Synthesis of Functionalized Long-Chain Thiols and Thiophenols for the Formation of Self-Assembled Monolayers on Gold

Frank Buckel,[a,1] Per Persson,[b,2] Franz Effenberger*[a]

[a] Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany
Fax +49(711)6854269; E-mail: franz.effenberger@po.uni-stuttgart.de
[b] Royal Institute of Technology, Department of Organic Chemistry, S-100 44 Stockholm, Sweden
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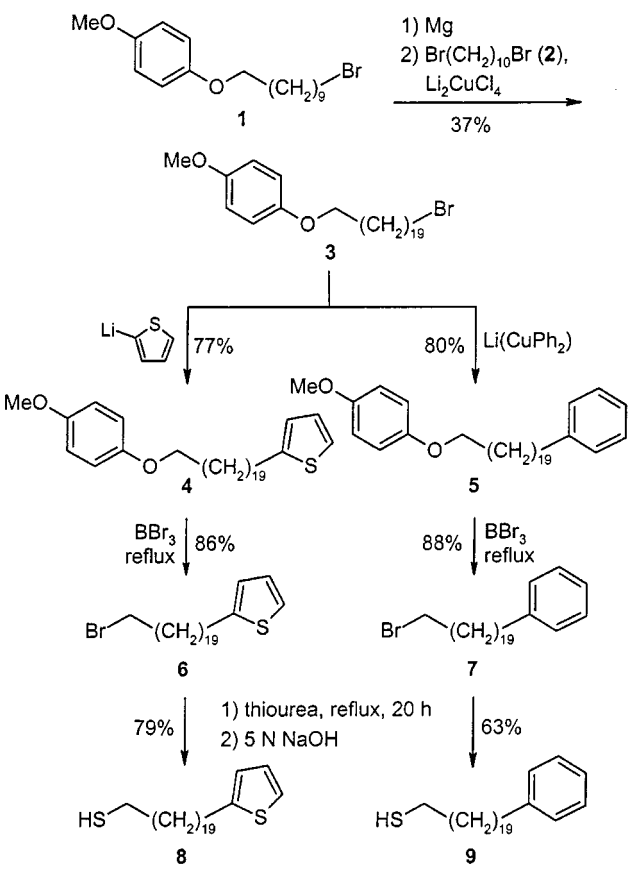
Abstract: The terminally 2-thienyl- and phenyl-substituted eicosane derivatives **4** and **5** were prepared by reacting 1-[(20-bromoeicosyl)oxy]-4-methoxybenzene (**3**) with 2-lithiothiophene and lithium diphenylcuprate, respectively. Reaction of **4** and **5** with BBr_3 leads to the corresponding bromides **6**, **7** which afforded the aryl-substituted eicosanethiols **8** and **9** by nucleophilic substitution with thiourea. 4-Eicosylthiophenol (**13**) was prepared from eicosylbenzene (**11**) by chlorosulfonation and subsequent reduction of the sulfonyl chloride. Synthesis of the thiol **22** with phenylenedioxy groups incorporated in the alkyl chain involves formation of **19** from allyloxy(bromobutoxy)benzene (**18**) and (4-(2-thienyl)butoxy)phenol (**17**). Hydroboration of **19** yields the corresponding alcohol **20**, which under Mitsunobu conditions and subsequent reduction with $LiAlH_4$ can be transformed to **22**.

Key words: functionalized long-chain alkanethiols, 4-alkylthiophenol, self-assembled monolayers on gold

Long-chain alkanethiols are known to form well ordered monolayers on gold.[3,4] These self-assembled monolayers (SAMs) are of interest due to their numerous applications.[4] The properties of SAMs (conductivity, wettability etc.) depend strongly on packing and orientation of the molecules in the layer. The two-dimensional order results from intermolecular interactions, e.g. van der Waals interactions. SAMs with aromatic systems incorporated may act as electron donors or acceptors, and furthermore, the π-systems could influence the layer structure sterically and by π-π interaction of the aromatic moiety. Compounds, suitable for formation of SAMs, can be structured in three parts: an anchor group for linkage to the substrate, a carbon chain of 2–3 nm length, and a terminal group with variable chemical functionalities.

In the present publication we report on the synthesis of terminally thienyl- and phenyl-substituted alkanethiols, a 4-alkylthiophenol as well as a long-chain thiol with phenylenedioxy groups incorporated in the alkyl chain. The formation and characterization of SAMs formed from these adsorbates will be published elsewhere.

Long-chain alkanethiols can be prepared simply by S_N reactions from the corresponding alkyl bromides.[5] In analogy to a literature-known procedure[6] bromide **1** was converted to the Grignard reagent which was coupled with 1,10-dibromodecane (**2**) in the presence of a catalytic amount of Li_2CuCl_4 to give the α,ω-substituted long-chain alkane **3** (Scheme 1). In bromide **1**[7] hydroquinonemonomethyl ether is used as a protecting group which can be transformed easily in a bromide function.[7,8]



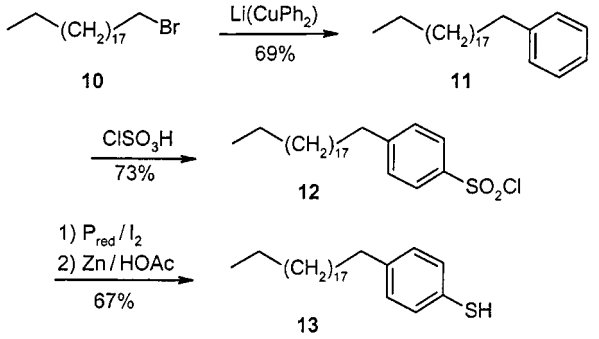
Scheme 1

Whereas **3** reacted with 2-lithiothiophene[9] to give the ω-protected α-(2-thienyl)alkane **4** in 77% yield, the conversion of **3** with phenyllithium was accompanied by numerous side-reactions.[10] The yield of the phenyl derivative **5** was only 14%. Replacing phenyllithium by lithium diphenylcuprate[10] afforded the coupling product **5** in 80% yield.

BBr_3 in boiling dichloromethane[8] was found to be more effective for simultaneous deprotection and bromination of **4** and **5** than the published system HBr/acetic anhydride at 100°C.[8] In HBr/acetic anhydride compound **6** with terminal thienyl group was isolated in only 42% yield after a

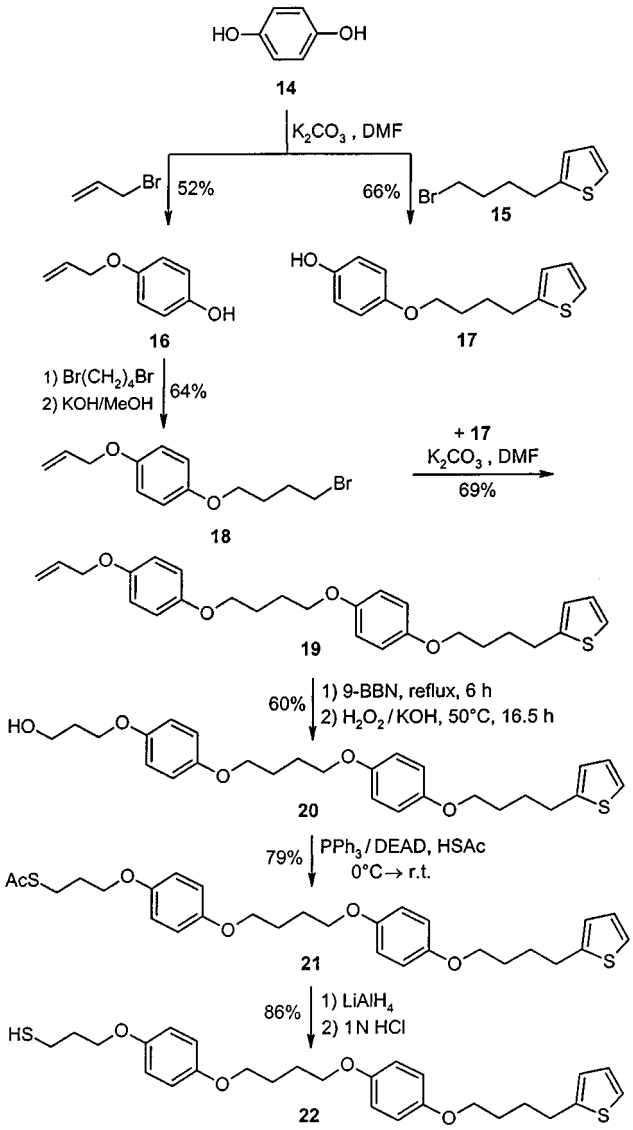
reaction time of 8 d. However, by using BBr_3 the ω-bromides **6** and **7** were available after 1.5 h in high chemical yields (Scheme 1). By reaction of **6** and **7** with thiourea in 95% ethanol and cleavage of the resultant isothiouronium salt with NaOH under argon atmosphere the terminally aryl-substituted eicosanethiols **8** and **9** were obtained.

In order to compare steric and electronic influences of alkylthiols with thiophenols as anchor groups for the formation of SAMs on gold, a 4-alkyl substituted thiophenol of comparable chain length had to be synthesized. The known eicosylbenzene (**11**)[11] could be prepared by reacting 1-bromoeicosane (**10**) with lithium diphenylcuprate (Scheme 2). The thiol function was introduced in the benzene ring of **11** in the common way[5] by chlorosulfonation to sulfonyl chloride **12** and subsequent reduction of the SO_2Cl group with red phosphorus/iodine. The intermediate disulfide formed owing to the easy oxidizability of thiophenols, could be reduced with zinc in glacial acetic acid giving 4-eicosylthiophenol (**13**) in 67% yield.



Scheme 2

The synthetic route to compound **22** with *p*-phenylenedioxy groups incorporated in the alkyl chain, which has been designed by molecular modelling[12] for formation of SAMs, is based on literature-known methodologies (Scheme 3).



Scheme 3

Monoalkylation of hydroquinone (**14**) with allyl bromide has been reported to give **16** in only 27% yield after distillation.[13] Therefore **16** has been purified by flash chromatography on silica gel. By this procedure the yield could be improved to 52% (Table 1). Analogously, **14** was reacted with bromide **15**[14] to give **17** in 66% yield (Table 1). Thereby the concentration of **14** was maintained at a high level throughout the reaction in order to minimize a disubstitution of **14**. The bromide **18** was prepared by alkylation of **16** with 1,4-dibromobutane. To avoid dialkylation, dibromobutane was added in fivefold excess (referred to **16**). By alkylation of the phenol **17** with bromide **18** compound **19** was obtained in 69% yield (Table 1).

Table 1 Synthesis of Compounds **16**, **17** and **19**

	Starting Materials				Reaction Conditions			Product	Yield %	Mp (°C); appearance
	14, **17** (mmol)		Bromide (mmol)	K_2CO_3 (mmol)	DMF (mL)	Temp (°C)	Time (h)			
14	41.3	allyl	8.6	20.6	30	60	20	**16**	52	40–42
14	114.0	**15**	23.0	57.0	60	80	4	**17**	66	44–45; pale solid
17	4.18	**18**	4.03	4.43	20	75	24	**19**	69	108–109; white solid

The terminal functionalization of **19** to a thiol was achieved by hydroboration with 9-borabicyclo[3.3.1]nonane[15] (9-BBN) and subsequent oxidation using H_2O_2. The regioselectivity of 9-BBN compared with that of BH_3 has been investigated in the transformation of **18** into the corresponding alcohol: in accordance to published results,[16] the sterically demanding 9-BBN was found to be significantly more regioselective than BH_3 (99.2%: 70%), and therefore it was used as hydroborating agent for **19**. The resulting alcohol **20**, which was isolated in 60% yield, was converted via Mitsunobu reaction with triphenylphosphine/diethyl azodicarboxylate (DEAD) and thioacetic acid as a nucleophile to give thioacetate **21** in 79% yield. The synthesis was accomplished by reduction of the thioacetate with $LiAlH_4$ yielding 86% of the desired functionalized thiol **22**.

^{1}H NMR spectra were recorded on a Bruker AC 250 F (250 MHz) or Bruker ARX 500 (500 MHz) spectrometer with TMS as internal standard. Mps were determined on a Büchi SMP 20 apparatus and are uncorrected. Preparative column chromatography was performed using glass columns of different size packed with silica gel S, grain size 0.032–0.063 mm (Riedel-de Haen). All solvents and educts were purified and dried. All experiments were carried out under Ar as inert gas in flame-dried apparatus. For reaction yielding thiols an Oxisorb filter (Messer-Griesheim) was additionally used and solvents were degassed.

1-[(20-Bromoeicosyl)oxy]-4-methoxybenzene (3)
According to reference 6, from **1**[7] (13.73 g, 40.0 mmol) and **2** (24.01 g, 80.0 mmol); after workup, the excess of **1** was distilled off (121°C/0.01 Torr), and crude **3** was chromatographed on silica gel with petroleum ether/CH_2Cl_2 (1:1); recrystallization from petroleum ether/CH_2Cl_2 gave **3** as colourless crystals (7.07 g, 37%); mp 84°C.

^{1}H NMR ($CDCl_3$): δ = 1.26–1.42 (m, 32 H, 16 CH_2), 1.69–1.78 (m, 2 H, CH_2), 1.82–1.91 (m, 2 H, CH_2), 3.41 (t, *J* = 6.9 Hz, 2 H, CH_2Br), 3.77 (s, 3 H, CH_3O), 3.90 (t, *J* = 6.6 Hz, 2 H, OCH_2), 6.83 (s, 4 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 26.07–29.69 (CH_2), 32.85 (CH_2), 34.05 (CH_2Br), 55.73 (CH_3), 68.66 (CH_2O), 114.60 (Ph), 115.41 (Ph), 153.31 (Ph), 153.65 (Ph).

Anal. calcd for $C_{27}H_{47}BrO_2$: C, 67.06; H, 9.80; Br, 16.52. Found: C, 67.28; H, 9.69; Br, 16.37.

2-[20-(4-Methoxyphenoxy)eicosyl]thiophene (4)
A solution of **3** (7.0 g, 14.47 mmol) in anhyd THF (180 mL) was added dropwise at r.t. to a stirred solution of 2-lithiothiophene, prepared from thiophene (2.78 mL, 35.12 mmol) and a 1.6 M solution of BuLi in hexane (18.1 mL, 28.96 mmol) diluted in THF (21 mL).[9] After 3 d, the mixture was hydrolyzed with ice-H_2O (70 mL), and the aqueous phase was extracted several times with Et_2O. The combined extracts were dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel with petroleum ether/CH_2Cl_2 (1:1). Recrystallization from MeOH gave **4** as yellow crystals (5.44 g, 77%); mp 76°C.

^{1}H NMR ($CDCl_3$): δ = 1.25–1.43 (m, 32 H, 16 CH_2), 1.61–1.80 (m, 4 H, 2 CH_2), 2.81 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.76 (s, 3 H, CH_3O), 3.89 (t, *J* = 6.6 Hz, 2 H, OCH_2), 6.77 (dd, *J* = 3.4, 1.0 Hz, 1 H, thienyl H-3), 6.83 (s, 4 H, Ph), 6.91 (dd, *J* = 5.1, 3.4 Hz, 1 H, thienyl H-4), 7.09 (dd, *J* = 5.1, 1.1 Hz, 1 H, thienyl H-5).

^{13}C NMR ($CDCl_3$): δ = 26.07–29.93 (CH_2), 31.82 (CH_2), 55.74 (CH_3), 68.68 (CH_2O), 114.61 (Ph), 115.43 (Ph), 122.69 (thienyl C-4), 123.87 (thienyl C-2), 126.62 (thienyl C-3), 145.90 (thienyl C-1), 153.32 (Ph), 153.65 (Ph).

Anal. calcd for $C_{31}H_{50}O_2S$: C, 76.49; H, 10.35; S, 6.59. Found: C, 76.48; H, 10.26; S, 6.83.

Preparation of Phenyl-Substituted Compounds 5 and 11; General Procedure
To an ice-cooled suspension of CuBr·Me_2S (12 mmol for **3**, 40 mmol for **10**) in anhyd Et_2O (30 or 100 mL) a 1.8 M solution of phenyllithium in cyclohexane/Et_2O (2 equiv based on CuBr·MeS) was added followed by a solution of **3** or **10** in anhyd THF (40 or 25 mL). The mixture was allowed to warm to r.t., and poured onto a solution of NH_4Cl . The aqueous phase was extracted several times with Et_2O, and the combined extracts were washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo.

(20-(4-Methoxyphenoxy)eicosyl)benzene (5)
From **3** (1.45 g, 3.0 mmol), 2.5 d reaction time, chromatography on silica gel with petroleum ether/CH_2Cl_2 (1:1) and recrystallization from MeOH was obtained 1.15 g (80%) of **5** as a colourless solid; mp 62–63°C.

^{1}H NMR ($CDCl_3$): δ = 1.25–1.45 (m, 32 H, 16 CH_2), 1.58–1.62 (m, 2 H, CH_2), 1.72–1.78 (m, 2 H, CH_2), 2.59 (t, *J* = 7.8 Hz, 2 H, CH_2Ph), 3.76 (s, 3 H, CH_3O), 3.90 (t, *J* = 6.6 Hz, 2 H, OCH_2), 6.83 (s, 4 H, Ph), 7.15–7.28 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 26.07–29.70 (CH_2), 31.54 (CH_2), 36.00 (CH_2Ph), 55.74 (CH_3), 68.68 (CH_2O), 114.60 (Ph), 115.43 (Ph), 125.53 (Ph), 128.20 (Ph), 128.39 (Ph), 142.97 (Ph), 153.32 (Ph), 153.65 (Ph).

Anal. calcd for $C_{33}H_{52}O_2$: C, 82.44; H, 10.90. Found: C, 82.49; H, 11.00.

Eicosylbenzene (11)
From **10** (3.61 g, 10.0 mmol), 1 d reaction time, and fractional distillation was obtained 2.48 g (69%) of **11** as a colourless solid; bp 175–182°C/0.1 Torr; mp 38–39°C.

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.22–1.30 (m, 34 H, 17 CH_2), 1.59–1.62 (m, 2 H, CH_2), 2.60 (t, *J* = 7.8 Hz, 2 H, CH_2Ph), 7.15–7.28 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 14.13 (CH_3), 22.71 (CH_2), 29.36–29.71 (CH_2), 31.55 (CH_2), 31.94 (CH_2), 36.01 (CH_2Ph), 125.54 (Ph), 128.21 (Ph), 128.40 (Ph), 142.98 (Ph).

Anal. calcd for $C_{26}H_{46}$: C, 87.07; H, 12.93. Found: C, 87.19; H, 12.95.

Deprotection and Bromination to Compounds 6 and 7; General Procedure
To a solution of **4** or **5** in CH_2Cl_2 (150 or 10 mL) an equimolar amount of BBr_3 was added dropwise within 5–30 min. After being refluxed for 1.5 h, the mixture was hydrolyzed with a solution of NH_4Cl, and the aqueous phase was extracted with CH_2Cl_2 . The combined extracts were washed with H_2O , a solution of $NaHCO_3$ and H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel with petroleum ether.

2-(20-Bromoeicosyl)thiophene (6)
From **4** (4.87 g, 10.0 mmol) was obtained 3.83 g (86%) of **6** as colourless crystals; mp 42–43°C.

^{1}H NMR ($CDCl_3$): δ = 1.25–1.45 (m, 32 H, 16 CH_2), 1.61–1.70 (m, 2 H, CH_2), 1.79–1.91 (m, 2 H, CH_2), 2.81 (t, *J* = 7.6 Hz, 2 H, CH_2), 3.40 (t, *J* = 6.9 Hz, 2 H, CH_2Br), 6.77 (dd, *J* = 3.4, 1.0 Hz, 1 H, thie-

nyl H-3), 6.91 (dd, *J* = 3.4, 5.1 Hz, 1 H, thienyl H-4), 7.10 (dd, *J* = 5.1, 1.1 Hz, 1 H, thienyl H-5).

^{13}C NMR ($CDCl_3$): δ = 28.20–29.93 (CH_2), 31.82 (CH_2), 32.86 (CH_2), 34.04 (CH_2Br), 122.69 (thienyl C-4), 123.87 (thienyl C-2), 126.62 (thienyl C-3), 142.89 (thienyl C-1).

Anal. calcd for $C_{24}H_{43}BrS$: C, 64.98; H, 9.77; Br, 18.01; S, 7.23. Found: C, 64.77; H, 9.84; Br, 18.22; S, 7.19.

20-Bromoeicosylbenzene (7)
From **5** (961.5 mg, 2.0 mmol) was obtained 766.9 mg (88%) of **7** as a colourless solid; mp 36°C.

^{1}H NMR ($CDCl_3$): δ = 1.25–1.43 (m, 32 H, 16 CH_2), 1.57–1.62 (m, 2 H, CH_2), 1.82–1.88 (m, 2 H, CH_2), 2.59 (t, *J* = 7.8 Hz, 2 H, C*H*$_2$Ph), 3.40 (t, *J* = 6.9 Hz, 2 H, CH_2Br), 7.15–7.28 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 28.19–29.69 (CH_2), 31.55 (CH_2), 32.85 (CH_2), 34.08 (CH_2Br), 36.00 (*C*H$_2$Ph), 125.53 (Ph), 128.20 (Ph), 128.39 (Ph), 142.96 (Ph).

Anal. calcd for $C_{26}H_{45}Br$: C, 71.37; H, 10.37; Br, 18.26. Found: C, 71.47; H, 10.40; Br, 17.98.

Preparation of Thiols 8 and 9; General Procedure
A solution of **6** or **7** and thiourea (1.1 equiv) in EtOH (95%) was heated to reflux for 20 h. Then 5 M NaOH (1.2 or 0.6 mL) was added, and the mixture was refluxed for a further 4 h. After being cooled to r.t., CH_2Cl_2 and H_2O were added. The aqueous phase was extracted with CH_2Cl_2 . The combined extracts were washed with H_2O, a solution of NH_4Cl and H_2O , dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel with petroleum ether/CH_2Cl_2 (10:1) (**8**) or petroleum ether (**9**).

20-(2-Thienyl)eicosanethiol (8)
From **6** (887.1 mg, 2.0 mmol) was obtained 623.2 mg (79%) of **8** as a colourless solid; mp 45–46°C.

^{1}H NMR ($CDCl_3$): δ = 1.25–1.36 (m, 32 H, 16 CH_2), 1.33 (t, *J* = 7.7 Hz, 1 H, SH), 1.58–1.70 (m, 4 H, CH_2), 2.48–2.56 (m, 2 H, C*H*$_2$SH), 2.81 (t, *J* = 7.6 Hz, 2 H, CH_2), 6.77 (dd, *J* = 3.4, 0.8 Hz, 1 H, thienyl H-3), 6.91 (dd, *J* = 5.1, 3.4 Hz, 1 H, thienyl H-4), 7.10 (dd, *J* = 5.1, 1.1 Hz, 1 H, thienyl H-5).

^{13}C NMR ($CDCl_3$): δ = 24.68 (CH_2SH), 28.40–29.93 (CH_2), 31.82 (CH_2), 34.07 (CH_2), 122.70 (thienyl C-4), 123.87 (thienyl C-2), 126.62 (thienyl C-3), 145.90 (thienyl C-1).

Anal. calcd for $C_{24}H_{44}S_2$: C, 72.66; H, 11.18; S, 16.16. Found: C, 72.67; H, 11.25; S, 16.29.

20-Phenyleicosanethiol (9)
From **7** (437.6 mg, 1.0 mmol) was obtained 245.7 mg (63%) of **9** as a colourless solid; mp 40–41°C.

^{1}H NMR ($CDCl_3$): δ = 1.25–1.38 (m, 32 H, 16 CH_2), 1.33 (t, *J* = 7.7 Hz, 1 H, SH), 1.57–1.63 (m, 4 H, CH_2), 2.50–2.54 (m, 2 H, C*H*$_2$SH), 2.60 (t, *J* = 7.8 Hz, 2 H, C*H*$_2$Ph), 7.15–7.29 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 24.67 (CH_2SH), 28.39–29.69 (CH_2), 31.54 (CH_2), 34.07 (CH_2), 36.00 (CH_2Ph), 125.53 (Ph), 128.20 (Ph), 128.39 (Ph), 142.97 (Ph).

Anal. calcd for $C_{26}H_{46}S$: C, 79.92; H, 11.87; S, 8.21. Found: C, 79.77; H, 11.88; S, 8.35.

4-Eicosylbenzenesulfonyl Chloride (12)
To a solution of **11** (1.79 g, 5.0 mmol) in $CHCl_3$ (5 mL) chlorosulfuric acid (1 mL, 15.0 mmol) was added, and the mixture was stirred at r.t. for 22 h. Then it was poured on ice, and the aqueous phase was extracted with CH_2Cl_2 . The combined extracts were washed with H_2O, a solution of $NaHCO_3$ and H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel with petroleum ether/CH_2Cl_2 (3:1) to give **12** as a colourless solid (1.67 g, 73%); mp 59°C.

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.25–1.32 (m, 34 H, 17 CH_2), 1.63–1.66 (m, 2 H, CH_2), 2.72 (t, *J* = 7.8 Hz, 2 H, C*H*$_2$Ph), 7.40 (d, *J* = 8.5 Hz, 2 H, Ph), 7.94 (d, *J* = 8.5 Hz, 2 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 14.13 (CH_3), 22.70 (CH_2), 29.20–29.71 (CH_2), 30.95 (CH_2), 31.93 (CH_2), 36.07 (*C*H$_2$Ph), 127.09 (Ph), 129.59 (Ph), 141.77 (Ph), 151.68 (Ph).

Anal. calcd for $C_{26}H_{45}ClO_2S$: C, 68.31; H, 9.92; Cl, 7.76; S, 7.01. Found: C, 68.51; H, 10.00; Cl, 7.60; S, 6.76.

4-Eicosylthiophenol (13)
To a boiling suspension of red phosphorus (83.6 mg, 2.7 mmol) and iodine (4.1 mg, 0.016 mmol) in glacial HOAc (7 mL) **12** (457.2 mg, 1.0 mmol) was added portionwise within 15 min. After being heated to reflux for 23 h, H_2O (1 mL) was added, and the mixture refluxed for a further 1 h. Then CH_2Cl_2 and H_2O were added, and the aqueous phase extracted with CH_2Cl_2. The combined extracts were washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel with petroleum ether to give 303.3 mg (78%) of disulfide.

To a solution of disulfide (288.0 mg, 0.37 mmol) in CH_2Cl_2 (20 mL) Zn dust (196.1 mg, 3.0 mmol) and glacial HOAc (0.5 mL) were added. After stirring for 15 h, the mixture was filtered through a silica gel column. The resulting solid was recrystallized from MeOH to give **13** as a colourless solid (246.9 mg, 86%); mp 54–55°C.

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.21–1.29 (m, 34 H, 17 CH_2), 1.55–1.58 (m, 2 H, CH_2), 2.54 (t, *J* = 7.7 Hz, 2 H, C*H*$_2$Ph), 3.38 (s, 1 H, SH), 7.05 (d, *J* = 8.1 Hz, 2 H, Ph), 7.20 (d, *J* = 8.1 Hz, 2 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 14.14 (CH_3), 22.71 (CH_2), 29.23–29.71 (CH_2), 31.44 (CH_2), 31.94 (CH_2), 35.40 (*C*H$_2$Ph), 126.76 (Ph), 129.20 (Ph), 129.86 (Ph), 140.79 (Ph).

Anal. calcd for $C_{26}H_{46}S$: C, 79.93; H, 11.87; S, 8.21. Found: C, 79.99; H, 11.98; S, 8.16.

Preparation of Compounds 16, 17 and 19; General Procedure
To a stirred solution of **14** and potassium carbonate in anhyd DMF under Ar allyl bromide or a solution of **15**[14] in DMF (10 mL) was added dropwise over 0.5–1 h. In the case of **19**, K_2CO_3 was added to a stirred solution of **18** and **17** in anhyd DMF (20 mL). After heating to 60–80°C (Table 1), the mixture was allowed to cool to r.t., hydrolyzed with ice–H_2O, and neutralized in the case of **16**, **17** with 1–2 M HCl. Then it was extracted with CH_2Cl_2. The combined extracts were washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2 or 2% MeOH in CH_2Cl_2 (for **17**) (Table 1 and 2).

Allyloxy-4-(4-bromobutoxy)benzene (18)
To a vigorously stirred solution of **16** (5.38 g, 36.0 mmol) and 1,4-dibromobutane (39.0 g, 180.0 mmol) in MeOH (30 mL) at 60°C under Ar was added dropwise a solution of KOH (2.02 g, 36.0 mmol) in MeOH (20 mL) within 3 h. After being refluxed for a further 6 h, the mixture was allowed to cool to r.t., mixed with ice–H_2O (300 mL) and left for 0.5 h. Then it was neutralized with dilute HCl and extracted with CH_2Cl_2 (3 x 150 mL each). The combined extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel with CH_2Cl_2. In order to remove dibromobutane completely, the remaining oil was distilled bulb-to-bulb at 40°C/0.2 Torr to give **18** as a white solid (6.57 g, 64%); mp 34°C.

^{1}H NMR ($CDCl_3$): δ = 1.85–2.12 (m, 4 H, 2 CH_2), 3.48 (t, *J* = 6.5 Hz, 2 H, CH_2Br), 3.94 (t, *J* = 5.9 Hz, 2 H, OCH_2), 4.46–4.50 (m, 2 H, =CHC*H*$_2$), 5.24–5.44 (m, 2 H, CH_2=), 5.97–6.12 (m, 1 H, =CH), 6.78–6.87 (m, 4 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 28.0, 29.5 (CH_2), 33.5 (CH_2Br), 67.4 (OCH_2), 69.5 (=$CHCH_2$), 115.3, 115.7 (Ph), 117.5 (CH_2=), 133.6 (CH), 152.8, 153.2 (Ph).

Anal. calcd for $C_{13}H_{17}BrO_2$: C, 54.75; H, 6.01; Br, 28.02. Found: C, 54.90; H, 5.95; Br, 27.98.

3-[4-(4-{4-[4-(2-Thienyl)butoxy]phenoxy}butoxy)phenoxy]-1-propanol (20)

To a solution of **19** (1.58 g, 3.49 mmol) in anhyd THF (25 mL) under N_2 a 0.5 M solution of 9-borabicyclo[3.3.1]nonane (9-BBN) in THF (9.0 mL, 4.50 mmol) was slowly added, and the mixture was heated to reflux for 6 h. After being allowed to cool to r.t., a mixture from 30% solution of H_2O_2 (2 mL, 17.0 mmol) and 5 M solution of KOH (4 mL, 20.0 mmol) was added. The mixture was heated to 50°C for 1.5 h, and stirred for a further 15 h. The precipitate was filtered off, and washed with a small volume of cold THF and H_2O. Recrystallization from THF and flash chromatography on silica gel with 2% MeOH in CH_2Cl_2 gave **20** as a white solid (979 mg, 60%); mp 128–129°C (Table 2).

S-3-[4-(4-{4-[4-(2-Thienyl)butoxy]phenoxy}butoxy)phenoxy]propyl Thioacetate (21)

To a solution of PPh_3 (262.3 mg, 1.0 mmol) in anhyd THF (5 mL) at 0°C was added dropwise DEAD (156 μL, 1.0 mmol), and the mixture was stirred for 0.5 h. Then a solution of **20** (235.3 mg, 0.5 mmol) and thioacetic acid (71 μL, 1.0 mmol) in anhyd THF (30 mL) was added dropwise within 20 min. After stirring at 0°C for a further 1 h, the mixture was allowed to warm to r.t. (17 h). The reaction was terminated by concentration in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2 to give **21** as a colourless solid (207.4 mg, 79%); mp 102–104°C (Table 2).

3-[4-(4-{4-[4-(2-Thienyl)butoxy]phenoxy}butoxy)phenoxy]-1-propanethiol (22)

To a solution of **21** (158.6 mg, 0.3 mmol) in anhyd THF (5 mL) at r.t. was added $LiAlH_4$ (22.8 mg, 0.6 mmol), and the mixture was stirred for 2 h. After addition of 1 M HCl (5 mL) followed by CH_2Cl_2 (10 mL) (ice-cooling) and 1 M HCl (5 mL) at r.t., the mixture was stirred for 0.5 h. The phases were separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined extracts were washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2 to give **22** as a colourless solid (125.0 mg, 86%); mp 105–106°C (Table 2).

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Table 2 Spectroscopic Data of Compounds **17**, and **19–22**

Product[b]	^1H NMR (500 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
17	1.81–1.88 (m, 4 H, CH_2), 2.89 (t, *J* = 6.9, 2 H, CH_2), 3.91 (t, *J* = 6.0, 2 H, OCH_2), 4.60 (s, 1 H, OH), 6.73–6.78 (m, 4 H, Ph), 6.80 (dd, *J* = 1.1, 3.4, 1 H, thienyl H-3), 6.91 (dd, *J* = 3.4, 5.1, 1 H, thienyl H-4), 7.11 (dd, *J* = 1.2, 5.1, 1 H, thienyl H-5)	28.3, 28.7 (CH_2), 29.6 (CH_2), 68.3 (OCH_2), 115.6, 116.0 (Ph), 123.0 (thienyl C-4), 124.2 (thienyl C-2), 126.7 (thienyl C-3), 145.1 (thienyl C-1), 149.4 (Ph C-1), 153.2 (Ph C-4)
19	1.80–1.87 (m, 4 H, CH_2), 1.91–1.96 (m, 4 H, CH_2), 2.90 (t, *J* = 6.9, 2 H, CH_2), 3.92 (t, *J* = 5.9, 2 H, OCH_2), 3.97 (t, *J* = 5.5, 4 H, 2 OCH_2), 4.47–4.49 (m, 2 H, =$CHCH_2$), 5.25–5.41 (m, 2 H, CH_2=), 6.00–6.08 (m, 1H, CH), 6.77-6.87 (m, 9 H, Ph, thienyl H-3), 6.91 (dd, *J* = 3.5, 5.1, 1 H, thienyl H-4), 7.11 (dd, *J* = 1.1, 5.1, 1 H, thienyl H-5)	26.5 (CH_2), 28.7, 29.2 (CH_2), 30.0 (CH_2), 68.5, 68.6, 69.9 (CH_2O), 115.8, 116.1 (Ph), 117.9 (CH_2=), 123.4 (thienyl C-4), 124.6 (thienyl C-2), 127.1 (thienyl C-3), 134.0 (CH), 145.5 (thienyl C-1), 153.1 (Ph C-4), 153.5, 153.6, 153.7 (Ph C-1,4)
20[a]	1.73–1.78 (m, 4 H, CH_2), 1.78–1.84 (m, 6 H, CH_2), 2.85 (t, *J* = 6.8, 2 H, CH_2), 3.52-3.55 (m, 2 H, CH_2OH), 3.90–3.96 (m, 8 H, CH_2O), 4.52 (t, *J* = 5.1, 1 H, OH), 6.82–6.88 (m, 9 H, Ph, thienyl H-3), 6.93 (dd, *J* = 3.4, 5.0, 1 H, thienyl H-4), 7.31 (dd, *J* = 0.8, 5.1, 1 H, thienyl H-5)	25.4 (CH_2), 27.8, 28.1, 28.7 (CH_2), 32.1 (CH_2), 57.2 (CH_2OH), 64.8, 67.4 (CH_2O), 115.1, 115.2 (Ph), 123.3 (thienyl C-4), 124.3 (thienyl C-2), 126.8 (thienyl C-3), 144.5 (thienyl C-1), 152.4, 152.5, 152.6 (Ph C-1,4)
21	1.82–1.89 (m, 4 H, CH_2), 1.92–1.96 (m, 4 H, CH_2), 2.04 (tt, *J* = 6.1, 7.1, 2 H, CH_2), 2.34 (s, 3 H, CH_3), 2.90 (t, *J* = 7.0, 2 H, CH_2), 3.05 (t, *J* = 7.1, 2 H, SCH_2), 3.93 (t, *J* = 6.1, 2 H, OCH_2), 3.96 (t, *J* = 6.1, 4 H, CH_2O), 3.97 (t, *J* = 5.9, 2 H, CH_2O), 6.80 (dd, *J* = 1.0, 3.4, 1 H, thienyl H-3), 6.82 (s, 8 H, Ph), 6.92 (dd, *J* = 3.4, 5.1, 1 H, thienyl H-4), 7.12 (dd, *J* = 1.1, 5.1, 1 H, thienyl H-5)	25.92-29.62 (CH_2), 30.65 (CH_3), 66.85, 68.11, 68.20 (CH_2O), 115.40, 115.47 (Ph), 122.95 (thienyl C-4), 124.18 (thienyl C-2), 126.70 (thienyl C-3), 145.11 (thienyl C-1), 152.90, 153.11, 153.17, 153.28 (Ph C-1,4), 195.81 (C=O)
22	1.39 (t, *J* = 8.1, 1 H, SH), 1.81–1.89 (m, 4 H, CH_2), 1.93–1.96 (m, 4 H, CH_2), 2.05 (tt, *J* = 7.1, 5.9, 2 H, CH_2), 2.73 (td, *J* = 6.9, 8.2, 2 H, CH_2SH), 2.90 (t, *J* = 6.9, 2 H, CH_2), 3.93 (t, *J* = 6.0, 2 H, OCH_2), 3.97 (t, *J* = 5.4, 4 H, CH_2O), 4.02 (t, *J* = 5.9, 2 H, CH_2O), 6.80 (dd, *J* = 1.1, 3.4, 1 H, thienyl H-3), 6.82, 6.83 (each s, 8 H, Ph), 6.92 (dd, *J* = 3.4, 5.1, 1 H, thienyl H-4), 7.12 (dd, *J* = 1.0, 5.1, 1 H, thienyl H-5)	21.31 (CH_2SH), 26.10-29.62 (CH_2), 33.46 (CH_2), 66.28, 68.12, 68.21 (CH_2O), 115.41, 115.44 (Ph), 122.96 (thienyl C-4), 124.19 (thienyl C-2), 126.71 (thienyl C-3), 145.12 (thienyl C-1), 152.95, 153.11, 153.17, 153.27 (Ph C-1,4)

[a] In DMSO-d_6.
[b] Satisfactory microanalysis found for each compound.

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