New Myocardial Imaging Agents: Synthesis of 15-(*p*-Iodophenyl)-3(*R*,*S*)-methylpentadecanoic Acid by Decomposition of a 3,3-(1,5-Pentanediyl)triazene Precursor

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Methods have been developed for the rapid, regiospecific introduction of iodine into the para position of the terminal phenyl ring of 15-(*p*-iodophenyl)-3(*R*,*S*)-methylpentadecanoic acid via the HI decomposition of a 3,3-(1,5-pentanediyl)triazene derivative of the *p*-amino substrate. The syntheses and physical properties of the triazene intermediate, 1-[4-(13(*R*,*S*)-methyl-14-carboxytetradecyl)phenyl]-3,3-(1,5-pentanediyl)triazene, and 15-(*p*-iodophenyl)-3(*R*,*S*)-methylpentadecanoic acid are described. Radioiodinated methyl-branched long-chain fatty acids such as 15-(*p*-iodophenyl)-3(*R*,*S*)-methylpentadecanoic acid are of interest as myocardial imaging agents as a result of the pronounced uptake and prolonged heart retention, which appears to result from the inhibition of fatty acid metabolism. Iodine was introduced into the para position of the terminal phenyl ring by treatment of the triazene intermediate at 0–5 °C with HI which was generated by in situ treatment of sodium iodide in acetone with trifluoroacetic acid. The triazene intermediate decomposed to yield exclusively the *p*-iodophenyl product in good yield (>50%). These results suggest that the decomposition of the 3,3-(1,5-pentanediyl)triazene derivative of terminal phenyl long-chain fatty acids is an attractive method for the preparation of high specific activity regiospecific radioiodinated agents.

Structurally modified long-chain fatty acids radiolabeled with iodine-123 have been widely used for the clinical evaluation of patients with heart disease.[1,2] These agents can be uniquely used to evaluate by noninvasive methods various aspects of regional fatty acid metabolism in relation to heart disease and thus aid in the diagnosis, prognosis, and management of the cardiac patient. One approach has involved the stabilization of radioiodide by attachment to the para position of the terminal phenyl ring of 15-phenylpentadecanoic acid (IPP). The iodine-123-labeled IPP has been used by several clinical investigators.[3-5] An extension of these studies has involved introduction of β-methyl branching into IPP to inhibit β-oxidation. The use of iodine-123-labeled 15-(*p*-iodophenyl)-3(*R*,*S*)-methylpentadecanoic acid (BMIPP) has been proposed to evaluate in vivo structurally modified fatty acids designed to inhibit a crucial metabolic step which results in trapping the tracer.[6] The BMIPP was prepared by iodide displacement of the crude bis(trifluoroacetoxy)thallium(III) intermediate prepared by in situ treatment of the methyl-branched fatty acid with thallium(III) trifluoroacetate. Because of the importance of the regioselectivity of the iodination on the biological properties of the resulting radioiodinated product, and the need for a simple rapid radioiodination method, a rapid synthetic method has now been developed for the preparation of 15-(*p*-iodophenyl)-3(*R*,*S*)-methylpentadecanoic acid (**12**, Scheme II).

Because the terminal phenyl, methyl-branched fatty acids are not commercially available, a synthetic method for the preparation of 15-phenyl-3(*R*,*S*)-methylpentadecanoic acid (**6**) was developed by utilizing the thiophene synthesis of long-chain fatty acids[7] as described in Scheme I. By the selection of substituents introduced into the 2- and 5-positions of the thiophene ring, a variety of 3-methyl-branched fatty acids of various chain lengths can be prepared. With use of this synthetic approach, 2-(6-phenylhexyl)thiophene (**3**) and 3(*R*,*S*)-methyl-4-carbomethoxybutanoyl chloride were subjected to Friedel–Crafts acylation to afford 2-(3(*R*,*S*)-methyl-1-oxo-4-carbomethoxybutyl)-5-(6-phenylhexyl)thiophene (**4**). The methyl ester **4** was then reduced under Wolff–Kishner (Huang–Minlon) conditions to give 2-(3(*R*,*S*)-methyl-4-carboxybutyl)-5-(6-phenylhexyl)thiophene (**5**). The pivotal step in this method involved the Raney nickel desulfurization and reduction of the acid **5** to yield the desired methyl-branched acid, 15-phenyl-3(*R*,*S*)-methylpentadecanoic acid (**6**).

Iodide was introduced (Scheme II) into the para position of the terminal phenyl ring of **6** via the HI decomposition of the 3,3-(1,5-pentanediyl)triazene derivative **11**. There are several advantages of this triazene decomposition reaction[8-15] in contrast to other methods available for the iodination of the phenyl ring. In the presence of HI the phenyltriazenes undergo decomposition to yield exclusively the *p*-iodophenyl products. Secondly, the reaction is rapid and generally proceeds in good yield (>50%) within 20 min at room temperature. An additional advantage is that this reaction can readily be adapted to the microscale, which

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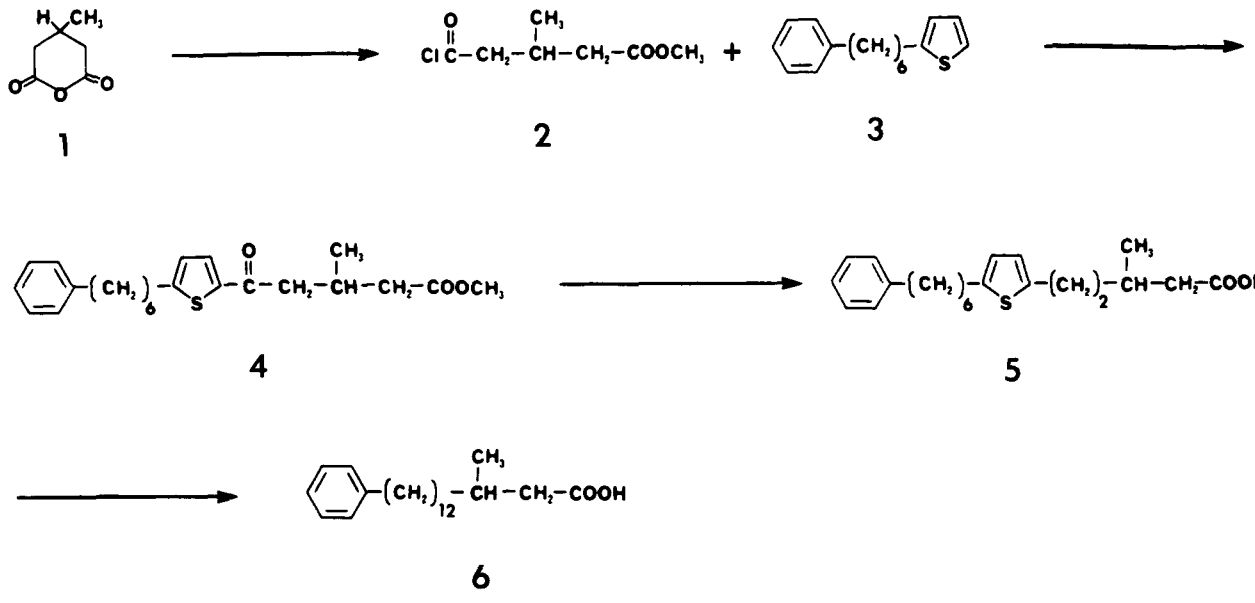
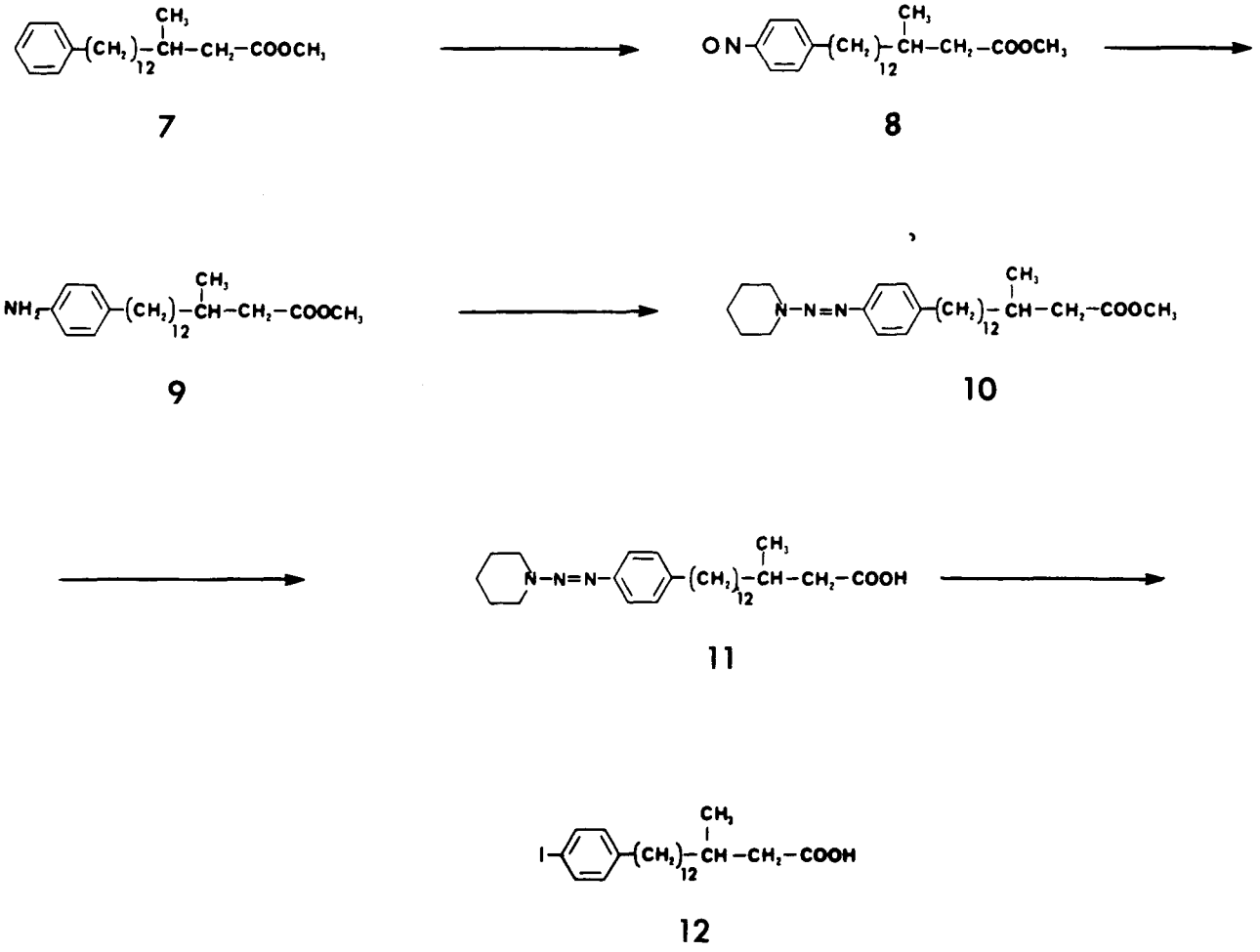
Scheme I



Scheme II



is important in the development of a radiopharmaceutical kit for the clinical preparation of high specific activity regiospecific radioiodinated products. Thus, this method appears to be superior to many classical iodination procedures,[16] including iodide displacement of the *p*-[bis(trifluoroacetoxy)thallium]phenyl substrates.[17,18] Generally, thallation of the phenyl moiety in a molecule containing functional groups such as a carboxylic acid[19] is slow at room temperature and requires reaction times greater

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than 24 h. Although the reaction times may be decreased by heating, thallation is a reversible reaction and substantial amounts of the more thermodynamically stable meta isomer may accumulate by an equilibrium process. The thallation method may, therefore, require high-pressure liquid chromatographic purification of the desired radioiodinated para isomer. A second disadvantage is the requirement for fresh preparation of the [bis(trifluoroacetoxy)thallium(III)]phenyl intermediate from highly corrosive reagents, which may be beyond the scope of many clinical facilities.

The key intermediate required for the regiospecific radioiodination of 15-phenyl-3(*R,S*)-methylpentadecanoic acid by the triazene route was 1-[4-(13(*R,S*)-methyl-14-carboxytetradecyl)phenyl]-3,3-(1,5-pentanediyl)triazene (**11**). The synthetic approach for the preparation of this triazene involved introduction of a nitroso group into the para position of the terminal phenyl group via aromatic thallation.[20] We selected aromatic thallation as a means of introducing a functionalized nitrogen group onto the phenyl group because of the regiospecificity and good yield for electrophilic substitution of the phenyl ring. In this synthetic approach, triazene compound **11** was prepared by the four-step sequence of reactions outlined in Scheme II. The methyl 15-phenyl-3(*R,S*)-methylpentadecanoate (**7**) was prepared by esterification of the corresponding free acid **6** with diazomethane. Aromatic thallation of the methyl ester **7** with thallium(III) trifluoroacetate in trifluoroacetic acid followed by treatment with nitrosyl chloride afforded methyl 15-(*p*-nitrosophenyl)-3(R,S)-methylpentadecanoate (**8**). Reduction of the nitroso compound **8** with $NaBH_4$ and 10% Pd/C in MeOH followed by column chromatographic purification gave pure methyl 15-(*p*-aminophenyl)-3(*R,S*)-methylpentadecanoate (**9**). Treatment of the aromatic amine **9** at 0 °C with nitrous acid followed by aqueous piperidine afforded 1-[4-(13-(*R,S*)-methyl-14-carbomethoxytetradecyl)phenyl]-3,3-(1,5-pentanediyl)triazene (**10**). Basic hydrolysis of the triazene methyl ester gave the desired triazene 1-[4-(13-(*R,S*)-methyl-14-carboxytetradecyl)phenyl]-3,3-(1,5-pentanediyl)triazene (**11**). The triazene **11** was rapidly converted to radiochemically pure radioiodinated 15-(*p*-iodophenyl)-3(*R,S*)-methylpentadecanoic acid (**12**) on a 22-μmol scale following filtration through a short silicic acid column.[21] The ^{123}I-labeled agent has been prepared, and excellent single photon tomographic images of the normal dog myocardium have been obtained,[21] indicating that this agent is an excellent candidate for potential testing in humans after studies in animals with normal and altered regional myocardial blood flow have been completed.

Experimental Section

General Methods. All chemicals and solvents were analytical grade and were used without further purification. Column chromatography was performed with acidic grade silicic acid, 60–200 mesh (Sigma Chemical Co.), and silica gel (Davison Chemical Co.). The melting points were determined in open capillary tubes on a Büchi SP apparatus and are uncorrected. The thin-layer chromatographic analyses (TLC) were performed on 250-μm thick layers of silica gel G PF-254 coated on glass plates (Analtech, Inc.). The low-resolution mass spectra (MS) were recorded on a Kratos MS-25 low-resolution instrument under the following conditions: ionizing energy, 70 eV; accelerating potential, 8000 V; trap current, 100 μA; probe temperature, 200–300 °C. The proton nuclear magnetic resonance spectra (^1H NMR) were obtained at 60 MHz with a Varian 360-A instrument or at 200 MHz with a Nicolet high-resolution instrument. Samples (30–40 mg) were dissolved in the solvents indicated and resonances are reported downfield (δ) from the internal tetramethylsilane standard. Elemental analyses were determined at Galbraith Laboratories, Knoxville, TN.

2-(3(*R,S*)-Methyl-1-oxo-4-carbomethoxybutyl)-5-(6-phenylhexyl)thiophene (4). A mixture of 3-methylglutaric anhydride (7.7 g, 0.06 mol) and MeOH (5 ml) was stirred at 100 °C for 90 min. The resulting clear, viscous oil was vacuum distilled (30 min, bath temperature at 30 °C) to remove the unreacted methanol. A solution of the crude half-ester and thionyl chloride (14.4 g, 0.122 mol) was then stirred at room temperature for 14 h. The resulting mixture was vacuum distilled (30 min, bath temperature at 80 °C) to remove the excess thionyl chloride. The pale yellow solution was cooled to room temperature to give 10.7 g (quantitative) of crude 3(*R,S*)-methyl-4-carbomethoxybutanoyl chloride (**2**). The crude acid chloride of the half-ester **2** (5.9 g, 0.033 mol) was added to a solution of 2-(6-phenylhexyl)thiophene[22] (**3**, 7.2 g, 0.03 mol) in 100 mL of CH_2Cl_2. The resulting mixture was cooled to 0 °C and anhydrous $SnCl_4$ (17.2 g, 0.066 mol) was added dropwise. The solution was allowed to warm to room temperature and stirring was continued for 16 h. The resulting purple mixture was then treated with 6 N HCl until a yellow solution was obtained. The CH_2Cl_2 layer was washed thoroughly with 10% HCl, H_2O, and 10% NaOH and dried over anhydrous Na_2SO_4. After evaporation of the CH_2Cl_2 in vacuo the crude product was chromatographed on silica gel. Elution with C_6H_6 gave 9.5 g (83%) of **4** as a colorless oil. A single component was observed on TLC (C_6H_6) R_f 0.20; MS, *m/z* (relative intensity) 386 (M^+, 75); ^1H NMR ($CDCl_3$) δ 1.07 (d, 3 H, J = 6 Hz, HCCH_3), 1.4 (m, 8 H, CH_2), 2.5 (m, 8 H, [PhCH_2, thienyl-CH_2, -CH_2C=O,-CH_2COOCH_3]), 3.67 (s, 3 H, -COOCH_3), 6.72 (d, 1 H, J = 4 Hz, Ar) 7.1 (s, 5 H, Ar), 7.5 (d, 1 H, J = 4 Hz, Ar. Anal. Calcd for $C_{23}H_{30}O_3S$: C, 71.50; H, 7.77. Found: C, 71.40; H, 7.93.

2-(3(*R,S*)-Methyl-4-carboxybutyl)-5-(6-phenylhexyl)-thiophene (5). The keto ester **4** (9.5 g, 0.025 mol) was suspended in 60 mL of diethylene glycol containing KOH (7.75 g, 0.138 mol) and 85% hydrazine hydrate (4.0 g, 0.08 mol) and the solution refluxed for 1 h. The resulting mixture was distilled until the liquid reached a temperature of 200 °C and then it was refluxed 3 h. The mixture was cooled to 90 °C, poured into 250 mL of H_2O, acidified to pH 2–3 with 12 N HCl, and extracted thoroughly with ether. The combined ether extracts were washed with H_2O (4 × 50 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed to give 8 g (90%) of the acid **5**: bp 195–200 °C (1.5 mm); a single component on TLC (4% CH_3OH–$CHCl_3$) R_f 0.50; ^1H NMR ($CDCl_3$) δ 1.0 (d, 3 H, J = 6 Hz, HCCH_3), 1.1 to 2.9 (m, 19 H), 6.45 (s, 2 H, Ar), 7.1 (s, 5 H, Ar). Anal. Calcd for $C_{22}H_{30}O_2S$: C, 73.70; H, 8.43. Found: C, 74.07; H, 8.51.

15-Phenyl-3(*R,S*)-methylpentadecanoic Acid (6). A suspension of Raney nickel (20 g) and the acid **5** (3.5 g, 0.01 mol) in a mixture of 100 mL of absolute ethanol and 200 mL of 10% sodium carbonate was vigorously stirred and heated under reflux for 16 h. The resulting hot solution was filtered and the filtrate was cooled to room temperature, cautiously acidified to pH 3 with 12 N HCl, and extracted with ether (3 × 100 mL). The combined ether extracts were washed with H_2O (4 × 100 mL) and dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. The crude product was dissolved in CH_2Cl_2 and chromatographed on silicic acid (acidic, 75 g) slurried in CH_2Cl_2. Elution with CH_2Cl_2 gave **6** in fractions 5–10 (2.2, 67%) as a white solid: mp 37–39 °C; a single component was detected by TLC (4% CH_3OH–$CHCl_3$) R_f 0.50; MS, *m/z* (relative intensity) 332 (M^+, 17); ^1H NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 6 Hz, HCCH_3), 1.27 (s, 22 H, -CH_2-), 2.17 (d, 2 H, J = 6 Hz, HCC$H_2$$CO_2$-), 2.57 (t, 2 H, J = 6 Hz, PhCH_2-), 7.17 (s, 5 H, Ar). Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.61; H, 10.33.

Methyl 15-Phenyl-3(*R,S*)-methylpentadecanoate (7). The acid **6** (2.00 g, 6 mmol) was added to an ether solution containing CH_2N_2, prepared from *N*-methyl-*N'*-nitrosoguanidine (MNNG). The resulting solution was stirred for 12 h at 0 °C and protected from light. The Et_2O solution was dried over anhydrous sodium sulfate and filtered and the ether removed to give an oil. The

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crude product was chromatographed on silicic acid (50 g). Elution with C_6H_6 (25 mL) gave **7** in fractions 6–9 (1.99 g, 96%) as a colorless oil: TLC (50% C_6H_6–hexane) R_f 0.45; MS, m/z (relative intensity) 346 (M^+, 10); ^1H NMR ($CDCl_3$) δ 0.9 (d, 3 H, J = 5 Hz, $HCCH_3$), 1.23 (s, 22 H, CH_2), 2.17 (d, 2 H, J = 6 Hz, $HCCH_2CO_2$-) 2.60 (t, 2 H, J = 6 Hz, $PhCH_2$-) 3.65 (s, 3 H, $COOCH_3$), 7.15 (s, 5 H, Ar). Anal. Calcd for $C_{23}H_{36}O_2$: C, 79.77; H, 10.98. Found: C, 80.00; H, 11.04.

Methyl 15-(*p*-Nitrosophenyl)-3(*R*,*S*)-methylpentadecanoate (8). The methyl ester **7** (1.6 g, 4.7 mmol) was added to a solution of trifluoroacetic acid (10 mL) containing thallium(III) trifluoroacetate (3.3 g, 6 mmol). The resulting mixture was protected from light and stirred at room temperature for 48 h. The resulting solution was vacuum distilled at 40 °C (0.6 mm) followed by several codistillations with 1,2-dichloroethane. The brown methyl 15-[*p*-[bis(trifluoroacetoxy)thallium]phenyl]-3(*R*,*S*)-methylpentadecanoate intermediate was used without further purification and added to a stirred mixture of CH_2Cl_2 (50 mL) and isoamyl nitrite (0.88 g, 7.5 mmol) under red lights. A solution of 12 N HCl (2 mL) and glacial acetic acid (3 mL) was added, and the reaction mixture was vigorously stirred for 10 min. After the addition of 1 N HCl (30 mL), the mixture was stirred an additional 10 min and filtered through Celite and the green colored CH_2Cl_2 layer separated. The CH_2Cl_2 extract was washed several times with 0.1 N HCl and water and dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo to leave a green colored oil. The resulting oil was chromatographed on silicic acid (75 g), slurried in 50% benzene–hexane. Fractions 25 mL in volume were eluted with 50% benzene–hexane. Fractions 18–31 were combined to give 800 mg (46%) of compound **8** as a green liquid. Analysis by TLC (50% benzene–hexane) indicated the presence of a single component: R_f 0.23; MS, m/z (relative intensity) 375 (M^+, 10); ^1H NMR ($CDCl_3$) δ 0.95 (d, 3 H, J = 6 Hz, $HCCH_3$), 1.27 (s, 22 H, $-CH_2-$), 2.17 (d, 2 H, J = 6 Hz, $HCCH_2CO_2$-), 2.75 (t, 2 H, J = 6 Hz, $PhCH_2$-), 3.70 (s, 3 H, $-CO_2CH_3$), 7.65 (AA'BB', 4 H, J = 18 Hz, Ar). Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.78; H, 9.77; N, 3.70.

Methyl 15-(*p*-Aminophenyl)-3(*R*,*S*)-methylpentadecanoate (9). A suspension of the nitroso intermediate **8** (375 mg, 1 mmol) and 10% palladium on charcoal (50 mg) was stirred in MeOH (10 mL) at room temperature under argon. Sodium borohydride ($NaBH_4$; 120 mg, 3 mmol) in MeOH (5 mL) was added with the aid of a syringe. The resulting mixture was stirred 30 min, filtered, added to H_2O (100 mL), and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with H_2O and dried over anhydrous Na_2SO_4, and the $CHCl_3$ was evaporated to yield an orange oil. The crude amine was applied to a silica gel column (25 g) slurried in $CHCl_3$. Fractions were eluted with $CHCl_3$ (10 mL). Fractions 16–23 (323 mg, 90%) were combined to give compound **9** as a yellow oil: TLC (C_6H_6) R_f 0.18; MS, m/z (relative intensity) 361 (M^+, 39); ^1H NMR ($CDCl_3$) δ 0.9 (d, 3 H, J = 6 Hz, $HCCH_3$), 1.25 (s, 22 H, CH_2), 2.17 (d, 2 H, J = 6 Hz, $HCCH_2CO_2$-), 2.5 (t, 2 H, J = 6 Hz, $PhCH_2$-), 3.6 (s, 3 H, $-COOCH_3$), 6.8 (AA'BB', 4 H, J = 14 Hz, Ar). Anal. Calcd for $C_{23}H_{39}NO_2$: C, 76.40, H, 10.87, N, 3.87. Found: C, 76.42; H, 10.70; N, 3.82.

1-[4-(13(*R*,*S*)-Methyl-14-carbomethoxytetradecyl)phenyl]-3,3-(1,5-pentanediyl)triazene (10). The amine **9** (180 mg, 0.5 mmol) was suspended in 2 mL of 0.5 N HCl and the mixture cooled to 0–5 °C. Sodium nitrite (35 mg, 0.5 mmole) in H_2O (1 mL) was added dropwise and the solution stirred for 5 min at 0–5 °C. Piperidine (200 mg, 2.25 mmol) in H_2O (1 ml) was added while maintaining the temperature of the reaction mixture at 0–5 °C for 20 min, and the mixture was poured into H_2O (25 mL) and extracted with $CHCl_3$ (2 × 25 mL). The $CHCl_3$ extracts were washed with H_2O (3 × 25 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The crude triazene was chromatographed on silica gel (25 g), slurried in benzene. Fractions (25 mL) were eluted with benzene. Fractions 7–11 were combined to give 140 mg (62%) of compound **10** as a yellow oil: TLC (C_6H_6) R_f 0.45; ^1H NMR ($CDCl_3$) δ 0.90 (d, 3 H, J = 6 Hz, $HCCH_3$), 1.27 (s, 22 H, CH_2), 1.67 (s, 6 H, piperidinyl $(CH_2)_3$-), 2.17 (d, 2 H, J = 6 Hz, $HCCH_2CO_2$-), 2.57 (t, 2 H, J = 6 Hz, $PhCH_2$-), 3.67 (s, 3 H, $-COOCH_3$), 3.77 (m, 4 H, piperidinyl CH_2NCH_2-), and 7.30 (AA'BB', 4 H, J = 8 Hz, Ar). Anal. Calcd for $C_{28}H_{47}N_3O_2$: C, 73.48; H, 10.35; N, 9.18. Found: C, 73.39; H, 10.32; N, 9.08.

1-[4-(13(*R*,*S*)-Methyl-14-carboxytetradecyl)phenyl]-3,3-(1,5-pentanediyl)triazene (11). The methyl ester **10** (140 mg, 0.31 mmol) was refluxed for 60 min in EtOH (12 mL) containing 1 N NaOH (2 mL). After cooling, the solution was poured into H_2O (100 mL) and acidified to pH 3 with 1 N HCl. The resulting mixture was extracted with ethyl ether (2 × 50 mL), the ether extracts were washed with H_2O (3 × 50 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed to give a tan solid. Crystallization from MeOH–H_2O gave **11** (72 mg, 53%) as a light solid powder: mp 65–66 °C; TLC (4% MeOH–$CHCl_3$) R_f 0.40; MS, m/z (relative intensity) 332 ($M^+-C_5H_9N_3$, 10); ^1H NMR ($CDCl_3$) δ 1.00 (d, 3 H, J = 6 Hz, $HCCH_3$), 1.27 (s, 22 H, CH_2), 1.70 (s, 6 H, piperipidinyl $(CH_2)_3$-), 2.17 (d, 2 H, J = 6 Hz, $HCCH_2CO_2$-), 2.57 (t, 2 H, J = 6 Hz, $PhCH_2$-), 3.75 (m, 4 H, piperidinyl CH_2NCH_2-), 7.28 (AA'BB', 4 H, J = 8 Hz, Ar).

15-(*p*-Iodophenyl)-3(*R*,*S*)-methylpentadecanoic Acid (12). The triazene **11** (44 mg, 0.1 mmol) in acetone (1 mL) was added dropwise to a mixture of trifluoroacetic acid (45 mg, 0.4 mmol) and sodium iodide (15 mg, 0.1 mmol) stirred at 0–5 °C. The resulting solution was stirred for 15 min at 25 °C, diluted with H_2O (50 mL), and extracted with Et_2O (3 × 50 mL). The combined Et_2O extracts were washed with 10% $NaHSO_3$ (50 mL) and H_2O (3 × 50 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The resulting residue was crystallized from petroleum ether (30–60 °C) to yield 30 mg (65%) of compound **12**: mp 48–49 °C (lit. mp 47–49 °C).[6]

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Registry No. **1**, 4166-53-4; (±)-**2**, 90046-92-7; **3**, 88336-89-4; (±)-**4**, 90046-93-8; (±)-**5**, 88336-91-8; (±)-**6**, 88336-87-2; (±)-**7**, 88336-88-3; (±)-**8**, 90046-94-9; (±)-**9**, 90046-95-0; (±)-**10**, 90046-96-1; (±)-**11**, 90046-97-2; (±)-**12**, 88336-95-2; methyl 15-[*p*-[bis(trifluoroacetoxy)thallium]phenyl]-3(*R*,*S*)-methylpentadecanoate, 90046-98-3.