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Synthesis, X-ray Structure, and Self-Assembly of Functionalized Bis(2,2′:6′,2″-terpyridinyl)arenes

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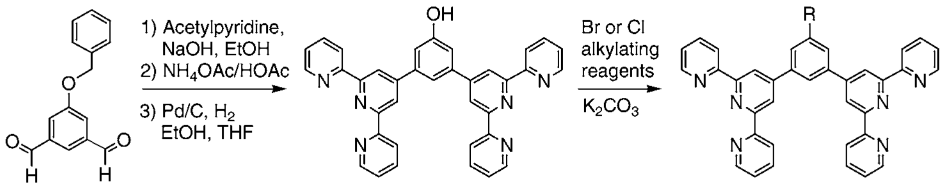
ABSTRACT

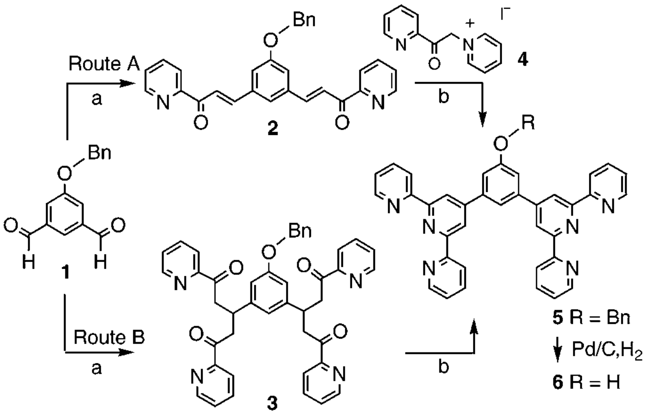


***meta*-Bis(terpyridinyl)phenol has been synthesized from *O*-benzyl-3,5-di(formyl)phenol in three steps. Its alkylation afforded a series of bisterpyridinylarenes, which can be self-assembled to afford the corresponding hexametallomacrocycles possessing Fe(II), Zn(II), or Ru(II) connectivity.**

Terpyridines[1] have found application in many fields such as luminescent materials,[2] molecular biology,[3−5] medical diagnostics and action sensors,[4] self-assembly,[5] preorganized molecular devices,[6] and photoactive molecular-scale wires.[7] More recently, linear and dendritic bisterpyridine complexes have played a fundamental role in supramolecular polymers, nonlinear optical materials, and nanosciences.[8,10−13] Thus, the terpyridine ligand is ubiquitous in molecular construction.

Our synthetic strategy for hexamer self-assembly is based on *m*-bis(terpyridinyl)arenes possessing the critical 120° angle with respect to the two ligating moieties. Herein, we describe a facile synthesis of the pivotal 3,5-di(terpyridinyl)phenol (**6**; Scheme 1), which can be readily functionalized by alkylation. Previously, we reported 1-(methyl, bromo, and hydroxymethyl)-3,5,-bis(terpyridinyl)arenes, which are useful in the self- and directed-assembly[14,15] of homonuclear

Scheme 1. Synthesis of the Key 3,5-Di(terpyridinyl)Phenol **6** from Dienone or Tetraketone Intermediates[a]



[a] Route A: (a) 2.2 equiv of acetylpyridine/NaOH; (b) pyridinium salt **4**, $NH_4OAc/HOAc$. Route B: (a) 4.4 equiv of acetylpyridine/NaOH; (b) $NH_4OAc/HOAc$.

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10.1021/ol0364529 CCC: $27.50

Fe(II) or Ru(II) metallomacrocycles (Figure 1) and their heteronuclear counterparts.[16]

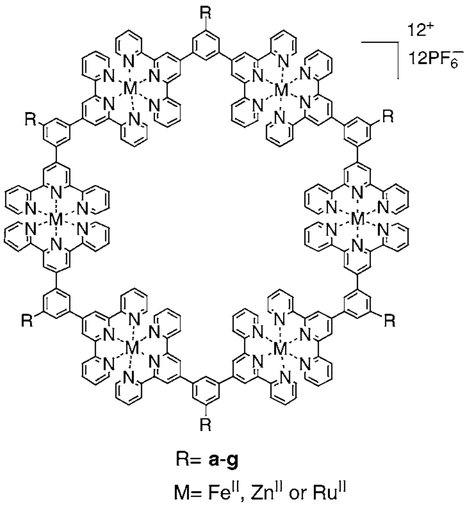

Figure 1. Hexameric metallomacrocycles by self- and directed-assembly from *O*-alkyl-3,5-bisterpyridinylphenol ligands.

To instill utilitarian functionality into these unique building blocks, the creation of 3,5-di(terpyridinyl)phenol was effected in three steps beginning with dialdehyde[17,18] **1**; two different routes (Scheme 1) were employed. In Route A, the addition of 2.2 equiv of 2-acetylpyridine to dialdehyde **1** in EtOH generated the pale yellow, crystalline dienone **2**. Without further purification, treatment of **2** with NH_4OAc and pyridinium salt **4** in AcOH afforded (12%) the desired benzyl-protected, bisligand **5**. Alternatively, the addition of 4.4 equiv of 2-acetylpyridine formed the tetraketone **3**, which was then reacted with excess NH_4OAc to give 22% of the same bisterpyridine **5** (see Supporting Information). These two methods have traditionally been used for over two decades in the synthesis of monoterpyridines; however, both methods are usually more efficient (ca. 50%). For the bisterpyridine derivatives, yields have approached 35% using a combination of prolonged reaction times, intermediate purification (i.e., **2** or **3**), and changing the solvent media from acetic acid to formamide.[19,20] The rationale in the simpler cases for the diminished conversions has been presented;[21,22] in these bisterpyridine formations, combinations of the proposed intermediates lead to further decline in yield.

Single crystals of dienone **2**, suitable for X-ray analysis, were grown from a mixed CH_2Cl_2 and EtOAc solvent (1:1 v/v); a triclinic structure was subsequently confirmed (Figure 2). Two molecules of the dienone were observed to be stacked 3.42 Å apart with respect to the distance between the two pyridine−benzene−pyridine planes. The benzyl rings are nearly perpendicular (88°) to the pyridine−benzene−pyridine plane, and the benzyl ring face-to-face distance averaged 3.53 Å.

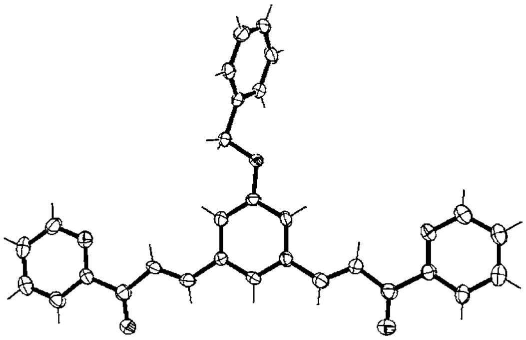

Figure 2. X-ray structure of 3,5-di(pyridylpropenonyl)-*O*-benzyl phenol **2**.

The structure of *O*-benzyl-3,5-di(terpyridinyl)phenol **5**, obtained from crystals grown in the mixed solvent $CHCl_3$ and EtOAc (2:1 v/v), was confirmed by X-ray analysis (Figure 3), which revealed one terpyridine to be coplanar with the phenol ring while the other terpyridine is twisted, relative to that plane, by 25°. The pyridine rings of the terpyridinyl moieties adapted an anti conformation typical of all such structures, and the benzyl and phenol planes are juxtaposed 41.8° relative to each other.

Deprotection of the phenol group in bisligand **5** (Scheme 1) was readily accomplished by hydrogenation[23] (10% Pd/C, 60 psi H_2) affording (87%) the desired alcohol **6**; notably, it was insoluble in $CHCl_3$. ^1H NMR (DMSO-d_6) spectra of alcohol **6** revealed the complete disappearance of the benzyl group absorptions at 7.57−7.39 ppm (C_6H_5) and 5.27 ppm (CH_2) along with the appearance of a new peak at 10.16 ppm (ArOH), thus supporting its formation. As well, upfield

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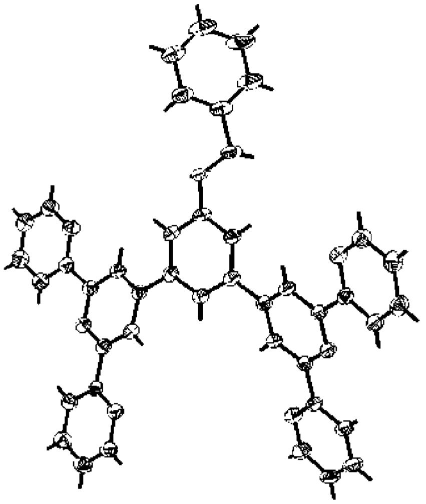
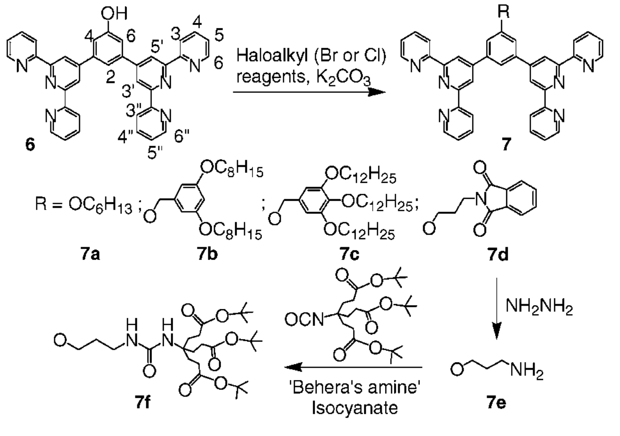


Figure 3. X-ray structure of *O*-benzyl-3,5-bis(terpyridinyl)-phenol **5**.

shifts of singlets from 7.59 to 7.44 ppm (2,6-Ar*H*) and from 7.95 to 7.77 ppm (4-ArH) were indicative of the transformation. Mass peaks (ESI-MS) at *m*/*z* 647.4 ($M^+ + H$, 100%) and *m*/*z* 579.2 amu ($M^+ + Na$, 100%) for **5** and **6**, respectively, further support the assignments.

The 3,5-di(terpyridinyl)phenol **6**, as a useful starting monomer, can be easily alkylated (Scheme 2) using a series of halogen-based reagents in the presence of K_2CO_3 using DMF as a solvent; in some cases, KI was added as a catalyst to afford (75−83%) the di(terpyridinyl)phenyl derivatives. Hence, an *n*-hexyloxy moiety was introduced to afford the white, crystalline **7a**, which greatly enhanced the solubility of both the ligand and corresponding hexametallomacrocycles whose properties and synthesis will be described elsewhere. Formation of ether **7a** was verified (^1H NMR) by a triplet at 4.17 ppm (OCH_2) and a mass peak (ESI-MS) appearing at *m*/*z* 641.5 amu ($M^+ + H$, 100%).

Scheme 2. Synthesis of *O*-Alkyl-di(terpyridinyl)phenol Derivatives



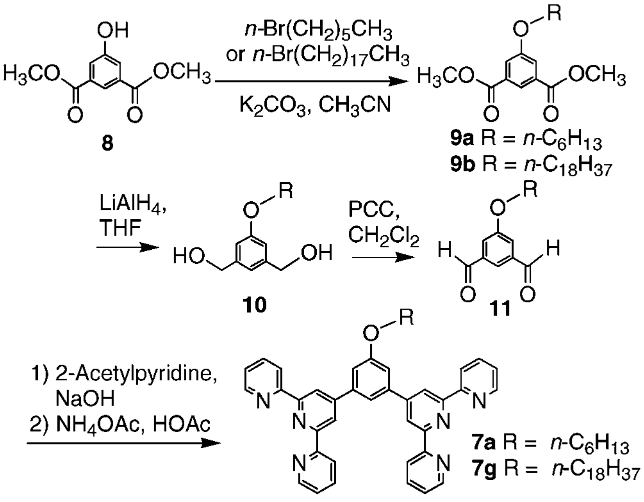
3,5-Di(octenyloxy)benzyl chloride was synthesized in two steps from 3,5-dihydroxybenzyl alcohol via alkylation using 8-bromo-1-octene. Subsequent treatment with $SOCl_2$ afforded the corresponding benzyl chloride, which, when reacted with **6**, afforded (82%) the white microcrystalline bisterpyridine **7b**. The ^1H NMR spectrum exhibited alkene absorptions at 5.88−5.78 and 5.04−4.94 ppm, as well as a triplet at 4.01 ppm (OCH_2) and singlet at δ 5.22 ppm (OCH_2Ar); ESI-MS data also confirmed the structure with mass peaks at *m*/*z* 899.6 ($M^+ + H$) and *m*/*z* 921.6 amu ($M^+ + Na$, 100%).

Attachment of the known, more lipophilic trisdodecyloxybenzyl group under similar conditions afforded **7c**, whose ^1H NMR spectrum exhibited similar absorption patterns, and ESI-mass data [*m*/*z* 1200.9 amu ($M^+ + H$, 100%)] confirmed the structure.

Treatment of phenol **6** with 3-bromopropyl phthalimide gave rise to the protected amine **7d**, which was subsequently deprotected by treatment with hydrazine to give the free amine **7e**. Conformation of the structure was supported (^1H NMR) by the disappearance of signals assigned to the phthalimide moiety and ESI mass data of the precursor **7d**, which showed a signature peak at 766.4 amu ($M^+ + Na$, 100%). Bisterpyridine **7f** possessing a triester dendron connected by urea functionality was generated (75%) by treatment of amine **7e** with the commercially available isocyanate[24,25] of Behera's amine. Characterization (^{13}C NMR) included the observation of two new signals at 173.1 and 157.5 ppm, corresponding to the ester and urea carbonyl moieties, respectively. The structure was further confirmed by the appearance in ESI-MS spectrum of a peak at *m*/*z* 1077.7 amu ($M^+ + Na$, 100%).

The second method to produce the desired *O*-alkyl-3,5-di(terpyridinyl)phenols was accomplished beginning with the phenolic diester **8** in five-steps.

Scheme 3. Synthesis of *O*-Alkyl-di(terpyridinyl)phenol Derivatives Directly from 3,5-Di(methoxycarbonyl)phenol **8**



Alkylation of **8** with either the C_6 or C_{18} alkyl halide gave the corresponding ethers, which were next reduced ($LiAlH_4$)

to the bishydroxymethyl derivatives (**10a** and **b**) in the anticipated high overall yields. Conversion to bisaldehydes **11a** and **b** was then accomplished (61−68%) by oxidization (pyridinium chlorochromate, PCC).

In the final two steps, aldehydes **11a** and **b** were each transformed to oily terpyridine intermediates via reaction with 2-acetylpyridine and, without the purification of intermediates, were treated with a large excess (20X) of NH_4OAc/HOAc and refluxed 4−8 h, to afford black solutions; workup and column chromatography (Al_2O_3) afforded (15−22%) pale yellow solids **7a** and **7g**. Both alkoxy derivatives were confirmed by NMR and ESI MS [*m*/*z* 641.5 amu ($M^+ + H$, 100%) and *m*/*z* 809.7 amu ($M^+ + H$, 100%) for **7a** and **7g**, respectively].

In a preliminary experiment, reaction of ligand **7a** with 1 equiv of $RuCl_3 \cdot nH_2O$ under reducing conditions (*N*-ethylmorpholine) afforded, via self-assembly, the desired hexameric, metallomacrocycle [Figure 1; R = *n*-C_6CH_{13}, M = Ru(II); 41% after column chromatography (SiO_2) eluting with H_2O/MeCN/KNO_3 (ratio of 1:7:1)]. Following exchange of the counterions to PF_6^-, the structure was confirmed by its ^1H NMR spectrum, which possessed a characteristic triplet absorption at 4.50 ppm (OCH_2) and a singlet at 9.28 ppm indicative of the 3′,5′-Py*H*. MALDI-TOF mass spectrometry showed peaks at *m*/*z* 7055.59 [$M^+ - 1PF_6^-$], 6911.03 [$MH^+ - 2PF_6^-$], and 6766.43 amu [$MH^+ - 3\ PF_6^-$]. Notably, this 12^+ charged hexamer possesses significantly enhanced solubilities in common organic solvents such as MeCN, acetone, DMSO, and $CHCl_3$, in contrast to that of nonalkylated metallohexamers. The analogous Fe(II) hexamer [Figure 1, R = *n*-C_6H_{13}, M = Fe(II)] was also prepared (91%) by a one-pot self-assembly method via reaction of the bisligand **7a** with $FeCl_2$.

In conclusion, 3,5-di(terpyridinyl)phenol has been synthesized and transformed to utilitarian derivatives for self-assembly to metallohexamacrocycles using Fe(II) and Ru(II). An alternative route, using 3,5-di(methoxy-carbonyl)phenol, has generated a five-step route to *O*-alkyl-3,5-di(terpyridinyl)phenols. The structures of these monomers were characterized by means of ^1H and ^{13}C NMR, as well as mass spectrometry. Experiments in further self-assembly are currently ongoing.

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Supporting Information Available: Synthetic procedures, spectral data, and crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

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