SYNTHESIS OF [18-^{14}C]OCTATRIACONTANE FROM [1-^{14}C]STEARIC ACID

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SUMMARY

A method was developed to synthesize ^{14}C-labelled n-alkanes for use in cigarette smoke studies. Specifically, n-[18-^{14}C]-octatriacontane was synthesized from 1 mCi [1-^{14}C]stearic acid in a radiochemical yield of 20%. The key features of this synthesis were two consecutive alkylations of tosylmethyl isocyanide followed by acid hydrolysis to [18-^{14}C]-19-octatriacontanone and modified Wolff-Kishner reduction to the n-alkane. After purification on silica gel 25 mg of [18-^{14}C]octatriacontane was obtained with a total radioactivity of 200 μCi, a specific activity of 4.3 mCi/mmol, and a radiochemical purity in excess of 98% by thin layer radiochromatography. The method has also been applied to the synthesis of unlabeled n-pentatriacontane and is considered to be generally applicable to the synthesis of radiolabeled alkanes from radiolabeled fatty acids.

Key Words: [18-^{14}C]octatriacontane, radiosynthesis, ^{14}C-labeled alkanes.

INTRODUCTION

During an ongoing study on the cigarette smoke chemistry of alkanes a need developed for ^{14}C-labeled alkanes with chain lengths greater than 32 carbon atoms. A survey of the literature revealed that a wide variety of approaches are utilized in the synthesis of unlabeled alkanes, up to and including $n\text{-}C_{390}H_{782}$[1–7]. The literature regarding the synthesis of ^{14}C-labeled long chain n-alkanes is less extensive[8]. The Wurtz reaction has been used in the synthesis of [16,17-$^{14}C_2$]dotriacontane ($n\text{-}C_{32}H_{66}$)[9] but is reported to be accompanied by formation of branched alkanes and olefins[5]. n-Alkanes have been synthesized via methyl ketones starting from $^{14}CO_2$ or ^{14}C-methyl iodide to yield terminally labeled alkanes[10]. Other methods that may be applicable to the synthesis of labeled alkanes can be found in the synthesis of labeled alkyl derivatives, olefins, and alkynes[8].

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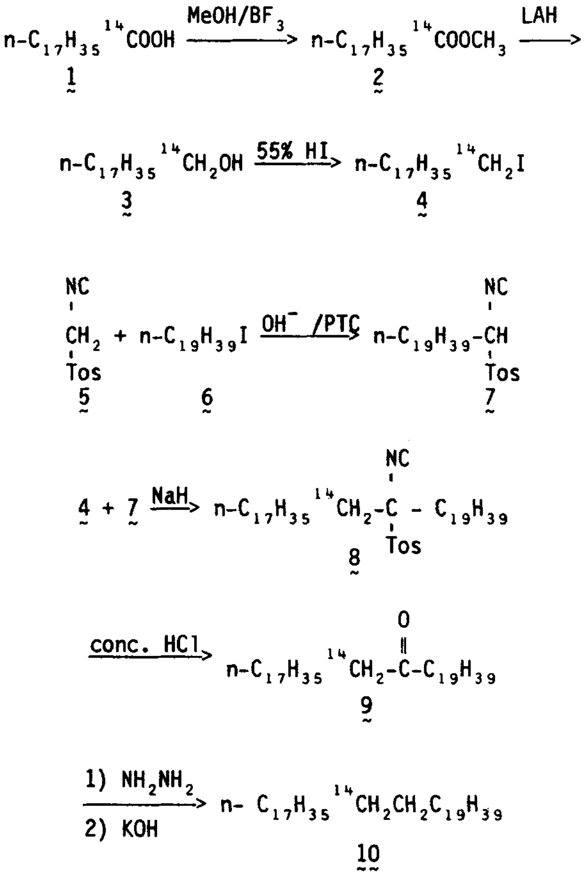
Octatriacontane, n-$C_{38}H_{78}$, is a naturally occurring wax in certain plants such as hibiscus[11] and has been isolated as a side-product in the syntheses of methyl octacosanoate[12] and of methyl 3-methyl-5-oxotetracosanoate[13]. Neither of the latter two methods was considered suitable for radiosynthesis of the alkane, in terms of a microscale synthesis and yield. In developing an alternative method other factors were also considered, such as using commercially available radiolabeled fatty acids or alcohols as starting materials. Initially a Grignard type cross-coupling reaction of 1-tosyloctadecane and 1-bromoeicosane was investigated, using dilithium tetrachlorocuprate as catalyst[14]. The reaction afforded only starting materials and side products and was not investigated further. Consequently an alternative method was developed and successfully applied to the synthesis of [18-^{14}C]octatriacontane from the readily available [1-^{14}C]stearic acid.

RESULTS AND DISCUSSION

All synthetic and analytic operations were first performed with unlabeled material, and the structures of various unlabeled intermediates and products were confirmed spectroscopically. The key feature of our synthetic approach is the coupling of two iodoalkanes by alkylation of tosylmethyl isocyanide (TosMIC) as shown in Scheme 1. TosMIC is a carbonyl anion equivalent that has been successfully utilized in the synthesis of ketones[5] and various substituted hydrocarbons[16]. The two building blocks [1-^{14}C]-1-iodooctadecane (4) and 1-iodononadecane (6) were prepared from commercially available materials. [1-^{14}C]stearic acid ([1-^{14}C]-1, 1 mCi, 4.9 mCi/mmol) was converted to the methyl ester 2 and reduced to the alcohol 3. Treatment of crude 3 with refluxing hydriodic acid followed by silica gel chromatography yielded [1-^{14}C]-1-iodooctadecane (4). The radiochemical yield of 4 was 58% based on 1. The intermediate 4 was also obtained in two steps by direct reduction of stearic acid to the alcohol followed by halogenation in an overall yield of 52%. The identity of [1-^{14}C]-4 was confirmed by co-chromatography with reference material by thin layer chromatography (TLC) and

Scheme 1



$$\underset{\mathbf{1}}{n\text{-}C_{17}H_{35}{}^{14}COOH} \xrightarrow{MeOH/BF_3} \underset{\mathbf{2}}{n\text{-}C_{17}H_{35}{}^{14}COOCH_3} \xrightarrow{LAH}$$

$$\underset{\mathbf{3}}{n\text{-}C_{17}H_{35}{}^{14}CH_2OH} \xrightarrow{55\%\ HI} \underset{\mathbf{4}}{n\text{-}C_{17}H_{35}{}^{14}CH_2I}$$

$$\underset{\mathbf{5}}{NC\text{-}CH_2\text{-}Tos} + \underset{\mathbf{6}}{n\text{-}C_{19}H_{39}I} \xrightarrow{OH^-/PTC} \underset{\mathbf{7}}{n\text{-}C_{19}H_{39}\text{-}CH(NC)(Tos)}$$

$$\mathbf{4} + \mathbf{7} \xrightarrow{NaH} \underset{\mathbf{8}}{n\text{-}C_{17}H_{35}{}^{14}CH_2\text{-}C(NC)(Tos)\text{-}C_{19}H_{39}}$$

$$\xrightarrow{conc.\ HCl} \underset{\mathbf{9}}{n\text{-}C_{17}H_{35}{}^{14}CH_2\text{-}C(=O)\text{-}C_{19}H_{39}}$$

$$\xrightarrow[2)\ KOH]{1)\ NH_2NH_2} \underset{\mathbf{10}}{n\text{-}C_{17}H_{35}{}^{14}CH_2CH_2C_{19}H_{39}}$$

PTC = Phase transfer catalysis
LAH = Lithium aluminum hydride
Tos = para-$CH_3C_6H_4SO_2$-

reversed-phase high performance liquid chromatography (RP-HPLC). The radiochemical purity of **4** was determined to be 96% by high performance liquid radiochromatography (HPLRC).

The second building block 1-iodononadecane (**6**) was prepared by treatment of 1-nonadecanol with refluxing hydriodic acid. Alkylation of TosMIC (**5**) with **6** by phase transfer catalysis yielded 1-tosyleicosanyl isocyanide (**7**). The coupling of [1-^{14}C]-**4** with **7** was carried out in DMSO-diethyl ether with sodium hydride as base. After purification by column chromatography, the dialkylated product [18-^{14}C]-19-isocyano-19-tosyloctatriacontane (**8**) was obtained in excellent radiochemical yield (92% based on **4**), with a radiochemical purity of 97% as determined by thin layer radiochromatography (TLRC). In experiments with unlabeled materials on a scale of 0.1 to 0.2 mmol the yield varied from 55 to 72%.

Hydrolysis of 8 with conc. HCl yielded [18-^{14}C]-19-octatriacontanone (9) . TLRC of the crude material showed 97% of the radioactivity to be associated with 9. The compound was used without further purification.

[18-^{14}C]octatriacontane (10) was obtained from [18-^{14}C]-9 using modified Wolff-Kishner conditions[14a]. Radioanalysis of the crude product showed about 70% of the total radioactivity to be associated with 10. The remaining 30% was associated with an unidentified polar material. Chromatography of the crude material yielded [18-^{14}C]-10 (25 mg, 200 μCi, 4.3 mCi/mmol). The radiochemical yield based on [1-^{14}C] stearic acid was 20%. TLC showed the compound to be homogeneous with a radiochemical purity in excess of 98%. Unlabeled $C_{38}H_{78}$ synthesized by this method was identified by MS and IR analyses and by capillary gas co-chromatography with reference material. In an alternative sequence the direct reduction of 8 to n-$C_{38}H_{78}$ with lithium in liquid ammonia[16] was carried out. However, the reaction was observed to be incomplete and was not investigated further.

The synthesis of n-pentatriacontane, $C_{35}H_{72}$, from 1-iodooctadecane and 1-iodohexadecane was also achieved by the above synthetic route. The method has been found to be amenable to microscale synthesis. The reactions are easily followed by TLC and the products are conveniently purified by silica gel column chromatography. By using other ^{14}C-fatty acids, this method can be applied to the synthesis of radiolabeled alkanes, uncontaminated by branched, unsaturated or homologous materials.

EXPERIMENTAL

General. Unless otherwise indicated, solvents were HPLC-grade (either J. T. Baker or Burdick and Jackson). Diethyl ether (Mallinckrodt, AR, anhydrous) was predried with KOH pellets, refluxed with calcium hydride, and distilled under argon. Dimethyl sulfoxide was predried and distilled from barium oxide. Hexane was predried and distilled from KOH. The distilled solvents were kept with Type 4A molecular sieves. Unless otherwise noted, reactions were run under dry nitrogen.

Stearic acid (99+%), 1-octadecanol (99%), tosylmethyl isocyanide (TosMIC), sodium hydride (60% dispersion in mineral oil), hydrazine sulfate and 2-ethoxyethyl ether (98+%) were obtained from Aldrich Chemical Co. Boron trifluoride in methanol (14% W/V), methyl stearate (99+%), and reference n-octatriacontane (99+%) were obtained from Alltech Assoc., Inc. 1-iodooctadecane was obtained from Crescent Chemical Corp. and 1-nonadecanol was obtained from Fluka Chemical Corp. Triethylene glycol was obtained from Mallinckrodt. [1-^{14}C]Stearic acid with a total activity of 1 mCi and specific activity of 57 mCi/mmol (199 μCi/mg) was obtained from Amersham Corp.

Column chromatography was performed on Kieselgel 60 (EM Reagents, 40-63μ). Thin layer chromatography (TLC) was carried out on 0.25 mm thickness silica gel 60 F-254 plates obtained from EM Reagents. The chromatograms were visualized with phosphomolybdic acid spray reagent (Alltech Assoc.) followed by heating, to give blue spots. Thin layer radiochromatography (TLRC) was carried out using a Berthold TLC Linear Analyzer Model LB 2832.

High performance liquid chromatography (HPLC) was carried out using a Waters M6000A pump with a U6K injector and a Waters Radial-Pak™ 10 μm C-18 cartridge, with methanol as eluting solvent. A Waters Model 401 refractometer was used for analyses of methyl stearate, 1-octadecanol, and 1-iodooctadecane. The UV detector (Waters Model 440 absorbance detector) was set at 254 nm and was used for analysis of 1-iodooctadecane. For radiolabeled samples the HPLC was interfaced with a Radiomatic Flo-One Beta HPLC radiofloflow monitor (RadioAnalytic, Inc., Tampa, Florida). A 0.5 mL flow cell was used with Radiomatic Flo-Scint III as the scintillation fluid at a flow rate of 2 mL/min. The electronic splitter of the Flo-One was set either at 50% or 90%, at 1-sec intervals. Total radioactivity measurements were determined in Beckman Ready-Solv NA cocktail using a Beckman LS 7500 liquid scintillation counter.

Infrared spectra (IR) were recorded using a Perkin Elmer spectrometer model 735B. Nuclear magnetic resonance (NMR) spectra were obtained using a

Varian XL-300 spectrometer. Mass spectra (MS) were obtained using a Finnegan 3300 spectrometer. A Hewlett-Packard gas chromatograph model 5880A equipped with a flame ionization detector was used for GC analyses. A fused silica capillary column (DB-5, 1 μM film thickness, 30 m X 0.322 mm, length X I.D., J&W Scientific Inc.) was used with helium as carrier gas.

Methyl [1-^{14}C]stearate (2). A solution of [1-^{14}C]stearic acid (4.8 mg, 0.017 mmol, 1 mCi) in toluene was combined with unlabeled stearic acid (53 mg, 0.186 mmol). The resultant solution of [1-^{14}C]stearic acid (57 mg, 0.203 mmol, 4.9 mCi/mmol) was evaporated under N_2 and the residue was refluxed with BF_3 /MeOH (5mL) for about 135 min. While still warm the clear colorless homogeneous solution was pipetted into ice-cold H_2O (5 mL) and extracted with CH_2Cl_2 (1x20 mL; 2x15 mL). The aqueous layer was made alkaline with saturated aqueous Na_2CO_3 and re-extracted with CH_2Cl_2 (15 mL). The combined organic phases were washed sequentially with saturated Na_2CO_3 (10 mL) and H_2O (3x10 mL). The organic phase was dried with $MgSO_4$, filtered and evaporated to give crude methyl [1-^{14}C]stearate (54 mg, 1 mCi).

TLC solvent system: CH_2Cl_2/hexane, 15:5 (Rf 0.67)

HPLC solvent system: MeOH, 1 mL/min (retention time 13.3 min)

Radiochemical purity by HPLRC: 93%

[1-^{14}C]-1-Octadecanol (3). A straight tube flask (5 mL) with a septum port was cooled in an ice bath and charged with dry freshly distilled Et_2O (400 μL). LAH (16.8 mg, 0.44 mmol) was added to the flask and a solution of methyl [1-^{14}C]stearate (54 mg, 0.18 mmol, 1 mCi) in dry ether (400 μL) was added dropwise though the syringe. Additional aliquots of ether (2 x 500 μL) were added to complete transfer of the radioactive material. The reaction mixture was stirred for 30 min at ice-bath temperature and for an additional 1.5 h at room temperature. The reaction was quenched at 0°C with H_2O (0.1 mL) and 15% NaOH (0.2 mL). After stirring for another 30 min the colorless supernatant was transferred to a separatory funnel with ether (15 mL). The white precipitate remaining in the flask was dissolved in H_2O (5 mL) and combined with the ethereal phase. After separation of the phases the aqueous phase was re-extracted with ether (3x10 mL). The combined organic phases were washed with H_2O (2x5 mL), dried ($MgSO_4$), filtered and evaporated to yield the crude alcohol (45 mg, 994 μCi).

TLC solvent system: CH_2Cl_2/MeOH, 25:1 (Rf 0.56)

Radiochemical purity by TLRC: 94%

HPLC solvent system: MeOH, 1 mL/min (Retention time 8.7 min)

Radiochemical purity by HPLRC: 93%

[1-^{14}C]-1-iodooctadecane (4). Hydriodic acid (55%, 1 mL) was added to [1-^{14}C]-1-octadecanol (45 mg, 0.16 mmol, 994 μCi) in a 5 mL flask. The mixture was refluxed gently for 90 min. After cooling to room temperature the reaction mixture was pipetted into ice cold H_2O (5 mL) and diluted with additional H_2O (5 mL). The product was extracted with CH_2Cl_2 (1x25 mL, 2x10 mL) and the combined organic phases (violet-colored) were washed sequentially with saturated Na_2CO_3 (5 mL), H_2O (5 mL), 5% $NaHSO_3$ (2x5 mL), saturated Na_2CO_3 (5 mL) and H_2O (3x5 ML). After drying over $MgSO_4$ the organic phase was filtered and evaporated to yield crude 1-iodooctadecane (61 mg, 900 μCi, 87% radiochemically pure). The crude material was chomatographed on silica gel (10 g, slurry-packed in hexane). The column was eluted with hexane and 2 mL fractions were collected, counted for radioactivity and analyzed by TLC. Four major fractions, each >98% radiochemically pure by TLC, were combined and after evaporation of solvent yielded 4 (57 mg, white crystalline wax, 586 μCi, 58% radiochemical yield based on [1-^{14}C]stearic acid).

TLC solvent system: Hexane (Rf 0.55)

HPLC solvent system: MeOH, 2 mL/min (Retention time 11.2 min) or 1 mL/min (Retention time 22.8 min)

Radiochemical purity by HPLRC: 96-97%

1-Iodononadecane (6). A stirred mixture of hydriodic acid (55%, 20 mL) and 1-nonadecanol (3 g, 10.5 mmol) was refluxed for 90 min. After cooling to room temperature the reaction mixture was poured into ice water (50 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were washed with

5% aqueous Na_2CO_3 (2x25 mL), 5% aqueous $NaHSO_3$ solution (2x25 mL) and H_2O (2x25 mL). After drying over $MgSO_4$, the organic phase was filtered and evaporated to yield crude 6 (3.8 g). The material was chomatographed on silica gel (70 g) slurry packed in hexane and eluted with hexane. The major fractions (analyzed by TLC) were combined to yield 6 (3.5 g, 85% yield).

TLC solvent system: Hexane (Rf 0.58)

HPLC solvent system: MeOH, 2 mL/min (retention time 13.4 min).

IR (CH_2Cl_2) ν cm^{-1} 2850, 2800, 1440. ^1H NMR ($CDCl_3$) δ 3.18 (2H, t, CH_2I).

EIMS m/e 394 (M^+), 267 $(M-I)^+$. m.p. 44°C.

<u>1-tosyleicosanyl isocyanide</u> (7). A mixture of 1-iodononadecane (6, 1.5 g, 3.9 mmol), TosMIC (5, 0.796 g, 4.0 mmol), CH_2Cl_2 (15 mL), 40% aqueous tetra-n--butyl ammonium hydroxide (0.6 mL, 0.9 mmol), and 40% aqueous NaOH (10 mL, 100 mmol) was placed in a flask cooled in an ice-batch. The mixture was stirred and warmed to room temperature overnight. TLC (hexane/CH_2Cl_2, 1:2) showed some unreacted 6 to be present. The reaction mixture was poured into ice-cold H_2O (15 mL) and extracted with CH_2Cl_2 (3x25 mL). The combined organic phases were washed with H_2O (20 mL) and saturated NaCl (2x25 mL). After drying (Na_2SO_4) the organic phase was filtered and evaporated to yield crude 7 (2 g). The crude product (1.0 g) was chomatographed on silica gel (46 g) slurry packed in hexane/CH_2Cl_2, 1:1. The column was eluted with mixtures of hexane and CH_2Cl_2, beginning with a 1:1 ratio and gradually increasing the amount of CH_2Cl_2. Fractions were analyzed by TLC using UV and phosphomolybdicacid spray reagent for visualization. Appropriate fractions were combined to yield 326 mg of 7.

TLC solvent system: hexane/CH_2Cl_2,1:2 (Rf of 7 , 0.32; Rf of 6, 0.73)

IR (CH_2Cl_2) ν cm^{-1} 2150 (-N=C:), 1350, 1160. 'H NMR ($CDCl_3$) δ 0.87 (3H, t, CH_3), 1.25(36H, br s, 18 x CH_2), 2.48 (3H, s, CH_3Ar), 4.43 (1H,m, -CHNC), 7.43 (2H, d, ArH), 7.86 (2H, d, ArH). EIMS m/e 306 $(M-SO_2C_6H_4CH_3)^+$, 155 $(SO_2C_6H_4CH_3)^+$.

[18-^{14}C]-19-Isocyano-19-tosyloctatriacontane (8). Sodium hydride (22 mg, 60% dispersion in mineral oil) was added to a 5 mL straight tube flask with a septum port. The sodium hydride was washed free of mineral oil with dry hexane (1 mL), and resuspended in freshly distilled dry Et_2O (0.5 mL). A biphasic solution of [1-^{14}C]-1-iodooctadecane (4, 57 mg, 0.15 mmol, 586 μCi) and 1-tosyleicosanyl isocyanide (7, 71 mg, 0.15 mmol) in 2.9 mL of Et_2O/DMSO (2.2:0.7) was added over 10 min using a 5 mL syringe. Additional Et_2O (1.0 mL) was used to complete transfer of the reactants into the flask. TLC after 2 h showed the reaction to be >75% complete. After 3 h the mixture was cooled to 0°C, quenched with H_2O (0.5 mL) and stirred for 5 min. The mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (5x15 mL). The combined organic phases were washed with saturated NaCl (10 mL), H_2O (10 mL), dried over Na_2SO_4, filtered and evaporated to yield crude 8. The crude material was chomatographed on silica gel (10 g) slurry packed in hexane/CH_2Cl_2, 5:3. The column was eluted with hexane/CH_2Cl_2, 5:3, (25 mL) followed by hexane/CH_2Cl_2, 1:1 (40 mL). All fractions were counted for radioactivity and were analyzed by TLC. Appropriate fractions were combined to yield 8 (98 mg, 541 μCi, 92% radiochemical yield based on 4). A fraction containing unreacted [1-^{14}C]-iodooctadecane was also obtained.

TLC solvent system: Hexane/CH_2Cl_2, 1:1 (Rf of 4, 0.69; Rf of 7, 0.17; Rf of 8, 0.28)

Radiochemical purity by TLRC: 97%

Spectroscopic analysis of unlabeled 8: ^{1}H NMR ($CDCl_3$) δ 0.87 (6H, m, 2 x CH_3), 1.25 (70H, br m, 35 x CH_2), 2.35-2.48 (7H, m, 2 x CH_2 and $ArCH_3$), 7.3-7.8 (4H, m, ArH). IR (CH_2Cl_2) ν cm^{-1} 2150 (-N=C:), 1340, 1160

[18-^{14}C]-19-octatriacontanone (9). A solution of 8 (98 mg, 0.13 mmol, 540 μCi) in CH_2Cl_2 (3 mL) and conc. HCl (0.2 mL, 38%) was stirred for 1 h.

Additional CH_2Cl_2 (2 mL) was added and the reaction was stirred for another hour. The reaction was quenched with 15% NaOH (1 mL) and after dilution with H_2O (5 mL) the crude product was extracted with $CHCl_3$ (1x20 mL; 2x15 mL). The combined organic phases were washed with H_2O (2x10 mL). TLRC of the organic phase (508 µCi) showed 97% of the radioactivity to be associated with the ketone. The organic phase was dried ($MgSO_4$), filtered and evaporated to yield crude 9 (75 mg), which was redissolved in chloroform (25 mL) to remove an insoluble impurity (11 mg). The crude ketone (64 mg) was used in the next step without further purification.

TLC solvent system: Hexane/CH_2Cl_2, 1:1, Rf 0.57

Spectroscopic analyses of unlabeled 9: IR ($CHCl_3$) ν cm^{-1} 1700 (C=O). ^1H NMR ($CDCl_3$) δ 0.88 (6H, br t, 2 x CH_3), 1.26 (66H, br s, 33 x CH_2), 2.37 (4H, br t, 2 x CH_2CO). CIMS m/e: 548 (M^+)

[18-^{14}C]-n-octatriacontane (10). The following reagents were added to crude 9 (64 mg, 0.1 mmol, 506 µCi) in a thee-necked round bottom flask (15 mL): $NH_2NH_2 \cdot H_2SO_4$ (272 mg, 2.09 mmol), triethylene glycol (2 mL), 2-ethoxyethyl ether (2 mL), and hydrazine (95%, 0.5 mL, 15 mmol). The heterogeneous mixture was gradually heated (1.5 h) in an oil bath to a temperature of 180-185°C. The reaction mixture was kept at 180-185°C for the next 4 h and then cooled to room temperature overnight. KOH (429 mg, 85% by assay) was added to the reaction mixture in 3 portions over 20 min. Simultaneously the oil bath temperature was raised to 160°C over 40 min. The reflux condenser was replaced with a micro-distillation column and the oil bath temperature was raised to 175°C over the next 30 min. During this period the excess hydrazine distilled off. The oil bath was kept at 175°C for 45 min after which the micro-distillation column was replaced with a reflux condenser. The oil bath temperature was gradually raised to 220-230°C (60-70 min) and kept at this temperature for the next 4 h. After cooling to room temperature overnight the reaction mixture was diluted with H_2O (5 mL) and extracted with cyclohexane (1x30 mL; 2x20 mL). A cyclohexane-insoluble precipitate remained in the flask. The combined organic phases were washed with 1N HCl (10 mL) and H_2O (3x10 mL). After drying ($MgSO_4$) the organic phase was filtered and on solvent evaporation a crystalline residue was obtained. The crude product (radiochemical purity 70% by TLRC) was chomatographed on silica gel (50 g) slurry-packed in cyclohexane. Fractions were eluted with cyclohexane, counted for radioactivity and analyzed by TLC. Appropriate fractions were combined to yield 10 (25 mg, 200 μCi). Based on [1-^{14}C]stearic acid the chemical yield was 23% and the radiochemical yield was 20%.

TLC solvent systems: (1) Cyclohexane (Rf 0.67), (2) Hexane: CH_2Cl_2, 9:1 (Rf 0.81), (3) Pentane (Rf 0.87)

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