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RESEARCH ARTICLE

# Gram-Scale Synthesis of the 1,1,*n*,*n*-Tetramethyl[*n*](2,11)teropyrenophanes

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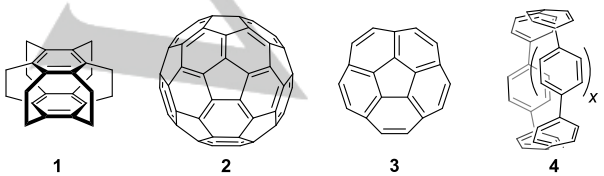
Supporting information for this article is given via a link at the end of the document.

**Abstract:** A gram-scale synthesis of a series of 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes (*n* = 7–9) has been accomplished as well as the first synthesis of the next higher homologue 1,1,10,10-tetramethyl[10](2,11)teropyrenophane. The scale-up of the original small-scale synthesis required the development of several heavily modified synthetic methods, including a chlorination / Friedel-Crafts alkylation protocol and an iodination / Wurtz coupling protocol, which were performed on 25-30 g and 30-60 g scales, respectively. Two separate sets of conditions for the key teropyrene-forming cyclodehydrogenation reaction at the end of the synthetic pathway were developed, an acid-promoted one for the two less strained congeners and an acid-free method for the two more strained homologues.

## Introduction

The design and efficient synthesis of π-electronic systems continues to be an area of considerable interest due to the very broad range of conceivable structures and properties, especially their optoelectronic properties, which may lead to applications in the field of materials science. Often, the first synthesis of a new designed π-system is a *tour de force*, which establishes access to the target compound on just a very small (milligram) scale. In some cases, e.g. superphane (**1**) (Chart 1),[1] the original synthesis (syntheses) ends up never being repeated/improved, but lives on as a classic piece of synthetic work in textbooks.[2] The lack of material limits the extent to which the molecule can be studied, let alone be used as a building block for more elaborate systems or to be incorporated into other interesting systems. In other cases, further generations of synthetic routes are developed and a molecule moves from being novel to being an abundant building block, e.g. buckminsterfullerene ($C_{60}$) (**2**), corannulene (**3**) and the [*n*]cycloparaphenylenes (CPP) (**4**) (Chart 1).




**1** **2** **3** **4**

***Chart 1.*** Structures of superphane (**1**), buckminsterfullerene ($C_{60}$) (**2**), corannulene (**3**) and the CPPs (**4**).

The original report of $C_{60}$ (**2**) by Kroto, Smalley and Curl[3] produced only minute quantities of the new carbon allotrope. Currently, $C_{60}$ is being produced commercially on a metric ton scale.[4] The first synthesis of corannulene by Barth and Lawton[5] was achieved in 0.4% overall yield using a 17-step synthesis. Later, more efficient syntheses were developed (9-12 steps), which improved the overall yield to up to 85%.[6] More recently, a kilogram-scale synthesis of corannulene (**3**) was disclosed.[7] In the same vein, Bertozzi *et al*.[8] reported the first synthesis of CPPs ([9]- (**4**, x=4), [12]- (**4**, x=7) and [18]CPP (**4**, x=13) with just a few milligrams of each compound bring produced. A few years later, Jasti *et al*.[9] reported gram-scale syntheses of [8]CPP (**4**, x=3) and [10]CPP (**4**, x=5), and Yamago et al.[10] communicated gram-scale syntheses of [10]CPP (**4**, x=5), [8]CPP (**4**, x=3) and [6]CPP (**4**, x=1). Several CPPs are commercially available.[11] The ability to produce tons, kilograms and grams, respectively, of these fascinating molecules has enabled the comprehensive investigation of their physical and chemical properties as well as their use in synthesis and as materials in ways that reflect the scale of their availability. More recent breakthrough syntheses of structurally novel and interesting π systems on a mg scale, e.g. carbon nanobelts and related systems,[12] highlight the need for the continued development of superior, larger scale synthetic approaches.

Our group has reported two synthetic approaches to a small series of 1,1,*n*,*n*-tetramethyl[*n*](2,11)teropyrenophanes (**5a-c**),[13] which feature a severely bent 36-carbon polycyclic aromatic system (teropyrene), a sizeable cavity and good solubility in common organic solvents (unlike the parent teropyrene,[14] which has extremely low solubility). The two synthetic routes are closely related, differing only in the method used for the installation of the first two-carbon bridge in the triply bridged pyrenophanes **6a-c** and **7a-c**, which served as direct synthetic precursors to the teropyrenophanes **5a-c** (Scheme 1). Dipyren-2-ylalkanes **8a-c** were employed as common starting points for the synthesis of **6a-c** and **7a-c**. The original syntheses delivered just 5-20 mg of material, which allowed for the determination of their crystal structures and the measurement of various physical and spectroscopic properties. However, insufficient amounts were available for the detailed investigation of their covalent and supramolecular chemistry.[15a] We recently reported the

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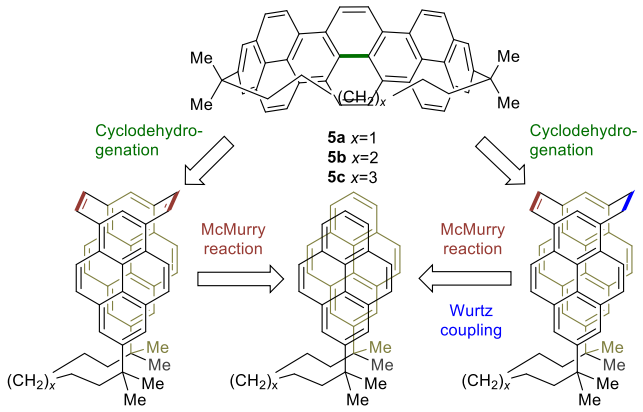
development of a gram-scale synthesis of **5c**,[15b] which underpinned the discovery of a highly regioselective four-fold bromination reaction. We now report the full details of the development of gram-scale syntheses of all three members of the series **5a-c** as well as the first synthesis of the next higher homolog **5d**.

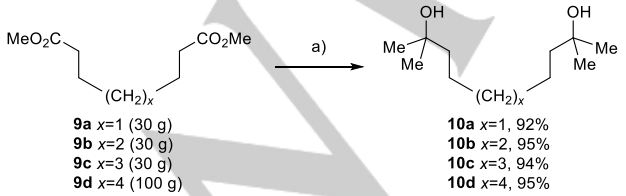



***Scheme 1***. Existing synthetic approaches to the teropyrenophanes **5a-c**.

## Results and Discussion

Initial work aimed at the synthesis of synthetically useful amounts of the teropyrenophanes **5a-c** involved direct scale-up of the existing Wurtz/McMurry route (via **7a**),[13b,c] but this proved to be problematic from the outset. Ultimately, almost every step of the synthesis had to be modified to accommodate scale-up. At the same time, a new teropyrenophane, **5d**, was added to the series.

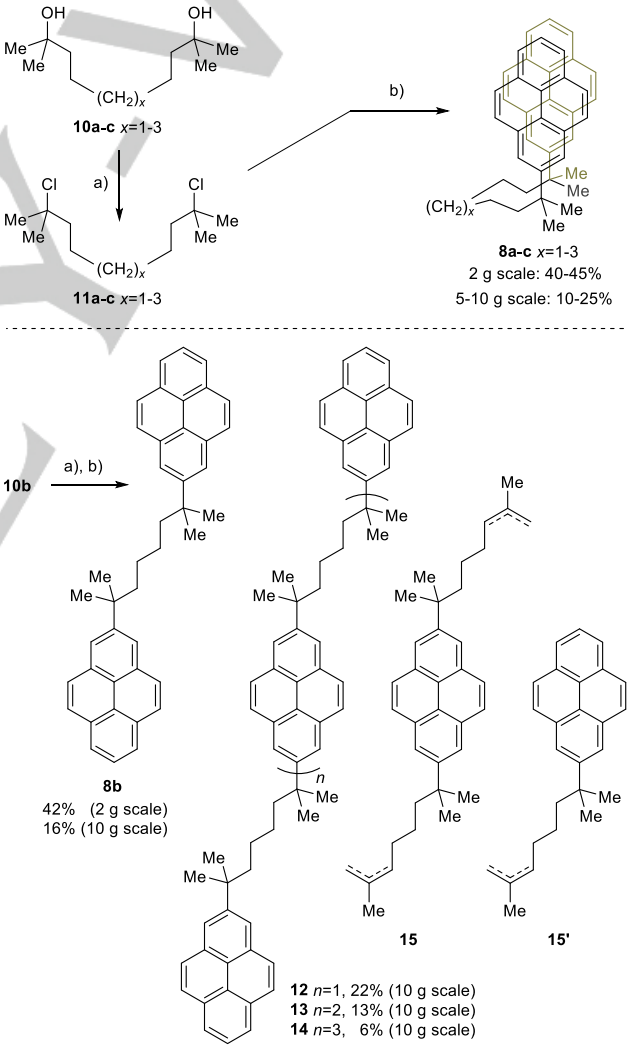
**Grignard Reactions.** The first step of the existing route, Grignard reaction between methylmagnesium bromide and diesters **9a-c** (Scheme 2), had always been limited to a <10 g scale (vigorous exotherm). For larger scale reactions, the commercially available solution of the Grignard reagent (3.0 M in diethyl ether) was diluted (*ca*. 1:1) with THF prior to the addition of the diesters **9a-d**, more efficient stirring was employed, and the rate of the addition of **9a-d** was carefully controlled. Using the new procedure, the Grignard reactions could be performed comfortably on a 30-100g scale of the diesters **9a-d** to afford diols **10a-d** in slightly improved yield (92-95%). It was also found that either drum THF or recovered THF from previous Grignard reactions could be used instead of dry THF, but an additional 0.5-1.0 equiv of the Grignard reagent was required to obtain equivalent yields.




***Scheme 2***. Synthesis of diols **10a-d**. Reaction conditions: a) MeMgBr (3.0 M in $Et_2O$), THF, –15 °C to reflux, 17-24 h.

**Chlorination and Friedel-Crafts Alkylation.** The second step in the synthesis was the conversion of diols **10a-d** into the corresponding dichlorides **11a-d** using concentrated aqueous HCl. These reactions were performed previously on up to a 2 g scale. Moving to a 10 g scale brought with it the formation of significant amounts of chloroalkene and diene side products arising from the elimination of one or two equivalents of HCl (Supporting Information, Sec. 3.1), the use of which in the subsequent Friedel-Crafts alkylation reactions resulted in a substantial lowering of the yield (10-25% for **8a-c**, *cf*. 40-45% on a 2 g scale).

The Friedel-Crafts alkylation reactions had always given rise to several side products (TLC analysis) and the scale-up work enabled the isolation and identification of some of them. For example, Friedel-Crafts alkylation of pyrene with dichloride **11b** (containing some chloroalkenes and dienes) on a 10 g scale led to the isolation of **8b** ($R_f$ = 0.22, 16% from diol **10b**) and linear oligomers **12** (22%, $R_f$ = 0.15), **13** (13%, $R_f$ = 0.10) and **14** (6%, $R_f$ = 0.05) (Scheme 3, Supporting Information, Sec. 3.2). The 41% combined yield of these products and the fact that 5.0 equivalents of pyrene were used suggest that monoalkylated pyrene systems are reacting significantly faster than unalkylated pyrene. The presence of alkenylpyrene side products **15** and **15'**, which would arise from the alkylation of pyrene by choloralkenes **S1**, was indicated by LCMS analysis of the crude product, but none of these compounds was isolated in pure form.

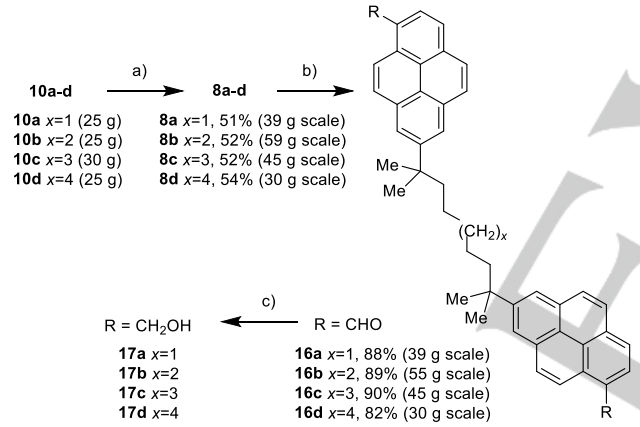



***Scheme 3***. Initial attempts to scale up the synthesis of dipyren-2-ylalkanes **8a-c** and side products obtained from them. Reaction conditions: a) conc. HCl, rt, 3 h. b) pyrene (5.0 equiv.), $AlCl_3$, $CH_2Cl_2$, rt, 4 h.

Various ways of minimizing the formation of linear oligomers were explored, including the use of other Lewis acids in conjunction with dichloride **11c**, the use of Brønsted acids in conjunction with diol **10c** and the introduction of substituents at one end of the

pyrene system (Supporting Information, Sec. 4). These approaches were largely unsuccessful and attention was returned to the original dichloride/$AlCl_3$ system. The main challenge was to minimize the amount of chloroalkene and diene side products in the dichlorides **11a-d** and this problem was solved by replacing the original chlorinating agent (37% aqueous HCl solution) with HCl gas. Bubbling gaseous HCl into a solution of diol **10c** in dry dichloromethane resulted in complete consumption of the starting diol **10c** in 4-5 h and the exclusive formation of **11c** (TLC analysis). No trace of chloroalkene or diene side products was observed. The resulting solution of **11c** was purged with nitrogen gas and then pyrene (5 equiv.) and $AlCl_3$ were added. This led to the formation of dipyren-2-ylalkane **8c** in 38% yield on a 2 g scale and 42% on a 10 g scale. In both cases, oligomers **12**, **13** and **14** were still present (TLC analysis), but there were clearly fewer additional spots than before (Scheme 3).

Raising the number of equiv. of pyrene from 5.0 to 10.0 improved the yield of **8c** to 53% on a 10 g scale. With a much-improved procedure in hand, the diols **10a-d** were then converted to the corresponding dipyren-2-ylalkanes **8a-d** on a 25-30 g scale[16] with no reduction in yield (51-54%) (Scheme 4). It was therefore possible to produce 35-40 g of **8a-d** in a single synthetic operation from diols **10a-d**. Furthermore, it found that replacing dry $CH_2Cl_2$ with drum grade $CH_2Cl_2$ had no detrimental effect on the yield. The odd-tethered compounds **8a** and **8c** were obtained as fluffy solids and were noticeably more soluble in $CH_2Cl_2$ than the even-tethered compounds **8b** and **8d**, which were obtained as crystalline solids.



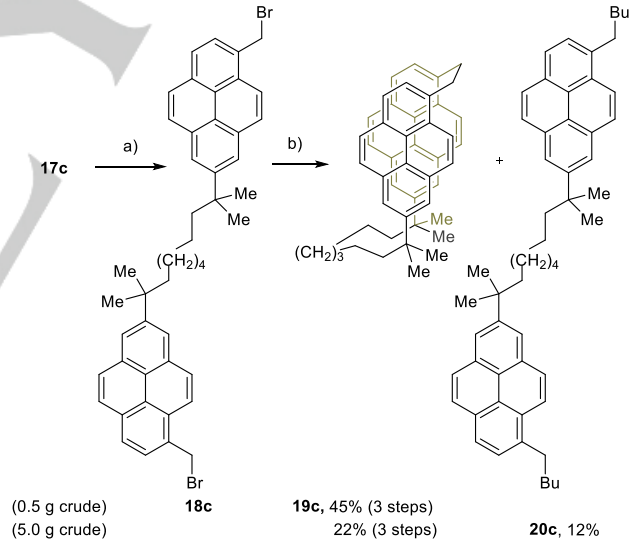

***Scheme 4.*** Reagents and conditions: Large scale synthesis of diols **17a-d**. a) i) HCl (gas), 4-5 h; ii) $N_2$ (gas), 20 min; iii) pyrene, $AlCl_3$, $CH_2Cl_2$, rt, 1 h; b) $Cl_2CHOCH_3$, $TiCl_4$, $CH_2Cl_2$, rt, 2 h; c) $NaBH_4$, THF, rt, 2 h.

**Rieche Formylation and Reduction.** Rieche formylation of the dipyren-2-ylalkanes **8a-d** required only minor changes to the original protocol. On a 0.5 g scale, 2.5 equiv. of both $TiCl_4$ and $Cl_2CHOCH_3$ were used to convert **8a-c** to the corresponding dialdehydes **16a-c** in 82-90% yield. Direct scale-up of these reactions to several grams of **8a-c** resulted in incomplete reaction and lower yields (40-44%). Therefore, 5.0 equiv. of $TiCl_4$ and $Cl_2CHOCH_3$ were employed and the temperature was changed from 0 °C to room temperature. With these modifications, the Rieche formylations of **8a-d** could be performed conveniently on a 30-59 g scale to produce the corresponding dialdehydes **16a-d** in 88-90% yields (Scheme 4). As before, it was found that drum grade $CH_2Cl_2$ could be used, but this required the addition of 0.5-1.0 additional equiv. of both $TiCl_4$ and $Cl_2CHOCH_3$. All of the dialdehydes **16a-d** exhibited good solubility in $CH_2Cl_2$, THF and ethyl acetate.

The next step in the synthetic pathway was the reduction of dialdehydes **16a-d** with $NaBH_4$, which proceeded efficiently to afford diols **17a-d** on a 30-55 g scale (Scheme 4). The only modifications that were made to the small-scale procedure were the use of drum THF instead of dry THF and a ten-fold increase in concentration. The recovered THF could be reused without any adverse effect on the reaction. The diols **17a-d** exhibited good solubility in $CH_2Cl_2$, THF and ethyl acetate. Attempted purification by column chromatography or crystallization resulted in substantial losses of material. $^1$H NMR analysis of the crude products indicated that they were easily of >90% purity, so they were used without purification in the following step.

**Bromination / Wurtz coupling reaction.** In the original small-scale synthesis, diols **17a-c** were brominated using $PBr_3$ to produce the corresponding dibromides **18a-c**, which were then used as substrates in intramolecular Wurtz coupling reactions.[13b] During initial attempts to increase the scale of the bromination of diol **17c**, it was found that hydrolysis of the resulting dibromide **18c** (to give back diol **17c**) during both workup and (to a greater extent) column chromatography on silica gel became increasingly prevalent as the scale of the reaction increased. For example, on a 10 g scale, **18c** was obtained in only 37% yield (2 steps from dialdehyde **16c**) after chromatography. The stability of the 1-pyrenylmethyl cation[17] is most likely the cause for the ease with which **18c** undergoes hydrolysis.

Since the majority of the hydrolysis appeared to occur during chromatography, it was decided to use the crude dibromide **18c** in the subsequent intramolecular Wurtz coupling reaction leading to [*n*.2]pyrenophane **19c** (Scheme 5). When this reaction was performed on a 0.5 g scale, cyclophane **27c** was obtained in 45% overall yield from dialdehyde **16c**. However, the yield for the three-step sequence dropped to 22% when the scale was increased to 5 g. Several side products were formed (TLC analysis) and the most abundant one **20c** (12%) was isolated in pure form.




***Scheme 5.*** Initial attempts to scale up the Wurtz coupling of **18c**. Reagents and conditions: a) $PBr_3$, $CH_2Cl_2$, 0 °C rt, 1 h; b) *n*-BuLi, THF, −15 °C, 10 min.

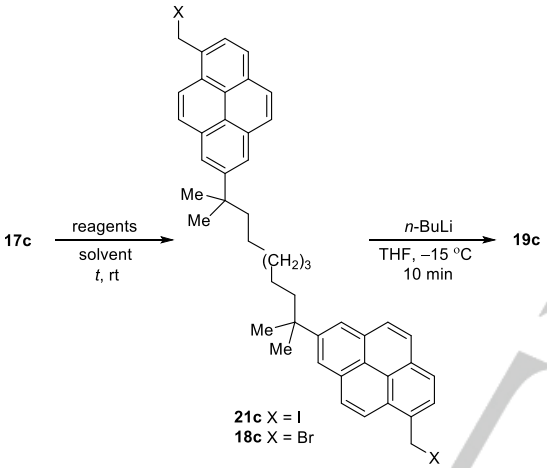
To avoid hydrolysis during both the aqueous workup and column chromatography, a further modification to the procedure was made. Treatment of diol **17c** (50 mg) with $PBr_3$ as before cleanly generated dibromide **18c** (TLC analysis). Switching the solvent to THF followed by addition of *n*-BuLi gave rise to a complex mixture of products from which cyclophane **19c** was isolated in 10% yield (from diol **17c**) (Table 1, Entry 1).

**Iodination / Wurtz coupling reaction.** Wurtz couplings are known to work better for alkyl iodides than the corresponding alkyl bromides,[18] so the possibility of replacing dibromide **18c** with diiodide **21c** was investigated. Attempted conversion of diol **17c** (50 mg) into diiodide **21c** using the Appel reaction ($PPh_3$/$I_2$/DMAP) gave a mixture of products (TLC analysis). Addition of *n*-BuLi to

this mixture gave an even more complex mixture (Table 1, Entry 2).

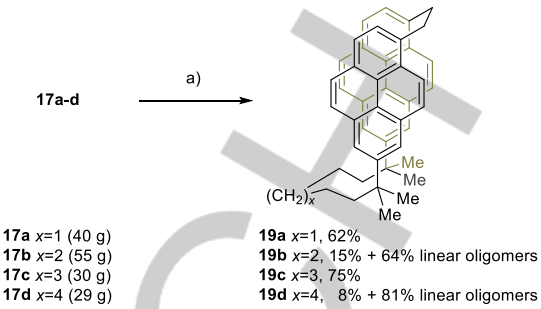
Das *et al*. reported the iodination of benzylic alcohols using PMHS/$I_2$ in $CHCl_3$.[19] Applying these conditions to diol **17c** (200 mg) resulted in clean conversion to what was presumed to be diiodide **21c** within 20 min at room temperature (TLC analysis). Replacement of the solvent with dry THF followed by the addition of 6.5 equiv. of *n*-BuLi at –15 °C led to the formation of **17c** in 61% yield (Table 1, Entry 3). Using THF for the iodination step removed the need for a change in solvent and gave an identical result (Table 1, Entry 4). More importantly, an increase in yield was observed as the reaction scale was increased to 2 g (61%), 9 g (66%) and then 30 g (75%) (Table 1, Entries 5 to 7). For the 30 g scale reaction, the concentration was increased (*ca*. two-fold) and it was found that drum THF could be used with no effect on the yield, but an additional 0.5-1.0 equiv. of *n*-BuLi was required to consume the starting material. An additional benefit of using diiodide **21c** instead of dibromide **18c** was that none of the side product **20c** was formed (TLC analysis).

***Table 1.*** Scale up of the halogenation / Wurtz coupling reactions of **17c**.



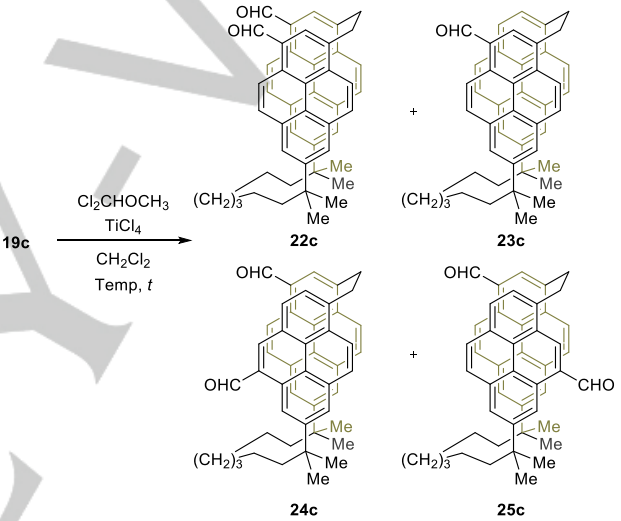

| entry | **17c** (g) | reagent(s)/solvent | *t* (min) | *n*-BuLi (equiv.) | **19c** (%) |
|---|---|---|---|---|---|
| 1 | 0.05 | $PBr_3/CH_2Cl_2$ | 120 | 1 - 8 | 10 |
| 2 | 0.05 | $I_2/PPh_3$/DMAP/$CHCl_3$ | 120 | 1 - 30 | mixture |
| 3 | 0.20 | $I_2$/PMHS/$CHCl_3$ | 20 | 6.2 | 61 |
| 4 | 0.20 | $I_2$/PMHS/THF | 20 | 6.2 | 61 |
| 5 | 2.00 | $I_2$/PMHS/THF | 20 | 6.2 | 61 |
| 6 | 8.90 | $I_2$/PMHS/THF | 20 | 6.2 | 66 |
| 7 | 30.0 | $I_2$/PMHS/THF | 20 | 6.2 | 66 |

With a reliable large-scale procedure in hand, the other diols **17a**, **17b** and **17d** were then subjected to the iodination/ Wurtz coupling sequence. The reaction of **17a** proceeded smoothly on a 40 g scale and cyclophane **19a** was obtained in 62% yield (Scheme 6). On the other hand, the reactions of the substrates with even-numbered tethers **17b** and **17d** gave much lower yields of **19b** (15%) and **19d** (8%). In contrast to the other reactions, a precipitate started to form as soon as the addition of *n*-BuLi commenced. The solids, which were found to be insoluble in a range of common organic solvents, are presumably linear oligomers arising from intermolecular Wurtz coupling reactions. The difference in the outcome between the odd and even series is likely a consequence of conformational preferences in the tether. Although the conformational behavior in these systems is surely complex, it is worth noting that the odd series has easy access to a fully staggered conformation that places the two pyrene units in a parallel, face-to-face orientation. The same is not true for the even series, where an *anti*-like conformation provides maximum separation of the two aromatic systems (Supporting Information, Sec. 12).




***Scheme 6.*** Optimized halogenation / Wurtz coupling reactions of **17a-d**. Reagents and conditions: a) 1. $I_2$/PMHS, THF, rt, 20 min; 2. *n*-BuLi, THF, −15 °C, 10 min.

***Table 2.*** Rieche formylation of **19c**.




| entry | **19c** (g) | $TiCl_4$ (equiv.) | $Cl_2CHOCH_3$ (equiv.) | *t* (h) | Temp (°C) | **22c** (%) | **24c** (%) | **25c** (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.05 | 2.5 | 2.5 | 2 | 0 | 75 | a | a |
| 2 | 0.25 | 2.5 | 2.5 | 2 | 0 | 30 | 20 | 18 |
| 3 | 0.25 | 6.0 | 6.0 | 2 | 0 | 63 | a | a |
| 4 | 0.25 | 6.0 | 6.0 | 2 | 0-rt | 54 | a | a |
| 5 | 0.25 | 6.0 | 6.0 | 2 | rt | 47 | a | a |
| 6 | 0.25 | 6.0 | 6.0 | 2 | 40 | 38 | a | a |
| 7 | 0.96 | 6.0 | 6.0 | 2 | 0 | 32 | a | a |
| 8 | 4.50 | 6.0 | 6.0 | 2 | 0 | 16 | a | a |
| 9 | 0.50 | 6.0 | 6.0 | 17 | 0-rt | 50 | a | a |
| 10 | 0.50 | 15.0 | 15.0 | 17 | 0-rt | 58 | a | a |
| 11 | 1.10 | 15.0 | 15.0 | 17 | 0-rt | 40 | a | a |
| 12 | 5.00 | 15.0 | 15.0 | 17 | 0-rt | 45 | 19 | 16 |

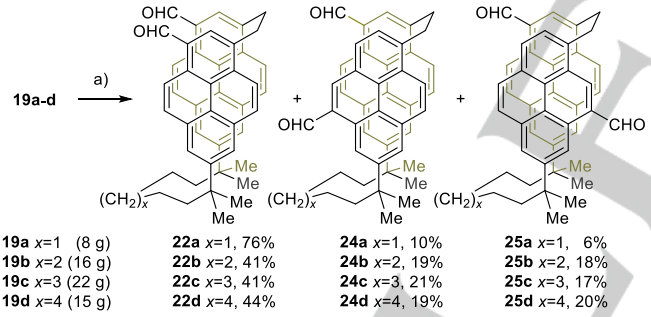
[a] This compound was formed (TLC analysis), but it was not isolated in pure form and the yield was not determined

**Second Rieche formylation.** To prepare for the final bridge-forming event, Rieche formylation was performed on the [*n*.2](7,1)pyrenophanes **19a-d**. As before, the system with the 9-membered bridge (**19c**) was selected for scale-up work. In the original synthesis of **5c**, Rieche formylation of **19c** on a 50 mg scale afforded the corresponding dialdehyde **22c** in 75% yield (Table 2, Entry 1). When the reaction scale was increased to 250 mg (Table 2, Entry 2), the reaction was sluggish and the yield of **22c** (30%) dropped significantly. Furthermore, in addition to a monoformylated species, two previously unobserved products

were isolated using careful chromatography (Table 2). These compounds were identified as regioisomeric dialdehydes **24c** and **25c** (Supporting Information, Sec. 3.3). To force the formylation of **19c** to completion, 6.0 equiv. of both $TiCl_4$ and $CHCl_2OCH_3$ were employed (Table 2, Entry 3) and the yield of **22c** improved to 63% (250 mg scale). The yield of **22c** dropped significantly with increasing temperature (Table 2, Entries 4 to 6) or with an increase in the scale of reaction up to 4.5 g (Table 2, Entries 7 and 8).

The order of addition of the reagents ($TiCl_4$ and $Cl_2CHOCH_3$) to **19c** was then changed. Instead of the direct addition of $Cl_2CHOCH_3$ and then $TiCl_4$ to a solution of cyclophane **19c** in $CH_2Cl_2$ at 0 °C, a freshly-prepared mixture of the two reagents in $CH_2Cl_2$ at 0 °C was added dropwise to a 0 °C solution of **19c** (500 mg scale) in $CH_2Cl_2$. The resulting reaction mixture was stirred at room temperature for a period of 17 h, which afforded **22c** in 50% yield (Table 2, Entry 9). Increasing the number of equiv. of $TiCl_4$ and $Cl_2CHOCH_3$ to 15 resulted in an increase in the yield to 58% (Table 2, Entry 10). Only a moderate reduction in yields was observed upon increasing the scale of the reaction to 5 g (Table 2, Entries 10 to 12). On this scale, significant amounts of the two regioisomeric side products **24c** (19%) and **25c** (16%) were still formed (Table 2, Entry 12).

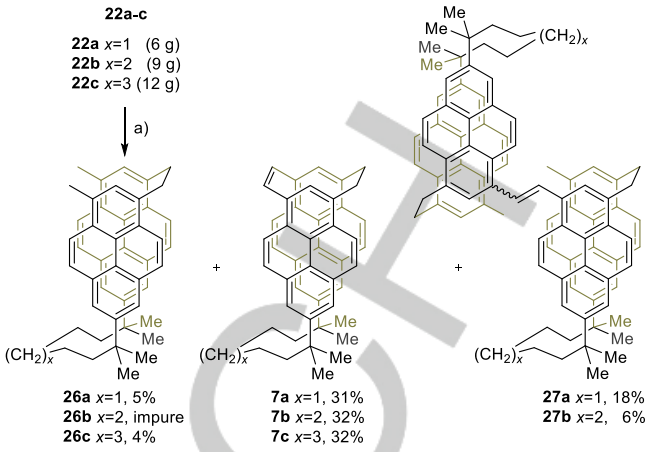
With improved conditions in hand, all of the cyclophanes **19a-d** were converted to the corresponding dialdehydes **22a-c** on 8-25 g scales (Scheme 7). The best result was obtained for the smallest member of the series **19a**, where the desired dialdehyde **22a** was isolated in 76% yield along with **24a** (10%) and **25a** (6%). The results for the higher homologues were less favorable (**22b-d** (41-44%), **24b-d** (19-21%) and **25b-d** (17-20%)), but nevertheless afforded multigram quantities of material. As before, drum grade $CH_2Cl_2$ could be used with no detrimental effect on the yield. All of the dialdehydes **22a-d**, **24a-d** and **25a-d** are readily soluble in $CH_2Cl_2$.




**19a** $x$=1 (8 g) **22a** $x$=1, 76% **24a** $x$=1, 10% **25a** $x$=1, 6%
**19b** $x$=2 (16 g) **22b** $x$=2, 41% **24b** $x$=2, 19% **25b** $x$=2, 18%
**19c** $x$=3 (22 g) **22c** $x$=3, 41% **24c** $x$=3, 21% **25c** $x$=3, 17%
**19d** $x$=4 (15 g) **22d** $x$=4, 44% **24d** $x$=4, 19% **25d** $x$=4, 20%

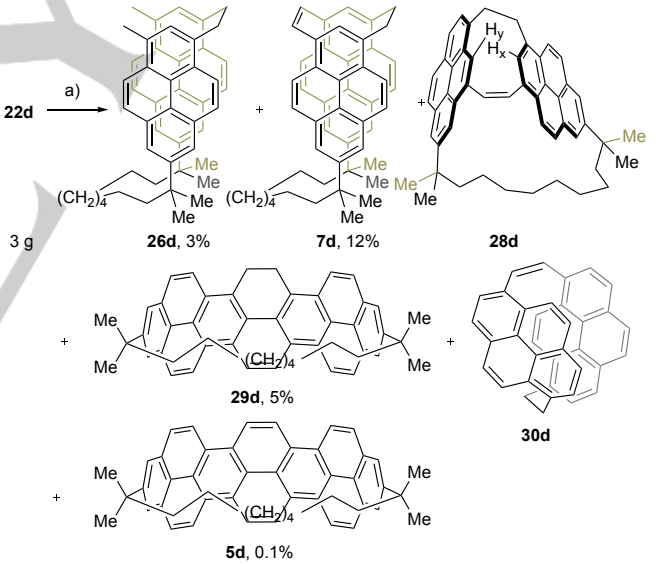
***Scheme 7.*** Modified Rieche formylation reactions of **19a-d**. Reagents and conditions: a) $TiCl_4$, $Cl_2CHOCH_3$, $CH_2Cl_2$, 0 °C rt, 17 h.

**McMurry reaction.** The scale-up of the intramolecular McMurry reactions of the three smallest cyclophanedialdehydes **22a-c** to afford [*n*.2.2](7,1,3)pyrenophanes **7a-c** was accomplished on a 6-12 g scale without changing the existing conditions. The reaction of **22d** to give **7d** was not as straightforward and is addressed separately below. The products **7a-c** were isolated in 30-32% yields, which are a little lower than those obtained previously on a 0.20 g scale (36-44%) (Scheme 8). As in the previously reported small-scale reactions, fully reduced compounds **26a-c** were formed (2-5%). Hydrocarbon **26b** was the only one that could not be isolated in pure form. Bright green fluorescent side products **27a-b** (*E/Z* mixtures, Supporting Information, Sec. 3.4), which evidently arose through intermolecular McMurry reaction and reduction (in either order), were also isolated.




***Scheme 8.*** McMurry reaction of cyclophanedialdehydes **22a-c**. Reagents and conditions: a) $TiCl_4$, Zn, pyridine, THF, reflux, 4 h.

When the largest cyclophanedialdehyde **22d** (3 g scale) was subjected to McMurry reaction under the conditions used for other members of the series, the reduction product **26d** (3%) and the intended intramolecular coupling product **7d** were again formed, but the latter was accompanied by the formation of several side products with very similar $R_f$ values ($R_f$ = 0.36-0.37, 30% dichloromethane / hexanes) (Scheme 9). This compound mixture was then subjected to *ca*. 15 further column chromatographic separations, which led to the isolation of five compounds with varying levels of purity.




***Scheme 9.*** McMurry reaction of dialdehyde **22d**. Reagents and conditions: a) $TiCl_4$, Zn, pyridine, THF, reflux, 4 h.

The first compound to be eluted (*ca*. 95% purity, $^1$H NMR analysis) was identified as **28d** by X-ray crystallography (Figure 1). This side product is the result of intramolecular McMurry coupling of dialdehyde **25d**. The starting material **22d** must therefore have been contaminated with a small amount of its regioisomer **25d**. In the crystal, the two pyrene systems of **28d** are essentially planar and the angle between the two best planes is 51.3°. The distance between the two internal carbon atoms is quite short (2.78 Å) (Supporting Information, Sec. 10).

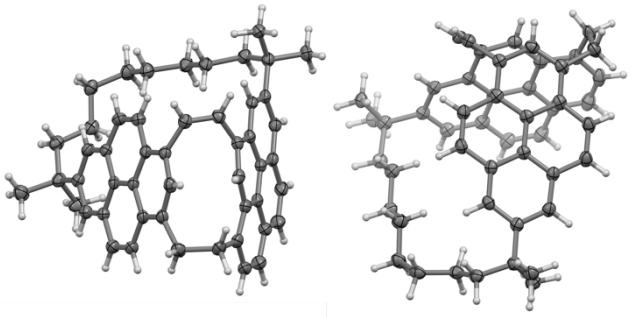


***Figure 1.*** Two views of a single molecule in the crystal structure **28d**, with 50% displacement ellipsoids. A second identical molecule in the asymmetric unit and lattice solvent molecules omitted for clarity.

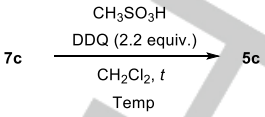
The second and third compounds to elute were dihydroteropyrenophane **29d** and teropyrenophane **5d**, which were isolated as the major components of *ca*. 80:20 and 70:30 mixtures with **28d**, respectively. The pathway to these two cyclophanes involves closure of the central C–C bond and this can be explained by the initial formation of cyclophanemonoene **7d**, followed either by a valence isomerization and then dehydrogenation, or a Scholl-type cycloaromatization. Either way, formal oxidations took place under reductive conditions. Similar unusual results were described previously in the synthesis of a porphyrin[20] and a (1,6)pyrenophane under McMurry conditions.[21] The closure of the central C–C bond was not observed in the reactions leading to **7a**-**c**, which is likely a consequence of the lower level of strain in teropyrenophane **5d** ($SE_{calc}$ = 38.7 kcal/mol) than in its lower homologues **5a**-**c** ($SE_{calc}$ = 44.7-61.8 kcal/mol).[22] This is reminiscent of what has been observed in the syntheses of [*n*](2,7)pyrenophanes, where precursors to the less strained members of the series undergo similar C–C bond-forming reactions under the conditions of their formation.[23]

The fourth compound to elute was the desired cyclophanemonoene **7d**, which was isolated in pure form in 12% yield. Considering how much chromatography was performed, this is very likely a substantial under-representation of the actual yield of this compound. The fifth and final compound to elute from the cluster of compounds was (1,6)(1,8)[2.2]pyrenophane-1-monoene **30d**. This compound clearly did not originate from **7d**. A discussion of its origin, structure and spectroscopic properties will be published elsewhere.

**Conversion of 7a-d to 5a-d.** The teropyrenophanes become increasingly strained as the bridge becomes shorter ($SE_{calc}$ = 38.7, 44.7, 54.2, 73.6 kcal/mol for **5d**-**a**, respectively (Supporting Information, Sec. 11), so they present quite different levels of synthetic challenge. The original small-scale syntheses of **5a**-**c** were performed on a 20-23 mg scale under quite harsh conditions (DDQ, *m*-xylene, 125-145 °C)[13b] and required a large excess of DDQ, presumably due to the reaction of DDQ with *m*-xylene.[24] It was immediately apparent that directly scaling up the reaction was not only impractical, but also tied to a sharp decrease in the yield. For example, **7c** afforded **5c** in just 21% yield on a 0.5 g scale (Supporting Information, Sec. 5).

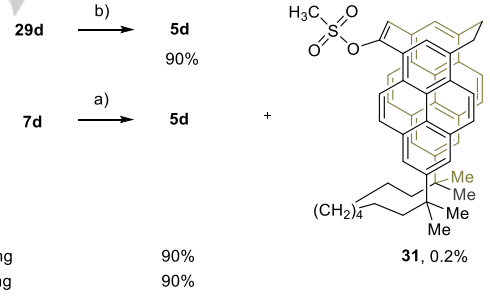
The use of Rathore's conditions[25] for intramolecular Scholl reactions (DDQ, 9:1 $CH_2Cl_2$ / $CH_3SO_3H$, 0 °C) resulted in complete consumption of **7c** in less than 2 min with only 2.0 equiv. of DDQ, but the product **5c** appeared to be reactive under the conditions of its formation and was isolated in just 5% yield. After some optimization (Table 3, Entries 1-3), it was found that the use of just 2.0 equiv. of $CH_3SO_3H$ along with 2.2 equiv. of DDQ in dichloromethane at ambient temperature afforded **5c** in very good yield (83-88%), in less than 10 min and on as much as a 2.2 g scale (Table 3, Entries 4-8). Even with the stoichiometric amount of acid, **5c** still appeared to be reactive under the conditions of its formation. If the reaction was allowed to proceed after **7c** had been completely consumed, the spot for **5c** diminished significantly in intensity (TLC analysis).

***Table 3.*** Scale-up of the conversion of **7c** to **5c**.




| entry | **7c** (g) | $CH_3SO_3H$ (equiv.) | *t* (min) | Temp (°C) | **5c** (%) |
|---|---|---|---|---|---|
| 1 | 0.01 | 9:1 $CH_2Cl_2$/$CH_3SO_3H$ | 2 | 0 | 5 |
| 2 | 0.01 | 9.5:0.5 $CH_2Cl_2$/$CH_3SO_3H$ | 2 | 0 | 12 |
| 3 | 0.01 | 1 | 120 | 40 | 75 |
| 4 | 0.01 | 2 | 8 | rt | 88 |
| 5 | 0.10 | 2 | 10 | rt | 88 |
| 6 | 0.50 | 2 | 10 | rt | 88 |
| 7 | 1.04 | 2 | 10 | rt | 85 |
| 8 | 2.20 | 2 | 10 | rt | 83 |

Curiously, the reaction of cyclophanemonoene **7d** to give the less strained teropyrenophane **5d** required somewhat more forcing conditions (6.0 equiv. of $CH_3SO_3H$ and 3.0 equiv. of DDQ). Under these conditions, teropyrenophane **5d** was isolated in 90% yield on both a 10 mg and 200 mg scale (Scheme 10). Dihydroteropyrenophane **29d**, which was obtained during the McMurry reaction of **7d**, was also smoothly converted to **5d** using 3.0 equiv. of $CH_3SO_3H$ and 1.5 equiv. of DDQ (Scheme 10). A very small amount of a side product was isolated from the 10 mg scale reaction. $^1$H NMR (e.g. $\delta$ 3.25 ppm) and HRMS analysis (*m/z* = 738.3222) were consistent with structure **31** (2%).




***Scheme 10.*** Conversion of **7d** to **5d**. Reagents and conditions: a) $CH_3SO_3H$ (6.0 equiv.), DDQ (3.0 equiv.), $CH_2Cl_2$, 40 min, rt. b) $CH_3SO_3H$ (3.0 equiv.), DDQ (1.5 equiv.), $CH_2Cl_2$, 30 min, rt, 90%.

**Crystal structure of [10](2,11)teropyrenophane**

Crystals suitable for the X-ray crystallographic studies of **5d** were obtained from an ethyl acetate / hexanes solution (Figure 2, Supporting Information, Sec. 10). The end-to-end bend angle ($\theta_{tot}$) for the teropyrene system in **5d** is 145.2º, which is (as expected) significantly smaller than that of its next smaller homologue **5c** (154.3°). The ß angles[26] are 4.0° and 4.5°. As seen in the other teropyrenophanes **5a**-**c**, the bend angle of the central pyrene system ($\theta_2$ = 81.0º) in **5d** is larger than those of the two flanking pyrene systems ($\theta_1$ = 57.6º and $\theta_3$ = 63.6º), but the differences in magnitude between them are smaller than those in **5a**-**c**.[13a-c] Nevertheless, the teropyrene system of **5d** still has a semi-elliptical profile rather than a semi-circular one. As in the case of **5a**-**c**, the bent teropyrene system has the effect of stretching the bridge. The C–C–C bond angles in the bridge of **5d** lie in the range of 113.1–115.9° (avg. = 114.5°).

10.1002/chem.202003828



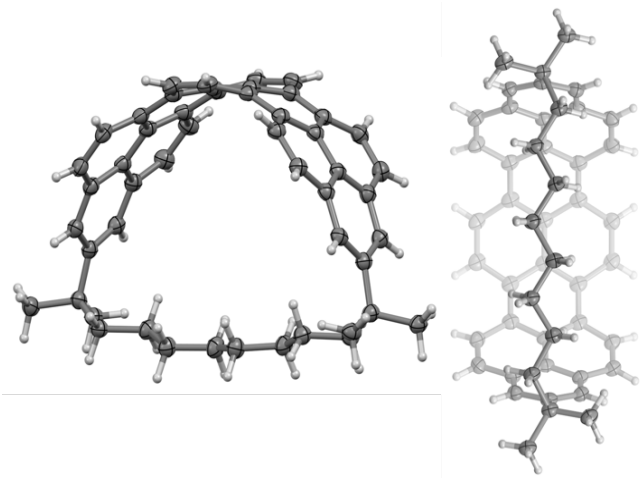



***Figure 2***. Two views of a single molecule in the crystal structure of **5d**, with 50% displacement ellipsoids. Disordered lattice solvent molecules omitted for clarity.

The aromatic signals of **5d** appear at $\delta$8.90 ($H_a$), 8.64 ($H_b$), 7.88 ($H_c$) and 7.62 ppm ($H_d$). These signals are all at lower field ($\Delta\delta$ = 0.08-0.13 ppm) than those of the corresponding protons in **5c**,[13a-c] which is in line with the previously observed trend that the aromatic signals all move to higher field with increasing bend in the teropyrene system. The highest field protons in the bridge resonate at $\delta$ –0.46 ppm, which compares to $\delta$ –1.00, –0.66 and –1.15 ppm for **5c**, **5b** and **5a**, respectively.[13a-c]

The lowest energy absorption envelope of **5d** has vibronic structure with $\lambda_{max}$ = 499, 469 and 438 nm (Figure 3). These values are at slightly lower energy than those of **5c** ($\lambda_{max}$ = 496, 464 and 435 nm) and fit with the trend of a small blue shift with increasing bend in the teropyrene system.[13b] By comparison, the longest wavelength absorptions of **5b** and **5a** are 489 and 484 nm, respectively. The emission spectrum of **5d** shows mirror image symmetry with the absorption spectrum ($\lambda_{max}$ = 516, 543 and 585(sh) nm, Figure 3). Again, these values are at slightly lower energy than those of **5c** ($\lambda_{max}$ = 512, and 533 nm).[13b] The results of a much more detailed study of the photophysical properties of **5a-d** will be published elsewhere.

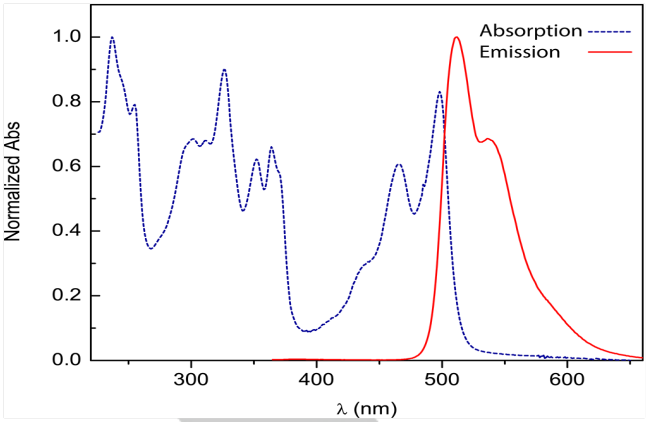
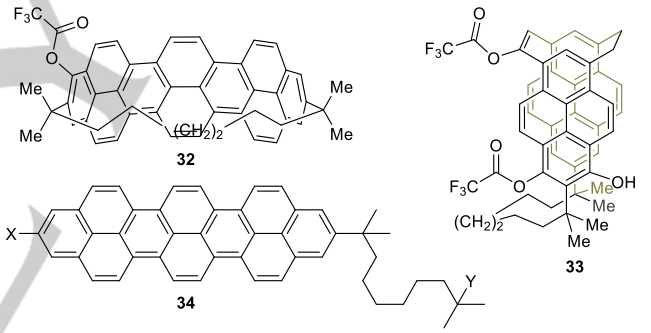



**Figure 3**. Normalized absorption and emission spectra of **5d** in acetonitrile. Irradiation wavelength = 350 nm.

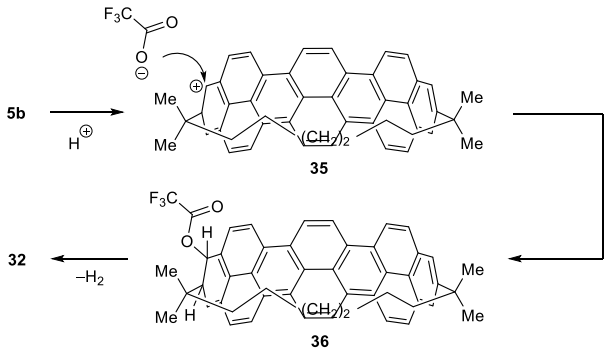
Using the previously established reaction conditions for the conversion of **7c** to **5c**, **7b** was consumed completely in 5 min, but **5b** was obtained in only 5% yield (Table S2), which suggested that **5b** is more reactive under the conditions of its formation than its less strained congener **5c**. In an attempt to find more suitable reaction conditions, the use of a variety of acids ($CH_3SO_3H$, $CF_3COOH$, $CHCl_2COOH$, $CH_3COOH$ and *p*-TsOH; p$K_a$ range –2.0 to 4.76), solvents, temperatures and reactions times were screened, all of which ended in no improvement in the yield of **5b** (Table S2). Additionally, replacing DDQ with other oxidizing agents delivered either moderate or no conversion of **7b** to **5b** or produced a complex mixture (Table S2).

From the reactions described in Table S2, Entries 8-13, three types of side products **32**, **33** and **34** were consistently observed, all of which could be isolated using column chromatography (Scheme 11, Supporting Information, Sec. 3.5). The formation of **32** involves protonation at the bridgehead carbon atom to give cation **35**, followed by the addition of trifluoroacetate anion to give **36** and then dehydrogenation by DDQ (Scheme 12). Several other sites of protonation of **7b** could also lead to **32**. Similarly, when dichloroacetic acid was used (Table S2, Entries 16-19) two side products containing at least one dichloroacetoxy group were observed (Supporting Information, Sec. 3.6). The isolation and characterization of these side products shed some light on the reactivity of the teropyrene system, which in turn helped with the development of new reaction conditions.

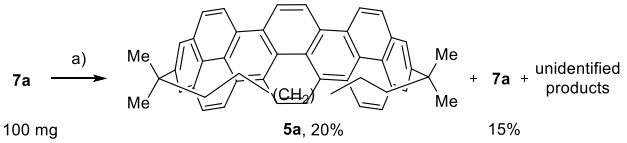
The scale-up of the conversion of monoene **7a** using DDQ / $CH_3SO_3H$ (1.0 equiv.) at 40 °C for 2 h afforded the most highly strained teropyrenophane **5a** in only 20% yield, along with some unreacted starting material **7a** (15%) (Scheme 13). Cyclophane **7a** was not completely consumed, even after increasing the amount of $CH_3SO_3H$ to 3.5 equiv. As with **7b**, it was evident that **5a** was reactive under the conditions of its formation (TLC analysis).




***Scheme 11.*** Side products formed in the conversion of **7b** to **5b** in the presence of $CF_3CO_2H$.




***Scheme 12.*** Proposed mechanism for the formation of compound **32**.




***Scheme 13.*** Conversion of **7a** to **5a**. Reagents and conditions: a) DDQ (2.2 equiv.), $CH_3SO_3H$ (1.0–3.5 equiv.), $CH_2Cl_2$, 30 min, 40 °C.

**Acid-free formation of 5a and 5b.** The observation of side products that contained structural units originating from the acids that were used to promote the formation of **5a** and **5b** prompted the reinvestigation of acid-free conditions. A parameter that had only received scant attention to this point was the solvent. Ten common organic solvents were screened for the conversion of **7a** to **5a** on a 5 mg scale with 2.2 equiv. of DDQ in 2 mL solvent under microwave irradiation (Table 4). Good conversion of **7a** into **5a** occurred only when DCE, $CH_3CN$ and $CHCl_3$ were used (Table 4, Entries 1-3) and no side products were observed when using $CH_3CN$ (TLC analysis). Modest conversion occurred in EtOAc, *m*-xylene and benzene (Table 4, Entries 4-6) and no reaction took place in hexanes, 1,4-dioxane, THF and toluene (Table 4, Entries 7-10). Due to the scale limitation under microwave conditions, attention was turned to the use of thermal conditions. Of the 4 different solvents (DCE, $CHCl_3$, EtOAc and $CH_3CN$) used on a 5 mg scale, almost all of the starting material was consumed in DCE and $CH_3CN$ (Table 4, Entries11-14). Increasing the scale in these two solvents to 25 mg and increasing the amount of DDQ to 2.7 equiv. led to the complete consumption of the starting material in 3 h (Table 4, Entries 15-18). The yields in $CH_3CN$ were superior, so further scale-up was performed using this solvent. Ultimately, **7a** was converted into **5a** on a 1.25 g scale in 81% yield (Table 4, Entries 19-20). The conversion of **7b** to **5b** also proceeded smoothly using these conditions on 5 mg, 25 mg and 1.29 g scales in 85-90% yields (Table 5). The reaction times (2-2.5 h) were significantly shorter than those leading to **5a** (3-4 h), which is presumably a reflection of the lower strain energy of **5b** (54.2 kcal/mol vs. 61.8 kcal/mol, Supporting Information, Sec. 11).

***Table 4.*** Optimized conditions for the conversion of **7a** to **5a**.

**7a** —(a or b)→ **5a**

| entry | **7a** (g) | DDQ (equiv.) | solvent | *t* (h) | **5a** (%) | dielectric constant ($\varepsilon$)[e] |
|---|---|---|---|---|---|---|
| 1 | 0.005 | 2.2[a] | 1,2-dichloroethane | 1.0 | 88[c] | 10.4 |
| 2 | 0.005 | 2.2[a] | acetonitrile | 1.0 | 91[c] | 36.6 |
| 3 | 0.005 | 2.2[a] | chloroform | 1.0 | 86[c] | 4.8 |
| 4 | 0.005 | 2.2[a] | ethyl acetate | 1.0 | <20[d] | 6.0 |
| 5 | 0.005 | 2.2[a] | *m*-xylene | 1.0 | <20[d] | 2.4 |
| 6 | 0.005 | 2.2[a] | benzene | 1.0 | <20[d] | 2.3 |
| 7 | 0.005 | 2.2[a] | hexanes | 1.0 | 0[d] | 1.9 |
| 8 | 0.005 | 2.2[a] | 1,4-dioxane | 1.0 | 0[d] | 2.3 |
| 9 | 0.005 | 2.2[a] | tetrahydrofuran | 1.0 | 0[d] | 7.5 |
| 10 | 0.005 | 2.2[a] | toluene | 1.0 | 0[d] | 2.4 |
| 11 | 0.005 | 2.2[b] | ethyl acetate | 4.0 | 55 | |
| 12 | 0.005 | 2.2[b] | 1,2-dichloroethane | 3.5 | 82 | |
| 13 | 0.005 | 2.2[b] | acetonitrile | 3.5 | 89 | |
| 14 | 0.005 | 2.2[b] | chloroform | 4.0 | 49 | |
| 15 | 0.025 | 2.2[b] | 1,2-dichloroethane | 3.5 | 61 | |
| 16 | 0.025 | 2.2[b] | acetonitrile | 3.5 | 71 | |
| 17 | 0.025 | 2.7[b] | 1,2-dichloroethane | 3.0 | 78 | |
| 18 | 0.025 | 2.7[b] | acetonitrile | 3.0 | 94 | |
| 19 | 0.10 | 2.7[b] | acetonitrile | 3.0 | 87 | |
| 20 | 1.25 | 2.7[b] | acetonitrile | 3.5 | 81 | |

[a] MW, 100 °C. [b] reflux. [c] isolated yield. [d] according to $^1$H NMR and TLC analysis. [e] the values were obtained from Vogel's Practical Organic Chemistry (5th ed.).

***Table 5.*** Optimized thermal conditions for the conversion of **7b** to **5b**.

**7b** —(DDQ (2.7 equiv.), $CH_3CN$, *t*, reflux)→ **5b**

| entry | **7b** (g) | *t* (h) | **5b** (%) |
|---|---|---|---|
| 1 | 0.005 | 2.0 | 90 |
| 2 | 0.025 | 2.5 | 88 |
| 3 | 1.298 | 2.5 | 85 |

The observation that the best result was observed in the solvent with the highest dielectric constant ($\varepsilon$ = 36.6) suggests that there is developing charge at the transition state of the reaction. It has been noted previously that some (2,7)pyrenophanes have relatively large calculated dipole moments that increase with the degree of bend in the pyrene system ($\mu$ = 0.87-1.74 D)[27] and an adamantano(2,7)pyrenophane was calculated to have a dipole moment 2.3 D.[28] Therefore, the dipole moments of **5a**-**d** were calculated at the B3LYP-D3/6-31G(d) level of theory and found to be almost identical ($\mu$ = 2.31-2.39 D), despite the range of bend in the teropyrene system (Supporting Information, Sec. 11). It thus seems that developing polarity in **5a**-**b** indeed plays a role in the success of the acid-free reaction in acetonitrile.

## Conclusion

A scaled-up, 8-step synthesis of the 1,1,*n*,*n*-tetramethyl[*n*](2,11)-teropyrenophanes **5a**-**c** leading to gram quantities of material has been developed and a first synthesis of **5d** has been accomplished on a 0.2 g scale. On the surface, the synthetic route closely resembles the previously reported synthetic pathway, but substantial modifications had to be made at almost every stage. The most important advances that enabled progress on a large scale were 1) the development of a chlorination / Friedel-Crafts reaction leading to **8a**-**d** on a 35-40 g scale, 2) the development of an iodination / Wurtz coupling reaction leading to **27a**-**d** on a 2-25 g scale and 3) the discovery of two sets of conditions (with and without acid) for the conversion of cyclophanemonoenes **7a**-**d** into teropyrenophanes **5a**-**d**. The two highest homologues **5c** and **5d** were generated at room temperature via and acid-promoted cyclodehydrogenation reaction, whereas the two lowest homologues were formed in a polar aprotic solvent (acetonitrile) at *ca*. 82 °C without acid. The need for different conditions is a reflection of the increasing level of molecular strain as the bridge becomes shorter. The overall yields for **5a**-**d** were 4.9% (1.0 g), 0.7% (1.3 g), 3.6% (1.9 g), and 0.2% (0.2 g), respectively. The lower yields for the **5b** and **5d** (even number of atoms in the long bridge) are a result of low yields in the intramolecular Wurtz coupling step. The new teropyrenophane **5d** features a bent teropyrene system with an end-to-end bend of 145.2°. The availability of synthetically useful amounts of **5a**-**d** will enable the study of the chemistry these systems and their use as starting points for the construction of cyclophanes with larger aromatic systems.

## Acknowledgements

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**Keywords:** cyclophanes • nonplanar aromatic compounds • teropyrene • pyrene • cyclodehydrogenation

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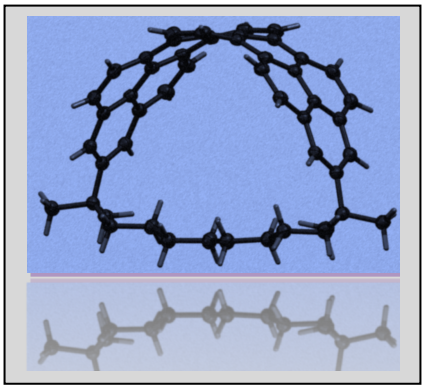

A large-scale synthetic route to a series of four [*n*](2,11)teropyrenophanes (*n*=7-10) has been developed, which delivered the three smallest homologues on a >1 g scale and enabled the first synthesis of the highest homologue. The synthetic pathway culminates with a teropyrene-forming cyclodehydrogenation, for which two sets of conditions had to be developed as a result of the broad range of strain (38.7-61.8 kcal/mol) in these bow-shaped cyclophanes.

Institute and/or researcher Twitter usernames: ((optional))