Tetrahedron 65 (2009) 8113–8119

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Highly substituted Schiff base macrocycles via hexasubstituted benzene: a convenient double Duff formylation of catechol derivatives

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ARTICLE INFO

Article history:
Received 5 May 2009
Received in revised form 30 July 2009
Accepted 30 July 2009
Available online 4 August 2009

ABSTRACT

The synthesis of soluble, shape-persistent macrocycles is important for developing new materials. Double Duff formylation of 4,5-dialkylcatechol derivatives yields 3,6-diformyl-4,5-dialkylcatechols in moderate yields. These hexasubstituted aromatics are useful precursors to highly substituted Schiff base macrocycles. We illustrate convenient routes to these compounds as well as structural studies of two new macrocycles with alkyl substituents.

1. Introduction

The development of shape-persistent macrocycles is important for creating new materials,[1] new liquid crystals,[2] and for studying the role of non-covalent interactions in supramolecular chemistry.[3] Cyclic molecules based on phenyleneethynylene and phenyleneebutadiyne moieties, for example, have been extensively studied and their self-assembly studied under different conditions.[4] Other macrocycles, such as cyclic *d*,*l*-peptides and bis-urea macrocycles have also garnered interest for their abilities to organize into tubular assemblies.[5–7] In the past decade, Schiff base macrocycles have emerged as a new class of shape-persistent molecules that can be easily synthesized and also show interesting supramolecular phenomena.[8]

Since the first Schiff base macrocycles prepared by Robson and Pilkington,[9] there has been a great deal of growth in this field.[10,11] New macrocycles are being designed for complexing multiple metal centers for studies of supramolecular chemistry,[12] catalysis,[13] magnetism,[14] and other applications. By changing the geometry of the diformylaromatics that are incorporated into the macrocycle, the structure of the macrocycle can be modified.[15] One of the most studied Schiff base macrocycles is the family of conjugated [3+3] macrocycles (e.g., **3a**) that are readily prepared by the condensation of 3,6-diformylcatechol **1a** with *o*-phenylenediamine derivatives (Scheme 1).[16] These shape-persistent macrocycles have proven useful as templates for multinuclear cluster complexes and as precursors to molecule-based nanotubes.[17,18]

A significant limitation of this macrocycle is that in order to make it soluble, the macrocycle needs to be substituted with alkoxy substituents on the phenylenediamine. The alkoxy groups on the phenylenediamine render that subunit very electron rich and, consequently, very oxygen sensitive. The ability to incorporate solubilizing groups on the diformyl component will avoid the problem of oxygen sensitivity and open access to macrocycles with new electronic and steric properties. Also, if more than six groups are desired on the periphery of the macrocycle, then substituents on the diformylcatechol group are necessary. Very little work has been done to explore the functionalization of the diformylcatechol component.[19] The goal of adding alkyl groups to the diformylcatechol group requires hexasubstituted benzenes, and we were uncertain that the precursors could be made, or would react to form macrocycles. Hexasubstituted benzene derivatives have been shown to have interesting physical properties[20] and are notoriously difficult to access.

In this paper, we describe the convenient preparation of new hexasubstituted benzene derivatives that are functionalized for the formation of Schiff base macrocycles when reacted with phenylenediamines. Two of these macrocycles have been studied by single crystal X-ray diffraction, and preliminary evidence of metalation of the cycles is reported.

2. Results and discussion

2.1. Synthesis of 4,5-dialkyl-3,6-diformylcatechols 1b–1d

To demonstrate the functionalization of the macrocycles with alkyl groups on the catechol moiety, we selected three different representative chain lengths: methyl, butyl, and hexyl substituents. 4,5-Dialkylcatechols were prepared as shown in Scheme 2. *o*-Dibutylbenzene **4c** and *o*-dihexylbenzene **4d** were prepared by Kumada coupling of *o*-dichlorobenzene with the corresponding Grignard reagent.[21] Bromination of **4b**–**4d** yielded **5b**–**5d** in good

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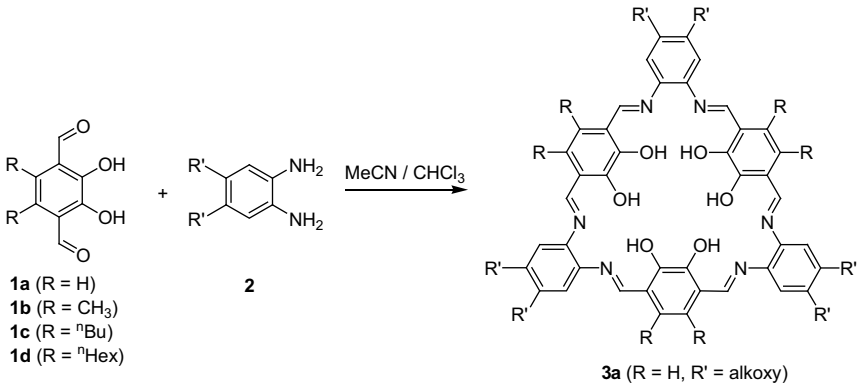
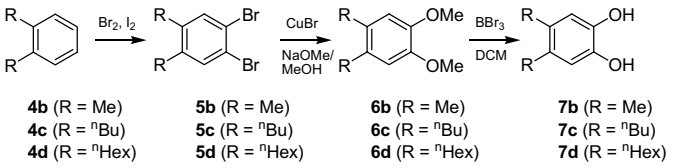
doi:10.1016/j.tet.2009.07.094



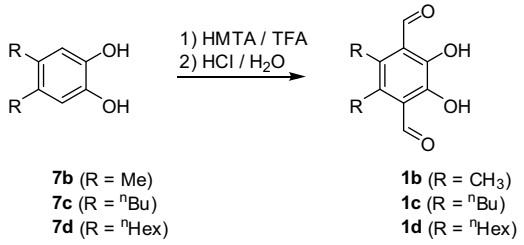
Scheme 1. Macrocycle synthesis.



Scheme 2. Synthesis of 4,5-dialkylcatechol derivatives **7b**–**7d**.

yield.[22] Ullman-type coupling of NaOMe with the brominated aromatics **5b**–**5d** afforded 4,5-dialkylveratrole derivatives **6b**–**6d**. Müllen and co-workers recently reported an alternative route to related compounds **7** that may be more amenable to scale-up.[23]

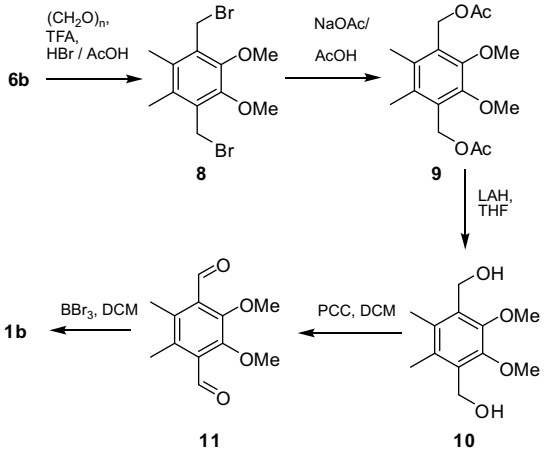
Duff formylation with hexamethylenetetraamine (HMTA) in trifluoroacetic acid (TFA) is a well-known route to salicylaldehyde derivatives, although it usually proceeds in low yield.[24,25] Duff formylation of catechol directly gives mostly unidentified products (possibly oligomers), with compound **1a** isolated in very low yield (<1%). In fact, there are no reports of formylation of any unprotected catechol derivative. To our surprise, Duff formylation of compounds **7b**–**7d** (obtained from the demethylation of **6b**–**d** with BBr_3 and used directly) gave the dialkyldiformylcatechol compounds **1b**–**1d**, Scheme 3. The yields for the preparation of **1c** and **1d** were ~30%, but the yield of **1b** was considerably lower (~10%). We do not have an explanation for the difference, but perhaps the longer alkyl chains shield the products or intermediates from side reactions.



Scheme 3. Synthesis of **1b**–**1d** via Duff formylation.

We tried other routes to **1c** and **1d** with limited success. For example, dilithiation of **6c** and **6d** followed by quenching with DMF gave mixtures of starting material, monoformylated compound, and diformylated compound. The desired diformylated compound was the minor product and was difficult to separate from the other components. Quenching the dilithiated compound with ethyl chloroformate gave the desired diester in good yield. However, clean conversion of the esters to aldehydes was problematic. We found the Duff formylation was the most effective route to **1c** and **1d**.

For **1b**, we developed an alternative route that gave the product in higher yield, though requiring more steps, Scheme 4. Bromomethylation of **6b** afforded **8** in 63% yield. Reaction with sodium acetate gave the diacetate product **9**, which was reduced in nearly quantitative yield to **10**. Oxidation with pyridinium chlorochromate (PCC) gave compound **11** in 73% yield. Deprotection with BBr_3 gave the desired compound **1b**. Our attempts to extend this route to the preparation of **1c** and **1d** were not successful as the bromomethylated compounds analogous to **8** could not be isolated in good yield.



Scheme 4. Synthesis of **1b** via bromomethylation.

2.2. Properties of the hexasubstituted molecules

Hexasubstituted molecules **1b**–**1d** were fully characterized. The ^1H NMR spectra of these molecules contain a downfield hydroxyl peak at ~12 ppm; the large downfield shift is characteristic of strong intramolecular hydrogen-bonding. This hydrogen bond was also evident in the red-shifted C–O stretch (ca. 1650 cm^{-1}) in the IR spectra. The structure of compound **1c** was determined by single crystal X-ray diffraction and is shown in Figure 1. Notably, the asymmetric unit contains two different molecules (A and B) of compound **1c**. In one conformation (A), both carbonyl groups are positioned for hydrogen-bonding with the two hydroxyl groups. In

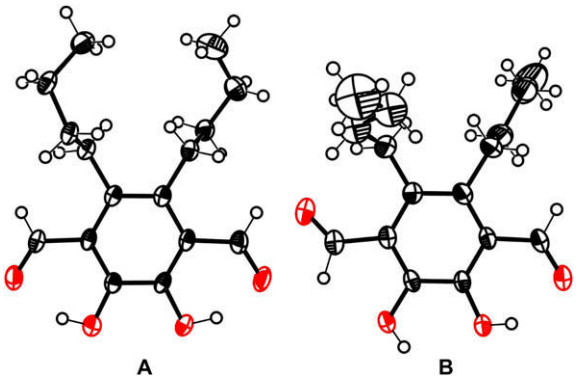


Figure 1. ORTEP depiction of molecules A and B in the solid-state structure of **1c**. Thermal ellipsoids are shown at 50% probability.

the second conformation (B), one of the carbonyl groups is involved in hydrogen-bonding while the other is rotated 180°. The hydroxyl group not involved in intramolecular hydrogen-bonding in B is hydrogen-bonded to the oxygen atoms of A in the solid state. Moreover, molecule A is arranged into dimers in the solid state, with π-stacking present.

As expected, the solid-state structure of **1c** shows considerable distortion. The C–C–C angle between the formyl group (not involved in hydrogen-bonding) and the benzene ring is 114°, substantially less than the expected 120° angle. Other bond angles around the ring show small, but significant distortions.

2.3. Macrocycle synthesis

With diols **1b**–**d** in hand, we set out to explore their reactivity. As these are hexasubstituted aromatics, we expected them to be much less reactive than **1a**, and perhaps unlikely to form a macrocycle. Reaction of **1b** with phenylenediamine **2** (R′=OEt) gave macrocycle **3b** in 87% yield, Scheme 1. A second macrocycle (**3c**) with R′=OC_5H_{11} was prepared by an analogous route (77%). The macrocycles were identified by NMR spectroscopy, mass spectrometry, and both gave satisfactory analysis. Notably, mass spectrometry confirmed that the products were the [3+3] macrocycles and not larger cycles. Each macrocycle showed a single imine C=N stretch in the IR spectrum at ca. 1600–1620 cm^{-1}. ^1H NMR spectra showed a single OH resonance near 14 ppm, and a single imine resonance at 9.0 ppm for both macrocycles. These data are consistent with the threefold symmetry of the macrocycles in solution.

Macrocycles **3d** and **3e**, with *n*-butyl and *n*-hexyl substituents, respectively, were readily prepared by condensation of **1c** and **1d** with phenylenediamines **2** (R′=H or R′=OMe), Scheme 1. The macrocycles were also characterized by NMR spectroscopy, mass spectrometry, and elemental analysis.

As expected, changing the substituents has a large effect on the optical properties of the macrocycles. Macrocycle **3a** with only alkoxy substituents displays an absorption peak around 400 nm that is associated with a π–π* transition of the ring. Macrocycles **3b**, **3c**, and **3e**, which have alkoxy substitutents on the diamine units and alkyl substituents on the diol units, all display absorption maxima near 410–415 nm in solution. On the other hand, macrocycle **3d**, which has no peripheral alkoxy chains has no strong absorption peaks in the visible region, and only λ_{max} at 370 nm. The alkoxy groups have a strong role in shifting the absorption spectra of the macrocycles, likely as a consequence of donating π-electron density to the cycle.

We were surprised that the macrocycles were easily formed, particularly considering the steric hindrance around the formyl groups. Compounds **1c** and **1d** also react with 4,5-dialkoxy-1,2-phenylenediamines to give macrocyclic products with longer alkoxy groups, but in this case the products were isolated as oils and we have not been able to fully purify them. Nevertheless, ^1H NMR data and mass spectrometry confirmed that they are the major products formed, and can be isolated in ca. 95% purity. We are hopeful that more dodecasubstituted macrocycles can be isolated, enabling access to liquid crystalline trimetallic complexes.

2.4. Macrocycle structures

To further investigate the influence of the alkyl groups on the sterics of the macrocycles, we undertook structural studies of macrocycles **3b** and **3d**. Single crystals of **3b** and **3d** suitable for X-ray diffraction were grown from DMF and CH_3CN/CH_2Cl_2, respectively. Figure 2 shows the solid-state structure of macrocycle **3b**, and Figure 3 shows the solid-state structure of macrocycle **3d**.

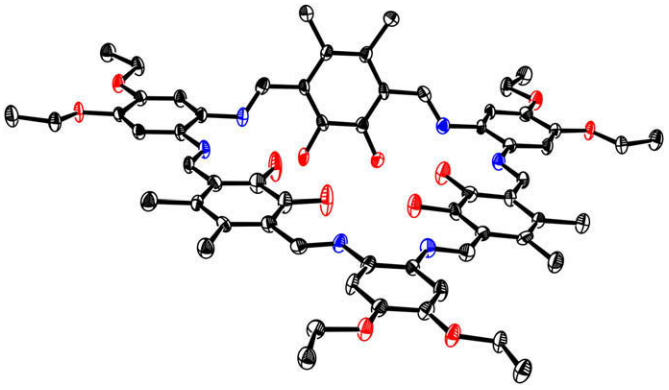


Figure 2. ORTEP depiction of the solid-state structure of macrocycle **3b**. Thermal ellipsoids are drawn at 50% probability level. (Black=C, Red=O, Blue=N).

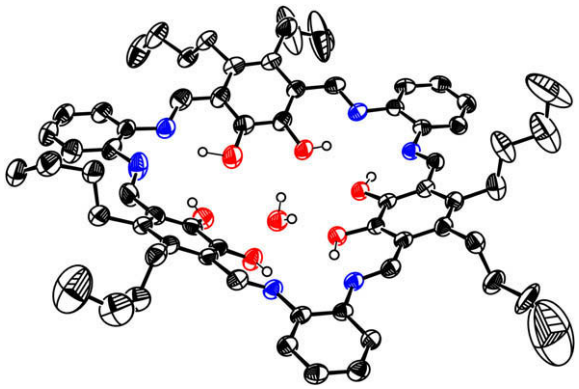


Figure 3. ORTEP depiction of the solid-state structure of macrocycle **3d**. Thermal ellipsoids are drawn at 50% probability level.

In the solid state, macrocycle **3b** is mostly planar, with one catechol unit rotated out of the plane, having a dihedral C–C–N=C angle of 46°, Figure 2. The hydrogen atoms on the hydroxyl groups were not located, but the imine groups are oriented for strong hydrogen-bonding with these groups as expected from the ^1H NMR solution data. We were surprised that the incorporation of alkyl groups did not lead to considerable torsion about the Ar–imine bond. The macrocycles pack in staggered planes to accommodate the twisted phenyl ring. A slight overlap of the macrocycles in different planes and an interplanar distance of 3.43 Å suggest that π–π interactions are occurring in the solid state.

The solid-state structure of macrocycle **3d**, as shown in Figure 3, is quite different from that of **3b**. Although the phenyl rings

associated with the diimine groups are nearly coplanar, the catechol groups are all rotated in one direction relative to the plane derived from the phenylenediimine rings. The interior hydroxyl groups are hydrogen-bonded to imine groups and to a water molecule at the center of the ring. This conformation produces a shallow bowl shape, analogous to that observed when macrocycles **3a** are metalated.[17] The macrocycles pack in staggered rows of alternating orientation, allowing for each pair of macrocycles to have strong π–π interactions between six phenyl rings at a distance of 3.56 Å.

We have been unable to freeze-out conformations of macrocycles **3a**, and DFT calculations indicate that the catechol groups can rotate within the macrocycle with a barrier of less than ~5 kcal mol^{-1}. Low temperature ^{1}H NMR studies of macrocycle **3c** also failed to freeze-out any conformations down to −60 °C, in spite of the bulky alkyl groups in the molecule.

Macrocycles **3a** have been shown to react with 7 equiv of zinc acetate in ethanol to form metallocavitands containing seven zinc ions, six bridging acetates, and one μ-oxo ligand.[17] The analogous reaction with macrocycle **3b** was carried out and MALDI-TOF mass spectrometry indicated that the expected heptazinc cluster was formed (spectrum in Supplementary data). Interestingly, the solubility properties of this new metallomacrocycle are quite unusual: the metallomacrocycle formed from **3b** is very soluble in ethanol and even ethanol/water mixtures while the metallomacrocycle formed from **3a** with ethoxy chains is insoluble in ethanol. This has so far frustrated crystallization of the zinc complex of **3b**. Further studies are underway to investigate the multimetallic complexes formed from these macrocycles.

3. Conclusion

We have demonstrated the first Duff formylation of catechol derivatives to yield dialkyldiformyldihydroxybenzenes, one of which was characterized in the solid state. These hexasubstituted aromatics undergo condensation with phenylenediamines to afford [3+3] Schiff base macrocycles in good yield. Structural studies of two new macrocycles, including the first dodecasubstituted triangular Schiff base macrocycle, indicate that these cycles are nearly flat, and that the steric hindrance of the additional alkyl groups does not substantially interfere with the chemistry of the formyl or imine groups. These macrocycles react with transition metals to form multinuclear metal complexes. We are now exploring the use of these macrocycles as templates for monodisperse cluster complexes, and as precursors to trimetallic discotic liquid crystals.

4. Experimental

4.1. General

Compounds **2b–d**,[26] **4c–d**,[27] **5b–d**,[21,22] **6b**,[28] and **8** were prepared by literature methods. Deuterated solvents were purchased from Cambridge Isotope Laboratories, and other reagents were obtained from Aldrich. All reactions were carried out under air unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker AV-300 or AV-400 spectrometer. ^{13}C NMR spectra were recorded using a proton decoupled pulse sequence. ^{1}H and ^{13}C NMR spectra were calibrated to the residual protonated solvent at δ 7.27 and 77.23, respectively, in $CDCl_3$ or at δ 5.32 and 54.00, respectively, in CD_2Cl_2. UV–vis spectra were obtained in DCM (ca. 1×10^{-6} mol L^{-1}) on a Varian Cary 5000 UV–vis–near-IR spectrophotometer using a 1 cm quartz cuvette. IR spectra were collected neat in the solid state on a Thermo Nicolet 6700 FT-IR spectrometer or in a KBr pellet on a Nicolet 4700 FT-IR spectrometer. All mass spectrometry experiments were conducted at the UBC Microanalytical Services Laboratory. EIMS was conducted on a Kratos MS-50 spectrometer. MALDI-TOF mass spectrometry was performed on a Bruker Biflex IV instrument with a dithranol matrix. Electrospray ionization (ESI) mass spectra were obtained on a Bruker Esquire LC instrument in MeOH (ca. 1×10^{-4} mol L^{-1}). Elemental analyses (CHN) were performed at the UBC Microanalytical Services Laboratory. Melting points were obtained on a Fisher-John's melting point apparatus.

X-ray crystal structures were obtained on a Bruker X8 APEX II diffractometer with graphite monochromated Mo Kα radiation. The structures were solved by direct methods[29] and refined using SHELXL-97.[30] Thermal ellipsoid plots of the molecular structures were prepared using ORTEP.

4.2. 1,2-Dimethoxy-4,5-dibutylbenzene (6c)

To 3.042 g (8.74 mmol) 1,2-dibromo-4,5-dibutylbenzene **5c** were added 100 mL of 25 wt % NaOMe in MeOH, three drops of ethyl acetate, and 27 mg CuBr (0.19 mmol, 2 mol %). This produced a dark blue suspension that was heated to reflux overnight under nitrogen. After confirming that the reaction had proceeded to completion by ^{1}H NMR spectroscopy, the mixture was poured into 100 mL of ice water. The resulting pale blue suspension was extracted with 3×60 mL diethylether. The organic layer was washed with 50 mL dilute (~0.1 M) $NH_4OH_{(aq)}$ then 2×50 mL water, dried over $MgSO_4$, and filtered. After solvent was removed under vacuum, compound **6c** (1.948 g, 7.78 mmol, 89% yield) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.62 (s, 2H, Ar–*H*), 3.84 (s, 6H, OC*H*$_3$), 2.53 (t, $^3J_{HH}$=7.6 Hz, 4H, Ar–C*H*$_2$), 1.53 (m, 4H, Ar–CH$_2$C*H*$_2$), 1.39 (m, 4H, Ar–CH$_2$CH$_2$C*H*$_2$), 0.94 (t, $^3J_{HH}$=7.2 Hz, 6H, CH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 146.8, 132.6, 112.6, 55.9, 33.9, 32.1, 22.8, 14.0. IR (neat) ν (cm^{-1})=2957, 2930, 2860, 1609, 1598, 1578, 1495, 1460, 1394, 1260, 1200, 1051, 875, 750. UV–vis (CH_2Cl_2) λ_{max} (nm) (ε): 284 nm (430 L mol^{-1} cm^{-1}). EIMS: *m*/*z*=250 [M]$^+$. Anal. Calcd for $C_{16}H_{26}O_2$: C 76.75, H 10.47. Found: C 76.59, H 10.44.

4.3. 1,2-Dimethoxy-4,5-dihexylbenzene (6d)

Conditions analogous to those for the preparation of 1,2-dimethoxy-4,5-dibutylbenzene (**6c**) were employed. Compound **6d** was obtained as a colorless oil (91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.64 (s, 2H, Ar–*H*), 3.84 (s, 6H, OC*H*$_3$), 2.52 (t, $^3J_{HH}$=7.6 Hz, 4H, Ar–C*H*$_2$), 1.3–1.6 (m, 16H, Ar–CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$), 0.89 (t, $^3J_{HH}$=7.2 Hz, 6H, CH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 146.8, 132.5, 112.6, 55.9, 33.9, 32.1, 31.6, 29.8, 22.8, 14.0. IR (neat) ν (cm^{-1}): 2956, 2928, 2856, 1610, 1519, 1465, 1266, 1224, 1115, 1036, 1006, 859, 742. UV–vis (CH_2Cl_2) λ_{max} (nm) (ε): 282 (380 L mol^{-1} cm^{-1}). EIMS: *m*/*z*=306 [M]$^+$. Anal. Calcd for $C_{20}H_{34}O_2$: C 78.38, H 11.18. Found: C 78.03, H 11.00.

4.4. 2,3-Dibutyl-5,6-dihydroxybenzene-1,4-dialdehyde (1c) via catechol 7c

To 2.332 g (9.31 mmol) 1,2-dimethoxy-4,5-dibutylbenzene **6c** was added 100 mL dicholoromethane and the resulting solution chilled to 0 °C under nitrogen. To this solution was added 3.8 mL (~40 mmol, ~2 equiv) boron tribromide by syringe. The solution was stirred under nitrogen overnight warming to room temperature then quenched by addition of 150 mL distilled water followed by three drops of concentrated HCl. The aqueous layer was extracted with 3×50 mL dichloromethane (DCM) and the organic fractions dried over Na_2SO_4, filtered, and the solvent removed in vacuo affording **7c** as a tan solid; this material was found to slowly degrade on standing in air and was used without additional purification (^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (s, 2H, Ar–*H*), 5.27 (br s, 2H, ArO*H*), 2.46 (t, 4H, Ar–C*H*$_2$), 1.48–1.52 (m, 4H, Ar–CH$_2$C*H*$_2$),

1.25–1.35 (m, 4H, Ar–$CH_2CH_2CH_2$), 0.88 (t, 6H, CH_2CH_3)). The solid was dissolved in 75 mL trifluoroacetic acid under nitrogen. To the resulting pink solution was added 5.430 g HMTA (38.7 mmol, ~2 equiv relative to 1,2-dimethoxy-4,5-dibutylbenzene), and the solution heated to reflux under nitrogen. On heating, the solution changed from pink to orange to dark red. After 3 h at reflux, the solution was cooled to room temperature and 100 mL ~4 M $HCl_{(aq)}$ was added. This solution was then heated to reflux overnight under nitrogen. The resulting orange/red solution was cooled to room temperature, transferred to a separatory funnel, and diluted with 100 mL distilled water. A suspension formed and was extracted with DCM (4×60 mL). The pooled organic extracts were rinsed with 60 mL distilled water, 80 mL 1% $NaHCO_{3(aq)}$, and another 60 mL distilled water then dried over Na_2SO_4, filtered, and the solvent removed by rotary evaporation. The crude material was obtained as a viscous orange/red tar and was purified by chromatography on silica using 0.5% acetone in DCM as the eluent. The desired product eluted first, with subsequent fractions containing a sizeable proportion of the product along with impurities. Later fractions were retained and resubjected to the column conditions. The product 2,3-dibutyl-5,6-dihydroxybenzene-1,4-dialdehyde was obtained as a waxy, bright orange solid (0.899 g, 3.23 mmol, 35% yield after chromatography). Crystals suitable for X-ray diffraction were grown by slow evaporation of a hexanes solution. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.95 (s, 2H, Ar–O*H*), 10.35 (s, 2H, Ar–C*H*O), 2.86 (t, $^3J_{HH}$=7.6 Hz, 4H, Ar–CH_2), 1.44–1.56 (m, 8H, Ar–$CH_2CH_2CH_2$), 0.98 (t, $^3J_{HH}$=7.2 Hz, 6H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 196.6, 151.2, 132.4, 120.9, 35.5, 26.2, 22.9, 13.8. IR (thin film) ν (cm^{-1}): 3388, 3085, 2959, 2929, 1646, 1554, 1439, 1397, 1294, 1247, 1195, 929, 758. UV–vis (CH_2Cl_2) λ_{max} (nm) (ε): 304 (1.5×10^4 L mol^{-1} cm^{-1}), 441 (3.5×10^3 L mol^{-1} cm^{-1}). EIMS: m/z=278 $[M]^+$. Anal. Calcd for $C_{16}H_{22}O_4$: C 69.04, H 7.97. Found: C 69.07, H 7.99. Mp: 52–55 °C.

4.5. 2,3-Dihexyl-5,6-dihydroxybenzene-1,4-dialdehyde (1d) via catechol 7d[31]

Conditions analogous to those for the preparation of 2,3-dibutyl-5,6-dihydroxybenzene-1,4-dialdehyde (**1c**) were employed. Analytically pure **1d** was obtained as a waxy, bright orange solid (31% yield after chromatography). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.96 (s, 2H, Ar–O*H*), 10.34 (s, 2H, Ar–C*H*O), 2.85 (t, $^3J_{HH}$=7.6 Hz, 4H, Ar–CH_2), 1.50 (m, 4H, Ar–CH_2CH_2), 1.30 (m, 12H, Ar–$CH_2CH_2CH_2CH_2CH_2$), 0.98 (t, $^3J_{HH}$=7.2 Hz, 6H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 196.6, 151.2, 132.4, 120.9, 35.5, 32.6, 29.6, 26.2, 22.9, 13.8. IR (neat) ν (cm^{-1}): 3387, 3085, 2956, 2856, 1645, 1555, 1440, 1397, 1296, 1236, 1117, 1094, 936, 764. UV–vis (CH_2Cl_2) λ_{max} (nm) (ε): 299 nm (1.4×10^4 L mol^{-1} cm^{-1}), 436 nm (3.1×10^3 L mol^{-1} cm^{-1}). EIMS: m/z=334 $[M]^+$. Anal. Calcd for $C_{20}H_{30}O_4$: C 71.82, H 9.04. Found: C 72.02, H 9.11. Mp: 39–41 °C.

4.6. 2,3-Dimethyl-5,6-dihydroxybenzene-1,4-dialdehyde (1b) via catechol 7b[32]

Conditions analogous to those for the preparation of 2,3-dibutyl-5,6-dihydroxybenzene-1,4-dialdehyde (**1c**) were employed. Analytically pure **1b** was obtained as a waxy, bright orange solid (11% yield after chromatography). Spectroscopic data are provided in Section 4.10.

4.7. 3,6-Diacetylmethyl-1,2-dimethoxy-4,5-dimethylbenzene (9)

A mixture of compound **8** (595 mg, 1.69 mmol), sodium acetate (1.54 g, 18.8 mmol), acetic anhydride (1.5 mL, 15 mmol), and acetic acid (45 mL) was heated to reflux under N_2 for 23 h. The solution was poured into ~300 mL of water. Upon cooling overnight, white crystals formed that were isolated by filtration and dried under vacuum. Compound **9** was obtained as white needles. Yield: 325 mg (0.98 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.22 (s, 4H, Ar–CH_2), 3.83 (s, 6H, OCH_3), 2.21 (s, 6H, CH_3), 2.05 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.0, 150.0, 133.8, 128.8, 61.3, 51.8, 20.8, 15.7. IR (neat) ν (cm^{-1}): 2983, 2939, 2830, 1732, 1587, 1457, 1380, 1221, 1101, 1015, 965, 710, 621, 582, 438. UV–vis (CH_2Cl_2) λ_{max} (nm) (ε): 288 (3.06×10^3 L mol^{-1} cm^{-1}), 226 (1.59×10^4 L mol^{-1} cm^{-1}). ESI-MS: m/z=333.1 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{22}O_6$: C 61.92, H 7.15. Found: C 62.20, H 7.21. Mp: 78–80 °C.

4.8. 3,6-Di(hydroxymethyl)-1,2-dimethoxy-4,5-dimethylbenzene (10)

Under N_2, a solution of **9** (300 mg, 0.90 mmol) in 40 mL of dry THF was added slowly with a syringe to a suspension of $LiAlH_4$ (137 mg, 3.6 mmol) in 50 mL dry THF. After heating the mixture to reflux for 20 h, the excess $LiAlH_4$ was slowly quenched with water (10 mL), then the reaction mixture was filtered through Celite. Rotary evaporation gave an off-white solid that was pure by ^{1}H NMR spectroscopy. Yield: 188 mg (0.83 mmol, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.78 (s, 4H, Ar–CH_2), 3.89 (s, 6H, OCH_3), 2.31 (s, 6H, Ar–CH_3), 1.87 (s, 2H, O*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 149.0, 132.8, 99.9, 60.8, 57.5, 15.8. IR (neat) ν (cm^{-1}): 3202, 2992, 2938, 2895, 2831, 2719, 1489, 1459, 1419, 1383, 1322, 1260, 1095, 999, 859, 674, 430. UV–vis (CH_2Cl_2) λ_{max} (nm) (ε): 286 nm (1.07×10^3 L mol^{-1} cm^{-1}), 225 nm (6.55×10^3 L mol^{-1} cm^{-1}). HRMS calcd for $C_{12}H_8O_4$ $[M]^+$: 226.12051. Found: 226.12085. Mp: 136–140 °C.

4.9. 3,6-Diformyl-1,2-dimethoxy-4,5-dimethylbenzene (11)

Compound **10** (50 mg, 0.221 mmol) was dissolved in ca. 50 mL of DCM at room temperature. Pyridinium chlorochromate (PCC) (229 mg, 1.06 mmol) was added slowly turning the reaction mixture orange-brown in color. The reaction mixture was left stirring for ca. 14 h at room temperature. Most of the solvent was removed under vacuum leaving ~3 mL of a dark brown oil. This was flushed through a silica plug with ~300 mL of DCM and the solvent was then removed under vacuum leaving behind a pale yellow solid (36 mg) that was pure by ^{1}H NMR spectroscopy. Yield: 36 mg (0.16 mmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.56 (s, 2H, C*H*O), 3.96 (s, 6H, OCH_3), 2.43 (s, 6H, Ar–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 193.1, 134.9, 133.1, 99.9, 62.1, 15.3. IR (neat) ν (cm^{-1}): 3365, 2978, 2944, 2865, 2759, 2560, 2359, 2341, 1915, 1690, 1557, 1453, 1396, 1259, 1047, 956, 789, 575. HRMS calcd for $C_{12}H_{14}O_4$ $[M]^+$: 222.08921. Found: 222.08938. Mp: 47–49 °C.

4.10. 3,6-Diformyl-1,2-dihydroxy-4,5-dimethylbenzene (1b)

Under a nitrogen atmosphere, compound **11** (482 mg, 2.2 mmol) was dissolved in ~50 mL of dry DCM cooled in an ice/water bath. BBr_3 (0.9 mL, 9.8 mmol) was added turning the reaction mixture red in color. After stirring for 14 h at room temperature, the reaction was quenched with water and the product extracted with DCM. The combined organic fractions were dried over $MgSO_4$, filtered, and dried under vacuum to leave an orange solid (431 mg, >100%) that was nearly pure by ^{1}H NMR spectroscopy. Recrystallization from a mixture of DCM/hexanes yielded **1b** as orange needles. Yield: 342 mg (1.76 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.89 (s, 2H, O*H*), 10.45 (s, 2H, C*H*O), 2.48 (s, 6H, Ar–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.6, 150.8, 127.8, 121.2, 13.3. IR ν (cm^{-1}): 3040, 2920, 2799, 1641, 1610, 1552, 1416, 1379, 1274, 1243, 1098, 922, 739, 595, 491. UV–vis (CH_2Cl_2) λ_{max} (nm) (ε): 443 (2.45×10^3 L mol^{-1} cm^{-1}), 302

(1.31×10^4 L mol^{-1} cm^{-1}), 226 (9.96×10^3 L mol^{-1} cm^{-1}). EIMS: m/z=194 $[M]^+$. Anal. Calcd for $C_{10}H_{10}O_4$: C 61.85, H 5.19. Found: C 62.00, H 5.55. Mp: 172–175 °C.

4.11. Macrocycle 3b (R=CH$_3$, R′=OC$_2$H$_5$)

Under a nitrogen atmosphere, 51 mg (0.26 mmol) of 1,2-diethoxy-4,5-diaminobenzene was dissolved in 10 mL of 1:1 degassed $CHCl_3$/MeCN. Diformyldiol **1b** (50 mg, 0.26 mmol) was added turning the solution from colorless to deep red. After heating at reflux (90 °C) for 4 h, the solution was cooled to room temperature, yielding a red microcrystalline solid of **3b**. Macrocycle **3b** was isolated on a Büchner funnel, washed with cold MeCN, and dried under vacuum. Yield: 81 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 13.93 (s, 6H, O*H*), 8.98 (s, 6H, C*H*=N), 6.80 (s, 6H, Ar–*H*), 4.15 (q, 12H, OCH_2), 2.36 (s, 18H, Ar–CH_3), 1.48 (t, $^3J_{HH}$=6.8 Hz, 18H, CH_2CH_3). IR ν (cm^{-1}): 3543, 2977, 2929, 1604, 1505, 1473, 1377, 1309, 1180, 1098, 1031, 978, 798, 619, 571. UV–vis (CH_2Cl_2) λ_{max} (nm) (ε): 412 (4.27×10^4 L mol^{-1} cm^{-1}), 349 (2.03×10^4 L mol^{-1} cm^{-1}), 229 (3.56×10^4 L mol^{-1} cm^{-1}). ESI-MS: m/z=1064 $[M+H]^+$, 1102 $[M+K]^+$. Anal. Calcd for **3b**·2H$_2$O ($C_{60}H_{70}N_6O_{14}$): C 65.56, H 6.42, N 7.65. Found: C 65.31, H 6.23, N 7.63. Single crystals were obtained from DMF. Mp: >260 °C.

4.12. Macrocycle 3c (R=CH$_3$, R′=O^{n}C$_5$H$_{11}$)

Macrocycle **3c** was prepared by a procedure analogous to that used to prepare macrocycle **3b**, but with 1,2-dipentyloxy-4,5-diaminobenzene. Yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 13.83 (br s, 6H, O*H*), 8.97 (s, 6H, C*H*=N), 6.81 (s, 6H, Ar–*H*), 4.03 (br t, 12H, OCH_2), 2.35 (s, 18H, Ar–CH_3), 1.84 (m, 12H, OCH_2CH_2), 1.42 (m, 24H, $OCH_2CH_2CH_2CH_2$), 0.95 (t, $^3J_{HH}$=7.0 Hz, 18H, CH_2CH_3). ^{13}C NMR δ (ppm): 161.1, 150.8, 149.1, 135.9, 124.7, 119.0, 105.8, 70.0, 29.1, 28.2, 22.5, 14.5, 14.1. IR ν (cm^{-1}): 2953, 2931, 2869, 1604, 1507, 1467, 1377, 1312, 1258, 1181, 984, 826, 624, 504. UV–vis (CH_2Cl_2) λ_{max} (nm) (ε): 415 (2.76×10^4 L mol^{-1} cm^{-1}), 350 (1.85×10^4 L mol^{-1} cm^{-1}), 228 (1.52×10^4 L mol^{-1} cm^{-1}). ESI-MS: m/z=1315.7 $[M+H]^+$, 1337.6 $[M+Na]^+$. Anal. Calcd for **3c**·H$_2$O ($C_{78}H_{102}N_6O_{13}$): C 70.24, H 7.86, N 6.30. Found: C 70.45, H 7.60, N 6.70. Mp: >260 °C.

4.13. Macrocycle 3d (R=^{n}C$_4$H$_9$, R′=H)

In a 100 mL round bottom flask, 2,3-dibutyl-5,6-dihydroxybenzene-1,4-dialdehyde (**1c**; 0.359 g, 1.29 mmol) was dissolved in 50 mL acetonitrile and 10 mL chloroform. *o*-Phenylenediamine (0.142 g, 1.35 mmol) was added and the resulting yellow solution stirred briefly under nitrogen for 5 min. A drop of piperidine was added immediately turning the solution dark red. This solution was heated at reflux overnight under nitrogen, then cooled to room temperature, at which point a fine precipitate formed. The solid was isolated by filtration on a Buchner funnel and washed with a small volume of ice-cold acetonitrile. After air drying, the product **3d** was obtained as an orange/brown powder (0.108 g, 0.103 mmol, 24% yield, >95% pure by NMR integration). Slow diffusion of acetonitrile into a concentrated dichloromethane solution afforded single crystals suitable for X-ray diffraction. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 14.00 (s, 6H, O*H*), 8.92 (s, 6H, C*H*=N), 7.36 (br d, 6H, Ar–*H*), 7.16 (br d, 6H, Ar–*H*), 2.79 (m, 12H, Ar–CH_2), 1.49 (br m, 24H, Ar–$CH_2CH_2CH_2$), 0.97 (br t, 18H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.0, 151.9, 143.6, 129.4, 127.6, 119.6, 118.5, 35.0, 27.6, 23.0, 13.9. IR (thin film) ν (cm^{-1}): 3339, 3198, 2955, 2924, 2856, 1618, 1556, 1493, 1465, 1383, 1327, 1215, 1140, 1101, 827, 748 cm^{-1}. UV–vis (CH_2Cl_2) λ_{max} (nm) (ε): 370 (1.58×10^5 L mol^{-1} cm^{-1}). MALDI-TOF: m/z=1051.3 $[M+H]^+$. Anal. Calcd for $C_{66}H_{78}N_6O_6$: C 75.40, H 7.48, N 7.99. Found: C 75.09, H 8.19, N 7.17. Mp: 199–202 °C.

4.14. Macrocycle 3e (R=^{n}C$_6$H$_{13}$, R′=OCH$_3$)

Macrocycle **3e** was prepared using a procedure analogous to that used to prepare macrocycle **3d**, but with compound **1d** in the place of **1c** and dialkoxyphenylenediamine **2b** in place of phenylenediamine. Compound **3e** was obtained as a black powder (28% yield, >95% pure by NMR integration). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 14.65 (s, 6H, OH), 8.97 (s, 6H, C*H*=N), 6.86 (s, 6H, Ar–*H*), 4.02 (s, 18H, O–CH_3), 2.84 (br m, 12H, Ar–CH_2), 1.58 (br m, 12H, Ar–CH_2CH_2), 1.49 (br m, 12H, Ar–$CH_2CH_2CH_2$), 1.35 (br m, 24H, $CH_2CH_2CH_3$), 0.91 (br t, 18H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.8, 152.5, 150.8, 136.1, 131.0, 119.2, 103.3, 46.2, 33.9, 32.7, 30.7, 28.8, 23.7, 15.1. IR (neat) ν (cm^{-1}): 2952, 2920, 2851, 1604, 1510, 1455, 1435, 1317, 1259, 1193, 1005, 842, 627, 554. UV–vis (CH_2Cl_2) λ_{max} (nm) (ε): 413 (4.35×10^4 L mol^{-1} cm^{-1}), 347 (3.05×10^4 L mol^{-1} cm^{-1}), 229 (5.27×10^4 L mol^{-1} cm^{-1}). HRMS calcd for $C_{84}H_{114}N_6O_{12}$ $[M+H]^+$: 1399.8567. Found: 1399.8519. Mp: 145–147 °C.

4.15. X-ray crystallography

Crystals of **1c** were obtained from hexanes. X-ray crystal data for **1c**: $C_{16}H_{22}O_4$, M_w=278.34 g mol^{-1}, orange plate (1.4×1.2×0.05 mm), monoclinic, space group $P2_1/a$ (#14), a=18.1497(6), b=7.2908(7), c=24.030(2) Å, α=90.00°, β=109.146(5)°, γ=90.00°, V=3003.8(5) Å^3, Z=8, ρ_{calcd}=1.231 g/cm^3, F_{000}=1200, Mo Kα radiation, λ=0.71073 Å, T=173(2) K, $2\theta_{max}$=27.23°, 56,005 reflections were collected, 6689 were unique (R_{int}=0.0528). Final GoF=0.991, R_1=0.0632, R_2=0.1605, R indices based on 4348 reflections with $I>2\sigma(I)$. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located through difference mapping or calculated positions and were refined isotropically.

Crystals of macrocycle **3b** suitable for X-ray diffraction were obtained from hot DMF. X-ray crystal data for **3b**: $C_{75}H_{101}N_{11}O_{18}$, M_w=1444.67 g mol^{-1}, red prism (0.70×0.15×0.10 mm), triclinic, space group P-1 (#2), a=12.3499(14), b=17.709(3), c=19.450(3) Å, α=64.827(5)°, β=84.172(6)°, γ=80.874(6)°, V=3798.3(9) Å^3, Z=2, ρ_{calcd}=1.263 g cm^{-3}, F_{000}=1544, Mo Kα radiation, λ=0.71073 Å, T=173(2) K, $2\theta_{max}$=22.72°, 45,369 reflections were collected, 9757 were unique (R_{int}=0.1080). Final GoF=1.020, R_1=0.0692, wR_2=0.1686, R indices based on 4641 reflections with $I>2\sigma(I)$. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located through difference mapping or calculated positions and were refined isotropically. An isolated oxygen atom is present in the structure that is believed to be a solvent water molecule. The long O–H bond (O4–H4) is likely due to strong hydrogen-bonding between H4 and the adjacent imine nitrogen.

Crystals of macrocycle **3d** suitable for X-ray diffraction were obtained by slow diffusion of acetonitrile into a concentrated DCM solution of **3d**. X-ray crystal data for **3d**: $C_{68}H_{83}N_7O_7$, M_w=1110.41 g mol^{-1}, red blade (0.50×0.10×0.05 mm), triclinic, space group P-1 (#2), a=13.2837(6), b=16.4922(7), c=16.7747(7) Å, α=61.505(2)°, β=68.968(2)°, γ=80.205(3)°, V=3014.6(3) Å^3, Z=2, ρ_{calcd}=1.223 g cm^{-3}, F_{000}=1192, Mo Kα radiation, λ=0.71073 Å, T=173(2) K, $2\theta_{max}$=21.81°, 34,184 reflections were collected, 7172 were unique (R_{int}=0.0292). Final GoF=1.036, R_1=0.0788, wR_2=0.2109, R indices based on 5467 reflections with $I>2\sigma(I)$. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located through difference mapping or calculated positions and were refined isotropically. The somewhat aberrant U_{eq} values for C49 and C56 are likely attributable to disorder in the alkyl side chains where they reside.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council (NSERC) of Canada for funding (Discovery Grant). K.E.S. and

A.J.G. thank NSERC for graduate scholarships. We are also grateful to Brian Patrick and Jonathan Chong for assistance with the X-ray crystallography.

Supplementary data

Supporting spectra are available for this article. CCDC 742116–742118 contain the crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK (fax: +44 1223 336 033; or email: deposit@ccdc.cam.ac.uk)). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.094.

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