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6,6′-Dibromo-4,4′-di(hexoxymethyl)-2,2′-bipyridine: A New Solubilizing Building Block for Macromolecular and Supramolecular Applications

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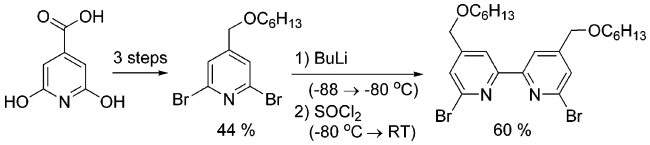
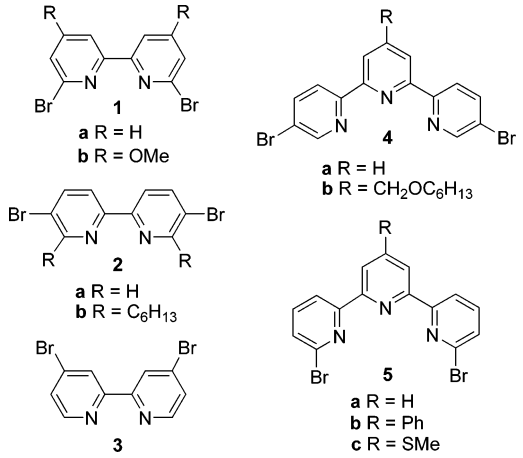


Although brominated bipyridines and terpyridines are highly desirable synthetic building blocks for both ligand design and macro- or supramolecular applications, few such synthetic precursors have been reported that include much-needed solubilizing groups. Reported here is an inexpensive route to 2,6-dibromo-4-(hexoxymethyl)pyridine from citrazinic acid with an overall yield of 44% and its efficient conversion (60%) to 6,6′-dibromo-4,4′-di(hexoxymethyl)-2,2′-bipyridine via oxidative coupling.

Dibromo-2,2′-bipyridines (Chart 1, **1**−**3**) and dibromo-2,2′;6′,2″-terpyridines (**4** and **5**) are highly desirable synthetic building blocks for a wide variety of ligand designs,[1] as well as macromolecular[2,3] and supramolecular applications.[1a,2−6] The incorporation of these units allows the production of a variety of macromolecular systems capable of binding metal ions. Such systems, however, often suffer from solubility problems and thus there is a need for synthetic units containing flexible side chains in order to render these rigid frames soluble in common organic solvents.[5] Unfortunately, the literature is limited in the synthesis of such dihalo building blocks containing additional functional groups and currently only two examples have been reported (**2b**[3] and **4b**[1d]) that contain solubilizing side chains.

CHART 1. Dibromobipyridines and Dibromoterpyridine Building Blocks



In the application of **1a** as a building block for larger, more complicated systems, we found that solubility quickly became a limiting factor that prohibited the successful production of the desired targets. Thus, it was realized that a functionalized analogue containing solubilizing side chains was required in order to maximize the versatility of the 6,6′-dibromo-2,2′-bipyridine unit as a useful building block. The unfunctionalized parent **1a** has been produced from 2,6-dibromopyridine by a variety of different coupling methods,[7−9] which are summarized in Table 1. The methoxy analogue **1b** has also been produced via oxidative coupling of 2,6-dibromo-4-methoxypyridine, using the $CuCl_2/O_2$ method shown in entry 2.[10] As far as we are aware, compound **1b** is currently the only reported example of a functionalized analogue of **1a**. Here we report an improved synthesis (3 steps, 44% overall yield) of the known compound 2,6-dibromo-4-(hexoxymethyl)pyridine (**7**), and its oxidative coupling to produce the desired functionalized analogue 6,6′-dibromo-4,4′-di(hexoxymethyl)-2,2′-bipyridine (**8**) in yields up to 60%.

To produce an analogue of **1a** containing the desired solubilizing side chains, we began investigating the application of the coupling methods from Table 1 above to the coupling of the functionalized precursor **7**. In the process, the synthesis of precursor **7** was also significantly improved as shown in Scheme 1. The initial step involves the treatment of citrazinic acid (**9**) with $POBr_3$, which was generated in situ from a mixture of PBr_3, Br_2, and P_2O_5. No special equipment is required for the $POBr_3$ generation and the resulting product separation is very simple, giving yields comparable with the previous methods of Fallahpour (50−55%).[11] In addition, the in situ generation is considerably less expensive than the use of reagent grade $POBr_3$, which reduces the cost of producing intermediate **10** to ∼$1/g in comparison to ∼$7/g with the previous procedure. This reduc-

(1) For examples, see: (a) Bai, X.-L. B.; Liu, X.-D.; Wang, M.; Kang, C.-Q.; Gao, L.-X. *Synthesis* **2005**, 485. (b) Collin, J.-P.; Jouvenot, D.; Koizumi, M.; Sauvage, J.-P. *Inorg. Chem.* **2005**, *44*, 4693. (c) Hilmey, D. G.; Paquette, L. A. *J. Org. Chem.* **2004**, *69*, 3262. (d) Lehmann, U.; Henze, O.; Schluter, A. D. *Chem. Eur. J.* **1999**, *5*, 854. (e) Grosshenny, V.; Romero, F. M.; Zeissel, R. *J. Org. Chem.* **1997**, *62*, 1491. (f) Giblin, G. M.; Box, P. C.; Campbell, I. B.; Hancock, A. P.; Roomans, S.; Mills, G. I.; Molloy, C.; Tranter, G. E.; Walker, A. L.; Doctrow, S. R.; Huffman, K.; Malfroy, B. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1367. (g) Heller, M.; Schubert, U. S. *Synlett* **2002**, 751.

(2) Newkome, G. R.; Patri, A. K.; Holder, E.; Schubert, U. S. *Eur. J. Org. Chem.* **2004**, 235.

(3) (a) Maruyama, T.; Yamamoto, T. *Synth. Met.* **1995**, *69*, 553. (b) Maruyama, T.; Kubota, K.; Yamamoto, T. *Macromolecules* **1993**, *26*, 4055.

(4) Henze, O.; Lehmann, U.; Schluter, A. D. *Synthesis* **1999**, 683.

(5) Schubert, U. S.; Eschbaumer, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2892.

(6) Grave, C.; Schluter, A. D. *Eur. J. Org. Chem.* **2002**, 3075.

(7) Garber, T.; Rillema, D. P. *Synth. Commun.* **1990**, *20*, 1233.

(8) Parks, J. E.; Wagner, B. E.; Holm, R. H. *J. Organomet. Chem.* **1973**, *56*, 53.

(9) Uchida, Y.; Echikawa, N.; Oae, S. *Heteroat. Chem.* **1994**, *5*, 409.

(10) Neumann, U.; Vögtle, F. *Chem. Ber.* **1989**, *122*, 589.

(11) Fallahpour, R.-A. *Synthesis* **2000**, 1138.

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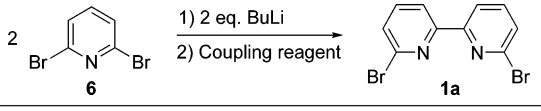
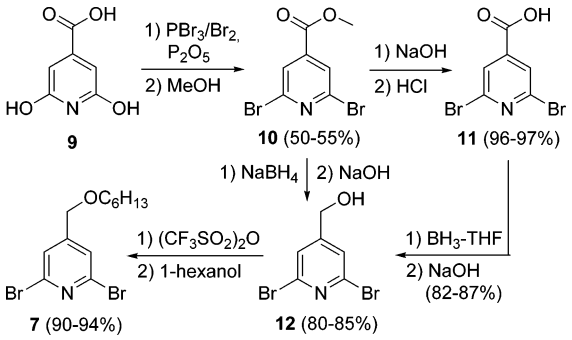
TABLE 1. Synthesis of 6,6′-Dibromo-2,2′-bipyridine



entry	coupling reagent	reported yield[a] (%)	ref
1	$CuBr/O_2$	72	7
2	$CuCl_2/O_2$	50	8
3	$SOCl_2$	51	9
4	$POCl_3$	35	9
5	PCl_3	5	9

[a] Yield based on 2,6-dibromopyridine.

SCHEME 1. Synthesis of 4-Hexoxymethyl-2,6-dibromopyridine (7)



tion in cost makes the routine production of multigram quantities of **10** quite feasible.

Initial attempts to reduce the methyl ester **10** directly to alcohol **12** via $LiAlH_4$ resulted in poor yields, as previously observed by Schluter[1d] and Schubert.[1g] Thus, while it added an additional synthetic step, it was found that saponification of **10** with aqueous NaOH to give acid **11** (96−97%), followed by borane reduction to give alcohol **12** (82−87%) gave significantly better yields. Revisiting the initial one-step reduction, however, revealed that changing the reducing agent from $LiAlH_4$ to $NaBH_4$ did allow the direction conversion of **10** to **12** in good yield (80−85%).[12] Finally, the hexyl functionality was then incorporated through a modification of Schluter's procedure[1d] to yield the desired 2,6-dibromo-4-(hexoxymethyl)pyridine (**7**) (90−94%). The overall yield of **7** from compound **9** was 44% in comparison to 19% with the previous conditions.[1d] This higher yield could be accomplished in as little as three steps, although there was no difference in the overall yield between the 3-step and 4-step routes.

Initial investigations of the oxidative coupling of **7** resulted in a mixture of products consisting primarily of the debrominated species 4,4′-di(hexoxymethyl)-2,2′-bipyridine (**13**). In addition, some byproducts indicated that deprotonation at the benzylic position was also a potential problem. As a result, it was decided to investigate the conditions of the initial lithiation step in more detail. To probe the competition between metal−halogen exchange and any competing deprotonation, the reaction was quenched with I_2 after lithiation and the resulting iodated products isolated (Scheme 2). The results of these studies are given in Table 2.

It was found that the literature conditions[7−9] for the monolithiation of **6** (Table 2, entry 1) gave rather poor results when

(12) Fallahpour, R.-A. *Synthesis* **2000**, 1665.

SCHEME 2. Species Produced during the Lithiation Studies

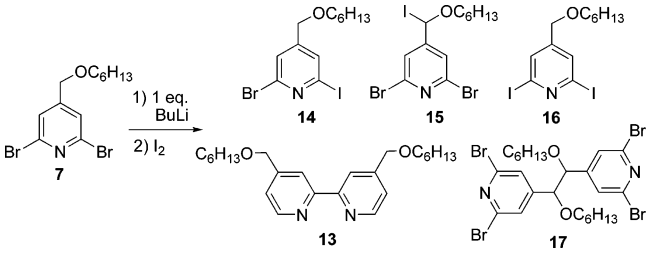
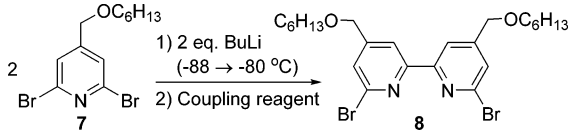


TABLE 2. Effect of Temperature on the Lithiation of Compound 7

entry	temp (°C)	time (min)	% yields of various products[a] 13[b]	14[c]	15[b]	16[c]	17
1	−40	20	40	27	4	∼1	trace
2	−80	15	-	73	13	∼4	∼1
3	−88 → −80	20	-	79	14	∼4	∼1
4	−90	50	-	67	14	∼3	∼1
5	−100	180	-	61	10	∼3	∼1

[a] Yield based on compound **7**. [b] Isolated yield. [c] Determined from NMR of the isolated fraction containing **14**, **7**, and **16**.

TABLE 3. Synthesis of 6,6′-Dibromo-4,4′-di(hexoxymethyl)-2,2′-bipyridine (8)

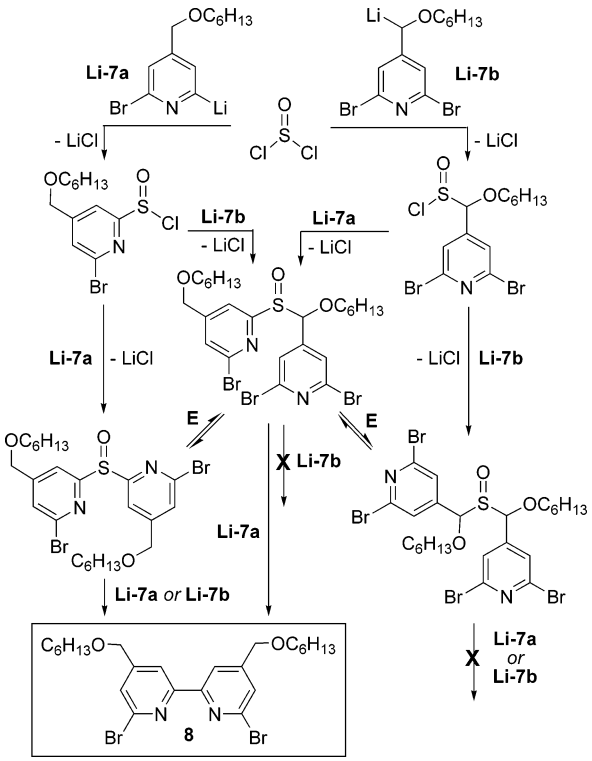


entry	coupling reagent	yield based on **7** (%)	yield based on coupling reagent (%)
1	$CuBr/O_2$	21	21
2	$CuCl_2/O_2$	25	25
3	$SOCl_2$	60	90
4	$POCl_3$	37	75
5	$R_2SnCl_2/Cu(NO)_3$	17	17

applied to the functionalized analogue **7**. Not only was it verified that benzylic deprotonation competes with metal−halogen exchange, but a large amount (40%) of the debrominated bipyridine **13** was also isolated. The formation of **13** is not dependent on the I_2 quench, as quenching with H_2O gave similar results. Lowering the temperature to −80 °C eliminated the production of **13** and greatly increased the amount of the 2-iodated product (Table 2, compound **14**). It is reasonable to propose that metal−halogen exchange readily occurs at −40 °C, but that the resulting organolithium reagent is not stable at that temperature and decomposes to produce **13**. It was found that lowering the temperature below −88 °C had a negative effect on lithiation of the 2-position, possibly because of the decreased solubility of **7** at these temperatures (compound **7** begins to precipitate from solution at ca. −80 °C). As a consequence, the optimum conditions were determined to be the utilization of temperatures between −88 and −80 °C and such conditions were then applied to all further coupling studies.

Conditions for coupling with each reaction were optimized and the resulting yields for the production of bipyridine **8** are given in Table 3. With the exception of entry 3, all methods gave fairly low yields based on the starting pyridine **7**. However, the use of either $SOCl_2$ or $POCl_3$ as coupling reagents requires >2 equiv of **7** for every equivalent of the product **8** produced.[9,13−15] Thus in terms of the coupling reagents, these two methods gave isolated yields of 90% and 75%, respectively.

SCHEME 3. Proposed Mechanism for the Production of Bipyridine 8 via Thionyl Chloride Coupling



From the results of the lithiation studies given in Table 2, it is known that even in the optimized conditions, the treatment of **7** with BuLi generates a significant amount (~15%) of an undesired organolithium intermediate via deprotonation of the benzylic carbon. Therefore, it is believed that the difference in the yields from various methods is due to differences in selectivity between the two organolithium species present in the coupling reactions. The methods that give the lowest yields depend on either transmetalation (entries 1 and 2) or metathesis/transmetalation (entry 5) in order to generate the reactive intermediates necessary for oxidative coupling. These reactions are driven by the transfer of the organyl to the less electropositive Cu center and the formation of the lithium halide byproduct. As such, there is little selectivity between the possible aryl or benzylic reagents and a variety of coupling products are possible.

In contrast, the use of $SOCl_2$ as the coupling reagent allows a degree of selectivity, resulting in a significantly higher yield of bipyridine **8**. A proposed coupling mechanism based on previous studies of $SOCl_2$-mediated aryl−aryl couplings is shown in Scheme 3.[2,15] As shown, the method involves the reaction of the generated organolithium species with $SOCl_2$ to form an intermediate sulfoxide. However, as treatment of **7** results in the generation of two organolithium species (**Li-7a** or **Li-7b**, respectively), three different sulfoxides are thus possible. The addition of **Li-7a** or **Li-7b** to one of the sulfoxides generates a four-coordinate sulfur species that can either give product via oxidative coupling or eliminate an equivalent of **Li-7a** or **Li-7b** in an exchange process to regenerate a sulfoxide.

(13) Oae, S.; Inabushi, Y.; Yoshihara, M. *Heteroat. Chem.* **1993**, *4*, 185.
(14) Oae, S.; Inabushi, Y.; Yoshihara, M.; Uchida, Y. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *95*−*96*, 361.
(15) Oae, S.; Inabushi, Y.; Yoshihara, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *103*, 101.

TABLE 4. Relative Solubilities of 1a and 8[a]

	solvent					
bipyridine	hexanes	EtOAc	$CHCl_3$	CH_2Cl_2	CH_3CN	CH_3OH
1a	ss	ss	s	s	ss	ss
8	s	s	vs	vs	s	s

[a] vs = very soluble; s = soluble; ss = sparingly soluble.

As such, all three possible sulfoxide intermediates are in equilibrium with one another and the higher ratio of **Li-7a** should favor sulfoxides containing this unit. In addition, Oae and co-workers have shown that the use of $SOCl_2$ *selectively* couples aryl species, in that mixtures of aryl and benzyl substrates strongly favor aryl−aryl coupling,[13] while the use of alkyllithium species results in a complete lack of oxidative coupling.[14] Similar selectivity is also observed for $POCl_3$.

As a result of this selectivity, these reagents produce higher yields of the desired product **8** and result in the generation of fewer byproducts. In addition, as these methods do not involve transition metal reagents, removal of metal ions coordinated by the bipyridine product is not required. The only significant weakness in the use of either $SOCl_2$ or $POCl_3$ is that 3 and 4 equiv of starting material are required in order to make each equivalent of the coupled bipyridine, respectively. However, the use of $SOCl_2$ reduces this weakness and the advantages of selectivity, reaction cleanliness, and ease of separation makes this method quite useful in the production of such bipyridine products.

As might be expected, the solubility of **8** is significantly enhanced in comparison to that of the unfunctionalized parent **1a**. Table 4 lists the relative solubilities of both compounds in a variety of solvents. While **1a** really only shows appreciable solubility in chlorinated solvents, compound **8** is also soluble in both nonpolar solvents such as hexanes and significantly polar organics such as acetonitrile and methanol. Quantification of the compounds solubility in $CHCl_3$ gives a maximum solubility of ~10 mg mL^{-1} for **1a**, while the solubility of **8** exceeds 530 mg mL^{-1}.

In conclusion, we have presented the efficient preparation of a new, solubilizing dibromo-2,2′-bipyridine building block from commercial citrazinic acid. This four-step synthesis has an overall yield of 26% and can be easily prepared on large scales. The utilization of such a building block should contribute solubility to the resulting macromolecular and supramolecular species, allowing both higher molecular weight materials and a greater diversity of possible assemblies.

Experimental Methods

Unless noted, all materials were reagent grade and used without further purification. Compound **1a** was synthesized according to Oae.[9] Anhydrous diethyl ether and THF were freshly distilled from sodium benzophenone and deoxygenated prior to use. Except for the saponification of **11**, all reactions were performed under nitrogen. Chromatographic separations were performed by using standard column methods with silica gel (230−400 mesh). ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Varian 400 MHz spectrometer and referenced to the chloroform signal, and peak multiplicity was reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet.

2,6-Dibromo-4-methoxycarbonylpyridine (10). PBr_3 (21.8 mL, 0.232 mol) was loaded into a 250-mL three-neck flask cooled in a rt water bath. Br_2 (11.9 mL, 0.231 mol) was then added dropwise with stirring to the PBr_3 to yield a yellow solid (PBr_5). P_2O_5 (12.0

g, 0.083 mol) was then added and this solid mixture was mixed well with a spatula under a flow of N_2. At this point, a reflux condenser was added that was connected to a water-filled bubbler to trap evolved HBr. Under a flow of N_2, the mixture was heated to 98 °C for 2 h and then cooled to rt. Citrazinic acid (20.0 g, 0.128 mol) was then added and the solids were mixed thoroughly with a spatula under a flow of N_2. The water bath was replaced with an oil bath and the mixture was heated at 185 °C for 8 h (**Caution**: large evolution of HBr gas occurs at ∼130 °C). The mixture was cooled back to rt and 150 mL of CH_3OH was *slowly* added (**Caution**: the reaction with CH_3OH is exothermic, causing the solution to reflux). The mixture was stirred for 30 min., after which solid $NaHCO_3$ was added slowly until bubbling stopped. CH_3OH was then removed in vacuo, resulting in a thick black sludge. CH_2Cl_2 (200 mL) was added, then the mixture stirred for 10 min and decanted. This was repeated 6 times. The combined organic fractions were then concentrated and purified by column chromatography (7.5% EtOAc/hexanes). Final recrystallization from hexane gave 20.94 g (55%). Mp 86.8−88.2 °C (lit.[1d] mp 88−89 °C). ^{1}H NMR ($CDCl_3$) δ 7.99 (s, 2H), 3.97 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 163.2, 141.7, 141.7, 126.9, 53.5.

2,6-Dibromopyridine-4-carboxylic Acid (11). Aqueous NaOH (1.2 M, 150 mL) was added to **10** (14.0 g, 0.047 mol) in 100 mL of THF, and the mixture was heated at reflux for 4 h. THF was removed in vacuo, and the aqueous solution was washed with ether, acidified with concentrated HCl, and extracted with CH_2Cl_2. The organic fraction was dried over $MgSO_4$ and evaporated to give 13.10 g (98%) of a light yellow powder. Recrystallization from H_2O gave mp 184.2−185.8 °C (lit.[11] mp 184−185 °C). ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 166.8, 142.0, 140.6, 127.2.

2,6-Dibromo-4-(hydroxymethyl)pyridine (12). From compound 11: A solution of **11** (6.72 g, 0.0239 mol) in 125 mL of dry THF was cooled to 0 °C and borane (1 M in THF, 60 mL) was slowly added. The cooling bath was then removed, and stirring was continued overnight. Water was slowly added until gas evolution ceased, and the solution was concentrated to ∼50%. NaOH (3 M, 75 mL) was added and the mixture was heated at reflux for 1 h. The remaining THF was then removed and the solution was extracted with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$ and evaporated. The residue was dissolved in a minimum of $CHCl_3$, loaded onto a silica column, and eluted with 30% EtOAc/hexane to yield 5.43 g (85%) of a white solid.

From compound 10: $NaBH_4$ (19.2 g, 510 mmol) was slowly added to a rt solution of **10** (30.0 g, 102 mmol) in 700 mL of dry ethanol and then heated at reflux for 2 h. This solution was cooled to toom temperature and 2 M HCl (100 mL) added slowly with stirring until bubbling stopped. The solution was then concentrated to ∼100 mL by rotary evaporation and solid NaOH was added until the solution became basic. The solution was then stirred for 2 h during which precipitation occurred. CH_2Cl_2 (300 mL) was added to dissolve the precipitate, then the mixture was poured into 500 mL of water and extracted with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$ and evaporated. The residue was purified as above to yield 21.70 g (80%) of a white solid. Mp 110.0−111.5 °C (lit.[1d] mp 110−111 °C). ^{1}H NMR ($CDCl_3$) δ 7.46 (s, 2H), 4.72 (d, 2H, J = 5.2 Hz), 2.37 (t, 1H, J = 5.2 Hz). ^{13}C NMR ($CDCl_3$) δ 155.7, 141.0, 124.5, 62.4.

2,6-Dibromo-4-(hexoxymethyl)pyridine (7). Triflic anhydride (6.35 mL, 37.6 mmol) was added to 50 mL of dry CH_2Cl_2 and cooled to 0 °C. A solution of **12** (10 g, 37.6 mmol) and Et_3N (4.71 mL, 33.7 mmol) in 200 mL of dry CH_2Cl_2 was then added dropwise over 30 min. The cooling bath was removed, and the solution was stirred for 1 h. 1-Hexanol (100 mL, 0.796 mol) was then added and the mixture was stirred for 1 h. Et_3N (30 mL) was then added, the solvents were evaporated, and the remaining mixture was poured into 200 mL of water. This was then extracted with hexane and the combined organic fractions were dried over $MgSO_4$, evaporated, and chromatographed on a silica column (3.5% EtOAc/hexane) to yield 12.43 g (94%) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 2H), 4.40 (s, 2H), 3.45 (t, 2H, J = 5.6 Hz), 1.58 (m, 2H), 1.33 (m, 2H), 1.26 (m, 4H), 0.85 (t, 3H, J = 5.6 Hz). ^{13}C NMR ($CDCl_3$) δ 154.0, 140.9, 125.0, 71.8, 69.9, 31.8, 29.73, 26.0, 22.8, 14.3.

6,6′-Dibromo-4,4′-di(hexoxymethyl)-2,2′-bipyridine (8). Compound **7** (1.0 g, 2.8 mmol) in 50 mL of ether was cooled to −88 °C producing a partially dissolved suspension. *n*-BuLi (1.14 mL, 2.84 mmol, 2.5 M in hexane) was added dropwise via syringe and the suspension was stirred for 20 min while warming to −80 °C, which resulted in a light red homogeneous solution. $SOCl_2$ (0.069 mL, 0.95 mmol) was added dropwise via syringe, causing the solution to first turn black then finally yellow upon complete addition. The solution was allowed to warm to −60 °C over 20 min, resulting in precipitation. The suspension was stirred for another 15 min at −60 °C and then warmed to rt. Water (20 mL) was added, then the mixture was stirred for 10 min and poured into 150 mL of water. The mixture was extracted with ether and the organic layers were dried over $MgSO_4$, evaporated, and applied to a silica column (3.5% EtOAc/hexane) to yield 0.46 g (60%) of a white solid. Recrystallization from CH_3CN gave mp 69.6−70.5 °C. ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 2H), 7.55 (s, 2H), 4.56 (s, 4H), 3.53 (t, 4H, J = 6.8 Hz), 1.66 (p, 4H, J = 6.8 Hz), 1.40 (m, 4H), 1.32 (m, 8H), 0.90 (t, 6H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ 155.5, 152.5, 142.2, 126.6, 118.6, 71.7, 70.8, 31.9, 29.8, 26.0, 22.8, 14.3.

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Supporting Information Available: Details of the lithiation studies, NMR data and spectra for the products **14**−**17**, and crystallographic data for **17**; synthetic methods for the preparation of **8** via alternate coupling methods, and NMR spectra of **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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