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Methoxy-substituted centrohexaindanes through the fenestrane route†

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Tetrahydroxyfenestrindane undergoes HPF_6-catalyzed condensation with anisole, 2-methylanisole and the three dimethoxybenzenes to furnish several centrohexaindanes bearing oxyfunctionalization at the opposite ends of one of the three [2,2′]-spirobiindane axes.

Centrohexaindane **1** (Fig. 1) is a unique hydrocarbon containing a rigid three-dimensional C_{17} core and six isolated benzene rings, each pointing into different directions of the Carthesian space.[1–3] Three independent syntheses have been developed by which gram amounts of **1** have become accessible.[2] Because of the strictly orthogonal orientation of the six aromatic rings, a directed introduction of functional groups at the molecular periphery of **1** should lead to highly interesting building blocks for supramolecular chemistry.[4] However, attempts to incorporate substituents in the course of the synthesis, or *a posteriori*, or activate the benzene rings by dearomatization, have remained rather limited to date.[5,6]

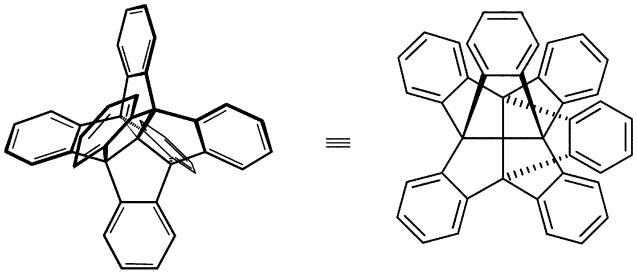

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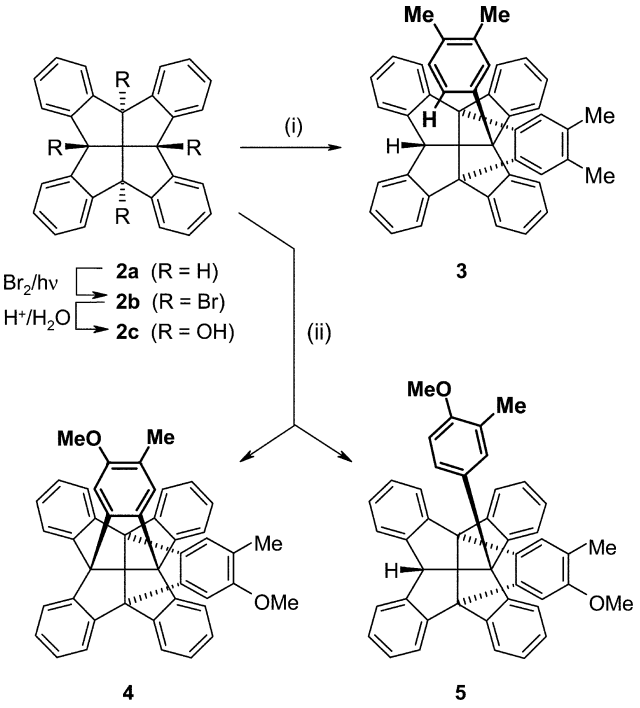
Fig. 1 Centrohexaindane **1**: 3D perspective view (left) and schematic view (right).

In this communication, we present the first directed syntheses of centrohexaindanes bearing methoxy-substituted benzene rings. In analogy to the so-called "fenestrane route" to the parent hydrocarbon, involving a fourfold Friedel–Crafts reaction between tetrabromofenestrindane **2b** and benzene in the last step,[2] we studied the condensation of fenestrindanetetrol **2c** with several electron-rich arenes in the presence of aqueous hexafluorophosphoric acid.[7–9] Tetrahydroxyfenestrane **2c** is easily prepared from fenestrindane (**2a**) *via* its tetrabromo derivative **2b** and subsequent hydrolysis.[2,10] It turned out that the incorporation of two arene units across the [5.5.5.5]fenestrane core of **2c** can be easily achieved with anisole and anisole derivatives which do not contain hydride-transferring methyl groups.

When *ortho*-xylene is used in a two-phase mixture with HPF_6–H_2O containing **2c**, the *seco*-centrohexaindane **3**[11] is isolated as the major product in moderate yield (Scheme 1).† Obviously, one molecule of *ortho*-xylene forms a new indane unit but the other one is incorporated as an *ortho*-xylyl group only. A similarly ambivalent behaviour was found when 2-methylanisole was used for condensation. In this case, centrohexaindane **4**, a new topologically nonplanar compound, is formed as the major product (isolated yield 30%), resulting from twofold arene incorporation, along with the *seco*-centrohexaindane **5** (10%) bearing a 5-methoxy-6-methylindane unit but also a 3-methyl-4-anisyl substituent.‡ This indicates that the more electron-rich arene undergoes aromatic substitution more readily but that its hydride donor ability can still compete with complete, fourfold condensation. It is not clear whether the hydride transfer occurs before or after incorporation of the first arene molecule.



Scheme 1 *Reagents, conditions and yields:* i, *ortho*-xylene, HPF_6 (60%), 25 °C, 24 h, 36%; ii, 2-methylanisole, HPF_6 (60%), 25 °C, 24 h, 30% (**4**) and 10% (**5**). For the conversion **2a** → **2b** → **2c**, see refs. 2 and 10.

By contrast, when the reaction is carried out with anisole instead of xylene or 2-methylanisole, hydride transfer no longer competes with the four-fold C–C bond formation. Obviously, a single methoxy group renders the arene sufficiently electron-rich to allow the complete condensation giving the chiral dimethoxycentrohexaindane **6** as the sole product (Scheme 2). Likewise, veratrole was found to undergo the corresponding condensation giving tetramethoxycentrohexaindane **7**. This topologically nonplanar compound was isolated in 95% yield and subjected to X-ray crystal structure analysis, which nicely confirmed the approximate T_d symmetry of the carbon framework and the regular orientation of the two pairs of methoxy substituents at the opposite sides of the initial fenestrane "plane" and at the opposite ends of the newly formed [2,2′]-spirobiindane axis (Fig. 2).§

† Electronic supplementary information (ESI) available: Syntheses procedures, physical and spectroscopic data of compounds **3**–**9**. See http://www.rsc.org/suppdata/ob/b4/b417837h/

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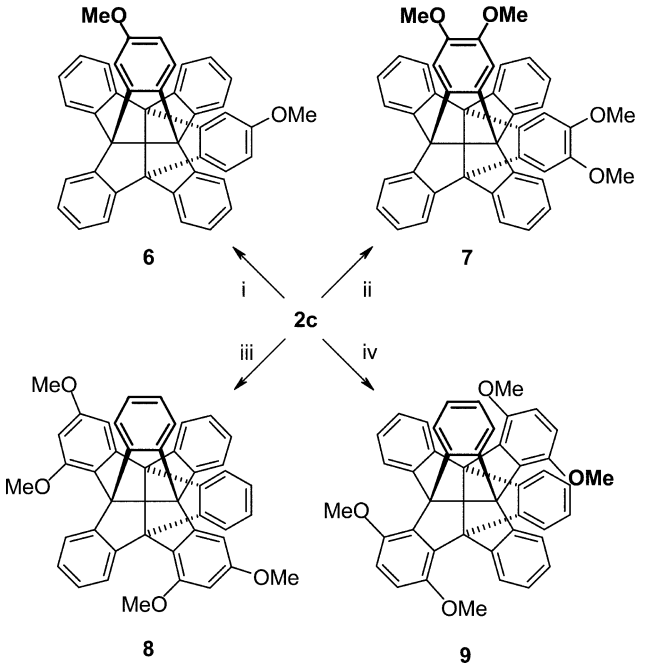

Scheme 2 *Reagents, conditions and yields:* i, anisole, HPF_6 (60%), 25 °C, 24 h, 71% (**7**); ii, 1,2-dimethoxybenzene, ditto, 95% (**7**): iii, 1,3-dimethoxybenzene, ditto, 51% (**8**); iv, 1,4-dimethoxybenzene, ditto, 58% (**9**).

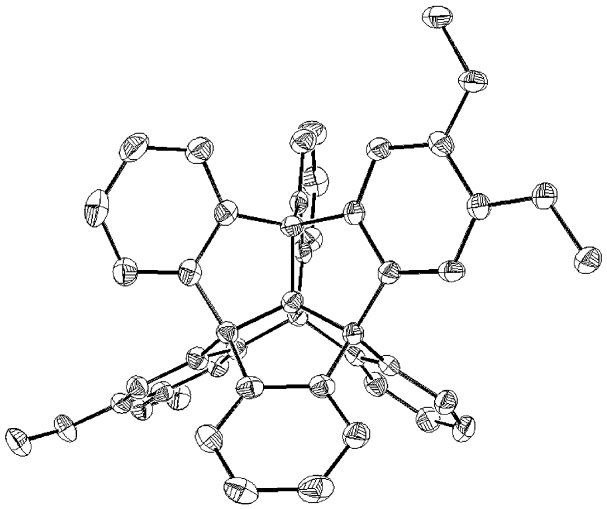

Fig. 2 Molecular structure of tetramethoxycentrohexaindane **7**, as determined by X-ray diffraction (ORTEP plot). Hydrogen atoms are omitted for the sake of clarity.

Even resorcinol dimethyl ether and hydroquinone dimethyl ether react in the same manner. Thus, centrohexaindanes **8** and **9** are formed bearing two or, respectively, even all of the four methoxy groups at the inner positions of the arene periphery. This is particularly remarkable because steric hindrance within the four rigid, C_{3v}-symmetrical triphenylmethane units comprised in the centrohexaindane framework is difficult to overcome in electrophilic aromatic substitution reactions at these highly shielded *ortho* positions.[12]

The results presented here are encouraging for the construction of various centrohexaindane-based building blocks bearing functional groups with spatially well defined orientation at the three-dimensional framework. Incorporation of other electron-rich arenes appears possible provided that hydride transfer processes can be suppressed. This may enable us to extend the polycyclic carbon skeleton of **1** and to introduce various coordination sites and host functionalities.¶

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Notes and references

‡ Hindered rotation of the 3,4-disubstituted phenyl group in compound **5** gives rise to nearly 1 : 1 splitting of several ^1H (and also ^{13}C) resonances at ambient temperature, which largely vanishes upon heating to 100 °C (see Supplementary Information). Formation of bis-*seco*-centrohexaindanes was not observed.

§ ***Tetramethoxycentrohexaindane*** **7**. 1,2-Dimethoxybenzene (1.48 mL, 11.6 mmol) is placed into a polyethylene bottle (30 mL) and stirred intensely while a red suspension prepared by mixing tetrahydroxyfenestrindane **2c** (50 mg, 116 mmol) and aqueous hexafluorophosphoric acid (60%, 6 mL) is added. The reaction vessel is closed loosely with a PE screwing lock. ***Due to the permanent release of hydrogen fluoride, experiments with hexafluorophosphoric acid require particular caution!*** After stirring for a total of 24 h at 25 °C, the reaction mixture is diluted by addition of ice–water and then extracted several times with trichloromethane. The combined extracts were dried over sodium sulfate, concentrated to dryness and the residue was recrystallized from trichloromethane to give tetramethoxycentrohexaindane **7** (74 mg, >95%) as a colourless, amorphous solid. Selected data for **7**: mp 360 °C; ^1H NMR (500 MHz, $CDCl_3$): [AA′BB′] spin system, $\delta_A = 7.74$ (8 H), $\delta_B = 7.26$ (8 H), 7.21 (s, 4 H), 3.90 (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 150.1$ (s), 148.2 (s), 139.9 (s), 128.4 (d), 123.9 (d), 106.7 (d), 96.6 (s), 72.6 (s), 56.3 (q); MS (EI, 70 eV): *m/z* 636 (100, $M^{\bullet+}$], 500 (13), 318 (6); accurate mass (EI-MS): $C_{45}H_{32}O_4$ calcd 636.2301, found 636.2306. *Crystal data of compound 7:* $C_{45}H_{32}O_4 \cdot H_2O \cdot CH_3OH$ (686.76 g mol^{-1}), orthorhombic, *Pnma*, $a = 17.357(8)$, $b = 13.487(5)$, $c = 14.830(6)$ Å, $V = 3472(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.314$ Mg m^{-3}, GoF = 1.018, *R* values for reflections with $I > 2\sigma(I)$ $R1 = 0.0753$, $wR2 = 0.1787$. CCDC reference number 250182. See http://www.rsc.org/suppdata/ob/b4/b417837h/ for crystallographic data in .cif or other electronic format.

¶ Preliminary experiments have shown that the fenestrane route is viable to annelate two crown ether units at the opposite sides of **1** by fusing fenestrindanetetrol **2c** with two molecules of benzo-18-crown-6 under HPF_6 catalysis.

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