

Gram-Scale Synthesis and Supramolecular Complex of Precursors of Clar's Hydrocarbon Triangulene

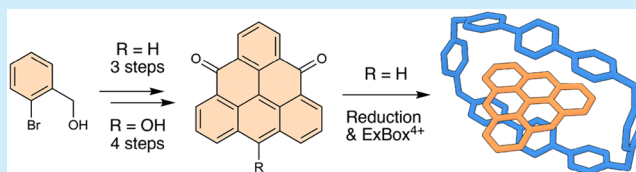
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S Supporting Information

ABSTRACT: We present to date the most efficient gram-scale synthesis of triangulene-4,8-dione and 12-hydroxytriangulene-4,8-dione, the precursors of Clar's hydrocarbon, in overall yields >50%. The direct dihydroprecursors of triangulene, obtained upon reduction of triangulene-4,8-dione, were stabilized in a supramolecular complex with a tetracationic cyclophane ExBox⁴⁺ and characterized by single-crystal X-ray crystallography. This result represents the first step in an endeavor to stabilize the fragile core of triangulene in an inclusion complex in solution and solid state.



The “odd” nature of triangulene has provoked the minds of chemists ever since the proposal of Eric Clar in 1950s.¹ On account of high reactivity, the synthesis of this compound known as Clar's hydrocarbon was not successful until 2001, when Kubo et al. confirmed for the first time the triplet ground state of its trisubstituted derivative by EPR spectroscopy in solution.² After 10 years of (EPR) silence, the chemistry of triangular graphene fragments started to flourish again, and this year, triangulene is featured in the logo of the Symposium on Novel Aromatic Compounds (ISNA) held in Sapporo, Japan. The most recent breakthrough is the imaging of the naked triangulene (2017) and its π -extended homologues (2019) on various surfaces by using STM/AFM techniques (Figure 1).³

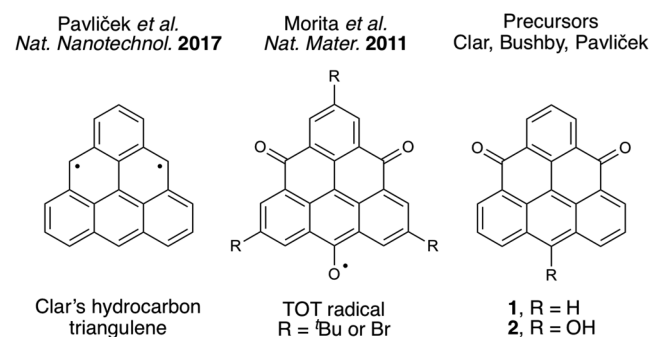
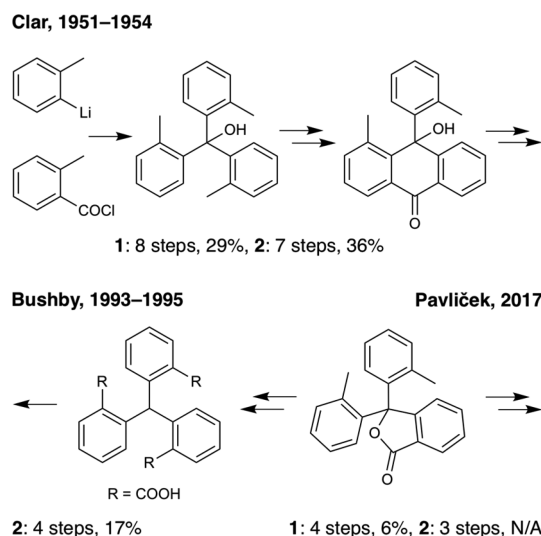


Figure 1. Recent breakthroughs in the chemistry of triangulene.

The first attempts to synthesize triangulene were carried out by Clar. His efforts using the old-days aromatic hydrocarbon chemistry gave rise to two oxo-functionalized precursors **1** and **2** (Figure 1) accessible in eight and seven steps with 29% and 36% yields, respectively (Scheme 1).⁴ Despite the incredible synthetic methodology advancements in the past 60 years, only two shorter pathways have been reported since then by

Scheme 1. Previous Strategies to Triangulene Precursors



Bushby⁵ et al. (1995) and Pavliček^{3a} et al. (2017). None of them, however, surpassed the synthesis of Clar in terms of overall chemical yields.

The oxo-substitution of the triangulene core endows the neutral trioxotriangulene (TOT) radical derived from **2** with chemical stability. This stabilization allowed the exploration of the rich redox properties of TOTs,⁶ which can store up to four electrons reversibly, and the use of this system as a molecular component of cathode-active materials in organic batteries. The tri-*tert*-butyl TOT exhibited a high discharge capacity of more than 300 A h kg⁻¹, exceeding those delivered by Li-ion

Received: July 30, 2019

Published: August 15, 2019

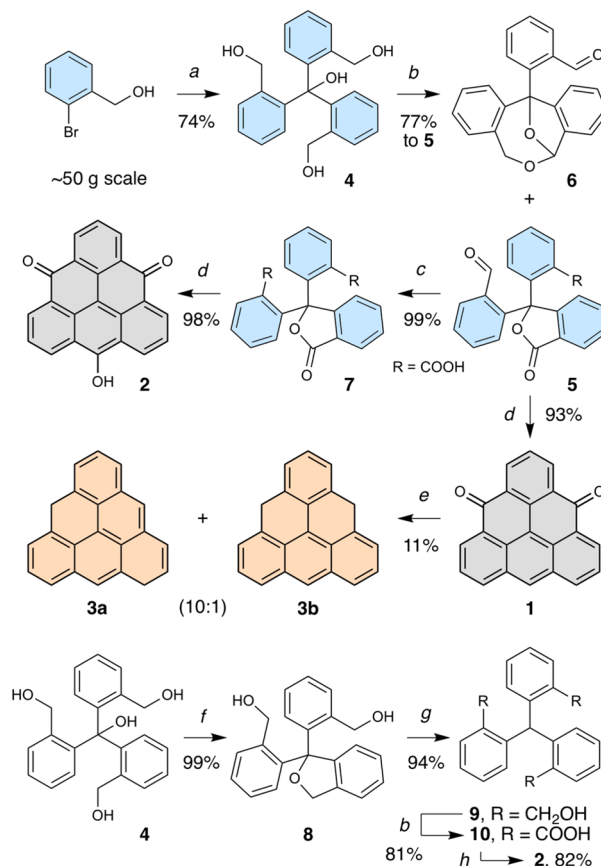
batteries. The unpaired electron in TOT radicals is responsible for the formation of one-dimensional assemblies in the solid state on account of weak π -stacking. Such assemblies show semiconducting properties with relatively high conductivities of $\sim 10^{-3}$ S cm^{-1} . Mixing of a sample of TOT radical with a sample of its reduced form results in a purely organic mixed-valence salt, exhibiting conductivity that can reach up to 125 S cm^{-1} . It has also been demonstrated that other TOT derivatives can act as promising metal-free electrocatalysts in the oxygen-reduction reaction. We showed that the tri-*tert*-butyl derivative of **2** can easily be converted into donor-acceptor dyads with rare layered solid-state packing motifs.⁷ Finally, because of the extra stabilization provided by the peripheral oxygen atoms, the doubly reduced conjugate base of **2** was the first TOT derivative with a triplet ground state detected by EPR spectroscopy.⁸

Considering the importance of these achievements, both fundamentally and from the standpoint of applications, there is a need for a high-yielding few-step synthesis of **1** and **2** that can be performed on a gram scale. The common feature of all previously published synthetic strategies (Scheme 1 and Schemes S1–S3) is the preparation of 3,3-di-*o*-tolylisobenzofuran-1(3*H*)-one. This precursor represents the point in synthesis where the approaches of Bushby and Pavliček shorten the original sequence of Clar, although they significantly forfeit the yield. The subsequent oxidation of the two methyl groups in this precursor to carboxylic acids is required to assemble the triangulenedione core in a final acid-catalyzed cyclization. Each strategy uses rather harsh ($\text{KMnO}_4/\text{reflux}$; Bushby, Pavliček) or even dangerous ($\text{HNO}_3/200$ °C; Clar; precursor on the right in Scheme 1) oxidation conditions. In fact, when we were reproducing the synthetic sequence of Clar, we encountered an explosion during this step in our attempt to oxidize the methyl groups using a pressure flask (Figure S1). A similar dangerous outcome was previously reported in the literature by Bushby et al.⁹ For this reason, we strongly discourage even skilled synthetic organic chemists to use this method.

To avoid these issues, we designed a new synthesis of **1** and **2** (Scheme 2), which employs an intermediate that is accessible in a single high-yielding step and which can be oxidized using a milder oxidant. This intermediate, a C_3 -symmetric tetraalcohol **4**, could be successfully obtained in a very good 74% yield through (1) a lithium-halogen exchange in commercially available 2-bromobenzylalcohol with two equiv of *n*-BuLi, followed by (2) a 3-fold nucleophilic addition of the resulting aryl lithium salt to diethylcarbonate. This reaction can be easily upscaled to ~ 50 g of the starting 2-bromobenzylalcohol without decreasing the yield. Compound **4** does not require purification by column chromatography and can be obtained pure by simple recrystallization from ethyl acetate.

The structure of **4** allows for using a milder oxidant to convert the three hydroxymethyl groups into the corresponding carboxylic acids. Our initial attempts with Jones oxidation provided a mixture of **5** and **6**. While the latter is a byproduct that cannot be oxidized to the desired compound **7**, the former possesses a formyl group in place of the expected carboxylic acid. This unexpected result was, however, a fortunate reaction outcome because **5** can be converted directly to **1**, a reduced form of **2** without the hydroxyl group in position 12. The optimized conditions of the Jones oxidation provided **5** in 77% (3.7 g) and **6** in 21% yield. This oxidation is the only step in our sequence that requires purification by column chromatog-

Scheme 2. Synthesis of Triangulene Precursors **1**, **2**, and **3**^a



^aReaction conditions: (a, 1) *n*-BuLi, THF, -78 °C, 2 h; (a, 2) $(\text{EtO})_2\text{CO}$, rt, 7 days, 74%; (b) CrO_3 , H_2SO_4 , acetone, reflux, 12 h, 77% (**5**), 21% (**6**), 81% (**10**); (c) H_2O_2 , NaH_2PO_4 , HCl, NaClO_2 , MeCN, 10 °C, 6 h, 99%; (d) Cu, H_2SO_4 , 120 °C, 93% (**1**), 98% (**2**); (e) LiAlH_4 , AlCl_3 , $\text{Et}_2\text{O}/\text{THF}$, 3.5 h, 11% (3 cycles); (f) Me_2SiCl_2 , MeCN, rt, 2 h, 99%; (g) Li, $\text{C}_{10}\text{H}_{10}$, THF, rt, 14 h, 94%; (h) H_2SO_4 , 120 °C, 2 h, 82%.

raphy. Subsequent Friedel–Crafts acylation of **5**, employing concentrated sulfuric acid as the solvent and copper as a reducing agent,⁴ resulted in the formation of **1** in excellent 93% yield (1.9 g). This three-step procedure with an overall 53% yield is the shortest and best-yielding synthesis of **1** to date.

Similar cyclization to form **2** requires that the formyl group in **5** is first oxidized to the carboxylic acid. This step was performed with a $\text{NaClO}_2/\text{H}_2\text{O}_2$ mixture,¹⁰ yielding **7** in a nearly quantitative yield (99%, 3.1 g) without the need for purification. Finally, cyclization using Cu/ H_2SO_4 afforded **2**, which was obtained pure upon filtration also almost quantitatively (98%, 2.6 g). This four-step synthetic route gives **2** in an overall 55% yield, which is ~ 1.5 times higher than that of the best available seven-step synthesis of Clar.⁴ Because of low solubility, the structures of both **1** and **2** were confirmed by 1D/2D NMR spectroscopy in D_2SO_4 , including the full assignment of ^1H and ^{13}C resonances reported here for the first time (see the Supporting Information).

Since our attempts to prevent the formation of **6** in the Jones oxidation of the key tetraalcohol **4** were not successful, we explored an alternative path (Scheme 1, bottom). The key was to avoid the formation of the acetal moiety in **6** by reducing the central hydroxy group in **4**. First, ether intermediate **8** was synthesized upon treatment of **4** with

dimethylsilyl dichloride¹¹ in almost a quantitative yield. Then, **8** was reduced by lithium naphthalenide¹² in 94% yield to triol **9**. Subsequent Jones oxidation provided the tricarboxylic acid **10** in a considerably better yield (81%) than the method of Bushby et al. (54%),⁵ which required oxidation of two methyl groups by potassium permanganate to form **10**. The final 3-fold Friedel–Crafts acylation afforded **2** in 82% yield. Although this alternative route added an extra synthetic step, its overall yield of 46% is superior to any of the previously reported syntheses.

To obtain the direct precursor of pristine triangulene, ketotriangulenes **1** or **2** must be further reduced. Reduction of **1** to a mixture of **3a** and **3b** was reported previously twice.^{3a,13} We felt, however, that both the method and the available spectroscopic data to characterize **3** were not sufficiently described, or the samples of **3** were produced in an unsatisfactory purity because of the sensitivity of **3** to oxygen. Our initial attempts to reduce **1** using original conditions $\text{AlCl}_3/\text{LiAlH}_4$ revealed that this protocol leads only to small quantities of the desired product. It appeared to us that the reason is the low solubility of **1**. As the reaction progressed, the surface of undissolved solid **1** would be covered by aluminum oxide, a reaction byproduct, which suppressed the reduction to proceed further. To partially overcome this problem, **1** was added into the mixture of $\text{AlCl}_3/\text{LiAlH}_4$ in small portions. The next important part of the protocol was to isolate soluble red byproducts, presumably various hydroxyl triangulenes formed upon contact with oxygen, during the column chromatography. Even though the presence of oxygen was minimized during the purification steps, formation of these byproducts could not be avoided. They were subjected again to the same reduction conditions, which afforded additional amounts of the desired product. After three cycles, the combined product samples were purified once again by oxygen-free column chromatography, to afford a pure sample of **3** in 11% overall yield. Although this yield is lower than the reported ones, our method is reliable for obtaining very pure material. The NMR spectroscopy revealed that **3** is formed as a 10:1 mixture of two inseparable dihydro isomers **3a** and **3b**. The experimental ratio of 10:1 is in an excellent agreement with the populations of 89% and 11% for **3a** and **3b**, respectively, calculated from our DFT data. Both compounds were fully characterized by 2D NMR spectroscopy, including the full assignment of ^1H and ^{13}C resonances, for the first time (see the Supporting Information).

It was reported by Kubo et al. that three *tert*-butyl groups in the apexes of triangulene improved its kinetic stability and permitted recording an EPR spectrum in a frozen toluene matrix at 123 K.² An intermediate increase of the temperature resulted, however, in a rapid oligo-/polymerization of the diradical in the sample. A better steric protection of triangulene would require introduction of bulky substituents at positions 4, 8, and 12, which is not a straightforward synthetic task because of the unexpected chemical reactivity of π -extended aromatic ketones such as **1** and **2**.¹⁴ An alternative strategy to prevent bimolecular reactions of triangulene in solution is an inclusion of the fragile triangulene core into a large protective molecular shell or, in other words, stabilizing triangulene in the form of a supramolecular host–guest complex. Such an approach has previously enabled kinetically stabilizing a number of well-known reactive intermediates.¹⁵ The first step in this endeavor is a successful formation of a supramolecular complex of triangulene precursors **3**. We selected a tetracationic cyclo-

phane ExBox⁴⁺ as a promising candidate.¹⁶ ExBox⁴⁺ is known to scavenge electron-rich polyaromatic hydrocarbons from their solutions on account of a favorable donor–acceptor interaction in the formed host–guest complexes, the strength of which correlates with the number of π -electrons. Dihydroprecursors **3** possess 20 π -electrons each and are expected to form a stable host–guest complex with ExBox⁴⁺. Indeed, formation of the $3\text{CExBox}\cdot 4\text{PF}_6$ complex was confirmed by ^1H NMR spectroscopy in solution (Figure 2) and X-ray crystallography in the solid state (Figure 3).¹⁷

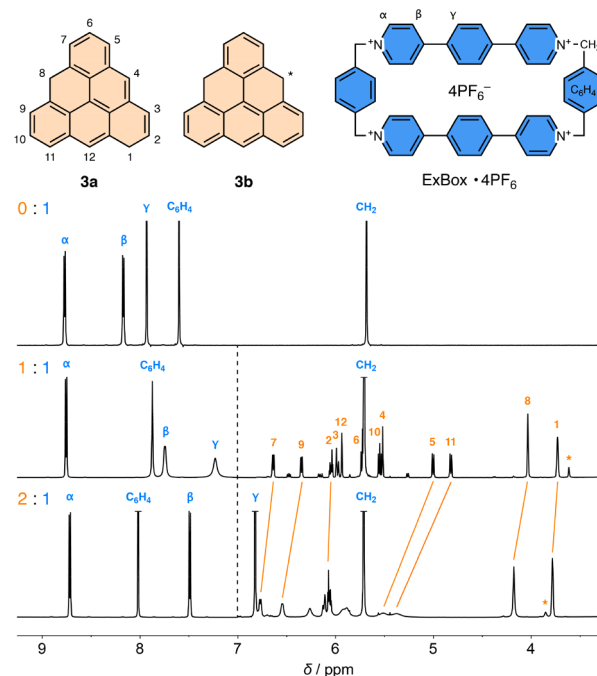


Figure 2. Structures of **3a**, **3b**, and ExBox·4PF₆ (top) and ^1H NMR spectra (CD₃CN, 25 °C; bottom) of ExBox·4PF₆ and its 1:1 and 1:2 complexes with **3** (**3a**/**3b** ~ 10:1). Intensity of the parts of spectra on the right from the dashed line was increased with respect to the left part for clarity.

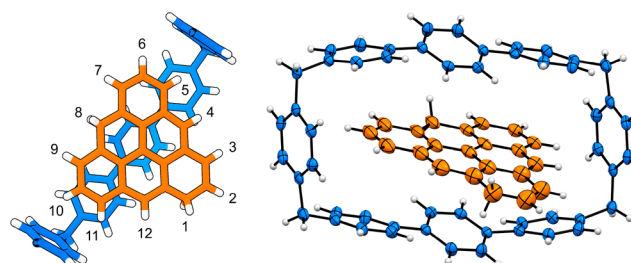


Figure 3. Different crystallographic views of the solid-state structure of $3\text{CExBox}\cdot 4\text{PF}_6$.¹⁷ The top part of ExBox⁴⁺ in the structure on the left is not displayed for clarity. Thermal ellipsoids are shown at a 50% probability level.

In the ^1H NMR spectrum of a 1:1 mixture of **3** and ExBox·4PF₆ in CD₃CN, upfield shifts of β and γ protons and a downfield shift of the C₆H₄ protons for ExBox·4PF₆ as well as upfield shifts for all signals of **3a** and **3b** were observed. These shifts are in agreement with those observed for inclusion of aromatic guests inside ExBox⁴⁺. X-ray diffraction (XRD) analysis of the single crystal of $3\text{CExBox}\cdot 4\text{PF}_6$, obtained by a slow vapor diffusion of diisopropyl ether into the acetonitrile

solution of **3** and ExBox-4PF₆, confirmed that **3** resides inside the cavity of ExBox⁴⁺. A comparison of the carbon–carbon bond lengths of **3a** (the major species) in the complex with those obtained from DFT calculations suggests that the prevalent of the three possible orientations of **3a** inside the cavity is the one shown in Figure 3 (the longest C_{sp3}–C_{sp2} bonds are in the range 1.45–1.47 Å by XRD and 1.50–1.52 Å by DFT). This orientation agrees well with the prevalent orientation in solution: the largest upfield shift is observed for protons 5 and 11, smaller shift for protons 7, 8, and 9, and only a very small shift for protons 1 and 2 (Figure 2, orange lines).

The association constant for the binding of **3** inside ExBox⁴⁺ elucidated by NMR titration (Figure S3) is $\sim 0.8 \times 10^4 \text{ M}^{-1}$, in between those of 18- π -electron [4]helicene ($\sim 0.6 \times 10^4 \text{ M}^{-1}$) and 20- π -electron perylene ($\sim 9 \times 10^4 \text{ M}^{-1}$).¹⁶ Although the affinity of **3** toward ExBox⁴⁺ is relatively high, so is the rate constant for the guest-exchange process, judging from the presence of only one set of averaged signals for the bound and unbound species (both **3** and ExBox⁴⁺) in the NMR spectrum at room temperature. As a result, our initial attempts to generate triangulene trapped in the supramolecular complex in solution at room temperature using oxidants such as chloranil or non-nucleophilic bases (NaH, ^tBuOK) were unsuccessful. Increasing the activation energy preventing triangulene from escaping from its inclusion complex is thus inevitable. A pursuit of such a goal is in progress in our laboratories.

In conclusion, we presented the most efficient synthesis to date of triangulene-4,8-dione and 12-hydroxytriangulene-4,8-dione. Both compounds were synthesized on gram scales in overall yields >50% using a common route with only a single purification by column chromatography. Our simple approach promises a rapid access to C₃-symmetrically oxo-substituted triangulenes. We also proposed a new strategy to stabilize triangulene in a solution or solid state within a supramolecular complex. By means of NMR spectroscopy and single-crystal X-ray diffraction, we demonstrated the first step of this strategy, namely, the complexation of ExBox-4PF₆ and the direct precursor of triangulene, the synthesis of which was here optimized to produce samples of high purity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02683.

Synthetic procedures and characterization data for all new compounds (PDF)

Accession Codes

CCDC 1943899 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (Grant Agreement 716139), the Swiss National Science Foundation (SNSF, T.S./PZ00P2_174175, M.J./PZ00P2_148043, PP00P2_170534), and Experientia Foundation (T.S.). We would like to thank our colleagues at the University of Basel, namely, PD Daniel Häussinger (2D NMR), Dr. Markus Neuburger and Dr. Alessandro Prescimone (XRD), and Prof. Marcel Mayor for supporting our research. We also acknowledge Leoš Valenta (University of Zurich) for help with NMR measurements.

■ DEDICATION

Dedicated to Miroslav Kozák on the occasion of his 60th birthday.

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- (17) Crystal parameters for 3CExBox·4PF₆: [C₂₂H₁₄CC₄₈H₄₀N₄·4(PF₆)·2.8(C₂H₃N)]; orange plate, 0.16 × 0.14 × 0.03 mm; triclinic, P $\bar{1}$ (no. 2); $a = 10.1937(7)$, $b = 10.6981(8)$, and $c = 18.2104(15)$ Å; $\alpha = 96.700(5)$, $\beta = 106.062(3)$, and $\gamma = 107.208(3)^\circ$; $V = 1779.80(14)$ Å³; $Z = 1$; $T = 123$ K; $\rho_{\text{calc}} = 1.536$ g cm⁻³; $\mu = 1.994$ mm⁻¹; $S = 1.1042$. CCDC no. 1943899. Molecules of **3** show rotational displacement disorder inside the cavity of ExBox⁴⁺ (Figure S2).