiomeric excess (ee = $[(R) - (S)/(R) + (S)] \cdot 100$; determined by enantioselective GC) depended slightly on the reaction conditions (*Table 1*) and strongly on the structure of the aziridine (*Table 2*). In some cases, yields and ee's reached considerable-to-excellent values.

To optimize the reaction conditions, the isomerization **1e**→(*R*)-**2e** was studied in some detail (*Table 1*). The catalytically active species was cob(I)alamin (= Cbl; green), obtained from red hydroxocob(III)alamin hydrochloride (= vitamin B_{12a} = OH–Cbl·HCl) by *in situ* two-electron reduction by Zn powder in presence of NH_4Cl (*Table 1, Entries 1–10*). Since usually only 1–5 mol-% of vitamin B_{12a} (with respect to **1e** (100 mol-%), corresponding to $c = 4 \cdot 10^{-3}$ mol/l) were used, the amount of consumed Zn was negligibly small. The solvent of choice was MeOH; a small amount of Et_3N (*ca.* 1 equiv. with respect to **1e**, corresponding to $c \approx 1 \cdot 10^{-1}$ mol/l) possibly enhanced the ee (*Table 1, Entries 2* and *6*). For complete isomerization (TLC monitoring), the reaction

Table 1. *Cbl-Catalyzed Isomerization of 7-Benzoyl-7-azabicyclo[4.1.0]heptane* (**1e**) *to (R)-N-(Cyclohex-2-en-1-yl)benzamide* (**2e**)[a])

Entry	Catalytic system		Reaction conditions			Product			
	mol-% OH–Cbl·HCl	reducing agent	solvent buffer system	temp. [°C]	time [h]	**2e** [%][b])	$[\alpha]_D^{23}$[c])	ee[d])	by-products [%]
1	0	Zn/NH_4Cl	MeOH	23	168	0	0	0	e)
2	5	Zn/NH_4Cl	MeOH	23	17	90	+139	79	8[f])
3	5	Zn/NH_4Cl	MeOH	5	47	91	+154	87	6[f])
4	5	Zn/NH_4Cl	MeOH	–20	192	93	+157	89	5[f])
5	3	Zn/NH_4Cl	MeOH	15	22.5	94	+139	79	4[f])
6	5	Zn/NH_4Cl	MeOH/Et_2N[g])	23	23	84	+154	87	16[f])
7	5	Zn/NH_4Cl	MeOH/Et_3N[g])	–20	168	90	+158	90	5[f])
8	1	Zn/NH_4Cl	MeOH/Et_3N[g])	0	132	53	+154	87	27[f])
9	10	Zn/NH_4Cl	MeOH/Et_3N[g])	–30	244	90	+159	91	3[f])
10	5	Zn/NH_4Cl	MeOH/dioxane 1:4	23	132	38	+132	76	47[f])
11	5	Zn[h])	H_2O/phthalic acid[h])	23	23	33	+110	63	2[f])
12	1[i])	Zn/NH_4Cl	MeOH/Et_3N[g])	0	288	10[h])	+132	76	55[f])
13	5[i])	Zn/NH_4Cl	MeOH	23	46	13	+139	79	77[f])

[a]) Reaction conditions: Hydroxocob(III)alamin hydrochloride (= vitamin B_{12a} = OH–Cbl·HCl; *Entries 1–11*) or dicyano(heptamethyl Cob(III)yrinate) (*Entries 12* and *13*) dissolved in the solvent/buffer system was reduced *in situ* by 'activated' Zn (excess) in presence of NH_4Cl under Ar. To the dark-green mixture, **1e** was added and stirred. For workup, the mixture was diluted with H_2O and extracted with Et_2O (see *Exper. Part*).

[b]) Yield of pure **2e** ((*R*)- and (*S*)-enantiomers) rel. to **1e**.

[c]) Optical rotation of crude **2e** before crystallization (conc. and solvent, see *Exper. Part*); limits of error *ca.* ±2%.

[d]) Determined by enantioselective GC (17% heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin and 25% heptakis(2,3,6-tri-*O*-propyl)-β-cyclodextrin in *OV-1701*, 130°).

[e]) *N*-(Chlorocyclohexyl)benzamide (39%), *N*-(2-methoxycyclohexyl)benzamide (27%), and *N*-cyclohexylbenzamide (9%).

[f]) Yield of *N*-cyclohexylbenzamide, as determined by GC in the raw products.

[g]) 1 mol-equiv. of Et_3N with respect to **1e**.

[h]) Phthalic acid (0.8 mol-equiv. with respect to **1e**) instead of NH_4Cl.

[i]) Dicyano(heptamethyl cob(III)yrinate) instead of OH–Cbl·HCl.

was run for *ca.* 20 h at room temperature or for more than 200 h at −30°. The influence of the temperature on yield and ee was not very marked (*Table 1*, *Entries 6* and *9*). Achiral *N*-cyclohexylbenzamide was detected as the main by-product. On workup in presence of air, cob(III)alamin was immediately regenerated and may be re-used. If, under otherwise the same conditions, dicyano(heptamethyl cob(III)yrinate) was used as catalyst instead of OH–Cbl·HCl, mainly *N*-cyclohexylbenzamide and only small amounts of **2e** ((*R*)) were obtained (*Table 1*, *Entries 12* and *13*). A control experiment in absence of any catalyst gave products mainly resulting from aziridine-ring opening by nucleophiles like Cl^- and MeOH and no **2e** (*Table 1*, *Entry 1*).

In case of the 5-ring acylaziridines, the (*tert*-butyloxy)carbonyl (Boc)-protected derivative **1a** (crude oil containing *ca.* 15% of *tert*-butyl cyclopentanecarbamate) isomerized at 0° within 8 days to **2a** ((*R*)) in 56% yield and 87% ee (*Table 2*, *Entry 2*). The Boc protecting group was removed with CF_3COOH *via* the ammonium trifluoroacetate **7a**·CF_3COOH (93% yield) to yield the free amine **7a** ((*R*)) with $NaOH/H_2O$ (volatile, not isolated; *Scheme 3*). Benzoylaziridine **1d** isomerized at room temperature within 18.5 h to **2d** ((*R*); 49% yield, 51% ee; *Table 2*, *Entry 1*).

Table 2. *Cbl-Catalyzed Isomerization of Achiral Aziridines to Optically Active Allylamines*[a])

Entry	Starting material		Reaction conditions				Product				
	Aziridine	*n*	R	buffer[b])	temp. [°C]	time [h]	allylamine	yield[c]) [%]	$[\alpha]_D^{23}$[d])	ee [%]	configuration
1	**1d**	1	Ph	–	*ca.* 22	18.5	**2d**	49	+76	51[e])	*R*[g])
2	**1a**	1	*t*-BuO	1.1	0	192	**2a**	56	+77	87[f])	*R*[g])
3	**1e**	2	Ph	1.0	–20	168	**2e**	90	+158	90[f])	*R*[h])
4	**1e**	2	Ph	1.2	*ca.* 22	23	**2e**	84	+154	87[f])	*R*[h])
5	**1b**	2	*t*-BuO	1.1	0	216	**2b**	64	+101	95[f])	*R*[h])
6	**1b**	2	*t*-BuO	1.2	*ca.* 22	20	**2b**	50	+98	92[f])	*R*[h])
7	**1f**	2	Et	–	*ca.* 22	20	**2f**	52	+58	54[f])	*R*[h])
8	**5b**[i])	2	[i])	[j])	*ca.* 22	17	**7c**	58	–3.8	10[k])	*S*[h])
9	**1c**	3	MeO	1.5	*ca.* 22	96	no isomerization				
10	**1g**	4	Ph	1.2	*ca.*22	168	no isomerization				

[a]) Reaction conditions: Hydroxocob(III)alamin hydrochloride (= vitamin B_{12a} = OH–Cbl·HCl; 5 mol-% with respect to aziridine (= 100 mol-%)) dissolved in MeOH/buffer was reduced *in situ* by 'activated' Zn (excess) in presence of NH_4Cl under Ar. To the dark-green mixture was added the aziridine and stirred. For workup, the mixture was diluted with H_2O and extracted with Et_2O (see *Exper. Part*).

[b]) Mol-equiv. of Et_3N with respect to aziridine.

[c]) Yield of pure allylamine ((*R*)- and (*S*)-enantiomers) rel. to pure aziridine. The main by-product was *N*-acylcycloalkylamine.

[d]) Optical rotation of crude allylamines before crystallization (conc. and solvent see *Exper. Part*). Limits of error *ca.* ±2%.

[e]) Determined by enantioselective GC of the *N*-methylated derivative **2d'**, prepared from **2d**.

[f]) Determined by enantioselective GC.

[g]) Chemical correlation with (–)-(*R*)-glutamic acid.

[h]) Chemical correlation with (+)-(*S*)-2-aminohexanedioic acid.

[i]) *N*-Unacylated aziridine.

[j]) Phthalic acid (0.5 mol-equiv. with respect to aziridine) instead of NH_4Cl.

[k]) Chemical correlation with **2b**.

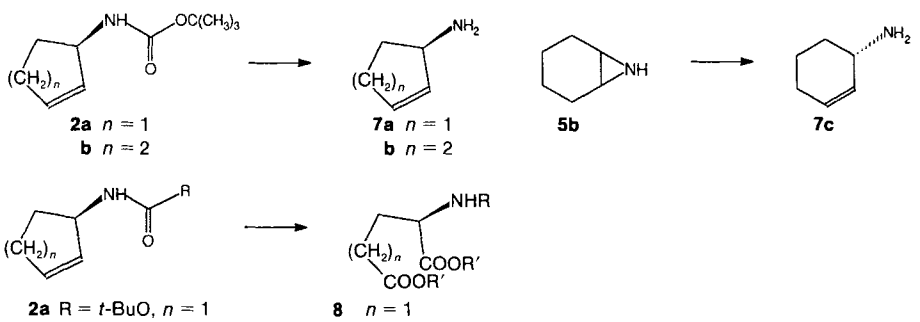
In case of the 6-ring aziridines, the Boc-protected derivative **1b** isomerized at 0° within 9 days to **2b** ((*R*)) in 64% yield and an impressive ee of 95% (*Table 2, Entry 5*). The Boc protecting group was removed as described above, affording (+)-(*R*)-(cyclohex-2-en-1-yl)amine (**7b**) in 90% yield. Benzoylaziridine **1e** (crude solid, containing *ca.* 12% of *N*-cyclohexylbenzamide) isomerized at –20° within 7 days to **2e** ((*R*)) in 90% yield and 90% ee (*Table 2, Entry 3*). Crystallization afforded enantiomerically pure **2e** ((*R*)) in 65% yield with respect to **1e**. *N*-Propanoylaziridine **1f**, however, afforded, after isomerization at room temperature for 20 h **2f** in only 52% yield and 54% ee. The main by-products of isomerization were the corresponding *N*-(cycloalkyl)carboxamides in all cases described above.

In case of the 7- and 8-ring aziridines **1c** and **1g**, respectively, no isomerization was observed (*Table 2, Entries 9* and *10*).

Configuration by Chemical Correlation. To establish the chirality of the acylamino-substituted cyclopent-2-enes **2a** and **2d**, they were converted to the corresponding (*R*)-glutamic acid (**8**) of known configuration [24]. To this end, **2a** was ozonized in CH_2Cl_2 (oxidative workup with H_2O_2), the Boc protecting group removed with CF_3COOH, and the salt purified by ion-exchange chromatography affording **8** ((*R*)) in 60% yield; its $[\alpha]_D^{23} = -18.9$ and all other properties corresponded to (*R*)-glutamic acid (60% ee).

Similarly, **2d** was ozonized, oxidized, and the benzoylamino function hydrolyzed with 6N HCl/H_2O affording **8** ((*R*)) in 87% yield; its $[\alpha]_D^{23} = -4.91$ and all other properties corresponded to (*R*)-glutamic acid of only 16% ee, due to partial racemization. The chirality of the acylamino-substituted cyclohex-2-enes **2e** and **2f** was correlated with that of known (*R*)-2-aminohexanedioic acid [25] (**9a**). As described above, **2e** was ozonized and oxidized. For hydrolysis of the amide function, the diacid was first transformed to the dimethyl ester (60%), the amide acylated with $(Boc)_2O$, and the diacylamino function solvolyzed with MeONa in MeOH [26]. Ion-exchange chromatography afforded **9** ((*R*)) in 75% yield; its $[\alpha]_D^{20} = -14.3$ and all other properties corresponded to (*R*)-2-aminohexanedioic acid (55% ee). Finally, **2f** was ozonized, oxidized, and the diacid esterified with CH_2N_2 to afford dimethyl (*R*)-2-(propanoylamino)hexanedioate (**9b**) in 16% yield ($[\alpha]_D^{23} = -4.1$, 12% ee). The enantiomer, to which it was correlated, was obtained from pure (*S*)-2-aminohexanedioic acid by esterification with CH_2N_2 and propanoylation with propanoyl chloride in 25% yield ($[\alpha]_D^{23} = +33.7$, 100% ee).

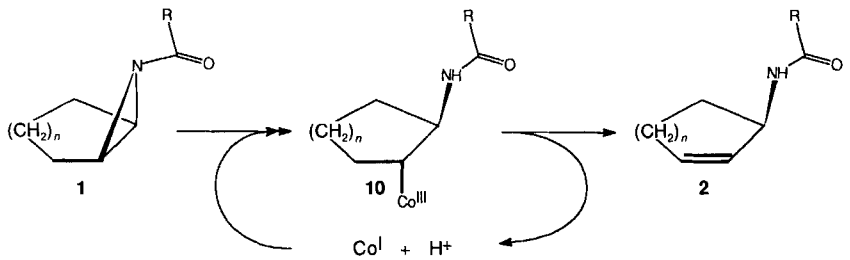
Scheme 3[a])



[a]) Only one enantiomer of **2**, **7**, **8**, and **9** is shown.

Mechanism of Isomerization. Even without having detailed information about kinetics, thermodynamics, or the structure of intermediates of the isomerization **1**→**2**, it is believed, that the reaction mechanism is generally the same as that described for the Cbl-catalyzed isomerization of epoxides to allylic alcohols [27]. However, there are two remarkable differences: *i*) there is no increase in the ee of **2e** in lowering the polarity of the solvent (*cf. Table 1, Entries 2* and *10*), *ii*) the colour of the reacting mixture is not orange-red (colour of alkylcob(III)alamins) but dark brown-grey; the UV/VIS spectrum of the mixture during the whole reaction is dominated by the sharp absorption signal at *ca.* 390 nm (signal of cob(I)alamin) and only a relatively weak shoulder at *ca.* 520 nm (signal of alkylcob(III)alamins). These observations suggest that the isomerization of **1** proceeds in two steps *via* intermediate organocobalamins as minor species in the steady state (*Scheme 4*). In the first step, the aziridin ring is opened by an S_N2-type displacement of the N-atom by the (chiral) Co^I nucleophil to afford a mixture of the two diastereoisomeric (1*R*,2*R*)- and (1*S*,2*S*)-*Coβ*-(2-(acylamino)cycloalkyl)cob(III)alamins **10** (only the (1*R*,2*R*)-diastereoisomer is shown) in different amounts (ratio in case of **1e**→**2e** *ca.* 20:1). This step is rate-limiting and responsable for the enantioselectivity. The intermediates **10**

Scheme 4[a])



[a]) Only one diastereoisomer of **10** and one enantiomer of **2** is shown.

decompose in the second and faster step to give **2** (only the (*R*)-enantiomer is shown) and recycled Co^{I} and H^+. The reason for the high enantioselectivity is not yet understood, but it has certainly to do with the β-axially oriented substituents at the periphery of the corrin nucleus, mainly by interactions with the *a*- and *c*-acetamido side chains of Cbl, acting as 'gate posts' [28] [29] in the approach of the aziridin to Co^{I} on its way to the S_N2 transition state.

The authors are grateful to PD Dr. *P. Bigler* and Dr. *Ch. Müller* for the NMR spectra, Mr. *A. Saxer* for anal. GC and enantioselective GC, and Prof. *U. P. Schlunegger* and his group for the MS and GC/MS, all from the University of Berne. This work was financially supported by the *Swiss National Science Foundation*.

Experimental Part

1. *General.* Chemicals and solvents: Vitamin B_{12a} (= hydroxocobalamin hydrochloride pyrogen-free *Fr. Ph. BP*, 10.7% loss on drying, < 2% cyanocobalamin) from *Roussel Uclaf*; cyclopentene oxide (**6a**; 98%) from *Aldrich*; cyclooctene oxide (**6d**; 99%) from *EGA-Chemie*; NH_4Cl (*purum*), 30% H_2O_2 (*Ph. Hvi.*), pyridine (*Ph. Hvi.*), 25% NH_4OH (*Ph. Hvi.*), and Zn powder from *Siegfried* ('activated': a 25-ml flask containing Zn powder (*ca.* 1 g), in MeOH (10 ml) was placed for 5 min in an ultrasonic cleaning bath (33 kHz, 50 W, Tec-15, *Telesonic*), Zn filtered off, and used immediately); AgNCO freshly prepared [30] from KNCO and $AgNO_3$ (*Fluka*); CH_2N_2 in Et_2O prepared from *N*-nitroso-*N*-methyltoluene-4-sulfonamide [31] (*Fluka*); all other reagents from *Fluka*: CII *pract.* and NH_4Cl, NaN_3, $Na_2S_2O_3$, $SOCl_2$, $LiAlH_4$, Et_3N, 4-(dimethylamino)pyridine, MeI, di-*tert*-butyl dicarbonate [$(Boc)_2O$], benzoyl chloride, propanoylchloride, and CF_3COOH all *purum*; solvents from *Fluka*: MeCN, *t*-BuOH, THF, Et_2O, CH_2Cl_2 all *purum* and distilled before use; sat. NaCl soln. in H_2O (brine). Ozonolysis: O_3/O_2 mixture generated by a *Fischer* ozoniser. Column chromatography (CC): silica gel from *Baker*; for 'Ag-activated' silica gel; silica gel was suspended in 5% $AgNO_3/H_2O$, filtered off, dried at 110° for 12 h and stored in the dark. Anal. TLC: precoated plates, silica gel *60* F_{254} from *Merck*; for 'Ag-activated' plates, plates were dipped in 5% $AgNO_3/H_2O$ and dried as above; same eluent as for the corresponding CC. Anal. GC: *Hewlett-Packard-5794* gas chromatograph; 20-m *Duran* glass cap. column coated with *SE-54* (*df* = 0.15 µm), temp. program from 40 to 250° at 3°/min; flame-ionization detector (FID). Enantioselective GC (t_R in min): *Hewlett-Packard-5890* with modified cyclodextrins as chiral stationary phase, *vide infra*; in all cases, the ee was determined from the % of relative intensities of base-line separated peaks of enantiomers and checked by parallel measurements of the corresponding racemic, enantiomerically enriched, or enantiomerically pure compounds. Amino-acid analysis: *Hewlett-Packard* liquid chromatograph, reversed-phase HPLC on a *Nova-Pak-C18* column. Melting point (uncorrected): *Büchi 510*. $[\alpha]_D$: *Perkin-Elmer-241* polarimeter. UV/VIS: *Hewlett-Packard-8451A* diode array spectrophotometer. IR: *Perkin-Elmer-782* spectrometer. ^{1}H-NMR: *Bruker-AM-400 WB* (400 MHz) and *Bruker-AC-300* (300 MHz) spectrometer; δ-values in ppm with respect to Me_4Si (= 0 ppm) as internal standard. ^{13}C-NMR: *Bruker-AM-400-WB* (100 MHz) and *Bruker-AC-300* (75 MHz) spectrometer; Me_4Si (= 0 ppm) as internal standard. MS (*m/z* (%)): *Varian-MAT-CH-7A*, ionization energy 70 eV. GC/MS: *Varian MAT-44S*. Elemental analyses: Mikroelementaranalytisches Laboratorium, ETH, Zürich.

2. *Starting Materials.* *(±)*-trans-*1-Azido-2-iodocyclopentane* (**4a**). To a stirred suspension of NaN_3 (16.3 g, 0.25 mol) in MeCN (100 ml) in a cooling bath (−20°) was added slowly a soln. of ClI (18.3 g, 0.113 mol) in MeCN (20 ml) within 20 min. After stirring for additional 10 min, cyclopentene (**3a**; 7.8 g, 0.10 mol) was added and the mixture allowed to warm up to r.t. under stirring for 10 h. The red-brown slurry was poured into H_2O (250 ml) and extracted with Et_2O (3 × 250 ml). The org. phase was washed with 5% $Na_2S_2O_3$ in H_2O (150 ml) and brine (2 × 300 ml), dried ($MgSO_4$) and evaporated: 26.7 g (100%) of **4a**. Slightly orange oil. IR (film): 2980*s*, 2890*w*, 2110*s*, 1475*w*, 1450*m*, 1355*m*, 1335*m*, 1255*s*, 1175*m*, 1125*m*, 1040*w*, 930*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.35–2.30 (*m*, 6H); 3.85–4.10 (*m*, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): 22.5 (*t*); 28.7 (*d*); 29.4 (*t*); 36.8 (*t*); 71.7 (*d*). MS: 237 (6, M^+), 197 (2), 195 (3), 167 (4), 155 (5), 154 (59), 128 (10), 127 (15), 111 (8), *110* (100), 81 (3), 80 (27), 68 (15), 67 (85), 55 (93), 41 (29), 18 (22).

(±)-trans-*2-Azidocyclopentan-1-ol* (**4a′**). A mixture of cyclopentene oxide (**6a**; 8.41 g, 0.10 mol) and NaN_3 (16.25 g, 0.25 mol) in acetone/H_2O 1:1 (120 ml) was heated under reflux for 22 h. After most of the acetone was evaporated, the soln. was extracted with Et_2O (3 × 80 ml) and CH_2Cl_2 (3 × 60 ml). The combined org. phase was washed with brine (2 × 20 ml), dried ($MgSO_4$), and evaporated: 14.0 g of a yellow oil. Bulb-to-bulb distillation (40° (oven temp.)/0.02 mbar) afforded 12.7 g of **4a′**. Pale yellow oil. GC: 96% purity (corresponding to 96.0% yield). IR (film): 3360*s* (br.), 2985*m*, 2100*s*, 1450*w*, 1250*m*, 1185*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.52–1.90 (*m*, 4 H); 1.92–2.13 (*m*, 2 H); 2.68 (*s*, OH, 1 H); 3.70 (*m*, 1 H); 4.08 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.4 (*t*); 28.6 (*t*); 32.1 (*t*); 68.7 (*d*); 77.6 (*d*). MS: 127 (2, M^+), 110 (1), 99 (9), 98 (8), 85 (2), 84 (5), 83 (14), 82 (11), 81 (8), 80 (5), 79 (3), 72 (3), 71 (63), 70 (14), 67 (15), 58 (4), 57 (30), 56 (14), 55 (18), 54 (16), 44 (98), *43* (100), 42 (22), 41 (35), 28 (31), 18 (21).

6-Azabicyclo[3.1.0]hexane (**5a**). i) *From* **4a**: A suspension of $LiAlH_4$ (3.50 g, 92.2 mmol) in Et_2O (100 ml) was cooled in an ice-bath. To the stirred slurry was added **4a** (11.85 g, 50 mmol) within 30 min under Ar. The mixture was then allowed to warm up to r.t. under stirring for 12 h. Workup was accomplished by slow addition of 20% NaOH in H_2O (20 ml), followed by 30 min of vigorous stirring. The white, granular salts were filtered off, and the filtrate was extracted with Et_2O (2 × 40 ml). The Et_2O phase was washed with brine (50 ml), dried ($MgSO_4$), and evaporated carefully *i.v.*: **5a** (2.91 g, 70%).

ii) *From* **4a′**: A soln. of **4a′** (12.7 g, 0.10 mol) and PPh_3 (31.5 g, 0.12 mol) in THF (120 ml) was heated under reflux for 15 h. After most of THF was distilled off at 80° (bath temp.), 10% NaOH in H_2O (100 ml) was added and the mixture heated under reflux for 5 h. Steam distillation at *ca.* 100° gave a total volume of *ca.* 90 ml of distillate which was extracted with Et_2O (6 × 80 ml) and CH_2Cl_2 (40 ml). The combined org. phases were washed with brine (2 × 20 ml) and dried ($MgSO_4$) and the solvents distilled off *i.v.*: 8.0 g of pale yellow liquid. GC: 55% of **5a** (53% yield rel. to **4a′**). For analysis, crude **5a** was distilled in a *Vigreux* column (90°/540 mbar). Volatile colorless liquid. IR ($CDCl_3$): 3310*w*, 3040*m*, 2960*s*, 2860*m*, 1445*w*, 1320*w*, 1215*w*, 1165*m*, 1115*w*, 1050*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.55 (*s*, NH); 1.10–1.85 (*m*, 6H); 2.44 (*s*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.1 (*t*); 27.2 (*t*); 35.5 (*d*). GC/MS: 83 (10, M^+), 82 (78), 80 (26), 69 (5), *68* (100), 67 (18), 65 (7), 56 (34), 55 (31), 54 (44), 53 (10), 51 (4), 42 (15), 41 (37), 39 (22), 38 (5).

N-*(*tert*-Butoxycarbonyl)-6-azabicyclo[3.1.0]hexane* (**1a**). To a stirred soln. of NaOH (1.60 g) in H_2O (40 ml) and *t*-BuOH (24 ml), **5a** (2.91 g, 35 mmol; from **4a**) was added at r.t. under Ar, followed by $(Boc)_2O$ (7.64 g, 35 mmol) in *t*-BuOH (15 ml) within 1 h (→white precipitate, temp. rise to 35°). After stirring for 12 h at r.t., the mixture was extracted with Et_2O (3 × 70 ml), the combined Et_2O phase washed with brine (2 × 40 ml), dried ($MgSO_4$), and evaporated: 6.40 g of yellowish oil (100%, calc. as $C_{10}H_{12}NO_2$). GC: 84% of **1a** (84% yield rel. to **5a**) and 15% of *tert*-butyl cyclopentanecarbamate.

Data of **1a**: IR (film): 2980*s*, 2940*s*, 2860*m*, 1710*s*, 1515*w*, 1480*m*, 1460*m*, 1440*w*, 1385*m*, 1370*m*, 1345*m*, 1315*m*, 1280*m*, 1255*m*, 1160*s*, 1100*w*, 1000*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.00–1.10 (*m*, 2 H); 1.30 (*s*, 9 H); 1.38–1.53 (*m*, 4 H); 1.85–1.98 (*m*, 2 H); 2.75 (*s*-like, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.4 (*t*); 26.4 (*t*); 27.9 (*q*); 42.9 (*d*); 80.4 (*s*); 161.4 (*s*). MS: 185 (1, $[M + 2]^+$), 184 (0.3, $[M + 1]^+$), 168 (2), 130 (7), 129 (8), 128 (10), 127 (51), 113 (10), 110 (22), 84 (21), 83 (85), 82 (68), 68 (70), 67 (59), *59* (43), 58 (17), *57* (100), 56 (25), 55 (24), 54 (12), 41 (56), 19 (23), 18 (8).

(±)-trans-*2-Azidocyclohexan-1-ol* (**4b**). A mixture of cyclohexene oxide (**6b**; 14.7 g, 0.15 mol) and NaN_3 (25 g, 0.38 mol) in acetone/H_2O 1:1 (160 ml) was heated under reflux for 14.5 h. After most of the solvent was evaporated, the soln. was extracted with Et_2O (3 × 80 ml) and CH_2Cl_2 (3 × 80 ml). The combined org. phase was washed with H_2O (2 × 20 ml), dried ($MgSO_4$), and evaporated: 21.5 g of **4b**. Pale yellow oil. GC: 93% purity, corresponding to 93% yield. IR (film): 3400*s* (br.), 2940*s*, 2860*s*, 2090*s* (N_3), 1450*m*, 1260*s*, 1070*s*, 990*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.15–1.42 (*m*, 4 H); 1.62–1.86 (*m*, 2 H); 1.90–2.10 (*m*, 2 H); 3.10 (*s*, OH); 3.12–3.27 (*m*, 1 H); 3.29–3.47 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.9 (*t*); 24.2 (*t*); 29.9 (*t*); 33.2 (*t*); 67.1 (*d*); 73.6 (*d*). MS: 142 (4, $[M + 1]^+$), 141 (48, M^+), 138 (3), 112 (6), 99 (9), 98 (10), 97 (3), 96 (8), 95 (6), 94 (6), 85 (8), 84 (38), 83 (6), 82 (28), 81 (88), 79 (18),

72 (5), 71 (22), 70 (58), 69 (24), 68 (26), 67 (37), 65 (7), 58 (18), 57 (90), 56 (86), 55 (39), 54 (47), 53 (15), 45 (13), 44 (73), *43* (100), 42 (44), 41 (62), 40 (18), 39 (34), 28 (53), 18 (19).

7-Azabicyclo[4.1.0]heptane (**5b**). A soln. of **4b** (18.3 g, 130 mmol) and PPh_3 (39.3 g, 150 mmol) in dry THF (150 ml) was heated under reflux for 15 h. After most of the THF was distilled off at 80° (bath temp.), 10% NaOH in H_2O (150 ml) was added and the mixture heated under reflux for 5 h. Steam distillation at *ca.* 100° gave a total of *ca.* 130 ml of distillate. It was extracted with Et_2O (6 × 80 ml) and CH_2Cl_2 (40 ml), and the combined org. phase washed with brine (2 × 20 ml), dried ($MgSO_4$), and evaporated: 11.8 g (90%) of **5b**. Colourless liquid. GC: 97% purity. IR (film): 3250*s*, 3000*s*, 2930*s*, 2850*s*, 1440*s*, 1245*m*, 1140*m*, 1070*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.00–1.50 (*m*, 5 H); 1.60–1.80 (*m*, 4 H); 2.18 (*s*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.9 (*t*); 24.4 (*t*); 29.1 (*d*). MS: 97 (7, $M^{+\cdot}$), 96 (38), 86 (25), 84 (61), 83 (4), *82* (100), 80 (8), 79 (6), 74 (8), 72 (30), 71 (38), 69 (61), 68 (79), 56 (10), 43 (25), 42 (44), 41 (38), 39 (13), 28 (20), 18 (7).

tert-*Butyl 7-Azabicyclo[4.1.0]heptane-7-carboxylate* (**1b**). To a stirred soln. of **5b** (0.58 g, 6.0 mmol), Et_3N (0.61 g, 6.0 mmol), and 4-(dimethylamino)pyridine (0.75 g, 6.0 mmol) in CH_2Cl_2 (20 ml) was added $(Boc)_2O$ (2.62 g, 12.0 mmol) at 0° within 10 min under Ar. The soln. was stirred for 1 h at 0° and for 18 h at r.t. Evaporation and CC (silica gel (100 g), pentane/Et_2O 3:7) afforded 0.81 g of a colourless oil (TLC: R_f 0.51). Bulb-to-bulb distillation (45° (oven temp.)/0.05 mbar) afforded 0.50 g of **1b** (42%). Colourless solid: M.p. 36.5°. IR (KBr): 3000*m*, 2980*s*, 2930*s*, 2860*m*, 1715*s*, 1480*m*, 1440*m*, 1415*m*, 1370*s*, 1295*s*, 1225*s*, 1160*s*, 1085*m*, 1010*m*, 950*w*, 930*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.14–1.28 (*m*, 2 H); 1.32–1.48 (*m*, 2 H); 1.46 (*s*, *t*-Bu); 1.70–1.86 (*m*, 2 H); 1.87–2.00 (*m*, 2 H); 2.55 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.9 (*t*); 23.7 (*t*); 27.9 (*q*); 36.9 (*d*); 80.5 (*s*); 163.3 (*s*). MS: 198 (0.4, $[M+1]^+$), 197 (0.1, $M^{+\cdot}$), 182 (0.5), 142 (11), 141 (54), 138 (4), 126 (22), 124 (11), 98 (11), 97 (70), 96 (93), 83 (9), 82 (90), 81 (62), 79 (16), 70 (6), 69 (67), 68 (27), 58 (30), *57* (100), 56 (11), 55 (13), 42 (24), 41 (39), 29 (9), 18 (6).

Methyl 8-Azabicyclo[5.1.0]octane-8-carboxylate (**1c**). To a suspension of freshly prepared AgNCO (4.30 g, 18.5 mmol) in THF (50 ml) and cycloheptene (**3c**; 2.15 g, 22.4 mmol) was added portionwise I_2 (5.47 g, 22 mmol). On stirring for 4 h at −20°, the originally dark-brown mixture became yellow. After warming to r.t., the inorg. salts were filtered off and the filtrate concentrated to *ca.* 28 ml. To this mixture was added MeOH (60 ml) and the soln. heated under reflux for 4 h. After most of the solvents were evaporated, H_2O (20 ml) was added, the mixture extracted with Et_2O (4 × 40 ml), and the combined org. phase washed with brine (2 × 40 ml), dried ($MgSO_4$), and evaporated: 6.45 g of **4c** as brown solid. This solid was dissolved in THF (40 ml), NaOMe (0.54 g) added, and the mixture heated under reflux for 5.5 h. After addition of H_2O (20 ml), the soln. was extracted with Et_2O (4 × 40 ml) and the org. phase washed with brine (2 × 20 ml), dried ($MgSO_4$), and evaporated: 1.45 g of **1c**. Pale yellow oil. GC: 80% purity (31% yield rel. to **3c**). IR (CH_2Cl_2): 2980*w*, 2960*s*, 2930*s*, 2860*s*, 1740*s*, 1440*s*, 1360*m*, 1300*s*, 1240*s*, 1100*m*, 1050*w*, 1025*w*, 910*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20–2.10 (*m*, 10 H, CH_2); 2.53 (*s*-like, 2 H, CH); 3.70 (*s*, MeO). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.3 (*t*); 29.2 (*t*); 30.5 (*t*); 41.9 (*d*); 53.3 (*d*); 164.8 (*s*). GC-MS: 169 (11, $M^{+\cdot}$), 168 (5), 155 (10), 154 (77), 142 (25), 141 (10), 140 (25), 128 (11), 126 (17), 110 (67), 101 (12), 95 (30), 83 (39), 82 (18), 81 (17), 68 (20), 67 (27), 59 (28), 56 (22), *55* (100), 41 (76), 28 (33).

6-*Benzoyl-6-azabicyclo[3.1.0]hexane* (**1d**). To a stirred soln. of crude **5a** (0.58 g, 7.0 mmol; from **4a**) and Et_3N (1.01 g, 10 mmol) in dry Et_2O (20 ml) was added benzoyl chloride (0.98 g, 7.0 mmol) within 30 min at 10°. After stirring for 15 h at r.t., H_2O (10 ml) was added and the mixture extracted with Et_2O (4 × 25 ml). The combined Et_2O fractions were washed with brine (10 ml), dried ($MgSO_4$), and evaporated: 0.80 g of yellowish oil. CC (silica gel (80 g), Et_2O/pentane 1:1) gave 0.57 g of **1d** (44% rel. to **5a**). Colourless solid. TLC: R_f 0.54. M.p. 57°. UV (MeOH): 208 (3.88), 240 (4.02). IR (CH_2Cl_2): 3040*m*, 2970*m*, 2930*m*, 2860*m*, 1670*s*, 1600*m*, 1580*m*, 1450*s*, 1380*s*, 1320*s*, 1270*s*, 1220*w*, 1130*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.25–1.50 (*m*, 1 H); 1.60–1.78 (*m*, 3 H); 2.03–2.21 (*m*, 2 H); 3.19 (*s*, 2 H); 7.32–7.58 (*m*, 3 H); 7.90–8.00 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.5 (*t*); 27.0 (*t*); 43.7 (*d*); 128.3 (*d*); 128.7 (*d*); 132.3 (*d*); 133.6 (*s*); 178.1 (*s*). GC/MS: 187 (1.2, $M^{+\cdot}$), 186 (2.6), 158 (1), 106 (8), *105* (100), 104 (1), 78 (4), 77 (62), 76 (2), 67 (3), 55 (15), 51 (17), 41 (6), 39 (7).

7-Benzoyl-7-azabicyclo[4.1.0]heptane (**1e**). As described for **1d**, **5b** (0.97 g, 10.0 mmol) was benzoylated affording 2.04 g of **1e** (89%). GC: 88% purity. For analysis, crude **1e** was crystallized from Et_2O/hexane 1:2 at 4°. Colourless solid. M.p. 77°. UV (MeOH): 192 (3.36), 208 (4.29), 240 (4.42). IR (KBr): 3440*w*, 3060*w*, 3005*w*, 2930*m*, 2860*m*, 1985*w*, 1310*w*, 1790*w*, 1670*s*, 1600*m*, 1580*w*, 1450*m*, 1410*m*, 1310*m*, 1290*s*, 1230*m*, 1185*w*, 1120*m*, 1070*m*, 1020*w*, 1000*w*, 700*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.28–1.48 (*m*, 2 H); 1.50–1.65 (*m*, 2 H); 1.82–2.00 (*m*, 2 H); 2.00–2.20 (*m*, 2 H); 2.75 (*m*, 2 H); 7.38–7.48 (*m*, 2 H); 7.50–7.58 (*m*, 1 H); 7.92–8.06 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.9 (*t*); 23.8 (*t*); 37.0 (*d*); 128.7 (*d*); 128.9 (*d*); 132.4 (*d*); 133.5 (*s*); 180.0 (*s*). MS: 203 (1, $[M+2]^+$), 202 (16, $[M^+ + 1]^+$), 201 (82, $M^{+\cdot}$), 200 (98), 199 (16), 173 (6), 172 (4), 146 (4), 123 (4), 122 (8), 106 (28), *105* (100), 104 (6), 97 (19), 96 (98), 82 (8), 80 (6), 79 (8), 78 (10), 77 (61), 76 (4), 69 (50), 68 (10), 67 (13), 51 (21), 42 (30), 41 (28).

7-Propanoyl-7-azabicyclo[4.1.0]heptane (**1f**). As described for **1d**, **5b** (0.98 g, 10.1 mmol) was propanoylated with Et_3N (1.10 g, 11.0 mmol) and propanoyl chloride (0.95 g, 10.3 mmol) affording 1.80 g of an oil. CC (silica gel

(100 g), Et_2O) gave 1.14 g (73%) of **1f**. Colourless liquid. IR ($CHCl_3$): 3000*s*, 2940*s*, 2865*m*, 1680*s*, 1610*w*, 1500*m*, 1460*m*, 1440*m*, 1420*m*, 1370*m*, 1270*w*, 1170*m*, 1080*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.18 (*t*, J = 7, Me); 1.20–1.33 (*m*, 2 H); 1.37–1.50 (*m*, 2 H); 1.75–2.00 (*m*, 4 H); 2.40 (*q*, J = 7, CH_2); 2.60 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.4 (*q*); 19.9 (*t*); 23.9 (*t*); 29.8 (*t*); 35.6 (*d*); 187.5 (*s*). MS: 153 (9, M^+), 125 (2), 98 (7), 97 (81), 96 (71), 82 (35), 81 (13), 80 (3), 79 (4), 70 (5), 69 (52), 68 (11), 67 (7), 57 (17), 56 (5), 55 (9), 54 (5), 42 (34), 41 (18), 28 (44), *18* (100).

(±)-trans-*2-Aminocyclooctan-1-ol* (**4d**). In a steel bomb equipped with stirrer, cyclooctene oxide (**6d**; 7.56 g, 60 mmol) and 25% aq. NH_4OH soln. (100 ml) were heated at 140° (bath temp. 194°) for 22 h. The brown soln. was then extracted with Et_2O (4 × 80 ml), the combined Et_2O phase washed with brine (2 × 20 ml), dried ($MgSO_4$), and evaporated, and the residue crystallized 2 × from benzene/petroleum ether 1:1: 2.58 g (30%) of **4d**. Colourless crystals. M.p. 71.5°. IR (CH_2Cl_2): 3610*w*, 3390*m* (br.), 2920*s*, 2860*s*, 1580*m*, 1470*m*, 1440*m*, 1420*s*, 1270*s*, 1100*w*, 1040*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.43–1.98 (*m*, 15 H); 2.67 (*m*, 1 H); 3.31 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.6 (*t*); 24.4 (*t*); 26.0 (*t*); 26.7 (*t*); 32.4 (*t*); 34.8 (*t*); 56.4 (*d*); 75.7 (*d*). MS: 144 (9, $[M + 1]^+$), 143 (42, M^+), 141 (4), 126 (10), 114 (21), 113 (10), 112 (65), 100 (70), 99 (15), 98 (18), 86 (13), 82 (16), 72 (14), 70 (40), 59 (14), 57 (23), *56* (100), 43 (36), 30 (28), 18 (10).

9-Azabicyclo[6.1.0]nonane (**5d**). Cold 95% H_2SO_4 soln. (0.90 g, 9.2 mmol) was cautiously added to a suspension of **4d** (1.14 g, 8.0 mmol) in H_2O (1 ml). The light brown soln. was heated for 20 min at 80° and then for 20 min at 130° (bath temp.), whereby H_2O slowly distilled off. The solid was dissolved in 20% NaOH in H_2O (30 ml) and heated under reflux (110° bath temp.) for 15 h. The soln. was extracted with Et_2O (5 × 30 ml) and the combined Et_2O phase washed with brine (2 × 20 ml), dried ($MgSO_4$), and evaporated: 0.36 g (36.0%) of **5d**. Colourless liquid. IR (film): 3250*m* (br.), 2900*s*, 2860*s*, 1470*s*, 1450*s*, 1330*w*, 1240*m*, 1150*w*, 1030*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.98–1.85 (*m*, 11 H); 1.82–1.95 (*d*-like *m*, 2 H); 2.05–2.18 (*d*, J = 15, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 27.2 (*t*); 27.4 (*t*); 27.5 (*t*); 34.0 (*d*). GC/MS: 125 (2, M^+), 110 (1.6), 108 (1.3), 96 (5), 93 (3), 82 (27), 80 (6), 79 (7), 70 (6), 69 (12), 68 (18), 67 (9), 57 (15), *56* (100), 54 (7), 43 (74), 41 (18), 39 (17).

9-Benzoyl-9-azabicyclo[6.1.0]nonane (**1g**). As described for **1d**, **5d** (0.37 g, 2.96 mmol) was benzoylated with Et_3N (0.51 g, 5 mmol) and benzoyl chloride (0.42 g, 3 mmol) affording 0.94 g of crude **1g** as a yellowish oil. CC (silica gel (80 g), Et_2O/pentane 1:1) afforded 0.32 g (47%) of **1g**. Pale yellow solid. TLC: R_f 0.65. M.p. 72.5°. IR (CH_2Cl_2): 3105*w*, 3080*w*, 3020*w*, 2980*w*, 2940*m*, 2860*w*, 1670*s*, 1600*w*, 1580*w*, 1460*w*, 1450*m*, 1430*m*, 1320*s*, 1300*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.38–1.79 (*m*, 10 H); 2.25 (*d*, J = 5, 2 H); 2.48 (*s*-like, 2 H); 7.40 (*dd*, J = 6, 7, 2 H); 7.55 (*dd*, J = 1, 6, 1 H); 7.95 (*d*, J = 7, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.5 (*t*); 26.6 (*t*); 26.9 (*t*); 41.7 (*d*); 128.5 (*d*); 129.2 (*d*); 132.6 (*d*); 133.8 (*s*); 179.9 (*s*). GC/MS: 229 (0.3, M^+), 228 (0.3), 201 (4.1), 125 (4), 124 (46), 122 (4), 105 (37), 97 (18), 96 (3), 78 (4), 77 (44), 69 (8), 56 (7), *55* (100), 51 (14), 41 (24).

3. *Cbl-Catalyzed Isomerizations. (R)*-tert-*Butyl Cyclopent-2-ene-1-carbamate* (**2a**; *Table 2, Entry 2*). To the red soln. of OH–Cbl·HCl (0.130 g, 0.09 mmol), Et_3N (0.20 g, 2.00 mmol), and MeOH (15 ml) was added at 0° activated Zn powder (1.5 g) under Ar. After stirring for *ca.* 1 h at 0° (→dark green (Cbl)), crude **1a** (0.405 g; containing 15% of *t*-butyl cyclopentanecarbamate, *i.e.* 1.88 mmol of **1a**) was then added by syringe (→brown-green). After stirring for 8 d at 0° (→dark-green), H_2O (10 ml) was added and the soln. extracted with Et_2O (4 × 40 ml). The combined Et_2O phase was washed with brine (2 × 20 ml), dried ($MgSO_4$), and evaporated: 0.395 g of yellowish solid. CC ('Ag-activated' silica gel (15 g), pentane/Et_2O 8:2) afforded 0.170 g (42% rel. to **1a**) of *tert*-butyl cyclopentanecarbamate and 0.194 g (48% rel. to crude **1a**, 56% rel. to **1a**) of **2a**.

Data of **2a**: Colourless solid. R_f 0.26. M.p. 87.5°. $[\alpha]_D^{23}$ = +77.0 (c = 5.14, CH_2Cl_2). Enantioselective GC (20% heptakis{2,3-di-*O*-propyl-6-[(*tert*-butyl)dimethylsilyl]}-β-cyclodextrin in *OV-1701*, 140°): t_R 82.8 (6.5%, (*S*)-enantiomer), 86.3 (93.5%, (*R*)-enantiomer); 87% ee. For analysis, **2a** was crystallized from Et_2O/pentane 1:2 at 4° and sublimed (*ca.* 70°/0.1 mbar). Colourless needles. M.p. 88°. $[\alpha]_D^{23}$ = +77.8 (c = 1.84, CH_2Cl_2). IR (CH_2Cl_2): 3440*m*, 3030*w*, 3005*m*, 3000*m*, 2985*m*, 2940*m*, 2860*w*, 1710*s*, 1610*w*, 1500*s*, 1370*m*, 1240*w*, 1170*s*, 1100*w*. ^{1}H-NMR ($CDCl_3$): 1.48 (*s*, 9 H); 1.50–1.51 (*m*, 1 H); 2.17–2.50 (*m*, 3 H); 4.54 (*s*, NH); 4.70 (*s*, 1 H); 5.64–5.70 (*m*, 1 H); 5.85–5.93 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$): 28.4 (*q*); 31.0 (*t*); 31.7 (*t*); 56.8 (*d*); 79.1 (*s*); 131.6 (*d*); 134.1 (*d*); 155.3 (*s*). MS: 185 (3, $[M + 2]^+$), 184 (1, $[M + 1]^+$), 183 (2, M^+), 130 (20), 129 (24), 128 (47), *127* (100), 126 (84), 125 (28), 118 (6), 100 (7), 83 (41), 82 (73), 81 (19), 80 (12), 68 (21), 67 (62), 66 (63), 62 (33), 57 (73), 41 (37), 29 (22), 18 (5). Anal. calc. for $C_{10}H_{17}NO_2$ (187.24): C 65.54, H 9.35, N 7.64; found: C 65.65, H 9.15, N 7.55.

Data of tert-*Butyl Cyclopentanecarbamate:* Colourless solid. R_f 0.40. M.p. 66.5°. IR (CH_2Cl_2): 3460*m*, 2980*m*, 2880*w*, 1710*s*, 1510*s*, 1400*w*, 1375*m*, 1245*m*, 1175*s*, 1105*w*. ^{1}H-NMR ($CDCl_3$): 1.30–1.43 (*m*, 2 H); 1.45 (*s*, 9 H); 1.50–1.72 (*m*, 4 H); 1.88–2.02 (*m*, 2 H); 3.92 (*m*, 1 H); 4.58 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 23.6 (*t*); 28.5 (*q*); 33.3 (*t*); 43.0 (*d*); 77.5 (*s*); 155.6 (*s*). MS: 186 (2, $[M + 1]^+$), 185 (22, M^+), 170 (5), 153 (7), 131 (12), 130 (94), 129 (93), 128 (37), 127 (10), 126 (12), 101 (8), 100 (52), 83 (21), 82 (15), 69 (24), 62 (32), 59 (57), *57* (100), 56 (77), 41 (43), 18 (4).

(R)-tert-*Butyl Cyclohex-2-ene-1-carbamate* (**2b**; *Table 2, Entry 5*). As described for **2a**, OH–Cbl·HCl (0.070 g, 0.05 mmol), Et_3N (0.12 g, 1.2 mmol), MeOH (10 ml), activated Zn powder (1.5 g), and **1b** (0.22 g, 1.1

mmol; added as solid) were reacted for 9 d at 0°. Workup as described afforded 0.25 g of colourless oil. GC: 3 fractions at t_R 27.19, 27.38, and 33.65 min. CC (silica gel (15 g), pentane/EtOH 100:2) gave minor fractions (see below) and one main fraction (R_f 0.43, t_R 27.38): 0.14 g (64%) **2b**. Colourless solid. M.p. 48°. $[\alpha]_D^{23} = +101$ ($c = 2.80$, $CHCl_3$). Enantioselective GC (17% heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin and 25% heptakis(2,3,6-tri-*O*-propyl)-β-cyclodextrin in *OV-1701*, 100°): t_R 58.9 (2.0%, (*S*)-enantiomer), 64.0 (77.6%, (*R*)-enantiomer); 95% ee. For analysis, **2b** was crystallized from Et_2O at −20° and sublimed (40°/0.1 mbar). Colourless solid. M.p. 48.5°. $[\alpha]_D^{23} = +102.9$ ($c = 3.31$, $CHCl_3$). IR (KBr): 3340*s*, 3030*w*, 2980*m*, 2940*m*, 1680*s*, 1520*s*, 1450*w*, 1380*w*, 1370*m*, 1340*w*, 1250*s*, 1170*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.43 (*s*, *t*-Bu); 1.45–1.74 (*m*, 3 H); 1.82–2.05 (*m*, 3 H); 4.15 (*s*, 1 H); 4.52 (*s*, 1 H); 5.53–5.66 (*m*, 1 H); 5.78–5.90 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.7 (*t*); 24.8 (*t*); 28.4 (*q*); 29.8 (*t*); 45.0 (*d*); 79.1 (*s*); 128.2 (*d*); 130.4 (*d*); 155.2 (*s*). MS: 199 (0.2, $[M + 2]^+$), 197 (0.15, M^+), 169 (0.6), 143 (5), 142 (22), *141* (100), 140 (56), 139 (7), 126 (13), 114 (6), 113 (57), 97 (10), 96 (15), 95 (5), 82 (18), 81 (61), 80 (79), 79 (8), 69 (39), 62 (14), 57 (62), 41 (15), 18 (7). Anal. calc. for $C_{11}H_{19}NO_2$ (197.28): C 66.97, H 9.71, N 7.10; found: C 67.08, H 9.65, N 7.10.

The GC peak at t_R 27.19 arose from tert-*butyl cyclohexanecarbamate*: GC/MS: 199 (0.3, M^+), 184 (0.1), 143 (7), 141 (13), 140 (6), 113 (6), 100 (4), 96 (6), 83 (4), 82 (12), 81 (18), 80 (21), 79 (7), 69 (17), 67 (5), 62 (11), 59 (16), *57* (100), 56 (39), 55 (10), 43 (8), 41 (31), 39 (7).

From the combined minor CC fractions, *(±)*-trans-*(*tert-*butyl) 2-chlorocyclohexane-1-carbamate* was isolated by repeated crystallization from Et_2O at −20°. GC: t_R 33.65. M.p. 104.5°. IR (KBr): 3260*s*, 3080*w*, 3000*w*, 2980*m*, 2940*s*, 2860*m*, 1715*s*, 1680*s*, 1560*s*, 1450*w*, 1400*w*, 1370*m*, 1320*m*, 1285*m*, 1250*w*, 1180*s*, 1120*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.18–1.44 (*m*, 3 H); 1.46 (*s*, *t*-Bu); 1.63–1.83 (*m*, 3 H); 2.10–2.31 (*m*, 2 H); 3.44–3.61 (*m*, 1 H); 3.68–3.78 (*m*, 1 H); 4.65 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.1 (*t*); 25.1 (*t*); 28.4 (*q*); 32.7 (*t*); 35.8 (*t*); 56.0 (*d*); 63.0 (*d*); 79.5 (*s*); 155.4 (*s*). MS: 235 (4, $[M + 2]^+$), 234 (0.2, $[M + 1]^+$), 233 (12, $M^{+\cdot}$), 218 (3), 198 (0.2), 180 (25), 179 (74), 178 (35), *177* (100), 174 (10), 143 (8), 142 (34), 141 (13), 135 (10), 133 (30), 118 (8), 116 (19), 100 (34), 98 (55), 90 (7), 82 (7), 81 (40), 80 (8), 62 (49), 59 (70), 57 (81), 56 (69), 41 (27), 18 (9).

(R)-N-*(Cyclopent-2-en-1-yl)benzamide* (**2d**; *Table 2, Entry 1*). As described for **2a**. OH–Cbl·HCl (0.084 g, 0.06 mmol), NH_4Cl (0.10 g, 1.9 mmol), MeOH (20 ml), activated Zn powder (1.0 g), and **1d** (0.23 g, 1.23 mmol; added as solid) were reacted for 18.5 h at 22° (TLC: no **1d** left). Workup as usual afforded 0.23 g of a yellowish solid ($[\alpha]_D^{23} = +69.85$ ($c = 1.37$, CH_2Cl_2)). CC ('Ag-activated' silica gel (40 g), Et_2O/pentane 8:2) gave 0.113 g (49%) of **2d** and 0.074 g (32%) of *N*-cyclopentylbenzamide.

Data of **2d**: Colourless solid. TLC: R_f 0.26. After sublimation at 105°/$2 \cdot 10^{-2}$ mbar, m.p. 123°. $[\alpha]_D^{23} = +76.3$ ($c = 0.72$, CH_2Cl_2). UV (MeOH, $c = 6.1 \cdot 10^{-5}$): 210 (4.13), 230 (4.28). IR (CH_2Cl_2): 3450*m*, 3090*w*, 3030*w*, 2970*m*, 2860*w*, 1660*s*, 1605*w*, 1580*w*, 1530*s*, 1490*s*, 1260*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.59–1.80 (*m*, 2 H); 2.30–2.58 (*m*, 2 H); 5.15–5.25 (*m*, 1 H); 5.75 (*m*, 1 H); 5.98 (*m*, 1 H); 6.14 (br. *s*, NH); 7.42–7.52 (*m*, 3 H); 7.74–7.80 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 31.1 (*t*); 31.4 (*t*); 56.0 (*d*); 126.8 (*d*); 128.3 (*d*); 130.9 (*d*); 131.2 (*d*); 134.8 (*d*); 135.0 (*s*); 166.9 (*s*). MS: 188 (4, $[M + 1]^+$), 187 (34, $M^{+\cdot}$), 159 (2), 123 (1), 122 (26), 106 (8), *105* (100), 82 (5), 79 (5), 78 (4), 77 (53), 67 (5), 66 (9), 65 (3), 51 (8), 41 (3), 18 (12). Anal. calc. for $C_{12}H_{13}NO$ (187.24): C 76.98, H 7.00, N 7.48; found: C 77.05, H 7.26, N 7.41.

Data of N-*Cyclopentylbenzamide*: Colourless solid. TLC: R_f 0.49. M.p. 148.5°. UV (MeOH, $c = 6.34 \cdot 10^{-5}$ M): 210 (4.12), 228 (4.25). IR (CH_2Cl_2): 3450*w*, 3050*w*, 3040*w*, 2970*m*, 2880*w*, 1660*s*, 1605*w*, 1580*w*, 1515*s*, 1490*s*, 1300*w*, 910*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.40–1.58 (*m*, 2 H); 1.60–1.82 (*m*, 4 H); 1.98–2.18 (*m*, 2 H); 4.41 (*m*, 1 H); 6.07 (*s*, 1 H); 7.36–7.57 (*m*, 3 H); 7.70–7.81 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.8 (*t*); 33.2 (*t*); 51.6 (*d*); 126.7 (*d*); 128.4 (*d*); 131.2 (*d*); 135.1 (*s*); 167.0 (*s*). GC/MS: 190 (2, $[M + 1]^+$), 189 (8, $M^{+\cdot}$), 188 (3), 123 (3), 122 (40), 106 (8), *105* (100), 104 (2), 84 (3), 79 (20), 77 (76), 68 (5), 51 (28), 41 (8).

(R)-N-*(Cyclopent-2-en-1-yl)*-N-*methylbenzamide* (**2d′**; *Table 2, Entry 1*). To a soln. of **2d** (0.028 g, 0.15 mmol; see previous exper.) in THF (15 ml), NaH (0.041 g, 0.92 mmol) was added. With stirring under N_2, MeI (0.043 g, 0.3 mmol) was added at 0° and the soln. stirred for 20 h at r.t. The excess NaH was cautiously decomposed by addition of 95% MeOH (*ca.* 1 ml). H_2O (5 ml) was added and the soln. extracted with Et_2O (2 × 20 ml). The combined org. phase was washed with brine (10 ml), dried ($MgSO_4$), and evaporated: 0.046 g of yellowish oil. CC (silica gel (10 g), Et_2O/pentane 6:4) afforded 0.20 g (70%) of **2d′**. TLC: R_f 0.22. Colourless oil. $[\alpha]_D^{23} = +49.7$ ($c = 0.394$, CH_2Cl_2). Enantioselective GC (100% heptakis{2,3-di-*O*-acetyl-6-*O*-[(*tert*-butyl)dimethylsilyl]}-β-cyclodextrin in *OV-1701*, 130°): t_R 286.6 (60.14%, (*R*)-enantiomer), 302.4 (19.70%, (*S*)-enantiomer); 50% ee. IR (CH_2Cl_2): 3040*w*, 2930*s*, 2860*s*, 1630*s*, 1605*m*, 1580*w*, 1500*w*, 1465*m*, 1450*m*, 1440*m*, 1400*s*, 1340*m*, 1150*w*, 1070*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.65–2.60 (*m*, 2 CH_2); 2.90 (*s*, Me); 4.90 (*s*-like, CH); 5.52–5.78 (*m*, 1 H); 5.85–6.15 (*m*, 1 H); 7.40 (*s*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 27.3 (*t*); 27.4 (*q*); 31.5 (*t*); 65.4 (*d*); 126.7 (*d*); 128.3 (*d*); 129.1 (*d*); 129.7 (*d*); 135.1 (*d*); 136.9 (*s*); 171.4 (*s*). GC/MS: 202 (4, $[M + 1]^+$), 201 (22, $M^{+\cdot}$), 200 (3), 186 (9), 136 (12), 106 (9), *105* (100), 96 (5), 77 (53), 67 (17), 66 (8), 51 (15), 41 (9).

(S)-Cyclohex-2-en-1-amine (**7c**; *Table 2, Entry 8*). As described for **2a**, OH–Cbl·HCl (0.28 g, 0.20 mmol), phthalic acid (0.33 g, 2.0 mmol), H_2O (12 ml), activated Zn powder (0.15 g), and **5b** (0.39 g, 4 mmol) were reacted for 17 h at r.t. under Ar. Then 20% NaOH in H_2O (4 ml) was added and the soln. extracted with Et_2O (5 × 30 ml). The combined org. phase was washed with brine (2 × 10 ml), dried ($MgSO_4$), and evaporated: 0.32 g (69%) of **7c**. GC: 85% purity. Yellowish oil. $[\alpha]_D^{23} = -3.8$ ($c = 0.97$, benzene). IR ($CHCl_3$): 3070*w*, 3010*w*, 2940*s*, 2860*m*, 1690*m*, 1605*w*, 1450*w*, 1240*w*, 1050*m*, 910*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.00–2.50 (*m*, 8 H); 3.37 (*m*, 1 H); 5.58–5.80 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.2 (*t*); 25.0 (*t*); 33.5 (*t*); 46.9 (*d*); 128.1 (*d*); 132.4 (*d*). GC/MS: 97 (16, M^+), 96 (32), 82 (23), 79 (14), 77 (8), 70 (4), *69* (100), 68 (14), 67 (5), 56 (13), 54 (14), 43 (30), 41 (16).

(R)-N-(Cyclohex-2-en-1-yl)benzamide (**2e**; *Table 1, Entry 7*, and *Table 2, Entry 3*). As described for **2a**, OH–Cbl·HCl (0.080 g, 0.06 mmol), Et_3N (0.13 g, 1.27 mmol), NH_4Cl (0.10 g, 1.9 mmol), MeOH (15 ml), activated Zn powder (1.5 g), and **1e** (0.255 g, 1.27 mmol; added as solid) were reacted for 7 d at −20°. Workup as usual afforded 0.23 g (90%) of **2e**. Yellowish solid. M.p. 106°. $[\alpha]_D^{23} = +157.9$ ($c = 6.07$, $CHCl_3$). Enantioselective GC (17% heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin and 25% heptakis(2,3,6-tri-*O*-propyl)-β-cyclodextrin in *OV-1701*, 130°): t_R 367.8 (5%, (*S*)-enantiomer), 373,9 (95%, (*R*)-enantiomer); 90% ee. For crystallization, the solid was dissolved in Et_2O (*ca.* 5 ml) and cooled gradually from 40° to 20° (1 h), 4° (10 h), and −20° (24 h), affording colourless crystals which were recrystallized from Et_2O: 0.17 g (65% rel. to **1e**) of **2e**. GC (as above): t_R 373.9 (> 99.5%, (*R*)-enantiomer). Crystallization of the substance in the mother liquor (pentane, 4°) gave *ca.* 5 mg of *N*-cyclohexylbenzamide. Enantioselective GC (as above): t_R 393.2.

Data of **2e**: M.p. 107.5°. $[\alpha]_D^{23} = +178.6$ ($c = 3.02$, $CHCl_3$). UV (MeOH, $c = 3.4 \cdot 10^{-5}$ M): 192 (3.34), 210 (4.40), 228 (4.49). IR (CCl_4): 3460*w*, 3070*w*, 3030*w*, 2930*m*, 2860*w*, 1670*s*, 1600*w*, 1580*w*, 1510*s*, 1480*s*, 1340*m*, 1260*m*, 1245*m*, 700*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.53–1.87 (*m*, 3 H); 1.92–2.12 (*m*, 3 H); 4.65–4.78 (*m*, 1 H); 5.62–5.75 (*m*, 1 H); 5.90–5.98 (*m*, 1 H); 6.14 (*d*, $J = 10$, NH); 7.40–7.53 (*m*, 3 H); 7.74–7.80 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.8 (*t*); 24.8 (*t*); 29.5 (*t*); 45.1 (*d*); 126.9 (*d*); 127.6 (*d*); 128.5 (*d*); 131.3 (*d*); 131.4 (*d*); 134.8 (*s*); 166.7 (*s*). MS: 203 (15, $[M + 2]^+$), 202 (19, $[M + 1]^+$), 201 (93, M^+), 173 (14), 172 (6), 160 (4), 145 (3), 123 (6), 122 (64), 121 (19), 106 (23), *105* (100), 96 (14), 80 (12), 79 (19), 78 (8), 77 (55), 51 (8), 18 (10). Anal. calc. for $C_{13}H_{15}NO$ (201.27): C 77.58, H 7.51, N 6.96; found: C 77.64, H 7.60, N 7.13.

Data of N-Cyclohexylbenzamide: M.p. 137°. IR (KBr): 3240*s*, 3270*w*, 3030*w*, 2940*s*, 2860*m*, 1645*s*, 1630*s*, 1605*w*, 1550*s*, 1490*w*, 1455*m*, 1330*m*, 1080*w*, 700*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.09–1.50 (*m*, 5 H); 1.55–1.83 (*m*, 3 H); 1.90–2.10 (*m*, 2 H); 3.85–4.20 (*m*, 1 H); 6.20–6.38 (*s*, NH); 7.32–7.55 (*m*, 3 H); 7.70–7.87 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.0 (*t*); 25.5 (*t*); 33.2 (*t*); 48.7 (*d*); 126.9 (*d*); 128.4 (*d*); 131.2 (*d*); 135.1 (*s*); 166.7 (*s*). MS: 205 (0.5, $[M + 2]^+$), 204 (8, $[M + 1]^+$), 203 (40, M^+), 202 (8), 201 (7), 174 (1), 160 (8), 146 (3), 123 (10), *122* (100), 106 (11), 105 (96), 98 (5), 79 (17), 78 (8), 77 (42), 76 (2), 74 (14), 59 (15), 51 (9), 45 (9), 31 (17), 28 (19), 18 (49).

(R)-N-(Cyclohex-2-en-1-yl)propanamide (**2f**; *Table 2, Entry 7*). As described for **2a**, OH–Cbl·HCl (0.11 g, 0.075 mmol), NH_4Cl (0.34 g), MeOH (10 ml), activated Zn powder (1.0 g), and **1f** (0.23 g, 1.5 mmol; added by syringe) were reacted for 20 h at r.t.: 0.25 g of yellowish oil. CC (silica gel (15 g), Et_2O) afforded 0.18 g (78%) of **2f** and 0.038 g (16%) of *N*-cyclohexylpropanamide.

Data of **2f**: TLC: R_f 0.44. $[\alpha]_D^{23} = +57.5$ ($c = 0.55$, CCl_4). Enantioselective GC (10% heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin in *OV-1701*, 110°): t_R 97.0 (17%, (*S*)-enantiomer), 99.2 (58%, (*R*)-enantiomer); 54% ee. Crystallization (Et_2O, 0°) afforded 0.12 g of **2f** (52% rel. to **1f**). Colourless needles. M.p. 80°. $[\alpha]_D^{23} = +58.1$ ($c = 0.44$, CCl_4). IR (CCl_4): 3450*m*, 3310*w*, 3060*w*, 3000*m*, 2940*m*, 2870*w*, 1660*s*, 1510*s*, 1450*w*, 1430*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.15 (*t*, $J = 7$, Me); 1.42–1.74 (*m*, 3 H); 1.82–2.08 (*m*, 3 H); 2.15–2.30 (*q*, $J = 7$, CH_2); 4.50 (*m*, 1 H); 5.50–5.60 (*m*, 1 H); 5.75–5.90 (*m*, 1 H); 6.15 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.9 (*q*); 19.8 (*t*); 24.8 (*t*); 29.5 (*t*); 29.9 (*t*); 44.5 (*d*); 127.9 (*d*); 130.8 (*d*); 172.9 (*s*). MS: 154 (12, $[M + 1]^+$), *153* (100), 152 (2), 138 (2), 125 (11), 124 (5), 110 (2), 98 (11), 97 (82), 96 (52), 95(9), 93(5), 82(20), 81 (34), 80 (24), 79 (20), 78 (4), 77(7), 74 (31), 70 (6), 69 (72), 57 (24), 41 (11), 29 (19). Anal. calc. for $C_9H_{15}NO$ (153.22): C 70.55, H 9.87, N 9.14; found: C 70.39, H 9.94, N 9.11.

Data of N-Cyclohexylpropanamide: Colourless solid. TLC: R_f 0.50. M.p. 80–81°. IR (CCl_4): 3445*w*, 3340*m*, 2930*s*, 2860*m*, 1680*s*, 1650*s*, 1540*m*, 1500*s*, 1450*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.05–1.25 (*m*, 6 H); 1.28–1.45 (*m*, 2 H); 1.55–1.80 (*m*, 3 H); 1.85–1.98 (*m*, 2 H); 2.05–2.25 (*q*, $J = 7$, CH_2); 3.65–3.85 (*m*, 1 H); 5.50–5.75 (*s*, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.0 (*q*); 25.0 (*t*); 25.6 (*t*); 29.9 (*t*); 33.2 (*t*); 48.1 (*d*); 172.9 (*s*). MS: 156 (4, $[M + 1]^+$), 155 (30, M^+), 126 (5), 112 (8), 99 (4), 98 (6), 97 (1), 96 (2), 83 (6), 82 (5), 75 (2), *74* (100), 70 (7), 67 (7), 58 (2), 57 (24), 56 (37), 55 (9), 43 (6), 41 (5), 28 (25), 18 (16).

Isomerization with **1c** (*Table 2, Entry 9*). As described for **2a**, OH–Cbl·HCl (0.035 g, 0.025 mmol), NH_4Cl (0.30 g), MeOH (10 ml), activated Zn powder (1.5 g) and **1c** (0.12 g, 0.71 mmol) were reacted for 4 d at r.t. under Ar. GC showed no change. Workup as usual afforded 0.105 g of **1c**, identified by NMR.

Isomerization with **1g** (*Table 2, Entry 10*). As described for **2a**, OH–Cbl·HCl (0.07 g, 0.05 mmol), Et_3N (0.10 g, 1 mmol), NH_4Cl (0.20 g), MeOH (15 ml), activated Zn powder (1 g) and **1g** (0.23 g, 1 mmol) were reacted

at r.t. for 7 d under Ar. Workup as usual afforded 0.26 g of colourless oil. GC: methyl benzoate (53%) and **1g** (45%).

4. *(R)-(Cycloalk-2-en-1-yl)amines. (R)-(Cyclopent-2-en-1-yl)ammonium Trifloroacetate* (**7a**·CF_3COOH). To a soln. of crude **2a** (0.060 g, 0.33 mmol; $[\alpha]_D^{23} = +67.0$; 78% ((*R*)) ee by GC) in CH_2Cl_2 (1.5 ml) was added CF_3COOH (*0.80* ml; freshly dist.) under Ar at 0°. After stirring for 5 *min* at 0° and 30 *min* at r.t., all volatile materials were evaporated at *ca.* 5 mbar: dark semisolid residue. H_2O (1 ml) was added, the soln. washed with Et_2O, and the aq. phase evaporated; 0.060 g (93%) of **7a**·CF_3COOH. Semisolid. $[\alpha]_D^{23} = +23.7$ ($c = 1.202$, MeOH). IR (KBr): 3450*m* (br., NH_2), 3120*s*, (br., NH_2), 3040*s*, 3010*s*, 3000*m*, 2980*m*, 2940*m*, 2890*m*, 1680*s*, 1520*w*, 1435*w*, 1205*s*, 1180*s*, 1135*s*. ^{1}H-NMR (300 MHz, D_2O): 1.73–1.99 (*m*, 2 H); 2.22–2.71 (*m*, 4 H); 4.31 (*s*, 1 H); 5.72 (*m*, 1 H); 6.21 (*m*, 1 H). ^{13}C-NMR (75 MHz, D_2O): 30.1 (*t*); 33.4 (*t*); 59.6 (*d*); 118.5 (*q*); 128.6 (*d*); 142.2 (*d*); *ca.* 163 (very weak *s*, COOH). MS: 199 (0.5, $[M + 2]^+$), 178 (1.5), 177 (1), 147 (3), 145 (1.5), 119 (8), 115 (7), 114 (20), 97 (30), 96 (18), 91 (11), 86 (12), 82 (30), 70 (15), *69* (100), 56 (20), 51 (61), 50 (31), 45 (87), 18 (48).

Treatment of **7a**·CF_3COOH with NaOH in H_2O gave the free amine **7a**; however, it was not isolated because of its high volatility.

(R)-(Cyclohex-2-en-1-yl)amine (**7b**). To a soln. of crude **2b** (0.110 g; $[\alpha]_D^{23} = +92.5$; containing 10% of *tert*-butyl cyclohexanecarbamate) in CH_2Cl_2 (2 ml) was added CF_3COOH (1.5 ml; freshly dist.) under Ar at 0° and stirred for 5 min at 0° and 30 min at r.t. Workup as described above afforded 0.115 g of **7b**·CF_3COOH as yellowish semisolid. To this semisolid was added 5% NaOH in H_2O (*ca.* 1.5 ml). The mixture was extracted with Et_2O (2 × 8 ml) and the combined Et_2O phase dried ($MgSO_4$) and evaporated 0.049 g of **7b**. GC: 90% purity, corresponding to 90% yield. Yellowish oil. $[\alpha]_D^{23} = +37.8$ ($c = 0.882$, CH_2Cl_2). IR ($CHCl_3$): 3070*w*, 3010*w*, 2940*s*, 2860*m*, 1690*m*, 1605*w*, 1450*w*, 1240*w*, 1050*m*, 910*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.00–2.50 (*m*, 8 H); 3.37 (*m*, 1 H); 5.58–5.80 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.2 (*t*); 25.0 (*t*); 33,5 (*t*); 46.9 (*d*); 128.1 (*d*); 132.4 (*d*). GC/MS: 97 (16, M^+), 96 (32), 82 (23), 79 (14), 77 (8), 70 (4), *69* (100), 68 (14), 67 (5), 56 (13), 54 (14), 43 (30), 41 (16).

5. *Determination of the Chirality by Chemical Correlation. (–)-(R)-Glutamic Acid* (**8**) *from* **2a**. A stream of O_3 (0.75 g/h) was passed through a soln. of crude **2a** (0.190 g, 1.04 mmol; $[\alpha]_D^{23} = +62.4$; 70% ee) in CH_2Cl_2 (30 ml) at −78° until no starting material was detected by TLC (*ca.* 7 h). Then, 30% H_2O_2 in H_2O (1.5 ml) was added and the soln. stirred at r.t. for 18 h. The soln. was evaporated, the white semifluid (0.210 g) dissolved in CH_2Cl_2 (1.5 ml), CF_3COOH (1.5 ml; freshly dist.) added at 0° and the mixture stirred for 1 h at r.t. The soln. was evaporated, the residue dissolved in H_2O (2 ml), this soln. washed with Et_2O (2 × 10 ml), the H_2O phase evaporated, and the residue purified by ion-exchange CC (*Dowex 50W* × *8* (12 g), 5% NH_4OH in H_2O): 0.095 g (62%) of **8**. M.p. 190° (dec.). $[\alpha]_D^{23} = -18.9$ ($c = 2.2$, 5N HCl); 60% ee [24]. HPLC (reversed phase): **8** was identical with authentic glutamic acid.

(–)-(R)-Glutamic Acid (**8**) from **2d**. A stream of O_3 (0.75 g/h) was passed through a soln. of crude **2d** (0.12 g, 0.37 mmol); $[\alpha]_D^{23} = +82.0$) in MeOH (20 ml) for 12.5 h at −20°. After stirring for 10 h r.t., the soln. was evaporated. The residue was dissolved in 90% formic acid (5 ml) and 30% H_2O_2 in H_2O (5 ml) and stirred for 5 h at 55–60°. The soln. was evaporated: 0.20 g of colourless oil ($[\alpha]_D^{23} = +1.9$ ($c = 5.4$, MeOH)). The oil was dissolved in 6N HCl/H_2O (10 ml) and heated under reflux for 6 h. The soln. was washed with Et_2O (2 × 20 ml) and CH_2Cl_2 (3 × 20 ml) and evaporated and the residue submitted to CC at an ion-exchange column (*Dowex 50W* × *8* (10 g), 5% HCl in H_2O): 0.044 g (87%) of **8**. Yellowish solid. M.p. 190° (dec.). $[\alpha]_D^{23} = -4.91$ ($c = 4.3$, 5N HCl); 16% ee [24]. HPLC: see above.

(R)-2-Aminohexanedioic Acid (**9a**) *from* **2e**. i) *Dimethyl (R)-2-(Benzoylamino)hexanedioate.* A stream of O_3 (0.5 g/h) was passed through a soln. of crude **2e** (0.25 g, 1.2 mmol; $[\alpha]_D^{23} = +110$; 63% ee) in MeOH (20 ml) for 10 h at −40°, 4 h at −25°, and 5 h at −20°. After stirring for 10 h at r.t., the soln. was evaporated. The residue was dissolved in 90% formic acid (10 ml) and 30% H_2O_2 in H_2O (10 ml) and stirred for 5.5 h at 55–60°. Evaporation afforded 0.42 g of a yellowish oil. The oil was dissolved in Et_2O (12 ml) and CH_2N_2 (16 ml of 0.5M CH_2N_2 in Et_2O; *ca.* 8 mmol) added at −20°. After 1 h at −20° and 15 h at r.t., the solvent was evaporated: 0.55 g of colourless oil. CC (silica gel (80 g), Et_2O/pentane 7:3) afforded 0.20 g (60%) of dimethyl (*R*)-2-(benzoylamino)hexanedioate. TLC: R_f 0.23. Colourless oil.

ii) *Amino Acid* (**9a**). To a soln. of dimethyl 2-(benzoylamino)hexanedioate (56 mg, 0.19 mmol; see above) in CH_2Cl_2 (20 ml) were added 4-(dimethylamino)pyridine (42 mg, 0.19 mmol), Et_3N (40 mg, 0.4 mmol), and $(Boc)_2O$ (218 mg, 1 mmol). After stirring for 26 h at r.t. under N_2, the volatiles were evaporated, and the residue was purified by CC (silica gel (20 g), Et_2O): 75 mg (100%) of dimethyl 2-{benzoyl[(*tert*-butyloxy)carbonyl]amino}hexanedioate. TLC: R_f 0.65. Yellowish solid. It was dissolved in MeOH (1 ml), and 2.0M NaOMe in MeOH (0.14 ml) was added. After stirring for 1 h at 0° and for 4 h at r.t., the soln. was poured into brine (1 ml) and extracted with Et_2O (3 × 10 ml). The org. phase was dried ($MgSO_4$) and evaporated and the residue chromatographed on a reversed-phase column (*Amberlite XAS-2* (styrene-divinylbenzoyl copolymer), *Servachrom* (200 g, H_2O/MeOH 2:1); 0.64 g of

white solid. The solid was dissolved in 7% HCl in H_2O (1.5 ml) and the soln. washed with Et_2O (3 × 20 ml) and purified by ion-exchange CC (*Dowex 50 WX8* (6 g), 5% NH_4OH in H_2O): 23 mg (75%) of **9a**.

Data of **9a**: Colourless solid. M.p. *ca.* 200° (dec.). $[\alpha]_D^{23} = -143$ ($c = 0.46$, 6N HCl); 55% ee [25]. IR (KBr): 3400*m* (br.), 3040*s* (br.), 1920*m*, 1680*s*, 1645*s*, 1580*m*, 1510*s*, 1420*m*, 1350*m*, 1330*m*, 1300*m*, 1220*m*, 1130*w*, 1030*w*, 765*m*. ^{1}H-NMR (60 MHz, D_2O): 1.10–1.90 (*m*, 4 H); 1.92–2.30 (*t*, $J = 7$, CH_2); 3.35–3.75 (*m*, 1 H). MS: 162 (0.2, $[M + 1]^+$), 144 (5), 143 (21), 117 (3), 116 (39), 115 (4), 100 (3), 99 (25), *98* (100), 97 (9), 74 (15), 70 (20), 69 (7), 60 (4), 57 (3), 56 (30), 55 (81), 44 (8), 43 (9), 42 (12), 28 (11), 18 (8).

*Data of Dimethyl (*R*)-2-(Benzoylamino)hexanediaote*: $[\alpha]_D^{23} = -27.2$ ($c = 2.23$, $CHCl_3$). IR ($CHCl_3$): 3440*m*, 3070*w*, 3040*w*, 3000*m*, 2960*m*, 1740*s*, 1665*s*, 1600*w*, 1585*w*, 1520*m*, 1490*m*, 1440*m*, 1360*m*, 1240*m*, 1180*m*, 1060*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.65–1.90 (*m*, 3 H); 1.91–2.08 (*m*, 1H); 2.38 (*t*, $J = 7$, 2 H); 3.67 (*s*, MeO); 3.77 (*s*, MeO); 4.78 (*m*, 1 H); 7.18 (*d*, $J = 10$, NH); 7.35–7.55 (*m*, 3 H); 7.78–7.88 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.8 (*t*); 31.5 (*t*); 33.1 (*t*); 51.9 (*d*); 52.4 (*d*); 52.5 (*d*); 127.2 (*d*); 128.5 (*d*); 131.7 (*d*); 133.8 (*s*); 167.3 (*s*); 172.8 (*s*); 173.6 (*s*). MS: 294 (4, $[M + 1]^+$), 293 (12, M^+), 279 (1), 263 (3), 262 (20), 261 (8), 235 (52), 234 (98), 230 (19), 229 (10), 220 (42), 202 (28), 193 (43), 189 (11), 188 (50), 174 (12), 172 (9), 161 (19), 156 (22), 152 (14), 140 (8), 113 (9), 112 (58), 104 (45), *105* (100), 98 (9), 77 (34), 59 (4), 43 (1).

*Data of 2-{Benzoyl[(*tert*-butyloxy)carbonyl]amino}hexanedioate*. IR (film): 3060*w*, 3040*m*, 2980*s*, 2960*s*, 1730*s*, 1680*s*, 1600*w*, 1585*w*, 1450*m*, 1440*m*, 1350*s*, 1250*s*, 1140*s*, 1090*m*, 1000*m*, 840*m*, 900*s*, 700*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.18 (*s*, *t*-Bu); 1.71–1.85 (*q*, $J = 7$, CH_2); 2.08–2.50 (*m*, 4 H); 3.68 (*s*, MeO); 3.78 (*s*, MeO); 5.08 (*q*, $J = 5.5$, 9.5, 1 H); 7.38–7.58 (*m*, 3 H); 7.60–7.68 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.8 (*t*); 27.3 (*q*); 28.6 (*t*); 33.3 (*t*); 51.5 (*q*); 52.4 (*q*); 57.4 (*d*); 83.7 (*s*); 127.7 (*d*); 128.2 (*d*); 131.4 (*d*); 137.3 (*s*); 152.8 (*s*); 170.9 (*s*), 172.8 (*s*); 173.5 (*s*).

*Dimethyl (*R*)-2-(Propanoylamino)hexanedioate* (**9b**) *from* **2f**. A stream of O_3 (0.50 g/h) was passed through an stirred soln. of **2f** (0.46 g, 3 mmol; $[\alpha]_D^{23} = +14.6$; 13% ee) in MeOH (20 ml) for 7 h at −78° and for 2 h at −20°. The soln. was evaporated and the residue dissolved in formic acid (10 ml) and 30% H_2O_2 in H_2O (10 ml). After stirring for 6 h at 55–60°, the soln. was evaporated: 0.35 g of a semisolid. It was dissolved in Et_2O (10 ml), and CH_2N_2 (14 ml of 0.5M CH_2N_2 in Et_2O, *ca.* 7 mmol) was added at −20°. After stirring for 1 h at −10° and 12 h at r.t., the solvent was evaporated: 1.04 g of yellowish oil. CC (silica gel (80 g), Et_2O) afforded 0.12 g (16%) of **9b**. TLC: R_f 0.23. Colourless oil. $[\alpha]_D^{23} = -4.1$ ($c = 0.80$, CCl_4). Enantioselective GC (17% heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin and 25% heptakis(2,3,6-tri-*O*-propyl)-β-cyclodextrin in *OV-1701*, 130°): t_R 264.4 (56.2%, (*R*)-enantiomer), 270.7 (43.8%, (*S*)-enantiomer); 12% ee. IR (CCl_4): 3440*w*, 2960*w*, 1745*s*, 1690*s*, 1500*m*, 1435*w*, 1330*w*, 1200*s*, 1170*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.17 (*t*, $J = 7$, Me); 1.20 (*m*, 1 H); 1.60–1.80 (*m*, 2 H); 1.80–1.95 (*m*, 1 H); 2.28 (*q*, $J = 7$, CH_2); 2.35 (*t*, CH_2); 3.68 (*s*, MeO); 3.75 (*s*, MeO); 4.65 (*m*, 1 H); 6.25 (*d*, $J = 10$, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.7 (*q*); 20.6 (*t*); 29.5 (*t*); 31.8 (*t*); 33.3 (*t*); 51.6 (*q*); 51.7 (*q*); 52.5 (*d*); 172.9 (*s*); 173.6 (*s*); 173.7 (*s*). MS: 246 (2, $[M + 1]^+$), 245 (4, M^+), 230 (2), 224 (3), 223 (4), 205 (6), 191 (5), 190 (3), 189 (10), 188 (14), 186 (72), 172 (10), 158 (61), 155 (33), 154 (37), 153 (16), 145 (13), 131 (10), *130* (100), 119 (11), 117 (15), 116 (12), 113 (11), 112 (29), 102 (8), 99 (13), 98 (72), 88 (10), 81 (20), 74 (65), 70 (13), 57 (41), 56 (52), 41 (12), 29 (15). Anal. calc. for $C_{11}H_{19}NO_5$ (245.28): C 53.87, H 7.81, N 5.71; found: C 53.58, H 7.86, N 5.30.

*Dimethyl (*S*)-2-(Propanoylamino)hexanedioate* ((*S*)-Enantiomer of **9b**) *from (+)-(*S*)-2-Aminohexanedioic Acid*. To a suspension of (+)-(*S*)-2-aminohexanedioic acid (0.08 g, 0.5 mmol; *Fluka*) in MeOH (2.5 ml) was added $SOCl_2$ (0.29 g, 24 mmol) at −10° under N_2. After stirring for 16 h at r.t. and 2 h at 50°, the volatiles were evaporated, and 25% NH_4OH in H_2O (0.4 ml) was added. The soln. was extracted with Et_2O (3 × 20 ml) and the Et_2O phase washed with brine (2 × 1 ml), dried ($MgSO_4$), and evaporated: 0.04 g of dimethyl (*S*)-2-aminohexanedioate. Colourless oil. $[\alpha]_D^{23} = +8.2$ ($c = 3.9$, $CHCl_3$). The oil (0.039 g, 0.21 mmol) was dissolved in Et_2O (1 ml), and Et_3N (0.02 g, 0.2 mmol) and propanoyl chloride (0.04 g, 0.4 mmol) were added dropewise at 0°. The soln. was stirred for 10 min at 0° and 10 min at r.t. H_2O (0.3 ml) was added, the soln. extracted with Et_2O (3 × 5 ml), and the Et_2O phase washed with brine (1 ml), dried ($MgSO_4$), and evaporated: 0.05 g of colourless oil. CC (silica gel (15 g), Et_2O) afforded 0.03 g (25%) of (*S*)-enantiomer of **9b**. TLC: R_f 0.28. Colourless oil. $[\alpha]_D^{23} = +33.7$ ($c = 0.40$, CCl_4). Enantioselective GC (17% heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin and 25% heptakis(2,3,6-tri-*O*-propyl)-β-cyclodextrin in *OV-1701*, 130°): t_R 269.5 (100%, (*S*)-enantiomer). GC (as above; mixture of **9b** prepared from **2f** and of (*S*)-enantiomer): t_R 264.4, 270.

REFERENCES

[1] A. Georgopoulos, G. Petranyi, H. Mieth, J. Drews, *Antimicrob. Agents Chemother.* **1981,** *19,* 386; G. Petranyi, A. Georgopoulos, H. Mieth, *ibid.* **1981,** *19,* 390.

[2] G. Petranyi, N. S. Ryder, A. Stütz, *Science* **1984,** *224,* 1239.

[3] *Sumitomo Chemical Company,* EP 0 128 006 B1, 1984.

[4] K. Kobayashi, S. Miyazawa, A. Terahara, H. Mishima, H. Kurihara, *Tetrahedron Lett.* **1976,** 537; R. R. Rando, F. Bangerter, *J. Am. Chem Soc.* **1976,** *98,* 6762; R. R. Rando, F. Bangerter, *ibid.* **1977,** *99,* 5141; R. D. Allan, G. A. R. Johnstone, B. Twitchin, *Neurosci. Lett.* **1977,** *4,* 51; *Chem. Abstr.* **1977,** *86,* 150390.

[5] T. Hashimoto, S. Kondo, H. Naganawa, T. Takita, K. Maeda, H. Umezawa, *J. Antibiot.* **1974,** *27,* 86; T. Hashimoto, S. Takahashi, H. Naganawa, T. Takita, K. Maeda, H. Umeazawa, *ibid.* **1972,** *25,* 350; C. Y. P.Teng, B. Ganem, *Tetrahedron Lett.* **1982,** *23,* 313.

[6] Review: D. M. Huryn, M. Okabe, *Chem. Rev.* **1992,** *92,* 1745.

[7] T. Kondo, H. Nakai, T. Goto, *Tetrahedron* **1973,** *29,* 1801.

[8] R. R. Copp, V. E. Marquez, *J. Med. Chem.* **1991,** *34,* 208.

[9] B. M. Trost, L. Li, D. G. Simon, *J. Am. Chem. Soc.* **1992,** *114,* 8745, and ref. cit. therein.

[10] Review: R. B. Cheikh, R. Chaabouni, A. Laurent, P. Mison, A. Nafti, *Synthesis* **1983,** 685; A. Laurent, P. Mison, A. Nafti, R. B. Cheikh, R. Chaabouni, *J. Chem. Res. (S)* **1984,** 354.

[11] J. K. Whitesell, H. K. Yaser, *J. Am. Chem. Soc.* **1991,** *113,* 3526.

[12] R. B. Grossman, W. M. Davis, S. L. Buchwald, *J. Am. Chem. Soc.* **1991,** *113,* 2321.

[13] T. Hayashi, A. Yamamoto, Y. Ito, E. Nishioka, H. Miura, K. Yanagi, *J. Am. Chem. Soc.* **1989,** *111,* 6301.

[14] Z. Li, K. R. Conser, E. N. Jacobsen, *J. Am. Chem. Soc.* **1993,** *115,* 5326; D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes, *ibid.* **1993,** *115,* 5328.

[15] R. Scheffold, H. Su, L. Walder, Z. da Zhang, *Helv. Chim. Acta* **1988,** *71,* 1073.

[16] J. A. Deyrup, 'Aziridines', Ed. A. Hassner, John Wiley and Sons, New York, 1983, p. 1–214.

[17] A. Hassner, G. T. Mattews, F. W. Fowler, *J. Am. Chem. Soc.* **1969,** *91,* 5046.

[18] J. Legters, T. B. Zwanenburg, *Tetrahedron Lett.* **1989,** *30,* 4881.

[19] J. Prandi, H. B. Kagan, H. Mimoun, *Tetrahedron Lett.* **1986,** *27,* 2617.

[20] D. V. Kashelikar, P. E. Fanta, *J. Am. Chem. Soc.* **1960,** *82,* 4927.

[21] A. Hassner, M. E. Lorber, C. Heathcock, *J. Org. Chem.* **1967,** *32,* 540.

[22] D. S. Tarbell, Y. Yamamoto, B. M. Pope, *Proc. Natl. Acad. Sci. U.S.A.* **1972,** *69,* 730.

[23] D. Dolphin, 'Methods Enzymol.', Vol. XVIII, 1971, Part C, p. 34.

[24] *Beilstein 4,* IV, 3028.

[25] *Beilstein 4,* IV, 3070.

[26] S. Danishefsky, J. Morris, L. A. Clizbe, *J. Am. Chem. Soc.* **1981,** *103,* 1602.

[27] P. Bonhote, R. Scheffold, *Helv. Chim. Acta* **1991,** *74,* 1425.

[28] V. B. Pett, M. N. Liebman, P. Murray-Rust, K. Prasad, J. P. Glusker, *J. Am. Chem. Soc.* **1987,** *109,* 3207.

[29] R. Scheffold, R. Härter, Ch. Weymuth, 'Modern Methodology in Organic Synthesis', Ed. T. Shono, Kodansha, Tokyo, 1992, p. 29.

[30] A. Hassner, C. Heathcock, *J. Org. Chem.* **1965,** *30,* 1748.

[31] Th. J. De Boer, H. J. Backer, *Org. Synth. Coll.* **1963,** *4,* 250.