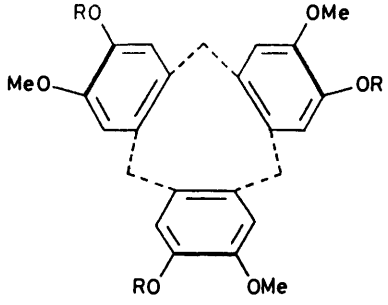
Synthesis and Absolute Configuration of Chiral (C_3) Cyclotriveratrylene Derivatives. Crystal Structure of (*M*)-(−)-2,7,12-Triethoxy-3,8,13-tris-[(*R*)-1-methoxycarbonylethoxy]-10,15-dihydro-5*H*-tribenzo[*a,d,g*]-cyclononene

By **André Collet,* Jacqueline Gabard,** and **Jean Jacques,** Laboratoire de Chimie organique des Hormones, Collège de France, 11 place Marcelin Berthelot, 75231 Paris Cedex 05, France
Michèle Cesario, Jean Guilhem, and **Claudine Pascard,** Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France

The absolute configuration of chiral C_3-cyclotriveratrylene derivatives has been determined unambiguously as follows. First, the absolute configuration of 2-(2-ethoxy-4-hydroxymethylphenoxy)propionic acid (5b) was established as *R*-(+) by chemical correlations and circular dichroism measurements. Upon treatment with perchloric acid, compound (+)-(5b) leads to the title compound (−)-(3), isolated in 14% yield, m.p. 127 °C, $[\alpha]_D^{25}$ −16.1° ($CHCl_3$). The crystal and molecular structure of (−)-(3) have been determined by single crystal *X*-ray analysis: orthorhombic, a = 23.428, b = 22.165, c = 15.145 Å; space group $P2_12_12_1$, Z = 8. The *M* absolute configuration has been ascribed to (−)-(3), on the basis of internal comparison with groups −CH(Me)CO_2Me whose absolute stereochemistry is derived from that of (+)-(5b). Seven chiral C_3-cyclotriveratrylene derivatives have been chemically related to (*M*)-(−)-(3). The absolute configurations so established are identical with those deduced independently from an exciton analysis of circular dichroism spectra.

CYCLOTRIVERATRYLENE [1,2] (1) (CTV) is a rigid molecule which exists as a single 'crown' conformer (C_{3v} symmetry), the activation free energy for interconversion of the nine-membered ring being [3] $\Delta G^{\ddagger}_{25}$ 26.5 kcal mol^{-1}. Several of its derivatives or analogues [4] exhibit a similar conformational behaviour and, whenever appropriately substituted, may be resolved into optically stable enantiomers [3,5,6] (Scheme 1). We have previously described such optically active compounds, of type (2), having C_3 symmetry.[3,6] We now report the synthesis of other chiral (C_3)-analogues, and the determination by single-crystal *X*-ray analysis of the structure of compound (−)-(3), which incorporates the group R* = −*CH(Me)CO_2Me of known absolute configuration as an internal reference.



(1) R=Me [achiral]
(*P*)-(−)-(2a) R=H
(*M*)-(−)-(2b) R=Ac
(*M*)-(−)-(2c) R=CD_3

The perspective view of (−)-(3) (Figure 1) displays the actual absolute stereochemistry which was found for this compound. The latter is represented conventionally in Scheme 2, and should be identified by the *M* stereoconformational descriptor (see Appendix). All other (C_3)-cyclotriveratrylene analogues described in this paper were chemically related to (*M*)-(−)-(3); the stereoformulae shown indicate the absolute configurations derived from these correlations. These unambiguous results confirm an independent assignment of stereochemistry, based on an exciton analysis of the circular dichroism spectra, which we discuss elsewhere.[7]

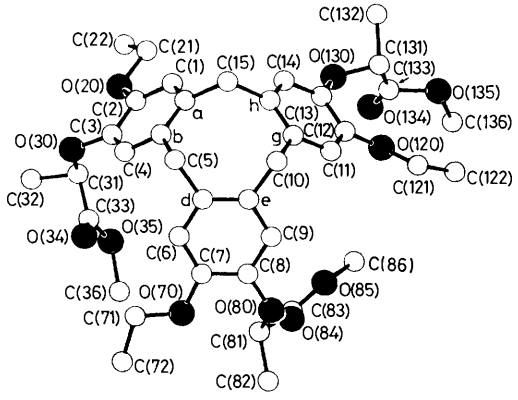
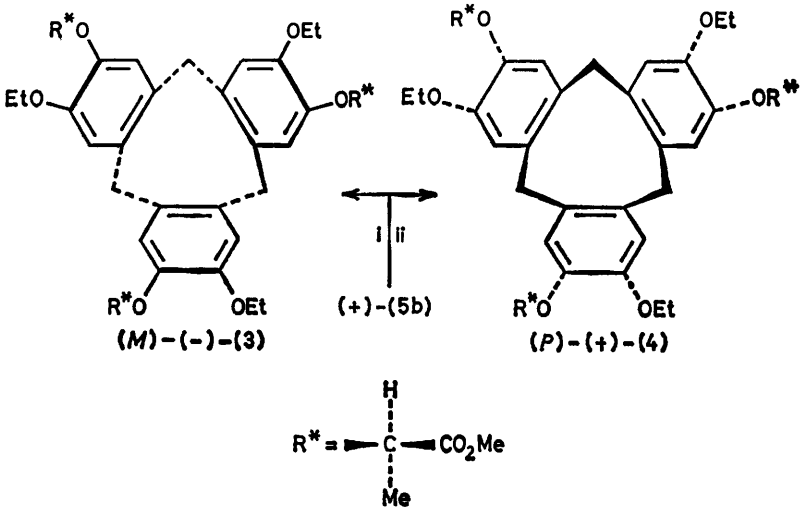


FIGURE 1 Perspective view of (*M*)-(−)-(3) showing its absolute configuration and atomic numbering

Syntheses and Chemical Correlations.—We followed the synthetic route described earlier,[6] starting from ethylvanillyl alcohol (instead of vanillyl alcohol), which was condensed with 2-bromopropionic acid to give racemic 2-(2-ethoxy-4-hydroxymethylphenoxy)propionic acid, (±)-(5b). Resolution with quinine afforded optically pure (+)-(5b), having the *R* absolute configuration, as shown below. Reaction of this substituted benzylic alcohol in 65% perchloric acid, followed by esterification of the resulting organic material with diazomethane afforded a complex mixture of polymers from which the cyclic diastereoisomeric triesters (−)-(3) (m.p. 127 °C) and (+)-(4) (m.p. 130 °C) were isolated in 14 and 3% yields,

respectively (Scheme 1). These values reflect more the difficulty of the chromatographic isolation of (4) than the actual ratio (3) : (4) in the original mixture, which is estimated to *ca.* 2 : 1 (n.m.r.). Taking into account the amount of uncompletely separated fractions, the total yield of trimeric products (3) + (4) is of the order of 30%. In 60% perchloric acid, cyclotriveratrylene is formed from veratryl alcohol in 35% yield.[8]



SCHEME 1 *Reagents*: i, $HClO_4$; ii, CH_2N_2

Compounds (−)-(3) and (+)-(4) exhibit ^1H n.m.r. spectra consistent with a cyclotriveratrylene-like structure having a locked crown conformation; the latter is characterized by the AB quartet of the methylene bridges (Table 1). These diastereoisomers only differ by the *configuration M* or *P*, respectively, of the crown structure. As a consequence, their circular dichroism (c.d.) spectra show a nearly mirror-image relationship [7] in the range 225—310 nm (Figure 2). These c.d. spectra

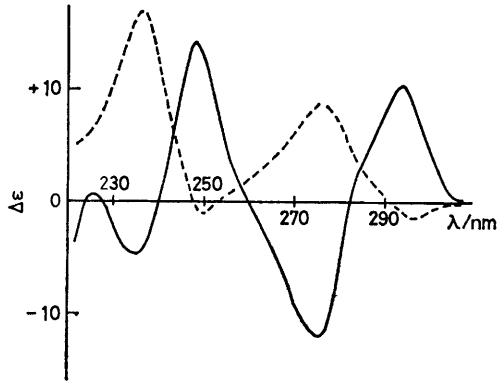
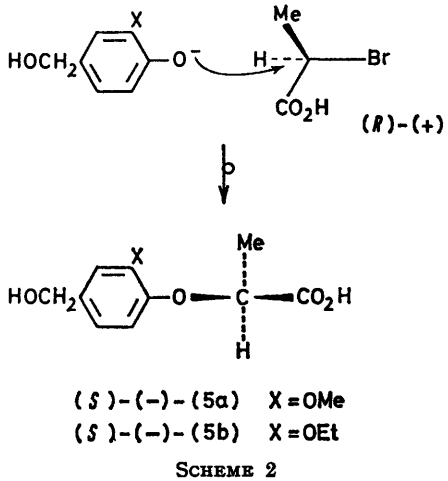


FIGURE 2 C.d. spectra in methanol solution: ——, (*M*)-(−)-(3); — — —, (*P*)-(+)-(4)

consist, for each compound (−)-(3) and (+)-(4), of two exciton patterns centred at *ca.* 246 and 285 nm, connected with the ^1L_a and ^1L_b transitions of the aryl chromophores, respectively.

The absolute configuration of the reference group R* in (−)-(3) was established principally on the basis of the stereochemical correlation described in Scheme 2. Reaction of sodium 2-ethoxy-4-hydroxymethylphenoxide with (*R*)-(+)-2-bromopropionic acid [9] [67% enantiomeric excess (e.e.)] in ethanol solution afforded (−)-(5b) (59% e.e.). Assuming an S_N2 process led to the assignment of *S*-configuration to (−)-(5b). A similar relation obtained for (5a), which has been involved [3,6] in the synthesis of (2a—c). Fredga *et al.*[10] have shown that the sign of the ^1L_b Cotton effect of configurationally related 2-phenoxypropionic acids is independent of the substitution pattern of the benzene ring, and that all members of the *R*-series should display a positive ^1L_b



SCHEME 2

c.d. band at 250—300 nm. This feature is observed in the c.d. spectra of (+)-(5a) and (+)-(5b) (Figure 3), which are nearly identical to that of (*R*)-(+)-2-(2-methoxyphenoxy)propionic acid [10] (5c), given for comparison. Additionally, it was observed that (+)-(5a), when dissolved into a nematic mesophase, induced the formation of a right-handed cholesteric phase, as did

(*R*)-(+)-2-phenoxypropionic acid under the same experimental conditions.[11]

We conclude from this set of independent experiments that (+)-(5a) and (+)-(5b) have *R*-configuration, which, in turn, gives the absolute stereochemistry of group R*.

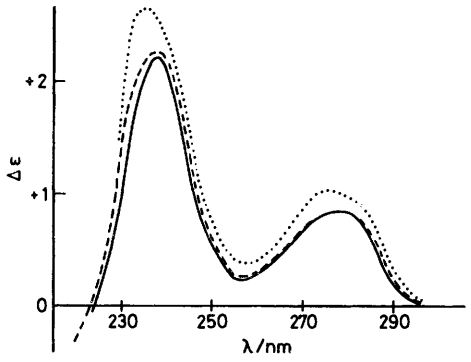


FIGURE 3 C.d. spectra of substituted (*R*)-2-phenoxypropionic acids in methanol solution: —— (+)-(5a); — — —, (+)-(5b); · · · · (+)-(5c)

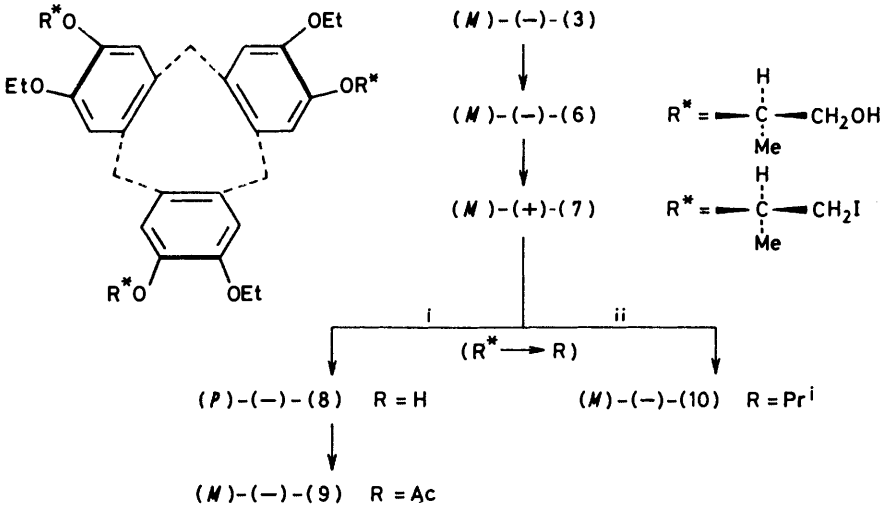
Removal of the chiral groups R* in the diastereoisomer (*M*)-(−)-(3) to obtain the enantiomers (8)—(10) involved the sequence of transformations summarized in Scheme 3. In order to prevent ring inversion, which is likely to occur even on moderate heating, all reactions and work-up were carried out at or below room temperature. The following racemization half-times, measured on (+)-(2c), are indicative of the resistance of the nine-membered ring to inversion:[3] $t_{\frac{1}{2}}$ *ca.* 36 days, 36 h, and 3 min at 20, 50, and 100 °C respectively.

Lithium aluminium hydride reduction of the pure diastereoisomer (*M*)-(−)-(3) in tetrahydrofuran (THF) (0 °C) afforded the triol (*M*)-(−)-(6), $[\alpha]_D^{25}$ −69°;* esterification with methanesulphonyl chloride (−20 °C), followed by reaction of the trimethanesulphonate with magnesium iodide–ether (20 °C) gave the tri-iodide (*M*)-(+)-(7), $[\alpha]_D^{25}$ +76°, in 78% overall yield from (−)-(3). It seems worth mentioning that $MgI_2 \cdot Et_2O$ is a very mild and efficient reagent for the conversion of primary methanesulphonates or toluene-*p*-sulphonates into iodides at room temperature.[12] ^{1}H N.m.r. spectral data for (*M*)-(−)-(6) and (*M*)-(+)-(7) are assembled in Table 1. No evidence for the presence of the *P*-diastereoisomer was found in the n.m.r. spectrum of (+)-(7), at a precision level better than 5%.

The three chiral groups –*CH(Me)CH_2I in (*M*)-(+)-(7) were finally removed and transformed into achiral substituents R as follows: (i) β-elimination with zinc powder in acetic acid (20 °C) furnished the triphenol (*P*)-(−)-(8), $[\alpha]_D^{25}$ −262°, which formed a triacetate, (*M*)-(−)-(9), $[\alpha]_D^{25}$ −217°; (ii) reduction of the iodide groups with sodium borohydride in hexamethylphosphoramide (HMPA)[13] (20 °C) afforded the tri-isopropyl compound (*M*)-(−)-(10), $[\alpha]_D^{25}$ −47°. Considering the above mentioned diastereoisomeric purity of (*M*)-(+)-(7), it may be expected that the enantiomeric purities of (8), (9), and (10) are within the range 90—100%; for the moment we have no direct criteria of enantiomeric purity for these compounds.

Compounds (2a—c) were connected to (*P*)-(−)-(8) as shown in Scheme 4. Methylation of the triphenol (*P*)-(−)-(8), and ethylation of the triphenol (+)-(2a) led to the same product, (*P*)-(−)-(11), having $[\alpha]_{578}^{25}$ −21°. The absolute configuration of (2a) is thus established as (*M*)-(+) [or (*P*)-(−)]; those of the other compounds, (*M*)-(−)-(2b) and (*M*)-(−)-(2c), follow.

As is apparent from the data assembled in Tables 1 and 2, the ^{1}H and ^{13}C n.m.r. spectra of the enantiomers (8)—(11) resemble closely that of cyclotriveratrylene (1). However, owing to the change of symmetry group, from C_{3v} to C_3, the six equivalent aromatic hydrogens in (1), which give a singlet at 6.82 p.p.m., are split into two



SCHEME 3 *Reagents*: i, Zn–AcOH; ii, $NaBH_4$

* All specific rotations of cyclotriveratrylene derivatives were measured in chloroform solution.

TABLE 1

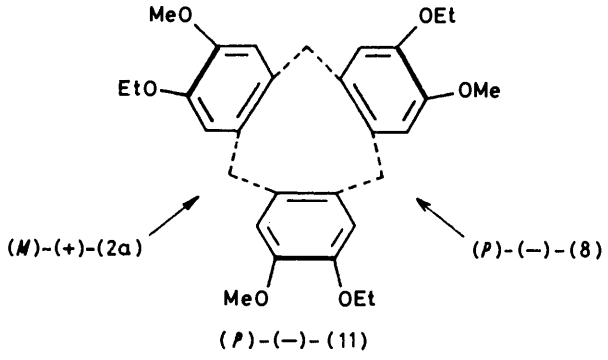
^{1}H N.m.r. spectral data [a] (δ from internal Me_4Si in $CDCl_3$ solution)

	Aromatic s		H_a † d ⟷ H_e d		O(Me, Et, R, R*)
CTV (1)	6.82		4.75	3.54	3.82 (s)
(*M*)-(−)-(3)	6.99	6.82	4.63	3.48	3.66 (s), 4.56 (q) ⟷ 1.56 (d), 4.09 (q) ⟷ 1.40 (t)
(*P*)-(+)-(4)	6.88	6.80	4.64	3.46	3.68 (s), 4.70 (q) ⟷ 1.54 (d), 4.07 (m) ⟷ 1.38 (t)
(*M*)-(−)-(6)	6.94	6.82	4.70	3.50	3.9—4.3 (m), 3.5—3.7 (m), 1.40 (t), 1.29 (d)
(*M*)-(+)-(7)	6.97	6.85	4.70	3.52	3.9—4.2 (m), 3.3 (m), 1.40 (t), 1.43 (d)
(*P*)-(−)-(8)	6.86	6.78	4.69	3.47	4.07 (q) ⟷ 1.39 (t), OH 5.4
(*M*)-(−)-(9)	6.96	6.85	4.70	3.52	3.93 (q) ⟷ 1.34 (t), 2.26 (s)
(*M*)-(−)-(10)	6.86	6.82	4.70	3.48	4.37 (m) ⟷ 1.30 (d), 4.01 (q) ⟷ 1.37 (t)
(*P*)-(−)-(11)	6.83	6.81	4.75	3.51	3.81 (s), 4.03 (q) ⟷ 1.40 (t)

[a] s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively; ⟷ indicates coupling.

† AB (nearly AX) quartet with ^3J *ca.* 14 Hz; H_a and H_e correspond to the *quasi*-axial (inner) and *quasi*-equatorial (outer) hydrogens of the methylene bridges.

sets of three equivalent hydrogens in (8)—(11), thus giving rise to two peaks. The same holds true in the proton-decoupled ^{13}C spectra; the (3 × 6) aromatic carbons, which appear as three resonances in (1), are now split into six singlets in (8)—(11).



SCHEME 4

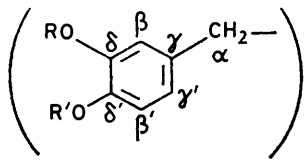
Crystal Structure of Compound (M)-(−)-(3).—The umbrella shape of the (*M*)-(−)-(3) molecule and the crown conformation of the nine-membered ring are visible on the perspective view in Figure 1. The torsion angles reported in Table 6 should be compared with the corresponding values for CTV given in ref. 2. In fact, if the side-chains are not considered, the two independent molecules (*1*) and (*2*) of (−)-(3) are nearly identical with respect to angles and distances. They are very close to a noncrystallographic C_3 symmetry, as shown by the common value (112 ± 4°) of the angles at C(5), C(10), and C(15), and by those of the corresponding sets of torsion angles (Table 6). In contrast, the C_{3v} molecular symmetry is not respected in the crystal of (1), one of the phenyl rings being pushed toward the centre of the molecular cavity; a pseudo-mirror plane, passing through the centre of this phenyl ring and the opposite methylene bridge obtains.

In (−)-(3), the ethoxy-side-chains are fully extended, lying approximately in the planes of the corresponding benzene rings; the deviation from planarity is smaller than 23° in all cases but one (Table 6). The preferred crystal state conformation of methoxybenzene derivatives is actually planar.[14] The 1-methoxycarbonyl-ethoxy-chains adopt several conformations, which differ by the orientation of the ArO–CH bonds, either downwards or upwards with respect to the plane defined by O(30)–O(80)–O(130) (see Figure 1). The carbonyl oxygens generally eclipse the ArO oxygens, except in one case where it is rotated by 180° from this position.

The molecular geometry of the tribenzocyclononatriene system may be defined by the angles (Φ) between

TABLE 2

^{13}C N.m.r. spectral data (δ from internal Me_4Si in $CDCl_3$ solution)



	Methylene	Aromatic						
	α	β, β'		γ, γ'		δ, δ'		R, R'
CTV (1)	36.3	113.2		131.7		147.7		56.0 (OCH_3)
(*P*)-(−)-(8)	36.3	113.3	115.4	131.2	132.5	144.3	144.5	64.7 (OCH_2), 14.9 (CH_3)
(*M*)-(−)-(9)	36.5	115.5	123.8	131.5	137.8	138.9	149.1	64.7 (OCH_2), 14.8 (CH_3), 20.6 (CH_3), 169 (CO)
(*M*)-(−)-(10)	36.5	116.3	119.9	132.3	133.3	146.5	148.9	64.8 (OCH_2), 15 (CH_3) 72.5 (OCH), 22.2, 22.4 (2 × CH_3)
(*P*)-(−)-(11)	36.5	114.1	115.6	132.0	132.2	(147.5	148.5) [a]	56.2 (OCH_3) 64.7 (OCH_2), 14.8 (CH_3)

[a] Uncertainty owing to an unfavourable signal-to-noise ratio.

TABLE 3

Atomic co-ordinates ($\times 10^4$) for molecules (*1*) and (*2*) of compound (*M*)-(−)-(3). The mean values of e.s.d.s for *x*, *y*, and *z* are 0.0012, 0.0013, and 0.0020, respectively

	(1)			(2)		
	x	*y*	*z*	*x*	*y*	*z*
C(1)	10 311	8 059	7 466	10 884	12 370	10 087
C(2)	10 061	8 621	7 311	11 302	12 750	9 742
C(3)	9 818	8 943	8 007	11 561	13 181	10 283
C(4)	9 825	8 704	8 859	11 401	13 230	11 167
b	10 076	8 143	9 015	10 983	12 849	11 511
a	10 318	7 821	8 318	10 724	12 419	10 971
C(6)	8 963	7 985	10 292	10 585	14 022	12 625
C(7)	8 409	7 759	10 369	10 208	14 508	12 657
C(8)	8 305	7 146	10 245	9 620	14 406	12 676
C(9)	8 755	6 757	10 045	9 410	13 817	12 662
e	9 309	6 982	9 968	9 788	13 331	12 630
d	9 413	7 596	10 092	10 375	13 433	12 611
C(11)	9 415	5 935	8 414	8 805	12 798	11 406
C(12)	9 396	5 807	7 512	8 591	12 689	10 561
C(13)	9 754	6 115	6 930	8 905	12 345	9 963
C(14)	10 131	6 550	7 250	9 433	12 108	10 210
h	10 150	6 678	8 151	9 647	12 216	11 055
g	9 793	6 370	8 733	9 333	12 561	11 653
C(5)	9 983	7 897	9 946	10 825	12 911	12 496
C(10)	9 759	6 529	9 747	9 501	12 715	12 626
C(15)	10 580	7 174	8 451	10 215	11 989	11 257
O(20)	10 026	8 917	6 486	11 470	12 791	8 928
C(21)	10 275	8 550	5 722	11 147	12 414	8 309
C(22)	10 128	8 947	4 887	11 446	12 549	7 344
O(70)	7 914	8 106	10 539	10 429	15 121	12 616
C(71)	8 023	8 715	10 837	11 030	15 217	12 838
C(72)	7 432	8 985	11 005	11 063	15 896	12 801
O(120)	9 004	5 390	7 178	8 117	12 991	10 212
C(121)	8 882	4 861	7 752	7 694	13 267	10 842
C(122)	8 529	4 451	7 104	7 235	13 525	10 327
O(30)	9 629	9 541	7 914	12 056	13 499	10 046
C(31)	9 113	9 575	7 445	11 932	13 986	9 477
C(32)	9 024	10 258	7 223	12 484	14 249	9 113
C(33)	8 650	9 456	8 128	11 621	14 510	10 132
O(34)	8 670	9 455	8 951	11 826	14 597	10 850
O(35)	8 169	9 257	7 733	11 264	14 810	9 672
C(36)	7 626	9 185	8 373	10 984	15 313	10 203
O(80)	7 777	6 899	10 362	9 273	14 911	12 771
C(81)	7 328	7 175	9 890	9 212	15 257	11 990
C(82)	6 770	7 105	10 429	9 039	15 954	12 349
C(83)	7 318	6 777	9 039	8 665	15 001	11 499
O(84)	6 990	6 892	8 357	8 374	14 659	11 785
O(85)	7 633	6 290	8 854	8 679	15 202	10 705
C(86)	7 599	5 953	7 891	8 093	15 074	10 292
O(130)	9 725	6 027	5 995	8 770	12 240	9 086
C(131)	9 745	5 408	5 691	8 196	12 054	8 941
C(132)	10 257	5 413	4 957	8 204	11 476	8 498
C(133)	9 238	5 385	5 291	7 945	12 326	8 183
O(134)	8 902	5 727	4 945	8 210	12 881	7 926
O(135)	9 087	4 740	5 074	7 484	12 633	8 215
C(136)	8 449	4 689	4 545	7 218	13 035	7 440

the planes of each phenyl ring and a pseudo-C_3 axis {approximated by a normal to the plane [C(5)–C(10)–C(15)]}, and by the distances (*d*) between the centres of the phenyl rings (Scheme 5). The values of Φ and *d* for (−)-(3) and (1) in the crystal state are assembled in Table 7; the ternary symmetry of (−)-(3) and the severe distortion of (1) are clearly apparent from these data.

Owing to the presence of two independent molecules the packing of (−)-(3) is fairly complex (Figure 4). The density of the crystal (D_c 1.195) is bracketed between that of the benzene–water CTV clathrate (D_c 1.26) and that of unsolvated CTV (calculated as D_c' 1.12 from the data of ref. 2). In fact all the intermolecular contacts in the

TABLE 4

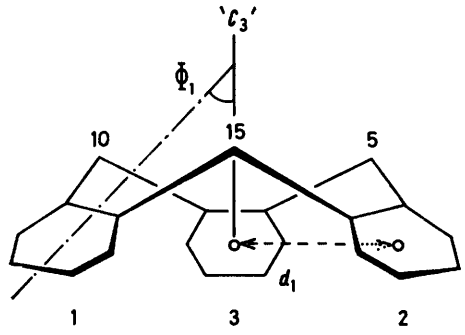
Bond distances (Å) for molecules (*1*) and (*2*) of compound (*M*)-(−)-(3) in the crystal state. Distances for the benzene rings are not reported. The mean value of e.s.d.s is 0.04 Å

	(1)	(2)		(1)	(2)
C(2)–O(20)	1.41	1.30	O(30)–C(31)	1.40	1.41
C(3)–O(30)	1.40	1.40	C(31)–C(32)	1.56	1.52
b–C(5)	1.53	1.54	C(31)–C(33)	1.52	1.69
a–C(15)	1.57	1.59	C(33)–O(34)	1.25	1.21
C(7)–O(70)	1.42	1.45	C(33)–O(35)	1.35	1.27
C(8)–O(80)	1.36	1.39	O(35)–C(36)	1.61	1.52
e–C(10)	1.49	1.52	O(80)–C(81)	1.41	1.42
d–C(5)	1.51	1.57	C(81)–C(82)	1.55	1.69
C(12)–O(120)	1.40	1.40	C(81)–C(83)	1.56	1.59
C(13)–O(130)	1.43	1.38	C(83)–O(84)	1.31	1.11
h–C(15)	1.56	1.46	C(83)–O(85)	1.33	1.28
g–C(10)	1.58	1.56	O(85)–C(86)	1.64	1.54
O(20)–C(21)	1.53	1.46	O(130)–C(131)	1.45	1.42
C(21)–C(22)	1.58	1.65	C(131)–C(132)	1.64	1.45
O(70)–C(71)	1.45	1.46	C(131)–C(133)	1.33	1.42
C(71)–C(72)	1.53	1.51	C(133)–O(134)	1.21	1.43
O(120)–C(121)	1.49	1.50	C(133)–O(135)	1.51	1.28
C(121)–C(122)	1.57	1.45	O(135)–C(136)	1.70	1.60

TABLE 5

Angles (°) for the molecules (*1*) and (*2*) of compound (*M*)-(−)-(3) in the crystal state. Angles for the benzene rings are not reported. The mean value for e.s.d.s is 3°

	(1)	(2)
C(3)–C(2)–O(20)	114	112
C(2)–C(3)–O(30)	122	124
a–b–C(5)	125	122
b–a–C(15)	122	125
C(8)–C(7)–O(70)	114	120
C(7)–C(8)–O(80)	122	117
d–e–C(10)	124	126
e–d–C(5)	124	123
C(13)–C(12)–O(120)	119	116
C(12)–C(13)–O(130)	122	126
g–h–C(15)	123	122
h–g–C(10)	122	127
b–C(5)–d	115	109
e–C(10)–g	114	108
a–C(15)–h	111	115
C(2)–O(20)–C(21)	114	114
O(20)–C(21)–C(22)	103	104
C(7)–O(70)–C(71)	115	118
O(70)–C(71)–C(72)	105	101
C(12)–O(120)–C(121)	116	118
O(120)–C(121)–C(122)	101	108
C(3)–O(30)–C(31)	112	112
O(30)–C(31)–C(32)	106	110
O(30)–C(31)–C(33)	105	105
C(32)–C(31)–C(33)	103	108
C(31)–C(33)–O(34)	131	118
C(31)–C(33)–O(35)	111	109
O(34)–C(33)–O(35)	118	132
C(33)–O(35)–C(36)	115	112
C(8)–O(80)–C(81)	116	114
O(80)–C(81)–C(82)	109	105
O(80)–C(81)–C(83)	101	106
C(82)–C(81)–C(83)	111	106
C(81)–C(83)–O(84)	123	124
C(81)–C(83)–O(85)	128	107
O(84)–C(83)–O(85)	108	128
C(83)–O(85)–C(86)	122	107
C(13)–O(130)–C(131)	116	114
O(130)–C(131)–C(132)	104	108
O(130)–C(131)–C(133)	99	113
C(132)–C(131)–C(133)	110	90
C(131)–C(133)–O(134)	139	114
C(131)–C(133)–O(135)	110	123
O(134)–C(133)–O(135)	110	85
C(133)–O(135)–C(136)	112	127



SCHEME 5

crystal structure of (−)-(3) are consistent with van der Waals radii, and no cavities which may accommodate small guest molecules are apparent.

TABLE 6

Torsion angles (°) for both independent molecules (*1*) and (*2*) of compound (−)-(3) in the crystal state. The mean standard deviation is 4°. The sign convention of Klyne and Prelog (see ref. 22) is used

	(*1*)	(*2*)
C(5)–b–a–C(15)	−6	5
C(15)–h–g–C(10)	5	−5
C(10)–e–d–C(5)	5	6
C(1)–C(2)–O(20)–C(21)	2	4
C(2)–O(20)–C(21)–C(22)	175	180
C(2)–C(3)–O(30)–C(31)	75	80
C(3)–O(30)–C(31)–C(33)	83	73
O(30)–C(31)–C(33)–O(35)	−157	−149
C(31)–C(33)–O(35)–C(36)	−173	−177
b–a–C(15)–h	99	93
h–g–C(10)–e	92	96
e–d–C(15)–b	91	94
C(6)–C(7)–O(70)–C(71)	−14	−20
C(7)–O(70)–C(71)–C(72)	182	184
C(7)–C(8)–O(80)–C(81)	55	77
C(8)–O(80)–C(81)–C(83)	93	92
O(80)–C(81)–C(83)–O(85)	3	−165
C(81)–C(83)–O(85)–C(86)	−175	−168
a–C(15)–h–g	−97	−91
g–C(10)–e–d	−99	−96
d–C(5)–b–a	−90	−97
C(11)–C(12)–O(120)–C(121)	−36	−23
C(12)–O(120)–C(121)–C(122)	190	183
C(12)–C(13)–O(130)–C(131)	−51	−48
C(13)–O(130)–C(131)–C(133)	119	139
O(130)–C(131)–C(133)–O(135)	−168	−123
C(131)–C(133)–O(135)–C(136)	−179	170

TABLE 7

Geometry of the cyclotribenzylene ring for compounds (1) and (*M*)-(−)-(3) in the crystal state [a]

	(1)	(*M*)-(−)-(3)	
		(*1*)	(*2*)
Φ_1	43.5	46	41.5
Φ_2	31	42	46
Φ_3	44.5	41.5	41
d_1	4.98	4.72	4.76
d_2	4.67	4.82	4.75
d_3	4.93	4.83	4.83

[a] Angles Φ in (°); distances *d* in Å.

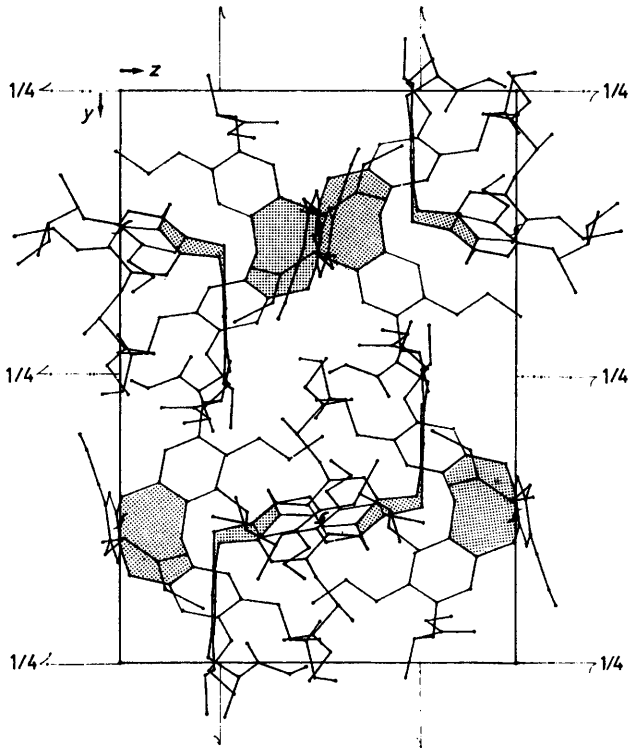


FIGURE 4 A view of the molecular packing of (−)-(3) along *a*

EXPERIMENTAL

Melting points were taken on a Kofler Hotbench apparatus or recorded, with simultaneous check of purity, on a Perkin-Elmer DSC 2 microcalorimeter. Rotations were measured on a Perkin-Elmer 241 automatic polarimeter. Circular dichroism spectra were recorded on a Jouan-Dichrograph III instrument. ^{1}H- and ^{13}C-N.m.r. spectra were run on Perkin-Elmer R 32 and Varian FT 80A instruments. All compounds studied gave routine i.r. spectra consistent with their structures, on a Perkin-Elmer 297 spectrometer (for Nujol mulls).

3-Ethoxy-4-hydroxybenzyl Alcohol (*Ethylvanillyl Alcohol*).—Ethylvanilline was reduced by sodium borohydride in 1.1M sodium hydroxide solution at 10—20 °C, for 30 min, by the method of Brink [15] to afford the crude alcohol (80—85%), m.p. 62—63 °C (lit.,[15] 63 °C), which was used without further purification.

(±)-*2-(2-Ethoxy-4-hydroxymethylphenoxy)propionic Acid* (±)-(5b).—2-Bromopropionic acid (10 g, 0 065 mol) dissolved in 95% ethanol (40 ml) was exactly neutralized by addition of aqueous 12M-sodium hydroxide (theory: 5.45 ml; found: 5.32). To this solution was added ethylvanillyl alcohol (11 g, 0.065 mol) and further 12M-NaOH (5.32 ml); the mixture was refluxed under nitrogen for 7 h. Water was added and ethanol was stripped off under vacuum; acidification with 6N-HCl (25 ml) and extraction with ether afforded a mixture of acidic and phenolic material. The latter was eliminated by redissolution of the mixture in 15% aqueous Na_2CO_3 and extraction with ether. Finally, the aqueous layer was acidified and extracted with ether, affording after usual work-up the acid (±)-(5b) (13 g, 88%), as a viscous syrup which was very difficult to crystallize and whose purity was checked by its n.m.r.

spectrum. The acid formed a *dicyclohexylamine salt* from ethyl acetate, m.p. 150 °C (solvated) (Found: C, 66.9; H, 9.2. $C_{12}H_{16}O_5 \cdot C_{12}H_{23}N \cdot 0.5AcOEt$ requires C, 67.1; H, 9.3%).

Resolution of (5b). (R)-(+)-2-(2-*Ethoxy*-4-*hydroxymethylphenoxy*)*propionic Acid*.—Racemic (5b) (12.7 g, 0.053 mol) and quinine (18 g, 0.055 mol) were mixed together in boiling ethyl acetate (100 ml), and the solution was allowed to crystallize at 0—5 °C. The crude salt was recrystallized twice from ethyl acetate to afford the pure salt [(+)-(5b)–quinine] (9.1 g), m.p. *ca.* 100—110 °C (solvated). A sample of this salt was decomposed with HCl, followed by extraction of (5b) with ethyl acetate to afford a viscous syrup, $[\alpha]_D^{25}$ +44.5°, $[\alpha]_{578}^{25}$ +46.6° (*c*, 1 in 95% ethanol). This acid exhibited a ^{1}H n.m.r. spectrum identical to that of racemic (5b), and formed a *dicyclohexylamine salt*, m.p. 138 °C (from ethyl acetate) (Found: C, 68.3; H, 9.2. $C_{12}H_{16}O_5 \cdot C_{12}H_{23}N$ requires C, 68.4; H, 9.3%) c.d. spectrum of (+)-(5b) (in methanol, *c* 1.5 g l^{-1}): $\lambda_{max.}$ ($\Delta\varepsilon$)238 (+2.3) and 278 nm (+0.86).

The quinine salt may be decomposed conveniently with ion-exchange resins. The following procedure is typical. The salt (8.5 g) was dissolved in methanol–water (85 ml; 7 : 3 v/v) and stirred for 30 min with Dowex 50X2 cation-exchange resin (H^+ form; 17 g dry weight). The resin was collected by filtration and washed with methanol, and the combined filtrates were evaporated to dryness to afford the acid (+)-(5b) (3.1 g), $[\alpha]_D^{25}$ +44.1° (*c*, 0.8 in 95% ethanol); the acid was contaminated with *ca.* 5% of its methyl ester (n.m.r.) and was used without further purification for the trimerization step.

Resolution of (5a). (R)-(+)- *and* (S)-(−)-2-(2-*Methoxy*-4-*hydroxymethylphenoxy*)*propionic Acid*.—Racemic (5a) was obtained as follows. To a stirred solution of vanillyl alcohol (20.3 g) and 2-bromopropionic acid (21 g) in ethanol (65 ml) was added dropwise with cooling a solution of NaOH (10.9 g) in H_2O (20 ml). The resulting mixture was set aside for 7 days at room temperature under nitrogen. Water was added and ethanol evaporated off. Upon acidification, the acid (5a) crystallized (25.1 g 84%), m.p. 134 °C.

This acid (25 g, 0.11 mol) was mixed with quinine (36 g, 0.11 mol) in boiling ethyl acetate (600 ml). After 3 h a salt (A) (37.8 g) was collected, and recrystallized from isopropyl alcohol at room temperature overnight to give the pure salt [(+)-(5a)–quinine] (25.2 g). The latter was decomposed by HCl, and (+)-(5a) was extracted with ethyl acetate, yielding a product (7.3 g) having $[\alpha]_{578}^{25}$ +42° (*c*, 0.9 in 95% ethanol), m.p. 150 °C.

The mother-liquors of the least soluble salt (A) were evaporated to dryness and decomposed by HCl as above, affording impure (−)-(5a) (7.5 g), $[\alpha]_{578}^{25}$ −33° (*c*, 1.3 in 95% ethanol), which corresponds to 78% enantiomeric excess (e.e). Owing to a favourable phase diagram, recrystallization of this partially resolved product in acetic acid yielded optically pure (−)-(5a) (5.1 g), $[\alpha]_{578}^{25}$ −42° (*c*, 0.9 in 95% ethanol), m.p. 150 °C; c.d. spectrum of (+)-(5a) (in methanol, *c* 0.6 g l^{-1}: $\lambda_{max.}$ ($\Delta\varepsilon$) 238 (+2.2) and 278 nm (+0.88).

(*R*)-(+)-*Ethyl* 2-*Bromopropionate*.—This compound was prepared by the method of Walker [9a] by reaction of (*S*)-(−)-ethyl lactate, $[\alpha]_D^{25}$ −8.9 (neat; *l*, 1 dm), with PBr_5 in chloroform solution. Distillation (b.p. 55—57 °C at 20 mmHg) gave the (+)-bromoester (48%), $[\alpha]_D^{22}$ +37.5, $[\alpha]_{578}^{22}$ +39.4° (neat; *l*, 1 dm). Determination of enantiomeric purity was carried out by ^{1}H n.m.r. spectroscopy using Eu(hfbc)$_3$ in CCl_4–C_6D_{12} (10 : 1 v/v). Integration of the secondary methyl peaks, at a separation $\Delta\Delta\delta$ *ca.* 0.2 p.p.m., indicated an e.e. of 68 ± 3%; this value corresponds to calculated maximum rotations $[\alpha]_D^{22}$ 55 ± 2°, $[\alpha]_{578}^{22}$ 58 ± 2° (neat; *l*, 1 dm). The maximum experimental value reported so far is $[\alpha]_{578}^{24}$ 55.5° (neat; *l*, 1 dm).[9b]

Absolute Configuration of (5b).—(*R*)-(+)-Ethyl 2-bromopropionate (0.9 g, 0.005 mol; 68% e.e.) was dissolved in ethanol (4 ml) and saponified at room temperature by adding dropwise 10M-NaOH solution in the presence of phenolphthalein; *ca.* 0.5 ml NaOH were consumed. To the resulting sodium 2-bromopropionate solution was added ethylvanillyl alcohol (0.84 g, 0.005 mol) and further 10M-NaOH (0.5 ml). The mixture was refluxed for 7 h and isolated as described for the synthesis of racemic (5b), to give (−)-(5b), $[\alpha]_{578}^{25}$ −27.6° (*c*, 1.1 in 95% ethanol), e.e. 59%; the compound exhibited an n.m.r. spectrum identical to that of racemic (5b).

Absolute Configuration of (5a).—(*R*)-(+)-Ethyl 2-bromopropionate and vanillyl alcohol afforded similarly (−)-(5a), 50% e.e., which was recrystallized from ethyl acetate to give optically pure (−)-(5a), $[\alpha]_{578}^{25}$ −41.5° (*c*, 1.2 in 95% ethanol), m.p. 150 °C.

Trimerization of (*R*)-(+)-(5b). 2,7,12-*Triethoxy*-3,8,13-*tris*-[(R)-1-*methoxycarbonylethoxy*]-10,15-*dihydro*-5H-*tribenzo*[a,d,g]*cyclononene* (M)-(−)-(3) *and* (P)-(+)-(4).—A solution of (*R*)-(+)-(5b) (3.1 g) in 1M-NaOH (13 ml) was added dropwise (30 min) with energetic stirring into 65% perchloric acid (100 ml). The dark purple suspension obtained was stirred for a further 30 min and then poured into water (1 l) and set aside for 2 h. The suspension of tiny particles was collected on a Büchner funnel, washed with water, and dried, giving a solid (2.8 g). Extraction of the mother-liquors with ethyl acetate afforded a further 0.2 g of material. The crops were combined in chloroform and the resulting suspension was treated with an excess of ethereal diazomethane, until complete esterification had occurred. The resulting product was chromatographed on silica gel (100 g; Merck Kieselgel 60, 230—400 mesh), using ethyl acetate–hexane (35 : 65, v/v) as the eluant.

The first fractions (560 mg) consisted of nearly pure (−)-(3); crystallization from ethanol (with brief and moderate heating) afforded the pure *triester* (0.44 g, 14%), m.p. 127 °C, $[\alpha]_D^{25}$ −16.1° (*c*, 0.5 in chloroform) (Found: C, 65.9. H, 6.7. $C_{39}H_{48}O_{12}$ requires C, 66.1; H, 6.8%).

The fractions eluted immediately thereafter were enriched in (+)-(4); of these, 180 mg of fairly pure product were collected. Crystallization from ethanol gave pure (+)-(4) (83 mg, 3%), m.p. 130 °C, $[\alpha]_D^{25}$ +115° (*c*, 0.3 in chloroform).

Both samples of (−)-(3) and (+)-(4) isolated were diastereoisomerically pure (^{1}H n.m.r.); c.d. spectra (in ethanol, *c* 0.3 g l^{-1}): $\lambda_{max.}$, ($\Delta\varepsilon$): (*M*)-(−)-(3), 210 (−70), 235 (−4.8), 248 (+14.3), 276 (−12), and 294 (+10.5); (*P*)-(+)-(4), 236 (+17), 250 (−1.1), 276 (+8.8), and 296 (−1.4).

(M)-(−)-2,7,12-*Triethoxy*-3,8,13-*tris*-[(R)-1-*hydroxymethylethoxy*]-10,15-*dihydro*-5H-*tribenzo*[a,d,g]*cyclononene* (M)-(−)-(6).—The triester (−)-(3) (326 mg) in tetrahydrofuran (THF) (3 ml) was added dropwise to a suspension of lithium aluminium hydride (100 mg) in THF (4 ml), stirred and cooled at 0 °C. After having been stirred for 1 h at 20 °C the mixture was hydrolysed with dilute sulphuric acid and the triol was extracted with dichloromethane.

Removal of the solvent under vacuum *without heating* afforded (*M*)-(−)-(6) (281 mg, 98%), homogeneous on t.l.c. [silica gel; chloroform–methanol (93 : 7 v/v) as eluant]. The product was obtained as a glass, and had $[\alpha]_D^{25}$ −69° (*c*, 0 4 in chloroform).

(M)-(+)-2,7,12-*Triethoxy*-3,8,13-*tris*-[(S)-1-*iodomethylethoxy*]-10,15-*dihydro*-5H-*tribenzo*[a,d,g]*cyclononene* (M)-(+)-(7).—The triol (−)-(6) (268 mg) was esterified by methanesulphonyl chloride (0.5 ml) in pyridine (4 ml) for 4 h at −20 °C. The mixture was poured onto ice and the trismethanesulphonate, extracted with dichloromethane, was used without further purification.

Conversion of the trismethanesulphonate into the triiodide (+)-(7) was performed as follows.[12] A solution of magnesium iodide–ether was prepared by reaction of iodine (1 g) with magnesium (0.2 g) in anhydrous ether (20 ml), under nitrogen. The clear solution, separated from unchanged magnesium, was transferred into a 50-ml flask, under nitrogen. To it was added, with stirring, a solution of the preceding trismethanesulphonate in dry dichloromethane (6 ml), which resulted in the immediate formation of a pale yellow precipitate. Stirring was continued until a clear iodine-coloured solution was finally formed [*ca.* 4 h; formation of (+)-(7) was monitored by t.l.c., using pure dichloromethane as eluant]. After the reaction had gone to completion the mixture was poured onto ice and extracted with dichloromethane. The organic layer was washed with water (containing a trace of sodium hydrogensulphite), dried, and evaporated to dryness, without heating. Column filtration over silica gel (20 g; Merck Kieselgel 60, 230—400 mesh) with pure dichloromethane as eluant furnished pure (*M*)-(+)-(7) [342 mg, 78% overall from (−)-(3)], m.p. 131 °C, $[\alpha]_D^{25}$ +76° (*c*, 0.3 in chloroform).

(P)-(−)-2,7,12-*Triethoxy*-3,8,13-*trihydroxy*-10,15-*dihydro*-5H-*tribenzo*[a,d,g]*cyclononene* (*P*)-(−)-(8).—A suspension of the tri-iodide (+)-(7) (200 mg) and zinc powder (2 g) in acetic acid (3 ml) was stirred for 2 h under nitrogen; further zinc (1 g) and acetic acid (3 ml) were added and stirring was continued for 1 h. The mixture was diluted with ethyl acetate and the supernatant solution was separated from the zinc powder and precipitated salts by filtration through a sintered glass Büchner funnel. The filtrate was washed with water and with sodium carbonate solution, dried over sodium sulphate and the solvent was finally removed under vacuum, at 20 °C. The resulting triphenol (−)-(8) (101 mg, 95%) exhibited $[\alpha]_D^{25}$ −249° (*c*, 0.3 in chloroform). T.l.c. on silica-gel [chloroform–methanol (49 : 1 v/v) as eluant] afforded a glass (90 mg), $[\alpha]_D^{25}$ −262° (*c*, 0.3 in chloroform).

(M)-(−)-2,7,12-*Triacetoxy*-3,8,13-*triethoxy*-10,15-*dihydro*-5H-*tribenzo*[a,d,g]*cyclononene* (*M*)-(−)-(9).—The preceding triphenol (−)-(8) (39 mg) was allowed to react with acetic anhydride (0.5 ml) at room temperature overnight. Dilution with water and extraction with ethyl acetate afforded a crude triacetate which was purified by t.l.c. on silica gel [ethyl acetate–hexane (1 : 1 v/v) as eluant]. Crystallization from methanol (no heating) gave the *triacetate* (40 mg) (−)-(9) (80%), m.p. (inst.) 205 °C, $[\alpha]_D^{25}$ −218° (c, 0.1 in chloroform) (Found: C, 68.5; H, 6.4. $C_{33}H_{36}O_9$ requires C, 68.7; H, 6.3%).

(M)-(−)-2,7,12-*Triethoxy*-3,8,13-*tri-isopropoxy*-10,15-*dihydro*-5H-*tribenzo*[a,d,g]*cyclononene* (*M*)-(−)-(10).—To the tri-iodide (+)-(7) (100 mg) dissolved in hexamethylphosphoramide (HMPA) (1.5 ml) was added sodium borohydride (45 mg); the mixture was stirred for 1 h at room temperature.[13] Dilute HCl was added and the product was extracted with ethyl acetate. The organic layer was washed with water containing a trace of sodium hydrogensulphite, dried, and evaporated to dryness at 20 °C. Recrystallization from methanol yielded the *tri-isopropyl compound* (*M*)-(−)-(10) (37 mg, 61%), m.p. 116 °C, $[\alpha]_D^{25}$ −47° (*c*, 0.6 in chloroform); (Found: C, 74.7; H, 8.6. $C_{36}H_{48}O_6$ requires C, 75.0; H, 8.4%).

(P)-(−)-2,7,12-*Triethoxy*-3,8,13-*trimethoxy*-10,15-*dihydro*-5H-*tribenzo*[a,d,g]*cyclononene* (P)-(11).—Attempted methylation of the triphenol (−)-(8) with diazomethane in ether–chloroform for 20 h at 20 °C failed. The following procedure [16] was effective. The triphenol (−)-(8) (39 mg) was dissolved in HMPA (1.5 ml); 25% aqueous NaOH (0.1 ml) was added and the solution was stirred for 5 min. This was followed by addition of methyl iodide (0.1 ml) and stirring of the mixture for 7 h. Similar work-up as for the preceding experiment afforded compound (*P*)-(−)-(11) (36 mg, 83%) which was recrystallized from methanol; m.p. 152, then 166 °C; $[\alpha]_D^{25}$ −20°, $[\alpha]_{578}^{25}$ −21° (*c*, 0.2 in chloroform) (Found: C, 72.7; H, 7.4. $C_{30}H_{36}O_6$ requires C, 73.1; H, 7.4%).

Absolute Configuration of (2a).—The triphenol (+)-(2a), previously described [6] (15 mg), was dissolved in HMPA (1.5 ml) with 25% aqueous NaOH (0.1 ml) and the solution was stirred for 5 min. Ethyl iodide (0.1 ml) was added and the reaction mixture was stirred for 6 h. Work-up as above afforded compound (*P*)-(−)-(11) (5 mg), $[\alpha]_{578}^{25}$ −21° (*c*, 0.2 in chloroform), identical (n.m.r.) with the sample obtained by methylation of (*P*)-(−)-(8) described in the preceding experiment.

Crystal Data for Compound (M)-(−)-(3).—$C_{39}H_{48}O_{12}$, M = 707.8. Orthorhombic, a = 23.428(3), b = 22.165(3), c = 15.145(2) Å, U = 7 864 Å^3, Z = 8, D_c = 1.195; Cu-K_α radiation, λ = 1.5418 Å, μ = 7.40 cm^{-1}; space group $P2_12_12_1$.

The crystal of (*M*)-(−)-(3) used for the *X*-ray structure determination was a colourless prism (0.34 × 0.60 × 0.17 mm^3) obtained from an ethanol solution at room temperature.

Data were collected using the ω–2θ scan technique up to 2θ = 137°, on a Philips PW 1100 four-circle diffractometer, with graphite monochromatized Cu-K_α radiation. Lorentz and polarization corrections were applied to the data, but none for absorption nor extinction.

Scanning data. Scan speed 0.04 deg s^{-1}; scan width 0.80°; number of scans 2; background time 2 × 10 s; number of measured data 5 435; number of independent data above the 3σ(I) level 2 325.

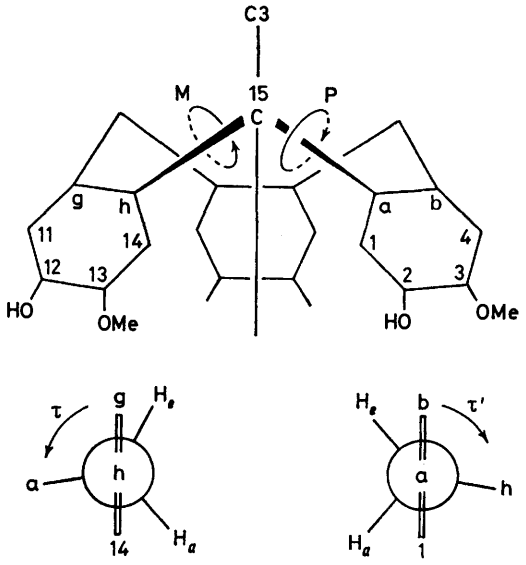
Structure analysis and refinement. The presence of two molecules of (*M*)-(−)-(3) per asymmetric unit requires the location of 102 non-hydrogen atoms. Probably owing to the small number and poor quality of the data, direct methods [17] did not lead to conclusive results. The structure was solved using a Patterson search program,[18] with CTV (1) as the model. At that time, the structure of the inclusion compound of (1) with benzene and water was published by Cerrini *et al.*,[2] and we used their results.* The best fit in a Patterson search gave the position of the central nucleus of one of the molecules. From this point successive Fourier syntheses revealed the whole structure. The atomic co-ordinates were refined by the least-squares

* In fact we had solved the crystal structure of the same clathrate when the paper by Cerrini [2] appeared; both sets of results are in agreement.

method, minimizing the function $\Sigma\ w(|F_o| - |F_c|)^2$. The weighting scheme [$w = 1/\sigma^2(F_o)$] was based on statistical counting errors. A rigid block refinement program [19] was used, on account of the comparatively small number of data with respect to the great number of possible variable parameters. Ideal phenyl groups were introduced (C–C 1.40 Å, angles 120°), and the other atoms were refined as independent. To the isotropic thermal parameters were arbitrarily assigned gradually increasing values, as a function of the distance of the atoms from the nine-membered ring. The atomic scattering factors were taken from ref. 20. The final discrepancy factors are $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o| = 14.5\%$, and $R_w = \Sigma w(|F_o| - |F_c|)/\Sigma w|F_o| = 14.1\%$. The final set of atomic co-ordinates for the two independent molecules is listed in Table 3. Bond distances and angles are assembled in Tables 4 and 5 respectively. Observed and calculated structure factors and isotropic thermal parameters are listed in Supplementary Publication No. SUP 23028 (13 pp.).*

APPENDIX

Professor Prelog transmitted to us the following comments relative to the specification of the absolute configuration of (C_3)-CTV derivatives in accordance with IUPAC



SCHEME 6

rules [21] (adapted from German; notes in brackets are by A. C ; see also ref. 22).

' Enantiomers [of CTV type] are conformers and consequently should be designated according to the *P* or *M* helicity of their preferred conformations. In these compounds, owing to the C_3 axis, there exist three equivalent pairs of conformations around six single bonds [*i.e.*, the CH_2–Ar bonds]. It suffices to consider one of these pairs, for example the conformations around bonds h–C(15) and a–C(15) [Scheme 6]. The selected torsion angles in these conformations are τ [g–h–C(15)–a] and τ' [b–a–C(15)–h] respectively. In the model shown, $\tau = (M)$, and $\tau' = (P)$. Examination of the sequence-rule-preferred path [from C(15)] indicates that, since OCH_3[13] > OH [2], then h > a [and $\tau > \tau'$]; it follows that the enantiomer shown [(+)-(2a)] corresponds to the *M* descriptor.'

We are particularly indebted to Professor V. Prelog for the specification of chirality summarized above. We are grateful to Mrs. Liliane Lacombe for recording and interpretation of n.m.r. spectra.

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REFERENCES

[1] H. Erdtman, F. Haglid, and R. Ryhage, *Acta Chem. Scand.*, 1964 **18**, 1249; B. Miller and B. D. Gesner, *Tetrahedron Lett.*, 1965, 3351; A. S. Lindsey, *J. Chem. Soc.*, 1965, 1685; R. C. Cookson, B. Halton, and I. D. R. Stevens, *J. Chem. Soc. B*, 1968, 767.

[2] S. Cerrini, E. Giglio, F. Mazza, and N. V. Pavel, *Acta Crystallogr., Sect. B*, 1979, **35**, 2605.

[3] A. Collet and J. Gabard, *J. Org. Chem.*, 1980, **45**, 5400.

[4] T. Sato, K. Uno, and M. Kainosho, *J. Chem. Soc., Chem. Commun.*, 1972, 579; T. Sato, T. Akima, and K. Uno, *J. Chem. Soc., Perkin Trans. 1*, 1973, 891; T. Sato and K. Uno, *ibid.*, p. 895.

[5] A. Lüttringhaus and K. C. Peters, *Angew. Chem.*, 1966, **78**, 603; *Angew. Chem. Internat. Edn. Eng.*, 1966, **5**, 593.

[6] A. Collet and J. Jacques, *Tetrahedron Lett.*, 1978, 1265.

[7] A. Collet and G. Gottarelli, *J. Am. Chem. Soc.*, 1981, **103**, 204.

[8] B. Umezawa, O. Hoshino, H. Hara, K. Ohyama, S. Mitsubayashi, and J. Sakakibara *Chem. Pharm. Bull.*, 1969, **17**, 2240.

[9] (*a*) J. W. Walker, *J. Chem. Soc.*, 1895, **67**, 921; (*b*) K. Freudenberg and L. Markert, *Ber.*, 1927, **60**, 2447; (*c*) W. Gerrard and M. J. Richmond, *J. Chem. Soc.*, 1945, 853; W. Gerrard, J. Kenyon, and H. Phillips, *ibid.*, 1937, 153; B. Holmberg, *Ber.*, 1926, **59**, 1558.

[10] A. Fredga, E. Gamstedt, and R. Håkansson, *Chemica Scripta*, 1973, **4**, 145.

[11] J. P. Berthault, Thèse Ingénieur Docteur, Paris, 1977.

[12] P. Place, M. L. Roumestant, and J. Goré, *Bull. Soc. Chim. Fr.*, 1976, 169.

[13] R. O. Hutchins, D. Kandasamy, F. Dux, tert., C. A. Marianoff, D. Rotstein, B. Goldsmith, W. Burgoyne, F. Cistone, J. Dalessandro, and J. Puglis, *J. Org. Chem.*, 1978, **43**, 2259.

[14] G. M. Anderson, tert., P A. Kollman, L. N. Domelsmith, and K. N. Houk, *J. Am. Chem. Soc.*, 1979, 101, 2344.

[15] M. Brink, *Acta Univ. Lund.*, Sect. II, no. 16, p. 1 (*Chem. Abstr.*, 1966, **64**, 9620).

[16] J. E. Shaw and D. C. Kunerth, *J. Org. Chem.*, 1974, **39**, 1968.

[17] (*a*) G. Germain, P. Main, and M. Woolfson, *Acta Crystallogr., Sect. A*, 1971, **27**, 368; (*b*) C. Riche, *ibid.*, 1973, **29**, 133.

[18] B. P. Braun, J. Hornstra, and J. L. Leenhouts, *Philips Research Report*, 1969, **24** 85.

[19] D. André, R. Fourme, and M. Renaud, *Acta Crystallogr., Sect. B*, 1971, **27**, 2371.

[20] ' International Tables for *X*-Ray Crystallography,' vol. IV, Kynoch Press, Birmingham, 1974.

[21] ' IUPAC 1968 Tentative Rules, Section E, Fundamental Stereochemistry ' in *J. Org. Chem.*, 1970, **35**, 2849.

[22] W. Klyne and V. Prelog, *Experientia*, 1960, **16**, 521.

* For details see Notice to Authors No. 7, *J. Chem. Soc., Perkin Trans. 1*, 1980, Index issue.