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An efficient synthesis of 4,4′,5,5′-tetraiododibenzo-24-crown-8 and its highly conjugated derivatives

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Abstract—4,4′,5,5′-Tetraiododibenzo-24-crown-8 (**9**), a practical building block, was prepared under efficient and mild reaction conditions starting from the simple starting material, catechol (**1**). Highly conjugated 4,4′,5,5′-tetraethynyldibenzo-24-crown-8 (**10a**,**b**) were prepared via a Sonogashira coupling reaction from tetraiodocrown ether **9**. These highly conjugated crown ethers form complexes in CD_2Cl_2 with dibenzylammonium hexafluorophosphate in a 1:1 ratio. Emission spectrum of pseudorotaxane **11** shows a dramatic shift from the non-complexed precursor.

1. Introduction

There is a continuing interest in the preparation of functionalized dibenzo-24-crown-8 ether (DB24C8) derivatives.[1] Since Pedersen's discovery[2] of crown ethers over three decades ago, interactions between crown ethers and guest entities, such as alkylammonium (RNH_3^+) ions, have generated much interest.[3] Specifically, DB24C8 derivatives bind with various cationic species such as alkyl ammonium ions. These self-assembly systems possess interesting properties. For example, DB24C8s have been used in the preparation of molecular receptors,[4] polymers,[5] (pseudo)rotaxanes,[6] catenanes,[7] switches,[8] and surface-bound materials.[9]

Recent synthetic advances in transition metal catalyzed C–C coupling reactions, such as the Sonogashira, Suzuki, and Stille coupling reactions, have provided efficient routes for the preparation of highly conjugated phenylacetylene containing compounds.[10] In particular, *ortho*-bisethynylbenzene moieties have been studied as integral parts of light-harvesting systems,[11] subunits of dehydrobenzoannulenes,[12] highly conjugated polymers,[13] and organic high-spin magnetism.[14] Despite recent advances, such coupling reactions between electron-rich arylhalides and alkynes remain challenging. For example, Sonogashira coupling reactions between 4,5-dibromoveratrole and terminal alkynes often require high temperatures and extended reaction periods. In this letter, we are focusing on the preparation of highly conjugated crown ethers containing *ortho*-bisethynylbenzene moieties. Herein, we present an efficient preparation of 4,4′,5,5′-tetraiododibenzo-24-crown-8 ether (**9**) starting from simple catechol followed by Pd catalyzed alkyne coupling reactions to afford highly conjugated 24-crown-8 ethers containing *ortho*-bisethynylbenzene subunits.

2. Results and discussion

In order to construct 4,4′,5,5′-tetraiododibenzo-24-crown-8 (**9**), we first prepared 4,5-diiodocatechol (**4**). A conventional strategy employs the diiodination of veratrole (**5**) with mercuric acetate and iodine followed by demethylation using BBr_3 to afford catechol **4** in high yield (Scheme 1).[15] Although this is a very efficient method, BBr_3 is highly corrosive and often limits incorporation of a wide variety of functional groups. As an alternative, we endeavored to prepare **4** directly from catechol (**1**) using a variety of iodonium sources, without much success. However, when catechol was protected as a ketal, compound **2** underwent an iodination reaction analogous to that for veratrole (**5**) to give diiodoketal **3** in good yield. Upon the preparation of diiodoketal **3**, we were able to obtain catechol **4** in

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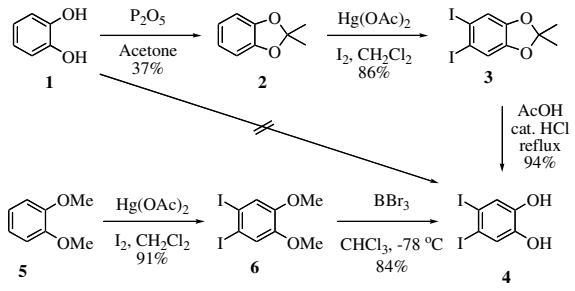


Scheme 1. Preparation of 4,5-diiodocatechol.

86% yield employing milder deprotection conditions. Deprotection was most effective providing 94% yield when a solution of compound **3** in acetic acid in the presence of catalytic amount of HCl was gently heated under reflux.

Upon the preparation of catechol **4**, tetraiodo crown ether derivative **9** was prepared following the standard crown ether procedure as shown in Scheme 2.[16] Catechol **4** was first reacted with triethylene glycol monotosylate[17] in basic solution to provide bisglycol **7** in 61% yield. Ditosylation of bisglycol **7** provided ditosylate **8** in 80% yield. Macrocycle **9** was then prepared using pseudo-dilution conditions in the presence of Cs_2CO_3 in high yield. Further conversion into the tetraethynyl derivatives by Sonogashira coupling reaction gave highly conjugated DB24C8 species **10a**,**b** (Table 1). The Pd coupling reaction yields are quite good (75–81%) considering that we are performing four simultaneous coupling reactions, which equates to above 95% conversion per coupling reaction.

The DB24C8 **10a**,**b** derivatives were characterized by ^{1}H NMR and UV–vis spectroscopy. The extended π-conjugation of these macrocycles were verified by the expected absorptions as shown in Figure 1. The absorption spectra of compounds **9** and **10a**,**b** exhibit the characteristic pattern associated with the *ortho*-disubstituted catechols. As expected, addition of alkynes to the DB24C8 core shifted λ max 1 and λ max 2 by approximately 40 and 50 nm, respectively, from their precursor **9** as depicted in Table 1. The general trend is also observed in compound **10b** as 4-*tert*-buylphenylacetylenes are coupled shifting peaks an additional 32 and 27 nm, respectively.

Table 1. Yields of Pd catalyzed coupling reactions and selected peaks (λ max 1 and 2 in nm) from the absorption spectra of **9** and **10a**,**b**

Compounds	Pd coupling yields	λ max 1	λ max 2
9	—	219	244
10a (R = TMS)	81%	252	292
10b (R = 4-*t*Bu-Ph)	75%	284	319

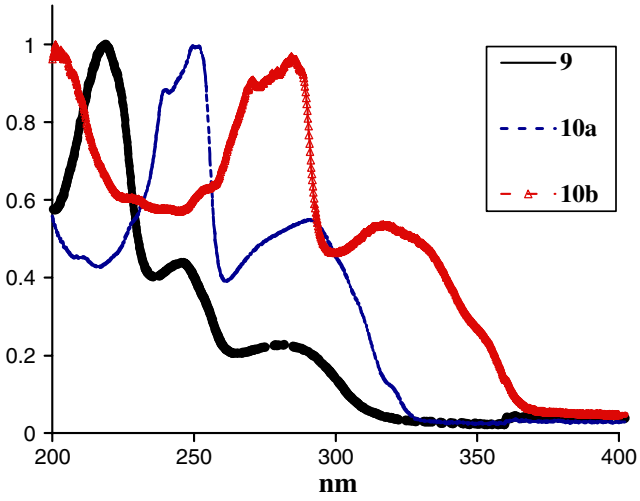
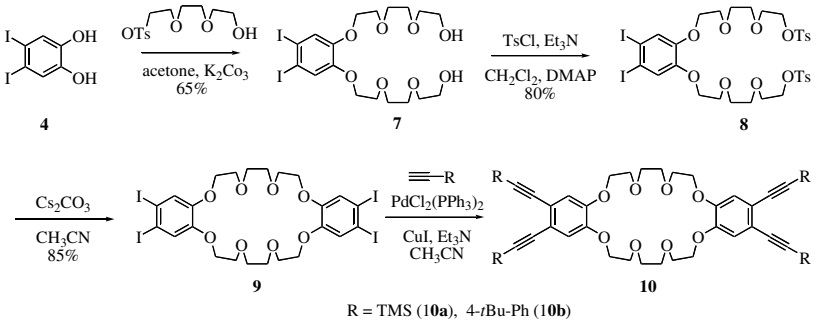


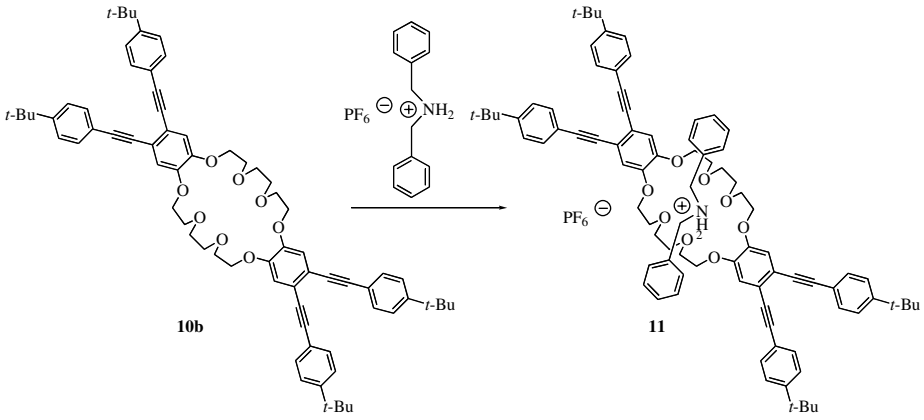
Figure 1. Absorption spectra of DB24C8 **9** and **10a**,**b**.

The interaction between macrocycle **10b** and the dibenzylammonium hexafluorophosphate salt in CD_2Cl_2 at room temperature results in a 1:1 complex as expected (Scheme 3). The ^{1}H NMR spectra suggest the formation of pseudorotaxane **11** host–guest complex as indicated by clear upfield shifts shown in Table 2. The most noticeable differences are in the ethylene moieties of the crown ether, where the 3.86 ppm resonance shifts to 3.58 ppm. Furthermore, the singlet representing the aromatic resonance of DB24C8 shifts 0.1 ppm as the complex forms. Based on the previous studies of similar systems, the observed chemical shifts and the absence of resonances from **10b** is consistent with the formation of pseudorotaxane.[6a]

Surprising evidence of the complexation between crown ether **10b** and the ammonium ion is also provided by the comparison of fluorescence spectra of **10b** and **11** as



Scheme 2. Preparation of DB24C8 **10a**,**b** from 4,5-diiodocatechol (**4**).



Scheme 3. Formation of pseudorotaxane **11**.

Table 2. Selected ^{1}H NMR resonances (ppm) of DB24C8 **10b** and complex **11**

10b	11	Δ (10b−11)
4.20	4.14	0.06
3.95	3.85	0.10
3.86	3.58	0.28
7.23	6.93	0.10

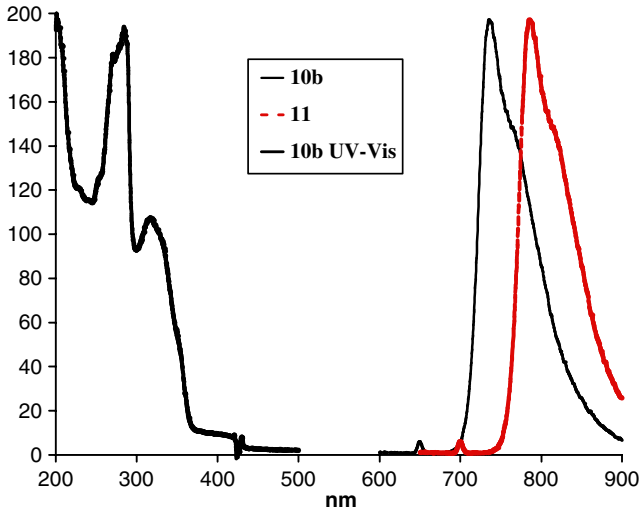


Figure 2. Fluorescence spectra of compound **10b** and complex **11**.

shown in Figure 2. When excited with a 325 nm laser, the macrocycles **10b** and **11** provided distinctively different fluorescence emissions. The fluorescence spectrum of complex **11** shows bathochromic shift of approximately 50 nm from compound **10b** as the result of the complexation. Currently, we are examining various cations, which might provide even larger changes in fluorescence emission for the purpose of optical switching.

In conclusion, we have developed an efficient synthetic method to prepare 4,4′,5,5′-tetraiododibenzo-24-crown-8 (**9**) and its highly conjugated derivatives. Further studies exploring the optical behavior of these compounds and their complexes will be reported in due course.

3. Experimental

3.1. 5,6-Diiodo-2,2-dimethylbenzo[1,3]dixole (3)

In a round bottom flask, ketal **2** (2.0 g, 13.3 mmol), I_2 (7.44 g, 29.3 mmol), and $Hg(OAc)_2$ (9.34 g, 29.3 mmol) were dissolved in CH_2Cl_2 (250 ml). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was filtered and washed with an aqueous solution of sodium thiosulfate and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried with magnesium sulfate and concentrated to give diiodoketal **3** as a light orange solid in 86% yield (4.59 g). Mp 143–145 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (s, 2H), 1.66 (s, 6H,). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.1, 95.7, 118.8, 120.2, 149.0. MS (*m*/*z*); 276 (M−I, 100), 261 (M−I−CH_3, 100), 134 (M−2I−CH_3, 24), IR (cm^{-1}) 2980, 1480, 1228. Anal. Calcd for $C_9H_8I_2O_2$ (401.861): C, 26.89; H, 2.01. Found: C, 26.95; H, 1.92.

3.2. 4,5-Diiodocatechol (4)

In a round bottom flask equipped with a reflux condenser, diiodoketal **3** (250 mg, 0.622 mmol) was dissolved in AcOH (15 ml), H_2O (5 ml), and 6 M HCl (2 ml). The reaction mixture was heated to gentle reflux for 2 h. The reaction mixture was concentrated and redissolved in ethylacetate. The solution was filtered through a plug of silica gel using ethylacetate. Upon concentration, diiodocatechol (**4**) as a solid was obtained in 94% yield (211 mg). Spectroscopic data are consistent with the literature values.[17] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (s, 2H) 1.76 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 96.2, 125.8, 144.5. MS (*m*/*z*) 361 (M+, 0.96), 236 (M−I, 30.2), 109 (M−2I, 14.9).

3.3. 4,5-Diiodo-1,2-bis[2-[2-(2-hydroxyethoxy)ethoxy]-ethoxy]benzene (7)

In a round bottom flask, diiodocatechol **4** (2.00 g, 5.52 mmol), triethylene glycol monotosylate[18] (4.13 g, 12.1 mmol), and K_2CO_3 (1.68 g, 12.1 mmol) were added and dissolved in dry acetone (100 ml) and refluxed overnight. The reaction mixture was concentrated and

filtered through a plug of silica gel with a MeOH/EtOAc (1:4) mixture. Column chromatography with MeOH/EtOAc (1:4) mixture yielded a yellowish viscous oil in 61% yield (2.10 g). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (s, 2H), 4.12 (t, $J = 5.7$, 4H), 3.86 (t, $J = 5.7$ Hz, 4H), 3.74–3.83 (m, 12H), 3.61 (t, $J = 3.6$ Hz, 4H), 2.96 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 61.7, 69.0, 69.5, 70.3, 70.8, 72.6, 96.8, 124.5, 149.3. MS (*m*/*z*) 626 (M+, 58.3), 500 (M−I, 17.8), 493 (M−$C_6H_{13}O_3$, 22.6), 388 (M−$C_{10}H_{22}O_6$, 100), 266 (M−2I−$C_4H_{10}O_3$, 43.7). IR (cm^{-1}) 3422, 2873, 2360, 1490, 1245, 1122. Anal. Calcd for $C_{18}H_{28}I_2O_8$ (626.987): C, 34.52; H, 4.51. Found: C, 34.39; H, 4.22.

3.4. 4,5-Diiodo-1,2-bis[2-[2-[2-[[(4-tosyl)sulfonyl]oxy]-ethoxy]ethoxy]ethoxy]benzene (8)

In a round bottom flask, diiodo catechol bisglycol **7** (9.78 g, 15.6 mmol), DMAP (20 mg) and Et_3N (8.0 ml) were dissolved in CH_2Cl_2 (100 ml) and the resulting solution was cooled to 0 °C. Via a dropping funnel, *p*-toluenesulfonyl chloride (6.53 g, 34.2 mmol) in CH_2Cl_2 (50 ml) was added over 2 h. After the addition, the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was concentrated and chromatographed over silica gel using MeOH/EtOAc (1:9). Compound **8** was isolated as a yellow viscous oil in 80% yield (11.6 g). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.806 (dd, $J = 8.1$, 13.7 Hz, 8H), 7.31 (s, 2H), 4.15 (t, $J = 4.8$ Hz, 4H), 4.09 (t, $J = 4.0$ Hz, 4H), 3.80 (t, $J = 4.0$ Hz, 4H), 3.72–3.52 (m, 12H), 2.44 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 68.7, 69.1, 69.2, 69.6, 70.8, 96.7, 124.6, 127.9, 129.8, 132.9, 144.8, 149.5. MS (*m*/*z*) 934 (M+, 0.02), 648 (M−$C_{14}H_{16}$, 1.00), 564 (M−$C_8H_9O_3S$, 1.36), 388 (M−$C_{10}H_{22}O_6$, 100). IR (cm^{-1}) 2949, 1356, 1174, 910, 727. Anal. Calcd for $C_{32}H_{40}I_2O_{12}S_2{\cdot}C_4H_8O_2$: C, 42.28; H, 4.73. Found $C_{32}H_{40}I_2O_{12}S_2{\cdot}C_4H_8O_2$: C, 42.09; H, 4.59.

3.5. 4,4′,5,5′-Tetraiododibenzo-24-crown-8 ether (9)

In a round bottom flask equipped with a condenser, Cs_2CO_3 (14.1 g, 43.2 mmol) was mixed with MeCN (334 ml) and refluxed under N_2. Compound **8** (8.1 g, 8.64 mmol) and diiodocatechol (**4**) (3.124 g, 8.635 mmol) were dissolved in 50 ml of MeCN and added drop wise via syringe pump over 24 h. The reaction mixture was heated under reflux for additional two days. The reaction mixture was concentrated and run through a plug of silica gel using an EtOAc/MeCN/hexane (3:3:4) mixture. White solid was isolated without further purification in 85% (7.0 g). Mp 183–184 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (s, 4H), 4.08 (t, $J = 3.6$ Hz, 8H), 3.88 (d, $J = 3.9$ Hz, 8H), 3.78 (s, 8H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 69.8, 71.5, 96.8, 124.1, 149.6. MS (*m*/*z*) 952.0 (M^+, 2.31), 826.1 (M−I, 3.32), 698.1 (M−2I−H, 4.20), 572.1 (M−3I−H, 23.8). IR (cm^{-1}) 3054, 2986, 2305, 1494, 1232, 896, 705. Anal. Calcd for $C_{24}H_{28}I_4O_8{\cdot}CH_3CN$ (992.822): C, 31.44; H, 3.15. Found: C, 31.45; H, 3.18.

3.6. 4,4′,5,5′-Tetra(trimethylsilylethynyl)dibenzo-24-crown-8 ether (10a)

In a pressure microwave vessel, compound **9** (100 mg, 0.11 mmol), CuI (40 mg, 0.21 mmol), and $PdCl_2(PPh_3)_2$ (15 mg, 0.021 mmol) were added in degassed Et_3N/MeCN (1:9, 10 ml) under N_2. Trimethylsilylacetylene (0.15 ml, 1.05 mmol) was added via syringe under N_2 and capped. The reaction mixture was irradiated by microwave 3 h at 85 °C. The crude mixture was concentrated and chromatographed on silica gel using an EtOAc/MeCN/hexane (3:3:4). A pale yellow solid was isolated in 81% yield (132 mg) as pure compound. Mp 150–152 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.89 (s, 4H), 4.11 (t, $J = 2.4$ Hz, 8H), 3.90 (t, $J = 2.4$, 8H), 3.81 (s, 8H), 0.26 (s, 36H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.0, 69.2, 69.5, 71.3, 96.7, 103.2, 115.9, 119.0, 148.5. MS (*m*/*z*) 855.3 (M+Na^+, 100), 759.2 (M−TMS, 60). IR (cm^{-1}) 2958, 1247, 833, 737. Anal. Calcd for $C_{44}H_{64}O_8Si_4{\cdot}C_4H_8O_2$: C, 62.57; H, 7.88. Found: C, 62.89; H, 7.99.

3.7. 4,4′,5,5′-Tetra(4-*tert*-butylphenylethynyl)dibenzo-24-crown-8 ether (10b)

In a pressure microwave vessel, compound **9** (50.0 mg, 0.053 mmol), CuI (3.0 mg, 0.016 mmol), and $PdCl_2$-$(PPh_3)_2$ (4.0 mg, 0.0032 mmol) were added in degassed Et_3N/MeCN (1:9, 10 ml) under N_2. 4-*tert*-Butylphenylacetylene (41 mg, 0.26 mmol) was added via syringe under N_2 and capped. The reaction mixture was irradiated by microwave 1.5 h at 90 °C. The crude mixture was concentrated and chromatographed on silica gel using EtOAc/MeCN/hexane (3:3:4). A pale yellow solid was isolated in 75% yield (42 mg). Dec. 196 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51 (d, $J = 8.4$ Hz, 8H), 7.37 (d, $J = 8.7$ Hz, 8H), 7.03 (s, 4H) 4.19 (t, $J = 3.9$ Hz, 8H), 3.94 (t, $J = 3.9$ Hz, 8H), 3.86 (s, 8H), 1.34 (s, 36H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.4, 35.0, 69.6, 69.9, 71.6, 88.0, 92.6, 116.1, 119.4, 120.7, 125.5, 131.5, 148.8, 151.5. HRMS Calcd for $C_{72}H_{80}O_8$· 1095.5751. Found 1095.5752. IR (cm^{-1}) 2958, 1511, 1248, 665.

4. Pseudorotaxane 11

Compound **10b** (5.0 mg, 0.0047 mmol) was dissolved in CD_2Cl_2 with dibenzylammonium hexafluorophosphate salt (3.0 mg, 0.0087 mmol) and sonicated for 30 min. The reaction mixture was filtered through cotton plug to eliminate any undissolved starting materials. The resulting solution was used without further purification to obtain proton NMR spectrum. ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 7.53–7.28 (m, 18H), 6.93 (s, 4H), 4.70 (t, $J = 5.4$ Hz, 4H), 4.21 (s, 4H), 4.18–4.10 (m, 8H), 3.85–3.82 (m, 8H), 3.58 (s, 8H), 2.47 (br s, 2H) 1.35 (s, 36H). ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 31.4, 35.3, 52.1, 68.9, 70.7, 71.3, 87.7, 93.4, 115.7, 120.0, 120.5, 126.2, 129.4, 129.6, 130.0, 130.2, 131.7, 147.8, 152.6.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.147.

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