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The preparation of three new partially deuterated hexadecanethiols for applications in surface chemistry

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The synthesis of three partially deuterated hexadecanethiols has been achieved. Thiols $CH_3(CH_2)_7(CD_2)_8SH$, $CD_3(CD_2)_7(CH_2)_8SH$ and $CD_3(CH_2)_{15}SH$ were targeted, as these compounds, after formation of self-assembled monolayers on Au(1 1 1) or Au nanoparticles, can provide mechanistic information pertaining to reactive atom migrations within the assembly. The syntheses of each of these compounds called upon Grignard coupling chemistry, which was activated by Li_2CuCl_4. Applicable deuterium containing fragments were either commercially obtained or constructed from by way of an inexpensive and efficient ring opening, protection and dimerization of THF-d_8. Sulfur incorporation was by thiolacetate substitution or addition reactions. The protocols presented possess general applicability in a number of syntheses requiring block-deuterated fattyalkyl sections.

Keywords: grignard reaction; self-assembled monolayers; thiol; deuterium

Introduction

Ordered monolayer-thick organic films present highly structured interfaces by which to protect metallic and inorganic supports, provide protein binding sites with controlled topographies and compositions, and function as controlled resist films for electron and photon-driven lithography and surface modifications.[1] In addition, the structured nature of these systems makes them ideal model systems for the study of molecular dynamics, condensed phase phenomena and energy transfer processes. These films can be prepared using Langmuir–Blodgett techniques for physisorbed films and self-assembly for covalently bound monolayers (i.e. SAMs). Much of the interest in these systems stems from the relative ease with which the composition of the film can be modified to fulfill specific *physical* or *chemical* design objectives. In this work we will describe the synthesis of three partially deuterated alkanethiol species that are designed to provide information related to both of these objectives for SAM systems.

Alkanethiols adsorbed onto gold substrates constitute the most studied family of systems in the vast literature on SAMs. Deuteration of an otherwise perhydrogenated molecule can be used to distinguish the vibrational properties and ordering characteristics at specific sites along the chain axis without significantly perturbing the van der Waals forces that provide the film's stability. Previous theoretical[2] and experimental work[3,4] has shown that isotopic segregation is not expected for these systems, and as such mixtures of hydrogenated and deuterated species can be considered as thermodynamically ideal solutions and adsorbed films. By diluting deuterated components within fully hydrogenated isotopomers it has been possible to identify and quantify the dynamic intermolecular and intramolecular coupling of the vibrational modes of two dimensional film,[4] and thus clarify the nature of the overall spectrum.

Selective deuteration of *n*-alkanethiol SAMs can also be used to explore the *chemical* consequences of the highly ordered condensed phase environment of the SAM. We have recently used perdeuterated alkanethiols to explore the mechanisms of molecular hydrogen formation when SAMs are exposed to low-energy (0–15 eV) electron beams.[3] By measuring the relative yields of HD and D_2 formed as the mole fraction of perdeuterated thiolates was varied, we have shown that the reaction is bimolecular in nature, with a primary hydrogen (deuterium) fragment produced by electron impact, and the molecular hydrogen being produced by the reactive encounters of these fragments with adjacent molecules; by unambiguously showing that the unimolecular fragmentation channels[5] has negligible probabilities, the interpretation of electron-beam induced chemistry in lithographic processes becomes more reliable.

The current series of partially deuterated target alkanethiols, compounds **1**, **2** and **3**, are designed to further our ability to study the physical and chemical implications of SAM structure. The films composed of these species present significantly simplified infrared spectra (e.g. with fully resolved spectral regions associated with the methyl and methylene vibrational modes), and have been used to observe the subtle bands associated with the α and β methylene sites[6,7] (relative to the methyl termination) as the films are thermally disordered. They have also been used to estimate effective range of the electron-

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impact produced fragment prior to the second reactive encounter with a nearby chain.

These synthetic methods outlined here may find further use in the syntheses of partially and/or fully deuterated alkyl chains for introduction into lipids which have already been be utilized for studies of chain dynamics in phospholipid bilayers.[8] Solid-state ^{2}H NMR techniques have also been used to observe the temperature-dependent chain librations using selectively deuterated alkanethiols bound to gold nanoparticles,[9] and quantify the progressive disordering of these quasi-spherical systems as the temperature is increased.

Results and discussions

Synthesis of 9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16,16-(heptadecyldeuterio) hexadecane-1-thiol (1)

The principal tool adopted for the constructions of all deuterated targets was Grignard coupling reactions. Tamura and Kochi[10] first investigated the use of dilithium tetrachlorocuprate for coupling of alkyl halides with Grignard reagents. This provided a selective catalyst to couple alkyl, aryl and vinyl Grignard reagents with primary alkyl halides. Johnson[11] demonstrated that in the presence of Li_2CuCl_4, alkyl Grignard reagents couple with only one bromide of an alkyl dibromide, with formation of the dicoupled product possible at higher temperatures and longer reaction time. Based on this and other precedents,[12–14] the Grignard reagent of commercially available perdeuterated bromooctane (**4**) was prepared and coupled to dibromooctane as the starting point for 9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16,16-(heptadecyldeuterio)hexadecanethiol-d_{17} (**1**, Scheme 1).

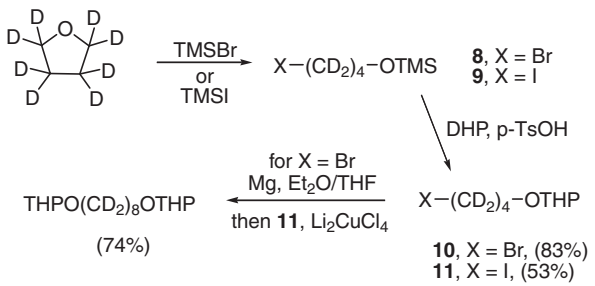
The perdeuterated bromooctane Grignard reagent was reproducibly obtained in refluxing THF in the presence of ether-rinsed magnesium turnings and an I_2 initiator. To ensure the production of significant monocoupled product, two equivalents of dibromooctane were reacted with the Grignard reagent in the presence of a catalytic amount of freshly prepared Li_2CuCl_4 (Scheme 1).

This reaction produced an inseparable mixture of the desired bromohexadecane **5** and leftover dibromooctane. Analysis of the NMR and mass spectral data indicated a 35% conversion with 65% starting material left over and $<2\%$ of the dicoupled product. The addition of potassium thioacetate to this crude mixture produced thiolacetate **6,** which was easily separated from doubly functionalized **7** by flash chromatography to yield 51% of compound **6** over two steps. The deacetylization of **6** to afford labelled thiol **1** was performed by treating the thiolacetate with one equivalent of LAH in THF for 15 min[15] producing thiol cleanly in 70% yield without disulfide contamination.

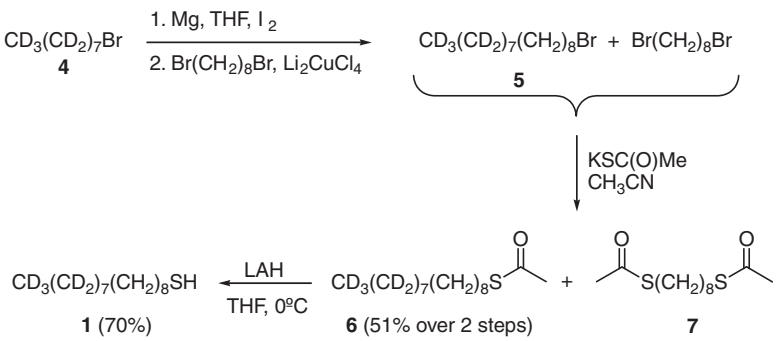
Synthesis of 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-(hexadecyldeuterio)hexadecane-1-thiol (2)

The synthesis of 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-(hexadecyldeuterio)hexadecane-1-thiol (**2**) proved much more difficult, as it required a fully deuterated eight carbon chain with orthogonal functionality permitting the coupling of bromooctane to one end while conserving the other end for a thiol. A procedure[16] has been described for the synthesis of (hexadecyldeuterio)-1,8-octanediol starting from THF-d_8 (Scheme 2). This procedure involves the ring opening of THF-d_8 with TMSBr and TMSI to form the silyl protected α-bromo-ω-alcohol **8** and α-iodo-ω-alcohol **9**, respectively. THP protection precedes magnesiobromide coupling to THP protected iodide **11** using Li_2CuCl_4.

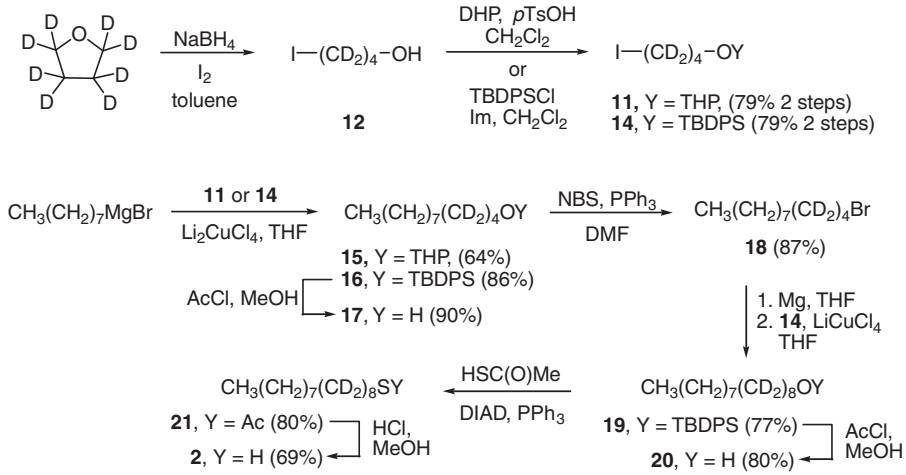
Given the cost of the TMSX reagents and the eventual need to differentiate the termini of the symmetric deuterated 8-carbon backbone, we sought a different approach, one that called on an iterative construction of the deuterated target **2**. Specifically, we wished to couple the THP-protected bromide **10** (or iodide **11**) to an eight carbon bromide through Grignard chemistry, then connect this to another molecule of bromide **10** (or iodide **11**) to give the 16 carbon, partially deuterated chain. Furthermore, we hoped to adapt a new protocol for opening THF[17,18] and apply it to the perdeuterated manifold, thus circumventing expensive TMSX reagents. The alternative procedure uses sodium borohydride and iodine in THF over 2 h to ring open THF (Scheme 3). Targeting the fully deuterated version, an alternative solvent had to be used as using THF-d_8 is not



Scheme 2.



Scheme 1.



Scheme 3.

economically viable. A variety of solvents were evaluated using hydrogenated THF and it was found that 1 equivalent of $NaBH_4$ and 2 equivalents of I_2 in toluene for 3 days at room temperature gave efficient formation of 4-iodobutanol, which could readily be converted to a THP protected iodoalcohol in 74% overall yield.

These same procedures were carried out for the THF-d_8 substrate. Secondary isotope effects resulted in a longer reaction time of 6 days giving 96% yield of the crude alcohol, which was carried through to THP protection to yield 79% of the protected perdeuterated compound **11**. To our knowledge, this is the first use of the $NaBH_4/I_2$ conditions[17] for the preparation of perdeuterio-4-iodobutan-1-ol and it is recommended as a convenient, high yielding and inexpensive protocol for the ring opening of THF-d_8.

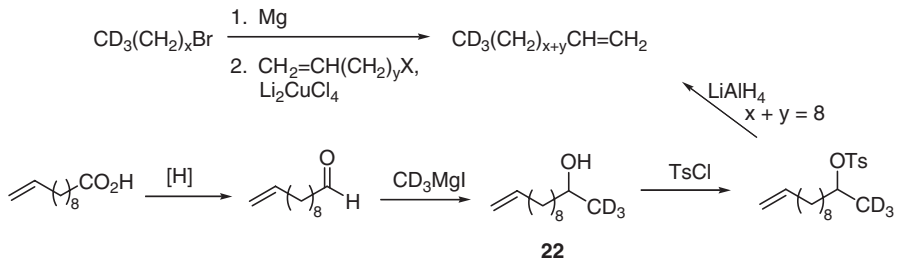
The synthesis was continued with coupling of compound **11** to the prepared octylmagnesium bromide. This resulted in THP protected **15** with deuterium incorporation on carbons 1–4. However, NMR analysis of **15** indicated some protium introduction α to the OTHP group. Adjusting reaction conditions did not remedy this, and subsequently a new oxygen-protecting group was sought for this chemistry.

Accordingly, TBDPS ether **14** was prepared from the corresponding alcohol in good yield using imidazole and TBDPSCl.[17] Freshly prepared octylmagnesium bromide was then connected to **14** affording 12-carbon protected alcohol **16**, which did not succumb to any undesirable deuterium–hydrogen exchange. Substrate **16** was efficiently deprotected[19] (AcCl, MeOH, 90%) to provide 1,1,2,2,3,3,4,4-(octadeuterio)dodeca-1-ol (**17**). The resulting alcohol was then converted to bromide **18** using NBS/Ph_3P in DMF.[20] Addition of another perdeuterated 4 carbon chain was accomplished using the identical Grignard coupling conditions affording 16-carbon compound **19**, which was readily deprotected to afford alcohol **20** for eventual conversion to thiolacetate **21** (Mitsunobu conditions: PPh_3, DIAD, AcSH, 80%).[21] The release of thiol **2** was effected in this case with HCl in refluxing methanol to give hexadecanethiol with deuterium incorporation on carbons 1–8 (**2**) in 17% overall yield over nine steps.

Synthesis of 16,16,16-(trideuterio)hexadecane-1-thiol

A number of synthetic schemes were considered for introduction of deuterium at the terminal methyl group of an alkanethiol. Long chain alkyl bromides with d_3-terminal methyl groups are commercially available in 4, 6, 8 and 10 carbon lengths. It was recognized from previous reactions that one of these could be converted to the Grignard reagent and coupled to an appropriate length α-halo-ω-olefin as outlined in Scheme 4.

The thiol could be incorporated through a radical reaction of thiolacetic acid with the double bond and subsequent deprotection of the thiolacetate to yield the thiol. Although this scheme seems feasible, the commercially available choices of $(x+y)=13$ proved expensive and in view of this, other synthetic routes were explored. A previous synthesis developed for the synthesis of 12,12,12-(trideuterio)-dodecane-1-thiol by Qin,[22] demonstrates the reduction of an unsaturated 11 carbon



Scheme 4.

acid and reaction of the resulting aldehyde with d_3-methylmagnesium iodide (Scheme 4). The secondary alcohol (**22**) was reduced through conversion to a tosylate and LAH reduction. Placement of the thiol at the double bond was accomplished as indicated above.

For a final chain length of 16 carbons, a 15 carbon ω-unsaturated alcohol would have to be made. Following a procedure by Christoffers,[23] 15-bromopentadecene was made from the Grignard reaction of allylmagnesium chloride and 1,12-dibromododecane. This produced an inseparable mixture of the product **23**, 1,12-dibromododecane and possibly 1,17-octadecadiene. This crude mixture was taken directly to the next step to convert the bromide to alcohol **24**,[24] by first displacing bromides with acetates and then hydrolyzing all acetates. Purification by flash chromatography afforded **24** in 21% yield over three steps.

At this point we were able to expedite CD_3 incorporation compared with the synthesis of Scheme 4. It has been shown that methyl group incorporation can be accomplished by reaction of a primary tosyl group with methyllithium[25,26] or methylmagnesium chloride[27] in the presence of copper (I) iodide.[28] The methyllithium was first attempted with tosylate **25,** which was prepared in 71% yield by the reaction of alcohol **24** with TsCl. While methyl incorporation was accomplished with MeLi in only 20%, the same reaction with methylmagnesium bromide was significantly more efficient, proceeding in 77% yield. Thus, by circumventing alcohol oxidation as required by Scheme 4, d_3-alkene **26** was obtained directly from primary tosylate **25** in 87% yield.

The addition of thiolacetic acid to the double bond of this alkene **21** was accomplished through a radical chain addition assisted by photoinitiated AIBN. Specifically, alkene **26**, thioacetic acid and AIBN in toluene exposed to UV irradiation for 5 h, and after chromatography, afforded addition product **27** in 84% yield. Deprotection of this thiolacetate was accomplished in 50% whether using $LiAlH_4$ or acidic methanol (75 mg scale). (Scheme 5).

Summary

This paper outlines the preparation of three heretofore unknown hexadecanethiols with different sections of perdeuteration. In studies to be submitted elsewhere two of the compounds have been used to secure valuable information regarding the mechanism of molecular hydrogen formation during low-energy (10 eV) electron irradiation of hexadecanethiol SAM's.

In addition to the construction of new useful compounds **1**–**3**, the methods adopted herein offer improvements over some existing protocols. We have demonstrated a facile and inexpensive approach to perdeuterated 4-iodobutan-1-ol. We have applied a more expeditious conversion of primary tosylate to alkane circumventing the partial reduction protocol of a carboxylic acid. We have established that the TBDPS group suitably protects alcohols during Grignard reactions while maintaining the isotopic integrity of the substrate. Finally, we have demonstrated an iterative method for the incorporation of C_4D_8 units into organic molecules. In principle, numerous deuterated targets can be assembled with this chemistry.

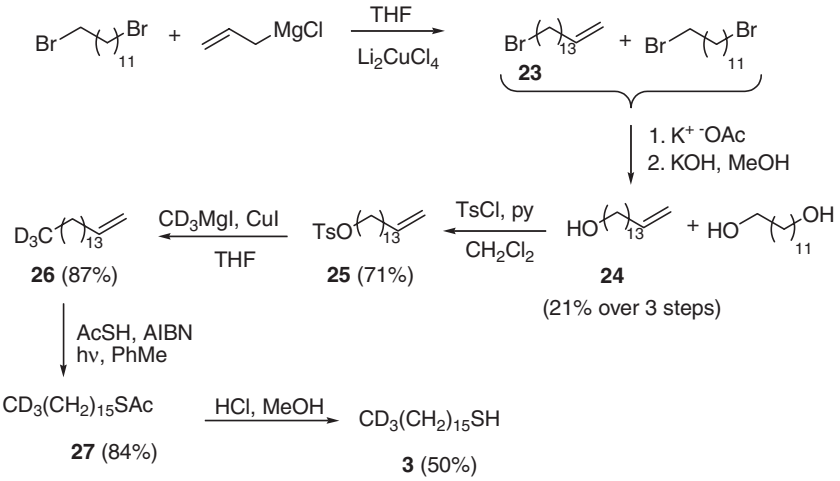
Experimental methods

General methods

The general procedures have been published elsewhere.[29] UV irradiation was performed with a Hanovia 200 W immersion lamp light source. Deuterium-labelled compounds were purchased from C-D-N isotopes. A 0.1 M solution of Li_2CuCl_4 in THF was prepared by drying LiCl and $CuCl_2 \bullet 2H_2O$ under vacuum for 4 h at 120°C.

9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16,16-(Heptadecyldeuterio)-1-bromohexadecane ***(5)***

To a flame dried RBF was added scratched magnesium turnings (348 mg, 1.43 mmol), a crystal of iodine and THF (5 mL). 1-Bromooctane-d_{17} (1.00 g, 4.76 mmol) was added dropwise and the reaction was stirred under reflux until complete formation of Grignard reagent was indicated by GC analysis (3.5 h). To another flame dried RBF was added 1,8-dibromooctane (2.59 g, 9.52 mmol), a freshly prepared 0.1 M solution of Li_2CuCl_4 (0.952 mL) and THF (5 mL). This mixture was cooled to 0°C and the prepared Grignard reagent was added dropwise. During addition, the reaction turned from orange to dark purple to clear and then remained dark purple. The reaction was stirred overnight at 0°C and was then quenched with 1 M HCl (30 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and



Scheme 5.

concentrated to yield an inseparable mixture of 1,8-dibromooctane and the product 9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16,16-(heptadecyldeuterio)-bromohexadecane (**5**) (2.81 g total mass). Characterization data for **5**:^{1}H NMR ($CDCl_3$)δ3.38 (t, J = 6.8 Hz, 2H), 1.83 (p, J = 7.1 Hz, 2H), 1.42–1.23 (m, 4H). ^{2}H NMR ($CHCl_3$)δ1.17 (s, 14H), 0.80 (s, 3H). ^{13}C NMR ($CDCl_3$)δ34.0, 33.9, 32.9, 32.7, 29.6, 29.4, 28.8, 28.5, 28.2, 28.0. IR (cm^{-1}): 2928, 2855, 2196, 2095, 1464. MS (EI), *m/z* (%):323 (M^+ ^{81}Br, 6), 321 (M^+ ^{79}Br, 6), 242 (12), 165 (3), 163 (3), 151 (22), 149 (22), 137 (98), 135 (100).

9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16-(Heptadecyldeuterio)-hexadecyl-1-thiolacetate ***(6)***

The crude mixture of 1,8-dibromooctane and bromohexadecane-d_{17} (2.81 g) was dissolved in CH_3CN (40 mL) to which was added potassium thiolacetate (2.18 g, 19.1 mmol). The mixture was stirred at room temperature until complete by TLC (3 h). The reaction was quenched with H_2O (40 mL), the layers were separated and the aqueous layer was extracted with pentanes (3 × 30 mL). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The mixture was purified by flash chromatography on silica gel (2% EtOAc/hexanes) to yield the pure **6** (767 mg, 51% over two steps). ^{1}H NMR ($CDCl_3$)δ2.84 (t, J = 7.3 Hz, 2H), 2.30 (s, 3H), 1.53 (m, 2H), 1.23 (m, 12H). ^{2}H NMR ($CHCl_3$)δ1.17 (s, 14H), 0.80 (s, 3H). ^{13}C NMR ($CDCl_3$)δ195.5, 30.6, 29.6, 29.5, 29.4, 29.1, 28.8. IR (cm^{-1}): 2917, 2851, 2191, 2090, 1687, 1469. MS (EI), *m/z* (%): 317 (M^+, 9), 274 (100), 257 (21), 241 (18).

9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16-(Heptadecyldeuterio)-hexadecane-1-thiol ***(1)***

To a flame dried RBF was added $LiAlH_4$ (23.9 mg, 0.630 mmol) and THF (0.5 mL). This mixture was cooled to 0°C and a mixture of hexadecanethiolacetate-d_{17} (**6**, 200 mg, 0.630 mmol) in THF (1.5 mL) was added dropwise. Reaction was stirred at this temperature for 30 min. The reaction quenched slowly with H_2O (5 mL) and the aluminum salts were filtered off and washed with CH_2Cl_2. The filtrate layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The mixture was isolated by flash chromatography on silica gel (100% hexanes) to yield pure **1** (122 mg, 70%). ^{1}H NMR ($CDCl_3$)δ2.50 (q, J = 7.4 Hz, 2H), 1.58 (m, 2H), 1.36–1.22 (m, 13H). ^{2}H NMR ($CHCl_3$)δ1.18 (s, 14H), 0.82 (s, 3H). ^{13}C NMR ($CDCl_3$)δ34.1, 29.6, 29.5, 29.1, 29.4, 24.7. IR (cm^{-1}): 2924, 2853, 2195, 2095, 1465, 1087. MS (EI), *m/z* (%): 275 (M^+, 100), 240 (49), 212 (10), 152 (4), 121 (9), 101 (20), 83 (32), 55 (41). HRMS (EI): Calc'd for $C_{16}H_{17}D_{17}S$, 275.3348; Found, 275.3443.

1,1,2,2,3,3,4,4-(octyldeuterio)-4-iodo-1-(Tetrahydropyranyloxy)butane ***(11)***

This protocol was adapted from a previous method.[30] To a flame dried RBF was added 1,1,2,2,3,3,4,4-(octyldeuterio)-4-iodobutan-1-ol (**12**, 3.10 g, 14.9 mmol), *p*-toluenesulfonic acid (567 mg, 2.98 mmol) and CH_2Cl_2 (20 mL). The mixture cooled to 0°C and 3,4-dihydro-2H-pyran (3.41 mL, 37.3 mmol) added dropwise. The reaction was warmed to room temperature and stirred in the dark until TLC indicated completion (4 h). The reaction was quenched with H_2O (20 mL), the layers were separated and aqueous layer was extracted with ether (3 × 15 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated. The mixture was purified by flash chromatography on silica gel (5% EtOAc/hexanes) to yield pure 11 (2.68 g, 62%). ^{1}H NMR ($CDCl_3$)δ4.55 (m, 1H), 3.88–3.81 (m, 1H), 3.74–3.66 (m, 1H), 3.50–3.45 (m, 1H), 3.39–3.31 (m, 1H), 1.83 (m, 8H), 1.2–1.3 (m, 18H), 0.85 (t, J = 6.5 Hz, 3H). ^{2}H NMR ($CHCl_3$)δ3.71 (1 H), 3.37 (1H), 3.19 (2H), 1.87 (2H), 1.63 (2H). ^{13}C NMR ($CDCl_3$)δ98.9, 67.7, 62.3, 31.9, 30.8, 29.8, 29.6, 29.5, 29.3, 26.2, 25.5, 22.7, 19.7, 14.1. MS (CI, NH_3), *m/z* (%): 288 ($(M+NH_4)^+$, 25), 186 (43), 169 (23), 102 (100), 85 (10), 53 (2).

1,1,2,2,3,3,4,4-(Octyldeuterio)-4-iodobutan-1-ol ***(12)***

To a solution of sodium borohydride (1.89 g, 50.0 mmol) and THF-d_8 (4.00 g, 50.0 mmol) was added dropwise a solution of iodine (25.4 g, 100 mmol) in toluene (130 mL). The mixture was stirred for 6 days in the dark, cooled to 0°C and slowly quenched with H_2O (80 mL). The layers were separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Crude **12** (10.0 g, 96%) was protected without further purification. ^{2}H NMR ($CHCl_3$)δ3.49 (s, 2D), 3.10 (s, 2D), 1.75 (s, 2D), 1.50 (s, 2D). ^{13}C NMR ($CDCl_3$)δ60.5 (m), 32.0 (m), 28.7 (m), 6.9 (m). IR (cm^{-1}): 3346, 2212, 2098.

t-Butyl-(1,1,2,2,3,3,4,4-(octyldeuterio)-4-iodobutoxy)diphenylsilane ***(14)***

This protocol was adapted from a previous method.[17] To a flame dried RBF was added a solution of crude 4-iodobutan-1-ol-d_8 (**12**, 6.80 g, 32.7 mmol), imidazole (5.57 g, 81.8 mmol) and CH_2Cl_2 (100 mL). *t*-Butylchlorodiphenylsilane (10.1 mL, 39.2 mmol) was added dropwise at 0°C. The mixture was warmed slowly to room temperature and stirred in the dark overnight. The reaction was quenched with saturated NH_4Cl solution (40 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated. Product was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to yield pure **14** (11.5 g, 79%). ^{1}H NMR ($CDCl_3$)δ7.67 (dd, J = 7.7, 1.5 Hz, 4H), 7.42–7.36 (m, 6H), 1.04 (s, 9H). ^{2}H NMR ($CHCl_3$)δ3.63 (s, 2H), 3.15 (s, 2H), 1.88 (s, 2H), 1.59 (s, 2H). ^{13}C NMR ($CDCl_3$)δ135.5, 133.8, 129.6, 127.6, 26.8, 19.2. IR (cm^{-1}): 3070, 2929, 2856, 2198, 2084, 1727, 1427, 1265, 1111, 1047. MS (CI, NH_3), *m/z* (%): 464 ($(M+NH_4)^+$, 100), 447 (8), 406 (19), 386 (5), 326 (1), 191 (6).

1,1,2,2,3,3,4,4-(Octyldeuterio)-(tetrahydropyranyloxy)dodecane ***(15)***

This protocol was adapted from a previous method.[16] To a flame dried RBF was added scratched magnesium turnings (189 mg, 7.77 mmol), a crystal of iodine and THF (3 mL). 1-bromooctane (500 mg, 2.59 mmol) was added dropwise and the reaction was stirred under reflux until complete formation of the Grignard reagent was indicated by GC analysis (3.5 h). To another flame dried RBF was added 1,1,2,2,3,3,4,4-(octyldeuterio)-4-iodo-1-(tetrahydropyranyloxy)butane (**14**, 380 mg, 1.30 mmol), a freshly prepared 0.1 M solution of Li_2CuCl_4 (0.260 mL) and THF (2 mL). This mixture was cooled to 0°C and the prepared Grignard reagent was added dropwise. The reaction was stirred at this temperature overnight and was quenched with 1 M HCl (5 mL) and then extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and

concentrated. The mixture was purified by flash chromatography on silica gel (100% hexanes) to yield 15 (230 mg, 64%). ^{1}H NMR ($CDCl_3$)δ4.56–4.55 (m, 1H), 3.87–3.82 (m, 1H), 3.74–3.66 (m, 0.2H), 3.50–3.48 (m, 1H), 3.37–3.31 (m, 0.2H), 1.83–1.81 (m, 1H), 1.80–1.67 (m, 1H), 1.59–1.48 (m, 6H), 1.30–1.24 (m, 12H), 0.86 (t, J = 6.9 Hz, 3H). ^{2}H NMR ($CHCl_3$)δ3.68 (s, 0.9H), 3.32 (s, 0.9H), 1.52 (s, 2H), 1.25 (s, 4H). ^{13}C NMR ($CDCl_3$)δ98.8, 67.7, 62.3, 31.9, 31.8, 30.8, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 26.2, 25.5, 22.7, 19.7, 14.1. IR (cm^{-1}): 3449, 2924, 2854, 1466, 1028. MS (CI, NH_3), *m/z* (%): 296 (($M+NH_4$)$^+$, 43), 277 (5), 102 (100), 85 (10).

t-Butyl-(1,1,2,2,3,3,4,4-(octyldeuterio)-dodecyl)diphenylsilane ***(16)***

To a flame dried RBF was added scratched magnesium turnings (758 mg, 31.2 mmol), a crystal of iodine and THF (10 mL). 1-bromooctane (2.00 g, 10.4 mmol) was added dropwise and the reaction was stirred under reflux until complete formation of Grignard reagent was indicated by GC analysis (3.5 h). To another flame dried RBF was added *t*-butyl-(1,1,2,2,3,3,4,4-(octyldeuterio)-4-iodobutoxy)diphenylsilane (**14**, 2.31 g, 5.18 mmol), a freshly prepared 0.1 M solution of Li_2CuCl_4 (2.08 mL) and THF (10 mL). This mixture was cooled to 0°C and the prepared Grignard reagent was added dropwise. Upon addition of the Grignard, the reaction turned from orange to dark purple to clear and then remained dark purple. The reaction stirred overnight at this temperature. Workup and purification as per **15** yielded pure **16** (1.93 g, 86%). ^{1}H NMR ($CDCl_3$)δ7.66 (d, J = 7.4 Hz, 4H), 7.40–7.24 (m, 6H), 1.29–1.25 (m, 14H), 1.04 (s, 9H), 0.88 (t, J = 5.1 Hz, 3H). ^{2}H NMR ($CHCl_3$)δ3.61 (s, 2H), 1.48 (s, 2H), 1.26 (s, 2H), 1.22 (s, 2H). ^{13}C NMR ($CDCl_3$)δ135.5, 133.8, 129.6, 127.6, 26.9, 19.2. IR (cm^{-1}): 3071, 2926, 2855, 2199, 2087, 1471, 1112, 1075. MS (CI, NH_3), *m/z* (%): 450 (($M+NH_4$)$^+$, 100), 433 (27), 392 (27), 372 (7), 338 (2), 256 (3).

1,1,2,2,3,3,4,4-(Octyldeuterio)-dodecan-1-ol ***(17)***

This protocol was adapted from a previous method.[19] To a flame dried RBF was added *t*-butyl-(1,1,2,2,3,3,4,4-(octyldeuterio)-dodecyl)diphenylsilane (**16,** 4.24 g, 9.80 mmol) in methanol (30 mL). The mixture was cooled to 0°C and acetyl chloride (115 mg, 1.47 mmol) was added dropwise. The reaction was warmed slowly to room temperature and stirred until TLC indicated completion (5 h). The reaction was diluted with CH_2Cl_2 (150 mL) and neutralized with 10% $NaHCO_3$ solution (9 mL). The organic layer was separated and washed with H_2O (20 mL), brine, dried over $MgSO_4$ and concentrated. The mixture was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to yield pure **17** (1.71 g, 90%). ^{1}H NMR ($CDCl_3$)δ1.24 (s, 14 H), 0.85 (t, J = 6.4 Hz, 3H). ^{2}H NMR ($CHCl_3$)δ3.58 (s, 2H), 1.49 (s, 2H), 1.26 (s, 4H). ^{13}C NMR ($CDCl_3$)δ31.9, 29.7, 29.6, 29.5, 29.3, 22.6, 14.1. IR (cm^{-1}): 3347, 2923, 2853, 2201, 2099, 1466, 1117. MS (CI, NH_3), *m/z* (%): 212 (($M+NH_4$)$^+$, 100), 52.4 (16).

1,1,2,2,3,3,4,4-(Octyldeuterio)-1-bromododecane ***(18)***

This protocol was adapted from a previous method.[20] To a flame dried RBF was added 1,1,2,2,3,3,4,4-(octyldeuterio)-dodecan-1-ol (**17**, 1.47 g, 7.56 mmol), PPh_3 (3.96 g, 15.1 mmol) and DMF (15 mL). *N*-bromosuccinimide (2.69 g, 15.1 mmol) was added slowly to the mixture and the reaction was stirred at 50°C for 15 min. The reaction was cooled to room temperature and methanol (9 mL) was added and stirred for an additional 5 min to destroy excess reagent. The reaction was extracted with ether (3 × 10 mL) and combined organic layers were washed with 1 M HCl (16 mL), brine, dried over $MgSO_4$ and concentrated. The mixture was purified by flash chromatography on silica gel (100% hexanes) to yield pure **18** (1.70 g, 87%). ^{1}H NMR ($CDCl_3$)δ1.24 (s, 14H), 0.86 (t, J = 6.8 Hz, 3H). ^{2}H NMR ($CHCl_3$)δ3.36 (s, 2H), 1.78 (s, 2H), 1.35 (s, 2H), 1.24 (s, 2H). ^{13}C NMR ($CDCl_3$)δ31.9, 29.6, 29.5, 29.3, 29.2, 22.7, 14.1. IR (cm^{-1}): 2924, 2853, 2197, 2099, 1466, 991. MS (EI), *m/z* (%): 258 (M^+ ^{81}Br, 3), 256 (M^+ ^{79}Br, 3), 159 (19), 157 (19), 143 (100), 145 (97), 104 (6), 90 (11), 76 (19), 57 (41).

t-Butyl-(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-(hexadecyldeuterio)-hexadecyl)diphenylsilane ***(19)***

To a flame dried RBF was added scratched magnesium turnings (425 mg, 17.5 mmol), a crystal of iodine and THF (8 mL). 1,1,2,2,3,3,4,4-(octyldeuterio)-1-bromododecane (**18**, 1.50 g, 5.83 mmol) was added dropwise and the reaction was stirred under reflux until complete formation of Grignard reagent was indicated by GC analysis (3.5 h). To another flame dried RBF was added *t*-butyl-(1,1,2,2,3,3,4,4-(octyldeuterio)-4-iodobutoxy)diphenylsilane (**12**, 1.30 g, 2.92 mmol), a freshly prepared 0.1 M solution of Li_2CuCl_4 (2.33 mL) and THF (8 mL). This mixture was cooled to 0°C and the prepared Grignard reagent was added dropwise. Upon Grignard addition, the reaction turned from orange to dark purple to clear and then remained dark purple. The reaction was stirred overnight at this temperature. Workup and purification as per **15** yielded pure **19** (1.12 g, 77%). ^{1}H NMR ($CDCl_3$)δ7.72 (d, J = 7.3 Hz, 4H), 7.45–7.39 (m, 6H), 1.31 (s, 14H), 1.10 (s, 9H), 0.93 (t, J = 5.3 Hz, 3H). ^{2}H NMR ($CHCl_3$)δ3.61 (s, 2H), 1.48 (s, 2H), 1.17 (s, 12H). ^{13}C NMR ($CDCl_3$)δ135.6, 134.2, 129.5, 127.6, 32.0, 29.8, 29.7, 29.5, 29.4, 26.9, 22.7, 19.2, 13.1. IR (cm^{-1}): 3071, 2925, 2855, 2197, 2095, 1463, 1427, 1112, 1047, 823. MS (CI, NH_3), *m/z* (%): 514 (($M+NH_4$)$^+$, 100), 498 (37) 456 (36), 437 (9), 338 (5), 321 (4), 280 (2), 256 (5).

1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-(Hexadecyldeuterio)-hexadecan-1-ol ***(20)***

This protocol was adapted from a previous method.[19] To a flame dried RBF was added *t*-butyl-(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-(hexadecyldeuterio)-hexadecyl)diphenylsilane (**19**, 1.00 g, 2.01 mmol) in methanol (6 mL). The mixture was cooled to 0°C and acetyl chloride (2.37 mg, 0.302 mmol) was added dropwise. The reaction was warmed slowly to room temperature and stirred until TLC indicated completion (5 h). Workup and purification as per compound **17** yielded pure **20** (0.418 g, 80%). ^{1}H NMR ($CDCl_3$)δ1.23 (s, 14H), 0.86 (t, J = 6.8 Hz, 3H). ^{2}H NMR ($CHCl_3$)δ3.59 (s, 2H), 1.50 (s, 2H), 1.27 (s, 2H), 1.19 (s, 10H). ^{13}C NMR ($CDCl_3$)δ31.9, 29.7, 29.6, 29.4, 29.3, 22.6, 14.1. IR (cm^{-1}): 3293, 2918, 2850, 2194, 2090, 1563, 1265, 908. MS (CI, NH_3), *m/z* (%): 276 (($M+NH_4$)$^+$, 100), 275 (6), 53 (10).

1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-(Hexadecyldeuterio)-hexadecyl-1-thiolacetate ***(21)***

This protocol was adapted from a previous method.[21] To a flame dried RBF was added PPh_3 (780 mg, 2.70 mmol) and THF (6 mL). The mixture was cooled to 0°C and diisopropylazodicarboxylate (546 mg, 2.70 mmol) was added dropwise. After the mixture was stirred at 0°C for 30 min, a solution of 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-(hexadecyldeuterio)-hexadecan-1-ol (**20**, 0.349 mg,

1.35 mmol) and thiolacetic acid (195 mg, 2.70 mmol) in THF (4 mL) was added at 0°C. The reaction was stirred at 0°C for 1 h then warmed to room temperature and stirred until TLC indicated completion (1.5 h). The solvent was evaporated and the mixture was purified by flash chromatography on silica gel (5% EtOAc/hexanes) to yield pure **21** (305 mg, 71%). ^{1}H NMR ($CDCl_3$)δ2.29 (s, 3H), 1.23 (s, 14H), 0.85 (t, J = 6.8 Hz, 3H). ^{2}H NMR ($CHCl_3$)δ2.81 (s, 2H), 1.26 (s, 2H), 1.17 (s, 2H). ^{13}C NMR ($CDCl_3$)δ196.0, 31.9, 30.6, 29.7, 29.6, 29.4, 29.3, 22.7, 14.1. IR (cm^{-1}): 2923, 2853, 2196, 2096, 1695, 1467, 1353, 1132, 957. MS (EI), *m/z* (%): 316 (M^+, 13), 273 (100), 252 (17), 239 (15).

1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-(Hexadecyldeuterio)-hexadecane-1-thiol ***(2)***

This protocol was adapted from a previous method.[22] To a flame dried RBF was added 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-(hexadecyldeuterio)-hexadecyl-1-thiolacetate (**21**, 54 mg, 0.170 mmol) and MeOH (2.5 mL). 1 drop of concentrated HCl was added to the reaction mixture and the reaction was refluxed overnight. The solvent was evaporated and the residue was dissolved in EtOAc (10 mL). The solution was washed with water (2 × 10 mL), brine, dried over $MgSO_4$ and concentrated. Purification by flash chromatography (100% hexanes) yielded pure **2** (32 mg, 69%). ^{1}H NMR ($CDCl_3$)δ1.27–1.24 (m, 15H), 0.86 (t, J = 6.6 Hz, 3H). ^{2}H NMR ($CHCl_3$)δ2.47 (2H), 1.53 (2H), 1.30 (2H), 1.19 (10H). ^{13}C NMR ($CDCl_3$)δ31.9, 29.7, 29.4, 29.3, 22.7, 14.1. IR (cm^{-1}): 2956, 2922, 2853, 2196, 2094, 1466. MS (EI), *m/z* (%): 274 (M^+, 100), 239 (40), 207 (8), 104 (14), 90 (20), 74 (20), 62 (27). HRMS (EI): Calc'd for $C_{16}H_{18}D_{16}S$, 274.3386; Found, 274.3386.

15-Bromo-1-pentadecene ***(23)***

Following an established protocol,[23] 1,12-dibromododecane (10.0 g, 3.05 mmol) was dissolved in a 0.15 M solution of Li_2CuCl_4 in THF (45 mL). The mixture was cooled to 0°C and allylmagnesium chloride (2.0 M, 22.8 mL, 4.58 mmol) was added slowly over a period of 30 min. The reaction was stirred at this temperature for 1 h and then quenched with 1 M HCl (72 mL) and stirred for an additional 30 min. The layers were separated and aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give an inseparable mixture of product **23** and starting 1,12-dibromododecane (7.70 g). This crude product was carried onto the next step without purification.

Pentadec-14-en-1-ol ***(24)***

The crude mixture of 15-bromo-1-pentadecene and 1,12-dibromododecane was dissolved in DMF (50 mL). Potassium acetate (10.2 g, 104 mmol) was added to the mixture and the reaction was stirred at 60°C for 2 h. After evaporation of the solvent, the residue was treated with KOH (5.84 g, 104 mmol) and MeOH (60 mL) and stirred at the same temperature for 1.5 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (50 mL). The layers were separated and the organic layer was washed with H_2O (2 × 50 mL), brine, dried over $MgSO_4$ and concentrated. Purification by flash chromatography on silica gel (20% EtOAc/hexanes) yielded pure **24**[31] (1.51 g, 21% over three steps). ^{1}H NMR ($CDCl_3$)δ5.83–5.75 (m, 1H), 4.97 (d, J = 17.4 Hz, 1H), 4.90 (d, J = 10.5 Hz, 1H), 3.62 (t, J = 6.6 Hz, 2H) 2.02 (q, J = 6.9 Hz, 2H), 1.56–1.50 (m, 2H), 1.24 (m, 20H). ^{13}C NMR ($CDCl_3$)δ179.0, 139.3, 114.1, 63.1, 33.8, 32.8, 29.6, 29.5, 29.4, 29.1, 28.9, 25.7.

Pentadec-14-en-1-yl tosylate ***(25)***

Pentadec-14-en-1-ol (**24**, 713 mg, 3.15 mmol) and *p*-toluenesulfonyl chloride (901 mg, 4.73 mmol) were dissolved in CH_2Cl_2 (3 mL) in a flame dried RBF and a catalytic amount of pyridine (0.510 mL) was added. The reaction was stirred at room temperature until TLC indicated completion (5 h). The reaction was diluted with CH_2Cl_2 (10 mL) and quenched with H_2O (10 mL). The layers were separated and the organic layer was washed with 1 M HCl (10 mL), saturated $NaHCO_3$ (10 mL), brine, dried over $MgSO_4$ and concentrated. The mixture was purified by flash chromatography on silica gel (50% toluene/hexanes) to yield pure **25** (850 mg, 71%). ^{1}H NMR ($CDCl_3$)δ7.77 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 5.86–4.89 (m, 1H), 4.97 (d, J = 20.7 Hz, 1H), 4.93 (d, J = 10.2 Hz, 1H), 4.00 (t, J = 6.5 Hz, 2H) 2.43 (s, 3H), 2.02 (q, J = 7.0 Hz, 2H), 1.61 (p, J = 6.9 Hz, 2H), 1.35–1.20 (m, 20H). ^{13}C NMR ($CDCl_3$)δ144.5, 139.2, 133.3, 129.7, 127.8, 114.0, 70.6, 33.8, 29.6, 29.5, 29.4, 29.3, 29.0, 28.9, 28.8, 25.3, 21.6. IR (cm^{-1}): 3074, 2925, 2854, 1640, 1599, 1466, 1364, 1189, 1178. MS (CI, NH_3), *m/z* (%): 398 ($(M+NH_4)^+$, 100), 356 (3), 316 (3).

16,16,16-(Trideuterio)-hexadec-1-ene ***(26)***

The protocol is based on a published method.[27] To a flame dried RBF was added pentadec-14-en-1-yl tosylate (**25**, 800 mg, 2.10 mmol), copper (I) iodide (80 mg, 0.420 mmol) and THF (8 mL). The mixture was cooled to 0°C and 1.0 M solution of d_3-methylmagnesium iodide in ether (5.25 mL, 5.25 mmol) was added dropwise by syringe. The reaction was brought slowly to room temperature and stirred overnight. The reaction was diluted with diethyl ether (10 mL) and quenched slowly with 1 M HCl (15 mL). The layers were separated and aqueous layer was extracted with ether (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Product was purified by flash chromatography on silica gel (100% hexanes) to yield pure **26** (416 mg, 87%). ^{1}H NMR ($CDCl_3$)δ7.77 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 5.86–4.89 (m, 1H), 4.97 (d, J = 20.7 Hz, 1H), 4.93 (d, J = 10.2 Hz, 1H), 4.00 (t, J = 6.5 Hz, 2H) 2.43 (s, 3H), 2.02 (q, J = 7.0 Hz, 2H), 1.61 (p, J = 6.9 Hz, 2H), 1.35–1.20 (m, 20H). ^{2}H NMR ($CDCl_3$)δ0.83. ^{13}C NMR ($CDCl_3$)δ139.3, 114.1, 33.9, 31.8, 29.7, 29.5, 29.4, 29.2, 29.0, 22.4. IR (cm^{-1}): 3078, 2924, 2854, 2214, 2075, 1641, 1466, 909. MS (EI), *m/z* (%): 227 (M^+, 55), 199 (13), 185 (5), 171 (5), 143 (10), 125 (20), 111 (45), 97 (94), 83 (100), 69 (68), 55 (80).

16,16,16-(Trideuterio)-hexadecyl-1-thiolacetate ***(27)***

To an oven dried quartz vial was added d_3-hexadec-1-ene (**26**, 750 mg, 3.30 mmol), AIBN (54 mg, 0.330 mmol) thiolacetic acid (0.891 mL, 13.2 mmol) and toluene (5 mL). The reaction was irradiated under UV light for 5 h. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched with saturated $NaHCO_3$ until no thiolacetic acid remained. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The mixture was purified by flash chromatography on silica gel (5%

EtOAc/hexanes) to yield pure **27** (838 mg, 84%). 1 H NMR ($CDCl_3$)δ2.84 (t, $J = 7.3$ Hz, 2H), 2.30 (s, 3H), 1.54 (p, $J = 7.5$ Hz, 2H), 1.32–1.23 (m, 26H). ^{2}H NMR ($CHCl_3$)δ0.83 (s). ^{13}C NMR ($CDCl_3$)δ31.9, 30.6, 29.7, 29.6, 29.4, 29.3, 28.3, 22.7, 14.1. IR (cm^{-1}): 2915, 2850, 2209, 1694, 1471. MS (EI), *m/z* (%): 303 (M^+, 10), 260 (100), 243 (19), 227 (18).

16,16,16-(Trideuterio)-hexadecane-1-thiol ***(3)***

To a flame dried RBF was added $LiAlH_4$ (75.1 mg, 1.98 mmol) and THF (2.5 mL). This mixture was cooled to 0°C and a solution of d_3-hexadecanethiolacetate (**27**, 600 mg, 1.98 mmol) in THF (3.5 mL) was added dropwise. The reaction was stirred at this temperature for 10 min and then quenched slowly with H_2O (10 mL). The aluminum salts were filtered off and washed with CH_2Cl_2. The layers of filtrate were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried and concentrated. The product was isolated by flash chromatography (100% hexanes) to yield pure **3** (257 mg, 50%). ^{1}H NMR ($CDCl_3$)δ2.49 (q, $J = 7.3$ Hz, 2H), 1.59 (m, 2H), 1.35–1.24 (m, 27H). ^{2}H NMR ($CHCl_3$)δ0.84 (s). ^{13}C NMR ($CDCl_3$)δ34.1, 31.8, 29.7, 29.5, 29.4, 29.1, 28.4, 24.7, 22.4. IR (cm^{-1}): 2923, 2853, 2213, 1465, 1055. MS (EI), *m/z* (%): 261 (M+, 100), 227 (70), 199 (22), 125 (17), 111 (36), 97 (75), 83 (87), 69 (64), 55 (63). HRMS (EI): Calc'd for $C_{16}H_{31}D_3S$, 261.2569; Found, 261.2574.

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