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New key compounds in cyclotriveratrylene chemistry. Synthesis, optical resolution, absolute configuration and circular dichroism of C3-cyclotriveratrylenes with sulfur substituents

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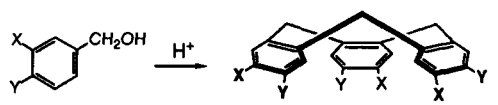
Vanillin 6a and isovanillin 6b were converted via a Newman-Kwart rearrangement to thiovanillin 9a and isothiovanillin 9b, which on S-methylation and subsequent reduction of the aldehyde function gave 3-methoxy-4-methylthio- (3a) and 4-methoxy-3-methylthio-benzylalcohol (3b), respectively. On reaction with formic acid, 3a and 3b afforded in excellent yield the new sulfur substituted cyclotriveratrylene 4. The latter could be desulfurized to cyclotrianisylene 2b, and selectively O-demethylated to the triphenol 11. Optical resolution of 11 gave access to a new family of chiral cyclotriveratrylenes incorporating sulfur substituents, which in turn can be used as starting units for the synthesis of new cryptophanes and related host structures. Analysis of the chiroptical properties of these sulfur substituted cyclotriveratrylenes provided information on the relative influence of the CH_3O and CH_3S substituents on the electronic transitions of the benzene chromophore. It was inferred from the exciton circular dichroism spectra of these compounds that the CH_3S group exerts a weaker effect than the CH_3O group on the polarization direction of the benzenoid ^1L_b transition, the reverse being true for the ^1L_a transition.

INTRODUCTION

Over the past years, we have shown that the acid catalyzed cyclodehydration of certain 3,4-disubstituted benzyl alcohols allowed practical access to functionalized C3-cyclotriveratrylenes (Scheme I).[1,2] These cone-shaped molecules have since found applications in the area of liquid crystals,[3] and have been used as shaping units in the design and synthesis of a number of cavitands and speleands,[4] such as the cryptophanes,[5] and related host molecules. Moreover, the recent finding that certain cryptophanes can form stable radical cations on oxidation and thus represent a new family of organic electron donors has opened new perspectives in the utilization of these systems as components of three-dimensional charge-transfer materials.[5d]

We report here that the reaction of Scheme I can now be applied to the preparation of C3-cyclotriveratrylenes bearing sulfur substituents (e.g., SCH_3), and we describe in detail our results on the synthesis, optical resolution, absolute configuration, and relevant properties of derivatives **4** and **5**, *new key intermediates* for the preparation of functionalized cyclotriveratrylenes and cryptophanes. We also discuss the chiroptical properties of sulfur substituted C3-cyclotriveratrylenes (**4**, **5**, and **11**) in light of the exciton



	X	Y		Yield (%)
1a	OCH_3	OH	2a	(0)[a]
1b	OCH_3	H	2b	(6)[a]
1c	OCH_3	Br	2c	(25-40)[a]
1d	OCH_3	$OCH_2CH{=}CH_2$	2d	(55)[a]
1e	OCH_3	OCH_3	2e	(70)[a]
3a	OCH_3	SCH_3	4	(60)[b]
3b	SCH_3	OCH_3	4	(70)[b]
3c	OC_2H_5	SCH_3	5	(71)[b]

Scheme I (a) See ref. 2; (b) this work.

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theory; we address the question of the effect of a sulfide group on the electronic transitions of benzenoid compounds, and we conclude that a CH_3S group exerts a weaker influence than does a CH_3O group on the polarization direction of the aromatic $\pi \rightarrow \pi^*$ ^1L_b transition, the inverse behavior being true for the ^1L_a transition. The syntheses (based on the chemistry described here) and properties of a new series of sulfur substituted cryptophanes will be reported in a forthcoming paper.

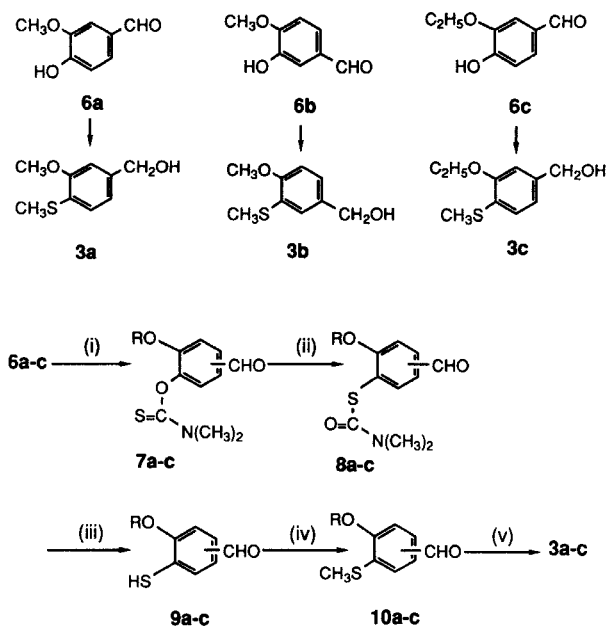
RESULTS AND DISCUSSION

Syntheses

The reaction of Scheme I is not general; position 6 of the alcohol must be activated towards electrophiles, which requires that substituent X at position 3 be a strong electron releasing group, and in almost all reported cases X was a methoxy group.[1] Although the role of substituent Y at position 4 is less evident, the following examples make clear that the outcome of the reaction is critically dependent on its nature. The reaction only affords tars with vanillyl alcohol **1a** (Y = OH),[6] alcohol **1b** (Y = H) gives *ca.* 6% of trimer **2b**,[7] and alcohol **1c** (Y = Br) trimerizes to **2c** in 25–40% yield.[7-9] So far, the best results (*ca.* 50%) have been obtained when the X and Y substituents of the alcohol were both oxygenated groups of structure OCH_2R; for instance the allyl protected vanillyl alcohol **1d** has been converted to trimer **2d** in 55% yield.[10] Cyclotriveratrylene **2d** is a key compound, because it can be prepared in multigram quantities, and then appropriate functional group transformations may generate derivatives which cannot be obtained by direct trimerization of benzyl alcohol precursors. Thus—*inter alia*—**2d** can be transformed into **2a**, then **2b**, by cleavage of the allyl groups, followed by selective deoxygenation of the phenol functions;[10] **2a** and **2b** are important intermediates in the template directed synthesis of cryptophanes.[1,2]

Along the same lines, we expected that the sulfur substituted cyclotriveratrylene **4** could be obtained from either 3-methoxy-4-methylthiobenzyl alcohol **3a** or its regioisomer **3b**, themselves accessible from vanillin **6a** and isovanillin **6b** by using the reaction sequence depicted in Scheme II. In a similar way, we anticipated that **5** could be prepared by cyclodehydration of **3c**, itself available from ethylvanillin **6c** by the same method.

The key step for the conversion of **6a–c** to **3a–c** is the replacement of the phenol by a thiophenol group, and this transformation was satisfactorily achieved by using the Newman-Kwart procedure which rests on the thermal rearrangement of a O-aryl thiocarbamate



Scheme II Reagents and conditions. **A** (**6a** to **3a**): (i) $(CH_3)_2NCSCl$, THF-H_2O, KOH, 0–20 °C, 85%; (ii) 240–250 °C, diphenyl ether, 15 min, 84%, or 240–255 °C, no solvent, 25 min, 72%; (iii) methanol, 2 M NaOH, reflux, 1 h 30, 90%; (iv) methanol, 2 M NaOH then CH_3I, 15 h, r.t., 92%; (v) methanol, $NaBH_4$, 15 h, r.t., 98%. **B** (**6b** to **3b**): (i) 90%; (iii) 87%; (iv) 80% and (v) 98%, same conditions as above; (ii) 245–250 °C, diphenyl ether, 2 h 10, 94%. **C** (**6c** to **3c**): (i) 80%; (iii) methanol, 2 M NaOH, reflux, 1 h, 88%; (iv) 93%; (v) 92%, same conditions as above; (ii) 240–260 °C, no solvent, 1 h, 80%.

to the corresponding S-aryl carbamate.[11-13] To this end the phenol groups of **6a–c** were esterified with *N,N*-dimethylthiocarbamoyl chloride to give **7a–c** in 80–90% yield. As the conditions for the rearrangement may vary widely from one compound to another,[11] we found it convenient to study this reaction by differential scanning calorimetry (DSC), by heating small samples of **7a–c** without solvent in a sealed aluminium cell, and observing the heat flow which follows the transformation.

On heating **7a** at a rate of 15 °C/min (Fig. 1), the DSC trace showed the expected melting endotherm at 115 °C, followed by an exotherm corresponding to the rearrangement (ΔH -12.4 kcal mol^{-1}), between *ca.* 160 °C and 290 °C, with a maximum at *ca.* 250 °C. The product recovered from the DSC pan and analysed by ^1H NMR consisted of essentially pure **8a**, the rearranged substrate, together with minor amounts of decomposition products. This experiment indicated that under these conditions the reaction had gone to completion in about 10 min. Accordingly, the preparative rearrangement of **7a** to **8a** was effected at 240–255 °C for 15 min in diphenyl ether (84%) or, in a more simple way, without solvent (72%).

The thermal behavior of **7c** was similar to that of **7a**. Under the same conditions the rearrangement

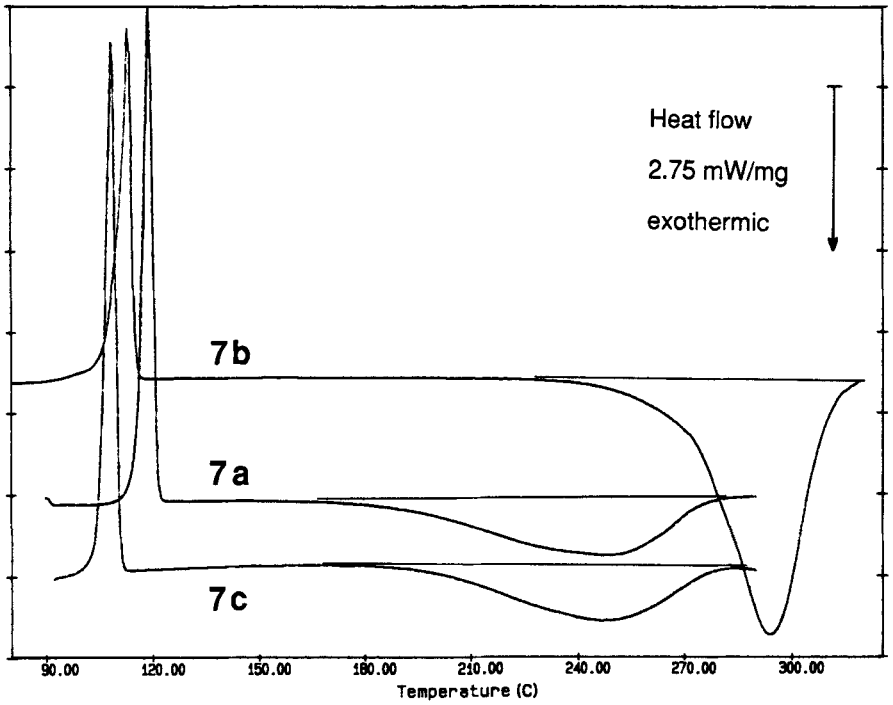


Figure 1 Normalized DSC scans of **7a–c** showing the melting endotherms and the rearrangement exotherms at a scanning rate of 15 °C/min.

exotherm (ΔH −11.8 kcal mol^{-1}) was observed between *ca.* 170 °C and 290 °C, with a maximum at 253 °C. The preparative rearrangement was effected without solvent at 240–260 °C for 1 h and gave **8c** in 80% isolated yield.

The conversion of **7b** to **8b** proved to be more difficult. The DSC experiments showed that the exotherm was shifted to a much higher temperature, between 215 °C and 330 °C, with a maximum at 300 °C, and that extensive decomposition occurred (the total heat evolved was approximately 20 kcal mol^{-1}). This result indicates that the presence of an electron withdrawing group (CHO) in the *meta* position makes the reaction more difficult.[14] In this case, the preparative rearrangement of **7b** was carried out at 245–250 °C in diphenyl ether for 2 h 10 min and gave **8b** in 94% yield.

Alkaline hydrolysis of **8a–c** afforded the corresponding thiols **9a–c** in excellent yield. Thiovanillin **9a** has a slightly pungent odor and a very unpleasant taste. The odor of ethylthiovanillin **9c** is very much stronger than that of **9a**, and may be described as a combination of sulfur and flower components. There is a previous report[15] on the synthesis of thiovanillin; the same method was employed, however the indicated mp (112 °C) differs from that of our product (47 °C). The spectroscopic data and elemental analysis (C, H, O, S) of our thiovanillin were as expected for structure **9a**.

Finally, the thiophenol groups of **9a–c** were methylated by reaction of their sodium salts with methyl iodide to give **10a–c** (80–93%),[16] and sodium borohydride reduction of the aldehyde function eventually provided the desired benzyl alcohols **3a–c** in almost quantitative yield.

The cyclodehydration of the sulfur substituted benzyl alcohols **3a–c** proved to be very much easier than that of their oxygenated analogues (e.g., **1c** or **1d**), which, as we have shown, required the presence of a strong mineral acid (perchloric acid).[8,10] In contrast, the cyclodehydration of **3a** and of its regioisomer **3b** proceeded in a satisfactory way in warm formic acid (0.38 M, 70 °C), to give the trimer **4** (mp 240 °C); the reaction time was shorter and the yield of **4** was better from **3b** (1 h 30, 70%) than from **3a** (3 h 30, 60%). The cyclodehydration of **3c** worked in a similar fashion (0.39 M, 1 h 30, 71%) to give the trimer **5** (mp 215 °C). In all cases the reaction of the sulfur substituted benzyl alcohols was attended by a transient green color, whereas that of the oxygenated analogues[8,10] always showed a violet coloration. This difference in color of the reactive species might be related to the ease of the reaction of the sulfur substituted precursors; more details on the mechanism of this reaction, including M.O. calculations, will be reported in a separate paper.

In order to take advantage of the ready availability of **4**, we sought simple reactions that would allow us to manipulate selectively the peripheral substituents. We first examined the desulfurization of **4** to C3-cyclotrianisylene **2b**, and we found that this reaction

could be effected in the presence of Raney nickel in a mixture of ethanol and THF (1:1) at room temperature (at a higher temperature, extensive hydrogenation of the aromatic rings occurred); **2b** was obtained in 86% yield by this procedure, which therefore represents a shorter and easier route to this important intermediate than the previously described 3-step sequence[10,21] starting from **2d**.

We next attempted to demethylate selectively either the OCH_3 or the SCH_3 groups of **4** to reach the corresponding phenol **11** and thiophenol **12**, respectively (see Scheme III). To this end, we first examined the reaction of **4** with boron tribromide and found that the selective O-demethylation of **4** occurred smoothly in refluxing dichloromethane to give the triphenol **11** (mp 270 °C) in 69% isolated yield. We also tried the procedures reported by Testaferri *et al.*[22] for the selective cleavage of the $O-CH_3$ or $S-CH_3$ bonds in methylthioanisoles. The O-demethylation of **4** to **11** could be effected in 79% yield by means of sodium isopropanethiolate; however, the reaction was much less easy with this reagent than with BBr_3, and required to be carried out in HMPA at 120 °C for 18 h. In contrast, all our attempts aiming to S-demethylate **4** selectively, by reaction with sodium (2.5 eq) in HMPA at 100 °C (as reported by Testaferri),[22] or under different conditions where the amount of sodium and/or the temperature were changed, were always attended with some O-demethylation, and we were unable to isolate even a small sample of the pure thiophenol **12**.

Inclusion compounds

Cyclotriveratrylene **2e** has been known for a long time to form crystalline inclusion compounds with small molecules,[1] and we anticipated that its sulfur analogue **4** might display the same property. In fact, when racemic **4** was crystallized from dichloromethane, chloroform, toluene, acetone, or ethanol, it invariably afforded unsolvated crystals. This difference in the inclusion properties of **2e** and **4** might be conformational in origin. The conformational preference of the CH_3-S-Ar group has been the object of several studies by NMR,[17] photoelectron spectroscopy,[18] UV, IR and Raman spectroscopies, and theoretical calculations.[19] It has generally been concluded that, in contrast with the behavior of the CH_3-O-Ar group which tends to lie in the plane of the benzene ring to which it is bound, the CH_3-S-Ar group does not show such a preference. We investigated the conformational preference of the methylthioether groups in **4** by molecular mechanics (PCMODEL),[20] and we found that in the MMX force field the lowest energy conformer had its three CH_3S groups almost perpendicular to the benzene rings and turned towards the cavity of the cyclotriveratrylene cone (Fig. 2), a situation which makes the overall shape of **4** different from that of **2e** and in turn might account for the absence of isomorphism between them.

Optical resolution and absolute configurations

In our earlier work[1] we had resolved several C3-cyclotriveratrylenes (triphenols **2a**, **2f**, **2g**) by formation and separation of their diastereomeric esters with chiral acids such as (−)-ω-camphanic acid and (+)-2-phenoxypropionic acid; (−)-ω-camphanic acid proved to be ineffective for the resolution of triphenol (±)-**11**; in this case the mixture of diastereomers showed a single spot by TLC. The resolution was satisfactorily achieved with *R*-(+)-2-(*p*-chlorophenoxy)-propionic acid **16**,[23] a chiral acid which, to the best of our knowledge, had never been used as a resolving agent before this work. The esterification of the phenol groups was effected by allowing (±)-**11** to react with (+)-**16** in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) in dichloromethane at room temperature. The diastereomers **13** and **14** were separated chromatographically (**13** was the faster running isomer) and showed the rotations indicated in Scheme III. The isolated diastereomers were pure by TLC and ^1H NMR spectroscopy, and their diastereomeric excess (*de*) was therefore assumed to be greater than 95%.

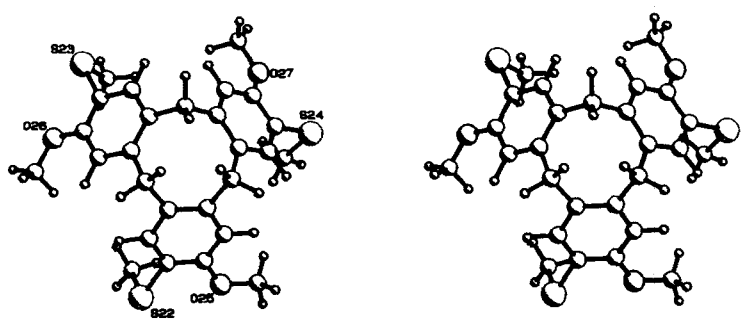
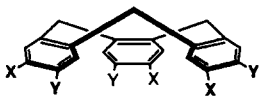
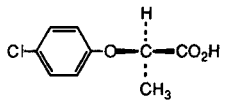


Figure 2 Stereo view of the preferred conformation of **4** (MMX force field[20]).



X	Y		Config.[a]	$[\alpha]_D^{25}$
OCH_3	OH	**2a**	*P*-(-)	-272[b]
OCH_3	H	**2b**	*P*-(-)	-165[b]
OH	H	**2f**	*P*-(-)	-199[c]
Br	OH	**2g**	*P*-(-)	-174[c]
OCH_3	SCH_3	**4**	*M*-(+)	+382[c]
OC_2H_5	SCH_3	**5**	*M*-(+)	+266c
OH	SCH_3	**11**	*M*-(+)	+354[c]
OCH_3	SH	**12**		
OCOZ*	SCH_3	**13**	*M*-(+)	+251[c]
SCH_3	OCOZ*	**14**	*P*-(-)	-18[c]
$OCOCH_3$	SCH_3	**15**	*M*-(+)	+460[c]



P-(+)-**16** (= Z*CO_2H)

Scheme III (a) The absolute configurations *M* or *P* indicated in the Scheme correspond to the stereoformula shown. For the use of the *P* and *M* descriptors see ref. 28; (b) rotation in $CHCl_3$; (c) in dioxane.

We found it preferable to cleave the diastereomers **13** and **14** to the enantiomers of **11** by reduction with lithium aluminium hydride at 0–20 °C rather than by alkaline hydrolysis. These conditions would ensure that no racemization due to ring inversion take place during the cleavage (see below). In this way, (+)-**13** and (−)**14** afforded (+)-**11**, $[\alpha]_D^{25}$ +354°, and (−)-**11**, $[\alpha]_D^{25}$ − 343° (dioxane), respectively; the enantiomeric excess (*ee*) of these compounds should be the same as the *de* of the starting diastereomers (>95%).

On methylation, the enantiomers (+)-**11** and (−)-**11** gave (+)-**4** and (−)-**4** having $[\alpha]_D^{25}$ +382° and −396° (dioxane), respectively, and similarly on ethylation (+)-**11** gave (+)-**5**, $[\alpha]_D^{25}$ +266° (dioxane). Finally, on acetylation (+)-**11** gave (+)-**15**, $[\alpha]_D^{25}$ +460° and (−)-**11** furnished (−)-**15**, $[\alpha]_D^{25}$ −467° (dioxane).

In order to determine the absolute configurations of the sulfur substituted cyclotriveratrylenes, a sample of (+)-**4** was submitted to the desulfurization reaction described above (Raney nickel in THF-ethanol, room temperature) and was converted in this way to the known *P*-(−)-C3-cyclotrianisylene **2b**, showing $[\alpha]_D^{25}$ −155° ($CHCl_3$); similarly a sample of (−)-**4** gave *M*-(+)-**2b** with $[\alpha]_D^{25}$ +164°. These figures are close to the maximum reported rotation of **2b** ($[\alpha]_D^{25}$ ±165°),[21] and it was thus confirmed that the enantiomeric excess of our samples of (+)- and (−)-**4** was excellent. This correlation, and the sequences of reaction described above thus established unambiguously that (+)-**4**, (+)-**5**, (+)-**11**, (+)-**13**, (−)-**14** and (+)-**15** have the absolute configurations indicated in Scheme III.

Conformation stability

The ^1H and ^{13}C NMR spectra of compounds **4**, **5**, **11**, **13**–**15**, and the existence of their optical activity, were consistent with a C3-cyclotriveratrylene structure in the usual rigid crown conformation (Tables 1 and 2). In particular, the ^1H NMR spectra of all these compounds exhibited for the methylene bridges the characteristic AX quartet,[1] in which the pseudo axial hydrogens (H_a), sterically congested at the top of the crown, resonate at *ca.* 1–1.2 ppm downfield with respect to their pseudo equatorial counterparts (H_e).

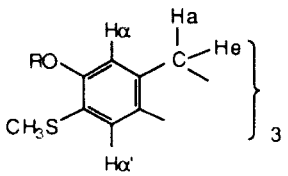
In order to study the effect of the sulfur substituents on the inversion barrier of the crown, we measured the racemization rate of (+)-**11** in dioxane at five temperatures in the range 37–58 °C. We calculated the following activation parameters (corresponding to the (+) to (−) inversion): $\Delta G^{\neq}$ 27.4 kcal mol^{-1} (298 K), $\Delta H^{\neq}$ 26.6 kcal mol^{-1} and $\Delta S^{\neq}$ −3 cal mol^{-1} K^{-1}. These figures are close to those reported[1] for other C3-cyclotriveratrylenes (including **2a** and **2b**), and confirm that in general the peripheral substituents have little effect on the conformational inversion barrier. The conformational stability of the crown in **11** can be best appreciated by considering that the time necessary to lose 1% of rotation ($t_{1/100}$) at 20 °C in solution is 59 h (instead of 40 h and 48 h for **2a** and **2b**, respectively). The crown in **11** is thus very slightly more rigid than it is in the other chiral cyclotriveratrylenes for which racemization data are available.

Circular dichroism

Chiral C3-cyclotriveratrylenes are useful systems for spectroscopic studies because their chiroptical properties, which are dominated by the coupled oscillator mechanism (exciton optical activity), can provide accurate information on the polarization direction of the transitions in substituted benzenoid derivatives.[21] We focus here on the polarization of the aromatic ^1L_b and ^1L_a transitions (in Platt's notation),[37] which correspond to the benzene $^1A_{1g} \rightarrow {}^1B_{2u}$ and $^1A_{1g} \rightarrow {}^1B_{1u}$ transitions, respectively, and we particularly address the problem of the relative influence of alkoxy *vs.* thioalkyl substituents on these transitions.

The circular dichroism of most C3-cyclotriveratrylenes can be interpreted by means of the simple analysis summarized in Scheme IV. In (**a**), the presence of two

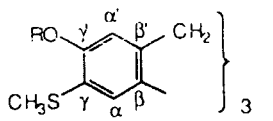
Table 1 ^{1}H-NMR spectral data for compounds **4**, **5**, **11**, **13**–**15** in $CDCl_3$[a]



	Hα'(s)	*Hα(s)*	*Ha(d)*	*← J(Hz) →*	*He(d)*	*SCH_3(s)*	*OR*
4	7.16	6.78	4.74	(13.7)	3.61	2.36	3.84 (s, OCH_3)
5	7.12	6.77	4.72	(13.6)	3.57	2.36	4.15 – 3.95 (m, diastereotopic $CH_3\underline{CH_2}$); 1.41 (*t*, J = 6.9 Hz, $\underline{CH_3}CH_2$)
11	7.46	6.97	4.63	(13.6)	3.59	2.24	6.40 (s, OH)
13	7.17	6.95	4.68	(13.8)	3.63	2.32	1.79 (d; J = 6.8; $\underline{CH_3}CH$) 4.95 (q; J = 6.8; $CH_3\underline{CH}$) 6.92 and 7.24 (2d; J = 9.0; Ph)
14	7.06	6.86	4.68	(13.7)	3.60	2.20	1.78(d; J = 6.8; $\underline{CH_3}CH$) 4.93 (q; J = 6.8; $CH_3\underline{CH}$) 6.91 and 7.25 (2d; J = 9.0; Ph)
15	7.22	7.03	4.73	(13.7)	3.67	2.30	2.38 (s, $OCOCH_3$)

[a] Spectra recorded at 200.13 MHz; the residual $CHCl_3$ peak was used as reference (δ = 7.24 ppm); racemates and enantiomers showed identical spectra.

Table 2 ^{13}C-NMR spectral data for compounds **4**, **5**, **11** and **15**[a]



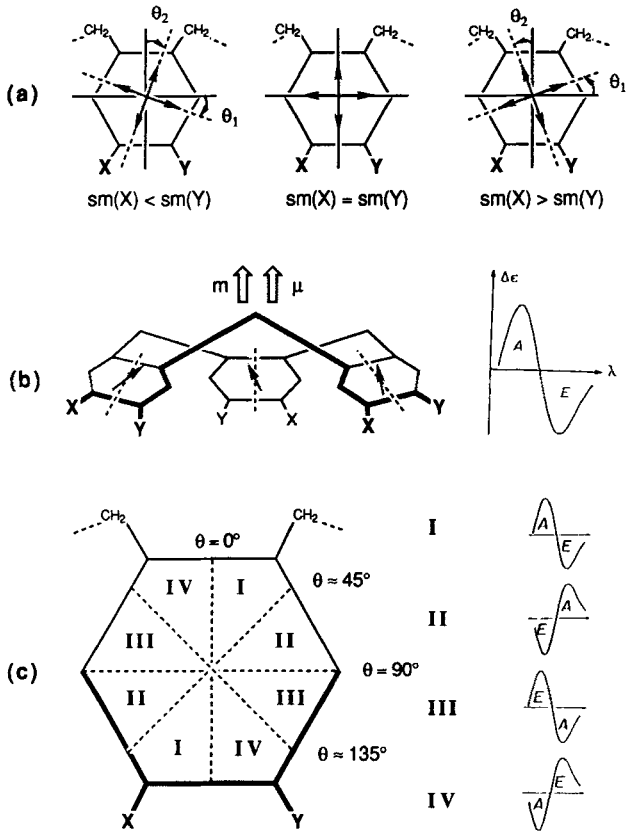
	α	α'	β	β'	γ	γ'	CH_2	SCH_3	R
4[b]	129.3	111.6	131.7	138.0	124.6	155.7	36.4	15.6	55.8 (OCH_3)
5[b]	129.0	112.8	131.6	137.8	124.7	154.9	36.3	15.3	64.2(OCH_2); 14.7(CH_3)
11[c]	131.9	115.9	136.7	143.1	120.1	155.6	36.3	20.2	
15[b]	124.5	123.6	137.6	137.2	130.3	147.6	36.2	16.2	20.8 (CH_3); 169.0 (CO)

[a] Spectra recorded at 50.4 MHz; [b] in $CDCl_3$; [c] in $C_2D_2Cl_2$.

substituents (X and Y) on each benzene ring is considered to cause a rotation of the ^1L_b (θ_2) and ^1L_a (θ_1) electric transition moments from the short and long axes (defined here by $\theta = 0$ and $\theta = 90°$, respectively). It is classically assumed[24] that θ_2 can be evaluated by vector addition of the substituent spectroscopic moments (sm), and that θ_1 is roughly perpendicular to θ_2. The coulombic coupling of each transition in the three benzene rings in turn generates two exciton couplets connected with the ^1L_b and ^1L_a systems, which in cyclotriveratrylenes such as **2a** occur at *ca.* 290 and 230 nm, respectively.[21]

As shown in Scheme IV (**b**), the in-phase *A*-coupling of the electric transition dipoles generates parallel electric (μ) and magnetic (m) overall transition moments along the three-fold axis, hence positive rotational strength for the *A*-component of the exciton couplet. Conversely, the out-of-phase *E*-coupling (not shown) could be assigned a negative rotational strength by similar reasoning. For the considered small value of θ, the coulombic interaction potential (V) of the transition dipoles is evidently repulsive in the A-coupling, and attractive in the *E*-coupling. The *A* component should therefore be found at higher energy, giving the exciton couplet a positive-negative sequence from high to low energy in the circular dichroism spectrum.

The dependence of the circular dichroism spectra on variation of θ is displayed in Scheme IV (**c**). There are four critical values of the angle where the exciton pattern is inverted as a consequence of the change of sign of either m, V, or μ. These *magic angles* correspond to $\theta = 0°$, $\approx 45°$, $90°$, and $\approx 135°$, and define the four sectors I–IV, each being characterized by a particular



Scheme IV The exciton mechanism in C3-cyclotriveratrylenes. (a) Polarization of the ^1L_b (θ_2) and ^1L_a (θ_1) transitions as a function of the spectroscopic moments (sm) of substituents X and Y; (b) in-phase *A*-coupling for a small positive value of θ, giving positive rotational strength at high energy. The out-of-phase *E*-coupling can be obtained by inverting one (or two) arrows; (c) the magic angles and the four sectors: a change in sign of m, V, μ, V occurs for $\theta = 0$, ≈ 45, 90, $\approx 135°$, respectively. The corresponding exciton couplets are shown on the right.

sequence of the *A* and *E* components of the exciton couplet as indicated on the Scheme. In all chiral C3-cyclotriveratrylenes that have been studied so far,[25] θ_2 was found in sectors I and IV, and θ_1 in sectors II or III.

The CD spectra of *M*-(+)-**4**, *M*-(+)-**5** and *M*-(+)-**11** are shown in Fig. 3, and relevant CD and UV data are assembled in Tables 3 and 4. These compounds display two well defined exciton couplets centered at *ca.* 295 and 260 nm, which we assign to the ^1L_b and ^1L_a systems. The presence of the sulfur substituents determines a red shift of the transitions, as may be expected.[36] These spectra indicate that the simple coupled oscillator mechanism dominates the chiroptical properties of **4**, **5**, and **11**, like in most chiral cyclotriveratrylenes. Since the absolute configurations of **4**, **5**, and **11** are known (X = OCH_3, OC_2H_5, or OH, Y = SCH_3), the diagram of Scheme IV (**c**) indicates that the polarization direction of the ^1L_b

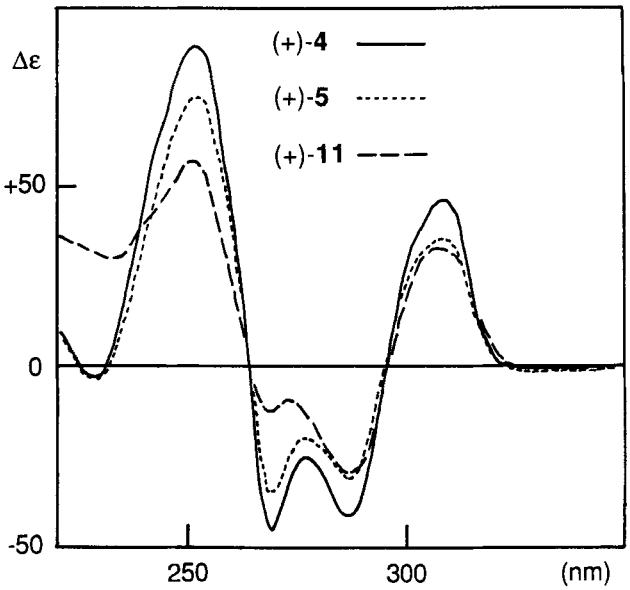


Figure 3 Circular dichroism spectra in methanol-dichloromethane 8:2 (v/v).

Table 3 Circular dichroism spectra[a,b]

	^1L_a		^1L_b	
No (X, Y)	λ_{max}	$\Delta\varepsilon$	λ_{max}	$\Delta\varepsilon$
(+)-**4** (OCH_3, SCH_3)	250	+89	287	−41
	(*255*)[c]		(*301*)[c]	
	270	−46	309.5	+46
(−)-**5** (OC_2H_5, SCH_3)	250	+74	287	−31
	(*255*)[c]		(*301*)[c]	
	268.5	−35	309	+35
(+)-**11** (OH, SCH_3)	250	+56	287	−31
	(*252*)[c]		(*301.5*)[c]	
	269	−11.7	308	+34

[a] In methanol-dichloromethane 8:2 (v/v); [b] λ_{max} in nm, $\Delta\varepsilon$ in $M^{-1}cm^{-1}$; c) λ_{max} in the isotropic ultraviolet absorption spectra.

Table 4 Ultraviolet isotropic absorption spectra[a,b]

	^1L_a		^1L_b		
No (X, Y)	λ_{max}	ε	λ_{max}	ε	**D**[c]
monomers					
1e (OCH_3, OCH_3)	230	8670	277.5	2820	2.4
3 (OCH_3, SCH_3)	255	10540	289	4800	3.9
trimers					
2e (OCH_3, OCH_3)	233	34200	290	11300	10.3
4 (OCH_3, SCH_3)	255	41260	301	19550	17.9
5 (OC_2H_5, SCH_3)	255	30800	301	14200	12.7
11 (OH, SCH_3)	252	29360	301.5	17750	16.2

[a] In methanol-dichloromethane 8:2 (v/v); [b] λ_{max} in nm, ε in $M^{-1}cm^{-1}$; [c] **D**, the dipole strength of the ^1L_b transition, was estimated from the band area by the relation $\mathbf{D} = 9.18 \times 10^{-3} (1/\lambda) \int \varepsilon \, d\lambda$, and is expressed in units of square Debye (D^2).

band should lie in sector II or IV, and that of the ^1L_a band in sectors I or III.

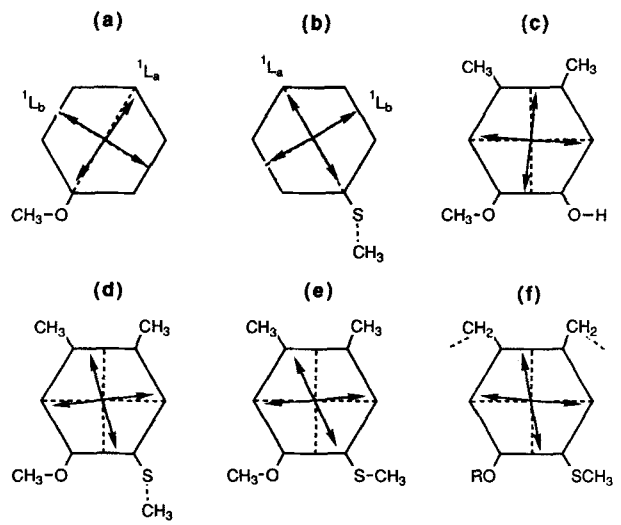
As noted above, the polarization θ_2 of the ^1L_b transition can, in principle be evaluated by vector addition of the substituent spectroscopic moments (sm).[24,27,37] The sm's of the two benzylic CH_2 group can be considered equal, but their magnitude is not known. In our previous work[21] we had suggested a value of $+19$ $((M^{-1}\,cm^{-1})^{1/2})$, a figure which should probably be taken as the higher limit; the lower limit would be around $+8$, the sm of the CH_3 group.[26] As the overall contribution of the CH_2 groups to the ^1L_b transition is parallel to the short axis ($\theta = 0$) of the benzene ring, the sign of θ_2 should depend only on the *relative magnitude* of the sm's of the X and Y groups. The values of the sm's of the OCH_3 and OH groups are *ca.* 30–35,[26] and that of the SCH_3 group is unknown. If the spectroscopic moment theory is still valid here, the experimental CD spectra of **4**, **5**, and **11** suggest that the sm of SCH_3 could be either slightly smaller (θ_2 in sector IV), or much greater (θ_2 in sector II), than that of a OCH_3 group; in the latter case, the vector addition of the spectroscopic moments would require that *a sm of at least +130* be assigned to SCH_3 to allow angle θ_2 to cross the magic angle of $\approx 45°$ and reach sector II. This figure is clearly out of the range of the usual spectroscopic moments, and the first hypothesis (θ_2 in sector IV and sm of SCH_3 *smaller* than that of OCH_3) therefore seems to be preferred here. The same arguments applied to the ^1L_a exciton couplet led us to an inverse conclusion: for this transition, the sequence of signs of the CD couplet implies that the sm of the SCH_3 group would be slightly *greater* than that of the OCH_3 group and the polarization θ_1 of the ^1L_a transition should then be found in sector III, rather than in sector I.

In the classical theory the absorption intensity of the lowest energy transition (^1L_b) of substituted benzenes is considered to comprise two separate contributions: the absorption due to the electronic perturbation caused by the substituents, and the vibrational absorption due to the symmetry-breaking atomic motions.[27] In this theory, the electronic contribution is represented by $(\Sigma sm_i)^2$, the square of the modulus of the vectorial summation of the sm's of the substituents, and the vibrational contribution is assumed to have a relatively constant value. The magnitude of $(\Sigma sm_i)^2$ is calculated from the UV band area, after subtraction of the estimated vibrational intensity. In practice, the total area of the UV band provides the dipole strength **D**, equal to μ^2, the square of the modulus of the transition dipole (see Table 4). Thus, $\mathbf{D} \approx (\Sigma sm_i)^2$ + vibrational intensity.

The experimental dipole strengths of monomers **1e** and **3**, and of trimers **2e**, **4**, **5** and **11** are assembled in Table 4. On going from veratryl alcohol **1e** to the related monosulfide **3**, the dipole strength of the ^1L_b transition increases from 2.4 to 3.95 square Debye. Similarly, the dipole strength of **4**, **5** and **11** is *ca.* 1.2 to 1.7 times greater than that of cyclotriveratrylene **2e**. If the above hypothesis is correct, then the increase in absorption intensity, on going from the oxygenated to the sulfur substituted derivatives, should be vibrational in origin, and should probably be related to the change of symmetry group between **1e** and **3**. This argument is supported by the observation that there is no increase in the absorption intensity on going from anisole to thioanisole, which belong to the same group of symmetry.[27]

Further support of these views was provided by CNDO/S calculation of the electronic transitions in suitable monomer structures (Scheme V).We used a program in which *d* orbitals were included in the basis set for sulfur. The substrate geometries were generated by means of PCMODEL,[20] and the OCH_3 or OH substituents were set coplanar to the aromatic ring, whereas the conformation of the SCH_3 group was fixed either perpendicular or coplanar to the ring. Details on the calculations are given in the Experimental section. Relevant results are summarized in Scheme V.

We first checked the reliability of the calculations by considering systems in which the polarization directions of the transitions are known. In anisole and thioanisole (Scheme V(**a**) and V(**b**), respectively), the calculations confirmed that the first two bands were similar to the benzene $^1A_{1g} \rightarrow {}^1B_{2u}$ and $^1A_{1g} \rightarrow {}^1B_{1u}$ transitions and were polarized, as expected, along the short and long axes of the molecules, respectively. In



Scheme V (a–e) CNDO/S calculation of the polarization directions of the ^1L_b and ^1L_a transitions in model structures; (f) experimental polarizations inferred from the CD spectra of (+)-**4**, (+)-**5**, and (+)-**11**.

(**c**), we found that the calculated polarization directions for the ^1L_b and ^1L_a systems were in agreement with those derived from the exciton analysis of the CD spectrum of *P*-(−)-**2a**,[10] assuming a spectroscopic moment of OH slightly greater than that of OCH_3 for both transitions. Next, we examined the case of 1,2-dimethyl-3-methoxy-4-methylthiobenzene, as a model of sulfur substituted cyclotriveratrylenes. In (**d**), for various calculations including or not *d* orbitals, the polarization of the ^1L_b band was always found in sector IV, in agreement with the hypothesis that the sm of OCH_3 would be greater than that of SCH_3 for this transition. This result was not qualitatively affected by the conformation of the SCH_3 group (compare (**d**) and (**e**)). For the ^1L_a band, the calculated polarization of the transition moment was found to be in sector II, very close to the long axis ($\theta = 90°$) of the molecule. The CNDO/S calculations thus suggests that the OCH_3 group would have a slightly stronger effect than the SCH_3 groups on the ^1L_a transition, whereas the exciton analysis of the CD spectra of **4**, **5**, and **11** would imply, for that transition, the inverse conclusion (polarization in sector III).

Our conclusion that the sm of SCH_3 is smaller than that of OCH_3 for the ^1L_b transition is in agreement with the analysis of Petruska,[36] based on the Perturbation theory. According to this author, the "*transition moment parameter*" *q*—which is considered to be roughly proportional to Platt's spectroscopic moments—is slightly smaller in magnitude for the SH group than for the CH_3O or OH groups. The same conclusion would probably hold for the CH_3S group. For Petruska, the magnitude of *q* is related to inductive effects, whereas for Platt[37] and Exner[27] the sm's are controlled primarily by mesomeric effects and the inductive effects are much less important. In the case discussed here, both contributions would lead to the same result: sulfur is less electronegative than oxygen, and the Ar-S bond (1.77 Å) being substantially longer than the Ar-O bond (1.39 Å) the conjugation of the sulfur lone pairs with the aromatic π orbitals (even in a planar conformation) should be much weaker than that of the oxygen lone pairs, as was pointed out by Palmieri *et al.*[19c] when comparing anisole and thioanisole.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

Melting points were measured on a Perkin-Elmer DSC7 microcalorimeter with simultaneous check of purity. Rotations and racemization kinetics were measured on a Perkin-Elmer 241 micropolarimeter, in thermostated 1-dm quartz cells and spectrometric grade solvents. Circular dichroism spectra (CD) were recorded on a Jobin-Yvon Dichrograph V instrument, and absorption spectra (UV) were obtained on a Cary 219 spectrophotometer. Infrared spectra (IR) were taken (in KBr) on a Perkin-Elmer 1600FTIR instrument; ^1H and ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer. Elemental analyses were performed by the Service Central d'Analyse du C.N.R.S.

Column chromatographic separations and filtrations were carried out over Merck silica gel 60 (0.040–0.063 mm); analytical and preparative thin-layer chromatography (TLC) were performed on Merck silica gel TLC plates F254.

Racemization kinetics

The racemization of (+)-**11** was followed polarimetrically at 436 nm in dioxane solution, using a 1-dm thermostated cell (±0.1 °C). The first order rate constant *k* corresponding to the (+) to (−) process (crown inversion) were derived from linear regression of $\alpha(t) = \exp(-2kt)$ at five temperatures between 37 and 58 °C. From these five points linear regression ($r = 0.999$) of $k = (RT/Nh)\exp(-\Delta H^{\neq}/RT + \Delta S^{\neq}/R)$ gave the Eyring activation parameters indicated in the text. The value of $t_{1/100}$ refers to $(0.5/k)\ln(100/99)$, where *k* is the calculated rate constant at 20 °C.

CNDO/S calculations

The program used was derived from QCPE 382. The set of parameters including or not the 3d atomic orbitals for the sulfur atom are given in Table 5. A constant K which distinguishes between σ, π, and δ components of overlap[29,30] was adopted and set to *1*, 0.585, and 0.3, respectively. The two-center repulsion integrals ν_{AB} were calculated from the Nishimoto-Mataga formula;[31] a total of 100 configurations were included in the CI procedure.

Table 5 Parameters used for the CNDO/S calculations

	$1/2\ (I_\mu + A_\mu)\ (eV)$[a]			$-\beta_{A\cdot}$ (eV)
	s	*p*	*d*	
H	7.176			12.0
C	14.051	5.572		17.0[b] or 17.5[c]
O	25.3902	9.111		45.0[d]
S	17.6494	6.989	0.7130	from 18.15[a] to 25.0[e]

[a] Ref. 32; [b] ref. 29; [c] ref. 34; [d] ref. 35; [e] ref. 34.

4-(*N,N*-dimethylthiocarbamoyloxy)-3-methoxybenzaldehyde (7a)

A solution of *N,N*-dimethylthiocarbamoyl chloride (18.5 g, 0.15 mol) in THF (40 mL) was added dropwise at 0 °C to a solution of vanillin **6a** (22.8 g, 0.15 mol) and potassium hydroxide (8.4 g) in water (100 mL). The reaction mixture was stirred for 15 min at room temperature, then 100 mL of 10% aqueous potassium hydroxide was added; the resulting white precipitate was collected by suction filtration, washed with water, and dried in air. Yield 30.5 g (85%) of pure **7a**, mp 115 °C. Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.47; N, 5.85; O, 20.06; S, 13.40. Found: C, 55.1; H, 5.6; N, 5.8; O, 20.4; S, 13.3 IR (KBr): ν max 1699 (C = O), 1539 (C = S). ^{1}H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 9.94 (s, CH = 0); 7.48 and 7.20 (broad m's, aromatic H's); 3.88 (s, OCH_3); 3.44 and 3.52 (2s, $(CH_3)_2N$).

4-(*N,N*-dimethyl-carbamoylthio)-3-methoxybenzaldehyde (8a)

Method A. a solution of **7a** (13 g, 0.054 mol) in diphenylether (180 mL) was heated in a metal bath at 240–250 °C for 15 min under argon. After cooling to room temperature the solution was poured into 1.56 L of pentane. The crystalline precipitate was filtrated off and washed with hot pentane; yield 10.9 g (84%) of beige needles of **8a**, mp 113 °C.

Method B. 4 g of **7a** (0.017 mol) were heated at 240–255 °C under argon for 25 min (metal bath). Recrystallization of the rearranged product from a dichloromethane-pentane mixture gave a first crop of pure **8a** (1.75 g) and a second crop (1.13 g) was obtained from the mother liquors by column chromatography using ethyl acetate-hexane 1:1 (v/v) as the eluant. Overall yield 2.88 g (72%), mp 113 °C. Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.47; N, 5.85; O, 20.06: S, 13.40. Found: C, 55.4; H, 5.3; N, 5.9; O, 20.3; S, 13.3. IR (KBr): ν max 1686 (HC = O), 1661 (SC = O). ^{1}H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 9.97 (s, CH = O); 7.67 and 7.46 (2d, 2 aromatic H's, J = 8 Hz); 7.42 (s, aromatic H); 3.92 (s, OCH_3); 3.08 (broad s, $(CH_3)_2N$).

4-Mercapto-3-methoxybenzaldehyde (9a) (Thiovanillin)

To a solution of **8a** (7.95 g, 0.033 mol) in methanol (51 mL) was added dropwise 19.9 mL of 2 M aqueous sodium hydroxide, and the mixture was refluxed for 1 h 30. The methanol was stripped off and the remaining aqueous phase was extracted with dichloromethane then acidified with concentrated hydrochloric acid. The desired product was extracted with diethyl ether, the organic phase was dried over sodium sulfate and evaporated to dryness to give **9a** as an oil which rapidly solidified (yield 5.2 g, 93%); pale yellow crystals (5.0 g, 90%) were obtained by recrystallization from hexane; mp 47 °C. Anal. Calcd for $C_8H_8O_2S$: C, 57.13; H, 4.79; O, 19.02; S, 19.06. Found: C, 56.8; H, 4.8; O, 19.2; S, 19.0. IR (KBr): ν max 1702 (HC = O), 2550 (SH). ^{1}H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 9.86 (s, CH = O); 7.30–7.40 (broad m, aromatic H's); 4.15 (s, SH); 3.95 (s, OCH_3).

3-Methoxy-4-methylthiobenzaldehyde (10a)

To a stirred solution of **9a** (4.57 g, 0.027 mol) in methanol (32 mL) at room temperature was added dropwide 16.2 mL (0.032 mol) of aqueous 2 M sodium hydroxide. After 30 min methyl iodide (3.4 mL, 0.054 mol) was added and the reaction mixture was stirred overnight at room temperature. Then water was added and the desired product was extracted with diethyl ether. The organic phase was washed with water, dried over sodium sulfate and evaporated to dryness to give **10a** (4.5 g, 92%) as yellow crystals, mp 42 °C. Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.5; H, 5.5. IR (KBr): ν max 1673 (C = O). ^{1}H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 9.89 (s, CH = O); 7.43 (dd, aromatic H, J = 1.5 and 7.9 Hz); 7.29 (d, aromatic H, J = 1.5 Hz); 7.19 (d, aromatic H, J = 7.9 Hz); 3.94 (s, OCH_3); 2.47 (s, SCH_3).

3-Methoxy-4-methylthiobenzyl alcohol (3a)

A solution of **10a** (4.4 g, 0.024 mol) in 28 mL of methanol was allowed to react for 15 h at room temperature with 1.32 g of sodium borohydride. Addition of water followed by extraction of the organic material with dichloromethane and usual workup gave **3a** (4.3 g, 98%) as a white solid (mp 64 °C). Anal. Calcd for $C_9H_{12}O_2S$: C, 58.67; H, 6.56; O, 17.37; S, 17.40. Found: C, 58.9; H, 6.6; O, 17.5; S, 17.2. ^{1}H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24):

δ 7.12 and 6.90 (2d, aromatic H's, J = 7.8 Hz); 6.87 (s, aromatic H); 4.64 (s, CH_2); 3.89 (s, OCH_3); 2.41 (s, SCH_3).

4-(*N,N*-dimethylthiocarbamoyloxy)-3-ethoxybenzaldehyde (7c)

A solution of *N,N*-dimethylthiocarbamoyl chloride (9.3 g, 0.075 mol) in 40 mL of THF was added dropwise to a stirred solution of ethylvanillin **6c** (12.5 g, 0.075 mol) and potassium hydroxide (4.2 g, 0.075 mol) in water (50 ml), at 0 °C. The resulting precipitate of **7c** was collected by suction filtration, washed with water and dried in air. Yield 15.2 g (80%), mp 104 °C. Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.89; H, 5.92; N, 5.53; O, 18.95; S, 12.66. Found: C, 56.7; H, 5.9; N, 5.6; O, 18.9; 12.4. ^{1}H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 9.92 (s, CHO); 7.46 (broad m, 2 aromatic H's); 7.22 (d, aromatic H, J = 8.6 Hz); 4.12 (q, CH_2, J = 6.9 Hz); 3.44 and 3.36 (2s, $N(CH_3)_2$); 1.38 (*t*, CH_3, J = 6.9 Hz).

4-(*N,N*-dimethyl-carbamoylthio)-3-ethoxybenzaldehyde (8c)

Compound **7c** (8.49 g, 0.033 mol) was heated in a metal bath at 240–260 °C for 1 h under argon. After cooling the resulting solid was recrystallized from 20 mL of 95% ethanol to give **8c**, 6.8 g (80%), mp 113 °C. Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.89; H, 5.92; N, 5.53; O, 18.95; S, 12.66. Found: C, 57.0; H, 5.9; N, 5.7; O, 19.2; S, 12.5. ^{1}H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 9.95 (s, CHO); 7.67 (d, aromatic H, J = 7.7 Hz); 7.41 (dd, aromatic H, J = 7.7 and 1.6 Hz); 7.39 (s, aromatic H); 4.15 (q, CH_2, J = 6.9 Hz); 3.06 (broad s, $N(CH_3)_2$); 1.42 (*t*, CH_3, J = 6.9 Hz).

4-Mercapto-3-ethoxybenzaldehyde (9c)

Compound **8c** (8 g, 0.031 mol) in 48 mL of methanol was hydrolyzed by 2 M aqueous NaOH (21.2 mL, 0.042 mol) for 1 h under reflux. After usual workup (see the preparation of **9a**) the product was purified by flash chromatography over 80 g of silica gel, using dichloromethane as the eluant. Yield 5 g (88%) of **9c** as a yellow solid, mp 36.5 °C. Anal. Calcd for $C_9H_{10}O_2S$: C. 59.32; H, 5.53; O, 17.56; S, 17.59. Found: C, 59.3; H, 5.5; O, 17.6; S, 17.8. ^{1}H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 9.86 (s, CHO); 7.40–7.29 (broad m, aromatic H's); 4.20 (s, SH); 4.17 (q, CH_2, J = 7.0 Hz); 1.48 (*t*, CH_3, J = 7.0 Hz).

3-Ethoxy-4-methylthiobenzaldehyde (10c)

A solution of **9c** (4.37 g, 0.024 mol) in 28 mL of methanol was treated with 14.1 mL of aqueous 2 M NaOH, then with 3 mL of methyl iodide. The reaction mixture was stirred overnight at room temperature and after workup (see the preparation of **10a**) a yellow solid was obtained and recrystallized from hexane. Yield 4.4 g of **10c** (93%), mp 69 °C. Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.19; H, 6.16; O, 16.30; S, 16.34. Found: C, 61.3; H, 6.2; O, 16.5; S, 16.2. ^{1}H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 9.87 (s, CHO); 7.41 (dd, aromatic H, J = 1.5 and 7.9 Hz); 7.27 (d, aromatic H, J = 1.5 Hz); 7.18 (d, aromatic H, J = 7.9 Hz); 4.16 (q, CH_2, J = 6.9 Hz); 2.45 (s, SCH_3); 1.46 (*t*, CH_3, J = 6.9 Hz).

3-Ethoxy-4-methylthiobenzyl alcohol (3c)

Reduction of **10c** (2.8 g, 0.014 mol) in 15 mL of methanol was carried out by reaction with 0.73 g of sodium borohydride at room temperature overnight. Addition of water and extraction with dichloromethane gave **3c** as a yellow solid (2.55 g, 92%), mp 47 °C. Anal. Calcd for $C_{10}H_{14}O_2S$: C, 60.57; H, 7.11; O, 16.14; S, 16.17. Found: C, 60.9; H, 6.9; O, 16.3; S, 16.0. ^{1}H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 7.10 (d, aromatic H, J = 7.8 Hz); 6.89 (d, aromatic H, J = 7.8 Hz); 6.84 (s, aromatic H); 4.62 (s, $C\underline{H}_2OH$); 4.10 (q, CH_2, J = 6.7 Hz); 2.40 (s, CH_3S); 1.44 (*t*, CH_2, 7.0 Hz).

3-(*N,N*-dimethylthiocarbamoyloxy)-4-methoxybenzaldehyde (7b)

A solution of *N,N*-dimethylthiocarbamoyl chloride (8.2 g, 0.066 mol) in THF (18 mL) was added dropwise at 0 °C to a solution of isovanillin **6b** (10 g, 0.066 mol) and potassium hydroxide (3.7 g, 0.066 mol) in water (44 mL). The white precipitate was collected by suction filtration, washed with water and dried in air. Yield 10.2 g (90%) of **7b**, mp 110 °C. Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; O, 20.06; S, 13.39. Found: C, 55.4; H, 5.6; N, 5.7; O, 20.2; S, 13.1. ^{1}H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 9.86 (s, CHO); 7.76 (dd, aromatic H, J = 2.0 and 8.5 Hz); 7.55 (d, aromatic H, J = 2 Hz); 7.10 (d, aromatic H, J = 8.4 Hz); 3.89 (s, OCH_3); 3.45 and 3.35 (2s, $N(CH_3)_2$).

3-(*N,N*-dimethylcarbamoylthio)-4-methoxybenzaldehyde (8b)

A solution of **7b** (10.2 g, 0.043 mol) in 100 mL of diphenyl ether was heated at 245–250 °C under argon for 2 h 10. Then the cooled solution was poured into 1 L of pentane and the resulting precipitate was collected by suction filtration, washed with pentane, and dried in air. Yield 9.6 g (94%) of **8b** as beige

needles, mp 126 °C. Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.47; N, 5.85; O, 20.06; S, 13.40. Found: C, 55.1; H, 5.5; N, 5.7; O, 20.2; S, 13.5. ^1H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 9.86 (s, CHO); 7.93 and 7.98 (dd, and d, aromatic H's, J = 2 and 8.5 Hz); 7.05 (d, aromatic H, J = 8.5 Hz); 3.94 (s, CH_3O); 3.10 (2 broad s, $N(CH_3)_2$).

4-Methoxy-3-mercaptobenzaldehyde (9b) (Isothiovanillin)

The alkaline hydrolysis of **8b** (7.9 g) was effected in refluxing methanol as described above for the hydrolysis of **8a**. The resulting **9b** was recrystallized from hexane; yield 4.8 g (87%), mp 58 °C. Anal. Calcd for $C_8H_8O_2S$: C, 57.13; H, 4.79; O, 19.02; S, 19.06. Found: C, 57.5; H, 4.8; O, 19.3; S, 19.4. ^1H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 9.81 (s, CHO); 7.79 (d, aromatic H, J = 2 Hz); 7.64 (dd, aromatic H, J = 8.4 and 2 Hz); 6.94 (d, aromatic H, J = 8.4 Hz); 3.97 (s, CH_3O); 3.86 (s, SH).

3-Methylthio-4-methoxybenzaldehyde (10b)

Thiol **9b** (4 g, 0.024 mol) in 28 mL of methanol was treated with 14.1 mL (0.028 mol) of aqueous 2 M sodium hydroxyde then 3 mL of methyl iodide as described above for the preparation of **10a**. Extraction of the resulting yellow oil by hot hexane gave 3.2 g (80%) of **10b**, mp 46 °C. Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53; O, 17.56; S, 17.59. Found: C, 59.4; H, 5.6; O, 17.6; S, 17.4. ^1H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 9.86 (s, CHO); 7.64 (d, aromatic H, J = 1.9 Hz); 7.62 (dd, aromatic H, J = 8.5 and 1.9 Hz); 6.92 (d, aromatic H, J = 8.5 Hz); 3.96 (s, CH_3O); 2.47 (s, CH_3S).

3-Methylthio-4-methoxybenzyl alcohol (3b)

A solution of **10b** (2.45 g, 0.013 mol) in 10 mL of methanol was treated with 0.73 g of sodium borohydride at room temperature overnight. Addition of water and extraction with dichloromethane gave 2.5 g (98%) of **3b** as a white solid, mp 65 °C. Anal. Calcd for $C_9H_{12}O_2S$: C, 58.67; H, 6.56; O, 17.37; S, 17.40. Found: C, 58.3; H, 6.6; O, 17.7; S, 17.2. ^1H NMR (in $CDCl_3$, δ of residual $CHCl_3$ set to 7.24): δ 7.15 (d, aromatic H, J = 1.9 Hz); 7.10 (dd, aromatic H; J = 1.9 and 8.2 Hz); 6.79 (d, aromatic H, J = 8.2 Hz); 4.61 (s, CH_2); 3.87 (s, CH_3O); 2.42 (s, CH_3S).

2,7,12-Trimethoxy-3,8,13-trimethylthio-10,15-dihydro-5H-tribenzo-[a,d,g]cyclononene ((±)-4)

A) From **3a**: **Alcohol 3a** (4.6 g, 0.025 mol) was dissolved in 65 mL of formic acid and the resulting pale green solution was stirred in an oil bath at 70 °C. The green color rapidly turned to pale yellow and after *ca.* 30 min a precipitate began to form. After 3 h 40 the solvent was evaporated to dryness under vacuum (rotatory evaporator). The solid residue was taken into water and collected by suction filtration, washed with water, and dried in air. The crude material (4 g) was chromatographed over 300 g of silica gel by using dichloromethane-hexane 99:1 (v/v) as the eluant, giving 2.5 g (60%) of pure (±)-**4** (see below).

B) From **3b**: alcohol **3b** (2 g, 0.0108 mol) was dissolved in 28 mL of formic acid and the pale green solution was heated in an oil bath at 70 °C with stirring. After 10 min a precipitate began to form. After 1 h 30 the solvent was stripped off under vacuum (rotatory evaporator) and the solid residue was recrystallized from dichoromethane-ethanol, yielding 1.26 g (70%) of pure (±)-**4**.

Samples of (±)-**4** obtained from either **3a** or **3c** showed the same mp's (240 °C), and ^1H and ^{13}C NMR spectra (Tables 1 and 2). Anal. Calcd for $C_{27}H_{30}O_3S_3$: C, 65.02; H, 6.06; O, 9.62; S, 19.28. Found: C, 65.2; H, 5.9; O, 9.9; S, 19.6.

2,7,12-Triethoxy-3,8,13-trimethylthio-10,15-dihydro-5H-tribenzo-[a,d,g]cyclononene ((±)-5)

Alcohol **3c** (2 g, 0.010 mol) was dissolved in 26 mL of formic acid. The pale green solution was stirred at 70 °C (oil bath). After 8 min the mixture turned to a beige color and a precipitate began to form. After 1 h 30 the solvent was evaporated under vacuum (rotatory evaporator) and the product was taken into water and collected by suction filtration. Column chromatography over 200 g of silica gel using dichloromethane-hexane 80:20 (v/v) as the eluant gave 1.3 g (71%) of pure (±)-**5**, mp 215 °C. Anal. Calcd for $C_{30}H_{36}O_3S_3$: C, 66.62; H, 6.71; O, 8.87; S, 17.78. Found: C, 66.4; H, 6.7; O, 9.0; O, 9.0; S, 17.3. ^1H and ^{13}C NMR spectra see Tables 1 and 2.

2,7,12-Trihydroxy-3,8,13-trimethylthio-10,15-dihydro-5H-tribenzo-[a,d,g]cyclononene ((±)-11).

Method A. To a solution of (±)-**4** (0.3 g, 0.6 mmol) in 10 mL of dichloromethane stirred at −78 °C under argon, was added dropwise 0.57 ml (6 mmol) of boron tribromide. The solution was stirred for 20 min at −70 °C then 1 h at room temperature (a white precipitate was observed) and finally it was refluxed overnight. The reaction mixture was cooled in a dry-ice acetone bath and hydrolyzed by 14 mL of water. The white solid was collected by suction filtration, washed with 10 mL of water, and dried in vacuum; yield 0.25 g of nearly pure **11** which was eventually chromatographed on a silica gel column (dichloromethane as the eluant)

to give 0.19 g (69%) of **11** as a white solid, mp 270 °C, identical with the product obtained by the method B below.

Method B. Sodium isopropanethiolate (1.95 g, 19.8 mmol) was added to a solution of (±)-**4** (1.16 g, 2.33 mmol) in 12 mL of HMPA at 120 °C. The resulting mixture was stirred at 120 °C under argon for 18 h, then it was cooled and poured into 80 mL of aqueous 8 M hydrochloric acid. The precipitate was collected by suction filtration, washed with water, and dried at 80 °C under vacuum, yielding 1 g of crude **11** (yellow solid). Column chromatography over 100 g of silica gel using dichloromethane as the eluant finally gave 0.84 g (79%) of (±)-**11** as a beige solid, mp 270 °C. Anal. Calcd for $C_{24}H_{24}O_3S_3$: C, 63.13; H, 5.29; O, 10.51; S, 21.06. Found: C, 63.5; H, 5.5; O, 10.6; S, 21.1. ^1H and ^{13}C NMR spectra are given in Table 1 and 2.

Optical resolution of (±)-11. To a solution of *R*-(+)-2-*p*-chlorophenoxy propionic acid[23] **16** (692 mg, 3.45 mmol) in 20 mL of dichloromethane were added 230 mg (1.92 mmol) of 4-dimethylaminopyridine (DMAP), 350 mg (0.77 mmol) of (±)-**11**, and 790 mg (3.8 mmol) of dicyclohexylcarbodiimide (DCC); this mixture was stirred for 15 h at room temperature. Then, 6 mL of 1 M aqueous HCl was added and the precipitate (dicyclohexylurea) was removed by filtration and washed with dichloromethane. The organic filtrate was washed with aqueous sodium hydrogenocarbonate then with water until neutral, and dried (Na_2SO_4). The solvent was evaporated, leaving 1 g of the crude 1:1 mixture of diastereomers **13** and **14**.

The resolution of **13** and **14** was effected by column chromatography over silica gel, using chloroform-diethyl ether 99:1 (v/v) as the eluant. In a first stage the above mixture was chromatographed over 280 g of silica gel giving 150 mg (39%) of pure **13** (first eluted) and several fractions containing an excess of **14**. In a second stage these unresolved fractions were chromatographed twice on a similar column eventually yielding a further amount of **13** (20 mg) and 145 mg (38%) of **14**. The pure diastereomers were crystallized (*without heating*!) from diethyl ether (**13**) and light petroleum (**14**).

The faster-running **13** showed $[\alpha]_D^{25}$ +251° (c 0.1, dioxane), mp > 135 °C (decomp., by DSC at 5 K/min). Anal. Calcd for $C_{51}H_{45}Cl_3O_9S_3$: C, 60.92, H, 4.63; O, 14.32; S, 9.56. Found: C, 61.2; H, 4.4; O, 14.2; S, 9.2.

The slower-running **14** showed $[\alpha]_D^{25}$ −18° (c 0.105, dioxane); on heating (Kofler bench) it became pasty at *ca.* 100 °C, eventually melting at *ca.* 150 °C (decomp.). Anal. was consistent with $C_{51}H_{45}Cl_3O_9S_3$. Found: C, 60.7; H, 4.5; O, 14.2; S, 9.3. For the ^1H NMR spectra of **13** and **14** see Table 1.

Cleavage of diastereomers (+)-13 and (−)-14 to enantiomers (+)-11 and (−)-11, respectively

A) The crystalline diastereomer (+)-**13** (150 mg, 0.15 mmol) was added by portions to a stirred suspension of lithium aluminium hydride (140 mg) in 5.5 mL of THF at 0 °C under argon. The mixture was stirred for 15 min at 0 °C then 1 h 15 at 20 °C. Hydrolysis was carried out at 0 °C by adding successively several drops of ethyl acetate, diethyl ether and water; the precipitated alumina was dissolved by addition of 1 N H_2SO_4. The organic material was extracted with diethyl ether, then with chloroform. The combined organic phases were dried (Na_2SO_4) and evaporated to dryness under vacuum *without heating*, and the crude product was purified by digestion in dichloromethane at room temperature; yield 62 mg (91%) of (+)-**11**, $[\alpha]_D^{25}$ +354° (c 0.2 in dioxane), mp 282 °C (by DSC at 10 K/min). Elemental analysis of the crystalline material suggested the presence of 0.25 eq. of water; Calcd for $C_{24}H_{24}O_3S_3$, 0.25 H_2O: C, 62.51; H, 5.35; O, 11.27; S, 20.85. Found: C, 62.6; H, 5.1; O, 11.1; S, 20.6.

B) In a similar way, 145 mg of (−)-**14** afforded 40 mg (61%) of (−)-**11** having $[\alpha]_D^{25}$ −343° (c 0.0615, dioxane), mp 279 °C (by DSC at 10 K/min). Anal. Consistent with $C_{24}H_{24}O_3S_3$, 0.25 H_2O. Found: C, 62.2; H, 5.25; O, 11.4.

The ^1H NMR of (+)- and (−)-**11** were identical with that of the racemate (Table 1).

Methylation of enantiomers (+)-11 and (−)-11 to (+)-4 and (−)-4, respectively

A) To a solution of triphenol (+)-**11** (15 mg, 0.033 mmol) in 1 mL of HMPA was added 0.1 mL of 25% aqueous NaOH and the mixture was stirred for 40 min at room temperature under argon. This was followed by the addition of methyl iodide (0.1 mL). After stirring for 1 h, ice was added and the resulting crystalline precipitate was collected by suction filtration, washed with water and dried under vacuum at room temperature. Then the product was purified by filtration through a short silica gel column using dichloromethane as the eluant. The fractions containing pure (+)-**4** were evaporated off under vacuum *without heating* to give 10.2 mg (62%), $[\alpha]_D^{25}$ +382° (c 0.07, dioxane), mp 238 °C (DSC, 5 K/min). Anal. Calcd for $C_{27}H_{30}O_3S_3$: C, 65.02; H, 6.06. Found: C, 65.1; H, 6.2.

B) Similarly, (−)-**11** (11.6 mg, 0.025 mmol) afforded (−)-**4** as a solid which was purified by TLC on silica gel (dichloromethane as the eluant); yield 8.7 mg (70%), $[\alpha]_D^{25}$ −396° (c 0.058, dioxane), mp 238 °C (DSC,

10 K/min). Both (+)- and (−)-**4** showed ^{1}H NMR spectra identical with that of (±)-**4** (Table 1).

Ethylation of (+)-11 to (+)-5

To a solution of (+)-**11** (10.5 mg, 0.023 mmol) in HMPA (0.8 mL) was added 0.07 mL of 25% aqueous NaOH, and the mixture was stirred for 25 min at room temperature under argon. Then 0.1 mL of ethyl iodide was added. After 2 h stirring at room temperature, water was added (20 mL) and the crystalline precipitate of (+)-**5** was filtered off and washed with water. It was purified by TLC (silica gel, dichloromethane); yield 10 mg (81%) of pure (+)-**5**, $[\alpha]_D^{25}$ +266° (c 0.095, dioxane). Elemental analysis of the crystalline solid suggested the presence of 0.5 eq. of water; Calcd for $C_{30}H_{36}O_3S_3$, 0.5 H_2O: C, 65.53; H, 6.78. Found: C, 65.3; H, 6.8. The ^{1}H NMR spectrum of (+)-**5** was identical with that of (±)-**5** (see Table 1).

Acetylation of enantiomers (+)- and (−)-11 to (+)- and (−)15, respectively. 2,7,12-Triacetyloxy-3,8,13-trimethylthio-10,15-dihydro-5H-tribenzo[a,d,g]cyclonene (15)

A) Triphenol (+)-**11** (15.2 mg) ($[\alpha]_D^{25}$ +354° in dioxane) was added to a chilled mixture of acetic anhydride (0.46 mL) and pyridine (0.9 mL). After 1 h stirring at 0 °C, ice was added, and the precipitate was collected by suction filtration, washed with water and dried in air. Digestion in diethyl ether afforded 14.8 mg (77%) of (+)-**15**, $[\alpha]_D^{25}$ +460° (c 0.108, dioxane), mp 224 °C (DSC, 5 K/min). Anal. Calcd for $C_{30}H_{30}O_6S_3$: C, 61.83; H, 5.19. Found: C, 61.7; H, 5.1.

B) Similarly, 15 mg of (−)-**11** ($[\alpha]_D^{25}$ −343° in dioxane) gave after purification by filtration on a short silica gel column (AcOEt) 13 mg of (−)-**15**, mp 225 °C (DSC, 5 K/min), $[\alpha]_D^{25}$ -467° (c 0.057, dioxane). The ^{1}H and ^{13}C NMR spectra of (+)- and (−)-**15** were identical (see Tables 1 and 2) and in agreement with the expected structure.

Desulfurization of (±)-4 to (±)-2b. 2,7,12-Trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (2b, cyclotrianisylene)

To a solution of (±)-**4** (0.202 g, 0.41 mmol) in a mixture of THF (10 mL) and 95% ethanol (10 mL) was added *ca.* 1.2 g of a slurry of Raney nickel in 95% ethanol (prepared from a commercial suspension in water (from Janssen Chimica)). The mixture was stirred at room temperature for 2 h 30 (the reaction was followed by TLC). The catalyst was filtrated off, rinsed with dichloromethane, and the colorless filtrate was evaporated to dryness, giving 0.15 g of crude **2b**, which was purified by column chromatography using dichloromethane as the eluant. Yield 0.125 g (86%), mp 230 °C (DSC, 5 K/min) (lit.[10] mp 235 °C). The ^{1}H NMR spectrum was identical with that of an authentic sample of **2b** prepared by Canceill *et al.*[10]

Absolute configuration of 4. Conversion of (+)-4 into *P*-(−)-2b and of (−)-4 into *M*-(+)-2b by desulfurization

A) A stirred solution of (+)-**4** (10 mg) in 1 mL of THF and 1 mL of 95% ethanol was treated with *ca.* 0.6 g of Raney nickel (washed with 95% ethanol). After 3 h at room temperature (the reaction progress was monitored by TLC), the catalyst was separated by filtration over celite and the filtrate was evaporated to dryness *without heating*. The crystalline material so obtained was purified by TLC (silica gel, dichloromethane) and digested in diethyl ether, yielding 4.3 mg (60%) of *P*-(−)-**2b** showing $[\alpha]_D^{25}$ −155° (c 0.167 in $CHCl_3$), ^{1}H NMR spectrum identical with that of (±)-**2b**.

B) Similarly, a sample of (−)-**4** gave *M*-(+)-**2b** showing $[\alpha]_D^{25}$ +164° (c 0.06, $CHCl_3$). The maximum reported rotation $[\alpha]_D^{25}$ of **2b** is in the range 161 to 165° (in $CHCl_3$).[21]

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