Ring Opening Reactions

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Hexaradialenes by Successive Ring Openings of Tris(alkoxytricyclobutabenzenes): Synthesis and Characterization**

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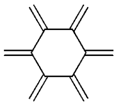
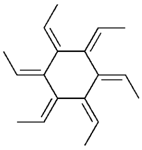
Hexaradialenes are alicyclic cross-conjugated hydrocarbons, in which all of the carbon atoms in the six-membered ring are sp^2 hybridized and have as many exocyclic double bonds as possible. Interesting physical properties and reactivities are expected from their unique structures, which also have potential utility for constructing polycyclic molecules.[1,2] The parent system (**I**),[3–5] however, is unstable and polymerizes immediately on formation; only a few substituted hexaradialenes have been structurally characterized, including hexamethyl,[6] dodecamethyl,[7] and hexabromo[8] derivatives **II**–**IV**.

One possible synthetic route to such systems is from the valence isomer, tricyclobutabenzene **V**; this route is particularly interesting as it considers the question of the relative thermodynamic preference of the two isomers. Although the corresponding interconversion between monocyclobutabenzene and quinodimethane has been thoroughly studied,[9] their tricyclobutabenzene analogues have remained unstudied, presumably owing to their poor availability.

We previously developed a flexible synthetic route to tricyclobutabenzenes that contain various oxygenated motifs by repeated [2+2] cycloadditions of benzyne and ketene silyl acetal (KSA),[10] which allowed the study of the thermal behavior of oxygenated triannelated systems, such as **VI**. Herein, we report that the thermal isomerization of **VI** indeed offers a highly stereoselective access to stereodefined hexaradialenes **VII**, given that the hydroxy groups on the four-membered rings were protected by bulky substituents.



I



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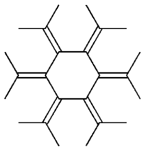

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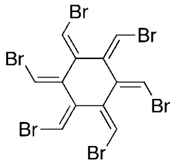

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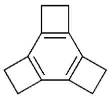
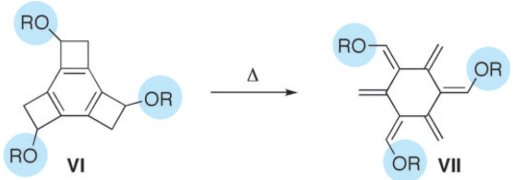


V



VI **VII**

Scheme 1 shows the preparation of tritosylate **7**, the key intermediate for introducing three alkoxy substituents using S_N2 reactions. Starting from iodide **1**, bromotosylate **2**[11] was selectively prepared by the repeated [2+2] cycloaddition reactions of benzyne in a similar manner to that previously reported.[10b] The third cycloaddition reaction occurred regioselectively[12] upon treatment of bromotosylate **2** with *n*BuLi in the presence of KSA **8** to give a single cycloadduct, which was converted into ketone **3** by selective hydrolysis. The carbonyl group in **3** was converted into a methylene group by a four-step sequence. Acid hydrolysis of triacetal **5** and subsequent reduction of the resulting C_3-symmetric triketone gave triol **6**. Tosylation of **6** afforded tritosylate **7** as a mixture of diastereomers, which were separated by preparative TLC to give the *syn–anti* isomer **7a** and the *syn–syn* isomer **7b** in 53 % and 32 % yields, respectively. The relative stereochemistry of **7a** and **7b** was easily assigned by NMR analysis with symmetry considerations.

Tritosylate **7** served as a versatile platform to introduce various oxygen nucleophiles onto the tricyclobutabenzene framework (Scheme 2). Upon treatment of **7a** with five equivalents of sodium 4-methoxyphenoxide in *N*,*N*-dimethylformamide at 45 °C, the three-fold S_N2 reactions occurred smoothly to give *syn–anti* ether **9a** in 75 % yield. Similarly, the reaction of *syn–syn* isomer **7b** proceeded cleanly and stereospecifically, affording *syn–syn* ether **9b** in 73 % yield. The corresponding sterically hindered 2,6-xylyloxy diastereomers **10a** and **10b** were also prepared in high yields.

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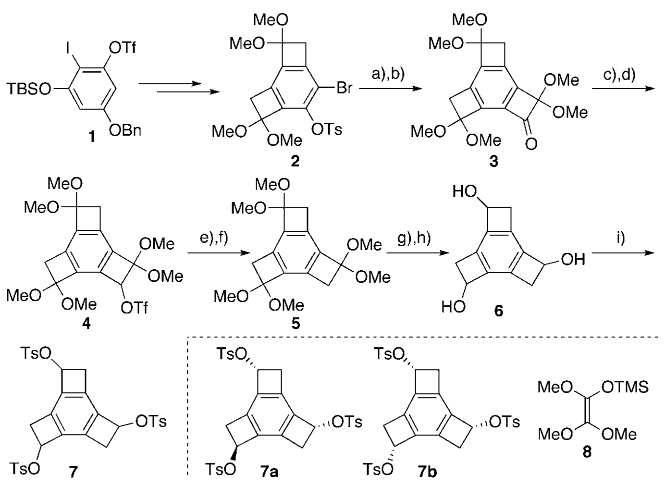


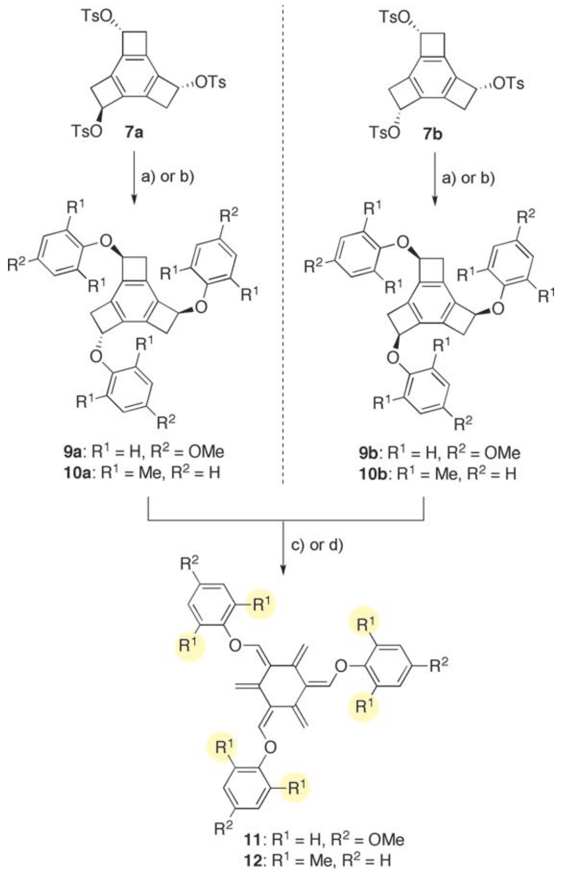
Scheme 1. Preparation of tris(ester) **7**. Reagents and conditions: a) **8**, *n*BuLi, Et_2O, −78 °C, 5 min. b) PPTS, MeOH, 25 °C, 2 h (**3**: 62 % yield, 2 steps). c) $NaBH_4$, MeOH, 0 °C, 15 min. d) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 15 min. e) nBu_4NI, toluene, 95 °C, 4.5 h. f) $LiEt_3BH$, Et_2O, 25 °C, 42 h. (**5**: 74 % yield, 4 steps). g) aq HF, CH_3CN, 25 °C, 2 h. h) $LiEt_3BH$, THF, −100→−78 °C (**6**: 71 % yield, 2 steps). i) TsCl, pyridine, CH_2Cl_2, 25 °C, 18 h (**7a**: 53 % yield, **7b**: 32 % yield). PPTS = pyridinium *para*-toluenesulfonate, Tf = trifluoromethanesulfonyl, Ts = *para*-toluenesulfonyl.

Upon heating of *syn–anti* ether **9a** in toluene at 110 °C, the expected hexaradialene **11** was not obtained: only a complex mixture of products was produced, and the starting material was completely consumed (Scheme 2).[13] On the other hand, when the bulkier 2,6-xylyloxy substrate **10a** (*syn–anti* isomer) was heated in toluene at 100 °C for 3 hours, the ring-opened product **12** was obtained in 74 % yield.[14] Importantly, the product was obtained as a stable white solid after purification by preparative TLC. It is interesting that the isomerization was rigorously stereoselective, irrespective of the stereochemistry of the starting material: the same C_3-symmetric product **12** was also cleanly obtained from the *syn–syn* isomer **10b** (Scheme 2).

Figure 1 shows the ^{1}H NMR spectroscopic monitoring of the thermal reaction of **10a** ([D$_8$]toluene, 100 °C). The reaction proceeded cleanly, and the peaks of the starting material were almost completely converted into those of the corresponding hexaradialene **12** after 3 hours (spectrum (d); Figure 1). During the reaction, neither quinodimethane (one-ring opening) nor bis(quinodimethane) (two ring openings) was observed (see below).

Slow crystallization of hexaradialene **12** gave single crystals suitable for X-ray analysis (hexane, −15 °C) as shown in Figure 2.[15,16] The central six-membered ring adopts a non-planar twist-boat conformation[17] so as to avoid the non-bonding interactions of the exocyclic double bonds.

Trisilyl ethers **14** and **15**, available from the silylation of triol **6**, were also subjected to thermal isomerization conditions (Scheme 3). Upon heating a mixture of *syn–syn* and *syn–anti* isomers of TBDMS-protected **14** (TBDMS = $tBuMe_2Si$; toluene, 105 °C), the ring opening reaction occurred cleanly and stereoselectively to give the C_3-symmetric



Scheme 2. S_N2 reaction of **7** and thermal isomerization of aryl ethers **9a** and **10a**. Reagents and conditions: a) NaH, 4-methoxyphenol, DMF, 45 °C, 36 h (**9a**: 75 % yield from **7a**; **9b**: 73 % yield from **7b**). b) NaH, 2,6-dimethylphenol, DMF, 45 °C, 28 h (**10a**: 77 % yield from **7a**; **10b**: 73 % yield from **7b**). c) Toluene, 110 °C, (**11**: 0 % yield from **9a** and **9b**). d) Toluene, 100 °C, 3 h. (**12**: 74 % yield from **10a**, 73 % yield from **10b**). DMF = *N*,*N*-dimethylformamide.

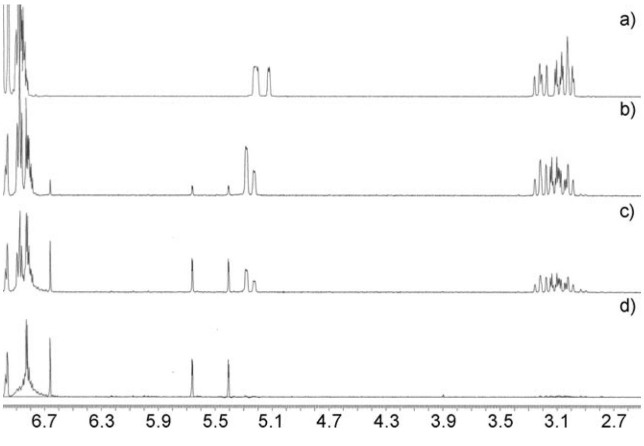


Figure 1. Thermal reaction of **10a** monitored by ^{1}H NMR spectroscopy (400 MHz, [D$_8$]toluene, 100 °C). a) **10a** (RT), b) 15 min (100 °C), c) 1 h (100 °C), d) 3 h (100 °C).

hexaradialene **16** as a single stereoisomer. Although clean formation of **16** was evident by the ^{1}H NMR analysis, it was highly prone to hydrolysis during chromatography on silica-gel, presumably owing to the lability of the enol silyl ether

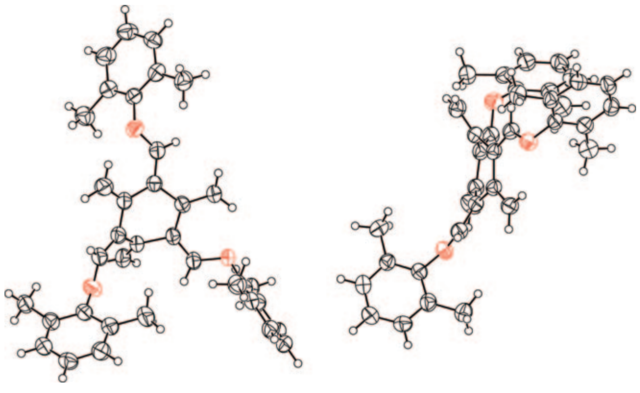
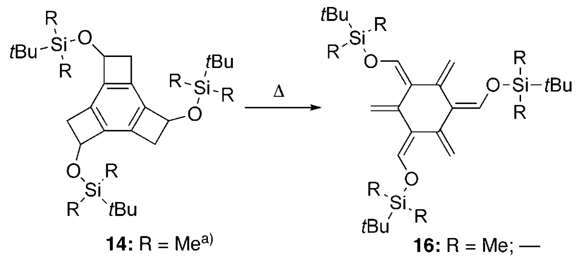


Figure 2. X-ray structure of **12**. Thermal ellipsoids drawn at 50% probability. The hexane molecule and the minor part of the disordered molecule are omitted for clarity, see reference [16].



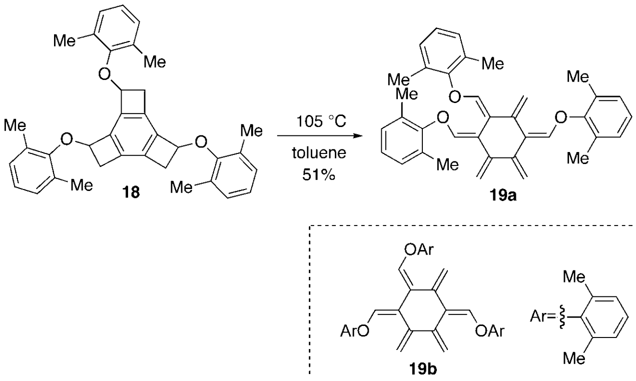
Scheme 3. Thermal isomerization of silyl ethers **14** and **15**. a) Toluene, 105 °C, 2.5 h. b) Chlorobenzene, 125 °C, 1 h (**17**: 75% yield).

moieties. On the other hand, the more sterically congested TBDPS (*t*BuPh$_2$Si) derivative **15** was cleanly converted (chlorobenzene, 125 °C) into the C_3-symmetric hexaradialene **17** as a stable, colorless oil after purification on preparative TLC.

The observed stereoselectivities in these reactions can be explained by the torquoselectivity of the substituted cyclobutene derivatives.[18] The outward rotation of the electron-donating oxy groups on the four-membered rings accounts for the ring-opened product. Also consistent with the formation of **17** would be the, albeit less likely, three-fold inward rotations of three alkoxy groups.

To address this point, the regioisomeric non-C_3-symmetric substrate **18**,[19] consisting of a mixture of four stereoisomers, was subjected to the thermal reaction (Scheme 4). Here again, a high stereoselectivity was observed, irrespective of the stereochemistry of the starting material, to afford **19a** as a single stereoisomer. The formation of **19b**, by the three-fold inward rotations was not observed. Thus, the energetically preferred outward rotation of the electron-donating three aryloxy groups accounts for the formation of the sterically congested product. The stereochemistry of **19a** was determined by NMR spectroscopic analysis (NOE, HMQC, HMBC).[20]

As for the reaction mechanism, we addressed the interesting question of whether the three ring openings proceed in a concerted or stepwise manner. To gain insight into these possibilities, trapping experiments were carried out.



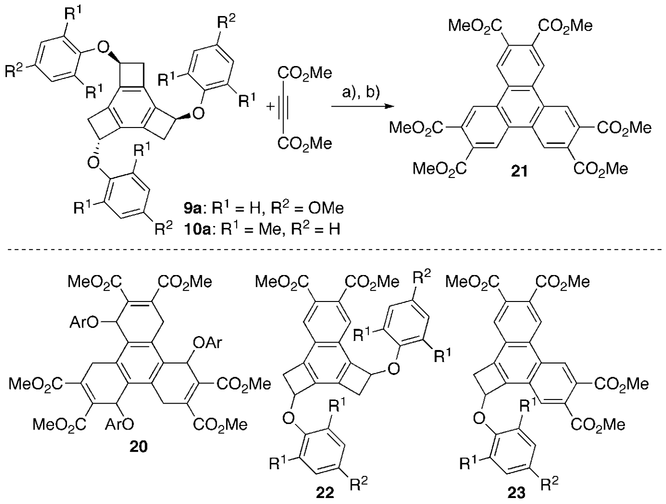
Scheme 4. Thermal isomerization of non-C_3-symmetric aryl ether **18**.

Upon heating of **10a** with dimethyl-2-butynedioate at 100 °C for 24 hours, three-fold [4+2] cycloadditions occurred smoothly, and subsequent treatment with acid effected three-fold eliminations of the tris(annelated) product **20**[21] to give triphenylene **21** in 60% yield (Scheme 5).[22] TLC analysis suggested that the initially observed products, which corresponded to the mono and the bis(cycloaddition) products were gradually converted into the cycloadduct **20**. Indeed, gentle heating of **10a** (toluene, 90 °C, 4 h) gave monoannelated product **22**[23] and diannelated product **23** in 30% and 15% yields, respectively, after acid treatment of the reaction mixture.[24]

It is interesting that the three-fold [4+2] cycloadditions occurred smoothly to give triphenylene **21** when phenyl ether **9a** was heated in the presence of the trapping agent. In contrast, simple heating of **9a** gave a complex mixture of products (see above).

These results suggest that the three ring opening reactions occur independently and the intermediary dienes and/or tetraenes undergo [4+2] cycloaddition to give the corresponding mono and/or diannelated cycloadducts.

In summary, tricyclobutabenzenes, which have bulky alkoxy groups on the four-membered rings, cleanly rearrange



Scheme 5. Three-fold [4+2] cycloaddition reactions of **12**. Reagents and conditions: a) Toluene, 100 °C. b) Conc H$_2$SO$_4$, toluene, RT (**20**: 67% yield from **9a**, 60% yield from **10a**).

into the corresponding hexaradialenes with high stereoselectivity. Further studies on the reactivity and physical properties of such oxygenated alicyclic cross-conjugated hydrocarbons are underway in our laboratory.

Experimental Section

Synthesis of hexaradialene **12**: A solution of tricyclobutabenzene **10a** (10.3 mg, 0.0199 mmol) was heated in toluene at 100 °C. After 3 h, the crude product was purified by column chromatography on silica-gel (hexane/EtOAc = 95:5) to give **12** (7.6 mg, 74 % yield) as a white solid. Recrystallization from hexane gave **12** as colorless prisms: m.p. = 118.3–120.4 °C.

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[11] For the preparation of **2**, see the Supporting Information. See also Ref. [10b].

[12] The regiochemistry of the [2+2] cycloadduct was determined by NMR spectroscopic analysis with symmetric consideration after converting into the C_3-symmetric triacetal **5**.

[13] The reaction has a threshold temperature for the ring opening: upon heating of **9a** at 105 °C, the starting material was gradually consumed, although the reaction did not occur in toluene at 100 °C.

[14] All new compounds were fully characterized by spectroscopic methods, combustion analysis, or high-resolution mass spectral analysis. For details, see the Supporting Information.

[15] Crystallographic data for **12**: $C_{39}H_{43}O_3$, $M_r = 559.7669$, colorless crystal, $0.40 \times 0.30 \times 0.20$ mm, monoclinic, space group $P\bar{1}$, $Z = 2$, $T = 123(2)$ K, $a = 7.608(3)$, $b = 12.346(3)$, $c = 18.172(7)$ Å, $\alpha = 100.71(2)$, $\beta = 100.99(2)$, $\gamma = 104.92(2)°$, $V = 1568.6(9)$ Å^3, $\lambda(\mathrm{Mo_{K\alpha}}) = 0.71075$ Å, $\mu = 0.073$ mm^{-1}. Intensity data were collected on a Bruker SMART 1000 diffractometer. The structure was solved by direct methods (SHELXS97) and refined with full-matrix least-squares on F^2 (SHELXL97). A total of 13951 reflections were measured and 6654 were independent. Final $R1 = 0.1153$, $wR2 = 0.2801$ (4411 refs; $I > 2\sigma(I)$), and GOF = 1.095 (for all data, $R1 = 0.1595$, $wR2 = 0.3101$). CCDC 759632 (**12**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] The high *R* factors are mainly due to the disorder of the hexane crystalline solvent molecules incorporated in the crystal. The hexane molecule is in a narrow channel structure along the *a* axis and is extremely disordered on two inversion centers (0, 0, 0 and 1/2, 0, 0), which results in the continuous carbon chain model without hydrogen atoms. The 2,6-xylyloxy groups of **12** are also disordered. The disorder consists of the flipping of the 2,6-xylyloxy groups and the occupancy for the minor part of the disorder is 12.6(4) %. In spite of the disorder, the conformation of the central six-membered ring has been clearly determined from the electron density map and refined.

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[19] For the preparation of **18**, see the Supporting Information.

[20] For details, see the Supporting Information.

[21] Tris(annelated) product **20** was highly prone to aromatization during column chromatography on silica gel, although its formation was confirmed by ^{1}H NMR analysis.

[22] For related reactions, see: a) H. Hopff, G. Kormany, *Helv. Chim. Acta* **1963**, *46*, 2533–2538; b) H. Hopff, G. Kormany, *Helv. Chim. Acta* **1965**, *48*, 437–443; c) W. E. Billups, D. J. McCord, B. R. Maughon, *J. Am. Chem. Soc.* **1994**, *116*, 8831–8832. See also Refs [4] and [5].

[23] Monoannelated product **22** consisted of two stereoisomers, which were not separable.

[24] Triphenylene **21** was also produced in 5 % yield, accompanied by the starting material **10a** (37 %).