Improved Methods for the Synthesis of [ω-^{11}C]Palmitic Acid

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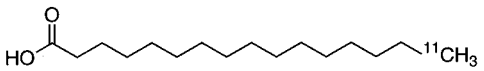
Introduction

The metabolism of fatty acids provides the major source of energy for the heart under normal physiological conditions. This metabolism proceeds via β-oxidation in two-carbon increments, starting at the carboxyl head and progressing along the aliphatic tail of the fatty acid. Each cycle of β-oxidation is catalyzed by a number of enzymes, including a family of acyl-CoA dehydrogenases, various members of which are specific for fatty acids of different chain lengths. A genetic deficiency for the long- or medium-chain acyl dehydrogenase (LCAD or MCAD) causes an accumulation of toxic fatty acid metabolic intermediates, which are potientially arrythmogenic and may cause sudden cardiac arrest.[1] Currently, there is no clinical method for evaluating cardiac metabolism for or predicting the severity of diseases such as MCAD deficiency.[2−5] We have previously reported the possibility of developing a noninvasive technique for the diagnosis of MCAD deficiency.[6] The rate of fatty acid metabolism could be evaluated by quantification of a positron emission tomographic (PET) image of the heart generated upon injection of a suitable radiolabeled fatty acid.[7,8] The rate at which the activity clears from the heart, compared to an appropriate control, would provide a measure of the presence and the severity of MCAD deficiency.

Two important issues in developing such a myocardial imaging agent are the type of radiolabel employed and its position. Isotopic substitution of a carbon atom would neither alter the natural structure of the fatty acid nor interfere with its normal metabolism. Because carbon-11 (half-life 20.4 min) is a positron-emitting isotope and a ^{11}C-substituted fatty acid would display predictable kinetics for metabolism of the radiolabel to $^{11}CO_2$, carbon-11 is the radioisotope of choice. With respect to its position in the fatty acid structure, a radiolabel placed at the head of a long-chain fatty acid would be metabolized before the MCAD enzyme is required and, thus, would provide no useful information. Shorter chain fatty acids with a headgroup label might circumvent this problem, but they display poor uptake into the myocardium.[6] Therefore, the imaging agent would ideally be a long-chain fatty acid labeled at the tail end, such as [ω-^{11}C]palmitic acid (**1**). Presented here are improved methods for the synthesis of **1**, using novel tracer-level techniques.



[ω-^{11}C]Palmitic acid (**1**)

Results and Discussion

Previous methods for the synthesis of [ω-^{11}C]palmitic acid (**1**) via incorporation of [^{11}C]CH_3I possess various drawbacks.[6,9,10] For example, a previous approach from this laboratory involves the tedious preparation of a precursor Grignard reagent that produces large amounts (ca. 60 mg) of unlabeled nor-acid and utilizes a harsh RuO_4 oxidation that generates a number of byproducts.[6] An alternate method described by others uses organocuprate chemistry;[10] while mild and general, this approach requires the use of air-sensitive organometallic reagents that must be freshly prepared. We sought to develop a method for the synthesis of **1** that would be convenient, reliable, and efficient and would produce minimal amounts of unlabeled byproducts.

Ishiama et al. have demonstrated the cross-coupling of a functionalized alkyl borane with a *saturated* primary alkyl iodide via a palladium-catalyzed Suzuki reaction.[11] Furthermore, this method has been shown to efficiently cross-couple a saturated alkyl borane with [^{11}C]CH_3I in good yields in less than 5 min at the tracer level, where the palladium catalyst is in large excess.[12] The reputed efficiency of this reaction combined with the stability and simple preparation of the trialkylborane precursor make application of the Suzuki coupling an attractive strategy for the synthesis of tail-labeled fatty acids through incorporation of [^{11}C]CH_3I, which can be routinely produced in large amounts (1.0 Ci) through an automated on-line synthesis.[13] In addition, the mild conditions of the Suzuki coupling permits the fatty acid to be protected as a *tert*-butyl ester, allowing facile deprotection with trifluoroacetic acid to provide the desired radiolabeled fatty acid directly (cf., Scheme 1). Alternatively, the acid

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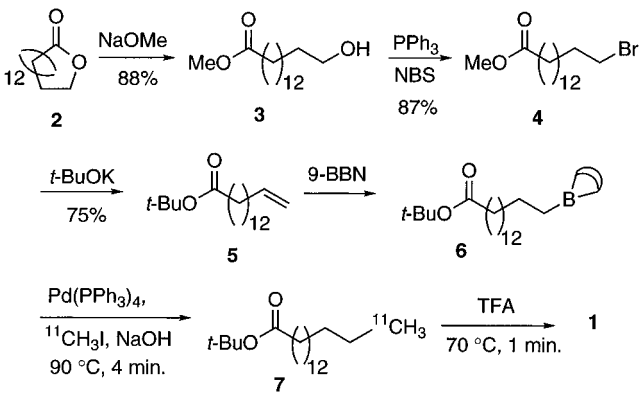
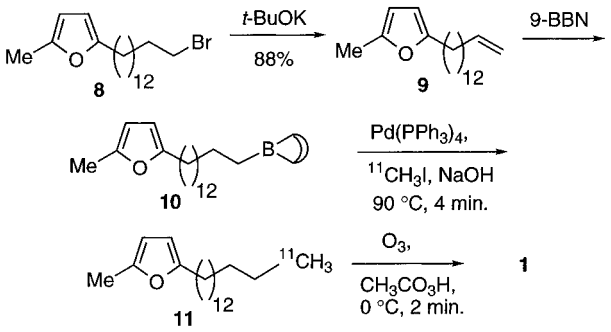
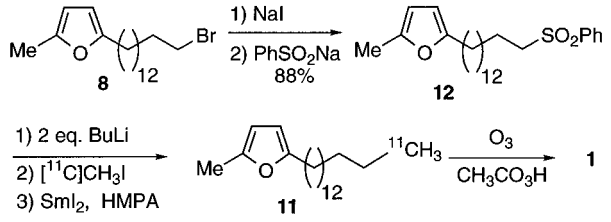
Scheme 1



Scheme 2



Scheme 3



may be masked as a furan and then revealed by oxidative cleavage (cf., Scheme 2).

Alkylation of a highly reactive phenyl sulfone dianion[14] provides an alternate pathway for the incorporation of [^{11}C]CH_3I. This strategy would require an additional step to reductively cleave the sulfone following alkylation with [^{11}C]methyl iodide, and the process is only compatible with the acid masked as the furan (cf., Scheme 3). However, the reductive cleavage can potentially be combined with the alkylation in a one-pot reaction.

An alternative to the use of the aggressive oxidant RuO_4 for the oxidative cleavage of the furan to the carboxylic acid is highly desirable[6] and could be applied to both methods. Because of the short half-life of carbon-11, a simple and rapid workup and purification of all intermediates is required. We envisioned using ozone for this purpose. Convenient ozone production in a manner compatible with the facilities of a hospital will ultimately be required if this radiopharmaceutical (**1**) is to be prepared for clinical use by either of the two routes that involve furan ozonolysis. We sought an alternative to the large, immobile ozone generators commonly utilized in chemistry laboratories. Thus, we have used a "pocket ozonolyzer", which can be conveniently assembled from a high-voltage vacuum leak finder and a few simple parts.[15] With this convenient, portable source of ozone, ozonolysis can be performed on millimole quantities of substrate in reasonable times (ca. 1 mmol/10 min). This translates to nearly instantaneous oxidation on the very small scale (several mg) that is typically used with radiochemical syntheses. The compact nature of this device makes it suitable to fit in the confined area of a shielded hot-cell.

To prepare the ester precursor needed for the synthesis of [ω-^{11}C]palmitic acid (**1**) by the Suzuki coupling method, we used commercially available, inexpensive ω-pentadecalactone (**2**) (Scheme 1). Ring opening of lactone **2** with NaOMe afforded the ω-hydroxy methyl ester **3** in high yield. Conversion of the hydroxy ester **3** to ω-bromo ester **4** was achieved using PPh_3/NBS. Treatment of the bromo methyl ester **4** with an excess of *t*-BuOK resulted in HBr elimination to provide the terminal alkene with concomitant transesterification to give the ω-unsaturated *tert*-butyl ester **5**. Synthesis of the furan precursor (Scheme 2) required only treatment of (ω-bromoalkyl)furan **8**[6] with *t*-BuOK to afford terminal alkene **9**. The same (ω-bromoalkyl)furan (**8**) was used to prepare the precursor for the synthesis of [ω-^{11}C]palmitic acid via the sulfone. One-pot conversion (Scheme 3) of bromide **8** to the iodide followed by displacement of the iodide with sodium benzenesulfinate furnished sulfone **12**.

Treatment of the terminal alkene **5** (Scheme 1) or **9** (Scheme 2) with a slight excess of 9-BBN provided the required substrate for the radiochemical synthesis of **1**. The resulting trialkylborane **6** or **10**, respectively, was not isolated but rather stored as a stock solution in THF. [^{11}C]Methyl iodide produced from the automated synthesis[13] was collected in 1 mL of THF at 0 °C, and $Pd(PPh_3)_4$, an aliquot of trialkylborane **6** or **10**, and NaOH were, added in succession. Alternate palladium ligands (P(*o*-tolyl)$_3$, $AsPh_3$, dppf) were not as effective as $Pd(PPh_3)_4$, and NaOH was determined to be a superior base to K_3PO_4. The reaction mixture was heated at reflux for 4 min, giving incorporation of [^{11}C]CH_3I with yields routinely between 65 and 75% for both the furan and ester substrates. Rapid elution of the reaction mixture through a short column of silica gel affords the Suzuki-coupled product **7** or **11**, respectively, in >99% radiochemical purity.

Deprotection of the ω-labeled ester **7** with neat TFA at 90 °C for 1 min affords the desired radiopharmaceutical **1** in quantitative radiochemical yield (RCY) and >99% radiochemical purity (RCP), as determined by HPLC. Likewise, ozonolysis of furan **11** for 2 min using the pocket ozonolyzer, followed by treatment with peracetic acid, provided **1** in >90% RCY and RCP. The chemical purity of **1** produced by both approaches is also high (see Experimental Section). The final product is efficiently synthesized in less than 45 min from ester **6** and in under 55 min from furan **10**, from the end of target bombardment. Preferably, a radiochemical synthesis should take no longer than 3 half-lives of the radioisotope being used. These syntheses are within this ideal for carbon-11 (half-life 20.4 min).

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(15) Beroza, M.; Bierl, B. A. *Mikrochim. Acta (Wein)* **1969**, 720. The metal tip of a vacuum leak tester (Tesla coil) is fitted with a glass sheath containing an inlet for oxygen and an outlet to the reaction. The sheath is wrapped with aluminum foil, grounded by a copper wire lead, and insulated with rubber tubing. Ozone is then produced by turning on the vacuum leak tester and commencing oxygen flow.

Application of the sulfone strategy for the synthesis of [ω-^{11}C]palmitic acid (**1**) required treatment of sulfone **12** (Scheme 3) with BuLi to form the desired geminal dianion. [^{11}C]Methyl iodide in THF was added, and analysis of a quenched aliquot after 2 min showed a radiochemical incorporation yield of 66%. The anion was quenched with NH_4Cl, and HMPA and SmI_2 were added to reductively cleave the sulfone. After stirring at reflux for 10 min, quenching with NH_4Cl afforded alkylfuran **11** in an overall radiochemical yield of 51%. The use of a sulfone dianion to incorporate the radiolabel is not as efficient as the Suzuki coupling, because of the extra step required for sulfone cleavage. However, the ability to perform the cleavage in the same reaction vessel as the alkylation facilitates the use of this strategy. Ozonolysis of furan **11** as before afforded [ω-^{11}C]palmitic acid (**1**) in 90% RCY and >90% RCP in 65 min from end of target bombardment. Material prepared by this approach does contain some unlabeled nor acid, pentadecanoic acid (see the Experimental Section).

We have described three new approaches to the synthesis of [ω-^{11}C]palmitic acid (**1**) from precursors **6**, **10**, and **12** in overall decay corrected yields of 75%, 68%, and 51% in 45, 55, and 65 min, respectively, from the end of target bombardment. Both the alkyl Suzuki and the sulfone dianion-based strategies present distinct advantages when compared to other methods. The sulfone strategy does not require tedious preparation of air-sensitive reagents in advance, rather only the addition of BuLi minutes before addition of [^{11}C]CH_3I. More impressively, the Suzuki coupling utilizes a stable trialkylborane precursor and requires no air-sensitive techniques to incorporate the radiolabel. This reaction does not rely on a rigorously exact quantity of any reagent, as does the sulfone method, which requires 2 equiv of BuLi. Robust preparative methods are especially important for a radiopharmaceutical synthesis, which must be highly reproducible. Both reactions operate well when relatively small amounts of precursor are used, and the unreacted trialkylborane from the Suzuki coupling is easily separated by flash chromatography during product isolation. Both of these factors are critical in minimizing the quantity of nonradiolabeled byproducts that are formed in these sequences. Removal of unalkylated compound created in the sulfone route (i.e., pentadecanoic acid) would require preparative HPLC, however.

Although the Suzuki method is more convenient and efficient than the sulfone route, the sulfone dianion approach can be used for the incorporation of longer chain radiolabeled alkyl halides such as [1-^{11}C]CH_3CH_2I, whereas we have so far been unable to use the Suzuki reaction for the incorporation of [1-^{11}C]CH_3CH_2I (unpublished results).[16] Thus, the sulfone dianion approach would allow the synthesis of [(ω-1)-^{11}C]palmitic acid, whose PET image of the heart would provide an interesting comparison with the image created by uptake of [ω-^{11}C]palmitic acid, due to the differing metabolic fate of the ω-1 carbon (ends as [1-^{11}C]acetate) vs the ω carbon (ends as [2-^{11}C]acetate).[17] Finally, a convenient method for producing ozone has been demonstrated and should find further use in radiochemical as well as traditional organic synthesis.

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Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were obtained at 400 or 500 MHz. Mass spectra were obtained by one of the following ionization techniques: fast atom bombardment (FAB), electron impact (EI), or chemical ionization (CI). Melting points are uncorrected. HPLC for the radiochemical experiments was performed on a chromatograph equipped with either a UV (operating at 215 nm) or a refractive index detector and a NaI-(Tl) radioactivity detector. All solvents were dried and distilled under N_2 prior to use. Flash chromatography was performed with Woelm silica gel (0.040−0.063 mm). All reactions except the Suzuki couplings were performed under a nitrogen atmosphere. Radiolabeled products were analyzed by comparison of retention times with a standard unlabeled compound via coinjection on HPLC (0.46 cm × 25 cm C8 analytical column, 85% CH_3CN/15% H_2O/0.1% TFA, 2 mL/min flow). All radiochemical yields are decay corrected.

Alkylboranes **6** and **10** were prepared according to standard literature procedure[11] and were stored at 0 °C as solutions in THF. The general workup procedure was as follows: Following the reaction quench, the aqueous layer was extracted with ether, and the combined organic layers were washed with water and brine and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration, and the filtrate was evaporated under reduced pressure to afford the crude product.

Methyl 15-Hydroxypentadecanoate (3). Sodium metal (1.4 g, 62 mmol) was added to MeOH (75 mL) at 0 °C with stirring. The mixture was warmed to room temperature and stirred until all of the sodium was consumed. ω-Pentadecalactone (**2**) (3.0 g, 12.5 mmol) was added with stirring, and the solution was stirred at 80 °C for 3 h. The reaction was quenched with 1 N HCl (100 mL) and diluted with water (100 mL). Workup afforded crude **3**. Flash chromatography on silica gel (2:1 hexanes:EtOAc) afforded 2.98 g (88%) of pure **3** as a white solid: mp 47.0−48.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.35 (bs, 20H), 1.52 (m, 2H), 1.57 (m, 2H), 2.26 (t, J = 7 Hz, 2H), 3.58 (t, J = 7 Hz, 2H), 3.62 (s, 3H); MS (FAB) 273 (M^+ + H, 100). Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84. Found: C, 70.20; H, 11.58.

Methyl 15-Bromopentadecanoate (4). To a solution of alcohol **3** (795 mg, 2.92 mmol) and PPh_3 (1.53 g, 5.83 mmol) in 5 mL of DMF was added NBS (1.04 g, 5.84 mmol) in portions. The reaction was heated at 55 °C for 30 min. Methanol (5 mL) was added followed by 1 N HCl (50 mL). Workup gave a crude pink solid. Hexanes were added to dissolve the product, leaving behind Ph_3P=O. Flash chromatography on silica gel (20:1 hexanes:EtOAc) afforded 850 mg (87%) of pure bromide **4** as a white solid: mp 38.0−39.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.35 (bs, 18H), 1.38 (m, 2H), 1.58 (m, 2H), 1.82 (m, 2H), 2.26 (t, J = 7 Hz, 2H), 3.36 (t, J = 7 Hz, 2H), 3.62 (s, 3H); MS (FAB) 337 (M^+(^{81}Br) + H, 69), 335 (M^+(^{79}Br) + H, 80). Anal. Calcd for $C_{16}H_{31}O_2Br$: C, 57.33; H, 9.32. Found: C, 57.59; H, 9.44.

***tert*-Butyl 14-Pentadecenoate (5).** To a 1.0 M solution of *t*-BuOK in THF (10 mL) was added bromide **4** (710 mg, 2.12 mmol). After the solution was stirred at room temperature for 1 h, 1 N HCl (50 mL) was added. Workup afforded crude alkene **5**. Flash chromatography on silica gel (hexanes) afforded 660 mg (75%) of pure **5** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.35 (bs, 18H), 1.37 (m, 2H), 1.43 (s, 9H), 2.03 (m, 2H), 2.19 (t, J = 7 Hz, 2H), 4.90 (ddt, J = 10.2, 2.2, 1.3 Hz, 1H), 4.97 (ddt, J = 17.2, 3.6, 1.6 Hz, 1H), 5.80 (ddt, J = 17.1, 10.5, 6.6, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 25.0, 27.9, 28.8, 28.9, 29.0 29.2, 29.3, 29.4 × 2, 29.5 × 2, 33.7, 35.4, 79.8, 114.0, 139.1, 173.3; MS (CI) 241 (M^+ − isobutylene, 100). Anal. Calcd for $C_{19}H_{36}O_2$: C, 76.97; H, 12.24. Found: C, 77.10; H, 12.37.

5-Methyl-2-(tetradec-13-en-1-yl)furan (9). To a solution of bromide **8**[6] (200 mg, 0.560 mmol) in THF (5 mL) at 0 °C was added *t*-BuOK (1.68 mL of 1.0 M in THF, 1.68 mmol). After the solution was stirred at room temperature for 1 h, 1 N HCl (50 mL) was added. Workup afforded crude alkene **9**. Flash chromatography on silica gel (hexanes) afforded 136 mg (88%)

of pure **9** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20−1.35 (bs, 18H), 1.61 (m, 2H), 2.04 (m, 2H), 2.26 (s, 3H), 2.56 (t, J = 7 Hz, 2H), 4.90 (ddt, J = 10.2, 2.2, 1.3 Hz, 1H), 4.97 (ddt, J = 17.2, 3.6, 1.6 Hz, 1H), 5.80 (ddt, J = 17.1, 10.5, 6.6, 1H), 5.84 (s, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) 13.5, 28.1, 28.2, 29.0, 29.2 (2 C). 29.4, 29.5, 29.6 (4 C), 33.8, 105.1, 105.7, 114.1, 139.3, 150.0, 154.8; MS (EI) 276 (M^+, 8), 95 (100). Anal. Calcd for $C_{19}H_{32}O$: C, 82.54; H, 11.67. Found: C, 82.65; H, 11.74.

5-Methyl-2-[14-(phenylsulfonyl)tetradecyl]furan (12). To a solution of bromide **8**[6] (500 mg, 1.40 mmol) in acetone (5 mL) was added NaI (231 mg, 1.54 mmol). The solution was stirred for 1 h, after which time DMF (5 mL) and sodium benzenesulfinate (276 mg, 1.68 mmol) were added. The reaction was heated to 60 °C and stirred overnight. The reaction was quenched by addition of 1 N HCl (50 mL). Workup afforded crude sulfone **12**. Recrystallization from hexanes afforded 450 mg (77%) of pure **12**: mp 71.0−72.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.40 (bs, 20H), 1.58 (m, 2H), 1.69 (m, 2H), 2.24 (s, 3H), 2.54 (t, J = 7 Hz, 2H), 3.07 (m, 2H), 5.82 (s, 2H), 7.56 (m, 2H), 7.63 (m, 1H), 7.90 (m, 2H); MS (EI) 418 (M^+, 9), 95 (100). Anal. Calcd for $C_{25}H_{38}O_3S$: C, 71.73; H, 9.15. Found: C, 71.36; H, 8.90.

[^{11}C]Methyl Iodide. [^{11}C]Carbon dioxide was produced by the ^{14}N(p,α)^{11}C nuclear reaction and was converted to [^{11}C]CH_3I using the PETtrace MeI Microlab (GE Medical Systems, Uppsala, Sweden) based on the technique described by Larsen et al.[13] [^{11}C]Methyl iodide produced in this way was trapped in THF (1.0 mL) at 0 °C.

[ω-^{11}C]Palmitic Acid (1). Via Ester 6. To a THF solution (300 μL) of [^{11}C]CH_3I at room temperature in a glass reaction vessel were added one crystal of $Pd(PPh_3)_4$, ester **6** (150 μL of 0.075 M, 11.3 μmol), and NaOH (10 μL, 5 M). The reaction vessel was capped and heated at 90 °C for 4 min and then cooled in an ice bath. The solvent was removed in vacuo, and the residue was loaded onto a silica gel column (column diameter, 1 cm; column height, 8 cm). The column was eluted with 5% Et_2O/pentanes (10 mL), and the collected eluant was evaporated in vacuo. Trifluoroacetic acid (200 μL) was added, and the mixture was heated at 90 °C for 1 min. Water (1 mL) and ether (1 mL) were added, and the organic layer was analyzed by HPLC. A single radioactive peak was recorded with a retention time identical with that of palmitic acid. When a refractive index detector was used in series with the radioactive detector, no corresponding mass peaks were observed near the time window of the radioactive peak, indicating very high chemical purity.

Via Furan 10. Substituting furan **10** for ester **6**, the procedure follows the synthesis of **1** via **6** through the point of the silica gel column elution. After the solvent was removed, CH_2Cl_2 (10 mL) was added and the solution was rapidly cooled to 0 °C with a dry ice−acetone bath. Ozone[15] was bubbled through the solution for 2 min, followed by addition of 30% peracetic acid. The solvent was removed in vacuo over a warm water bath (60 °C). Water (1 mL) and ether (1 mL) were added, and the organic layer was analyzed by HPLC. The HPLC traces for both the radioactivity and mass detectors were identical with those observed for production of **1** via **6**, indicating very high chemical purity.

Via Sulfone 12. To a solution of **12** (15 mg, 35.8 μmol) and DMPU (0.1 mL) in THF (0.5 mL) at 0 °C in a 35 mL round-bottomed flask was added *n*-BuLi (0.059 mL of 1.22 M in hexanes, 71.7 μmol). The bright yellow solution was stirred for 5 min, after which a mixture of [^{11}C]CH_3I and CH_3I (0.5 μL) in THF (1.0 mL) was added. The ice bath was removed, and the reaction was stirred for 2 min. Saturated NH_4Cl (5 μL) was added, followed by HMPA (300 μL) and SmI_2 (15 mL of 0.1 M in THF, 1.5 mmol) via cannula. The purple solution was heated at 90 °C for 10 min, after which time saturated NH_4Cl (100 μL) was added. The solvent was evaporated, and the residue was loaded onto a silica gel column (column diameter, 1 cm; column height, 7 cm). The column was eluted with 5% Et_2O/pentanes (10 mL), the collected eluant was evaporated in vacuo, CH_2Cl_2 (10 mL) was added, and the solution was rapidly cooled to 0 °C with a dry ice−acetone bath. Ozone was bubbled through the solution for 2 min followed by addition of 30% peracetic acid. The solvent was removed in vacuo over a warm water bath. Water (1 mL) and ether (1 mL) were added, and the organic layer was analyzed by HPLC. A single radioactive peak was recorded with a retention time identical with that of palmitic acid. When a UV detector was used in series with the radioactive detector, mass peaks were observed corresponding to palmitic acid (resulting from the use of carrier CH_3I) and pentadecanoic acid (resulting from unalkylated starting material).

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