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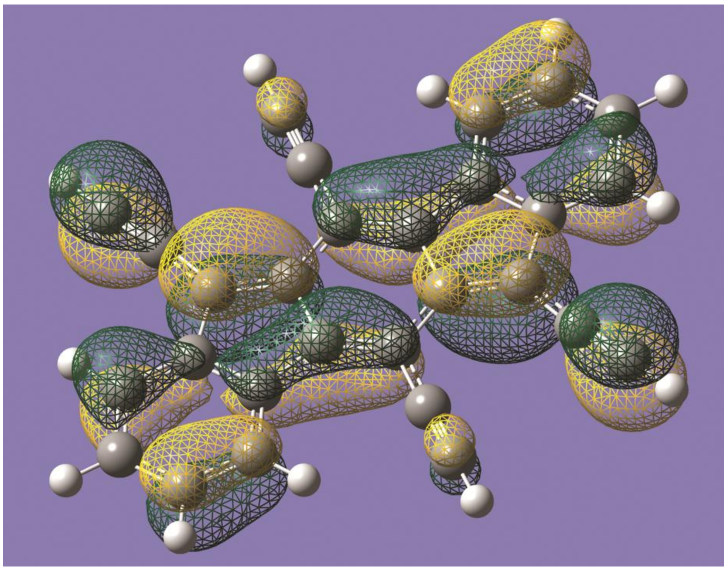

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COMMUNICATION

Concise, aromatization-based approach to an elaborate C_2-symmetric pyrenophane†‡

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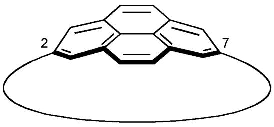
A very short synthesis (5 steps), the crystal structure and resolution of an elaborate, inherently chiral [*n*](1,6)pyrenophane is reported. The synthesis hinges upon two very productive events: a multicomponent reaction and an unprecedented double-McMurry/valence isomerization/dehydrogenation step. Aromatization reactions are involved in the formation of all four of the rings of the pyrene system.

For the [*n*]cyclophanes, *i.e.* those composed of one aromatic system and one bridge, pyrene is the largest aromatic system to have been used frequently. All but one of the known [*n*]pyrenophanes are [*n*](2,7)pyrenophanes (**1**),[1] which have C_{2v} symmetry and are thus inherently achiral systems.[2] The exception is [10](1,6)pyrenophane (**2**),[3] which is C_2-symmetric and thus an inherently chiral cyclophane.[4]



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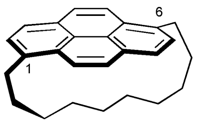

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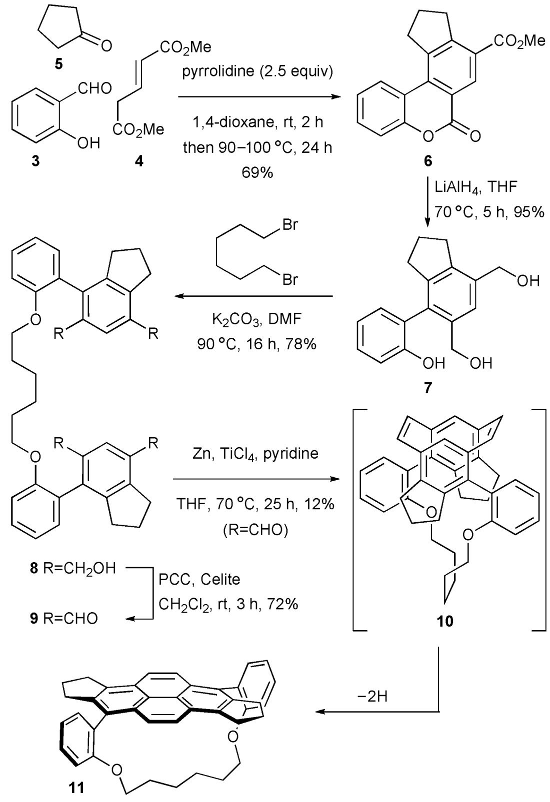
The synthesis of **2** was modeled on the general synthetic approach to the [*n*](2,7)pyrenophanes (**1**),[1] but proved to be problematic.[3] As a result, work aimed at the development of an improved synthetic approach to [*n*](1,6)pyrenophanes (as well as [*n*](2,7)pyrenophanes) was initiated. The initial results of this work are presented herein.

Inspiration for a new synthetic approach came from a recently reported multicomponent reaction (MCR) that affords 6*H*-dibenzo[*b*,*d*]pyran-6-ones (DBP).[5] In one example of this reaction, salicylaldehyde (**3**) reacted with dimethyl glutaconate (**4**) and cyclopentanone (**5**) in the presence of pyrrolidine to afford DBP **6** in 69% yield (Scheme 1). Within **6** can be seen the elements of a 4-substituted isophthalate, which corresponds to the type of starting material used for the synthesis of **2**.[3] Reduction of **6** with $LiAlH_4$ afforded triol **7** (95%). The difference in acidity of the different types of OH groups (benzylic and phenolic) enabled two units of **7** to be tethered by way of a highly chemoselective *O*-alkylation reaction with 1,6-dibromohexane, which afforded tetraol **8** (78%). At this point, the synthesis deviated from the standard route, which would have involved conversion of the four alcohols to bromides, formation of a dithiacyclophane, conversion of the dithiacyclophane into a cyclophanediene (*e.g.* **10**) and a valence isomerization/dehydrogenation (VID) reaction to afford



Scheme 1 Synthesis of (1,6)pyrenophane **11**.

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‡ Electronic supplementary information (ESI) available: Experimental procedures; characterization data and copies of ^1H and ^{13}C NMR spectra; details of the resolution; details of the absorption and emission spectra; Beer's law plot; supplementary crystallographic information for **11**. CIF for **11**. CCDC 880434. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc33611a

the pyrenophane (7 steps overall). Instead, tetraol **8** was oxidized with PCC/Celite® to afford tetraaldehyde **9** (72%) and this compound was subjected to McMurry reaction conditions[6] with the intention of forming cyclophanediene **10** (along with an isomeric cyclophanediene) directly. However, the only compound isolated from this reaction was [12](1,6)pyrenophane derivative **11** (12%).

The (1,6) bridging motif in **11** was evident from its ^{1}H NMR spectrum, which contained an AB system (δ 7.89 and 7.69 ppm, J = 9.2 Hz) for the protons attached to the pyrene system and high field signals for some of the bridge protons (2H multiplets centered at δ 0.36, 0.14, −0.39 and −0.51 ppm), which lie across the face of the pyrene system. The (1,8) isomer of **11** would have exhibited two singlets for the pyrenyl protons and would not have been expected to exhibit aliphatic signals at such high field.[3]

Although the yield of **11** was low, the result is noteworthy for several reasons. First, the reaction delivers the target pyrenophane directly, thereby replacing a 7-step sequence with a 2-step sequence. The reaction is also very productive, as it leads to the formation of three new carbon–carbon bonds and two new aromatic rings. A likely order of events is two successive intramolecular McMurry reactions leading to metacyclophanediene **10** followed by a VID reaction. The observation of dehydrogenation under reductive (McMurry) conditions is not without precedent when it results in the formation of an aromatic system.[7] In the present case, the high aromatic stabilization energy of pyrene (74.6 kcal mol^{-1})[8] provides ample driving force for dehydrogenation. Assuming that the reaction indeed proceeds through metacyclophanediene **10**, this is a very rare example of a McMurry reaction leading to a [2.2]metacyclophane[9] and the first example of the McMurry reaction being used to form *both* bridges of a [2.2]metacyclophanediene. The presence of a tether between the two isophthalaldehyde units in **9** is presumably advantageous in this regard. Finally, it is interesting to note that (1,6)pyrenophane **11** was formed to the exclusion of its (1,8) isomer. This is in contrast to the dithiacyclophane-derived [10](1,6)pyrenophane (**2**), which was formed as the minor component of a 4 : 7 mixture with [10](1,8)pyrenophane.[3]

Pyrenophane **11** is a rather elaborate derivative of [12](1,6)pyrenophane, which means that the pyrene system would be expected to be less distorted from planarity than that of [10](1,6)pyrenophane (**2**).[3] Indeed, the solid-state structure of **11** (Fig. 1 and ESI‡)[10] revealed a pyrene system that is less twisted than the one in **2**. The twist in the pyrene system can be assessed using the torsion angles through its middle (C6-C7-C26-C27-C28-C16-C17-C29). For **11**, the five angles range from 160.0 to 174.1° and the average deviation from 180° (the value for a planar pyrene system) is 10.8°. This compares to a range of 159.9 to 170.5° and an average deviation from 180° of 14.1° in **2**.[3] The bend in the pyrene system of **11** (as indicated by the smallest angle formed by C7-C8-C26 and C17-C18-C16) is 17.4°, which is also smaller than the corresponding value in **2** (27.3°).[3,11] Relatively long intramolecular C(sp^3)–H···π interactions[12] (3.30 Å) between protons attached to C37 and C38 and the apical rings of the pyrene system are also observed.[12] The unit cell (space group $P\bar{1}$, Fig. S3) consists of two enantiomeric molecules in a face-to-face arrangement with a closest π···π contact of 3.47 Å.[13]

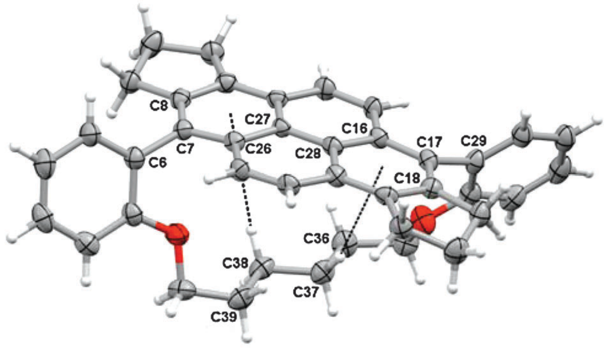


Fig. 1 Asymmetric unit of **11** with 50% probability ellipsoids showing intramolecular C(sp^3)–H···π contacts.

The absorption spectrum for **11** (Fig. 2) exhibits significant complexity in the low energy absorption band envelope with bands λ_{max} (ε, M^{-1} cm^{-1}) at 392 (1.4 × 10^4), 373 (3.2 × 10^4), 365 (3.0 × 10^4), 355 (2.5 × 10^4), 295 (3.9 × 10^4) and 283 (2.5 × 10^4) nm.[14] Based on the linearity of Beer's law plots (ESI‡), there is no evidence for aggregation below 6.0 × 10^{-5} M. The fluorescence quantum yield (Φ) for **11** is 0.40 and the fluorescence lifetime (τ_f) is 1.7 ns. This compares to Φ = 0.64 and τ_f = 480 ns for pyrene.[15] The absorption features at 392 nm and the barely resolved band at 362 nm are not apparent in the emission profile (Fig. 2). As a result, the mirror image symmetry between the absorption and emission spectra expected for a 2-state system is absent. These observations imply that the lowest energy absorption band envelope is comprised of two overlapping transitions and their vibronic components, one of which leads to emission and the other to non-radiative decay. At this juncture, a cautious interpretation is that there is an inversion of the energetics and the nature of the absorbing and emitting states, consistent with observations made in other pyrene-based derivatives.[15,16] A detailed study of the excited state dynamics of **11** is underway.

Small samples (*ca.* 10 mg) of (+)-**11** (>99% *ee* by HPLC) and (−)-**11** (>99% *ee* by HPLC) were obtained by preparative chiral phase HPLC (Chiralpak OD-H column: 40% ethanol (0.1% diethylamine)/CO$_2$, 100 bar). The CD spectra (Fig. 3) of

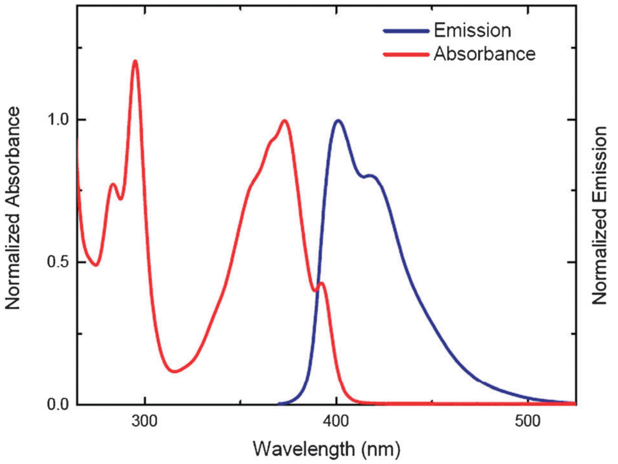


Fig. 2 Normalized absorption (red) and emission spectra (blue) for **11** in CHCl$_3$ (1 atm N$_2$) at 298 ± 3 K. [**11**] = 1.32 μM and λ_{exc} = 350 nm.

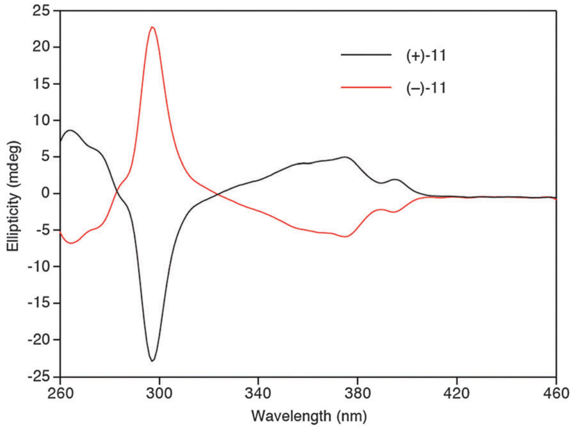
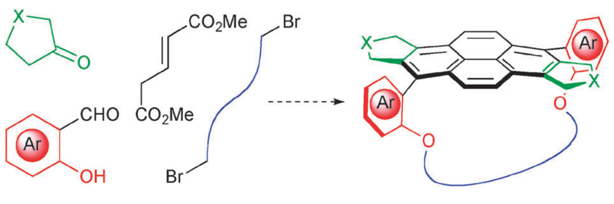


Fig. 3 CD spectra for (+)-**11** (black line) and (−)-**11** (red line).

the two enantiomers are nearly perfect mirror images and the specific rotations ($[\alpha]_D^{23}$ = +130 ± 20° (c = 0.13, CHCl$_3$) and $[\alpha]_D^{23}$ −120 ± 20° (c = 0.14, CHCl$_3$)) agree well. The low precision is due to the small quantities of the pure enantiomers.

In summary, (1,6)pyrenophane **11** was synthesized in 4.4% overall yield by a route that both starts and ends with a highly productive reaction. The initial multicomponent reaction not only brought together most of the atoms required for the pyrenophane **11**, but also generated a new aromatic ring that ultimately manifested itself as the two apical rings in the pyrene system. The synthesis culminated in a very unusual twofold intramolecular McMurry/VID reaction, which generated the two central aromatic rings of the pyrene system. As such, all four of the rings in the pyrene unit were created during the synthesis. Looking forward, the multicomponent reaction holds promise for the synthesis of related pyrenophanes through variation of the ketone and salicylaldehyde components of the MCR (Scheme 2). There is also potential to vary the length of the bridge (and thus the degree of deformation of the pyrene system) by varying the length of the dihalide used in the *O*-alkylation reaction. Asymmetric syntheses of these inherently chiral cyclophanes are also conceivable. Work aimed at exploiting these opportunities is underway.



Scheme 2 Points of diversity for future (1,6)pyrenophane syntheses.

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10 Crystal data for **11**: $C_{40}H_{36}O_2$, M = 548.69, triclinic, a = 9.395(5) Å, b = 12.771(6) Å, c = 13.799(7) Å, α = 104.045(8)°, β = 107.143(4)°, γ = 106.279(6)°, V = 1419.9(12) Å^3, T = 153(2) K, space group $P\bar{1}$, Z = 2, μ(Mo-Kα) = 0.077 mm^{-1}, 13837 reflections measured, 5859 independent reflections ($R_{\rm int}$ = 0.0590). The final R_1 values were 0.0884 ($I > 2\sigma(I)$)and 0.1271 (all data). The final $wR(F^2)$ values were 0.1702 ($I > 2\sigma(I)$) and 0.1924 (all data). The goodness of fit on F^2 was 1.150. CCDC 880434.

11 The evaluation of bend using this metric requires the torsion angle for C8-C26-C18-C16 to be close to 180°. For **11**, the angle is 175.1°, which is comparable to 174.5° in **2** (ref. 3).

12 The C–H···centroid angles are 157.6° and 159.8°, which qualifies these interactions as meaningful, according to: E. Arunan, G. R. Desiraju, R. A. Klein, J. Sadlej, S. Scheiner, I. Alkorta, D. C. Clary, R. H. Crabtree, J. J. Dannenberg, P. Hobza, H. G. Kjaergaard, A. C. Legon, B. Mennucci and D. J. Nesbitt, *Pure Appl. Chem.*, 2011, **83**, 1619. Slightly longer C(sp^3)–H···π interactions (3.39–3.51 Å) between protons on C36 and C39 and the two central rings of the pyrene system are not meaningful because the C–H···centroid angles are less than 130° (128.1–128.5°). For discussions of the C–H···π hydrogen bond, see: G. R. Desiraju, *Angew. Chem., Int. Ed.*, 2011, **50**, 52, and references cited therein.

13 While this distance may evoke thoughts of nascent π stacking, it is important to bear in mind that the pyrene systems are twisted and bent away from one another. Thus, the 3.47 Å distance applies only to the closest contact and not the full pyrene surfaces.

14 The photophysical properties of pyrene and pyrenyl derivatives have been extensively documented.[15,16] Briefly, following the discussion of Hynes[15] and based on the extensive studies of Thulstrup,[16] the assignments of four transitions and their vibronic components that dominate the UV-vis absorption spectrum are outlined below. The lowest energy transition is assigned to a $So \rightarrow {}^1L_b$ transition which formally forbidden. The $So \rightarrow {}^1L_b$ picks up intensity through vibronic coupling with the $So \rightarrow {}^1L_a$ state that is 2700 cm^{-1} higher in energy. This is clearly reflected in the ratio of the oscillator strengths ($f_{\rm osc}$) of the $So \rightarrow {}^1L_a$ and $So \rightarrow {}^1L_b$ transitions respectively where $f_{\rm osc}({}^1L_a)/f_{\rm osc}({}^1L_b)$ = 120, and gives rise to the complex vibronic structure observed in the UV-vis spectra for pyrene. The two major higher lying transitions are assigned $So \rightarrow {}^1B_b$ (36200 cm^{-1}) and $So \rightarrow {}^1B_a$ (41000 cm^{-1}), respectively.

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