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Helix-forming self-assembly of enantiopure 2,2′-dimethylbiphenyl-6,6′-dipropiolic acid and amide organized by hydrogen bonds

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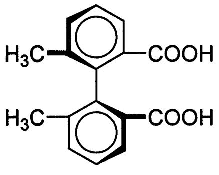
Abstract—Single-crystal X-ray diffraction revealed that the molecules of both the title compounds (*S*)-**5** and (*S*)-**6** are linked, via double hydrogen bonds, in infinite chains which follow the crystallographic symmetry of the three- and four-fold screw axis, respectively. To our knowledge this represents the first documented case when intermolecular carboxylic hydrogen bond constitutes an integral part of a helix backbone set up from repeating homochiral subunits. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Recently, we have found[1] that enantiopure 2,2′-dimethylbiphenyl-6,6′-dicarboxylic acid **1** self-assembles in the form of hydrogen-bonded, chiral (D_4 symmetry) cyclotetramers (‘chiral squares’) in solution as well as in the solid phase (Fig. 1; only (*S*)-**1** is shown).

In the crystal, moreover, the cyclotetrameric species have been found to stack[†] into open columns, presenting in this way a simple model of a chiral microporous structure. Since the pores arising by self-assembly of the parent tecton **1** are impractically small,[‡] we have now investigated self-assembly of the homologous acetylenic diacid (*S*)-**5**. It was expected that the rigidity of its molecular framework may sustain the intended expansion of the micropores. Owing to the analogy in hydrogen bonding behavior which exists[3,4] between carboxylic acids and amides, we have also examined the corresponding acetylenic diamide (*S*)-**6**.


(*S*)-**1**

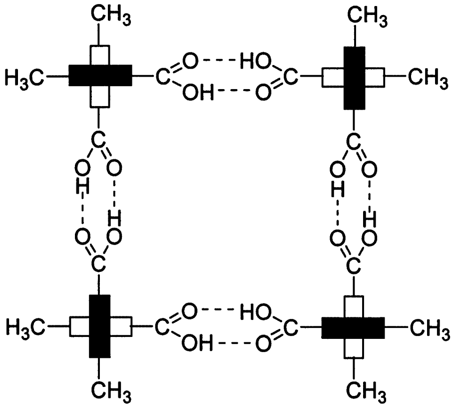


Figure 1. Formation of tetramers from (*S*)-**1**.

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[†] In the meantime, we have reported analogous stacking of a chiral cyclotrimer exhibiting D_3 symmetry which also gave rise to chiral micropores; cf. Ref. 2.

[‡] The van der Waals space inside the distorted cyclotetramer of **1** is approximately 6.8×1.8 Å; cf. Ref. 1.

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2. Results and discussion

2.1. Synthesis

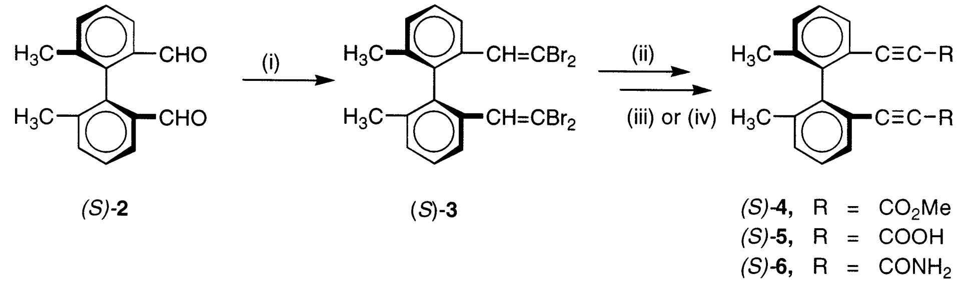
The starting dialdehyde **2** ((*RS*)- as well as (*S*)-form[5]) on treatment with tetrabromomethane and triphenylphosphine was transformed into the bis(dibromoethenyl) derivative **3** which on exhaustive dehydrohalogenation with butyllithium, followed by carbomethoxylation of the resulting carbanion and subsequent alkaline hydrolysis afforded the target diacid **5**. Ammonolysis of the intermediary diester **4** afforded smoothly the corresponding diamide **5** (Scheme 1; only synthesis of the (*S*)-enantiomer of **5** is shown).

2.2. Molecular structure and hydrogen bonding in crystals of (*S*)-5 and (*S*)-6

At first glance, the molecular structure of the enantiopure acetylenic diacid (*S*)-**5** is similar to that of the homochiral parent[1] compound (*S*)-**1**.

The molecule of (*S*)-**5** (Fig. 2a) is composed of two halves related by the crystallographic C_2 axis passing through the midpoint of the $C(1)–C(1^{i})(-x, y-x, 1/3-z)$ bond. The aromatic ring is planar within ±0.010(3) Å and the largest deviation of the pivot atoms of the substituents from this plane is 0.069(4) Å for $C(1^{i})$. The triple bond is slightly bent with the bond angles of 171.1(1) and 175.8(1)° and a torsion angle of −12(1)°. Notably, the dihedral angle of the aromatic ring planes, which is 66.02(5)° for (*S*)-**5**, is markedly smaller than the values of 80° found earlier[1,6] for (*S*)- and (*RS*)-**1**.

In contrast to the molecular structure, the crystal packing of the acetylenic diacid (*S*)-**5** is totally different from that of the homochiral parent diacid (*S*)-**1**. The carboxyl group of (*S*)-**5** is joined to its counterpart at *y*, *x*, −*z* through the familiar, albeit remarkably distorted, double hydrogen bond. However, by means of this intermolecular hydrogen bond, the molecules are not assembled into squares (as in (*S*)-**1**; Fig. 1), but are



Scheme 1. (i) CBr_4, CH_2Cl_2, 0°C, 1 h; (ii) BuLi, THF, −70°C to 0°C, 1 h, then $ClCO_2Me$, rt, 30 min; (iii) NaOH, H_2O, rt, 3 h; (iv) NH_3/MeOH, rt, 3 h.

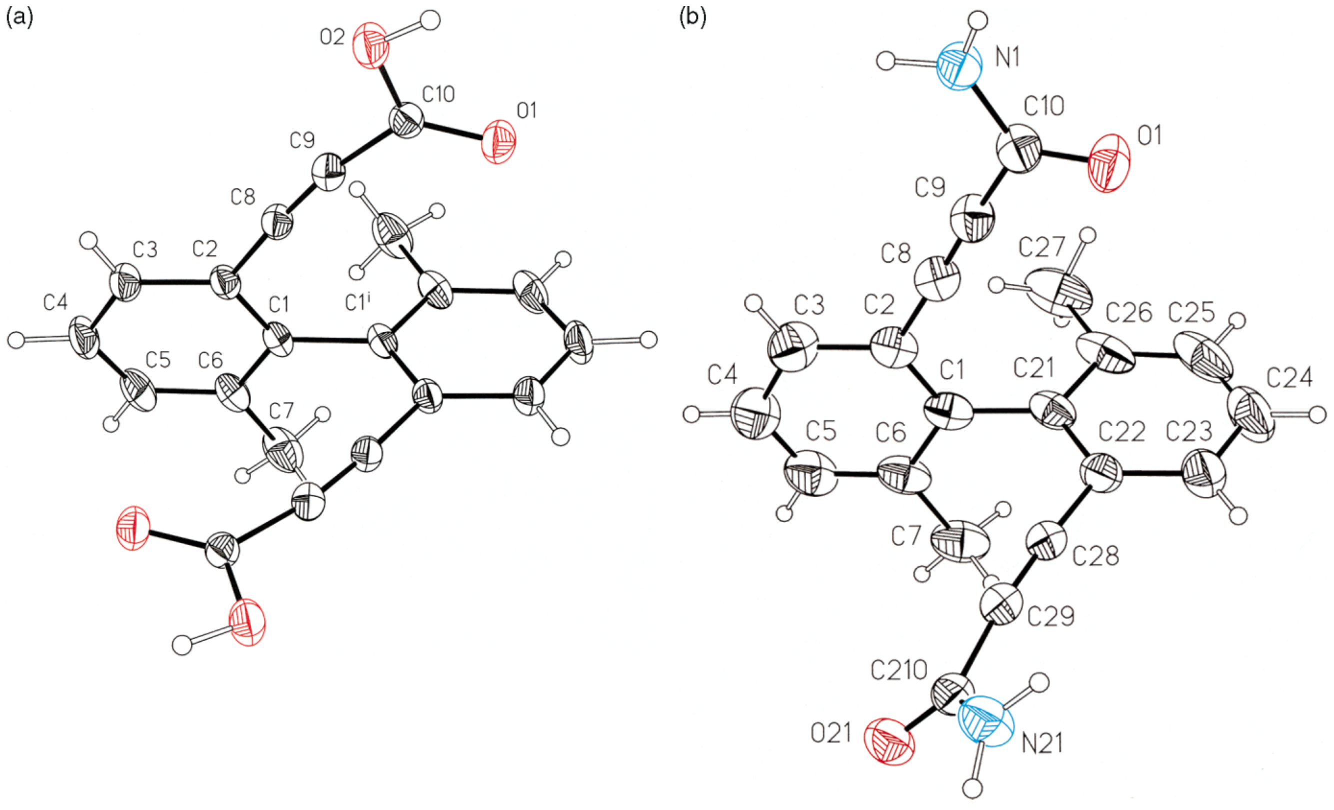


Figure 2. View of the molecule of (a) (*S*)-**5** and (b) (*S*)-**6** (ORTEP, 30% probability ellipsoids).

linked in a chain which follows the crystallographic symmetry of the three-fold screw axis propagating along the *c*-direction (Fig. 3a). To our best knowledge, this represents *the first documented case when carboxylic hydrogen bond between repeating homochiral subunits constitutes an integral part of a helix backbone.*[§]

The trigonal motif of the helix is presumably related to the unusually high mutual inclination of aromatic rings and to the torsional distortion of the hydrogen bridge (the dihedral angle of the least-squares COOH planes is 48.2(3)°, while the atoms of the carboxyl group remain coplanar within ±0.04 Å).

The individual helix chains partly interpenetrate one another from the sides of their peripheral methyl groups (Fig. 4a), but remain well separated at the van der Waals distances without any further interaction between the aromatic rings of the individual chains. As can be seen from the view along the helical axis, space remains inside the chain. The approximate diameter of the 'free' channel is 5.2 Å in terms of covalent radii and 2.8 Å in van der Waals ones. Whether suitable rod-shaped molecules might be capable of entering this chiral channel, at least under forcing conditions, remains a matter of speculation at this stage.

A complementary insight into this intriguing problem has been provided by the crystal packing of the corresponding acetylenic diamide[¶] (*S*)-**6**. In accord with expectation, the amide grouping of (*S*)-**6** has been found to be joined to its counterpart again through the double hydrogen bond. In contrast to the *three-fold screw axis* established for the dicarboxylic acid (*S*)-**5**, however, the intermolecular hydrogen bonds of the diamide (*S*)-**6** are linked to a chain which follows *a four-fold screw axis* propagating along the *c*-direction (Fig. 3b). Although the resulting tetragonal (square-like) helix chains also partly interpenetrate each other (Fig. 4b), similarly as in the case of the diacid (*S*)-**5**, there now remains more space inside the helices, as evidenced by the molecules of solvent (ethyl acetate) which entered these voids.

The solvent molecules do not exhibit any contact shorter than 3.2 Å in respect to the channel atoms. The guest molecules are severely disordered and occupy the voids with non-integral stoichiometry, thus precluding exact determination of the host–guest crystal structure. To obviate the unsurmountable problem, we have used the SQUEEZE procedure[9] which ignores, in an iterative manner, molecules of solvent in the refinement step. This routine, which was originally intended to treat structures of higher molecularity, allowed us to solve the host amide structure (Fig. 2b and Fig. 3b) with a reasonable precision ($R = 0.049$).

When the absolute configuration of the starting enantiopure molecules is known, the absolute configuration of the resulting supramolecular helix can be drawn

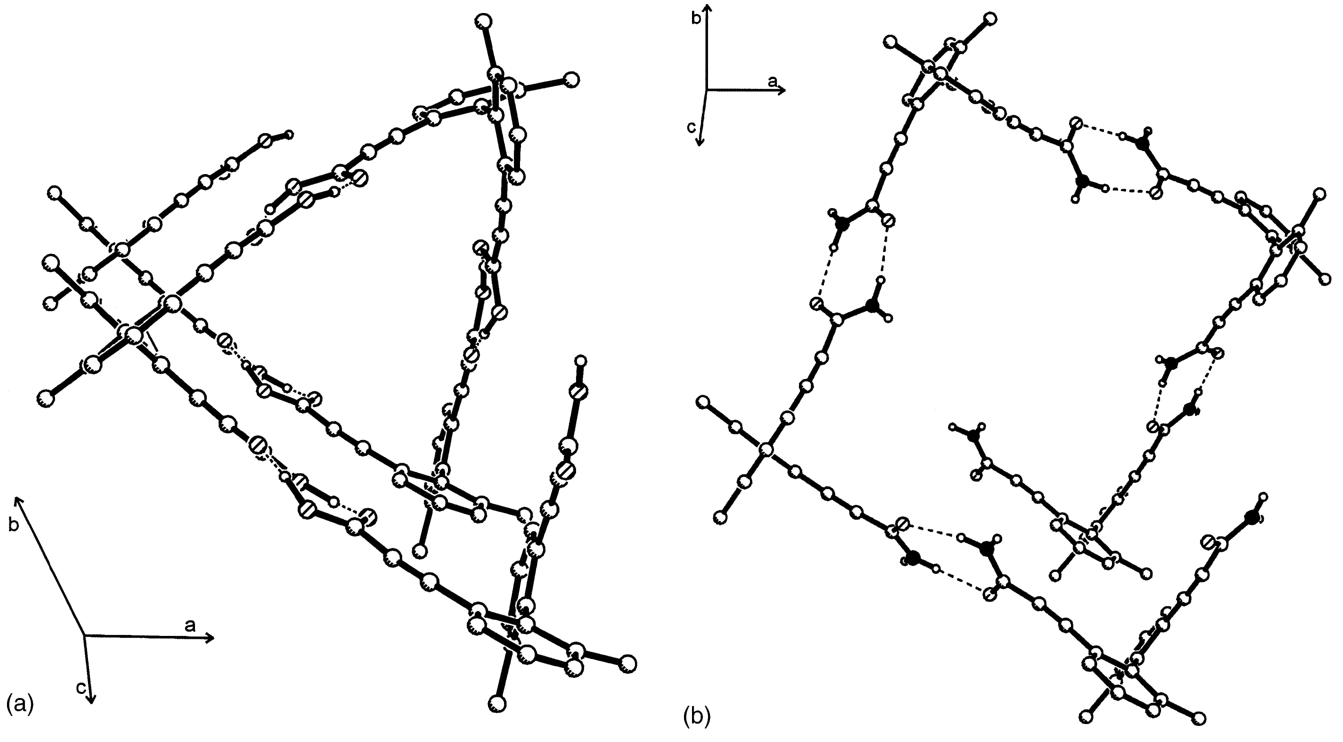


Figure 3. Helical segments arising in crystals of (a) (*S*)-**5** 'trigonal helix' and (b) (*S*)-**6** 'tetragonal helix'.

[§] As a rule, the helix backbone is formed *exclusively by covalent bonds*. Hydrogen bonding and other non-covalent forces usually contribute to helix formation only via their participation in secondary structure, the prominent examples being polypeptide, polysaccharide or nucleic acid chains. However, a solitary case when carboxylic hydrogen bond between repeating *achiral* subunits yielded a racemic set of helices is known (Ref. 7).

[¶] After the present study had been completed, a related case of a helical assembly was reported resulting from a combination of intra- and intermolecular amide hydrogen bonds (Ref. 8).

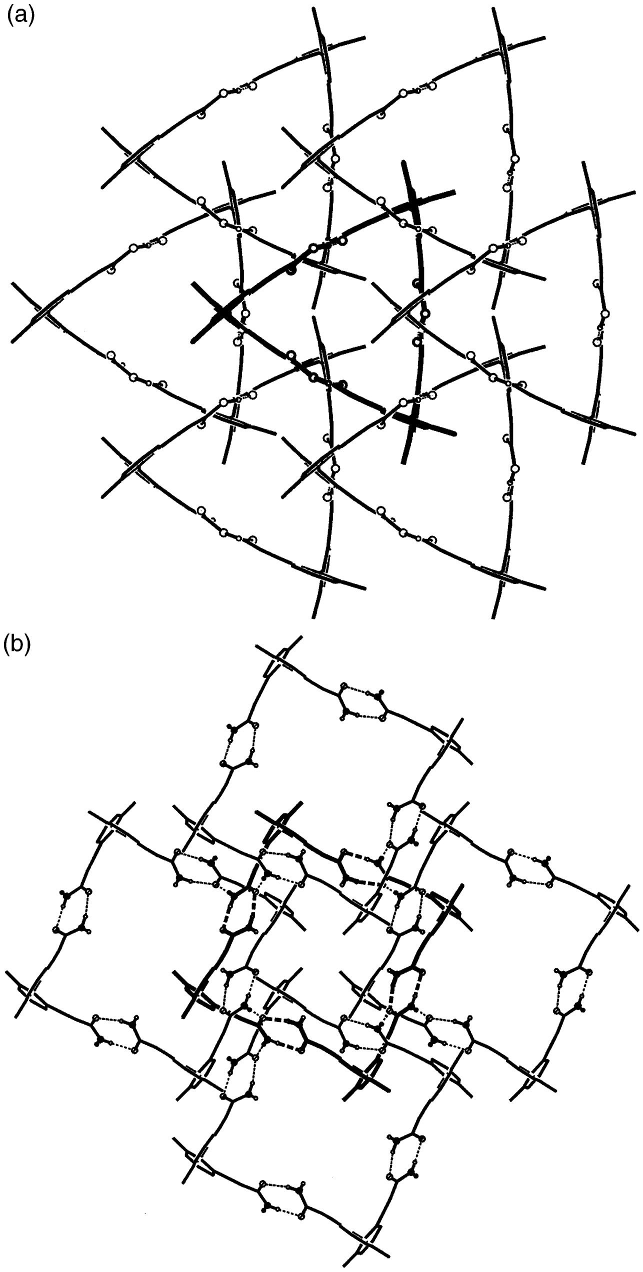


Figure 4. Packing of individual helices in crystals of (a) (*S*)-**5** and (b) (*S*)-**6**, as projected onto *ab* plane.

from the crystal structure; accordingly, the helices arising from (*S*)-**5** as well as (*S*)-**6** possess the (*P*)-configuration.

2.3. Crystal packing of the racemate (*RS*)-5

Helix formation is characteristic of homochiral molecules. Moreover, the observed self-assembling pattern of the racemate (*RS*)-**5** does not allow a direct comparison with the enantiopure (*S*)-**5**, since water molecules participate in the intermolecular hydrogen bonding. This gives rise to 2D layers which are two molecules thick and are arranged parallel to the crystallographic *ac* plane. Instead of being the usual double type, the hydrogen bonds are branched: three of them directly to other three carboxyl groups and one through the molecule of water to the fourth carboxyl (Fig. 5a). Another important intermolecular interaction in the racemate is π-stacking of the aromatic rings which holds the layers together (Fig. 5b).

There are two crystallographically independent stacking interactions of neighboring symmetry-related aromatic rings at the perpendicular distances between the coplanar rings of 3.223 and 2.892 Å, respectively, and with a mutual slippage of the rings by approximately a half of their diameter, indicating a strong π-interaction according to the usual criteria.[10]

3. Conclusion

Contrary to simple expectation, the extended acetylenic models (*S*)-**5** and (*S*)-**6** do not self-assemble to chiral

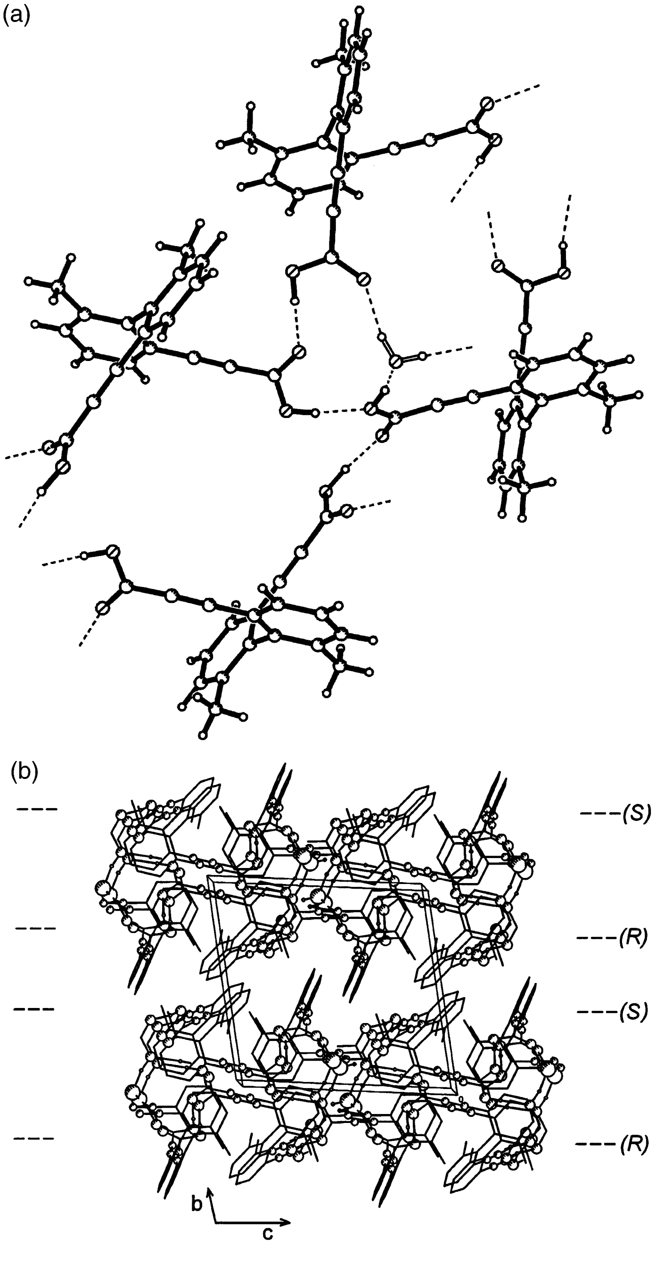


Figure 5. (a) Hydrogen bonding and (b) stacking of (*RS*)-**5**.

squares as the parent homochiral compound (*S*)-**1** does, but are linked, via intermolecular double hydrogen bonds, in infinite chains that follow the crystallographic symmetry of the three- and four-fold screw axis, respectively. The resulting helix chains interpenetrate one another, however, there remains space inside the chains which may give rise to free chiral channels. In this way, the crystallographic results suggest a novel approach to the design of chiral microporous structures.

4. Experimental

4.1. (*RS*)-2,2′-Bis(2,2-dibromoethenyl)-6,6′-dimethyl-1,1′-biphenyl (*RS*)-3

A solution of racemic aldehyde (*RS*)-**2** (2.4 g, 10 mmol) in dry dichloromethane (20 mL) was added at 0°C to a mixture of CBr_4 (13.1 g, 40 mmol) and triphenylphosphine (20.9 g, 80 mmol) in dry dichloromethane (40 mL). The mixture was stirred for 1 h at this temperature, then diluted with light petroleum (400 mL), the precipitate was filtered off, stirred with light petroleum and filtered again. The combined filtrates were concentrated in vacuo, the residue was triturated with light petroleum, and the insoluble material was removed by filtration. The filtrate was concentrated and the residue chromatographed on a 30×5 cm column of silica gel with light petroleum as eluent. The product fractions gave (*RS*)-**3** as an oil which slowly solidified (5.24 g, 95%); mp 58–59°C (ethanol at 0°C). ^1H NMR ($CDCl_3$) δ 7.3–7.6 (m, 6H); 6.8 (s, 2H); 1.9 (s, 6H). Anal. calcd for $C_{18}H_{14}Br_4$: C, 39.31; H, 2.57; Br, 58.12. Found C, 39.21; H, 2.48; Br 58.20%.

4.2. (*S*)-2,2′-Bis(2,2-dibromoethenyl)-6,6′-dimethyl-1,1′-biphenyl (*S*)-(+)-3

Prepared from dialdehyde[6] (*S*)-(−)-**2** in the same manner as (*RS*)-**3** in 95% yield; mp 33–35°C, $[\alpha]_D^{20}$ +65.1 (*c* 1.1, ethanol); enantiomerically pure according to chiral HPLC (cellulose triacetate, ethanol). NMR spectrum was identical with that of the racemate.

4.3. (*RS*)-2,2′-Bis(methoxycarbonylethynyl)-6,6′-dimethyl-1,1′-biphenyl (*RS*)-4

Tetrabromide (*RS*)-**3** (4.95 g; 9 mmol) in tetrahydrofuran (30 mL) was treated with *n*-butyl lithium in pentane (2 M, 36 mL, 72 mmol) at −70°C. After stirring for 1 h at 20°C the mixture was cooled again to −70°C and methyl chloroformate (3.4 g, 36 mmol) in tetrahydrofuran (15 mL) was rapidly added with stirring. After warming to room temperature the mixture was stirred for 30 min and then decomposed by careful addition of saturated aqueous ammonium chloride under cooling. Ether was added, the organic phase was washed several times with water, dried and taken down. The product was precipitated with light petroleum, collected and recrystallized from methanol, mp 114–116°C. Total yield, including an additional amount obtained from the mother liquors, was 1.6 g (51%). ^1H NMR ($CDCl_3$) δ 7.2–7.4 (m, 6H), 3.65 (s, 6H), 2.03 (s, 6H). IR: ν_{max} (cm^{-1}) 2215, 2235 (C≡C), 1713 (C=O), 1495, 1590, 1608 (arom.), 1209, 1298 (C-O). Anal. calcd for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found C, 76.23; H, 5.25%.

4.4. (*S*)-2,2′-Bis(methoxycarbonylethynyl)-6,6′-dimethyl-1,1′-biphenyl (*S*)-(+)-4

The ester was obtained from (*S*)-(+)-**3** (1.1 g) in a yield of 63%, in the same manner as the racemic compound. The product was purified by chromatography on silica gel in ether–light petroleum 1:3. Mp 88–91.5°C; $[\alpha]_D^{20}$ +185.4 (*c* 0.5, methanol). The NMR and IR spectra were identical with those of the racemic compound. Anal. calcd for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found C, 76.12; H, 5.40%.

4.5. (*RS*)-2,2′-Bis(carboxyethynyl)-6,6′-dimethyl-1,1′-biphenyl (*RS*)-5

To a solution of diester (*RS*)-**4** (1.05 g, 3 mmol) in methanol (10 mL) was added a solution of NaOH (1.2 g, 30 mmol) in water (6 mL) and the mixture was stirred at room temperature for 3 h. After evaporation to dryness, the residue was dissolved in water and acidified with dilute HCl. The product was taken up in ether and dried. Evaporation gave 920 mg (96%) of a solid which on pressure crystallization from ether (40°C) afforded crystals of (*RS*)-**5** (650 mg, 68%); mp 189–191°C. ^1H NMR ($CDCl_3$) δ 7.3–7.6 (m, 6H), 2.03 (s, 6H). Anal. calcd for $C_{20}H_{14}O_4$: C, 75.45; H, 4.43. Found C, 75.63; H, 4.48%.

4.6. (*S*)-2,2′-Bis(carboxyethynyl)-6,6′-dimethyl-1,1′-biphenyl (*S*)-(+)-5

Prepared in exactly the same manner as (*RS*)-**5** in a yield of 70%; $[\alpha]_D^{20}$ +148.8 (*c* 0.5, ethanol). ^1H NMR spectrum was identical with that of the racemic diacid.

4.7. (*RS*)-2,2′-Bis(carbamoylethynyl)-6,6′-dimethyl-1,1′-biphenyl (*RS*)-6

A solution of diester (*RS*)-**4** (100 mg, 0.29 mmol) in a saturated (0°C) methanolic solution of anhydrous ammonia (5 mL) was left aside for 3 h at room temperature. Evaporation in vacuo, followed by crystallization from methanol gave the diamide, (54 mg, 55%); mp 200–201°C.

^1H NMR (DMSO-d_6) δ 7.3–7.8 (m, 10H), 1.96 (s, 6H). IR (KBr), ν_{max} (cm^{-1}): 2205, 2220 (C≡C), 3437, 3280, 3143 (N-H), 1641 (amide I), 1606 (amide II). Anal. calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found C, 75.68; H, 5.16; N, 8.71%. MS(FAB): 317 (M+1).

4.8. (*S*)-2,2′-Bis(carbamoylethynyl)-6,6′-dimethyl-1,1′-biphenyl (*S*)-(−)-6

The optically active diamide (*S*)-(−)-**6** was prepared in the same manner and yield as (*RS*)-**6**. Mp 80–83°C (dec.) (ethyl acetate). $[\alpha]_D^{20}$ +153.5 (*c* 0.5, methanol). ^1H

NMR (DMSO-d_6) δ 7.3–7.8 (m, 10H), 1.96 (s, 6H)+ EtOAc: 4.02 (q), 2.00 (s), 1.17 (t). The signal intensities showed an approximate ratio (−)-**6**: EtOAc = 1.5:1.

4.9. Single-crystal X-ray diffraction analysis

4.9.1. (*RS*)-5. Single crystals were obtained by slow evaporation from ether–heptane solution. Crystal data: $C_{20}H_{14}O_4$, $M = 327.32$, triclinic, space group P (No. 2), $a = 11.1570(2)$, $b = 12.2790(3)$, $c = 13.4910(3)$ Å, $\alpha = 80.948(1)$, $\beta = 68.599(1)$, $\gamma = 89.788(1)°$, $V = 1696.46(6)$ Å^3, $F(000) = 684$, $D_c = 1.282$ g cm^{-3} for $Z = 4$. A colorless crystal of the dimensions 0.2×0.45×0.50 mm was measured on a Nonius Kappa CCD diffractometer with graphite monochromator (MoK_α radiation, $\lambda = 0.71070$ Å) at 150(2) K. A total of 31671 reflections were measured in the range $h = -14$ to 14, $k = -15$ to 15, $l = -15$ to 17, from which 8418 were unique ($R_{\text{int}} = 0.025$) and 5996 were regarded as observed according to the $I > 2\sigma(I)$ criterion. Absorption was neglected ($\mu = 0.091$ mm^{-3}). The structure was solved by direct methods and refined by full-matrix least squares based on F^2 (SHELXL-97).[11] The hydrogen atoms were refined isotropically. The refinement converged to $R = 0.0396$, $wR = 0.0908$, $GOF = 1.030$ for 563 parameters and 5996 observed reflections. Secondary extinction correction with the refined coefficient of 0.0155(16) was applied. The final difference map displayed no peaks of chemical significance.

4.9.2. (*S*)-5. Single crystals were obtained by slow evaporation from ether–heptane solution. Crystal data: $C_{20}H_{14}O_4$, $M = 318.34$, trigonal, space group $P3_12$ (No. 152), $a = 9.150(2)$, $c = 17.500(3)$ Å, $V = 1268.85(4)$ Å^3, $F(000) = 498$, $D_c = 1.250$ g cm^{-3} for $Z = 3$, $T = 150(2)$ K. Colorless crystal, 0.3×0.6×0.7 mm, total 22815 reflections, $h = -11$ to 11, $k = -5$ to 5, $l = -21$ to 21, 1673 were unique ($R_{\text{int}} = 0.027$), 1588 observed ($I > 2\sigma(I)$), $\mu = 0.087$ mm^{-3}, $R = 0.0318$, $wR = 0.0826$, $GOF = 1.129$ for 125 parameters and 1586 observed reflections. Other details as for (*RS*)-**5**.

4.9.3. (*S*)-6. Single crystals were obtained by slow diffusion of ether vapors into an ethyl acetate solution. Crystal data: $C_{20}H_{14}O_4 \cdot 0.6EtOAc$, tetragonal, space group $P4_1$ (No. 76), $a = 11.9810(3)$, $c = 16.1440(4)$ Å, $V = 2317.4(1)$ Å^3, total 34335 reflections measured at 190 K, 3998 ($R_{\text{int}} = 0.026$) used for structure solution and refinement. Routine procedures as above yielded the host structure without problems. The difference density map revealed regions of diffuse residual electron density which were attempted to be modeled as (disordered and partly occupied) ethyl acetate molecule. Despite extensive trials involving also fixation of the proposed ethyl acetate geometry, no chemically reasonable model could be found. At this stage, six most intense peaks of residual electron density were isotropically refined as carbon atoms of 0.5 fractional occupancy (according to their intensity) which resulted in an unsatisfactory value of $R = 0.092$. The procedure SQUEEZE was applied, followed by a standard least-squares refinement. This straightforwardly resulted in a reasonably precise solvent-free model which converged at $R = 0.049$. It is important that the total residual electron density within the voids as determined by SQUEEZE corresponds to 0.6 ethyl acetate per host molecule, in good accordance with the ^{1}H NMR spectrum. All further geometrical parameters of the guest are related to this solvent-free model. Because of the poor quality of the structure determination including the solvent, data for this structure have not been deposited with CCDC, but are available from the authors on request.

Crystallographic data (excluding structure factors) for the structures (*RS*)-**5** and (*S*)-**5** have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication numbers CCDC 166565 and CCDC 166566, respectively. Full crystallographic data in the form of standard CIF files as produced by SHELX are available by e-mail from the author (I.C.).

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