(C_3)-Tris-(*O*-allyl)-cyclotriguaiacylene, a Key Intermediate in Cyclotriveratrylene Chemistry. Short and Efficient Synthesis of Cyclotriguaiacylene

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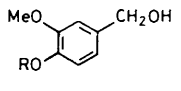
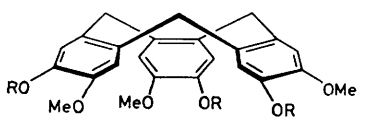
Straightforward access to (C_3)-functionalized derivatives of cyclotriveratrylene can be attained *via* the readily accessible intermediate (C_3)-tris-(*O*-allyl)-cyclotriguaiacylene.

The cone-shaped molecule cyclotriveratrylene (CTV) has recently been incorporated as a rigid, lipophilic unit in the structure of new synthetic hosts[1,2] capable of complexing small organic guests (*e.g.*, $MeNH_3^+$) within a molecular cavity. The design and synthesis of such molecular receptors (speleands)[1b] require the ready availability of appropriate (C_3)-functionalized CTV derivatives. Such intermediates can, in principle, be obtained regiospecifically by allowing suitable 3,4-disubstituted benzyl alcohols to react in the presence of strong acids. These reactions are, however, extremely sensitive to the nature of the substituents employed, and few successful examples have been reported.[3] Particularly, it has not been possible to 'trimerize' directly vanillyl alcohol (**1**) into the triphenol (C_3)-cyclotriguaiacylene (**6**), an important compound in CTV chemistry.[1a,4] This difficulty was originally circumvented[1a] by using a circuitous procedure involving the phenol-protected vanillyl alcohol (**2**), which upon reaction with perchloric acid afforded the (C_3)-triacid (**4**) in 45% yield. Unfortunately, cleavage of the three $-CH_2CO_2H$ groups in (**4**) needed five additional steps, making this route impracticable for preparing reasonable quantities of (**6**).



(1) R = H
(2) R = CH_2CO_2H
(3) R = $CH_2CH{=}CH_2$



CTV R = OMe
(4) R = CH_2CO_2H
(6) R = H

This communication describes a new synthetic process allowing access to multigram quantities of (**6**), from vanillyl alcohol (**1**), in only *three simple steps*. This can be achieved *via* the key intermediate (**5**), (C_3)-tris-(*O*-allyl)-cyclotriguaiacylene, which appears to be the most easily accessible (C_3)-functionalized CTV derivative known to date.

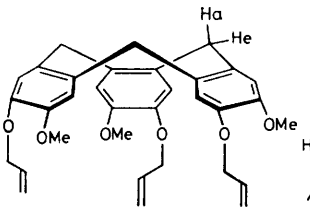
The allyl ether (**3**)† was prepared from vanillyl alcohol (**1**) and allyl bromide (K_2CO_3 in refluxing acetone; 4 h) and was

† Satisfactory elemental analyses were obtained for (**3**); ^{1}H n.m.r. spectrum: (Me_4Si; $CDCl_3$): δ 2.1 (OH), 3.82 (s, OMe), 4.55 (s + m, CH_2OH and $OCH_2CH{=}$), 5.1—5.5 (m, $CH_2{=}$), 5.8—6.3 (m, $-CH{=}$), 6.80 and 6.87 (s, 2 × ArH and s, ArH).

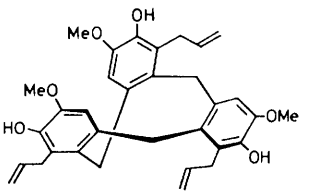
isolated in >80% yield after crystallization from di-isopropyl ether, m.p. 86 °C. Attempted trimerization of (3) into (5), by using conditions (65% $HClO_4$; 20 °C) under which (2) gave the trimer (4) in fair yield, was unsuccessful, presumably because the *O*-allyl group did not survive the strongly acidic medium. However, the trimerization of (3) did proceed smoothly after dilution of the perchloric acid by addition of methanol. In a typical experiment, 65% perchloric acid (85 ml) was added dropwise to a chilled, well stirred solution of (3) (29 g) in methanol (170 ml). The resulting pink solution was then stirred (room temp.) for 18 h, affording a whitish crystalline precipitate. Dilution with water followed by extraction of the organic material into dichloromethane gave a solid, which was purified by digestion in diethyl ether, yielding 16 g of (5), m.p. 170 °C. An analytically pure sample was obtained by crystallization from tetrahydrofuran as small white needles, m.p. 172 °C.

Structure (5) was confirmed by its ^1H and ^{13}C n.m.r. spectra.‡ In particular, (5) adopts the locked 'crown' conformation of the parent CTV system, as shown by the characteristic[1] AB quartet of the methylene bridges at δ 3.74 and 4.71 in the ^1H n.m.r. spectrum. Incidentally, the presence of three conformationally adjustable allyl groups, connected to three electron-rich aromatic rings forming a rigid 'cup,' makes compound (5) promising for π-complexation of certain metallic ions or clusters.[5]

Since the allyl group is amenable to a variety of chemical transformations, (5) is expected to be a useful intermediate in the synthesis of CTV analogues having three-fold symmetry. For example, a Claisen rearrangement was effected easily (dimethylaniline; 1 h reflux) to give (7), whose structure was assigned on the basis of its ^1H and ^{13}C n.m.r. spectra.§ In contrast to (5), compound (7) probably exhibits a flexible 'saddle' conformation, as indicated by its ^1H n.m.r. spectrum, in which the methylene bridge hydrogens resonate as a sharp singlet at δ 3.89. Such behaviour has been observed previously in several CTV analogues bearing bulky substituents *ortho* to the nine-membered ring.[4,6]



(5)



(7)

Cleavage of the three allyl groups in (5) was carried out in about 80% yield by using the method of Scheffold.[7] A solution of (5) (15 g) in ethanol–dioxan (2:1; 230 ml) was stirred at 60 °C (20 h; N_2) in the presence of 10% palladium on charcoal (3 g) and 65% perchloric acid (3 ml), yielding 9.4 g of the crude triphenol (6), m.p. 300—305 °C (decomp.), which was pure enough for most subsequent chemical transformations. Crystallization from ethanol–tetrahydrofuran afforded colourless needles of a monohydrate (from C and H analysis), m.p. 307—309 °C (by differential scanning calorimetry).

We have also found that (6) can be resolved into enantiomers *via* separation of its diastereoisomeric triesters with (+)- or (−)-ω-camphanic acid,[8] and the readily accessible intermediates (5) and (6) should aid the development of the chemistry of optically active CTV derivatives.

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‡ Satisfactory elemental analyses were obtained for (5); ^1H n.m.r. spectrum: (Me_4Si; $CDCl_3$): δ 3.74 (d, *J* 14 Hz, H_e), 4.71 (d, *J* 14 Hz, H_a), 3.80 (s, OMe), 6.77 and 6.82 (2 × s, ArH), 4.55 (m, OCH_2), 5.12—5.50 (m, CH_2=), and 5.72—6.30 (m, –CH=); ^{13}C n.m.r. spectrum (Me_4Si; $CDCl_3$): δ 36.3 (CH_2 bridges), 55.9 (OMe), 70.0 (OCH_2), 113.5 and 115.5 (Ar *C*H), 117.2 (CH_2=), 131.6 and 132.2 (Ar *C*–CH_2), 133.6 (–CH=), and 146.6 and 148.1 p.p.m. (Ar *C*–O).

§ Compound (7) was isolated as a crystalline complex with di-isopropyl ether, m.p. 153 °C; unsolvated (7) had m.p. *ca.* 179 °C; ^1H n.m.r. spectrum (Me_4Si; $CDCl_3$): δ 3.45 (m, CH_2CH=), 3.76 (s, OMe), 3.89 (s, CH_2 bridges), 4.8—5.1 (m, CH_2=), 5.5 (OH), 5.6—6.1 (m, –CH=), 6.52 (s, Ar H); ^{13}C n.m.r. spectrum (Me_4Si; $CDCl_3$): δ 30.2 (CH_2CH=), 34.3 (CH_2 bridges), 55.9 (OMe), 111.9 (Ar *C*H), 114.4 (CH_2=), 136.4 (–CH=), 124.0, 130.8, 131.0, 142.4, and 144.5 p.p.m. (Ar *C*–O and *C*–H).

References

1 (a) J. Gabard and A. Collet, *J. Chem. Soc., Chem. Commun.*, 1981, 1137; (b) J. Canceill, A. Collet, J. Gabard, F. Kotzyba-Hibert, and J.-M. Lehn, *Helv. Chim. Acta*, 1982, **65**, 1894.
2 J. A. Hyatt, *J. Org. Chem.*, 1978, **43**, 1808; K. Frensch and F. Vögtle, *Liebigs Ann. Chem.*, 1979, 2121; F. M. Menger, M. Takeshita, and J. F. Chow, *J. Am. Chem. Soc.*, 1981, **103**, 5938.
3 A. Collet, J. Gabard, J. Jacques, M. Cesario, J. Guilhem, and C. Pascard, *J. Chem. Soc., Perkin Trans.* 1, 1981, 1630.
4 A. Collet and G. Gottarelli, *J. Am. Chem. Soc.*, 1981, **103**, 5912; A. Collet and J. Gabard, *J. Org. Chem.*, 1980, **45**, 5400 and references therein.
5 J. L. Pierre, P. Baret, P. Chautemps, and M. Armand, *J. Am. Chem. Soc.*, 1981, **103**, 2986.
6 J. F. Manville and G. E. Troughton, *J. Org. Chem.*, 1973, **38**, 4278; G. Combaut, J.-M. Chantraine, J. Teste, J. Soulier, and K.-W. Glombitza, *Tetrahedron Lett.*, 1978, 1699.
7 R. Boss and R. Scheffold, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 558.
8 Unpublished work.