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Synthesis of a new apiol-derived cyclotriveratrylene analog

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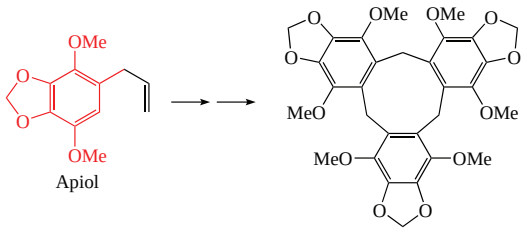
1,4,6,9,11,14-Hexamethoxy-2,3,7,8,12,13-tris(methylenedioxy)-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*][9]annulene, a new representative of a cyclotriveratrylene family, was prepared in high yield by acid-catalyzed trimerization of 2,5-dimethoxy-3,4-(methylenedioxy)benzyl alcohol. Structure of the product was confirmed by X-ray diffraction.



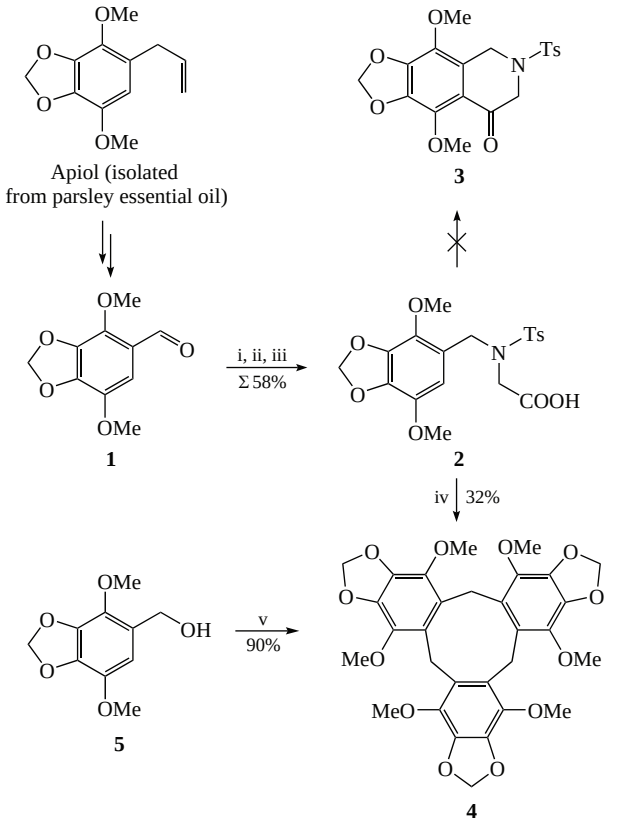
Keywords: cyclotriveratrylene, molecular hosts, tribenzo[*a*,*d*,*g*][9]annulenes, apiol, 2,5-dimethoxy-3,4-(methylenedioxy)benzyl alcohol, trimerization.

Dedicated to Academician M. P. Egorov on the occasion of his 70th birthday anniversary.

Cyclotriveratrylenes (CTVs) represent an important family of molecular hosts extensively investigated since the 1960s.[1,2] They have found numerous applications in supramolecular chemistry, *i.e.*, for binding and recognition of small neutral organic molecules and ions, construction of organogels and liquid crystals or formation of cages and capsules (in particular, for drug delivery).[3–7] Also, they are used as starting compounds in the synthesis of other types of molecular hosts such as cryptophanes and hemicryptophanes.[8,9]

When studying the synthetic transformations of allylbenzene plant metabolites (like apiol and dillapiol),[10–14] we attempted to perform an acidic cyclization of *N*-benzyl-*N*-tosylglycine derivative **2** (produced from apiolaldehyde **1**[10]) in order to prepare isoquinolone product **3** (Scheme 1).[15] Unexpectedly, instead we obtained a CTV derivative **4** in moderate yield.† The same CTV derivative **4** was then prepared in excellent yield by $HClO_4$-catalyzed[16] trimerization of 2,5-dimethoxy-3,4-(methylenedioxy)benzyl alcohol **5**[10] (see Scheme 1).

^{1}H NMR spectra of the compound **4** recorded in $CDCl_3$ and $(CD_3)_2SO$ featured a singlet corresponding to CH_2-protons [at 3.95 ppm in $CDCl_3$ and at 3.82 ppm in $(CD_3)_2SO$]. This fact provides evidence for a saddle (or twist) conformation of **4**.[17–19] This is a rather rare case since CTV derivatives usually would



Scheme 1 *Reagents and conditions*: i, $H_2NCH_2COOEt \cdot HCl$, $NaBH_3CN$, EtOH; ii, TsCl, Et_3N, CH_2Cl_2; iii, NaOH, MeOH; iv, 5% oleum, Et_2O–CH_2Cl_2; v, $HClO_4$, MeOH.

† *Synthesis of 1,4,6,9,11,14-hexamethoxy-2,3,7,8,12,13-tris(methylenedioxy)-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*][9]annulene* **4**.

Method 1 from **2**. Oleum (5%, 15 ml) was added dropwise to diethyl ether (30 ml) cooled to –60 °C, and the resulting mixture was added dropwise at –60 °C to a solution of acid **2** (1.50 g, 3.5 mmol) in CH_2Cl_2 (30 ml). The temperature was gradually raised to 0–5 °C, the mixture was stirred for 10 min, poured into water and extracted with CH_2Cl_2. The solvent was evaporated, and product **4** was isolated by column chromatography (EtOAc/petroleum ether = 1 : 4, R_f = 0.5). Yield 0.55 g (32%).

Method 2 from **5**. To a suspension of benzylic alcohol **5** (2.0 g, 9.43 mmol) in MeOH (15 ml), 70% $HClO_4$ (4 ml) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 3 h and left overnight. The resulting precipitate was filtered off and washed with cold MeOH to yield 1.65 g (90%) of trimer **4** (purity >90%). The substance was then recrystallized from EtOAc.

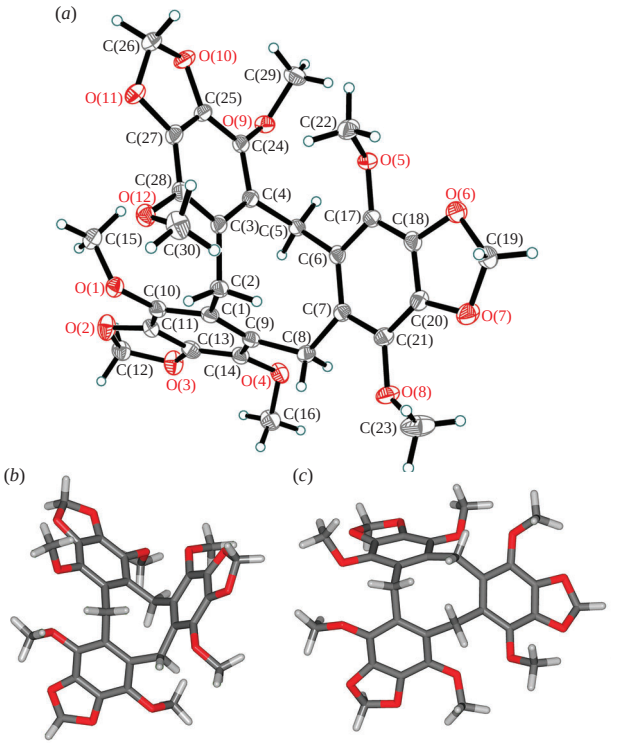


Figure 1 (*a*) Single crystal structure of **4**, calculated structures of (*b*) the saddle conformer and (*c*) the crown conformer.

adopt a crown conformation where CH_2-protons are non-equivalent and resonate as two doublets in ^{1}H NMR.[17] The saddle conformation of compound **4** was further confirmed by X-ray diffraction (Figure 1).‡ Probably, such a conformation is due to steric hindrance induced by two MeO-substituents in both *ortho*-positions of the benzene rings.[18,19]

‡ *Crystal data for* **4**. $C_{30}H_{30}O_{12}$, M = 582.54 g mol^{-1}, T = 100.0(1) K, monoclinic, space group $P2_1/n$, a = 8.43220(10), b = 13.88340(10) and c = 22.1875(2) Å, β = 97.1820(10)°, V = 2577.06(4) Å^3, Z = 4, μ(CuK$_\alpha$) = 0.988 mm^{-1}, d_{calc} = 1.501 g cm^{-3}, 33741 reflections measured (3.764° ⩽ 2θ ⩽ 79.614°), 5579 unique (R_{int} = 0.0340) which were used in all calculations. The final R_1 was 0.0442 [$I > 2\sigma(I)$] and wR_2 was 0.1198 (all data).

X-ray diffraction data were collected at 100 K on a four-circle Rigaku Synergy S diffractometer equipped with a HyPix600HE area-detector (kappa geometry, shutterless ω-scan technique), using monochromatized CuK$_\alpha$-radiation. The intensity data were integrated and corrected for absorption and decay by the CrysAlisPro program.[20] The structure was solved by direct methods using SHELXT[21] and refined on F^2 using SHELXL-2018[22] in the OLEX2 program.[23] All non-hydrogen atoms were refined with individual anisotropic displacement parameters. All hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. A rotating group model was applied for methyl groups.

CCDC 2283620 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

In conclusion, a new apiol-derived CTV derivative, that could be of interest as a molecular host, was prepared in 90% yield by acid-catalyzed trimerization of 2,5-dimethoxy-3,4-(methylenedioxy)benzyl alcohol.

Crystal structure determination was performed in the Department of Structural Studies of Zelinsky Institute of Organic Chemistry, Moscow.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.011.

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