JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis, Crystal Structure, and Resolution of [10](1,6)Pyrenophane: An Inherently Chiral [*n*]Cyclophane

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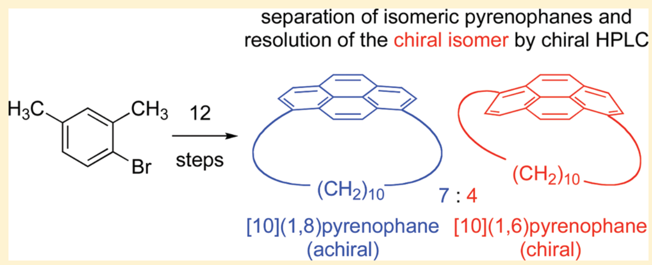
S *Supporting Information*

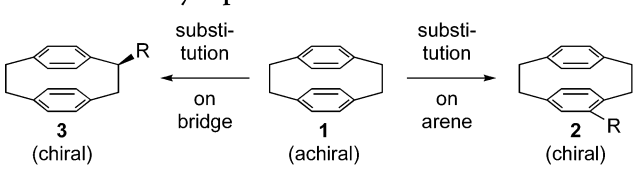
ABSTRACT: A synthetic approach to a set of three inherently chiral [*n*]cyclophanes, [*n*](1,6)pyrenophanes (**29a**–**c**, $n = 8-10$) was investigated. Progress toward **29a** was thwarted by the failure of the key dithiacyclophane-forming reaction. For the next higher homologue, the synthesis was completed, but the desired [9](1,6)pyrenophane (**29b**) could only be partially separated from an isomeric pyrenophane, [9](1,8)pyrenophane (**28b**), and an unidentified byproduct. Work aimed at the synthesis of the next higher homologue resulted in the isolation of a 7:4 mixture of [10](1,8)pyrenophane (**28c**) and [10](1,6)pyrenophane (**29c**), which could not be separated by column chromatography or crystallization. However, single-crystal X-ray structures of **28c** and **29c** were obtained after manual separation of two crystals with different morphologies from the same batch of crystals obtained from the 7:4 mixture of **28c** and **29c**. The pyrene system of **29c** was found to have a gentle end-to-end bend as well as a significant longitudinal twist. Short intermolecular C(sp^3)–H···π contacts (2.64 to 2.76 Å) between H-atoms on the bridge and the centroids of three of the four six-membered rings of the pyrene system of a neighboring pyrenophane of like chirality give rise to the formation of single enantiomer columns. From a DNMR study of the mixture of **28c** and **29c**, the bridge in [10](1,8)pyrenophane (**28c**) was found to undergo a conformational flip from one side of the pyrene system to the other with $\Delta G^{\ddagger} = 14.9 \pm 0.2$ kcal/mol. A two-stage preparative HPLC protocol was subsequently developed for the separation of **28c** and **29c** (Chiralpak AD-H column) and then the enantiomers of **29c** (Chiralcel OJ-H column). This enabled the measurement of their optical rotations and CD spectra.



■ INTRODUCTION

Stereochemistry is one of the many interesting facets of cyclophane chemistry,[1] and a significant body of literature on chiral cyclophanes exists.[2] Parent cyclophanes, i.e., the bare-bones assemblies of aromatic units and bridges, can be achiral or chiral, but most of the quintessential cyclophane systems, e.g., [2.2]paracyclophane (**1**), are of the achiral variety. These, however, can become chiral when appropriately substituted, either on the aromatic system, e.g., **2**, or, less commonly, on the bridge, e.g. **3** (Scheme 1). Indeed, a large majority of known chiral cyclophanes are derivatives of inherently achiral cyclophanes (especially [2.2]paracyclophane (**1**)).[2] Nevertheless, a considerable number of inherently chiral parent cyclophanes are known, a small selection of which (**4**,[3] **5**,[4] **6**,[5] and **7**[6]) is shown below. Only a few inherently chiral parent cyclophanes have been resolved, e.g., **5** and **7**. Furthermore, virtually all of the inherently chiral cyclophanes reported so far are composed of more than one aromatic system.[7] A series of [*n*](2,5)-pyridinophanes ($n = 8-12$; compound **7** when $n = 9$) are the only examples of inherently chiral [*n*]cyclophanes (i.e., those composed of a single aromatic system and one bridge).[6] Remarkably, the resolved enantiomers of pyridinophane **7** were reported to be configurationally very stable, maintaining their optical activity after prolonged heating at 250 °C! Only the highest homologue of **7** ($n = 12$) was found to be configurationally unstable at room temperature.

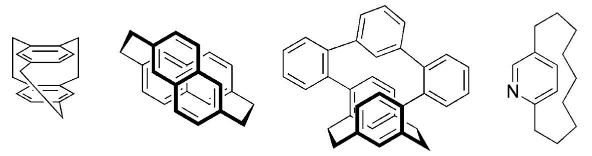
Scheme 1. Substitution of an Inherently Achiral Cyclophane to Give Chiral Cyclophanes



The synthesis of inherently chiral and configurationally stable parent [*n*]cyclophanes requires an aromatic system with enantiotopic faces (including consideration of the bridging motif) and this rules out benzene, regardless of the bridging

Received: May 20, 2011
Published: November 27, 2011

motif. Larger benzenoid aromatic systems with particular bridging motifs (e.g., [*n*](2,6)naphthalenophanes) and various mononuclear heteroaromatic systems with particular bridging motifs (e.g., [*n*](2,5)pyridinophanes) are therefore needed, as are concise, general synthetic approaches. The bridge must also be short enough to provide configurational stability. With these issues in mind, it is interesting to note that there are relatively few reports of [*n*]cyclophanes derived from aromatic systems larger than benzene regardless of whether they are inherently chiral or not.[8]



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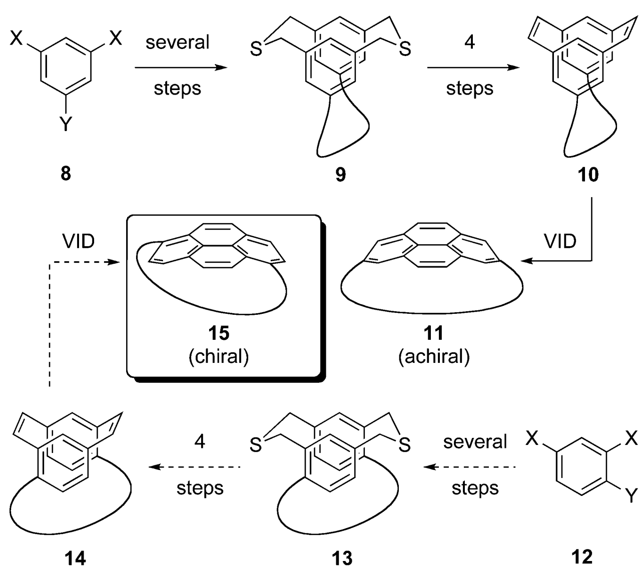
Pyrene is a promising aromatic system for incorporation into a chiral and configurationally stable [*n*]cyclophane. There are several bridging motifs that render the faces of this polynuclear aromatic system enantiotopic, and it is large enough that interconversion of the enantiomers by way of a "skipping rope" process is likely to be difficult, even with reasonably long bridges (cf. [9](2,5)pyridinophane (**7**)). Lastly, and perhaps most importantly, a range of [*n*]pyrenophanes has been reported over the past two decades using a common synthetic approach.[9] Although these systems have all been inherently achiral (2,7)pyrenophanes (**11**), the general synthetic approach should be easily adapted for the synthesis of inherently chiral (C_2-symmetric) [*n*](1,6)pyrenophanes (**15**) simply by changing the substitution pattern of the starting material from a 1,3,5-trisubstituted benzene (**8**) to a 1,2,4-trisubstituted benzene (**12**) (Scheme 2). Instead of just an end-to-end bend, which is

Scheme 2. Synthetic Approach to [*n*](2,7)Pyrenophanes (11) and Proposed Approach to [*n*](1,6)Pyrenophanes (15) (VID = Valence Isomerization/Dehydrogenation)

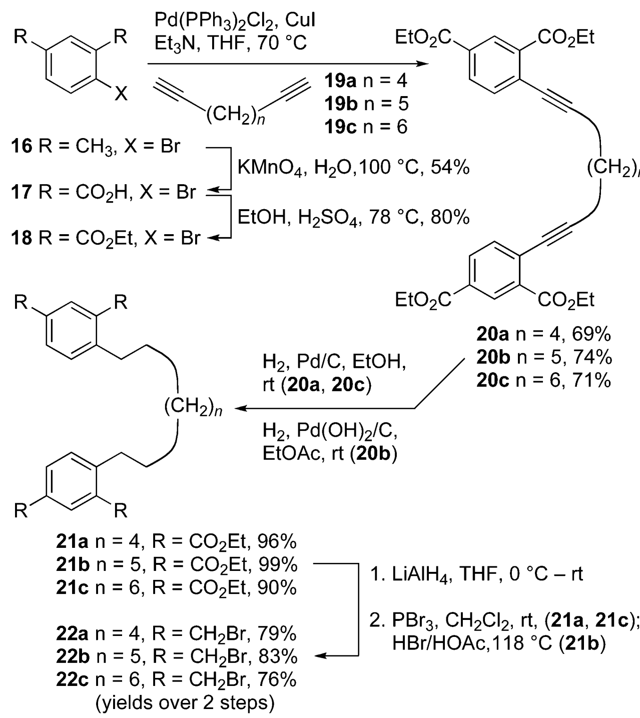


present in the pyrene system of the [*n*](2,7)pyrenophanes (**11**) and the pyridine system in **7**, the bridge of the [*n*](1,6)-pyrenophanes (**15**) would be expected to also impose a longitudinal twist, or torsion, around the long axis of the pyrene system. If the enantiomers of such a pyrenophane could be separated, this would allow the chiroptical and photophysical properties of a chiral pyrene system (a much more interesting chromophore than pyridine) to be studied.

■ RESULTS AND DISCUSSION

The key 1,2,4-trisubstituted building block, diethyl 4-bromoisophthalate (**18**), was synthesized from 4-bromo-*m*-xylene (**16**) using an oxidation/esterification sequence (43%, two steps) (Scheme 3). At this point, an eight-carbon bridge

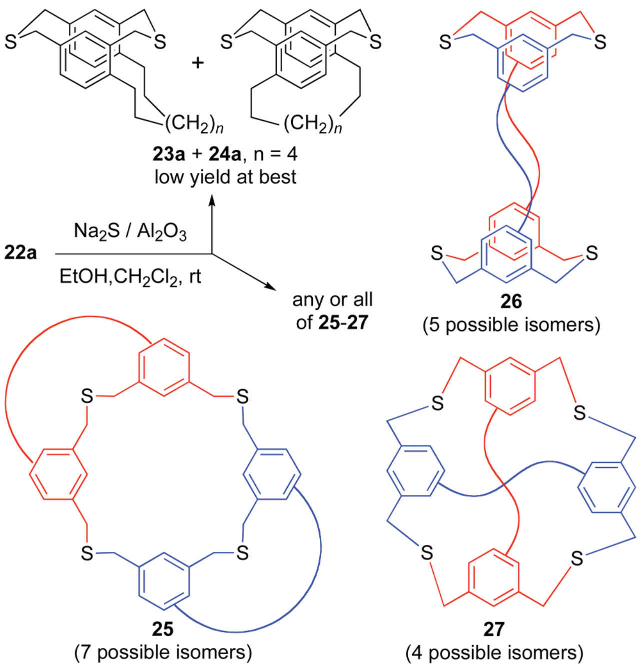
Scheme 3. Synthesis of Tetrabromides 22a−c



was chosen to link two aromatic building blocks because it was expected to impart significant, but not excessive, twist to the pyrene system in the target [8](1,6)pyrenophane. Accordingly, Sonogashira reaction of **18** with 1,7-octadiyne (**19a**) afforded diynetetraester **20a** (69%). The alkyne functionalities were removed by catalytic hydrogenation (96%), and the resulting tetraester **21a** was converted into tetrabromide **22a** by sequential reaction with $LiAlH_4$ and PBr_3 (79%, two steps).

The reaction of tetrabromide **22a** with Na_2S/Al_2O_3 was expected to give a mixture of isomeric dithiacyclophanes **23a** and **24a** (Scheme 4). Two isomers can form because the faces of the two benzene rings are prochiral and can therefore be connected in a face-to-face or face-to-back fashion. Obtaining a mixture at this point was expected to be unavoidable, and separation at this stage or later in the synthesis was a part of the plan. However, treatment of tetrabromide **22a** with Na_2S/Al_2O_3 gave little or none of the desired dithiacyclophanes **23a** and **24a**. The ^1H NMR spectrum of the crude product was more complicated than expected for a mixture of **23a** and **24a**, and the APCI(+) mass spectrum showed a base peak at m/z = 765. This corresponds to $[M + 1]^+$ for tetrathiacyclophanes resulting from the coupling of two molecules of tetrabromide **22a**. The situation, however, is complicated as 16 isomeric structures are possible. These can be broadly categorized according to the way in which the CH_2SCH_2 bridges connect the two sets of tethered arenes, i.e., **25−27** (Scheme 4).

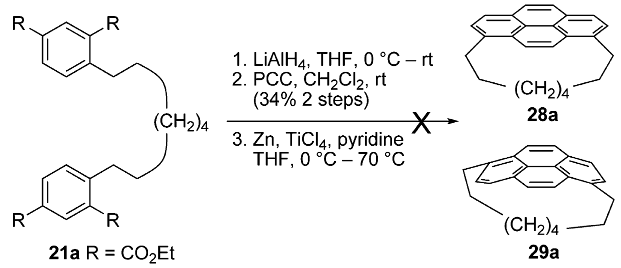
Scheme 4. Reaction of Tetrabromide 22a with Na_2S/Al_2O_3



Isomers of **25** arise when each benzene ring forms one CH_2SCH_2 bridge to the other benzene ring that came from the same molecule of **22a** (an "intramolecular" bridge)[10] and one of the benzene rings that came from a different molecule of **22a** (an "intermolecular" bridge).[10] There are two ways in which a benzene ring can form two "intermolecular" bridges, and these lead to isomer groups **26** and **27**. When each benzene ring forms two intermolecular CH_2SCH_2 bridges to one of the benzene rings originating from a different molecule of **22a**, an isomer of **26** is produced. If the two intermolecular CH_2SCH_2 bridges from a particular benzene ring are to different benzene rings of the other molecule of **22a**, the product is an isomer of **27**. Individual members of each category (see the Supporting Information) differ in the attachment points of the long bridge to the common tetrathiacyclophane skeleton. Of course, when both new CH_2SCH_2 bridges are intramolecular, the products are dithiacyclophanes **23a** and **24a**. Although a small peak corresponding to $[M + 1]^+$ for these dithiacyclophanes (m/z = 383, 6%) was also observed in the APCI(+) mass spectrum, the most optimistic interpretation of this observation would be that only a small proportion of **23a** and **24a** was generated. Neither **23a** nor **24a** appears to be strained significantly, so the origin of the preference for intermolecular reaction at some point during the coupling reaction is unclear.

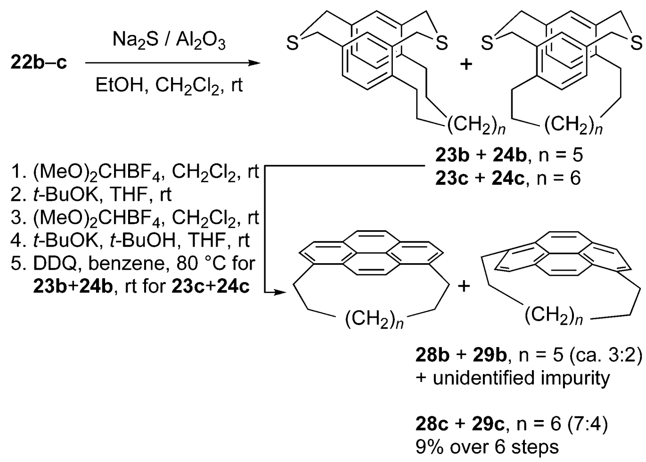
In an attempt to circumvent the failed sulfide coupling, the use of a 2-fold intramolecular McMurry reaction was briefly investigated. Despite its generally poor record in the synthesis of [2.2]metacyclophanes,[11] intramolecular McMurry reactions have recently been applied successfully.[8c,12] Tetraester **21a** was therefore reduced with $LiAlH_4$, and the crude tetraol was oxidized with PCC to afford the corresponding tetraaldehyde (34%, two steps) (Scheme 5). Subjection of this compound to McMurry reaction conditions[13] resulted in the complete consumption of the starting material, but no mobile compounds, e.g. **28a** and/or **29a** (TLC analysis) were formed during this reaction. At this point, work with an eight-carbon tether was terminated, and attention was turned to systems with longer tethers.

Scheme 5. Attempted Intramolecular McMurry Reaction of 28a



Tetrabromides **22b** (9-carbon tether) and **22c** (10-carbon tether) were synthesized from 1,8-nonadiyne (**19b**) and 1,9-decadiyne (**19c**), respectively, according to the approach used for **22a** (Scheme 3). For **22b**, some of the reagents were different, but there was little change in the yields. However, the outcome of the reactions of **22b** and **22c** with Na_2S/Al_2O_3 (Scheme 6) was different than that observed for **22a**.

Scheme 6. Synthesis of Pyrenophanes 28b,c and 29b,c



For **22b**, column chromatography of the crude reaction mixture afforded a mixture consisting mainly of dithiacyclophanes **23b** and **24b**. The EI mass spectrum exhibited the expected molecular ion peak at m/z = 396 (35) and no peaks at higher mass. The ^1H NMR spectrum of this mixture is consistent with a ca. 3:1 mixture of the two dithiacyclophanes (ca. 90% purity), but it could not be determined which one was the major product. For the thioether bridges, the major isomer gives rise to an AB system (δ 3.98, 3.83, J = 14.8 Hz) and a singlet (δ 3.80, degenerate AB system). The minor isomer exhibited two AB systems (δ 3.89, 3.87, J = 14.8 Hz; δ 3.87, 3.74, J = 15.4 Hz). In the aromatic region, signals attributable to the internal protons of the major and minor isomers were observed at δ 7.13 and 7.48, respectively, in a ca. 3:1 ratio, along with a broad singlet at δ 6.84, which is attributable to the external protons for both isomers. All attempts to purify or separate **23b** and **24b** by column chromatography or crystallization were unsuccessful. In fact, product losses and decreases in purity accompanied the attempted purifications and separations. Consequently, the mixture was taken through the standard five-step series of reactions for the conversion of a tethered dithiacyclophane into a pyrenophane that has been used for all of the (2,7)pyrenophanes reported previously by our group.[9,14] This consists of *S*-methylation, Stevens rearrangement, *S*-methylation, Hofmann elimination, and cyclodehydrogenation (Scheme 6).

Another mixture of compounds was obtained following column chromatography (single spot by TLC analysis). The ^{1}H NMR spectrum of this mixture was rather complex but contained some signals at higher field than δ 0 ppm, which strongly suggested the presence of [9](1,6)pyrenophane (**29b**). No such high field signals would be expected for [9](1,8)-pyrenophane (**28b**) because the bridge is not constrained to lie across the face of the pyrene system, as it is in **29b**. Crystallization of this mixture from hexanes afforded colorless needles, which were determined by analysis of their ^{1}H NMR spectrum (see the Supporting Information) to be a ca. 4:1 mixture of [9](1,8)pyrenophane (**28b**) and an unidentified impurity.[15] Further crystallizations did not improve the purity. The aromatic region of the spectrum was dominated by two singlets (δ 8.29 and 7.94 ppm) and an AX system (δ 8.02, 7.72 ppm, J = 7.8 Hz), which is characteristic of a 1,8-disubstituted pyrene unit. Since the spectrum was devoid of signals above δ 0 ppm, it was concluded that the impurity was neither [9](1,6)pyrenophane (**29b**) nor a [9](1,6)-dihydropyrenophane.[16] The ^{1}H NMR spectrum of the material obtained from the mother liquor (see the Supporting Information) indicated that it was a ca. 3:8:1 mixture of **28b** and **29b** and the same unidentified impurity as before.[15] Attempted crystallization of this mixture did not afford a purer sample of **29b**. Signals attributable to **29b** include two AX systems in the aromatic region (δ 8.20, 7.98 ppm, J = 9.2 Hz; δ 8.00, 7.71 ppm, J = 7.6 Hz) and three broad high-field multiplets centered at δ −0.24 (2 H), −1.30 (4 H), and −1.70 (2 H) ppm. Having identified which aromatic signals correspond to **28b** and **29b**, the ratio of these two pyrenophanes in the crude mixture was estimated to be ca. 3:2.

The benzylic protons of **28b** appear as two well-resolved ddd at δ 3.75 (J = 14.0, 8.5, 4.3 Hz) and 3.14 (J = 14.0, 7.7, 4.4 Hz). This, in addition to the observation of nine aliphatic signals, indicated that the bridge in this cyclophane lies to one side of the plane defined by the pyrene system (cf. the crystal structure of **28c** below) and that the flip of the bridge from one side of the pyrene system to the other is slow on the NMR time scale.[17] This conformational process interconverts two identical species. In the spectrum of **29b**, the benzylic protons are observed as two well-resolved ddd at δ 3.73 (J = 13.3, 6.7, 6.7 Hz) and 2.92 (J = 13.4, 6.7, 6.7 Hz), and a total of nine aliphatic signals (two of them virtually coincident) can be identified.[17] Again, a slow flip of the bridge from one face of the pyrene system to the other can be inferred, but now the bridge flip interconverts the two enantiomeric forms of **29b**. Thus, at room temperature, **29b** is at least reasonably configurationally stable. Determination of the energy barrier for the bridge flip, e.g., using variable-temperature NMR studies, will have to await the availability of a pure (or purer) sample of **29b**.

Moving to the next higher homologue of the series, reaction of tetrabromide **22c** with Na_2S/Al_2O_3 again afforded a mixture of the desired dithiacyclophanes **23c** and **24c**. Standard column chromatography of the crude reaction mixture afforded a mixture of **23c** and **24c** of ca. 90% purity (by ^{1}H NMR analysis) in ca. 40% yield. The ^{1}H NMR spectrum of the mixture of **23c** and **24c** was very similar to that of **23b** and **24b**, with the exception of the signals for the internal protons of the two isomers, which overlapped to give a single broad singlet at δ 7.26. The only signals in the ^{1}H NMR spectrum of **23c** and **24c** that exhibited only slight overlap were those due to one of the benzylic protons of the long bridge and one of the benzylic protons of a thioether bridge. An approximate ratio of 1.7:1 was determined using these signals. The APCI(+) mass spectrum showed the expected $[M + 1]^+$ peak at m/z = 411 (39) as well as a peak at m/z = 821 (21) corresponding to the $[M + 1]^+$ peaks of dimeric tetrathiacyclophanes (cf. **25**−**27**).

Like their lower homologues **23b** and **24b**, **23c** and **24c** were found to be somewhat unstable toward chromatography and general handling under air. To minimize losses during workup and chromatography, it was found to be practical to filter the reaction mixture through a plug of Celite and use the crude material immediately in the subsequent series of steps. Accordingly, the crude mixture of **23c** and **24c** was subjected to an *S*-methylation/Stevens rearrangement/*S*-methylation/Hofmann elimination sequence of reactions. At this point, the ^{1}H NMR spectrum of the product mixture indicated that it already consisted mainly of the target pyrenophanes **28c** and **29c**, but with one or more minor (<10%) byproducts. The peak in the APCI(+) mass spectrum at m/z = 343 (36), two mass units greater than the $[M + 1]^+$ peak of **28c** and **29c**, suggested that the byproducts were cyclophanedienes and/or dihydropyrenophanes.[16] Whatever the case, treatment of this mixture with DDQ at room temperature afforded a clean mixture of [10](1,8)pyrenophane (**28c**) and [10](1,6)pyrenophane (**29c**) in a combined 9% yield over six steps from tetrabromide **22c**. Again, all attempts to separate the two products by chromatography or crystallization were unsuccessful.

The ratio of [10](1,8)pyrenophane (**28c**) to [10](1,6)-pyrenophane (**29c**) was determined to be 7:4 by integration of the signals in the aromatic region of the ^{1}H NMR spectrum (Supporting Information). The aromatic signals for [10](1,8)-pyrenophane (**28c**) were essentially the same as those for **28b** ($\Delta\delta$ < 0.04 ppm), which is not surprising because the pyrene system in both compounds is expected to be planar. On the other hand, the aromatic signals for the C_2-symmetric [10](1,6)pyrenophane (**29c**) (two AX systems: δ 8.34, 8.01 ppm, J = 9.3 Hz; δ 8.04, 7.82 ppm, J = 7.8 Hz) are all at slightly lower field ($\Delta\delta$ = 0.03−0.14 ppm) than those of **29b**. This is consistent with the trend observed for the [n](2,7)-pyrenophanes, in which the aromatic protons consistently move to higher field as the aromatic system becomes more distorted from planarity.[9,14] As with **29b**, the bridge of **29c** lies across one face of the pyrene system, which gives rise to some very high field signals in the ^{1}H NMR spectrum, including two 2 H multiplets centered at δ −1.95 ppm and −2.65 ppm. Remarkably, the highest field signal appears at more than half a ppm higher field than the highest field signal observed in any of the [n](2,7)pyrenophanes (δ −2.10 ppm).[9b]

In the aliphatic region of the ^{1}H NMR spectrum of the 7:4 mixture of **28c** and **29c**, the benzylic signals for **29c** were observed as two well-resolved ddd at δ 3.70 (J = 13.1, 11.2, 4.7 Hz) and 3.14 (J = 13.2, 4.4, 4.4 Hz). In contrast, those of **28c** appeared as very broad singlets, which were suggestive of a conformational process near coalescence. A DNMR experiment (Figure S1, Supporting Information) was performed (toluene-d_8 solution), and an energy barrier of $\Delta G^{\ddagger}$ = 14.9 ± 0.2 kcal/mol for the process was determined (T_c = 325 K, ν_{AB} = 297.7 Hz).[18] It was also observed that the benzylic signals of **29c** gradually lost resolution upon warming to 366 K (the limit of the instrument) but had not yet assumed the appearance of the signals for **28c** at 278 K (45 K below coalescence). If **29c** is assumed to be ≈100 K below coalescence, this would correspond to an energy barrier of $\Delta G^{\ddagger}$ ≈ 22 kcal/mol.

However, in view of the report that enantiomerically pure [9](2,5)pyridinophane (7) retained its optical activity after prolonged heating at 250 °C,[6] it would be quite surprising for **29c** to have such a low energy barrier.

The 7:4 ratio (1.75:1) of **28c**:**29c**, where it is clear which isomer is more abundant, is consistent with the approximate ratio observed for **23c**:**24c** (1.7:1), where it could not be determined which isomer is more abundant. The same trend was observed for the lower homologues **23b**:**24b** (3:1 in favor of one of them) and **28b**:**29b** (ca. 1.5:1 in favor of **28b**). If **23b** and **23c** are indeed the major isomers, then it suggests that there is a significant difference in the rate of S_N2 reactions at the two different types of benzylic bromides in **22b** and **22c**. Under this scenario, like benzylic positions of the two aromatic systems in **22b** and **22c** will be coupled preferentially. In other words, the two less hindered positions will be coupled selectively and the two more hindered positions will be coupled selectively, resulting in the formation of an excess of **23b** and **23c** (the precursors to **28b** and **28c**).

The mixture of [10](1,8)pyrenophane **28c** and [10](1,6)-pyrenophane **29c** could not be separated either by crystallization or column chromatography. However, one attempted crystallization afforded a sample from which two different types of crystals, a rod and a plate,[20] were manually separated under a microscope. X-ray crystallographic analysis of the rod revealed that it was [10](1,8)pyrenophane **28c**. The asymmetric unit consists of two closely associated, chemically identical molecules (one of these is shown in Figure 1). The pyrene

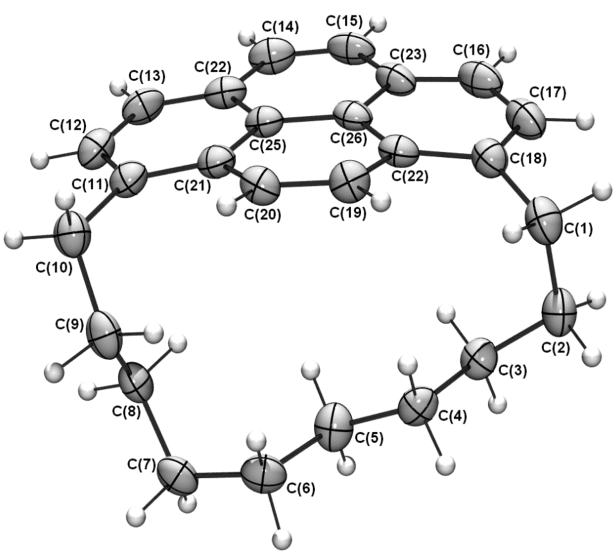


Figure 1. One of the two chemically identical molecules in the asymmetric unit of **28c** with 50% probability ellipsoids.

system is bowed slightly from planarity, the end-to-end bend angle (θ)[9d,21] being 11.3° and 14.0° for the two molecules in the asymmetric unit. Considering how little energy is required to bend pyrene slightly from its planar conformation,[22] the nonplanarity observed here could easily be accounted for entirely by crystal packing forces. Some short intermolecular C···H contacts (2.80–2.87 Å) between C(H) atoms and carbons that form part of the pyrene systems of a neighboring molecule were observed in the packed unit cell (Figures S2 and S3, Supporting Information), but no noteworthy C–H···π interactions (H to aromatic ring centroid) were observed.

The plate-shaped crystal was found to be [10](1,6)-pyrenophane **29c** (Figure 2). The asymmetric unit consists of

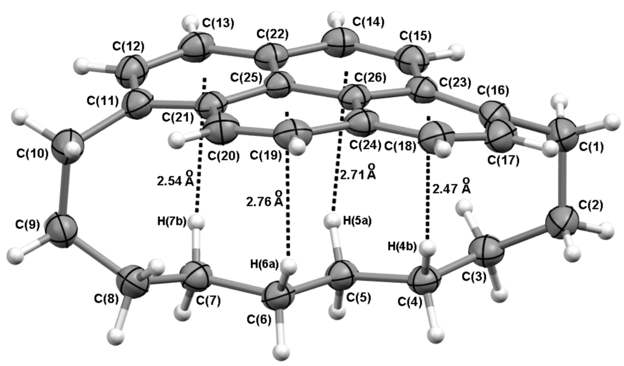


Figure 2. Asymmetric unit of **29c** with 50% probability ellipsoids showing intramolecular $C(sp^3)$–H···π contacts.

a single molecule (Figure 2 and Figures S4,5, Supporting Information), in which the pyrene system exhibits both an end-to-end bend and a longitudinal twist. The bend in the pyrene system cannot be meaningfully described using the bend angle θ, which is used for (2,7)pyrenophanes. However, a related angle in (1,6)pyrenophanes, i.e., the smallest angle formed by the planes defined by C(11)–C(12)–C(21) and C(16)–C(17)–C(23) in **29c**, may prove to be useful provided certain conditions are met. For comparisons between (1,6)-pyrenophanes, the torsion angle formed by C(12)–C(21)–C(23)–C(17) (numbering from **29c**) should remain constant. For meaningful comparisons to (2,7)pyrenophanes to be made, this torsion angle should be 180°, or very close to it. For **29c**, the torsion angle is 174.5° and the bend angle is 27.3°. This compares to a θ value of 34.6° for 1,12-dioxa[12](2,7)-pyrenophane,[9e,23] which is the [*n*](2,7)pyrenophane with the most gently bent pyrene to have been reported. On the other hand, the β-angles[24] of **29c** are 8.5° and 8.0°, which are similar to those for 1,7-dioxa[7](2,7)pyrenophane (8.2° and 8.7°),[9b] which is the [*n*](2,7)pyrenophane with the most severely bent pyrene to have been reported. The twist in the pyrene system in **29c** can be quantified by the dihedral angles along the pathway that connects the two benzylic carbon atoms through the middle of the pyrene system: C(1)–C(16)–C(23)–C(26)–C(25)–C(21)–C(11)–C(10). In a completely planar system, all five of the dihedral angles would be 180°. For **29c**, the angles (starting from the C(1) end of the chain) are 161.43(18)°, −170.51(18)°, 168.73(18)°, −168.70(19)°, and 159.9(2)°. These numbers will now serve as a basis for comparison to other [*n*](1,6)pyrenophanes as they become available.

A final noteworthy feature of the crystal structure of **29c** is the presence of several short $C(sp^3)$–H···π contacts. Intramolecular contacts (2.47 to 2.76 Å) are observed between H-atoms on contiguous bridge carbon atoms (H(4b), H(5a), H(6a) and H(7b)) and the centroids of all four of the six-membered rings of the pyrene system (Figure 2). Comparably short intermolecular contacts (2.64 to 2.76 Å) exist between another set of H-atoms on the bridge (H(3b), H(4a) and H(5b)) and the centroids of three of the four six-membered rings of the pyrene system of a neighboring molecule (Figure 3). The intermolecular $C(sp^3)$–H···π contacts occur between molecules of like chirality such that enantiomerically pure, slipped columns (slippage angle[25] = 12.7°) are present in the

dx.doi.org/10.1021/jo201013q | J. Org. Chem. 2012, 77, 57–67

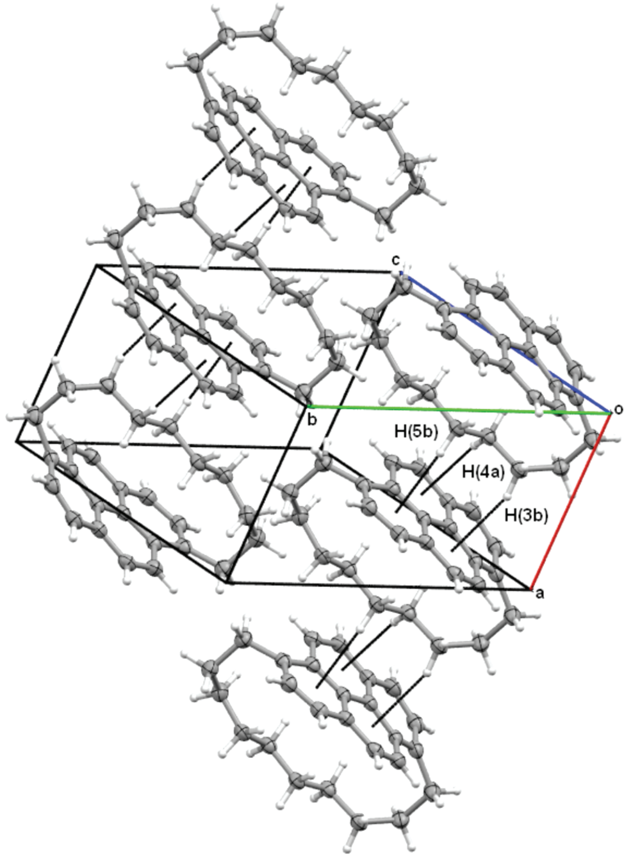


Figure 3. Packed unit cell of **29c** in the crystal showing C(sp^3)−H···π contacts.

crystal. All columns composed of molecules of like chirality point in the same direction and all columns composed of molecules of opposite chirality point in opposite directions. All columns run parallel to the a axis. The prevalence of short C(sp^3)−H···π contacts here and in a recently reported pyrenophane crystal structure[14c] may be indicative of this being a generally important phenomenon for pyrenophanes. As such, it would be worthwhile to revisit older pyrenophane structures to check for overlooked C(sp^3)−H···π contacts.

Whereas the originally obtained mixture of **28c** and **29c** could be used to provide the ^{1}H NMR properties and (fortunately) the crystal structures of the individual cyclophanes, measurement of the chiroptical properties of **29c** required the separation of this inherently chiral cyclophane from its achiral isomer **28c** in addition to the separation of its two enantiomers. The use of chiral HPLC was investigated, and after considerable experimentation, an effective two-stage procedure was developed. In the first stage, **29b** was isolated (ratio of **28c** to (+)-**29c** = 98.7:1.3 and 99.8:0.2 in two separate batches) using a Chiralpak AD-H column. The two enantiomers of **29c** were then separated in the second stage using a Chiralcel OJ-H column. A total of 3−4 mg each of (+)-**29c** and (−)-**29c** with an er of >99.8:0.2 was obtained (see the Supporting Information). The two enantiomers of **29c** exhibit perfectly complementary CD traces (Supporting Information), but because of the small quantities of the pure enantiomers, the specific rotations could not be determined with high precision ($[\alpha]^{24}_D = -210 \pm 20$ (c = 0.05 in $CHCl_3$) and $[\alpha]^{24}_D = +270 \pm 40$ (c = 0.04 in $CHCl_3$)). The numbers do just agree within the large experimental error. The magnitude of the rotations for the PAH-based cyclophane **29c** is slightly larger than that reported for the heterocycle-based cyclophane (+)-7 (+152).[6] However, the question of how the rotations change as the pyrene system becomes increasingly distorted from planarity will have to await the availability of enantiomerically pure samples of the lower homologues.

The absorption spectra of **28c** and **29c** are very similar to one another. Both cyclophanes exhibit β', β, and p bands that are characteristic of simple pyrene systems. Like the [n](2,7)-pyrenophanes,[9e,19] all of these bands are red-shifted (10−32 nm) from those of pyrene. While much of this red shift can be attributed to substitution of the pyrene system, it is interesting to note that the p bands of **28c** and **29c** are significantly red-shifted from those of [10](2,7)pyrenophane. For example, λ_{max} for the lowest energy p bands of **28c** and **29c** are observed at 354 and 356 nm, respectively, whereas those of pyrene and [10](2,7)pyrenophane are observed at 336 and 341 nm,[19] respectively. One noteworthy feature in the spectra of **28c** and **29c** is the presence of a weak absorption band at 384 and 386 nm, respectively. These are presumably α bands, which have become less forbidden due to the lowering of the symmetry.

■ CONCLUSIONS

The approach used here for the synthesis of [n](1,6)-pyrenophanes **29a−c** (n = 8−10) met with limited success. The major source of problems was the Na_2S/Al_2O_3-mediated self-coupling of tetrabromides **22a−c**. In the case of **22a**, the desired dithiacyclophane **24a** was not obtained due to intermolecular reaction. For **22b,c**, dithiacyclophanes **23b,c** were certainly formed, but only as components of mixtures of products. Although they were successfully converted into the respective [n](1,6)pyrenophanes **29b,c**, they could not be separated from the corresponding [n](1,8)pyrenophanes **28b,c**, and in the case of **29b**, an unidentified byproduct using column chromatography or crystallization. Nevertheless, manual separation of crystals enabled the determination of the crystal structures of [10](1,6)pyrenophane **29c** and [10](1,8)-pyrenophane **28c**. A small-scale separation of **28c** and **29c**, and the two enantiomers of **29c** was achieved using chiral HPLC. This enabled the measurement of the specific rotations, absorption and CD spectra. Ongoing work is directed toward the development of an improved synthetic route that leads exclusively, or at least selectively, to [n](1,6)pyrenophanes. Access to a series of [n](1,6)pyrenophanes will enable the study of how the chiroptical properties change with increasing distortion from planarity.

■ EXPERIMENTAL SECTION

General Methods. All reactions were performed under the protection of nitrogen gas unless otherwise indicated. THF was freshly distilled from sodium benzophenone ketyl. Dichloromethane was freshly distilled from calcium hydride. Hexanes were distilled before use for column chromatography. Flash chromatography was performed using Silicycle silica gel 60, particle size 40−63 μm. Compounds on tlc plates were visualized under UV light (254 and 365 nm). Melting points are uncorrected. CD spectra were recorded in a cell with a 1 mm (0.01 dm) path length at a concentration of 1.7 × 10^{-4} M (5.7 × 10^{-5} g/mL).

Diethyl 4-Bromoisophthalic Acid (17). A mixture of 4-bromo-m-xylene (**16**) (25.3 g, 137 mmol), $KMnO_4$ (100 g, 633 mmol), and water (1.5 L) was heated at reflux for 16 h. The mixture was cooled to room temperature and suction filtered. The filtrate was acidified by the addition of aqueous 6 M HCl solution (100 mL), and the white precipitate formed was isolated by suction filtration and air-dried to afford **17** (18.2 g, 54%) as a white solid: mp 286−290 °C (lit.[26] mp = 287 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 13.56 (br s, 2 H), 8.37 (d, *J* = 2.1 Hz, 1 H), 7.99 (dd, *J* = 8.1, 2.1 Hz, 1 H), 7.90 (d, *J* = 8.1 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 166.8, 166.3, 134.7, 133.8, 133.0, 131.6, 130.5, 125.5.

Diethyl 4-Bromoisophthalate (18). A mixture of 4-bromoisophthalic acid (**17**) (13.0 g, 53.2 mmol), concentrated sulfuric acid (4 mL), and absolute ethanol (100 mL) was heated at reflux for 16 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether and the resulting solution was washed with water (2 ×), washed with saturated aqueous $NaHCO_3$ solution (3 ×), washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (20% diethyl ether/hexanes) to afford **18**[27] as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.40 (d, *J* = 2.1 Hz, 1 H), 7.95 (dd, *J* = 8.4, 2.2 Hz, 1 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 4.43, (q, *J* = 7.2 Hz, 2 H), 4.39, (q, *J* = 7.1 Hz, 2 H), 1.43, (t, *J* = 7.2 Hz, 3 H), 1.41, (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.4, 165.0, 134.4, 132.7, 132.0, 129.6, 126.6, 61.9, 61.5, 14.2, 14.1.

1,8-Bis(2,4-bis(ethoxycarbonyl)phenyl)octa-1,7-diyne (20a). To a degassed mixture of diethyl 4-bromoisophthalate (**18**) (12.0 g, 40.0 mmol), $Pd(PPh_3)Cl_2$ (560 mg, 0.803 mmol), CuI (152 mg, 0.802 mmol), and 1:1 THF/Et_3N (200 mL) was added 1,7-octadiyne (**19a**) (2.55 g, 24.0 mmol) in one portion. The reaction was stirred at 80 °C for 18 h and cooled to room temperature. The precipitate was removed by suction filtration, and the filter cake was washed with ethyl acetate (50 mL). The filtrate was washed with saturated aqueous NH_4Cl solution, washed with H_2O, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (20:80 ethyl acetate/hexanes) to afford **9a** as pale yellow needles (7.33 g, 13.5 mmol, 69%): R_f (20:80 ethyl acetate/hexanes) 0.27; mp (ethanol) 73.0−74.0 °C; IR (neat) ν = 2976 (w), 1718 (s), 1368 (m), 1298 (s), 1259 (s), 1147 (m), 1109 (s), 1009 (s), 764 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.53 (d, *J* = 1.4 Hz, 2 H), 8.06 (dd, *J* = 8.1, 1.6 Hz, 2 H), 7.57 (d, *J* = 8.1 Hz, 2 H), 4.40 (q, *J* = 7.1 Hz, 4 H), 4.39 (q, *J* = 7.1 Hz, 4 H), 2.59−2.57 (m, 4 H), 1.87−1.86 (m, 4 H), 1.41 (t, *J* = 7.1 Hz, 6 H), 1.40 (t, *J* = 7.1 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 165.7, 134.7, 132.9, 132.2, 132.6, 129.5, 128.9, 99.2, 79.8, 61.71, 61.69, 28.0, 19.9, 14.67, 14.66; LCMS [APCl(+)] *m/z* 547 ([M + 1]$^+$, 100), 519 (10); HRMS [EI] calcd for $C_{32}H_{34}O_8$ 546.2254, found 546.2245.

1,9-Bis(2,4-bis(ethoxycarbonyl)phenyl)nona-1,8-diyne (20b). To a degassed solution of diethyl 4-bromoisophthalate (**18**) (10.8 g, 35.9 mmol) and 1,8-nonadiyne (**19b**) (2.16 g, 18.0 mmol) in Et_3N (80 mL) were added $Pd(PPh_3)_2Cl_2$ (0.50 g, 0.71 mmol) and CuI (0.60 g, 3.2 mmol). The resulting mixture was heated at reflux for 18 h and then cooled to room temperature. The reaction mixture was suction filtered and the filter cake was washed with diethyl ether. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (35% diethyl ether/hexanes) to afford **20b** as a colorless solid (8.00 g, 70%): mp (diethyl ether/hexanes) 63−64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.53 (d, *J* = 1.7 Hz, 2 H), 8.03 (dd, *J* = 8.1, 1.8 Hz, 2 H), 7.55 (d, *J* = 8.1 Hz, 2 H), 4.41 (q, *J* = 7.2 Hz, 4 H), 4.39 (q, *J* = 7.1 Hz, 4 H), 2.55−2.53 (m, 4 H), 1.74−1.71 (m, 6 H), 1.42 (t, *J* = 7.1 Hz, 6 H), 1.41 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.6, 165.2, 134.2, 132.3, 131.7, 131.1, 129.0, 128.5, 99.1, 79.2, 61.2, 28.1, 27.9, 19.7, 14.2; MS [EI] *m/z* M$^+$ not observed, 531 (38), 457 (34), 441 (40). Anal. Calcd for $C_{33}H_{36}O_8$: C, 70.69; H, 6.41. Found: C, 70.74; H, 6.60.

1,10-Bis(2,4-bis(ethoxycarbonyl)phenyl)deca-1,9-diyne (20c). To a degassed mixture of diethyl 4-bromoisophthalate (**18**) (1.00 g, 3.33 mmol), $Pd(PPh_3)Cl_2$ (47 mg, 0.067 mmol), CuI (13 mg, 0.067 mol) and 1:1 THF/Et_3N (40 mL) was added 1,9-decadiyne (268 mg, 2.00 mmol) in one portion. The reaction was stirred at 80 °C for 18 h and cooled to room temperature. The reaction mixture was suction filtered, and the filter cake was washed with ethyl acetate (50 mL). The filtrate was washed with saturated aqueous NH_4Cl solution, washed with H_2O and brine (25 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (20:80 ethyl acetate/hexanes) to afford **9c** as a colorless oil (1.35 g, 2.35 mmol, 71%): R_f (20:80 ethyl acetate/hexanes) 0.21; IR (neat) ν = 2955 (m), 1716 (s), 1366 (w), 1285 (m), 1173 (s), 1071 (s), 762 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.53 (d, *J* = 1.4 Hz, 2 H), 8.05 (dd, *J* = 8.1, 1.6 Hz, 2 H), 7,57 (d, *J* = 8.1 Hz, 2 H), 4.42 (q, *J* = 7.2 Hz, 4 H), 4.39 (q, *J* = 7.2 Hz, 4 H), 2.53 (t, *J* = 7.1 Hz, 4 H), 1.71−1.68 (m, 4 H), 1.57−1.54 (m, 4 H), 1.42 (t, *J* = 6.9 Hz, 6 H), 1.40 (t, *J* = 7.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.1, 165.8, 134.7, 132.8, 132.2, 132.6, 129.4, 129.1, 99.8, 79.6, 61.72, 61.69, 28.8, 28.7, 20.3, 14.7; LCMS [APCl(+)] *m/z* 575 ([M + 1]$^+$, 100), 529 (6); HRMS [CI(+)] calcd for $C_{34}H_{39}O_8$ 575.2645, found 575.2643.

1,8-Bis(2,4-bis(ethoxycarbonyl)phenyl)octane (21a). A mixture of diyne tetraester **20a** (14.7 g, 27.7 mmol), 10% Pd/C (3.12 g), and absolute ethanol (200 mL) was stirred vigorously under an atmosphere of H_2 (balloon) for 18 h (monitored by ^{1}H NMR). The mixture was concentrated under reduced pressure, and the residue was dissolved in dichloromethane (200 mL). The catalyst was removed by suction filtration, and the filtrate was concentrated under reduced pressure. Crystallization of the residue from ethanol afforded **21a** as a white solid (14.4 g, 96%): R_f (dichloromethane) 0.14; mp (ethanol): 96.0−96.5 °C; IR (neat) ν = 2935 (w), 1719 (s), 1364 (w), 1297 (s), 1219 (m), 1130 (m), 1067 (m), 1024 (m), 764 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.51 (d, *J* = 1.6 Hz, 2 H), 8.07 (dd, *J* = 8.0, 1.4 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 4.41 (q, *J* = 7.2 Hz, 4 H), 4.40 (q, *J* = 7.2 Hz, 4 H), 3.01−2.98 (m, 4 H), 1.64−1.58 (m, 4 H), 1.43 (t, *J* = 7.2 Hz, 6 H), 1.42 (t, *J* = 7.2 Hz, 6 H), 1.38−1.30 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.5, 166.3, 149.9, 132.7, 132.1, 131.4, 130.6, 128.6, 61.51, 61.48, 34.9, 32.0, 30.1, 29.8, 14.74, 14.70; LCMS [APCl(+)] *m/z* 555 ([M + 1]$^+$, 100), 541 (20), 509 (46); HRMS [EI] calcd for $C_{32}H_{42}O_8$ 554.2880, found 554.2883.

1,9-Bis(2,4-bis(ethoxycarbonyl)phenyl)nonane (21b). A mixture of diyne tetraester **20b** (4.19 g, 7.47 mmol), 20% wet palladium hydroxide on C (Pearlman's catalyst) (0.803 g), and ethyl acetate (200 mL) was stirred under an atmosphere of hydrogen (hydrogenation apparatus) for 3 h. The reaction mixture was suction filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to afford tetraester **21b** as an oily white solid (4.21 g, 99%): mp (ethyl acetate/heptane) 47−49 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.50 (d, *J* = 1.8 Hz, 2 H), 8.05 (dd, *J* = 8.0, 1.9 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 4.39 (q, *J* = 7.1 Hz, 8 H), 3.01−2.96 (m, 4 H), 1.62−1.54 (m, 4 H), 1.41 (t, *J* = 7.1 Hz, 6 H), 1.40 (t, *J* = 7.1 Hz, 6 H), 1.34−1.25 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.9, 165.7, 149.4, 132.1, 131.6, 130.9, 130.1, 128.0, 60.9, 34.4, 31.5, 29.5, 29.3, 14.2; MS [EI] *m/z* M$^+$ not observed, 523 (40), 203 (100). Anal. Calcd for $C_{33}H_{44}O_8$: C, 69.69; H, 7.80. Found: C, 69.44; H, 7.99.

1,10-Bis(2,4-bis(ethoxycarbonyl)phenyl)decane (21c). A mixture of diynetetraester **20c** (9.46 g, 16.5 mmol), 10% Pd/C (3.74 g), and absolute ethanol (250 mL) was stirred vigorously under an atmosphere of H_2 (balloon) for 18 h (monitored by ^{1}H NMR). The mixture was concentrated under reduced pressure, and the residue was dissolved in dichloromethane (200 mL). The catalyst was removed by suction filtration, and the filtrate was concentrated under reduced pressure. Crystallization of the residue from ethanol afforded **21c** as a white solid (8.61 g, 90%): R_f (20:80 ethyl acetate/hexanes) 0.21; mp (ethanol) 77.0−78.0 °C; IR (neat) ν = 2925 (w), 1722 (m), 1289 (w), 1238 (m), 1096 (w), 1071 (w), 1026 (w), 762 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.49 (d, *J* = 1.4 Hz, 2 H), 8.05 (dd, *J* = 8.0, 1.6 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 4.39 (q, *J* = 7.1 Hz, 4H), 4.38 (q, *J* = 7.1 Hz, 4 H), 3.00−2.96 (m, 4 H), 1.62−1.56 (m, 4 H), 1.41 (t, *J* = 7.0 Hz, 6 H), 1.40 (t, *J* = 7.0 Hz, 6 H), 1.36−1.34 (m, 4 H), 1.27−1.25 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.6, 166.3, 149.9, 132.7, 132.1, 131.4, 130.7, 128.6, 61.51, 61.48, 34.9, 32.0, 30.1, 30.0, 29.9, 14.74, 14.70; LCMS [APCl(+)] *m/z* 583 ([M + 1]$^+$, 100), 537 (71); HRMS [CI(+)] calcd for $C_{34}H_{47}O_8$ 583.3271, found 583.3264.

1,8-Bis(2,4-bis(bromomethyl)phenyl)octane (22a). To a 0 °C solution of tetraester **21a** (5.00 g, 9.02 mmol) in THF (200 mL) was added dropwise a slurry of $LiAlH_4$ (1.93 g, 50.9 mmol) in THF (20 mL). The resulting mixture was stirred at room temperature for 16 h and then quenched by the careful sequential addition of ethyl acetate (50 mL) and absolute ethanol (25 mL). The resulting mixture was poured into a 1 M aqueous HCl solution (100 mL) and extracted with ethyl acetate. The organic layer was washed with brine and concentrated under reduced pressure to afford a white solid (3.07 g), which was used without purification in the next step. The crude tetraalcohol exhibited the following spectroscopic data: IR (neat) ν = 3301 (m), 2922 (m), 1467 (w), 1224 (w), 1157 (m), 1049 (s), 1021 (s), 889 (m), 828 (m), 724 (m) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.32 (s, 2 H), 7.11−7.05 (m, 4 H), 5.12 (t, *J* = 5.7 Hz, 2 H), 5.08 (t, *J* = 5.4 Hz, 2 H), 4.50 (d, *J* = 5.3 Hz, 4 H), 4.44 (d, *J* = 5.6 Hz, 4 H), 2.56−2.52 (m, 4 H), 1.49 (br m, 4 H), 1.30 (br s, 8 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 140.4, 140.2, 138.8, 129.3, 126.7, 125.8, 63.8, 61.5, 32.1, 31.4, 29.9, 29.8.

To a well-stirred mixture of the crude tetraalcohol (1.00 g, 2.61 mmol) in dichloromethane (50 mL) was added PBr_3 (2.89 g, 10.7 mmol). The resulting mixture was stirred at room temperature for 18 h, and H_2O (100 mL) was added. The layers were separated, and the organic layer was washed with saturated aqueous $NaHSO_4$ solution, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (50:50 dichloromethane/hexanes) to afford **12c** as a white solid (0.773 g, 79% from **21a**): R_f (20:80 dichloromethane/hexanes) 0.20; mp (dichloromethane/hexanes) 142.0−143.0 °C; IR (neat) ν = 2929 (w), 2851 (w), 1464 (w), 1209 (m), 904 (w), 827 (w), 737 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 1.6 Hz, 2 H), 7.27 (dd, *J* = 7.9, 1.8 Hz, 2 H), 7.17 (d, *J* = 7.9 Hz, 2 H), 4.51 (s, 4 H), 4.48 (s, 4 H), 2.72−2.69 (m, 4 H), 1.67−1.61 (m, 4 H), 1.41−1.37 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 142.5, 136.23, 136.21, 131.4, 130.7, 129.9, 33.4, 32.5, 31.5, 31.2, 30.1, 29.8. LCMS [APCl(+)] *m*/*z* [M + 1]$^+$ not observed; HRMS [CI(+)] calcd for $C_{24}H_{30}{}^{79}Br_4$ 633.9081, found 633.9087.

1,9-Bis(2,4-bis(bromomethyl)phenyl)nonane (22b). A solution of tetraester **21b** (2.20 g, 3.87 mmol) in THF (75 mL) was added dropwise to a slurry of $LiAlH_4$ (0.81 g, 0.021 mol) in THF (75 mL), and the resulting mixture was stirred at room temperature for 6 h. The reaction was quenched by the careful addition of ethyl acetate (10 mL). The resulting mixture was poured into a 1 M aqueous HCl solution (100 mL) and extracted with ethyl acetate. The organic layer was washed with brine and concentrated under reduced pressure to afford a white solid (1.40 g), which was used without purification in the next step.

The crude tetraalcohol (0.83 g, 2.1 mmol) was slurried in glacial acetic acid (30 mL) and 30% HBr in AcOH (3.5 mL, 17 mmol HBr) was added. The resulting solution was heated at reflux for 16 h. The reaction mixture was cooled to room temperature and water (50 mL) was added. The resulting mixture was extracted with diethyl ether and the organic phase was washed with H_2O, washed with aqueous saturated $NaHCO_3$ solution, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography (25% dichloromethane/hexanes) to afford tetrabromide **22b** as a white solid (1.24 g, 83% from **21b**): mp (dichloromethane/hexanes) 112−114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 1.7 Hz, 2 H), 7.27 (dd, *J* = 7.8, 1.7 Hz, 2 H), 7.18 (d, *J* = 7.8 Hz, 2 H), 4.51 (s, 4 H), 4.46 (s, 4 H), 2.73−2.68 (m, 4 H), 1.66−1.60 (m, 4 H), 1.39−1.33 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 142.2, 135.8, 131.0, 130.2, 129.5, 119.9, 33.0, 32.1, 31.1, 30.8, 29.6, 29.4; MS [EI] *m*/*z* M$^+$ not observed, 492 (6), 199 (56), 197 (60), 119 (68), 118 (55). Anal. Calcd for $C_{25}H_{32}Br_4$: C, 46.04; H, 4.95. Found: C, 46.03; H, 4.89.

1,10-Bis(2,4-bis(bromomethyl)phenyl)decane (22c). To a 0 °C solution of tetraester **21c** (8.30 g, 14.2 mmol) in THF (250 mL) was added dropwise a slurry of $LiAlH_4$ (2.97 g, 78.3 mmol) in THF (20 mL). The resulting mixture was stirred at room temperature for 16 h and then quenched by the careful sequential addition of ethyl acetate (50 mL) and absolute ethanol (25 mL). The resulting mixture was poured into a 1 M aqueous HCl solution (100 mL) and extracted with ethyl acetate. The organic layer was washed with brine and concentrated under reduced pressure to afford a white solid (5.89 g), which was used without purification in the next step. The crude tetraalcohol exhibited the following spectroscopic data: IR (neat) ν = 3311 (w), 2920 (m), 1465 (w), 1233 (w), 1041 (s), 985 (m), 924 (w), 822 (m), 705 (m) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.33 (s, 2 H), 7.10−7.06 (m, 4 H), 5.08−5.03 (m, 4 H), 4.51 (s, 4 H), 4.45 (s, 4 H), 2.59−2.55 (m, 4 H), 1.50 (br m, 4 H), 1.29−1.18 (m, 12 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 140.4, 140.1, 138.8, 129.3, 126.6, 125.8, 63.8, 61.5, 32.1, 31.4, 29.93, 29.90, 29.8.

To a well-stirred mixture of the crude tetraalcohol (3.00 g, 7.30 mmol) in dichloromethane (100 mL) was added PBr_3 (7.84 g, 29.0 mmol) under N_2. The resulting mixture was stirred at room temperature for 18 h and then H_2O (100 mL) was added. The layers were separated and the organic layer was washed with saturated aqueous $NaHSO_4$ solution, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography (50:50 dichloromethane/hexanes) to afford **22c** as a white solid (3.67 g, 76% from **21c**): R_f (50:50 dichloromethane/hexanes) 0.57; mp 111.0−113.0 °C; IR (neat) ν = 2926 (m), 2849 (m), 1503 (w), 1465 (m), 1210 (s), 1162 (w), 904 (w), 864 (m), 737 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 1.3 Hz, 2 H), 7.27 (dd, *J* = 7.9, 1.4 Hz, 2 H), 7.17 (d, *J* = 7.9 Hz, 2 H), 4.51 (s, 4 H), 4.46 (s, 4 H), 2.72−2.68 (m, 4 H), 1.66−1.60 (m, 4 H), 1.41−1.33 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 142.6, 136.22, 136.18, 131.4, 130.7, 129.9, 33.4, 32.5, 31.5, 31.2, 30.1, 29.91, 29.86. LCMS [APCl(+)] *m*/*z* [M + 1]$^+$ not observed; HRMS [CI(+)] calcd for $C_{26}H_{34}{}^{79}Br_4$ 661.9394, found 661.9388.

17,26-Dithia[9.3.3](1,2,4)cyclophane (23b) and 17,26-Dithia[9.3.3](1,2,4)(1,4,6)cyclophane (24b). To a solution of tetrabromide **22b** (0.57 g, 0.87 mmol) in 10% absolute ethanol/dichloromethane (400 mL) was added Na_2S/Al_2O_3 (1.4 g, 3.5 mmol) in several portions over 30 min.[28] The resulting mixture was stirred vigorously at room temperature for 2 h and then suction filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was subjected to column chromatography (40:60 dichloromethane/hexanes) to afford a white solid (0.25 g), which consisted primarily of ca. 3:1 mixture of **23b** and **24b**: ^{1}H NMR (300 MHz, $CDCl_3$) (signals attributable to **23b**) δ = 7.13 (s, 2 H), 6.84 (s, 4 H), 3.98 (d, *J* = 14.8 Hz, 2 H), 3.83 (d, *J* = 14.8 Hz, 2 H), 3.80 (s, 4 H), 2.85−2.75 (m, 2 H), 2.23−2.12 (m, 2 H), 1.58−0.71 (m, 16 H); (signals attributable to **24b**) δ = 7.48 (s, 2 H), 6.84 (s, 4 H), 3.89 (d, *J* = 14.8 Hz, 2 H), 3.87 (d, *J* = 14.8 Hz, 2 H), 3.87 (d, *J* = 15.4 Hz, 2 H), 3.74 (d, *J* = 15.4 Hz, 2 H), 2.77−2.70 (m, 2 H), 2.31−2.21 (m, 2 H), 1.58−0.71 (m, 16 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.2, 134.3, 134.0, 132.3, 132.2, 129.7, 127.5, 127.1, 126.9, 39.2, 38.7, 38.6, 30.5, 29.2, 27.4, 27.3, 26.2, 25.7, 25.3, 24.3, 22.8; MS [EI(+)] *m*/*z* 396 (M$^+$, 35), 148 (28), 105 (27).

18,27-Dithia[10.3.3](1,2,4)cyclophane (23c) and 18,27-Dithia[10.3.3](1,2,4)(1,4,6)cyclophane (24c). To a solution of tetrabromide **22c** (1.00 g, 1.51 mmol) in 10% absolute ethanol/dichloromethane (250 mL) was added Na_2S/Al_2O_3 (2.33 g, 6.04 mmol).[28] The resulting mixture was stirred at room temperature for 16 h and then suction filtered. The filtrate was concentrated under reduced pressure, and the residue was subjected to column chromatography (50:50 dichloromethane/hexanes) to afford a white solid, which consisted primarily of a ca. 1.7:1 mixture of **23c** and **24c** (254 mg, 41%): R_f (50:50 dichloromethane/hexanes) 0.43; ^{1}H NMR (500 MHz, $CDCl_3$) (signals attributable to **23c**) δ = 7.26 (s, 2 H), 6.87−6.81 (m, 4 H), 4.05 (d, *J* = 14.8 Hz, 2 H), 3.84−3.78 (m, 6 H), 2.69 (ddd, *J* = 14.9, 10.7, 5.3 Hz, 2 H), 2.23 (ddd, *J* = 14.8, 11.1, 4.9 Hz, 2 H), 1.74−1.67 (m, 2 H), 1.76−0.96 (m, 16 H); (signals attributable to **24c**) δ = 7.26 (s, 2 H), 6.87−6.81 (m, 4 H), 3.88 (d, *J* = 14.8 Hz, 2 H), 3.84−3.78 (m, 6 H), 2.76 (ddd, *J* = 15.0, 10.2, 3.5 Hz, 2 H), 2.29 (ddd, *J* = 15.0, 7.4, 3.1 Hz, 2 H), 1.76−0.96 (m, 16 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 139.2, 138.1, 135.4, 134.7, 132.9, 132.5, 128.8, 128.5, 127.7, 127.5, 39.1, 39.0, 31.3, 30.2, 28.8, 28.1, 27.9, 27.54, 27.47, 27.2, 27.08, 27.05; LCMS [APCl(+)] *m*/*z* 839 (M_{dimer} + 19]$^+$, 21), 821 (M_{dimer} + 1]$^+$, 21), 427 ([M + 17]$^+$, 100), 411 ([M + 1]$^+$, 39); HRMS [EI] calcd for $C_{26}H_{34}S_2$ 410.2102, found 410.2110.

[9](1,8)Pyrenophane (28b) and [9](1,6)Pyrenophane (29b). To a solution of dithiacyclophanes **23b** and **24b** (0.25 g, max. 0.63

mmol) in dichloromethane (15 mL) was added $(MeO)_2CHBF_4$ (Borch reagent)[29] (0.5 g, 3 mmol) slowly over 5 min by syringe. The resulting mixture was stirred for 1 h, and the solvent was removed under reduced pressure. To the resulting oily residue was added 4:1 methanol/water (2 mL), and after the mixture was stirred for a few minutes, the solvent was removed under reduced pressure. The resulting oily solid was suspended in THF (20 mL), and to this mixture was added *t*-BuOK (0.60 g, 5.3 mmol). The reaction mixture was stirred at room temperature for 14 h, and water (1 mL) was added. The solvent was removed under reduced pressure, and the residue was taken up in dichloromethane (60 mL). The resulting solution was washed with aqueous 1 M HCl solution, water, and brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford a foamy white solid (0.101 g).

To a solution of this solid (0.060 g) in dichloromethane (15 mL) was added $(MeO)_2CHBF_4$ (Borch reagent)[29] (0.4 g, 2 mmol) slowly over 5 min by syringe. The resulting mixture was stirred for 1 h, and the solvent was removed under reduced pressure. The oily brown residue was suspended in 1:1 THF/*t*-BuOH (40 mL), and *t*-BuOK (0.51 g, 4.5 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 14 h, and the solvent was removed under reduced pressure. The residue was taken up in dichloromethane (50 mL) and water (50 mL), and the layers were separated. The organic layer was washed with aqueous 1 M HCl solution, water, and brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford a yellow-brown oil.

This oil was dissolved in benzene (20 mL), and DDQ (0.100 g, 0.441 mmol) was added. The reaction mixture was heated at reflux for 1 h and cooled to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (10% dichloromethane/hexanes) to afford a mixture of **28b**, **29b** and an unidentified impurity as a white solid: ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.4, 130.1, 129.4, 129.2, 128.7, 128.4, 127.3, 127.1, 126.9, 126.7, 126.2, 126.1, 126.0, 125.4, 124.9, 124.7, 124.0, 123.9, 123.63, 123.55, 55.4, 33.2, 33.1, 32.9, 32.4, 31.0, 30.91, 30.87, 30.23, 30.15, 29.6, 29.0, 27.9, 27.5, 27.0, 24.7, 24.1; MS [EI] *m*/*z* (%): 326 (M^+, 79), 324 (31), 253 (32), 241 (43), 239 (37), 228, (100), 215 (35). Crystallization of this mixture from hexanes afforded white needles that consisted of a ca. 4:1 mixture of **28b** and the unidentified impurity: ^1H NMR (300 MHz, $CDCl_3$) (signals attributable to **28b**) δ = 8.29 (s, 2 H), 8.02 (d, *J* = 7.8 Hz, 2 H), 7.94 (s, 2 H), 7.72 (d, *J* = 7.7 Hz, 2 H), 3.75 (ddd, *J* = 14.0, 8.5, 4.3 Hz, 2 H), 3.14 (ddd, *J* = 14.0, 7.7, 4.4 Hz), 2.21−2.08 (m, 2 H), 1.37−1.24 (m, 2 H), 1.08−0.96, (m, 2 H), 0.76−0.61 (m, 2 H), 0.56−0.43 (m, 2 H), 0.45−0.33 (m, 2 H), 0.17−0.05 (m, 2 H). The mother liquor was concentrated under reduced pressure to afford a ca. 8:3:1 mixture of **29b**, **28b**, and the unidentified impurity: ^1H NMR (300 MHz, $CDCl_3$) (signals attributable to **29b**) δ 8.20 (d, *J* = 9.2 Hz, 2 H), 8.00 (d, *J* = 7.8 Hz, 2 H), 7.98 (d, *J* = 9.2 Hz, 2 H), 7.71 (d, *J* = 7.6 Hz, 2 H), 3.73 (ddd, *J* = 13.3, 6.7, 6.7 Hz, 2 H), 2.92 (ddd, *J* = 13.4, 6.7, 6.7 Hz, 2 H), 1.64−1.52 (m, 2 H), 1.28−1.14 (m, 2 H), 0.42−0.29 (m, 2 H), −0.18 to −0.30 (m, 2 H), −1.25 to −1.35 (m, 4 H), −1.64 to −1.75 (m, 2 H).

[10](1,8)Pyrenophane (28c) and [10](1,6)Pyrenophane (29c). To a solution of dithiacyclophanes **23c** and **24c** (254 mg, max. 0.620 mmol) in dichloromethane (10 mL) was added $(MeO)_2CHBF_4$ (Borch reagent)[29] (457 mg, 2.74 mmol) slowly over 5 min by syringe. The resulting mixture was stirred for 1 h, and the solvent was removed under reduced pressure. To the resulting residue was added ethyl acetate (6 mL), and this mixture was stirred vigorously for 5 min. The supernatant was decanted, and the residue was dried under vacuum. The residue was slurried in THF (15 mL), and *t*-BuOK (352 mg, 3.12 mmol) was added in one portion. The reaction was stirred overnight and then quenched by the addition of saturated aqueous NH_4Cl solution (1 mL). The reaction mixture was concentrated under reduced pressure, and the residue was filtered through a plug of Celite (dichloromethane) to afford a yellow oil (253 mg).

To a solution of this yellow oil (253 mg, 0.620 mmol) in dichloromethane (10 mL) was added $(MeO)_2CHBF_4$ (Borch reagent)[29] (269 mg, 1.61 mmol), and the resulting mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure, and the residue was suspended in THF (15 mL). To this mixture was added *t*-BuOK (253 mg, 2.23 mmol) in one portion, and the resulting mixture was sonicated for 1 h. The mixture was then stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (25:75 dichloromethane/hexanes) to yield a mixture of compounds consisting mainly of pyrenophanes **28c** and **29c** (^1H NMR analysis) as a colorless oil (85 mg): R_f (20:80 dichloromethane/hexanes) 0.50; LCMS [APCl(+)] *m*/*z* 343 ($[M_{cyclophanedienes} + 1]^+$, 36), 342 (25), 341 ($[M_{pyrenophanes} + 1]^+$, 78), 340 (65).

To a well-stirred solution of the product mixture from the previous reaction in degassed benzene (8 mL) was added a solution of DDQ (227 mg, 0.714 mmol) in degassed benzene (2 mL). The reaction mixture turned green, then orange, then dark red within 10 min. The mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was subjected to column chromatography (10:90 dichloromethane/hexanes) to afford a 7:4 mixture of pyrenophanes **28c** and **29c** as a white solid (43 mg, 0.16 mmol, 9%, six steps from tetrabromide **22c**): R_f (10:90 dichloromethane/hexanes) 0.14; mp 140.0−143.5 °C; ^1H NMR (500 MHz, $CDCl_3$) (signals attributable to **28c**) δ = 8.33 (s, 2 H), 8.06 (d, *J* = 7.7 Hz, 2 H), 7.96 (s, 2 H), 7.76 (d, *J* = 7.7 Hz, 2 H), 3.76 (v br s, 2 H), 3.18 (v br s, 2 H), 2.08 (v br s, 2 H), 1.75 to −0.16 (m, 14 H); 1.15−1.09 (m, 10 H), 1.06−1.01 (m, 12 H), 0.58−0.51 (m, 2 H), 0.80 to −0.12 (m, 4 H); (signals attributable to **29c**) δ = 8.34 (d, *J* = 9.3 Hz, 2 H), 8.04 (d, *J* = 7.5 Hz, 2 H), 8.01 (d, *J* = 9.2 Hz, 2 H), 7.82 (d, *J* = 7.8 Hz, 2 H), 3.70 (ddd, *J* = 13.1, 11.2, 4.7 Hz, 2 H), 3.14 (ddd, *J* = 13.2, 4.4, 4.4 Hz, 2 H), 1.98−1.91 (m, 2 H), 1.17−0.79 (m, 6 H), 0.58−0.51 (m, 2H), −0.01 to −0.14 (m, 2 H), −1.94 to −2.00 (m, 2 H), −2.61 to −2.68 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 138.1, 137.0, 130.4, 129.92, 129.87, 129.2, 127.7, 126.8, 126.5, 126.3, 125.5, 125.1, 124.9, 124.2, 123.7, 33.5, 32.3, 31.5, 30.7, 30.4, 30.1, 29.78, 29.77, 28.33, 28.27, 28.0, 25.9; LCMS [APCl(+)] *m*/*z* 341 ($[M + 1]^+$, 100), 340 (29); HRMS [CI(+)] calcd for $C_{26}H_{29}$ 341.2269, found 341.2263.

Two samples of **28c** and **29c** remaining from multiple attempted crystallizations and chromatographic separations were subjected to a two-stage preparative chiral HPLC protocol. In the first stage, **28c** was isolated (Chiralpak AD-H column, 2 × 15 cm, 30% methanol/CO_2, 100 bar, 65 mL/min, 280 nm). The two enantiomers of **29c** were then separated in the second stage (Chiralcel OJ-H column, 2 × 15 cm, 30% methanol/CO_2, 100 bar, 65 mL/min, 280 nm). Peak 1 (3 mg combined) was found to be (−)-**29c**: $[\alpha]^{24}_D = -210 \pm 20$ (*c* = 0.05 in $CHCl_3$); UV−vis ($CHCl_3$) λ_{max} (log ε) 274 (4.3), 284 (4.4), 326 (sh, 4.0), 340 (4.3), 356 (4.5), 386 (3.5) nm; CD ($CHCl_3$) $[\theta]_{283} = -2.4 \times 10^5$ deg·cm^2·dmol^{-1}. Peak 2 (4 mg combined) was found to be (+)-**29c**: $[\alpha]^{24}_D = +270 \pm 40$ (*c* = 0.04 in $CHCl_3$); UV−vis ($CHCl_3$) λ_{max} (log ε) 274 (4.3), 284 (4.4), 326 (sh, 4.0), 340 (4.3), 356 (4.5), 386 (3.5) nm; CD ($CHCl_3$) $[\theta]_{283} = +2.0 \times 10^5$ deg·cm^2·dmol^{-1}. Peak 3 was found to be **28c**: UV−vis ($CHCl_3$) λ_{max} (log ε) 274 (3.9), 284 (4.1), 324 (sh, 3.6), 338 (4.0), 354 (4.1), 384 (2.8) nm.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H NMR and ^{13}C NMR spectra for compounds **20a−c**, **21a−c**, **22a−c**, **23b+24b**, **23c+24c**, **28b+29b**, and **28c+29c**. DNMR spectra for compounds **28c** and **29c**. Mass spectra for compounds **23c+24c** and **25−27**. Structures of possible isomers for compounds **25−27**. Other views of **28c** and **29c** in the crystal. CIF files for **28c** and **29c**. HPLC traces for **28c** and **29c** before and after separation. CD spectra of (+)-**29c** and (−)-**29c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENTS

Financial support of this work from the Natural Sciences and Engineering Research Council (NSERC) of Canada (G.J.B.) and the National Science Foundation (Grant No. CHE-0936862) (R.A.P.) is gratefully acknowledged.

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(15) This ratio was determined using the integral ratio between the 2 H singlet at δ 8.29 for **28b** and the doublet at δ 8.37 for the impurity. This assumes that the doublet at δ 8.37 for the impurity is also a 2 H signal. Thus, the ratios may change if the structure of the impurity is determined.

(16) 4,5-Dihydropyrenophanes have been observed following the Hofmann elimination step in several syntheses of [*n*](2,7) pyrenophanes. For example, see ref 9e.

(17) For both the [*n*](1,8)pyrenophanes and [*n*](1,6)pyrenophanes, each of the carbon atoms on the bridge has a pair of diastereotopic protons that exchange their environments upon flipping of the bridge from one face of the pyrene system to the other. The one exception is the pair of protons bonded to the central carbon atom of the bridge when *n* is odd. These two protons are homotopic. For even values of *n*, $n/2$ aliphatic signals are expected when bridge flipping is fast on the NMR time scale and *n* aliphatic signals are expected when bridge flipping is slow. For odd values of *n*, $(n + 1)/2$ aliphatic signals are expected when bridge flipping is fast on the NMR time scale and *n* aliphatic signals are expected when bridge flipping is slow.

(18) The Holm−Gutowsky equation was used, even though the exchanging nuclei are coupled: Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228−1234. The application of an equation for coupled nuclei assuming J_{AB} = 13.2 Hz (the observed value for J_{AB} in **29c**) also gave a value of $\Delta G^{\ddagger}$ = 14.9 kcal/mol: Heidberg, J.; Weil, J. A.; Janusonis, G. A.; Anderson, J. K. *J. Chem. Phys.* **1964**, *41*, 1033−1044.

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(20) Only one crystal of each type was separated, and this was only for one of several attempted crystallizations. While this allowed for the crystal structures of **28c** and **29c** to be determined, manual separation is clearly not something that can be relied upon as a means of separation.

(21) Strictly speaking, the angle θ was defined to describe the bend of the pyrene system in (2,7)pyrenophanes, so its use here may be loose. However, the pyrene system in **28c** is bent in very much the same way as those in the (2,7)pyrenophanes, and the magnitude of the bend is small.

(22) The distortion energy of the pyrene system in [12](2,7) pyrenophane (θ = 27.7°) was calculated to be 3.1 kcal/mol: (a) Dobrowolski, M. A.; Cyrański, M. K.; Merner, B. L.; Bodwell, G. J.; Wu, J. I.; Schleyer, P. v. R. *J. Org. Chem.* **2008**, *73*, 8001−8009. (b) Wu, J. I.; Dobrowolski, M. A.; Cyrański, M. K.; Merner, B. L.; Bodwell, G. J.; Mo, Y.; Schleyer, P. v. R. *Mol. Phys.* **2009**, *107*, 1177−1186.

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(25) The slippage angle is defined as 90° minus the smallest angle between the mean plane for [C(14), C(15), C(19), C(20), C(25), C(26)] and the mean plane for [C(25), C(26), C(25′) and C(26′)] with C(25′) and C(26′) generated by the operation (1 + *x*, *y*, *z*). For **29c**, the slippage angle is 90.0° − 77.3° = 12.7°.
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