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Nanoscale Tripodal 1,3,5,7-Tetrasubstituted Adamantanes for AFM Applications

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The synthesis of four novel nanoscale 1,3,5,7-tetrasubstituted adamantanes **22** and **25**−**27** designed for atomic force microscopy (AFM) applications is described. Each tetrahedrally shaped molecule incorporates a broad tripodal base made up of three identical legs that terminate with a sulfur-containing moiety, which is either a 4-acetylsulfanylmethylphenyl unit or else a (1,2,5-dithiazepan-1-yl)phenyl unit. The sulfur atoms are intended for eventual binding of the molecule multivalently to the apex of a gold-coated commercial AFM tip through formation of multiple S−Au bonds. In each molecule, the fourth terminus is a para-substituted benzoic acid methyl ester that is designed to scan the sample. We demonstrate that **27** is sufficiently large and rigid to be imaged by a conventional AFM tip. Adamantanes **22** and **25**−**27** may also find application as chemically well-defined nanoscale objects for calibration of AFM tips.

Introduction

Within the family of scanning probe microscopies,[1] atomic force microscopy(AFM) is enjoying the widest usage in biomedical research.[2,3] AFM has the unique feature of being able to operate in aqueous buffer, thus allowing the imaging of individual biological structures[4] as they lay on an atomically flat surface under essentially physiological conditions. Resolution is limited by the sharpness of the tip. Aspect ratio (tip height/base)[5] is another important tip feature. Multiwalled (MWNT)[6,7] (∼9 nm radius) or single walled (SWNT) carbon nanotubes (∼3 nm, ultimate limit, ∼0.5−0.7 nm radius[7]) have the best combination of aspect ratio and sharpness reported to date.[8] A major limitation is that methods of attachment of the nanotubes to conventional tips require specialized equipment.

Nanoscale molecules with potential as single molecule tips for AFM are beginning to appear and include the tripodal oligophenylenes described by Cai et al.,[9] the caltrop-shaped tetrasubstituted silanes described by Yao and Tour,[10] and a prototypic tower-shaped molecule **1** (Chart 1) from our laboratory.[11,12] Recently,[13] we described the synthesis of two symmetrically substituted tetraphenylmethanes **2** and **3** and the 1,3,5,7-symmetrically substituted tetraphenyladamantane **4**. These nanoscale molecules are designed to bind multivalently to the apex of a gold-coated commercial tip through formation of an Au−S bond while the fourth terminus is available to scan the sample. Herein, we describe the synthesis of several related tetrahedrally shaped tripodal adamantane-based molecules **22** and **25**−**27** in which one terminus is an ester group while the other three contain sulfur atoms for eventual binding to a gold surface. We also demonstrated that **27** is sufficiently large and rigid to be imaged by a conventional AFM tip.

Results and Discussion

We once again adaped the elegant, convergent, stepwise synthesis of oligo(4-phenyleneethynylenes) used by Moore[14,15] and others[16] for the synthesis of rigid units of

(1) Hansma, H. G. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 14678−14680.
(2) Hansma, H. G.; Pietrasanta, L. *Curr. Opin. Chem. Biol.* **1998**, *2*, 579−584.
(3) Jandt, K. D. *Surf. Sci.* **2001**, *491*, 303−332.
(4) For a review see: Shao, Z. F.; Yang, J.; Somlyo, A. P. *Annu. Rev. Cell Devel. Biol.* **1995**, *11*, 241−265.
(5) Skårman, B.; Wallenberg, L. R.; Jacobsen, S. N.; Helmersson, U.; Thelander, C. *Langmuir* **2000**, *16*, 6267.
(6) Dai, H.; Hafner, J. H.; Rinzler, A. G.; Colbert, D. T.; Smalley, R. E. *Nature* **1996**, *384*, 147.
(7) Wong, S. S.; Harper, J. D.; Lansbury, P. T., Jr.; Lieber, C. M. *J. Am. Chem. Soc.* **1998**, *120*, 603.
(8) For a review on imaging with carbon nanotube AFM probes, see: Hafner, J. H.; Cheung, C.-L.; Woolley, A. T.; Lieber, C. M. *Prog. Biophys. Mol. Biol.* **2001**, *77*, 73.
(9) (a) Deng, X.; Mayeux, A.; Cai, C. *J. Org. Chem.* **2002**, *67*, 5279. (b) Deng, X.; Cai, C. *Tetrahedron Lett.* **2003**, *44*, 815.
(10) Yao, Y.; Tour, J. M. *J. Org. Chem.* **1999**, *68*, 1968.
(11) Keana, J. F. W.; Petukhov, P. A.; Rukavishnikov, A. V.; Phadke, A.; LaMunyon, D. H.; Lee, M. D. Abstract of Papers, Proceedings of the 217th ACS National Meeting, March 21−25, 1999, Anaheim CA; American Chemical Society: Washington, DC, 1999; p 72-ORG.
(12) Rukavishnikov, A. V.; Phadke, A.; Lee, M. D.; LaMunyon, D. H.; Petukhov, P. A.; Keana. J. F. W. *Tetrahedron Lett.* **1999**, *40*, 6353.
(13) Li, Q.; Rukavishnikov, A. V.; Petukhov, P. A.; Zaikova, T. O.; Keana, J. F. W. *Org. Lett.* **2002**, *21*, 3631−3634.
(14) Zhang, J.; Pesak, D. J.; Ludwick. J. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4227−4239.
(15) Young, J. K. and Moore, J. S. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; Weinheim: New York. 1995.
(16) See, for example: Jones, L.; Schumm, J. S.; Tour, J. M. *J. Org. Chem.* **1997**, *62*, 1388−1410. Aujard, I.; Baltaze, J.-P.; Baudin, J.-B.; Cogne, E.; Ferrage, F.; Jullien, L.; Perez, E.; Prevost, V.; Qian, L. M.; Ruel, O. *J. Am. Chem. Soc.* **2001**, *123*, 8177−8188.

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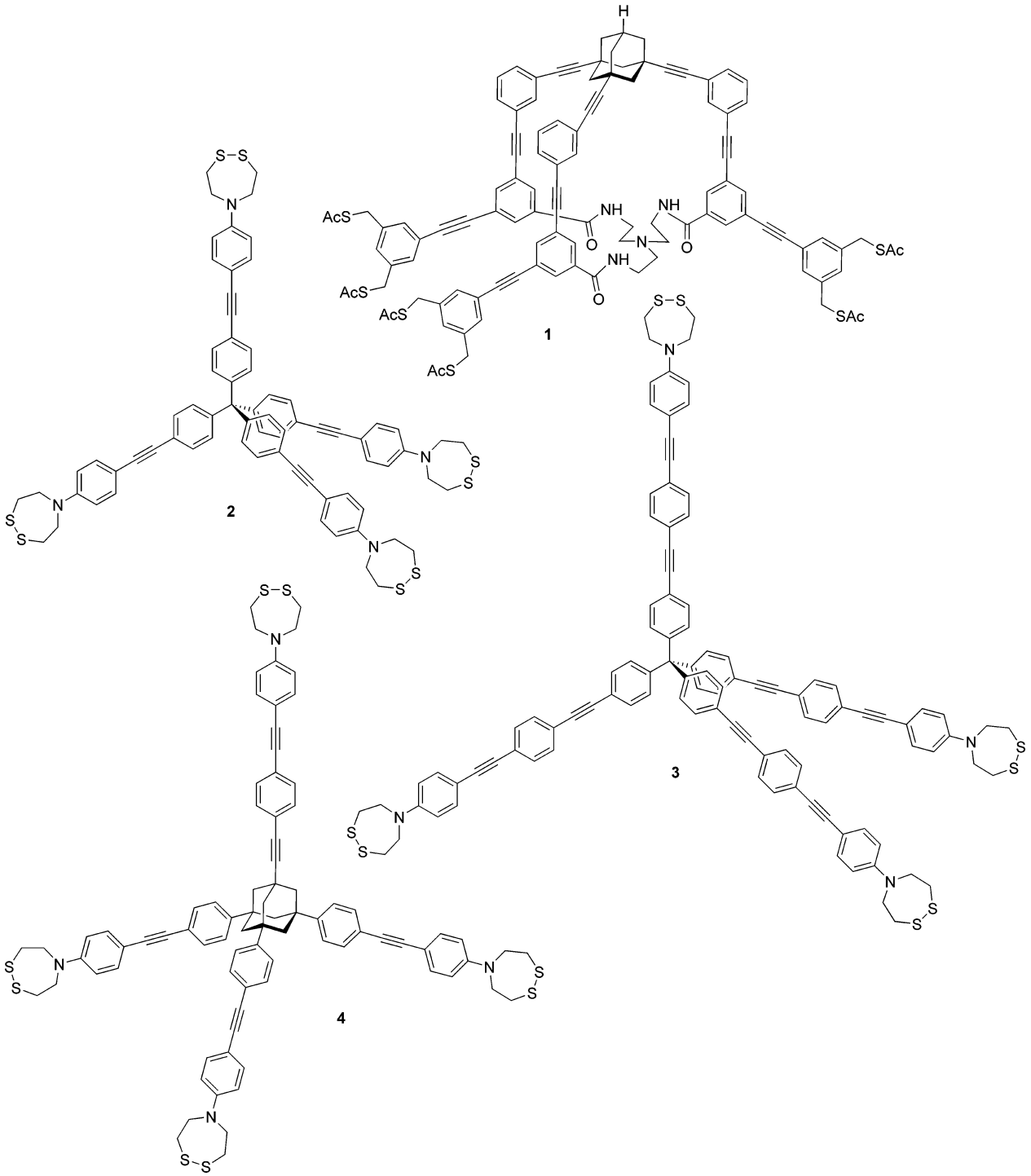
CHART 1



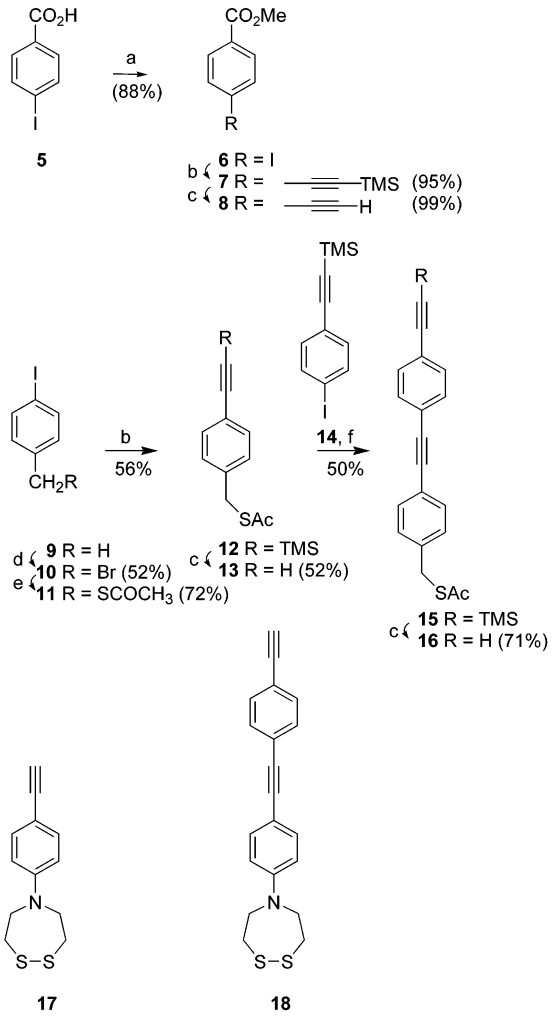
well-defined conformation. We chose 4-ethynylbenzoic acid methyl ester (**8**)[17] as the ester segment. Ester **8** was synthesized by modifying the procedure of Lau et al.[17] to employ 4-iodobenzoic acid (**5**) as the starting material rather than 4-bromobenzoic acid (Scheme 1). Thus, 4-iodobenzoic acid (**5**) was converted into methyl 4-iodobenzoate (**6**), which was coupled to TMSA to give TMS-protected alkyne **7** in 95% yield. Deprotection of **7** with Bu_4NF gave alkyne **8** in 99% yield.

We chose two sulfur-containing moieties, a 4-acetylsulfanylmethylphenyl unit represented by **13**[18] and **16**, and a (1,2,5-dithiazepan-1-yl)phenyl unit represented by **17**[13] and **18**[13] for the feet of the nanoscale molecules with the intent of determining operationally which foot unit is preferred for attachment to the commercial gold-coated AFM tips. These sulfur-containing moieties proved to be compatible with a series of Sonogashira coupling reactions and TMS deprotection steps.

(17) Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, *46*, 2280−2286.

(18) Gryko, D. T.; Clausen, C.; Roth, K. M.; Dontha, N.; Bocian, D. F.; Kuhr, W. G.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7345−7355.

SCHEME 1[a]

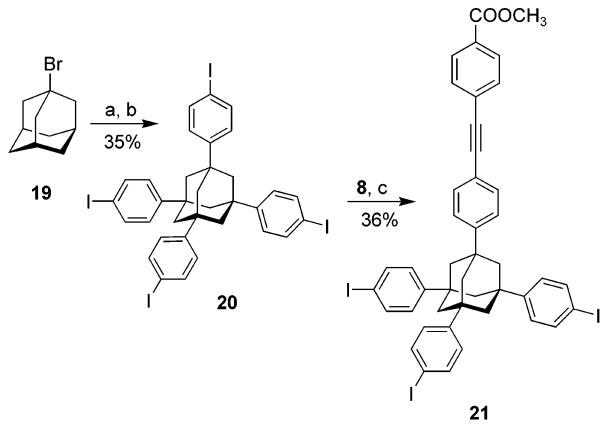


[a] Key: (a) CH_3I, DMSO, K_2CO_3; (b) TMSA, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF; (c) BuN_4F, THF; (d) NBS, $CHCl_3$; (e) CH_3COSH, Et_3N, THF; (f) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF.

Alkynes **13**[18] and **16** were synthesized by a modification of the method of Gryko et al.[18] 4-Iodotoluene (**9**) was treated with NBS in $CHCl_3$ affording 4-iodobenzyl bromide (**10**),[19] which was converted into thioester **11** by treatment with triethylammonium thioacetate. Thioester **11** was then coupled with TMSA to give alkyne **12**. Desilylation of **12** with Bu_4NF gave terminal alkyne **13**. Sonogashira coupling of **13** with iodide **14**[20] gave thioester **15**, desilylation of which with Bu_4NF gave thioacetic acid *S*-[4-(4-ethynylphenylethynyl)benzyl] ester (**16**). Terminal alkynes **17** and **18** were described previously by us.

Our molecular tip design required a 1,3,5,7-tetrasubstituted adamantane in which one of the substituents was differentiated from the other three sulfur-containing substituents. To this end, 1,3,5,7-tetrakis(4-iodophenyl)-adamantane (**20**) was prepared from 1-bromoadamantane (**19**) as described earlier[13] (Scheme 2) and then allowed to react with alkyne ester **8** in a Sonogashira coupling reaction. 4-[4-[3,5,7-Tris(4-iodophenyl)adamantan-1-yl]-

SCHEME 2[a]



[a] Key: (a) *t*-BuBr, $AlCl_3$, PhH; (b) [bis(trifluoroacetoxy)iodo]-benzene, I_2, $CHCl_3$; (c) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF.

phenylethynyl]benzoic acid methyl ester (**21**) was thus obtained in 36% yield after chromatography.

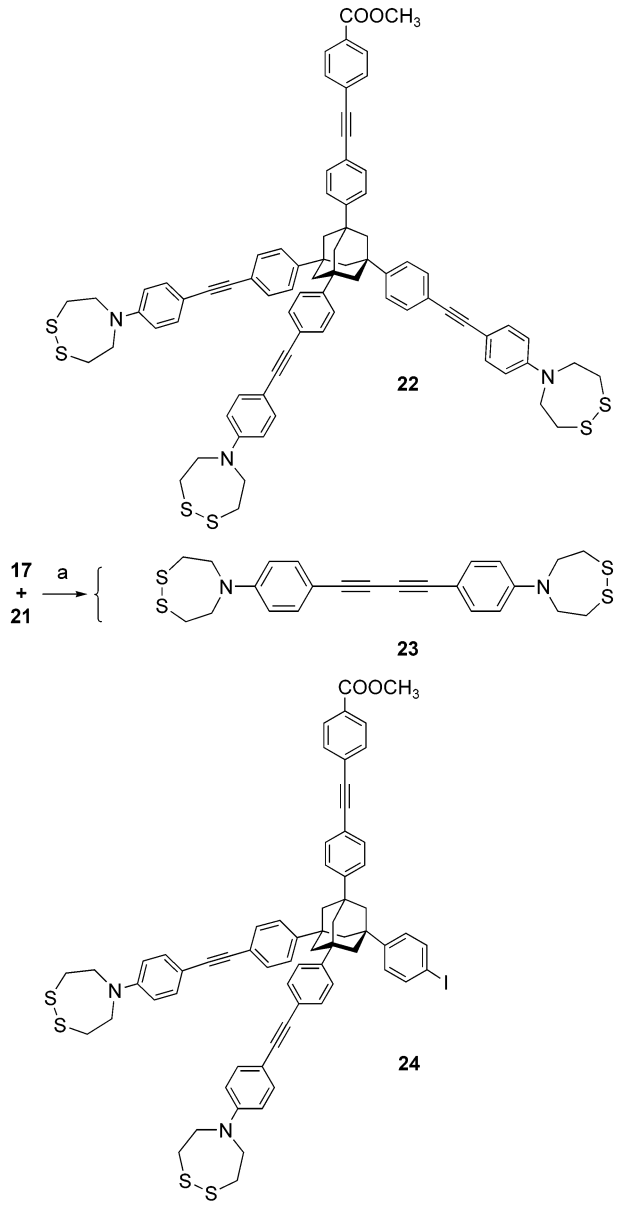
We chose tripodal 1,3,5,7-tetraphenyladamantane **22** as our first target (Scheme 3). A Sonogashira coupling reaction between alkyne **17** and ester **21** gave ester **22** in low yield after a rather difficult column chromatography together with comparable amounts of diyne **23** and ester **24**. Ester **24** resulted from coupling at only two of the three iodophenyl groups in **21**. Diyne **23** resulted from a competing Glaser-type oxidative homocoupling reaction of **17** despite efforts to exclude oxygen from the reaction.[21,22] Thorand and Krause[23] were able to minimize homocoupling by performing the Sonogashira reaction in THF instead of an amine as solvent, although that approach was unsuccessful in our hands. The need to effect a 3-fold coupling in the case of ester **21** required a balance between the use of excess alkyne **17** to drive the reaction to completion and the separation of pure **22** from diyne **23**.

^{1}H NMR spectroscopy proved to be particularly useful for monitoring the purification of esters **22** and **24** (Figure 1). Precursor **21** and coupling products **22** and **24** all show a three-proton methyl ester singlet at δ 3.93 and a somewhat broadened 12-proton singlet or doublet at δ 2.16 due to the adamantane core. Also, in **22**−**24**, the two four-proton triplets due to the dithiazepane ring have essentially the same chemical shift (δ 3.09 and 3.99). Fortunately, the relative integrals of the δ 3.93 (3H) and 2.16 (12H) peaks to the two dithiazepane triplets easily reveal the relative amounts of precursor **21**, coupling products **22** and **24**, and diyne **23** in the chromatography fractions.

The versatile ester triiodide **21** was next employed for the synthesis of a larger analogue of **22** as well as two other nanoscale molecules, which incorporate three acetylthioester feet in place of a [1,2,5]dithiazepane heterocycle unit. Thus, terminal alkyne **18** was coupled to 4-[4-[3,5,7-

(19) Wilson, A. A.; Dannals, R. F.; Ravert, H. T.; Frest, J. J.; Wagner, H. N., Jr. *J. Med. Chem.* **1989**, *32*, 1057−1062.
(20) Hsung, R. P.; Chidsey, C. E. D.; Sita, L. R. *Organometallics* **1995**, *14*, 4808−4815.
(21) (a) Ziener, U.; Godt, A. *J. Org. Chem.* **1997**, *62*, 6137. (b) Xu, Z.; Moore, J. S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 246. (c) Wagner, R. W.; Johnson, T. E.; Li, F.; Lindsey, J. S. *J. Org. Chem.* **1995**, *60*, 5266−5273.
(22) Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, *66*, 1910−1913.
(23) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551−8553.
(24) Ramachandran, T. R.; Baur, C.; Bugacov, A.; Madhukar, A.; Koel, B. E.; Requicha, A.; Gazen, C. *Nanotechnology* **1998**, *9*, 237.

SCHEME 3[a]



[a] Key: $Pd(Ph_3)_2Cl_2$, CuI, Et_3N, THF.

tris-(4-iodophenyl)adamantan-1-yl]phenylethynyl]benzoic acid methyl ester (**21**) under Sonogashira conditions to give tripodal tetraphenyladamantane **25** (Scheme 4). The ^{1}H NMR spectrum of ester **25** has the same characteristic peaks as those of **22** but differs in the integration.

Terminal alkynes **13** and **16** were next coupled to ester **21** giving tripodal nanoscale molecules **26** and **27**, respectively. The ^{1}H NMR spectra of tripodal tetraphenyladamantane **26** and **27** are characteristic as well, displaying prominently two distinct singlets for the CH_3-COSCH_2 groups in the molecule. Integration of these two singlets with respect to the three-proton methyl ester singlet allowed the separation of **26** and **27** from incompletely coupled intermediates to be monitored conveniently.

Visualization of Individual Molecules of Ester 27 Using a Conventional AFM Tip. Like single molecules of tetrapodal molecule **3**,[13] molecules of ester **27** are of sufficient size and rigidity that they can be imaged individually using a conventional AFM tip. Solutions of ester **27** in CH_2Cl_2 were separately spin-coated onto freshly cleaved mica and examined in air and ambient humidity by AFM in tapping mode (Figure 2A,B). The light dots are images of individual molecules laying on the mica surface. Images A and B were obtained using different concentrations (1.0 and 0.25 μM, respectively) of **27** in CH_2Cl_2 and demonstrate that the number of individual molecules appearing in the images is concentration dependent. As a control, freshly cleaved mica was spin-coated with a CH_2Cl_2 solution of segment **16** and examined by AFM (Figure 2C). Segment **16** is much smaller than ester **27** and can lay flat on the mica surface. Consequently, only the mica surface is seen.

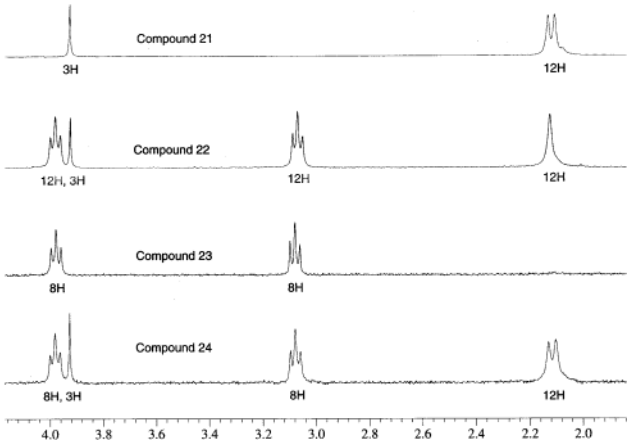


FIGURE 1. Distinctive region in the ^{1}H NMR (300 MHz) spectra for compounds **21**−**24**.

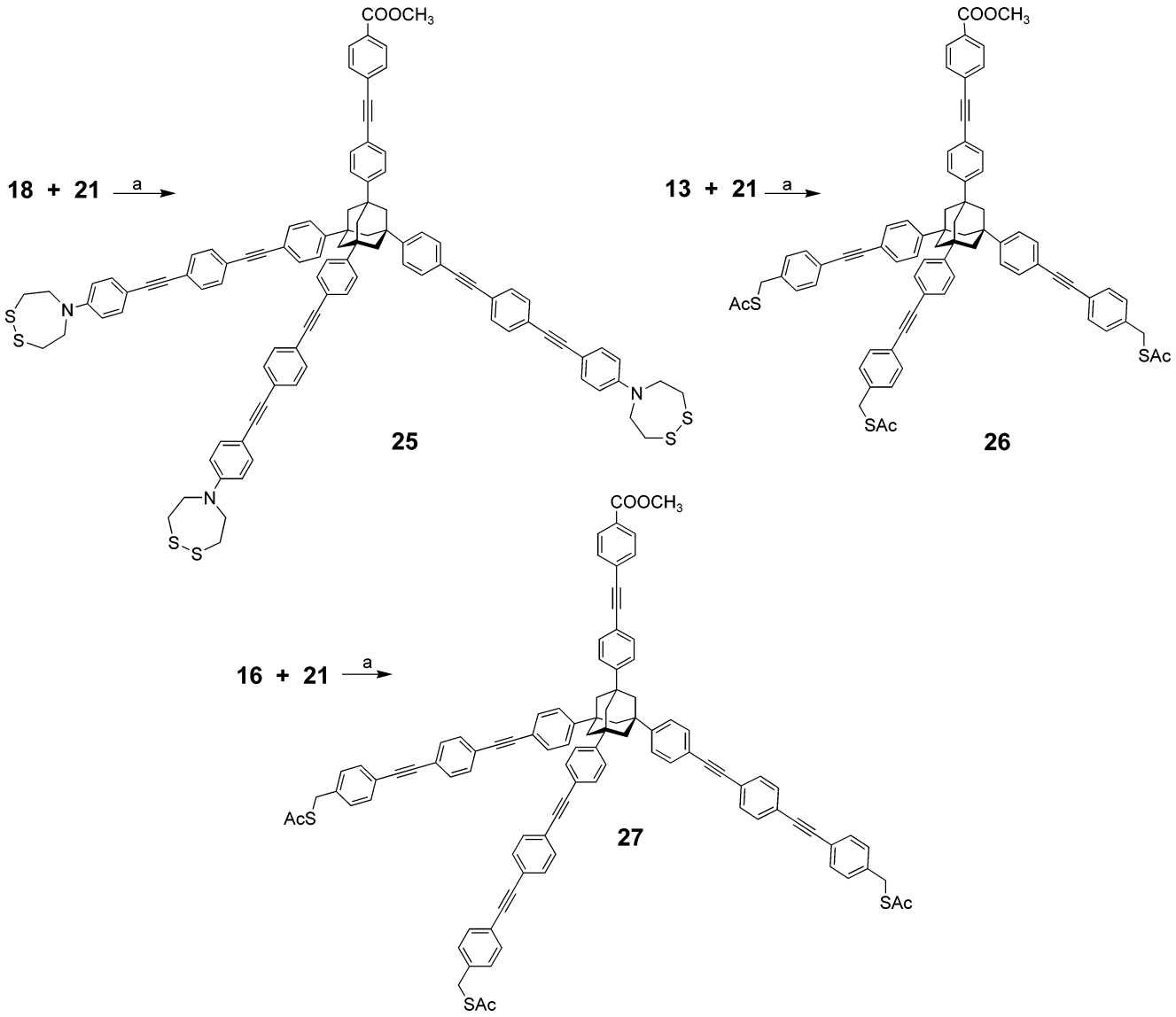
Studies directed at attaching these nanoscale molecules to a gold-coated commercial AFM tip are in progress. These molecules may also find application as chemically well-defined nanoscale objects for calibration of AFM tips.

Experimental Section

General Information. All reagents were purchased from commercial suppliers and used without further purification. Tetrahydrofuran (99.9%, anhydrous, inhibitor free) and triethylamine (99.5%) were used as received. Solvents were well deoxygenated with N_2 before use in Sonogashira coupling reactions. Brine refers to a saturated aqueous solution of NaCl. Melting points are uncorrected. A decomposition point is indicated by dec. PHB means that the sample was placed in a preheated block just below the decomposition temperature. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ unless otherwise noted. Chemical shifts are expressed in δ units (ppm) with the residual solvent peak (^{1}H $CHCl_3$, δ7.26; ^{13}C $CDCl_3$, δ77) as the internal standard. Coupling constants (J) are reported in hertz (Hz). NMR splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. Column chromatography was carried out on silica gel (60−200 mesh). Analytical TLC was performed on commercially coated 60 mesh F_{254} plastic plates. Spots were rendered visible by exposing the plate to UV light. Mass spectra were recorded on an LC/MS system.

4-Trimethylsilylethynylbenzoic Acid Methyl Ester (7). A suspension of methyl 4-iodobenzoate (**6**, 1.00 g, 3.82 mmol), trimethylsilylacetylene (0.64 mL), $Pd(PPh_3)_2Cl_2$ (0.080 g, 0.114 mmol), and CuI (0.044 g, 0.229 mmol) in deoxygenated Et_3N (2 mL) and THF (8 mL) in a thick-walled reaction tube was heated with stirring at 80 °C for 1.5 h. The reaction mixture

SCHEME 4[a]



[a] Key: $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF.

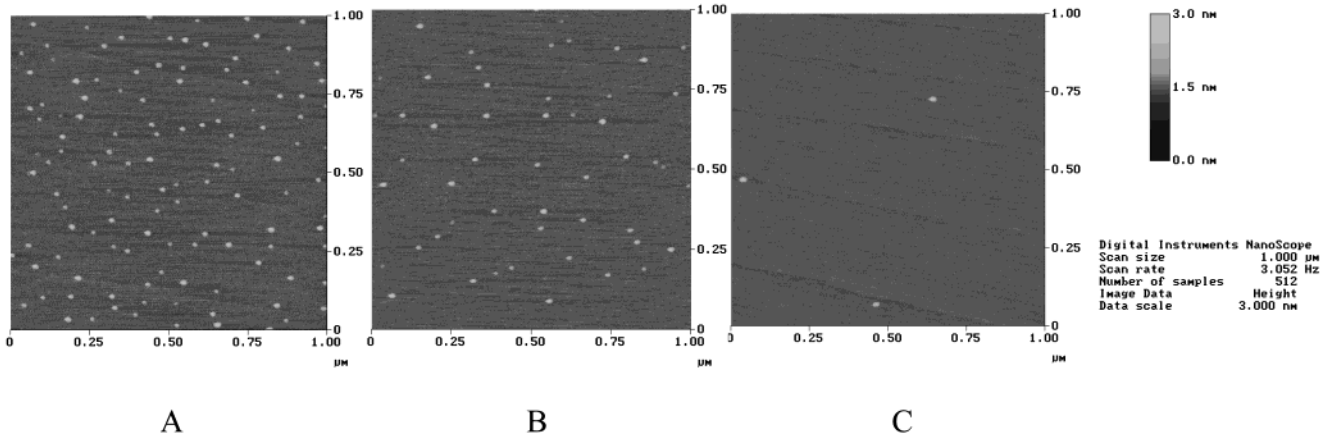


FIGURE 2. AFM images (1.00 × 1.00 μm) of freshly cleaved mica after spin-coating with the following: (A) 1.00 μM solution of ester **27** in CH_2Cl_2; (B) 0.25 μM solution of ester **27** in CH_2Cl_2; (C) 0.25 μM solution of segment **16** in CH_2Cl_2. Note the dependence of ester **27** image density on concentration (A vs B). Nanoscale features such as those seen in C are occasionally seen on certain regions of the surface when imaging freshly cleaved mica and may represent mica particulates produced as the result of the cleavage.[13,24]

was filtered, and the solid was washed with ether (50 mL). The combined organic solutions were evaporated to dryness. The residue was purified by chromatography with 10:1 hexanes/ether as an eluent to give **7** (0.84 g, 95%) as colorless crystals, which were pure by TLC and NMR: mp 55−56 °C (lit.[17] 69%, mp 55−55.5 °C); ^{1}H NMR δ 0.25 (s, 9H), 3.89 (s, 3H), 7.50 (d, J = 8.6 Hz, 2H), 7.95 (d, J = 8.6 Hz, 2H); ^{13}C NMR δ −0.31, 51.99, 97.47, 127.64, 129.24, 129.57, 131.57, 166.22; MS calcd for $C_{13}H_{17}O_2Si$ (M + 1) 233.1, found 233.1. Anal. Calcd for $C_{13}H_{16}O_2Si$: C, 67.20; H, 6.94. Found: C, 67.29; H, 6.90.

4-Ethynylbenzoic Acid Methyl Ester (8). To a suspension of ester **7** (0.96 g, 4.13 mmol) in THF (6 mL) was added a 1.0 M solution of *n*-Bu_4NF in THF (4.2 mL, 4.20 mmol) with stirring at −20 °C. The solution was stirred for 30 min at −20 °C, and then it was diluted with water (100 mL) and extracted with ether (2 × 50 mL). The combined extracts were washed with brine (2 × 30 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by chromatography with 10:1 hexanes/ether as an eluent to give **8** (0.69 g, 99%) as a colorless power, which was pure by TLC and NMR: mp 93−94 °C (lit.[17] 73%; mp 92.5−93.5 °C); ^{1}H NMR δ 3.23 (s, 1H), 3.91(s, 3H), 7.54 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 52.25, 80.02, 82.74, 126.69, 129.42, 130.09, 132.05, 166.38; MS calcd for $C_{10}H_9O_2$ (M + 1) 161.0, found 161.0. Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 75.08; H, 5.04.

4-Iodobenzyl bromide (10): colorless crystals, which were pure by TLC and NMR: mp 78.5−79.5 °C (lit.[19] mp 78−79.5 °C); ^{1}H NMR δ 4.42 (s, 2H), 7.13 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H); ^{13}C NMR δ 32.48, 94.13, 130.82, 137.39, 137.93.

Thioacetic acid *S*-(4-iodobenzyl) ester (11):[18] colorless solid, which was pure by TLC and NMR; mp 41−42 °C (lit.[18] mp 40−41 °C); ^{1}H NMR δ 2.34 (s, 3H), 4.04 (s, 2H), 7.04 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 30.30, 32.85, 92.65, 130.75, 137.44, 137.64, 194.82; MS calcd for $C_9H_{10}IOS$ (M + 1) 292.94, found 293.0.

Thioacetic acid *S*-(4-trimethylsilylethynylbenzyl) ester (12):[18] light yellow solid, which was pure by TLC and NMR; mp 41−42 °C (lit.[18] mp 41−42 °C); ^{1}H NMR δ 0.27 (s, 9H), 2.37 (s, 3H), 4.12 (s, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ −0.08, 30.27, 33.18, 94.38, 104.71, 122.05, 128.66, 132.13, 138.09, 194.83; MS calcd for $C_{14}H_{19}OSSi$ (M + 1) 263.1, found 263.1. Anal. Calcd for $C_{14}H_{18}OSSi$: C, 64.07; H, 6.91. Found: C, 63.94; H, 6.73.

1-[4-(*S*-Acetylthiomethyl)phenyl]acetylene (13).[18] yellow oil, which was pure by TLC and NMR; ^{1}H NMR δ 2.35 (s, 3H), 3.08 (s, 1H), 4.01 (s, 2H), 7.25 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H); ^{13}C NMR δ 30.23, 33.09, 77.00, 83.26, 120.96, 128.74, 132.28, 138.49, 194.74; MS calcd for $C_{11}H_9OS$ (M − 1) 189.0, found 189.0. Anal. Calcd for $C_{11}H_{10}OS$: C, 69.44; H, 5.30. Found: C, 69.65; H, 5.31.

1-(Trimethylsilylethynyl)-4-iodobenzene (14):[20] colorless crystals, which were pure by TLC and NMR; mp 68−70 °C (lit.[20] mp 56−58 °C); ^{1}H NMR δ 0.24 (s, 9H), 7.18 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ −0.15, 94.46, 95.86, 103.95, 122.59, 133.41, 137.34; MS calcd for $C_{11}H_{12}ISi$ (M − 1) 299.0, found 299.0. Anal. Calcd for $C_{11}H_{13}ISi$: C, 44.01; H, 4.36. Found: C, 43.72; H, 4.16.

Thioacetic Acid *S*-[4-(4-Trimethylsilylethynylphenylethynyl)benzyl] Ester (15). A thick-walled reaction tube was charged with alkyne **13** (0.304 g, 1.60 mmol), iodide **14** (0.540 g, 1.800 mmol), $Pd(PPh_3)_2Cl_2$ (0.0285 g, 0.0405 mmol), CuI (0.0154 g, 0.0808 mmol), triethylamine (3 mL), and THF (7 mL). The mixture was flushed with N_2 and capped with a Teflon screwcap. The mixture was heated with stirring at 40−50 °C for 20 h and filtered, and the solid was washed with CH_2Cl_2 (50 mL). The filtrate was evaporated to dryness, and the residue was purified by chromatography. Elution with 1:9 CH_2Cl_2/hexanes gave **15** (0.49 g, 85%) as light yellow crystals that were pure by TLC and NMR: mp 124−125 °C; ^{1}H NMR δ 0.25 (s, 9H), 2.36 (s, 3H), 4.12 (s, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.436 (s, 4H), 7.443 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ −0.11, 30.31, 33.22, 89.25, 90.97, 96.24, 104.59, 121.91, 122.87, 123.23, 128.87, 131.35, 131.80, 131.86, 138.14, 194.88; MS calcd for $C_{22}H_{22}OSSiNa$ (M + Na) 385.1, found 385.1. Anal. Calcd for $C_{22}H_{22}OSSi\cdot{}^1/_4H_2O$: C, 71.99; H, 6.18. Found: C, 72.22; H, 5.94.

Thioacetic Acid *S*-[4-(4-Ethynylphenylethynyl)benzyl] Ester (16). A 1.0 M solution of *n*-Bu_4NF in THF (0.58 mL, 0.58 mmol) was added dropwise to a stirred solution of TMS alkyne **15** (0.21 g, 0.58 mmol) in THF (10 mL) at −20 °C over 1 h. The solution was stirred for 30 min, and then it was diluted with water (50 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by chromatography. Elution with 1:9 CH_2Cl_2/hexanes gave **16** (0.14 g, 83%) as light yellow crystals, which were pure by TLC and NMR: mp 115−117 °C; ^{1}H NMR δ 2.33 (s, 3H), 3.15 (s, 1H), 4.09 (s, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.44 (s, 4H); ^{13}C NMR δ 30.31, 32.22, 78.91, 83.24, 89.05, 91.05, 99.93, 121.85, 123.66, 128.88, 131.43, 131.84, 132.04, 138.22, 194.90; MS calcd for $C_{19}H_{15}OS$ (M + 1) 291.1, found 291.1. Anal. Calcd for $C_{19}H_{14}OS$: C, 78.59; H, 4.86. Found: C, 78.36; H, 4.75.

5-(4-Ethynylphenyl)-1,2,5-dithiazepane (17):[13] colorless crystals, which were pure by TLC and NMR: mp 119−121 °C; ^{1}H NMR δ 2.97 (s, 1H), 3.07 (t, J = 5.55 Hz, 4H), 3.97 (t, J = 5.55 Hz, 4H), 6.56 (d, J = 9 Hz, 2H), 7.37 (d, J = 9.0 Hz, 2H); ^{13}C NMR δ 36.64, 52.39, 74.97, 84.49, 109.19, 110.96, 133.66, 146.63; MS calcd for $C_{12}H_{13}NS_2$ (M + 1) 236.0, found 236.0. Anal. Calcd for $C_{12}H_{13}NS_2$: C, 61.23; H, 5.57; N, 5.95. Found: C, 61.35; H, 5.53; N, 5.95.

5-[4-(4-Ethynylphenylethynyl)phenyl]-1,2,5-dithiazepane (18):[13] yellow crystals, which were pure by TLC and NMR: mp 159−161 °C; ^{1}H NMR δ 3.09 (t, J = 5.6 Hz, 4H), 3.15 (s, 1H), 3.99 (t, J = 5.6 Hz, 4H), 6.60 (d, J = 9.0 Hz, 2H), 7.40 (d, J = 9.0 Hz, 2H), 7.40 (s, 4H); ^{13}C NMR δ 36.67, 52.45, 78.50, 83.46, 87.12, 92.51, 99.94, 111.12, 120.92, 124.60, 131.09, 131.97, 133.25, 146.55; MS calcd for $C_{20}H_{18}NS_2$ (M + 1) 336.1, found 336.1. Anal. Calcd for $C_{20}H_{17}NS_2$: C, 71.60; H, 5.11; N, 4.18. Found: C, 71.37; H, 4.96; N, 3.99.

1,3,5,7-Tetrakis(4-iodophenyl)adamantane (20):[13] colorless crystals, which were pure by TLC and NMR; mp >250 °C; ^{1}H NMR δ 2.06 (s, 12H), 7.18 (d, J = 8.6 Hz, 8H), 7.67 (d, J = 8.6 Hz, 8H); ^{13}C NMR δ 39.30, 46.94, 91.99, 127.38, 137.78, 148.66; MS calcd for $C_{34}H_{29}I_4$ (M + 1) 944.8, found 944.8. Anal. Calcd for $C_{34}H_{28}I_4$: C, 43.25; H, 2.99. Found: C, 43.52; H, 2.89.

4-[4-[3,5,7-Tris(4-iodophenyl)adamantan-1-yl]phenylethynyl]benzoic Acid Methyl Ester (21). A solution of 4-ethynylbenzoic acid methyl ester (**8**, 0.150 g, 0.936 mmol) in THF (10 mL) was added dropwise over 2 h to a stirred suspension of tetraiodide **20** (1.330 g, 1.404 mmol), $Pd(PPh_3)_2Cl_2$ (0.0328 g, 0.0468 mmol), and CuI (0.0178 g, 0.0936 mmol) in deoxygenated triethylamine (8 mL) and tetrahydrofuran (50 mL). The mixture stirred at rt for 8 h, and then it was evaporated to dryness. The residue was extracted with ether (100 mL), washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4, and evaporated to give crude **21**. The residue was purified by chromatography with 1:1 $CHCl_3$/hexanes as an eluent to afford **21** (0.33 g, 36%) as a colorless solid, which was pure by TLC and NMR: mp 174−176 °C; ^{1}H NMR δ 2.07 (s, 6H), 2.10 (s, 6 H), 3.93 (s, 3H), 7.20 (d, J = 8.9 Hz, 6H), 7.44 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.68 (dd, J_1 = 2.1 Hz, J_2 = 8.9 Hz, 6H); ^{13}C NMR δ 39.02, 39.25, 46.50, 46.63, 52.23, 88.62, 91.70, 92.17, 120.70, 125.09, 127.12, 127.95, 129.39, 129.50, 131.45, 131.84, 137.47, 148.42, 149.41, 166.50; MS calcd for $C_{44}H_{36}O_2I_3$ (M + 1) 976.9, found 976.9. Anal. Calcd for $C_{44}H_{35}I_3O_2\cdot H_2O$: C, 53.14; H, 3.75. Found: C, 53.19; H, 3.58.

4-[4-[3,5,7-Tris-[4-[4-(1,2,5-dithiazepan-5-yl)phenylethynyl]phenyl]adamantan-1-yl]phenylethynyl]benzoic Acid Methyl Ester (Nanoscale Molecule 22), 5-[[4-[4-[4-(1,2,5-Dithiazepan-5-yl)phenyl]]buta-1,3-diynyl]phenyl]-1,2,5-

dithiazepane (23), and 4-[4-[3,7-Bis[4-[4-(1,2,5-dithiazepan-5-yl)phenylethynyl]phenyl]-5-(4-iodophenyl)adamantan-1-yl]phenylethynyl]benzoic Acid Methyl Ester (24). A thick-walled reaction tube was charged with ester (21, 25 mg, 0.026 mmol), 5-(4-ethynylphenyl)-1,2,5-dithiazepane (**17**, 18.0 mg, 0.104 mmol), $Pd(PPh_3)_2Cl_2$ (5.0 mg, 0.071 mmol), and CuI (3.0 mg, 0.015 mmol) in triethylamine (2 mL) and tetrahydrofuran (8 mL). The suspension was flushed with N_2 and capped with a Teflon screwcap. The mixture was heated with stirring at 50−55 °C for 20 h and then filtered, and the solid was washed with $CHCl_3$ (30 mL). The filtrate was evaporated to dryness, and the residue was purified by chromatography. Elution with 1:1 $CHCl_3$/hexanes first gave alkyne dimer **23** (6.0 mg, 18%) as a colorless solid, which was pure by TLC and NMR: mp >250 °C; ^{1}H NMR δ 3.08 (t, J = 5.6 Hz, 8H), 3.97 (t, J = 5.6 Hz, 8H), 6.56 (d, J = 9.0 Hz, 4H), 7.39 (d, J = 9.0 Hz, 4H); ^{13}C NMR δ 36.63, 52.49, 77.20, 82.06, 109.20, 111.12, 134.12, 146.77; MS calcd for $C_{24}H_{25}N_2S_4$ (M + 1) 469.1, found 469.1. Continued elution gave the incompletely coupled ester **24** as a colorless solid (4.1 mg, 13%), which was pure by TLC and NMR: mp ∼180−225 °C (PHB, dark brown to dark red solid); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.13 (s, 6H), 2.15 (s, 6H), 3.09 (t, J = 5.5 Hz, 8H), 3.93 (s, 3H), 3.99 (t, J = 5.5 Hz, 8H), 6.60 (d, J = 9.0 Hz, 4H), 7.24 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 9.3 Hz, 4H), 7.42 (d, J = 9.3 Hz, 4H), 7.47 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.5 Hz, 4H), 7.54 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.5 Hz, 2H), 8.02 (d, J = 8.5 Hz, 2H); ^{13}C NMR δ 29.70, 36.74, 39.22, 39.38, 46.81, 52.23, 52.44, 87.31, 88.53, 90.13, 91.61, 92.31, 110.53, 111.12, 120.59, 122.03, 124.94, 125.20, 127.24, 129.51, 131.38, 131.49, 131.84, 133.18, 137.47, 146.30, 148.30, 148.78, 149.80, 166.58; MS calcd for $C_{68}H_{60}IN_2O_2S_4$ (M + 1) 1191.3, found 1191.3. Continued elution gave **22** (3.2 mg, 10%) as a pale white solid, which was pure by TLC and NMR: dec ∼175−210 °C (PHB, yellow to dark yellow solid); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.16 (s, 12H), 3.09 (t, J = 5.5 Hz, 12H), 3.93 (s, 3H), 3.98 (t, J = 5.5 Hz, 12H), 6.59 (d, J = 8.5 Hz, 6H), 7.41 (d, J = 9.0 Hz, 6H), 7.44 (d, J = 8.5 Hz, 6H), 7.49 (d, J = 8.0 Hz, 8H), 7.54 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 8.04 (d, J = 8.5 Hz, 2H); ^{13}C NMR δ 29.68, 36.75, 39.26, 46.86, 52.23, 52.44, 77.20, 87.36, 88.47, 90.06, 110.57, 111.12, 120.52, 121.95, 125.00, 125.24, 128.12, 129.50, 131.37, 131.49, 131.82, 133.18, 146.29, 148.49, 149.98, 166.61; MS calcd for $C_{80}H_{72}N_3O_2S_6$ (M + 1) 1298.4, found 1298.4.

4-[[4-[3,5,7-Tris-[4-[4-[4-(1,2,5-dithiazepan-5-yl)phenylethynyl]phenylethynyl]phenyl]adamantan-1-yl]phenylethynyl]benzoic Acid Methyl Ester (25). A thick walled reaction tube was charged with 4-[4-[3,5,7-tris-(4-iodophenyl)-adamantan-1-yl]phenylethynyl]benzoic acid methyl ester (**21**, 25.0 mg, 0.026 mmol), 5-[4-(4-ethynylphenylethynyl)phenyl]-1,2,5-dithiazepane (**18**, 34.4 mg, 0.103 mmol), $Pd(PPh_3)_2Cl_2$ (5.0 mg, 0.071 mmol), and CuI (3.0 mg, 0.015 mmol) in triethylamine (2 mL) and tetrahydrofuran (8 mL). The suspension was flushed with N_2 and capped with a Teflon screwcap. The mixture was heated with stirring at 50−55 °C for 20 h and then filtered, and the solid was washed with $CHCl_3$ (30 mL). The filtrate was evaporated to dryness, and the residue was purified by chromatography with 1:1 $CHCl_3$/hexanes as an eluent to give **25** (3.2 mg, 8%) as a pale white solid, which was pure by TLC and NMR: dec ∼220 °C (PHB, orange solid); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.19 (s, 12H), 3.10 (t, J = 5.5 Hz, 12H), 3.93 (s, 3H), 3.99 (t, J = 5.5 Hz, 12H), 6.61 (d, J = 9.0 Hz, 6H), 7.41 (d, J = 9.0 Hz, 6H), 7.46 (d, J = 8.5 Hz, 6H), 7.48 (d, J = 8.5 Hz, 12H), 7.50 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.0 Hz, 6H), 7.56 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 8.02 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.68, 36.74, 39.38, 46.82, 52.49, 81.35, 87.41, 89.26, 90.78, 92.35, 96.12, 110.27, 111.16, 121.16, 122.27, 123.93, 125.13, 129.52, 131.18, 131.47, 131.72, 133.27, 146.54, 149.26, 166.60; MS calcd for $C_{104}H_{84}N_3O_2S_6$ (M + 1) 1598.5, found 1598.5. Anal. Calcd for $C_{104}H_{83}N_3O_2S_6 \cdot 6H_2O$: C, 73.16; H, 5.61; N, 2.46. Found: C,73.22; H, 5.66; N, 2.54.

4-[4-[3,5,7-Tris-[4-(4-acetylsulfanylmethylphenylethynyl)phenyl]adamantan-1-yl]phenylethynyl]benzoic Acid Methyl Ester (26). A thick-walled reaction tube was charged with 4-[4-[3,5,7-tris(4-iodophenyl)adamantan-1-yl]-phenylethynyl]benzoic acid methyl ester (**21**, 25 mg, 0.026 mmol), 1-[4-(*S*-acetylthiomethyl)phenyl]acetylene (**13**, 19.5 mg, 0.102 mmol), $Pd(PPh_3)_2Cl_2$ (5 mg, 0.071 mmol), CuI (3 mg, 0.015 mmol), triethylamine (2 mL), and THF (8 mL). The mixture was flushed with N_2 and capped with a Teflon screwcap. The mixture was heated with stirring at 60−65 °C for 20 h and then filtered, and the solid was washed with CH_2Cl_2 (50 mL). The filtrate was evaporated to dryness, and the residue was purified by chromatography. Elution with 1:1 CH_2Cl_2/hexanes gave **26** (5.6 mg, 19%) as a white solid, which was pure by TLC and NMR: dec ∼130 °C (PHB, yellow solid); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.17 (s, 12H), 2.36 (s, 9H), 3.93 (s, 3H), 4.12 (s, 6H), 7.26 (d, J = 8.5 Hz, 6H), 7.45 (d, J = 8.0 Hz, 6H), 7.46 (d, J = 8.5 Hz, 6H), 7.49 (d, J = 9.0 Hz, 2H), 7.52 (d, J = 8.5 Hz, 6H), 7.55 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 8.02 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz) δ 30.31, 33.24, 39.30, 39.38, 46.77, 52.21, 88.54, 88.98, 89.49, 92.28, 120.60, 121.15, 122.26, 125.06, 125.18, 128.03, 128.83, 129.36, 129.48, 131.46, 131.69, 131.78, 131.82, 137.82, 149.16, 149.76, 166.56, 194.94; MS calcd for $C_{77}H_{64}O_5S_3$ (M + 2) 1164.4, found 1164.4.

4-[[4-[3,5,7-Tris[4-(4-acetylsulfanylmethylphenylethynyl)phenylethynyl]phenyl]adamantan-1-yl]phenylethynyl]benzoic Acid Methyl Ester (27). A thick-walled reaction tube was charged with ester **21** (25.0 mg, 0.0270 mmol), thioacetic acid *S*-[4-(4-ethynylphenylethynyl)benzyl] ester (**16**, 37.9 mg, 0.128 mmol), $Pd(PPh_3)_2Cl_2$ (5.0 mg, 0.071 mmol), CuI (3.0 mg, 0.015 mmol), triethylamine (2 mL), and THF (8 mL). The mixture was flushed with N_2 and capped with a Teflon screwcap. The mixture was heated with stirring at 50−55 °C for 20 h and then filtered, and the solid was washed with CH_2Cl_2 (50 mL). The filtrate was evaporated to dryness, and the residue was purified by chromatography. Elution with 1:1 CH_2Cl_2/hexanes gave **27** (3.5 mg, 10%) as a pale white solid, which was pure by TLC and NMR: dec ∼142 °C (PHB, yellow solid); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.19 (s, 12H), 2.36 (s, 9H), 3.93 (s, 3H), 4.12 (s, 6H), 7.28 (d, J = 8.0 Hz, 6H), 7.46 (d, J = 8.5 Hz, 6H), 7.49 (d, J = 9.0 Hz, 6H), 7.50 (s, 18H), 7.51 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.0 Hz, 6H), 7.56 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.33, 33.26, 39.38, 46.80, 52.22, 88.58, 89.05, 89.36, 90.94, 91.14, 92.27, 96.11, 120.68, 121.04, 122.00, 122.98, 123.16, 125.15, 128.06, 128.90, 129.51, 131.52, 131.80, 131.83, 138.15, 149.37, 149.73, 166.57, 194.89; MS calcd for $C_{101}H_{74}O_5S_3$ (M) 1462.47, found 1462.4. Anal. Calcd for $C_{101}H_{74}O_5S_3 \cdot 5H_2O$: C, 78.06; H, 5.45. Found: C, 77.71; H, 5.41.

Atomic Force Microscopy Experiments. AFM measurements were carried out with a Nanoscope IIIa Multimode AFM (Digital Instruments, Santa Barbara, CA) using a 10 μm scanner. Tapping mode AFM (TMAFM) scans were performed in air with NANO*SENSORS* silicon cantilevers/tips: type NCH, cantilever resonance frequency f_0 = 289−332 kHz and force constant 24.0−37.0 N/m.

The instrument was operated at frequencies slightly lower than the natural resonance frequency in air. All data were recorded in height mode. Set point values were chosen so that the interaction of the tip and sample provided a good compromise between stability and resolution, without damaging the tip or the sample. Scan rates ranged from 1 to 3 Hz. Images were taken at a 512 × 512-pixel resolution to increase the detail in the images. All TMAFM studies were carried out on freshly cleaved muscovite mica, grade V-4 (Structure Probe, Inc.).

Sample Preparation. Spectroscopic grade solvents were used for sample preparation. **Ester 27 on Mica.** One drop of a 0.25 or 1.0 μM solution of ester **27** in CH_2Cl_2 was spin-coated onto freshly cleaved mica (cleaved with Scotch tape) for 15−

20 s under ambient conditions at a speed of 2000 rpm. Scanning of the sample by AFM began immediately after completion of the spin-coating step.

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Supporting Information Available: ^{1}H NMR (300 MHz) spectra for **7**, **8**, **10**−**18**, and **20**−**24**; ^{1}H NMR (500 MHz) for **22** and **24**−**27**; ^{13}C NMR (75 MHz) spectra for **7**, **8**, **10**−**18**, **20**−**24**, and **26**; ^{13}C NMR (125 MHz) spectra for **25** and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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