Synthesis of Linear Alkyl-Bridged 2,2'-Bipyridine/Catechol Ligands

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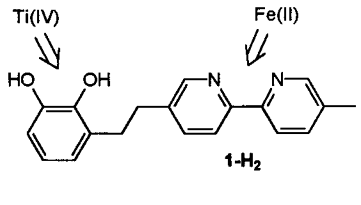
Linear alkyl-bridged 2,2'-bipyridine/catechol compounds **[1,12–14,19]-H$_2$** and **[2,20]-H$_4$** can be easily prepared by the addition of lithiated 5,5'-methyl-2,2'-bipyridine (**3**) to 3-(ω-haloalkyl)-substituted 1,2-dimethoxybenzenes **4**, **9**, **11**, **18** followed by cleavage of the methylaryl ethers.

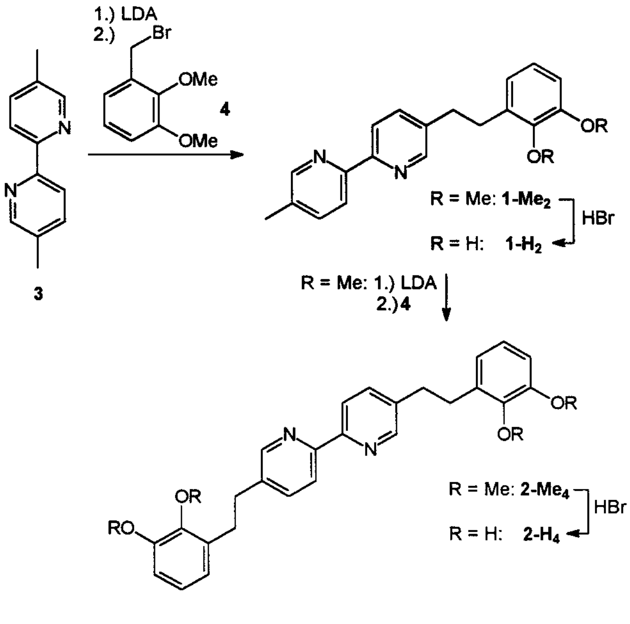
Sequential oligodonor ligands are of considerable interest for the formation of heterodi- or heterooligonuclear coordination compounds.[1] Artificial metal complexes with defined intermetallic distances can be obtained either in spontaneous self-assembly processes by simply mixing different components (oligodonor ligands and metal ions)[2–4] and forming many bonds in one reaction step or by consecutive formation of bonds using a multi-step synthetic sequence.[5] Recently we communicated a procedure for the synthesis of an ethylene-linked catechol/2,2'-bipyridine ligand **1-H$_2$**. First coordination studies showed that it is possible to selectively bind different metal ions to the different binding sites of the ligand **1**.[6]



To allow systematic studies of the coordination chemistry of sequential 2,2'-bipyridine/catechol ligands we synthesized a series of different derivatives of **1** with different lengths of the spacer. To control the solubility of metal complexes, alkyl chains were attached to one or both binding sites of the ligand. Additionally, catechol/2,2'-bipyridine/catechol compounds with three chelating units were synthesized. In this paper we describe detailed synthetic procedures and full characterization of the sequential ligands **[1,12–14,19]-H$_2$** and **[2,20]-H$_4$**.

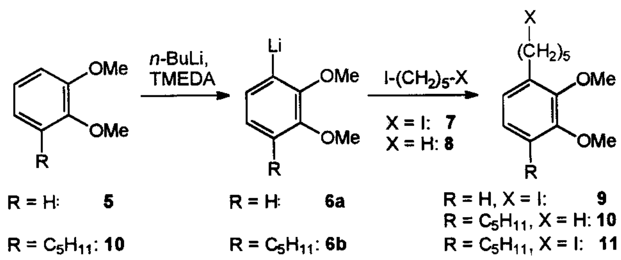
Ligands **1-H$_2$** and **2-H$_4$** possessing ethylene spacers were synthesized as described before.[6] 5,5'-Dimethyl-2,2'-bipyridine (**3**) is deprotonated at first with LDA (lithium diisopropylamide).[7] Addition of one equivalent of 2,3-dimethoxybenzyl bromide (**4**)[8] to the in situ generated benzyllithium derivative affords the methyl protected ligand **1-Me$_2$** in 59% yield as a pale yellow solid. The derivative **1-Me$_2$** can be deprotonated again (LDA) and after addition of benzyl bromide **4** the ligand precursor **2-Me$_4$** is obtained in 46% yield as a yellow crystalline solid. In the final step the ligands **1-H$_2$** and **2-H$_4$** are generated by ether cleavage with aqueous HBr under reflux in 96% (**1-H$_2$**) or 70% (**2-H$_4$**) yield, respectively.

For the preparation of compounds with longer spacer length, 3-(ω-haloalkyl)-substituted 1,2-dimethoxybenzene derivatives had to be synthesized first. Addition of



Scheme 1

butyllithium and TMEDA (*N,N,N',N'*-tetramethylethylenediamine) to a solution of veratrole (1,2-dimethoxybenzene, **5**) in diethyl ether generates 2,3-dimethoxyphenyllithium (**6**). This in situ generated lithium derivative **6**[9] can be trapped by the addition of 1,5-diiodopentane (**7**) or 1-iodopentane (**8**). The alkyl-substituted derivatives **9** and **10** are obtained in 34% (**9**) or 47% yield (**10**). Derivative **10** can be again ortho-lithiated and, after addition of diiodopentane **7**, the derivative **11** is isolated in 46% yield.



Scheme 2

The iodo-substituted derivatives **9** and **11** are ideal starting materials for the synthesis of the alkyl-bridged 2,2'-bipyridine/catechol derivatives **12-H$_2$** and **13-H$_2$** which possess a hexamethylene spacer connecting the binding sites of the sequential ligand. Therefore, bipyridine **3** is deprotonated with LDA and the formed lithiated species

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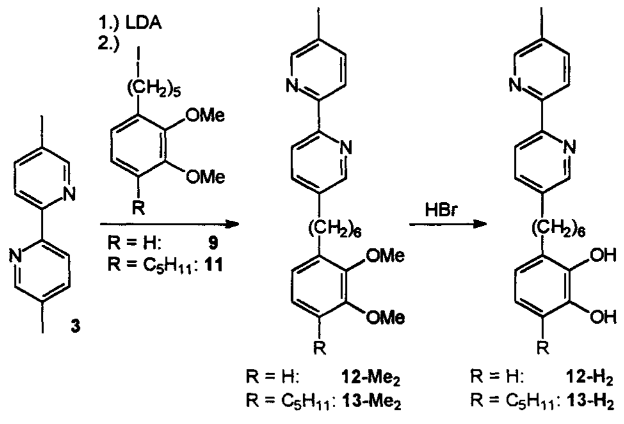
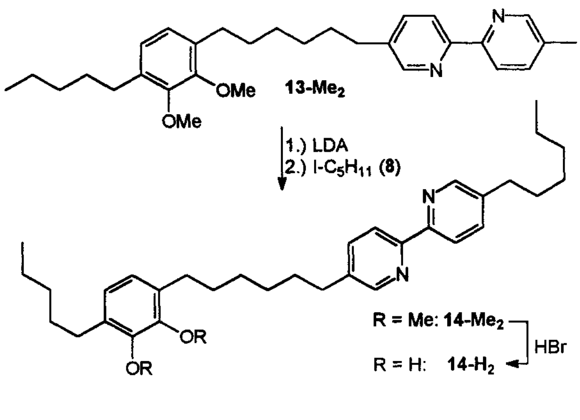
is coupled with the alkyliodo compounds **9** or **11** to obtain **12-Me₂** or **13-Me₂** in 53 % or 47 % yield, respectively. Finally, the methyl ethers of **12-Me₂** and **13-Me₂** are cleaved by refluxing in aqueous HBr and the free ligands are isolated in 97 % **(12-H₂)** and 100 % yield **(13-H₂)**.



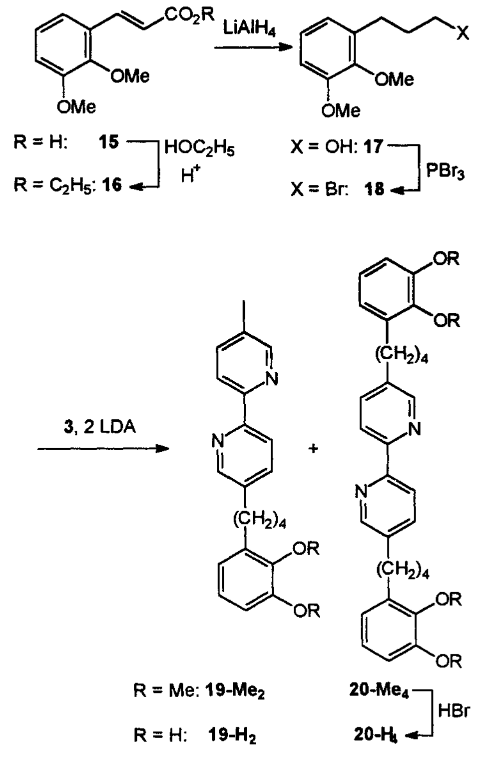
Scheme 3

Compound **13-Me₂** – an intermediate of this reaction sequence – is a useful building block for the preparation of a ligand which bears two terminal alkyl chains connected to both the bipyridine and the catechol moiety. Deprotonation of **13-Me₂** generates a lithium species which upon trapping with 1-iodopentane **(8)** affords **14-Me₂** in 68 % yield. Deprotection of the catechol units of **14-Me₂** with aqueous HBr at reflux proceeds in 89 % yield to obtain **14-H₂** as a waxy solid.



Scheme 4

As a further spacer we introduced a $(CH_2)_4$ chain as a bridge between the bipyridine and the catechol unit. 2,3-Dimethoxycinnamic acid **(15)** proved to be the ideal starting material. The cinnamic acid **15** is transformed into the ethyl ester **16** (93 %) which can be reduced with lithium aluminum hydride to obtain the propanol derivative **17** in 96 % yield. Reaction with PBr_3 affords the corresponding bromide **18** in 80–90 % yield (crude product). However, after column chromatography (silica gel, dichloromethane) only 33 % of analytically pure **18** can be isolated.



Scheme 5

In analogy to the earlier discussed coupling reaction, **18** is reacted with the lithium species derived from bipyridine **3** and LDA (2 equiv). Due to the conditions which were chosen for this reaction, a mixture of the $(CH_2)_4$ bridged 2,2′-bipyridine/veratrole **(19-Me₂**, 47 %) and veratrole/2,2′-bipyridine/veratrole derivative **(20-Me₄**, 31 %) is obtained. Compounds **19-Me₂** and **20-Me₄** can be easily separated by chromatography (silica gel, hexane/ethyl acetate/triethylamine 20:1:2) and are both important ligand precursors. Therefore no attempts were made to optimize this reaction to produce exclusively one of the products **19-Me₂** or **20-Me₄**. The free ligands are obtained after ether cleavage (HBr) in 90 % **(19-H₂)** or 97 % yield **(20-H₄)**.

In this paper we describe procedures for the preparation of a number of sequential 2,2′-bipyridine/catechol ligands. As a key step the coupling of an in situ generated lithium bipyridine derivative with various easily accessible iodo- or bromoalkyl-substituted veratrole derivatives was used. The ability of the obtained ligands to form heterodi- or heterotrimetallic coordination compounds with defined metal–metal distances is now under investigation in our laboratories.

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Table 1. NMR, MS and IR Data of the Veratrole/Bipyridine Derivatives **1-Me$_2$**, **2-Me$_4$**, **12-Me$_2$**, **13-Me$_2$**, **14-Me$_2$**, **19-Me$_2$**, and **20-Me$_4$**

Product	^{1}H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ	IR ν (cm^{-1})	MS m/z (%)
1-Me$_2$	8.47 (br, 2H), 8.24 (m, 2H), 7.59 (m, 2H), 6.94 (dd, J = 8.1, 7.7, 1H), 6.78 (dd, J = 8.1, 1.3, 1H), 6.71 (dd, J = 7.7, 1.3, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 2.95 (s, 4H), 2.37 (s, 3H)	154.1 (C), 153.7 (C), 152.8 (C), 149.5 (CH), 149.3 (CH), 147.1 (C), 137.4 (CH), 137.1 (C), 136.9 (CH), 134.6 (C), 133.0 (C), 123.8 (CH), 121.9 (CH), 120.3 (CH, double intensity), 110.6 (CH), 60.6 (CH_3), 55.6 (CH_3), 33.8 (CH_2), 31.8 (CH_2), 18.3 (CH_3)	3009, 2936, 2838, 1598, 1583, 1554, 1480, 1447, 1222	334 (M$^+$, 100), 183 (42), 151 (70), 91 (39)
2-Me$_4$	8.47 (m, 2H), 8.25 (m, 2H), 7.59 (m, 2H), 6.95 (m, 2H), 6.76 (m, 2H), 6.76 (m, 2H), 6.71 (m, 2H), 3.86 (s, 6H), 3.81 (s, 6H), 2.95 (s, 8H)	154.2 (C), 152.9 (C), 149.5 (CH), 147.3 (C), 137.3 (C), 137.1 (CH), 134.8 (C), 124.0 (CH), 122.1 (CH), 120.6 (CH), 110.7 (CH), 60.8 (CH_3), 55.8 (CH_3), 34.0 (CH_2), 31.9 (CH_2)	3009, 2935, 2837, 1583, 1479, 1278, 1269, 1077, 1010, 751	484 (M$^+$, 5), 334 (100), 183 (37), 151 (83), 91 (56)
12-Me$_2$	8.47 (dd, J = 4.0, 2.0, 2H), 8.24 (dd, J = 8.1, 4.0, 2H), 7.59 (dd, J = 8.1, 2.0, 2H), 6.96 (t, J = 7.9, 1H), 6.75 (d, J = 7.9, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.62 (m, 4H), 2.37 (s, 3H), 1.61 (br m, 4H), 1.38 (m, 4H)	153.9 (C), 153.8 (C), 152.7 (C), 149.5 (CH), 149.2 (CH), 147.1 (C), 137.9 (C), 137.4 (CH), 136.7 (CH), 136.5 (C), 133.0 (C), 123.7 (CH), 121.8 (CH), 120.4 (CH), 120.3 (CH), 109.9 (CH), 60.6 (CH_3), 55.6 (CH_3), 32.8 (CH_2), 31.0 (CH_2), 30.6 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 18.3 (CH_3)	2929, 2852, 1597, 1584, 1555, 1480, 1462, 1279, 1220, 1087, 830, 754	390 (M$^+$, 100), 375 (53), 197 (92)
13-Me$_2$	8.48 (br, 2H), 8.25 (m, 2H), 7.60 (dd, J = 8.1, 2.0, 2H), 6.82 (s, 2H), 3.83 (2s, 3H each), 2.65 (t, J = 7.6, 2H), 2.57 (t, J = 7.8, 4H), 2.37 (s, 3H), 1.66 (m, 2H), 1.58 (m, 4H), 1.41 (m, 4H), 1.35 (m, 4H), 0.90 (m, 3H)	154.0 (C), 153.8 (C), 151.0 (C, double intensity), 149.5 (CH), 149.2 (CH), 137.8 (C), 137.4 (CH), 136.7 (CH), 134.6 (C), 134.3 (C), 133.0 (C), 124.4 (CH), 124.3 (CH), 120.4 (CH), 120.3 (CH), 60.3 (CH_3 double intensity), 32.8 (CH_2), 31.9 (CH_2), 31.0 (CH_2), 30.8 (2 × CH_3), 29.7 (CH_2, double intensity), 29.4 (CH_2), 29.0 (CH_2), 22.6 (CH_2), 18.3 (CH_3), 14.1 (CH_3)	2999, 2928, 2854, 1552, 1490, 1464, 1275, 1024, 828, 816, 651	460 (M$^+$, 100)
14-Me$_2$	8.48 (br, 2H), 8.27 (d, J = 8.1, 2H), 7.60 (dt, J = 8.1, 2.4, 2H), 6.82 (m, 2H), 3.83 (2s, 3H each), 2.65 (t, J = 7.7, 4H), 2.57 (t, J = 7.9, 4H), 1.65 (m, 4H), 1.58 (m, 4H), 1.34 (m, 4H), 1.30 (m, 4H), 0.89 (m, 6H)	154.0 (2C), 151.1 (C, double intensity), 149.3 (CH, double intensity), 137.9 (C), 137.8 (C), 136.7 (CH, double intensity), 134.6 (C), 134.3 (C), 124.3 (2CH), 120.4 (CH, double intensity), 60.3 (CH_3, double intensity), 32.8 (CH_2, double intensity), 31.9 (CH_2), 31.6 (CH_2), 31.1 (CH_2), 31.0 (CH_2), 30.8 (CH_2), 30.6 (CH_2), 29.7 (CH_2, double intensity), 29.4 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 22.6 (CH_2, double intensity), 14.1 (CH_3, double intensity)	2929, 2857, 1466, 1412, 1275, 1027, 742	530 (M$^+$, 60), 487 (37), 268 (100)
19-Me$_2$	8.48 (brs, 2H), 8.24 (dd, J = 8.0, 4.0, 2H), 7.60 (m, 2H), 6.96 (t, J = 7.9, 1H), 6.76 (m, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.67 (m, 4H), 2.37 (s, 3H), 1.71 (brm, 4H)	154.0 (C), 153.8 (C), 152.8 (C), 149.5 (CH), 149.3 (CH), 147.1 (C), 137.7 (C), 137.4 (CH), 136.8 (CH), 136.1 (C), 133.0 (C), 123.8 (CH), 121.8 (CH), 120.4 (CH), 120.3 (CH), 110.1 (CH), 60.6 (CH_3), 55.6 (CH_3), 32.7 (CH_2), 30.9 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 18.3 (CH_3)	2941, 2859, 1584, 1473, 1440, 1272, 1217, 1084, 828, 749	362 (M$^+$, 82), 197 (100), 184 (90)
20-Me$_4$	8.49 (d, J = 2.0, 2H), 8.25 (d, J = 8.1, 2H), 7.61 (dd, J = 8.1, 2.0, 2H), 6.97 (m, 2H), 6.76 (m, 4H), 3.85 (s, 6H), 3.81 (s, 6H), 2.68 (m, 8H), 1.71 (brm, 8H)	154.0 (C), 152.7 (C), 149.3 (CH), 147.1 (C), 137.7 (C), 136.8 (CH), 136.1 (C), 123.8 (CH), 121.9 (CH), 120.4 (CH), 110.1 (CH), 60.6 (CH_3), 55.6 (CH_3), 32.7 (CH_2), 30.9 (CH_2), 30.2 (CH_2), 29.6 (CH_2)	2941, 2857, 1584, 1469, 1440, 1271, 1219, 1083, 818, 750	540 (M$^+$, 100), 376 (63), 362 (61)

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Melting points were measured on a Büchi 535 apparatus (uncorrected). IR spectra were obtained on a Bruker IFS 88 spectrometer (diffuse reflection (KBr) or as film on KBr plates). MS and HRMS spectra were recorded on a Finnigan MAT 90 spectrometer (EI, 70 eV). For ^{1}H NMR and ^{13}C NMR (BB/DEPT) spectra a Bruker DRX 500, AM 400, or a AC 250 was used; internal standard: $CHCl_3$, DMSO or MeOH; coupling constants J in Hz. Reactions with air or moisture sensitive materials were carried out under argon. Compounds **3**[7] and **4**[8] were prepared as described before. Correct HRMS were obtained for all new compounds ± 0.0035.

5-[2-(2,3-Dimethoxyphenyl)ethyl]-5′-methyl-2,2′-bipyridine (1-Me$_2$):
A solution of **3** (0.4 g, 2.17 mmol) in anhyd THF (6 mL) was added to freshly prepared LDA from i-Pr_2NH (0.3 mL, 2.14 mmol) and BuLi (1.6 M in hexanes, 1.3 mL, 2.08 mmol) in anhyd THF (6 mL) at −78 °C.[7] The mixture was allowed to warm to 0 °C and 2,3-dimethoxybenzyl bromide (**4**; 0.5 g, 2.14 mmol) in anhyd THF (6 mL) was added slowly. After 65 h at r.t. the solvent was removed and the residue extracted with H_2O and Et_2O. The organic phases were combined, dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 95:5) to afford 407 mg of **1-Me$_2$** (59%) as pale yellow crystals; mp 96 °C.

Calcd. for $C_{21}H_{22}N_2O_2$ (334.4): C 75.45, H 6.63, N 8.38; found: C 75.19, H 6.69, N 8.64.

5,5′-Bis[2-(2,3-dimethoxyphenyl)ethyl]-2,2′-bipyridine (2-Me$_4$):
A solution of **1-Me$_2$** (412 mg, 1.23 mmol) in anhyd THF (5 mL) was added to a freshly prepared solution of LDA (1.23 mmol) in anhyd THF (4 mL) at −78 °C. After warming to 0 °C a solution

Table 2. NMR, MS and IR Data of the Catechol/Bipyridine Derivatives **1-H$_2$**, **2-H$_4$**, **12-H$_2$**, **13-H$_2$**, **14-H$_2$**, **19-H$_2$**, and **20-H$_4$**

Product	^{1}H NMR[a] δ, J (Hz)	^{13}C NMR[a] δ	IR ν (cm^{-1})	MS m/z (%)
1-H$_2$	8.39 (m, 1 H), 8.24 (m, 1 H), 8.02 (m, 2 H), 7.54 (m, 2 H), 6.51 (m, 1 H), 6.45 (m, 1 H), 6.36 (m, 1 H), 6.36 (m, 1 H), 2.85–2.94 (m, 4 H), 2.28 (s, 3 H)	153.2 (C), 153.0 (C), 149.5 (CH), 149.3 (CH), 144.6 (C), 143.3 (C), 138.1 (CH), 138.0 (C), 137.8 (CH), 133.6 (C), 127.3 (C), 121.5 (CH), 121.1 (CH), 121.0 (CH), 119.7 (CH), 113.9 (CH), 32.7 (CH_2), 32.0 (CH_2), 18.3 (CH_3)	3046, 2860, 1594, 1475, 1378, 1059	306 (M$^+$, 50), 184 (100), 183 (14)
2-H$_4$	9.17 (s, 2 H), 8.44 (s, 2 H), 8.23 (d, J = 8.1, 2 H), 8.20 (s, 2 H), 7.72 (dd, J = 8.1, 1.6, 2 H), 6.62 (m, 2 H), 6.50 (m, 4 H), 2.89 (m, 4 H), 2.84 (m, 4 H)	153.1 (C), 149.1 (CH), 144.9 (C), 143.2 (C), 137.5 (C), 136.9 (CH), 127.8 (C), 120.4 (CH), 119.7 (CH), 118.6 (CH), 113.4 (CH), 32.2 (CH_2), 31.3 (CH_2)	3274, 3042, 2930, 1596, 1475, 1272, 834, 739	428 (M$^+$, 99), 306 (100), 183 (67)
12-H$_2$	8.46 (br s, 1 H), 8.43 (br s, 1 H), 8.09 (d, J = 8.1, 2 H), 7.60 (t, J = 8.1, 2 H), 6.61 (m, 3 H), 2.60 (m, 4 H), 2.35 (s, 3 H), 1.60 (m, 4 H), 1.35 (m, 4 H)	153.0 (C), 152.9 (C), 149.3 (CH), 149.0 (CH), 144.4 (C), 143.1 (C), 138.6 (C), 138.3 (CH), 137.6 (CH), 133.7 (C), 129.5 (C), 121.3 (CH, double intensity), 121.2 (CH), 119.6 (CH), 113.2 (CH), 32.7 (CH_2), 30.8 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 18.3 (CH_3)	3426, 2924, 2852, 1557, 1473, 1269, 1234, 829, 744	362 (M$^+$, 100), 239 (55), 197 (72), 184 (68)
13-H$_2$	8.47 (br s, 1 H), 8.42 (d, J = 1.5, 1 H), 8.08 (d, J = 8.1, 2 H), 7.68 (dd, J = 8.1, 1.5, 1 H), 7.57 (dd, J = 8.1, 2.0, 1 H), 7.4 (br, OH, 2 H), 6.62 (s, 2 H), 2.58 (m, 6 H), 2.37 (s, 3 H), 1.59 (m, 6 H), 1.31 (m, 8 H), 0.88 (t, J = 6.9, 3 H)	153.3 (C), 153.2 (C), 149.5 (CH), 149.2 (CH), 142.8 (C), 142.6 (C), 138.3 (C), 137.9 (CH), 137.2 (CH), 133.4 (C), 127.5 (C), 127.1 (C), 121.0 (CH), 120.9 (CH), 120.7 (CH), 120.6 (CH), 32.7 (CH_2), 31.8 (CH_2), 30.9 (CH_2), 30.0 (CH_2), 29.8 (CH_2, double intensity), 29.7 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 22.6 (CH_2), 18.3 (CH_3), 14.1 (CH_3)	3378, 2929, 2856, 1469, 1225, 1031, 830	432 (M$^+$, 100), 197 (42), 184 (43)
14-H$_2$	8.46 (s, 1 H), 8.40 (s, 1 H), 8.10 (m, 2 H), 7.60 (d, J = 6.8, 1 H), 7.56 (d, J = 7.8, 1 H), 6.60 (s, 2 H), 2.60 (br m, 8 H), 1.61 (m, 8 H), 1.30 (m, 16 H), 0.88 (m, 6 H)	153.4 (C), 149.2 (CH, double intensity), 142.7 (C, double intensity), 142.5 (C), 138.2 (C), 138.3 (C), 137.2 (CH, double intensity), 127.5 (C), 127.0 (C), 121.0 (CH), 120.7 (CH), 120.6 (CH, double intensity), 32.8 (CH_2), 32.7 (CH_2), 31.8 (CH_2), 31.6 (CH_2), 31.0 (CH_2), 30.8 (CH_2), 30.0 (CH_2), 29.7 (CH_2, triple intensity), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 22.6 (2 × CH_2), 14.1 (CH_3, double intensity)	3180, 2927, 2854, 1465, 829	502 (M$^+$, 100), 267 (26)
19-H$_2$	8.58 (m, 1 H), 8.56 (m, 1 H), 8.28 (m, 2 H), 8.01 (m, 2 H), 6.61 (dd, J = 6.9, 2.6, 1 H), 6.55 (m, 2 H), 2.78 (t, J = 7.3, 2 H), 2.63 (t, J = 7.2, 2 H), 2.47 (s, 3 H), 1.69 (m, 4 H)	149.4 (C), 149.2 (C), 148.5 (CH), 147.9 (CH), 145.9 (C), 144.4 (C), 142.5 (C), 142.4 (CH), 142.1 (CH), 137.9 (C), 130.1 (C), 123.3 (CH), 123.1 (CH), 122.0 (CH), 120.2 (CH), 113.8 (CH), 33.3 (CH_2), 31.6 (CH_2), 30.6 (CH_2), 30.3 (CH_2), 18.3 (CH_3)	3210, 2929, 2859, 1547, 1475, 1284, 831, 739	334 (M$^+$, 76), 184 (100)
20-H$_4$	8.48 (s, 2 H), 8.24 (d, J = 8.1, 2 H), 7.71 (dd, J = 8.2, 1.8, 2 H), 6.60 (dd, J = 6.4, 2.3, 2 H), 6.50 (m, 4 H), 2.64 (t, J = 7.2, 4 H), 2.54 (t, J = 7.3, 4 H), 1.60 (m, 4 H), 1.55 (m, 4 H)	153.2 (C), 149.1 (CH), 144.9 (C), 143.1 (C), 137.9 (C), 136.9 (CH), 128.9 (C), 120.2 (CH), 119.8 (CH), 118.5 (CH), 113.0 (CH), 31.8 (CH_2), 30.6 (CH_2), 29.4 (CH_2), 29.1 (CH_2)	3449, 2929, 2858, 1609, 1557, 1474, 1265, 737	484 (M$^+$, 100), 361 (46), 347 (42), 334 (51)

[a] Solvents for NMR: **1-H$_2$**, **12-H$_2$**, **13-H$_2$**, **14-H$_2$** = $CDCl_3$; **2-H$_4$**, **20-H$_4$** = DMSO-d_6; **19-H$_2$** = CD_3OD.

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of the benzyl bromide **4** (285 mg, 1.23 mmol) in anhyd THF (4 mL) was added. After 65 h at r.t., the solvent was removed and the residue suspended in H_2O. Extraction with CH_2Cl_2, drying of the organic phase ($MgSO_4$), and removal of the solvent afforded a beige solid which was recrystallized from MeOH to give 276 mg of **2-Me$_4$** (46%) as pale yellow crystals; mp 152 °C.

Calcd. for $C_{30}H_{32}N_2O_4 \cdot ¼H_2O$ (489.1): C 73.67, H 6.70, N 5.73; found: C 73.80, H 6.63, N 6.24.

Alkyl-Substituted Veratroles 9–11; General Procedure:

TMEDA (1 equiv) and BuLi (1 equiv) were added at r.t. to the 1,2-dimethoxybenzene derivative **5** or **10** (1 equiv) in Et_2O.[9] The iodoalkane **7** or **8** was added after 3 h and the mixture stirred overnight. After quenching with H_2O the Et_2O phase was dried ($MgSO_4$), evaporated, and the residue purified by column chromatography (silica gel, CH_2Cl_2/hexane, 1:1).

3-(5-Iodopentyl)-1,2-dimethoxybenzene (**9**):

Yield: 34% of a yellow oil.

IR (film): ν = 2997, 2932, 2857, 1599, 1584, 1481, 1274, 1223, 785, 748 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.98 (t, J = 7.9 Hz, 1 H), 6.77 (d, J = 7.9 Hz, 2 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.16 (t, J = 7.1 Hz, 2 H), 2.65 (t, J = 7.7 Hz, 2 H), 1.86 (m, 2 H), 1.63 (m, 2 H), 1.46 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 152.7 (C), 147.1 (C), 136.0 (C), 123.8 (CH), 121.9 (CH), 110.2 (CH), 60.6 (CH_3), 55.7 (CH_3), 33.5 (CH_2), 30.4 (CH_2), 29.7 (CH_2, double intensity), 7.2 (CH_2).

MS: m/z = 334 (M$^+$, 34), 206 (100), 151 (77), 136 (55).

1,2-Dimethoxy-3-pentylbenzene (**10**):

Yield: 47% of a colorless oil.

IR (film): ν = 2956, 2931, 2858, 1599, 1585, 1481, 1277, 1223, 747 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.99 (t, J = 7.9 Hz, 1 H), 6.79 (m, 2 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 2.64 (t, J = 7.8 Hz, 2 H), 1.61 (m, 2 H), 1.36 (m, 4 H), 0.91 (t, J = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 152.7 (C), 147.1 (C), 136.8 (C), 123.7 (CH), 121.9 (CH), 109.9 (CH), 60.6 (CH_3), 55.6 (CH_3), 31.8 (CH_2), 30.5 (CH_2), 29.8 (CH_2), 22.6 (CH_2), 14.0 (CH_3).

MS: m/z = 208 (M^+, 100), 151 (34), 136 (44).

1-(5-Iodopentyl)-2,3-dimethoxy-4-pentylbenzene (**11**):

Yield: 46 % of a colorless oil.

IR (film): ν = 2955, 2930, 2858, 1459, 1412, 1274, 1224, 1028, 816 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.85 (m, 2 H), 3.87 (2 s, 3 H each), 3.23 (t, J = 7.1 Hz, 2 H), 2.61 (m, 4 H), 1.91 (m, 2 H), 1.62 (m, 4 H), 1.51 (m, 2 H), 1.39 (m, 4 H), 0.94 (m, 3 H).

^{13}C NMR ($CDCl_3$): δ = 151.1 (C, double intensity), 134.8 (C), 133.9 (C), 124.4 (CH), 124.3 (CH), 60.3 (CH_3, double intensity), 33.4 (CH_2), 31.9 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 29.7 (CH_2, double intensity), 22.6 (CH_2), 14.1 (CH_3), 7.0 (CH_2).

MS: m/z = 404 (M^+, 39), 137 (100).

Coupling of Iodoalkyl Derivatives 8, 9, 11 with 5-Methyl-2,2′-bipyridines 3, 13-Me$_2$; General Procedure:

The bipyridine derivative **3** or **13-Me$_2$** (1 equiv) in anhyd THF (20 mL) was added to freshly prepared LDA (1.05 equiv) in anhyd THF (20 mL) at −78 °C. The solution was allowed to warm to 0 °C and the iodo compound **8**, **9**, or **11** was added. After stirring the mixture at r.t. overnight, the solvent was removed and the residue dissolved in CH_2Cl_2/water (30/30 mL). Phases were separated and the organic phase dried ($MgSO_4$) and evaporated. Unreacted **3** can be removed by Kugelrohr distillation (75 °C/10^{-2} Torr). Purification was done by column chromatography (silica gel, hexane/EtOAc/Et_3N, 20:1:2).

5-[6-(2,3-Dimethoxyphenyl)hexyl]-5′-methyl-2,2′-bipyridine (**12-Me$_2$**):

Yield: 53 % of a white solid; mp 58–59 °C.

Calcd. for $C_{25}H_{30}N_2O_2$ (390.5): C 76.89, H 7.74, N 7.17; found: C 76.78, H 7.14, N 7.18.

5-[6-(2,3-Dimethoxy-4-pentylphenyl)hexyl]-5′-methyl-2,2′-bipyridine (**13-Me$_2$**):

Yield: 47 % of a white solid; mp 52–53 °C.

Calcd. for $C_{30}H_{40}N_2O_2$ (460.7): C 78.22, H 8.75, N 6.08; found: C 77.78, H 8.74, N 6.00.

5′-Hexyl-5-[6-(2,3-dimethoxy-4-pentylphenyl)hexyl]-2,2′-bipyridine (**14-Me$_2$**):

Yield: 68 % of a yellow oil.

Ethyl-2,3-dimethoxycinnamate (16):

A solution of **15** (10.4 g, 50 mmol) in EtOH (40 mL) containing concd H_2SO_4 (3 mL) was refluxed for 6 h. Most of the EtOH was removed in vacuum and satd aq Na_2CO_3 was added. After extraction with Et_2O the organic phase was washed with satd aq Na_2CO_3, H_2O and dried ($MgSO_4$). Removal of solvent afforded 11.03 g (93 %) of a colorless oil.

IR (KBr): ν = 2937, 1712, 1635, 1580, 1480, 1428, 1269, 1180, 1004 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.97 (d, J = 16.2 Hz, 1 H), 7.12 (d, J = 8.0 Hz, 1 H), 7.02 (t, J = 8.0 Hz, 1 H), 6.91 (d, J = 8.0 Hz, 1 H), 6.46 (d, J = 16.2 Hz, 1 H), 4.24 (q, J = 7.1 Hz, 2 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 1.31 (t, J = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 167.1 (C), 153.1 (C), 148.4 (C), 139.3 (CH), 128.6 (C), 124.1 (CH), 119.6 (CH), 119.2 (CH), 113.9 (CH), 61.2 (CH_3), 60.4 (CH_2), 55.8 (CH_3), 14.3 (CH_3).

MS: m/z = 236 (M^+, 72), 205 (69), 177 (100).

3-(2,3-Dimethoxyphenyl)propan-1-ol (17):

A solution of **16** (11.03 g, 46.7 mmol) in Et_2O (35 mL) at 0 °C was added to a suspension of $LiAlH_4$ (4.44 g, 117 mmol) in Et_2O (85 mL). The mixture was stirred at 0 °C for 1 h and additionaly for 2 h at r.t. EtOAc (20 mL) was added and the organic phase was washed with satd aq NH_4Cl and with aq HCl. Drying ($MgSO_4$) and removal of solvent afforded 8.77 g (96 %) of a yellow oil.

IR (film): ν = 3403, 2937, 2835, 1600, 1584, 1481, 1269, 1222, 1085, 749 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.99 (t, J = 7.9 Hz, 1 H), 6.77 (d, J = 7.9 Hz, 2 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.57 (t, J = 6.8 Hz, 2 H), 2.72 (t, J = 6.8 Hz, 2 H), 2.44 (br, OH, 1 H), 1.83 (quint, J = 6.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 152.6 (C), 147.0 (C), 135.3 (C), 124.2 (CH), 122.0 (CH), 110.2 (CH), 61.5 (CH_2), 60.8 (CH_3), 55.6 (CH_3), 33.4 (CH_2), 25.6 (CH_2).

MS: m/z = 196 (M^+, 100), 152 (74), 136 (32), 91 (33).

1-Bromo-3-(2,3-dimethoxyphenyl)propane (18):

A solution of PBr_3 (1.8 mL, 20 mmol) in Et_2O (10 mL) was added to a solution of **17** (8.05 g, 41 mmol) in Et_2O (50 mL) containing pyridine (1 mL) at 0 °C. The mixture was stirred at 0 °C (1 h) and then at r.t. (2 h), and H_2O was added. The organic phase was dried ($MgSO_4$) and the solvent removed to give 9.43 g of a brown oil which can be used for further reactions. However, purification can be done by column chromatography (silica gel, CH_2Cl_2) to furnish 3.45 g (33 %) of a colorless oil.

IR (film): ν = 2960, 2935, 2835, 1599, 1585, 1481, 1272, 1083, 749 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.99 (t, J = 7.9 Hz, 1 H), 6.80 (d, J = 7.9 Hz, 2 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.42 (t, J = 7.0 Hz, 2 H), 2.79 (t, J = 7.0 Hz, 2 H), 2.16 (quin, J = 7.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 152.8 (C), 147.2 (C), 134.4 (C), 123.9 (CH), 122.1 (CH), 110.5 (CH), 60.6 (CH_3), 55.7 (CH_3), 33.6 (CH_2), 33.5 (CH_2), 28.5 (CH_2).

MS: m/z = 260 (M^+, 87), 258 (M^+, 92), 178 (100), 151 (65), 136 (53), 91 (54).

5-[4-(2,3-Dimethoxyphenyl)butyl]-5′-methyl-2,2′-bipyridine (19-Me$_2$) and 5,5′-Bis[4-(2,3-dimethoxyphenyl)butyl]-2,2′-bipyridine (20-Me$_4$):

A solution of **3** (461 mg, 2.5 mmol) in anhyd THF (20 mL) was added to freshly prepared LDA (5 mmol) in THF (20 mL) at −78 °C. The solution was allowed to warm to 0 °C and a solution of **18** in THF (20 mL) was added. After 18 h at r.t., the solvent was removed and the residue extracted with H_2O/CH_2Cl_2 mixture (30/30 mL). The organic phase was dried ($MgSO_4$) and solvent removed in vacuum. Column chromatography (silica gel, hexane/EtOAc/Et_3N 20:1:2) afforded the pure **19-Me$_2$** and **20-Me$_4$**.

19-Me$_2$:

Yield: 428 mg (47 %) of a white solid; mp 71–72 °C.

Calcd. for $C_{23}H_{26}N_2O_2 \cdot \frac{1}{4}H_2O$ (367.0): C 75.28, H 7.28, N 7.63; found: C 75.56, H 7.31, N 7.42.

20-Me$_4$:

Yield: 412 mg (31 %) of a colorless solid; mp 92–93 °C.

Calcd. for $C_{34}H_{40}N_2O_4$ (540.7): C 75.53, H 7.46, N 5.18; found: C 75.18, H 7.63, N 4.78.

Cleavage of Methyl Aryl Ethers; General Procedure:

The veratrole derivative was refluxed with 48 % aq HBr (40 mL) for 2 h. Satd aq $NaHCO_3$ was added until the pH of the solution became neutral. The precipitate was collected by filtration and dried in vacuum to give hygroscopic solids.

5-[2-(2,3-Dihydroxyphenyl)ethyl]-5′-methyl-2,2′-bipyridine (**1-H$_2$**):

Yield: 96 % of a light pink solid; mp 144 °C.

Calcd. for $C_{19}H_{18}N_2O_2 \cdot H_2O$ (324.4): C 70.35, H 6.21, N 8.64; found: C 70.82, H 5.95, N 8.54.

5,5′-Bis[2-(2,3-hydroxyphenyl)ethyl]-2,2′-bipyridine (**2-H$_4$**):

Yield: 302 mg (70 %) of a white solid; mp 232–234 °C.

Calcd. for $C_{26}H_{24}N_2O_4 \cdot \frac{1}{2}H_2O$ (436.5): C 71.38, H 5.76, N 6.40; found: C 71.32, H 5.68, N 6.42.

5-[6-(2,3-Dihydroxyphenyl)hexyl]-5′-methyl-2,2′-bipyridine (**12-H$_2$**):

Yield: 97 % of a light pink solid; mp 130–132 °C.

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Calcd. for $C_{23}H_{26}N_2O_2 \cdot \frac{1}{2}H_2O$ (370.5): C 74.37, H 7.33, N 7.54; found: C 74.67, H 7.08, N 7.21.

5-[6-(2,3-Dihydroxy-4-pentylphenyl)hexyl]-5'-methyl-2,2'-bipyridine **(13-H$_2$)**:

Yield: 100% of a red waxy solid.

Calcd. for $C_{28}H_{36}N_2O_2$ (432.6): C 77.74, H 8.39, N 6.48; found: C 77.64, H 8.37, N 6.17.

5'-Hexyl-5-[6-(2,3-dihydroxy-4-pentylphenyl)hexyl]-2,2'-bipyridine **(14-H$_2$)**:

Yield: 89% of a light pink waxy solid.

Calcd. for $C_{33}H_{46}N_2O_2$ (502.7): C 78.84, H 9.22, N 5.57; found: C 78.65, H 9.15, N 5.43.

5-[2-(2,3-Dihydroxyphenyl)butyl]-5'-methyl-2,2'-bipyridine **(19-H$_2$)**:

Yield: 90% of a white solid; mp 137–138 °C.

5,5'-Bis[2-(2,3-dihydroxyphenyl)butyl]-2,2'-bipyridine **(20-H$_4$)**:

Yield: 97% of a white solid; mp 172–173 °C.

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