The First Efficient Synthesis and Optical Resolution of Monosubstituted Cyclotribenzylenes

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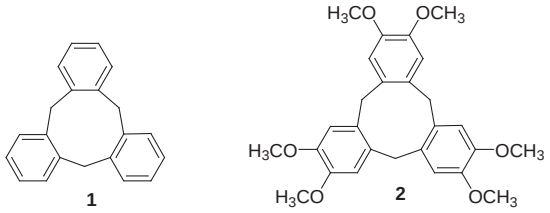
Dedicated to Professor Emanuel Vogel on the occasion of his 75th birthday

Abstract: A new and high yielding synthetic route to monosubstituted cyclotribenzylenes **6** via the cyclocondensation of benzene with a suitably monosubstituted diol **20**, obtained from ozonolysis of the corresponding dibenzosuberene precursor **19**, was developed for the first time! The dibenzosuberene itself could be readily prepared in large quantities from inexpensive starting materials in five steps. Using this synthetic approach, a mono bromosubstituted cyclotribenzylene **12a** was synthesized on large scale. Another four monosubstituted cyclotribenzylenes **21**−**24** were also prepared either via bromine/lithium exchange followed by subsequent quenching with external electrophiles or a copper mediated reaction with cyanide. These molecules adopt a rigid crown conformation as shown by X-ray analysis and temperature dependent NMR studies. The barrier to inversion is quite high, requiring temperatures well above 120 °C before inversion takes place. Futhermore, such monosubstituted cyclotribenzylenes are planar chiral and after optical resolution, using HPLC, we were able to obtain the first planar chiral C1-symmetric cyclotribenzylenes in form of the optically pure enantiomers of **12a**, the CD spectra of which are exact mirror images over the entire spectral range.

Key words: carbocycles, cyclophanes, CD spectroscopy, planar chirality

For the design of supramolecular receptors that also function in aqueous solvents, hydrophobic binding pockets and therefore concave shaped hydrocarbons are useful building blocks. They assure strong complexation, especially in combination with other binding sites, which allow the formation of additional ion pairs or cation-π interactions.[2] One such possible concave binding pocket is the cyclotribenzylene unit **1** ([1.1.1]-*ortho*-cyclophane or 10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene, respectively).[3,4] This molecule has a rather rigid bowl shaped conformation which should make it an ideal binding motif for the complexation of other unpolar groups, such as methyl, in its shallow cavity in water.[5] Interestingly, the supramolecular chemistry of cyclotribenzylenes is largely unexplored so far. This is in striking contrast to the closely related cyclotriveratrylenes **2**[6] which have already been used in this context (Figure).[2,7] Probably, this is mainly due to the straightforward synthesis of the later compounds by cyclocondensation of the veratryl cation and the possibilities of a further functionalization at the upper rim of the bowl using the phenolic OH groups there.[6] However, cyclotriveratrylenes are susceptible to easy ring cleavage under certain chemical conditions, which limits their further functionalization and use in chemical syntheses in general.[6,8] We are therefore interested in using the more stable parent compound, the cyclotribenzylene unit **1** itself, as a hydrophobic binding pocket in supramolecular assemblies.



Figure

To be able to incorporate the cyclotribenzylene moiety into supramolecular binding motifs, at least one anchoring point, for example a halosubstituent, at the periphery of the cyclotribenzylene is needed. Unfortunately, monosubstituted cyclotribenzylenes have not yet been described in the literature at all, except for one preliminary communication which claims the preparation of a mononitro and a monoformyl derivative by the corresponding functionalization of the parent hydrocarbon **1**, while the attempted bromination was reported not to give a monobrominated derivative but only intractable product mixtures.[9] However, the syntheses were only performed on a sub millimolar scale, the reported yields were rather low (21% and 46%, respectively) and only crude spectroscopic data were presented for the isolated products. In our attempts to reproduce this result, we were not able, for example, to isolate any mononitrated derivative but always ended up with isomeric mixtures of various multiply substituted products. This is not surprising taking into account, that there are two sets of six equivalent aromatic positions in the parent hydrocarbon and a selective functionalization of just one of them is rather difficult to achieve. Indeed, very similar reaction conditions that were claimed in this report to give the mononitrated cyclotribenzylene (large excess of concentrated nitric acid and sulfuric acid at 100 °C) were used by Kuck et al. to prepare a hexanitro derivative of tribenzotriquinacene, a closely related molecule.[10] Hence, even if it might work in low yields the mono-func-

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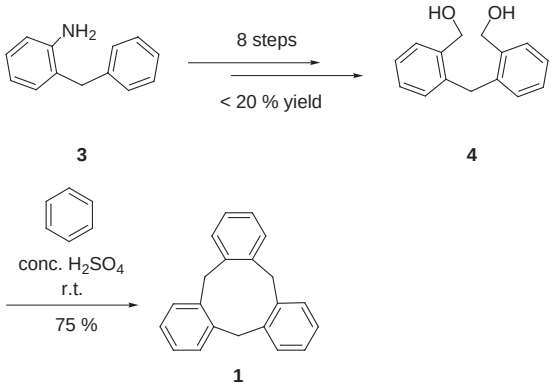
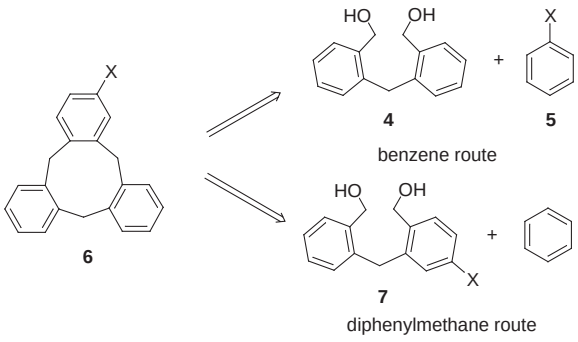
tionalization of cyclotribenzylene **1** itself is not useful for a general large scale synthesis of monosubstituted cyclotribenzylenes. Consequently, a new and general approach for the deliberate synthesis of selectively monosubstituted cyclotribenzylenes **6** is still needed and we wish to report here the successful completion of this objective.



Scheme 1 The original synthesis of **1** by Sato et al.

Synthetic Strategy

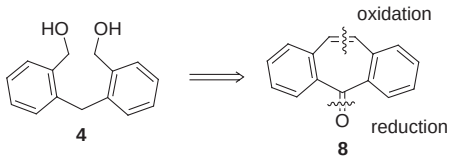
The parent hydrocarbon cyclotribenzylene (**1**) itself was first synthesized by Sato et al. in 1973 by a surprisingly high yielding Friedel–Crafts cyclocondensation (75%) of a bis-benzylic alcohol **4** with benzene in the presence of concentrated sulfuric acid as catalyst using high dilution conditions (Scheme 1).[2] Based on this synthetic approach,[11] the incorporation of a substituent into the molecule should, in general, be achievable by either one of two strategies (Scheme 2). One possibility is the cyclocondensation of the unsubstituted diol **4** with a monosubstituted benzene derivative **5** (the 'benzene route'). Alternatively, a monosubstituted diol building block **7** can be condensed with unsubstituted benzene (the 'diphenylmethane route'). To the best of our knowledge, none of these two approaches to monosubstituted cyclotribenzylenes **6** has been tested before.



Scheme 2 Two possible routes to monosubstituted cyclotribenzylenes **6**.

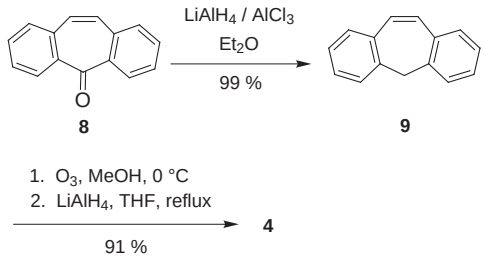
The 'Benzene Route'

We set out to test the usefulness of the benzene route by applying the cyclocondensation conditions to the reaction of diol **4** with benzene derivatives **5** such as acetanilide (X = NHAc), bromobenzene (X = Br), and anisole (X = OCH_3), respectively. However, the initial synthesis for the unsubstituted diol **4** reported by Sato et al. takes eight steps and has an overall yield of less than 20% (Scheme 1).[3,12] Therefore, we decided to first develop an improved synthetic approach to the unsubstituted diol **4** to make it readily accessible on large scale for the subsequent condensation studies. We reasoned that diol **4** could be prepared starting from commercially available dibenzosuberenone (**8**) by reductive removal of the carbonyl group and oxidative cleavage of the double bond with subsequent reductive work-up (Scheme 3).



Scheme 3 The retrosynthetic approach to diol **4** starting from dibenzosuberenone **8**.

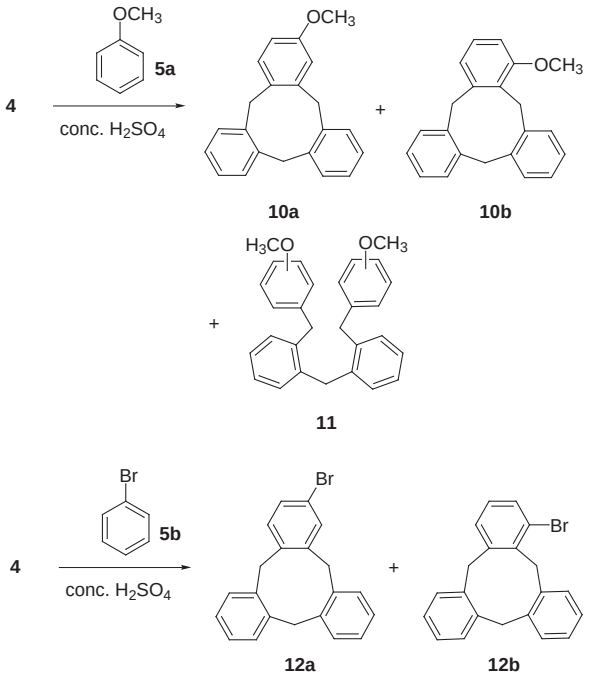
Starting from dibenzosuberenone (**8**), the carbonyl group was first reductively removed with lithium aluminium hydride and aluminium trichloride to obtain dibenzosuberene (**9**) in quantitative yield.[13] We then used ozonolysis to cleave the double bond, and after reductive work-up with lithium aluminium hydride in THF under reflux, diol **4** was directly obtained in 91% isolated yield. Thus, diol **4** is now readily available in two steps and 90% overall yield from the inexpensive commercial starting material dibenzosuberenone (**8**) (Scheme 4).[14]



Scheme 4 Our new synthetic approach to diol **4**.

Different monosubstituted benzene derivatives **5** were then used to attempt the cyclocondensation with diol **4** in the presence of concentrated sulfuric acid. None of these reactions, however, gave satisfactory results for the formation of an isomerically pure monosubstituted cyclotribenzylene **6**. The reaction of diol **4** with acetanilide in nitrobenzene as a solvent failed completely, probably either due to the low reactivity of acetanilide under such acidic conditions or due to the low solubility of its protonated form in the organic layer of this biphasic reaction

mixture. The much more reactive anisole (**5a**) did react under these conditions with diol **4**, but as GC-MS analysis showed, a complex mixture of various regioisomers of both cyclic mono- (**10a/b**) and several acyclic diadducts **11** was obtained in a ratio of approximately 1:1 (Scheme 5). Bromobenzene (**5b**) gave only the desired mono-cyclocondensation product **12** in very good yields of 66%, with only traces of the disubstituted acyclic adducts being formed. But again a mixture of two regioisomers **12a/b** was obtained as could be shown by NMR analysis. Unfortunately, we were not able to separate the two regioisomers using HPLC or any other chromatographic technique. Therefore, although monosubstituted cyclotribenzylenes can be synthesized following the 'benzene route', a large scale preparation of isomerically pure compounds using this approach is rather difficult. There might be a chance of either improving the isomeric ratio or facilitating the isomer separation if additional monosubstituted benzene derivatives are tested, but we did not pursue this synthetic route any further.

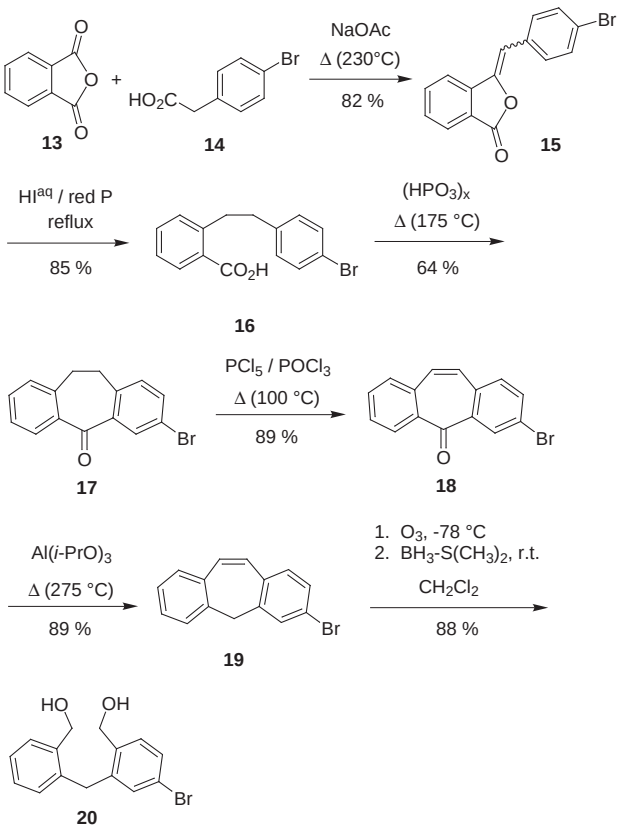


Scheme 5 Applying the 'benzene route' to the synthesis of monosubstituted cyclotribenzylenes.

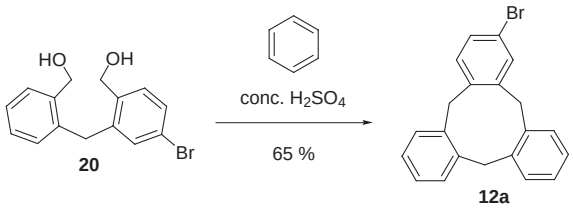
The 'Diphenylmethane Route'

The cyclocondensation of an already substituted diol **7** with benzene, according to our second synthetic strategy (Scheme 2), offers the advantage that the formation of different regioisomers such as **12a/b** in the cyclization step is not possible and only one pure product is expected, the structure of which depends on the position of the substituent in diol **7**. However, this route requires the synthesis of suitably monosubstituted diols or of the corresponding monosubstituted dibenzosuberene precursors (such as **19** for example). The attempted introduction of a bromo or nitro substituent into readily available unsubstituted dibenzosuberene (**9**) or dibenzosuberenone (**8**) failed for the same reasons as the direct derivatization of cyclotribenzylene (**1**) itself. In our hands, only disubstituted products were obtained in decent amounts.[15] These reactions were further complicated by undesired side reactions at the double bond or the benzylic positions, respectively. Therefore, it appeared that the substituent had at best already to be introduced before the formation of the tricyclic dibenzo[*a*,*d*]cycloheptene ring system. However, most of the syntheses reported for this class of compounds, which have been of interest in the past as potential antipsychotic agents (e.g. clozapine analogues),[16] so far either led to unsubstituted or symmetrically disubstituted derivatives.[17] We therefore developed a new and efficient six step synthesis to the previously unknown 5-bromo-2,2'-bis(hydroxymethyl)diphenylmethane **20**.[18] The synthesis is described in Scheme 6. Following a known procedure, 3-bromo-dibenzosuberone (**17**) was prepared in three steps from commercially available starting materials.[19,20] Condensation of *p*-bromophenyl acetic acid **14** with phthalic anhydride (**13**) in the presence of sodium acetate at 230−240 °C gave the corresponding phthalide **15** in 82% yield.[20,21] Subsequent reductive ring opening with aq hydroiodic acid/red phosphorus lead to the corresponding benzoic acid derivative **16** in 85% yield, which could be cyclized to the 3-bromo-dibenzosuberone (**17**) using polyphosphoric acid (64%). In analogy to work by Slates and Looker,[19c,22] the introduction of the double bond in the bromo derivative **17** was achieved in very good yields (89%) by reaction with phosphorus pentachloride in phosphorus oxychloride. Due to the bromo-substituent, the reduction of the carbonyl group in **18** was not possible with lithium aluminum hydride and aluminium trichloride according to the protocol that we used before in the synthesis of the unsubstituted diol **4,** since this would also cause debromination. Wolff−Kishner reduction[15] did work without debromination, but also caused substantial reduction of the double bond. A clean reductive removal of the carbonyl group in **18** in the presence of the bromine substituent was finally achieved in 89% yield by using modified Meerwein−Pondorf−Verley conditions (aluminium trisisopropylate at 275 °C).[23] However, the reductive work-up after ozonolysis of **19** proved to be more difficult than expected.[24,25] Finally, the use of the borane/dimethyl sulfide complex[26] in dichloromethane was successful and yielded the 5-bromo-2,2′-bis(hydroxymethyl)diphenylmethane (**20**) in 88% isolated yield. Thus, diol **20** can now be prepared for the first time, even in multi-gram quantities, within a few days!

With the necessary bromosubstituted diol **20** in hand, we attempted the cyclocondensation with benzene (Scheme 7) using slightly modified conditions (high dilution conditions at room temperature over 3 days). The reaction proceeded smoothly and the corresponding bromosubstituted cyclotribenzylene **12a** was finally obtained in 65% yield as a white crystalline solid.



Scheme 6 Synthesis of monosubstituted diol **20**.

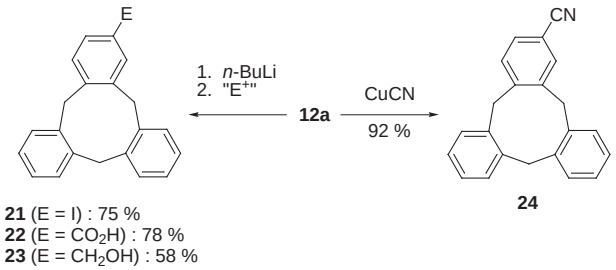


Scheme 7 Cyclocondensation of **20** with benzene to yield the monosubstituted cyclotribenzylene **12a**.

Therefore, to the best of our knowledge, this newly developed synthetic approach starting from inexpensive commercially available compounds with a total yield of more than 20% over seven steps provides the first successful and efficient synthesis of monosubstituted cyclotribenzylenes. The reactions can be readily performed on large scale and allow the synthesis of gram-quantities of **12a** within a few days.

Further Derivatization

Even though preliminary experiments suggest, that starting from other para-substituted phenyl acetic acids a whole variety of various monosubstituted cyclotribenzylenes **6** can be prepared following this route, the bromo substituent in **12a** already provides a useful synthetic handle for the introduction of other substituents into the cyclotribenzylene unit. Using bromine/lithium exchange and subsequent reaction of the resulting lithium organyl with an external electrophile, another three new monosubstituted cyclotribenzylenes **21**–**23** were prepared in good yields using iodine, carbon dioxide and paraformaldehyde as electrophiles, respectively (Scheme 8). Furthermore, by reaction of **12a** with copper(I) cyanide the corresponding nitrile **24** could be prepared in excellent yield (92%). All new compounds were fully characterized and gave satisfactory spectroscopic data. Hence, a variety of monosubstituted cyclotribenzylenes can now be prepared in large quantities via our new synthetic approach to **12a**. They can be employed for further studies or for the incorporation into other molecular assemblies using the various functional groups in those derivatives. The halo substituent could for example be used for palladium catalyzed coupling reactions, and the carboxyl or benzylic alcohol group for amidation or esterification reactions.



Scheme 8 Further derivatization of the bromosubstituted cyclotribenzylene **12a**.

Characterization and Physical Properties

NMR studies showed that **12a** was formed as a pure and single isomer in the cyclocondensation reaction in contrast to the reaction of bromobenzene **5b** with the unsubstituted diol **4**. There is one aromatic proton at $\delta = 7.39$ which is significantly shifted to lower field relative to the other aromatic protons, which give signals in the range from $\delta = 6.75$–7.16. This signal must therefore correspond to one of the α positions next to the electronegative bromo substituent, as could also be established by 2D NMR coupling experiments. The coupling constant furthermore shows that there is no direct neighbouring proton next to this specific one ($^4J_{H,H} = 4$ Hz). As this proton also shows a NOE with the protons of the neighbouring methylene bridge, it must be *ortho* to the ring junction, which means that the bromo substituent is in the *meta* position. Hence, the 2-substituted regioisomer **12a** was formed, and not the 1-substituted isomer **12b** for which one would not expect a NOE between the aromatic proton next to the bromine and the methylene bridge. A complete assignment of the full NMR spectrum of **12a** was also possible using 2D NMR experiments (see supplementary material). Although the regiochemistry of the substitution could already be assigned from the NMR, the structure and correct substitution pattern were further established without doubt by X-ray structure analysis of both the bro-

mosubstituted cyclotribenzylene **12a** and the iodo derivative **21**. Suitable crystals for the structure determination were obtained from acetone solns. The structures clearly proved that the halo substituents are in the *meta* position relative to the ring junction and that the molecule adopts a similar crown conformation as the parent hydrocarbon **1** (Figure 1).[2]

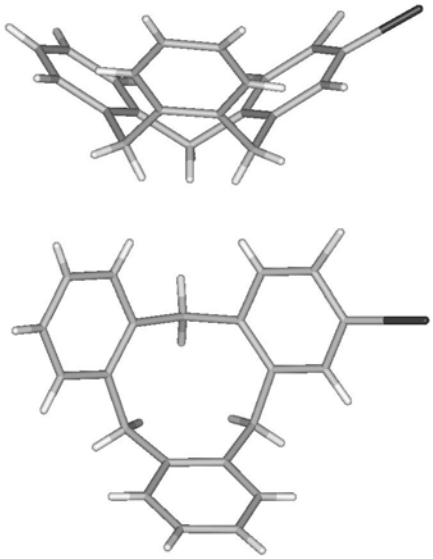


Figure 1 X-ray structure of the iodosubstituted cyclotribenzylene **21** (top: side view; below: view from top into the cavity).

In contrast to the parent hydrocarbon **1**, monosubstituted cyclotribenzylenes such as **12a** or **21**–**24** are asymmetric molecules giving rise to planar chirality. Hence, all these compounds are formed as a racemic mixture of the two corresponding enantiomers. To the best of our knowledge, we were able to resolve for the first time such a C1 symmetric cyclotribenzylene into its enantiomers. Using an analytical HPLC (Chiralpak AD) a small amount of the bromo derivative **12a** was separated into its enantiomers achieving nearly base line separation. The CD spectra for the two enantiomers are exact mirror images over the entire spectral range (Figure 2) reaching five extrema in the aromatic region centering around 205, 225, 240, 275, and 280 nm, respectively. So far, we were not able to determine the absolute configurations of the two enantiomers of **12a** from the CD spectra, which are quite different from the ones for C3- and D3-symmetric cyclotriveratrylenes and cyclotribenzylenes reported previously by Collet.[6,27]

Preliminary temperature dependent NMR studies showed that the energy barrier for the interconversion of the two enantiomeric crown conformations of **12a** is probably higher than 25 kcal/mol, requiring temperatures well above 120 °C before inversion takes place: The NMR spectrum of a sample of **12a** in toluene did not show any signs of coalescence of the methylene AB-signals up to this temperature. These data correspond well with those for the unsubstituted cyclotribenzylene **1** itself, which also

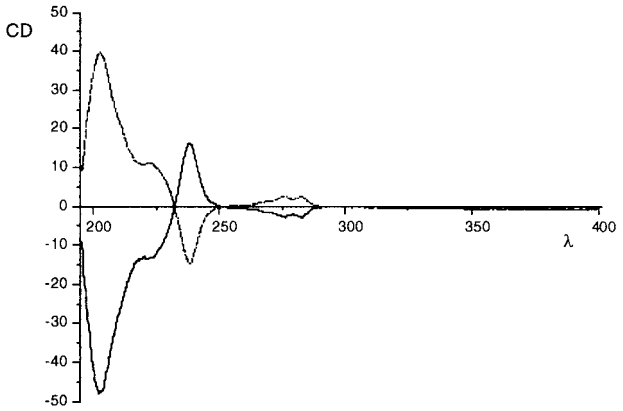


Figure 2 CD spectra of both enantiomers of **12a** in EtOH.

has a barrier to inversion of approximately 25 kcal/mol.[6] Obviously the bromo substitution neither affects the general conformational structure nor the stereoelectronic features of the cyclotribenzylene core unit dramatically.

In conclusion, following our newly developed synthetic route monosubstituted cyclotribenzylenes such as the bromo derivative **12a** can now for the first time be readily prepared in large quantities from inexpensive starting materials. As the bromo substituent in **12a** is easily replaced by various other substituents, this approach opens the way to monosubstituted cyclotribenzylenes in general. A physical organic characterization using various spectroscopic techniques (X-ray structure determination, temperature dependent NMR studies, and CD spectroscopy) of these monosubstituted cyclotribenzylenes showed that they exhibit planar chirality adopting a rather rigid crown conformation with a barrier to inversion of more than 25 kcal/mol. This means that at least at room temperature these molecules are conformationally stable, which should make them ideal chiral building blocks for the preparation of supramolecular systems with hydrophobic binding pockets.

Reaction solvents were dried and distilled under argon before use. All other reagents were used as obtained from either Aldrich or Fluka. ^{1}H and ^{13}C NMR shifts are reported relative to the deuterated solvents. Peak assignments are based on either DEPT, 2D NMR studies and/or comparison with literature data. Melting points are not corrected.

5*H*-Dibenzo[*a*,*d*]cycloheptene (9)

A soln of $AlCl_3$ (14.2 g, 107 mmol) in anhyd Et_2O (50 mL) was added to a suspension of $LiAlH_4$ (4.05 g, 107 mmol) in anhyd Et_2O (75 mL) and the resulting mixture was stirred for 15 min at r.t. To this slurry was slowly added a soln of dibenzosuberenone (**8**; 20.0 g, 97.0 mmol) in anhyd THF (110 mL) at 0 °C. To complete the reaction, the mixture was heated to reflux for 3 h followed by stirring at r.t. overnight (TLC control). To decompose excess of $LiAlH_4$, H_2O (100 mL) was added followed by acidification of the resulting suspension with 10% H_2SO_4 to pH 3 at 0 °C. The aq layer was separated and extracted with CH_2Cl_2 (5 × 100 mL) and Et_2O (5 × 100 mL). The combined organic layers were washed with a sat. soln of $NaHCO_3$ (100 mL), H_2O (100 mL), brine (100 mL) and dried with

$MgSO_4$. Chromatographic work-up (CH_2Cl_2, R_f 0.92) gave a fawn crystalline powder (18.4 g, 95.9 mmol, 99%); mp 130 °C.

IR (CsI): = 3067, 3026, 1491, 1459, 1438, 1426, 951, 807, 759, 736, 728, 621 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.68 (s, 2 H, benzylic CH_2), 7.06 (s, 2 H, olefinic CH), 7.19−7.33 (m, 8 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 40.6 (benzyl CH_2), 126.3, 128.06, 128.14, 128.7, 131.5, 135.0, 137.9 (olefinic C, ArC).

MS (EI): *m/z* = 192 $[M]^+$ (100), 165 $[M - CO]^+$ (15), 152 (5), 139 (5), 94 (5).

HRMS (EI): *m/z* calcd for $C_{15}H_{12}$: 192.0939; found: 192.093.

2,2´-Bis(hydroxymethyl)diphenylmethane (4)

A stream of O_2/O_3 was bubbled through a suspension of compound **9** (7.50 g, 39.0 mmol) in anhyd MeOH (225 mL) for 3 h at 0 °C. After 1 h the solid starting material had disappeared resulting in a slightly yellow soln. To remove any dissolved ozone, a stream of Ar was bubbled through the reaction mixture at r.t. After complete evaporation of the solvent (distillation temperature not higher than 30 °C) the remaining yellow oil was dissolved in anhyd Et_2O (200 mL) and then slowly added to a suspension of $LiAlH_4$ (7.40 g, 195 mmol) in anhyd Et_2O (300 mL) at 0 °C. To complete the reaction the mixture was heated to reflux for 2 h and then stirred at r.t. overnight (TLC control). The excess of $LiAlH_4$ was decomposed by adding a sat. aq soln of Na_2SO_4 (50 mL), and the pH of the suspension was then adjusted to 1−2 by the addition of 10% H_2SO_4. The resulting colorless precipitate was filtered off and washed extensively with Et_2O (3 × 100 mL) and EtOH (3 × 100 mL). The organic layer of the filtrate was separated and the aq layer was extracted with Et_2O (3 × 100 mL) and $CHCl_3$−EtOH, 2:1 (3 × 100 mL). The combined organic layers were washed with 2% HCl (50 mL) which was reextracted afterwards with $CHCl_3$−EtOH, 2:1 (50 mL). To remove traces of acid, some solid Na_2CO_3 was added before drying with $MgSO_4$. The solvent was evaporated and the resulting solid recrystallised from benzene to give **4** as a white powder (8.14 g, 35.7 mmol, 91%) of a white powder; mp 159 °C.

IR (CsI): 3268, 3245, 1482, 1456, 1444, 1047, 1009, 758, 741 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.96 (s, 2 H, benzylic CH_2), 4.46 (d, *J* = 4.4 Hz, 4 H, benzylic C*H*$_2$OH), 5.14 (t, *J* = 4.9 Hz, 2 H, CH_2O*H*), 6.82−7.41 (m, 8 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 33.8 (benzylic CH_2), 61.0 (benzylic CH_2OH), 126.2, 127.0, 127.2, 129.1, 137.5, 140.4 (ArC).

MS (EI): *m/z* = 210 $[M - H_2O]^+$ (25), 192 $[M - 2H_2O]^+$ (45), 179 $[M - H_2O - CH_2OH]^+$ (100), 165 (20), 152 (5), 91 (15).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{15}H_{16}O_2 \cdot H_2O$: 210.1045; found: 210.104.

***p*-Bromo-3-benzylidene Phthalide (15)**

A mixture of phthalic anhydride (**13**, 3.13 g, 21.1 mmol), (*p*-bromophenyl) acetic acid (**14**; 5.0 g, 23.3 mmol), and anhyd NaOAc (0.18 g, 2.19 mmol) was heated at 230−240 °C for 3 h in an Ar atm. The reaction mixture was cooled and the resulting slightly yellow solid recrystallized from EtOH. Consecutive work-up of the remaining mother liquid finally afforded pure **15** as yellow needles (5.22 g, 17.3 mmol, 82%); mp 174–175 °C.

IR (CsI): 1797, 1654, 1488, 1473, 1355, 1201, 1073, 1009, 976, 869, 851, 805, 760, 749, 687, 515 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.34 (s, 1 H, olefinic CH), 7.50–7.58 (m, 3 H, ArH), 7.68–7.77 (m, 4 H, ArH), 7.92–7.95 (m, 1 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 105.8 (olefinic CH), 119.9, 122.6, 123.5, 125.7, 130.1, 131.5, 132.0, 134.6, 140.4 (ArC), 145.1 (enol C), 166.8 (C=O).

MS (EI): *m/z* = 302, 300 $[M]^+$ (100), 221 $[M^+ - Br]$ (5), 193 $[M - Br - CO]^+$ (15), 165 (20).

HRMS (EI): *m/z* calcd for $C_{15}H_9BrO_2$: 299.9786; found: 299.978.

2-[2-(*p*-Bromophenyl)ethyl]benzoic Acid (16)

Aq HI (25 mL, 55–58%) was heated with a heat gun (ca. 150 °C) while H_3PO_2 was added dropwise until the I_2 color had disappeared. Compound **15** (5.0 g, 16.6 mmol) and red phosphorus (3.30 g, 107 mmol) were added, and the mixture was heated to reflux for 24 h. H_2O (25 mL) was slowly added and the reaction mixture was cooled to 0 °C overnight. The red solid was collected by filtration, then suspended in concd aq NH_4OH soln (50 mL) and heated to reflux for 1 h. The excessive red phosphorus was removed by filtration and washed with conc. NH_4OH soln (10 mL). The combined aq layers were then acidified (pH = 1−2) at 0 °C using concd HCl. Pure **16** precipitated as a colourless crystalline powder and was isolated by filtration (4.30 g, 14.1 mmol, 85%): mp 128–129 °C.

IR (CsI): 3050–2950, 1698, 1680, 1574, 1486, 1401, 1299, 1274, 1262, 1011, 800, 748, 530 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.79 (m, 2 H, benzylic CH_2), 3.16 (m, 2 H, benzylic CH_2), 7.16–7.82 (m, 8 H, ArH), 12.91 (br s, 1 H, CO_2H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 35.9, 36.9 (benzylic CH_2), 119.0, 126.4, 130.6, 130.8, 131.2, 131.3, 131.9, 141.3, 142.6 (ArC), 168.9 (CO_2H).

MS (EI): *m/z* = 306, 304 $[M]^+$ (65), 288, 286 $[M - OH]^+$ (25), 225 $[M - Br]^+$ (5), 207 $[M - Br - H_2O]^+$ (35), 178 (10), 171, 169 [M – benzyl$CO_2H]^+$ (100), 135 (15), 90 (20), 77 (15).

HRMS (EI): *m/z* calcd for $C_{15}H_{13}BrO_2$: 304.0099; found: 304.009.

3-Bromo-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-one (17)

Benzoic acid (**16**; 7.39 g, 24.2 mmol) and polyphosphoric acid (40 g) were heated 5 h at 175 °C. The hot reaction mixture was poured under stirring into ice H_2O (200 mL) and, after cooling to r.t., extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were washed with a sat. aq soln of Na_2CO_3 (3 × 100 mL), H_2O (100 mL), brine (100 mL) and dried with $MgSO_4$. After evaporation to dryness, the residue was purified by column chromatography (SiO_2, hexane−MeOH, 95:5; R_f 0.57). Recrystallisation from EtOH yielded **17** as slightly yellow crystals (4.45 g, 15.5 mmol, 64%); mp 79–80 °C.

IR (CsI): 2962, 1715, 1637, 1598, 1580, 1473, 1448, 1389, 1354, 1299, 1267, 1238, 1149, 833, 755, 628, 580 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.11–3.20 (m, 4 H, benzylic CH_2), 7.08–7.53 (m, 5 H, ArH), 7.95–8.13 (m, 2 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 34.4, 34.7 (benylic CH_2), 120.5, 126.8, 129.3, 130.7, 131.1, 132.7, 133.3, 135.0, 138.0, 140.1, 140.8, 141.8 (ArC), 194.0 (C=O).

MS (EI): *m/z* = 288, 286 $[M]^+$ (100), 260, 258 $[M - CO]^+$ (20), 207 $[M - Br]^+$ (20), 178 (60), 152 (10), 89 (15).

HRMS (EI): *m/z* calcd for $C_{15}H_{11}BrO$: 285.9993; found: 285.999.

3-Bromo-5*H*-dibenzo[*a,d*]cyclohepten-5-one (18)

A mixture of compound **17** (4.14 g, 14.4 mmol), PCl_5 (9.0 g, 43.2 mmol) and $POCl_3$ (16 mL) was heated to 100 °C for 3 h resulting in a deep red soln. The excess $POCl_3$ was removed in vacuo at 75 °C. The residue was dissolved in toluene (60 mL) and stirred overnight at r.t. After removal of the solvent in vacuo, the resulting red oil was carefully hydrolysed at 0 °C by dropwise addition of of MeOH–

H_2O, (5:1, 50 mL). The resulting suspension was stirred for 2 h at r.t. before evaporation of the MeOH. The aq suspension was then extracted with CH_2Cl_2 (5 × 25 mL), the combined organic layers were washed with H_2O (3 × 20 mL), brine (20 mL) and dried with $MgSO_4$. After evaporation to dryness, the residue was recrystallised from MeOH yielding **18** as yellow crystals (3.64 g, 12.8 mmol, 89% after consecutive work-up of the mother liquids); mp 107–108 °C.

IR (CsI): 1718, 1617, 1597, 1580, 1560, 1477, 1328, 1276, 835, 823, 728, 497 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.97, 7.06 (2 × d, *J* = 12.1 Hz, 2 H, olefinic CH), 7.37–7.72 (m, 5 H, ArH), 8.17–8.20 (m, 1 H, ArH), 8.34 (d, *J* = 2.2 Hz, 1 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 106.1, 107.4 (olefinic CH_2), 123.2, 129.1, 130.4, 130.6, 131.0, 132.3, 132.4, 132.9, 134.9, 138.1, 138.3, 139.7 (ArC), 191.4 (C=O).

MS (EI): *m/z* = 286, 284 $[M]^+$ (100), 258, 256 $[M – CO]^+$ (85), 207 $[M – Br]^+$, 176 $[M – CO – Br]^+$ (50), 151 (15), 88 (10).

HRMS (EI): *m/z* calcd for $C_{15}H_9BrO$: 283.9836; found: 283.983.

3-Bromo-5*H*-dibenzo[*a,d*]cycloheptene (19)

A mixture of ketone **18** (0.50 g, 1.75 mmol) and aluminium triisopropylate (1.07 g, 5.26 mmol) was heated to 275 °C for 3 h in an atmosphere of Ar until the melt had become solid. After cooling to r.t. the precipitate was suspended in 2 N HCl (15 mL)and stirred for 1 h. The aq suspension was then extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were evaporated to dryness, and the residue was purified by column chromatography (SiO_2, hexane–CH_2Cl_2, 5:1; R_f 0.59) yielding **19** as a slightly yellow crystalline powder (0.42 g, 1.55 mmol, 89%); mp 128–129 °C.

IR (CsI): 2959, 1653, 1583, 1483, 1420, 1076, 906, 836, 812, 794, 765, 732, 512, 447 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.67 (s, 2 H, benzylic CH_2), 6.91–7.05 (2 × d, *J* = 11.6 Hz, 2 H, olefinic CH), 7.11–7.32 (m, 7 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 41.1 (benzylic CH_2), 126.3, 127.9, 128.15, 128.17, 128.7, 129.02, 129.04, 129.5, 130.3, 130.4, 130.63, 130.64, 132.1 (olefinic C, ArC).

MS (EI): *m/z* = 272, 270 $[M]^+$ (100), 191, $[M – Br]^+$ (40), 163 (5), 95 (10), 82 (5).

HRMS (EI): *m/z* calcd for $C_{15}H_{11}Br$: 270.0044; found: 299.004.

Anal. Calcd for $C_{15}H_{11}Br$: C, 66.44; H, 4.09. Found: C, 66.45; H, 4.10.

5-Bromo-2,2´-bis(hydroxymethyl)diphenylmethane (20)

A stream of O_2/O_3 was bubbled through a solution of compound **19** (0.42 g, 1.55 mmol) in anhyd CH_2Cl_2 (15 mL) for 2 h at –78 °C. After 1 h the blue color of unreacted ozone was noticeable. The reaction mixture was allowed to warm to r.t., and Ar was bubbled through to remove any dissolved ozone. $BH_3{\cdot}S(CH_3)_2$ (6.20 mL of a 1 M soln in CH_2Cl_2, 6.20 mmol) was slowly added via a syringe, and the reaction mixture was stirred for additional 24 h resulting in a yellow soln containing some flaky precipitate. To decompose excess of borane, aq EtOH (10 mL) followed by 5% HCl (0.5 mL) were dropwise added followed by stirring for 1 h at r.t. The pH was adjusted at 5–6 by adding solid $NaHCO_3$, and the resulting mixture was dried with $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, CH_2Cl_2–EtOAc,1:1; R_f 0.48) yielding **20** as a colorless crystalline powder (0.42 g, 1.36 mmol, 88%); mp 109–110 °C.

IR (CsI): 3313, 2922, 1593, 1478, 1445, 1399, 1049, 1017, 1007, 754 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.97 (s, 2 H, bibenzylic CH_2), 4.44, 4.46 (2 × s, 4 H, benzylic CH_2OH), 5.14 (t, *J* = 5.5 Hz, 1 H, benzylic CH_2O*H*), 5.23 (t, *J* = 5.5 Hz, 1 H, benzylic CH_2O*H*), 6.86–7.45 (m, 7 H, ArH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 33.3 (bibenzylic CH_2), 60.3, 60.9 (benzylic CH_2OH), 119.9, 126.5, 127.1, 127.3, 129.0, 129.1, 129.2, 131.3, 136.7, 140.0, 140.37, 140.4 (Ar C).

MS (EI): *m/z* = 290, 288 $[M – H_2O]^+$ (5), 272, 270 $[M – 2H_2O]^+$ (20), 259, 257 $[M^+ – H_2O – CH_2OH]$ (10), 209 (25), 191 (30), 178 (100), 165 (25), 152 (10), 91 (25).

HRMS (EI): *m/z* $[M – H_2O]^+$ calcd for $C_{15}H_{15}BrO_2 – H_2O$: 288.015; found: 288.014.

Anal. Calcd for $C_{15}H_{15}BrO_2$: C, 58.65; H, 4.92. Found: C, 58.75; H, 4.82.

2-Bromo-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene (12a)

A soln of compound **20** (305 mg, 0.99 mmol) in anhyd benzene (100 mL) was added dropwise over 30 h to a mixture of concd H_2SO_4 (20 mL) and of anhyd benzene (20 mL) at r.t. After additional stirring for 48 h the reaction mixture was poured into ice H_2O (150 mL). The aq layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were washed with a sat. aq soln of $NaHCO_3$ (100 mL), H_2O (100 mL), brine (100 mL), and dried with $MgSO_4$. After evaporation of solvent to dryness, the residue was purified by column chromatography (SiO_2, hexane–acetone, 20:1; R_f 0.42) yielding **12a** as a colorless crystalline powder (225 mg, 0.65 mmol, 65%); mp 230 °C.

IR (CsI): 3059, 3018, 2929, 1586, 1492, 1482, 1476, 1447, 1104, 778, 751, 720 cm^{-1}.

^1H NMR (500 MHz, benzene-d_6): δ = 3.21–3.42 (3 × d, *J* = 11–13 Hz, 3 H, 3 benzylic C*H*H), 4.33–4.43 (3d, *J* = 13 Hz, 3 H, 3 benzylic CH*H*), 6.75–7.17 (m, 10 H, ArH), 7.39 (d, *J* = 2.2 Hz, 1 H, ArH).

^{13}C NMR (125.8 MHz, benzene–d_6): δ = 36.6, 36.8, 37.1 (benzylic CH_2), 120.6 (ArCBr), 127.1, 127.25, 127.29, 127.3, 130.1, 130.2 (2 × C), 130.3, 130.4, 132.0, 132.9, 138.7, 138.8, 139.2, 139.6, 139.8, 142.0 (ArC).

MS (EI): *m/z* = 350, 348 $[M]^+$ (60), 335, 333 $[M – CH_3]^+$ (10), 269 $[M – Br]^+$ (45), 252 (25), 191 (20), 178 (100), 165 (15), 126 (5), 91 (15).

HRMS (EI): *m/z* calcd for $C_{21}H_{17}Br$: 348.051; found: 348.051.

Anal. Calcd for $C_{21}H_{17}Br$: C, 72.22; H, 4.91. Found: C, 72.11; H, 4.91.

2-Iodo-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene (21)

Compound **12a** (930 mg, 2.66 mmol, dried under high vacuum) was dissolved in anhyd THF (93 mL) under Ar, and the soln was cooled to –78 °C. *n*-BuLi (1.6 M in hexane, 5.0 mL, 8.0 mmol) was added via a syringe. After stirring for 30 min at –78 °C I_2 (2.03 g, 7.99 mmol, dried over P_2O_5) was added in one portion and the cooling bath was removed. After stirring overnight, the organic solvent was removed under vacuum and the resulting red oil was dissolved in CH_2Cl_2 (100 mL). The organic layer was washed with sat. aq sodium hydrogensulfite soln (3 × 100 mL) and dried with $MgSO_4$. After evaporation to dryness, the residue was purified by column chromatography (SiO_2, hexane–acetone, 20:1; R_f 0.44) to afford **21** as a white solid (784 mg, 1.98 mmol, 75%); mp 214–215 °C.

IR (CsI): = 3057, 3017, 2928, 2362, 1475, 1445, 1099, 749, 718 cm^{-1}.

^1H NMR (300 MHz, CDCl3): δ = 3.65–3.76 (3 × d, *J* = 13.5 Hz, *J* = 13.4 Hz, *J* = 13.7 Hz, 3 H, 3 benzylic C*H*H), 4.79–4.85 (m, 3 H, 3 benzylic CH*H*), 7.06–7.13 (m, 5 H, ArH), 7.29–7.40 (m, 5 H, ArH), 7.69 (d, *J* = 1.9 Hz, 1 H, ArH).

^{13}C NMR (75.5 MHz, CDCl3): δ = 36.7, 37.1 (3 benzylic CH_2), 92.0 (ArCI), 118.8, 127.1, 127.17, 127.2, 127.3, 129.9, 130.1, 130.2, 131.9, 135.9, 138.6, 138.7, 138.8, 139.2, 139.4, 139.5, 141.8 (ArC).

MS (EI): *m/z* = 396 $[M]^+$ (85), 381 $[M - CH_3]^+$ (10), 318 (10), 305 $[M$ – benzyl$]^+$ (15), 269 $[M - I]^+$ (30), 252 (20), 239 (10), 191 (20), 178 (100), 152 (10), 126 (15), 91 (35).

HRMS (EI): *m/z* calcd for $C_{21}H_{17}I$: 396.0375; found: 396.038.

Anal. Calcd for $C_{21}H_{17}I$: C, 63.65; H, 4.32. Found: C, 64.03; H, 4.40.

2-Carboxy-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene (22)
Compound **12a** (175 mg, 0.50 mmol, dried under high vacuum) was dissolved in anhyd THF (30 mL) under Ar, and the soln was cooled to –78 °C. *n*-BuLi (1.6 M in hexane, 1.6 mL, 2.5 mmol) was added via a syringe. After stirring for 30 min at –78 °C anhyd CO_2 was passed rapidly through the reaction mixture and the cooling bath was removed after 30 min. When the temperature had risen to r.t. the CO_2 supply was disconnected and dilute HCl (25 mL) was added carefully. The organic solvent was removed under vacuum and the resulting aq suspension extracted with CH_2Cl_2–EtOH, 2:1 (5 × 25 mL). The combined organic layers were evaporated in vacuo, and the crude was purified by column chromatography (SiO_2, CH_2Cl_2–EtOAc; 7:1 + 1 mL of glacial HOAc per 1 L of eluent; R_f 0.65) to afford **22** as a white solid (123 mg, 0.39 mmol, 78%); mp > 310°C.

IR (CsI): 3019, 2926, 2668, 1695, 1612, 1574, 1476, 1432, 1304, 1280, 1093, 949, 750, 721 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.70–3.85 (m, 3 H, 3 benzylic C*H*H), 4.92–5.03 (m, 3 H, 3 benzylic CH*H*), 7.07–7.11 (m, 4 H, ArH), 7.44–7.65 (m, 6 H, ArH), 8.01 (d, *J* = 1.5 Hz, 1 H, ArH), 12.77 (br s, 1 H, CO_2H).

^{13}C NMR (75.5 MHz, DMSO–d_6): δ = 36.0, 36.1, 36.2 (3 benzylic CH_2), 126.9, 127.0, 127.1, 127.7, 129.3, 130.1, 130.28, 130.3, 130.6, 131.3, 139.1, 139.5, 140.0, 140.1, 140.3, 145.1 (ArC), 167.3 (CO_2H).

MS (EI): 314 $[M]^+$ (30), 299 $[M - CH_3]^+$ (5), 269 $[M - CO_2H]^+$ (20), 252 (15), 236 (15), 223 $[M$ – benzyl$]^+$ (20), 191 (15), 178 (100), 165 (15), 126 (10), 91 (25).

HRMS (EI): *m/z* calcd for $C_{22}H_{18}O_2$: 314.1306; found: 314.132.

2-Hydroxymethyl-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene (23)
Compound **12a** (100 mg, 0.29 mmol, dried under high vacuum) was dissolved in anhyd THF (20 mL) under Ar, and the soln was cooled to –78 °C. *n*-BuLi (1.6 M in hexane, 0.27 mL, 0.43 mmol) was added via a syringe. After stirring for 15 min at –78 °C paraformaldehyde (86 mg, 2.86 mmol, dried over P_2O_5) was added in one portion and the cooling bath was removed. When the temperature had risen to r.t., 5% HCl (20 mL) was added carefully. The organic solvent was removed under vacuum and the resulting aq suspension extracted with CH_2Cl_2–EtOH, 2:1 (5 × 20 mL). The combined organic layers were concentrated in vacuo, and the crude was purified by column chromatography (SiO_2, CH_2Cl_2–EtOAc, 5:1; R_f 0.72) to afford **23** as a white solid (50 mg, 0.17 mmol, 58%); mp 220°C.

IR (CsI): 3317, 3057, 3017, 2926, 2362, 1494, 1475, 1445, 1095, 1029, 742, 721 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73–3.77 (m, 3 H, 3 benzylic C*H*H), 4.56 (s, 2 H, benzylic CH_2OH), 4.86–4.92 (m, 3 H, 3 benzylic CH*H*), 5.28 (s, 1 H, CH_2OH), 7.06–7.10 (m, 5 H, ArH), 7.33–7.40 (m, 6 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 36.9, 37.0, 37.1 (3 benzylic CH_2), 65.2 (benzylic CH_2OH), 125.8, 127.0, 127.03, 127.04, 128.8, 130.0, 130.08, 130.09, 130.1, 130.3, 139.1, 139.3, 139.37, 139.38, 139.46, 139.5, 139.6 (ArC).

MS (EI): *m/z* = 300 $[M]^+$ (30), 282 $[M^+–H_2O]$ (5), 269 $[M–CH_2OH]^+$ (35), 252 (10), 191 (25), 178 (100), 165 (15), 91 (30).

HRMS (EI): *m/z* calcd for $C_{22}H_{20}$: 300.1514; found: 300.152.

2-Cyano-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene (24)
To a soln of compound **12a** (50 mg, 0.14 mmol) in anhyd DMF (5.0 mL) was added CuCN (39 mg, 0.43 mmol). The resulting heterogeneous mixture was poured in a thick wall glass autoclave and then heated at 200 °C overnight. After cooling to r.t., H_2O was added (20 mL) and the resulting suspension extracted with CH_2Cl_2 (6 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL) and the solvent was completely evaporated in vacuo. Purification of the residue by column chromatography (SiO_2, CH_2Cl_2–hexane, 5:1, R_f = 0.75) afforded **24** as a colorless solid (39 mg, 0.13 mmol, 92%); mp 258–259 °C.

IR (CsI): 3061, 3019, 2925, 2362, 2229, 1490, 1477, 1445, 1095, 756, 724 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73–3.80 (m, 3 H, 3 benzylic C*H*H), 4.80–4.95 (3 × d, *J* = 13.5 Hz, *J* = 13.5 Hz, 13.2 Hz, 3 H, 3 benzylic CH*H*), 7.10–7.14 (m, 4 H, Ar C*H*), 7.34–7.47 (m, 6 H, ArH), 7.65 (d, *J* = 1.6 Hz, 1 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 36.8, 37.1, 37.2 (3 benzylic CH_2), 110.7 (Ar *C*CN), 118.9 (C*C*N), 127.3, 127.4, 127.6, 129.9, 130.27, 130.32, 130.34, 130.9, 133.9, 137.8, 138.1, 139.4, 139.5, 140.8, 144.9 (ArC).

MS (EI): *m/z* = 295 $[M]^+$ (45), 280 $[M^+ - CH_3]$ (20), 264 (5), 253 (5), 217 (40), 204 $[M^+$ – benzyl] (100), 178 (45), 165 (10), 126 (10), 91 (15).

HRMS (EI): *m/z* calcd for $C_{22}H_{19}N$: 295.1361; found: 295.136.

X-ray Crystallographic Data of 21
Nonius KappaCCD diffractometer (20 °C), Mo–*K*α radiation, 2Θmax = 56°; structure determination by direct methods (SHELXS-97, SHELXL-97). $C_{21}H_{17}I$, monoclinic, space group P21/n, *a* = 4.669(1), *b* = 36.311(1), *c* = 9.544(1) Å, α = 90.00, β = 99.00(1), γ = 90.00, *V* = 1598.1(5) Å3, *Z* = 4, ρ calcd = 1.647 gcm^{-3}, μ = 1.998 mm^{-1}, 3552 data measured, *R1* = 0.0348, *R*w = 0.0838 (based on refinement of 2842 observed reflections with $I > 2\sigma$ and 268 variable parameters). The final difference density was less than 0.673 $eÅ^{-3}$.

Enantiomer Separation of *rac*-2-Bromo-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene (12a) and CD Spectroscopy
Column: Chiralpak AD (25 × 0.46 cm; Daicel Chemical Industries); eluent: hexane–EtOH, 98:2; flow rate: 0.5 mL min^{-1}; sample: 2 mg mL^{-1} (hexane–EtOH– CH_2Cl_2, 5:3:2); injection volume: 10–15 μL; retention times: 12.05 min and 12.91 min. For the CD spectra solns of the enantiomers in EtOH were used with a concentration of 0.36 mg mL^{-1}. Analytical HPLC of these solutions showed that enantiomer 1 was optically pure, with no traces of the second enantiomer present, while enantiomer 2 had an optical purity of 90% ee (5% of enantiomer 1 were present). Hence, the maximum absorbance of enantiomer 2 in the CD spectra was slightly lower than that of enantiomer 1.

Supporting Information Available: Crystallograpic data on **12a** and **21**; ^{13}C NMR spectroscopic data for compounds **12a** and **19**–**24**; full NMR shift assignment for **12a**.

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References

(1) Former address: Institut für Organische Chemie, Universität zu Köln, Greinstrasse 4, 50939 Köln, Germany.
(2) (a) Steed, J. W.; Atwood, J. L. In *Supramolecular Chemistry*; Wiley: Chichester, **2000**. (b) Lehn, J.-M. In *Supramolecular Chemistry, Concepts and Perspectives*; VCH: Weinheim, **1995**. (c) Vögtle, F. In *Supramolecular Chemistry*; Wiley & Sons: Chichester, **1991**.
(3) (a) Sato, T.; Uno, K. *J. Chem. Soc., Chem. Commun.* **1972**, 579. (b) Sato, T.; Uno, K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 895.
(4) For a general review on cyclophanes see: Vögtle, F. In *Cyclophane Chemistry*; Wiley & Sons: Chichester, **1993**.
(5) Diedrich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362.
(6) For a comprehensive review on the synthesis and properties of cyclotriveratrylenes see: Collet, A. *Tetrahedron* **1987**, *43*, 5725.
(7) For an extensive review see: Collet, A.; Dutasta, J.-P.; Lozach, B.; Canceil, J. *Top. Curr. Chem.* **1993**, *165*, 103.
(8) Sato, T.; Akima, T.; Uno, K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 891.
(9) Yamato, T.; Sakaue, N. *J. Chem. Res. (M)* **1997**, *12*, 2614.
(10) Tellenbröker, J.; Kuck, D. *Angew. Chem. Int. Ed.* **1999**, *38*, 919.
(11) For further synthetic approaches to unsubstituted cyclotribenzylene **1** see: (a) Lee, W. Y.; Sim, W.; Choi, K. D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 881. (b) Kodomari, M.; Taguchi, S. *J. Chem. Res. (S)* **1996**, 240. (c) Yamamoto, T.; Sakaue, N.; Furusawa, T.; Tashiro, M.; Surya Prakash, G. K.; Olah, G. A. *J. Chem. Res. (S)* **1991**, 242. (d) Canceill, J.; Collet, A.; Gottarelli, G. *J. Am. Chem. Soc.* **1984**, *106*, 5997. (e) Canceill, J.; Collet, A. *J. Chem. Soc., Chem. Commun.* **1983**, 1145.
(12) For other similar low yielding multi-step approaches to diol **4** see also: (a) Lee, W. Y.; Park, C. H.; Kim, Y. D. *J. Org. Chem.* **1992**, *57*, 4074. (b) Bergmann, E. D.; Pelchowicz, Z. *J. Am. Chem. Soc.* **1953**, *75*, 4281.
(13) Platzek, J.; Snatzke, G. *Tetrahedron* **1987**, *43*, 4947.
(14) A related approach was used by Renaud and coworkers. However, their route requires four steps and was rather low yielding with 58% yield at best: Renaud, R. N.; Layton, R. B.; Fraser, R. R. *Can. J. Chem.* **1973**, *51*, 3380.
(15) This is in accordance with other reports in the literature; see e.g. for a double nitration of dibenzosuberenone: Campbell, T. W.; Ginsig, R.; Schmid, H. *Helv. Chim. Acta* **1953**, *36*, 1489.
(16) Gringauz, A. In *Medicinal Chemistry*; Wiley-VCH: New York, **1997**.
(17) (a) Thompson, W. J.; Anderson, S.; Britcher, S. F.; Lyle, T. A.; Thies, J. E. *J. Med. Chem.* **1990**, *33*, 789. (b) Weiler-Feilchenfeld, H.; Solomonovici, A. *J. Chem. Soc. B* **1971**, 869. (c) Jung, M. E.; Miller, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 1984. (d) Inoue, J.; Cui, Y.-S.; Rodriguez, L.; Chen, Z.; Kador, P. F. *Eur. J. Med. Chem. Chim. Ther.* **1999**, *34*, 399.
(18) A regioisomer of this compound had been prepared earlier by Renaud in a very low yielding 12 step synthesis: (a) Fraser, R. R.; Renaud, R. N. *Can. J. Chem.* **1971**, *49*, 746. (b) Renaud, R. N.; Bovenkamp, J. W.; Fraser, R. R.; Capoor, R. *Can. J. Chem.* **1977**, *55*, 2642.
(19) (a) Engelhardt, E. L.; Zell, H. C.; Saari, W. S.; Christy, M. E.; Colton, C. D.; Stone, C. A.; Stavorski, J. M.; Wenger, H. C.; Ludden, C. T. *J. Med. Chem.* **1965**, *8*, 829. (b) Remy, D. C.; Rittle, K. E.; Hunt, C. A.; Anderson, P. S.; Arison, B. H.; Engelhardt, E. L.; Hirschmann, R.; Clineschmidt, B. V.; Lotti, V. J.; Bunting, P. R.; Ballentine, R. J.; Papp, N. L.; Flataker, L.; Witoslawski, J. J.; Stone, C. A. *J. Med. Chem.* **1977**, *20*, 1013. (c) Davis, D. A.; de Paulis, T.; Janowsky, A.; Smith, H. E. *J. Med. Chem.* **1990**, *33*, 809.
(20) Mikotic-Mihun, Z.; Dogan, J.; Litvic, M.; Cepanec, I.; Karminski-Zamola, G. M. *Synth. Commun.* **1998**, *28*, 2191.
(21) Manning, C.; McClory, M. R.; McCullough, J. J. *J. Org. Chem.* **1981**, *46*, 919.
(22) (a) Slates, H. L.; Wendler, N. L. *J. Med. Chem.* **1965**, *8*, 886. (b) Looker, J. J. *J. Org. Chem.* **1966**, *31*, 3599.
(23) In analogy to a patented procedure: Wendler, N. L.; Taub, D.; Hoffsommer, R. D. U. S. Patent 2,247,272, **1966**.
(24) $LiAlH_4$ even in equimolar amounts at low temperatures caused substantial debromination and gave only 23%, at most, of the desired bromosubstituted diol **20**. Other reducing agents such as sodium boronate or lithium boronate only gave complex product mixtures in which the desired diol **20** was only present in small amounts (according to TLC and GC-MS analysis), no matter which reaction conditions we tried (e.g. by variation of temperature and solvent, respectively). Borane in THF did not react at all.
(25) For various reductive work-up procedures after ozonolysis see: (a) Thiem, J. In *Houben-Weyl: Methoden der Organischen Chemie*, Vol. VI/1a; Thieme: Stuttgart, **1980**, 853. (b) For the use of lithium boronate see also: Brown, H. C.; Narasimhan, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702.
(26) Flippin, L. A.; Gallagher, D. W.; Jalali-Araghi, K. *J. Org. Chem.* **1989**, *54*, 1430.
(27) (a) Canceill, J.; Collet, A.; Gotarelli, G.; Plamieri, P. *J. Am. Chem. Soc.* **1987**, *109*, 6454. (b) Canceill, J.; Collet, A. *New J. Chem.* **1986**, *10*, 17. (c) Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1985**, *107*, 6993. (d) Canceill, J.; Collet, A.; Gabard, J.; Gotarelli, G.; Spada, G. P. *J. Am. Chem. Soc.* **1985**, *107*, 1299. (e) Collet, A. *J. Am. Chem. Soc.* **1981**, *103*, 5912.