Optical Activity due to Isotopic Substitution. Synthesis and Absolute Configuration of (+)- and (−)-(C_3)-[$^2H_3$]Cyclotribenzylene ([$^2H_3$][1.1.1.]Orthocyclophane)

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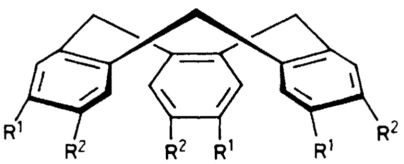
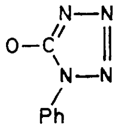
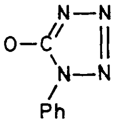
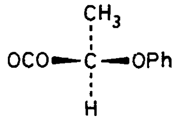
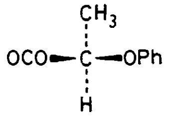
The (+)- and (−)-enantiomers of (C_3)-[$^2H_3$]cyclotribenzylene (or [2,7,12-$^2H_3$]-10,15-dihydro-5*H*-tribenzo[*a,d,g*]cyclononene), whose chirality is due to isotopic substitution, were synthesized from (C_3)-cyclotriguaiacylene, and their absolute configuration was established as *P*-(+) or *M*-(−).

In previous papers,[1] we reported the synthesis and circular dichroism (c.d.) of *M*-(+)-(C_3)-[$^2H_9$]cyclotriveratrylene, (**1**), whose chirality is due to the selective replacement of three OCH_3 by three OCD_3 groups. This compound exhibited the first example of isotopically engendered exciton c.d., the origin of which was tentatively ascribed to the difference in the rotamer populations of Ar–O–CH_3 *vs.* Ar–O–CD_3. In order to investigate the primary effect of an isotope on the chiroptical properties we have now synthesized the enantiomers of (C_3)-[$^2H_3$]cyclotribenzylene, (**3**), where no such conformational changes can occur. To our knowledge there is only one previous example of a compound whose optical activity is due to the presence of a deuterium atom bound directly to an aromatic ring; *S*-(−)-[4-$^2H_1$][2,2]paracyclophane.[2]

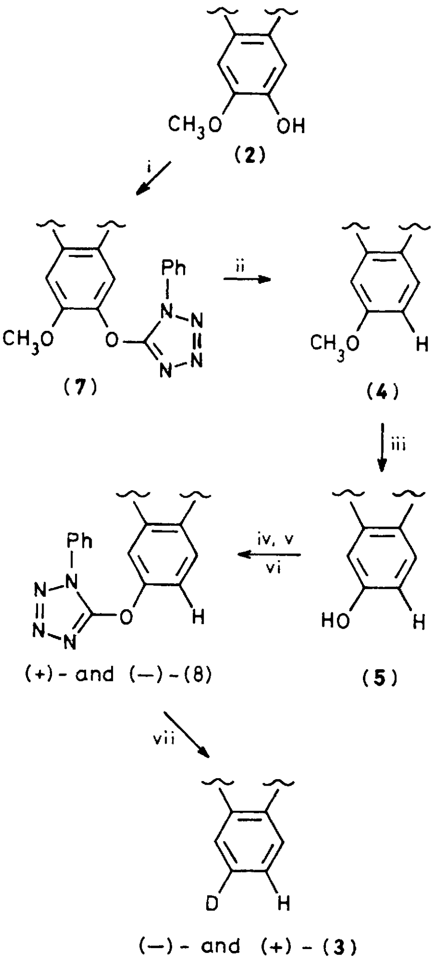
We have previously developed an efficient, multigram route to the racemic triphenol (C_3)-cyclotriguaiacylene[3] (**2**), which was therefore chosen as the starting material for the synthesis of (**3**), as outlined in Scheme 1. As chiral cyclotriveratrylenes may undergo crown inversion[1] even on moderate heating, with a barrier of *ca.* 26.5 kcal mol^{-1} (1 kcal = 4.184 kJ), we were faced with the major problem of performing all the reactions involving optically active material, at temperatures ⩽20 °C to prevent racemization.

We expected that replacement of the three OH groups in (**2**) or (**5**) by hydrogen or deuterium could be effected under mild conditions using the recent catalytic transfer hydrogenation procedure of Johnstone *et al.*[4] Accordingly, (±)-(**2**) was converted into the tris-*O*-(2-phenyltetrazolyl) derivative (±)-(**7**), m.p. *ca.* 255 °C (decomp.), which unfortunately



	R1	R2	
(1)	OCH_3	OCD_3	M-(−)
(2)	OCH_3	OH	P-(−)
(3)	D	H	P-(+)
(4)	OCH_3	H	P-(−)
(5)	OH	H	P-(−)
(6)	H	H	
(7)	OCH_3		M-(−)
(8)		H	P-(−)
(9)	 $OCO-C(CH_3)(H)-OPh$	H	P-(−)
(10)	H	 $OCO-C(CH_3)(H)-OPh$	M-(+)

proved to be totally inert when submitted to hydrogenolysis conditions[4] (10% palladium on charcoal in C_6H_6–EtOH–H_2O, using hydrazine as the H-donor). We therefore turned to an earlier procedure[5] using molecular hydrogen although it was reported to require prolonged reaction time at 35—40 °C under 2—3 atm of hydrogen. Nevertheless, we found that when a dichloromethane–methanol 2:1 mixture was employed as the solvent instead of benzene,[5] hydrogenolysis took place at 15—20 °C and (**7**) afforded the new compound (±)-(C_3)-cyclotrianisylene, (**4**), m.p. 235 °C, in 90% yield.† This compound on reaction with boron tribromide provided the desired triphenol (±)-(**5**), (C_3)-cyclotriphenolene, as a crystalline, high melting solid which was characterized as the triacetate, m.p. 218—222 °C.‡ Both (**4**) and (**5**) adopt the locked 'crown' conformation usually found in this series as revealed by the ^1H and ^{13}C n.m.r. spectra. As a further structural proof (**5**) was converted into the tetrazolyl ether (±)-(**8**) which in turn on hydrogenolysis as above afforded the known hydrocarbon (**6**), cyclotribenzylene, m.p. 278 °C (lit.[6] m.p. 274—276 °C).



Scheme 1. i, Bu^tOK, 1-chloro-2-phenyltetrazole, dimethylformamide (DMF), 95%; ii, H_2 (1 atm), 10% Pd/C, CH_2Cl_2–CH_3OH 2:1, 20 h, 90%; iii, BBr_3, CH_2Cl_2, 0—20 °C, 90%; iv, (+)-2-phenoxypropionic acid, dicyclohexylcarbodiimide, dimethylaminopyridine, DMF, 20 °C, 80%, then t.l.c.; v, $LiAlH_4$ or $LiEt_3BH$, THF, 0 °C; vi, Bu^tOK, 1-chloro-2-phenyltetrazole, DMF; vii, D_2 (1 atm), 10% Pd/C, CD_2Cl_2–CD_3OD 2:1.

We then investigated the optical resolution of (**5**) by formation of diastereoisomeric triesters with various optically active acids; (−)-ω-camphanic acid as well as *N*-toluene-*p*-sulphonyl- and *N*-methanesulphonyl-(*S*)-proline furnished diastereoisomer mixtures which we could not separate by chromatographic or crystallization methods. Finally, (+)-2-phenoxypropionic acid[7] and (±)-(**5**) gave[8] a mixture of (**9**) and (**10**) which could be separated chromatographically on silica gel using dichloromethane as an eluant. The first eluted compound (−)-(**9**) was washed with diethyl ether and exhibited $[\alpha]^{25}_{D}$ −86° (*c* 1, $CHCl_3$) and m.p. 187 °C; the diastereoisomer (+)-(**10**) after recrystallization from ethanol–dichloromethane at 0—20 °C showed $[\alpha]^{25}_{D}$ +195° and m.p. 162 °C. Both (−)-(**9**) and (+)-(**10**) had identical ^1H and ^{13}C n.m.r. spectra. These compounds were cleaved back to resolved (**5**) by reduction with either lithium triethylborohydride or lithium aluminium hydride in tetrahydrofuran at 0 °C. In this way (−)-(**9**) and (+)-(**10**) yielded (−)-(**5**) and (+)-(**5**), respectively, exhibiting $[\alpha]^{25}_{D}$ 186 ± 5° (*c* 0.25, dioxane). Compound (**5**) was assigned *P*-(−) absolute stereo-

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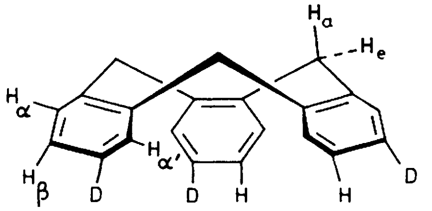
† Satisfactory elemental analyses (C, H) were obtained for (**4**); ^1H n.m.r. spectrum (Me_4Si; $CDCl_3$): δ 3.64 (d, *J* 14 Hz, H_e), 3.73 (s, OCH_3), 4.76 (d, *J* 14 Hz, H_a), 6.56—6.89 (m, 3 × Ar H); ^{13}C n.m.r. spectrum (Me_4Si, $CDCl_3$ + a small quantity of CD_3COCD_3): δ 36.1 (CH_2), 54.8 (OCH_3), 117.7, 115.0, 130.6 (3 × Ar CH), 131.2 and 140.8 (2 × Ar *C*–CH_2), 157.9 p.p.m. (Ar *C*–OCH_3).

‡ Satisfactory elemental analyses were obtained for the triacetate of (**5**); ^1H n.m.r. spectrum of the triacetate (Me_4Si, $CDCl_3$): δ 2.26 (s, $OCOCH_3$), 3.72 (d, *J* 14 Hz, H_e), 4.82 (d, *J* 14 Hz, H_a), 6.77—7.28 (m, 3 × Ar H); ^1H n.m.r. spectrum of (**5**) (Me_4Si, CD_3SOCD_3 + a small quantity of D_2O): δ 3.44 (d, *J* 14 Hz, H_e), 4.67 (d, *J* 14 Hz, H_a), 6.42—7.20 (3 × Ar H).



M-(−) (**3**)

chemistry by chemical connection to P-(−)-(**2**).[9] This was achieved by first converting a sample of (−)-(**2**) (>90% e.e.) into (−)-(**7**), $[\alpha]_D^{25}$ −81° (c 2, $CHCl_3$), which on hydrogenolysis by the same method as described above gave (−)-(**4**), $[\alpha]_D^{25}$ −157° (c 0.25, $CHCl_3$). On the other hand, (+)-(**5**) on methylation (ICH_3, 25% aqueous NaOH, room temp.) afforded (+)-(**4**), $[\alpha]_D^{25}$ +160° (c 0.25, $CHCl_3$).

In order to replace the OH groups in (+)- and (−)-(**5**) by deuterium these triphenols were first transformed into the tetrazolyl ethers M-(+)- and P-(−)-(**8**), respectively, exhibiting $[\alpha]_D^{25}$ +259° and −255° (c 0.25, $CHCl_3$). Deuteriolysis was achieved using 99.4% isotopically enriched deuterium gas in a CD_2Cl_2–CD_3OD 2:1 mixture, under similar conditions to those used for the conversion of (**7**) into (**4**). We used deuteriated solvents to avoid palladium-catalysed hydrogen exchange between deuterium gas and solvent which sometimes occurs in such reactions.[10] The resulting hydrocarbons (**3**) were carefully purified, first by t.l.c. on silica gel (hexane–dichloromethane 7:3 as the eluant), in order to eliminate any residual optically active starting material or incompletely transformed intermediates, then by digestion in pentane at 20 °C. Compound (+)-(**8**) thus gave (−)-(**3**), m.p. 281 °C; this exhibited a relatively high rotation, $[\alpha]_D^{25}$ −2.3°, $[\alpha]_{546}^{25}$ −2.9°, $[\alpha]_{436}^{25}$ −5.2°, and $[\alpha]_{365}^{25}$ −8.9° (c 2, $CHCl_3$, ±5%). Similarly (+)-(**3**), $[\alpha]_{365}^{25}$ +8.7°, was obtained from (−)-(**8**). Assuming that the deuterium atoms have replaced the oxygen groups regioselectively (see below), these reactions also provide the absolute stereochemistry of (**3**), M-(−) or P-(+).

The degree of incorporation and the location of the deuterium atoms in (**3**) were investigated by ^1H n.m.r. and mass spectroscopy. The n.m.r. spectrum (250 MHz) displayed the AX quartet of the methylene bridges *intact* ($CDCl_3$, δ 4.91 and 3.76 for H_a and H_e, respectively, J 13.7 Hz), indicating that no deuterium substitution had taken place at the benzylic positions; this is in contrast with earlier works involving tetralin derivatives.[10] The aromatic part of the spectrum was consistent with the presence of one deuterium atom on each phenyl ring at the expected position [H_α δ 7.38 (d, J 8 Hz), $H_{\alpha'}$ 7.38 (s), H_β 7.09 (d, J 8 Hz)]. The overall deuterium content was estimated by integration to be 0.97 D atom per phenyl ring, which on the basis of a statistical repartition would correspond to 91% of D_3- and 8% of D_2H-molecules in the 'trimer'. This result is in excellent agreement with mass spectroscopic measurements, which showed an intense molecular ion peak at M^+ m/z 273 ($C_{21}H_{15}D_3$); from the relative intensities of the M^+ and M^+-1 peaks in (**3**) and in the non-deuteriated hydrocarbon (**6**) it followed that the D_3/D_2H ratio was about 91:9.

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References

1 A. Collet and J. Gabard, *J. Org. Chem.*, 1980, **45**, 5400; A. Collet and G. Gottarelli, *J. Am. Chem. Soc.*, 1981, **103**, 5912.
2 P. H. Hoffman, E. C. Hong, O. Weigang, Jr., and M. J. Nugent, *J. Am. Chem. Soc.*, 1974, **96**, 2620; see also G. Barth and C. Djerassi, *Tetrahedron*, 1981, **37**, 4123.
3 J. Canceill, J. Gabard, and A. Collet, *J. Chem. Soc., Chem. Commun.*, 1983, 122.
4 I. D. Entwistle, B. J. Hussey, and R. A. W. Johnstone, *Tetrahedron Lett.*, 1980, **21**, 4747.
5 W. J. Musliner and J. W. Gates, Jr., *Org. Synth.*, 1971, **51**, 82; W. J. Musliner and J. W. Gates, Jr., *J. Am. Chem. Soc.*, 1966, **88**, 4271.
6 T. Sato and K. Uno, *J. Chem. Soc., Perkin Trans. 1*, 1973, 895; T. Sato, K. Uno, and M. Kainosho, *J. Chem. Soc., Chem. Commun.*, 1972, 579.
7 E. Fourneau and G. Sandulesco, *Bull. Soc. Chim. Fr.*, 1922, **31**, 988; A. Fredga and M. Matell, *Ark. Kemi*, 1951, **4**, 325.
8 B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522.
9 A. Collet and J. Jacques, *Tetrahedron Lett.*, 1978, 1265; A. Collet, J. Gabard, J. Jacques, M. Cesario, J. Guilhem, and C. Pascard, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1630.
10 P. J. van der Jagt, W. den Hollander, and B. van Zanten, *Tetrahedron*, 1971, **27**, 1049; W. den Hollander, P. J. van der Jagt, and B. van Zanten, *Recl. Trav. Chim. Pays-Bas*, 1971, **90**, 1214.