Synthesis and base-induced epimerization of *cis,cis,cis,trans*-tribenzo[5.5.5.6]fenestranes

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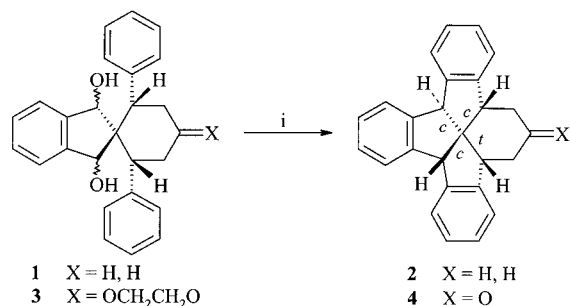 *E-mail: dietmar.kuck@uni-bielefeld.de*

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Strained *cis,cis,cis,trans*-tribenzo[5.5.5.6]fenestranes are accessible in good yield by two-fold cyclodehydration of *cis*-2,6-diphenylspiro[cyclohexane-1,2′-indane]-1′,3′-diols and the particularly high acidity of their 'inverted' benzylic bridgehead C–H bonds, causing facile epimerization to the more stable all-*cis*-tribenzo[5.5.5.6]fenestranes, is shown.

Strained stereoisomers of all-*cis*-[*m.n.o.p*]fenestranes have been of particular interest with respect to the quest for planar tetracoordinate carbon.[1–3] While extensive computational work has been published on strain and geometry of stereoisomeric fenestranes,[3a–c,4–6] only a few small-ring congeners bearing a single *trans*-fused pair of rings together with three *cis*-annelated ones, *i.e.* the *cis,cis,cis,trans*-fenestranes, are known by experiment.[7–9] Fenestranes bearing more than one *trans* junction have remained unknown to-date,[3,10] and even normal-ring fenestranes containing the *cis,cis,cis,trans* skeleton have only recently been realized in a single case.[11] Herein we report the first synthesis of a *cis,cis,cis,trans*-tribenzo[5.5.5.6]fenestrane **2** and some of its derivatives, and demonstrate the ease and some mechanistic details of its epimerization to the corresponding all-*cis* stabilomers.

Benzoannelated all-*cis*-[5.5.5.6]- and all-*cis*-[5.5.5.5]-fenestranes have been synthesized by two-fold cyclodehydration of the stereochemically suitable *trans*-2,6-diarylspiro[cyclohexane-1,2′-indane]-1′,3′-diols.[12,13] In these tandem cyclization reactions, the *trans* orientation of the two aryl groups translates directly into the all-*cis* stereochemistry of the fenestrane nucleus. Surprisingly, and contra-intuitively, we found that, under similar conditions, isomeric *cis*-diarylspirodiols such as **1** and **3**,[14] which are readily accessible from the corresponding spirotriketones,[15,16] undergo two-fold cyclization as well, giving the corresponding *cis,cis,cis,trans*-[5.5.5.6]fenestranes, such as **2** and **4**,† in good yields (Scheme 1). Force-field and semi-empirical MO calculations (MM+ and PM3, respectively) suggest that *cis,cis,cis,trans*-[5.5.5.6]fenestranes are, by *ca.* 10 kcalmol⁻¹, more strained than the all-*cis* isomers,[3a] in agreement with previous estimates on alicyclic analogues,[4,6] and that one of the unbridged bond angles of the fenestrane nucleus is also considerably increased.‡ Moreover, the cyclohexane ring
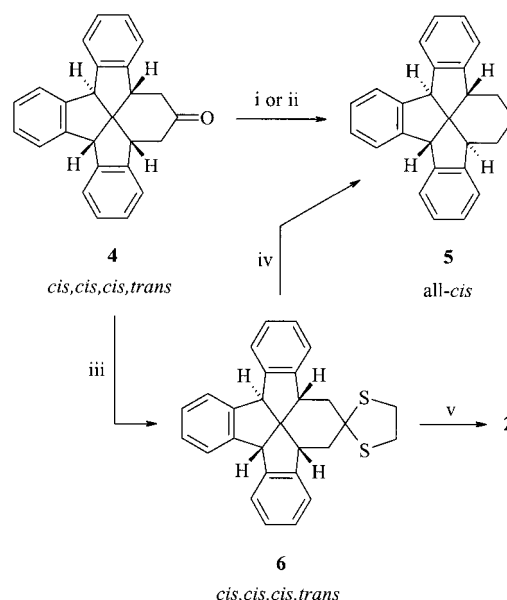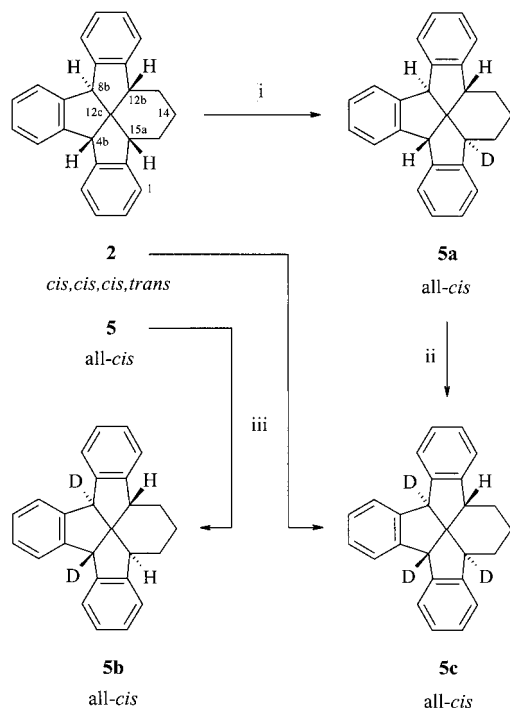
adopts a boat conformation in the most stable conformer of **2** and **4**.[14]

Reduction of fenestranone **4** under Wolff–Kishner–Huang–Minlon conditions, as well as reduction of its hydrazone with KOBuᵗ in DMSO at 20 °C and even Raney nickel-catalyzed hydrogenolysis of thioacetal **6**,[14] all resulted in the formation of the all-*cis* hydrocarbon **5** instead of **2** (Scheme 2). Obviously, the basic conditions used are sufficiently harsh to induce epimerization by a deprotonation–reprotonation sequence. In contrast, radical-induced desulfurization of **6** using Bu₃SnH and AIBN afforded retention of configuration at the 'inverted' bridgehead during reduction, giving the *cis,cis,cis,trans*-tribenzo[5.5.5.6]fenestrane **2** in good yield. These results suggest that C–H acidity at the strained fenestrane nucleus is the origin of epimerization, irrespective of the presence of a functional group at C(14).

In fact, independent experiments carried out with fenestranes **2** and **5** under essentially the same conditions used for reduction of **4** and its hydrazone revealed that base-induced epimerization occurs with high selectivity by deprotonation at the 'inverted' bridgehead (C-15a). Thus, treatment of all-*cis*-fenestrane **5** with KOBuᵗ in [²H₆]DMSO gave rise to complete H/D exchange at the benzhydrylic bridgeheads to generate **5b**, whereas the *cis,cis,cis,trans* isomer **2** underwent complete epimerization with concomitant incorporation of three deuterium atoms at the benzhydrylic and one of the benzylic positions to yield **5c**

Scheme 2 *Reagents and conditions*: i, N₂H₄·H₂O, KOH, diethylene glycol, 120 → 180 °C, 73%; ii, (a) N₂H₄·H₂O, EtOH, Δ, 92%, (b) KOBuᵗ, DMSO, 20 °C, 80%; iii, (CH₂SH)₂, BF₃·Et₂O, AcOH, 20 °C, 95%; iv, Raney-Ni (W2, 'neutral'), 1,4-dioxane, Δ, 80%; v, Bu₃SnH, AIBN, benzene, Δ, 87%.

1	X = H, H	2	X = H, H
3	X = OCH₂CH₂O	4	X = O

Scheme 1 *Reagents and conditions*: i, H₃PO₄, toluene, Δ; **1 → 2**, 24 h, 82%; **3 → 4**, 15 h, 87%.

Scheme 3 *Reagents and conditions*: i, KOD, [*O*,*O*′-²H₂]diethylene glycol, 180 °C, 3 h; ii, KOD, [*O*,*O*′-²H₂]diethylene glycol, 240 °C, >4 h; iii, KOBuᵗ, [²H₆]DMSO, 20 °C, 15 h; >90% in both cases.

(Scheme 3, paths iii). Moreover, use of KOD in *O*,*O*′-dideuterated diethylene glycol revealed that the C(15a)–H bond of **2** is far more acidic than the benzhydrylic C–H bonds in both **2** and **5**. When heated to 180 °C for 3 h, the *cis,cis,cis,trans* isomer **2** was partially epimerized (path i) to give a mixture consisting exclusively of monodeuterated all-*cis*-fenestrane **5a** and unlabelled starting material ([**5a**]:[**2**] ≈ 46:54 by ¹H NMR). Only prolongated heating at 240 °C effected relatively slow incorporation of deuterium into the benzhydrylic bridge-heads of **5a** to eventually give **5c** (path ii).

The results clearly show that benzoannelated *cis,cis,cis,-trans*-[5.5.5.6]fenestranes are easily accessible by directed synthesis, in spite of the considerable increase of strain in the tetracyclic framework, but that the additional strain also induces facile base-induced epimerization of the 'inverted' bridgehead to give the more stable all-*cis* isomers. This sheds some light on the extraordinary challenge to synthesize benzoannelated *cis,cis,cis,trans*-[5.5.5.5]fenestranes.³ᵃ

Notes and references

† *Selected data* for **2**: mp 222–223 °C; δ_H(CDCl₃, 500 MHz) 7.41–7.45 (m, 2 H), 7.00-7.20 (m, 10 H), 4.43 (s, 2 H), 3.79–3.82 (m, 2 H), 2.32–2.37 (m, 1 H), 2.21–2.24 (m, 1 H), 1.68–1.71 (m, 1 H), 1.53–1.59 (m, 2 H), 1.00–1.09 (m, 1 H); δ_C(CDCl₃, 125.8 MHz) 146.6 (s), 146.3 (s), 145.9 (s), 144.8 (s), 144.7 (s), 143.8 (s), 126.9 (d), 126.8 (d), 126.7 (d), 126.6 (d), 126.4 (d), 126.2 (d), 125.1 (d), 124.6 (d), 124.5 (d), 123.2 (d), 122.8 (d), 120.9 (d), 66.8 (s, *centro*-C), 59.7 (d), 56.4 (d), 47.0 (d), 45.3 (d), 28.1 (t), 18.3 (t), 15.4

(t); *m/z* (EI, 70 eV) 334 (100, M⁺), 305 (34), 291 (34), 257 (24). For **4**: mp 293–297 °C; δ_H(CDCl₃, 500 MHz) 7.47–7.50 (m, 1 H), 7.38–7.41 (m, 1 H), 7.02–7.21 (m, 10 H), 4.58 (s, 1 H), 4.43 (s, 1 H), 4.28 (dd, ³*J* 3.4, ³*J* 14.6, 1 H), 4.28 (d, *J* 5.1, 1 H), 3.38 (dd, ³*J* 6.2, ²*J* 15.1, 1 H), 2.94 (dd, ³*J* 3.6, ²*J* 18.6, 1 H), 2.70 (dd, ³*J* 1.8, ²*J* 15.1, 1 H), 2.27 (dd, ³*J* 14.8, ²*J* 18.6, 1 H); δ_C(CDCl₃, 125.8 MHz) 211.2 (s), 145.6 (s), 145.0 (s), 144.7 (s), 143.9 (s), 143.7 (s), 141.0 (s), 127.9 (d), 127.8 (d), 127.2 (d), 127.1 (d), 127.0 (d), 126.6 (d), 125.6 (d), 125.1 (d), 124.5 (d), 123.3 (d), 123.2 (d), 121.0 (d), 67.2 (s, *centro*-C), 58.7 (d), 56.7 (d), 47.1 (d), 47.0 (t), 44.3 (d), 37.8 (t); *m/z* (EI, 70 eV) 348 (100, M⁺), 305 (37), 290 (39).

‡ Increase of strain in the *cis,cis,cis,trans*-hydrocarbon, as calculated by MM+ (PM3): ΔE_strain = ΔH_f(**2**) − ΔH_f(**5**) = 9.1 (10.4) kcal mol⁻¹; bond angles calculated for **2**: C(4b)–C(12c)–C(12b) = 118.7° (120.0°), C(8b)–C(12c)–C(15a) = 115.8° (116.5°).

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