ORGANIC LETTERS

2000
Vol. 2, No. 1
37−39

# Synthesis of Multiply Substituted, Ion Channel Forming Octi(*p*-phenylene)s: Theme and Variations

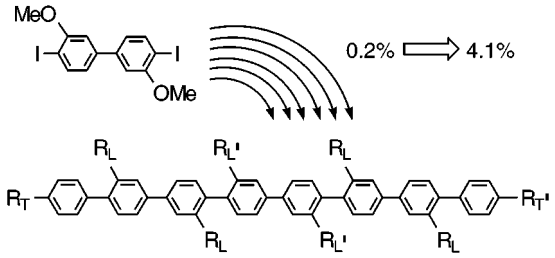
**Fabien Robert,[†] Jean-Yves Winum,[†,‡] Naomi Sakai,[†,‡] David Gerard,[†] and Stefan Matile*[,†,‡]**

*Department of Organic Chemistry, University of Geneva, CH-1211 Geneva, Switzerland, and Department of Chemistry, Georgetown University, Washington, D.C. 20057*

*stefan.matile@chiorg.unige.ch*

**Received November 2, 1999**

## ABSTRACT




**To facilitate the access to unique models for biological processes, we examined six different synthetic routes to octi(*p*-phenylene) rods with lateral and terminal substitutents $R_L$ and $R_T$. This systematic study allowed us to increase to overall yield for the synthesis of a new class of oligo(*p*-phenylene) ionophores about 20 times and to provide general insights into the practicability of synthetic routes to multiply substituted molecular rods.**

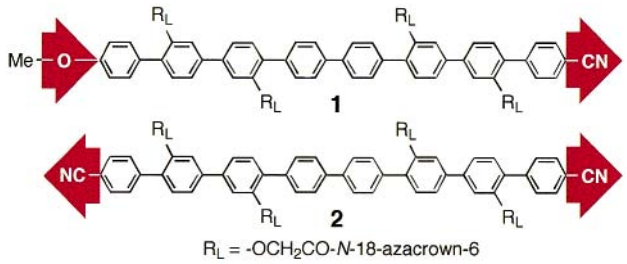
Push−pull octi(*p*-phenylene) rod **1** but not the structurally almost identical pull-pull rod **2** was recently found to recognize and depolarize polarized biomembranes.[1] Because this finding identified a new route toward cell membrane recognition,[2] voltage-dependent ion channel formation,[3] and, perhaps, biomimetic antibiotics that we hope can be used to resist microbial resistance,[4] we felt that increased efforts to improve the unsatisfactory synthesis of multiply substituted oligo(*p*-phenylene) rods were appropriate.[5]

Push−push rod **3** was selected as a target molecule for this study for the following reasons. It can be converted

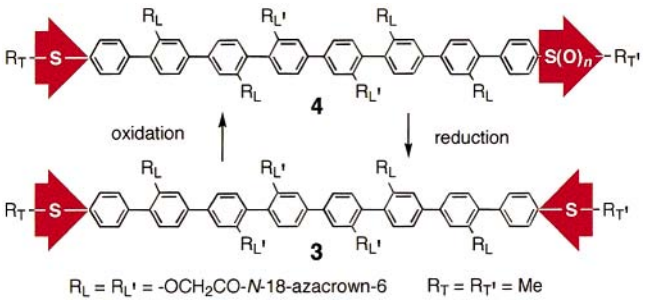
[†] University of Geneva.
[‡] Georgetown University.

(1) Winum, J.-Y.; Matile, S. *J. Am. Chem. Soc.* **1999**, *121*, 7961.
(2) Ghebremariam, B.; Sidorov, V.; Matile, S. *Tetrahedron Lett.* **1999**, *40*, 1445 and references therein.
(3) Reviews on nonpeptide ion channels and channel models: (a) Gokel, G. W.; Murillo, O. *Acc. Chem. Res.* **1996**, *29*, 425. (b) Fyles, T. M.; van Straaten-Nijenhuis, W. F. In *Comprehensive Supramolecular Chemistry;* Reinhoudt, N. D., Ed.; Elsevier: Oxford, 1996; Vol. 10, p 53. (c) Voyer, N. *Top. Curr. Chem.* **1996**, *184*, 1. Some recent references: (d) Qi, Z.; Sokabe, M.; Donowaki, K.; Ishida, H. *Biophys. J.* **1999**, *76*, 631. (e) Abel, E.; Maguire, E. M.; Murillo, O.; Suzuki, I.; DeWall, S. L.; Gokel, G. W. *J. Am. Chem. Soc.* **1999**, *121*, 9043. (f) Otto, S.; Osifshin, M.; Regen, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 7276. (g) Li, C.; Budge, L. P.; Driscoll, C. D.; Willardson, B. M.; Allman, G. W.; Savage, P. B. *J. Am. Chem. Soc.* **1999**, *121*, 931. (h) Fritz, M. G.; Walde, P.; Seebach, D. *Macromolecules* **1999**, *32*, 574. (i) de Mendoza, J.; Cuevas, F.; Prados, P.; Meadows, E. S.; Gokel, G. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1534. (j) Fyles, T. M.; Loock, D.; Zhou, X. *J. Am. Chem. Soc.* **1998**, *120*, 2997. (k) Meillon, J.-C.; Voyer, N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 967. (l) Pechulis, A. D.; Thompson, R. J.; Fojtik, J. P.; Schwartz, H. M.; Lisek, C. A.; Frye, L. L. *Bioorg. Med. Chem.* **1997**, *5*, 1893. (m) Wagner, H.; Harms, K.; Koert, U.; Meder, S.; Boheim, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2643. (n) Tanaka, Y.; Kobuke, Y.; Sokabe, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 693.
(4) (a) Niccolai, D.; Tarsi, L.; Thomas, R. *Chem. Commun.* **1997**, 2333. (b) Travis, J. *Science* **1994**, *264*, 360, references therein and in this *Science* issue. (c) Bechinger, B. *J. Membr. Biol.* **1997**, *156*, 197. (d) Wieprecht, T.; Dathe, M.; Beyermann, M.; Krause, E.; Maloy, W. L.; MacDonald, D. L.; Bienert, M. *Biochemistry* **1997**, *36*, 6124. (e) Saberwal, G.; Nagaraj, R. *Biochim. Biophys. Acta* **1994**, *1197*, 109. (f) Lear, J. D.; Schneider, J. P.; Kienker, P. K.; DeGrado, W. F. *J. Am. Chem. Soc.* **1997**, *119*, 3212. (g) Juvvadi, P.; Vunnam, S.; Merrifield, R. B. *J. Am. Chem. Soc.* **1996**, *118*, 8989. (h) Oiki, S.; Koeppe II, R. E.; Andersen, O. S. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 2121.

10.1021/ol991210n CCC: $19.00 
**Published on Web 12/15/1999**

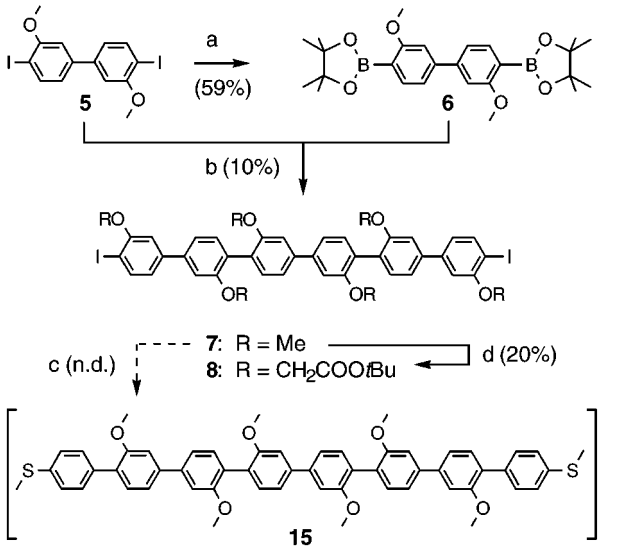



directly into push−pull rod **4** by partial sulfide oxidation, allowing, *in principle*, functional switching between push−push, push−pull (and pull−pull) systems in situ by simple redox chemistry.[6,7] These terminal $\pi$ donors and acceptors are further compatible with future elaboration of the terminal side chains $R_T$ and $R_{T'}$.[4] Moreover, octi(*p*-phenylene) **4** contains six lateral azacrowns compared to four in push−pull rod **1**. This addition of two central ion-conducting "relays" is expected to improve the capacity to mediate ion transport across biomembranes.[3]




The route previously employed to synthesize octi(*p*-phenylene) **2** consists of two distinct sequences: The octi(*p*-phenylene) rod is constructed in three steps including two Suzuki couplings; elaboration of the lateral side chains in four steps follows.[1,8] To synthesize push−push rod **3** along this previously established route, iodide **5** was converted into boronic acid pinacol ester **6** (Scheme 1). The key intermediate of this route, the terminally iodinated hexamer **7**, was subsequently obtained in 5% yield by Suzuki coupling[9] of bianisol **5** with dioxaborolane **6** under the conditions reported previously.[1,8] The yield of this conversion could be significantly increased to 10% by minimizing the undesired competing polymerization with very slow, continuous addition of dimer **5** to the reaction mixture over a period of 24 h. However, the synthesis of **3** along this route could not be completed because of the near intractability of sexi(*p*-phenylene) **7** (Table 1, variation 1).

**Scheme 1**[a]




[a] (a) 4,4,5,5-Tetramethyl-[1,3,2]-dioxaborolane, $PdCl_2$(dppf); (b) $PdCl_2$(dppf), $Na_2CO_3$ (9% from **5** without isolation of **6**); (c) *p*-thiomethylphenylboronic acid, Pd($PPh_3$)$_4$; (d) 1. $BBr_3$; 2. *tert*-butyl bromoacetate, $Cs_2CO_3$. nd = not determined.

**Table 1.** Six Routes to Octi(*p*-phenylene)s

| variation | yield (%)[a] | route[b] | bi[c] | sexi[c] | octi[c] |
|---|---|---|---|---|---|
| 1 | n.d. | **5** → **6** → **7** → **15** → **9** → **3** | 1 | 1 | 5 |
| 2 | 0.2 | **5** → **6** → **7** → **8** → **9** → **3** | 1 | 3 | 3 |
| 3 | 0.4 | **5** → **6** → **7** → **8** → **10** → **3** | 1 | 5 | 1 |
| 4 | 0.8 | **5** → **11** → **13** → **8** → **9** → **3** | 3 | 1 | 3 |
| 5 | 2.1 | **5** → **11** → **13** → **8** → **10** → **3** | 3 | 3 | 1 |
| 6 | 4.1 | **5** → **11** → **12** → **14** → **10** → **3** | 5 | 1 | 1 |

[a] Overall yield from **5**. Biphenyl **5** was obtained in 70% yield from fast blue B salt (Aldrich).[8d] [b] See schemes and Supporting Information for structures and conditions. [c] Number of biphenyl (bi), sexiphenyl (sexi), and octiphenyl (octi) intermediates synthesized along this route.

We have previously reported that lateral *tert*-butyl glycolate (but not methyl glycolate) side chains dramatically improve the solubility of oligo(*p*-phenylene)s.[8b] This was also true for hexamer **7** (Scheme 1). Successful conversion of the "solubilized" hexamer **8** into octamer **9** followed by deprotection and PyBOP-mediated[10] coupling with 12-azacrown-6 gave push−push rod **3** in 0.2% overall yield from **5** (Scheme 2 and Table 1, variation 2). Attachment of the

(5) For excellent, very recent reviews on synthesis and physical properties of rigid-rod molecules, see: (a) Schwab, P. F. H.; Levin, M. D.; Michl, J. *Chem. Rev.* **1999**, *99*, 1863. (b) Berresheim, A. J.; Müller, M.; Müllen, K. *Chem. Rev.* **1999**, *99*, 1747. (c) Martin, R. E.; Diederich, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1351.

(6) For a methionine-based redox-"switch" of peptide conformation, see: Schenck, H. L.; Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 12487.

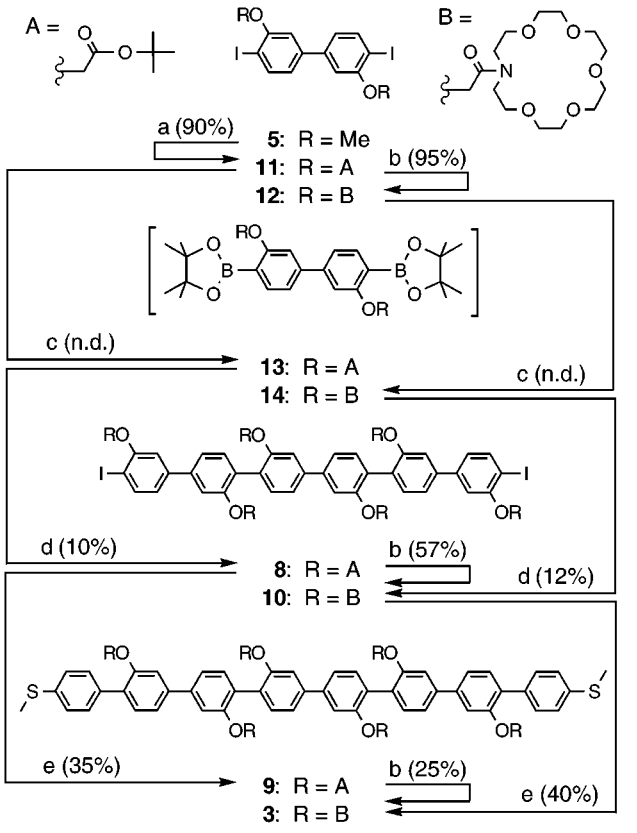
(7) Preliminary results corroborated that push−push rod **3** can be partially oxidized with 2 equiv of potassium hydrogen persulfate in a 1:1:1 mixture of THF, MeOH, and water to give push−pull rod **4** ($n$ = 2) in 50% yield. Compare Supporting Information and Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

(8) (a) Baumeister, B.; de Dios, A. C.; Matile, S. *Tetrahedron Lett.* **1999**, *40*, 4623. (b) Sakai, N.; Majumdar, N.; Matile, S. *J. Am. Chem. Soc.* **1999**, *121*, 4294. (c) Ni, C.; Matile, S. *Chem. Commun.* **1998**, 755. (d) Ghebremariam, B.; Matile, S. *Tetrahedron Lett.* **1998**, *39*, 5335. (e) Sakai, N.; Brennan, K. C.; Weiss, L. A.; Matile, S. *J. Am. Chem. Soc.* **1997**, *119*, 8726.

(9) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Giroux, A.; Han, Y.; Prasit, P. *Tetrahedron Lett.* **1997**, *38*, 3841.

(10) Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205.

**Scheme 2**[a]




[a] (a) 1. $BBr_3$; 2. *tert*-butyl bromoacetate, $Cs_2CO_3$; (b) 1. TFA/$CH_2Cl_2$, 2. 18-azacrown-6, PyBOP, DIPEA; (c) 4,4,5,5-tetramethyl[1,3,2]dioxaborolane, $PdCl_2$(dppf); (d) $PdCl_2$(dppf), $Na_2CO_3$ (yields from **11** / **12**); (e) *p*-thiomethylphenylboronic acid, Pd($PPh_3$)$_4$. nd = not determined.

lateral crowns on the hexamer level to give diiodide **10** allowed for the doubling of the overall yield for **3** and proved that, in this case, the presence of crown ethers is fully compatible with the conditions of Suzuki coupling (Table 1, variation 3).

Partial and complete elaboration of the lateral side chains *before* construction of the oligo(*p*-phenylene) scaffold was feasible in high yields (Scheme 2). Giroux−Suzuki coupling[9] with diiodides **11** and **12** under high dilution conditions gave hexamers **8** and **10**, respectively, as main reaction products. However, the intermediate dioxaborolanes **13** and **14** could not be isolated due to their instability under the purification conditions. Completion of the synthesis of **3** from hexamers **8** and **10**, respectively, gave overall yields of up to 4.1% (Scheme 2 and Table 1, variations 4−6).

Analysis of the six variations of the synthesis of push−push rod **3** revealed several trends (Table 1). Namely, the overall yield for the synthesis of multiply substituted oligo(*p*-phenylene)s increased parallel to the number of reactions performed on the dimeric (variations 1−6) and, less preferable, on the hexameric level (variations 1−3). This trend related directly to the reactions involved in side chain construction (90−95% for dimers, 20−57% for hexamers, nd-25% for octamers, Scheme 2), while the yields for scaffold elongation were practically independent of lateral substitution. The surprisingly modest effect of "solubilizing" side chains on the outcome of palladium-catalyzed arene−arene C−C bond formations was unexpected in light of established rules for the synthesis of rigid-rod oligomers.[5] These two observations lead to the seemingly counterintuitive conclusion that complete elaboration of lateral side chains before arene oligomerization is preferable despite consistently low yields during the latter synthetic sequence.

In summary, we here reported six variations of the synthesis of new, multiply substituted oligo(*p*-phenylene) ionophores to secure perfect synthetic access to molecular rods with variable permanent dipole and fixed charges designed to recognize and depolarize bacterial cell membranes. This systematic study revealed that high yield side chain construction before low yield oligomerization results in more than 20 times higher overall yields compared to the inverse sequence. Ongoing studies on the biological activity of push−push and push−pull rods **3** and **4** will be reported in due course.[11]

**Acknowledgment.** We thank the Swiss NSF (21-57059.99), the NIH (GM56147), and Suntory Institute for Bioorganic Research (SUNBOR Grant) for financial support of this work.

**Supporting Information Available:** Experimental procedure and characterization for compounds **3**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991210N

(11) Preliminary results with unpolarized vesicles (EYPC-SUVs) indicated that hexacrowns **3**/**4** are up to *100 times more active* than tetracrowns **1**/**2** under the conditions previously employed to characterize **1**/**2**.[1] Preliminary results in black lipid membranes (EYPC-BLMs) revealed single channel currents in the range of 1−40 pA at high voltages. Detailed studies on structure and activity of **3**/**4** and their now accessible positively charged analogues in SUVs, BLMs, and bacteria are ongoing.