Synthesis, resolution and absolute configuration determination of (*S*)- and (*R*)-4-formyl-5-hydroxy[2.2]paracyclophane and its application in the asymmetric synthesis of α-amino acids

Dmitri Yu. Antonov, Yuri N. Belokon,* Nikolai S. Ikonnikov, Svetlana A. Orlova, Aleksander P. Pisarevsky, Nikolai I. Raevski, Valeria I. Rozenberg,* Elena V. Sergeeva, Yuri T. Struchkov, Vitali I. Tararov and Evgeni V. Vorontsov

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow, Russia

Racemic (*R,S*)-4-formyl-5-hydroxy[2.2]paracyclophane (FHPC) was resolved into enantiomers *via* its Schiff's base with (*S*)- and (*R*)-α-phenylethylamine (α-PEAM) and its absolute configuration was determined by an X-ray diffraction structural study. Scalemic FHPC or its derivatives can be used as chiral auxiliaries for the asymmetric synthesis of β-hydroxy-α-amino acids and α-methylphenylalanine with ees ranging mostly from 45 to 98%.

Introduction

The burgeoning field of asymmetric synthesis relies mainly on the use of chiral natural compounds or their derivatives as chiral auxiliaries for stoichiometric asymmetric synthesis or chiral ligands for transition-metal-based catalysis.[1] Still, purely synthetic chiral auxiliaries are found to be among the most efficient ligands for asymmetric catalysis.[2] Among those auxiliaries feature prominently molecules with planar chirality, such as derivatives of ferrocene.[3] Chiral arenechromium complexes have been used in many stoichiometric asymmetric reactions,[4a] and also very recently to catalyse the addition reactions of organozinc compounds to aldehydes.[4b] Furthermore, a chiral pyridoxal derivative was shown to function as an auxiliary in the asymmetric synthesis of β-hydroxy-α-amino acids.[5]

Unfortunately, the compounds with planar chirality derived from arene– or cyclopentadiene–transition metal complexes are either readily oxidized or are unstable under certain reaction conditions.

We have therefore investigated whether other compounds with planar chirality, derived from [2.2]paracyclophane **1**, are also suitable as chiral auxiliaries, since here the starting material is very stable towards light, oxidation, acids, bases, and relatively high temperatures.[6]

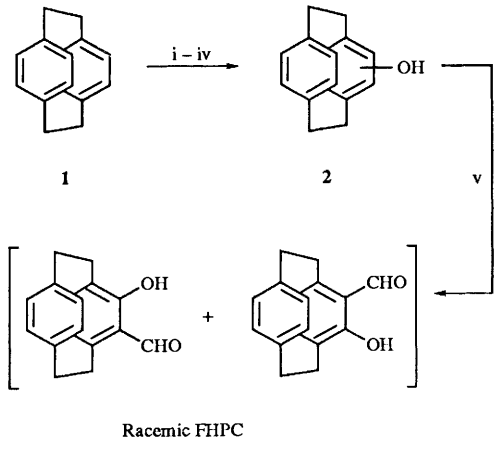
We believed that a salicylaldehyde analogue derived from [2.2]paracyclophane might be a very useful chiral auxiliary or a chiral ligand in the range of chemical reactions catalysed by salicylaldehyde or its derivatives. It was already well documented that metal complexes of chiral Schiff's bases derived from salicylaldehyde (or substituted salicylaldehyde) and chiral amines (or diamines of β-hydroxy amines) could be used for asymmetric cyclopropanation,[7] oxidation of sulfides,[8] epoxidation of olefins[9] and silylcyanation of aldehydes.[10] Finally, Cu^{II} complexes of the Schiff's bases derived from salicylaldehyde and glycine were used for the stoichiometric synthesis of racemic β-hydroxy-α-amino acids,[11] and Schiff's bases of amino acid esters and substituted benzaldehydes were employed for the synthesis of racemic α-amino acids.[12]

We report here the synthesis, resolution and absolute configuration determination of 4-formyl-5-hydroxy[2.2]paracyclophane (FHPC), a chiral analogue of salicylaldehyde, and also its application for the stoichiometric asymmetric synthesis of α-amino acids. Preliminary results of a part of the work were published earlier.[13]

Results and discussion

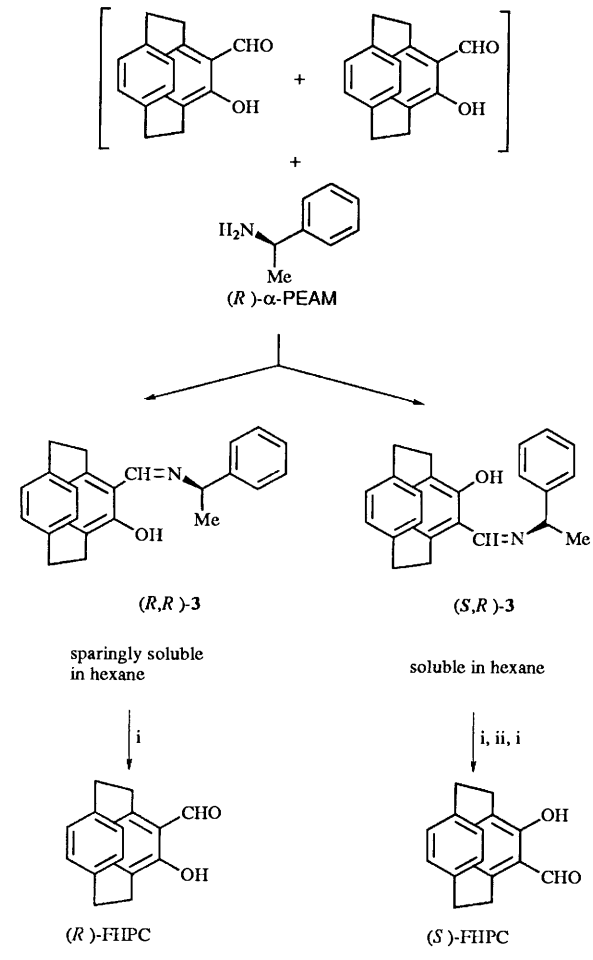
Synthesis and resolution of racemic FHPC

Synthesis of FHPC was carried out according to Scheme 1 in a multistage reaction; bromination of the parent paracyclophane **1**, Li–Br exchange, reaction of the organometallic intermediate with trimethyl borate, and oxidation with H_2O_2 furnishing the phenol **2**.[14] The *ortho* formylation with $(CH_2O)_n$, catalysed by $SnCl_4$ and Bu_3N,[15] gave the expected racemic FHPC.[16] Although the overall yield of the reaction was low (20–30%), the initial remaining phenol **2** could be almost quantitatively isolated from the reaction mixture and reused.



Scheme 1 *Reagents:* i, Br_2 (Fe); ii, BuLi; iii, $B(OMe)_3$; iv, H_2O_2, NaOH; v, $(CH_2O)_n$, $SnCl_4$, Bu_3N

The differing solubility, in hexane, of the Schiff's bases **3** derived from (*S*)-FHPC or (*R*)-FHPC and (*R*)-α-phenylethylamine [(*R*)-α-PEAM] was used for the resolution of racemic FHPC (see Scheme 2). A single crystallization of the mixture of the (*R,R*)-**3** and (*S,R*)-**3** diastereoisomers gave almost diastereoisomerically pure compound in the precipitate [de > 90% according to ^1H NMR spectroscopy, by measuring the areas of the resonances of the aldimine hydrogen atoms (N=CH)]. The diastereoisomeric purity of the isomer could be improved and brought to almost 96% by another crystallization. X-ray analysis of the sparingly soluble diastereoisomer revealed it to have the (*R,R*)-configuration (see Fig. 1). (*R*)-FHPC



Scheme 2 *Reagents:* i, aq. HCl, MeOH; ii, (*S*)-α-PEAM

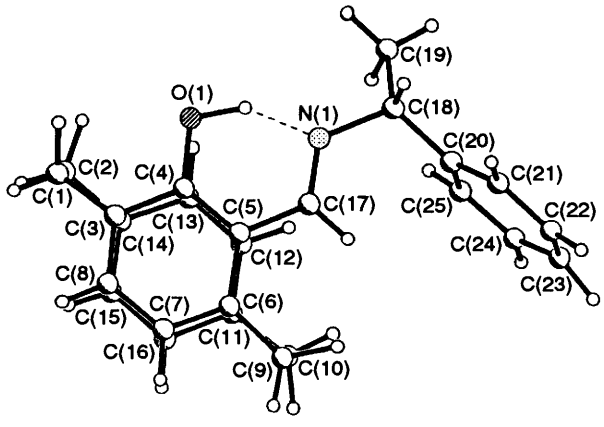
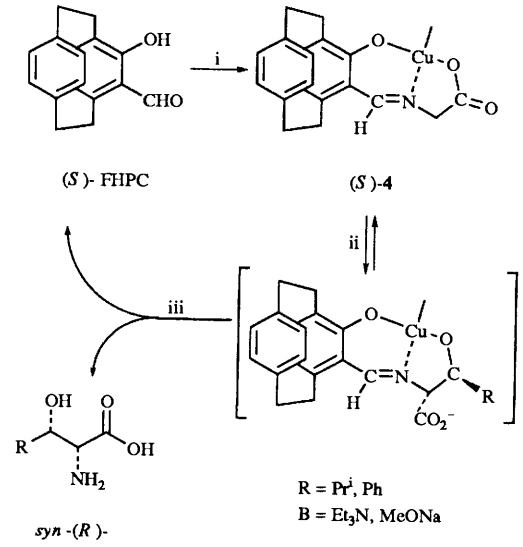


Fig. 1 Structure of the Schiff's base derived from (*R*)-α-phenylethylamine and (*R*)-FHPC as revealed by X-ray analysis

(having positive optical rotation at 589 nm) could be recovered from the pure diastereoisomer after the decomposition of the latter with a solution of aq. HCl in MeOH. The enantiomeric purity of the resolved material was additionally checked by ^{1}H NMR spectroscopy, employing europium tris(heptafluorobutyrylcamphorate) [Eu(hfc)$_3$] as a shift reagent. Another enantiomer [partially resolved (*S*)-FHPC] could be recovered from the remaining hexane solution as described above. One molar equivalent of (*S*)-α-phenylethylamine [(*S*)-α-PEAM] was added to it and the thus formed diastereoisomer (*S*,*S*)-**3** was



Scheme 3 *Reagents and conditions:* i, Gly, $Cu(OAc)_2$, MeONa, 50 °C; ii, RCHO, B; iii, aq. HCl, MeOH

recrystallized from hexane solution. In this way enantiomerically pure (*S*)-FHPC (having negative rotation at 589 nm) was easily obtained. On the other hand, (*S*)-FHPC could be obtained from racemic FHPC and (*S*)-α-PEAM, and (*R*)-FHPC—from partially resolved (*R*)-FHPC and (*R*)-α-PEAM. The novel procedure greatly simplifed the resolution technique, in comparison with one reported by us earlier.[13]

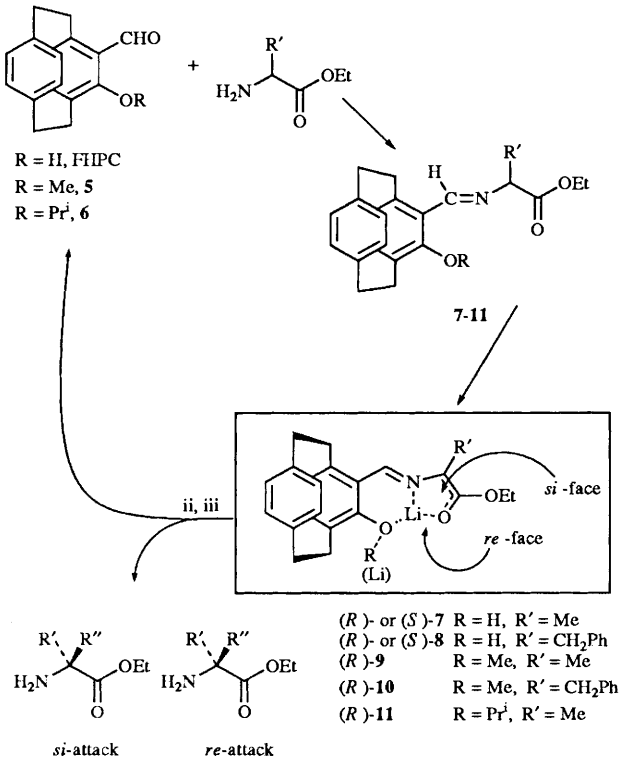
Asymmetric synthesis of β-hydroxy α-amino acids

The reaction involves condensation of the chiral Cu^{II} complexes (*S*)- and (*R*)-**4** derived from glycine and (*S*)- or (*R*)-FHPC respectively with isobutyraldehyde and benzaldehyde in MeOH (Scheme 3). After completion of the reaction, the mixture was quenched with aq. HCl, the unchanged initial chiral auxiliary was recovered, and the amino acids were isolated. FHPC retained its optical purity under all experimental conditions. The chemical yield, enantiomeric purity of the isolated amino acids, and their *syn*/*anti* (*threo*/*allo*) ratio were dependent on the pH of the solution (see Table 1). At a low pH (Et_3N catalysis), formation of almost racemic β-hydroxyleucine from complex (*S*)-**4** was observed (Table 1, run 1), although the yield and *syn*/*anti* ratio were also disappointing. However, at a higher pH (MeONa catalysis) the enantiomeric purity *syn*/*anti* ratio of the recovered amino acids were greatly improved and complex (*S*)-**4** gave rise to *syn*-(*R*)-β-hydroxy-α-amino acids (Table 1, runs 5–7), whereas complex **4** (*R*)-**4** produced their (*S*)-enantiomers (Table 1, runs 2–4, 8). Thermodynamic control of the stereochemistry of the reaction and a mechanism incorporating intermediate formation of a complex with the coordinated, ionized hydroxy group of the amino acid moiety (see Scheme 3) at a high pH can be invoked to rationalize the observations in the same manner as was discussed earlier for the condensations with other chiral Schiff's base complexes of Ni^{II} and Cu^{II} derived from glycine.[18] As can be seen from Scheme 3, chelation of the ionized hydroxy group and C=N moiety forces the ionized carboxy group to take up a pseudo-axial position to avoid a non-bonding interaction with the H-atom of the HC=N group whereas the R-substituent has to position itself on the other side of the chelate ring to minimize its unfavourable interaction with the carboxy group. The situation corresponded to *syn*-diastereoisomers of the amino acid moiety as the most energetically favourable in the equilibrated mixture of the complexes. At the same time unfavourable interaction of the axial carboxy group with the (*S*)-paracyclophane moiety was

Table 1 Condensation of complexes (*S*)- and (*R*)-**4** with isobutyraldehyde and benzaldehyde in MeOH, catalysed by base, under Ar, at 50 °C

Run	R in RCHO	Catalyst	Configuration of compound **4**	Time (*t*/h)	*syn*/*anti* quotient	d.e. %[a] (conf.)
1	Pr^i	Et_3N	(*S*)	11.5	4/1	0[b]
2	Pr^i	MeONa	(*R*)	1.5	28/1	90 (*S*)
3	Pr^i	MeONa	(*R*)	4.5	33/1	92 (*S*)
4	Pr^i	MeONa	(*R*)	7.5	58/1	93 (*S*)
5	Pr^i	MeONa	(*S*)	1.3	13/1	94 (*R*)
6	Pr^i	MeONa	(*S*)	4.5	20/1	96 (*R*)
7	Pr^i	MeONa	(*S*)	7.5	15/1	98 (*R*)
8	Ph	MeONa	(*R*)	0.5	*c*	77 (*S*)

[a] GLC enantiomeric analyses of the *syn*-β-hydroxy-α-amino acids were performed on a Chirasil-Val-type phase.[17] The chemical yields were in the range of 60–80%. [b] Almost racemic product, chemical yield 22%. [c] The amount of *anti*-isomer was too small to allow us to carry out any meaningful measurements.



Scheme 4 *Reagents:* i, LDA; ii, R″X; iii, aq. HCl

minimal if the configuration of the amino acid α-carbon atom was (*R*)-, with the CO_2^- group projected away from the basket of the paracyclophane moiety.

Whatever the mechanism of the reaction, the chemical yields, *syn*/*anti* ratio and enantiomeric purity of the β-hydroxy-α-amino acids obtained *via* FHPC-assisted reaction compare favourably with the earlier results on the use of a chiral pyridoxal-like pyridinophane for the synthesis of similar amino acids.[5] For example, their *syn*/*anti* values (1.1–2/1) and des 24–85% should be rated against the quotients 15–58/1 and de 77–98% in our case (see Table 1).

Synthesis of the *O*-alkylated derivatives of FHPC

(*R*)-FHPC was alkylated with MeI and Pr^{i}Br to give 4-formyl-5-methoxy[2.2]paracyclophane (*R*)-**5** and 4-formyl-5-isopropoxy[2.2]paracyclophane (*R*)-**6**, respectively.

C-Alkylation of the Schiff's bases derived from (*S*,*R*)-Ala-OEt [or (*S*,*R*)-Phe-OEt] and (*S*)- or (*R*)-FHPC [or its derivatives]

Syntheses of the Schiff's bases were carried out by the condensation of FHPC and its derivatives with the amino acid esters[19] (see Scheme 4), as described in the **Experimental** section. The Schiff's bases, derived from (*S*)- or (*R*)-FHPC and (*S*,*R*)-Ala-OEt, (*S*)-**7** or (*R*)-**7** respectively, and (*S*)- or (*R*)-FHPC and (*S*,*R*)-Phe-OEt, (*S*)-**8** or (*R*)-**8**, respectively, were alkylated in tetrahydrofuran (THF) [some hexamethylphosphnic triamide (HMPT) was added] in the presence of at least 2 mol equiv. of lithium diisopropylamide (LDA).[12a] Imines (*S*)-**7** and (*R*)-**7** were alkylated with BzlBr, and imines (*S*)-**8** and (*R*)-**8** were alkylated with MeI to afford α-methylphenylalanine (α-Me-Phe) in both cases. The Schiff's bases synthesized from substrates (*R*)-**5** and (*R*)-**6** [compounds (*R*)-**9**, (*R*)-**10** and (*R*)-**11**; see Scheme 4 for the designations], were alkylated in the presence of 1 mol equiv. of LDA. The results of the experiments are summarized in Table 2.

As could be seen from the data (Table 2, run 1), (*R*)-FHPC promoted alkylation of the AlaOEt moiety in imine (*R*)-**7** with BzlBr from the *re*-face of the intermediate Li-enolate (see Scheme 4), giving (*R*)-α-Me-Phe, whereas (*S*)-FHPC, as expected, induced *si*-attack, producing (*S*)-α-Me-Phe (Table 2, run 2). Alkylation of the PheOEt moiety in compound (*R*)-**8** with MeI gave (*S*)-α-Me-Phe (Table 2, run 3). The amino acid was also derived as a result of the *re*-face attack of a small electrophile on an amino acid ester enolate, having a larger side chain. As expected, compound (*S*)-**8** gave (*R*)-α-Me-Ph (Table 2, run 4). The stereochemical course of the reaction could be simply (and rather naïvely) accommodated by assuming significant shielding of the *si*-face in the enolates of imines (*R*)-**7** and (*R*)-**8** [or *re*-face in the corresponding enolates of imines (*S*)-**7** or (*S*)-**8**] by the phenyl ring of the paracyclophane moiety, situated over the enolate plane (see Scheme 4). Examination of runs 1–4 (Table 2) indicated that the diastereoselectivity (de) of the alkylation depended to some extent on the type of the amino acid side moiety and the alkylating agent. Larger des were obtained in cases of a large electrophile attacking a small amino acid moiety (runs 1,2), as compared with a small electrophile reacting with a large enolate (runs 3,4). The obvious explanation seems to be an increase in the value of the difference in energy between the two diastereoisomeric transition states accompanying the enlargement in the size of the attacking electrophile. Nevertheless, the predominant influence of the paracyclophane, shielding the *si*-face of the enolates of imines (*R*)-**7** and (*R*)-**8** and the *re*-face of the enolates derived from imines (*S*)-**7** and (*S*)-**8**, was retained.

Substitution of OH by OMe or OPr^i (conversion of FHPC into the ether **5** or **6**) reversed the stereochemical sense of the asymmetric alkylation of the AlaOEt moiety, giving (*S*)-α-Me-Phe from compounds (*R*)-**9** and (*R*)-**11** (see Table 2, runs 5 and 7). The computer-generated [minimal neglect of differential overlap (MNDO)-calculated] structure of the Li-enolate derived from compound (*R*)-**11** revealed that the RO group was

Table 2 Asymmetric synthesis of α-Me-Phe *via* alkylation of the Schiff's bases of (*S*,*R*)-AlaOEt [or (*S*,*R*)-PheOEt] and (*S*)- or (*R*)-FHPC and its derivatives[a]

Run	Initial substrate			Alkylating agent R″X	de %[c] (Conf.)	Recovery of the chiral auxiliary (%)
	Des.[b]	R	R′			
1	(*R*)-**7**	H	Me	BzlBr	79 (*R*)	70[d]
2	(*S*)-**7**	H	Me	BzlBr	82 (*S*)	80[d]
3	(*R*)-**8**	H	Bzl	MeI	60 (*S*)	69
4	(*S*)-**8**	H	Bzl	MeI	50 (*R*)	71
5	(*R*)-**9**	Me	Me	BzlBr	45 (*S*)	80[e]
6	(*R*)-**10**	Me	Bzl	MeI	8 (*R*)	70[e]
7	(*R*)-**11**	Pr^i	Me	BzlBr	49 (*S*)	80

[a] 2 h, at −78 °C, LDA, THF–HMPTA (7:1), overnight at 20 °C. [b] See Scheme 4 for the designations. [c] GLC enantiomeric analyses of α-Me-Phe were performed on a β-cyclodextrin-type phase.[20] Chemical yields of the amino acids were in the range 50–100%. [d] 10% of (*R*)-**4** [or (*S*)-**4**] was found in the reaction mixture. [e] 10% of (*R*)-FHPC was detected in the mixture.

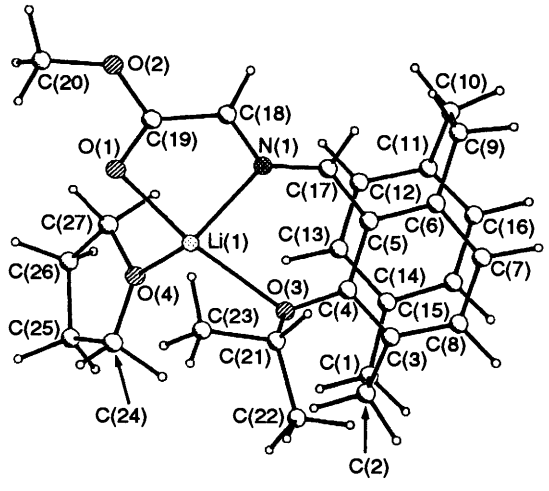


Fig. 2 The computer-generated (MNDO-calculated) structure of the Li-enolate of the Schiff's base derived from 4-formyl-5-isopropoxy[2.2]-paracyclophane and glycine ethyl ester

situated over the enolate plane, thereby shielding the *re*-face of the enolate, whereas the phenyl ring, situated on the other side of the plane, shielded the *si*-face (see Fig. 2). Thus the two shielding effects acted in opposite directions; however, the shielding provided by the RO substituent exerted a greater influence on the stereochemical outcome of the reaction in cases of BzlBr alkylation of the AlaOEt moiety. As expected, the size of the attacking electrophile influenced the d.e. of the reaction (compare runs 6 and 5). The attack of MeI on the PheOEt moiety in compound (*R*)-**10** gave almost racemic product (Table 2, run 6).

Among the chiral auxiliaries used, compound (*R*)-**5** were found to possess the greatest stability. FHPC was partly alkylated under the experimental conditions (up to 10%) and compound (*R*)-**4** was partly hydrolysed (up to 10%) in the course of work-up, following the alkylation step.

Conclusions

The data reported in this work clearly indicated that chiral auxiliaries based on derivatives of [2.2]paracyclophanes can be successfully employed for asymmetric syntheses. We believe that FHPC itself can be effectively used in future as a ligand for the salen–transition-metal complex-catalysed asymmetric reactions discussed in the introduction.[7–10] In addition, the molecule of FHPC could be easily modified and a set of new chiral derivatives of paracyclophane capable of serving as chiral ligands or auxiliaries synthesized.

Experimental

General

^{1}H NMR spectra were obtained on a Bruker WP-200-SY or at 400 MHz on a Bruker AMX-400 instrument with $CHCl_3$ (δ 7.27) as internal standard. Optical rotations were measured with a Perkin-Elmer-241 polarimeter in a thermostated cell at 25 °C; $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. TLC analysis was performed on silica gel precoated plates 'Silufol UV-254' (Chemapol). Column chromatography was performed on Kieselgel 60 (Merck). Dichloromethane was washed successively with conc. H_2SO_4, water and saturated aq. Na_2CO_3, predried with $CaCl_2$, distilled twice (successively) over P_2O_5 and CaH_2, and stored over 3 Å molecular sieves. Acetone and benzene were dried over molecular sieves 3 Å and were used without further purification. Ethanol was distilled from its magnesium alkoxide under argon. THF was distilled from sodium benzophenone ketyl under argon immediately before use. (*R*)- and (*S*)-α-phenylethylamine [(*R*)- and (*S*)-α-PEAM] were purchased from Fluka and diisopropylamine was purchased from Merck; all three were used without further purification. The hydrochlorides of α-amino acid ethyl esters were prepared according to literature procedures.[19] Compound (*R*)-**10** was obtained as an inseparable mixture with starting material (*R*)-**4**; its identification arose from ^{1}H NMR analyses of the mixture.

GLC enantiomeric analyses of α-amino acids

The enantiomeric purity of β-hydroxyleucine and β-phenylserine was checked by GLC analysis of their *N*-trifluoroacetyl isopropyl esters on a Chirasil-Val-type phase,[17] fused silica capillary column (23 m × 0.22 mm); 100 and 142 °C; carrier gas He at 1.4 and 1.8 bar (1 bar = 10^5 Pa). The samples of α-Me-Phe was analysed as their *N*-trifluoroacetyl propyl esters on a heptakis(2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl)-β-cyclodextrin phase[20] (DP-TFA-β-CD), glass capillary column (40 m × 0.23 mm); 143 °C; carrier gas He at 1.6 bar.

Quantum mechanics calculations

The calculations were performed on an IBM-compatible 486-processor computer, using a MNDO approach.

X-ray analysis of Schiff's base (*R*,*R*)-3

Red crystals of the Schiff's base were obtained by crystallization from hexane. Crystal data: $C_{25}H_{25}NO$, M = 355.5, orthorhombic (although the *a* and *b* parameters are, in fact, equal, the orthorhombic space group was chosen because of the lack of tetragonal symmetry in the intensities of reflections), *a* = 11.070(2), *b* = 11.077(2), *c* = 15.743(4) Å, *V* = 1930.3(7) Å^3, *Z* = 4, D_c = 1.223 g cm^{-3}, space group $P2_12_12_1$, μ = 0.074

mm^{-1}, $F(000)$ = 760. The unit-cell parameters and reflection intensities from a prismatic crystal with dimensions of 0.2 × 0.2 × 0.2 mm were measured with a four-circle automated Siemens P3/PC diffractometer (T 293 K, Mo-Kα) radiation, λ 0.710 73 Å, graphite monochromator, $\theta/2\theta$ scan, $2° < 2\theta < 56°$, scan speed 2–15 deg min^{-1}, scan width of 1.7°; no crystal decay was observed. 1591 Independent observed reflections with $I > 2\sigma(I)$. The structure was solved by direct methods. No absorption correction was applied. All non-hydrogen atoms were located in the difference map and refined anisotropically, hydrogen atoms were refined in isotropic approximation. The weighting scheme $w = [\sigma^2(F) + 0.0001 F^2]^{-1}$ was used. Full-matrix least-squares refinement led to R = 0.0451 (R_w = 0.0467) for the absolute configuration to the known (*R*)-configuration of the asymmetric centre of the PEAM moiety; refinement of the inverted structure led to approximately the same R- and R_w-values. The calculations were carried out with an IBM PC/AT-386 computer using the SHELXTL PLUS (PC Version) programs. Atomic coordinates, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.

In the molecule (Fig. 1), aromatic rings of paracyclophane moieties [C(3)–C(8) and C(11)–C(16)] are planar to within 0.10 and 0.11 Å, respectively, and form a dihedral angle of 1.4°. The phenyl ring C(20)–C(25) in the side chain is planar to within 0.01 Å and forms, with the aforementioned planes, angles of 82.5 and 81.3°, respectively. Bonds C(1)–C(2) and C(9)–C(10) are collinear to within 0.9°. The intramolecular hydrogen bond has the following parameters: O(1)···N(1) 2.533 Å, O(1)–H(10) 1.10 Å, H(10)–N(1) 1.54 Å, O(1)–H(10)···N(1) 148°. The H(10)···N(1) line runs almost parallel to the best-fit least-squares planes described by the paracyclophane rings (the angle is approximately 5°). The C(4)–O(1) bond has a length of 1.353 Å, and the deviation of the O(1) atom from the C(3)–C(8) plane is 0.07 Å. The N(1) atom has a planar configuration with the following parameters: N(1)–C(17) 1.275 Å, N(1)–C(18) 1.482 Å, C(17)–N(1)–C(18) 121.8°.

Synthesis of racemic FHPC

Published procedures were used for the synthesis of compounds **1**[14a] and **2**.[14b] *ortho*-Formylation was carried out similarly to a literature method described for the *ortho*-formylation of phenols as follows. To a solution of compound **2** (5.23 g, 23.3 mmol) in absolute toluene (250 cm^3) were added $SnCl_4$ (1.1 g, 0.49 cm^3, 4.2 mmol) and Bu_3N (3.02 g, 3.88 cm^3, 1.63 mmol) and the mixture was kept at ambient temp. for 0.5 h. Then $(CH_2O)_n$ (2.8 g, 9.32 mmol) was added and the mixture was kept at 100 °C for 1 h. After that the mixture was diluted with water and acidified with 2 mol dm^{-3} HCl. The organic layer was separated and the water layer was extracted with Et_2O (2 × 50 cm^3). The combined organic layers were evaporated to dryness and the residue was separated by column chromatography on SiO_2, with benzene as eluent (R_f of FHPC > R_f of **2**), and the fractions containing FHPC were combined and evaporated to afford *title compound* (1.17 g, 20%). Starting material **2** (3.14 g, 60%) was recovered as the next fraction. After recrystallization from heptane, FHPC (1.1 g, 19%) had mp 201–204 °C (Found: C, 80.95; H, 6.35. $C_{17}H_{16}O_2$ requires C, 80.88; H, 6.41%); $\delta_H(C_6D_6)$ 12.61 (1 H, s, OH), 9.47 (1 H, s, CHO), 7.00 (1 H, dd, *J* 8.0 and 1.8), 6.40 (1 H, dd, *J* 8.0 and 1.8), 6.30 (1 H, d, *J* 8), 6.26–6.16 (2 H, m), 5.98 (1 H, d, *J* 8) and 3.62–2.24 (8 H, m, bridge); λ_{max}(benzene)/nm 304 and 399; $\nu_{max}(CDCl_3)/cm^{-1}$ 1630 (C=O).

Resolution of FHPC

A solution of racemic FHPC (1.38 g, 5.48 mmol) and (*R*)-α-PEAM (0.63 g, 0.7 cm^3, 5.48 mmol) in benzene (38 cm^3)–EtOH (10 cm^3) was refluxed in a flask equipped with a Dean–Stark trap filled with $MgSO_4$ for 3 h. The resulting mixture of diastereoisomeric (*R,R*)- and (*S,R*)-**3** was recrystallized twice from hexane. *Isomer* (*R,R*)-**3** (0.70 g, 36%) had mp 158–160 °C (Found: C, 84.6; H, 7.1; N, 3.7. $C_{25}H_{25}NO$ requires C, 84.47; H, 7.09; N, 3.94%); $[\alpha]_D^{25}$ +365 (*c* 0.60, benzene); $\delta_H(CDCl_3)$ 14.4 (1 H, s, OH), 8.27 (1 H, s, N=CH), 7.52–7.25 (5 H, m, Ph), 6.75 (1 H, d, *J* 7.8 and 1.8), 6.51 (2 H, m), 6.35 (1 H, dd, *J* 7.8 and 1.8), 6.22 (1 H, d, *J* 7.8), 5.76 (1 H, d, *J* 7.8), 4.52 (1 H, q, α-H), 2.38–3.52 (8 H, m, bridge) and 1.7 (3 H, d, Me); λ_{max}(benzene)/nm 293, 317sh and 375.

Compound (*R,R*)-**3** was hydrolysed by being refluxed with aq. HCl in MeOH, the organic material was taken up into benzene (2 × 15 cm^3), and the extracts were dried over $MgSO_4$ and evaporated to give (*R*)-FHPC as yellow crystals. (*R*)-FHPC (0.46 g, 33%) had $[\alpha]_D^{25}$ +572.9 (*c* 0.55, benzene).

The combined hexane filtrates, containing partially enriched (*S,R*)-**3**, after evaporation and hydrolysis gave a partially resolved (*S*)-FHPC (0.86 g, 62%) with $[\alpha]_D^{25}$ −222.7 (*c* 0.58, benzene). This compound and (*S*)-α-PEAM (0.43 cm^3, 0.41 g, 3.41 mmol) afforded isomer (*S,S*)-**3** (0.52 g, 27.2%) with $[\alpha]_D^{25}$ +345 (*c* 0.60, benzene), mp 161–162.5 °C. Hydrolysis of compound (*S,S*)-**3** gave (*S*)-FHPC (0.35 g, 25%) with $[\alpha]_D^{25}$ −573.9 (*c* 0.38, benzene).

Determination of the enantiomeric purity of (*R*)-FHPC

^1H NMR investigation of the samples, containing racemic FHPC (0.02 mmol) and $Eu(hfc)_3$ (0.02 mmol) in $CDCl_3$ (0.5 cm^3), gave well resolved resonances of the H–C=O protons of the enantiomers of FHPC with a $\Delta\delta$-value of 0.73 ppm. Examination of the samples containing shift reagent and (*R*)-FHPC with $[\alpha]_D^{25}$ +472 (*c* 0.45, benzene) under the same experimental conditions indicated that the sample had 82% enantiomeric purity.

(*R*)-4-Formyl-5-methoxy[2.2]paracyclophane, (*R*)-5

A mixture of FHPC (0.1 g, 0.40 mmol), MeI (0.6 g, 0.26 cm^3, 4.0 mmol) and K_2CO_3 (0.5 g) in acetone (4 cm^3) was refluxed for 12 h. Then the mixture was diluted with benzene (5 cm^3), washed successively with saturated aq. Na_2CO_3 and water (2 × 10 cm^3), and the organic layer was separated, evaporated to dryness, and the resulting oily residue was recrystallized from hexane. *Compound* (R)-**5** (0.056 g, 53%) had mp 105–106 °C (Found: C, 81.5; H, 7.0. $C_{18}H_{18}O_2$ requires C, 81.17; H, 6.81%); $\delta_H(CDCl_3)$ 10.15 (1 H, s, CHO), 6.79 (1 H, dd, *J* 7.8 and 1.8), 6.67 (1 H, d, *J* 7.8), 6.58 (1 H, dd, *J* 7.8 and 1.8), 6.59–6.30 (3 H, m, ArH of paracycl.), 4.15–3.98 (1 H, m, bridge), 3.8 (3 H, s, OMe) and 3.45–2.60 (7 H, m, bridge). Compound (*R*)-**4** had mp 85–86 °C; $[\alpha]_D^{25}$ −130.15 (*c* 0.43, benzene); λ_{max}(benzene)/nm 294 and 358.

(*R*)-4-Formyl-5-isopropoxy[2.2]paracyclophane, (*R*)-6

To a solution of (*R*)-FHPC (0.167 g, 0.63 mmol) in DMF (2 cm^3) at 0 °C was added Bu^{t}OK (0.148 g, 1.32 mmol) and the mixture was allowed to reach room temp. Then 2-bromopropane (0.65 g, 0.5 cm^3, 5.3 mmol) was added to the resulting orange solution and the reaction mixture was stirred at 90 °C for 5 min. Then the reaction mixture was cooled, diluted with Et_2O, washed successively with saturated aq. $NaHCO_3$ and water, and extracted with Et_2O (2 × 10 cm^3). The combined extracts were evaporated to dryness and the oily residue was chromatographed on SiO_2 with benzene as the eluent to give the starting material (*R*)-FHPC (0.0204 g, 2% recovery) and compound (*R*)-**6** (0.14 g, 71.7%), which was recrystallized from hexane. Compound (*R*)-**6** (0.113 g, 57.7%) had mp 79–81 °C (Found: C, 81.1; H, 7.7. $C_{20}H_{22}O_2$ requires C, 81.59; H, 7.53%); $\delta_H(CDCl_3)$ 10.18 (1 H, s, CHO), 6.83 (1 H, dd, *J* 7.9 and 1.9), 6.66 (1 H, d, *J* 7.8), 6.59 (1 H, dd, *J* 7.9 and 1.7), 6.45 (1 H, dd,

J 7.8 and 1.8), 6.40 (1 H, d, *J* 7.8), 6.37 (1 H, dd, *J* 7.8 and 1.8), 4.15 (1 H, sept, *J* 6.15, C*H*Me$_2$), 4.08 (1 H, m, bridge), 3.36–2.71 (7 H, m, bridge), 1.48 (3 H, d, CHMe$_2$), and 1.10 (3 H, d, CH*Me*$_2$); $[\alpha]_D^{25}$ −143.0 (*c* 0.28, benzene).

Synthesis of the chiral Cu^{II}-complexes of the Schiff's bases derived from FHPC and Gly, (*S*)- and (*R*)-4

A mixture of (*R*)- or (*S*)-FHPC (0.15 g, 0.595 mmol), Gly (0.05 g, 0.67 mmol) and Cu(OAc)$_2$·H$_2$O (0.14 g, 0.7 mmol) in 0.23 mol dm^{-3} MeONa solution in MeOH (5 cm^3) was stirred at 50 °C for 5 h. Then the mixture was evaporated and the residue was purified on a Sephadex LH-20 column with benzene–methanol (3:1) as eluent, to yield Schiff's base complex (*S*)- or (*R*)-**4** (0.215 g, 93%).

Condensation of complex (*S*)- or (*R*)-4 with aldehydes

General procedure is illustrated by the synthesis of β-hydroxyleucine employing complex (*R*)-**4** as the starting material and MeONa as catalyst. A mixture of (*R*)-**4** (0.27 g, 0.59 mmol), a 0.28 mol dm^{-3} solution of MeONa in MeOH (6 cm^3) and isobutyraldehyde (0.22 cm^3, 0.174 g, 2.36 mmol) was stirred at 50 °C for several hours and worked up as described below.

Recovery of FHPC and amino acids from the Cu^{II} complexes

To a solution of the complex in MeOH was added 2 mol dm^{-3} HCl (8–10 mol equiv.) and the mixture was refluxed until FHPC precipitated from the solution. The mixture was extracted with benzene, the combined extracts were evaporated, and FHPC was purified on SiO_2 (benzene). The amino acid was isolated from the aqueous solution by ion-exchange chromatography on Dowex-50 (H^+).

Synthesis of the Schiff's bases 7–11

The general procedure is illustrated by the synthesis of compound (*R*)-**7**. To a solution of (*R*)-FHPC (0.075 g, 0.298 mmol) in benzene (3 cm^3) were added a solution of (*S*,*R*)-alanine ethyl ester hydrochloride (0.068 g, 0.298 mmol) in EtOH (1 cm^3) and a solution of Et$_3$N (0.030 g, 0.04 cm^3, 0.298 mmol) in EtOH (0.24 cm^3). The mixture was refluxed for 3 h in a flask equipped with a Dean–Stark trap filled with $MgSO_4$, then the solvent was evaporated off under reduced pressure, the residue was mixed with benzene (5 cm^3) and the insoluble material was filtered off. The remaining solution was evaporated under reduced pressure and the oily residue was purified by column chromatography on SiO_2. Initial elution with benzene gave starting (*R*)-FHPC (0.0015 g, 2% recovery), then a mixture of benzene and EtOH (15:1) was used to eluate a mixture (0.123 g, 97%) of two diastereoisomeric Schiff's bases of compound (*R*)-**7** which had δ_H(CDCl$_3$) 13.77 (0.5 H, s, OH), 13.73 (0.5 H, s, OH), 8.31 (0.5 H, s, N=CH) and 8.29 (0.5 H, s, N=CH), 6.88 (1 H, m, ArH of paracycl.), 6.63–6.17 (5 H, m, ArH of paracycl.), 4.42–3.99 [3 H, m, C*H*(CO$_2$Et)(Me)(N=CR) and OC*H*$_2$Me], 3.52–2.48 (8 H, m, bridge), 1.67 [3 × 0.5 H, d, CH(CO$_2$*Me*)(N=CHR)], 1.58 [3 × 0.5 H, d, CH(CO$_2$Et)(*Me*)(N=CR)], 1.35 (3 × 0.5 H, t, OCH$_2$*Me*) and 1.27 (3 × 0.5 H, t, OCH$_2$*Me*). Compound (*S*)-**7** has the same set of ^{1}H NMR parameters.

Compound (*R*)-**8** was isolated as a mixture of two diastereoisomers and had δ_H(CDCl$_3$) 14.4 (0.5 H, s, OH), 13.6 (0.5 H, s, OH), 8.08 (0.5 H, s, N=CH), 7.97 (0.5 H, s, N=CH), 7.35–7.20 (5 H, m, Ph), 6.90–6.10 (5 H, m, ArH of paracycl.), 6.60 (0.5 H, d, ArH or paracycl.), 5.05 (0.5 H, d, ArH of paracycl.), 4.38–4.10 (3 H, m, OC*H*$_2$Me and C*H*$_2$Ph), 3.52–2.28 [9 H, m, bridge and C*H*(CO$_2$Et)(CH$_2$Ph)(N=CHR)], 1.39 (3 × 0.5 H, t, OCH$_2$*Me*) and 1.25 (3 × 0.5 H, t, OCH$_2$*Me*). The mixture of diastereoisomers (*S*)-**8** has the same ^{1}H NMR parameters.

Compound (*R*)-**9** as a mixture of two diastereoisomers had δ_H(CDCl$_3$) 8.37 (0.5 H, s, N=CH), 8.34 (0.5 H, s, N=CH), 6.84–6.34 (6 H, m, ArH of paracycl.), 4.41–4.00 [3 H, m, C*H*(CO$_2$Et)-(Me)(N=CHR) and OC*H*$_2$Me], 3.66 (3 H, s, OMe), 3.41–2.36 (8 H, m, bridge), 1.66 [3 × 0.5 H, d, CH(CO$_2$Et)(*Me*)(N=CHR)], 1.52 [3 × 0.5 H, d, CH(CO$_2$Et)(*Me*)(N=CHR)], 1.36 (3 × 0.5 H, t, OCH$_2$*Me*) and 1.25 (3 × 0.5 H, t, OCH$_2$*Me*); λ_{max}(benzene)/nm 289 and 347.

Compound (*R*)-**10** as a mixture of two diastereoisomers had δ_H(CDCl$_3$) 8.23 (0.5 H, s, N=CH), 7.9 (0.5 H, s, N=CH), 7.40–7.05 (5 H, m, Ph), 6.64–5.80 (6 H, m, ArH of paracycl.), 4.32 (2 H, q, OC*H*$_2$Me), 3.58 (3 × 0.5 H, s, OMe), 3.10 (3 × 0.5 H, s, OMe), 3.45–2.48 [11 H, m, bridge, C*H*$_2$Ph and C*H*(CO$_2$Et)-(CH$_2$Ph)(N=CHR)] and 1.33 (3 H, t, OCH$_2$Me); λ_{max}(benzene)/nm 289 and 345.

Compound (*R*)-**11** as a mixture of two diastereoisomers had δ_H(CDCl$_3$) 8.30 (1 H, s, N=CH), 6.80–6.10 (6 H, m, ArH of paracycl.), 4.30–3.95 [3 H, m, OC*H*$_2$Me and C*H*(CO$_2$Et)-(Me)(N=CHR)], 3.86 (1 H, sept, *J* 6.15, OC*H*Me$_2$), 3.10–2.38 (8 H, bridge) and 1.60–0.90 [12 H, m, OCH$_2$*Me*, OCH*Me*$_2$ and CH(CO$_2$Et)(*Me*)(N=CHR)].

Alkylation of the Schiff's bases 7–11

General procedure is illustrated by the synthesis of α-Me-Phe *via* alkylation of compound (*R*)-**7**. To a solution of diisopropylamide (0.019 g, 0.027 cm^3, 0.38 mmol) in absolute THF (0.8 cm^3) at −78 °C was added a 2.9 mol dm^{-3} BuLi solution in hexane (0.13 cm^3, 0.38 mmol) and the mixture was stirred for 0.5 h at that temp. Then solutions of HMPT (0.5 cm^3) in THF (1 cm^3) and compound (*R*)-**7** (0.067 g, 0.19 mmol) in THF (1.5 cm^3) were successively added. After stirring of this mixture for another 0.5 h a solution of benzyl bromide (0.070 g, 0.05 cm^3, 0.4 mmol) in THF (0.2 cm^3) was added and the mixture was allowed to warm slowly to ambient temp. (within several hours) and was left overnight. Finally the reaction was quenched with saturated aq. NH_4Cl (10 cm^3) and extracted with benzene (3 × 10 cm^3). The combined benzene layers were washed with water (2 × 10 cm^3), the solvent was evaporated off under reduced pressure, and the residue was treated as described below.

Recovery of FHPC and α-Me-Phe after alkylation of Schiff's bases 7–11

To a solution of alkylated Schiff's base (*R*)-**7** in MeOH was added an aq. solution of (*S*)-Leu (0.012 g, 0.095 mmol in 2.1 cm^3) (as an internal standard for GLC) and aq. 2 mol dm^{-3} HCl (8–10 mol equiv.) and the mixture was refluxed for 2 h before being extracted with benzene (2 × 10 cm^3), and the combined organic extracts containing (*R*)-FHPC was purified on SiO_2 (with benzene as eluent). The water layer was evaporated to dryness. To the residue was added 6 mol dm^{-3} HCl (5–7 mol equiv.) and the mixture was heated for 6–8 h. The resulting amino acids were isolated from the aq. solution by ion-exchange chromatography on Dowex-50 (H^+).

Acknowledgements

This work was supported by Russian Fund of Fundamental Sciences (grant 93-03-5246), International Science Foundation (grant MKROOO), East European Funds of the Swiss National Science Foundation Grant (7 GUP J 041269) and INTAS (grant 94-1393).

References

1 H. Blaser, *Chem. Rev.*, 1992, **92**, 935.
2 R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994.
3 T. Hayashi, M. Konishi, M. Fukushima, M. Kagotani, M. Tajika and M. Kumada, *J. Am. Chem. Soc.*, 1982, **104**, 180; T. Hayashi, *Pure Appl. Chem.*, 1988, **60**, 712; A. Togni and S. Pastor, *J. Org. Chem.*, 1990, **55**, 1649; W. Cullen, F. Einstein, C. Huang, A. Willis and E. Yeh, *J. Am. Chem. Soc.*, 1980, **102**, 988.

4 (*a*) S. Davies, R. Newton and J. Williams, *Tetrahedron Lett.*, 1989, **30**, 2967; J. Blagg and S. Davies, *J. Chem. Soc., Chem. Commun.*, 1985, 653; (*b*) M. Uemura, R. Miyaka, K. Nakayama, M. Shiro and Y. Hayashi, *J. Org. Chem.*, 1993, **58**, 1238.
5 M. Ando, I. Watanabe and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 88.
6 S. Rosenfield and P. Keehn, *The Cyclophanes*, Academic Press, New York, 1993, vols. 1, 2.
7 T. Aratani, *Pure Appl. Chem.*, 1985, **57**, 1839.
8 S. Colonna, A. Manfredi, M. Spadoni, L. Casella and M. Gullotti, *J. Chem. Soc., Perkin Trans. 1*, 1987, 71.
9 E. Jacobsen, W. Zhang, A. Muci, J. Ecker and L. Deng, *J. Am. Chem. Soc.*, 1991, **113**, 7063; B. D. Brandes and E. N. Jacobsen, *J. Org. Chem.*, 1994, **59**, 4378.
10 M. Hayashi, Y. Miyamoto, T. Inoue and N. Oguni, *J. Org. Chem.*, 1993, **58**, 1515.
11 K. Harada, S. Suzuki, H. Narita and H. Watanabe, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2203.
12 (*a*) G. Stork, A. Y. W. Leong and A. M. Touzin, *J. Org. Chem.*, 1976, **41**, 3491; (*b*) A. van der Werf and R. M. Kellogg, *Tetrahedron Lett.*, 1988, **29**, 4981; G. Wulff, H. Bohnke and H. Klinken, *Liebigs Ann. Chem.*, 1988, 501; Sh. Kanemasa, O. Uchuda, E. Wada and H. Yamamoto, *Chem. Lett.*, 1990, 105.
13 V. Rozenberg, V. Kharitonov, D. Antonov, E. Sergeeva, A. Aleshkin, N. Ikonnikov, S. Orlova and Yu. Belokon, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 91.
14 (*a*) H. Reich and D. Cram, *J. Am. Chem. Soc.*, 1969, **91**, 3534; (*b*) W. Hoffman and K. Ditrich, *Synthesis*, 1983, 107; K. Krohn, H. Rieger, H. Hopf, D. Barrett, P. G. Jones and D. Doring, *Chem. Ber.*, 1990, **123**, 1729.
15 G. Casiraghi, G. Casnati, G. Puglia, G. Sartori and G. Terenghi, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1862.
16 H. Hopf and D. G. Barrett, *Liebigs Ann. Chem.*, 1995, 449.
17 M. Saporovskaya, L. Volkova and V. Pavlov, *Zh. Anal. Khim.*, 1989, **44**, 525.
18 Yu. Belokon, A. Bulychev, S. Vitt, Yu. Struchkov, A. Batsanov, T. Timofeeva, V. Tsyryapkin, M. Ryzov, L. Lysova, V. Bakhmutov and V. Belikov, *J. Am. Chem. Soc.*, 1985, **107**, 4252; V. Soloshonok, V. Kukhar, S. Galushko, N. Svistunova, D. Avilov, N. Kuzmina, N. Raevski, Yu. Struchkov, A. Pysarevski and Yu. Belokon, *J. Chem. Soc., Perkin Trans. 1*, 1993, 3143.
19 R. A. Boissonnas, St. Guttmann, P.-A. Jaquenoud and J.-P. Waller, *Helv. Chim. Acta*, 1955, **38**, 1491.
20 A. P. Croft and R. A. Bartsch, *Tetrahedron*, 1983, **39**, 1417.

Paper 5/00155B
Received 10*th January* 1995
Accepted 20*th March* 1995