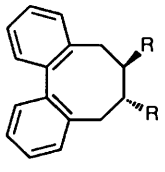
Synthesis and Chromatographic Resolution of some Chiral Four-Carbon 2,2'-Bridged Biphenyls. Some unusually High Selectivity Factors

Roland Isaksson, Parviz Rashidi-Ranjbar† and Jan Sandström *
Division of Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 124, S-221 00 Lund, Sweden

5,6,7,8-Tetrahydrodibenzocyclooctene and 14 of its 6-monosubstituted and *cis*- and *trans*-6,7-disubstituted derivatives have been prepared and resolved into enantiomers and diastereoisomers on a preparative scale by chromatography on swollen, microcrystalline triacetylcellulose. The solvent and structure dependence of capacity and selectivity factors is discussed in relation to the absolute configurations of the biphenyl units, the orientations of the substituents, and the symmetry of the molecules. Several remarkably high selectivity factors were observed, with 51.6 for the *trans*-6,7-dimethyl derivative with ethanol as the mobile phase as the most impressive one.

Bridged biaryls have been thoroughly studied over a long period of time,[1] and in several investigations the focus has been on chiroptical properties in relation to absolute configuration. However, little is known about the CD spectrum of the simple biphenyl chromophore at wavelengths below 230 nm. For a study of the spectral and conformational properties of biphenyls with known twist angle, we have searched for pure enantiomers of chiral 2,2'-bridged biphenyls. In recent years, optically active compounds without polar substituents have become available thanks to the development of chromatographic methods for resolution of enantiomers.[2,3] We have reported on the resolution of a number of dibenzo[*a*,*c*]cyclooctadiene derivatives[4,5] by liquid chromatography with swollen microcrystalline triacetylcellulose (TAC)[6] as the chiral stationary phase (CSP). In the present work, the preparation, and enantiomer and diastereoisomer resolution, of 5,6,7,8-tetrahydrodibenzo[*a*,*c*]cyclooctene **1** and a number of its 6-mono- and 6,7-di-substituted derivatives (Scheme 1) will be described. The ring system of compound **1** has been shown by X-ray crystallography[5] and by empirical force-field calculations[7] to have a twist-boat-chair (TBC) form with *ca.* 60° dihedral angle between the benzene rings as the favoured conformation, with substituents in positions 6 and 7 either in equatorial (e) or axial (a) orientation. In 6-mono-and in *trans*-6,7-disubstituted derivatives the e and e,e forms, respectively, are favoured (Fig. 1). The e,e form has also been found in an X-ray crystallographic study of a diprotonated 5,8-diaza analogue of compound **3**.[8] Conformational [(+)-TBC $\rightleftharpoons$ (−)-TBC] interchanges involving inversion of the biphenyl moiety have been shown to take place with barriers in the range 95–102 kJ mol^{-1}.[4,5,7,9]



1; R = H
2; R = Br
3; R = Me

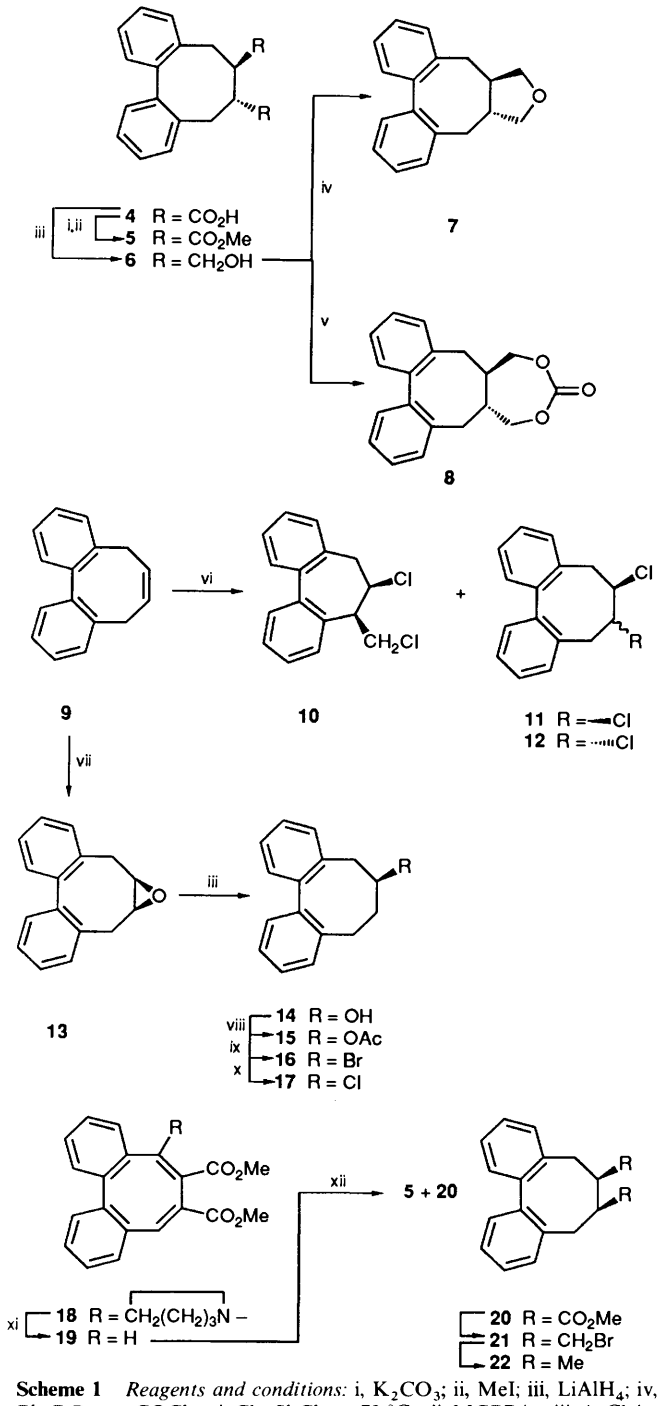
Synthesis.—A key compound in the synthesis is the *trans*-6,7-dicarboxylic acid **4**, which was prepared by known methods.[9] Reduction of acid **4** with $LiAlH_4$ gave the *trans*-bis(hydroxymethyl) compound **6**, treatment of which with triphenylphosphine followed by addition of bromine gave the *trans*-tetrahydrofuran compound **7**; similarly, treatment with phosgene gave the cyclic carbonate **8**. The preparation of the parent hydrocarbon **1** and the *trans*-dibromo compound **2** from diacid **4** followed the published procedures[5,10] with 5,8-dihydrodibenzo[*a*,*c*]cyclooctene **9** as intermediate. Addition of chlorine to compound **9** with or without $SbCl_5$ as catalyst gave a complex reaction mixture, from which three compounds, the *trans*-dichloro compound **12**, the *cis* analogue **11** and *cis*-6-chloro-5-chloromethyl-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene **10**, could be isolated. These compounds may have been formed with the phenonium ion **23** as intermediate. Formation of a similar phenonium ion has been proposed in order to explain the fast reaction and the products formed in the acetolysis of (5,6,7,8-tetrahydrodibenzo[*a*,*c*]cyclohepten-5-yl)-methyl tosate.[11]

Epoxidation of alkene **9** with *m*-chloroperbenzoic acid (MCPBA) gave the epoxide **13**, which was reduced by $LiAlH_4$ to the 6-hydroxy compound **14**. Acetylation with acetyl chloride gave the 6-acetoxy compound **15**. Treatment of alcohol **14** with PBr_5 gave the 6-bromo compound **16**, and, similarly, reaction with $SOCl_2$ gave the chloro analogue **17**.

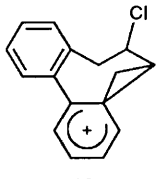
Synthesis of the *cis*-6,7-dimethyl derivative **22** started with dimethyl 5-pyrrolidinodibenzo[*a*,*c*]cyclooctene-6,7-dicarboxylate **18**.[12] Reduction with diborane gave dimethyl dibenzo-[*a*,*c*]cyclooctene-6,7-dicarboxylate **19**, which on hydrogenation with H_2/Pd gave a 1:2 mixture of compound **5** and its *cis*-analogue **20**. Reduction of this mixture with $LiAlH_4$ gave a mixture of diol **6** and its *cis*-analogue. Reaction with PBr_5 gave a complex mixture, from which the *cis*-6,7-bis(bromomethyl) compound **21** was isolated as the major product. Reduction of compound **21** with $LiAlH_4$ gave target compound **22**. The *trans*-analogue **3** was prepared by a literature method.[13]

Chromatographic Separations.—As mentioned in the Introduction, the eight-membered ring in the tetrahydrodibenzo-[*a*,*c*]cyclooctenes prefers a twist-boat-chair (TBC) conformation with equatorial (e) or axial (a) substituents in positions 6 and 7. For the 6-monosubstituted compounds, the e-form dominates over the a-stereoisomer, and for the *trans*-6,7-disubstituted analogues the e,e forms dominate over the a,a forms, and for compounds **3**–**6** quite strongly so. The *cis*-6,7-disubstituted analogues exist only in one enantiomeric pair, with one axial and one equatorial substituent.[7] Chromatography of a compound such as **2** on a TAC column leads to

† On leave of absence from the Department of Chemistry, Faculty of Science, Tehran University.



Scheme 1 *Reagents and conditions:* i, K_2CO_3; ii, MeI; iii, $LiAlH_4$; iv, $Ph_3P{\cdot}Br_2$; v, $COCl_2$; vi, Cl_2, $SbCl_5$, −78 °C; vii, MCPBA; viii, AcCl; ix, PBr_5; x, $SOCl_2$; xi, $BH_3{\cdot}THF$; xii, H_2, Pd/C



23

separation both of a diastereoisomers, e,e- and a,a-forms, and of enantiomers, (+)-e,e from (−)-e,e and (+)-a,a from (−)-a,a. A typical chromatogram is shown in Fig. 2.

The results of the enantiomer resolutions are expressed as selectivity factors α (Table 1), defined by eqn. (1), where k'_1

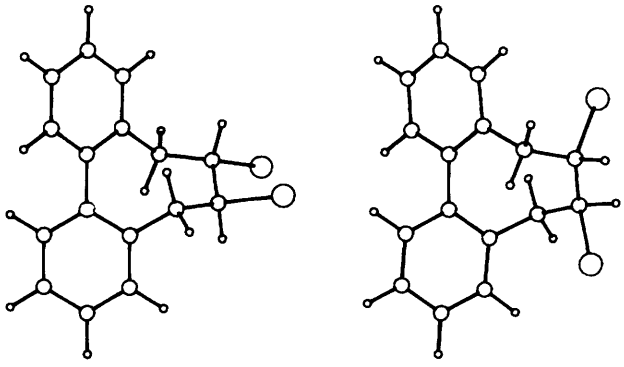


Fig. 1 The e,e and a,a forms of a *trans*-6,7-disubstituted 5,6,7,8-tetrahydrodibenzo[*a*,*c*]cyclooctene derivative

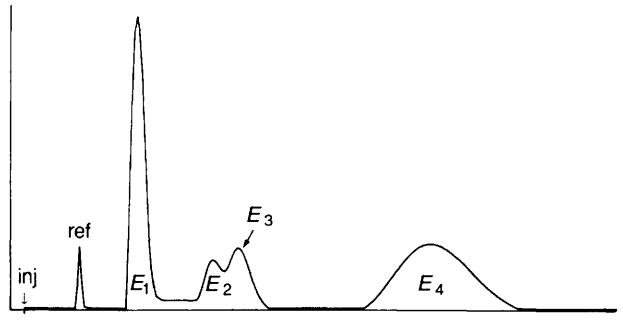


Fig. 2 Chromatogram of compound **2** at +20 °C [2.5 mg in methanol (1 cm^3) injected]. The chromatographic peaks are assigned to the following stereoisomers. E_1: (+)-e,e, E_2: (−)-a,a, E_3: (+)-a,a, and E_4: (−)-e,e, where (+) and (−) refer to *R* and *S* configurations of the biphenyl unit. UV detector trace (254 nm). Methanol flow rate 0.5 cm^3 min^{-1}. Reference compound is 1,3,5-tri-t-butylbenzene.

$$\alpha = k'_2/k'_1 \quad (1)$$

and k'_2 are the capacity factors for the first and second eluted enantiomer, respectively, with respect to a supposedly non-retained reference compound. The capacity factors are calculated from eqn. (2), where t_i and t_0 are the retention times of enantiomer and reference compound, respectively.[14]

$$k'_i = (t_i - t_0)/t_0 \quad (2)$$

The absolute configurations of 2,2′-bridged biphenyls were established by Mislow by asymmetric reduction of dibenzo- and dinaphtho-suberones.[15] In subsequent work on the chiroptical properties of bridged biaryls, Mislow and co-workers[16–20] established rules relating signs of Cotton effects to absolute configurations. For 2,2′-bridged biphenyls without polar substituents in the rings it was found that the rotational strength of the *A* transition[21,22] was always positive when the biphenyl unit had the *R* configuration. This regularity has recently been verified by an X-ray crystallographic study of optically active e,e- and a,a-forms of compound **2** by means of anomalous scattering.[5]

The CD spectra of a selection of the enantiomers and diastereoisomers listed in the Scheme are found in Table 2, and UV spectra of the racemic compounds with equilibrium diastereoisomer composition are found in Table 3. It is well established that the *A*-transition gives an absorption band in the range 235–238 nm for biphenyls with a saturated four-carbon bridge.[24,25] The notable hypsochromic shifts of the bands in the spectra of the *trans*-tetrahydrofurano compound **7** reflect a larger angle between the phenyl rings, 66° as compared with 58–62° for the other compounds as calculated by the MMP2-(85) force field method.[7]

Table 1 Capacity and selectivity factors

Compound		Methanol			Ethanol		
		k'_1	k'_2	α	k'_1	k'_2	α
1	*R*[a]	1.13	2.46	2.17	3.79	15.8	4.18
2 (e,e)	*R*	0.92	5.73	6.23	1.10	13.4	12.2
(a,a)	*S*	2.13	2.61	1.22	3.20	6.29	1.96
3 (e,e)	*R*	0.35	9.54	27.6	0.85	44.2	51.6
4	*R*				0.33	0.52	1.57
5	*R*				0.96	1.71	1.77
6	*R*				0.30	0.87	2.80
7	*R*	0.69	2.25	3.24	0.64	7.38	11.5
8	*R*				1.45	3.37	2.32
11	*R*	1.38	5.42	3.91	3.87	44.1	11.4
12 (e,e)	*R*	0.75	10.4	13.9			
(a,a)	*S*	1.46	9.07	6.21			
14 (e)	*R*				1.26	4.11	3.26
(a)	*S*				2.26	3.07	1.35
15 (e)	*R*				0.54	3.02	5.57
(a)	*S*				1.98	3.02	1.52
16 (e)	*R*	1.70	9.8	5.76	4.37	79	18.2
(a)	*S*	3.73	9.8	2.62	9.62	79	8.27
17 (e)	*R*	1.75	10.2	5.8			
(a)	*S*	2.07	10.2	4.9			
22	*R*	1.00	2.40	2.40	2.64	9.57	3.62

[a] Absolute configuration of the biphenyl unit in the first eluted enantiomer (E_1).

Table 2 CD spectra of (*R*)-5,6,7,8-tetrahydrodibenzo[*a*,*c*]cyclooctene **1** and some of its derivatives, all with the *R* configuration of the biphenyl unit. Solvent ethanol unless otherwise stated.

Compound	λ_{max}/nm ($\Delta\varepsilon$)
1[a,b]	277 (+0.57), 266sh[c] (+0.83), 232 (+36.7), 217 (+77.3), 200sh (−96), 192.5 (−101)
2[b,d] (e,e)	277 (+0.93), 266.5 (+1.26), 235sh (+31), 221.5 (+102), 200 (−104)
2[b,d] (a,a)	275.5 (+0.21), 267.5 (+0.20), 233.5 (+41.6), 216.5 (+95), 195sh (−142)
3	275 (+0.52), 267.5 (+0.85), 234 (+22.7), 218 (+46.2), 201 (−53.5)
5	275 (+0.70), 267 (+0.74), 230sh[d] (+20), 217 (+76.0), 198.5 (−78.0)
6	275 (+0.4), 232.5 (+21.5), 219 (+44.1), 202 (−51.4)
7	270 (+0.32), 225 (+29.6), 213 (+59.2), 197 (−86.0)
8	278 (+0.62), 268 (+0.80), 235 (+23.3), 218 (+50.2), 202 (−55.8)
11	277 (+0.86), 266 (+1.12), 233.5 (+34.3), 217 (+77.3), 201 (−83.4)

[a] From ref. 23. [b] Solvent MeOH. [c] Shoulder [d] From ref. 5.

The first eluted enantiomer (E_1) of compounds **1**, **2** (e,e), **3** (e,e), **5** (e,e), **6** (e,e), **7**, **8**, **11**, **15** (e), **16** (e) and **22** displays a positive *A* band near 235 nm, showing that this enantiomer has the *R* configuration of the biphenyl unit (Table 1). For the dicarboxylic acid **4** (e,e) the qualitative CD spectrum, and for the monohydroxy compound **14** (e) the positive rotations of the E_1 enantiomer, indicate the same configuration. On the other hand, the first eluted enantiomers of **2** (a,a), **12** (a,a), **14** (a), **15** (a) and **16** (a), have the *S* configuration. Information about the absolute configuration is missing for the monochloro compound **17** (e and a), but the similarity of the k_i and α values with those for the monobromo compound **16** leave little doubt that the elution orders of the enantiomers are the same for the two compounds. It seems to be a general rule that the *S* enantiomers with respect to the biphenyl unit without substituents, or with at least one equatorial substituent, interact more strongly with TAC than do the *R* enantiomers, and for some compounds, such as **3** (e,e) and **16** (e), the difference is substantial. Likewise, *R* enantiomers with only axial substituents are more strongly retained than are the corresponding *S* enantiomers.

Table 3 UV spectra of 5,6,7,8-tetrahydrodibenzo[*a*,*c*]cyclooctene **1** and some of its derivatives. Solvent ethanol

Compound	λ_{max}/nm ($\Delta\varepsilon$)
1	273 (520), 263 (1 040), 234.5 (11 200), 212 (44 000), 208 (44 300)
2	275sh (500), 235 (12 100), 209.5 (46 900)
3	275 (750), 266.5 (1 170), 237 (10 800), 213.5 (40 200), 209.5 (40 800)
5	275 (840), 266 (1 180), 235 (11 500), 210 (44 000)
6	275 (650), 266 (1 180), 237.5 (11 300), 210 (42 900)
7	273 (460), 264 (720), 231.5 (8 500), 207 (35 000)
8	275 (520), 265 (930), 236 (11 500), 212 (43 700), 210 (43 600)
11	276 (340), 266 (420), 235.5 (10 700), 205 (42 900)
15	275 (480), 265.5 (800), 235.5 (11 900), 208 (44 200)

Besides these general rules, it is obvious that the capacity factors depend on the nature and orientation of the 6,7-substituents. It appears that compounds containing polar groups, which may confer high solubility in the mobile phase, such as the dicarboxylic acid **4**, the diester **5**, the bis-(hydroxymethyl) compound **6**, and the monohydroxy and monoacetoxy compounds **14** and **15**, have small capacity factors and also rather low selectivity factors. Another observation is that the a,a-conformers of *trans*-6,7-disubstituted compounds have lower selectivity factors than do the corresponding e,e-conformers (**2**, **12**), and the same difference seems to exist between the a and e forms of the monosubstituted compounds **14**–**17**. For compounds **2** and **12** the selectivity differences come both from an increase in k'_1 and from a decrease in k'_2 when going from e,e to a,a,. For the monosubstituted compounds the effect seems to be due mainly to k'_1, the k'_2-values being rather similar for e and a forms.

For the two *cis* compounds **11** and **22** the selectivity factors are lower than for the e,e-forms of the *trans* analogues **12** and **3**, and for *cis*-dichloride **11** it is even lower than for the a,a-form of its *trans*-analogue **12**. Except for isomer **12** (a,a,), this is a consequence of higher k'_1- and lower k'_2-values for the *cis* compounds. The k'_1-values show that a compound with an *R*-biphenyl unit and one axial and one equatorial substituent is more strongly bound to TAC than is the analogue with two equatorial substituents, but not the one with two axial substituents. The lower selectivity factors for the *cis* compounds with C_1 symmetry than for the *trans* analogues with C_2 symmetry is a further illustration of the favourable effect of C_n axes on chiral separation previously observed and analysed.[26]

The effect of changing the mobile phase from methanol to ethanol is quite striking. Both k'_1 and k'_2 are generally increased, the latter most strongly, resulting in improved selectivity. For some of the compounds, such as the e- and a-form of the monobromo compound **16**, the effect is drastic, k'_2 increasing from 9.8 to 79. Impressive increases of k'_2 are also observed for the *cis*-dichloro compound **11** and for the *trans*-dimethyl compound **3**. These effects may be explained if it is assumed that the substrates interact with a TAC surface covered by a layer of adsorbed eluent molecules. If methanol is replaced by ethanol as eluent, stronger hydrophobic interaction effects between substrate and CSP can be expected, which outweigh any effects of increased solubility of the substrate in the mobile phase. (According to the *Z*- and E_T-values,[27] even 95% aq. ethanol is considerably less polar than methanol). The high selectivity factors and the low retention of E_1 permit relatively large

Table 4 Retention times (min) in reversed-phase chromatography

Compound	Solvent				
	EtOH (abs.)	EtOH (95%)	MeOH (100%)	MeOH–water (9:1)	MeOH–water (8:2)
1	36.5	33.0	37.5	59.0	137.0
2 (e,e)	37.5	33.0	37.2	55.0	174.0
2 (a,a)	37.5	33.0	37.2	59.0	144.0
3	33.0	34.0	40.0	74.0	215.0
4	26.2	20.5	25.0	27.5	22.0
5	35.0	27.5	31.5	40.0	70.0
6	33.5	25.0	28.5	30.0	40.0
7	36.0	29.0	33.5	43.5	77.0
12 (e,e)	37.2	32.0	35.5	58.0	143.0
12 (a,a)	37.2	32.0	35.5	53.0	121.0

loadings, and also a change of eluent to obtain higher mass 'throughput' per unit time.

The effect of the hydrophobicity of the substrates on their partition between mobile and stationary phases was further confirmed by reversed-phase HPLC experiments (Table 4). The compounds studied show very similar retention with pure methanol, abs. ethanol, or 95% aq. ethanol as the stationary phase. Gradually increased water content does not have much effect on the retention of the hydrophilic diacid **4** or bis-(hydroxymethyl) compound **6**, but increases the retention of the more hydrophobic compounds. The effect is not so strong for the diester **5** or the tetrahydrofuran **7**, but is quite striking for the *trans*-dimethyl compound **3**. It is worth noting that the di-equatorial *trans*-compounds **2** and **12**, which have large dipole moments, are more strongly retained than are the less polar diaxial conformers, although the opposite order had been expected based on interactions with the polar solvent.

The usefulness of reversed-phase chromatography for studying the hydrophobicity of organic compounds has been demonstrated by Kaliszan *et al.*[28]

In conclusion, this study has provided a truly remarkable separation factor, 51.6, for the e,e-form of dimethyl compound **3** in ethanol. To our knowledge this is by far the highest separation factor ever reported for a separation on TAC. However, the α-values in the range 11–12 observed for compounds **2** (e,e) **7**. **11** and **16** (e) are also quite impressive. It seems as if the retention of *S*-biphenyl on TAC is moderately strong, especially with ethanol as the mobile phase, but it also follows from a comparison of the k'_2-value for compound **1** with those for other compounds that the interaction energy may be either increased or decreased by the substituents.

Experimental

Syntheses.—All the prepared compounds are solids, but m.p.s are not always given since the products are conformationally inhomogeneous. Hence the dibromo compound **2** shows m.p. 84–86 °C, whereas the a,a-and e,e-form melt at 103–104 and 105–106 °C, respectively. It was not always possible to obtain the individual forms crystalline. Purification was by flash chromatography[29] on silica gel (Merck 60, mesh 230–240). The structures follow from the ^1H and ^{13}C NMR (Varian XL-300 NMR spectrometer, Me_4Si as reference) and mass spectra (Finnigan 1021 mass spectrometer). DMSO is dimethyl sulphoxide.

The chromatographic separations using ethanol as the mobile phase were performed with the equipment already described,[30] using both a UV (225 nm) and a polarimetric (365 nm) detector. The separations with methanol were performed with a Conbrio-TAC column* attached to a Varian LDC Model 5000 HPLC instrument, working at 38 atm with the UV detector at 254 nm. When diastereoisomers and enantiomers were separated in order to record their CD spectra the columns were enclosed in glass mantles, through which cooled ethanol (0–5 °C) was circulated. 1,3,5-Tri-*tert*-butylbenzene was used as the non-retained reference. The methanol used as mobile phase was HPLC grade, and the ethanol contained 5% of water. Normally, samples (1–3 mg) dissolved in the mobile phase (1 cm^3) were injected. The flow rate was 0.5 cm^3 min^{-1} with methanol and 1.0 cm^3 min^{-1} with ethanol. The CD spectra were recorded directly on the chromatography fractions, using a Jasco Model J-500A spectropolarimeter, and the concentrations were determined from the UV spectra, recorded on a Cary Model 2290 spectrophotometer. The CD spectra of both enantiomers have been recorded for all compounds. The reversed-phase chromatography was performed with a Chromasil-C_8 column† with 10 mμ particle size and 250 × 10 mm inner volume.

trans-5,6,7,8-Tetrahydrodibenzo[*a,c*]cyclooctene-6,7-dicarboxylic acid **4** was prepared as described before.[9] δ_H(DMSO; 300 MHz) e,e-form: 2.16 (2 H, m, 5- and 8-H^a), 2.75 (2 H, m, 6- and 7-H), 2.88 (2 H, d, 5- and 8-H^b) and 7.35 (8 H, m). The a,a-form was not observed in the ^1H NMR spectrum; δ_C(DMSO; 75 MHz) e,e-form: 33.37, 48.05, 126.74, 128.28, 128.41, 129.26, 138.84, 139.65 and 175.76; a,a-form: 30.77, 42.02, 126.62, 127.2, 129.11, 130.19, 136.97, 140.74 and 174.63; *m/z* [70 eV (rel. intensity)] 296 (M^+, 14.3), 278 (13.8), 250 (38.8), 205 (36), 178 (100), 165 (80.5) and 89 (28.7).

Dimethyl trans-5,6,7,8-*Tetrahydrodibenzo*[a,c]*cyclooctene*-6,7-*dicarboxylate* **5**.—Treatment of diacid **4** (200 mg) with K_2CO_3 (500 mg) in MeOH (50 cm^3) and addition of MeI (220 mg) gave the corresponding diester **5** (170 mg, 78%), which was purified by flash chromatography on silica with methylene dichloride as mobile phase; δ_H($CDCl_3$; 300 MHz) e,e-form: 2.39 (2 H, m, 5- and 8-H^a), 2.94 (2 H, d, 5- and 8-H^b), 3.24 (2 H, m, 6- and 7-H), 3.72 (6 H, s, Me) and 7.35 (8 H, m). The a,a-form was detected in the region of the methyl ester absorption; δ_C($CDCl_3$; 75 MHz) e,e-form: 33.80, 48.17, 52.20, 126.82, 128.26, 128.85, 129.60, 138.85, 140.29 and 175.36; a,a-form: 31.43, 42.67, 51.39, 127.44, 128.52, 129.71, 129.77, 137.00, 141.44 and 174.01; *m/z* 324 (M^+, 30.8), 264 (54.3), 205 (58.5), 178 (100), 165 (67.2) and 59 (25.8).

trans-5,6,7,8-Tetrahydro-6,7-bis(hydroxymethyl)dibenzo-[*a,c*]cyclooctene **6** was prepared essentially as described before,[13] the main difference being that the acid **4** instead of the ester **5** was reduced (2 mol equiv. $LiAlH_4$, 3 h reflux in dry THF, yield nearly quantitative); δ_H($CDCl_3$; 300 MHz) e,e-form: 1.7 (2 H, OH), 1.7 (2 H, m, 6- and 7-H), 2.25 (2 H, m, 5- and 8-H^a), 2.76 (2 H, d, 5- and 8-H^b), 3.62 (1 H, dd), 3.82 (1 H, dd) and 7.3 (8 H, m); a,a-form: 1.7 (2 H, OH), 2.11 (2 H, m, 6-and 7-H), 2.51 (1 H, dd), 2.8 (2 H, d) and 3.4 (1 H, dd); other peaks are hidden under the e,e-form peaks; δ_C($CDCl_3$; 75 MHz) e,e-form: 35.57, 45.15, 67.60, 126.07, 127.81, 128.51, 129.36, 140.50 and 140.91; a,a-form: 30.52, 38.14, 65.07, 126.96, 129.79, 130.61, 135.70 and 137.13; *m/z* 268 (M^+, 36), 250 (59), 232 (38), 219 (68.5), 203 (42), 191 (65.7), 179 (100), 165 (84), 69 (79.6) and 41 (75).

trans-1,3,3a,4,13,13a,14-Hexahydrodibenzo[4′,5′,6′,7′]cyclo-octeno[*c*]furan **7** was prepared by treatment of diol **6** (150 mg) with Ph_3P (160 cm^3) followed by addition of bromine (100 mg) in dry 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (DMPU; 20 cm^3); the reaction mixture was heated to 50 °C for 1 h, then worked up with water, diethyl ether was added, and the organic layer was separated, dried with $MgSO_4$, and evaporated. The solid material was flash chromatographed on silica with hexane

* Perstorp Biolytica AB, Lund, Sweden.

† EKA Nobel (Kungälv, Sweden).

to give compound **7** (75 mg, 55%), m.p. 142–143 °C; $\delta_H(CDCl_3$; 300 MHz) 1.91 (2 H, m, 3- and 13-H), 2.31 (2 H, m, 4- and 13-H^a), 2.68 (2 H, d, 4- and 13-H^b), 3.44 (2 H, m), 4.08 (2 H, m) and 7.25 (8 H, m); $\delta_C(CDCl_3$; 75 MHz) 33.04, 49.13, 73.06, 126.18, 128.17, 129.17, 130.73, 140.50 and 140.59; *m/z* 250 (M^+, 100) and 69 (17).

trans-1,5,5a,6,15,15a-*Hexahydrodibenzo*[4′,5′,6′,7′]*cyclooct-eno*[*e*][1,3]*dioxepin*-3-*one* **8**.—A 20% phosgene–toluene solution (0.5 cm^3) was injected into a solution of compound **6** (100 mg) in dry toluene (50 cm^3). The reaction mixture was stirred overnight, then worked up with water, diethyl ether was added, and the organic layer was separated, and dried over $MgSO_4$. Evaporation of the solvents gave a solid material, identified as carbonate **8** (74 mg, 68%), m.p. 176–178 °C; $\delta_H(CDCl_3$; 300 MHz) 1.93 (2 H, m, 5a- and 15a-H), 2.23 (2 H, m, 6- and 15-H^a), 2.42 (2 H, d, 6- and 15-H^b), 4.00 (2 H, m), 4.27 (2 H, m) and 7.32 (8 H, m); $\delta_C(CDCl_3$; 75 MHz) 34.79, 47.13, 76.12, 126.77, 128.40, 129.10, 129.32, 139.21, 139.94 and 154.78; ν_{max}(KBr)/cm^{-1} 3040w, 3020w, 2980w, 2960w, 2920w, 2860w, 1770s, 1760s, 1630w, 1480, 1465, 1243, 1200, 1095, 1060, 765, 760 and 755; *m/z* 294 (M^+, 91), 250 (13), 217 (43.5), 191 (33.8), 178 (100), 165 (78.7) and 44 (37).

5,6,7,8-Tetrahydrodibenzo[*a*,*c*]cyclooctene **1** and *trans*-6,7-dibromo-5,6,7,8-tetrahydrodibenzo[*a*,*c*]cyclooctene **2** were prepared as described before.[4,5,10,23]

trans-6,7-*Dichloro*-5,6,7,8-*tetrahydrodibenzo*[a,c]*cyclooctene* **12**.—Addition of Cl_2 (50 cm^3 of a saturated solution in CCl_4) to 5,8-dihydrodibenzo[*a*,*c*]cyclooctene **9**[10] (250 mg) in CCl_4 (50 cm^3) at −78 °C with or without $SbCl_5$ as catalyst gave a mixture of compounds. The reaction mixture was purified by flash chromatography over silica with pentane as mobile phase. All fractions were found by GLC to contain the three compounds **10**, **11** and **12**, which were separated by HPLC on silica with pentane as mobile phase. The first peak in GLC was identified as compound **12**, the second peak as a rearrangement product **10**, and the last one as the *cis*-isomer **11** of compound **12**.

Data for compound **12**; $\delta_H(CDCl_3$; 300 MHz) e,e-form: 2.87 (2 H, m, 5- and 8-H^a), 3.21 (2 H, dd, 5- and 8-H^b), 4.2 (2 H, m, 6- and 7-H) and 7.3 (8 H, m); a,a-form: 2.88 (2 H, m, 5- and 8-H^a), 3.09 (2 H, d, 5- and 8-H^b), 4.57 (2 H, m, 6- and 7-H) and 7.3 (hidden); $\delta_C(CDCl_3$; 75 MHz) e,e-form: 41.64, 67.79, 127.77, 128.49, 129.03, 130.14, 136.36 and 140.10; a,a-form: 32.58, 61.29, 126.66, 127.18, 129.86 and 133.78; two quaternary carbon resonances are hidden; *m/z* 278 (M^+, 45), 276 (M^+, 69), 205 (100), 178 (80.5), 165 (91.6) and 89 (50).

Spectral data for compound **10**; $\delta_H(CDCl_3$; 300 MHz) 2.59 (1 H, dd), 3.18 (1 H, dd), 3.22 (1 H, dd), 3.97 (1 H, dd), 4.21 (1 H, dd), 4.92 (1 H, ddd) and 7.3 (8 H, m); $\delta_C(CDCl_3$; 75 MHz) 42.24, 43.96, 46.22, 65.87, 125.93, 127.72, 127.81, 128.02, 128.06, 128.60, 128.62, 136.08, 140.22 and 143.87; *m/z* 280 (M^+, 3.7), 278 (M^+, 25), 276 (M^+, 38.8), 205 (37.9), 191 (100), 178 (47.2) and 165 (30.5).

cis-6,7-Dichloro-5,6,7,8-tetrahydrodibenzo[*a*,*c*]cyclooctene **11** was obtained as described above; $\delta_H(CDCl_3$; 300 MHz) 2.89 (1 H, dd, 5-H^a), 2.95 (1 H, d, 8-H^a), 3.15 (1 H, dd, 8-H^b), 3.22 (1 H, dd, 5-H^b), 4.39 (1 H, ddd, 7-H), 4.56 (1 H, tdd, 6-H) 7.3 (8 H, m); $\delta_C(CDCl_3$; 75 MHz) 38.19, 38.29, 61.54, 65.16, 126.99, 127.38, 127.45, 128.47, 129.84, 129.89, 130.16, 133.33, 133.71, 133.81, 137.73 and 140.47; *m/z* 278 (M^+, 24), 276 (M^+, 45), 205 (100), 178 (89.8), 165 (97.7), 89 (51) and 75 (35.6).

5,6,7,8-*Tetrahydrodibenzo*[a,c]*cycloocten*-6-*ol* **14**.—Epoxidation of compound **9** (350 mg) with MCPBA (325 mg) in CH_2Cl_2 (50 cm^3) gave the corresponding epoxide **13**, which was purified by flash chromatography on silica with CH_2Cl_2–hexane (25 : 75) as mobile phase (295 mg, 78%).

The epoxide (250 mg) was then treated with $LiAlH_4$ in dry THF (50 cm^3) and the mixture was refluxed for 1 h before being worked up by addition of saturated aq. NaCl. Diethyl ether was added and the organic layer was separated and dried with Na_2SO_4. Evaporation of solvent produced title compound **14** (240 mg, 95%), m.p. 76–78 °C.

Spectral data for compound **13** (m.p. 93–94 °C); $\delta_H(CDCl_3$; 300 MHz) 2.50 (1 H, dd, 5-H^a), 3.10 (1 H, d, 8-H^a), 3.4 (1 H, dd, 5-H^b), 3.43 (1 H, ddd, 7-H), 3.56 (1 H, dd, 8-H^b) and 3.59 (1 H, ddd, 6-H); $\delta_C(CDCl_3$; 75 MHz) 32.06, 33.10, 52.80, 56.51, 126.23, 126.28, 126.94, 127.30, 127.48, 127.79, 127.95, 128.42, 131.14, 135.39, 136.54, 140.67 and 141.87; *m/z* 222 (M^+, 29.7), 193 (21.7), 225 (100) and 165 (36.4).

Spectral data for compound **14**; $\delta_H(CDCl_3$; 300 MHz) e-form: 1.55 (1 H, m), 1.6 (1 H, s, OH), 2.19 (1 H, m), 2.35 (1 H, m), 2.56 (1 H, dd, 5-H^a), 2.63 (1 H, dd), 2.80 (1 H, d, 5-H^b), 3.9 (1 H, m, 6-H) and 7.3 (8 H, m); a-form: 1.77 (1 H, m), 2.98 (1 H, ddd), 4.16 (1 H, m, 6-H), other peaks are hidden under those of the e-form; $\delta_C(CDCl_3$; 75 MHz) e-form: 28.71, 38.15, 42.87, 73.53, 126.19, 126.48, 127.79, 128.03, 128.95, 129.29 (two overlapping peaks), 129.92, 137.46, 140.09, 141.08 and 141.55; a-form: 26.50, 37.80, 38.39, 65.30, 125.90, 126.92, 127.23, 127.97, 129.06, 129.15, 129.85, 131.72, 134.31, 140.30, 142.16 and 142.29; *m/z* 224 (M^+, 11.9), 222 (41.6), 194 (20), 179 (100), 165 (48.6) and 89 (16).

5,6,7,8-*Tetrahydrodibenzo*[a,c]*cycloocten*-6-*yl Acetate* **15**.—To a solution of the alcohol **14** (50 mg) in methylene dichloride (20 cm^3) was added acetyl chloride (20 mg). The reaction mixture was stirred and kept overnight, and then worked up by addition of water. Diethyl ether was added, and the organic layer separated and dried over Na_2SO_4. Evaporation of the solvent produced the acetate **15** (51 mg, 87%), m.p. 82–84 °C; $\delta_H(CDCl_3$; 300 MHz) e-form: 1.69 (1 H, m), 2.07 (3 H, s), 2.22 (1 H, m), 2.51 (1 H, d), 2.57 (1 H, dd, 5-H^a), 2.71 (1 H, ddd), 2.81 (1 H, d, 5-H^b), 4.94 (1 H, m, 6-H) and 7.3 (8 H, m); a-form: 1.83 (1 H, m), 2.05 (3 H, s), 2.32 (1 H, m), 3.21 (1 H, dd), 5.21 (1 H, m, 6-H), other peaks are hidden under those of the e-form; $\delta_C(CDCl_3$; 75 MHz) e-form: 21.67, 28.85, 34.20, 39.32, 75.60, 126.33, 126.73, 128.02, 128.05, 129.02, 129.12, 129.37, 130.26, 136.57, 140.04, 140.92, 141.25 and 170.41; a-form: 21.25, 27.60, 34.94, 35.58, 68.99, 126.02, 126.94, 126.86, 129.16, 129.24, 131.36, 135.19, 140.47, 141.49, 141.94 and 170.71. Two other peaks are hidden under those of the e-form; *m/z* 266 (M^+, 6), 206 (53), 191 (30.6), 178 (49), 165 (36.5) and 43 (100).

6-*Bromo*-5,6,7,8-*tetrahydrodibenzo*[a,c]*cyclooctene* **16**.—Treatment of hydroxy compound **14** (60 mg) with PBr_5 (125 mg) in methylene dichloride (50 cm^3) and stirring of the reaction mixture overnight afforded the corresponding monobromo compound **16**, which was purified by chromatography on silica with hexane as the mobile phase (46 mg, 72%); $\delta_H(CDCl_3$; 300 MHz) e-form: 2.2 (2 H, m), 2.7 (2 H, m), 2.95 (1 H, dd, 5-H^a), 3.37 (1 H, d, 5-H^b), 4.33 (1 H, m, 6-H) and 7.3 (8 H, m); a-form: 2.83 (1 H, dd, 5-H^a), 3.14 (1 H, dd, 5-H^b), 4.79 (1 H, m, 6-H), other peaks are hidden under those of the e-form; $\delta_C(CDCl_3$; 75 MHz) e-form: 32.52, 41.12, 44.26, 53.85, 126.48, 127.13, 128.18, 128.31, 128.97, 129.35, 129.42, 130.12, 138.40, 139.75, 140.60 and 140.68; a-form: 28.04, 39.44, 40.50, 53.39, 126.11, 126.99, 128.14, 129.54, 129.65, 133.45, 135.30, 140.28, 141.45 and 141.54. Two other peaks are hidden under those of the e-form; *m/z* 288 (M^+, 19), 286 (M^+, 20.4), 207 (61.5), 191 (37.5), 178 (90.7), 165 (100) and 89 (51.4).

6-*Chloro*-5,6,7,8-*tetrahydrodibenzo*[a,c]*cyclooctene* **17**.—To a solution of hydroxy compound **14** (65 mg) in methylene dichloride (25 cm^3) was added gradually the calculated amount of $SOCl_2$ (50 mg). The reaction mixture was stirred overnight and worked up by addition of water. Purification of the chloride

17 was carried out as described for the bromide **16** (48 mg, 68%); $\delta_H(CDCl_3$; 300 MHz) e-form: 1.98 (1 H, m), 2.22 (1 H, m), 2.62 (1 H, m), 2.74 (1 H, dd), 2.85 (1 H, dd, 5-H^a), 3.2 (1 H, d, 5-H^b), 4.19 (1 H, m, 6-H) and 7.3 (8 H, m); a-form: 2.11 (1 H, m), 2.49 (1 H, m), 3.11 (1 H, dd, 5-H^b), 4.62 (1 H, m, 6-H), other peaks are hidden under those of the e-form; $\delta_C(CDCl_3$; 75 MHz) e-form: 30.93, 39.99, 43.54, 61.86, 126.50, 127.15, 128.16, 128.33, 129.04, 129.41, 129.46, 130.18, 137.61, 139.88, 140.87 and 140.90; a-form: 27.07, 38.73, 39.65, 58.43, 126.13, 126.62, 126.93, 129.35, 129.53, 133.51, 134.64, 140.42, 141.52 and 141.85, other peaks are hidden under those of the e-form; *m/z* 244 (M^+, 22.5), 242 (M^+, 75), 207 (31), 191 (27), 178 (76), 165 (100) and 89 (55.3).

cis-5,6,7,8-*Tetrahydro*-6,7-*dimethyldibenzo*[a,c]*cyclooctene* **22**.—This was prepared by a multi-step procedure starting from dimethyl 5-pyrrolidinodibenzo[*a,c*]cyclooctene-6,7-dicarboxylate **18** (600 mg).[12] Reduction with BH_3–THF [31] gave the diester **19** (220 mg, 45%). Catalytic hydrogenation of diester **19** (200 mg) with H_2 and Pd/C as catalyst gave a mixture of *cis*-**20** and *trans*-**5** in the ratio 2:1. $LiAlH_4$ reduction of this mixture gave the corresponding *cis*-and *trans*-bis(hydroxymethyl) compounds **6**. This mixture was treated with PBr_5 in methylene dichloride and the reaction products were purified by chromatography on silica with hexane as mobile phase. The major fraction was identified as *cis*-6,7-bis(bromomethyl)-5,6,7,8-tetrahydrodibenzo[*a,c*]cyclooctene **21** (115 mg). Reduction of dibromide **21** (80 mg) with $LiAlH_4$ in THF gave compound **22** (38 mg, 82%), $\delta_H(CDCl_3$; 300 MHz) 0.81 (3 H, d, Me), 1.05 (3 H, d, Me), 1.96 (2 H, m), 2.18 (1 H, d, 8-H^a), 2.34 (1 H, dd, 8-H^b), 2.54 (1 H, dd, 5-H^a), 2.74 (1 H, dd, 5-H^b) and 7.3 (8 H, m); $\delta_C(CDCl_3$; 75 MHz) 12.33, 21.75, 33.23, 35.40, 39.05, 40.42, 125.62, 125.88, 126.43, 127.66, 129.06, 129.42, 129.68, 131.76, 137.76, 140.53, 141.47 and 142.87; *m/z* 236 (M^+, 47), 207 (32.2), 193 (24), 179 (100), 165 (44) and 41 (21.7).

trans-5,6,7,8-Tetrahydro-6,7-dimethyldibenzo[*a,c*]cyclooctene **3** was prepared as described before;[13] $\delta_H(CDCl_3$; 300 MHz) e,e-form: 1.1 (6 H, d, Me), 1.4 (2 H, m, 6- and 7-H), 2.24 (2 H, m, 5- and 8-H^a), 2.46 (2 H, d, 5- and 8-H^b) and 7.3 (8 H, m); a,a-form: 0.94 (6 H, d), 1.8 (2 H, m), 2.56 (2 H, dd), other peaks are hidden under those of the e,e-form; $\delta_C(CDCl_3$; 75 MHz) e,e-form: 23.66, 40.90, 42.51, 125.77, 127.61, 128.40, 129.45, 140.38 and 141.95; a,a-form: 20.00, 32.89, 35.40, 125.82, 126.32, 129.82, 131.79, 137.98, 141.78, other peaks are hidden under those of the e,e-form; *m/z* 236 (M^+, 48), 207 (27.9), 193 (21.2), 179 (100), 165 (42) and 41 (18.5).

Spectral data for compound **19**; $\delta_H(CDCl_3$; 300 MHz) 3.73 (6 H, s), 7.15 (2 H, m), 7.23 (2 H, m), 7.37 (4 H, m) and 7.92 (2 H, s); $\delta_C(CDCl_3$; 75 MHz) 52.21, 127.23, 127.59, 128.42, 130.90, 131.16, 135.73, 140.76, 143.45 and 166.04; *m/z* 320 (M^+, 2.8), 289 (9.6), 261 (41.3), 229 (44.2), 217 (32.7), 202 (100), 189 (21), 178 (13.4) and 59 (53.8).

Spectral data for compound **20**; $\delta_H(CDCl_3$; 300 MHz): 2.58 (1 H, dd, 5-H^a), 2.69 (1 H, dd, 7-H), 2.80 (1 H, dd, 8-H^a), 3.20 (3 H, s), 3.26 (1 H, dd, 5-H^b), 3.46 (1 H, d, 8-H^b), 3.56 (1 H, m, 6-H), 3.67 (3 H, s) and 7.3 (8 H, m); $\delta_C(CDCl_3$; 75 MHz): 30.40, 33.13, 43.27, 48.27, 51.20, 52.21, 126.38, 127.06, 127.49, 128.24, 129.17, 129.33, 129.59, 130.03, 136.24, 140.75, 141.26, 141.30, 173.09 and 173.88.

Spectral data for compound **21**; $\delta_H(CDCl_3$; 300 MHz) 2.25 (2 H, m), 2.48–2.58 (3 H, m), 3.2 (2 H, m), 3.44 (2 H, m) and 3.55 (1 H, dd); $\delta_C(CDCl_3$; 75 MHz) 30.77, 32.21, 34.06, 37.84, 41.10, 49.04, 126.42, 126.91, 127.29, 128.19, 128.71, 129.66, 130.29, 131.41, 135.42, 140.20, 140.39 and 141.35.

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