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Optical resolution of medium-size lactones by inclusion crystallization with optically active host compounds: remarkable odd–even effects on the chiral recognition

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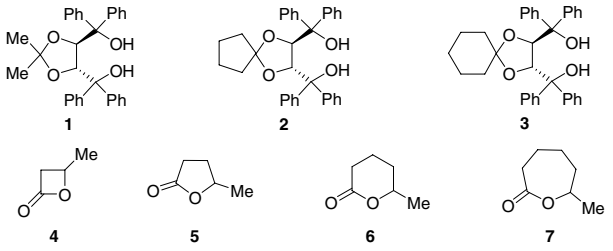
Abstract—Molecular recognition of medium-size lactones by inclusion complexation with optically active hosts derived from tartaric acid is described. Odd–even effects on the chiral recognition were observed in the enantioselective inclusion with the optically active host compounds in the solid state.

1. Introduction

Optically active lactones are present in a wide variety of natural products (e.g., fragrances, attractants and pheromones) isolated from insects, plants, fungi and marine organisms.[1] In addition, they are useful building blocks for the synthesis of biologically active substances, such as antitumour and antiviral agents,[2] and for the preparation of optically active biodegradable polymers.[3] Herein, we report a simple optical resolution of medium-size lactones **4**–**7** by inclusion crystallization with the optically active host compounds **1**–**3** derived from tartaric acid.[4]



2. Results and discussion

We first examined the inclusion properties of optically active host compounds **1**–**3** with lactones **4**–**7**. The host–guest ratios and the guest release temperatures of the inclusion crystals are summarized in Table 1. Host compounds **1**–**3** included several lactones **4**–**7** to form stable inclusion complexes in stoichiometric host–guest ratios, ranging from 3:1 to 1:1, except in the case of host **1** and lactone **7**, which did not produce an inclusion complex. We then examined the optical resolution of lactones **4**–**7** with (*R*,*R*)-(−)-**1**, (*R*,*R*)-(−)-**2** and (*R*,*R*)-(−)-**3**, respectively. A solution of (*R*,*R*)-(−)-**2** (14.8 g, 30.0 mmol) and (±)-**4** (5.2 g, 60.0 mmol) in ether–hexane (1:2, 18 ml) was kept at room temperature for 12 h, during which time crystals formed. Four recrystallizations of the crystals from ether–hexane gave the 1:1 inclusion complex of (*R*,*R*)-(−)-**2** and (*S*)-(−)-**4** as colourless prisms (3.6 g), which upon heating at 170 °C in vacuo afforded (*S*)-(−)-**4** in 99% ee (0.49 g, 19% yield). The enantiomeric excess was determined using a Chiralcel OA (HPLC column). The opposite enantiomer, (*R*)-(+)-**4**, was obtained in 99% ee in 14% yield by an inclusion complexation with (*S*,*S*)-(+)-**2** as the host compound instead of (*R*,*R*)-(−)-**2**. Using a similar procedure, the optical resolutions of the lactones **5**–**7** were carried out and the results are summarized in Table 2. Lactones **4** and **6** were resolved most efficiently with host compound **2**, while lactones **5** and **7** were resolved only moderately with the same host.

Interestingly, a remarkable 'odd–even' effect on the enantioselectivity in the inclusion complexation was observed. For example, the host (*R*,*R*)-(−)-**2** included the

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Table 1. Host–guest ratios and guest release temperatures of inclusion crystals of the optically active hosts **1**–**3** with lactones **4**–**7**

No.	Host	Lactones	H:G ratios[a]	Release temp (°C)[a]
1a	**1**	**4**	2:1	79
1b	**1**	**5**	2:1	77
1c	**1**	**6**	1:1	95
1d	**1**	**7**	No inclusion	—
2a	**2**	**4**	1:1	97
2b	**2**	**5**	1:1	94
2c	**2**	**6**	1:1	101
2d	**2**	**7**	2:1	120
3a	**3**	**4**	1:1	96
3b	**3**	**5**	3:2	104
3c	**3**	**6**	1:1	123
3d	**3**	**7**	3:1	132

[a] Determined by TGA.

(*S*)-(−)-enantiomer of the four-membered ring lactone **4** and the six-membered ring lactone **6**, whereas (*R*,*R*)-(−)-**2** included the (*R*)-(−)-enantiomer of five-membered ring lactone **5** and seven-membered ring lactone **7**. As far as we are able to determine, this is the first example of an odd–even effect on the enantioselectivity.

2.1. X-ray analyses

The crystal structures of several selected inclusion compounds were determined in order to confirm the corresponding chiral selectivities reported above. These include the compounds numbered **1b** and **1c**, illustrating the odd–even enantioselective effect for host **1** with two guests, and the series **2a**, **2b** and **2c**, illustrating the same phenomenon for host **2** and three different guests. In all cases, the known chirality of the host used for the preparation of a given complex enabled the unequivocal assignment of the chirality of the included guest. The reliance on the Flack parameter (often not definitive for structures containing only C, H, O and Mo K_α radiation for determination of absolute structure) was thus avoided. Tables 3 and 4 list crystallographic data for the five compounds described above.

Table 3. Crystallographic data for compounds **1b** and **1c**

	1b	**1c**
Formula	$2(C_{31}H_{30}O_4)\cdot C_5H_8O_2$	$C_{31}H_{30}O_4\cdot C_6H_{10}O_2$
Formula weight	1033.21	580.69
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$
a, Å	9.5875(1)	9.486(2)
b, Å	24.1902(3)	35.788(7)
c, Å	11.8234(2)	8.939(2)
α, °	90.0	90.0
β, °	99.807(1)	90.0
γ, °	90.0	90.0
Z	2	4
λ, Å	0.71073 (Mo K_α)	0.71073 (Mo K_α)
R_1	0.0381	0.0738
wR_2	0.0849	0.1792
Goodness of fit	1.038	1.139
Flack parameter	−0.3(5)	−1(2)

Figure 1 shows the asymmetric units of complexes **1b** and **1c**. The complex of **1b** comprises two molecules of host **1** and one molecule of lactone **5**, while that of **1c** contains one molecule of host **1** and a single molecule of lactone **6**.

In compound **1b**, a twofold disorder of the guest carbon atom at the asymmetric centre was observed, both components bearing the common methyl group, thus indicating the presence of both guest enantiomers in the crystal. The predominant one (site-occupancy 73%) corresponds to that shown with the (*S*)-configuration at the dominant asym-

Table 2. Absolute configurations, enantiomeric excesses and yields[a] of **4**–**7** obtained by complexation with the optically active hosts **1**–**3**

Guest	(*R*,*R*)-(−)-**1**	(*R*,*R*)-(−)-**2**	(*R*,*R*)-(−)-**3**
4	(*S*)-(−)-, 59% ee, 15% yield	(*S*)-(−)-, 99% ee, 19% yield	(*S*)-(−)-, 44% ee, 21% yield
5	(*S*)-(−)-, 38% ee, 22% yield	(*R*)-(+)-, 52% ee, 9% yield	(*R*)-(+)-, 11% ee, 26% yield
6	(*R*)-(+)-, 45% ee, 23% yield	(*S*)-(−)-, 80% ee, 19% yield	(*S*)-(−)-, 17% ee, 20% yield
7	No complexation	(*R*)-(+)-, 44% ee, 7% yield	(*R*)-(+)-, 11% ee, 27% yield

[a] Enantiomeric excess of the enantiomer obtained by four recrystallizations of the inclusion complex is shown.

Table 4. Crystallographic data for compounds **2a**–**c**

	2a	**2b**	**2c**
Formula	$C_{33}H_{32}O_4\cdot C_4H_6O_2$	$C_{33}H_{32}O_4\cdot C_5H_8O_2$	$C_{33}H_{32}O_4\cdot C_6H_{10}O_2$
Formula weight	578.71	592.70	606.73
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a, Å	9.3289(2)	9.3199(1)	9.2103(2)
b, Å	12.3371(2)	12.7212(2)	16.2752(3)
c, Å	26.0572(5)	26.3100(5)	21.4835(6)
Z	4	4	4
λ, Å	0.71073 (Mo K_α)	0.71073 (Mo K_α)	0.71073 (Mo K_α)
R_1	0.0447	0.0401	0.0407
wR_2	0.0804	0.0792	0.0794
Goodness of fit	1.032	1.009	0.972
Flack parameter	0.4(8)	1.4(8)	0.3(8)

metric centre (labelled * in Fig. 1). Careful examination of the guest tertiary H atom environments revealed that the preference for the (*S*)-enantiomer can be attributed to a favourable C*–H···π interaction that the corresponding tertiary H atom engages in with a host phenyl group (H···Cg 3.29 Å and C*–H···Cg 152°, Cg = ring centroid). In contrast, for the tertiary H atom corresponding to the (*R*)-enantiomer, which engages in an analogous interaction, the geometry is less favourable (H···Cg 3.35 Å, C–H···Cg 133°), indicating a weaker interaction. There is a continuous chain comprising four hydrogen bonds O–H···O that involve the four hydroxyl groups of the two independent host molecules and the carbonyl oxygen atom of the guest. The shortest of these H-bonds are the two intramolecular O–H···O bonds with distances O23···O1 2.655(2) Å and O58···O36 2.671(2) Å. The longest H-bond is that linking the host molecules [O23···O36 2.910(2) Å], while that between the host and guest has intermediate length [O1···O71 2.765(2) Å]. The resulting independent 2:1 hydrogen bonded unit is repeated by the 2_1-axis and by translation in the crystal.

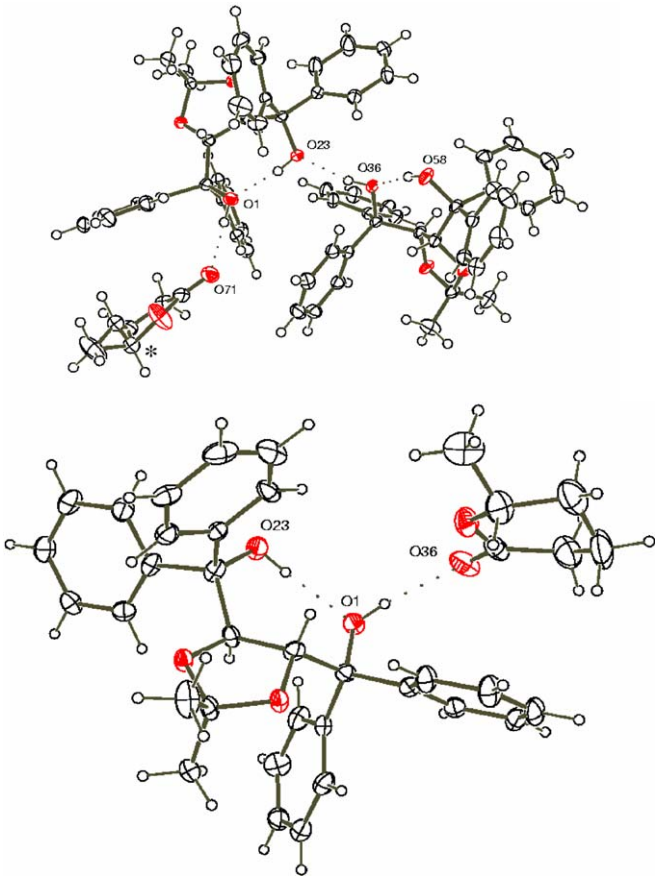

Figure 1. ORTEP diagrams showing the asymmetric units in compounds **1b** (top) and **1c** (bottom). Thermal ellipsoids are represented at the 50% level.

Compound **1c** on the other hand has 1:1 host–guest stoichiometry (Fig. 1) and no guest disorder was observed. In this case, the (*R*)-enantiomer is exclusively present in the crystal. As for the host in **1b**, there is intramolecular H-bonding between the hydroxyl groups, with O23···O1 2.747(6) Å, that is, somewhat longer than those observed in **1b**, owing to a small difference in host conformation. Host and guest are linked via the O1–H···O36 hydrogen bond of length 2.808(6) Å. The only other interactions stabilizing inclusion of the guest (*R*)-enantiomer are of the type C–H···π (host phenyl), one involving the guest tertiary H atom (H···Cg 3.20 Å) and the other involving a methylene H atom (H···Cg 3.07 Å). The crystal structure of **1c** is based on close packing of the 1:1 asymmetric units shown, with no H-bonding linking these units. Thus, the crystallographic results for **1b** and **1c**, confirming preferential inclusion by the host (*R*,*R*)-(−)-**1** of the (*S*)-enantiomer of the five-membered ring lactone **5** and the (*R*)-enantiomer of the six-membered ring lactone **6**, are in accord with those established analytically (Table 2), confirming the 'odd–even' effect on enantioselectivity.

X-ray analysis of compound **2a** revealed that the guest is disordered. Figure 2 shows the 1:1 host–guest asymmetric unit as well as details of the guest disorder.

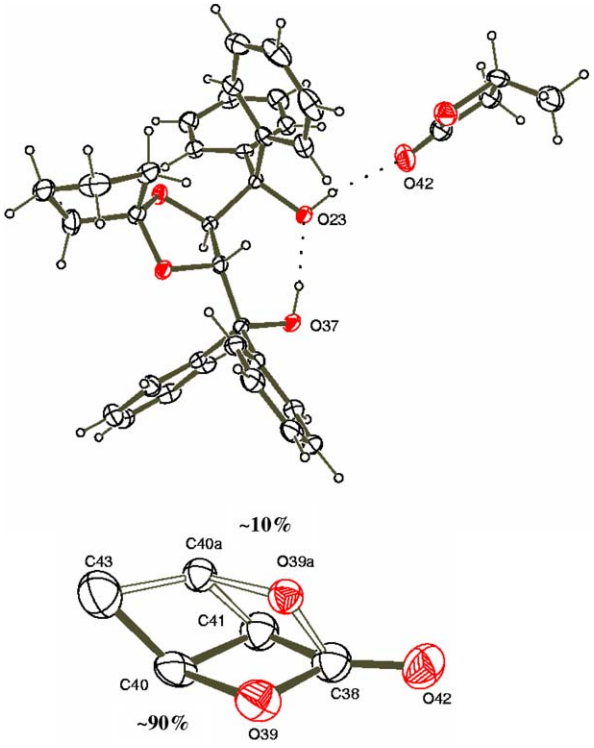

Figure 2. ORTEP diagrams showing the asymmetric unit in compound **2a** (top, major disordered guest component only) and details of the guest disorder (bottom, H atoms omitted for clarity).

Atoms C40 and O39 of lactone **4** occupy two sites each, such that both C40 and C40a are bonded to the common methyl carbon atom C43, corresponding to the major and minor enantiomeric populations of ~90% of (*S*)- and ~10% of (*R*)-4-methyloxetan-2-one. The guest tertiary H atom located at the stereogenic centre C40 [(*S*)-, with major occupancy, Fig. 2] engages in a stabilizing C–H···π interaction with a host phenyl ring (H···Cg 2.79 Å, C–H···Cg 142°). Instead, for the tertiary H atom corresponding to

the guest (*R*)-enantiomer, the shortest analogous interaction has much less favourable geometry (H···Cg 3.27 Å, C–H···Cg 113°). Hence, the preference for the (*S*)-enantiomer in this crystal can be rationalized. As found in host **1**, there is intramolecular H-bonding between the hydroxyl groups in host **2**, the distance O37···O23 being 2.662(2) Å, while the host–guest H-bond has O23···O42 2.819(2) Å. Analysis of the crystal structure shows that the asymmetric unit above forms a close-packed arrangement with only one weak C–H···O bond and van der Waals forces contributing to stabilization of the structure.

The other members in this series containing host **2**, whose X-ray structures were determined viz. **2b** and **2c**, also have 1:1 host–guest stoichiometries and their asymmetric units are shown in Figure 3. In the crystal of compound **2b**, the guest is ordered and its chirality is (*R*)-. The intramolecular hydrogen bond in host **2** has O1···O25 2.656(2) Å, while the host–guest hydrogen bond has O1···O38 2.757(2) Å. Analysis of the lactone ring conformation shows that it is an envelope form (flap at C42).

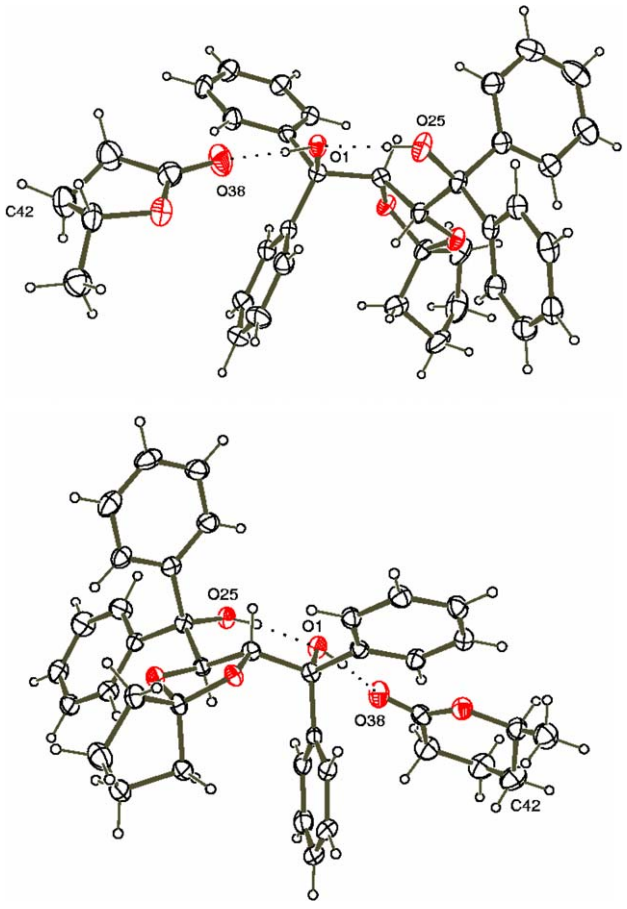

Figure 3. ORTEP diagrams showing the asymmetric units in compounds **2b** (top) and **2c** (bottom).

Lactone **6** in the crystal of compound **2c** exclusively occurs as the (*S*)-enantiomer. Atom C42 deviates significantly from the plane formed by the remaining five ring atoms. The H-bonding arrangement is analogous to the schemes found in **2a** and **2b**. Here, there is a short host–host intramolecular hydrogen bond (O1···O25 2.657(2) Å) but an almost equally strong host–guest hydrogen bond (O1···O38 2.687(2) Å).

Thus, also for the series **2a**, **2b** and **2c**, X-ray analyses confirmed the existence of the 'odd–even' effect with regards to the enantioselectivity of host **2**, in accordance with the results reported in Table 1. An interesting and highly relevant feature of this series of inclusion compounds is that the host arrays in crystals of **2a** and **2b** are isostructural, but they are not isostructural with that in **2c**. This is suggested by the unit cell parameters for these three compounds reported in Table 4 and was confirmed by detailed analysis of the packing arrangements shown in Figure 4.

As with the compounds described above, the types of host–guest interaction that mediate guest selectivities can be identified. Furthermore, the occurrence of host isostructurality in crystals of **2a** and **2b** is fortuitous, providing further clues as to the factors responsible for the inclusion of lactones **4** and **5** with opposite chiralities in essentially the same environments. It is clear from Figure 4 that the host frameworks are virtually identical in **2a** and **2b**, and that the guest molecules are located in analogous layers parallel to (0 0 1). For comparison, the structure of **2c** is drawn viewed down the *a*-axis, whose length is very similar to the *a*-axis lengths in the isostructural pair. The mode of the guest inclusion in **2c** clearly differs from that in **2a** and **2b**.

A detailed view of the inclusion of the guests in compounds **2a** and **2b** is shown as a stereoview in Figure 5, where fragments of surrounding hosts and the guest molecules are superimposed for comparison. Isostructurality of the host framework is evident. A comparison of the dispositions of the guest molecules shows that their carbonyl oxygen atoms occupy similar positions, each being hydrogen bonded to the corresponding host hydroxyl groups. Their molecular planes are rotated by ~45°, but their methyl C atoms practically overlap and the tertiary H atoms at the chiral centres point in opposite directions. In addition to the host–guest hydrogen bonds shown, for guest **4** there is one C–H···O hydrogen bond involving the ring O atom [H(phenyl)···O = 2.62 Å], and three CH···π interactions, two involving the guest methylene H atoms (with H_A···Cg 2.88 and H_B···Cg 3.22 Å, Cg = ring centroid), and one involving the tertiary H atom (H···Cg 2.78 Å). For guest **5**, there is an analogous C–H···O hydrogen bond with H(phenyl)···O = 2.56 Å, and two CH···π interactions involving the guest methylene H atoms (with H_A···Cg 2.61, H_B···Cg 2.84 Å). However, the tertiary H atom of guest **5** does not engage in any significant CH···π interaction. Thus, as regards the stereoselectivities manifested in **2a** and **2b**, anchoring of both guest molecules by common, strong host–guest O–H···O hydrogen bonding and accommodation of their sterically bulky methyl groups in common host environments appear to be the main factors that determine their modes of inclusion. The precise orientations of the guest molecules are dictated by the subtle secondary interactions described above. Evidently, the

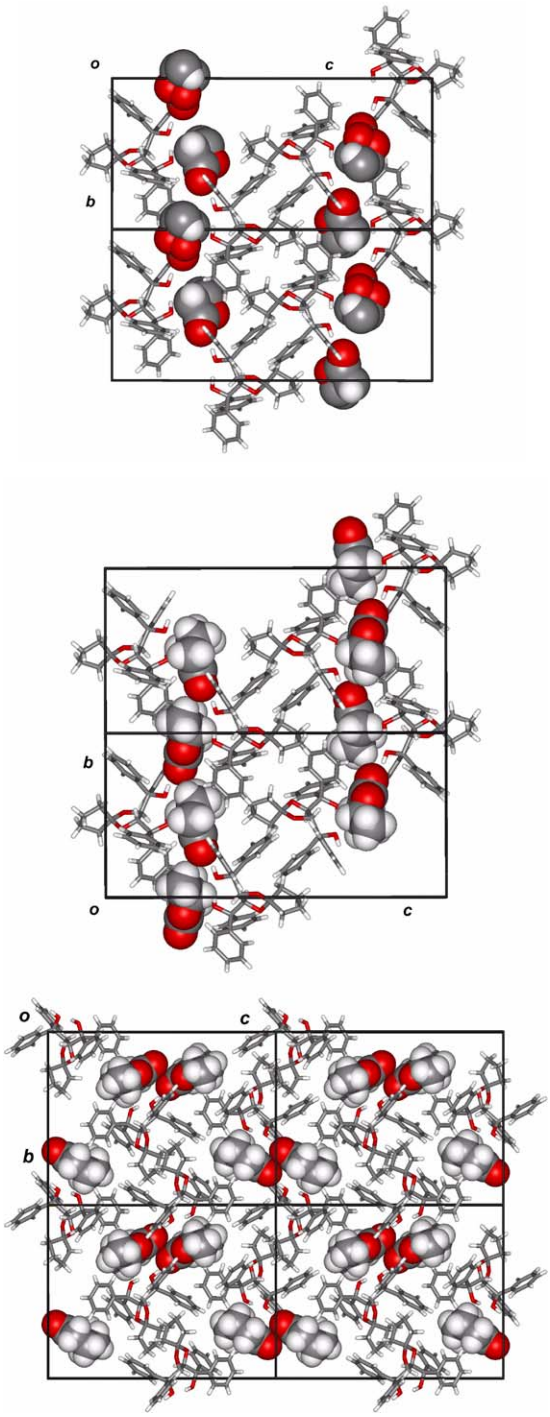

Figure 4. (1 0 0) projections of the crystal structures of **2a** (top), **2b** (centre) and **2c** (bottom). Two unit cells are shown for **2a** and **2b**, and four unit cells for **2c**. Host molecules are in stick representation and the guests are drawn in space-filling mode.

common host structure found in **2a** and **2b** is no longer able to accommodate the larger guest lactone **6**, so that compound **2c**, containing the latter guest, crystallizes in a different arrangement. Examination of host–guest interactions in that structure revealed only one host phenyl(C–H)···O(guest ring) hydrogen bond interaction in addition to the strong O–H···O hydrogen bond.

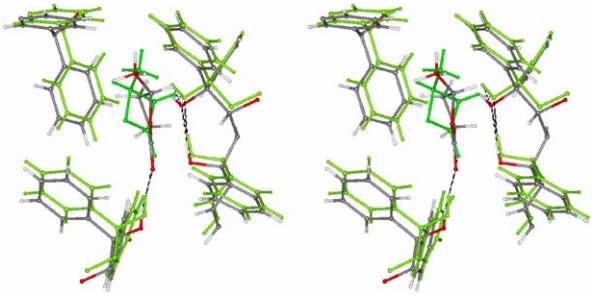

Figure 5. Stereoview showing the superposition of common fragments of the host molecules that surround complete guest molecules in **2a** (green, major component with s.o.f. ~90%) and **2b** (standard colours). Hydrogen bonding (O–H···O) is indicated by dashed lines.

3. Conclusions

Inclusion experiments with the host molecules **1**–**3** revealed a remarkable 'odd–even' effect with medium-size lactone guest molecules. In the absence of comprehensive X-ray structural data, it was not possible to explain all of the observed selectivities. However, a subset of these compounds **1b**–**c** and **2a**–**c** has been analyzed by X-ray diffraction and the results (a) confirm the selectivities determined by HPLC/polarimetry and (b) reveal host–guest interactions that can be used as a basis for explaining the selectivities in specific instances. Thus, in cases where less-than-perfect enantioselectivities occur for the crystals selected and analyzed (compounds **1b** and **2a**), both enantiomers of a given guest were located in the inclusion crystal meaning it was possible to identify specific host–guest interactions that account for the preferential inclusion of the predominant enantiomer. The occurrence of host isostructurality in the case of compounds **2a** and **2b**, on the other hand, provided a rare opportunity to identify the interactions that enable guest molecules differing only by a methylene group and having opposite chirality, to occupy a void with common topology in their inclusion crystals. In addition to the strong, ubiquitous host–guest O–H···O hydrogen bonds, other interactions that mediate the enantioselectivity in these series of compounds are generally weak (e.g., of type C–H···O, C–H···π), but do play a decisive role.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on JEOL JNM-GSX 400 spectrometer, with tetramethylsilane (TMS) as the internal standard. The optical rotations were measured with a ATAGAO AP-100 polarimeter. HPLC data were obtained on JASCO PU-980, UV-970 system. Thermogravimetric analyses (TGA) were performed on a Rigaku TG-8120 instrument.

4.2. General procedure for the optical resolution by inclusion crystallization

The optical resolution of lactones (**4**–**7**) was carried out as follows: a mixture of the lactone and the host compound

was dissolved with heating in ether–hexane solution. When this solution was kept at room temperature for 12 h, inclusion crystals of lactones **4**–**7** and optically active hosts **1**–**3** with the host–guest ratios listed in Table 1 were formed. The host–guest ratios were determined by ^{1}H NMR spectra. The purification of each complex was achieved by four recrystallizations from ether–hexane solution. The optically active lactones **4**–**7** with the enantiomeric excesses listed in Table 2 were isolated by heating the inclusion crystals in vacuo. The enantiomeric excesses of lactones **4** and **5** were determined by HPLC using Chiralcel OA and Chiralpak AS (Daicel Chemical Industries, Ltd.), respectively. The enantiomeric excesses of lactones **6**[5] and **7**[6] were determined by comparison with their reported $[\alpha]_D$ values.

Typical procedure for the optical resolution of (±)-**4** *with* (*R*,*R*)-(−)-**2**. When a solution of (*R*,*R*)-(−)-**2** (14.8 g, 30.0 mmol) and (±)-**4** (5.2 g, 60.0 mmol) in ether–hexane (1:2, 18 ml) was kept at room temperature for 12 h, a 1:1 inclusion complex of (*R*,*R*)-(−)-**2** and (*S*)-(−)-**4** of 40% ee (17.2 g) was obtained. Four recrystallizations of the crystals from ether–hexane (1:2) gave the pure 1:1 inclusion complex of (*R*,*R*)-(−)-**2** and (*S*)-(−)-**4** as colourless prisms (3.6 g), which upon heating at 170 °C in vacuo afforded (*S*)-(−)-**4** of 99% ee (0.49 g, 19% yield). The enantiomeric excess was determined by HPLC analysis with Chiralcel OA (Daicel Chemical Industries, Ltd.); eluent, hexane–2-propanol = 90:10; flow rate, 1.0 ml/min; detection, UV 220 nm; retention time, 18 [(*S*)-enantiomer] and 24 [(*R*)-enantiomer] min. The absolute configuration of **4** was determined by X-ray analysis.

Optical resolutions of other cases were carried out by the same procedures. The enantiomeric excess of **5** was determined by HPLC analysis with Chiralpak AS (Daicel Chemical Industries, Ltd.); eluent, hexane–2-propanol = 90:10; flow rate, 1.0 ml/min; detection, UV 220 nm; retention time, 15 (*S*-enantiomer) and 16 (*R*-enantiomer) min. The absolute configuration of **5** was determined by X-ray analysis. The enantiomeric excesses and absolute configurations of **6**[5] and **7**[6] were determined by comparison of their $[\alpha]_D$ values and specific rotation signs, respectively, with those reported.

4.3. X-ray diffraction

All crystal intensity data were collected on a Nonius Kappa CCD diffractometer using Mo K_α radiation and appropriate ϕ- and ω-scans. Crystals were coated in Paratone N oil (Exxon) and cooled in a stream of nitrogen vapour at the selected temperature. Unit cell dimensions before and after cooling were comparable, indicating that no phase changes occurred on altering the crystal temperature. The data-collection strategy indicated by the program COLLECT[7] involved suitable combinations of ϕ- and ω-scans. The program DENZO-SMN[8] was used for cell refinement and data reduction. Intensity statistics indicated non-centric space groups in all cases. The structures were solved by direct methods using the program SHELXS86[9] and refined by full-matrix least-squares against F^2 using the program SHELX-97.[10] Molecular parameters were calculated with PLATON.[11] The programs ORTEP[12] and WebLab ViewerPro 3.7[13] were used for illustrations. The CIF files for the structures have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 60444–60448).

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