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Synthesis and Absolute Stereostructure of Dinaphth[2,1- *c*:1′,2′–e]oxepin–3–(5*H*)–one[1]

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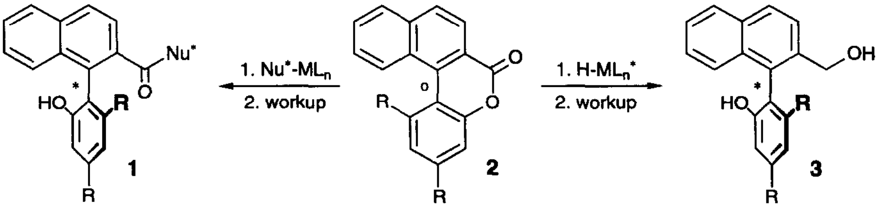
Abstract: The synthesis, enantiomer analysis, and configurational assignment of dinaphth[2,1–c:1′,2′–e]oxepin–3–(5*H*)–one, a seven–membered lactone–bridged chiral binaphthalene, is reported. The elucidation of the absolute configuration has been performed, independently by multiple scattering X–ray experiments and by circular dichroism (CD).

INTRODUCTION

Compared with the synthesis of molecules containing chiral *centers*, which is a well established field, the enantio– and diastereoselective synthesis of *axially* chiral compounds is still remarkably underdeveloped. And also the methods for the elucidation of the absolute axial configuration are not as well elaborated as for chiral centers.

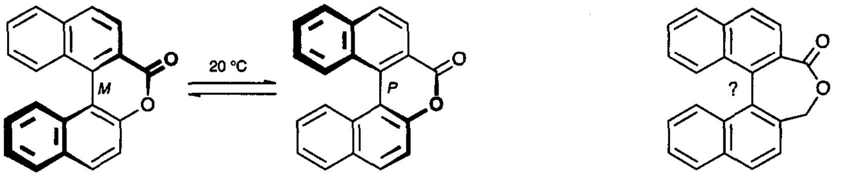
For the regio– and stereoselective synthesis of even highly sterically hindered biaryl systems, we have developed a synthetic strategy (Scheme 1) that allows the directed, *i.e.* stereo–controlled access to optionally any of the two possible atropo–isomers.[2,3] A key role within this concept is occupied by lactone–bridged biaryls such as **2**: they can easily be built up by intramolecular aryl coupling of the ester–type prefixed molecular moieties, thus allowing the *C*,*C*–bond formation to take place in high yields.[4] Due to a very low isomerization barrier, these bridged biaryls are configuratively labile at the axis, but can be ring–opened atropo–diastereoselectively,



Scheme 1. The directed ring–opening of helically twisted but configuratively labile ester–bridged biaryls with asymmetric induction at the axis using chiral reagents (stable elements of chirality are marked by "*", instable ones by "o".[5]).

using chiral metalated *O*– or *N*–nucleophiles ("Nu*–ML$_n$"), to give configuratively stable biaryl esters or amides **1**,[6,7] or even atropo–enantioselectively, using chiral hydride transfer reagents ("H–ML$_n$"), leading to the likewise stereochemically stable biaryl alcohols **3** in excellent enantiomeric excesses.[8,9]

Recently, we have reported on the synthesis[10] and optical resolution of the related pentacyclic lactone **4**[11] and have described its enantiomerization at room temperature (Scheme 2). For mechanistic and synthetic aspects, the preparation of the homologous bridged biaryl **5**, *i.e.* with a seven-membered ring, and the investigation of its structure and dynamics, would be of high interest. In this paper, we describe the synthesis of **5**, its configurational stability at room temperature, its enantiomer resolution by HPLC on a chiral stationary phase as well as the stereochemical attribution of its enantiomers, independently by comparison of its predicted and its experimental CD spectra and by multiple scattering X–ray experiments.



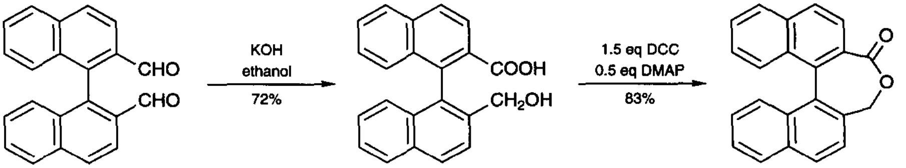
(M)-**4** *(P)*-**4** **5**

Scheme 2. Interconversion of the two helimeric enantiomers of **4** ($\Delta G = 91.1$ kJ·mol^{-1} at 20 °C),[11] and constitution of the homologous lactone **5**.

RESULTS AND DISCUSSION

1. Preparation of lactone 5:

In the literature, the structure of our target lactone had already been mentioned, yet without any spectroscopic and preparative details.[12] Our synthesis starts with the easily available dialdehyde **6**,[13] which can be disproportionated by an intramolecular Cannizzaro reaction, to give the hydroxy carboxylic acid **7**. This compound had previously been prepared by *Miyano et al.*, albeit starting from different precursors.[14] For the cyclization of **7** to the title compound **5**, methods for the acid catalyzed ring closure to 7–membered ring lactones, as described in the literature,[15] proved to be difficult. Whereas for reactions on a small scale, **5** can be prepared from **7** by heating in vacuo, under simultaneous sublimation, **5** was obtained in excellent yields by the use of



6 **7** **5**

Scheme 3. Synthetic pathway, that leads to the target compound **5**, starting from the binaphthyl dialdehyde **6**.

dicyclohexylcarbodiimide (DCC) / 4–dimethylaminopyridine (DMAP). Thus, the bridged binaphthyl **5** could be prepared on a multi–gram scale.

With this material in hands, suited crystals could be obtained for an X–ray structure analysis,[16] which showed that, starting from racemic **5**, this chiral helicene–like distorted molecule crystallizes in an enantiomerically pure form.

In this respect, **5** clearly differs from **4**[11] and the complete series of the related lactones **2**[4,17,18] (with R = H, Me, OMe, Et, *i*–Pr, *t*–Bu), which all crystallize in centric space groups, *i.e.* as racemates. This prompted us to investigate the stereochemical properties of this interesting bridged biaryl **5** more closely, including the elucidation of the absolute configuration of the enantiomers by two independent methods: experimental and theoretical CD spectroscopy as well as X–ray diffraction.

2. Chromatographic Enantiomer Resolution

For a stereochemical correlation of the absolute configuration of the material in different single crystals, but also in order to get a first idea about the configurative stability of **5**, as a precondition of performing CD spectroscopic investigations, we needed a reliable chromatographic analysis on a chiral phase, for which a "Chiracel OF" (Diacel Chem. Ind.) [length: 20 cm; eluent: isopropanol/n–hexane = 30:70; UV detection at 280 nm] proved to be the method of choice, see Fig. 1a.

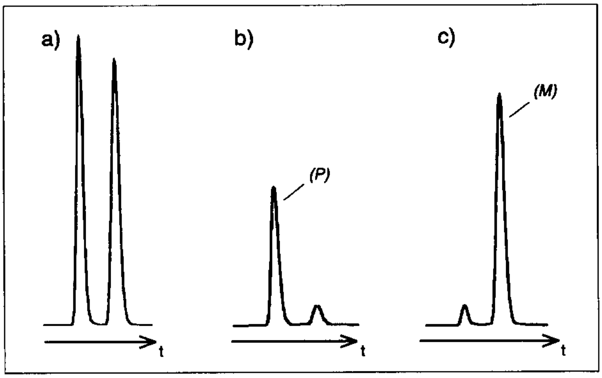
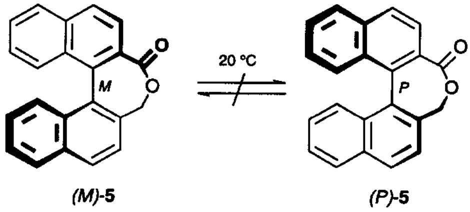


Fig. 1. Chromatography of **5** on a chiral phase: a) resolution of racemic **5**. — b) chromatogram of a typical crystal predominantly containing the (*P*)–enantiomer. — c) chromatogram of a typical crystal that mostly consists of the (*M*)–enantiomer.

These investigations showed already that, in contrast to the 6–membered ring lactone **4**, the larger size of the bridge between the two biaryl "halves" of **5**, now consisting of three instead of two atoms, leads to a distinctly higher atropisomerization barrier, giving the atropo–enantiomers (*M*)–**5** and (*P*)–**5** (see Scheme 4) that are configuratively stable, at least during the chromatographic process.

With this chromatographic enantiomer analysis in hands, we have then stereochemically analyzed single pure crystals of **5**, which indeed showed a high (though not complete) stereochemical homogeneity: In the crystals, either the *P*– (Fig. 1b) or the *M*–enantiomer (Fig. 1c) strongly predominates. The fact that the enantiomeric ratios of (*M*)–**5**/(*P*)–**5** do not subsequently change in solution, even not when heating the sample to 60 °C for 1 h, reveals that, different from the 6–membered lactone **4**, the title compound **5** is configuratively stable, *i.e.* the two helimeric enantiomers **5**–(*M*) and **5**–(*P*) do not interconvert.

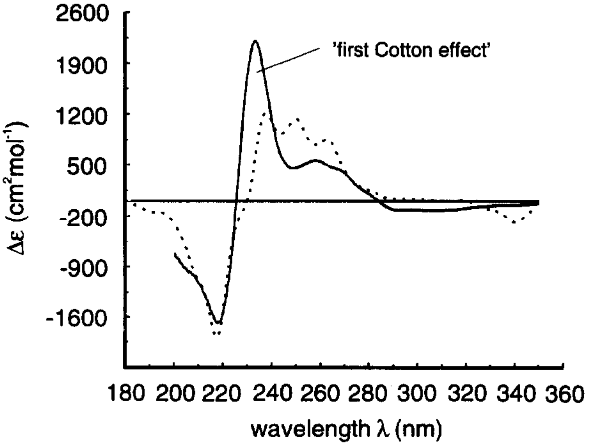


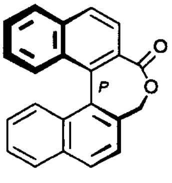
Scheme 4. Configurative stability of the 7–membered ring lactone **5**.

3. Elucidation of the Absolute Configuration of the Helimeric Enantiomers by Circular Dichroism

A rapid and reliable method for the determination of the absolute configuration of axially chiral biaryls is the investigation of the circular dichroism (CD). Fig. 2 (full line) shows the CD spectrum of the material corresponding to the chromatogram shown in Fig. 1b, *i.e.* with the more rapidly eluting isomer predominating. The enantiomeric character of the two compounds separated on the chiral phase is demonstrated by the opposite CD spectrum (not shown) resulting from material corresponding to the chromatogram in Fig. 1c. Moreover and more importantly, the CD spectroscopy offers the possibility of establishing the absolute configuration, which is often done by an empirical comparison with the spectral data of a related compound of known absolute configuration.

A better approach to the interpretation of CD spectra is the application of the exciton chirality method,[19] the use of which however is restricted, on principle, to systems containing two intensive and almost degenerate electronic transitions. For the lactone **5**, this condition is fulfilled to a nearly ideal degree, due to the far–reaching similarity of the two naphthalene systems. Of high diagnostic value in the experimental CD spectrum of the rapidly eluting atropo–enantiomer of **5** is the positive sign (+) of the so-called first Cotton–effect, belonging to the couplet at 223 nm, from which, according to the exciton chirality method, the configuration at the stereogenic





(P)-5

Fig. 2. CD spectra of the reference 5–(*P*) helimer. The experimental spectrum (——) was measured in an ethanol solution. The theoretical CD spectrum (- - - - -) was calculated by AM1 → CNDO/S and scaled by a factor[22] of 1.5.

axis can be deduced to be *P*.

A more reliable assignment of the absolute configuration at the axis can be obtained by comparison with the theoretically predicted CD spectrum obtained through semiempirical CNDO/2S–CI calculations,[20,21] a procedure that has already given excellent results in the field of non–bridged naturally occurring biaryl alkaloids.[22] For this purpose, **5** is a very good substrate: Due to the 3–membered bridge, the structure is quite rigid, and therefore allows to predict the conformation of the molecule very precisely. Thus, for the calculation of the CD spectrum, tentatively only the one minimum structure for *P*–**5**, as determined by energy–optimization by the AM1 method,[23] was taken into account. For the determination of the wave functions of the ground state and the excited states, a CI expansion of 100 singly occupied and the ground state determinant were used. Using procedures established earlier,[22] we obtained the calculated CD spectrum for *P*–**5** (see Fig. 2) (dotted line), which, despite the restriction to only one particular conformation, indeed matches very well with the experimental curve (Table 1) and especially reproduces the crucial positive Cotton effect of the couplet at 223 nm.

Table 1. Comparison of experimental CD data[a] of (*P*)–**5** with calculated data obtained by CNDO/2S–CI.

experimental		theoretical[b]	
−1687.5	(217.5)	−1885.3	(217.5)
+2206.3	(233.0)	+1214.6	(237.6)
+555.9	(258.0)	+1138.9	(249.9)
+430.6	(268.0)	+854.7	(262.7)

[a] $\Delta\varepsilon[\mathrm{cm}^2 \cdot \mathrm{mol}^{-1}]$ ($\lambda_{\max}$[nm]).

[b] $\Delta\varepsilon$ values scaled by an empirical factor of 1.5 due to comparison reasons.

Thus, as already probable from the exciton chirality approach, experimental and theoretical CD spectra clearly indicate the more rapidly eluting enantiomer to have *P*–configuration at the axis.

4. Independent Stereochemical Assignment by X–Ray Structure Analysis

Due to the importance of an unambiguous configurational assignment of this helimeric compound for our further stereochemical work, we tried to independently determine the stereostructure by a completely different method. Therefore, in addition to the mentioned "normal" X–ray structure analysis,[16] we now performed an absolute determination of the configuration at the axis by multiple scattering X–ray experiments.

As there are only two oxygen atoms per molecule, it is nearly impossible to determine the absolute structure by Bijvoet differences. Thus another method had to be applied.

Three structure factors form a triplet if their scattering vectors $\underline{h}_1$, $\underline{h}_2$ and $\underline{h}_3$ add up to zero. The sum of their phases Φ does not change under shifts of origin:

$$\underline{h}_1 + \underline{h}_2 + \underline{h}_3 = 0 \qquad \phi_1 + \phi_2 + \phi_3 = \Phi = \text{const.}$$

Structural enantiomorphs differ in the signs of structure invariants.

According to *Hümmer et al.*[24] three–beam scattering X–ray experiments deliver information on the sign of structure invariant triplet phases. They confirmed this statement experimentally[25] using a six–circle diffractometer[26] that allows the positioning of a scattering vector into a hardware–Ψ–axis with high angular resolution (0.001 degrees).

For three–beam experiments the primary scattering vector $\underline{h}$ is brought into the Ψ–axis and to the scattering position, *i.e.* the starting and the end point of $\underline{h}$ lie on the Ewald sphere. The intensity of $\underline{h}$ is observed while a Ψ–rotation around $\underline{h}$ is performed. If a secondary vector $\underline{h}'$ is moved with its end point through the surface of the Ewald sphere, the Bragg condition for this vector is fulfilled; an additional wave–field inside the crystal is excited influencing the wave–field related to the primary vector $\underline{h}$ *via* the difference vector $\underline{h}'' = \underline{h} - \underline{h}'$. Since the three vectors $-\underline{h}$, $\underline{h}'$ and $\underline{h}''$ add up to zero, they form a triplet. Both wave fields give reason for interference effects, since they refer to the same wavelength λ changing the intensity of the primary reflection during the rotation around Ψ. The changes are related to the structure invariant Φ unambiguously. For $\Phi = 90°$ the intensity is decreased, for $\Phi = -90°$ it is increased provided that the relation of the involved structure factor moduli does not differ too much from the ratio 1:2:2.

Since the variation of intensity depends also on some other physical effects not related to phases of structure factors (Aufhellung and Umweganregung resulting from energy conservation[27]), other centrosymmetric triplet phases, $\Phi^{+}[-\underline{h}, \underline{h}', \underline{h}'']$ and $\Phi^{-}[\underline{h}, -\underline{h}', -\underline{h}'']$ must be investigated.

No special properties, such as anomalous dispersion, are necessary; thus this procedure is especially suitable for structures containing only light atoms. It has been successfully used for several light atom structures.[28–30]

The determination of the absolute structure was preceded by a redetermination of the structure using the same specimen. The refinement led to $R = 0.047$ and $R_w = 0.029$. The result is in very good agreement with the data previously obtained,[16] especially the large dihedral angle at the pseudoaxis of the molecule and the nearly planar arrangement of both of the naphthalene systems were confirmed (cf. also Fig. 3, see below). Table 2 shows the structure factors and their phases used for the determination and the changes of the recorded intensities on an arbitrary scale. The investigation clearly established a *P*–configuration for the molecules (Fig. 3).

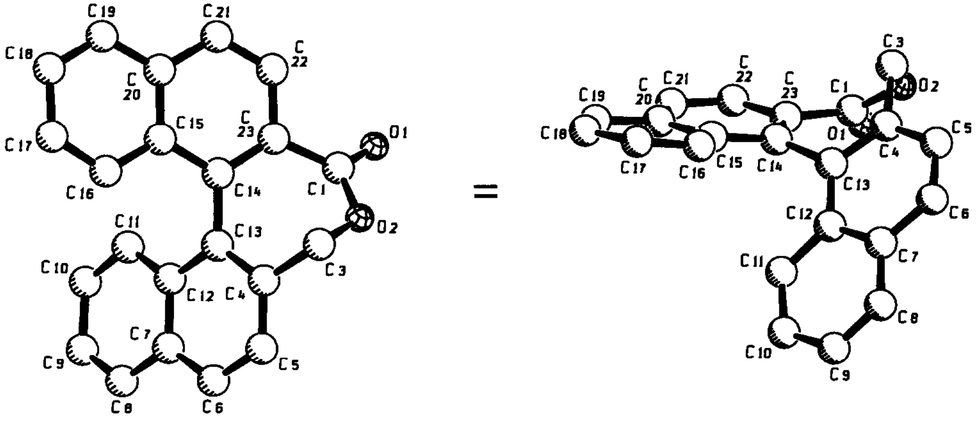
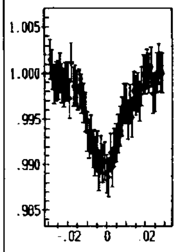
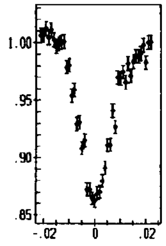
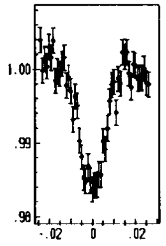
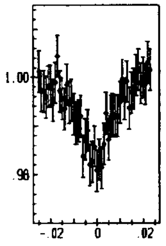
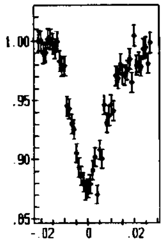
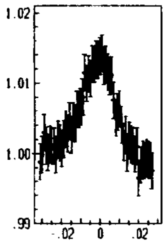
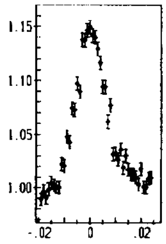
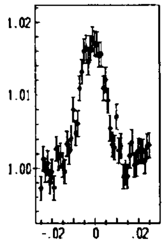
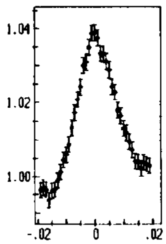
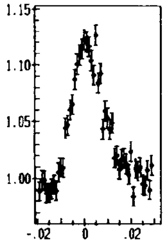


Fig. 3. The absolute stereostructure of (*P*)–**5** in the crystal, as determined by multiscattering X–ray measurements.

For a correlation of this stereochemical assignment with the information obtained from CD spectroscopy, the crystal that had been utilized for the X–ray structure analysis (which thus had been found to consist of *P*–configurated material) was submitted to the enantiomer analysis described above, giving a chromatogram identical to that of Fig. 1b, showing that again the more rapid eluting enantiomer, which already had been attributed to be *P*–configurated by CD spectroscopy (see above), was predominant. This demonstrates that both

Table 2. Data used for the determination of the absolute structure. The basic line is always indicated by 1.000. The results are in very good agreement with the triplet phases calculated on the basis of the refined atomic coordinates. It should be emphasized that the full–width at half–maximum of the changes does not exceed 0.02°. The triplets Φ_2, Φ_3 and Φ_5 were corrected for Umweganregung. The experiments were performed with a six–circle diffractometer installed at a rotating anode generator (radiation: Cu–$K_{\alpha 1}$).

Structure factors used with moduli (measured) and phases (calculated)								
hkl	F_{obs}	ϕ_{cal}	hkl	F_{obs}	ϕ_{cal}	hkl	F_{obs}	ϕ_{cal}
0 1 1	75.4	90°	2 1 1	70.4	11°	6 1 1	37.8	−111°
9 2 1	45.0	71°	2 0 2	31.2	180°	2 1 2	36.9	−37°
4 1 2	25.7	−62°	3 3 2	25.6	102°	4 4 2	28.8	147°
2 5 0	49.9	0°	0 2 1	47.7	180°	4 1 1	34.2	39°

Triplets used										
triplet	hkl	ϕ	hkl	ϕ	hkl	ϕ	hkl	ϕ	hkl	ϕ
−h −k −l	3 3 2	102°	$\bar{2}$ 0 $\bar{2}$	180°	4 $\bar{4}$ 2	−147°	4 $\bar{1}$ $\bar{2}$	118°	$\bar{2}$ 0 $\bar{2}$	180°
h′ k′ l′	$\bar{9}$ $\bar{2}$ $\bar{1}$	−71°	2 1 1	11°	$\bar{2}$ 5 0	180°	0 2 1	180°	0 $\bar{1}$ 1	−90°
h″ k″ l″	6 $\bar{1}$ $\bar{1}$	69°	0 $\bar{1}$ 1	−90°	$\bar{2}$ $\bar{1}$ $\bar{2}$	37°	$\bar{4}$ $\bar{1}$ 1	141°	2 1 1	11°
Φ	$\Phi_1^+ = 100°$		$\Phi_2^+ = 101°$		$\Phi_3^+ = 70°$		$\Phi_4^+ = 79°$		$\Phi_5^+ = 101°$	
										
h k l	$\bar{3}$ $\bar{3}$ $\bar{2}$	−102°	2 0 2	180°	$\bar{4}$ 4 $\bar{2}$	147°	$\bar{4}$ 1 2	−118°	2 0 2	180°
−h′ −k′ −l′	9 2 1	71°	$\bar{2}$ $\bar{1}$ $\bar{1}$	−11°	2 $\bar{5}$ 0	180°	0 $\bar{2}$ $\bar{1}$	180°	0 1 $\bar{1}$	90°
−h″ −k″ −l″	$\bar{6}$ 1 1	−69°	0 1 $\bar{1}$	90°	2 1 2	−37°	4 1 $\bar{1}$	−141°	2 1 1	−11°
Φ	$\Phi_1^- = -100°$		$\Phi_2^- = -101°$		$\Phi_3^- = -70°$		$\Phi_4^- = -79°$		$\Phi_5^- = -101°$	
										

methods yield the same result, independently!

5. Conclusions

In summary, the bridged biaryl **5** has been prepared and structurally investigated. Different from the corresponding 6–membered ring lactone **4**, the longer, since *three*–atomed bridge of **5** allows the two aromatic systems to adopt a relatively large dihedral angle. Thus, whereas **4** shows a helicene–like structure with all aromatic rings inherently twisted,[11] **5** seems to be a nearly strainless bridged biaryl, such that each of the two naphthalene systems is non–distorted but practically planar. On the other hand, the specific size and composition of this bridge distinctly enhances the atropisomerization barrier, so that **5**, different from **4**, is configuratively stable at room temperature. Using two independent methods, the stereochemical assignment of the axial configuration of the two atropo–enantiomers (*M*)–**5** and (*P*)–**5** was established. Further work aiming at an investigation of the synthetic use of this interesting biaryl, *e.g.* in directed ring–opening reactions, is in progress.

EXPERIMENTAL

Melting points were measured on a Reichert–Jung Thermovar hot–plate apparatus and are uncorrected. NMR spectra were recorded with a Bruker AC 200 and a Bruker WM 400 spectrometer in $CDCl_3$. The chemical shifts δ are given in parts per million (ppm) using the proton–signals of $CHCl_3$ in the deuterated solvents as internal reference for ^{1}H and ^{13}C NMR. The coupling constants, *J*, are given in Hertz. HPLC analyses: combination of Knauer HPLC pump 64, a 20 μl injection loop and a Chiracel OF column. The CD spectra were measured on a Jobin Yvon Model CD6 spectrograph at room temperature in ethanol ranging from 200 to 350 nm. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. Mass spectra were determined with a Finnigan MAT 8200 mass spectrometer. IR spectra were performed on a Perkin–Elmer 1420 infrared spectrophotometer. The intensities of the vibrational absorptions are denoted by: s (strong), m (middle), w (weak) and br (broad).

2′–Hydroxymethyl–1,1′–binaphthalene–2–carboxylic Acid (**7**): A solution of 460 mg (1.48 mmol) 1,1′–binaphthalene–2,2′–dialdehyde (**6**)[13] and 2.5 g (44.6 mmol) potassium hydroxide in 50 ml ethanol was refluxed for 3 h. After concentration of the solution to ca. 10 ml, the reaction mixture was treated with 10 ml water and washed with 8 ml diethyl ether. The aqueous phase was acidified with dilute hydrochloric acid and extracted with diethyl ether (3 x 10 ml). The combined organic phases were dried ($MgSO_4$), concentrated and the residue was recrystallized from ethanol, giving **7**·CH_3CH_2OH (397 mg, 72%) as colorless needles: mp 193–194°C (lit.:[14] 188–189 °C); IR (KBr): $\tilde{\nu}$ 3350 cm^{-1} (br, OH), 3040 (w, aromatic H) 2950 (w, CH), 1690 (s, C=O) 1580 (m, C=C), 1450, 1380 (m, CH), 1240 (s, C–O); ^{1}H NMR : δ = 1.19 (t, *J* = 7.0 Hz, 3H, CH_3CH$_2$OH), 3.66 (q, *J* = 7.0 Hz, 2H, CH$_3$CH_2OH), 4.09 and 4.22 (2d, *J* = 11.4 Hz, 1H each, 2′–CH_2OH), 4.67 (br, 3H, 3 OH), 6.85–7.58 (m, 7H, aromatic H), 7.72–7.98 (m, 5H, aromatic H); MS (70 eV): *m/z* (%) = 328 (62) [M$^+$], 310 (82) [M$^+$–H$_2$O], 281 (100) [310–CHO], 265 (55) [281–O], 252 (67) [281–CHO]; Anal. Calcd. for $C_{22}H_{16}O_3 \cdot CH_3CH_2OH$ (374.4): C, 76.99; H, 5.92. Found: C, 77.05; H, 5.47.

Dinaphth[2,1–c:1′,2′–e]oxepin–3–(5H)–one (**5**): An HCl–saturated solution of 71.0 mg (0.58 mmol) 4–dimethylaminopyridine (DMAP) in 200 ml dichloromethane was added to 382 mg (1.16 mmol) 2′–hydroxymethyl–1,1′–binaphthalene–2–carboxylic acid (**7**) and 360 mg (1.74 mmol) dicyclohexylcarbodiimide (DCC) and the mixture was refluxed overnight under N_2 atmosphere. After cooling to room temp., excessive DCC was removed by the addition of several drops methanol and acetic acid. After stirring for 30 min, the mixture was diluted with 100 ml dichloromethane and filtrated over silica gel. The solution was washed with 100 ml water and 100 ml sat. aqueous NaCl. The combined organic layers were dried over sodium sulfate and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography (SiO_2/CH_2Cl_2) and recrystallized from dichloromethane/n–pentane, yielding **5** (301 mg, 83%) as pale yellow needles: mp 229–230°C; $[\alpha]_D^{25}$ of (*P*)–**5**: +121° ($c = 0.035$ in CH_2Cl_2), $[\alpha]_D^{25}$ of (*M*)–**5**: –189° ($c = 0.016$ in CH_2Cl_2)[31]; IR (KBr): $\tilde{\nu}$ 3040 cm^{-1} (w, aromatic H), 2940 (w, CH) 1700 (s, C=O), 1580 (m, C=C) 1455, 1325 (m, CH), 1265 (s, C–O); ^1H NMR : $\delta = 5.07$ and 5.22 (2d, $J = 12.0$ Hz, 1H each, OCH_2), 7.23–7.72 (m, 7H, aromatic H) 7.91–8.12 (m, 5H, aromatic H); ^{13}C NMR : $\delta = 69.99$ (s, CH_2), 125.81, 126.41, 126.63, 127.36, 127.77, 128.30, 128.34, 128.42, 129.35, 129.61 (s, aromatic *C*H), 130.15, 130.68, 132.17, 133.66, 133.90, 134.03, 134.60, 134.88 (s, aromatic C_q), 170.33 (s, CO); MS (70 eV): *m/z* (%) = 310 (99) [M^+], 282 (23) [M^+–CO], 266 (39) [$M^+–CO_2$], 265 (100) [$M^+–CHO_2^+$], 263 (44) [$M^+–CH_3O_2^+$], 252 (74) [$M^+–C_2H_2O_2^+$], 250 (33) [266–O], 140 (23) [$C_{11}H_8^+$], 126 (48) [$C_{10}H_6^+$], 125 (51) [$C_{10}H_5^+$]; Anal. Calcd. for $C_{24}H_{14}O_2$ (310.4): C, 85.14; H, 4.55. Found: C, 85.49; H, 4.58.

*Multiple scattering X–ray experimental investigation of (P)–***5***:* Suited crystals of **5** were obtained from dichloromethane/petroleum ether. The dimension of the specimen used was $0.2 \cdot 0.2 \cdot 0.3$ mm^3 with brick shape. Space group is $P2_12_12_1$, $Z = 4$, lattice parameters are a = 19.1812(4) Å, b = 12.8703(3) Å, c = 6.3721(2) Å, $\alpha = 90°$, $\beta = 90°$ and $\gamma = 90°$. Radiation: $Mo–K_{\alpha 1}$, with a modified PW1100 diffractometer type. Number of measured refections was 9489, number of independent reflections 2645. Θ_{max} was 30.0° and $R_{int} = 0.036$.

The number of reflections used in the refinement was 2645 and the number of refined parameters 261. The weighting scheme was $w = \frac{1}{\sigma(F)}$ and the $(\Delta/\sigma)_{max}$–value was less than 0.01. Applying the extinction correction method of Larson,[32] a secondary–extinction value of 44814 was reached. The refined difference density minimum– and maximum–values are: $(\Delta\rho)_{min} = -0.27$ $eÅ^{-3}$ and $(\Delta\rho)_{max} = 0.23$ $eÅ^{-3}$.

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