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Synthesis of optically active bihelicenols

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Abstract—All six stereoisomers of dimethyl 5,5′-dihydroxy-1,1′,12,12′-tetramethyl-[6,6′]bi(benzo[*c*]phenanthrenyl)-8,8′-dicarboxylate (bihelicenol) were synthesized by the oxidative coupling of methyl 8-hydroxy-1,12-dimethylbenzo[*c*]phenanthrene-5-carboxylate (helicenol), and their structures were determined by X-ray analysis. © 2003 Elsevier Science Ltd. All rights reserved.

Previously we developed a multigram synthesis of an optically pure helicene,[1] 1,12-dimethylbenzo[*c*]-phenanthrene-5,8-dicarboxylic acid, and the derivatives have been used for the studies on chiral recognition in the complexation with cyclodextrins[2] or DNA,[3] chiral LB film formation,[4] chiral catalysis,[1] chiral charge-transfer (CT) complexation,[5] and folding in the water.[6] Of various potential uses of the helicene, we have regarded the compound in the present work as a chiral equivalent of naphthalene.[7] In view of successful achievement of 2,2′-binaphthol **1** in asymmetric catalysis,[8] it was wondered whether a bihelicenol **2**, because it should form a larger chiral pocket at the catalytic metal center, would be even a better ligand (Fig. 1). Also wondered was that the isomeric **2** might exhibit different stereoselectivity among all six isomers (*P*,*P*,*S*)-**2**, (*P*,*P*,*R*)-**2**, (*M*,*M*,*S*)-**2**, (*M*,*M*,*R*)-**2**, (*P*,*M*,*S*)-**2** and (*P*,*M*,*R*)-**2**. Described here are synthesis and structure determination of all the bihelicenols. As a related helicenol dimer, Katz prepared a bis[5]helicenediol ligand ([5]HELOL) in nonracemic form, and demonstrated the catalytic activity in the asymmetric addition of diethylzinc to aldehydes.[9]

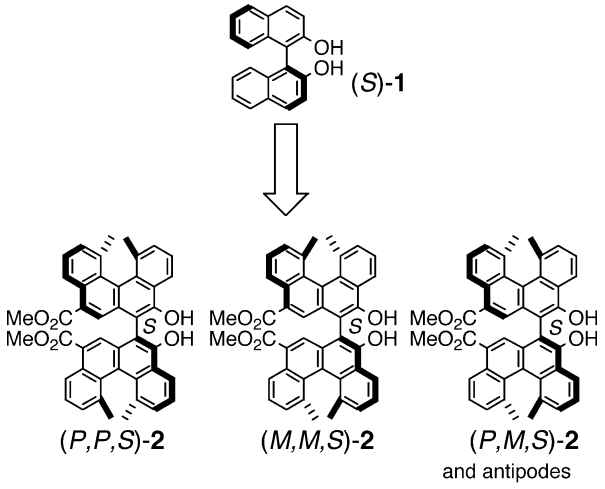

Figure 1. Structures of bihelicenols.

An aldehyde (*P*)-**4** obtained from (*P*)-**3**[10] was converted to a helicenol (*P*)-**5** by the Baeyer–Villiger oxidation with *m*-chloroperbenzoic acid followed by hydrolysis of the resulted formate[11] in 80% yield (Scheme 1). Treatment of (*P*)-**5** with Cu·TMEDA complex[12] under air gave an olefin dimer (*Z*,*P*,*P*)-**6** in 99% yield,[16] where (*Z*)-isomer was obtained exclusively without any trace of the (*E*)-isomer. The structure of (*Z*,*P*,*P*)-**6** was determined by X-ray analysis (Fig. 3a).[15] Although a number of diphenoquinone derivatives have been obtained by the oxidative dimerization of phenols,[9,13,14] the double bond stereochemistry was not determined unambiguously.[14] It may be interesting that the (*Z*)-isomer is obtained selectively in the present synthesis.

(*Z*,*P*,*P*)-**6** was hydrogenated to (*P*,*P*,*R*)-**2**[16] stereoselectively in the presence of palladium charcoal (99% yield), where no trace of (*P*,*P*,*S*)-**2** was detected. (*P*,*P*,*R*)-**2** was converted to dibenzyl ether (*P*,*P*,*R*)-**7**, and its structure was analyzed by X-ray (Fig. 2a).[15] The bihelicenol (*P*,*P*,*R*)-**2** epimerized by refluxing in degassed toluene for 3 h giving (*P*,*P*,*R*)-**2** and (*P*,*P*,*S*)-**2**[16] in

Keywords: helicene; binaphthol; oxidative coupling.

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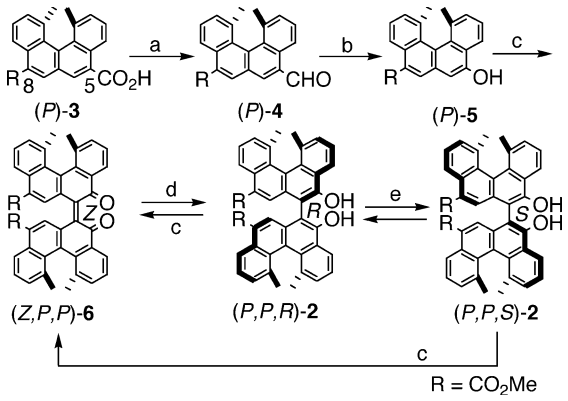


Scheme 1. *Reagents and conditions*: (a) i. BH_3–THF complex, ii. MnO_2; (b) i. *m*-CPBA, ii. K_2CO_3; (c) Cu(I)–TMEDA complex, air; (d) H_2, Pd/C; (e) toluene reflux.

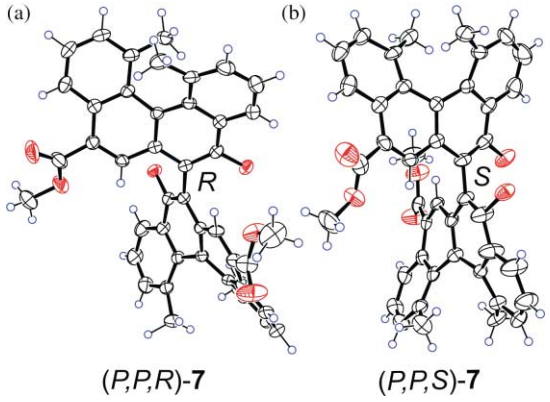


Figure 2. ORTEP drawings of (*P*,*P*,*R*)-**7** (a) and (*P*,*P*,*S*)-**7** (b). Benzyl groups have been omitted for clarity.

comparable amounts, which could be separated by silica gel chromatography. The structure of (*P*,*P*,*S*)-**7** was also confirmed by X-ray crystallographic analysis (Fig. 2b).[15] Comparable thermodynamic stability of (*P*,*P*,*R*)-**2** and (*P*,*P*,*S*)-**2** indicates that the stereoselectivity in the reduction of (*Z*,*P*,*P*)-**6** to (*P*,*P*,*R*)-**2** is under kinetic control. Examination of the X-ray structure of (*Z*,*P*,*P*)-**6** revealed a (*M*)-helical structure at H7–C7–C6a–C6–C6′–C6a′–C7′–H7′ moiety (Fig. 3b), which indicates that (*Z*,*P*,*P*)-**6** already possesses latent axis (*R*)-chirality at the C6–C6′ double bond moiety. Probably, this is the origin of the selectivity in the reduction of (*Z*,*P*,*P*)-**6** to (*P*,*P*,*R*)-**2**. Analogously, (*M*,*M*,*S*)-**2** and (*M*,*M*,*R*)-**2** were synthesized from (*M*)-**3**.

Both (*P*,*P*,*R*)-**2** and (*P*,*P*,*S*)-**2** were oxidized to (*Z*,*P*,*P*)-**6** using Cu·TMEDA complex (Scheme 1). The (*Z*)-selectivity in the formation of (*Z*,*P*,*P*)-**6** therefore may be ascribed to the thermodynamical stability of this compound.

The other two isomers (*P*,*M*,*R*)-**2** and (*P*,*M*,*S*)-**2** were synthesized from (±)-**5**. Oxidative coupling of (±)-**5**

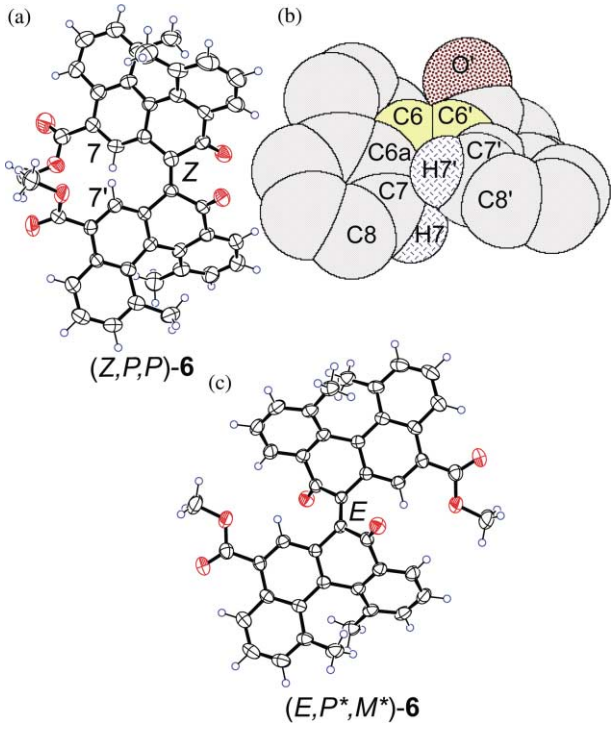
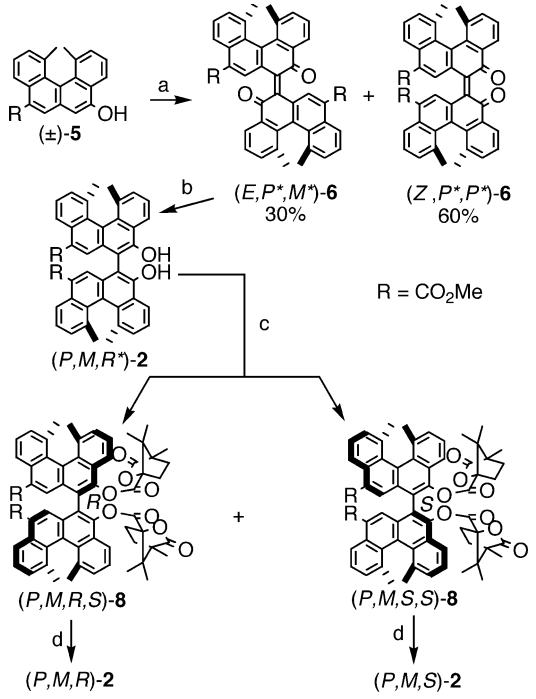


Figure 3. X-Ray structures of (*Z*,*P*,*P*)-**6** (a,b) and (*E*,*P**,*M**)-**6** (c). Aromatic A and D rings of helicene have been omitted in (b).



Scheme 2. *Reagents and conditions*: (a) air, Cu·TMEDA; (b) H_2, Pd/C; (c) (1*S*)-camphanic chloride, Et_3N; (d) $Ba(OH)_2 \cdot 8H_2O$.

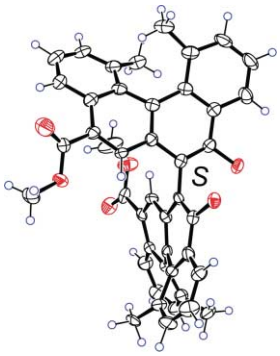


Figure 4. An ORTEP drawing of (*P*,*M*,*S*,*S*)-**8**. Camphanyl groups have been omitted for clarity.

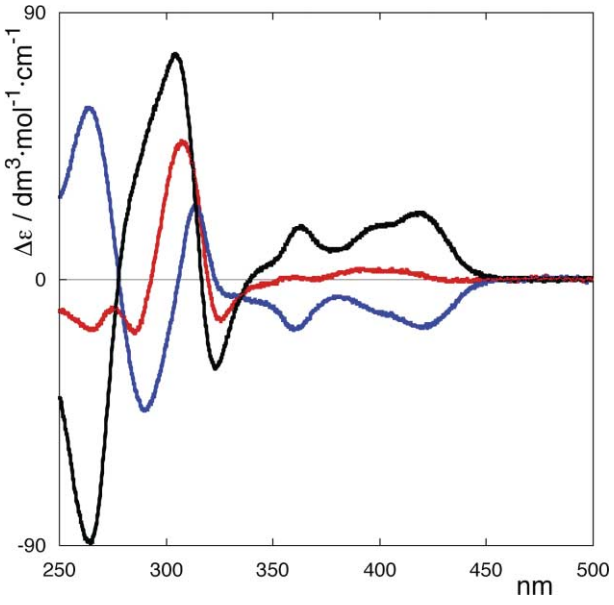


Figure 5. CD spectra ($CHCl_3$, 25°C) of (*P*,*M*,*R*)-**2** (red line) and (*P*,*P*,*R*)-**2** (blue line) and (*M*,*M*,*R*)-**2** (black line) at a concentration of 0.1 mM.

gave (*Z*,*P**,*P**)-**6** and (*E*,*P**,*M**)-**6**[16] in 60 and 30%, respectively (Scheme 2). The formation of the former isomer in a greater amount indicates that the homo-coupling of (*P*)-**5** and (*P*)-**5** predominates the hetero-coupling of (*P*)-**5** and (*M*)-**5**. Such chiral recognition of helicenes favoring the compound of the same helicity was observed in our group in the folding in the water,[3] and CT complexation.[5] It was noticed that (*Z*,*P**,*P**)-**6** possessed the (*Z*)-double bond, while (*E*,*P**,*M**)-**6** the (*E*)-double bond. The structure of (*E*,*P**,*M**)-**6** was determined by X-ray crystallographic analysis (Fig. 3c).[15] Then, (*E*,*P**,*M**)-**6** was hydrogenated to the racemic (*P*,*M*,*R**)-**2**, and was resolved by converting to (1*S*)-camphanic ester followed by chromatographic separation giving (*P*,*M*,*R*,*S*)-**8** and (*P*,*M*,*S*,*S*)-**8**. The structure of (*P*,*M*,*S*,*S*)-**8** was determined by the X-ray crystallographic analysis (Fig. 4).[15] The camphonyl moieties of (*P*,*M*,*R*,*S*)-**8** and (*P*,*M*,*S*,*S*)-**8** were removed by treatment with barium hydroxide at –35°C to give optically pure (*P*,*M*,*R*)-**2** and (*P*,*M*,*S*)-**2**,[16] respectively. No racemization occurred during the hydrolysis, which was confirmed by HPLC analysis. The methyl ester of **8** resisted to hydrolysis under the conditions.

The CD spectra of (*P*,*P*,*R*)-**2** and (*M*,*M*,*R*)-**2** are almost symmetrical between 350 and 450 nm (Fig. 5), which may be the absorption due to the helical chirality. In accordance, the CD absorption of (*P*,*M*,*R*)-**2** is weak at the region.

Use of bihelicenols **2** in asymmetric catalysis is now in progress.

Acknowledgements

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15. Crystallographic data (excluding structure factors) for (*P*,*P*,*R*)-**7**, (*P*,*P*,*S*)-**7**, (*Z*,*P*,*P*)-**6**, (*E*,*P**,*M**)-**6** and (*P*,*M*,*S*,*S*)-**8** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 202612, 202613, 202614, 202615 and 202616, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
16. (*P*,*P*,*R*)-**2**: Mp 198°C dec. (toluene). $[\alpha]_D^{25}$ −515 (*c* 0.6, $CHCl_3$). LRMS (EI, 70 eV) *m*/*z* 658 (M^+, 96%), 626 (78%). HRMS (EI, 70 eV) calcd for $C_{22}H_{20}O_6$: 658.2355. Found: 658.2341. Anal. ($C_{44}H_{34}O_6$) calcd for C, 80.21; H, 5.21%. Found: C, 79.75; H, 5.46%. IR (KBr) 3524, 3398, 1715 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (6H, s), 2.07 (6H, s), 3.75 (6H, s), 5.65 (2H, br), 7.47 (2H, d, J=7 Hz), 7.59–7.64 (4H, m), 7.72 (2H, t, J=8 Hz), 7.79 (2H, s), 8.40 (2H, d, J=8 Hz), 8.61 (2H, d, J=8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 24.0, 52.4, 106.5, 120.4, 123.0, 124.5, 125.4, 125.7, 126.4, 127.0, 128.1, 128.7, 129.0, 130.4, 130.5, 131.7, 132.5, 135.9, 137.2, 151.1, 168.1.

(*P*,*P*,*S*)-**2**: Mp 188°C dec. (toluene). $[\alpha]_D^{25}$ −649 (*c* 0.2, $CHCl_3$). LRMS (EI, 70 eV) *m*/*z* 658 (M^+, 85%), 626 (41%). HRMS (EI, 70 eV) calcd for $C_{44}H_{34}O_6$: 658.2355. Found: 658.2346. Anal. ($C_{44}H_{34}O_6$) calcd for C, 80.21; H, 5.21%. Found: C, 80.03; H, 5.26%. IR (KBr) 3519, 3409, 1703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (6H, s), 2.06 (6H, s), 3.63 (6H, s), 5.66 (2H, br), 7.47 (2H, d, J=7 Hz), 7.59 (2H, t, J=8 Hz), 7.60 (2H, d, J=8 Hz), 7.75 (2H, dd, J=8, 8 Hz), 7.80 (2H, s), 8.48 (2H, d, J=8 Hz), 8.66 (2H, d, J=8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.6, 23.8, 52.0, 106.0, 120.3, 123.0, 124.6, 125.2, 126.3, 126.3, 127.0, 127.2, 128.6, 128.7, 130.3, 131.2, 131.8, 132.3, 135.8, 137.1, 150.4, 167.5.

(*P*,*M*,*S*)-**2**: Mp >300°C (^{i}PrOH/hexane). $[\alpha]_D^{25}$ −42 (*c* 0.3, $CHCl_3$). LRMS (EI, 70 eV) *m*/*z* 658 (M^+, 42%), 109 (100%). HRMS (EI, 70 eV) calcd for $C_{44}H_{34}O_6$: 658.2355. Found: 658.2357. Anal. ($C_{44}H_{34}O_6$) calcd for C, 80.21; H, 5.21%. Found: C, 79.65; H, 5.33%. IR (KBr) 3406, 1716 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (3H, s), 2.03 (3H, s), 2.06 (6H, s), 3.60 (3H, s), 3.72 (3H, s), 5.64 (1H, br), 5.69 (1H, br), 7.45 (1H, d, J=7 Hz), 7.48 (1H, d, J=7 Hz), 7.57–7.63 (4H, m), 7.70 (1H, t, J=8 Hz), 7.73 (1H, t, J=8 Hz), 7.78 (1H, s), 7.79 (1H, s), 8.41 (d, 1H, J=8 Hz), 8.45 (d, 1H, J=8 Hz), 8.62 (d, 1H, J=8 Hz), 8.63 (d, 2H, J=8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 23.6, 24.0, 52.1, 52.1, 52.3, 52.3, 106.3, 106.6, 120.3, 120.4, 123.1, 124.5, 124.6, 125.3, 125.3, 125.4, 125.6, 125.8, 126.4, 127.0, 127.8, 127.9, 128.2, 128.7, 128.7, 128.9, 129.0, 130.4, 130.7, 130.8, 131.8, 132.0, 132.4, 132.6, 135.8, 136.0, 137.2, 137.3, 137.8, 150.3, 151.3, 167.7, 168.0.

(*Z*,*P*,*P*)-**6**: Mp 277°C dec. (toluene). $[\alpha]_D^{25}$ +1520 (*c* 0.5, $CHCl_3$). LRMS (EI, 70 eV) *m*/*z* 656 (M^+, 100%), 628 (M^+–CO, 66%). HRMS (EI, 70 eV) calcd for $C_{22}H_{18}O_6$: 656.2199. Found: 656.2181. Anal. ($C_{44}H_{32}O_6$) calcd for C, 80.47; H, 4.91%. Found: C, 80.41; H, 5.37%. IR (KBr) 1715, 1504 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (6H, s), 1.97 (6H, s), 3.71 (6H, s), 7.33 (2H, d, J=7 Hz), 7.47–7.55 (6H, m), 7.84 (2H, dd, J=7, 9 Hz), 8.18 (2H, s), 8.71 (2H, d, J=9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 23.7, 52.2, 123.3, 123.9, 125.8, 127.0, 128.1, 128.3, 129.2, 130.2, 132.2, 132.6, 133.2, 135.21, 135.22, 135.8, 137.5, 138.2, 138.6, 166.8, 193.6.

(*E*,*P**,*M**)-**6**: Mp 250°C dec. (CH_2Cl_2). LRMS (EI, 70 eV) *m*/*z* 656 (M^+, 16%), 628 (M^+–CO, 12%), 372 (100%). HRMS (EI, 70 eV) calcd for $C_{22}H_{18}O_3$: 656.2199. Found: 656.2200. Anal. ($C_{44}H_{32}O_6$) calcd for C, 80.47; H, 4.91%. Found: C, 80.41; H, 5.37%. IR (KBr) 1716, 1505 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (6H, s), 1.97 (6H, s), 4.10 (6H, s), 7.30 (2H, d, J=7 Hz), 7.48–7.59 (6H, m), 7.85 (2H, dd, J=7, 9 Hz), 8.03 (2H, s), 8.85 (2H, d, J=9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 23.9, 52.3, 122.5, 124.2, 125.8, 126.7, 127.9, 128.5, 128.8, 130.0, 132.0, 132.9, 133.5, 134.8, 134.9, 135.9, 138.5, 138.7, 139.0, 166.8, 196.3.