The Regiospecific Preparation of 2-Substituted Tribenzotriquinacenes

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Received: 20.11.2012; Accepted after revision: 10.01.2013

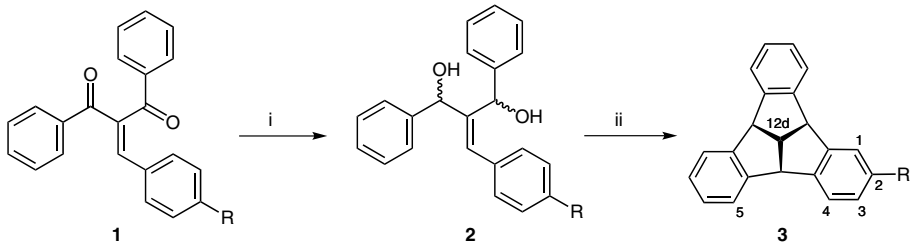
Abstract: Several substituted tribenzotriquinacene derivatives (TBTQ) carrying functional groups exclusively in the 2-position (OMe, OH, Br, CHO, CN, styryl, etc.) have been prepared by our new synthesis of the tribenzotriquinacene framework. The route has been extended to the preparation of a double-cup molecule in which two TBTQ moieties are fused by a benzene ring. The *trans* configuration of one of the diastereomers of this hydrocarbon was established by X-ray structural analysis.

Key words: cuplike aromatics, Friedel–Crafts cyclizations, cycloeliminations, convex molecules, chiral aromatics, double-cup structures, single-crystal X-ray structural analysis

Recently, we have reported on a versatile new synthesis for the preparation of tribenzotriquinacene (**3a**, Scheme 1) and also of several derivatives bearing one or more substituents (1-TBTQ) in their (sterically hindered) *ortho* position(s) (e.g., position 1 in compound **3**).[1]

In this route, cross-conjugated diones **1** – obtained by Knoevenagel condensation of the corresponding 1,3-diketones with aromatic aldehydes (selected yields are given in Scheme 1) – are reduced to the diols **2** (mixture of diastereomers), which, in a final step, are cyclodehydrated by treatment with polyphosphoric acid to the parent hydrocarbon **3a** or to various 1-substituted derivatives (inter alia: Br, Me, OMe).[1] These derivatives are chiral, and their enantiomers were resolved by chromatography using an optically active stationary phase (e.g., Chiralcel OD, Chiralcel OJH, and Chiralpak AS). Whereas the parent system **3a** had already been prepared by Kuck during his classical investigations of tribenzotriquinacene derivatives,[2] derivatives bearing substituents or functional groups in the sterically shielded 1-position are generally not readily accessible.[3]

In principle, our new route offers numerous possibilities to introduce functionality at all positions except for the central position 12d, since the aromatic substituents in substrate **1** can carry functional groups at every available carbon atom. Furthermore, the aromatic substituents can be replaced by heteroaromatic (e.g., thienyl) or condensed substituents (e.g., naphthyl). The benzhydrylic hydrogen atoms in **3** in principle could be replaced by substituents by performing for example, a Grignard reaction on appropriately substituted derivatives of **1** followed by cyclode-



	1		2		3		
	R	%	R	%	R	%	
a	H	66	H	93	H	32	
b	OMe	82	OMe	86	OMe	15	iii
c	–		–		OH	68	
d	Br	73	Br	83	Br	17	iv
e	–		–		TMS	81	v
f	–		–		H	92	vi
g	–		–		Tol-NH	68	

Scheme 1 Preparation of 2-substituted tribenzotriquinacenes by cyclodehydration. *Reagents and conditions*: i) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, CH_2Cl_2, –78 °C to 20 °C, 12 h; ii) polyphoshoric acid or H_3PO_4, chlorobenzene, 130 °C, 20 h; iii) BBr_3, CH_2Cl_2, –78 °C to 20 °C, 12 h; iv) $PdCl_2(PPh_3)_2$, TMSA, CuI, Ph_3P, Et_3N, toluene, 80 °C, 10 h; v) K_2CO_3, MeOH–THF (1:1), 20 °C, 3 h; vi) $Pd_2(dba)_3$, Xanthphos, NaO*t*-Bu, *p*-toluidine, reflux, 24 h.

SYNLETT 2013, 24, 0453–0456
Advanced online publication: 25.01.2013
DOI: 10.1055/s-0032-1318143; Art ID: ST-2013-B0995-L

hydration of the resulting tertiary diol. In all these cases, with a substituent already introduced at the substrate level, regiospecifically functionalized tribenzotriquinacenes would result. This is a priori not the case if the substituents are introduced after construction of the tribenzotriquinacene framework (e.g. by electrophilic substitution).

In the present communication we describe the preparation of 2-substituted TBTQs, compounds which could be of use, for example, for the construction of larger bowl-shaped molecules (see below).

We illustrate first the preparation of 2-substituted tribenzotriquinacenes by the examples collected in Scheme 1. Thus the *p*-methoxy-substituted substrate **1b** was reduced with sodium borohydride/cerium trichloride·heptahydrate (Luche conditions)[4] in good yield to diol mixture **2b**, which on treatment with polyphosphoric acid in chlorobenzene furnished 2-methoxytribenzotriquinacene **3b** (15%). Likewise, the bromo compound **3d** resulted when dione **1d** was subjected to the same sequence (total yield over all three steps: ca. 10%). The BBr_3-catalyzed ether cleavage of **3b** caused the formation of phenol **3c** (68%), whereas Sonogashira coupling of **3d** with trimethylsilylacetylene yielded **3e** (81%), which was desilylated to the ethynyl derivative **3f** by treatment with potassium carbonate in MeOH–THF in 92% yield. Finally, the secondary amine **3g** was obtained from **3c** by Buchwald coupling with *p*-toluidine in the presence of Xanthphos, sodium *tert*-butoxide, and $Pd_2(dba)_3$ (68%).[5] All new compounds were characterized by the usual analytical and spectroscopic data.[6]

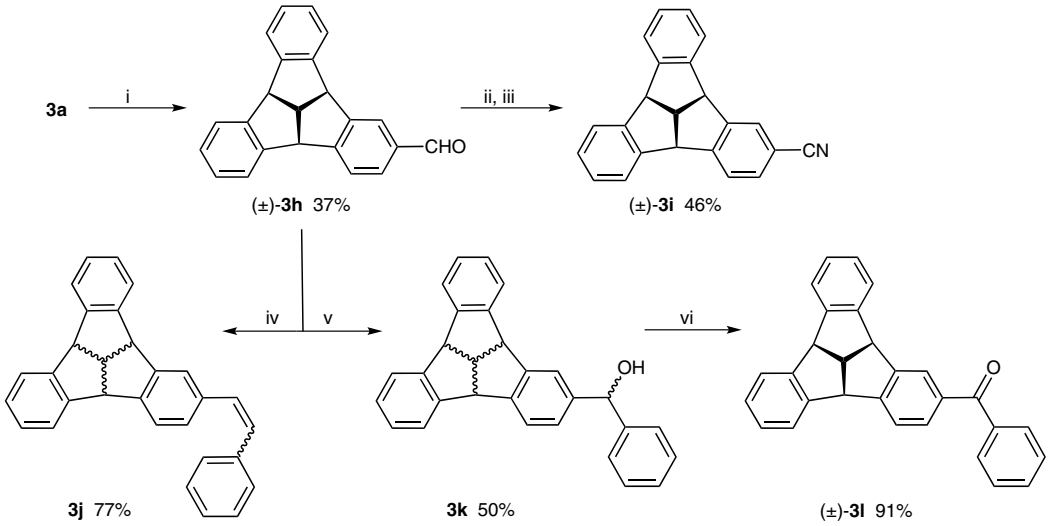
To investigate the above-mentioned electrophilic substitution of **3a** we subjected this parent system to the Rieche formylation.[7,8] As expected, the substitution took place exclusively at the outer rim of tribenzotriquinacene. However, the yield of this (not optimized) transformation was poor (37%), most likely due to the low solubility of the starting material. Conversion of the aldehyde **3h** into the corresponding oxime proceeded readily ($NH_2OH·HCl$, 76%) and its dehydration yielded nitrile **3i** (Ac_2O, EtOH, 60%; Scheme 2).

Wittig reaction of **3h** with benzyltriphenylphosponium bromide and sodium hydroxide furnished the expected styrene derivative **3j** (77%) as a mixture of diastereomers. Conversion of **3h** into phenyl ketone **3l** was accomplished by first carrying out a Grignard reaction with phenyl magnesium bromide (formation of **3k**, 50%) followed by a Swern oxidation (91%). Clearly, both **3j** and **3l** are useful starting materials for the preparation of tribenzotriquinacenes with a single-wing extension.[9]

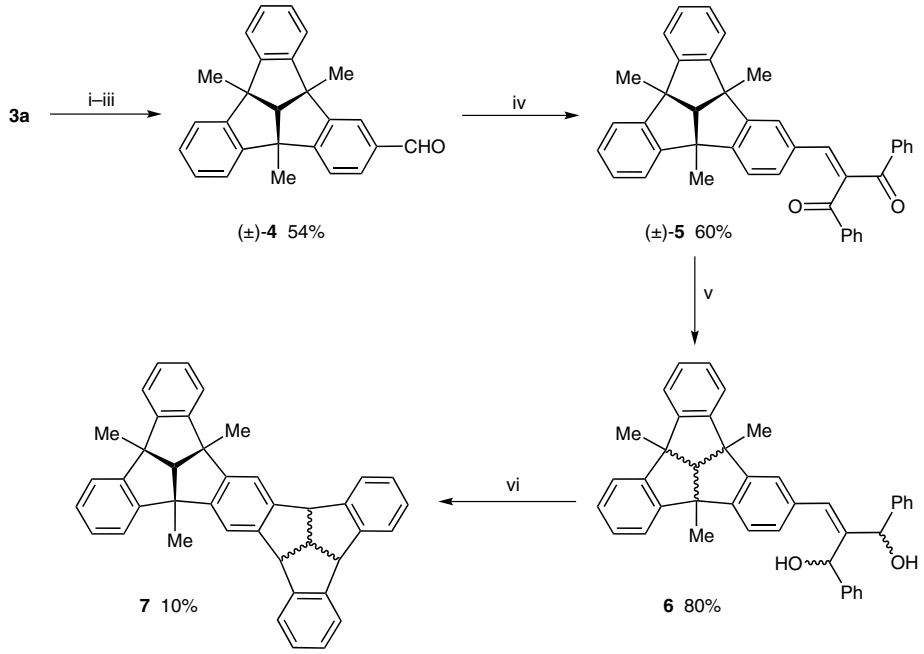
We are also interested in the preparation of derivatives containing more than one TBTQ moiety (e.g., compounds with a double or multiple cup structure).[8,9] As a first experiment in this direction we prepared the 'dimeric' structure **7** using our new TBTQ synthesis (Scheme 3). Since the direct formylation of **3a** to **3h** was low-yielding (see above), we decided to prepare the more soluble trimethyl derivative **4** in a sequence developed by Kuck[10] (overall yield from **3a** to **4**: 54%).

Condensation of aldehyde **4** with dibenzoylmethane furnished diketone **5** in good yield. And after reduction of this intermediate to the diastereomeric diols **6**, the latter were cyclized as above to hydrocarbon **7**, which was also obtained as a mixture of diastereomers. Although we were able to separate this mixture partially by column chromatography on silica gel, single crystals suitable for an X-ray investigation have so far been obtained only for the *anti*-isomer. The results of this study are shown in Figure 1.

The molecule of *anti*-**7** displays bond lengths and angles essentially as expected for the strained triquinacene system; thus the single bonds to the central carbons (C18D and C18E) are slightly lengthened at ca. 1.56 Å, and two of the three bond angles at the formally sp^2 atoms (e.g.,



Scheme 2 Preparation of 2-substituted tribenzotriquinacenes via initial electrophilic aromatic substitution. *Reagents and conditions*: i) $TiCl_4$, $MeOCHCl_2$, CH_2Cl_2, 20 °C, 24 h; ii) $NH_2OH·HCl$, KOH, EtOH–H_2O (1:1), reflux, 8 h; iii) Ac_2O, reflux, 2 h; iv) $[PhCH_2PPh_3]^+Br^-$, NaOH, CH_2Cl_2, 20 °C, 2 h; v) PhMgBr, THF, 20 °C, 0.5 h; vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to 20 °C, 2 h.



Scheme 3 Preparation of the double bowl-shaped hydrocarbon *anti*-**7**. *Reagents and conditions*: i) Br_2, *hv*, $CHCl_3$, 20 °C, 30 min; ii) $Al(CH_3)_3$, *n*-heptane, 50 °C, 15 min; iii) $TiCl_4$, $MeOCHCl_2$, CH_2Cl_2, 20 °C, 24 h; iv) dibenzoylmethane, piperidine, toluene, reflux 18 h; v) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, CH_2Cl_2, –78 °C to 20 °C, 12 h; vi) polyphosphoric acid, chlorobenzene, reflux, 24 h.

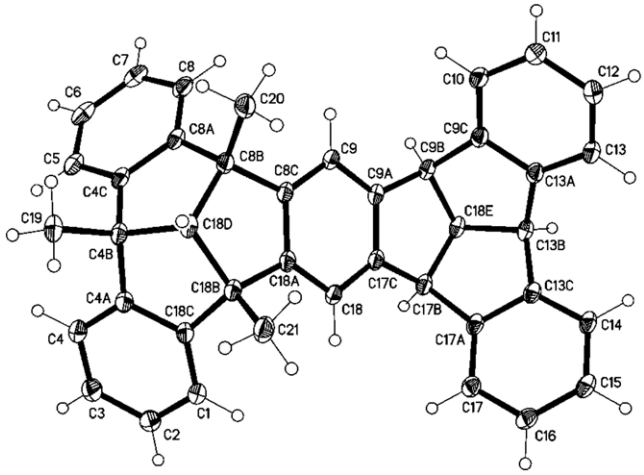


Figure 1 Structure of *anti*-**7** in the solid state (top view, ellipsoids represent 30% probability levels)

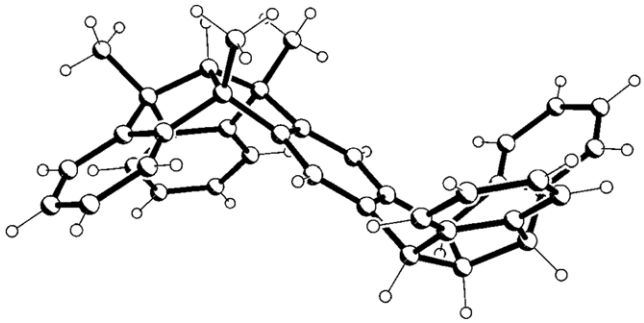


Figure 2 Side view of *anti*-**7** in the solid state

C4C, C8A) common to five-membered and benzo rings are distorted by ca. 7–8° from the ideal 120° [e.g., C5–C4C–C4B 127.50(15)° and C8A–C4C–C4B 112.07(14)°]. The central carbons lie ca. 1.4 Å out of the plane of the appropriate sp^2 atoms (for C18D defined by C4C, C8A, C8C, C18A, C18C, C4A and for C18E defined by C13A, C9C, C9A, C17C, C17A, C13C). The molecules stack parallel to the *a*-axis; neighboring molecules are related by inversion. The average stacking repeat distance is *a*/2 = 5.299 Å.[11] The steplike structure of the hydrocarbon is recognizable particularly well in the side view of *anti*-**7** (Figure 2).

Acknowledgment

G. M. thanks the *Fonds der Chemischen Industrie* and the *Studienstiftung des deutschen Volkes* for scholarships; R. S. was supported by a scholarship from the INDIGO program. We thank Prof. D. Kuck (University of Bielefeld) very much for numerous helpful discussions.

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(6) **Preparation of the Amine 3g as Typical Experimental Procedure**

An oven-dried, two-necked round-bottomed flask was charged with 2-bromotribenzotriquinacene (**3d**, 300 mg, 0.83 mmol), *p*-toluidine (107 mg, 1.0 mmol), Xanthphos [4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, 29 mg, 0.05 mmol], NaO*t*-Bu (112 mg, 1.16 mmol), and $Pd_2(dba)_3$ [tris(dibenzylideneacetone)dipalladium(0), 23 mg, 0.02 mmol]. The flask was evacuated and refilled with argon three times. Toluene (100 mL) was added, and the reaction mixture was refluxed for 20 h. After cooling to r.t., the reaction mixture was diluted with EtOAc and passed through a pad of silica gel. The solvent was removed in vacuo, and the analytically pure amine **3g** was obtained by flash chromatography using silica and 5% EtOAc in pentane as the eluent: 220 mg (68%) of **3g**, mp 215–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.46–7.34 (m, 4 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.17–7.13 (m, 5 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 6.92 (d, *J* = 8.0 Hz, 2 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 5.54 (br s, 1 H), 4.95–4.86 (m, 3 H), 4.47 (q, *J* = 9.6 Hz, 1 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 147.0, 146.2, 145.9, 145.7, 145.6, 143.1, 140.9, 138.2, 130.2, 129.8, 127.3, 127.3, 127.2, 124.7, 124.2, 124.2, 118.0, 117.5, 113.2, 55.8, 55.8, 55.2, 51.6, 20.6 ppm. UV (CH_2Cl_2): λ_{max} (lg ε) = 228 (4.21), 278 (4.18), 290 (4.25) nm. IR (powder): ν = 3395 (s), 3018 (s), 1606 (m), 1517 (ms), 1492 (m), 1478 (m), 1330 (m), 806 (ms), 742 (vs), 573 (m) cm^{-1}. MS: *m/z* calcd: 385.18250; found: 385.18243. Anal. Calcd. for $C_{29}H_{23}N$ (385.50): C, 89.23; H, 6.02; N, 3.58. Found: C, 89.07; H, 6.03; N, 3.27.

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(11) **X-Ray Structure Determination of *anti*-7**

Crystal Data

Monoclinic, $P2_1/c$, a = 10.5987(8), b = 25.6904(16), c = 10.5725(8) Å, β = 104.749(8)°, V = 2783.9(3) Å^3, Z = 4, μ = 0.5 mm^{-1}, D_x = 1.252 mg/m^3.

Data Collection and Reduction

A colorless hexagonal plate 0.15 × 0.1 × 0.02 mm was mounted on a glass fiber in inert oil and transferred to the cold gas stream of the diffractometer (Oxford Diffraction Nova A). A total of 53127 intensities were recorded to $2\theta_{max}$ 152° using mirror-focussed Cu Kα radiation (λ = 1.54184 Å); 5783 of these were independent (R_{int} = 0.073). Absorption corrections were performed on the basis of multiscans.

Structure Refinement

The structure was refined anisotropically on F^2 using the program SHELXL-97.[12] Hydrogen atoms were included using a riding model starting from calculated positions. The final *wR*2 for all reflections was 0.134 for 373 parameters, with *R*1 = 0.049 for reflections with $I > 2\sigma(I)$; S = 1.02, max. Δρ = 0.58 e Å^{-3}.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 909301. Copies of the data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.

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