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Synthesis of {323}-*p*-Octiphenyls: Orthogonal Functionalization along a Rigid-Rod Scaffold for Refined Supramolecular Architecture

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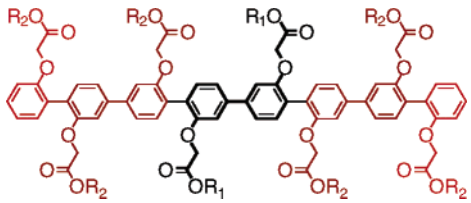
ABSTRACT



The synthesis of *p*-octiphenyls carrying orthogonal *tert*-butyl esters in the peripheral positions 1^2, 2^2, 3^3, 6^2, 7^3, and 8^2 and either *p*-methoxybenzyl or benzyl ester substituents in the central positions 4^2 and 5^3 is described. Resolution-enhanced HSQC/HMBC two-dimensional NMR spectroscopy is implemented as an attractive method for the complete characterization of complex *p*-oligophenyl scaffolds.

Conventional rigid-rod β-barrels, the first and only artificial β-barrels known to date, are versatile barrel-stave supramolecules composed of *p*-oligophenyl staves and β-sheet hoops (Figure 1).[1] The *p*-oligophenyl staves serve to preorganize the supramolecular architecture, and the β-sheet hoops serve to position functional groups at both the outer and the inner barrel surface. Internal barrel design was developed to construct rigid-rod β-barrels that function as variably regulated ion channels and pores,[2] supramolecular hosts,[1−4] enzyme sensors,[3] and catalysts.[4] These studies identified the confined and oriented "nanospace" within multifunctional rigid-rod β-barrel pores as a superb platform to couple, steer, and detect chemical processes.

In view of these attractive applications, the limitation to one peptide sequence per barrel is bothersome (Figure 1). In this Letter, we report synthetic access to {323}-*p*-octiphenyls **1** with orthogonal protecting groups OPG_1 and OPG_2 along their scaffold. This refined rigid-rod scaffold is expected to serve as a universal precursor for supramolecular barrel-stave architecture with distinct domains. Removal of OPG_2 in {323}-rod **1** and coupling of the produced six peripheral carboxylic acids with the N terminus of peripheral peptides followed by deprotection of two central carboxylic acids and attachment of central peptides should, for example, afford a {323}-conjugate **2** that self-assembles into a rigid-rod {323}-β-barrel with active-sites contracted to the middle of the supramolecule.

Several attractive routes to oligophenyls and related rigid rods exist.[2,5] Access to target molecule **1** was envisioned using Suzuki coupling[6] of central biphenyl subunits with *p*-methoxybenzyl (*p*MeOBn) and benzyl (Bn) protection,

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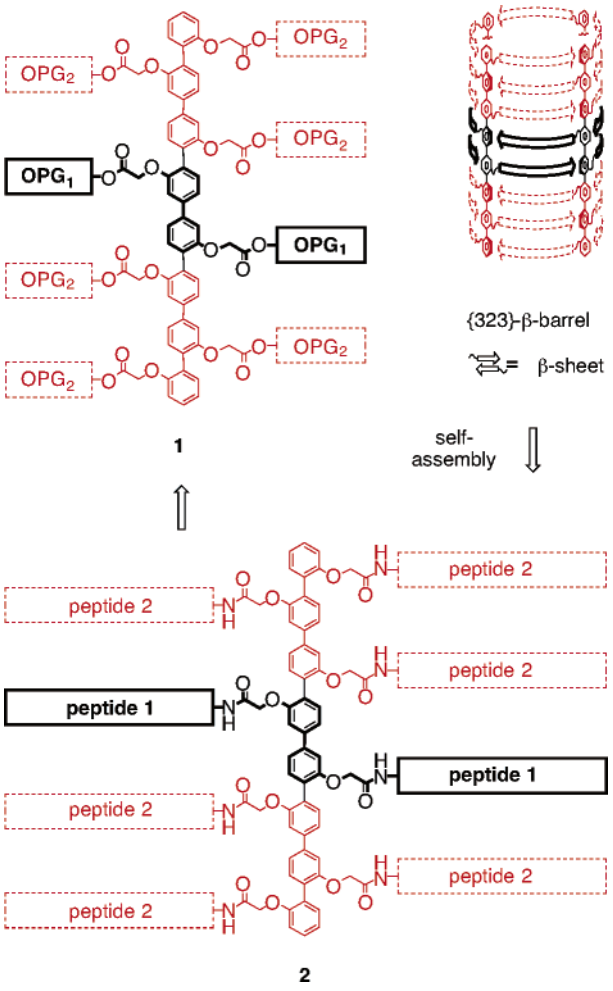

Figure 1. {323}-*p*-Octiphenyl **1** with orthogonal protection groups (OPGs) along the scaffold is synthesized to secure access to, e.g., rigid-rod {323}-*β*-barrels with distinct central (solid) and peripheral *β*-sheet domains (dotted) by selective introduction of peptide 1 and 2 in conjugate **2**.

respectively, and two peripheral *p*-terphenyl subunits with *tert*-butyl protection. The former can be removed by catalytic hydrogenation and are more (Bn) or less (*p*MeOBn) stable toward TFA; the latter is cleaved by TFA but resists catalytic hydrogenation.[7]

The central biphenyls **3** and **4** were accessible from commercial biphenyl **5**. Transformation of **5** into diiodide **6** and diphenol **7** as previously described[4b,5c] followed by introduction of di-*tert*-butyl esters in **8**, esterolysis, and esterification of diacid **9** with *p*MeOBn alcohol gave the desired di-*p*MeOBn-ester **3** (Scheme 1). Di-Bn-ester **4** was directly accessible from diphenol **7** by reaction with the commercially available benzylbromoacetate.

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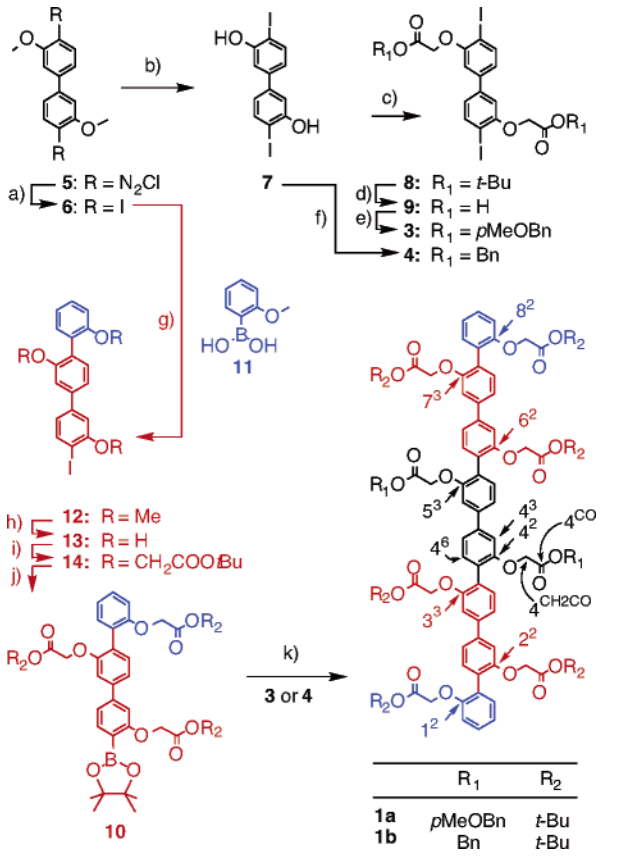
Scheme 1[a]



[a] Conditions: (a) KI, 70%;[4b] (b) BBr_3, 100%; (c) *tert*-butylbromoacetate, Cs_2CO_3, 90%; (d) TFA; (e) *p*-methoxybenzyl alcohol, EDC, HOBt, 70% from **8**; (f) benzylbromoacetate, Cs_2CO_3, 84%; (g) $Pd(PPh_3)_4$, K_2CO_3, acetone/water 5:1, 37%; (h) BBr_3, 92%; (i) *tert*-butylbromoacetate, Cs_2CO_3, 90%; (j) pinacolborane, $PdCl_2$(dppf), TEA, acetonitrile; (k) $Pd(PPh_3)_4$, K_2CO_3, DMSO, 48% **1b** from **14**.

The same starting material **5** was used to prepare the peripheral *p*-terphenyl subunit **10**. Although routine conditions yielded the *p*-quarterphenyl as the main product, slow addition of the commercially available boronic acid **11** for controlled Suzuki coupling with excess biphenyl **6** instead afforded *p*-terphenyl **12** as the main product. Side chain introduction via triphenol **13** was unproblematic. Among several conditions tested to convert the tri-*tert*-butyl ester **14** into boronate **10**, pinacolborane (rather than bispinacolatodiboron), $PdCl_2$(dppf), and TEA in acetonitrile gave the best substrate conversion.[8] Because of its poor stability on silica, *p*-terphenyl **10** was used as a crude product without further purification and characterization. Suzuki coupling of central and terminal *p*-oligophenyls **3**/**4** and **10**, respectively, was more challenging because of the instability of benzyl esters in basic protic solvents.[7] Combining insights from different reports, the best couplings were found using $Pd(PPh_3)_4$ and 6 equiv of K_2CO_3 in DMSO at 80 °C to afford pure {323}-*p*-octiphenyl **1b** in 48% yield.[6,9] Coupling

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conditions for {323}-rod **1a** were not optimized because orthogonality of Bn/*t*-Bu pairs was found to be superior compared to *p*MeOBn/*t*-Bu pairs. This identified rod **1b** as the precursor of choice for refined supramolecular architecture.

The characterization of refined oligomers by NMR spectroscopy is traditionally troublesome. Reminiscent of the spectra of polymers, similar chemical shifts of nearly identical nuclei result in poor peak separation. Satisfactory interpretation of the ^{1}H as well as the ^{13}C NMR spectrum of {323}-*p*-octiphenyl **1a** was possible only using a combination of traditional experiments (DEPT, COSY, and so on) together with the less common aliased versions of HSQC and HMBC NMR spectroscopy.[10] Without going into details,[10,11] this underappreciated method provides rapid access to high-resolution, within a few hertz per point, in the carbon dimension of the two-dimensional spectra.

High-resolution (aliased) HSQC and HMBC NMR spectroscopy is based on a violation of the Nyquist condition. In the present case, the spectral width was optimized on the basis of carbon chemical shifts of **1a** using the program "simple alias"[10c] and set to 325.7 and 970.2 Hz for the HSQC and HMBC, respectively. The resulting digital resolution of 0.96 and 1.88 Hz/point reduced the required number of time increments by a factor 40 and 18, respectively. The non-standard scale in the carbon dimension of the resulting "aliased" spectra (Figure 2c−f) was converted readily into the conventional ppm scale (Figure 2g).

Probably the most challenging aspect of the spectra of {323}-*p*-octiphenyl **1a** concerns the signals of carbons 2^2, 3^3, and 4^2 in the rigid-rod scaffold. Separated by only 4.6 Hz, these signals could not be resolved by conventional HMBC spectroscopy under comparable conditions (Figure 2b).[11] With the high-resolution of the aliased NMR spectrum, however, the fine structure of signals under the effect of scalar coupling was resolved. Symmetry considerations then permitted the identification of the center of each fine structure unambiguously (Figure 2d,e, blue lines). From these centers, identification of both chemical shifts and connectivities was straightforward (Figure 2, gray lines). For example, hydrogen 4^6 connected to carbon 4^2 (Figure 2, a→c→d), which in turn connected to hydrogen 4^3 in the scaffold (Figure 2, d→e→c→a) as well as hydrogen 4^{CH_2CO} in the side chain (Figure 2, d→f→c→a).

The synthesis of {323}-*p*-octiphenyl **1** rigid-rods reported herein secures access to refined supramolecular {323}-architecture, including {323}-*β*-barrels (Figure 1). The synthetic strategy is compatible with continuing refinement at the rod termini, including {12221}-*p*-octiphenyls, terminal

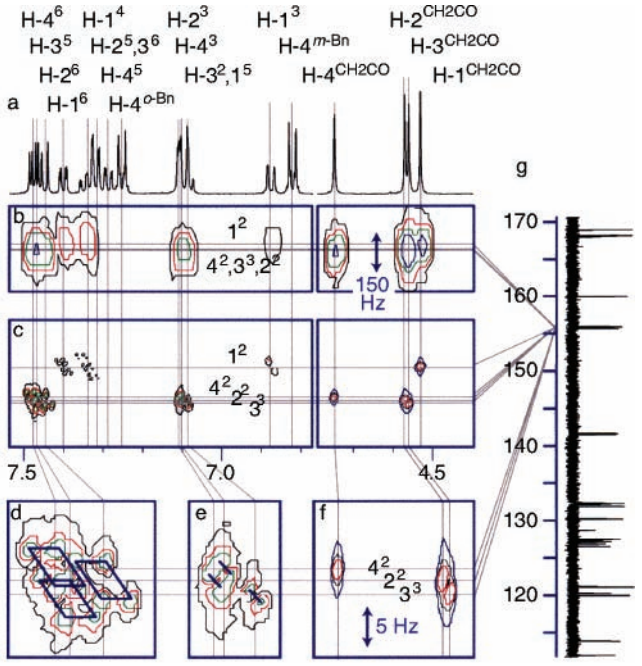

Figure 2. Resolution of three signals in the ^{13}C NMR spectrum of {323}-*p*-octiphenyl **1a** (i.e., 2^2, 3^3, 4^2) that are separated by only 4.6 Hz using aliased HMBC NMR spectroscopy (for the full spectrum, see Figure S2). (a) ^{1}H NMR and sections of (b) conventional and (c) aliased HMBC NMR with enlargements (d−f), signal fine structure (bold lines), correlations (gray lines), and transformation into the ^{13}C NMR scale (g).

extension from position 1^4 and 8^4, and so on. Another attractive perspective is to compare the 1^2,2^2,3^3,4^2,5^3,6^2,7^3,8^2-motif of {323}-*p*-octiphenyls **1** and the 1^3,2^3,3^2,4^3,5^2,6^3,7^2,8^3-sequence in conventional "staves" to assess, for the first time, the influence of the substitution pattern of isomeric "staves" on formation and stability of rigid-rod *β*-barrels. Studies along these lines are ongoing and will be reported in due course.[11]

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Supporting Information Available: Full details for all new compounds and ^{1}H−^{1}H−DQF−COSY and aliased HMBC NMR spectra of **1a** . This material is available free of charge via the Internet at http://pubs.acs.org.

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