Synthesis and Evaluation of Radioiodinated Terminal *p*-Iodophenyl-Substituted α- and β-Methyl-Branched Fatty Acids

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Methods have been developed for the preparation of terminal *p*-iodophenyl-substituted α- and β-methyl-branched long-chain fatty acids. The syntheses and physical properties of 14-(*p*-iodophenyl)-2(*RS*)-methyltetradecanoic acid and 15-*p*-iodophenyl)-3(*RS*)-methylpentadecanoic acid are described. The radioiodinated agents are of interest as a result of the expected pronounced uptake and prolonged myocardial retention that may result from the inhibition of fatty acid metabolism. Tissue distribution studies in rats with 14-(*p*-[^{125}I]iodophenyl)-2(*RS*)-methyltetradecanoic acid and 15-(*p*-[^{125}I]iodophenyl)-3(*RS*)-methylpentadecanoic acid show significant heart uptake and prolonged retention accompanied by low in vivo deiodination and high blood levels. A comparison of the heart uptake of the radioiodinated methyl-branched fatty acids and their unbranched analogues has demonstrated a greater myocardial retention of the methyl-branched fatty acids than the unbranched analogues. These results suggest that the mechanism of myocardial retention results from steric or chemical inhibition of the metabolism of these fatty acids by the presence of the methyl group.

Fatty acid analogues radiolabeled with γ-emitting isotopes have important applications for the identification of regions of impaired myocardial perfusion by nuclear medicine imaging procedures. The most extensively investigated agents are carbon-11-labeled and iodine-123-labeled terminal long-chain fatty acids. Regional myocardial metabolism has been measured with 1-[^{11}C]palmitic acid by emission computerized tomography.[1,2] Several workers have used 17-[^{123}I]iodoheptadecanoic acid to measure the difference in myocardial fatty acid metabolism between normal and ischemic tissue and in several types of cardiomyopathies.[3,4] However, this agent shows relatively rapid myocardial washout and undergoes facile in vivo deiodination. The high levels of radioiodide in the blood require a special background correction technique to quantitate the levels of radioiodide in the myocardium. More recently, radioiodide has been stabilized on the phenyl ring of 15-(*p*-iodophenyl)pentadecanoic acid,[5-7] and the iodine-123-labeled agent has been evaluated in patients with coronary artery disease.[8,9]

Structurally modified radiolabeled fatty acids have been developed to overcome the problems of rapid myocardial washout and high blood background. Studies with 9-[^{123m}Te]telluraheptadecanoic acid (9-THDA),[10-13] in which the tellurium heteroatom has been inserted in the alkyl chain to interfere with metabolism, have demonstrated that this model agent is rapidly extracted from the blood and concentrates in the myocardium in significant levels by an unusual trapping mechanism. These studies represent the first example of a radiolabeled fatty acid exhibiting prolonged retention (trapping) in the heart. Because of the attractive radionuclidic properties of iodine-123 (13.2-h half-life; 159-keV photon), we have recently reported the synthesis and evaluation of new agents labeled with radioiodide that contain nonradioactive tellurium.[14-18] In one model agent, 15-(*p*-[^{125}I]iodophenyl)-6-tellurapentadecanoic acid, the radioiodide has been stabilized to overcome in vivo deiodination by attachment to the para position of a terminal phenyl ring.[14-16] This agent shows rapid myocardial extraction in rats and dogs and prolonged myocardial retention similar to that observed with 9-THDA.[16] We have also stabilized radioiodide by fabrication of a tellurium fatty acid containing a terminal vinyl iodide moiety.[17] A model agent, 18-[^{125}I]iodo-7-tellura-17-octadecenoic acid, shows low in vivo deiodination, pronounced uptake, and prolonged myocardial retention in rats.[18]

One approach that has been evaluated as a means of inhibiting β-oxidation and, thus, lead to increased myocardial retention of radiolabeled long-chain fatty acids is the introduction of methyl branching. In rats and dogs, 3(*RS*)-methyl[1-^{11}C]heptadecanoic acid exhibits rapid myocardial extraction and shows high heart/blood ratios for up to 1 h after injection.[19,20] The mechanism resulting in the prolonged retention probably involves inhibition of a crucial metabolic transformation. Since the long-chain

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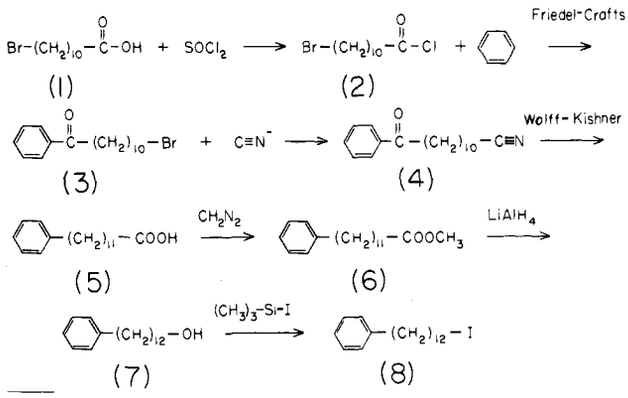
Scheme I



fatty acids are catabolized in the myocardium by β-oxidation, the presence of methyl branching may sterically or chemically inhibit this process analogous to the inhibition of glucose metabolism observed with 2-fluoro-2-deoxy-D-glucose in the heart and brain.[21] Introduction of methyl branching in the β-position would prevent oxidation of the β-hydroxyl intermediate to the β-keto acid. The latter intermediate is normally formed prior to carbon–carbon bond cleavage during the first cycle of β-oxidation.

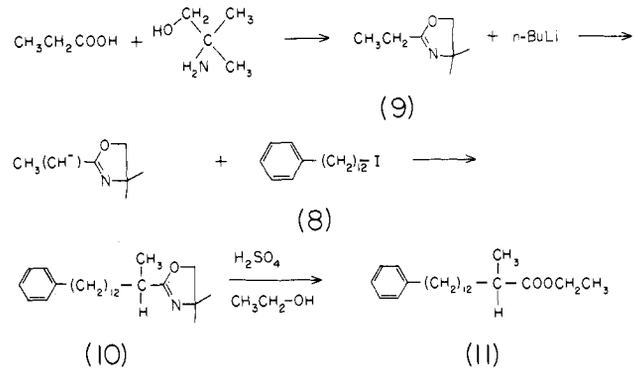
Because of the short physical half-life ($T_{1/2}$ = 20 min) of carbon-11 and the specialized imaging devices required for tomographic reconstruction of the 511-keV annihilation photons, radioiodinated terminal *p*-iodophenyl-substituted alkanoic fatty acids have been prepared in which methyl branching has been introduced to increase myocardial retention.[22-25] The *p*-[^{123}I]iodophenyl agents would be superior to carbon-11 agents for distribution to a large patient population.

The goals of the present investigation were to develop methods for the synthesis of the model agents, 14-(*p*-[^{125}I]iodophenyl)-2(*RS*)-methyltetradecanoic acid and 15-(*p*-[^{125}I]iodophenyl)-3(*RS*)-methylpentadecanoic acid, and to compare the distribution properties of these agents in rats with the 14-(*p*-[^{125}I]iodophenyl)tetradecanoic acid and 15-(*p*-[^{125}I]iodophenyl)pentadecanoic acid unbranched analogues.

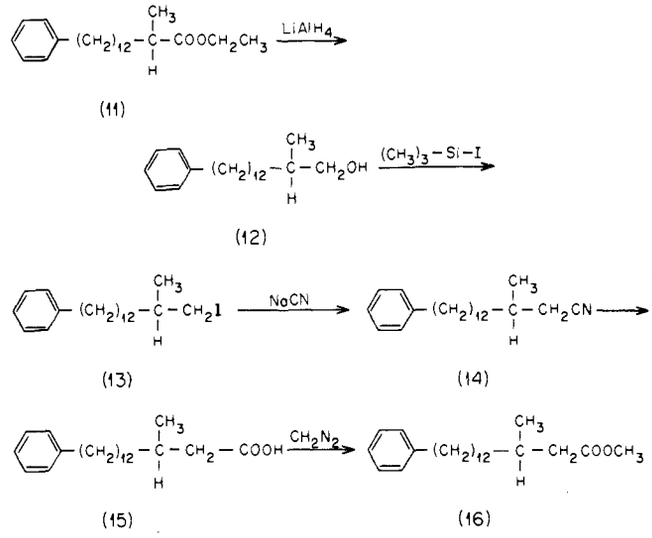
Results and Discussion

Chemistry. The initial stages of this investigated entailed the synthesis of ethyl 14-phenyl-2(*RS*)-methyltetradecanoate (11). The synthetic approach for the preparation of this racemic methyl-branched fatty acid involved homologation of a masked acetic acid via a 2-substituted oxazoline.[26] We chose this versatile homologation technique because of the mild reaction conditions for alkylation of the 2-substituted oxazoline (9). In addition, optically active 2-oxazolines[27] can potentially be used for the synthesis of the 2(*R*)- and 2(*S*)-methyl isomers. In this synthetic approach, 12-phenyldodecyl iodide (8) was the key intermediate employed in the alkylation step and

Scheme II



Scheme III



was prepared by the six-step sequence of reactions outlined in Scheme I. Commercially available 11-bromoundecanoic acid (1) was treated with dimethylformamidium chloride, and the crude acid chloride **2** was subjected to Friedel–Crafts acylation to afford 11-bromo-1-phenylundecan-1-one (**3**). The bromo ketone **3** was converted to the nitrile **4** by treatment with NaCN. The carbonyl function of the nitrile **4** was then reduced under Wolff–Kishner (Huang–Minlon) conditions. These reaction conditions concomitantly hydrolyze the nitrile function to give 12-phenyldodecanoic acid (**5**). Esterification of acid **5** with diazomethane (CH_2N_2) gave the corresponding methyl ester **6**, which was then reduced with $LiAlH_4$ to 12-phenyldodecan-1-ol (**7**). The alcohol **7** was converted to 12-phenyldodecyl iodide (**8**) by treatment with iodotrimethylsilane.[28,29]

The pivotal step in the synthesis of compound **11** (Scheme II) involved introduction of the methyl branching via alkylation of the anion of 2-ethyl-4,4-dimethyl-2-oxazoline (**9**).[26] Treatment of compound **9** with *n*-butyllithium, followed by addition of 12-phenyldodecyl iodide (**8**), gave 2(*RS*)-(4,4-dimethyl-2-oxazolin-2-yl)-14-phenyltetradecane (**10**). The disubstituted 2-oxazoline **10** was treated with ethanolic H_2SO_4 to afford the desired ethyl 14-phenyl-2(*RS*)-methyltetradecanoate (**11**). Utilizing this same approach, we used the 12-phenyldodecyl iodide (**8**) substrate to prepare the unbranched analogue, ethyl 14-phenyltetradecanoate (**32**), by reaction with 2,4,4-trimethyl-2-oxazoline.

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Table I. Distribution of Radioactivity in Tissues of Fischer 344 Rats Following Intravenous Administration of 15-(*p*-[^{125}I]Iodophenyl)-3(*RS*)-methylpentadecanoic Acid[a]

tissue	mean % injected dose/g (range) at the following times after injection			
	5 min	30 min	60 min	4 h
heart	4.62 (3.61-6.35)	3.63 (2.93-4.57)	4.26 (3.80-4.65)	2.27 (1.83-3.10)
blood	0.71 (0.31-1.19)	1.60 (1.49-1.71)	1.70 (1.31-1.42)	1.13 (1.01-1.36)
lungs	1.45 (1.20-1.85)	1.15 (0.92-1.44)	1.21 (1.10-1.31)	0.91 (0.78-1.11)
liver	8.32 (7.33-9.30)	3.66 (3.18-4.05)	1.92 (1.65-2.32)	0.95 (0.87-1.14)
kidneys	1.08 (0.94-1.22)	1.71 (1.64-1.75)	2.14 (2.02-2.55)	1.49 (1.35-1.56)
thyroids	6.78 (6.12-7.91)	9.26 (7.58-10.12)	10.66 (9.92-13.02)	9.69 (8.63-10.83)

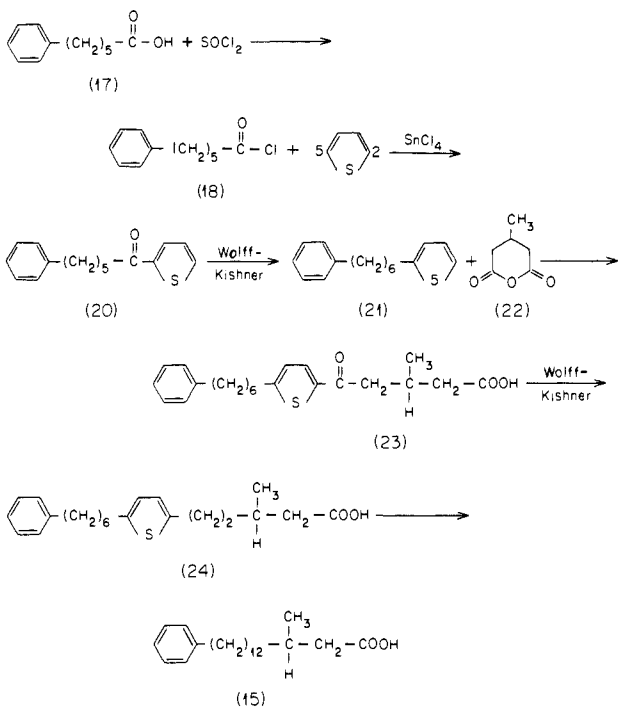
[a] Four rats were used for each time period. Each rat received ~8.2 μCi of the ^{125}I-labeled fatty acid administered by injection in a lateral tail vein in 6% bovine serum albumin solution (0.5 mL).

Two synthetic routes were developed for the preparation of the racemic 3-methyl-branched long-chain phenyl fatty acid. In one route, ethyl 14-phenyl-2(*RS*)-methyltetradecanoate (**11**) was converted to methyl 15-phenyl-3(*RS*)-methylpentadecanoate (**16**) by the five-step sequence of reactions outlined in Scheme III. Lithium aluminum hydride reduction of ester **11**, followed by treatment of the resulting alcohol with iodotrimethylsilane, gave 1-iodo-2(*RS*)-methyl-14-phenyltetradecane (**13**). Conversion of compound **13** to the nitrile **14**, followed by basic hydrolysis, afforded 3(*RS*)-methyl-15-phenylpentadecanoic acid (**15**), and esterification with CH_2N_2 gave methyl 3(*RS*)-methyl-15-phenylpentadecanoate (**16**).

The second route developed for the preparation of compound **15** utilized the classical thiophene synthesis of long-chain fatty acids (Scheme IV). By selection of the substituents introduced into the 2- and 5-positions of the thiophene ring, a variety of methyl-branched fatty acids varying in chain length and position of the methyl group can be prepared. Utilizing this synthetic approach, we converted commercially available 6-phenylhexanoic acid (**17**) to 6-phenylhexanoyl chloride (**18**). Friedel–Crafts coupling of the acid chloride[30] with thiophene (**19**) gave the substituted ketone **20**. Wolff–Kishner (Huang–Minlon) reduction of **20** gave 2-(6-phenylhexyl)thiophene (**21**). Friedel–Crafts acylation of **21** with 3-methylglutaric anhydride (**22**) and $AlCl_3$ then gave 2-[3(*RS*)-methyl-1-oxo-5-hydroxypentanoyl]-5-(6-phenylhexyl)thiophene (**23**). Wolff–Kishner reduction of **23** gave 2-[3(*RS*)-methyl-1-hydroxypentanoyl]-5-(6-phenylhexyl)thiophene (**24**). The pivotal step in this synthesis involved the Raney nickel desulfurization of compound **24** to 3(*RS*)-methyl-15-phenylpentadecanoic acid (**15**). Esterificaiton of acid **15** with CH_2N_2 gave the corresponding methyl ester **16**. The ester **16** obtained from both synthetic routes (Schemes III and IV) possessed identical physical and spectral properties.

Iodide was introduced into the para position of the terminal phenyl ring of the methyl-branched fatty acid esters **11** and **16** by decomposition of the arylthallium intermediates **25** and **26**, respectively (Scheme V). Aromatic thallation of compounds **11** and **16** with thallium(III)trifluoroacetate in trifluoroacetic acid[31-33] gave the corresponding *p*-bis(trifluoroacetoxy)thallium derivatives **25** and **26**, respectively. The crude thallium products **25** and **26** were treated with excess potassium iodide, followed by basic hydrolysis, to give 2(*RS*)-methyl-14-(*p*-iodophenyl)tetradecanoic acid (**29**) and 3(*RS*)-methyl-15-(*p*-iodophenyl)pentadecanoic acid (**30**). The NMR spectra of **29** and **30** exhibited characteristic AA'BB' coupling patterns for the ortho and meta protons centered at δ 6.8 (J = Hz). Although the formation of small amounts of the isomeric ortho- and meta-iodinated isomers of **29** and **30** could possibly occur by thermal isomerization of the thallium intermediates **25** and **26**, the expected resonances for the aromatic protons of these isomers in the NMR spectra of the crystallized compounds were not observed.

Scheme IV



The radioiodinated analogues, 15-(*p*-[^{125}I]iodophenyl)-3(*RS*)-methypentadecanoic acid, 14-(*p*-[^{125}I]iodophenyl)-2(*RS*)-methyltetradecanoic acid, 15-(*p*-[^{125}I]iodophenyl)pentadecanoic acid, and 14-(*p*-[^{125}I]iodophenyl)-tetradecanoic acid, were prepared by K–^{125}I treatment of the *p*-bis(trifluoroacetoxy)thallium derivatives[34] of the corresponding methyl esters as described for the preparation of the unlabeled compounds. The radioiodinated products each exhibited a single radioactive component upon thin-layer radiochromatographic analyses (SiO_2) and cochromatographed with the unlabeled standards. The radioiodinated phenyl fatty acids were assumed to contain greater than 90% of the *p*-iodo isomer based upon an analysis of the NMR spectra of the unlabeled compounds prepared on the same scale (0.10 mmol).

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Scheme V

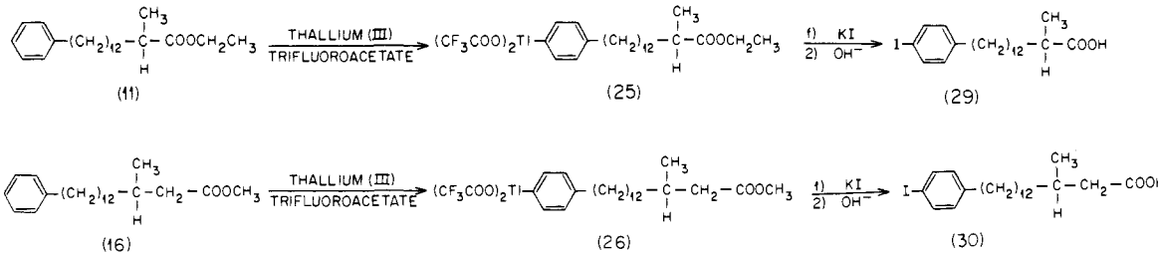

Table II. Distribution of Radioactivity in Tissues of Fischer 344 Rats Following Intravenous Administration of 15-(*p*-[^{125}I]Iodophenyl)pentadecanoic Acid[a]

tissue	mean % injected dose/g (range) at the following times after injection			
	5 min	30 min	60 min	4 h
heart	2.98 (2.34-3.47)	2.67 (2.44-3.10)	2.34 (2.20-2.47)	0.93 (0.90-0.95)
blood	0.91 (0.67-1.18)	1.50 (1.35-1.62)	1.32 (1.17-1.41)	0.70 (0.65-0.74)
lungs	1.26 (0.87-1.72)	1.36 (1.31-1.45)	1.29 (1.22-1.39)	0.97 (0.97-0.98)
liver	6.69 (4.4-8.1)	5.31 (5.10-6.25)	3.76 (5.25-4.07)	1.72 (1.37-1.95)
kidneys	0.84 (0.64-1.04)	1.08 (0.98-1.20)	1.05 (0.94-1.14)	0.88 (0.85-0.91)
thyroids	7.08 (5.64-9.54)	10.28 (9.89-10.76)	7.37 (7.19-7.63)	8.54 (6.74-10.19)

[a] Three rats were used for each time period. Each rat received ~11 μCi of the ^{125}I-labeled fatty acid administered by injection in a lateral tail vein in 6% bovine serum albumin solution (0.5 mL).

Table III. Distribution of Radioactivity in Tissues of Fischer 344 Rats Following Intravenous Administration of 14-(*p*-[^{125}I]Iodophenyl)-2(*RS*)-methyltetradecanoic Acid

tissue	mean % injected dose/g (range) at the following times after injection			
	5 min	30 min	60 min	5 h
heart	1.71 (1.70-2.00)	1.58 (1.35-1.80)	1.52 (1.28-1.63)	0.59 (0.50-0.63)
blood	1.80 (1.18-2.22)	1.83 (1.49-2.21)	1.64 (1.44-1.81)	1.07 (0.95-1.28)
lungs	1.13 (0.92-1.31)	1.03 (0.92-1.18)	1.13 (1.06-1.23)	0.77 (0.70-0.89)
liver	7.61 (6.21-9.90)	3.85 (2.92-4.42)	2.94 (2.71-3.38)	1.52 (1.44-1.59)
kidneys	1.68 (1.22-2.11)	1.95 (1.67-2.19)	1.85 (1.44-2.07)	1.36 (1.21-1.53)
thyroids	7.56 (6.41-9.82)	5.30 (8.63-10.59)	11.50 (8.90-13.00)	13.95 (11.10-17.18)

[a] Four rats were used for each time period. Each rat received ~11.7 μCi of the ^{125}I-labeled fatty acid administered by injection in a lateral tail vein in 6% bovine serum albumin solution (0.5 mL).

Biological Studies. The distribution of radioactivity in tissues of female rats at 5 min, 30 min, 60 min and 4 h after intravenous administration of 15-(*p*-[^{125}I]iodophenyl)-3(*RS*)-methylpentadecanoic acid is shown in Table I. The level of accumulation of radioactivity in the myocardium after injection of this agent was significant, but the blood levels were also high, resulting in low heart/blood ratios. This agent exhibited the expected prolonged retention in the myocardium. The myocardium uptake reached a maximum at 5 min (4.62% dose/g) and exhibited a slight decrease at 60 min (4.26% dose/g). After 4 h, the heart uptake (2.27% dose/g) had decreased 50% when compared with the peak uptake at 5 min. The heart/blood ratio reached a maximum of 9:1 at 5 min and decreased to 2.4:1 at 4 h. The accumulation of activity in the thyroid was low, 9.69% dose/g at 4 h, which demonstrated the stability of this agent to in vivo deiodination. The effect of methyl branching at the 3-position on myocardial retention was assessed by a comparison of the myocardial uptake in Fischer rats after administration of 15-(*p*-[^{125}I]iodophenyl)pentadecanoic acid (Table II). The myocardial uptake of activity at 5 min (2.98% dose/g) followed administration of the unbranched analogue was slightly lower and exhibited a 22% elimination at 60 min (2.34% dose/g) and a 67% elimination at 4 h (0.93% dose/g). The heart/blood ratio of the unbranched agent reached a maximum of 3.27:1 at 5 min and decreased to 1.77:1 at 60 min.

The increased myocardial retention of radioactivity following injection of 15-(*p*-[^{125}I]iodophenyl)-3(*RS*)-methylpentadecanoic acid in comparison to the unbranched analogue, 15-(*p*-[^{125}I]iodophenyl)pentadecanoic acid, suggests that methyl branching at the 3-position may be an effective means of inhibiting myocardial metabolism of radioiodinated phenyl fatty acids.

Table IV. Distribution of Radioactivity in Tissues of Fischer 344 Rats Following Intravenous Administration of 14-(*p*-[^{125}I]Iodophenyl)tetradecanoic Acid[a]

tissue	mean % injected dose/g (range) at the following times after injection	
	5 min	60 min
heart	2.72 (2.42-3.10)	1.78 (1.32-2.01)
blood	1.58 (1.51-1.79)	1.48 (1.43-1.62)
lungs	1.55 (1.41-1.82)	1.39 (1.23-1.58)
liver	4.82 (4.66-5.02)	2.04 (1.73-2.22)
kidneys	1.64 (1.54-1.77)	1.94 (1.81-2.01)
thyroids	1.64 (0.90-1.97)	2.56 (1.89-3.99)

[a] Three rats were used for each time period. Each rat received ~3.2 μCi of the ^{125}I-labeled fatty acid administered by injection in a lateral tail vein in 6% bovine serum albumin solution (0.5 mL).

Tissue distribution studies in female Fischer rats (Table III) after injection of 14-(*p*-[^{125}I]iodophenyl)-2(*RS*)-methyltetradecanoic acid gave results similar to those observed with 15-(*p*-[^{125}I]iodophenyl)-3(*RS*)-methylpentadecanoic acid (Table I). The level of accumulation of radioactivity in the myocardium after injection of the 2(*RS*)-methyl agent reached a maximum at 5 min (1.71% dose/g) and decreased only to 1.52% dose/g at 60 min. The heart/blood ratios reached a maximum of 0.95:1 at 5 min and decreased only to 0.93:1 at 60 min. The myocardial uptake of activity in rats (Table IV) at 5 min (2.72% dose/g) following administration of 14-(*p*-[^{125}I]-

iodophenyl)tetradecanoic acid, the unbranched analogue, was considerably higher but exhibited a 35% elimination after 60 min (2.72–1.78% dose/g).

Although the absolute uptake of the 2(*RS*)-methyl-branched fatty acid was not as high as that observed with the 3(*RS*)-methyl-branched fatty acid, both agents showed significant myocardial retention in rats over a 60-min period. The similarity of myocardial retention of radioactivity from the methyl-branched fatty acids strongly suggests that myocardial clearance is significantly inhibited by the introduction of methyl branching in the 2- and 3-positions of the fatty acid chain. The undesired property accompanying prolonged myocardial retention is the high blood level that results in low heart/blood ratios. The identity of the radioiodinated species remaining in the blood is not known, although it is not radioiodide, since thyroid uptake even after 60 min is very low. The anion generated by *n*-butyllithium treatment of 2-ethyl-4,4-dimethyl-2-oxazoline led to the formation of racemic mixtures of the methyl-branched analogues. The ratios of the *R* and *S* isomers have not been determined for these compounds, but the high myocardial uptake observed with the radioiodinated agents indicates that resolution of the racemic mixtures should be performed and that the radioiodinated *R* and *S* isomers of **29** and **30** should be evaluated individually in laboratory animals.

Conclusion

Novel synthetic routes have been developed for the syntheses of 15-(*p*-[^{125}I]iodophenyl)-3(*RS*)-methylpentadecanoic acid and 14-(*p*-[^{125}I]iodophenyl)-2(*RS*)-methyltetradecanoic acid. The model radioiodinated methyl-branched agents show significant myocardial uptake and retention in rats with little in vivo deiodination.

Experimental Section

General. The melting points (mp) were determined in capillary tubes with a Buchi SP apparatus and are uncorrected. The thin-layer chromatographic analyses (TLC) were performed with 250-μm thick layers of silica gel G PF-254 coated on glass plates (Analtech, Inc.). The free fatty acids **15**, **29**, **30**, **36** and **37** were analyzed in two solvent systems: S-1, MeOH/$CHCl_3$, 4:96; S-2, petroleum ether/ether/acetic acid, 70:30:1. Other compds. were analyzed with the systems indicated. The infrared spectra (IR) were recorded on a Beckman 18-A spectrophotometer with NaCl plates or KBr pellets. The low-resolution mass spectra (MS) were determined on a Kratos MS-25 instrument at 70 eV. The proton nuclear magnetic resonance spectra (NMR) were obtained at 60 MHz with a Varian 360-L instrument or at 200 MHz with a Nicolet high-resolution instrument. Samples (30–40 mg) were dissolved in $CDCl_3$ or CCl_4, and the resonances are reported downfield (δ) from the internal tetramethylsilane standard. All chemicals and solvents were analytical grade and were used without further purification. The petroleum ether had a 30–60 °C boiling range. The sodium [^{125}I]iodide was purchased from New England Nuclear, Inc. (North Billerica, MA). The elemental analyses were determined at Galbraith Laboratories, Knoxville, TN.

Animal Tissue Distribution Experiments. The distribution of radioactivity was determined in tissues of 10–12-week old female Fischer 344 rats (170–200 g) after intravenous administration of the radiolabeled fatty acid. The animals were allowed food and water ad libitum prior to and during the course of the experiment. The radioiodinated fatty acid was dissolved in 0.5 mL of absolute ethanol and added dropwise to a stirred solution of 6% bovine serum albumin at 40 °C. The final ethanol concentration was 10%. The solution was filtered through a 0.22-μm Millipore filter and injected via a lateral tail vein into the ether-anesthetized animals. The animals were anesthetized with ether, killed by cervical fracture, and the organs were excised, rinsed, and blotted dry. The organs were then placed in tared vials. The vials were weighed, the radioactive contents were determined in a Packard autogamma counter, and the percent injected dose per gram of tissue values were then calculated.

11-Bromo-1-phenylundecan-1-one (3). A solution of 11-bromoundecanoic acid (10.6 g, 0.04 mol) and thionyl chloride (4 mL, 0.07 mol) in dimethylformamide (DMF, 0.5 mL) was stirred at 80 °C for 1 h. The yellow-colored solution of 11-bromoundecanoyl chloride was cooled to room temperature and added to 200 mL of dry thiophene-free benzene. The resulting mixture was cooled to 10 °C, and $AlCl_3$ (8 g, 0.045 mol) was added in small portions. The resulting mixture was then stirred at 90 °C for 60 min, cooled, poured into ice-water (200 mL), and treated with 6 N HCl (200 mL). The organic layer was washed thoroughly with H_2O and 1 N NaOH and dried over anhydrous Na_2SO_4 and the C_6H_6 was removed to give a yellow oil. The crude product was crystallized from petroleum ether to give (10.44 g, 81%) of **3**: mp 43–44 °C; analysis by TLC (SiO_2-GF) in C_6H_6 indicated the presence of a single component (R_f 0.5); IR (KBr) 2910, 2840 (CH), 1680 (C=O), 730, 685 (aromatic) cm^{-1}; NMR ($CDCl_3$) δ 1.33 (s, 12 H, CH_2), 1.7 (m, 4 H, CH_2), 2.97 (t, J = 7 Hz, 2 H, CH_2C=O), 3.4 (t, J = 6 Hz, 2 H, CH_2Br), 7.5 (m, 3 H, aromatic), 7.97 (m, 2 H, aromatic); MS, m/z 326 [M^+ (^{81}Br), 3], 133 [M^+ – $(CH_2)_8{}^{81}$Br,9) 120 [M^+ – $CH(CH_2)_8{}^{81}$Br, 100], 105 [M^+ – $(CH_2)_{10}{}^{81}$Br, 80%], 77 [M^+ – $CO(CH_2)_{10}{}^{81}$Br, 30].

11-Cyano-1-phenylundecan-1-one (4). A mixture of (**3**; 13 g, 0.04 mol) and NaCN (2.5 g, 0.05 mol) was stirred at 80 °C for 2 h in 30 mL of dimethyl sulfoxide. The mixture was cooled to room temperature, poured into 200 mL of H_2O, and extracted several times with Et_2O. The combined ether extracts were washed thoroughly with H_2O and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The crude product was crystallized from petroleum ether to give (9.5 g, 85%) of **4**, mp 55–56 °C; analysis by TLC (SiO_2-GF) in C_6H_6 indicated the presence of a single component (R_f 0.33); IR (KBr) 2915, 2850 (CH), 2250 (C≡N), 1685 (C=O), 710, 670 (aromatic) cm^{-1}; NMR ($CDCl_3$) δ 1.33 (s, 14 H, CH_2), 1.7 (m, 2 H, CH_2), 2.33 (t, J = 6 Hz, 2 H, CH_2C≡N), 2.97 (t, J = 7 Hz, 2 H, CH_2C=O), 7.5 (m, 3 H, aromatic), 7.97 (m, 2 H, aromatic); MS, m/z 271 (M^+, 3), 120 [M^+ – $(CH)(CH_2)_7CN$, 100], 105 [M^+ – $(CH_2)_9CN$, 95], 77 [M^+ – $C(=O)(CH_2)_9CN$, 33].

12-Phenyldodecanoic Acid (5). The nitrile 4 (5.6 g, 0.02 mol) was added to 30 mL of diethylene glycol containing KOH (4.56 g, 0.08 mol) and 85% hydrazine hydrate (1.6 g, 0.05 mol), and the mixture was refluxed for 1 h. The mixture was distilled until the solution reached a temperature of 210 °C and then heated under reflux for 3 h. After cooling to 90 °C, a solution of 15 mL of 12 N HCl in 50 mL of H_2O was added, and the resulting mixture was cooled to room temperature and extracted several times with Et_2O. The combined Et_2O extracts were washed thoroughly with H_2O and dried over anhydrous Na_2SO_4, and the Et_2O was removed in vacuo to afford a white solid. The crude product was crystallized from methanol to give 5.25 g (95%) of **5**: mp 57–58 °C; analysis by TLC (SiO_2-GF) in 8% MeOH–$CHCl_3$ indicated the presence of a single component (R_f 0.55); NMR (CCl_4) δ 1.27 (s, 18 H, CH_2), 2.3 (t, J = 7 Hz, 2 H, CH_2COO), 2.57 (t, J = 7 Hz, 2 H, $PhCH_2$) and 7.13 (s, 5 H, aromatic); MS, m/z 276 (M^+, 6), 258 (M^+ – H_2O, 3%), 230 (M^+ – HCO_2H, 3), 92 [M^+ – $(CH)(CH_2)_8CO_2H$, 80], 91 [M^+ – $(CH_2)_9CO_2H$, 100].

Methyl 12-Phenyldodecanoate (6). The acid **5** (5.24 g, 0.019 mol) was added to an ether solution (100 mL) containing CH_2N_2, prepared from *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG; 5 g). The mixture was stirred at 0 °C under red lights for 12 h. The Et_2O solution was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to yield an oil. The crude product was applied to a silicic acid (75 g, basic grade) column slurried in C_6H_6. Fractions (100 mL in volume) were eluted with C_6H_6. Fractions 5–7 were combined to give methyl 12-phenyldodecanoate (**6**; 5.17 g, 95%) as a colorless oil: TLC (C_6H_6) R_f 0.50; NMR ($CDCl_3$) δ 1.27 (s, 16 H, CH_2), 1.6 (m, 2 H, CH_2), 2.3 (t, J = 7 Hz, 2 H, CH_2C=O), 2.57 (t, J = 7 Hz, 2 H, $PhCH_2$) 3.67 (s, 3 H, CO_2CH_3), 7.2 (s, 5 , aromatic); MS, m/z 290 (M^+, 10%), 258 (M^+ – CH_3OH, 20), 105 [M^+ – $(CH_2)_9COOCH_3$, 20], 92 [M^+ – $CH(CH_2)_8COOCH_3$, 70], 91 [M^+ – $(CH_2)_9COOCH_3$, 100].

12-Phenyldodecan-1-ol (7). The ester **6** (5.08 g, 0.017 mol) was added dropwise over a 60-min period to a stirred suspension of $LiAlH_4$ (2.28 g, 0.06 mol) in 80 mL of Et_2O under an argon atmosphere at room temperature. The resulting mixture was

heated under reflux for 4 h and cooled. The unreacted $LiAlH_4$ was decomposed by a dropwise addition of ethyl acetate (5 mL) and H_2O (5 mL). The mixture was carefully poured into ice–H_2O (100 mL), acidified with 10% H_2SO_4, and extracted thoroughly with Et_2O. The combined Et_2O extracts were washed several times with H_2O and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The crude product was crystallized from petroleum ether to afford 12-phenyldodecan-1-ol (**7**) as a white solid (4.1 g, 90%): mp 39–40 °C; TLC (C_6H_6) R_f 0.30; NMR ($CDCl_3$) δ 1.27 (s, 18 H, CH_2), 1.8 (m, 2 H, CH_2), 2.60 (t, J = 8 Hz, 2 H, $PhCH_2$), 3.60 (t, J = 6 Hz, 2 H, CH_2OH, 7.25 (s, 5 H, aromatic); MS, m/z 262 (M^+, 8), 244 (M^+, 8), 244 ($M^+ - H_2O$, 4), 104 [$M^+ - CH_3(CH_2)_9OH$, 100], 91 [$M^+ - (CH_2)_{11}OH$, 70].

12-Phenyldodecyl Iodide (8). A mixture of the alcohol **7** (2.62 g, 0.01 mol) and iodotrimethylsilane (4.00 g, 0.02 mol) in 15 mL of CH_2Cl_2 was stirred at room temperature under an argon atmosphere for 24 h. The mixture was poured into 100 mL of 10% sodium bisulfite and extracted several times with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed once with 10% sodium bisulfite and then thoroughly with H_2O and dried over anhydrous Na_2SO_4, and the CH_2Cl_2 was concentrated in vacuo to afford a yellow oil. The crude product was dissolved in petroleum ether and applied to a silicic acid (100 g) column (basic grade) slurried in petroleum ether. The column was eluted with petroleum ether, and fractions 4–6 (100 mL in volume) were combined to give **8** (3.3 g, 88%) as a colorless oil: TLC (C_6H_6) R_f 0.75; NMR ($CDCl_3$) δ 1.27 (s, 18 H, CH_2), 1.7 (s, 2 H, CH_2), 2.67 (t, J = 7 Hz, 2 H, $PhCH_2$), 3.2 (t, J = 7 Hz, 2 H, CH_2I), 7.25 (s, 5 H, aromatic); MS, m/z 372 (M^+, 8), 91 [$M^+ - (CH_2)_{11}I$, 100].

2(*RS*)-(4,4-Dimethyl-2-oxazolin-2-yl)-14-phenyltetradecane (10). 2-Ethyl-4,4-dimethyl-2-oxazoline (**9**; 990 mg, 7.8 mmol) in 10 mL of dry THF under argon was cooled to −78 °C, and 5 mL of a 1.7 M *n*-butyllithium solution was added with a syringe through a rubber septum. The resulting mixture was stirred at −78 °C for 60 min. After the dropwise addition of 12-phenyldodecyl iodide (**8**; 2.1 g, 5.7 mmol) in 5 mL of THF, the resulting mixture was stirred at −78 °C for 30 min and at room temperature for 45 min. The mixture was added to 100 mL of saturated NaCl and extracted several times with Et_2O. The combined Et_2O extracts were washed thoroughly with H_2O and dried over anhydrous Na_2SO_4, and the Et_2O was concentrated in vacuo to give a yellow oil. The crude material was dissolved in petroleum ether (2 mL) and applied to a silicic acid column (25 g, basic grade) slurried in petroleum ether. Fractions (100 mL in volume) were eluted with petroleum ether (1–5), followed by fractions (25 mL in volume) with ether (6–15). Fractions 7–9 were combined to give **10** (1.25 g, 60%) as a colorless oil: TLC (ether) R_f 0.75; NMR (CCl_4) δ 1.3 (s, 22 H, CH_2, and 9 H, CH_3), 2.3 (m, 1 H, CH), 2.7 (t, J = 7 Hz, 2 H, $PhCH_2$), 3.0 (s, 2 H, CH_2O), 7.25 (s, 5 H, aromatic); MS, m/z 371 (M^+, 75), 356 ($M^+ - CH_3$, 25).

Ethyl 14-Phenyl-2(*RS*)-methyltetradecanoate (11). A mixture of the oxazoline **10** (1.85 g, 5 mmol) and concentrated H_2SO_4 (1.6 mL) was refluxed in 95% ethanol (38.4 mL for 24 h. The mixture was cooled, poured into 150 mL of H_2O, and extracted several times with Et_2O. The combined Et_2O extracts were washed 4 times with 50 mL of saturated NaCl and dried over Na_2SO_4, and the Et_2O was evaporated in vacuo to afford **11** (1.52 g, 89%) as a colorless oil: TLC (C_6H_6) R_f 0.50; NMR ($CDCl_3$) δ 1.13 (d, J = 2 Hz, 3 H, $HCCH_3$), 1.27 (s, 20 H, CH_2), 1.27 (t, J = 6 Hz, 3 H, OCH_2CH_3), 2.37 (m, 1 H, $CHCO_2$), 2.67 (t, J = 6 Hz, 2 H, $PhCH_2$), 4.13 (q, J = 6 Hz, 2 H, OCH_2CH_3), 7.23 (s, 5 H, aromatic); MS, m/z 346 (M^+, 16), 322 ($M^+ - CH_2$, 18), 300 ($M^+ - OCH_2CH_3$, 20), 287 ($M^+ - CH_2OCH_2CH_3$, 46), 91 [$M^+ - (CH_2)_{11}CH(CH_3)CO_2CH_2CH_3$, 100].

14-Phenyl-2(*RS*)-methyltetradecan-1-ol (12). The ester **11** (346 mg, 1 mmol) in 5 mL of anhydrous Et_2O was added dropwise over 15 min to a stirred suspension of $LiAlH_4$ (160 mg, 4 mmol) and 25 mL of Et_2O as described for **7**. The dried Et_2O extracts were evaporated in vacuo to afford 290 mg of **12** (95%) as a colorless oil: TLC (C_6H_6) R_f 0.30; NMR ($CDCl_3$) δ 0.90 (d, J = 5 Hz, 3 H, $HCCH_3$), 1.23 (s, 20 H, CH_2), 2.60 (t, J = 7 Hz, 2 H, $PhCH_2$), 3.47 (d, J = 5 Hz, 2 H, CH_2OH), 7.25 (s, 5 H, aromatic); MS, m/z 304 (M^+, 20), 286 ($M^+ - H_2O$, 98), 230 [$M^+ - CH_3CH(CH_3)CH_2OH$, 40], 104 [$M^+ - CH_3(CH_2)_9CH(CH_3)CH_2OH$, 100], 91 [$M^+ - (CH_2)_{11}CHCH_3CH_2OH$, 76].

14-Phenyl-2(*RS*)-methyltetradecyl Iodide (13). The alcohol **12** (912 mg, 3 mmol) and iodotrimethylsilane (2.8 g, 14 mmol) were reacted in 15 mL of CH_2Cl_2 as described for **8**. The product was worked up in the usual manner, and the product was chromatographed on basic-grade SiO_2 by elution with petroleum ether. Fractions 5–11 (20 mL in volume) were combined to give 1.05 g of **13** (85%) as a colorless oil: TLC (C_6H_6) R_f 0.75; NMR ($CDCl_3$) δ 0.97 (d, J = 4 Hz, 2 H, $HCCH_3$), 1.25 (s, 20 H, CH_2), 2.62 (t, J = 7 Hz, 2 H, $PhCH_2$), 3.23 (d, J = 4 Hz, 2 H, $HCCH_2I$), 7.23 (s, 5 H, aromatic); MS, m/z 414 (M^+, 3), 287 ($M^+ - I$, 7), 91 [$M^+ - (CH_2)_{11}CHCH_3CH_2I$, 100].

14-Phenyl-2(*RS*)-methyltetradecanenitrile (14). A mixture of **13** (414 mg, 1 mmol) and NaCN (200 mg, 4 mmol) in 15 mL of Me_2SO were reacted as described for **4**. The dried ether extracts were evaporated in vacuo to afford an oil. The crude product was dissolved in petroleum ether and applied to a silicic acid (25 g, basic grade) column slurried in petroleum ether. Fractions 1–10 (25 mL) were eluted with petroleum ether, and fractions 11–20 (25 mL) were eluted with C_6H_6. Fractions 15–17 were combined and concentrated in vacuo to afford 256 mg of **14** (82%) as a colorless oil: TLC (C_6H_6) R_f 0.67; IR (NaCl) 2930, 2850 (CH), 2250 (C≡N), and 750, 700 (aromatic) cm^{-1}; NMR ($CDCl_3$) δ 1.17 (d, J = 5 Hz, 3 H, $HCCH_3$), 1.27 (s, 20 H, CH_2), 2.27 (d, J = 5 Hz, 2 H, $CH_2C{\equiv}N$), 2.63 (t, J = 7 Hz, 2 H, $PhCH_2$), 7.23 (s, 5 H, aromatic); MS, m/z 313 (M^+, 15), 92 [$M^+ - HC(CH_2)_{10}CH(CH_3)CH_2CN$, 100], 91 [$M^+ - (CH_2)_{11}CH(CH_3)CH_2CN$, 80].

15-Phenyl-3(*RS*)-methylpentadecanoic Acid (15). Method A. A mixture of nitrile **14** (235 mg, 0.75 mmol) and KOH (150 mg, 2.3 mmol) was refluxed for 6 h in 25 mL of ethylene glycol. The mixture was cooled to room temperature, poured into 100 mL of H_2O, and extracted several times with Et_2O. The ether extracts were washed with two 50-mL portions of water. The combined H_2O phases were acidified to pH 3 with 12 N HCl and extracted several times with benzene. The combined benzene extracts were washed several times with H_2O and once with 100 mL of saturated NaCl and dried over anhydrous Na_2SO_4, and the benzene was concentrated in vacuo to a white solid. Crystallization from methanol gave 216 mg of **15** (91%) as a white solid: mp 38–39 °C; analysis by TLC (SiO_2-GF) indicated the presence of a single component, R_f (S-1) 0.50 and R_f (S-2) 0.70; NMR ($CDCl_3$) δ 0.97 (d, J = 5 Hz, 3 H, $CHCH_3$), 1.27 (s, 23, CH, CH_2), 2.17 (d, J = 4 Hz, 2 H, $CH_3C{=}O$), 2.57 (t, J = 6 Hz, 2 H, $PhCH_2$), 7.17 (s, 5 H, aromatic); MS, m/z 332 (M^+, 17), 314 ($M^+ - H_2O$, 15) 104 [$M^+ - H_3C(CH_2)_9CH(CH_3)CH_2CO_2H$, 30], 92 [$M^+ - HC(CH_2)_{10}CH(CH_3)CH_2CO_2H$, 100], 91 [$M^+ - (CH_2)_{11}CH(CH_3)CH_2CO_2H$, 90].

Method B. Raney nickel (10 g) and acid **24** (2.5 g, 7 mmol) were vigorously stirred and refluxed in 50 mL of 10% NaOH for 18 h. The resulting mixture was filtered, and the cooled filtrate was acidified to pH 3 with 12 N HCl, and extracted several times with ether. The combined ether extracts were throughly washed with water and dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo to give compound **15**, which was identical with the sample prepared by method A. Crystallization from MeOH gave 1.8 g (77%) as a white solid, mp 37–39 °C.

Methyl 15-Phenyl-3(*RS*)-methylpentadecanoate (16). The acid **15** (2.00 g, 6 mmol) was added to an ether solution (100 mL) containing CH_2N_2, prepared from MNNG (2 g). The mixture was reacted as described for **6**. The dried Et_2O solution was concentrated in vacuo to give **16** (2.00 g, 95%) as an oil: TLC (C_6H_6) R_f 0.5; NMR ($CDCl_3$) δ 0.9 (d, J = 5 Hz, 3 H, $CHCH_3$), 1.23 (s, 23 H, CH, CH_2), 2.1 (d, J = 4 Hz, 2 H, $CHCH_2C{=}O$), 2.6 (t, J = 6 Hz, 2 H, $C_6H_5CH_2$) 3.65 (s, 3 H, OCH_3), 7.15 (s, 5 H, C_6H_5); MS, m/z 346 (M^+, 10), 314 ($M^+ - CH_3OH$, 40), 91 [$M^+ - (CH_2)_{11}CH(CH_3)CH_2CO_2CH_3$, 100).

2-(6-Phenyl-1-oxohexyl)thiophene (20). Anhydrous $SnCl_4$ (30.3 g, 0.12 mmol) was added dropwise to a solution of 6-phenylhexanoyl choloride (**18**; 21 g, 0.10 mmol) and thiophene (**19**; 9.2 g, 0.11 mmol) in CH_2Cl_2 (200 mL) stirred at 0 °C. The resulting purple mixture was then stirred at 0 °C for 30 min and then at room temperature for 2 h and treated with 6 N HCl until a yellow solution was obtained. The organic layer was washed thoroughly with 10% HCl, H_2O, and 10% NaOH and dried over anhydrous Na_2SO_4, and the CH_2Cl_2 was removed in vacuo to afford 18 h (70%) of **20**: bp 155–157 °C (1.8 mm); IR (Neat) 1660 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.6 (m, 6 H, CH_2), 2.8 (m, 4 H, $C_6H_5CH_2$,

Table V. Radioiodinated Phenyl Fatty Acid Yields[a]

no.	radiochem yield, %	no.	radiochem yield, %
27	36	33	17
28	42	35	28
29	91	36	65
30	89	37	80

[a] All radioiodinated products exhibited a single radioactive component upon thin-layer radiochromatographic analysis (SiO_2) and cochromatographed with the unlabeled standard. Radiochemical yields are reported for isolated, chromatographically homogeneous products.

and $CH_2C{=}O$), 7.1 (m, 6 H, aromatic), 7.45 (m, 1 H, aromatic), 7.65 (m, 1 H, aromatic).

2-(6-Phenylhexyl)thiophene (21). The ketone **20** (16.7 g, 0.06 mmol) was added to 60 mL of diethylene glycol containing KOH (9 g, 0.16 mmol) and 85% hydrazine (6 g, 0.20 mmol), and the mixture was reacted as described for **5**. The dried Et_2O extracts were evaporated in vacuo to yield 12 g (82%) of **21**: bp 160–162 °C (2.5 mm); NMR ($CDCl_3$) δ 1.45 (m, 8 H, CH_2), 2.65 (m, 4 H, $PhCH_2$ and thienyl CH_2), 6.65 (m, 1 H, aromatic), 6.8 (m, 1 H, aromatic), 6.95 (m, 1 H, aromatic), 7.1 (s, 5 H, aromatic).

2-[3(*RS*)-Methyl-1-oxo-5-hydroxypentanoyl]-5-(6-phenylhexyl)thiophene (23). A mixture of 2-(6-phenylhexyl)thiophene (**21**; 4.0 g, 0.02 mol) and 3-methylglutaric anhydride (**22**; 2.84 g, 0.022 mol) was stirred at 0 °C in 60 mL of nitrobenzene. Anhydrous $AlCl_3$ (6.75 g, 0.05 mol) was added to the resulting mixture in small portions. The mixture was stirred at 0 °C for 30 min and at room temperature for 4 h, poured into ice–water (200 mL), and treated with 6 N HCl (200 mL). After decomposition of the $AlCl_3$ complex with HCl, the nitrobenzene was removed by steam distillation. The crude product was collected by filtration of the supernatant liquid and crystallized from MeOH–H_2O (1:1) to give (4.8 g, 65%) of **23**: mp 71–72 °C; IR (KBr) 1660 (C=O), 1710 (C=O of COOH) cm^{-1}; NMR ($CDCl_3$) δ 1.11 (d, J = 5 Hz, 3 H, $CHCH_3$), 1.4 (m, 8 H, CH_2), 2.5 (m, 9 H), 6.72 (d, J = 4 Hz, 1 H, aromatic), 7.1 (s, 5 H, aromatic), 7.5 (d, J = 4 Hz, 1 H, aromatic).

2-[3(*RS*)-Methyl-1-hydroxypentanoyl]-5-(6-phenylhexyl)thiophene (24). The keto acid **23** (3.2 g, 8.7 mmol) was added to 10 mL of diethylene glycol containing KOH (1.5 g, 26.7 mmol) and 85% hydrazine (1 g, 30 mmol), and the mixture was reacted as described for **5**. The dried Et_2O extracts were evaporated in vacuo to give 3 g (96%) of **24**: bp 195–200 °C (1.5 mm); IR (Neat) 1710 (C=O of COOH), 850 2,5-disubstituted thiophene), 690 (monosubstituted benzene) cm^{-1}; NMR ($CDCl_3$) δ 1.0 (d, J = 5 Hz, 3 H, $CHCH_3$), 1.1–2.9 (m, 19 H), 6.45 (s, 2 H, aromatic), 7.1 (s, 5 H, aromatic).

Ethyl 14-(*p*-Iodophenyl)-2(*RS*)-methyltetradecanoate (27). The ester **11** (692 mg, 2 mmol) and thallium(III) trifluoroacetate (1.7 g, 3.1 mmol) in 6 mL of trifluoroacetic acid were stirred at room temperature under red lights for 5 days. Potassium iodide (1.33 g, 10 mmol) in 10 mL of H_2O was added, and the resulting mixture was stirred for 15 min. Sodium thiosulfate (1 g) was then added, and the mixture was stirred for an additional 15 min, poured into 50 mL of H_2O, and extracted several times with Et_2O. The Et_2O extracts were thoroughly washed with 0.1 N HCl and H_2O and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to afford a yellow oil. The crude material was dissolved in 2 mL of C_6H_6 and applied to a silicic acid column (25 g, basic form) slurried in C_6H_6. Fractions 5–7 (20 mL in volume) were combined, and the solvent was removed in vacuo to afford 700 mg of **27** (85%) a colorless oil: TLC (C_6H_6) R_f 0.50; NMR ($CDCl_3$) δ 1.13 (d, J = 4 Hz, 3 H, $CHCH_3$), 1.27 (s, 20 H, CH_2), 1.27 (t, J = 6 Hz, 3 H, OCH_2CH_3), 2.30 (m, 1 H, $CHCO_2$), 2.62 (t, J = 6 Hz, 2 H, $PhCH_2$), 4.2 (q, J = 6 Hz, 2 H, OCH_2CH_3), 7.32 (AA'BB', J = 8 Hz, 4 H); MS (m/z 472 (M^+, 30), 427 ($M^+ - OCH_2CH_3$, 15), 399 ($M^+ - CO_2CH_2CH_3$, 10), 345 (M^+ – I, 100), 299 (M^+ – I, $HOCH_2CH_3$, 100), 102 [M^+ – I, $(CH_2)_5CO_2CH_2CH_3$, 100).

Methyl 15-(*p*-Iodophenyl)-3(*RS*)-methylpentadecanoate (28). The ester **16** (520 mg, 1.5 mmol) and the thallium(III) trifluoroacetate (810 mg, 1.5 mmol) in 3 mL of trifluoroacetic acid were reacted as described for compound **27**. The C_6H_6 fractions (20 mL) 5–7 were concentrated in vacuo to give 616 mg of **28** (87%) as a colorless oil: NMR ($CDCl_3$) δ 0.9 (d, J = 6 Hz, 3 H, $CHCH_3$), 1.27 (s, 22 H, CH_2), 2.17 (d, J = 6 Hz, 2 H, $CHCH_2C{=}O$) 2.57 (t, J = 6 Hz, 2 H, $PhCH_2$) 3.67 (s, 3 H, $COOCH_3$), 7.27 (AA'BB', J = 8 Hz, 4 H); MS, m/z 472 (M^+, 4), 345 (M^+ – I, 3), 91 [M^+ – I, 3), 91 [M^+ – I, $CH(CH_2)_8CH(CH_3)CH_2CO_2CH_3$, 100].

14-(*p*-Iodophenyl)-2(*RS*)-methyltetradecanoic Acid (29). The ethyl ester **27** (378 mg, 0.8 mmol) was dissolved in EtOH (10 mL) and refluxed with 1 N NaOH (2 mL) for 90 min. The mixture was cooled, poured into H_2O, acidified to pH 2–3 with 1 N HCl, and extracted twice with Et_2O. Following thorough washing with H_2O, the organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo to give compound **29**. Crystallization from MeOH gave 302 mg of **29** (85%) as a white solid: mp 59–60 °C; analysis by two TLC solvent systems indicated the presence of a single component: R_f (S-1) 0.50 and R_f (S-2) 0.70; NMR ($CDCl_3$) δ 1.13 (d, J = 4 Hz, 3 H $CHCH_3$), 1.27 (s, 20 H, CH_2), 2.30 (M, 1 H, $CHCO_2$), 2.55 (t, J = 6 Hz, 2 H, $PhCH_2$), 7.27 (AA'BB', J = 8 Hz, 4 H); MS, m/z 444 (M^+, 3), 300 N^+ – I, HO, 13), 299 (M^+ – I, H_2O, 31), 217 [M^+ – I, H_2O – $CH_2CH(CH_3)CO_2H$, 43], 131 [M^+ – I, $CH(CH_2)_7CH(CH_3)CO_2H$, 50), 92 [M^+ – I, $(CH_2)_9CH(CH_3)CO_2H$, 44].

15-(*p*-Iodophenyl)-3(*RS*)-methylpentadecanoic Acid (30). The methyl ester **28** (378 mg, 0.8 mmol) was dissolved in EtOH (10 mL) and treated with 1 N NaOH (2 mL) as described for compound **29**. Crystallization from MeOH yielded 345 mg of **30** (95%) as a white solid: mp 47–49 °C; NMR ($CDCl_3$) δ 1.00 (d, J = 6 Hz, 3 H, $CHCH_3$), 1.27 (s, 20 H, CH_2), 2.17 (d, J = 6 Hz, 2 H, $CHCH_2CO_2$), 2.57 (t, J = 6 Hz, 2 H, $PhCH_2$), 7.27 (AA'BB', J = 8 Hz, 4 H); MS, m/z 458 (M^+, 3), 314 (M^+ – I, HO, 20), 313 (M^+ – I, H_2O, 37), 217 [M^+ – I, $CHCH_2CH(CH_3)CH_2CO_2H$, 31], 131 [M^+ – I, $CH(CH_2)_7CH(CH_3)CH_2CO_2H$], 92 [$M^+$ – I, $(CH_2)_9CH(CH_3)CH_2CO_2H$].

1-(4,4-Dimethyl-2-oxazolin-2-yl)-13-phenyltridecane (31). 2,4,4-Trimethyl-2-oxazoline (339 mg, 3 mmol) in 20 mL of dry THF under argon was cooled to −78 °C, and 2 mL of 1.6 M *n*-butyllithium was added with the aid of a syringe through a rubber septum. After the formation of a yellow solid, 12-phenyldodecyl iodide (**8**; 1.13 g, 3 mmol) in 5 mL of THF was added dropwise, and the resulting mixture was stirred at −78 °C for 10 min and then allowed to slowly reach room temperature. The mixture was added to 50 mL of saturated NaCl solution and extracted several times with Et_2O. The combined Et_2O extracts were washed several times with H_2O and dried over anhydrous Na_2SO_4, and the Et_2O was concentrated in vacuo to give 842 mg of **31** (76%) as a colorless oil: TLC (ether) R_f 0.75; NMR ($CDCl_3$) δ 1.27 (s, 22 H, CH_2; 6 H, CH_3), 2.25 (t, J = 6 Hz, 2 H, $N{=}CCH_2$), 2.65 (t, J = 7 Hz, 2 H, $PhCH_2$), 3.9 (s, 2 H, OCH_2), 7.2 (s, 5 H, aromatic); MS, m/z 357 (M^+, 2), 102 ($M^+ - CH(CH_2)_{11} - C_4H_8NO$, 60), 91 ($M^+ - (CH_2)_{12} - C_4H_8NO$, 100).

Ethyl 14-Phenyltetradecanoate (32). A mixture of oxazoline (**31**; 842 mg, 2.27 mmol), concentrated H_2SO_4 (0.8 mL), and 95% ethanol (24.2 mL) was reacted as described for compound **11**. The dried ether extracts were evaporated in vacuo to give 643 mg, (86%) of **32** as a colorless oil: TLC (benzene) R_f 0.50; NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.23 (s, 22 H, CH_2), 2.28 (t, J = 6 Hz, 2 H, $CH_2C{=}O$), 2.53 (t, J = 6 Hz, 2 H, $PhCH_2$) 4.1 (q, J = 7 Hz, 2 H, OCH_2CH_3), 7.2 (s, 5 H, aroatic); MS, m/z 332 (M^+, 6), 286 ($M^+ - HOCH_2CH_3$, 18) 258 ($M^+ - HCO_2CH_2CH_3$, 20), 92 ($M^+ - CH(CH_2)_{11}CO_2CH_2CH_3$, 100).

Ethyl 14-(*p*-Iodophenyl)tetradecanoate (33). The ester **32** (332 mg, 1 mmol) and thallium(III) trifluoroacetate (810 mg, 1.5 mmol) in 3 mL of trifluoroacetic acid were reacted as described for compound **27**, and the product was obtained and chromatographed on SiO_2 in the usual manner. The C_6H_6 fractions (20 mL) 5–7 were concentrated in vacuo to give 396 mg of **33** (82%) as a colorless oil: NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.23 (s, 22 H, CH_2), 2.28 (t, J = 6 Hz, 2 H, $CH_2C{=}O$), 2.53 (t, J = 6 Hz, 2 H, $PhCH_2$), 4.1 (q, J = 7 Hz, 2 H, OCH_2CH_3), 7.27 (AA'BB', J = 8 Hz, 4 H, aromatic); MS, m/z 458 (M^+, 6), 413 ($M^+ - OCH_2CH_3$, 7), 331 (M^+ – I, 15), 285 ($M^+ - HIOCH_2CH_3$, 50), 119 ($M^+ - ICH_2(CH_2)_9CO_2CH_2CH_3$, 60), 91 ($M^+ - ICH(CH_2)_{11}CO_2CH_2CH_3$, 100).

Methyl 15-Phenylpentadecanoate (34). 15-Phenylpentadecanoic acid (EMKA; 3.18 g, 0.01 mmol) was added to an ether solution (100 mL) containing CH_2N_2 as described for com-

pound 6. Crystallization from methanol yielded 3.10 g of 34 (94%) as a white solid: mp 38–39 °C; NMR (CCl_4) δ 1.27 (s, 24 H, CH_2), 2.23 (t, J = 6 Hz, 2 H, CH_2C=O), 2.57 (t, J = 6 Hz, 2 H, $PhCH_2$), 3.6 (s, 3 H, OCH_3), 7.15 (s, 5 H, aromatic); MS, m/z 332 (M^+, 18), 300 ($M^+ - CH_3OH$, 55), 91 [$M^+ - (CH_2)_{13}CO_2CH_3$, 100].

Methyl 15-(*p*-Iodophenyl)pentadecanoate (35). The ester 34 (664 mg, 2 mmol) and thallium(III) trifluoroacetate (1.62 g, 3 mmol) in 3 mL of trifluoroacetic acid were reacted and then treated with KI as described for compound 27. The C_6H_6 fractions (20 mL) 5–7 were concentrated in vacuo to yield 816 mg (89%) of a solid. Crystallization from methanol yielded 35 as a pale yellow solid: mp 55–56 °C; NMR ($CDCl_3$) δ 1.27 (s, 24 H, CH_2), 2.23 (t, J = 6 Hz, 2 H, CH_2C=O), 2.57 (t, J = 6 Hz, 2 H, $PhCH_2$), 3.6 (s, 3 H, OCH_3), 7.27 (AA'BB', J = 8 Hz, 4 H, aromatic); MS, m/z 458 (M^+, 3), 427 ($M^+ - CH_3O$, 2), 332 ($M^+ + 1 - I$, 70), 331 ($M^+ - I$, 35), 91 [$M^+ - I$, $CH(CH_2)_{12}CO_2CH_3$, 100].

14-(*p*-Iodophenyl)tetradecanoic Acid (36). The ethyl ester 33 (366 mg, 0.8 mmol) was dissolved in EtOH (10 mL) and treated with 1 N NaOH (2 mL) as described for compound 29. Crystallization from MeOH yielded 310 mg of 36 (90%) as a white solid: mp 86–87 °C; analysis by TLC in two solvent systems indicated the presence of a single component: R_f (S-1) 0.50; R_f (S-2) 0.70; NMR ($CDCl_3$) δ 1.27 (s, 24 H, CH_2), 2.3 (t, J = 6 Hz, 2 H, CH_2C=O), 2.57 (t, J = 6 Hz, 2 H, $PhCH_2$), 7.27 (AA'BB', J = 8 Hz, 4 H, aromatic); MS, m/z 430 (M^+, 5), 285 ($M^+ - I, H_2O$, 54) 217 [$M^+ - I$, $CH(CH_2)_2CO_2H$, 50], 91 [$M^+ - I$, $CH(CH_2)_{11}CO_2H$, 100].

15-(*p*-Iodophenyl)pentadecanoic Acid (37). The methyl ester 34 (458 mg, 1 mmol) was dissolved in EtOH (10 mL) and treated with 1 N NaOH (2 mL) as described for compound 29. Crystallization from MeOH yielded 400 mg of 37 (90%) as a white solid: mp 92–93 °C (lit.[24] mp 94 °C); analysis by TLC in two solvent systems indicated the presence of a single component: R_f (S-1) 0.50; R_f (S-2) 0.70; NMR ($CDCl_3$) δ 1.27 (s, 26 H, CH_2), 2.3 (t, J = 6 Hz, 2 H, CH_2C=O), 2.57 (t, J = 6 Hz, 2 H, $PhCH_2$), 7.27 (AA'BB', J = 8 Hz, 4 H, aromatic); MS, m/z 444 M^+, 5), 299 ($M^+ - I, H_2O$, 52), 217 [$M^+ - I$, $CH(CH_2)_2CO_2H$, 43], 91 [$M^+ - I$, $CH(CH_2)_{12}CO_2H$, 100].

Radioiodinated Phenyl Fatty Acids. General Procedure. The ester (0.1 mmol) and thallium(III) trifluoroacetate (0.15 mmol) in 3 mL of trifluoroacetic acid were stirred under red lights for 5 days. Sodium [^{125}I]iodide (no carrier added) in 1 mL of H_2O was added, and the resulting mixture was stirred for 5 min. Potassium iodide (17 mg, 0.1 mmol) in 1 mL of H_2O was then added, the mixture was stirred for 5 min, followed by a second addition of potassium iodide (66 mg, 0.4 mmol) in 1 mL of H_2O, and the resultant mixture was stirred for 20 min. Sodium thiosulfate (1 g) was added, and the mixture was stirred for 5 min, poured into 50 mL of H_2O, and extracted several times with Et_2O. The Et_2O extracts were washed once with 50 mL of 10% sodium bisulfite and then thoroughly with H_2O and dried over anhydrous Na_2SO_4, and the solvent was removed via a stream of argon. The crude material was dissolved in 1 mL of C_6H_6 and applied to a silicic acid column (25 g, basic form) slurried in C_6H_6. Fractions 3–5 (20 mL in volume) were combined, and the solvent was removed by a stream of argon to afford the radioiodinated product. The radiochemical and chemical purity were confirmed by TLC (SiO_2-GF) in C_6H_6, R_f (0.50).

The radioiodinated ester was dissolved in EtOH (10 mL) and refluxed with 1 N NaOH (2 mL) for 90 min. The mixture was cooled, poured into H_2O, acidified to pH 2-3 with 1 N HCl, and extracted twice with Et_2O. Followed thorough washing with H_2O, the organic layer was dried over anhydrous Na_2SO_4 and the Et_2O evaporated by a stream of argon (See Table V). The free acids were analyzed in S-1 and S-2 solvent systems as described earlier.

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Phosphorus–Nitrogen Compounds. 24. Phosphoramide Mustard Carrier Derivatives[1,2]

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Diethylstilbestrol, psoralen, and propranolol were used as potential carrier molecules for selective concentrations of a nitrogen mustard moiety in breast, skin, and lung tissues, respectively. The propranolol derivative gave two racemic mixtures, which were tested to ascertain any differences in anticancer activity. The insertion of a P=O group between the carrier and oncolytic portions offsets the excess lipophilic contribution of the latter and possibly provides for latentiation of alkylating activity. Murine tumor testing of the phosphoramide mustard derivatives and two intermediates indicated that two compounds possessed marginal activity against mammary carcinoma and lymphocytic leukemia.

The concept of carrier molecules has been employed in the design of some of the earliest nitrogen mustard derivatives used in cancer chemotherapy. L-Phenylalanine mustard (melphalan), for example, was synthesized in an attempt to localize an oncolytic moiety in melanomas.[3] It was hoped that phenylalanine, being a precursor of melanin, would serve as a carrier molecule by selectively transporting and concentrating *N*,*N*-bis(2-chloroethyl)-amine (nornitrogen mustard, nor-NH_2) in these tumors.

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