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Notes

Optical Resolution of Bicyclo[2.2.1]heptanone, Bicyclo[2.2.2]octanone, and Bicyclo[3.2.1]octanone Derivatives by Inclusion Complexation with Optically Active Host Compounds

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It is not easy to prepare optically pure enantiomers of the title bicyclic ketone derivatives, although these are useful synthons of various important compounds. We report a simple and efficient optical resolution method of such ketones by inclusion complexation with the optically active host compounds:[1] (*S*,*S*)-(−)-1,6-bis(*o*-chlorophenyl)-1,6-diphenyl-2,4-diyne-1,6-diol (**1**),[2] (*R*,*R*)-(−)-*trans*-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (**2**),[3] and (*S*)-(−)-10,10′-dihydroxy-9,9′-biphenanthryl (**3**).[4] The crystal structures of two inclusion compounds were analyzed by X-ray diffraction in order to learn about the structural mechanism of the efficient chiral recognition between the host and guest compounds (Chart I).

Experimental Section

Determination of Optical Purity. Optical purity of the ketone derivatives was determined primarily by HPLC, using a column containing an optically active solid phase, Chiralcel OC.[5] In a few cases (as specified below) it was determined by comparison of the $[\alpha]_D$ value with that reported for the resolved material.

Optical Resolution of Bicyclo[2.2.1]hept-2-en-5-one (4). When a solution of **2** (5.0 g, 10.8 mmol) and *rac*-**4** (2.32 g, 21.5 mmol) in benzene–hexane (1:1, 20 mL) was kept at room temperature for 12 h, a 1:1 complex of **2** and (−)-**4** was obtained as colorless prisms (5.89 g, 95%), which upon heating in vacuo gave (−)-**4** of 8.1% ee [1.03 g, 89%, $[\alpha]_D$ −92.7° (*c* 0.11, octane)]. When the resolution was carried out by complexation with **1**, (−)-**4** of 0.5% ee was obtained in 91% yield. In both cases, the optical purity of (−)-**4** was not improved by recrystallization of the complex. The optical purity of (−)-**4** was determined by comparison of measured $[\alpha]_D$ with the literature value.[6]

Optical Resolution of *endo*-Tricyclo[5.2.1.0^{2,6}]deca-3,8-dien-5-one (5). When a solution of **1** (4.83 g, 10.0 mmol) and *rac*-**5** (2.92 g, 20.0 mmol) in ether–petroleum ether (1:2, 20 mL) was kept at room temperature for 12 h, 1:1 complex of **1** and (+)-**5** was obtained as colorless prisms (6.21 g, 98%). Four recrystallizations of the solid complex from the same solvent mixture gave pure crystals (2.55 g, 40%, mp 79–80 °C), which upon heating in vacuo gave (+)-**5** of 59% ee [0.48 g, 33%, $[\alpha]_D$ +83.3° (*c* 0.96, MeOH)]. The optical purity was determined by comparison of measured $[\alpha]_D$ with the literature value.[7]

Optical Resolution of *endo*-Tricyclo[5.2.1.0^{2,6}]deca-3,8-diene-5,10-dione (6). When a solution of **1** (4.83 g, 10.0 mmol) and *rac*-**6** (3.20 g, 20.0 mmol) in butane (20 mL) was kept at room temperature for 12 h, a 1:1 complex of **1** and (−)-**6** was obtained, after three recrystallizations from butane, as colorless prisms (1.31 g, 20%, mp 149–151 °C), which upon heating in vacuo gave (−)-**6** of 100% ee [0.25 g, 16%, $[\alpha]_D$ −165° (*c* 0.2, MeOH)].

Optical Resolution of *endo*,*exo*-4-Oxatetracyclo[6.2.1.0^{2,7}0^{3,5}]undec-9-en-6-one (7). When a solution of **1** (4.83 g, 10.0 mmol) in ether–petroleum ether (1:1, 20 mL) was kept at room temperature for 12 h, a 1:1 complex of **1** and (+)-**7** was obtained, after two recrystallizations from a 1:1 ether–petroleum ether mixture, as colorless prisms (4.40 g, 70%, mp 127–129 °C), which upon heating in vacuo gave (+)-**7** of 100% ee [0.97 g, 60%, $[\alpha]_D$ +176° (*c* 1.2, MeOH)].

Optical Resolution of 4-Methoxybicyclo[2.2.2]oct-2-en-5-one (8). When a solution of **2** (2.30 g, 4.94 mmol) and *rac*-**8** (1.50 g, 9.87 mmol) in benzene–hexane (1:1, 10.0 mL) was kept at room temperature for 12 h, a 1:1 complex of **2** and (+)-**8** was obtained as colorless needles (2.99 g, 98%, mp 116–119 °C), which upon heating gave (+)-**8** of 5% ee [0.69 g, 90%, $[\alpha]_D$ +27.2° (*c* 1.2, $CHCl_3$)]. The optical purity of (+)-**8** in the complex was not improved by recrystallization.

Optical Resolution of 1-Methyl-4-methoxybicyclo[2.2.2]oct-2-en-5-one (9). When a solution of **1** (0.83 g, 1.72 mmol) and *rac*-**9** (0.58 g, 3.45 mmol) in ether–hexane (1:1, 10.0 mL) was kept at room temperature for 12 h, a 1:1 complex of **1** and (−)-**9** was obtained, after three recrystallizations from ether–hexane (1:1), as colorless plates (0.5 g, 45%, mp 119–120 °C), which upon heating in vacuo gave (−)-**9** of 100% ee [0.12 g, 41%, $[\alpha]_D$ −265° (*c* 0.6, $CHCl_3$)].

Optical Resolution of 1,2-Dimethyl-4-methoxybicyclo[2.2.2]oct-2-en-5-one (10). When a solution of **2** (0.98 g, 2.10 mmol) and *rac*-**10** (0.76 g, 4.20 mmol) in benzene–hexane (1:1, 10 mL) was kept at room temperature for 12 h, a 1:1 complex of **2** and (−)-**10** was obtained, after two recrystallizations from benzene–hexane, as colorless needles (0.9 g, 66%, mp 117–120 °C), which upon heating in vacuo gave (−)-**10** of 100% ee [0.21 g, 56%, $[\alpha]_D$ −359° (*c* 0.7, $CHCl_3$)].

Optical Resolution of Bicyclo[2.2.2]oct-2-ene-5,7-dione (11). When a solution of **3** (1.0 g, 2.59 mmol) and *rac*-**11** (0.7 g, 5.15 mmol) in benzene–hexane (1:1, 10 mL) was kept at room temperature for 12 h, a 1:1 complex of **3** and (−)-**11** was obtained, after three recrystallizations from benzene–hexane (1:1), as colorless needles (0.6 g, 44%, mp 189–190 °C), which upon heating in vacuo gave (−)-**11** of 100% ee [0.11 g, 31%, $[\alpha]_D$ −123.5° (*c* 0.12, CCl_4)]. The optical purity was determined by comparison of the observed $[\alpha]_D$ value with that reported previously.[8,9] Similar complexation of *rac*-**11** with hosts **1** and **2** gave (−)-**11** of 6.9% ee (92% yield) and 1.9% ee (8.3% yield), respectively.

Optical Resolution of 5-Methoxybicyclo[3.2.1]oct-2-en-4-one (12). When a solution of **2** (1.99 g, 4.27 mmol) and *rac*-**12** in benzene–hexane (1:1, 10 mL) was kept at room temperature for 12 h, a 1:1 complex of **2** and (−)-**12** was obtained, after one recrystallization from benzene–hexane (1:1), as colorless needles

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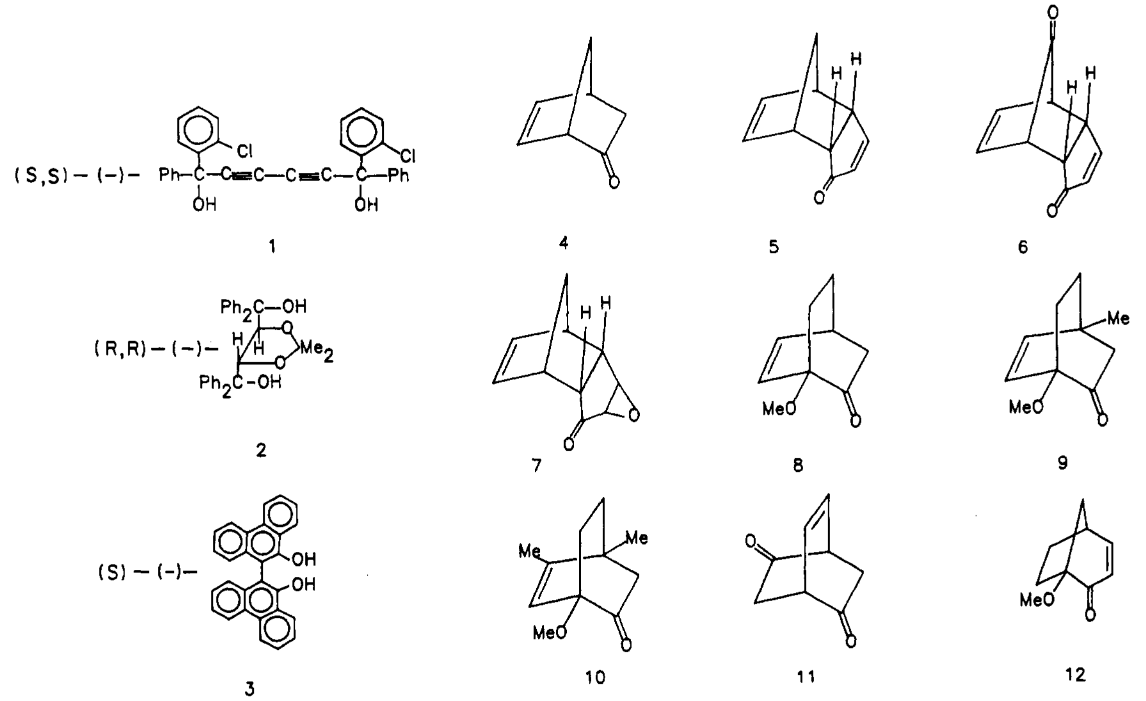
Chart I



(0.15 g, 57%, mp 126–128 °C), which upon heating in vacuo gave (-)-**12** of 100% ee [0.31 g, 48%, $[\alpha]_D$ -206° (*c* 0.28, $CHCl_3$)].

Additional experiments with other combinations of host and guest have also been carried out (see Table I below).

Crystal Structure Analyses. The 1:1 complexes of **1** with (-)-**6** (structure I) and of **2** with (-)-**12** (structure II) formed single crystals suitable for a detailed structural investigation. The X-ray diffraction experiments were carried out at room temperature (ca. 298 K) on automated CAD4 and Huber diffractometers equipped with a graphite monochromator. Intensity data were collected by the ω–2θ scan mode with a constant scan speed of 3 deg/min. No corrections for absorption or secondary extinction effects were applied. Possible deterioration of the analyzed crystals was tested by detecting periodically the intensities of standard reflections and was found negligible during the measurements. The two structures were solved by direct methods (SHELX-86)[9] and refined by full-matrix least squares (SHELX-76),[10] including the positional and anisotropic thermal parameters of the non-hydrogen atoms. The final refinements were based on experimental weights $w = 1/\sigma^2(F_o)$, minimizing $w(\Delta F)^2$.

For structure I, data were collected to $2\theta_{max} = 132°$, using Cu Kα radiation ($\lambda = 1.5418$ Å). Crystal data are $C_{30}H_{20}Cl_2O_2 \cdot C_9H_8O_2$, formula weight 631.55, space group tetragonal $P4_12_12$, $a = 7.958$ (4) and $c = 52.682$ (8) Å, $V = 3336.3$ Å^3, $Z = 4$, $D_{calc} = 1.257$ g·cm^{-3}.

A total of 2567 unique reflections with positive intensities were measured, assuming the 4/m Laue symmetry of the diffraction pattern. Subsequently, these were merged to yield 1753 unique observations in the 4/mmm Laue group, $R_i = 0.053$, to better reflect the symmetry of the diffraction pattern and conform with the final space group assignment for this crystal structure. In space group $P4_12_12$, the host and guest constituents have to reside on axes of twofold rotational symmetry, the asymmetric unit consisting of ($^1/_2$:$^1/_2$) host:guest entity. This requirement is perfectly consistent with the internal molecular symmetry of **1**, but not so with that of the (-)-**6** guest molecule. The latter was, therefore, assumed to be statistically disordered in the crystal lattice, adopting one of two possible orientations (at 50% probability) with respect to the 2-symmetry axes at the different guest sites. In the refinement calculations such model of the disorder can conveniently be described by allowing for only one atom, the peripheral carbon α to carbonyl, to be positioned at two different sites (about 1.28 Å apart) with 50% occupancy at each (Figure 1). The five other guest atoms contained in the asymmetric unit represent reasonably well the atomic positions of both orientations. In fact, the guest molecule appeared similarly disordered when the crystal structure was refined in space group $P4_1$ with the originally unmerged data set and (1:1) host:guest entity in the asymmetric unit. This provides a clear indication that the orientational disorder of the guest molecule was not imposed by assigning a higher $P4_12_12$ space symmetry to the lattice but is a genuine feature of this structure.

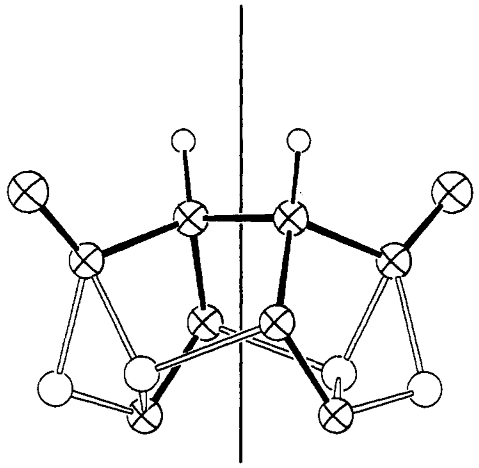


Figure 1. Orientational disorder of **6** around axes of crystallographic twofold rotational symmetry (marked by the vertical line) in structure I. Within the carbon framework, atoms and bonds with full occupancy are represented by cross circles and dark lines, respectively; those with an overall occupancy of 0.5 are indicated by empty bonds and clear circles. Two of the H-atoms are also shown, the others being omitted for clarity.

The refinement calculations converged at $R = 0.084$, $wR = 0.080$ for 999 observations having $I > 3\sigma(I)$. The relatively low data-to-parameters ratio, as well as the guest disorder around the twofold axes, affected the precision of the crystallographic determination, resulting in relatively large esd's of the structural and thermal parameters. Moreover, the geometry of the peripheral fragment of the guest species most affected by the orientational disorder is somewhat distorted. This indicates that the structural model used in the refinement calculations, although generally correct, may still be incomplete. Hydrogen atoms of the phenyl

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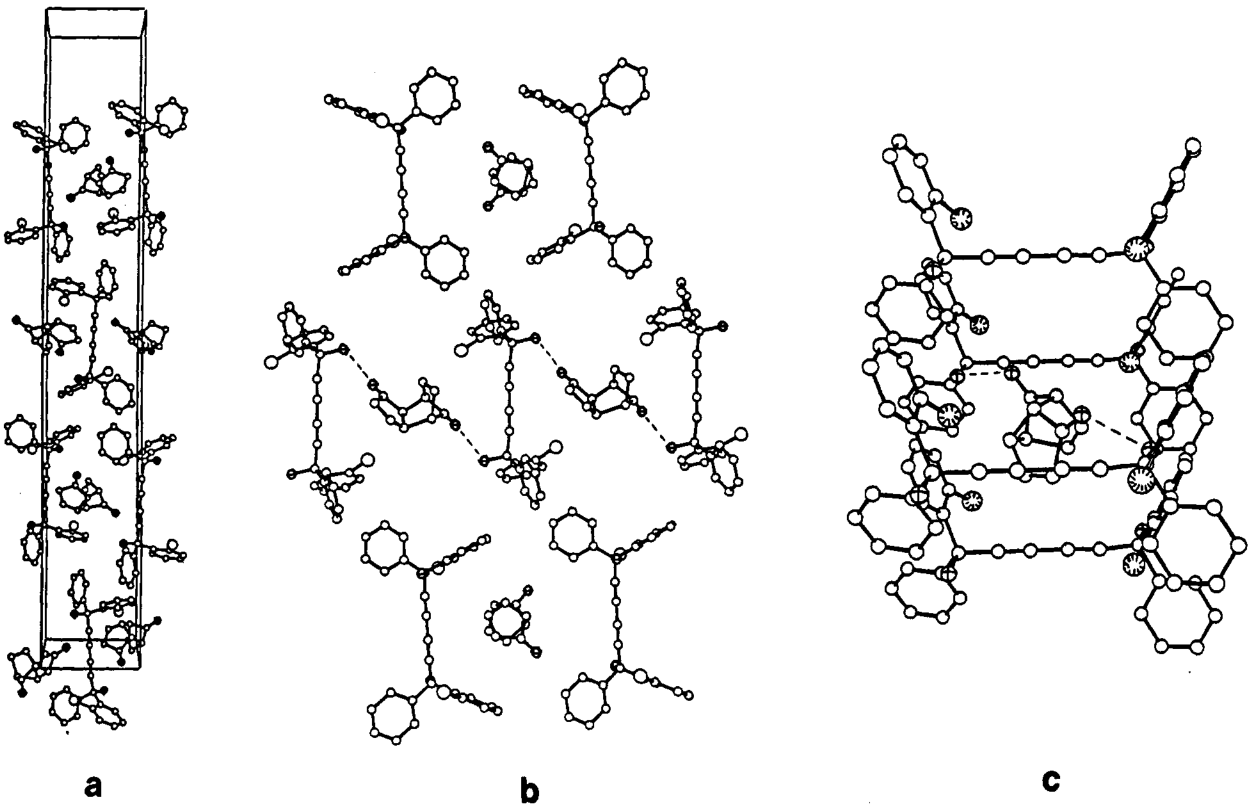

Figure 2. Illustration of structure I. (a) Contents of the unit cell viewed down the *a* axis, *c* is vertical. (b) Intermolecular arrangement of and H-bonding interaction between host and guest in sections parallel to the (1, 1, 0) planes of the crystal lattice. (c) Illustration of the molecular cage formed by four adjacent hosts around the included guest.

rings were introduced in calculated positions; that attached to O was located directly from a difference-Fourier map (H-atoms of the disordered guest were not included). At convergence, the peaks and troughs of the difference density map did not exceed 0.31 and −0.32 e·Å^{-3}.

For structure II, data were collected to $2\theta_{max} = 50°$, using Mo Kα radiation ($\lambda = 0.7107$ Å). Crystal data are $C_{31}H_{30}O_4 \cdot C_9H_{12}O_2$, formula weight 618.77, space group orthorhombic $P2_12_12_1$, $a = 9.737$ (1), $b = 15.347$ (2), and $c = 22.426$ (2) Å, $V = 3351.2$ Å^3, $Z = 4$, $D_{calc} = 1.226$ g·cm^{-3}. The refinement converged smoothly at $R = 0.055$, $wR = 0.055$ for 1797 observations above the threshold of $3\sigma(I)$ (out of 2862 unique data above zero). At convergence, the peaks and troughs of the difference density map did not exceed 0.24 and −0.22 e·Å^{-3}, respectively. All hydrogen atoms attached to carbon were introduced in calculated positions, the methyl substituents being treated as rigid groups. Approximate positions of the hydroxy H-atoms were found directly in difference-Fourier maps.

The X-ray data (atomic coordinates, temperature factors, bond lengths and bond angles) have been deposited in the supplementary material.

Results and Discussion

The results of the optical resolution experiments, involving crystalline complexations between the optically active host compounds (**1**–**3**) and bicyclic ketone derivatives (**4**–**12**) are summarized in Table I. Hosts show varying degrees of specificity in the complexation. Thus, from the above guest variety, **3** forms an inclusion complex only with **11**. Less specific are hosts **1** and **2**, as successful interactions occurred in some host–guest combinations but not in the others. No special relationships emerge from experimental resolution data between the formation of host–guest compounds, the efficiency of the resolution, and the detailed structure of the guest constituents. For example, host **1** includes **9** enantioselectively, but does not complex with either **8** or **10**, which have a similar structure. Further, host **2** is very effective in resolving *rac*-**10**, but it exhibits only a marginal resolution capability toward **8**. These observations suggest that fine structural details play, among other factors, an important role in enhancing selectivity in the inclusion complexation.

Table I. Yields and Optical Purities of the Enantiomers Resolved by Complexation with Optically Active Host Compounds 1, 2, and 3

	host 1		host 2		host 3	
ketone	yield (%)	% ee	yield (%)	% ee	yield (%)	% ee
4	91	0.5	89	8.1	–	–[a]
5	33	59	–	–	–	–
6	16	100	–	–	–	–
7	60	100	–	–	–	–
8	–	–	90	5	–	–
9	41	100	–	–	–	–
10	–	–	56	100	–	–
11	92	6.9	83	1.9	31	100
12	–	–	48	100	–	–

[a] No complexation occurred.

It is valuable, therefore, to clarify the relationships between efficiency of the resolution and the structures of host and guest from the viewpoint of interest in basic features of molecular recognition in these compounds and their significance to optical resolution. In this context, the crystal structures of two inclusion complexes of **1** with (−)-**6** and of **2** with (−)-**12** have been analyzed.

The uniquely beautiful crystal structure of **1**·(−)-**6** is illustrated in Figure 2. It can be best described as consisting of continuous chains of hydrogen-bonded species which are aligned in an alternating manner parallel to the (1, 1, 0) and (1, −1, 0) lattice planes of the crystal. Chains related by the fourfold screw axis stack along *c*; those centered at $z = 0$ and 0.5 point in the $\mathbf{a} + \mathbf{b}$ and $-\mathbf{a} - \mathbf{b}$ directions of the crystal, while those at $z = 0.25$ and 0.75 are directed along $\mathbf{a} - \mathbf{b}$ and $-\mathbf{a} + \mathbf{b}$, respectively. Along

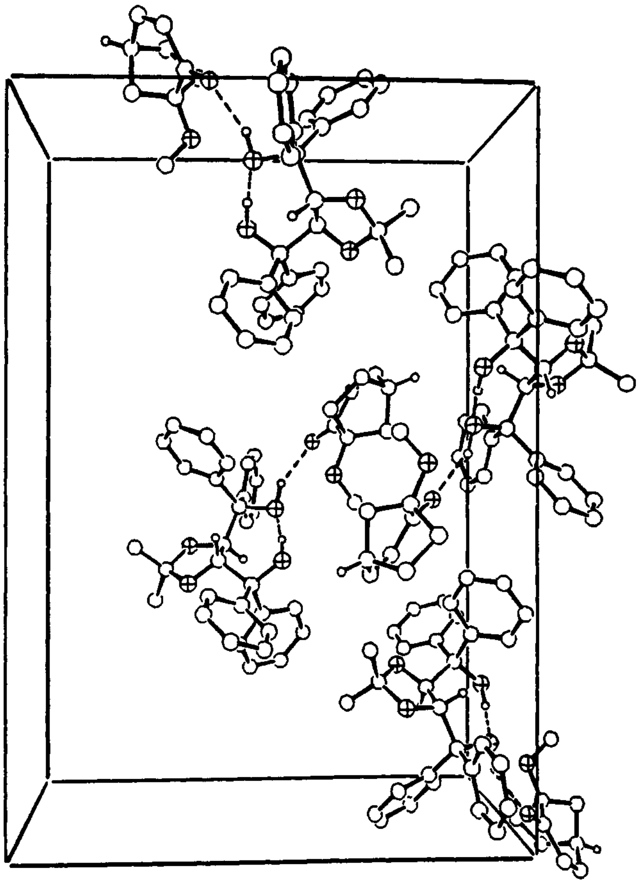

Figure 3. Packing diagram of structure II, viewed down the *a* axis (*c* is vertical). The localized H-bonding interactions between host and guest are indicated. For clarity, only selected H-atoms are shown. The O-atoms are represented by crossed circles.

the chain, every guest component is enclosed between, and H-bonded through its carbonyl groups to, two neighboring host molecules displaced by **a** + **b** or **a** − **b** [at OH···O = 2.75 (1) Å, O–H···O = 165°]. Correspondingly, each one of the hosts donates its two hydroxyl protons to different guests located in adjacent sites along the chain. Enclosure of the guest moiety is completed by two chlorophenyl groups approaching complementarily from opposite directions. The shortest Cl···C(guest) distance is 3.45 (2) Å, indicating a rather tight packing. The parallel chains at the different *z*-coordinate levels of the unit cell are displaced one with respect to the other in such a way that every guest site becomes surrounded by host molecules from above and below as well (Figure 2). The cage thus formed by four hosts provides a well-defined chiral environment around the guest constituent. The structural data reveal the important role played by the PhCl substituents in asymmetrically shaping the guest cavity.

It appears that due to its particular shape, consisting of thick ends and a thin center, and its rigidity, host **1** can also complex selectively enantiomeric guests that contain only one H-bonding function (e.g., **7** and **9**). In fact, **1** was found to be an effective resolving agent in many different applications.[11] Similar phenomena, where the mode of intermolecular arrangement in host–guest crystals is determined primarily by the shape of the bulkier component, have previously been observed in inclusion complexations with likely shaped host systems.[12]

Figure 3 illustrates the packing arrangement in the crystals of **2**·(−)-**12**. Here the structure consists of locally hydrogen-bonded (1:1) entities of host-to-guest at an OH···O distance of 2.871 (8) Å (O–H···O = 155°). In this structure the guest species are located one on top of the other in channel-type cavities formed between the hosts, which extend along the *a* axis of the crystal. The asymmetric environment around each guest is thus provided not only by the surrounding hosts but also by the neighboring guests displaced in both directions along these "channels". Undoubtedly, bulkiness of the included guest has a significant effect on the formation and stability of crystalline complexes of this type.[12,13]

The detailed structural features of **2** have been discussed in an earlier publication.[14] This host is conformationally rigid with the two hydroxyl groups located on the same side of the molecular framework and H-bonding to one another. The remaining surface of the molecule consists mainly of C–H bonds and is hydrophobic. Correspondingly, the hosts cluster in pairs or form bilayered arrangements, having their nonpolar surfaces turned inward in such cluster. Interaction with guest species may thus readily take place at the exposed polar sites between adjacent bilayers. In some respects the structural properties of **2** are similar to those exhibited by the naturally occurring alkaloids (e.g., brucine and strychnine).[15] Crystal structures of complexes with the latter reveal only a small number of characteristic layered or bilayered packing modes of the hosts. The possible packing arrangements are, therefore, restricted by the particular molecular shape, which makes the alkaloids effective as resolving agents of optically active guests by crystalline inclusion.

The high selectivity of **3** toward **11** is consistent with previous observations on the inclusion behavior of this host with other guests.[16] It has been shown that **3** complexes preferentially with guest molecules containing two hydrogen-bonding functions which are located on opposite sides of the molecular framework. Consistently, structural studies of some of these compounds revealed a common pattern of continuous –host–guest–host–guest– association in the solid phase. From among the present ketone derivatives only **6** and **11** are characterized by similarly suitable features. Efforts are currently being made to widen the scope of the above-described applications of optical resultion, as well as to improve the structural interpretations by comparable crystallographic studies of diastereoisomeric pairs of the inclusion complexes.

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Registry No. **1**, 86436-20-6; **1·6** (1:1), 136954-30-8; (*R*,*R*)-**2**, 93379-49-8; (*R*,*R*)-**2·12** (1:1), 136984-69-5; **3**, 95033-74-2; **4**, 16620-79-4; **5**, 105500-35-4; **6**, 14224-63-6; **7**, 123930-74-5; **8**, 136954-28-4; **9**, 136954-29-5; **10**, 124948-47-6; **11**, 76478-52-9; **12**, 124948-48-7.

Supplementary Material Available: X-ray data for the 1:1 inclusion complexes **1**·(−)-**6** and **2**·(−)-**12** (8 pages). Ordering information is given on any current masthead page.

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