Efficient Synthesis of Enantiomerically and Diastereomerically Pure [2.2]Paracyclophane-Based N,O-Ligands

Valeria I. Rozenberg,*[a] Tat'yana I. Danilova,[a] Elena V. Sergeeva,[a] Ivan. A. Shouklov,[a] Zoya A. Starikova,[a] Henning Hopf,*[b] and Klaus Kühlein*[c]

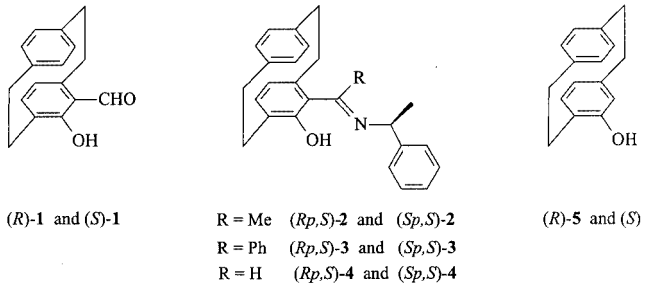
Keywords: Asymmetric synthesis / Chirality / Cyclophanes / Metallation / N,O ligands

Efficient syntheses of different enantiomerically and diastereomerically pure N,O-ligands with alkylamino and phenol groups attached to the [2.2]paracyclophane framework are described. Several transformations of the *ortho*-lithiated [2.2]paracyclophan-4-yl diethylcarbamate **7** and the reduction of the [2.2]paracyclophane imino derivatives **3**, **4**, **17**, **18**, and **21** allow the preparation of a wide range of compounds in which the chiral environment can be controlled by the planar chiral fragment and modified by the presence of one or two additional chiral centers in the alkylamino group.

Introduction

The catalytic asymmetric synthesis of enantiopure compounds is one of the most important tasks in academic and industrial organic chemistry. Among the currently employed ligand systems applicable for various types of asymmetric transformations, nitrogen-containing compounds stand out, as they can easily be prepared and inexpensively recycled. Over the last two decades, many promising results have been obtained by application of nitrogen-containing auxiliaries in asymmetric synthesis.[1] In particular, ligands bearing both an amine and an alcohol function (N,O-ligands) show good results in asymmetric catalysis.[2]

During the course of our ongoing project directed at the application of planar chiral [2.2]paracyclophanes in stereoselective synthesis we concentrated our efforts on N,O-ligands derived from 5-formyl-4-hydroxy[2.2]paracyclophane (FHPC, **1**, a chiral analogue of salicylaldehyde, Scheme 1). Thus, stoichiometric asymmetric synthesis of α-amino acids with the aid of Schiff bases of FHPC[3,4] and Ti^{IV}-catalyzed trimethylsilylcyanation of benzaldehyde with salene-type ligands derived from enantiomers of FHPC and different diamines[5] were elaborated. On the other hand, 4-(salicylidenamino)[2.2]paracyclophanes,[6] Schiff bases of FHPC with amino alcohols,[7] [2.2]paracyclophane-derived *N*-acyloxazol-2(3*H*)-one,[8] and 4-(hydroxydiphenylmethyl)[2.2]paracyclophane bearing a chiral oxazolinyl group in a *pseudo-gem* position[9] have been used by others as sources of asymmetric induction in different stereoselective reactions. Other examples of N,O-bifunctional [2.2]paracyclophanes involve chiral dendrimers,[10] and amidophenols with different types of substitution pattern.[11]



(*R*)-**1** and (*S*)-**1** | R = Me (*Rp*,*S*)-**2** and (*Sp*,*S*)-**2**; R = Ph (*Rp*,*S*)-**3** and (*Sp*,*S*)-**3**; R = H (*Rp*,*S*)-**4** and (*Sp*,*S*)-**4** | (*R*)-**5** and (*S*)

Scheme 1

We have recently described two general approaches to *ortho*-acylhydroxy[2.2]paracyclophanes,[12] and these compounds (close relatives of FHPC) obviously suggest themselves for use as starting materials for the synthesis of novel N,O-ligands. We thus identified specific conditions under which some of them [5-acetyl-4-hydroxy- (AHPC) and 5-benzoyl-4-hydroxy[2.2]paracyclophane (BHPC)] would form Schiff bases with (*S*)-α-phenylethylamine, and we have been able to separate the corresponding diastereomers (*Rp*,*S*)-**2** and (*Sp*,*S*)-**2** as well as (*Rp*,*S*)-**3** and (*Sp*,*S*)-**3** (Scheme 1).

[a] A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Science,
Vavilova 28, 119913 Moscow, Russia
Fax: (internat.) + 7-095/135-5085
E-mail: lera@ineos.ac.ru
[b] Institute of Organic Chemistry, Technical University of Braunschweig,
Hagenring 30, 38106, Germany
Fax: (internat.) + 49-531/391-5388
E-mail: H.Hopf@tu-bs.de
[c] Fasanenstrasse 41, 65779 Kelkheim, Germany
Fax: (internat.) + 49-6195/997-717
E-mail: Klaus.Kuehlein@t-online.de

  1434−193X/03/0203−0432 $ 20.00+.50/0 *Eur. J. Org. Chem.* **2003**, 432−440

Several months ago, Dahmen and Bräse demonstrated the efficient application of our diastereomeric Schiff bases **2** and **3** in the stereoselective addition of diethyl-[13] and alkenylzinc[14] to aldehydes and diethylzinc to imines.[15] They also reported three approaches towards the synthesis of [2.2]paracyclophane-based aminophenols, consisting of reductive amination of FHPC, reduction of the diastereomeric Schiff bases **4** of FHPC with (*S*)-α-phenylethylamine and some ketimines **2** and **3**, and 1,2-addition of methyllithium to **4**.[16]

Needless to say, since our report of the synthesis of *ortho*-acylhydroxy[2.2]paracyclophanes and their Schiff bases we have worked on the preparation of novel N,O-ligands starting from these compounds. In this paper we present our results on the synthesis of different primary and secondary aminophenols based on the [2.2]paracyclophane framework. The chiral environment in these ligands can either be provided solely by the planar chiral [2.2]paracyclophane fragment (Figure 1, type 1) or can also be modified by the introduction of one (Figure 1, type 2) or two additional chiral centers (Figure 1, type 3) in the side chain.

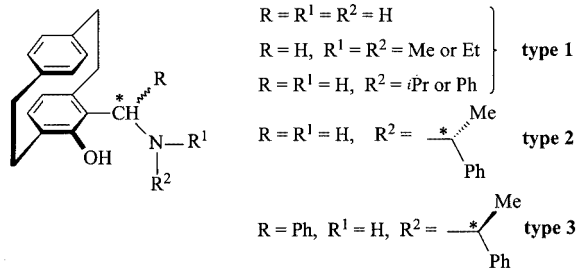


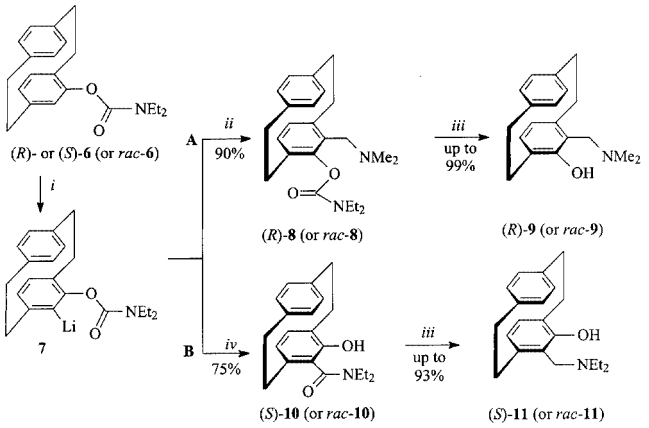
Figure 1. Chiral N,O-ligands derived from [2.2]paracyclophane

Results and Discussion

1. Transformations of *ortho*-Lithiated [2.2]Paracyclophan-4-yl Diethylcarbamate

The first route for the preparation of [2.2]paracyclophane-based N,O-ligands exploits the regularities of the *ortho*-regioselective lithiation of [2.2]paracyclophan-4-yl diethylcarbamate (**6**) investigated by us earlier;[17,18] we have also previously described the synthesis of the racemic amino phenols.[19] We now present the synthesis of both the racemic and the enantiomerically pure 5-[(dialkylamino)-methyl][2.2]paracyclophan-4-ols, starting from *rac*-, (*R*)-, and (*S*)-4-hydroxy[2.2]paracyclophanes (**5**). The racemic phenol **5** (Scheme 1) was resolved into its enantiomers by way of its diastereomeric esters with (1*S*)-camphanic acid, as recently reported by us.[20] Racemic, (*R*)-, and (*S*)-**6** were obtained by our standard carbamoylation procedure.[17]

ortho-Regioselective lithiation of *rac*-**6** or (*R*)-**6** at −78 °C, followed by treatment of the corresponding lithiated intermediate **7** with $CH_2{=}N^+Me_2I^-$ as the electrophile, produced *rac*- or (*R*)-**8** in high yield (Scheme 2, route A). After reductive deprotection of the hydroxy group of **8** with $LiAlH_4$, the *ortho*-substituted phenols *rac*-**9** or (*R*)-**9** were obtained in excellent yields.



Scheme 2. Preparation of the chiral N,O-ligands **9** and **11**: *i*: *s*BuLi, TMEDA, THF, −78 °C; *ii*: $CH_2{=}N^+Me_2I^-$; *iii*: $LiAlH_4$, Et_2O; *iv*: −78 °C → 20 °C

The other known pathway for the transformation of the *ortho*-lithiated intermediate **7** consists of its anionic Fries rearrangement to the corresponding diethylamido derivative **10**,[17] an obvious precursor to the *ortho*-substituted phenol **11** (Scheme 2, route B). In practice, we carried out this transformation by the lithiation of *rac*- and (*S*)-**6** to obtain the corresponding *rac*- and (*S*)-**10**. Reduction of the C=O double bond of **10** with $LiAlH_4$ produced *rac*- and (*S*)-**11** in high chemical yields. Single crystals of racemic **11** suitable for an X-ray diffraction study were obtained; the result is reproduced in Figure 2.

The first two members of the class of 5-[(dialkylamino)-methyl][2.2]paracyclophan-4-ols have thus been obtained in optically pure form from the readily available, easily resolvable precursor 4-hydroxy[2.2]paracyclophane (**5**), in overall yields of up to 70−89%. It should be noted that different *N*,*N*′-disubstituted amidophenols could in principle be obtained from optically pure 5-carboxy-4-hydroxy[2.2]paracyclophane, recently obtained in the laboratories of one of us,[21] and so the reduction of the amide carbonyl group could be regarded as a general route to N,O-ligands with hydroxy- and *N*,*N*′-disubstituted aminomethyl groups.

We next investigated the scope of the Fries rearrangement for the synthesis of the aminophenols with a secondary amino group. According to literature data, *N*-substituted carbamoyl derivatives of phenols can also be rearranged under the influence of basic reagents.[22] For this purpose we carried out the acylation of **5** with phenyl isocyanate and ethyl isocyanate in the presence of bases (B^-) to obtain the corresponding *O*-acyl derivatives **12** and **13** (Scheme 3).

Attempted rearrangement of **12** was carried out under the conditions developed for the rearrangement of **6** (*s*BuLi, TMEDA, −78 °C to room temperature, 12 h). However, not even traces of the desired product **14** could be detected after workup, only deprotected phenol **5** being recoverable in quantitative yield. The same negative result was obtained

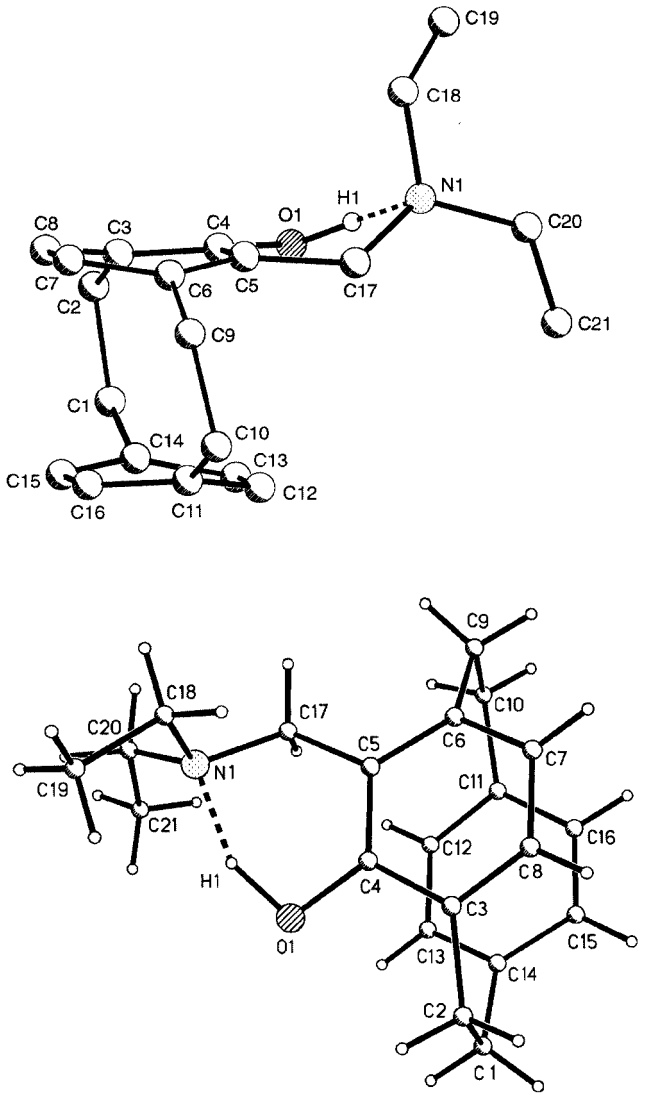
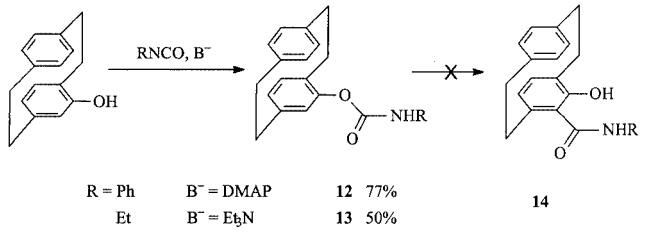


Figure 2. Structure of racemic **11** in the solid state (two projections)



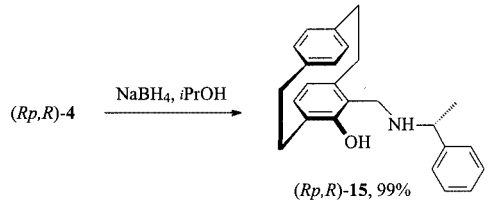
Scheme 3. Attempted preparation of paracyclophane N,O-ligands by Fries rearrangement

with derivative **13**. Attempts to carry out the classical Fries rearrangement[12] of **12** or **13** in the presence of $TiCl_4$ or $AlCl_3$ also failed.

2. Reduction of Schiff Bases

An alternative route to planar chiral aminophenols with secondary amino groups consists in the reduction of Schiff bases of FHPC or *ortho*-acylhydroxy[2.2]paracyclophanes. As mentioned above, Dahmen and Bräse recently exploited this approach in the reduction of a diastereomer pair (*Sp*,*S*)-**4** and (*Sp*,*R*)-**4**, as well as single diastereomers (*Rp*,*S*)-**2** and (*Sp*,*S*)-**3**.[16] Our more detailed results on this matter are presented here.

Racemic FHPC was synthesized by our novel procedure, which includes Friedel−Crafts oxaloylation of the phenol **5**, followed by reduction of the obtained α-oxo ester and oxidation of the intermediate triol.[20] Diastereomeric imine (*Rp*,*R*)-**4** was obtained in accordance with our already described procedure.[4] Treatment of (*Rp*,*R*)-**4** with $NaBH_4$ in refluxing 2-propanol for 1 h (Scheme 4) gave the amino phenol (*Rp*,*R*)-**15** in quantitative yield after preparative chromatography.



Scheme 4. Sodium borohydride reduction of the Schiff base (*Rp*,*R*)-**4**

After crystallization from heptane, this compound was obtained as fine, colorless crystals with $[\alpha]_D^{22} = +168.4$. Single crystals of (*Rp*,*R*)-**15** of suitable quality for an X-ray structural analysis could be obtained, and the results are shown in Figure 3 (top). The optimized reduction and purification of (*Rp*,*R*)-**15** is clearly more efficient than the reported procedure,[16] in which 12-h room-temperature reduction of (*Sp*,*S*)-**4** with the same reagent in methanol provided (*Sp*,*S*)-**15** in 84% chemical yield, and as a colorless oil with $[\alpha]_D^{22} = -131.0$.

Our previously reported technique[12] for the separation of the diastereomeric ketimines **3** of BHPC with α-phenylethylamine was improved in this study; we were fortunately able to find a suitable eluent to allow complete separation of the diastereomers **3** on silica gel. Thus, by starting from a 1:1 mixture of diastereomers, individual (*Rp*,*R*)-**3** and (*Sp*,*R*)-**3** were isolated in chemical yields of 50 and 48%, respectively, and their individual diastereomeric purities were determined as > 99% by ^1H NMR analysis.

We carried out reductions of (*Rp*,*R*)-**3** and (*Sp*,*R*)-**3** with $LiAlH_4$ in Et_2O and obtained the corresponding diastereomeric amino phenols **16** in quantitative yield and with complete stereoselectivity for each diastereomer (Scheme 5). The relative configuration of the product **16** obtained from (*Sp*,*R*)-**3** was unambiguously determined by X-ray crystallography[23] as (*Sp*,*S*,*R*) (Figure 3, bottom).

The above stereochemical result allows us to propose that diastereomeric ketimine **3** enters the reaction in a conformation in which the imino group is situated *syn* to the hydroxy group. Therefore, attack of $LiAlH_4$ from the side of the C=N double bond not shielded by the protons of the unsubstituted [2.2]paracyclophane ring should give rise to the formation of a new asymmetric center, with (*S*) configuration. For (*Rp*,*R*)-**3**, hydrogen incorporation from the less shielded side of the *syn*-oriented (with respect to the

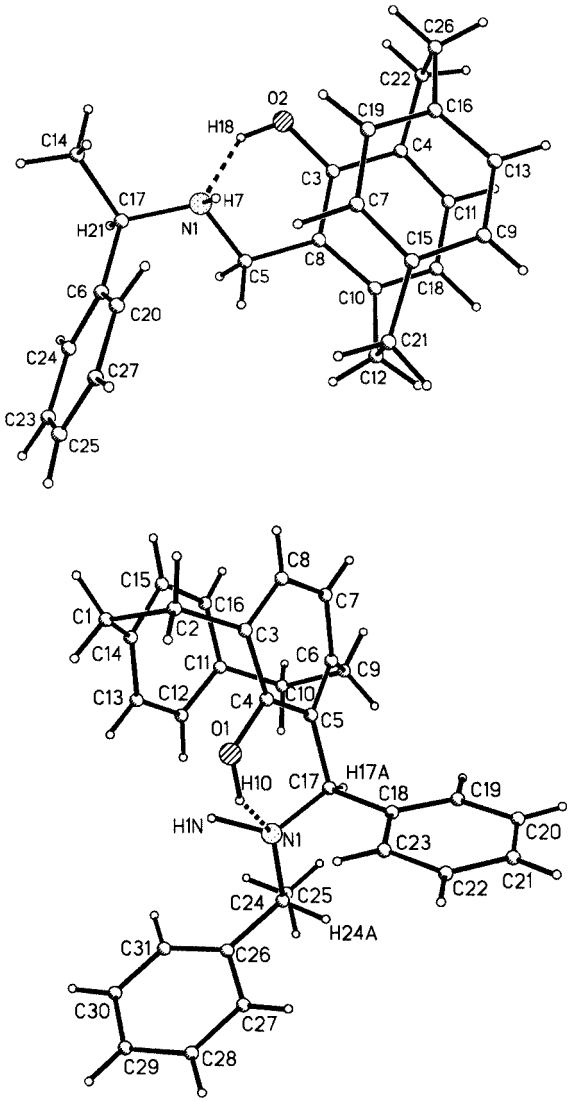
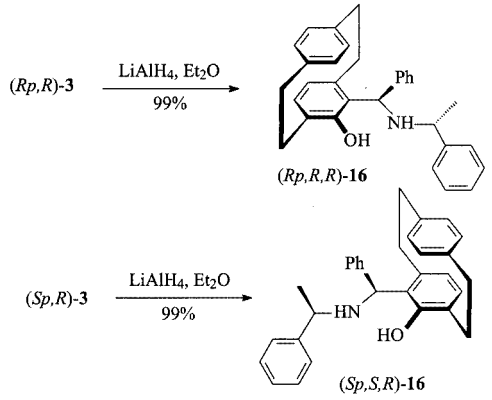


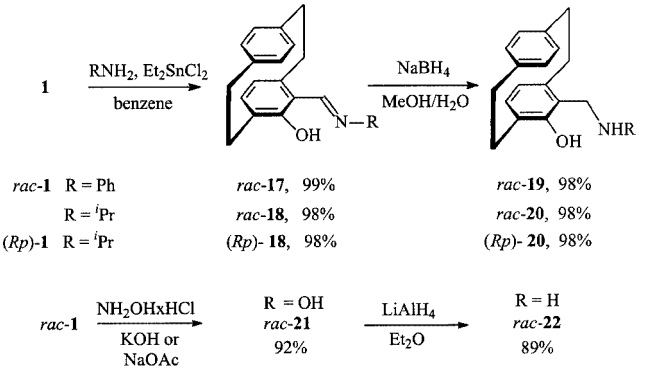
Figure 3. The crystal structures of (*Rp*,*R*)-**15** (top) and of (*Sp*,*S*,*R*)-**16** (bottom)



Scheme 5. Synthesis of the N,O-ligands **16** with three elements of chirality

hydroxy group) C=N double bond should similarly produce (*Rp*,*R*,*R*)-**16**. It should be noted that the reduction of (*Sp*,*S*)-**3** with $NaBH_4$ yielded (*Sp*,*S*,*S*)-**16** in only 78% *de*,[16] in contrast to the completely stereoselective reduction of both diastereomers of **3** with $LiAlH_4$.

We have also synthesized planar chiral aminophenols without extra asymmetric centers by the reduction approach. (*Rp*)-FHPC was obtained according to the described resolution procedure.[4] The imines *rac*-**17** and *rac*- and (*Rp*)-**18** were prepared in quantitative yields by heating of *rac*- and (*Rp*)-FHPC solutions at reflux with aniline or isopropylamine in the presence of Et_2SnCl_2 (Scheme 6).



Scheme 6. Preparation of N,O-ligands derived from FHPC (**1**)

The reductions of *rac*-**17** and of (*Rp*)- and *rac*-**18** were carried out with $NaBH_4$ in methanol to yield the corresponding aminophenols *rac*-**19**, *rac*-**20**, and (*Rp*)-**20** in quantitative yields. The described approach was also found to be applicable to the synthesis of the primary aminophenol **22**. By starting from racemic FHPC and hydroxylamine in the presence of bases (KOH or NaOAc) we synthesized oxime **21**, which was subsequently reduced in high yield to aminophenol **22** by use of $LiAlH_4$ in diethyl ether.

Conclusion

An efficient synthesis of chiral primary, secondary, and tertiary aminophenols, the chirality of which is determined by the planar chirality of the [2.2]paracyclophane framework, has been developed. One or two additional chiral centers can be incorporated into the new ligand. These readily accessible ligands, together with their precursors (amido phenols and Schiff bases), are promising chiral auxiliaries for a wide range of stereoselective reactions.

Experimental Section

General: Benzene and toluene were distilled from sodium; Et_2O and THF were distilled from sodium benzophenone ketyl under argon before use. $LiAlH_4$ and *s*BuLi were purchased from Merck. NaH (60% dispersion in mineral oil) was purchased from Aldrich. NMR: Bruker AMX 400 (400.13 and 100.61 MHz, for ^1H and ^{13}C, respectively). For ^1H NMR spectroscopy the residual proton signals of the deuterated solvents were used as internal standards; PC = [2.2]paracyclophanyl. MS: KRATOS MS890A (70 eV). IR: SPECORD M 82. Optical rotations: EPO-1 in thermostatted cell at 22

°C. TLC: Silica gel precoated plates "Silufol UV-254" (Chemapol) and "SORBFIL" PTLC-A-UV. Column chromatography: Kieselgel 60 (Merck). 5-Formyl-4-hydroxy[2.2]paracyclophane (**1**) and 4-hydroxy[2.2]paracyclophane (**5**) were prepared and resolved into enantiomers by literature procedures.[4,20] Enantiomeric [2.2]paracyclophan-4-yl diethylcarbamates (*Rp*)- and (*Sp*)-**6** were synthesized from (*Rp*)- and (*Sp*)-4-hydroxy[2.2]paracyclophanes (**5**), respectively, by a literature approach.[17] Schiff bases (*Rp*,*R*)-**3**, (*Sp*,*R*)-**3**, and (*Rp*,*R*)-**4** were prepared according to refs.[4,12]

(*Rp*)-5-[(Dimethylamino)methyl][2.2]paracyclophan-4-yl Diethylcarbamate [(*Rp*)-8]: *s*BuLi (1.3 N in cyclohexane, 0.82 mL, 1.07 mmol) was added at −76 °C under argon to a solution of (*R*)-**6** (288 mg, 0.89 mmol) and TMEDA (0.16 mL, 124 mg, 1.07 mmol) in anhydrous THF (23 mL), and the yellow solution was stirred for 1 h. $CH_2N^+Me_2I^-$ (200 mg, 1.07 mmol) was then added and the resulting mixture was left overnight at room temp. Aqueous hydrolysis afforded the crude product mixture, which was purified by silica gel chromatography with benzene/ethanol (10:1) and then ethanol as eluents to yield 305 mg (90%) of (*R*)-**8**. An analytically pure sample of (*R*)-**8** (106 mg, 31%) was obtained as colorless plates by crystallization from heptane. M.p. 151−152 °C. $[\alpha]_D^{22}$ = +25.4 (*c* = 0.4, C_6H_6). ^{1}H NMR ([D$_6$]acetone): δ = 1.15 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.43 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 2.02 (s, 6 H, NCH_3), 2.65−3.10 (m, 7 H, $CHHCH_2$), 3.13 [s, 2 H, $CH_2N(CH_2CH_3)_2$], 3.22−3.46 (m, 2 H, NCH_2CH_3), 3.49−3.58 (m, 1 H, $CHHCH_2$), 3.59−3.82 (m, 2 H, NCH_2CH_3), 6.46 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.49−6.52 (m, 2 H, PC arom. H), 6.56 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.60 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.71 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H) ppm. MS (EI): *m*/*z* (%) = 380 (20) [M$^+$], 337 (25), 280 (17), 264 (22), 236 (9), 176 (49), 104 (73). $C_{24}H_{32}N_2O_2$ (380.26): calcd. C 75.75, H 8.42, N 7.36; found C 75.81, H 8.64, N 7.44.

5-[(Dimethylamino)methyl][2.2]paracyclophan-4-yl Diethylcarbamate (*rac*-8): The synthesis was carried out as described for (*R*)-**8**, starting from *rac*-**6** (500 mg, 1.55 mmol), TMEDA (0.28 mL, 1.85 mmol), *s*BuLi in cyclohexane (1.3 N, 1.42 mL, 1.85 mmol), and $CH_2N^+Me_2I^-$ (340 mg, 1.85 mmol), to yield 530 mg (90%) of *rac*-**8** as a colorless oil. Its ^{1}H NMR spectrum agrees with that of (*R*)-**8**.

(*Rp*)-5-[(Dimethylamino)methyl][2.2]paracyclophan-4-ol [(*Rp*)-9]: $LiAlH_4$ (62 mg, 1.62 mmol) was added in portions to a solution of (*R*)-**8** (112 mg, 0.29 mmol) in anhydrous Et_2O (15 mL), and the reaction mixture was heated at reflux for 7 h. After the mixture had been allowed to cool to room temp., an excess of aqueous 0.5 N KOH solution was added and the mixture was thoroughly extracted with Et_2O, washed with H_2O, and dried with Na_2SO_4. Removal of the solvent in vacuo yielded 82 mg (99%) of (*R*)-**9**. An analytically pure sample (33 mg, 40%) was obtained by recrystallization from hexane, as pale yellow needles. M.p. 116.5−117 °C. $[\alpha]_D^{22}$ = +238.2 (*c* = 0.4, C_6H_6). ^{1}H NMR ($CDCl_3$): δ = 2.23 (br. s, 6 H, NCH_3), 2.53−2.61 (m, 1 H, $CHHCH_2$), 2.65−2.76 (m, 2 H, $CHHCH_2$), 2.96−3.12 (m, 4 H, $CHHCH_2$), 3.20 [d, *J* = 13.3 Hz, 1 H, $CH_2N(CH_3)_2$], 3.40 [d, *J* = 13.3 Hz, 1 H, $CH_2N(CH_3)_2$], 3.30−3.40 (m, 1 H, $CHHCH_2$), 6.10 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.42 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.51 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.55 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.67 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.85 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H) ppm. MS (EI): *m*/*z* (%) = 281 (24) [M$^+$], 237 (24), 236 (66), 176 (34), 104 (100). $C_{19}H_{23}ON$ (281.40): calcd. C 81.10, H 8.24, N 4.98; found C 80.97, H 8.18, N 5.04.

5-[(Dimethylamino)methyl][2.2]paracyclophan-4-ol (*rac*-9): The synthesis was carried out as described for (*R*)-**9**, from *rac*-**8** (230 mg, 0.61 mmol) and $LiAlH_4$ (125 mg, 3.30 mmol), to yield 130 mg (76%) of *rac*-**9** as a colorless oil. Its ^{1}H NMR spectrum agrees with that of (*R*)-**9**.

(*Sp*)-*N*,*N*-Diethyl-4-hydroxy[2.2]paracyclophane-5-carboxamide [(*Sp*)-10]: This compound was prepared according to the procedure described for *rac*-**10**,[16] from (*S*)-**6** (320 mg, 0.99 mmol), TMEDA (0.20 mL, 1.20 mmol), and *s*BuLi (1.3 N in cyclohexane, 1.03 mL, 0.99 mmol) in a chemical yield of 240 mg (75%). Colorless oil. $[\alpha]_D^{22}$ = −2.9 (*c* = 0.5, C_6H_6), $[\alpha]_D^{22}$ = −4.5 (*c* = 0.3, $CHCl_3$) {ref.[11] $[\alpha]_D^{22}$ = −17.9 (no solvent mentioned)}. $C_{21}H_{25}NO_2$ (323.44): calcd. C 77.99, H 7.79, N 4.33; found C 78.03, H 7.61, N 4.13.

(*Sp*)-5-[(Diethylamino)methyl][2.2]paracyclophan-4-ol [(*Sp*)-11]: $LiAlH_4$ (120 mg, 3.10 mmol) was added in portions to a solution of (*S*)-**10** (185 mg, 0.57 mmol) in anhydrous Et_2O (12 mL). The reaction mixture was heated at reflux for 4 h, allowed to cool to room temp., and carefully hydrolyzed with excess 0.5 N KOH solution. The reaction mixture was extracted with Et_2O, and the combined organic layers were washed with H_2O and dried with Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography with CH_2Cl_2/EtOH (10:1) to yield 160 mg (90%) of (*S*)-**11**. An analytically pure sample of (*S*)-**11** (64 mg, 36%) was obtained by crystallization from heptane. M.p. 90.5−91.5 °C. $[\alpha]_D^{22}$ = −145.9 (*c* = 0.4, C_6H_6). ^{1}H NMR ($CDCl_3$): δ = 1.10 (br. s, 6 H, CH_2CH_3), 2.28−2.42 (m, 2 H, NCH_2Me), 2.51−2.62 (m, 1 H, $CHHCH_2$), 2.65−2.79 (m, 2 H, $CHHCH_2$, 2 H, NCH_2Me), 2.95−3.12 (m, 4 H, $CHHCH_2$), 3.25−3.35 (m, 1 H, $CHHCH_2$), 3.35−3.48 (m, 2 H, CH_2NEt_2), 6.09 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.42 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.52 (br. d, ^3J = 7.8 Hz, 1 H, 15-H or 16-H), 6.55 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, 15-H or 16-H), 6.70 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, 12-H or 13-H), 6.87 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, 12-H or 13-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.36 (NCH_2CH_3), 29.76, 32.40, 33.98, 33.99 (C-1, C-2, C-9, C-10), 46.68 (NCH_2CH_3), 53.97 (CH_2NEt_2), 121.53, 123.97, 125.38, 126.02, 127.03 (C-3, C-5, C-6, C-11, C-14), 132.48, 132.64, 132.98, 137.40, 139.51, 140.34 (C-7, C-8, C-12, C-13, C-15, C-16), 157.00 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3442 cm^{-1}, 3096, 2967, 1600, 1463, 1455. MS (EI): *m*/*z* (%) = 309 (59) [M$^+$], 205 (100) [M$^+$ − 104], 104 (100). $C_{21}H_{27}NO$ (309.23): calcd. C 81.51, H 8.79, N 4.53; found C 81.74, H 8.76, N 4.51.

5-[(Diethylamino)methyl][2.2]paracyclophan-4-ol (*rac*-11): This compound was synthesized as described for (*R*)-**11**, from *rac*-**10** (280 mg, 0.87 mmol) and $LiAlH_4$ (182 mg, 4.79 mmol) in a chemical yield of 250 mg (93%). An analytically pure sample was obtained by crystallization from heptane. M.p. 109.5−111 °C. $C_{21}H_{27}NO$ (309.45): calcd. C 81.51, H 8.79, N 4.53; found C 81.76, H 8.76, N 4.53. The ^{1}H NMR spectrum agrees with that of (*R*)-**11**.

[2.2]Paracyclophan-4-yl Phenylcarbamate (*rac*-12): Phenyl isocyanate (0.10 mL, 108 mg, 0.91 mmol) was added to a solution of *rac*-**5** (204 mg, 0.91 mmol) and 4-(dimethylamino)pyridine (DMAP, 110 mg, 0.91 mmol) in anhydrous benzene (10 mL), and the mixture was heated at reflux for 3 h. The resulting mixture was allowed to cool to room temp. and acidified with HCl (1 N, 20 mL), extracted with Et_2O, washed successively with aq. saturated $NaHCO_3$ and H_2O, and dried with Na_2SO_4. The solvent was evaporated in vacuo. The crude product was purified by preparative chromatography (silica gel, CH_2Cl_2) to yield 240 mg (77%) of *rac*-**12** as a colorless powder. M.p. 175−177 °C. ^{1}H NMR ($CDCl_3$): δ = 2.75−2.85 (m, 1 H, $CHHCH_2$), 3.00−3.20 (m, 6 H, $CHHCH_2$), 3.35−3.45 (m, 1 H, $CHHCH_2$), 6.14 (d, ^4J = 1.8 Hz, 1 H, 5-H), 6.48−6.63 (m, 4 H, PC arom. H), 7.17 (m, 1 H, Ph arom. *p*-H), 7.32 (d, ^3J = 7.8 Hz, 1 H, 13-H), 7.40 (m, 2 H, Ph arom. *m*-H),

7.55 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 2 H, Ph arom. *o*-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.48, 34.38, 34.85, 35.27 (C-1, C-2, C-9, C-10), 120.77, 123.88, 127.91, 129.15, 129.17 (2 C), 129.39, 130.29, 131.39, 132.30, 132.96, 133.42, 135.36, 137.46, 138.13, 139.22, 139.48, 141.66, 148.59 ppm. MS (EI): *m*/*z* (%) = 343 (10) [M^+], 224 (22), 120 (51).

[2.2]Paracyclophan-4-yl Ethylcarbamate (*rac*-13): Ethyl isocyanate (0.12 mL, 92 mg, 1.30 mmol) was added to a solution of *rac*-**5** (250 mg, 1.12 mmol) and Et_3N (0.20 mL, 140 mg, 1.40 mmol) in anhydrous CH_2Cl_2 (20 mL), and the mixture was heated at reflux for 6 h. The reaction mixture was worked up as described for *rac*-**12**. The crude product was purified by silica gel chromatography with CH_2Cl_2 to yield 170 mg (52%) of *rac*-**13** as a colorless powder. M.p. 154−158 °C. ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, 3 H, C*H*$_3$), 2.60−2.80 (m, 1 H, C*H*HCH$_2$), 2.90−3.40 (m, 7 H, C*H*HCH$_2$), 3.02 (m, 2 H, NHC*H*$_2$CH$_3$), 5.00 (br. s, 1 H, N*H*CH$_2$CH$_3$), 6.02 (d, ^4J = 1.8 Hz, 1 H, 5-H), 6.40−6.60 (m, 5 H, PC arom. H), 6.88 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.01, 30.60, 31.21, 34.42, 35.20, 35.40 (C-1, 2, 9, 10), 120.61, 129.43, 130.30, 131.40 (C-3, C-6, C-11, C-14), 132.28, 133.42, 135.41, 135.46, 139.51, 141.19, 148.60 (C-5, C-7, C-8, C-12, C-13, C-15, C-16), 155.47 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3011 cm^{-1}, 3022, 1609, 1224 (s). MS (EI): *m*/*z* (%) = 295 (5) [M^+], 224 (60), 120 (100), 104 (40).

(*Rp*,*R*)-5-{[(1-Phenylethyl)amino]methyl}[2.2]paracyclophan-4-ol [(*Rp*,*R*)-15]: A solution of (*Rp*,*R*)-**4** (277 mg, 0.78 mmol) and $NaBH_4$ (230 mg, 5.93 mmol) in 2-propanol (50 mL) was heated at reflux for 1 h. The mixture was allowed to cool to room temp., hydrolyzed with excess aqueous 0.5 N KOH solution, concentrated to 1/3 of its volume, extracted with Et_2O, washed with H_2O, and dried with Na_2SO_4, and the solvents were evaporated in vacuo to yield 277 mg (99%) of (*Rp*,*R*)-**15** as a colorless oil. An analytically pure sample (191 mg, 69%) was obtained as pale yellow crystals by crystallization from hexane/heptane (1:1). M.p. 127.5−128 °C. $[\alpha]_D^{22}$ = +174.8 (*c* = 0.36, C_6H_6), $[\alpha]_D^{22}$ = +168.36 (*c* = 0.35, $CHCl_3$) {ref.[16] for (*Sp*,*S*)-**15** $[\alpha]_D^{22}$ = −131.00 (*c* = 0.5, $CHCl_3$), described as a colorless oil}. ^{1}H NMR (C_6D_6): δ = 1.02 [d, *J* = 7.1 Hz, 3 H, NCH(Ph)C*H*$_3$], 2.28−2.39 (m, 1 H, C*H*HCH$_2$), 2.42−2.53 (m, 1 H, C*H*HCH$_2$), 2.55−2.72 (m, 2 H, C*H*HCH$_2$), 2.75−2.89 (m, 1 H, C*H*HCH$_2$), 3.01 [d, *J* = 13.3 Hz, 1 H, C*H*$_2$NH(Ph)CH$_3$], 2.95−3.07 (m, 1 H, C*H*HCH$_2$), 3.25 [d, *J* = 13.3 Hz, 1 H, C*H*$_2$NH(Ph)CH$_3$], 3.20−3.32 (m, 1 H, C*H*HCH$_2$), 3.70−3.80 (m, 1 H, C*H*HCH$_2$), 6.15 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.39 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.45−6.55 (m, 3 H, PC arom. H), 7.05−7.17 (m, 4 H, arom. H), 7.18−7.25 (t, 2 H, arom. H) ppm. MS (EI): *m*/*z* (%) = 357 (21) [M^+], 252 (11), 236 (61), 148 (37), 132 (29), 104 (100). $C_{25}H_{27}NO$ (357.50): calcd. C 83.99, H 7.61, N 3.92; found C 83.91, H 7.67, N 3.65.

Separation of the Diastereomeric Mixture of (*Rp*,*R*)- and (*Sp*,*R*)-3: The diastereomeric mixture of (*Rp*,*R*)-**3** and (*Sp*,*R*)-**3** (240 mg, 100%) was obtained as described in ref.[12] from 5-benzoyl-4-hydroxy[2.2]paracyclophane (204 mg, 0.62 mmol), (*R*)-α-phenylethylamine (0.25 mL, 230 mg, 1.87 mmol), and $TiCl_4$ (0.07 mL, 120 mg, 0.62 mmol). The mixture was separated by preparative chromatography on silica gel with hexane/ethyl acetate/Et_3N (100:5:1). Diastereomer (*Rp*,*R*)-**3** (*de* > 99% according to ^{1}H NMR analysis, 120 mg, 50%) was isolated from the combined fractions with R_f = 0.15, diastereomer (*Sp*,*R*)-**3** (*de* > 99% according to ^{1}H NMR analysis, 115 mg, 48%) from the combined fractions with R_f = 0.10.

(*Rp*,*R*,*R*)-{Phenyl[(1-phenylethyl)amino]methyl}[2.2]paracyclophan-4-ol [(*Rp*,*R*,*R*)-16]: $LiAlH_4$ (99 mg, 2.66 mmol) was added to a solution of (*Rp*,*R*)-**3** (115 mg, 0.27 mmol) in anhydrous Et_2O (20 mL), and the mixture was heated at reflux for 6 h. After hydrolysis with excess aqueous KOH solution, the mixture was extracted with Et_2O, the solvent was removed in vacuo, and 139 mg of crude product was passed through a short column (silica gel; benzene) to yield (*Rp*,*R*,*R*)-**16** (113 mg, 98%) as a colorless oil. $[\alpha]_D^{22}$ = +12.9 (*c* = 0.42, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.32 [d, 3 H, NCH(Ph)C*H*$_3$], 1.57 (br. s, 1 H, NH), 2.45−2.55 (m, 1 H, C*H*HCH$_2$), 2.68−2.90 (m, 4 H, C*H*HCH$_2$), 2.92−3.05 (m, 1 H, C*H*HCH$_2$), 3.12−3.22 (m, 1 H, C*H*HCH$_2$), 3.42−3.52 [m, 2 H, C*H*HCH$_2$, NHC*H*(Ph)Me], 4.52 (d, 1 H, 12-H or 13-H), 4.6 [s, 1 H, C*H*(Ph)NH], 5.93 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.29 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.43 (d, ^3J = 7.8, 1 H), 6.55 (m, 2 H, 15-H, 16-H), 6.99 (d, ^3J = 7.8, 2 H, arom. H), 7.14−7.22 (m, 1 H, arom. H), 7.25−7.35 (m, 3 H, arom. H), 7.36−7.44 (m, 1 H, arom. H), 7.45−7.52 (m, 2 H, arom. H), 7.79 (d, ^3J = 7.8 Hz, 2 H, arom. H), 12.05 (br. s, 1 H, OH) ppm. MS (EI): *m*/*z* (%) = 433 (4) [M^+], 313 (14), 312 (27), 209 (33), 208 (75), 177 (41), 120 (31). $C_{31}H_{31}NO$ (433.59): calcd. C 85.87, H 7.21, N 3.23; found C 86.07, H 7.07, N 3.00.

(*Sp*,*S*,*R*)-{Phenyl[(1-phenylethyl)amino]methyl}[2.2]paracyclophan-4-ol [(*Sp*,*S*,*R*)-16]: This compound was obtained in 98% yield (92 mg) by the reduction of (*Sp*,*R*)-**3** (93 mg, 0.22 mmol). An analytically pure sample of (*Sp*,*S*,*R*)-**16** (46 mg, 49%) was obtained by recrystallization from hexane/heptane (1:1). M.p. 171−172 °C. $[\alpha]_D^{22}$ = +206.8 (*c* = 0.32, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.66 [d, *J* = 7.1 Hz, 3 H, NCH(Ph)C*H*$_3$], 2.20 [br. s, 1 H, N*H*CH(Ph)CH$_3$], 2.42−2.56 (m, 1 H, C*H*HCH$_2$), 2.57−2.68 (m, 1 H, C*H*HCH$_2$), 2.73−2.95 (m, 2 H, C*H*HCH$_2$), 3.02−3.16 (m, 2 H, C*H*HCH$_2$), 3.16−3.28 (m, 1 H, C*H*HCH$_2$), 3.38−3.50 (m, 1 H, C*H*HCH$_2$), 3.95−4.09 [m, 1 H, NHC*H*(Ph)CH$_3$], 4.89 [s, 1 H, C*H*(Ph)NH(Ph)CH$_3$], 5.98 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.33 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.55 (d, ^3J = 7.8, 1 H, PC arom. H), 6.63 (d, ^3J = 7.8, 1 H, PC arom. H), 6.80 (d, ^3J = 7.8, 1 H, PC arom. H), 6.97−7.04 (m, 2 H, arom. H), 7.07 (d, ^3J = 7.8, 1 H, PC arom. H), 7.13−7.22 (m, 3 H, arom. H), 7.23−7.29 (m, 2 H, arom. H), 7.30−7.55 (m, 3 H, arom. H), 13.31 (br. s, 1 H, OH) ppm. MS (EI): *m*/*z* (%) = 433 (4) [M^+], 313 (14), 312 (27), 209 (33), 208 (75), 177 (41), 120 (31). $C_{31}H_{31}NO$ (433.59) calcd. C 85.87, H 7.21, N 3.23; found C 85.87, H 7.42, N 3.17.

5-[(Phenylimino)methyl][2.2]paracyclophan-4-ol (*rac*-17): A mixture of *rac*-**1** (105 mg, 0.42 mmol), aniline (0.076 mL, 77 mg, 0.83 mmol), Et_2SnCl_2 (catalytic quantity), and anhydrous benzene (20 mL) was heated at reflux for 48 h in a flask equipped with a Dean−Stark trap filled with molecular sieves (3 Å). The solution was concentrated and passed through a short column filled with silica gel (eluent: benzene) to provide *rac*-**17** (135 mg, 99%) as an orange powder. M.p. 105−106 °C. ^{1}H NMR ([D$_6$]acetone): δ = 2.59−2.75 (m, 1 H, C*H*HCH$_2$), 2.81−3.30 (m, 5 H, C*H*HCH$_2$), 3.37−3.49 (m, 1 H, C*H*HCH$_2$), 3.68−3.85 (m, 1 H, C*H*HCH$_2$), 6.29 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.34 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.48 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.62 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.67 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.88 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 7.25−7.40 (m, 2 H, arom. H), 7.45−7.60 (m, 3 H, arom. H), 8.80 (s, 1 H, C*H*=N), 14.00 (s, 1 H, O*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.00, 33.50, 34.50, 37.00 (C-1, C-2, C-9, C-10), 122.00 (2 C), 124.10, 125.60, 125.80, 127.30 (3 C), 131.50 (2 C), 133.00, 134.30, 137.30, 137.60, 139.00, 139.20, 141.20, 147.70, 161.60 ppm. IR (KBr): $\tilde{\nu}$ = 3445 cm^{-1}, 2983, 1607, 1436.

$C_{23}H_{21}NO$ (327.43): calcd. C 84.37, H 6.46, N 4.28; found C 84.56, H 6.32, N 4.13.

(*Rp*)-5-[(Isopropylimino)methyl][2.2]paracyclophan-4-ol [(*Rp*)-18)]: A mixture of (*R*)-**1** (404 mg, 1.60 mmol), 2-aminopropane (0.55 mL, 380 mg, 6.40 mmol), Et_2SnCl_2 (catalytic quantity), and anhydrous benzene (20 mL) was heated at reflux for 4 h in a flask equipped with a Dean−Stark trap filled with $MgSO_4$. The mixture was concentrated and passed through a short column filled with silica gel (eluent: benzene) to produce (*R*)-**18** (469 mg, 98%). An analytically pure sample was prepared by recrystallization from hexane. M.p. 139−140 °C. $[\alpha]_D^{22}$ = +677.8 (*c* = 0.4, C_6H_6). ^{1}H NMR ($CDCl_3$): δ = 1.24 (d, *J* = 7.1 Hz, 3 H, NCHC*H*$_3$), 1.34 (d, *J* = 7.1 Hz, 3 H, NCHC*H*$_3$), 2.52−2.63 (m, 1 H, C*H*HCH$_2$), 2.67−2.76 (m, 1 H, C*H*HCH$_2$), 2.80−2.90 (m, 1 H, C*H*HCH$_2$), 3.02−3.08 (m, 1 H, C*H*HCH$_2$), 3.08−3.30 (m, 2 H, C*H*HCH$_2$), 3.37−3.50 (m, 2 H, C*H*HCH$_2$), 3.53−3.62 [m, 1 H, C*H*(CH$_3$)$_2$], 6.18 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.25 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.43 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.50 (d, ^3J = 7.8 sHz, 1 H, 7-H or 8-H), 6.60 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.90 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 8.20 (s, 1 H, C*H*=N), 14.5 (s, 1 H, O*H*). ^{13}C NMR ($CDCl_3$): δ = 24.20 [NCH(*C*H$_3$)$_2$], 24.61 [NCH(*C*H$_3$)$_2$], 29.92, 32.24, 33.82, 35.30 (C-1, C-2, C-9, C-10), 59.30 [N*C*H(CH$_3$)$_2$], 118.80, 123.60, 126.50, 128.20, 130.20 (C-3, C-5, C-6, C-11, C-14), 131.90, 133.40, 137.20, 137.30, 140.10, 141.90 (C-7, C-8, C-12, C-13, C-15, C-16), 159.30 (C-4), 163.10 (C=N) ppm. IR (KBr): $\tilde{\nu}$ = 3425 cm^{-1}, 1616, 1498, 1381. MS (EI): *m*/*z* (%) = 293 (60) [M$^+$], 189 (100); 147 (46), 104 (52). $C_{20}H_{23}NO$ (293.41) calcd. C 81.87, H 7.90, N 4.77; found C 81.81, H 7.85, N 4.76.

5-[(Isopropylimino)methyl][2.2]paracyclophan-4-ol (*rac*-18): The synthesis was carried out as described for (*R*)-**18**, starting from *rac*-**1** (105 mg, 0.42 mmol), 2-aminopropane (0.04 mL, 30 mg, 1.60 mmol), and Et_2SnCl_2 (catalytic quantity) to yield *rac*-**18** (120 mg, 98%). An analytically pure sample of **18** was obtained by recrystallization from hexane. M.p. 102−103 °C. $C_{20}H_{23}NO$ (293.41): calcd. C 81.87, H 7.90, N 4.77; found C 81.76, H 7.76, N 4.68. The ^{1}H NMR spectroscopic data agree with those for (*R*)-**18**.

5-[(Phenylamino)methyl][2.2]paracyclophan-4-ol (*rac*-19): A solution of *rac*-**17** (120 mg, 0.38 mmol) and $NaBH_4$ (114 mg, 3.00 mmol) in anhydrous methanol was stirred for 3 h at room temp. The mixture was hydrolyzed with excess aqueous KOH solution (0.5 N), concentrated, extracted with Et_2O, washed with H_2O, and dried with Na_2SO_4, and the solvents were evaporated in vacuo to yield 0.118 g (98%) of *rac*-**19** as a colorless powder. M.p. 170−180 °C (decomp.). ^{1}H NMR ($CDCl_3$): δ = 2.50−3.30 (m, 8 H, C*H*HCH$_2$), 3.85 (d, *J* = 13.3 Hz, 1 H, C*H*HNH$_2$), 3.98 (d, *J* = 13.3 Hz, 1 H, CH*H*NH$_2$), 6.15 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.40 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.42−6.45 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.49 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.61 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.78 (m, 1 H, Ph arom. H), 6.80−6.82 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.86 (m, 1 H, Ph arom. H), 7.18 (m, 2 H, Ph arom. H), 8.10 (s, 1 H, O*H*) ppm. ^{13}C NMR: δ = 29.85, 32.90, 33.90, 34.40 (C-1, C-2, C-9, C-10), 45.30 (*C*H$_2$NHPh), 115.90 (2 C), 120.80, 122.90, 125.30, 126.50, 126.90, 127.20, 129.3 (2 C), 132.50, 133.30, 133.49, 137.70, 139.50, 139.90, 147.20, 155.20. IR (KBr): $\tilde{\nu}$ = 3419 cm^{-1}, 3045, 2930, 1566, 1354 ppm. MS (EI): *m*/*z* (%) = 329 (4) [M$^+$], 327 (19), 223 (100).

(*Rp*)-5-[(Isopropylamino)methyl][2.2]paracyclophan-4-ol [(*Rp*)-20]: A mixture of (*R*)-**18** (303 mg, 1.03 mmol) and $NaBH_4$ (300 mg, 7.80 mmol) was stirred for 3 h at room temp. in methanol (75 mL) to which water (0.6 mL) had been added. The mixture was hydrolyzed with excess aqueous KOH solution (0.5 N), concentrated, extracted with Et_2O, washed with H_2O, and dried with Na_2SO_4, and the solvent was evaporated in vacuo to yield (*R*)-**20** (301 mg, 99%) as a colorless powder. An analytically pure sample (256 mg, 84%) was obtained as pale yellow crystals by recrystallization from heptane. M.p. 100−102 °C. $[\alpha]_D^{22}$ = +214.8 (*c* = 0.36, C_6H_6). ^{1}H NMR (C_6D_6): δ = 0.68 (d, ^3J = 7.1 Hz, 3 H, NHCHC*H*$_3$), 0.81 (d, ^3J = 7.1 Hz, 3 H, NHCHC*H*$_3$), 2.30−2.40 (sept, 1 H, NHC*H*(CH$_3$)$_2$], 2.52−2.65 (m, 3 H, CH*H*CH$_2$), 2.80−3.07 (m, 3 H, CH*H*CH$_2$), 3.12 (d, *J* = 13.3 Hz, 1 H, CH*H*NH*i*Pr), 3.20−3.31 (m, 1 H, CH*H*CH$_2$), 3.42 (d, *J* = 13.3 Hz, 1 H, CH*H*NH*i*Pr), 3.68−3.79 (m, 1 H, CH*H*CH$_2$), 6.17 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.46 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.54 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, 15-H or 16-H), 6.57 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 15-H or 16-H), 6.72 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, 12-H or 13-H), 7.18 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, 12-H or 13-H). ^{13}C NMR ($CDCl_3$): δ = 22.2, 22.9 [NHCH(*C*H$_3$)$_2$], 29.7, 32.6, 33.9, 34.1 (C-1, C-2, C-9, C-10), 46.97 (*C*H$_2$NH*i*Pr), 48.45 [NH*C*H(CH$_3$)$_2$], 122.8, 124.12 (C-7 or C-8), 125.90, 126.45, 127.11 (C-12, C-13), 132.40 (C-15 or C-16), 132.90 (C-7 or C-8), 133.10 (C-15 or C-16), 137.50, 139.10, 140.00, 156.92 (C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3447 cm^{-1}, 3017, 2928, 1568, 1425. MS (EI): *m*/*z* (%) = 295 (68) [M$^+$], 191 (73), 104 (100). $C_{20}H_{25}NO$ (295.42): calcd. C 81.31, H 8.53, N 4.74; found C 81.70, H 8.49, N 4.63.

5-[(Isopropylamino)methyl][2.2]paracyclophan-4-ol (*rac*-20): The synthesis was carried out as described for (*R*)-**20**, from *rac*-**18** (100 mg, 0.34 mmol) and $NaBH_4$ (100 mg, 2.58 mmol), to yield *rac*-**20** (98 mg, 98%). An analytically pure sample was obtained by recrystallization from hexane. M.p. 84−86 °C. $C_{20}H_{25}NO$ (295.42): calcd. C 81.31, H 8.53, N 4.74; found C 81.37, H 8.37, N 4.26. The ^{1}H NMR spectroscopic data agree with those for (*R*)-**20**.

5-Hydroxy[2.2]paracyclophane-4-carbaldehyde Oxime (*rac*-21): NaOAc (500 mg, 3.40 mmol) was added to a yellow solution of FHPC (**1**, 132 mg, 0.53 mmol) in anhydrous EtOH (30 mL), followed by hydroxylamine hydrochloride (100 mg, 1.4 mmol), and the reaction mixture was heated at reflux for 2 h. The resulting colorless solution was filtered and concentrated to dryness, and the crude solid was dissolved in Et_2O (30 mL), washed successively with $NaHCO_3$ solution and H_2O, and dried with Na_2SO_4. The solvent was evaporated in vacuo to yield the oxime *rac*-**21** (137 mg, 98%) as a pale yellow solid. Crystallization from benzene/pentane (1:1) produced 129 mg (92%) of analytically pure *rac*-**21**. M.p. = 110−112 °C. ^{1}H NMR ($CDCl_3$): δ = 2.48−2.55 (m, 1 H, C*H*HCH$_2$), 2.67−2.85 (m, 2 H, CH*H*CH$_2$), 2.93−3.17 (m, 3 H, CH*HCH*$_2$), 3.20−3.30 (m, 1 H, C*H*HCH$_2$), 3.35−3.42 (m, 1 H, C*H*HCH$_2$), 6.20 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.32 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.35 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.43 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.48 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.78 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 8.17 (s, 1 H, C*H*=N), 10.05 (s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.00, 32.74, 33.81, 34.93 (C-1, C-2, C-9, C-10), 117.40, 125.50, 126.80, 127.60, 130.00 (C-3, C-5, C-6, C-11, C-14), 132.10, 133.40, 136.40, 137.60, 139.89, 141.60 (C-7, C-8, C-12, C-13, C-15, C-16), 150.40 (C-4), 155.00 (*C*H=N) ppm. IR (KBr): $\tilde{\nu}$ = 3416 cm^{-1}, 2912, 1626, 1597, 1439. MS (EI): *m*/*z* (%) = 267 (100) [M$^+$], 250 (13), 234 (26), 162 (55), 146 (100), 104 (45). $C_{17}H_{17}NO_2$ (267.33): calcd. C 76.38, H 6.41, N 5.24; found C 76.47, H 6.43, N 5.14.

5-(Aminomethyl)[2.2]paracyclophan-4-ol (*rac*-22): A solution of *rac*-**21** (100 mg, 0.37 mmol) and $LiAlH_4$ (100 mg, 2.60 mmol) in anhyd-

rous Et_2O (25 mL) was stirred at room temp. for 48 h and additionally heated at reflux for 1 h. After cooling and hydrolysis with H_2O (10 mL), the reaction mixture was extracted with Et_2O, washed successively with H_2O and $NaHCO_3$, and dried with Na_2SO_4. The solvent was removed in vacuo to yield a solid residue (95 mg), which was purified by silica gel chromatography with ethanol to yield *rac*-**22** (84 mg, 89%) as a slightly yellow powder. M.p. 110−120 °C (decomp.). ^{1}H NMR ($CDCl_3$): δ = 2.50−2.80 (m, 3 H, C*H*HCH$_2$), 2.85−3.10 (m, 4 H, C*H*HCH$_2$), 3.20−3.35 (m, 1 H, C*H*HCH$_2$), 3.40 (d, J = 13.3 Hz, 1 H, CH_2NH$_2$), 3.95 (d, J = 13.3 Hz, 1 H, CH_2NH$_2$), 6.05 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.35 (d, ^3J = 7.8 Hz, 1 H, 7-H or 8-H), 6.42 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.50 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.55 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H), 6.80 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC arom. H) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.70, 32.70, 33.97, 34.10 (C-1, C-2, C-9, C-10), 41.90 (*C*H$_2$NH$_2$), 123.73, 124.30, 126.34, 126.71, 127.20 (C-3, C-5, C-6, C-11, C-14), 132.40, 132.90, 133.10, 137.60, 139.0, 140.0 (C-7, C-8, C-12, C-13, C-15, C-16), 157.0 (C-4). IR (KBr): $\tilde{\nu}$ = 3416 cm^{-1}, 3363, 1602, 1568, 1317, 1261 ppm. MS (EI): *m*/*z* (%) = 253 (46) [M$^+$], 236 (39), 132 (21), 104 (100).

Crystal Structure Determinations of *rac*-11, (*Rp*,*R*)-15, and (*Sp*,*S*,*R*)-16. ***rac*-11:** $C_{21}H_{27}NO$ (309.44), orthorhombic, space group *Pbca* (no. 61), 293 K, a = 12.309(4), b = 11.942(6), c = 23.965(9) Å, V = 3523(2) Å^3, Z = 8, $d_{calcd.}$ = 1.167 g cm^{-3}, μ = 0.071 mm^{-1}, F(000) = 1344, crystal size 0.60 × 0.40 × 0.20 mm. **(*Rp*,*R*)-15:** $C_{25}H_{27}NO$ (357.48), orthorhombic, space group $P2_12_12_1$,(no. 19), 110 K, a = 10.947(2), b = 11.205(1), c = 15.539(2) Å, V = 1906.1(4) Å^3, Z = 4, $d_{calcd.}$ = 1.246 g cm^{-3}, μ = 0.075 mm^{-1}, F(000) = 768, crystal size 0.30 × 0.40 × 0.70 mm. **(*Sp*,*S*,*R*)-16:** $C_{31}H_{31}NO$ (433.57), monoclinic, space group $P2_1$ (no. 4), 153 K, a = 7.639(3), b = 12.492(6), c = 12.525(5) Å, β = 103.19(3) °, V = 1163.7(8) Å^3, Z = 2, $d_{calcd.}$ = 1.237 g cm^{-3}, μ = 0.074 mm^{-1}, F(000) = 464, crystal size 0.20 × 0.15 × 0.04 mm. Single-crystal X-ray diffraction experiments for **15** were carried out with a Bruker SMART 1000 CCD area detector, by use of graphite-monochromated Mo-K$_\alpha$ radiation (λ = 0.71073 Å, ω-scans with a 0.3° step in ω and 10 s per frame exposure, 2θ < 60°) at 110 K. The low temperature of the crystals was maintained with a Cryostream (Oxford Cryosystems) open-flow N_2 gas cryostat. Reflection intensities were integrated with SAINT software [SMART V5.051 and SAINT V5.00, Area detector control and integration software, Bruker AXS Inc., Madison, WI 53719, USA, **1998**] and by semiempirical methods SADABS [G. M. Sheldrick, SADABS, Bruker AXS Inc., Madison, WI 53719, USA, **1997**]. A total of 15963 reflections was measured, 5520 (R_{int} = 0.0512) independent reflections were used in further calculations and refinement. Single-crystal X-ray diffraction experiments were carried out with a Siemens P3/PC diffractometer at 293 K for **11**, and with a Syntex P2$_1$ at 153 K for **16** [graphite-monochromated Mo-K_α radiation, θ/2θ scans, 2θ < 40° (**11**), 48° (**16**)]. A total of 1627 and 3981 reflections were measured, 1627 and 3601 (R_{int} = 0.0668) independent reflections were used in further calculations and refinement.The structures were solved by direct methods and refined by full-matrix, least squares against F^2 in anisotropic (for non-hydrogen atoms) approximation. All hydrogen atoms were located by difference Fourier synthesis and were refined by the riding model. The final refinements converged to $R1$ = 0.0563 [from 816 unique reflections with $I > 2\sigma(I)$] and $wR2$ = 0.1540 (from all unique reflections) for **11**; 0.0580 [from 2544 unique reflections with $I > 2\sigma(I)$] and $wR2$ = 0.1499 (from all unique reflections) for **15**; 0.1529 [from 1647 unique reflections with $I > 2\sigma(I)$] and $wR2$ = 0.4128 (from all unique reflections) for **16**, the number of the refined parameters being 208, 244 and 306 for **11**, **15**, and **16**, respectively. The high R factor for **16** was due to the low quality of the crystal. All attempts to obtain a well-formed single crystal from different solvents resulted in the growth of twins composed of thin, colorless needles. The X-ray diffraction analysis was therefore performed for an extremely small twinned sample with predominance of one component. The resolution of the two components was unsuccessful. All calculations were performed with an IBM PC/AT with SHELXTL software [G. M. Sheldrick, SHELXTL-97, Version 5.10, Bruker AXS Inc., Madison, WI 53719, USA]. CCDC-186186 to -186188 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

The financial support of Symyx Technologies, Santa Clara, CA, U.S.A., the Fonds der Chemischen Industrie, and the Russian Science Foundation (00-03-32683a and 00-03-32807a) is gratefully acknowledged. The authors are grateful to Dr. E. V. Vorontsov (Moscow, Russia) for NMR spectra analysis and for helpful discussion.

[1] F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159−2212.
[2] Y. Pu, P. Yu, *Chem. Rev.* **2001**, *101*, 757−824.
[3] V. Rozenberg, V. Kharitonov, D. Antonov, E. Sergeeva, A. Aleshkin, N. Ikonnikov, S. Orlova, Yu. Belokon′, *Angew. Chem.* **1994**, *106*, 106−108; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 91−92.
[4] D. Y. Antonov, Yu. N. Belokon′, N. S. Ikonnikov, S. A. Orlova, A. P. Pisarevskij, N. I. Raevskij, V. I. Rozenberg, E. V. Sergeeva, E. Struchkov, V. I. Tararov, E.V. Vorontsov, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1873−1879.
[5] Yu. Belokon′, M. Moscalenko, N. Ikonnikov, L. Yashkina, D. Antonov, E. Vorontsov, V. Rozenberg, *Tetrahedron: Asymmetry* **1997**, *8*, 3245−3250.
[6] D. S. Masterson, T. L. Hobbs, D. T. Glatzhofer, *J. Mol. Catal. A: Chem.* **1999**, *145*, 75−81; D. S. Masterson, D. T. Glatzhofer, *J. Mol. Catal. A: Chem.* **2000**, *161*, 65−68.
[7] A. H. Vetter, A. Berkessel, *Tetrahedron Lett.* **1998**, *39*, 1741−1744.
[8] F. Fringuelli, O. Piermatti, F. Pizzo, R. Ruzziconi, *Chem. Lett.* **2000**, 38−39.
[9] X.-W. Wu, X.-L. Hou, L.-D. Dai, J. Tao, B.-X. Cao, J. Sun, *Tetrahedron: Asymmetry* **2001**, *12*, 529−532.
[10] J. Issberner, M. Boehme, S. Grimme, M. Nieger, W. Paulus, F. Vögtle, *Tetrahedron: Asymmetry* **1996**, *7*, 2223−2232.
[11] A. Pelter, B. Mootoo, A. Maxwell, A. Reid, *Tetrahedron Lett.* **2001**, *42*, 8391−8394.
[12] V. Rozenberg, T. Danilova, E. Sergeeva, E. Vorontsov, Z. Starikova, K. Lysenko, Yu. Belokon′, *Eur. J. Org. Chem.* **2000**, 3295−3303.
[13] S. Dahmen, S. Bräse, *Chem. Commun.* **2001**, 26−27.
[14] S. Dahmen, S. Bräse, *Org. Lett.* **2001**, 4119−4122.
[15] S. Dahmen, S. Bräse, *J. Am. Chem. Soc.* **2002**, *124*, 5940−5941.
[16] S. Dahmen, S. Bräse, *Tetrahedron: Asymmetry* **2001**, *12*, 2845−2850.
[17] H. Hopf, D. G. Barret, *Liebigs Ann.* **1995**, 449−451.
[18] T. Focken, H. Hopf, V. Snieckus, I. Dix, P. G. Jones, *Eur. J. Org. Chem.* **2001**, 2221−2228.

[19] T. I. Danilova, Master Dissertation, Moscow, **1997**.
[20] V. I. Rozenberg, T. I. Danilova, E. V. Sergeeva, E. Vorontsov, Z. Starikova, A. Korlyukov, H. Hopf, *Eur. J. Org. Chem.* **2002**, 468−477.
[21] C. Schulz, PhD Dissertation, Braunschweig, **1999**.
[22] G. I. Gershzon, *Zh. Org. Khim.* **1943**, *13*, 68−81; G. Mann, H. Wilde, S. Hauptmann, J. Lehmann, M. Naumann, P. Lepom, *J. Prakt. Chem.* **1981**, *323*, 785−792.
[23] G. M. Sheldrick, *SHELXTL PC, An integrated system for solving, refining, and displaying crystal structures from diffraction data*, version 5.0, Siemens Analytical X-ray Instruments Inc., Madison, WI, **1994**.

Received May 27, 2002
[O02285]