Table I. Positional parameters and their estimated standard deviations for non-hydrogen atoms in **1d**[a].

Atom	x	y	z	B ($Å^2$)
O1	0.6397(4)	0.4828(4)	0.4049(3)	8.0(2)
O2	0.5948(4)	0.1337(3)	0.6164(3)	6.4(1)
O3	0.6244(4)	0.1111(3)	0.1666(4)	8.0(2)
O4	0.6004(5)	0.4581(5)	0.5377(4)	10.2(2)
O5	0.6590(4)	0.2399(3)	0.1507(3)	7.2(2)
O6	0.6173(4)	0.0414(2)	0.5044(3)	5.8(1)
O7	0.8490(4)	0.2403(3)	0.6430(3)	6.7(1)
O8	0.8829(5)	0.1114(3)	0.6254(3)	7.9(2)
O9	0.9124(4)	0.1335(3)	0.1764(3)	7.0(2)
O10	0.8709(3)	0.4804(3)	0.3881(3)	7.1(2)
O11	0.9070(4)	0.4575(4)	0.2537(3)	9.3(2)
O12	0.8919(3)	0.0401(3)	0.2878(3)	5.9(1)
C1	0.4769(3)	0.3463(3)	0.3783(3)	5.5(1)
C2	0.4619(3)	0.3349(3)	0.4485(3)	5.2(1)
C3	0.5012(3)	0.3707(3)	0.5034(3)	5.2(1)
C4	0.5585(3)	0.4191(3)	0.4869(3)	6.2(1)
C5	0.5773(3)	0.4329(3)	0.4167(3)	5.5(1)
C6	0.5377(3)	0.3969(3)	0.3603(3)	5.2(1)
C7	0.6690(5)	0.4877(5)	0.3323(4)	8.9(2)
C8	0.4034(3)	0.2755(3)	0.4731(3)	5.7(1)
C9	0.4542(3)	0.2057(3)	0.4785(3)	5.1(1)
C10	0.4608(3)	0.1595(3)	0.4241(3)	5.3(1)
C11	0.5130(3)	0.1035(3)	0.4310(3)	5.2(1)
C12	0.5619(3)	0.0946(2)	0.4917(3)	5.1(1)
C13	0.5542(3)	0.1407(2)	0.5511(3)	4.7(1)
C14	0.5013(3)	0.1968(3)	0.5436(3)	5.6(1)
C15	0.6841(4)	0.1335(4)	0.6174(4)	7.4(2)
C16	0.4132(4)	0.1624(3)	0.3524(3)	6.2(1)
C17	0.4710(3)	0.1850(3)	0.2947(3)	5.9(1)
C18	0.5188(4)	0.1373(3)	0.2531(3)	6.5(2)
C19	0.5813(4)	0.1580(4)	0.2100(4)	7.0(2)
C20	0.5969(4)	0.2265(3)	0.1962(3)	5.8(1)
C21	0.5483(4)	0.2736(3)	0.2513(3)	6.0(1)
C22	0.4868(3)	0.2546(3)	0.2801(3)	5.6(1)
C23	0.6082(6)	0.0381(4)	0.1760(5)	10.7(3)
C24	0.4351(3)	0.3101(3)	0.3142(3)	5.8(1)
C25	0.6227(7)	0.4202(8)	0.6064(4)	21.2(7)
C26	0.6943(4)	0.4358(3)	0.6413(3)	6.8(2)
C27	0.7130(4)	0.3857(4)	0.6942(4)	8.5(2)
C28	0.7494(4)	0.3140(4)	0.6941(3)	6.9(2)
C29	0.8252(3)	0.3111(3)	0.6463(3)	5.7(1)
C30	0.9131(4)	0.2223(3)	0.5951(3)	6.2(1)
C31	0.9608(3)	0.2731(3)	0.5603(3)	6.0(1)
C32	1.0242(3)	0.2549(3)	0.5115(3)	5.5(1)
C33	1.0367(3)	0.1879(3)	0.4990(3)	5.6(1)
C34	0.9920(3)	0.1370(3)	0.5338(3)	5.9(1)
C35	0.9322(4)	0.1533(3)	0.5857(3)	5.6(1)
C36	0.9060(6)	0.0435(4)	0.6223(4)	9.4(2)
C37	1.0955(3)	0.1607(3)	0.4404(3)	6.3(1)
C38	1.0503(3)	0.1567(2)	0.3669(3)	5.4(1)
C39	0.9947(3)	0.1011(2)	0.3558(3)	5.1(1)
C40	0.9474(3)	0.0935(2)	0.2949(3)	4.7(1)
C41	0.9535(4)	0.1426(3)	0.2427(3)	5.9(1)
C42	1.0069(3)	0.1968(2)	0.2529(3)	5.2(1)
C43	1.0539(3)	0.2085(3)	0.3131(3)	5.2(1)
C44	0.8248(4)	0.1398(4)	0.1801(4)	8.0(2)
C45	1.1014(3)	0.2701(3)	0.3214(3)	5.8(1)
C46	1.0471(3)	0.3288(3)	0.3426(3)	5.2(1)
C47	1.0066(3)	0.3682(3)	0.2896(3)	6.6(2)
C48	0.9485(4)	0.4193(3)	0.3035(3)	6.4(1)
C49	0.9291(3)	0.4330(3)	0.3769(3)	6.1(1)
C50	0.9726(4)	0.4000(3)	0.4274(3)	6.0(1)
C51	1.0299(3)	0.3471(3)	0.4164(3)	5.0(1)
C52	0.8405(4)	0.4896(4)	0.4594(4)	9.3(2)
C53	1.0729(3)	0.3148(3)	0.4794(3)	5.9(1)
C54	0.8968(4)	0.4281(6)	0.1849(4)	12.1(3)
C55	0.8336(5)	0.3932(3)	0.1785(3)	7.4(2)
C56	0.7943(5)	0.3853(5)	0.0921(4)	9.6(2)
C57	0.7611(4)	0.3156(4)	0.0992(3)	6.5(2)
C58	0.6860(4)	0.3091(3)	0.1477(3)	7.1(2)
C59	0.8593(5)	0.0099(3)	0.3510(5)	5.7(2)
C60	0.7873(5)	−0.0342(4)	0.3327(5)	6.3(2)
C61	0.7571(7)	−0.0756(2)	0.3977(7)	6.6(1)
C62	0.7227(5)	−0.0342(4)	0.4604(4)	5.8(2)
C63	0.6495(4)	0.0106(4)	0.4385(4)	5.1(2)
Ca1*	0.8370(9)	0.233(1)	0.393(1)	8.0(7)
Ca2*	0.7469(9)	0.3186(8)	0.4539(9)	8.3(4)
Ca*	0.730(1)	0.1646(8)	0.374(2)	14.3(9)
Ca3*	0.816(2)	0.281(2)	0.342(2)	18(2)
Ca5*	0.692(2)	0.268(1)	0.454(2)	13.3(9)
Ca6*	0.756(1)	0.199(2)	0.414(2)	28(2)
Ca7*	0.775(5)	0.268(2)	0.407(3)	28(2)

[a] Monoclinic C_c, a = 15.950(1), b = 19.598(2), c = 18.534(3) Å, β = 90.61 deg, V = 5793 $Å^3$; 5135 reflexions were observed (Cu$K\alpha$, $\theta \leqslant 70°$), 4252 with $I > \sigma(I)$ were used, R = 0.068 and R_w = 0.075. Starred atoms (*) were refined with a multiplicity of 0.5 and are highly disordered. Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as $(4/3)[a^2 \times B(1,1) + b^2 \times B(2,2) + c^2 \times B(3,3) + ab(\cos\gamma) \times B(1,2) + ac(\cos\beta) \times B(1,3) + bc(\cos\alpha) \times B(2,3)]$.

in diameter and 0.12 nm^3 in volume, respectively. In this crystal structure, the cavity is apparently filled with at least one disordered solvent molecule (acetone or dichloromethane), albeit if other crystalline samples obtained from acetone gave combustion analyses consistent with the presence of two water molecules per cryptophane.

Relevant data on the synthesis of D_3 and C_{3h} cryptophanes by the template method and by the direct method (taken from [19]) for comparison are assembled in table II. We have shown earlier that on reaction with formic acid, **13a** (n = 2) yielded the *anti* isomer **1a** (cryptophane-A) with a total stereoselectivity [4], while **13b** (n = 3) yielded the *syn* isomer **2b** (cryptophane-**F**) in 30% diastereomeric excess (de) with respect to the minor *anti* isomer **1b** (cryptophane-E) [10]. In the present work, we observed that this odd–even dependence of the stereochemistry still holds up to n = 8.

Table II. Cryptophane synthesis by the template method and the direct method[a].

Bridge structure		*Template method*		*Direct method*	
	1/2	***1*** anti	***2*** syn	***1*** anti	***2*** syn
$O(CH_2)_2O$	**a**	80	0	5	0
$O(CH_2)_3O$	**b**	27	50	17	3
$O(CH_2)_4O$	**c**	57 [66]	25 [34]	8	2
$O(CH_2)_5O$	**d**	38 [42]	59 [58]	15	6
$O(CH_2)_6O$	**e**	31 [65]	7 [35]	8	2
$O(CH_2)_7O$	**f**	41[b] [51]	40[b] [49]	5	1
$O(CH_2)_8O$	**g**	41 [59]	16 [41]	0	0
$O(CH_2)_9O$	**h**	38[b] [50]	38[b] [50]	–	–
$O(CH_2)_{10}O$	**i**	36[b] [50]	36[b] [50]	–	–
E $OCH_2CH{=}CHCH_2O$	**j**	34	5	5	1
Z $OCH_2CH{=}CHCH_2O$	**k**	25	50	10	8
$OCH_2C{\equiv}CCH_2O$	**l**	43	20	0	0

[a] Figures in brackets represent the relative amount (percent) of *syn* and *anti* isomers in the crude reaction product, whereas the other figures represent isolated yields. [b] The *syn* and *anti* isomers were not separated in this case.

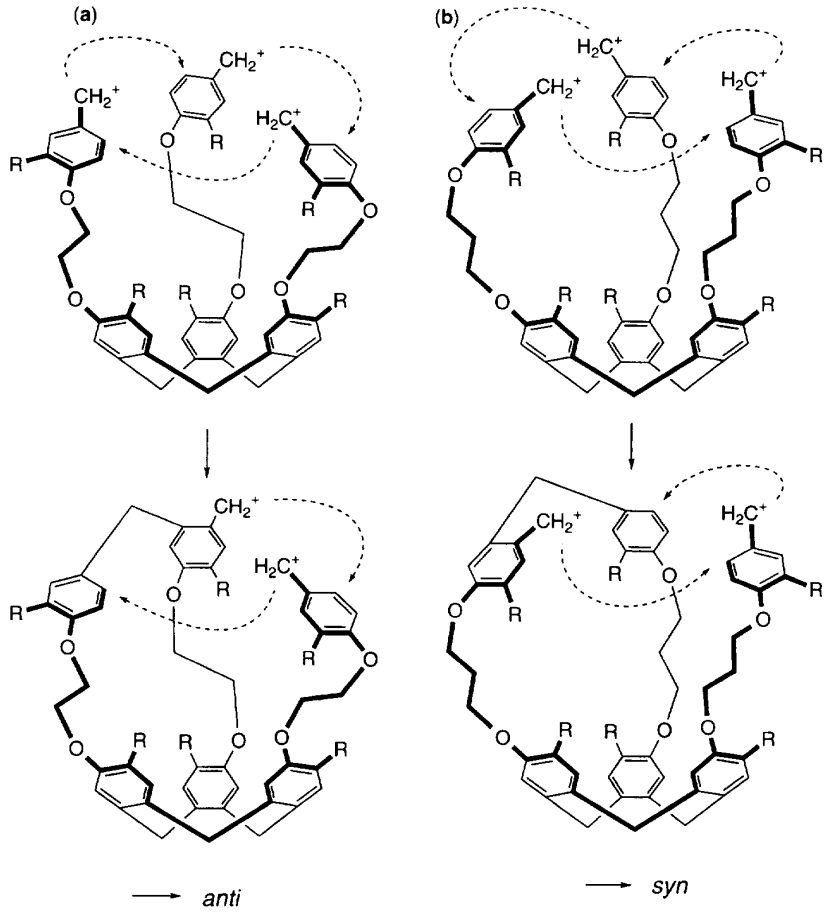

Fig 6

Thus, **13c** ($n = 4$) and **13e** ($n = 6$) were preferentially converted to the *anti* isomers **1c** (cryptophane-M) and **1e** (cryptophane-Q) in ca 30% de with respect to the *syn* isomers **2c** (N) and **2e** (R), whereas **13d** ($n = 5$) afforded the *syn* isomer **2d** (P) in 20% de with respect to **1d** (O). Precursor **13g** ($n = 8$) consistently furnished the *anti* isomer **1g** (cryptophane-U) in 18% de with respect to the *syn* isomer **2g** (V). The reaction showed no significant stereoselectivity in the cases of **13f,h,i** ($n = 7$, 9, 10) for which 1:1 mixtures of **1** (S, W, Y) and **2** (T, X, Z) were obtained. These mixtures proved impossible to resolve into their pure components by crystallization or chromatography over silica gel.

The observed product stereochemistry suggests that the orientation of the reactive ends (fig 6), which is dependent on the odd or even number of methylenes in the aliphatic spacer chains, plays an important role on the course of the cyclization leading to cryptophanes. For the *M* configuration depicted, even chains induce a counterclockwise attack (a) (as observed from the template ring), odd chains favor a clockwise attack (b), and the direction of the first attack in turn determines that of the entire cyclization sequence. A similar dependence has been observed in the template-directed synthesis of cryptophanes **1/2j** and **1/2k** having unsaturated bridges [16] (table II). On going from *trans* to *cis* $OCH_2CH{=}CHCH_2O$ spacers, the stereoselectivity is reversed from *anti* to *syn*. In even aliphatic chains in the zig-zag conformation the relative orientation of the terminal bonds is in fact the same as in a *trans* double bond, and conversely an odd chain is equivalent to a *cis* double bond. The fact that the direct method does not show such a dependence and invariably affords the *anti* isomers whatever the parity of the spacer indicates that it does not proceed through the same intermediates (for a discussion, see [1]). Concerning the cyclization kinetics, it is likely that the rate-determining step of the template-directed synthesis is the creation of the first bond (fig 6), and that the subsequent formation of the next two bonds is fast. The main argument in support of this view is the fact that we could neither isolate nor observe partially cyclized cryptophane intermediates lacking one or two $ArCH_2Ar$ bridges.

The ^1H NMR spectra of the crude cryptophanes mixtures with $n \geqslant 6$ showed the presence of additional species which we consider to be the in–out topoisomers **1′** and **2′**. The existence of such cryptophane topoisomers for $n \geqslant 3$ has already been noticed in previous studies of this laboratory [22] and the stereochemical consequences of their formation has been discussed [1]. In–out cryptophane topoisomers have more complicated spectra than the out–out ones because their CTV caps

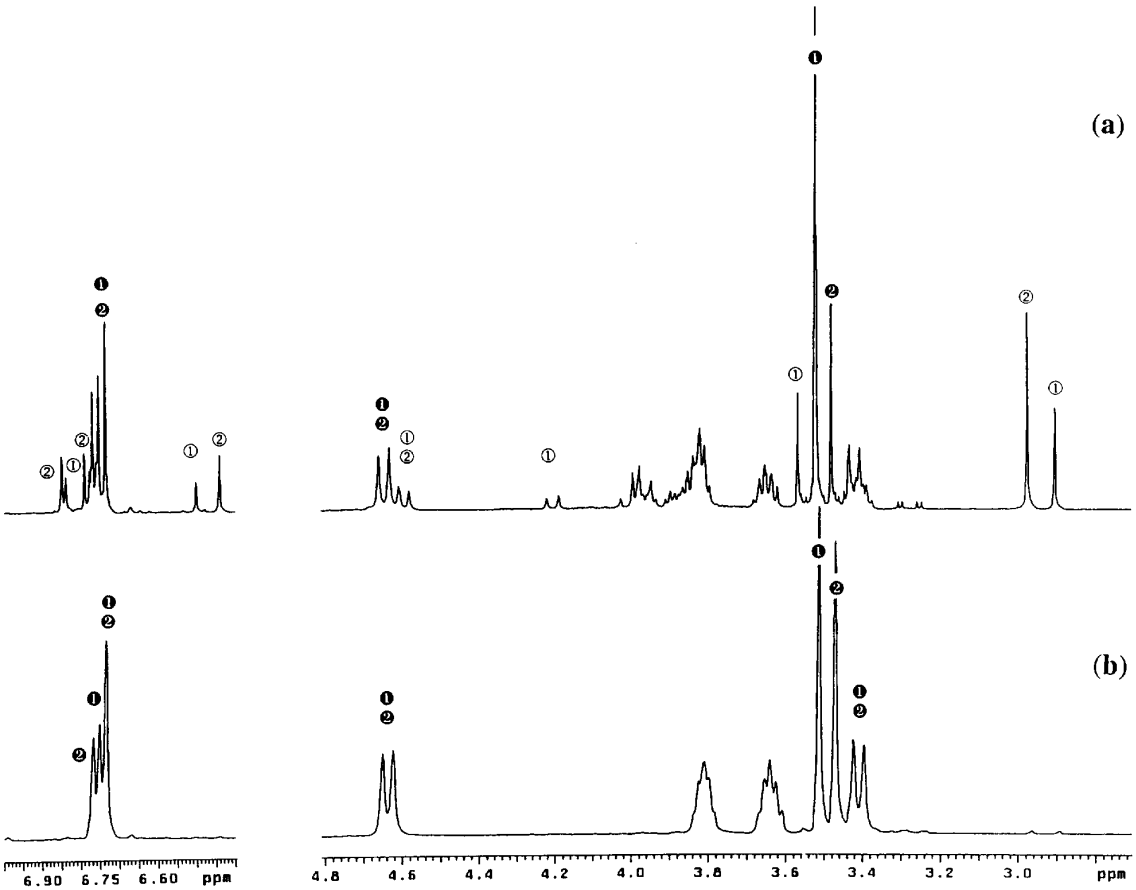

Fig 7. a 500 MHz ^{1}H NMR spectrum of a C_6D_6 solution containing **1f** (❶), **1f'** (①), **2f** (❷), **2f'** (②); b spectrum of the same solution after standing for 2 weeks at room temperature, showing only **1f** and **2f** (the aliphatic region is not shown and only selected resonances are labeled).

are no longer equivalent and the symmetry of the structure is reduced from D_3 to C_3 (**1'**) or from C_{3h} to C_3 (**2'**). For $n = 6$, only minor amounts of **1e'** and **2e'** were observed in the just isolated cryptophane mixture and these species slowly transformed into the 'swollen' out–out isomers **1e** and **2e** on standing for a few days at room temperature in chloroform solution. Conversely, transformation of the out–out into the in–out isomers was easily accomplished by warming the solution, leading to mixtures containing the four species **1e,e'** and **2e,e'**. For $n = 7$, the amount of in–out forms in the reaction product was more significant, and it was possible to obtain by chromatography samples enriched in these topoisomers. A typical ^{1}H NMR spectrum of such a fraction is shown figure 7. In spectrum (a) the presence of 16% of **1f'** and 31% of **2f'** is evidenced inter alia by the pairs of resonances of the methoxy groups at 2.89 and 3.55 ppm (**1f'**), and 2.96 and 3.51 ppm (**2f'**). In spectrum (b) of the same sample solution recorded after a couple of weeks standing at room temperature the in–out forms have almost completely disappeared and the out–out isomers **1f** and **2f** are present in ca 1:1 ratio. In order to take advantage of the information conveyed by optical activity, we examined this conformational behavior in the case of the product resulting from the cyclization of (+)-**13f**. The crude cryptophane mixture (free of foreign impurities by chromatographic filtration) showed $[\alpha]_D^{25}$ −11.8 ($CHCl_3$) and consisted of **1f** (49%), **2f** (44%), **1f'** (3%) and **2f'** (4%). This mixture was column chromatographed and split into four main fractions, the rotation (in $CHCl_3$) and composition (500 MHz ^{1}H NMR in C_6D_6) of which were monitored for several weeks. These experiments are summarized in table III.

Table III. Equilibration at room temperature of cryptophane topoisomers with $n = 7$ (**1f**, **1f'**, **2f**, **2f'**).

Fraction	*Time*	$[\alpha]_D^{25}$ *(CHCl₃)*	*% 1f*	*% 1f'*	*% 2f*	*% 2f'*
1	0	+14.4	26	33	36	5
	2 weeks	−7.4	48	9	43	–
2	0	+9.1	37	31	27	5
	2 weeks	−8.3	55	12	33	–
3	0	+1.8	49	25	24	3
	2 weeks	−11.2	63	11	25	–
	1 month	−14.7	66	6	28	–
4	0	−1.1	12	4	11	74
	2 weeks	−4.2	16	–	74	10

The faster running isomers are **1f'** and **2f**, followed by **1f** then **2f'**, but the R_f differences were not sufficient to allow a complete separation of these species. Nevertheless, from the composition and rotation data of the various fractions assembled in table III it was possible to estimate the specific rotation of **1f** at $-29 < [\alpha]_D^{25} < -27$ and that of its in–out topoisomer **1f'** at $+53.5 < [\alpha]_D^{25} < +64$. In principle, the in–out topoisomer **2f'** is also chiral, but it should be racemic because it is in equilibrium with **2f** which is achiral. However, there are conceivably two processes leading to in–out cryptophane topoisomers. These species can simply result from the conformational equilibration of their out–out counterparts, occurring during the isolation workup, or they can be formed together with the out–out isomers during the cyclization of **13** (fig 4). In this case, the in–out isomer **2'** just isolated from the cyclization of (+)-**13** should also be optically active. We have at present no clear answer to this question, although we suspect that most of the in–out forms are in fact formed during the isolation process and, particularly, during the evaporation of formic acid.

The chiroptical properties (circular dichroism) of the smallest D_3 cryptophanes **1a**, **1b**, **1l** and derivatives have been satisfactorily interpreted in the light of the exciton theory [17]. In these systems, the optical activity is dominated by a strong coulombic coupling of the electronic transitions of the aromatic rings within each CTV unit, and between these units, resulting in a strong circular dichroism in the regions of these transitions. For the larger cryptophanes considered in the present work, due to the flexibility of the spacers and the large separation between the two CTV caps, it is difficult, if at all possible, to perform such an analysis, because the geometry of these molecules cannot be defined with enough precision (the circular dichroism spectra of **1c–g** were in fact not interpreted). The decrease in the coupling between the two CTV moieties as the spacer length increases actually has a strong effect on the magnitude of the rotation of these compounds, which decreases from $[\alpha]_D - 254$ to ca -12 on going from $n = 2$ to 8. This overall decrease of the rotation is, however, modulated by a strong odd–even dependence on the number of methylenes in the spacer bridges, at least up to $n = 6$ (the figures for $n = 7$ and 8 are not reliable). As was stated above to account for the stereochemistry of the template-directed synthesis, this phenomenon is probably related to differences in the conformational properties of these two series. It is striking that such a dependence has also been observed in the host–guest complexation kinetics of cryptophanes **1a–d** and derivatives (n in the range 2 to 5); odd cryptophanes are slower than their even analogues when they bind or release their guests [1].

Table IV. Optical activity of *anti* D_3 cryptophanes of *MM*-(−) absolute configuration (see fig 1).

Name	*Bridge structure*	$[\alpha]_\lambda^{25}$ *(CHCl₃)* 589	578	546	436
1a (A)	$O(CH_2)_2O$[a]	−253	−265	−306	−574
1b (E)	$O(CH_2)_3O$[a]	−49	−51	−60	−110
1c (M)	$O(CH_2)_4O$	−117	−122	−141	−238
1d (O)	$O(CH_2)_5O$	−14	−15	−16	−21
1e (Q)	$O(CH_2)_6O$	−44	−46	−54	−100
1f (S)	$O(CH_2)_7O$	≈ −28			
1g (U)	$O(CH_2)_8O$	≈ −12	−13	−14	−29
1j (I)	$OCH_2CH{=}CHCH_2O$ E[b]	−154	−162	−185	
1k (K)	$OCH_2CH{=}CHCH_2O$ Z[b,c]	−83	−88	−112	
1l (G)	$OCH_2C{\equiv}CCH_2O$[a]	−201	−211	−242	

[a] Ref [17]; [b] ref [16]; [c] measured on the (+)-enantiomer.

Experimental section

^1H NMR spectra were recorded at 200 or 500 MHz on Bruker AC 200 or Varian Unity 500 spectrometers, respectively. Melting points were measured on a Kofler hotbench or by means of a Perkin-Elmer DSC7 microcalorimeter, with simultaneous check of purity. Rotations (in 10^{-1} deg cm^2 g^{-1}) were measured in a 1 dm thermostated quartz cell (25 °C) on a Perkin-Elmer 241 micropolarimeter. Chromatographic separations were performed over silica gel 60 (Merck). Combustion analyses and FAB+ mass spectra were carried out by the Service central d'analyse du CNRS.

4-[(4-Bromobutyl)oxy]-3-methoxybenzaldehyde **5c**

To a stirred solution of vanillin (7.61 g, 50 mmol) in 95% ethanol (90 mL) at rt, was added dropwise aqueous 12 M NaOH (4.2 mL, 50 mmol) (white precipitate) and then 1,4-dibromobutane (10.85 mL, 90 mmol); the reaction mixture was refluxed for 5 h. The solvent was stripped off and the residue was taken up in a mixture of water and diethyl ether, which resulted in the crystallization of the dialkylated byproduct **9c** which was separated by filtration (0.94 g, 10.5%). The ether layer was washed with aqueous (10%) KOH, with water, dried over sodium sulfate and evaporated to dryness to give a yellow oil. Column chromatography (silica gel, dichloromethane) yielded **5c** (7.82 g, 54%), as white crystals mp 49 °C.

^1H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3 = 7.24$): 9.83 (s, CHO); 7.41 (d, arom H, $J = 7.9$ Hz); 7.39 (s, arom H); 6.94 (d, arom H, $J = 7.9$ Hz); 4.12 (t, OCH_2, $J = 5.8$ Hz); 3.89 (s, OCH_3); 3.48 (t, CH_2Br, $J = 6.2$ Hz); 2.1–2.03 (m, CH_2CH_2).

Anal calc for $C_{12}H_{15}BrO_3$: C, 50.19; H, 5.26; Br, 27.83. Found: C, 50.4; H, 5.1; Br, 27.7.

2,2'-Dimethoxy-4,4'-[butane-1,4-diylbis(oxy)]-dibenzaldehyde **9c**

By-product in the preparation of **5c** above. Mp 149 °C (from 95% ethanol).

Anal calc for $[C_{20}H_{22}O_6 + 0.5\ H_2O]$: C, 65.38; H, 6.31. Found: C, 65.2; H, 6.3.

4-[(7-Bromoheptyl)oxy]-3-methoxybenzaldehyde **5f**

A mixture of vanillin (3.19 g, 21 mmol), aqueous 12 M NaOH (1.75 mL, 21 mmol), 1,7-dibromoheptane (10 g, 39 mmol) in 37 mL of 95% ethanol was refluxed for 5 h. The solvent was stripped off and the residue was taken up in a mixture of water and ether. The ether layer was washed with aqueous (10%) KOH, with water, dried over sodium sulfate and evaporated to dryness. Column chromatography (silica gel, dichloromethane/hexane (1:9) then pure dichloromethane) gave **5f** (3.5 g, 51%), as white crystals mp 50 °C.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 9.81 (s, CHO); 7.40 (dd, arom H, J = 7.9 and 1.7 Hz); 7.37 (broad s, arom H); 6.93 (d, arom H, J = 7.9 Hz); 4.06 (t, OCH_2, J = 6.7 Hz); 3.89 (s, OCH_3); 3.37 (t, CH_2Br, J = 6.8 Hz); 1.85–1.77 (m, CH_2CH_2); 1.54–1.36 (m, $(CH_2)_3$).

Anal calc for $C_{15}H_{21}BrO_3$: C, 54.72; H, 6.43; Br, 24.27. Found: C, 54.9; H, 6.2; Br, 24.1.

4-[(9-Bromononyl)oxy]-3-methoxybenzaldehyde **5h**

A mixture of vanillin (3.04 g, 20 mmol), aqueous 12 M NaOH (1.66 mL, 20 mmol), 1,9-dibromononane (8.1 mL, 40 mmol) in 95% ethanol (36 mL) was refluxed for 5 h. Usual workup followed by column chromatography (dichloromethane) gave 3.9 g (55%) of **5h**, white crystals, mp 38 °C, followed by the dialkylated byproduct **9h** (0.42 g, 10%).

^{1}H NMR of **5h** ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 9.82 (s, CHO); 7.41 (d, arom H, J = 7.8 Hz); 7.39 (broad s, arom H); 6.94 (d, arom H, J = 7.8 Hz); 4.07 (t, OCH_2, J = 6.7 Hz); 3.91 (s, OCH_3); 3.38 (t, CH_2Br, J = 6.8 Hz); 1.89–1.76 and 1.5–1.3 (m, $(CH_2)_7$).

Anal calc for $C_{17}H_{25}BrO_3$: C, 57.15; H, 7.05; Br, 22.36. Found: C, 57.2; H, 7.2; Br, 22.0.

2,2′-Dimethoxy-4,4′-[nonane-1,9-diylbis(oxy)]-dibenzaldehyde **9h**

Byproduct in the preparation of **5h** above. Mp 92.5 °C (from methanol).

^{1}H NMR ($CDCl_3$, δ $CHCl_3$ = 7.24): 9.83 (s, CHO); 7.43 (d, arom H; J = 7.9 Hz); 7.39 (s, arom H); 6.94 (d, arom H, J = 7.9 Hz); 4.07 (t, OCH_2, J = 6.8 Hz); 3.91 (s, OCH_3); 1.89–1.83 and 1.5–1.36 (m, $(CH_2)_7$).

Anal calc for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.8; H, 7.4.

4-[(10-Bromodecyl)oxy]-3-methoxybenzaldehyde **5i**

A mixture of vanillin (6.99 g, 46 mmol), aqueous 12 M NaOH (3.83 mL, 46 mmol), 1,10-dibromodecane (18.6 mL, 83 mmol) in 95% ethanol (83 mL) was refluxed for 5 h. Usual workup followed by column chromatography (dichloromethane/hexane (1:9) then pure dichloromethane) gave **5i** (10.4 g, 60%), white crystals mp 62 °C, followed by the dialkylated byproduct **9i** (0.25 g, 2.5%).

^{1}H NMR of **5i** ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 9.83 (s, CHO); 7.42 (d, arom H, J = 7.9 Hz); 7.39 (s, arom H); 6.94 (d, arom H, J = 7.9 Hz); 4.08 (t, OCH_2, J = 6.8 Hz); 3.91 (s, OCH_3); 3.38 (t, CH_2Br, J = 6.9 Hz); 1.90–1.76 and 1.49–1.28 (m, $(CH_2)_8$).

Anal calc for $C_{18}H_{27}BrO_3$: C, 58.22; H, 7.33; Br, 21.52; O, 12.93. Found: C, 58.4; H, 7.4; Br, 21.6; O, 13.1.

2,2′-Dimethoxy-4,4′-[decane-1,10-diylbis(oxy)]-dibenzaldehyde **9i**

Byproduct in the preparation of **5i** above. Mp 103.5 °C (from ethanol).

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 9.83 (s, CHO); 7.41 (d, arom H; J = 8 Hz); 7.39 (s, arom H); 6.94 (d, arom H, J = 8 Hz); 4.08 (t, OCH_2, J = 6.8 Hz); 3.91 (s, OCH_3); 1.86 and 1.32 (m, $(CH_2)_8$).

Anal calc for $C_{26}H_{34}O_6$ + 0.5 H_2O: C, 69.16; H, 7.81. Found: C, 69.4; H, 7.9.

4-[(5-Bromopentyl)oxy]-3-methoxybenzenemethanol **6d**

A heterogeneous mixture of vanillyl alcohol (6 g, 39 mmol), K_2CO_3 (5.4 g, 39 mmol), and 1,5-dibromopentane (7.95 mL, 58 mmol) in acetone (60 mL) was refluxed for 22 h. The solvent was stripped off and the residue was taken up in a mixture of water and diethyl ether, which resulted in the crystallization of the dialkylated byproduct **10d** which was separated by filtration (1.05 g, 14%). The organic layer of the filtrate was washed with aqueous (10%) KOH, with water, dried over sodium sulfate and evaporated. Column chromatography (dichloromethane/ethyl acetate 9:1), gave 8.21 g (69%) of pure **6d**. Mp 48 °C.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 6.91 and 6.83 (2s, arom H); 4.6 (d, CH_2OH, J = 5.9 Hz); 4.0 (t, OCH_2, J = 6.6 Hz); 3.85 (s, OCH_3); 3.41 (t, CH_2Br, J = 6.7 Hz); 2.02–1.53 (m, $(CH_2)_3$ and OH).

Anal calc for $C_{13}H_{19}BrO_3$: C, 51.49; H, 6.32; Br, 26.35. Found: C, 51.5; H, 6.1; Br, 26.5.

2,2′-Dimethoxy-4,4′-[pentane-1,5-diylbis(oxy)]-dibenzenemethanol **10d**

Byproduct in the preparation of **6d** above. Mp 114.5 °C from methanol (lit [19] Mp 115 °C).

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 6.91 and 6.83 (2s, arom H); 4.6 (d, CH_2OH, J = 5.9 Hz); 4.02 (t, OCH_2, J = 6.6 Hz); 3.85 (s, OCH_3); 1.94–1.85 and 1.7–1.56 (m, $(CH_2)_3$ and OH).

Anal calc for [$C_{21}H_{28}O_6$, 0.25 H_2O]: C, 66.21; H, 7.54. Found: C, 66.3; H, 7.4.

4-[(6-Bromohexyl)oxy]-3-methoxybenzenemethanol **6e**

In a similar way, vanillyl alcohol (6 g) and 1,6-dibromohexane (9 mL) afforded the insoluble dialkylated byproduct **10e** which was separated by filtration (1.7 g, 22%), and column chromatography of the mother liquors (dichloromethane/ethyl acetate 9:1) gave 7.76 g (63%) of **6e**. Mp 52 °C.

^{1}H NMR ($CDCl_3$, δ $CHCl_3$ = 7.24): 6.91 and 6.84 (2s, arom H); 4.6 (d, CH_2OH, J = 5.9 Hz); 3.99 (t, OCH_2, J = 6.6 Hz); 3.86 (s, OCH_3); 3.39 (t, CH_2Br, J = 6.8 Hz); 1.87–1.82 and 1.53–1.47 (m, $(CH_2)_4$ and OH).

Anal calc for $C_{14}H_{21}BrO_3$: C, 53.00; H, 6.67; Br, 25.19. Found: C, 53.1; H, 6.7; Br, 24.9.

2,2′-Dimethoxy-4,4′-[hexane-1,6-diylbis(oxy)]-dibenzenemethanol **10e**

Byproduct in the preparation of **6e** above. Mp 122 °C (from aqueous methanol).

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 6.90 and 6.83 (2s, arom H); 4.6 (d, CH_2OH, J = 5.9 Hz); 4.0 (t, OCH_2, J = 6.7 Hz); 3.85 (s, OCH_3); 1.85–1.81 and 1.59–1.53 (m, $(CH_2)_2$ and OH).

Anal calc for [$C_{22}H_{30}O_6$ + 0.8 H_2O]: C, 65.26; H, 7.86. Found: C, 65.4; H, 7.4.

4-[(8-Bromooctyl)oxy]-3-methoxybenzenemethanol **6g**

A mixture of vanillyl alcohol (5.53 g, 36 mmol), K_2CO_3 (4.97 g, 36 mmol), and 1,8-dibromooctane (10 mL, 54 mmol) in acetone (55 mL) was refluxed for 20 h. The insoluble dialkylated byproduct **10g** was separated (1.79 g, 24%). Column chromatography of the filtrate (dichloromethane/ethyl acetate 9:1) gave **6g** (7.5 g, 60%). Mp 40 °C.

^{1}H NMR ($CDCl_3$, δ $CHCl_3$ = 7.24): 6.90 and 6.83 (2s, arom H); 4.59 (d, CH_2OH, J = 5.7 Hz); 3.98 (t, OCH_2, J = 6.8 Hz); 3.85 (s, OCH_3); 3.38 (t, CH_2Br, J = 6.8 Hz); 1.87–1.75 and 1.59–1.36 (m, $(CH_2)_6$); 1.57 (t, OH, J = 5.7 Hz).

Anal calc for $C_{16}H_{25}BrO_3$: C, 55.66; H, 7.29; Br, 23.14. Found: C, 55.9; H, 7.4; Br, 23.1

2,2'-Dimethoxy-4,4'-[octane-1,8-diylbis(oxy)]-dibenzenemethanol **10g**

Byproduct in the preparation of **6g** above. Mp 110 °C (from ethanol).

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 6.90 and 6.83 (2s, arom H); 4.59 (d, CH_2OH, J = 5.9 Hz); 3.98 (t, OCH_2, J = 6.8 Hz); 3.85 (s, OCH_3); 1.85–1.37 (m, $(CH_2)_6$ + OH).

4-[(4-Iodobutyl)oxy]-3-methoxybenzaldehyde **7c**

A mixture of bromide **5c** (7 g, 24 mmol) and NaI (7.3 g, 48 mmol) in acetone (69 mL) was refluxed for 6 h 30 min. The solvent was evaporated, the residue was taken up in water and filtered to give 8.14 g (99%) of **7c**. Mp 38 °C.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 9.83 (s, CHO); 7.41 (d, arom H, J = 7.9 Hz); 7.39 (s, arom H); 6.94 (d, arom H, J = 7.9 Hz); 4.11 (t, OCH_2, J = 5.9 Hz); 3.90 (s, OCH_3); 3.26 (t, CH_2Br, J = 6.4 Hz); 2.05–1.99 (m, $(CH_2)_2$).

Anal calc for $C_{12}H_{15}IO_3$: C, 43.13; H, 4.52; I, 37.98. Found: C, 43.2; H, 4.5; I, 37.8.

4-[(7-Iodoheptyl)oxy]-3-methoxybenzaldehyde **7f**

A mixture of bromide **5f** (3.4 g, 10.3 mmol) and NaI (3.09 g, 20.6 mmol) in acetone (29 mL), was refluxed overnight. Column chromatography (dichloromethane) gave **7f** (3.48 g, 90%). Mp 53 °C.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 9.83 (s, CHO); 7.42 (dd, arom H, J = 1.9 Hz, J = 8 Hz,); 7.39 (d, arom H, J = 1.9 Hz); 6.94 (d, arom H, J = 8 Hz); 4.08 (t, OCH_2, J = 6.7 Hz); 3.91 (s, OCH_3); 3.17 (t, CH_2I, J = 6.9 Hz); 1.87–1.75 and 1.51–1.20 (m, $(CH_2)_5$).

Anal calc for $C_{15}H_{21}IO_3$: C, 47.89; H, 5.63; I, 33.73. Found: C, 48.1; H, 5.5; I, 33.7.

4-[(9-Iodononyl)oxy]-3-methoxybenzaldehylde **7h**

A mixture of bromide **5h** (2.97 g, 8.4 mmol) and NaI (2.49 g, 17 mmol) in acetone (23 mL) was refluxed for 8 h. The solvent was evaporated, the residue was taken up in water and filter to give **7h** (3.34 g, 99%). Mp 49 °C.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 9.82 (s, CHO); 7.40 (d, arom H, J = 7.8 Hz); 7.39 (s, arom H); 6.95 (d, arom H, J = 7.8 Hz); 4.07 (t, OCH_2, J = 6.8 Hz); 3.91 (s, OCH_3); 3.16 (t, CH_2I, J = 6.9 Hz); 1.9–1.7 and 1.5–1.3 (m, $(CH_2)_7$).

Anal calc for [$C_{17}H_{25}IO_3$ + 0.5 H_2O]: C, 49.40; H, 6.34; I, 30.70. Found: C, 49.1; H, 6.2; I, 30.6.

4-[(10-Iododecyl)oxy]-3-methoxybenzaldehyde **7i**

A mixture of bromide **5i** (5 g, 13.5 mmol) and NaI (4.04 g, 27 mmol) in acetone (37 mL) was refluxed for 8 h. The solvent was evaporated, the residue was taken up in water and filter to give **7i** (5.5 g, 98%). Mp 76 °C.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 9.83 (s, CHO); 7.42 (d, arom H, J = 7.9 Hz); 7.39 (s, arom H); 6.94 (d, arom H, J = 7.9 Hz); 4.08 (t, OCH_2, J = 6.8 Hz); 3.91 (s, OCH_3); 3.17 (t, CH_2I, J = 7.0 Hz); 1.9–1.73 and 1.5–1.29 (m, $(CH_2)_8$).

Anal calc for $C_{18}H_{27}IO_3$: C, 51.68; H, 6.50; I, 30.33; O, 11.47. Found: C, 52.0; H, 6.5; I, 30.1; O, 11.7.

4-[(5-Iodopentyl)oxy]-3-methoxybenzenemethanol **8d**

A mixture of bromide **6d** (7.55 g, 25 mmol) and NaI (7.46 g, 49 mmol) in acetone (75 mL), was refluxed for 6 h. The solvent was evaporated, the residue was taken up in water, extracted with dichloromethane and chromatographed (dichloromethane/ethyl acetate 9:1) to give **8d** (7.89 g, 90%). Mp 50 °C.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 6.90 and 6.83 (2s, arom H); 4.60 (d, CH_2OH, J = 5.8 Hz); 3.99 (t, OCH_2, J = 6.6 Hz); 3.85 (s, OCH_3); 3.19 (t, CH_2I, J = 6.9 Hz); 1.93–1.80 and 1.63–1.52 (m, $(CH_2)_3$ and OH).

Anal calc for $C_{13}H_{19}IO_3$: C, 44.59; H, 5.47. Found: C, 44.6; H, 5.4.

4-[(6-Iodohexyl)oxy]-3-methoxybenzenemethanol **8e**

A mixture of bromide **6e** (7 g, 22 mmol) and NaI (6.6 g, 44 mmol) in acetone (70 mL), was refluxed for 4 h 30 min. The solvent was stripped off, the residue was taken up in water and extracted with dichloromethane to give **8e** (7.9 g, 99%). Mp 53 °C.

^{1}H NMR ($CDCl_3$, δ $CHCl_3$ = 7.24): 6.90–6.83 (m, arom H); 4.59 (d, CH_2OH, J = 5.9 Hz); 3.99 (t, OCH_2, J = 6.6 Hz); 3.85 (s, OCH_3); 3.17 (t, CH_2I, J = 6.9 Hz); 1.87–1.77 and 1.60–1.42 (m, $(CH_2)_4$ + OH).

Anal calc for $C_{14}H_{21}IO_3$: C, 46.17; H, 5.81; I, 34.84. Found: C, 46.3; H, 5.9; I, 34.9.

4-[(8-Iodooctyl)oxy]-3-methoxybenzenemethanol **8g**

A mixture of bromide **6g** (7 g, 20 mmol) and NaI (6 g, 40 mmol) in acetone (70 mL) was refluxed for 7 h. The solvent was stripped, the residue was taken up in water and extracted with diethyl ether to give **8g** (7.95 g, 100%). Mp 37 °C.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 6.90–6.83 (m, arom H); 4.6 (d, CH_2OH, J = 5.8 Hz); 3.98 (t, OCH_2, J = 6.8 Hz); 3.85 (s, OCH_3); 3.16 (t, CH_2I, J = 6.9 Hz); 1.81–1.76 and 1.50–1.30 (m, $(CH_2)_6$); 1.55 (t, OH, J = 5.8 Hz).

Anal calc for $C_{16}H_{25}IO_3$: C, 48.99; H, 6.42. Found: C, 48.9; H, 6.4.

*2,7,12-Tris[4-(4-formyl-2-methoxyphenoxy)butyloxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[a,d,g]-cyclononene (±)-***12c*** and* M*-(+)-***12c***

Trialdehyde (±)-**12c** was prepared from (±)-cyclotriguaiacylene **11** (0.6 g, 1.48 mmol) in 36 mL of DMF/HMPA (1:1); 0.71 mL (4.44 mmol) of aqueous NaOH (6.25 M) was added and the mixture was stirred under argon for 10 min, followed by addition of iodide **7c** (1.48 g, 4.44 mmol). After the mixture was stirred at rt for 1 h, further amounts of NaOH (0.47 mL) and **7c** (0.99 g) were added. After 19 h, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with aqueous HCl (1 M), with water, dried over sodium sulfate

and evaporated to dryness to give a yellow oil. Column chromatography (dichloromethane/ethyl acetate 9:1) gave **12c** (1.02 g, 67%) as an amorphous powder.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 9.81 (s, CHO); 7.39 (d, arom H, J = 7.9 Hz); 7.36 (s, arom H); 6.94 (d, arom H, J = 7.9 Hz); 6.82 and 6.78 (2s, arom H); 4.73 (d, CH_2, J = 13.5 Hz); 4.17–3.97 (m, OCH_2); 3.84 and 3.73 (2s, OCH_3); 3.5 (d, CH_2, J = 13.5 Hz); 2.02 (m, $(CH_2)_2$).

Anal calc for $C_{60}H_{66}O_{15}$: C, 70.16; H, 6.47. Found: C, 70.5; H, 6.3.

Similarly, *P*-(−)-cyclotriguaiacylene **11** (66 mg) $[\alpha]_D^{25}$ −276 ($CHCl_3$), in 4 mL of DMF/HMPA was first treated with 0.08 mL of aqueous NaOH (6.25 M) and 163 mg of **7c** for 1 h at rt. Then, 0.05 mL of NaOH and 109 mg **7c** were added. After one night at rt, the mixture was treated as above; 150 mg (91%) of (+)-**12c** were obtained by TLC on silica gel (dichloromethane/ethyl acetate 7:3); amorphous powder, $[\alpha]_D^{25}$ +45.8 (*c* 0.35, $CHCl_3$). The ^{1}H NMR spectrum was identical to that of (±)-**12c**.

*2,7,12-Tris[7-(4-(formyl-2-methoxyphenoxy)heptyloxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a,d,g*]-cyclononene* (±)-**12f** *and* M-(+)-**12f**

Trialdehyde (±)-**12f** was prepared from (±)-cyclotriguaiacylene **11** (0.4 g, 0.99 mmol); 0.8 mL (4.93 mmol) of aqueous NaOH (6.25 M) and (1.85 g, 4.44 mmol) of iodide **7f** in 24 mL of DMF/HMPA (1:1), at rt overnight under argon. The crude material was chromatographed (dichloromethane/ethyl acetate 9:1) giving 0.996 g (87%) of pure **12f**. Mp 388 °C (decomp).

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 9.82 (s, CHO); 7.40 (d, arom H, J = 7.9 Hz); 7.37 (s, arom H); 6.93 (d, arom H, J = 7.9 Hz); 6.80 and 6.79 (2s, arom H); 4.72 (d, CH_2, J = 13.8 Hz); 4.11–4.05 (m, OCH_2); 3.88 and 3.78 (2s, OCH_3); 3.5 (d, CH_2, J = 13.8 Hz); 1.89–1.75 and 1.42 (m, $(CH_2)_5$).

Anal calc for [$C_{69}H_{84}O_{15}$ + H_2O]: C, 70.75; H, 7.39. Found: C, 70.8; H, 7.1.

Similarly, *P*-(−)-cyclotriguaiacylene **11** (55 mg) with $[\alpha]_D^{25}$ −276 ($CHCl_3$), in 3.4 mL of DMF/HMPA, was treated with 0.109 mL of aqueous NaOH (6.25 M) and 255 mg of **7f** at rt overnight; 125 mg (80%) of pure (+)-**12f** were obtained by TLC on silica gel (dichloromethane/ethyl acetate 8:2); $[\alpha]_D^{25}$ +44 (*c* 0.20, $CHCl_3$). The ^{1}H NMR spectrum was identical to that of (±)-**12f**.

*2,7,12-Tris[9-(4-formyl-2-methoxyphenoxy)nonyloxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a,d,g*]-cyclononene* (±)-**12h** *and* M-(+)-**12h**

Trialdehyde (±)-**12h** was similarly prepared from (±)-cyclotriguaiacylene **11** (0.3 g, 0.74 mmol); 0.6 mL (3.70 mmol) of aqueous NaOH (6.25 M) and (1.49 g, 3.70 mmol) of iodide **7h** in 18.2 mL of DMF/HMPA (1:1), at rt overnight under argon. The crude material was chromatographed (dichloromethane/ethyl acetate 9:1) giving 0.78 g (85%) of pure **12h** as an amorphous powder.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 9.81 (s, CHO); 7.40 (d, arom H, J = 7.9 Hz); 7.38 (s, arom H); 6.93 (d, arom H, J = 7.9 Hz); 6.80 and 6.79 (2s, arom H); 4.72 (d, CH_2, J = 14 Hz); 4.12–3.91 (m, OCH_2); 3.89 and 3.78 (2s, OCH_3); 3.49 (d, CH_2, J = 14 Hz); 1.88–1.73 and 1.50–1.27 (m, $(CH_2)_7$).

Anal calc for $C_{75}H_{96}O_{15}$: C, 72.78; H, 7.82. Found: C, 72.4; H, 7.8.

Similarly, *P*-(−)-cyclotriguaiacylene **11** (50 mg) with $[\alpha]_D^{25}$ −273 ($CHCl_3$), in 3 mL of DMF/HMPA, was treated with 0.1 mL of aqueous NaOH (6.25 M) and 249 mg of **7h** at rt overnight; 128 mg (84%) of (+)-**12h** was obtained by column chromatography (dichloromethane/ethyl acetate 9:1); $[\alpha]_D^{25}$ +43.5 (*c* 0.31, $CHCl_3$). The ^{1}H NMR spectrum was identical to that of (±)-**12h**.

*2,7,12-Tris[10-(4-formyl-2-methoxyphenoxy)decyloxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a,d,g*]-cyclononene* (±)-**12i** *and* M-(+)-**12i**

In the same way, trialdehyde (±)-**12i** was prepared from (±)-cyclotriguaiacylene **11** (0.2 g, 0.49 mmol); 0.4 mL (2.46 mmol) of aqueous NaOH (6.25 M) and (1.03 g, 2.46 mmol) of iodide **7i** in 12 mL of DMF/HMPA (1:1), at rt overnight under argon. The crude material was chromatographed (dichloromethane/ethyl acetate 92:8) giving 0.554 g (88%) of **12i** as an amorphous powder.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 9.82 (s, CHO); 7.41 (dd, arom H, J = 7.9 Hz, J = 1.8 Hz); 7.38 (d, arom H, J = 1.8 Hz); 6.94 (d, arom H, J = 7.9 Hz); 6.81 and 6.79 (2s, arom H); 4.72 (d, CH_2, J = 13.7 Hz); 4.07 (t, OCH_2, J = 6.8 Hz); 3.98 and 3.89 (m, OCH_2); 3.89 and 3.78 (2s, OCH_3); 3.50 (d, CH_2, J = 13.7 Hz); 1.89–1.73 and 1.50–1.24 (m, $(CH_2)_8$).

Anal calc for $C_{76}H_{98}O_{15}$: C, 73.19; H, 7.93. Found: C, 72.9; H, 7.9.

Similarly, *P*-(−)-cyclotriguaiacylene **11** (40 mg) with $[\alpha]_D^{25}$ −276 ($CHCl_3$), in 2.4 mL of DMF/HMPA, was treated with 0.08 mL of aqueous NaOH (6.25 M) and 257 mg of **7i** overnight at rt; 106 mg (84%) of (+)-**12i** were obtained by TLC on silica gel (dichloromethane/ethyl acetate 9:1); $[\alpha]_D^{25}$ +41.2 (*c* 0.29, $CHCl_3$). The ^{1}H NMR spectrum was identical to that of (±)-**12i**.

*2,7,12-Tris[4-[4-(hydroxymethyl)-2-methoxyphenoxy]-butyloxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene* (±)-**13c** *and* M-(+)-**13c**

This triol was prepared by reduction of the corresponding trialdehyde (±)-**12c** (0.897 g, 0.87 mmol) in 50 mL of methanol with 1.63 g of $NaBH_4$ at rt overnight. Evaporation of the solvent, addition of water, extraction with dichloromethane and column chromatography (dichloromethane/acetone 7:3) yielded 0.786 g (87%) of **13c**, as an amorphous powder.

^{1}H NMR (500 MHz, $CDCl_3$, δ $CHCl_3$ = 7.24): 6.84–6.76 (m, arom H); 4.72 (d, CH_2, J = 13.8 Hz); 4.57 (d, CH_2OH, J = 5.9 Hz); 4.04–4.01 (m, CH_2O); 3.70 and 3.69 (2s, OCH_3); 3.49 (d, CH_2, J = 13.8 Hz); 1.98 (m, $(CH_2)_2$); 1.73 (t, OH, J = 5.9 Hz).

Anal calc for $C_{60}H_{72}O_{15}$: C, 69.75; H, 7.02. Found: C, 69.6; H, 7.1.

Similarly, M-(+)-**12c** (0.12 g, 0.117 mmol) in 13 mL of methanol was allowed to react with 0.177 g of $NaBH_4$ at rt overnight. The crude material was purified by digestion in hexane (without heating). Yield 0.11 g (91%) of (+)-**13c**, $[\alpha]_D^{25}$ +36.5 (*c* 0.32, $CHCl_3$). The ^{1}H NMR was identical to that of (±)-**13c**.

*2,7,12-Tris[5-[4-(hydroxymethyl)-2-methoxyphenoxy]-pentyloxy]-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (±)-***13d** *and M-(+)-***13d**

Triol (±)-**13d** was prepared from (±)-cyclotriguaiacylene **11** (0.5 g, 1.22 mmol), 0.98 mL (6.12 mmol) of aqueous NaOH (6.25 M) and 2.15 g (6.12 mmol) of iodide **8d** in 30 mL of DMF/HMPA (1:1), at rt overnight under argon. Column chromatography (dichloromethane/acetone 7:3) gave 0.91 g (70%) of **13d** as an amorphous powder.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 6.88–6.78 (m, arom H); 4.72 (d, CH_2, J = 13.6 Hz); 4.52 (d, CH_2OH, J = 5.7 Hz) 4.02–3.85 (m, OCH_2); 3.81–3.76 (2s, OCH_3); 3.49 (d, CH_2, J = 13.6 Hz); 1.88–1.58 (m, $(CH_2)_3$); 1.72 (t, OH, J = 5.7 Hz). The ^{1}H NMR spectrum showed the presence of ca 0.5 mol of dichloromethane per mole of triol.

Anal calc for [$C_{63}H_{78}O_{15}$ + 1/2 CH_2Cl_2]: C, 68.23; H, 7.12. Found C, 68.0; H, 7.3.

*2,7,12-Tris[6-[4-(hydroxymethyl)-2-methoxyphenoxy]-hexyloxy]-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (±)-***13e** *and* M-*(+)-***13e**

Triol (±)-**13e** was similarly prepared from (±)-cyclotriguaiacylene **11** (0.4 g, 0.98 mmol), 0.78 mL (4.90 mmol) of aqueous NaOH (6.25 M) and (1.78 g, 4.90 mmol) of iodide **8e** in 24 mL of DMF/HMPA (1:1), at rt overnight under argon. Column chromatography (dichloromethane/acetone 7:3) gave 0.83 g (76%) of **13e** as an amorphous powder.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 6.91–6.78 (m, arom H); 4.73 (d, CH_2, J = 14 Hz); 4.58 (d, CH_2OH, J = 5.9 Hz); 4.03–3.85 (m, OCH_2); 3.81 and 3.76 (2s, OCH_3); 3.49 (d, CH_2, J = 14 Hz); 1.82–1.70 and 1.63–1.48 (m, $(CH_2)_4$); 1.66 (t, OH, J = 5.9 Hz).

Anal calc for $C_{66}H_{84}O_{15}$: C, 70.95; H, 7.57. Found: C, 70.9; H, 8.1.

Similarly, *P*-(−)-cyclotriguaiacylene **11** (58 mg) with $[\alpha]_D^{25}$ −276 ($CHCl_3$), in 3.4 mL of DMF/HMPA, was treated with 0.113 mL of aqueous NaOH (6.25 M) and 258 mg of **8e** at rt overnight, yielding 106 mg (67%) of (+)-**13e** after TLC on silica gel (dichloromethane/acetone 6:4) followed by a digestion in diethyl ether (without heating); $[\alpha]_D^{25}$ +35 (*c* 0.36, $CHCl_3$). The ^{1}H NMR spectrum was identical to that of (±)-**13e**.

*2,7,12-Tris[7-[4-(hydroxymethyl)-2-methoxyphenoxy]-heptyloxy]-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (±)-***13f** *and* M-*(+)-***13f**

Reduction of (±)-**12f** (0.895 g, 0.78 mmol) in 100 mL of methanol was effected by reaction with 1.2 g of $NaBH_4$ at rt for 2 days. Column chromatography (dichloromethane/acetone 7:3) yielded 0.736 g (82%) of **13f**. Mp 88 °C.

^{1}H NMR ($CDCl_3$, δ $CHCl_3$ = 7.24): 6.88–6.78 (m, arom H); 4.72 (d, CH_2, J = 13.7 Hz); 4.58 (d, CH_2OH, J = 5.9 Hz); 4.00–3.89 (m, CH_2O); 3.82 and 3.77 (2s, OCH_3); 3.49 (d, CH_2, J = 13.7 Hz); 1.88–1.77 (m, $(CH_2)_2$); 1.65 (t, OH, J = 5.9 Hz); 1.40 (m, $(CH_2)_3$).

Anal calc for [$C_{60}H_{90}O_{15}$ + 0.5 H_2O]: C, 70.93; H, 7.85. Found: C, 70.8; H, 7.8.

Similarly, M-(+)-**12f** (0.1 g, 0.087 mmol) in 10 mL of methanol was treated with 0.24 g of $NaBH_4$ at rt for 24 h. TLC (dichloromethane/acetone 7:3) yielded 94 mg (94%) of (+)-**13f**, $[\alpha]_D^{25}$ +33.6 (*c* 0.71, $CHCl_3$). The ^{1}H NMR spectrum was identical to that of (±)-**13f**.

*2,7,12-Tris[8-[4-(hydroxymethyl)-2-methoxyphenoxy]-octyloxy]-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (±)-***13g** *and* M-*(+)-***13g**

Triol (±)-**13g** was prepared from (±)-cyclotriguaiacylene **11** (0.4 g, 0.98 mmol), 0.78 mL (4.90 mmol) of aqueous NaOH (6.25 M) and (1.92 g, 4.90 mmol) of iodide **8g** in 24 mL of DMF/HMPA (1:1), 3 h at rt, under argon. Column chromatography (dichloromethane/acetone 8:2) gave 0.82 g (69%) of **13g** (oil).

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 6.89–6.79 (m, arom H); 4.72 (d, CH_2, J = 14 Hz); 4.0–3.85 (m, CH_2O); 4.58 (d, CH_2OH, J = 5.6 Hz); 3.84 and 3.77 (2s, OCH_3); 3.49 (d, CH_2, J = 14 Hz); 1.80–1.30 (m, OH + $(CH_2)_6$).

Anal calc for [$C_{72}H_{96}O_{15}$, H_2O]: C, 70.91; H, 8.09. Found: C, 71.0; H, 8.1.

Similarly, *P*-(−)-cyclotriguaiacylene **11** (61 mg) with $[\alpha]_D^{25}$ −276 ($CHCl_3$), in 3.6 mL of DMF/HMPA, was treated with 0.12 mL of aqueous NaOH (6.25 M) and 395 mg of **8g** for 15 h at rt TLC (dichloromethane/acetone 7:3) yielded 123 mg (68%) of (+)-**13g**; $[\alpha]_D^{25}$ +21 (*c* 0.36, $CHCl_3$). The ^{1}H NMR spectrum was identical to that of (±)-**13g**.

*2,7,12-Tris[9-[4-(hydroxymethyl)-2-methoxyphenoxy]-nonyloxy]-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (±)-***13h** *and* M-*(+)-***13h**

The reduction of (±)-**12h** (0.705 g, 0.57 mmol) in 10 mL methanol was carried out by reaction with 0.194 g of $NaBH_4$ at rt for 2 days. After concentration of the solvent, addition of water and extraction with dichloromethane, 0.67 g (94%) of **13h** was obtained.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 6.85–6.78 (m, arom H); 4.72 (d, CH_2, J = 14 Hz); 4.58 (s, CH_2OH); 4.00–3.89 (m, CH_2O); 3.83 and 3.78 (2s, OCH_3); 3.50 (d, CH_2, J = 14 Hz); 1.86–1.73 and 1.40–1.23 (m, $(CH_2)_7$ + OH).

Anal calc for [$C_{75}H_{98}O_{15}$ + CH_2Cl_2]: C, 68.92; H, 7.61. Found: C, 68.8 H, 7.9.

Similarly, reduction of M-(+)-**12h** (99 mg, 0.08 mmol) in 2 mL methanol by reaction with 0.03 g of $NaBH_4$ at rt overnight afforded 77 mg (78%) of (+)-**13h**, $[\alpha]_D^{25}$ +35.4 (*c* 0.31, $CHCl_3$). The ^{1}H NMR spectrum was identical to that of (±)-**13h**.

*2,7,12-Tris[10-[4-(hydroxymethyl)-2-methoxyphenoxy]-decyloxy]-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (±)-***13i** *and* M-*(+)-***13i**

Trialdehyde (±)-**12i** (0.45 g, 0.35 mmol) in 10 mL methanol was allowed to react with 0.4 g of $NaBH_4$ at rt for 2 days. After concentration, addition of water and extraction with dichloromethane, 0.43 g (95%) of **13i** (oil) was obtained.

^{1}H NMR ($CDCl_3$, 200 MHz, δ $CHCl_3$ = 7.24): 6.89–6.79 (m, arom H); 4.72 (d, CH_2, J = 13.6 Hz); 4.59 (d, CH_2OH, J = 5.8 Hz); 4.01–3.89 (m, CH_2O); 3.84 and 3.78 (2s,

OCH_3); 3.50 (d, CH_2, J = 13.6 Hz); 1.87–1.73 and 1.36–1.22 (m, $(CH_2)_8$ and OH).

Similarly, reduction of M-(+)-**12i** (98.2 mg, 0.076 mmol) in 3.5 mL of methanol by reaction with 0.24 g of $NaBH_4$ at rt for 24 h, yielded 71 mg (72%) of (+)-**13i**, $[\alpha]_D^{25}$ +25.8 (*c* 0.33, $CHCl_3$). The ^1H NMR spectrum was identical to that of (±)-**13i**.

Cryptophane-M (±)-**1c** *and (-)*-**1c** *and cryptophane*-N **2c**

The racemic triol (±)-**13c** (200 mg, 0.194 mmol) in 6 mL $CHCl_3$ was placed in a 1 L rotatory evaporator flask, and 466 mL of 99% formic acid was added (concentration 4.1×10^{-4} M). The flask was fitted to the evaporator and heated in the water bath at 55 °C for 3 h, with slow rotation. The solvent was evaporated under vacuum (some $CHCl_3$ was added at the end in order to facilitate formic acid removal through azeotrope formation), affording a mixture of *anti* **1c** and *syn* **2c** in a 66:34 ratio (^1H NMR). The materials from two such preparations were combined and the stereomers were separated by column chromatography (dichloromethane/acetone 92:8), yielding 0.216 g (57%) of **1c** (faster running) and 0.094 g (25%) of **2c** (slower running).

(±)-Cryptophane-M **1c**: ^1H NMR ($CDCl_3$, 500 MHz, δ $CHCl_3$ = 7.24): 6.65 and 6.38 (2s, arom H); 4.61 (d, CH_2, J = 14 Hz); 4.07–4.03 (m, OCH_2); 3.98–3.95 (m, OCH_2); 3.74 (s, OCH_3); 3.39 (d, CH_2, J = 14 Hz); 1.85–1.82 and 1.76–1.74 (m, $(CH_2)_2$).

MS (FAB) m/z 978.9; calcd for $C_{60}H_{66}O_{12}$: 979.

Anal calc for $[C_{60}H_{66}O_{12} + 2.5\ H_2O]$: C, 70.36; H, 6.98. Found: C, 70.4; H, 6.9.

Cryptophane-N **2c**: ^1H NMR (500 MHz, $CDCl_3$, δ $CHCl_3$ = 7.24): 6.75 and 6.65 (2s, arom H); 4.59 (d, CH_2, J = 14 Hz); 4.05–4.00 (m, OCH_2); 3.86–3.81 (m, OCH_2); 3.69 (s, OCH_3); 3.39 (d, CH_2, J = 14 Hz); 1.95–1.91 and 1.78–1.75 (m, $(CH_2)_2$).

MS (FAB) m/z 978.5; calcd for $C_{60}H_{66}O_{12}$: 979.

Anal calc for $C_{60}H_{66}O_{12}$: C, 73.59; H, 6.79. Found: C, 73.6; H, 7.0.

The optically active triol (+)-**13c** (100 mg, 0.096 mmol) was dissolved in 3 mL $CHCl_3$ and 233 mL formic acid was added (concentration 4.1×10^{-4} M). The solution was stirred at rt for 23 h. The solvent was evaporated under vacuum, affording a mixture of *anti* **1c** and *syn* **2c** in a 66:34 ratio (^1H NMR). Purification by TLC on silica gel (dichloromethane/acetone 9:1) led to (-)-cryptophane-M **1c** (35 mg, 37%, purified by digestion in diethyl ether), $[\alpha]_D^{25}$ −117 (*c* 0.25, $CHCl_3$), and cryptophane-N **2c** (20 mg, 24%), showing no rotation.

Cryptophanes-O (±)-**1d** *and cryptophane*-P **2d**

Each preparation was carried out in a 1 L rotatory evaporator flask in which was placed (±)-**13d** (200 mg, 0.186 mmol) in 5.8 mL of $CHCl_3$ and then 448 mL of formic acid (concentration 4.1×10^{-4} M). The solution was kept in the water bath at 55 °C for 3 h, with slow rotation. Evaporation of the solvent under vacuum provided a mixture of the desired *anti* **1d** and *syn* **2d** in a 42:58 ratio (by ^1H NMR). The materials of two such preparations were combined and column chromatographed (dichloromethane/diethyl ether 9:1), providing 0.144 g (38%) of the faster running **1d** (crystallized from acetone) and 0.224 g (59%) of the slower running **2d**.

(±)-Cryptophane-O **1d**: ^1H NMR (500 MHz, $CDCl_3$, δ $CHCl_3$ = 7.24): 6.69 and 6.67 (2s, arom H); 4.63 (d, CH_2, J = 14 Hz); 4.03 (m, OCH_2); 3.76 (m, OCH_2); 3.73 (s, OCH_3); 3.40 (d, CH_2, J = 14 Hz); 1.81–1.74 and 1.52–1.47 (m, $(CH_2)_3$).

MS (FAB) m/z 1020.8; calcd for $C_{63}H_{72}O_{12}$: 1021.

Anal calc for $[C_{63}H_{72}O_{12} + 2\ H_2O]$: C, 71.56; H, 7.12. Found: C, 71.7; H, 7.1.

Cryptophane-P **2d**: ^1H NMR (500 MHz, $CDCl_3$, δ $CHCl_3$ = 7.24): 6.69 and 6.66 (2s, arom H); 4.61 (d, CH_2, J = 14 Hz); 4.05 (m, OCH_2); 3.71–3.75 (m, OCH_2); 3.67 (s, OCH_3); 3.39 (d, CH_2, J = 14 Hz); 1.93–1.90 and 1.80–1.66 (m, $(CH_2)_3$).

MS (FAB) m/z 1020.7; calcd for $C_{63}H_{72}O_{12}$: 1021.

Anal calc for $[C_{63}H_{72}O_{12} + 2\ H_2O]$: C, 71.56; H, 7.12. Found: C, 71.6; H, 7.0.

Cryptophane-Q (±)-**1e** *and (-)*-**1e** *and cryptophane*-R **2e**

A solution of triol (±)-**13e** (216 mg, 0.193 mmol) in $CHCl_3$ (6 mL) was placed in a 1 L rotatory evaporator flask and 465 mL of formic acid was added (concentration 4.1×10^{-4} M). The flask was fitted to the evaporator and heated in the water bath at 55 °C for 3 h, with slow rotation. Evaporation to dryness under vacuum provided a mixture of *anti* **1e** and *syn* **2e** in a 65:35 ratio (^1H NMR). Column chromatography (benzene/acetone, 85:15) yielded cryptophane-R **2e** (14 mg, 7%, faster running) and cryptophane-Q **1e** (63 mg, 31%, slower running, crystallized from a mixture of methanol and acetone). The ^1H NMR spectra of the chloroform solutions showed the presence of small amounts of the in–out topoisomers **1e′** and **2e′**, which transformed into the out–out isomers on standing.

(±)-Cryptophane-Q **1e**: ^1H NMR (500 MHz, $CDCl_3$, δ $CHCl_3$ = 7.24): 6.73 and 6.68 (2s, arom H); 4.64 (d, CH_2, J = 14 Hz); 4.04–3.99 (m, OCH_2); 3.98–3.94 (m, OCH_2); 3.74 (s, OCH_3); 3.41 (d, CH_2, J = 14 Hz); 1.73–1.67 and 1.45–1.35 (m, $(CH_2)_4$).

MS (FAB) m/z 1062.7; calcd for $C_{66}H_{78}O_{12}$: 1063.

Anal calc for $[C_{66}H_{72}O_{12} + 0.5\ H_2O]$: C, 73.92; H, 7.42. Found: C, 74.1; H, 7.5.

Cryptophane-R **2e**: ^1H NMR (500 MHz, $CDCl_3$, δ $CHCl_3$ = 7.24): 6.78 and 6.73 (2s, arom H); 4.66 (d, CH_2, J = 14 Hz); 4.99–4.95 and 3.83–3.78 (m, OCH_2); 3.74 (s, OCH_3); 3.44 (d, CH_2, J = 14 Hz); 1.77–1.73, 1.67 and 1.35 (m, $(CH_2)_4$).

MS (FAB) m/z 1062.6; calcd for $C_{66}H_{78}O_{12}$: 1063.

Anal calc for $[C_{66}H_{78}O_{12} + H_2O]$: C, 73.31; H, 7.45. Found: C, 73.5 H, 7.8.

Similarly, a solution of triol (+)-**13e** (100 mg, 0.089 mmol) in 2.8 mL $CHCl_3$ and 217 mL formic acid (concentration 4.07×10^{-4} M) was stirred at rt for 24 h. The solvent was evaporated under vacuum, affording a mixture of *anti* **1e** and *syn* **2e** in a 63:37 ratio (^1H NMR). Purification by TLC on silica gel (benzene/acetone 85:15) yielded cryptophane-R **2e** (16 mg, 17%) and (-)-cryptophane-Q **1e** (48 mg, 51%, purifed by digestion in acetone/methanol), $[\alpha]_D^{25}$ −44 (*c* 0.48, $CHCl_3$).

Cryptophane-S (±)-**1f** *and (-)*-**1f** *and cryptophane*-T **2f**

The triol (±)-**13f** (100 mg, 0.095 mmol) in 3 mL $CHCl_3$ was placed in a 500 mL rotatory evaporator flask and 227 mL formic acid was then added (concentration 4.12×10^{-4} M). The flask was fitted to the evaporator and heated in the water bath at 55 °C for 3 h, with slow rotation. The solvent was evaporated under vacuum and the residue was purified by TLC (dichloromethane/diethyl ether 95:5) giving 85 mg (81%) of a mixture of cryptophane-S **1f** (44%), cryptophane-T **2f** (39%), together with their in–out topoisomers **1f′** and **2f′** (6 and 11%, respectively, from 500 MHz ^1H NMR

in C_6D_6). After 8 days, the NMR spectra of the C_6D_6 solution only showed **1f** and **2f** in 51:49 ratio. Attempts to separate these stereo and topoisomers by column chromatography was unsuccessful.

MS (FAB) (mixture of cryptophanes S **1f** and T **2f**): m/z 1105; calcd for $C_{69}H_{84}O_{12}$: 1105.

Anal (mixture of cryptophanes S **1f** and T **2f**) calc for $[C_{69}H_{84}O_{12} + H_2O]$: C, 73.77; H, 7.72. Found: C, 73.5; H, 7.6.

Similarly, the trimerization of (+)-**13f** (71 mg, 0.061 mmol) in 1.9 mL of chloroform and 147 mL formic acid at rt for 24 h, gave after purification by TLC (dichloromethane/diethyl ether 9:1), 60 mg (90%) of a mixture showing $[\alpha]_D^{25}$ −11.8 (c 0.32, $CHCl_3$), and consisting of **2f** (44%) and **2f'** (4%), and of **1f** (49%) and **1f'** (3%). This mixture was column chromatographed (dichloromethane/diethyl ether 97:3), and separated into four main fractions characterized by their rotation in $CDCl_3$ and their 500 MHz ^1H NMR spectrum in C_6D_6; details on these experiments are given in the text.

^1H NMR (500 MHz, C_6D_6, δ C_6D_5H = 7.15): Cryptophane-S **1f**: 6.75 and 6.732 (2s, arom H); 4.63 (d, CH_2, J = 13.5 Hz); 3.82–3.78 and 3.65–3.62 (m, OCH_2); 3.512 (s, OCH_3); 3.41 (d, CH_2, J = 13.5 Hz); 1.64–1.59, 1.50–1.45 and 1.37–0.99 (m, $(CH_2)_5$). Cryptophane-T **2f**: 6.766 and 6.732 (2s, arom H); 4.63 (d, CH_2, J = 13.5 Hz); 3.82–3.78 and 3.65–3.62 (m, OCH_2); 3.469 (s, OCH_3); 3.41 (d, CH_2, J = 13.5 Hz); 1.66–1.59 and 1.49–1.44 and 1.31–1.09 (m, $(CH_2)_5$). Cryptophane-S **1f'** (in–out): 6.83, 6.77, 6.76 and 6.49 (4s, arom H); 4.61 (d, CH_2, J = 15 Hz); 4.19 (d, CH_2, J = 16 Hz); 3.95 (d, CH_2, J = 16 Hz); 3.85–3.78 and 3.67–3.61 (m, OCH_2); 3.55 (s, OCH_3); 3.39 (d, CH_2, J = 15 Hz); 2.89 (s, OCH_3); 1.64–1.00 (m, $(CH_2)_5$). Cryptophane-T **2f'** (in–out): 6.84, 6.79, 6.77 and 6.44 (4s, arom H); 4.58 (d, CH_2, J = 13.5 Hz); 3.98–3.80 (m, OCH_2); 3.507 (s, OCH_3); 3.42–3.37 (d, CH_2, J = 15 Hz); 2.96 (s, OCH_3); 1.60–1.00 (m, $(CH_2)_5$).

Cryptophane-U (±)-**1g** *and (–)*-**1g** *and cryptophane*-V **2g**

Triol (±)-**13g** (209 mg, 0.174 mmol) in 5.4 mL of $CHCl_3$ was placed in a 1 L rotatory evaporator flask and 419 mL formic acid was then added (concentration 4.1×10^{-4} M). The flask was fitted to the evaporator and heated in the water bath at 55 °C for 3 h, with slow rotation. The solvent was evaporated under vacuum to give a mixture of **1g** and **2g** in 59:41 ratio. Separation by column chromatography of the crude materials obtained from two such experiments (dichloromethane/diethyl ether 96:4) yielded 61 mg (16%) of **2g** (faster running) and 160 mg (41%) of **1g** (slower running). These cryptophanes were crystallized from diethyl ether.

(±)-Cryptophane-U **1g**: ^1H NMR (500 MHz, $CDCl_3$, δ $CHCl_3$ = 7.24): 6.79 and 6.75 (2s, arom H); 4.70 (d, CH_2, J = 13.5 Hz); 3.99–3.96 (m, OCH_2); 3.76 (s, OCH_3); 3.47 (d, CH_2, J = 13.5 Hz); 1.68–1.65 and 1.29–1.17 (m, $(CH_2)_6$).

MS (FAB) m/z 1146.5; calcd for $C_{60}H_{66}O_{12}$: 1147.5.

Anal calc for $[C_{72}H_{90}O_{12} + H_2O]$: C, 74.19; H, 7.95. Found: C, 74.2; H, 8.0.

Cryptophane-V **2g**: ^1H NMR (500 MHz, $CDCl_3$, δ $CHCl_3$ = 7.24): 6.81 and 6.75 (2s, arom H); 4.69 (d, CH_2, J = 14 Hz); 4.00–3.96 and 3.86–3.82 (m, OCH_2); 3.76 (s, OCH_3); 3.47 (d, CH_2, J = 14 Hz); 1.72–1.64 and 1.29–1.21 (m, $(CH_2)_6$).

MS (FAB) m/z 1146.8; calcd for $C_{72}H_{90}O_{12}$: 1147.5.

Anal calc for $C_{72}H_{90}O_{12}$: C, 75.36; H, 7.90. Found: C, 75.2 H, 8.1.

A solution of triol (+)-**13g** (69 mg, 0.057 mmol) in 2 mL $CHCl_3$ and 139 mL formic acid (concentration 4.04×10^{-4} M) was stirred for 24 h at rt. The solvent was evaporated under vacuum to give a material containing (–)-**1g** and **2g** in a 64:36 ratio. Separation by column chromatography (dichloromethane/diethyl ether 96:4) yielded **2g** (9 mg, 14%, no rotation) and (–)-**1g** (20 mg, 31%, crystallized from diethyl ether), $[\alpha]_D^{25}$ −12 (c 0.30, $CHCl_3$). The ^1H NMR spectrum of (–)-cryptophane-U **1g** was identical to that of the racemate.

Cryptophane-W (±)-**1h** *and cryptophane*-X **2h**

Triol (±)-**13h** (279 mg, 0.225 mmol) in 6.9 mL $CHCl_3$ was placed in a 1 L rotatory evaporator flask and 500 mL of formic acid were then added (concentration 4.44×10^{-4} M). The flask was fitted to the evaporator and heated in the water bath at 55 °C for 3 h, with slow rotation. The solvent was evaporated under vacuum and column chromatography (dichloromethane/diethyl ether 96:4) gave a first fraction (163 mg, 61%, amorphous powder) consisting of a 50:50 mixture of **1h** and **2h** together with ca 28% of their topoisomers which disappeared on standing for 1 month in chloroform. The second fraction (43 mg, 16%) contained ca 50% of **1h** and **2h** and 50% of their in–out topoisomers.

^1H NMR (mixture of **1h** and **2h**, 500 MHz, $CDCl_3$, δ $CHCl_3$ = 7.24): 6.76 (s, arom H); 4.69 (d, CH_2, J = 14 Hz); 4.04–4.00 and 3.86–3.80 (m, OCH_2); 3.767 and 3.762 (2s, OCH_3); 3.47 (d, CH_2, J = 14 Hz); 1.77–1.74 and 1.68–1.65 (m, OCH_2CH_2); 1.36–1.20 (m, $(CH_2)_5$). For the in–out topoisomers: main peaks at 6.80, 6.789 and 6.782 (3s, arom H); 6.587 and 6.526 (2s, arom H); 3.78 and 3.74 (2s, OCH_3); 3.67 and 3.66 (2s, OCH_3).

^1H NMR (mixture of **1h** and **2h**, 500 MHz, in C_6D_6, δ C_6D_6 = 7.15): 6.890, 6.781, 6.762 and 6.756 (4s, arom H); 4.65 (d, CH_2, J = 13.5 Hz); 3.86–3.83 and 3.66–3.65 (m, OCH_2); 3.535 and 3.522 (2s, OCH_3); 3.43 (d, CH_2, J = 13.5 Hz); 1.67–0.99 (m, $(CH_2)_7$).

MS (FAB, mixture of **1h** and **2h**) m/z 1188.3; calcd for $C_{75}H_{96}O_{12}$: 1189.6.

Anal (mixture of **1h** and **2h**) calc for $[C_{75}H_{96}O_{12} + H_2O]$: C, 74.59; H, 8.19. Found: C, 74.4 H, 8.1.

Similarly, a solution of (+)-**13h** (71 mg, 0.056 mmol) in 2 mL $CHCl_3$ and 134 mL formic acid (concentration 4.12×10^{-4} M) was stirred for 3 h at 55 °C. The solvent was evaporated under vacuum and a purification by TLC (dichloromethane/diethyl ether 95:5) gave 44 mg (66%) of a 50:50 mixture of (–)-**1h** and **2h**, together with about 33% of in–out topoisomers. This mixture showed practically no rotation ($[\alpha]_D^{25}$ 0 (c 0.27, $CHCl_3$)).

Cryptophane-Y (±)-**1i** *and cryptophane*-Z **2i**

Triol (±)-**13i** (280 mg, 0.217 mmol) in 7 mL $CHCl_3$ was placed in a 1 L rotatory evaporator flask and 485 mL of formic acid were then added (concentration 4.43×10^{-4} M). The flask was fitted to the evaporator and heated in the water bath at 55 °C for 3 h, with slow rotation. The solvent was evaporated under vacuum and column chromatography (dichloromethane/diethyl ether 96:4) gave 159 mg (59%) of a 50:50 mixture of **1i** and **2i** (^1H NMR) and less than 10% of their in–out and possibly in–in topoisomers, which transformed into the out–out forms on standing several days in chloroform. The cyclization of **13i** (34 mg) was also carried out at rt for 30 h. The same workup gave 22 mg (68%) of a 50:50 mixture of cryptophanes Y **1i** and Z **2i**.

^1H NMR (mixture of **1i** and **2i**, 500 MHz, $CDCl_3$, δ $CHCl_3$ = 7.24): 6.80, 6.79 and 6.76 (3s, arom H); 4.69

(d, CH_2, J = 14 Hz); 3.99–3.77 (m, OCH_2); 3.764 (s, OCH_3); 3.47 (d, CH_2, J = 14 Hz); 1.76–1.67 and 1.35–1.18 (m, $(CH_2)_8$).

MS (FAB, mixture of **1i** and **2i**) m/z 1230.7; calcd for $C_{78}H_{102}O_{12}$: 1231.7.

Anal of the mixture of **1i** and **2i** calc for [$C_{78}H_{102}O_{12}$ + 0.5 H_2O]: C, 75.51; H, 8.37. Found: C, 75.4 H, 8.1.

The trimerization of (+)-**13i** (49 mg, 0.038 mmol) in 1.4 mL of $CHCl_3$ and 93 mL formic acid (concentration 4.02 × 10^{-4} M) at rt for 26 h, followed by TLC (dichloromethane/diethyl ether 95:5) provided 30 mg (64%) of a 50:50 mixture of **1i** and **2i** which also contained ca 20% of topoisomers. This mixture showed practically no rotation (c 0.67, $CHCl_3$).

Acknowledgments

We are grateful to Région Rhône-Alpes (X0712500 01) and to the European Commission (CHRXCT940484 and COST D7/006/93) for additional financial support. We thank JC Lanet and Rhône-Poulenc for a generous supply of vanillin.

Supplementary material

Table of positional parameters and their esd (including hydrogens), table of refined displacement parameters expressions, bond angles, bond distances, for cryptophane-O (8 pages). Supplementary material data have been deposited with the British Library, Document Supply Centre at Boston Spa, Wetherby, West Yorkshire, LS23 7 BQ, UK, as supplementary publication N° = SUP 90433 and are available on request from the Document Supply Centre.

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Bull Soc Chim Fr (1996) 133, 869-874

Synthesis and characterization of a new pyrimidine derivative: 5-[1-phenyl-2-(3-chlorophenyl)ethyl]-2,4,6-trichloropyrimidine

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Summary — The synthesis of 5-[1-phenyl-2-(3-chlorophenyl)ethyl]-2,4,6-trichloropyrimidine is described. The compound was prepared by chlorination of the 5-substituted barbituric acid obtained by treatment of the 5-benzylidenebarbituric acid with an organozinc reagent in the preceding step. The new trichloropyrimidine belongs to a series of new pyrimidine derivatives which show antibacterial activity against the human bacterial flora of the axilla and foot. The characterization of this compound was performed by spectroscopy and X-ray structure determination.

barbituric acid / benzylzinc bromide / trichloropyrimidine / X-ray diffraction / FTIR / Raman spectroscopy

Résumé — Synthèse et caractérisation d'un nouveau dérivé de la pyrimidine : la 5-[1-phényl-2-(3-chlorophényl)éthyl]-2,4,6-trichloropyrimidine. *La synthèse de la 5-[1-phényl-2-(3-chlorophényl)éthyl]-2,4,6-trichloropyrimidine a été réalisée en deux étapes à partir de l'acide 5-benzylidènebarbiturique. Elle consiste à préparer l'acide 5-[1-phényl-2-(3-chlorophényl)éthyl]-barbiturique par la voie organozincique, puis à traiter cet acide par un agent chlorant. Cette trichloropyrimidine appartient à une série de nouveaux dérivés pyrimidiques qui manifestent une activité antibactérienne contre la flore microbienne des aisselles et des pieds. Sa structure a été déterminée par des méthodes spectrographiques et ses cristaux analysés par diffraction de rayons X.*

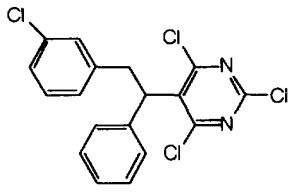
acide barbiturique / bromure de benzylzinc / trichloropyrimidine / diffraction de rayons X / FTIR / spectroscopie Raman

Introduction

Pyrimidine derivatives are usually synthesized according to the literature [1–7], by condensing a β-diamino reagent with a β-bifunctional compound, in order to form the pyrimidine ring. There have also been reports of pyrimidine ring formation starting with aminomethylene groups [8–10], β-diamides [11–13] or β-diamidines [14].

A new synthetic route was proposed for the preparation of barbituric acids by reacting a Grignard [15] or an organozinc reagent [16] with a 5-benzylidenebarbituric acid. This method was clearly useful for the synthesis of 5-[1-phenyl-2-(3-chlorophenyl)ethyl]-2,4,6-trichloropyrimidine **1** by reacting the organozinc reagent with the corresponding 5-substituted barbituric acid.

Compound **1** was characterized by the usual spectroscopic techniques. It belongs to a new series of 5-(1,2-diarylethyl)-2,4,6-trichloropyrimidines which are interesting for their activity against the human bacterial flora of the axilla and foot [17]. Trichloropyrimidine **1** was also the first product of the series to be crystallized for X-ray structure determination.



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X-ray structural characterization is necessary for a better understanding of the structure–activity relationship towards developing more active antibacterial analogues of the type of trichloropyrimidine **1**.

* Correspondence and reprints

Results and discussion

The precursor of 5-[1-phenyl-2-(3-chlorophenyl)ethyl]-2,4,6-trichloropyrimidine **1** was 5-[1-phenyl-2-(3-chlorophenyl)ethyl]barbituric acid **4** (fig 1). Compound **4** was obtained following 1,4-addition of (3-chlorobenzyl)zinc bromide **3** to 5-benzylidenebarbituric acid **2** [17]. Product **2** was easily prepared by condensing barbituric acid with benzaldehyde [18]. In our previous paper [17], we proved that the organozinc reagent **3** also undergoes hydrogen-metal exchange with both NH sites of the substrate **2**. The reaction therefore only led to substantial yields of product **4** if three molecular equivalents of organozinc reagent **3** were used. Compound **4** was purified by sodium hydroxide treatment before use in trichloropyrimidine synthesis. The reaction yielded 85% of barbituric acid **4**.

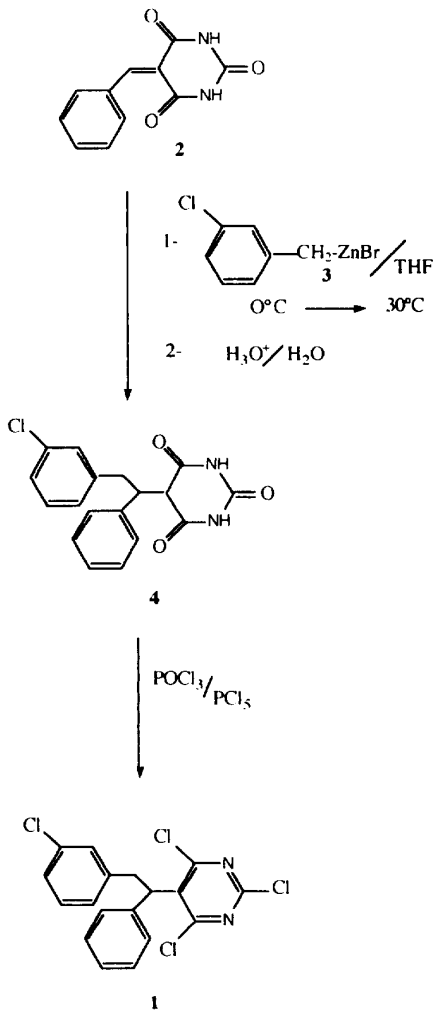

Fig 1. Synthesis of 5-[1-phenyl-2-(3-chlorophenyl)ethyl]-2,4,6-trichloropyrimidine **1**.

The reaction of the mixture of phosphorus oxychloride and phosphorus pentachloride with 5-[1-phenyl-2-(3-chlorophenyl)ethyl]barbituric acid **4**, according to the procedure of Gershon et al [19], gave the corresponding 5-[1-phenyl-2-(3-chlorophenyl)ethyl]-2,4,6-trichloropyrimidine **1**, which was purified first by sodium hydroxide treatment to remove the residual starting material **4**. The purification was then improved by recrystallization with ethanol, and colorless crystals were obtained. The purity was checked on the basis of their elution profile in a capillary gas chromatography procedure. Gas chromatography was coupled with a mass spectrometer to analyse the compound **1**.

Purity was controlled by high performance liquid chromatography using a silica-gel column packed with porasil particles and *n*-hexane with 0.05% of acetonitrile as eluent (R_t = 22.2 min). Synthesis yielded 57% compound **1**. In ethanol as solvent, compound **1** gave an ultraviolet spectrum with a band at 269.5 nm and a shoulder at 240 nm which were assigned to the absorptions of pyrimidine and benzene rings. This spectrum is different from the UV spectrum of barbituric acid **4** which shows absorption bands at 216 and 267 nm. The infrared and Raman spectra were obtained with crystalline compound **1**. The vibrational mode analysis given in table I was made qualitatively using the data found for related compounds [20–30]. The IR and Raman bands at 2 935 and 2 865 cm^{-1} were assigned to the -CH_2-alkyl stretching asymmetric and symmetric modes respectively [27–30]. The CH in- and out-of-plane bending modes in the CH_2-CH- group were characterized by bands at 1 454, 1 300, 1 210, 1 159, 1 030 and 860 cm^{-1}, which sometimes overlap with stretching or deformation aromatic ring modes [27–30]. The IR and Raman bands at 3 100–3 000 cm^{-1} range were assigned to the benzene ring CH stretching modes. The pyrimidine and benzene rings have five characteristic bands in the 1 600–1 400 cm^{-1} range, which correspond to the ν_{8a}, ν_{8b}, ν_{19a} and ν_{19b} modes [28–30]. The IR bands with high intensities at 1 597 and 1 528 cm^{-1} were assigned to benzene and pyrimidine C=C and C=N stretching modes. The Raman spectrum exhibits analogous bands at 1 600 and 1 527 cm^{-1}. The IR peaks at 1 499 and 1 428 cm^{-1}, which are absent in the Raman spectrum, can be attributed to the asymmetric aromatic ring vibrations. The frequencies in the 1 600–1 400 cm^{-1} range are relatively independent of substituent effects. However, some peak intensities may vary drastically [20–22, 25]. The strong IR band at 1 092 cm^{-1} and the very strong Raman band at 997 cm^{-1} can be attributed to the asymmetric and symmetric aromatic ring breathing (benzene and pyrimidine rings) respectively [20–22, 25, 27–30]. In the 450–100 cm^{-1} frequency range, the assignments of the vibrations are quite difficult. However, these vibrations can be caused by C-halogen or C–H alkyl deformation [27–30]. Thus, the 2,4,6-trichloropyrimidine IR and Raman spectra [22] show four C–Cl bending vibrations at 458, 205, 179 and 149 cm^{-1}. The C–Cl Raman or IR vibrations of 5 or 2-chloropyrimidine [22–25] are located at 433, 290, 197 and 436, 323, 177 cm^{-1} respectively. Therefore, the compound **1** frequencies at 416, 269, 207, 168 and 130 cm^{-1} could be assigned as C–Cl deformation modes.

Nevertheless, the frequencies with high intensities at 387, 349, 218, 194 and 153 cm^{-1} could also be caused by C–Cl bending vibrations. The observed hypsochromic

Table I. Observed FT-Raman and IR frequencies (cm^{-1}) of 5-[1-phenyl-2-(3-chlorophenyl)ethyl]-2,4,6-trichloropyrimidine **1**.

Infrared	*Raman*	*Assignment*[a]
	130 s	C–Cl def
	153 s	C–Cl def
	168 m	C–Cl def
	194 s	C–Cl def
	207 s	C–Cl def
	218 s	C–Cl def wag
	243 m	C–Cl def
	269 m	C–Cl band
	349 m	C–Cl def
	387 s	C–Cl str
	416 m	Pyrim ring def
	453 w	Benz ring def out of plane
	471 w	Benz ring def out of plane
	597 w	Pyrim ring def
695 vs	703 w	Benz ring def out of plane
757 vs	760 mw	Arom ring def in plane
775 s	775 mw	and CH_2 rock
811 s		Arom ring def
844 ms	843 m	C–H out of plane (benz ring)
861 vs	859 w	C–H out of plane (benz ring)
875 m		C–H out of plane (benz ring)
960 m	961 vw	Benz ring def
995 vw	997 vs	Arom ring breathing (as)
1030 w	1032 m	CH in plane def
		(arom mono substituted)
1092 m		Arom ring breathing (s)
1122 w	1121 m	C–C str (skel alkyl)
1159 m	1153 w	CH def and
1184 m	1185 m	C–C str (skel alkyl)
		and CH def benz ring
1210 s	1209 m	CH in plane def
1300 mw	1295 vw	CH twist and wag
1320 (sh)		CH tertiary def and
1331 ms	1330 f (sh)	CH def in plane arom
1428 ms		C=N, C=C str (as)
1454 ms	1456 w	$-CH_2-$ def sci
1499 vs		C=N, C=C str (as)
1528 vs	1527 s	C=N, C=C str
1575 ms	1582 m	C=N, C=C str
1597 vs	1600 s	C=N, C=C str
1700 to 2000 w		Benz combination bands
2865 vs	2874 w	$-CH_2-$ str (sym)
	2930 (sh)	$-CH_2-$ str (asym)
2935 w	2935 m	$-CH_2-$ str (asym)
3020 m	3028 w	CH benz str
3060 vw	3062 s	CH benz str
3080 w	3090 w	CH benz str

[a] Relative intensities are denoted by v = very, s = strong, w = weak, m = medium, (sh) = shoulder, str = stretch, def = deformation, skel = skeleton, sci = scissoring, arom = aromatic, pyrim = pyrimidine, benz = benzol, asym = asymmetric, sym = symmetric.

effect of these frequencies could be due to steric intermolecular interaction. Thus, the great number of frequencies with strong intensities in the 450–100 cm^{-1} range corresponding to C–Cl vibrations could mainly be caused by C–Cl intermolecular interaction revealed in the crystal structure.

^1H NMR analysis at 200 MHz of 5-substituted barbituric acid **4** displayed a doublet at 3.45 ppm for COCHCO proton with a coupling constant $^3J = 3.6$ Hz.

The barbituric acid ring of compound **4** exhibited a broad singlet at 9.90 ppm for the two NH protons. The tertiary proton CH of the ethyl chain gave a multiplet at 3.82 ppm. Each proton of the methylene group showed a doublet of doublets at 3.09 ppm ($^2J = 13.7$ Hz and $^3J = 6.7$ Hz) and 3.50 ppm ($^2J = 13.7$ Hz and $^3J = 9.9$ Hz) for the ethyl chain. This suggests that free rotation is hindered between the barbituric ring and its substituent in position 5 due to the steric hindrance of the 1-phenyl-2-(3-chlorophenyl)ethyl group. As expected, the characteristic signals of the barbituric ring of precursor **4** disappeared in the ^1H NMR spectrum of the corresponding trichloropyrimidine **1**. Moreover, the ^1H NMR structure of the ethyl chain was modified. In particular, the tertiary proton exhibited a triplet at 5.19 ppm with a coupling constant $^3J = 8.5$ Hz and the two protons of the methylene group gave a doublet at 3.57 ppm with the coupling constant $^3J = 8.5$ Hz. The down-field shift of the tertiary proton resonance for trichloropyrimidine **1** compared to its barbituric acid precursor **4** characterized the out-magnetic anisotropy effect of the pyrimidine ring of compound **1**. The mass spectrum (electronic impact at 70 eV) of compound **1** gave five molecular peaks at $m/z = 396$, 398, 400, 402 and 404 due to the presence of the isotopes 35 and 37 of chlorine in the molecular formula $C_{18}H_{12}Cl_4N_2$. For the same reason, the fragment $(C_{11}H_6Cl_3N_2)^+$ resulting from the cleavage with the 3-chlorobenzyl group was assigned to four peaks at $m/z = 271$, 273, 275 and 277.

X-ray crystal analysis confirmed the structure of compound **1** (fig 2). The experimental bond lengths and bond angles reported in table IV were similar to those observed in related compounds [31, 32]. The crystal structure of compound **1** was built of one type of the enantiomeric forms (fig 3) when single crystals were prepared by slow evaporation of the ethanol solution of the racemic mixture. The molecules were located in general positions of orthorombic $P2_12_12_1$ space group (table II). Examination of the intermolecular bond distances in the crystal showed that cohesion of molecules was only due to the van der Waals interactions. However, short Cl(1)···Cl(2) (3.49 Å) atomic contacts between two molecules occurred.

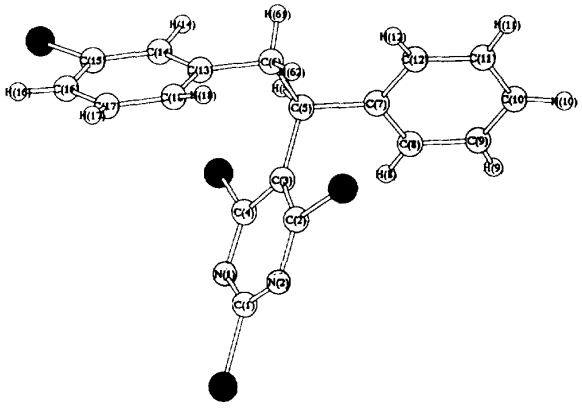

Fig 2. MolDraw molecular structure and atomic numbering of 5-[1-phenyl-2-(3-chlorophenyl)ethyl]-2,4,6-trichloropyrimidine **1** with C(18)-C(13)-C(6)-C(5) dihedral = 111.3°.