Synthesis of Half-Deuterated Palmitic and Palmitoleic Acids from THF-d_8

Donghui Qin, Hoe-Sup Byun, and Robert Bittman*

Department of Chemistry and Biochemistry, Queens College of the City University of New York, Flushing, New York 11367-1597

Received July 25, 1996

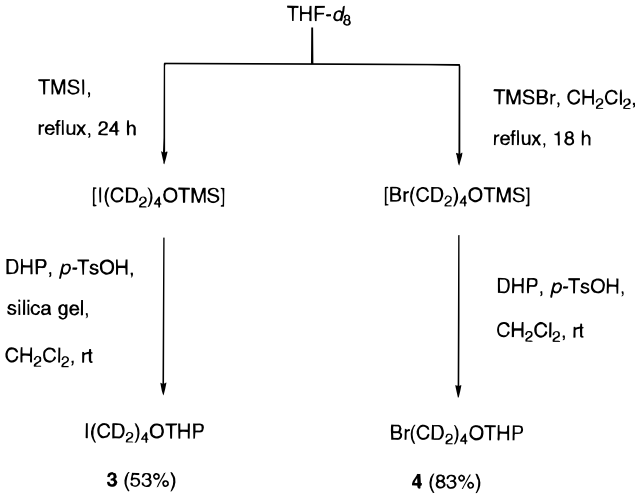
Phospholipids containing fatty acyl chains deuterated at different positions are required for detailed biophysical studies of the conformational order of the hydrocarbon chains in vesicles.[1] The quantitative determination of conformational disorder in the phospholipid acyl chains has been studied in bilayers utilizing the CD_2 rocking modes and CH_2 wagging modes of specifically deuterated 1,2-dipalmitoylphosphatidylcholine (DPPC).[2] For example, studies of the relative populations of *trans* and *gauche* bonds have been carried out using DPPC with a CD_2 group at positions 2, 3, 4, 6, 10, 12, or 13 of the acyl chain.[2]

The current paper describes the synthesis of half-deuterated palmitic acid **1** in which the "top half" (C_2−C_8) is perdeuterated. In future work, **1** will be converted into DPPC with half-deuterated acyl chains, which will be used to estimate *gauche* bond concentrations in separate halves of the phospholipid acyl chain as a function of temperature and bilayer cholesterol content.

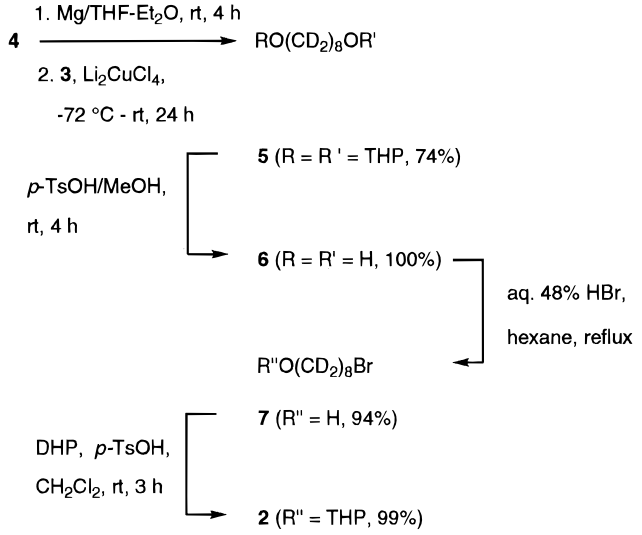
Results and Discussion

The synthesis of **1** started from commercially available deuterated tetrahydrofuran (THF-d_8) (Scheme 1). After the THF ring was opened with either TMS-I or TMS-Br,[3] the TMS group was replaced in situ by a THP group to give THPO$(CD_2)_4$I (**3**) or THPO$(CD_2)_4$Br (**4**), with yields of 53% and 83%, respectively. The in situ replacement of the TMS group by a THP moiety was carried out because we found that it was not possible to couple the THF ring-opened products, i.e., TMS ethers of 4-bromo- (or 4-iodo)butane, with the corresponding Grignard reagent in the presence of copper catalyst due to the lability of the TMS group. Attempted homocoupling of **3** or **4** catalyzed by soluble silver[4] in THF was unsuccessful (≤15% yield). However, the Grignard reagent of bromide **4** was coupled successfully with iodide **3** with a copper(II) catalyst[5] at −72 °C (dry ice/EtOH), giving **5** in 74% yield (Scheme 2). Deprotection of THP ether **5** gave 1,8-octanediol-d_{16} **6** in quantitative yield. The reaction of

Scheme 1. Ring Opening of THF-d_8



Scheme 2. Synthesis of 1,8-Octanediol-d_{16} 6 and Bromide 2



diol-d_{16} **6** with 48% aqueous HBr in hexane provided the monobromo alcohol,[6] 8-bromo-1-octanol-d_{16} **7**, in 94% yield. Acid-catalyzed protection of **7** gave 8-bromo-1-tetrahydropyranyloxy-octane-d_{16} **2**.[7]

Cross-coupling of deuterated bromooctyl THP ether **2** with *n*-octylmagnesium bromide in the presence of Li_2CuCl_4 in THF provided tetrahydropyranyl hexadecyl-d_{16} ether **8** in 60% yield (Scheme 3). Deprotection of the THP group of **8** (*p*-TsOH/MeOH) gave 1-hexadecanol-*1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8*-d_{16} (**9**) in high yield, and oxidation of **9** (PDC/DMF, rt) gave palmitic acid-*2,2,3,3,4,4,5,5,6,6,7,7,8,8*-d_{14} (**1**) (Scheme 3).

Scheme 4 shows an alternate route for the preparation of **1**. Coupling of bromide **2** with octynyllithium in HMPA/THF (1:1) at −72 °C gave hexadecynyl ether **10** in 83% yield.[8] Deprotection and catalytic hydrogenation with Wilkinson's catalyst (to avoid scrambling of deuterium)[1b,2a] gave **9** in 89% yield. Hydrogenation of **10** with Wilkinson's catalyst also gave hexadecyl tetrahydroxypyranyl ether **8** in 93% yield. An advantage of this route is that partial hydrogenation of **11** with Lindlar catalyst gave *cis*-9-hexadecen-1-ol-*1,1,2,2,3,3,4,4,*

(1) (a) Tulloch, A. P. *Prog. Lipid Res.* **1983**, *22*, 235−256. (b) Rakoff, H. *Prog. Lipid Res.* **1982**, *21*, 225−254.

(2) (a) Mendelsohn, R.; Davies, M. A.; Schuster, H. F.; Xu, Z.; Bittman, R. *Biochemistry* **1991**, *30*, 8558−8563. (b) Mendelsohn, R.; Davies, M. A.; Brauner, J. W.; Schuster, H. F.; Dluhy, R. A. *Biochemistry* **1989**, *28*, 8934−8939.

(3) Kricheldorf, H. R.; Mörber, G.; Regel, W. *Synthesis* **1981**, 383−384.

(4) (a) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303−305. (b) Berkowitz, W. F.; Pan, D.; Bittman, R. *Tetrahedron Lett.* **1993**, *34*, 4297−4300.

(5) Fuganti, C.; Grasselli, P.; Servi, S.; Höegberg, H.-E. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3061−3065.

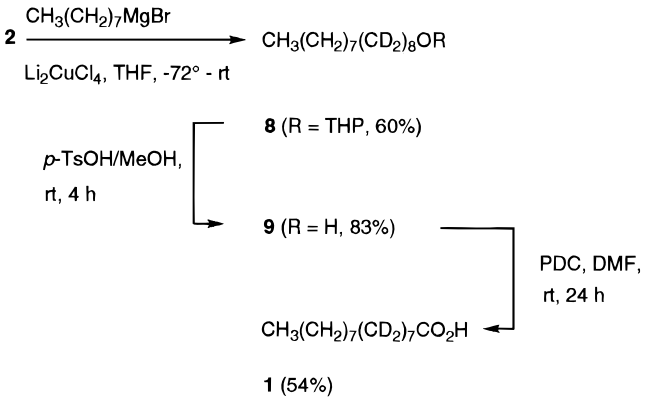
(6) Valicenti, A. J.; Pusch, F. J.; Holman, R. T. *Lipids* **1985**, *20*, 234−242.

(7) Attempts to prepare **2** via conversion of **5** into a half-protected analog, 8-(tetrahydropyranyloxy)-1-octanol-d_{16} (**5′**), by using a variety of acid catalysts, e.g., AcOH, HCO_2H, $KHSO_4$, Dowex-50 (H^+), and potassium hydrogen phthalate, resulted in poor yields. Similarly, ≤50% yield was obtained for conversion of **6** into **5′** using DHP and catalytic *p*-TsOH.

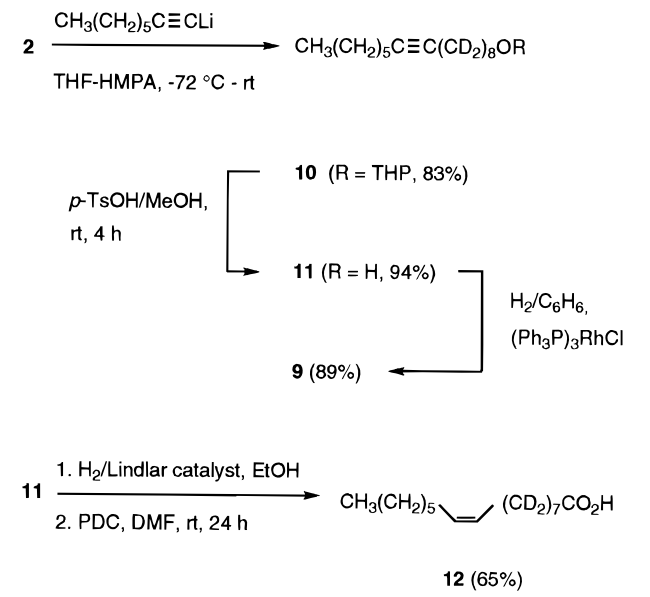
(8) Xu, Z.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **1991**, *56*, 7183−7186.

S0022-3263(96)01423-5 CCC: $12.00

Scheme 3. Synthesis of Hexadecanol-d_{16} 9 and Palmitic Acid-d_{14} 1



Scheme 4. An Alternate Route to Hexadecanol-d_{16} 9 and Synthesis of Palmitoleic Acid-d_{14} 12



5,5,6,6,7,7,8,8-d_{16}, which when oxidized by PDC afforded another deuterated fatty acid, palmitoleic acid-*2,2,3,3,4,4,5,5,6,6,7,7,8,8-*d_{14} (**12**).

In conclusion, the preparation of specifically deuterated palmitic acid **1** was readily obtained from commercially available THF-d_8. THF ring opening and in situ substitution of the TMS group by a THP group provided two very stable synthons, **3** and **4,** which have contiguous CD_2 groups and are convenient precursors of selectively deuterated fatty acyl chains.

Experimental Section

General Information. See refs 8 and 9 for general experimental protocols. Hexamethyldisilane, *p*-TsOH monohydrate, 1-bromooctane, and *p*-TsCl were purchased from Aldrich. 3,4-Dihydropyran (DHP) was from Eastman Organic Co. THF-d_8 was from Cambridge Isotope Laboratories (Andover, MA). Silica gel 60 (230−400 ASTM mesh) was used for flash chromatography and as the reagent in Scheme 1. ^{1}H NMR spectra were recorded at 400 MHz. ^{13}C NMR spectra were recorded at 100 MHz. GC/MS analyses were performed by Professor David C. Locke and Mr. Kevin Y. Xie at Queens College of CUNY on a Hewlett-Packard 5988a GC/MS instrument with a cross-linked methylsilicone column.

4-Iodo-1-(tetrahydropyranyloxy)butane-d_8 (3). A mixture of iodine (25.4 g, 100 mmol) and hexamethyldisilane (14.6 g, 100 mmol) was heated at 60 °C. After the mixture became a homogeneous solution, the temperature was raised to reflux for 1.5 h (oil bath temperature 135 °C). The iodine color disappeared after 10 min, and then the mixture was heated to reflux for 1 h. THF-d_8 (7.57 g, 94.4 mmol) was added, and the mixture was refluxed for 24 h. To the reaction mixture were added DHP (28.4 g, 337 mmol), *p*-TsOH (56.7 mg, 0.277 mmol), silica gel (7.2 g),[10] and dry ether (60 mL). The reaction was stirred for an additional 4 h, then diluted with ether (100 mL), and filtered through a Celite pad. The ether solution was washed with saturated aqueous $NaHCO_3$ solution (5 mL) and water (20 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation. The residue was purified by column chromatography on silica gel (elution with hexane/EtOAc 20:1) to give 14.5 g (53%) of **3** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.56−4.58 (m, 1H), 3.82−3.87 (m, 1H), 3.48−3.53 (m, 1H), 1.78−1.88 (m, 1H), 1.67−1.74 (m, 1H), 1.50−1.58 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 98.77, 64.94−65.79 (quintet, J = 21.53 Hz), 62.32, 30.68, 28.89−29.80 (m, 2C), 25.43, 19.60, 5.87−6.77 (quintet, J = 22.98 Hz); FAB HRMS calcd for $C_9H_8D_8O_2I$ (M − H)$^+$ m/z 291.0697, found 291.0683.

4-Bromo-1-(tetrahydropyranyloxy)butane-d_8 (4). To a solution of TMS-Br (19.14 g, 125 mmol) in 70 mL of CH_2Cl_2 was added THF-d_8 (5.0 g, 62.5 mmol) at 0 °C. The solution was heated to reflux at 55 °C for 18 h and then cooled to 0 °C. After DHP (13.14 g, 156 mmol) and *p*-TsOH (24 mg, 12 mmol) were added, the reaction mixture was warmed to rt and stirred for 4 h. The solvents were evaporated under vacuum to give a brown residue that was purified by silica gel flash chromatography (elution with hexane/EtOAc 15:1) to give 12.66 g (51.7 mmol, 83%) of **4** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.56−4.58 (m, 1H), 3.82−3.88 (m, 1H), 3.49−3.53 (m, 1H), 1.73−1.77 (m, 1H), 1.62−1.66 (m, 1H), 1.46−1.50 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 98.82, 65.17−66.02 (quintet, J = 21.47 Hz), 62.37, 32.62−33.54 (quintet, J = 23.09 Hz), 31.59, 28.5−29.9 (quintet, J = 19.42 Hz), 26.83−27.39 (quintet, J = 19.18 Hz), 25.46, 19.79; FAB HRMS calcd for $C_9H_8D_8O_2Br$ (M − H)$^+$ m/z 245.0815, found 245.0815.

1,8-Bis(tetrahydropyranyloxy)octane-*1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-*d_{16} (5). A mixture of 1-(tetrahydropyranyloxy)-4-bromobutane-d_8 **4** (2.0 g, 8.16 mmol) and magnesium turnings (294 mg, 12.24 mmol) in 40 mL of THF and Et_2O (1:1) was stirred at rt until complete formation of the Grignard reagent. The reaction mixture was cooled to −72 °C. A solution of **3** (2.4 g, 8.16 mmol) in 20 mL of THF and 200 μL of 0.2 M Li_2CuCl_4 in THF was added dropwise under argon. The resulting reaction mixture was slowly warmed to rt and stirred for 24 h, then diluted with 100 mL of ether, washed with saturated aqueous $NaHCO_3$ solution and water, and dried over Na_2SO_4. The solvents were evaporated on a rotary evaporator to give 2.0 g (74%) of **5** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 4.49−4.50 (m, 1H), 3.77−3.81 (m, 1H), 3.41−3.43 (m, 1H), 1.73−1.77 (m, 1H), 1.62−1.66 (m, 1H), 1.46−1.50 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 98.77, 66.33−67.18 (quintet, J = 21.43 Hz, 2C), 62.28, 30.81, 28.12−28.89 (m, 4C), 25.55, 24.53−24.31 (quintet, J = 19.44 Hz, 2C), 19.75; EI HRMS calcd for $C_{18}H_{17}D_{16}O_4$ (M - H)$^+$ m/z 329.3383, found 329.3380.

1,8-Octanediol-*1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-*d_{16} (6). A solution of bis(THP) ether **5** (0.61 g, 1.85 mmol) and *p*-TsOH (28 mg, 0.15 mmol) in 25 mL of MeOH was stirred at rt for 4 h. After the solvent was evaporated, 100 mL of ether was added, and the resulting solution was washed twice with water and brine. The ether solution was dried over Na_2SO_4 and purified by flash chromatography (hexane/EtOAc 1:1) to give 300 mg (100%) of needlelike white crystals: ^{13}C NMR ($CDCl_3$) δ 62.57−61.73 (quintet, J = 21.28 Hz, 2C), 31.10−31.86 (quintet, J = 18.94 Hz, 2C), 28.40−27.656 (quintet, J = 18.71 Hz, 2C), 24.74−23.99 (quintet, J = 19.96 Hz, 2C); FAB HRMS calcd for $C_8H_3D_{16}O_2$ (M + H)$^+$ m/z 163.2389, found 163.2392.

8-Bromo-1-octanol-*1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-*d_{16} (7). A suspension of diol **6** (500 mg, 3.09 mmol) in 25 mL of 48% aqueous hydrobromic acid was heated with 25 mL of hexane to reflux. The hexane was decanted into anhydrous K_2CO_3 and replaced with fresh hexane every 4 h for a total of six times. After K_2CO_3 was removed by filtration from the combined

(9) Byun, H.-S.; Bittman, R. *J. Org. Chem.* **1994**, *59*, 668−671.

(10) Silica gel was added to provide the reaction with a proton source. Substitution of the TMS group of $TMSO(CD_2)_4I$ by a THP group did not take place without silica gel.

hexane solution, the solvent was evaporated. The product was purified by flash chromatography to give 653 mg (94%) of **7** as a colorless oil: ^{13}C NMR ($CDCl_3$) δ 62.18−61.33 (quintet, J = 21.39 Hz, 1C), 32.89−33.81 (quintet, J = 22.99 Hz), 30.97−31.95 (m, 2C), 26.42−28.27 (m, 3C), 23.98−24.73 (quintet, J = 18.97 Hz, 1C); EI MS calcd for $C_8D_{15}Br$ $(M - DOH)^+$ m/z 205.13 and 207.13, found 205.10 and 207.15.

8-Bromo-1-(tetrahydropyranyloxy)octane-*1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-d*$_{16}$ (2). A solution of **7** (208 mg, 0.92 mmol), DHP (93.3 mg, 1.11 mmol), and *p*-TsOH (9.0 mg, 0.046 mmol) in 4 mL of CH_2Cl_2 was stirred at rt for 3 h. The solution was diluted with 50 mL of CH_2Cl_2 and then washed with saturated aqueous $NaHCO_3$ solution, water, and brine. The solvent was evaporated under vacuum, and the residue was purified by flash chromatography (hexane/EtOAc 20:1) to give 280 mg (99%) of **2** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.49−4.50 (m, 1H), 3.77−3.81 (m, 1H), 3.41−3.43 (m, 1H), 1.73−1.77 (m, 1H), 1.62−1.66 (m, 1H), 1.46−1.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 98.77, 66.24−67.09 (quintet, J = 21.46 Hz, 1C), 32.75−33.67 (quintet, J = 23.07 Hz), 31.21−31.98 (quintet, J = 19.33), 30.79, 29.69, 26.38−29.00 (m, 4C), 26.42−28.27 (m, 3C), 24.46−25.22 (quintet, J = 19.15 Hz), 19.71; EI MS calcd for $C_{13}H_8D_{16}O_2Br$ $(M - H)^+$ m/z 309.19 and 307.20, found 309.25 and 307.25.

Tetrahydropyranyl Hexadecyl-*1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-d*$_{16}$ Ether (8). A mixture of 1-bromooctane (282 mg, 1.46 mmol) and Mg (42 mg, 1.46 mmol) in 5 mL of THF was stirred for 3 h at rt until the magnesium metal disappeared**.** After the solution was cooled to −72 °C, a solution of **2** (150 mg, 0.49 mmol) in 2 mL of THF and 60 μL of 0.2 M Li_2CuCl_4 in THF was added dropwise under argon. The resulting solution was slowly warmed to rt and stirred at rt overnight. The reaction mixture was diluted with 50 mL of Et_2O, and the solution was washed with water and brine and then dried over Na_2SO_4. The solvents were evaporated under vacuum, and the residue was purified by flash chromatography to give 98 mg (60%) of **8** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.56−4.58 (m, 1H), 3.84−3.90 (m, 1H), 3.47−3.52 (m, 1H), 1.73−1.77 (m, 1H), 1.62−1.66 (m, 1H), 1.46−1.50 (m, 4H), 1.26−1.49 (m, 14H), 0.86−0.90 (t, J = 6.77 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 98.81, 66.41−67.27 (quintet, J = 21.60 Hz), 62.33, 31.96, 30.83, 31.19−31.96 (quintet, J = 19.03 Hz), 31.96, 29.75, 29.70, 29.49, 29.40, 27.73−28.95 (m, 4C), 25.55, 24.60−25.33 (quintet, J = 18.24 Hz), 22.73, 14.14; EI MS calcd for $C_{21}H_{25}D_{16}O_2$ $(M - H)^+$ m/z 341.41, found 341.35.

1-Hexadecanol-*1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-d*$_{16}$ (9). A solution of **8** (98 mg, 0.29 mmol) and *p*-TsOH (3.8 mg, 0.020 mmol) in 4 mL of MeOH was stirred at rt for 4 h. The reaction mixture was diluted with 40 mL of ether, and the solution was washed with saturated aqueous $NaHCO_3$ solution, water, and brine. The ether solution was dried over Na_2SO_4. After the solvents was evaporated, the residue was purified by flash chromatography to give 62 mg (83%) of **9** as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 14H), 0.86−0.90 (t, J = 6.77 Hz, 3H); ^{13}C NMR ($CDCl_3$) 61.77−62.62 (quintet, J = 21.52 Hz), 31.96, 31.19−31.87 (quintet, J = 18.9 Hz), 30.32, 29.74, 29.69, 29.47, 29.39, 27.86−28.97 (m, 4C), 24.10−24.85 (quintet, J = 19.23 Hz), 22.71, 14.13; EI MS calcd for $C_{16}H_{18}D_{16}O$ $(M - H)^+$ m/z 258.36, found 257.34.

1-(Tetrahydropyranyloxy)-9-hexadecyne-*1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-d*$_{16}$ (10). To a solution of 1-octyne (150 mg, 1.36 mmol) in 6 mL of THF was added 543 μL of *n*-butyllithium (1.36 mmol, 2.5 M in hexane) at −72 °C. The resulting solution was stirred for 1 h. Bromo ether **2** (300 mg, 0.97 mmol) in 6 mL of HMPA was added dropwise, followed by 2 mL of THF to wash the residue on the dropping funnel. The solution was slowly warmed to rt and stirred for 8 h. The reaction mixture was poured into water and extracted with ether. The ether solution was dried over Na_2SO_4. After the evaporation of solvents, the residue was purified by flash chromatography to give 274 mg (83%) of **10** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.56−4.58 (m, 1H), 3.85−3.90 (m, 1H), 3.47−3.53 (m, 1H), 2.12−2.15 (t, J = 7.03 Hz, 2H), 1.79−1.87 (m, 1H), 1.69−1.75 (m, 1H), 1.43−1.61 (m, 6H), 1.22−1.41 (m, 6H), 0.87−0.91 (t, J = 7.03 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 98.83, 66.37−67.24 (quintet, J = 21.88 Hz), 32.75−33.67 (quintet, J = 23.07 Hz), 31.39, 30.81, 29.15, 28.56, 27.11−29.02 (m, 4C), 24.56−25.68 (m, 2C), 25.52, 22.59, 19.74, 18.77, 17.43−18.42 (quintet, J = 20.42 Hz), 14.07; FAB HRMS calcd for $C_{21}H_{23}D_{16}O_2$ $(M + H)^+$ m/z 339.3954, found 339.3953.

9-Hexadecyn-1-ol-*1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-d*$_{16}$ (11). To a solution of **10** (194 mg, 0.57 mmol) in 7 mL of MeOH was added *p*-TsOH (7 mg, 0.036 mmol). The reaction mixture was stirred at rt for 1 h. Evaporation on a rotary evaporator gave a residue that was purified by flash chromatography, yielding 136 mg (94%) of **11** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.12−2.15 (t, J = 7.00 Hz, 2H), 1.44−1.51 (quintet, J = 7.02 Hz, 2H), 1.35−1.41 (m, 2H), 1.25−1.33 (m, 6H), 0.87−0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 80.28, 80.16, 61.78−62.63 (quintet, J = 21.46 Hz), 31.39, 30.95−32.14 (m), 29.15, 28.56, 27.11−28.37 (m, 4C), 24.02−24.83 (m, 2C), 22.59, 18.77, 17.51−18.3 (quintet, J = 19.91 Hz), 14.07; FAB HRMS calcd for $C_{16}H_{15}D_{16}O$ $(M + H)^+$ m/z 255.3379, found 255.3379.

1-Hexadecanol-*1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-d*$_{16}$ (9) from 11. To a solution of **11** (21 mg, 0.083 mmol) in 2 mL of dry C_6H_6 was added Wilkinson's catalyst $[(Ph_3P)_3RhCl]$[11] (8 mg, 0.008 mmol). A hydrogen balloon was applied. After being degassed with hydrogen gas, the homogeneous solution was stirred for 12 h. The solvent was evaporated and the resulting residue was purified by flash chromatography to give 19 mg (89%) of **9** as a white solid. The ^{1}H and ^{13}C NMR spectra were identical to those for the preparation of **9** from **8**.

Palmitic Acid-2,2,3,3,4,4,5,5,6,6,7,7,8,8-*d*$_{14}$ (1). A mixture of 1-hexadecanol-d_{16} (**9**; 61 mg, 0.24 mmol) and PDC (723 mg, 1.92 mmol) in 4 mL of DMF was stirred at rt for 24 h. The reaction mixture was poured into 10 volumes of water, acidified with 3 N HCl, and extracted with ether. Removal of the solvents gave a residue that was purified by flash chromatography (elution with 500:100:5 hexane/EtOAc/85% formic acid) to yield 33 mg (54%) of palmitic acid-d_{14} **1** as a white solid: ^{1}H NMR ($CDCl_3$) δ 11.34 (br, s, 1H), 1.25 (s, 14H), 0.86−0.90 (t, J = 7.03 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.20 (CO_2H), 32.75−34.06 (m), 31.94, 29.72, 29.67, 29.44, 29.38, 27.38−28.94 (m, 4C), 23.19−23.98 (m, 2C), 22.71, 14.14; FAB HRMS calcd for $C_{16}H_{19}D_{14}O_2$ $(M + H)^+$ m/z 271.3359, found 271.3349; EI MS calcd for methyl palmitate-d_{14} $C_{17}H_{20}D_{14}O_2$ (prepared by using excess BF_3-methanol)[12] (M^+) m/z 284.34, found 284.30.

Palmitoleic Acid-2,2,3,3,4,4,5,5,6,6,7,7,8,8-*d*$_{14}$ (12). To a mixture of **11** (80 mg, 0.31 mmol) in 2 mL of EtOH was added Lindlar catalyst (2 mg). After being degassed with hydrogen gas, the reaction mixture was stirred for 2 h under H_2. The catalyst was filtered, and the filtrate was concentrated under reduced pressure. After being dried under vacuum for 4 h, the residue was dissolved in a suspension of PDC in 4 mL of dry DMF and stirred for 24 h at rt. The reaction mixture was poured into 10 volumes of water, acidified with 3 N HCl, and extracted with ether. Removal of the solvents gave a residue that was purified by flash chromatography (elution with 500:100:5 hexane/EtOAc/85% formic acid) to yield 54 mg (65%) of palmitoleic acid-d_{14} **12** as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 10.53 (br, s, 1H), 5.29−5.39 (m, 2H), 1.98−2.03 (q, J = 6.58 Hz, 2H), 1.28 (s, 8H), 0.86−0.90 (t, J = 6.21 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.02 (CO_2H), 130.05, 129.67, 32.81−34.04 (m), 31.80, 29.76, 29.01, 27.37−28.34 (m), 27.24, 25.84−26.59 (m), 23.19−24.13 (m), 22.68, 14.12; FAB HRMS calcd for $C_{16}H_{17}D_{14}O_2$ $(M + H)^+$ m/z 269.3203, found 269.3191.

Acknowledgment. This work was supported in part by NIH Grant HL-16660. We thank the mass spectrometry facility at Michigan State University for the FAB HRMS. We gratefully acknowledge support from the National Science Foundation (Grant CHE-9408535) for funds for the purchase of the 400-MHz NMR spectrometer.

JO961423F

(11) (a) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711−1732. (b) Birch, A. J.; Williamson, D. H. *Org. React.* **1976**, *24*, 1−186.

(12) Metcalfe, L. D.; Schmitz, A. A. *Anal. Chem.* **1961**, *33*, 363−364.