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Solid-phase approaches toward cyclic oligomers

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Abstract—Strategies were sought to effect cyclizations of oligo(*m*-phenylene ethynylene) by exploiting pseudo-high dilution effects on polymer supports. Using Pd/Cu-catalyzed coupling protocols, Merrifield's resin (1% crosslinked chloromethylated polystyrene) proved inadequate for site isolation; inter-site couplings ensued on the flexible support. Conversely, use of the Argopore resin, a more highly crosslinked polystyrene, inhibited inter-site interactions, and no identifiable final product could be separated from the resin. Spectroscopic and mass spectrometric methods indicated that the product from the Argopore resin might be a threaded catenane. © 2001 Elsevier Science Ltd. All rights reserved.

1. Supramolecular synthesis

Over the last two decades, there has been a surge of development in the field of supramolecular chemistry. The preparation of well-defined molecular architectures has played a large role in the exploration of this discipline.[1–5] Both the creation of exactly specified chemical structures and the methodologies to their syntheses are crucial for the advancement of supramolecular and materials chemistry.[6–13] The controlled incorporation of moieties that define the steric, electronic, and chemical properties of the supramolecular frameworks has been critical for effecting the syntheses.[7] Some specific methods include step-wise divergent/convergent syntheses,[14–18] templated approaches,[19–21] and geometrically controlled routes.[22,23] Initially we sought to improve the synthesis of cyclic oligo(*m*-phenylene ethynylene)s by employing a resin-supported route for a pseudo-high dilution effect. However, as we will show, lightly crosslinked resins did not provide the needed site isolation due to their inherent flexibilities.[24] While the more rigid resins did inhibit inter-site interactions, we were not able to separate identifiable products, and spectroscopic and mass spectrometric methods indicated that the final product might be a threaded catenane.[3]

2. Benefits of solid-supported chemistry

Solid-supported chemistry in the preparation of oligomers has several potential advantages over conventional solution-phase organic syntheses including simplified purification of intermediates, use of easily filterable excess reagents to drive reactions, minimization of orthogonal protection group protocols, and simple adaptation to combinatorial and automated approaches.[14–18,25,26] While targeting the cyclic oligo(*m*-phenylene ethynylene) **1**, we considered a resin-supported strategy as illustrated by Fig. 1. We were emboldened by Moore's success in obtaining higher yields using resin based-macrocyclic synthesis versus the solution phase.[27]

3. Attempted coupling of resin-bound pentamer with 1,3-diethynylbenzene

Specifically, a resin-immobilized oligomer could be constructed (Scheme 1), affording a diiodo-functionalized pentamer that could be reacted with 1,3-diethynylbenzene to form a cyclic hexamer **1**. Accordingly, 1,3-diiodobenzyl alcohol (**2**) was prepared by borane reduction of the known 1,3-diiodobenzoic acid. **3**, a resin suitable for immobilizing alcohol functionalized molecules,[28] was prepared from commercially available Merrifield's resin (1% crosslinked polystyrene with chloromethylation at 1.00 mequiv./g Cl). Treatment with the sodium salt of 2-(hydroxymethyl)-3,4-dihydro-2*H*-pyran in dimethylacetamide gave the desired resin with 100% expected mass gain after drying. **2** was bound to the resin by heating at 60°C in the presence of *p*-toluenesulfonic acid in 1,2-dichloroethane[28] to give **4**. The yield of 67% was determined by mass increase and by cleaving a small sample from the polymer support under literature conditions[28] to measure the loading. This diiodo-functionalized resin **4** is the starting material for the two-directional oligomer growth.

Keywords: supramolecular; macrocycle; pseudo-high dilution.

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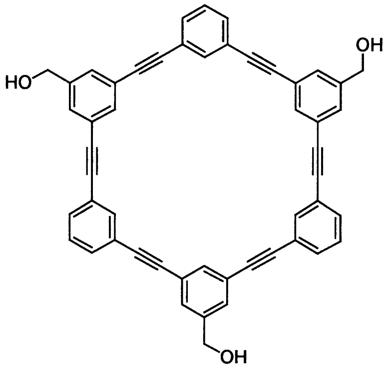

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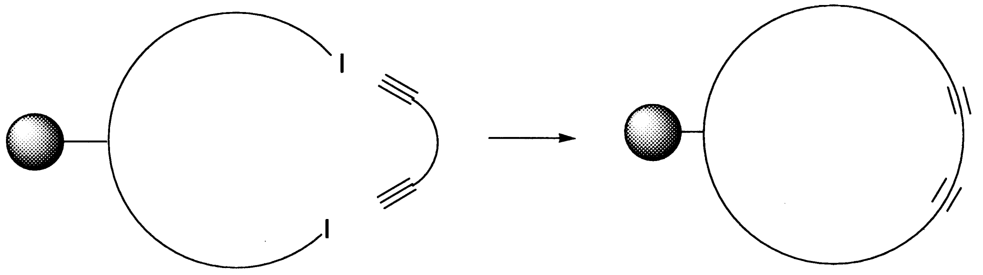
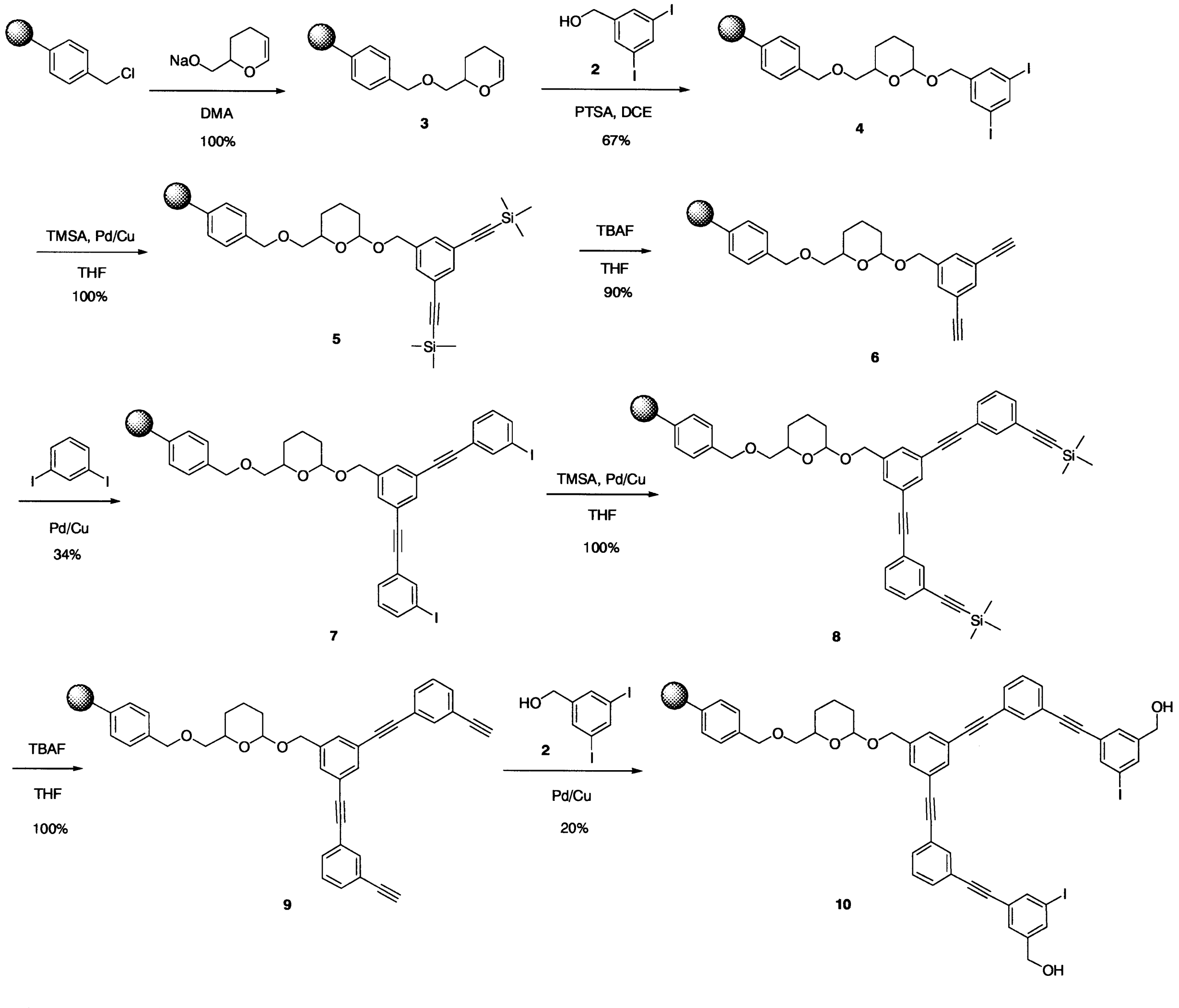


Figure 1. Strategy 1 for the preparation of resin-immobilized cyclic oligo(*m*-phenylene ethynylene)s.



Scheme 1. Preparation of a resin-immobilized pentamer.

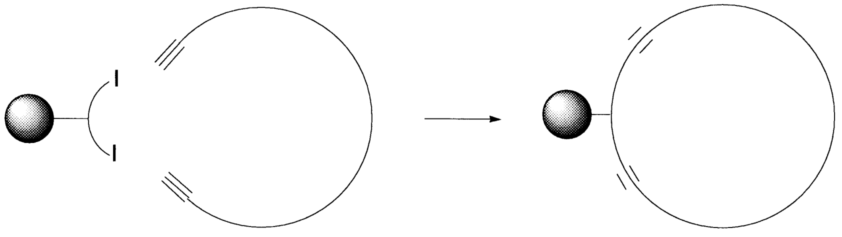
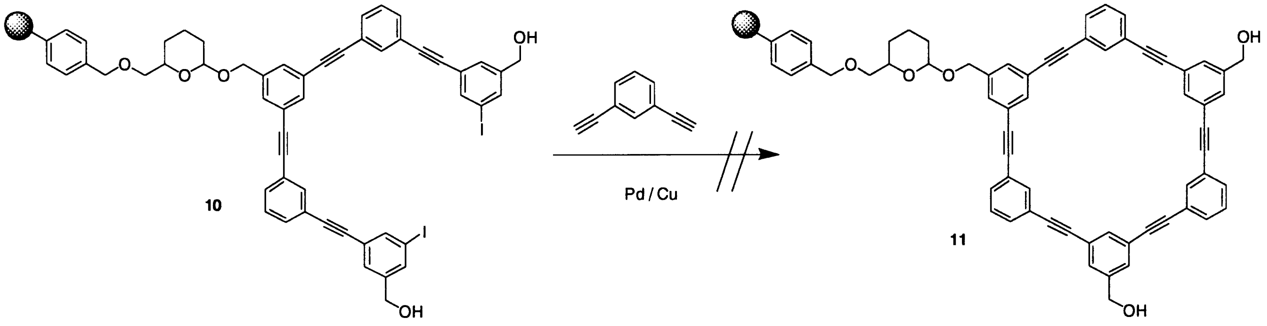


Figure 2. Strategy 2 for the preparation of resin-immobilized cyclic oligo(*m*-phenylene ethynylene)s.



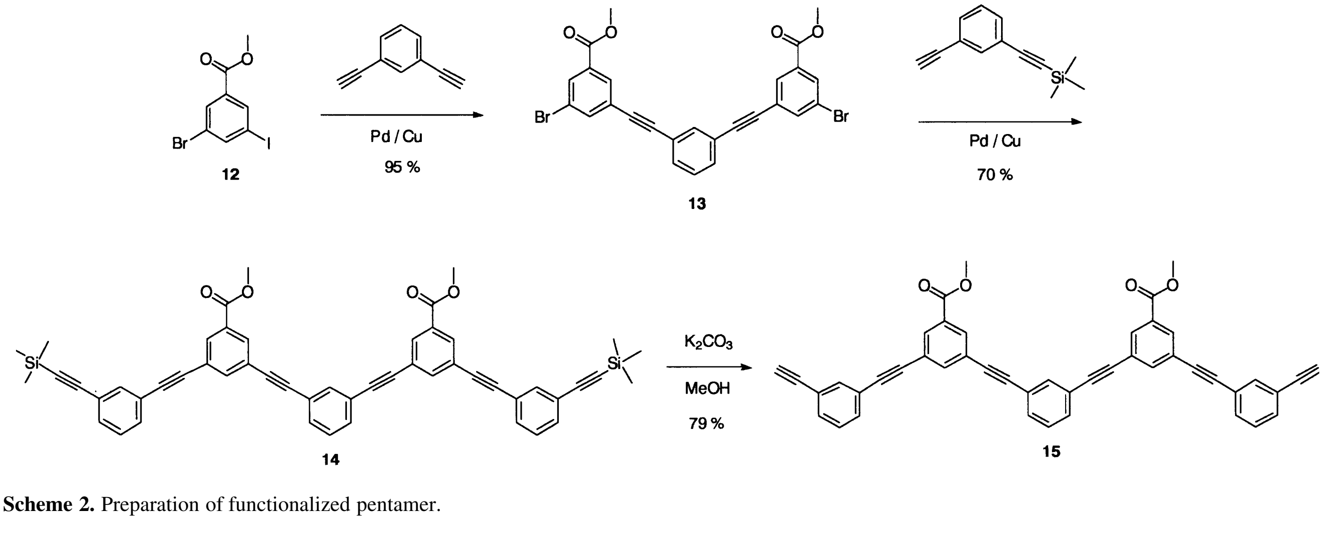
(1)

Reaction of **4** with trimethylsilylacetylene under palladium-catalyzed cross-coupling conditions[29,30] gave **5** (Scheme 1). Resin **5** shows a strong infrared absorbance at 2156 cm^{-1} due to the trimethylsilyl-terminated alkynes. Upon treatment with tetrabutylammonium fluoride, this absorbance was replaced by the absorbance at 3292 cm^{-1} of resin **6**. These infrared bands have been used previously to determine the efficacy of polystyrene-supported reactions.[15,18,24] Treatment with 1,3-diiodobenzene, again under palladium-catalyzed cross-coupling conditions,[29,30] gave **7**. Assuming that the dialkyne was site-isolated while binding to the support, there was no danger of oligomerization. The mass increase was only 34% of the expected increase, but the terminal alkyne proton infrared absorbance disappeared, indicating that the starting material had been consumed.[15,18,24] Reaction of **7** with trimethylsilylacetylene under palladium catalyzed cross-coupling conditions gave **8**, which was desilylated to give **9**, again accompanied by the expected infrared signatures. Finally, treatment with 1,3-diiodobenzyl alcohol gave **10** as indicated by the disappearance of the infrared absorbance at 3292 cm^{-1}. This entire transformation resulted in only 20% of the expected mass gain.

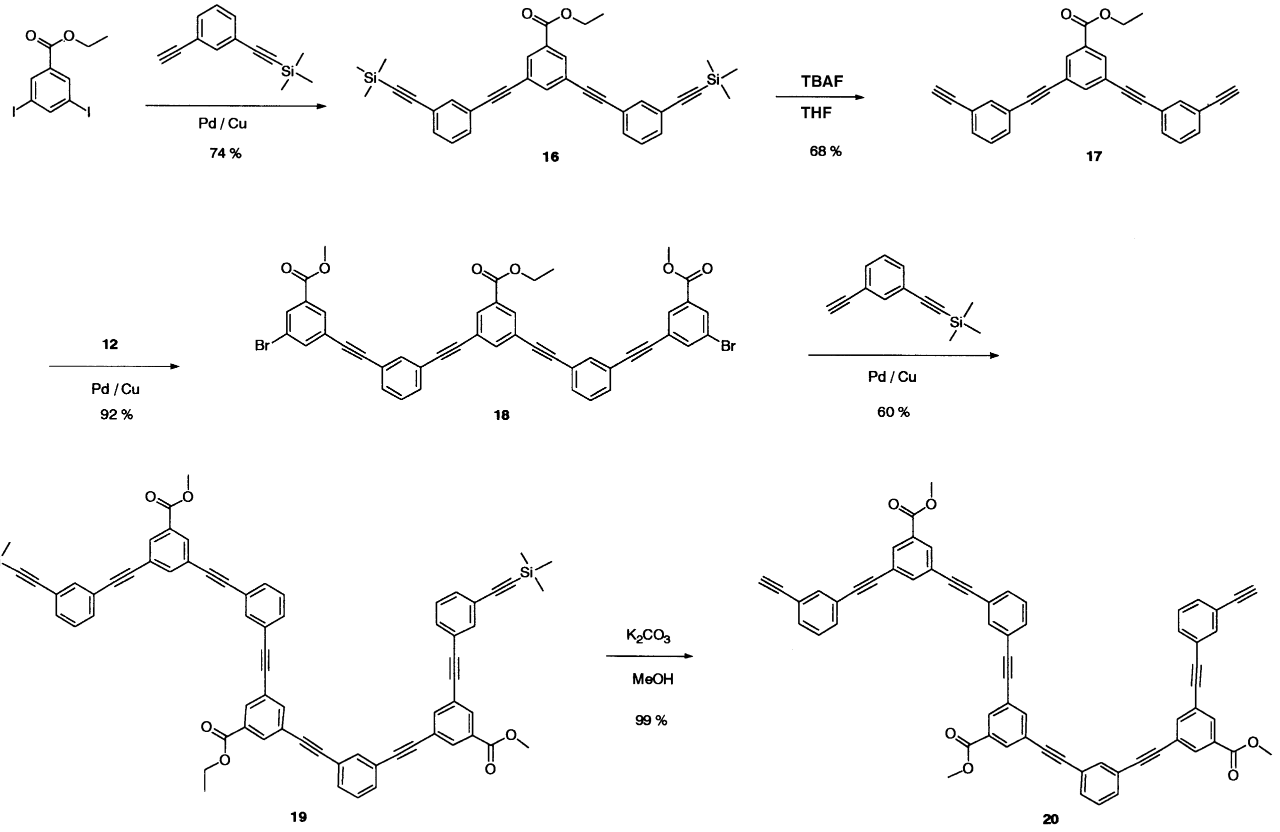
Cyclization was attempted with 1,3-diethynylbenzene (Eq. (1)). However, the desired cyclic hexamer **1** was not obtained upon cleavage from the polymer support with pyridinium *p*-toluenesulfonate in *n*-butanol and 1,2-dichloroethane.[24,28] Analysis of the cleaved material suggests that inter-site reactions had taken place during the oligomer growth; this behavior has been previously reported.[24,31,32] The occurrence of reactions between the resin-supported oligomers also explains the low mass increase of later reactions in the sequence.

4. Attempted coupling of α,ω-diethynyl pentamer to resin-bound diiodoarene

Turning to a different strategy, as depicted in Fig. 2, an



Scheme 2. Preparation of functionalized pentamer.



Scheme 3. Preparation of functionalized heptamer.

oligomer would be prepared by solution-phase two-directional synthesis and reacted with a resin-immobilized small molecule containing the appropriate diiodo-functionality.

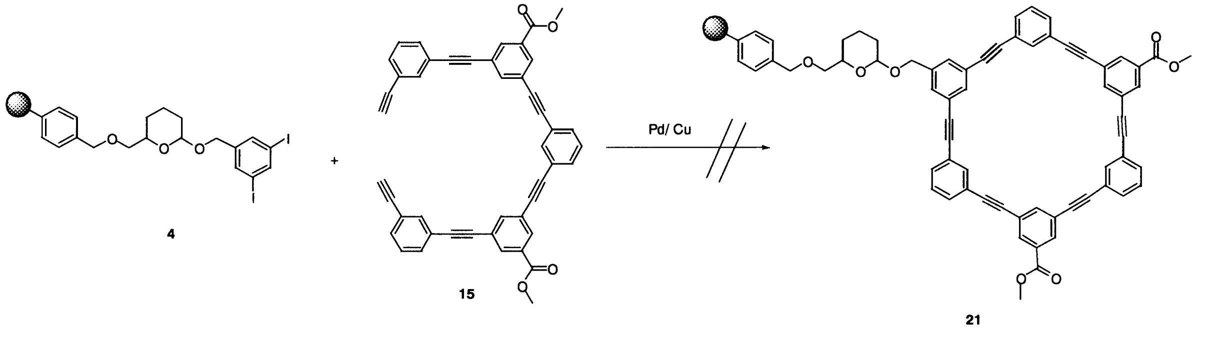
Strategy 2 would enjoy the same streamlined synthetic route as in the first method; however, because the oligomer would not be bound to a polymer support during growth reactions, suitably protected functionalities would be required in order to avoid polymerization.

As we wished to target a cyclic hexamer, efforts turned to the preparation of an appropriately functionalized pentamer (Scheme 2).

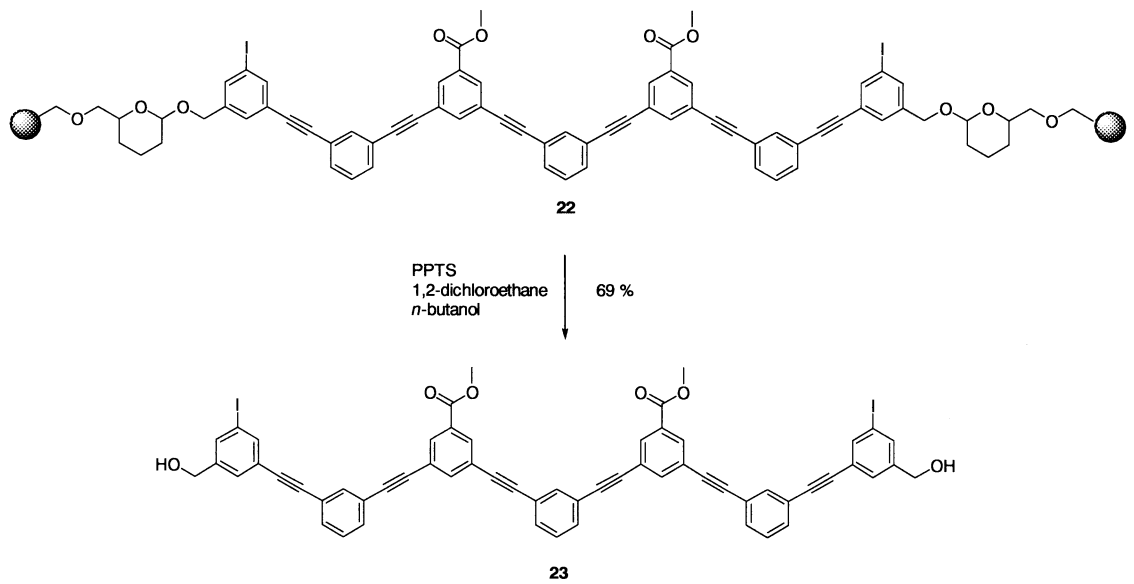
Coupling of an excess of the known methyl 3-bromo-5-iodobenzoate (**12**) with 1,3-diethynylbenzene gave **13**. **12** rather than the dibromo- or diiodo-derivative was required in order to avoid polymerization; experiments using the latter compounds with 1,3-diethynylbenzene, even with slow addition of the dialkyne to a solution of excess dihalide, gave polymeric products. The resulting trimer **13** was treated with excess mono-silylated 1,3-diethynylbenzene[24,33] to give pentameric material **14** that was deprotected with potassium carbonate in methanol to give **15**.

In addition to the pentamer **15**, we sought a heptamer in the hope of polymer-supported cyclization to form a cyclic octamer since previously used methods were ineffective.[22,23]

Treatment of ethyl 3,5-diiodobenzoate with excess mono-silylated 1,3-diethynylbenzene in the presence of palladium and copper gave **16** (Scheme 3). Desilylation[34] gave **17**, which was coupled with excess **12** to give pentamer **18**. Treatment with excess mono-silylated 1,3-diethynylbenzene in the presence of palladium and copper gave the desired heptamer **19**. Reaction with methanolic potassium



(2)



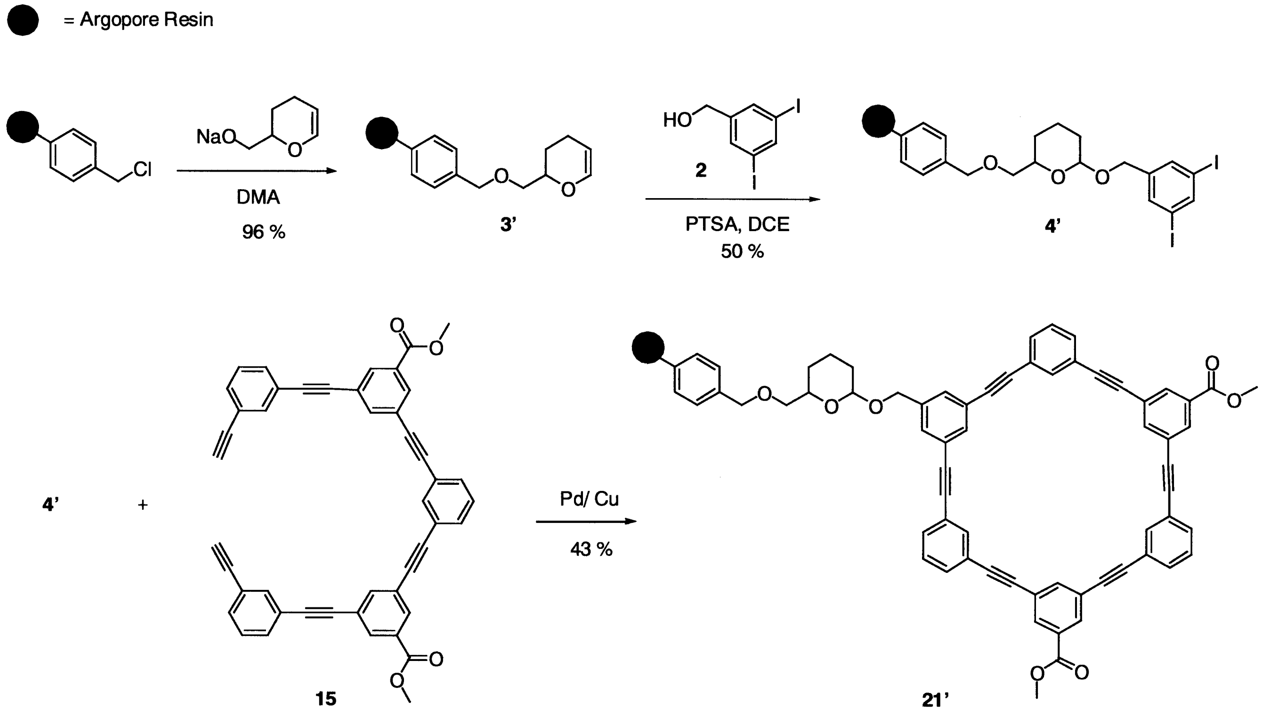
(3)

carbonate gave the desired desilylated material as the trimethyl triester **20**.

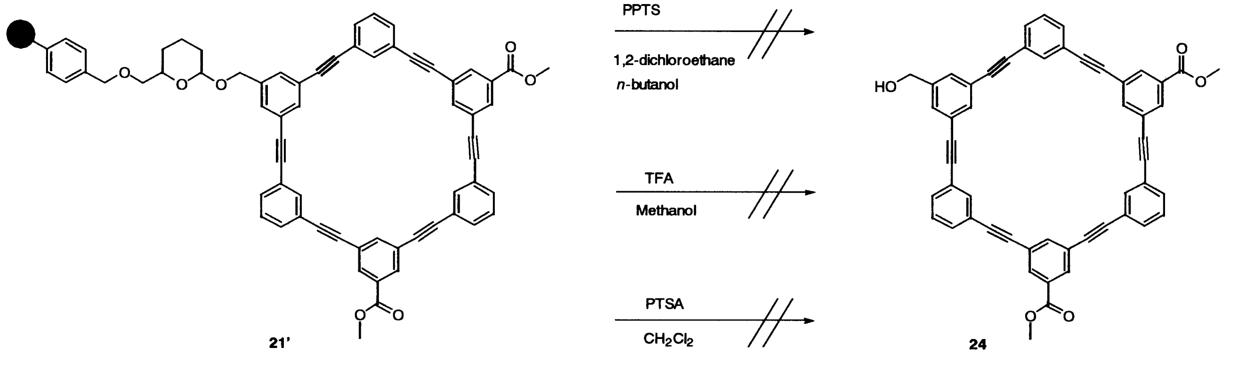
Attempts to react oligomer **15** with resin-immobilized diiodide **4** did not result in the desired cyclic hexamer, **21** (Eq. (2)). As in our previous strategy, it seems that in the resin-supported compounds molecules are not truly site-isolated, resulting in reaction between separate resin-bound functionalities.[31,32] We instead obtained **22** as confirmed by treatment with acid to afford **23** (Eq. (3)). Likewise cyclic octamer derived from **4** and **20** did not form.

5. Use of the Argopore resin

Due to the side-reaction between resin-functionalities, truly site-isolated reactions to form cyclic oligomers are disfavored with this solid-support. Therefore, we turned our attention to a more highly cross-linked system, namely the Argopore resin. This highly cross-linked chloromethylated polystyrene has been previously used to maximize site isolation, although the precise crosslinking level is not disclosed by the manufacturer.[31,32] Our preliminary experiments have shown that the material swells very little in



Scheme 4. Preparation of the cyclic hexamer on the Argopore resin.



Scheme 5. Attempted cleavage reactions to liberate cyclic hexamer.

solvents such as THF (which greatly swell Merrifield's resin) thereby attesting to the high crosslink density. It was hoped that this rigid resin would minimize the probability of inter-site reactions of the resin-supported oligomers.

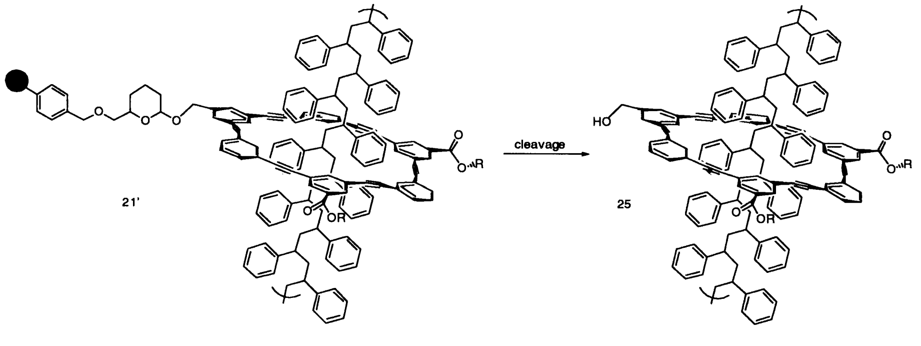
As shown in Scheme 4, resin-immobilized diiodobenzyl alcohol (**4′**) was prepared on the Argopore resin. Reaction of the pentamer **15** with the functionalized Argopore resin **4′** gave a bright yellow resin with the expected mass increase and an infrared absorbance at 1733 cm^{-1}, indicating that ester functionality had indeed been incorporated in the polymer support. Oddly, standard cleavage conditions did not provide the desired cyclic oligomer, **24** (Scheme 5), which is a precursor to **1**. In fact, no oligomeric material could be cleaved from the resin. The only spectroscopically observable product was a small amount of **2**. Since cyclics similar to **24** are generally soluble,[22,23,27] we did not believe we had a simple solubility problem in product isolation. More rigorous cleavage conditions[28] were attempted, as shown in Scheme 5. Using trifluoroacetic acid–methanol (95:5), followed by overnight continuous extraction with THF gave no product. Additionally, treatment with *p*-toluenesulfonic acid in CH_2Cl_2 also failed to remove product from the polymer support.

First assuming that the material was physically entrapped in the pores of the polymer matrix, we attempted to mechanically liberate the macrocycle. By cooling the solid resin with liquid N_2 and pulverizing with an agate mortar and pestle, we reduced the resin to a fine paste. This paste was then treated again with the above extraction conditions, resulting in no observed oligomer. The pulverized resin was further subjected to sonication for 24 h in dimethylformamide; some physical decomposition of the polymer was observed, but no product was isolated.

We then theorized that the material, once cyclized, was physically entangled with the highly cross-linked polymer in a threaded (catenane) structure (Scheme 6).

6. Some evidence for a resin-threaded catenane

Thus we performed matrix-assisted laser-desorption ionization mass spectrometry (MALDI-MS) on the suspected resin/catenane (**25**) with the hope of cleaving either the resin or the macrocycle, and detecting the macrocycle's fragments.[35] We assumed that the material had been transesterified to the di(butyl) ester during the attempted cleavage reaction conditions (*n*-butanol and acid). Thus, the product alcohol di(butyl) ester has a predicted mass spectrometric distribution for $C_{59}H_{42}O_5$ of 830.3 (100% intensity), 831.2 (65% intensity), and 832.3 (20% intensity) amu. Ions from the MALDI-MS of **25** (R=*n*-butyl) were centered at 815, 774, 756, 712, 694, and 692 amu that must correspond to our oligomeric material; control experiments with the matrix alone, as well as the resin **4′** prior to reaction with pentamer **15**, did not show these fragments. Note that peak differences of a few mass units are difficult to distinguish in this MALDI-MS since intense energy was required to decompose the host resin. Moreover, the insoluble beads' macroscopic contour contributed to the need for averaging over 200 scans.[35] The observed peak at 815 corresponds to loss of methyl from the parent ion. The peak at 774 (−56 amu) corresponds to the ion formed by a



Scheme 6. Effect of the cleavage reaction on the Argopore resin-bound cyclic hexamer.

McLafferty rearrangement (loss of C_4H_8). The peak centered at 756 corresponds to the ion formed by loss of a butoxy group ($-OC_4H_9$). As each of these ions are higher in molecular weight than that of the starting pentamer **15** (or even its di(butyl) ester derivative), we concluded that **15** had reacted with functionality on resin **4′** to produce a compound that could fragment under the MALDI conditions to give the observed species. The spectrometric information, coupled with the clear 1733 cm^{-1} IR signature for the ester and our inability to remove the product from the resin using vigorous conditions suggested that the catenane **25** had formed. Further work is needed to confirm this interesting result.

7. Conclusions

In summary, we initiated a study to mimic high dilution conditions for macrocycle formation by conducting the cyclization step on a polymer support. However, the lightly crosslinked Merrifield's resin was inadequate to provide the desired site isolation. Use of the Argopore resin, a more highly crosslinked polystyrene, inhibited inter-site interactions; some evidence that the cyclized products were threaded by the resin to form resin/macrocycle catenanes was obtained. Although a resin that could be decomposed after reaction could likely be used to achieve the desired macrocyclization with site isolation and subsequent liberation, the resin/macrocycle structures provide a unique avenue to catenanes,[5] should our preliminary conclusion be confirmed with further work. It is possible that a functionalized, decomposable resin could be used to provide a general synthesis to such threaded catenanes.

8. Experimental

8.1. General procedure

All operations, unless otherwise noted, were carried out under a dry, oxygen-free, atmosphere. Infrared spectra of resin-immobilized compounds were obtained by swelling the polymer with CCl_4 and pressing the sample between two NaCl plates. THF and Et_2O were distilled under N_2 over sodium benzophenone ketyl. Reagent grade CH_2Cl_2 was distilled under N_2 from CaH_2. Bulk grade hexanes were distilled prior to use. Column chromatography was carried out on silica gel (230–400 mesh from EM Science). Merrifield resin (1% crosslinked, 200–400 mesh, 1.00 mequiv./g Cl, Aldrich #22,148-1) and Argopore resin (highly crosslinked, 200–400 mesh, 0.96 mequiv./g Cl, Aldrich #45,250-1) were purchased from Aldrich Chemical Co. and used without additional purification. When referring to the approximate number of mmol on a resin, it refers to the active synthetic component. Flash chromatography refers to column chromatography with a N_2 head pressure as described by Still.[36]

8.2. General resin washing procedure

The solvent-suspended resin was isolated by filtration through a dry pre-weighed sintered glass funnel. The mother liquor was set aside, and the filtrant was then washed successively in the funnel with THF (3×250 mL), DMF (3×250 mL), 1:1 DMF–water (3×250 mL), acetone (3×250 mL), CH_2Cl_2 (3×250 mL), and Et_2O (3×250 mL). The resin was allowed to pre-dry in the funnel, followed by rigorous drying in a vacuum oven for 8 h (60°C at <2.5 mmHg pressure).

8.3. General procedure for cleavage of immobilized compounds from polymer resin[28]

Approximately 0.50 g of the loaded polymer was added to a flask containing $C_6H_5N-TsOH$ (0.15 g, 0.60 mmol), 1-butanol (50 mL), and CH_2ClCH_2Cl (50 mL). The reaction was stirred overnight at 60°C. The reaction mixture was then poured through a fritted funnel and the filter cake was washed extensively with CH_2Cl_2. The filtrate was washed with water (3×) and the organics concentrated in vacuo to give the cleaved compound. The loading was determined from isolated product; yield was calculated from the loading compared to the theoretical loading based on Merrifield's resin (1.00 mequiv./g).

8.3.1. 3,5-Diiodobenzyl alcohol (2). To a dry flask at 0°C containing 3,5-diiodobenzoic acid (0.10 g, 0.27 mmol) was slowly added BH_3-THF (3.0 mL, 3.0 mmol) via syringe. This was stirred for 1 h, then allowed to warm to room temperature. The reaction was quenched with 15:1 THF–water. The crude mixture was extracted with ether (3×20 mL), dried over $MgSO_4$, and concentrated in vacuo. This was dissolved in CH_2Cl_2 and filtered through a silica gel plug and reconcentrated to yield 0.10 g (100%) of a white solid. FTIR (KBr) 3422, 3213, 1638, 1386 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.66 (s, 2H), 4.60 (s, 2H), 1.57 (s, 1H plus additional water). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 144.0, 134.8, 94.8, 63.5. HRMS Calcd for $C_7H_6I_2O$: 359.8508. Found: 359.8504.

8.3.2. Dihydropyran functionalized resin (3).[28] To a dry N_2-purged flask containing 2-(hydroxymethyl)-3,4-dihydro-2*H*-pyran (6.85 g, 60.0 mmol) and THF (100 mL) was slowly added NaH (1.67 g, 66.0 mmol). Vigorous bubbling accompanied the addition, and the reaction was stirred for 2 h at room temperature. The resulting solution was concentrated and dissolved in dimethylacetamide (300 mL). Merrifield's resin was then added to the solution, and the reaction was stirred for 12 h. The product was isolated and purified by the general resin washing procedure according to Section 8.2. A total of 22.1 g (100% of expected mass change) of white powder was obtained. FTIR (CCl_4) 3411.5, 3029.7, 2921.0, 1947.2, 1600.4, 1445.6, 1380.6, 1380.6, 1238.9 cm^{-1}.

8.3.3. Diiodoarene-functionalized resin (4). A method analogous to that of Thompson was used.[28] To a dry N_2-purged flask containing resin **3** (11.5 g, 10 mmol DHP), CH_2ClCH_2Cl (200 mL), and $TsOH-H_2O$ (1.00 g, 5.26 mmol) was added 3,5-diiodobenzyl alcohol (7.75 g, 21.5 mmol). The reaction was heated to 60°C for 12 h. Afterwards, the product was isolated according to the general resin washing procedure according to Section 8.2. A total of 13.9 g (67% of expected mass change) of product was obtained as a pale yellow powder. FTIR (CCl_4) 3398.5, 3032.7, 2922.4, 2320.6, 1949.4, 1871.6, 1597.3, 1443.8, 1368.5 cm^{-1}.

8.4. General coupling procedures 1 and 2

The resin was loaded into a flame-dried, N_2-purged screw-cap tube containing ~0.008 mol equiv. $[(C_6H_5)_3P]_2PdCl_2$, ~0.06 mol equiv. CuI, ~3.25 mol equiv. *i*Pr_2NEt and 100 mL THF. ~3 mol equiv. of trimethylsilylacetylene (procedure 1) or diiodoarene (procedure 2) was added, the tube was sealed and the mixture was stirred at room temperature for 12 h. The product was isolated by the general resin washing procedure according to Section 8.2.

8.4.1. 1,3-Bis(trimethylsilylethynyl)arene-functionalized resin (5). Using coupling procedure 1, **4** (12.63 g, 8.79 mmol) gave 12.11 g (100% of expected mass change) of product that as a yellow powder. FTIR (CCl_4) 3025.8, 2909.3, 2156.3, 1598.1, 1488.0, 1446.8, 1360.3, 1250.7, 1032.1, 851.3, 795.4, 740.6, 682.6 cm^{-1}.

8.4.2. 1,3-Bis(ethynyl)arene-functionalized resin (6). To a dry flask containing resin **5** (11.4 g, 8.79 mmol) and THF (250 mL) was added $(C_4H_9)_4NF$ (25.0 mL, 25.0 mmol, 1.0 M in THF). The resultant black solution was stirred at room temperature for 1 h. Afterwards, the product was isolated according to the general resin washing procedure according to Section 8.2. A total of 10.30 g (90% of expected mass change) of product was obtained as an orange powder. FTIR (CCl_4) 3291.9, 3026.8, 2912.4, 1551.9, 1360.3, 1244.9, 994.6, 784.0 cm^{-1}.

8.4.3. Resin 7. Using coupling procedure 2, **6** (9.72 g, 7.90 mmol) and 1,3-diiodobenzene gave 10.79 g (34% of expected mass change) of product as a yellow powder. FTIR (CCl_4) 3021.3, 2926.0, 1596.3, 1448.2, 1112.2, 789.8 cm^{-1}.

8.4.4. Resin 8. Using coupling procedure 1, **7** (9.45 g, 5.77 mmol), gave 9.41 g (100% of expected mass change) of product as a yellow powder. FTIR (CCl_4) 3054.6, 2912.8, 2155.5, 1596.8, 1449.6, 785.6 cm^{-1}.

8.4.5. Resin 9. To a dry flask containing resin **8** (8.4 g, 5.2 mmol) and THF (150 mL) was added $(C_4H_9)_4NF$ (20.0 mL, 20.0 mmol, 1.0 M in THF). The resultant black solution was stirred at room temperature for 1 h. Afterwards, the product was isolated according to the general resin washing procedure according to Section 8.2. A total of 8.07 g (105% of expected mass change) of product was obtained as an orange powder. FTIR (CCl_4) 3291.7, 3030.6, 2921.7, 1594.4, 1451.3, 787.8 cm^{-1}.

8.4.6. Resin 10. Using coupling procedure 2, **9** (7.4 g, 5 mmol), and 1,3-diiodobenzyl alcohol gave 7.85 g (20% of expected mass change) of product was obtained as a yellow powder. FTIR (CCl_4) 3420 (br), 3034.6, 2916.3, 1599.6, 1447.5, 1370.0, 1034.6, 790.1 cm^{-1}.

8.4.7. Trimer 13. An oven-dried, N_2-purged screw-cap tube containing 1,3-diethynylbenzene (213 mg, 1.69 mmol), **12** (1.15 g, 3.37 mmol), $[(C_6H_5)_3P]_2PdCl_2$ (20 mg, 0.029 mmol), CuI (20 mg, 0.11 mmol), THF (5.0 mL) and *i*Pr_2NEt (1.0 mL, 5.7 mmol) was sealed, and the reaction was stirred at room temperature for 12 h. The reaction mixture was poured into water, extracted with CH_2Cl_2, washed with water, and concentrated in vacuo to give a crude solid. The product was further purified by flash column chromatography (silica, 2:1 hexane–CH_2Cl_2) to yield 0.8822 g (95%) of the desired trimer as a white solid. FTIR (film) 3075.3, 2999.4, 2952.2, 2847.8, 1727.9, 1597.4, 1583.0, 1478.8, 1439.0, 1267.0, 1195.3, 1165.1, 1130.7, 997.7, 952.7, 907.8, 829.9, 792.9, 765.4, 731.6, 676.9 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (t, J=1.5 Hz, 2H), 8.04 (t, J=1.5 Hz, 2H), 7.75 (t, J=1.6 Hz, 2H), 7.63 (s, 1H), 7.45 (dd, J=7.7, 1.3 Hz, 2H), 7.30 (t, J=7.7 Hz, 1H), 3.90 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0, 139.2, 135.9, 133.5, 133.1, 133.0, 132.4, 129.8, 126.3, 124.0, 123.4, 91.8, 88.9, 53.9. HRMS Calcd for $C_{26}H_{16}Br_2O_4$: 549.9415. Found: 549.9424.

8.4.8. Bis-silylated pentamer 14. To a flame-dried, N_2-purged screw-cap tube containing trimer **13** (0.78 g, 1.42 mmol), $[(C_6H_5)_3P]_2PdCl_2$ (20 mg, 0.029 mmol), CuI (20 mg, 0.11 mmol), and a 3:1 mixture of mono- and disilyl-1,3-diethynylbenzene (0.91 g, 3.0 mmol monosilyl) was added *i*Pr_2NEt (1.0 mL, 5.7 mmol) and THF (10 mL) via syringe. The tube was evacuated and back-filled with dry N_2 (3×) then sealed, and the reaction was stirred at 80°C for 2 d. The reaction mixture was poured into water, extracted with CH_2Cl_2, washed with water, and concentrated in vacuo to give a crude solid. The product was further purified by flash column chromatography (silica, 2:1 hexane–CH_2Cl_2) to yield 0.78 g (70%) of the desired pentamer as a pale yellow solid. FTIR (film) 3066.9, 2956.8, 2158.6, 1727.6, 1595.6, 1478.1, 1441.3, 1355.1, 1263.2, 1112.5, 1001.5, 887.9, 847.6, 794.2, 763.9, 732.0, 682.3, 646.5 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (d, J=1.7 Hz, 2H), 8.10 (d, J=1.5 Hz, 2H), 7.79 (s, 2H), 7.70 (s, 1H), 7.65 (s, 2H), 7.50–7.42 (m, 6H), 7.33 (t, J=7.7 Hz, 1H), 7.28 (t, J=7.8 Hz, 2H), 3.93 (s, 6H), 0.27 (s, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 139.3, 136.2, 135.9, 133.4, 133.1, 132.9, 132.7, 131.9, 129.8, 129.6, 125.1, 125.0, 124.8, 124.3, 124.0, 105.2, 96.4, 91.3, 91.2, 89.5, 89.3, 53.7, 1.3. HRMS Calcd for $C_{52}H_{42}O_4Si_2$: 786.2622. Found: 786.2651.

8.4.9. Pentamer 15. To a dry flask containing pentamer **14** (124 mg, 0.158 mmol), MeOH (50 mL), and CH_2Cl_2 (50 mL) was added K_2CO_3 (100 mg, 0.724 mmol) at room temperature. The suspension was stirred at room temperature for 3 h, at which time the starting material had been completely consumed by TLC analysis. The crude mixture was filtered through a silica gel plug and concentrated in vacuo. The concentrate was dissolved in CH_2Cl_2, washed with water, and reconcentrated to give the desired pentamer as 80 mg (79%) of a pale yellow solid. FTIR (film) 3292.1, 2924.9, 2854.5, 1726.6, 1596.2, 1476.8, 1441.2, 1355.0, 1264.3, 1199.8, 1111.4, 1001.5, 895.1, 793.8, 766.3 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (t, J=1.7 Hz, 2H), 8.13 (t, J=1.7 Hz, 2H), 7.83 (t, J=1.5 Hz, 2H), 7.72 (t, J=1.1 Hz, 1H), 7.66 (t, J=1.3 Hz, 2H), 7.52–7.45 (m, 6H), 7.36 (t, J=7.7 Hz, 1H), 7.31 (t, J=7.7 Hz, 2H) 3.95 (s, 6H), 3.12 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 139.3, 136.3, 135.9, 133.5, 133.3, 133.0, 132.9, 132.0, 129.8, 129.7, 125.0, 124.3, 124.1, 123.8, 91.2, 91.1, 89.5, 89.4, 83.9, 79.3, 53.8. HRMS Calcd for $C_{46}H_{26}O_4$: 642.1831. Found: 642.1843.

8.4.10. Bis-silylated trimer 16. To an oven-dried, N_2-purged screw-cap tube containing ethyl 3,5-diiodobenzoate (0.80 g, 2.0 mmol), $[(C_6H_5)_3P]_2PdCl_2$ (70 mg, 0.10 mmol), CuI (70 mg, 0.37 mmol), THF (20 mL), and a 3:1 mixture of mono- and disilyl-1,3-diethynylbenzene (1.21 g, 4.03 mmol monosilyl) was added *i*Pr_2NEt (1.0 mL, 5.7 mmol) via syringe. The tube was sealed, and the reaction was stirred at room temperature for 12 h. The crude mixture was then dissolved in Et_2O, washed with water, dried over anhydrous $MgSO_4$, passed through a short silica gel plug, and concentrated in vacuo. The crude product was further purified by flash column chromatography (silica, 3:1 hexane–CH_2Cl_2) to yield 0.80 g (74%) of the desired trimer as a yellow solid. FTIR (film) 3066.7, 2961.8, 2158.4, 1948.1, 1724.5, 1593.8, 1475.5, 1442.9, 1406.7, 1368.5, 1258.5, 1217.8, 1140.6, 1111.4, 1025.4, 990.9, 960.0, 848.5, 794.4, 763.0, 730.9, 685.3, 646.5 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, J=1.6 Hz, 2H), 7.80 (t, J=1.5 Hz, 1H), 7.67 (td, J=1.4, 0.6 Hz, 2H), 7.47 (dt, J=7.7, 1.3 Hz, 2H), 7.44 (dt, J=8.0, 1.4 Hz, 2H), 7.29 (td, J=7.7, 0.6 Hz, 2H), 4.40 (q, 7.1 Hz, 2H), 1.42 (t, J=7.1 Hz, 3H), 0.27 (s, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.2, 139.2, 136.3, 133.4, 133.1, 132.7, 132.4, 129.6, 125.0, 124.8, 124.0, 105.2, 96.4, 91.2, 89.4, 62.8, 15.7, 1.3. HRMS Calcd for $C_{35}H_{34}O_2Si_2$: 542.2097. Found: 542.2039.

8.4.11. Trimer 17. To a dry flask containing trimer **16** (0.80 g, 1.5 mmol) and THF (15 mL) was slowly added $(C_4H_9)_4NF$ (6.0 mL, 6.0 mmol, 1.0 M in THF) via syringe at room temperature. The reaction was stirred at room temperature for 30 min, and the crude mixture was filtered through a silica gel plug and concentrated in vacuo. The concentrate was dissolved in CH_2Cl_2, washed with water, and re-concentrated before further purification by flash column chromatography (silica, 2:1 hexane–CH_2Cl_2) to give 0.40 g (68%) of the desired trimer as a golden oil. FTIR (film) 3293.5, 3068.5, 2982.3, 1723.1, 1595.8, 1476.4, 1442.4, 1369.9, 1258.1, 1204.5, 1111.2, 1025.0, 896.0, 795.1, 768.5, 733.0, 879.3 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, J=1.0 Hz, 2H), 7.78 (s, 1H), 7.66 (s, 2H), 7.48 (td, J=7.7 Hz, 2H), 7.45 (d, J=7.8 Hz, 2H), 7.28 (t, J=7.7 Hz, 2H), 4.38 (q, J=7.1 Hz, 2H), 3.13 (s, 2H), 1.41 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 138.1, 135.1, 132.3, 132.2, 131.9, 131.1, 128.5, 123.7, 123.0, 122.6, 89.9, 88.3, 82.7, 78.2, 61.6, 14.5. HRMS Calcd for $C_{29}H_{18}O_2$: 398.1307. Found: 398.1316.

8.4.12. Pentamer 18. To an oven-dried, N_2-purged screw-cap tube containing trimer **17** (0.38 g, 0.95 mmol), **12** (0.65 g, 1.91 mmol), $[(C_6H_5)_3P]_2PdCl_2$ (14 mg, 0.020 mmol), and CuI (14 mg, 0.074 mmol) was added THF (10 mL) and *i*Pr_2NEt (1.0 mL, 5.7 mmol) via syringe. Upon addition of the amine, the clear pale yellow solution darkened to orange-brown within 10 min. The tube was sealed, and the reaction was stirred at room temperature for 12 h. The reaction mixture was poured into water, extracted with CH_2Cl_2, and concentrated in vacuo to give a crude brown solid. The product was further purified by flash column chromatography (silica, 2:1 hexane–CH_2Cl_2) to yield 0.72 g (92%) of the desired pentamer as a slightly pink solid. FTIR (film) 3073.1, 2952.2, 2215.2, 1726.0, 1596.8, 1563.9, 1478.0, 1439.2, 1369.4, 1317.6, 1266.7, 1111.1, 1000.4, 905.2, 794.7, 765.0, 731.0, 676.9 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, J=1.5 Hz, 2H), 8.13 (t, J=1.7 Hz, 2H), 8.11 (t, J=1.5 Hz, 2H), 7.85 (t, 1.4 Hz, 1H), 7.83 (t, J=1.6 Hz, 2H), 7.72 (s, 2H), 7.52 (app td, J=7.8, 1.3 Hz, 4H), 7.37 (t, J=7.7 Hz, 2H), 4.41 (q, J=7.1 Hz, 2H), 3.94 (s, 6H), 1.43 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.05, 164.97, 138.1, 134.8, 132.3, 132.0, 131.9, 131.8, 131.3, 131.2, 128.7, 125.2, 123.8, 123.1, 122.8, 122.3, 90.6, 89.8, 88.4, 87.6, 61.6, 52.7, 14.5. HRMS Calcd for $C_{45}H_{28}Br_2O_6$: 822.0253. Found: 822.0235.

8.4.13. Bis-silylated heptamer 19. A flame-dried, N_2-purged screw-cap tube containing pentamer **18** (0.59 g, 0.71 mmol), $[(C_6H_5)_3P]_2PdCl_2$ (100 mg, 0.143 mmol), CuI (100 mg, 0.53 mmol), THF (20.0 mL), and a 3:1 mixture of mono- and disilyated 1,3-diethynylbenzene (1.00 g, 3.33 mmol monosilylated) was evacuated and back-filled with dry N_2 (3×). To this solution was added *i*Pr_2NEt (1.0 mL, 5.7 mmol) via syringe. The tube was sealed, and the reaction was heated at 80°C for 3 d. The reaction mixture was poured into water, extracted with CH_2Cl_2, washed with water, filtered through a silica gel plug, and concentrated in vacuo to give a black tar. The product was further purified by flash column chromatography (silica, 1:1 hexane–CH_2Cl_2) to yield 0.45 g (60%) of the desired heptamer as a brown semi-solid. FTIR (film) 3065.5, 2955.8, 2158.5, 1729.5, 1597.9, 1478.0, 1441.5, 1357.8, 1265.3, 1240.5, 1206.7, 1169.3, 1137.2, 1111.1, 1026.1, 1004.0, 894.9, 844.8, 793.4, 767.4, 733.0, 682.8, 647.3 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.15 (t, J=1.2 Hz, 2H), 8.14 (t, J=1.5 Hz, 2H), 8.12 (t, J=1.5 Hz, 2H), 7.85 (t, J=1.3 Hz, 1H), 7.83 (t, J=1.7 Hz, 1H), 7.73 (s, 2H), 7.66 (s, 2H), 7.53 (t, J=1.5 Hz, 2H), 7.51 (t, J=1.8 Hz, 2H), 7.48–7.43 (m, 4H), 7.36 (t, J=7.9 Hz, 2H), 7.29 (t, J=7.7 Hz, 2H), 4.41 (q, J=7.2 Hz, 2H), 3.95 (s, 6H), 1.44 (t, J=7.2 Hz, 3H), 0.27 (s, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4, 164.9, 138.1, 138.0, 135.0, 134.6, 132.21, 132.18, 131.9, 131.7, 131.4, 131.1, 130.7, 128.5, 128.3, 123.8, 123.73, 123.69, 123.5, 123.0, 122.7, 103.8, 95.1, 90.0, 89.9, 89.8, 88.3, 88.2, 88.0, 61.5, 52.6, 52.5, 14.4, 0.0. HRMS Calcd for $C_{71}H_{54}O_6Si_2$: 1058.3459. Found: 1058.3480.

8.4.14. Heptamer 20. To a dry flask containing heptamer **19** (0.26 g, 0.25 mmol), MeOH (25 mL), and CH_2Cl_2 (25 mL) was added K_2CO_3 (0.25 g, 1.8 mmol) at room temperature. The suspension was stirred at room temperature for 90 min, at which time the starting material had been completely consumed by TLC analysis. The crude mixture was filtered through a silica gel plug and concentrated in vacuo. The concentrate was dissolved in CH_2Cl_2, washed with water, and re-concentrated to give 0.22 g (99%) of the desired heptamer as a yellow solid. FTIR (film) 3293.4, 2951.1, 1725.3, 1595.8, 1476.9, 1440.2, 1355.6, 1264.1, 1112.5, 1002.2, 902.2, 793.4, 731.5 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.13 (m, 4H), 8.12 (t, J=1.1 Hz, 2H), 7.84 (t, J=1.6 Hz, 1H), 7.82 (t, J=1.5 Hz, 2H), 7.72 (t, J=1.6 Hz, 2H), 7.66 (t, J=1.5 Hz, 2H), 7.52–7.45 (m, 8H), 7.35 (t, J=8.1 Hz, 2H), 7.30 (t, J=7.8 Hz, 2H), 3.95 (s, 3H), 3.94 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 138.1, 135.1, 134.7, 132.3, 132.2, 131.8, 131.7, 130.8, 128.6, 128.5, 123.8, 123.1, 122.9, 122.6, 90.0, 89.9, 88.3, 88.2, 82.7, 78.1, 52.6.

8.4.15. Resin-immobilized heptamer 22. A flame-dried N_2-purged screw-cap tube containing resin **4** (0.500 g, 0.225 mmol arene, 0.45 mequiv./g resin), bis(dibenzylideneacetone)palladium(0) (5.8 mg, 0.010 mmol), CuI (10.0 mg, 0.0525 mmol), $(C_6H_5)_3P$ (5.3 mg, 0.020 mmol), and pentamer **15** (70.0 mg, 0.109 mmol) was evacuated and back-filled with dry N_2 (3×). To this solution was added *i*Pr_2NEt (1.0 mL, 5.7 mmol) and THF (5.0 mL). Upon addition of the amine, the clear red solution became a brownish-tan suspension over ca. 1 min. The tube was sealed, and the reaction was stirred at 80°C for 36 h. Afterwards, the product was isolated according to the general resin washing procedure according to Section 8.2. A total of 546.2 mg (550.8 mg theory=91% of expected mass change) of product was obtained as a bright yellow powder. FTIR (CCl_4) 3026.0, 2918.8, 1944.6, 1874.0, 1804.9, 1729.4, 1593.6, 1549.5, 1489.4, 1447.2, 1359.8, 1252.7, 1109.3, 789.8 cm^{-1}.

8.4.16. Heptamer 23. Resin-immobilized heptamer **22** (546 mg) was suspended in a solution of C_6H_5N–TsOH (50 mg, 0.20 mmol) in CH_2ClCH_2Cl (25 mL) and *n*-butanol (25 mL). The suspension was heated at 70°C for 24 h. The polymer was removed by filtration and the crude filtrant was concentrated in vacuo to give a crude solid. The crude mass was further purified by flash column chromatography (silica, 9:1 CH_2Cl_2/acetone) to obtain a small amount of residual 3,5-diiodobenzyl alcohol and 92 mg (0.083 mmol, 0.15 mequiv./g resin, 0.22 mequiv./g resin theory, 69% of expected mass) of the expected heptamer as a yellow film. FTIR (film) 3401.1, 2925.2, 2854.5, 1726.8, 1597.3, 1556.1, 1478.3, 1440.6, 1354.3, 1253.8, 1198.5, 1110.5, 1003.3, 907.4, 792.8, 768.1, 732.1, 681.5 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.16 (m, 4H), 7.86 (t, $J=1.7$ Hz, 2H), 7.80 (t, $J=1.5$ Hz, 2H), 7.74 (t, $J=1.6$ Hz, 1H), 7.70 (m, 4H), 7.54–7.48 (m, 8H), 7.38 (t, $J=8.4$ Hz, 1H), 7.36 (t, $J=7.8$ Hz, 2H), 4.67 (s, 4H), 3.96 (s, 6H), 1.25 (br s, 2H+H_2O). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 143.0, 139.2, 138.3, 135.8, 134.8, 134.8, 132.4, 131.8, 131.8, 131.7, 130.9, 129.1, 128.7, 125.0, 123.9, 123.2, 123.10, 123.05, 93.9, 89.95, 89.92, 89.7, 88.3, 88.2, 63.9, 52.5. HRMS Calcd for $C_{60}H_{36}I_2O_6$: 1106.0601. Found: 1106.0640.

8.4.17. Dihydropyran functionalized Argopore resin (3′).[28] To a dry N_2-purged flask containing 2-(hydroxymethyl)-3,4-dihydro-2*H*-pyran (1.71 g, 15.0 mmol) and THF (25 mL) was slowly added NaH (0.45 g, 18.80 mmol). Vigorous bubbling accompanied the addition, and the reaction was stirred for 2 h at room temperature. The resulting solution was concentrated and then dissolved in dimethylacetamide (75 mL). Argopore resin (highly cross-linked, 200–400 mesh, 0.96 mequiv./g Cl) was then added to the solution, and the reaction was stirred for 12 h. The product was isolated and purified by the general resin washing procedure according to Section 8.2. A total of 5.20 g (96% of expected mass change) of white powder was obtained. The resin showed an identical infrared spectrum to that of compound **3**.

8.4.18. Diiodoarene-functionalized Argopore resin (4′). A method analogous to that of Thompson was used.[28] To a dry N_2-purged flask containing resin **3′** (3.00 g, ~2.76 mmol DHP), CH_2ClCH_2Cl (100 mL), and C_6H_5N–TsOH (0.50 g) was added 3,5-diiodobenzyl alcohol (3.00 g, 8.33 mmol). The reaction was heated to 60°C for 12 h. Afterwards, the product was isolated according to the general resin washing procedure according to Section 8.2. A total of 3.50 g (50% of expected mass change) of product was obtained as a pale yellow powder. The resin showed an identical infrared spectrum to that of compound **4**.

8.4.19. Argopore-resin-immobilized hexamer 21′. A flame-dried N_2-purged screw-cap tube containing resin **4′** (1.19 g, 0.454 mmol arene, 0.38 mequiv./g resin), bis(dibenzylideneacetone)palladium(0) (25 mg, 0.043 mmol), CuI (25 mg, 0.13 mmol), $(C_6H_5)_3P$ (25 mg, 0.10 mmol), and pentamer **15** (145 mg, 0.226 mmol) was evacuated and back-filled with dry N_2 (3×). To this solution was added *i*Pr_2NEt (1.0 mL, 5.7 mmol) and THF (20.0 mL). Upon addition of the amine, the suspension darkened to brown over ca. 1 min. The tube was sealed, and the reaction was stirred at 80°C for 2 d. Afterwards, the product was isolated according to the general resin washing procedure according to Section 8.2. A total of 1.24 g (1.30 g theory, 43% of expected mass change) of product was obtained as a yellow powder. FTIR (KBr) 3025.6, 2927.5, 1733.8, 1600.8, 1491.2, 1449.3, 1384.7, 1262.9, 1117.1, 1036.4, 898.5, 834.4, 795.9, 763.9, 704.9 cm^{-1}. MALDI-MS (The sample was suspended in 100% MeCN and then placed atop a dried layer of matrix made from α-cyano-4-hydroxycinnamic acid in 70% MeCN and 0.1% trifluoroacetic acid. The sample was run in positive ion mode and the data was calibrated by external calibration with peptide standards Angiotensin I and Bovine Insulin.) 815.89 (6.4%), 774.16 (3.2%), 756.03 (16.0%), 712.02 (11.2%), 694.04 (100%), 692.07 (94.4%).

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35. Note that fragmentation of an even-numbered molecular ion yields an odd-numbered fragment. Conversely, rearrangement is recognized as having taken place by an even-numbered molecular ion yielding an even-numbered fragment (due to rearrangement of a hydrogen atom accompanying fragmentation). For examples, see (a) *Spectrometric Identification of Organic Compounds*; Silverstein, R. M., Bassler, G. C., Morrill, T. C., Eds.; 5th ed, Wiley: New York, 1991. (b) Creel, H. S. *Trends Polym. Sci.* **1993**, *1*, 336.
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