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Design and Synthesis of a Class of Twin-Chain Amphiphiles for Self-Assembled Monolayer-Based Electrochemical Biosensor Applications

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A new class of twin-chain hydroxyalkylthiols (mercaptoalkanols) is described that features a nearly constant cross section and the potential for modification at one or both termini. These compounds are regioselectively available through Pd-mediated couplings of benzene diiododitriflate, and their syntheses include an example of a previously unreported coupling reaction to generate an *ortho*-substituted arene bis(acetic acid). In an electrochemical sensor system, the self-assembled monolayers (SAMs) that were prepared from the new amphiphiles demonstrate an improved stability in comparison to the monolayers prepared from analogous single-chain thiols.

Introduction

The use of functionalized amphiphiles is central to a wide array of applications and disciplines.[1–3] One of the most important classes of amphiphiles is constructed from long-chain thiols. The strength of the gold-sulfur interaction, combined with the selectivity of gold for thiols and related functional groups, provides the basis for creating robust self-assembled monolayers (SAMs) that can tolerate a diverse array of functionality (commonly, –OH, $–N_3$, or $–CH_3$ groups) at the terminus or "tail" of the amphiphile.[4] When incorporated into SAM-based electrochemical biosensors, these functionalized amphiphiles serve to passivate and provide stability to the sensing element and to tether the sensing element to the surface. The stability of the SAM, and therefore of the sensor, increases with the chain length of the thiol component.[5] However, in electrochemical biosensor applications, the use of very long-chain thiol backbones would result in the formation of highly resistive monolayers, which consequently would impede electrochemical readouts. To address this, we now report the synthesis of a new class of arene cross-linked twin-chain dithiol amphiphiles. The new amphiphiles, which feature a nearly constant cross section and functionalized termini, form stable SAM-based sensors that are more capable of withstanding multiple electrochemical perturbations than the single-chain amphiphiles of similar length.

The vast majority of amphiphiles that are utilized for surface passivation or substrate attachment in gold-thiolate biosensors are single-chain mercaptoalkanols (hydroxyalkylthiols),[6] the limitations of which have been reported elsewhere.[7] A number of multidentate thiol-based amphiphiles have also been reported (see Figure 1). Amphiphiles based upon multidentate thiols have several advantages over their single-chain counterparts, that is, they absorb more rapidly onto the gold surface, and they generate more stable SAMs.[8,9] These properties are directly relevant to the performance, stability, and reusability of biosensors. However, existing multidentate thiols either possess unfunctionalized termini, which limit the ability to create functional monolayers, or feature a significant mismatch between the multivalent "head" and the termini.[10–12] As part of a collaboration that targets the creation of SAM-based sensors on

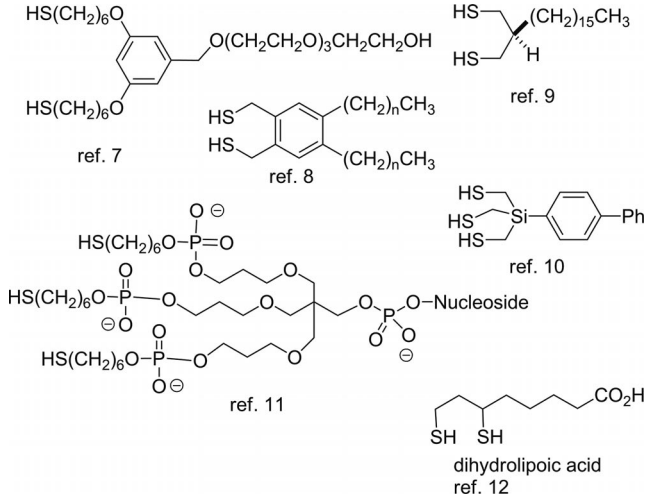

Figure 1. Examples of multidentate thiol amphiphiles.

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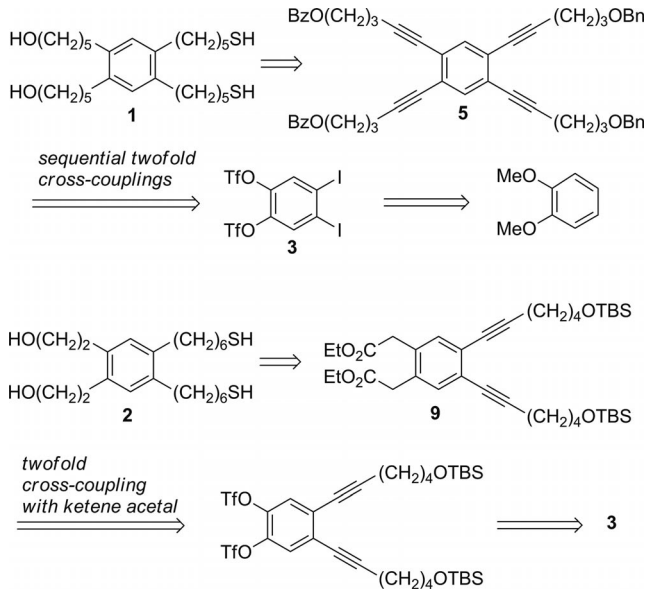
nanomaterial surfaces, we became interested in multivalent amphiphiles that incorporate functionalized termini and maintain a nearly constant cross section down the long axis. Herein, we report the synthesis of a new class of twin-chain thiols, which, upon incorporation into electrochemical biosensors, result in SAMs that possess improved stability in comparison to those prepared from an analogous single-chain thiol.

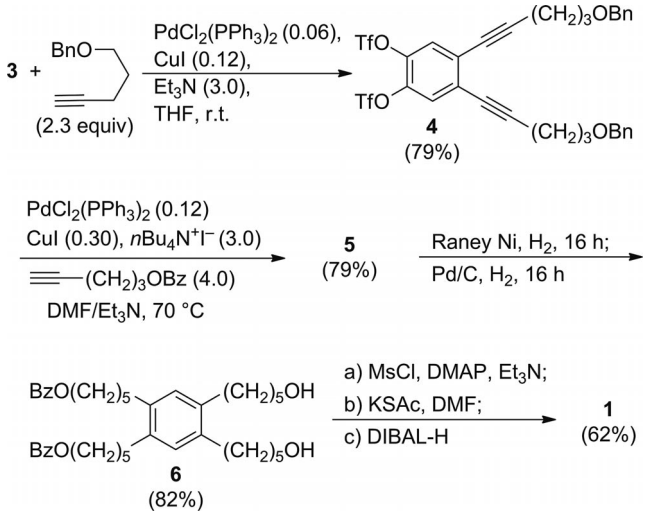
Results and Discussion

Our initial investigations focused on amphiphiles **1** and **2**, which were chosen for their comparability to 13- and 11-carbon single-chain thiol amphiphiles, respectively. The key steps for the construction of the molecular frameworks involve sequential cross-coupling reactions of diiododitriflate **3** (see Scheme 1). The synthesis for 13-carbon twin-chain amphiphile **1** is made on the basis of research from our lab that demonstrates the ability to prepare 1,2,4,5-tetralkynylarenes from **3** with complete regiochemical control through two sequential Sonagashira reactions.[13] The synthesis of the shorter 11-carbon amphiphile **2** requires a new approach, in which the two chains that comprise the terminus are introduced through two cross-coupling reactions between the bis(triflate) and a silyl ketene acetal.



Scheme 1. Retrosynthetic analysis for the 13- and 11-carbon amphiphiles (Bn = benzyl, Bz = benzoyl, Tf = trifluoromethylsulfonyl, TBS = *tert*-butyldimethylsilyl).

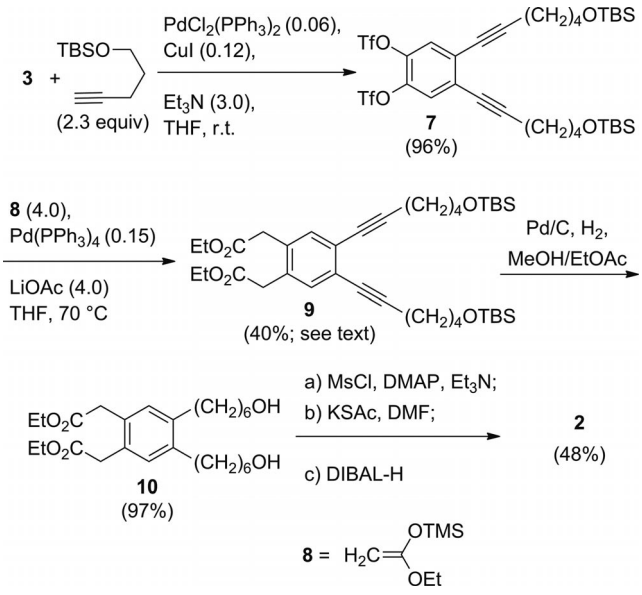
The synthesis of **1** commenced with the two Sonogashira cross-coupling reactions of **3** with the benzyl ether of 4-pentyn-1-ol (see Scheme 2). Subsequent couplings of the resulting dialkynylditriflate **4** with the benzoyl ester of 4-pentyn-1-ol generated tetraalkyne **5**. We had originally planned to employ a Pd-catalyzed reaction with H_2 to achieve saturation of all four alkynes and hydrogenolytic deprotection of both benzyl ethers. However, the reaction at room temperature and atmospheric pressure delivered a mixture of partially saturated products.[14] The reaction at 40 °C and at 2 atm pressure furnished a modest yield (40%, not shown) of diol **6**, which was accompanied by byproducts that were saturated but retained one (30%) or both (10%) of the benzyl ethers. Although the overall yield could be improved by resubjecting the isolated byproducts to the reaction conditions, we found that complete saturation and deprotection of **5** were easily achieved in high yield by the tandem application of Raney nickel (Raney Ni) and Pd/H_2. The alcohol moieties of **6** were then activated as methanesulfonates, which were displaced by treatment with KSAc to provide the bis(thioester) in 74% yield over the two steps. Reduction with diisobutylaluminum hydride (DIBAL-H) removed both the benzoate and thioacetate protecting groups to provide the 13-carbon twin-chain amphiphile **1**.



Scheme 2. Synthesis of amphiphile **1**.

The synthesis of 11-carbon amphiphile **2**, as illustrated in Scheme 3, also began with two Sonagashira coupling reactions of **3**. The product dialkynylditriflate **7** was then subjected to Pd-mediated coupling reactions with silyl ketene acetal **8** to provide bis(ester) **9** in moderate yield. Although the coupling of silyl ketene acetals with iodoarenes or aryl triflates has been previously described, our experiment was the first example of its application to *ortho*-positioned bis(functionalization).[15] The ketene acetal couplings proved considerably more challenging than the Sonagashira reactions described earlier. Attaining even moderate yields of the twofold coupling product **9** required the use of dry lithium acetate and relatively pure silyl ketene acetal, and the latter was frequently contaminated with the C-silylated isomer ethyl 2-trimethylsilylacetate.[16,17] However, even after the reaction was optimized, the monocarboxymethyl/monotriflate that was derived from a single cross-coupling reaction was often observed as a major byproduct.[18]

The monotriflate byproduct readily underwent a Sonagashira coupling reaction with simple alkynes (not shown), which suggested a potentially general pathway to introduce



Scheme 3. Synthesis of amphiphile **2**.

differentially functionalized termini into future generations of twin-chain amphiphiles. In marked contrast to what we had observed for the tetraalkynylarenes, the bis(alkynes) were easily saturated using Pd/C and hydrogen to furnish a nearly quantitative yield of diol **10**, which reflected concomitant desilylation under the protic reaction conditions.[19] The conversion of **10** into the corresponding diol/dithiol **2** was achieved in a good yield by using a similar method as that for the 13-carbon substrate above. No oxidative degradation of the thiol moieties was observed during the reaction, workup, or purification processes. The twin-chain amphiphiles **1** and **2** are easily handled oils and stable indefinitely when stored in the cold in the absence of light and oxygen.

Electrochemical DNA Sensor

The synthesized amphiphiles were applied to the fabrication of a folding-based electrochemical DNA (E-DNA) sensor. An electrochemically cleaned gold disc electrode was immersed for 10 min in a 2 mM ethanolic solution of either 11-hydroxyundecanethiol, **1**, or **2**. The resulting SAMs were further modified (drop casting, 3 h) with a stem-loop DNA sensing element that was thiolated at the 5′-terminus and modified with methylene blue (MB) at the 3′-terminus.[20] The fabricated sensors were then rinsed with deionized (DI) water and placed in an electrochemical cell. The stability of the sensors was assessed by monitoring the MB current through alternating current voltammetry (ACV), scanning every 12 h over a period of 72 h (see Figure 2). Although the sensor that was prepared with the single-chain amphiphile exhibited significant loss of response after 24–36 h, the sensors fabricated with **1** and **2** retained nearly 100% of the original response after 72 h, highlighting the stability of the SAMs that were derived from the twin-chain amphiphiles.

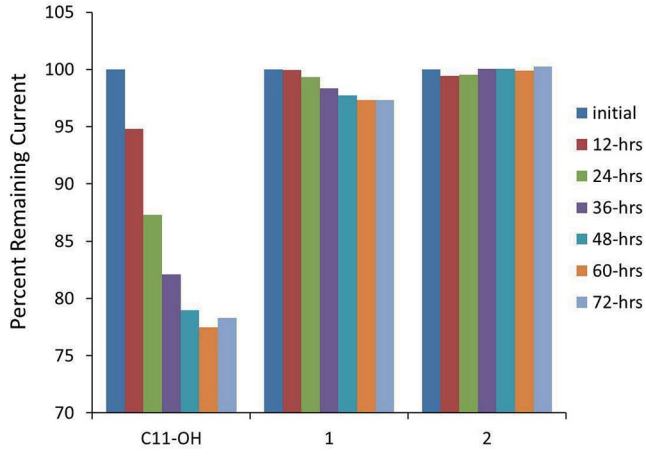


Figure 2. Comparison of stability of E-DNA sensors formed from 11-hydroxyundecanethiol, **1**, and **2**.

As a final test of stability, the sensors that were recovered from the ACV monitoring after 72 h (see above) were challenged/hybridized with 1.0 μM complete complementary target DNA, to which all the sensors responded. Upon sensor regeneration with deionized water, the MB signal was also regenerated, as expected for this class of sensors (see Figure 3).[20]

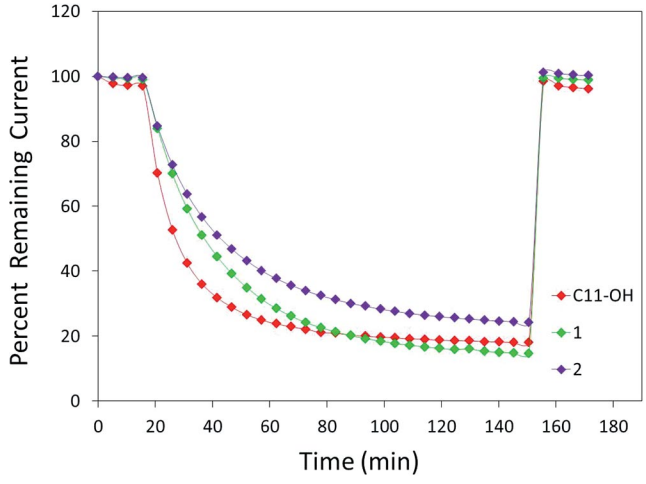


Figure 3. Hybridization curves obtained from sensors passivated with 11-hydroxyundecanethiol (red), **1** (green), and **2** (purple) in the presence of 1.0 μM target DNA in Phys2 buffer after the 72 h stability run. *K-ras* probe sequence: 5′ HS-$(CH_2)_{11}$-CCGTTACGCCACCAGCTCCAAACGG–C7–MB-3′. *K-ras* target sequence: 5′-TTGGAGCTGGTGGCGTA-3′.

Conclusions

A new class of twin-chain amphiphiles was prepared using routes that should be easily adaptable to a range of backbones and functional groups. The hydroxy groups of

the new amphiphiles, which were applied here as part of a wettable passivation layer, provide the foundation for the syntheses of functionalized nanomaterials and allow control of nearest neighbor interactions at the surface of the monolayer.

In initial tests, the sensors fabricated that use the new amphiphiles showed improved stability compared to those prepared from the single-chain thiol. Electrochemical characterization of the SAMs derived from **1** and **2** along with details of the performance of E-DNA sensors that were fabricated from these amphiphiles will be reported separately.

Experimental Section

General Information: All reactions were carried out in flame-dried glassware under dry nitrogen and using magnetic stirring. The solvents were used as purchased with the exception of tetrahydrofuran (THF) and CH_2Cl_2, which were distilled from Na/Ph_2CO and CaH_2, respectively. Thin layer chromatography was performed with 0.25 mm hard-layer silica G plates, and the developed plates were visualized with a UV lamp and by staining with 1% aqueous $KMnO_4$ solution (for unsaturated compounds), I_2 (general), and vanillin or phosphomolybdic acid (general, after charring). The NMR spectroscopic data were obtained by using $CDCl_3$ as the solvent with the data reported in parts per million (δ, ppm), [multiplicity, coupling constant (Hz), integration]. The ^{13}C NMR spectroscopic data are reported in parts per million (δ, ppm). The ^1H and ^{13}C NMR spectroscopic data were referenced to the residual proton in $CDCl_3$ and $CDCl_3$, respectively. Infrared spectra were recorded as neat films using attenuated total reflectance (ATR). Selected absorptions were reported in wavenumbers (cm^{-1}). HRMS analysis was obtained with the ionization source listed for each compound.

1,2-Diiodo-4,5-dimethoxybenzene:[13,21] To a flame-dried 100 mL round-bottomed flask (RBF) equipped with a short air condenser were added H_5IO_6 (5.84 g, 25.6 mmol, 0.41 equiv.) and methanol (36 mL). The mixture was stirred at room temp., and then I_2 (12.76 g, 50.2 mmol, 0.8 equiv.) was added. The reaction was stirred vigorously for 10 min, and then 1,2-dimethoxybenzene (8.0 mL, 8.7 g, 63 mmol, 1 equiv.) was added through a syringe in one portion. The reaction was heated to 70 °C in an oil bath for 5 h, which resulted in the formation of a white solid. The solid made stirring difficult, but the reaction proceeded in the absence of efficient stirring. The hot solution was poured into dilute aqueous $Na_2S_2O_5$ (approximately 100 mL), and the mixture was cooled to room temp. The solid was collected by filtration through a glass frit, washed quickly with cold MeOH (2 × 30 mL), and dried in vacuo to afford the diiodoarene (21.07 g, 54 mmol, 86%) as a white solid, which was considered pure by NMR analysis and used without further purification, m.p. 134.5–136.0 °C; R_f = 0.49 [20% ethyl acetate (EtOAc)/hexane (Hex)]. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.25 (s, 2 H), 3.85 (s, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 149.6, 121.7, 96.1, 56.2 ppm.

1,2-Dihydroxy-4,5-diiodobenzene:[13,22] A flame-dried 250 mL RBF was charged with 1,2-diiodo-4,5-dimethoxybenzene (3.90 g, 10 mmol, 1 equiv.) and then evacuated/backfilled with nitrogen (3×). CH_2Cl_2 (70 mL) was added. The solution was cooled to 0 °C, and BBr_3 (1.0 M solution in CH_2Cl_2, 25 mL, 25 mmol, 2.5 equiv.) was added by using a syringe pump over 20 min. The reaction was stirred at 0 °C for 4 h and then quenched with H_2O (50 mL). The separated aqueous layer was extracted with Et_2O (2 × 75 mL). The combined organic layers were dried with $MgSO_4$, filtered through a pad of silica, and concentrated in vacuo to afford 1,2-dihydroxy-4,5-diiodobenzene (3.61 g, 9.99 mmol, quantitative) as an off-white solid, which was considered pure by NMR analysis and used without further purification, m.p. 116.0–116.5 °C; R_f = 0.50 (50% EtOAc/Hex). ^1H NMR (400 MHz, [D_6]acetone): δ = 8.48 (br. s, 2 H), 7.38 (s, 2 H) ppm. ^{13}C NMR (150 MHz, [D_6]acetone): δ = 146.5, 125.6, 93.7 ppm.

4,5-Diiodo-1,2-phenylene Bis(trifluoromethanesulfonate) (3):[13] To a flame-dried 100 mL RBF were added 1,2-dihydroxy-4,5-diiodobenzene (2.84 g, 7.85 mmol, 1 equiv.), CH_2Cl_2 (55 mL), and pyridine (3.16 mL, 3.10 g, 39 mmol, 5 equiv.). The solution was cooled to 0 °C, and Tf_2O (2.91 mL, 4.88 g, 17.3 mmol, 2.2 equiv.) was added dropwise through a syringe over 10 min. The reaction was stirred for 6 h, as the mixture warmed to ambient temperature. The reaction mixture was then cooled to 0 °C and quenched with H_2O (30 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried with $MgSO_4$ and filtered through a tall pad of silica. The pad was washed carefully with CH_2Cl_2 to avoid the elution of impurities, and the filtrate was concentrated in vacuo to afford **3** (4.90 g, 7.82 mmol, quantitative) as an off-white solid, which was considered pure by NMR analysis and used without further purification. [Note: For reactions in which small amounts of impurities were observed after filtration, the product was obtained in pure form by column chromatography (10% EtOAc/Hex).] M.p. 46.5–47.7 °C; R_f = 0.60 (10% EtOAc/Hex). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.6, 133.4, 118.5 (q, $J_{C,F}$ = 321.0 Hz), 108.0 ppm. FTIR: $\tilde{\nu}$ = 1429, 1335, 1215, 1125, 1105, 868, 788, 745, 689 cm^{-1}. HRMS (ESI): calcd. for $C_8H_2F_6I_2NaO_6S_2$ $[M + Na]^+$ 648.7184; found 648.7164.

5-Benzyloxypentyne:[23] To a flame-dried 250 mL RBF was added NaH (60% dispersion in mineral oil, 1.9 g, 47.6 mmol, 2 equiv.). The solid was washed with hexanes (15 mL). THF (95 mL) was added, and the suspension was cooled to 0 °C. Pentynol (2.0 g, 23.8 mmol, 1 equiv.) in THF (5 mL) was added dropwise. BnBr (2.60 mL, 21.9 mmol, 0.92 equiv.) was added dropwise. The reaction was then warmed to room temp. over 16 h and then quenched with a saturated aqueous solution of NH_4Cl (25 mL). The mixture was diluted with H_2O (20 mL), and the resulting solution was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (40 mL), dried with Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (4% EtOAc/Hex) afforded the benzyl ether (3.60 g, 20.7 mmol, 94%) as a colorless liquid; R_f = 0.41 (5% EtOAc/Hex). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.44 (5 H), 4.55 (s, 2 H), 3.61 (t, J = 6.2 Hz, 2 H), 2.36 (td, J = 7.1, 2.6 Hz, 2 H), 1.97 (t, J = 2.6 Hz, 1 H), 1.81–1.93 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5, 128.4, 127.63, 127.58, 84.0, 73.0, 68.7, 68.5, 28.7, 15.3 ppm. CAS: 57618-47-0.

4,5-Bis(5-benzyloxypent-1-yn-1-yl)-1,2-phenylene Bis(trifluoromethanesulfonate) (4):[13] A flame-dried 20 mL vial fitted with a screw-cap septum was charged with $PdCl_2(PPh_3)_2$ (84 mg, 0.12 mmol, 0.06 equiv.), CuI (45.6 mg, 0.24 mmol, 0.12 equiv.), and compound **3** (1.25 g, 2 mmol, 1 equiv.). The vessel was evacuated/backfilled with nitrogen (3×), and to this were sequentially added THF (4 mL), Et_3N (0.85 mL, 6 mmol, 3 equiv.), and 5-benzyloxypentyne (802 mg, 4.6 mmol, 2.3 equiv.) in THF (1 mL). The reaction was stirred for 3 h at room temp. and filtered through a pad of silica, which was washed with Et_2O. The filtrate was concentrated in vacuo and purified by flash chromatography (gradient from Hex to 10% EtOAc/Hex) to afford **4** (1.14 g, 1.59 mmol, 79%); R_f = 0.27

(10% EtOAc/Hex). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42 (s, 2 H), 7.27–7.39 (10 H), 4.56 (s, 4 H), 3.65 (t, J = 6.0 Hz, 4 H), 2.62 (t, J = 7.1 Hz, 4 H), 1.92–1.98 (m, 4 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.8, 138.3, 128.4, 128.2, 127.59, 127.56, 126.3, 121.7, 119.6, 117.5, 115.3, 98.1, 77.4, 73.0, 68.5, 28.6, 16.5 ppm. FTIR: $\tilde{\nu}$ = 2859, 2230, 1489, 1433, 1210, 1178, 1135, 1080, 732 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{28}F_6O_8S_2Na$ [M + Na]$^+$ 741.1027; found 741.1039.

5-Benzoyloxypentyne:[24] To a flame-dried 100 mL RBF were added pentynol (2.0 g, 24 mmol, 1 equiv.) and CH_2Cl_2 (80 mL). The reaction was cooled to 0 °C, and BzCl (3.3 mL, 28 mmol, 1.2 equiv.) was added dropwise followed by the addition of *N*,*N*-dimethylaminopyridine (DMAP, 300 mg, 2.4 mmol, 0.1 equiv.) and Et_3N (7 mL). The reaction was warmed to room temp. over 12 h and then quenched with HCl (2 N solution, 10 mL). The solution was extracted with EtOAc (2 × 40 mL), and the combined extracts were washed with brine (40 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (2.5% EtOAc/Hex) to afford the protected alkynol (4.02 g, 21.4 mmol, 89%) as a colorless oil; R_f = 0.57 (10% EtOAc/Hex). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.03–8.07 (2 H), 7.53–7.60 (1 H), 7.42–7.48 (2 H), 4.44 (t, J = 6.1 Hz, 2 H), 2.40 (td, J = 7.3, 2.7 Hz, 2 H), 1.98–2.05 (overlapping signals, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.5, 132.9, 130.3, 129.6, 128.3, 83.0, 69.1, 63.4, 27.7, 15.4 ppm. CAS: 5390-04-5.

4,5-Bis(5-benzyloxypent-1-yn-1-yl)-1,2-phenylene Bis(pent-4-yn-1-ol-5-yl, Benzoate Ester) (5): A flame-dried 20 mL vial fitted with a screw-cap septum was charged with $PdCl_2(PPh_3)_2$ (127 mg, 0.18 mmol, 0.12 equiv.), CuI (89.4 mg, 0.45 mmol, 0.30 equiv.), and Bu_4NI (1.65 g, 4.5 mmol, 3 equiv.). The vessel was evacuated/backfilled with nitrogen (3×), followed by the addition of bis(triflate) **4** in a mixture of *N*,*N*-dimethylformamide (DMF)/Et_3N (5:1, 7 mL). The mixture was stirred for 5 min at room temp., and 5-benzoyloxypentyne (980 mg, 6.1 mmol, 4.1 equiv.) in DMF/Et_3N (5:1, 1.5 mL) was then added. The reaction was heated to 70 °C (oil bath) for 5.5 h and then cooled to room temp. The crude reaction mixture was filtered through a pad of silica, which was washed with Et_2O. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (15% EtOAc/Hex) to afford **5** (930 mg, 1.17 mmol, 79%) as a colorless oil; R_f = 0.39 (20% EtOAc/Hex). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.04–8.10 (4 H), 7.54–7.60 (2 H), 7.42–7.47 (4 H), 7.39–7.41 (2 H), 7.33–7.38 (8 H), 7.27–7.31 (2 H), 4.55 (s, 4 H), 4.53 (t, J = 6.3 Hz, 4 H), 3.66 (t, J = 6.2 Hz, 4 H), 2.70 (t, J = 7.0 Hz, 4 H), 2.60 (t, J = 7.0 Hz, 4 H), 2.11 (quint, J = 6.6 Hz, 4 H), 1.94 (quint, J = 6.6 Hz, 4 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.5, 138.5, 135.3, 133.0, 130.2, 129.6, 128.38, 128.36, 127.60, 127.56, 125.3, 124.9, 95.0, 93.9, 79.6, 79.1, 73.0, 68.7, 63.7, 28.9, 28.0, 16.7, 16.6 ppm. FTIR: $\tilde{\nu}$ = 3675, 2988, 2972, 2901, 2229, 1716, 1451, 1394, 1269, 1107, 1068, 1027, 900 cm^{-1}. HRMS (ESI): calcd. for $C_{54}H_{50}O_6Na$ [M + Na]$^+$ 817.3505; found 817.3503. Note: This procedure differs from a previous report in the use of 12 mol-% $PdCl_2(PPh_3)_2$ rather than 6 mol-%.[13]

1,2-Bis(5-benzoyloxypentyl)-4,5-bis(5-hydroxypentyl)benzene (6): Raney Ni (50% in water, 120 mg) was added to an 8 mL vial. The solid was collected on a stir bar and washed with MeOH (3 × 5 mL). The vial was then fitted with a screw-cap septum and charged with a solution of **5** (199 mg, 0.25 mmol, 1 equiv.) in MeOH/EtOAc (3:1, 4 mL). The vial was placed under an atmosphere of H_2 (balloon), and the reaction was stirred for 16 h. The reaction mixture was filtered through a plug of silica, and the filtrate was concentrated under vacuum. The residue was dissolved in THF (3 mL) and added to an 8 mL vial, which had been charged with 10 wt.-% Pd/C (20 mg). The reaction was placed under an atmosphere of H_2 for 16 h and then filtered through a plug of silica. The filtrate was concentrated in vacuo, and the resulting residue was purified by flash chromatography (55% EtOAc/Hex) to afford **6** (129 mg, 0.21 mmol, 82%) as a colorless oil; R_f = 0.30 (60% EtOAc/Hex). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.04–8.10 (4 H), 7.54–7.61 (2 H), 7.42–7.50 (4 H), 6.94 (s, 2 H), 4.36 (t, J = 6.7 Hz, 4 H), 3.67 (t, J = 6.6 Hz, 4 H), 2.53–2.68 (8 H), 1.80–1.91 (6 H), 1.53–1.72 (16 H), 1.44–1.51 (4 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.7, 137.6, 137.3, 132.8, 130.4, 129.9, 129.5, 128.3, 65.0, 62.7, 32.5, 32.21, 32.15, 31.2, 30.9, 28.6, 26.1, 25.8 ppm. FTIR: $\tilde{\nu}$ = 3776, 2988, 2972, 2901, 1717, 1334, 1271, 1067, 1057, 1028 cm^{-1}. HRMS (ESI): calcd. for $C_{40}H_{54}O_6Na$ [M + Na]$^+$ 653.3818; found 653.3823.

1,2-Bis(5-benzoyloxypentyl)-4,5-bis(5-methylsulfonylpentyl)benzene: To a flamed-dried 20 mL vial fitted with a screw-cap septum were added **6** (215 mg, 0.34 mmol, 1 equiv.), CH_2Cl_2 (4 mL), and Et_3N (0.19 mL, 1.36 mmol, 4 equiv.). DMAP (4.2 mg, 0.034 mmol, 0.1 equiv.) was added followed by the dropwise addition of methanesulfonyl chloride (MsCl, 0.08 mL, 1.02 mmol, 3 equiv.). The reaction was stirred for 3 h and quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (20 mL), dried with Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (45% EtOAc/Hex) afforded the bis(methanesulfonate) (294 mg, 0.37 mmol, 91%) as a colorless oil; R_f = 0.27 (40% EtOAc/Hex). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.01–8.11 (4 H), 7.54–7.62 (2 H), 7.46 (t, J = 7.6 Hz, 4 H), 6.92 (s, 2 H), 4.35 (t, J = 6.6 Hz, 4 H), 4.26 (t, J = 6.6 Hz, 4 H), 3.02 (s, 6 H), 2.60 (br. t, J = 8.0 Hz, 4 H), 2.57 (br. t, J = 8.0 Hz, 4 H), 1.77–1.88 (8 H), 1.48–1.70 (16 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.7, 137.6, 137.3, 132.9, 130.5, 129.9, 129.5, 128.3, 70.1, 65.0, 37.4, 32.2, 32.1, 31.1, 30.8, 29.1, 28.7, 26.2, 25.6 ppm. FTIR: $\tilde{\nu}$ = 2937, 1714, 1352, 1272, 1173, 1114, 1070, 944, 908 cm^{-1}. HRMS (ESI): calcd. for $C_{42}H_{58}O_{10}S_2Na$ [M + Na]$^+$ 809.3369; found 809.3367.

1,2-Bis(5-benzoyloxypentyl)-4,5-bis[5-(acetylthiyl)pentyl]benzene: To a flame-dried 8 mL vial fitted with screw-cap septum were added the bis(methanesulfonate) (222 mg, 0.282 mmol, 1 equiv.) and DMF (2.5 mL) followed by KSAc (97 mg, 0.85 mmol, 3 equiv.). The reaction was stirred for 14 h and then diluted with Et_2O (20 mL) and H_2O (10 mL). The layers were separated, and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 10 mL), dried with Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (10% EtOAc/Hex) afforded the bis(thioacetate) (170 mg, 0.228 mmol, 81%) as a colorless oil; R_f = 0.32 (15% EtOAc/Hex). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.07 (d, J = 7.3 Hz, 4 H), 7.58 (t, J = 7.4 Hz, 2 H), 7.46 (t, J = 7.8 Hz, 4 H), 6.92 (s, 2 H), 4.36 (t, J = 6.7 Hz, 4 H), 2.90 (t, J = 7.3 Hz, 4 H), 2.60 (br. t, J = 7.9 Hz, 4 H), 2.55 (br. t, J = 7.9 Hz, 4 H), 2.35 (s, 6 H), 1.80–1.89 (8 H), 1.54–1.70 (8 H), 1.44–1.51 (4 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.9, 166.7, 137.5, 137.3, 132.8, 130.5, 129.9, 129.5, 128.3, 65.0, 32.3, 32.2, 31.1, 30.9, 30.7, 29.5, 29.1, 28.7, 26.3 ppm. FTIR: $\tilde{\nu}$ = 3684, 3675, 2988, 2972, 2901, 1717, 1688, 1406, 1394, 1383, 1230, 1057, 1028 cm^{-1}. HRMS (ESI): calcd. for $C_{44}H_{58}O_6S_2Na$ [M + Na]$^+$ 769.3573; found 769.3568.

1,2-Bis(5-hydroxypentyl)-4,5-bis(5-thiylpentyl)benzene (1): A flame-dried 8 mL vial fitted with a screw-cap septum was charged with the bis(thioacetate) (144 mg, 0.193 mmol, 1 equiv.) and THF (2.5 mL). DIBAL-H (nominally 1.5 M solution in toluene, 1.55 mL,

2.3 mmol, 12 equiv.) was added dropwise. The reaction was stirred at room temp. for 2.5 h, cooled to 0 °C, and quenched by the careful addition of HCl (2 N solution, 4 mL). The solution was diluted with H_2O (10 mL), and the resulting mixture was extracted with Et_2O (3 × 10 mL). The organic layers were washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (50% EtOAc/Hex) to afford **1** (74 mg, 0.163 mmol, 84%) of a colorless oil; R_f = 0.19 (45% EtOAc/Hex). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.92 (s, 2 H), 3.68 (t, J = 6.6 Hz, 4 H), 2.53–2.61 (12 H), 1.56–1.72 (18 H), 1.45–1.53 (8 H), 1.37 (t, J = 7.9 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 137.6, 137.4, 129.9, 62.9, 33.9, 32.6, 32.3, 32.2, 31.2, 30.8, 28.5, 25.9, 24.6 ppm. FTIR: $\tilde{\nu}$ = 3353, 2930, 2857, 2358, 2338, 1775, 1460, 1143 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{46}O_2S_2Na$ [M + Na]$^+$ 477.2837; found 477.2821.

6-(*tert*-Butyldimethylsilyloxy)hexyne:[25] A flame-dried 100 mL RBF was charged with hexynol (2.50 g, 25.5 mmol, 1 equiv.), CH_2Cl_2 (60 mL), TBSCl (4.23 g, 28.1 mmol, 1.1 equiv.), and imidazole (3.82 g, 56.1 mmol, 2.2 equiv.). The reaction was stirred for 1.5 h, and then quenched with a saturated aqueous solution of $NaHCO_3$ (40 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was filtered through a pad of silica to afford the silyl-protected alkynol (4.93 g, 23.2 mmol, 91%) as a colorless oil; R_f = 0.70 (5% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.65 (t, J = 6.0 Hz, 2 H), 2.24 (td, J = 6.8 Hz, 2.7 Hz, 2 H), 1.96 (t, J = 2.5 Hz, 1 H), 1.56–1.70 (2 H), 0.92 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.5, 68.2, 62.6, 31.8, 25.9, 25.0, 18.3, 18.2, –5.3 ppm. CAS: 73448-13-2.

4,5-Bis[6-(*tert*-butyldimethylsilyloxy)hex-1-ynyl]-1,2-phenylene Bis-(trifluoromethanesulfonate) (7): A flame-dried 20 mL vial fitted with a screw-cap septum was charged with $PdCl_2(PPh_3)_2$ (126 mg, 0.18 mmol, 0.06 equiv.), CuI (68 mg, 0.36 mmol, 0.12 equiv.), and **3** (1.88 g, 3 mmol, 1 equiv.). The vessel was evacuated/backfilled with nitrogen (3×), and to this were sequentially added THF (5 mL), Et_3N (1.29 mL, 9 mmol, 3 equiv.), and a solution of 6-(*tert*-butyldimethylsilyloxy)hexyne (1.46 g, 6.9 mmol, 2.3 equiv.) in THF (2.5 mL). The reaction was stirred for 3 h at room temp. and then filtered through a pad of silica, which was washed with Et_2O. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (gradient from 0 to 2% EtOAc/Hex) to afford **7** (2.29 g, 2.29 mmol, 96%) as a colorless oil; R_f = 0.27 (2.5 % EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 2 H), 3.66–3.72 (4 H), 2.49–2.61 (4 H), 1.66–1.77 (8 H), 0.92 (s, 18 H), 0.08 (s, 12 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.8, 128.3, 126.3, 118.5 (q, $J_{C,F}$ = 320.9 Hz), 98.6, 77.3, 62.5, 31.9, 25.9, 24.9, 19.4, 18.3, –5.3 ppm. FTIR: $\tilde{\nu}$ = 2945, 2930, 2858, 2230, 1489, 1436, 11247, 1211, 1179, 1137, 1087, 834, 807, 774 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{48}F_6O_8S_2Na$ [M + Na]$^+$ 817.2131; found 817.2120.

[(1-Ethoxyvinyl)oxy]trimethylsilane (8):[26] To a flame-dried 250 mL RBF were added iPr$_2$NH (4.8 mL, 34.1 mmol, 1.2 equiv.) and THF (33 mL). The solution was cooled to 0 °C, and BuLi (nominally 1.6 M solution in hexane, 19.5 mL, 31.2 mmol, 1.1 equiv.) was added dropwise. The mixture was stirred for 15 min and then cooled to –78 °C. A mixture of EtOAc (2.8 mL, 28.4 mmol, 1 equiv.) and trimethylsilyl chloride (TMSCl, 4.4 mL, 34.3 mmol, 1.2 equiv.) in THF (15 mL) was added over 5 min, and the cooling bath was removed. The reaction was warmed to room temp. and then stirred for 4 h. The solvent was removed in vacuo, and the resulting residue was dissolved in hexane (50 mL). The solution was filtered through a pad of Celite, which was washed with hexane (2 × 15 mL). Concentration in vacuo followed by distillation (70–80 °C, 40–50 Torr) provided **8** as a colorless liquid (see NMR spectrum for approximate composition). CAS: 18295-66-4.

Diethyl 2,2′-(4,5-Bis{6-[(*tert*-butyldimethylsilyl)oxy]hex-1-ynyl}-1,2-phenylene)diacetate (9): A flame-dried 8 mL vial fitted with a screw-top septum was charged with $Pd(PPh_3)_4$ (87 mg, 0.075 mmol, 0.15 equiv.) and anhydrous LiOAc (133 mg, 2 mmol, 4 equiv.). The vessel was evacuated and backfilled with dry nitrogen (3×) followed by the addition of **7** (398 mg, 0.5 mmol, 1 equiv.) and **8** [321 mg, 2 mmol, 4 equiv. (based on mass, approximately 75% pure by ^{1}H NMR analysis)] in THF (3.5 mL). The sealed reaction vessel was placed in a 70 °C oil bath for 5 h and then cooled to room temp. followed by dilution with H_2O (10 mL) and EtOAc (10 mL). The separated aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic layers were washed with brine (1 × 20 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (8% EtOAc/Hex) to afford **9** (134 mg, 0.20 mmol, 40%) as a colorless oil; R_f = 0.30 (10% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (s, 2 H), 4.14 (q, J = 7.1 Hz, 4 H), 3.68 (t, J = 5.8 Hz, 4 H), 3.64 (s, 4 H), 2.49 (t, J = 6.5 Hz, 4 H), 1.64–1.78 (8 H), 1.25 (t, J = 7.1 Hz, 6 H), 0.92 (s, 18 H), 0.07 (s, 12 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.8, 134.1, 132.5, 125.5, 94.0, 79.3, 62.7, 61.0, 38.7, 31.9, 26.0, 25.2, 19.4, 18.4, 14.1, –5.3 ppm. FTIR: $\tilde{\nu}$ = 2987, 2856, 1735, 1250, 1211, 1102, 1030, 833, 773 cm^{-1}. HRMS (ESI): calcd. for $C_{38}H_{62}O_6Si_2Na$ [M + Na]$^+$ 693.3983; found 693.3961.

Diethyl 2,2′-[4,5-Bis(6-hydroxyhexyl)-1,2-phenylene]diacetate (10): A flame-dried 20 mL vial fitted with a screw-cap septum was charged with 10% (w/w) Pd/C (10 mg) followed by the addition of a solution of **9** (103 mg, 0.155 mmol, 1 equiv.) in MeOH/EtOAc (1:1, 8 mL). The reaction was placed under an atmosphere of H_2 (balloon) and stirred for 18 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to provide **10** (66 mg, 0.149 mmol, 97%) as a colorless oil; R_f = 0.41 (75% EtOAc/Hex). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.03 (s, 2 H), 4.15 (q, J = 7.1 Hz, 4 H), 3.63–3.70 (overlapping s/t, 8 H), 2.54–2.62 (m, 4 H), 1.55–1.64 (10 H), 1.39–1.45 (8 H), 1.27 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.7, 139.6, 131.5, 130.4, 62.9, 60.8, 38.6, 32.7, 32.2, 31.0, 29.4, 25.6, 14.2 ppm. FTIR: $\tilde{\nu}$ = 3346, 2930, 2856, 1729, 1367, 1256, 1155, 1027 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{42}O_6Na$ [M + Na]$^+$ 473.2879; found 473.2888.

Diethyl 2,2′-(4,5-Bis{6-[(methylsulfonyl)oxy]hexyl}-1,2-phenylene)-diacetate: To a flamed-dried 8 mL vial fitted with a screw-cap septum were sequentially added **10** (55 mg, 0.124 mmol, 1 equiv.), CH_2Cl_2 (1.5 mL), Et_3N (0.075 mL, 0.5 mmol, 4 equiv.), DMAP (1.6 mg, 0.013 mmol, 0.1 equiv.), and MsCl (0.031 mL, 0.372 mmol, 3 equiv.) dropwise. The reaction was stirred for 3 h and then quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (55% EtOAc/Hex) to afford the bis(methanesulfonate) (64 mg, 0.105 mmol, 85%) as a colorless oil; R_f = 0.86 (75% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (s, 2 H), 4.25 (t, J = 6.5 Hz, 4 H), 4.15 (q, J = 7.1 Hz, 4 H), 3.66 (s, 4 H), 2.60 (s, 6 H), 2.54–2.62 (m, 4 H), 1.79 (4 H), 1.55–1.65 (4 H), 1.39–1.45 (8 H), 1.27 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.6, 139.3, 131.5, 130.5, 70.1, 60.8, 38.6, 37.4, 32.1, 30.9, 29.1, 25.4, 14.2 ppm. FTIR: $\tilde{\nu}$ = 2935, 2860, 1729, 1349, 1332, 1170, 1028, 948, 914, 729 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{46}O_{10}S_2Na$ [M + Na]$^+$ 629.2430; found 629.2459.

Diethyl 2,2′-{4,5-Bis[6-(acetylthio)hexyl]-1,2-phenylene}diacetate: To a flamed-dried 8 mL vial fitted with a screw-cap septum was added diethyl 2,2′-(4,5-bis{6-[(methylsulfonyl)oxy]hexyl}-1,2-phenylene)diacetate (61 mg, 0.101 mmol, 1 equiv.) in DMF (1.5 mL) followed by KSAc (58 mg, 0.505 mmol, 5 equiv.). The reaction was stirred for 14 h and then quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL). The mixture was diluted with Et_2O (20 mL), and the separated organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 5 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (15% EtOAc/Hex) to afford the bis(thioacetate) (46 mg, 0.081 mmol, 80%) as a colorless oil; R_f = 0.22 (10% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (s, 2 H), 4.15 (q, J = 7.1 Hz, 4 H), 3.66 (s, 4 H), 2.89 (t, J = 7.3 Hz, 4 H), 2.52–2.60 (m, 4 H), 2.35 (s, 6 H), 1.52–1.64 (8 H), 1.38–1.46 (8 H), 1.27 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.0, 171.6, 139.5, 131.5, 130.4, 60.8, 38.6, 32.2, 31.0, 30.6, 29.5, 29.2, 29.1, 28.7, 14.2 ppm. FTIR: $\tilde{\nu}$ = 2927, 2855, 1732, 1688, 1254, 1133, 1029, 950 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{46}O_6S_2Na$ [M + Na]$^+$ 589.2634; found 589.2651.

2,2′-[4,5-Bis(6-thiylhexyl)-1,2-phenylene]diethanol (2): A flame-dried 8 mL vial fitted with a screw-cap septum was charged with the bis(thioacetate) (44 mg, 0.078 mmol, 1 equiv.) and THF (1 mL) followed by the dropwise addition of DIBAl-H (nominally 1.5 M solution in toluene, 0.65 mL, 0.93 mmol, 12 equiv.). The reaction was stirred for 3 h and then quenched by the slow dropwise addition of HCl (2 N solution, 2 mL) at 0 °C. The mixture was diluted with H_2O (10 mL), and the resulting solution was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (70% EtOAc/Hex) to afford **2** (22 mg, 0.055 mmol, 71%) as a colorless oil; R_f = 0.22, (50% EtOAc/Hex). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.98 (s, 2 H), 3.85 (t, J = 6.5 Hz, 4 H), 2.90 (t, J = 6.7 Hz, 4 H), 2.52–2.60 (m, 8 H), 2.12 (s, 2 H), 1.65 (quint, J = 7.2 Hz, 4 H), 1.58 (quint, J = 7.5 Hz, 4 H), 1.38–1.49 (8 H), 1.36 (t, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.8, 134.3, 130.8, 63.6, 35.3, 33.9, 32.2, 31.2, 29.2, 28.2, 24.6 ppm. FTIR: $\tilde{\nu}$ = 3332, 2925, 2853, 1503, 1460, 1040 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{38}O_2S_2Na$ [M + Na]$^+$ 421.2211; found 421.2212.

E-DNA Sensor Fabrication: Prior to SAM formation, gold disc electrodes (2 mm diameter, CHI, Instruments, Austin, TX) were electrochemically cleaned by cycling between –0.4 and 1.6 V versus Ag/AgCl in sulfuric acid (0.5 M) until the gold oxide formation region of the voltammogram displayed three distinct peaks and successive scans showed minimal to no change. The E-DNA sensors were fabricated in two steps: (1) The electrochemically cleaned gold disc electrodes were immersed in a 2 mM ethanolic solution of either **1**, **2**, or 11-hydroxyundecaneundecanol for 10 min. The electrodes were then rinsed with deionized water and dried under N_2. (2) A stem-loop DNA sensing element thiolated at the 5′-end and modified with methylene blue (MB) at the 3′-end (see representation of sensor construct below) was then drop casted on the preformed SAMs for 3 h.[19] Electrochemical measurements were performed at room temperature (22 ± 1 °C) with a CHI 1040A Electrochemical Workstation (CH Instruments, Austin, TX). The modified electrodes were analyzed using alternating current voltammetry (ACV) at a frequency of 10 Hz and an amplitude of 25 mV. All voltammograms were recorded in a physiological buffer solution (Phys2) that consisted of Tris (20 mM), NaCl (140 mM), KCl (5 mM), $MgCl_2$ (1 mM), and $CaCl_2$ (1 mM). The solution was adjusted to pH = 7.4 with hydrochloric acid. For sensor stability monitoring, ACV scans were collected every 12 h for a total of 72 h. The sensors were then interrogated/hybridized with 1.0 μM complete complementary target DNA (see sequence below) until no change in the MB current was observed. The sensors were then regenerated by rinsing continuously with deionized water for 30 s. The sensors were subsequently transferred to a fresh Phys2 buffer solution for electrochemical monitoring of the regenerated current [*K-ras* probe sequence: 5′ HS-$(CH_2)_{11}$-CCGTTACGCCAC-CAGCTCCAAACGG–C7–MB-3′; *K-ras* target sequence: 5′-TTGGAGCTGGTGGCGTA-3′].

Supporting Information (see footnote on the first page of this article): NMR spectra for major compounds.

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