bromo sugar [prepared from 3.40 g (10 mmol) of 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinose] in CH_2Cl_2 (50 mL). The mixture was stirred for 7 days at room temperature, and then saturated $NaHCO_3$ solution (30 mL) was added. The mixture was filtered through a Celite pad, and the Celite was washed with CH_2Cl_2. The combined organic solutions were washed with $NaHCO_3$ solution and water, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed over a silica gel column using n-C_3H_{14}–EtOAc (3:2) as the eluent. The β-anomer (**3a**, R^1 = Ac) was obtained as the major product (1.82 g, 43%) as a syrup. This product slowly decomposed upon long standing at room temperature. The ^1H NMR data are given in Table II.

5(*E*)-(2-Bromovinyl)-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (4c). Compound **3c** (R^1 = H; 450 mg) was dissolved in saturated NH_3/MeOH (50 mL). After 24 h, the solvent was removed in vacuo, and the residue was triturated several times with Et_2O and CH_2Cl_2. The solid residue (contaminated with a minute amount of impurities) was chromatographed over a silica gel column using $CHCl_3$–MeOH (20:1, v/v) as the eluent. The major nucleoside fraction was concentrated to dryness, and the residue was triturated with Et_2O to crystallize the product **4c** (315 mg, 91%), mp 189–190 °C dec. The same compound **4c** was also obtained in a similar manner from **3c** (R′ = Ac).

In a similar manner, **4b**, mp 225–225.5 °C, and **4d**, mp 178–179 °C dec, were obtained from the corresponding protected nucleosides. For the ^1H NMR data of **4b–d**, see Table II. The 5-ethyluracil analogue (**4e**), mp 163–164 °C, was also prepared similarly from **3e**: ^1H NMR (Me_2SO-d_6) δ 1.03 (3 H, t, CH_2CH_3), 2.22 (2 H, q, CH_2Me), 3.70–3.78 (3 H, m, H-5′, H-5″), 4.23 (1 H, dq, H-3′, $J_{2',3'} = J_{3',4'} = 4.3$ Hz, $J_{3',F} = 18$ Hz), 5.07 (1 H, ddd, H-2′, $J_{1',2'} = J_{2',3'} = 4.3$ Hz, $J_{2',F} = 53.0$ Hz), 6.13 (1 H, dd, H-1′, $J_{1',2'} = 4.3$, $J_{1',F} = 14.0$ Hz), 7.57 (1 H, s, H-6), 11.43 (1 H, br s, NH).

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-vinyluracil (4a). Compound **3a** (1.8 g) was dissolved in NH_3/MeOH (150 mL), and the solution was left standing for 24 h at room temperature. After concentration of the mixture in vacuo, the residue was crystallized from EtOH to give pure **4a**: yield 650 mg (58%); mp 170 °C (sinter), 235–270 °C (dec). The ^1H NMR spectral data of **4a** are given in Table II.

Antiviral Activity. Antiviral activity was determined by the plaque-reduction assay.[2] Vero cell monolayers were infected with approximately 20–30 plaque-forming units (pfu) of HSV-1 (strain 2931) or HSV-2 (strain G) per well and incubated for 2 h. Maintenance media containing various concentrations of drugs were used to overlay the monolayers. When the plates were fully developed (2 days), the number of plaques were counted, and a linear regression was developed in order to calculate concentration of the drug required to reduce plaque formation by 50% (ED_{50}).

Cytotoxicity. Cytotoxicity was determined by the method reported previously[2,14] using normal, PHA-stimulated human lymphoblasts. The concentration of drug causing a 50% inhibition of replication (ID_{50}) was determined.

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Registry No. **1a**, 37107-81-6; **2a**, 55520-62-2; **2b**, 87782-42-1; **2c**, 73446-72-7; **2d**, 73446-76-1; **2e**, 31167-05-2; **3a** (R′ = Ac), 87782-45-4; **3b** (R′ = H), 87782-43-2; **3c** (R′ = H), 87782-40-9; **3c** (R′ = Ac), 87782-46-5; **3d** (R′ = H), 87782-44-3; **3e** (R′ = Ac), 87782-41-0; **4a**, 87782-49-8; **4b**, 87782-48-7; **4c**, 79637-79-9; **4d**, 87782-47-6; **4e**, 83546-42-3; 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranose, 84025-00-3; 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide, 56632-81-6.

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Synthesis and Evaluation of Radioiodinated (*E*)-18-Iodo-17-octadecenoic Acid as a Model Iodoalkenyl Fatty Acid for Myocardial Imaging

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^{125}I-labeled (*E*)-18-iodo-17-octadecenoic acid (**13**) has been prepared and evaluated in rats to determine the myocardial uptake and retention and degree of in vivo deiodination of this model iodivinyl-substituted fatty acid, which contains no structural perturbation to inhibit metabolism. This new agent was prepared by NaI–chloramine-T treatment of (17-carbomethoxyheptadec-1-en-1-yl)boronic acid (**11**) prepared by catecholborane treatment of methyl 17-octadecynoate (**10**), followed by basic hydrolysis to the free acid (**13**). The pivotal substrate, 17-octadecynoic acid (**9**), was prepared by two new routes. The ^{125}I-labeled acid **13** showed high myocardial uptake (1 h, 1.90–2.28% dose/g) with 45% washout after 2 h but lower heart/blood ratios in comparison to analogues containing the tellurium heteroatom. Deiodination was low for the first 2 h after injection (2 h, 61% dose/g). Excellent myocardial images were obtained in a dog with the ^{123}I-labeled agent.

The use of radioiodinated fatty acids for the evaluation of coronary artery disease is well established.[1] A variety of structurally modified long-chain fatty acids labeled with radioiodide are extracted by the myocardial tissue like normal plasma fatty acids, and the uptake and subsequent metabolism can be used to measure regional fatty acid metabolism. Iodine-123 is the most attractive single-photon radionuclide for labeling fatty acids because of the ease of iodine chemistry and the attractive properties of this isotope. These properties include an attractive 13-h half-life, which makes radiosynthesis, purification, and distribution of these agents feasible. In addition, the abundant 159-keV γ photon is in the optimal region for detection with Anger cameras, and single photon emission tomography with this radioisotope is feasible. We have recently described the stablization of radioiodide as a vinyl iodide on tellurium fatty acids,[2] and more recently, the

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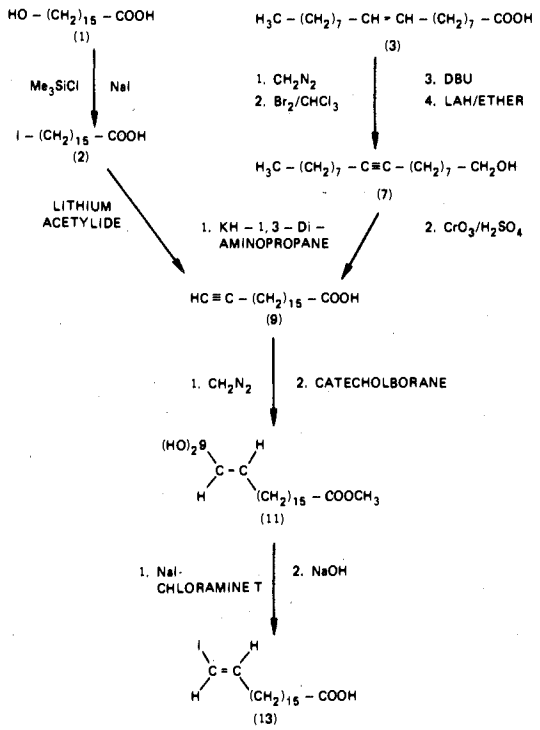
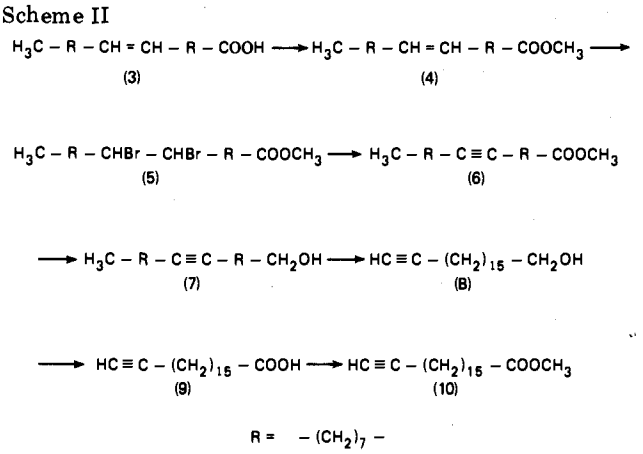
0022-2623/84/1827-0094$01.50/0

Scheme I



Scheme II



effect of tellurium position on the myocardial uptake of 18-[^{125}I]iodo-*n*-tellura-17-octadecenoic acid analogues has been studied.[3] The purpose of the present study was to develop a synthesis of 18-iodo-17-octadecenoic acid and to evaluate the biodistribution properties of the ^{125}I-labeled agent in rats. Comparison of the blood levels, myocardial uptake, and retention properties of this agent (**13**) with analogues containing tellurium in various positions of the fatty acid chain[3] has demonstrated the important role played by the tellurium heteroatom in targeting and "trapping" these agents in the myocardium.

Results and Discussion

Chemistry. The 17-octadecynoic acid (**9**) was prepared by two routes (Scheme I). In the first route, commercially available 16-hydroxyhexadecanoic acid (**1**; juniperic acid) was treated with Me_3SiCl and NaI in acetonitrile to yield the 16-iodohexadecanoic acid (**2**). Treatment with lithium acetylide in hexamethylphosphoramide (HMPA)[4] then gave 17-octadecynoic acid (**9**), which was esterified with CH_2N_2 to give the methyl ester (**10**). Esterification following the coupling reaction was required, since repeated attempts to couple lithium acetylide with methyl 16-iodohexadecanoate were unsuccessful. A second new route for the synthesis of **9** involved formation of 9-octadecyn-1-ol (**7**), followed by the series of transformations summarized in Scheme II. Following methylation of 9-octadecenoic acid (**3**), the ester **4** was treated with Br_2 to give dibromide **5**, which was then dehydrobrominated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give methyl 9-octadecynoate (**6**). Following reduction to the alcohol **7**, the acetylenic linkage was isomerized to the terminal position with KH and 1,3-diaminopropane.[5] The resulting alcohol **8** was then oxidized with CrO_3–H_2SO_4 to give 17-octadecynoic acid (**9**).

Formation of (*E*)-18-iodo-17-octadecenoic acid (**13**) was achieved by treatment of the boronic acid **11** with NaI–chloramine-T,[6] followed by basic hydrolysis of the ester **12**. The boronic acid **11** was prepared by catecholborane treatment of **10**. The methyl ester **10** was used since only low yields of the boronic acid were obtained with the free acid **9**. These studies have also demonstrated that reaction of catecholborane with acetylenic acids, such as **10**, must be conducted at <45 °C to eliminate concomitant reduction of the carbomethoxy group to give (17-hydroxyheptadec-1-en-1-yl)boronic acid.

Table I. Distribution of Radioactivity in Tissues of Female Fischer 344 Rats After Intravenous Administration of 18-[^{125}I]Iodo-17-octadecenoic Acid (13)

	Mean (range) percent injected dose/g tissue					
	Tissue					
Tissue	5 min	30 min	1 h	2 h	4 h	1 d
Heart	3.17 (2.11-3.73)	2.69 (2.40-3.08)	2.09 (1.90-2.28)	1.72 (1.30-2.36)	0.94 (0.67-1.17)	0.32 (0.27-0.37)
Blood	0.30 (0.21-0.42)	0.40 (0.35-0.44)	0.28 (0.26-0.29)	0.28 (0.22-0.31)	0.27 (0.24-0.29)	0.07 (0.06-0.08)
Lungs	1.02 (0.68-1.21)	1.03 (0.88-1.15)	0.82 (0.82-0.83)	0.90 (0.87-0.92)	0.85 (0.74-0.98)	0.59 (0.51-0.56)
Liver	8.65 (5.32-11.9)	7.81 (6.98-8.99)	4.83 (4.45-5.47)	4.04 (3.83-4.38)	3.08 (2.63-3.65)	0.60 (0.53-0.67)
Kidney	0.82 (0.53-0.94)	0.70 (0.61-0.79)	0.62 (0.59-0.66)	0.63 (0.58-0.67)	0.55 (0.50-0.64)	0.32 (0.31-0.34)
Thyroid	9.29 (6.36-10.8)	20.88 (18.3-24.9)	27.18 (18.9-24.9)	61.81 (45.1-73.5)	153 (264-416)	350 (264-416)
Mean Heart:Blood (Range)	10.6 (8.2-12.5)	6.7 (5.6-7.4)	7.6 (7.3-7.8)	6.6 (4.3-10.7)	3.5 (2.5-4.2)	4.8 (4.2-6.0)

Table II. Comparison of the Heart Uptake and Heart/Blood Ratios of 18-[^{125}I]Iodo-17-octadecenoic Acid ([^{125}I]13) and 18-[^{125}I]Iodo-*n*-tellura-17-octadecenoic Acid Analogues After Intravenous Administration to Female Fischer 344 Rats

	Mean heart, % dose/g (Mean heart:blood)	
[^{125}I] labeled agent[a]	5 min	120 min
18-Iodo-17-octadecenoic acid (13)	3.2 (11)	1.7 (8)
18-Iodo-5-tellura-17-octadecenoic acid	3.9 (37)	3.6 (20)
18-Iodo-7-tellura-17-octadecenoic acid	3.5 (13)	2.9 (12)
18-Iodo-9-tellura-17-octadecenoic acid	4.8 (21)	3.9 (9)
18-Iodo-11-tellura-17-octadecenoic acid	3.1 (7)	3.8 (5)
18-Iodo-13-tellura-17-octadecenoic acid	1.5 (10)	1.0 (1.5)

[a] Values for the 18-[^{125}I]iodo-*n*-tellura-17-octadecenoic acid analogues are taken from ref 3.

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Figure 1. Left anterior oblique γ camera image (500 ks^{-1}) of the myocardium of a dog 10 min after intravenous administration of 1.5 mCi of 18-[^{123}I]iodo-17-octadecenoic acid obtained with a Phogamma camera.

Biological Studies. The ^{125}I-labeled 18-iodo-17-octadecenoic acid was prepared in the same manner by treatment of **11** with Na^{125}I, followed by SiO_2 column purification and basic hydrolysis. The tissue distribution of 18-[^{125}I]iodo-17-octadecenoic acid was evaluated in female rats (Table I). In comparison with agents with Te in the alkyl chain, this agent shows similar initial heart uptake but more rapid washout with about 45% loss after 2 h. In addition, the heart/blood ratios (Table I) are considerably lower than observed with several analogues containing tellurium in the fatty acid chain (Table II). Significant in vivo deiodination did not occur until 2 h after injection (Table I), and excellent myocardial images were obtained in a dog with the ^{123}I-labeled agent (Figure 1).

Conclusion

These studies indicate that attachment of radioiodine on a fatty acid as a vinyl iodide moiety is an effective means of stabilizing the iodine and does not alter the initial pronounced myocardial uptake observed with terminal radioiodinated long-chain fatty acids. In addition, we have shown that the myocardial uptake and distribution properties of 18-[^{125}I]iodo-17-octadecenoic acid (**13**) are similar to analogues containing the Te heteroatom.[3] The 45% washout of **13** after 2 h, however, illustrates the unique role played by the Te heteroatom in retaining the modified fatty acids in the myocardium. Several of the Te analogues also show much lower blood levels (Table II). Further evaluation of the 18-[^{123}I]iodo-17-octadecenoic acid as a potential myocardial imaging agent should be pursued, since this agent can be readily radiolabeled in the final step of the synthesis and shows good properties in dogs.

Experimental Section

The 70-eV low-resolution mass spectra (MS), 60-MHz nuclear magnetic resonance spectra (NMR), and infrared spectra (IR) were determined as described earlier.[2] The melting points (mp) were determined in capillary tubes with a Buchi SP instrument and are uncorrected. For thin-layer chromatography (TLC), 250-μm thick layers of SiO_2 G PF-254 were used (Analtech, Inc.). The Na^{125}I was purchased from New England Nuclear, Inc. (North Billerica, MA). All chemicals and solvents were analytical grade and were used without further purification. The elemental analyses were determined at Galbraith Laboratories (Knoxville, TN). The analyses indicated were within ±0.4% of the theoretical values. The tissue distribution studies were performed in female Fischer 344 rats as previously described.[2] The ^{125}I- and ^{123}I-labeled fatty acids were formulated in 6% bovine serum albumin solution (10% EtOH) and filtered through a 0.22-μm Millipore filter and injected in a lateral tail vein.

16-Iodohexadecanoic Acid (2). A mixture of 16-hydroxyhexadecanoic acid (**1**; 1.36 g, 5 mmol), chlorotrimethylsilane (3.24 g, 15 mmol), and sodium iodide (3.00 g, 20 mmol) was heated for 90 min at 70 °C in 50 mL of acetonitrile. The mixture was cooled to room temperature, poured into 200 mL of 10% sodium thiosulfate, and extracted several times with Et_2O. The combined Et_2O extracts were washed thoroughly with 10% sodium thiosulfate 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 petroleum ether (30–60 °C) to afford 1.85 g (97%) of **2**: mp 74–75 °C (lit.[4] 74–74.5 °C). Analysis by TLC (SiO_2–GF) in MeOH–$CHCl_3$ (8:92) indicated the presence of a single component (R_f 0.60): NMR ($CDCl_3$) δ 1.25 (s, 26 H, CH_2), 2.25 (t, J = 6 Hz, 2 H, $CH_2C{=}O$, 3.10 (t, J = 7 Hz, 2 H, CH_2I).

Methyl 9-Octadecynoate (6). Oleic acid (**3**; 28.2 g, 100 mmol) was treated in ether with excess diazomethane generated from *N*-methyl-*N'*-nitrosoguanidine (MNNG). The solution was stirred for 2 h at room temperature, and the solvent was evaporated to give methyl 9-octadecenoate (29.6 g) in quantitative yield. The ester (29.6 g, 100 mmol) was dissolved in $CHCl_3$ (50 mL), and the solution was cooled in an ice bath. A solution of Br_2 (16 g, 100 mmol) in $CHCl_3$ was added slowly, and the solvent was removed in vacuo from the orange-colored solution to give methyl dibromooctadecanoate (**5**; 45.6 g, 100%). The dibromide (18.2 g, 40 mmol) was treated under nitrogen with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 24 g, 160 mmol). The mixture was heated to 140 °C for 12 h, cooled, and, after the addition of H_2O (150 mL), extracted with petroleum ether. The organic extract was washed with dilute HCl (100 mL), H_2O, and saturated NaCl solution. Removal of the solvent gave 11.1 g (95%) of methyl 9-octadecynoate (**6**): NMR ($CDCl_3$) δ 0.85 (m, 3 H, CH_3), 1.23 (CH_2 envelope, 24 H), 2.03 (m, 6 H, $CH_2C{\equiv}CCH_2$ and CH_2COOCH_3), 3.53 (s, 3 H, $COOCH_3$).

17-Octadecynoic Acid (9). Method A. Lithium acetylide–ethylenediamine (1.86 g, 20 mmol) and dry hexamethylphosphoramide (HMPA, 10 mL) were stirred at room temperature under an argon atmosphere for 45 min.[4] The resulting slurry was cooled to 0 °C, and a mixture of 16-iodohexadecanoic acid (**2**; 1.91 g, 5 mmol) in 5 mL of argon-purged HMPA was added dropwise. The resulting solution was stirred at 0 °C for 30 min, poured into crushed ice (50 g), acidified with 5 N H_2SO_4, and extracted several times with Et_2O. The combined ether extracts were washed thoroughly with H_2O and then dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The crude product was crystallized from petroleum ether (30–60 °C) to yield 1.10 g (79%) of **9**: mp 64–65 °C; IR (KBr) 3280 (C≡CH), 3000 (OH), 2900, 2850 (CH), 1700 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (s, 28 H, CH_2), 1.9 (m, 1 H, C≡CH), 2.33 (t, J = 6 Hz, 2 H, CH_2COO); MS, m/z 280 (M^+, O), 255 [$M^+ - (CH_2)_{15}COOH$, 20]. Anal. ($C_{17}H_{32}O_2$) C, H.

Method B. Methyl 9-octadecynoate (**6**; 8.82 g, 30 mmol) was dissolved in ether (100 mL), and the solution was added slowly to a slurry of LAH (1.14 g, 30 mmol) in ether (100 mL) at 0 °C under nitrogen. After the solution was stirred for 4 h, H_2O (1.14 mL) was cautiously added, followed by 15% NaOH (1.14 mL) and additional H_2O (2.3 mL). The mixture was filtered through Celite and then dried over Na_2SO_4, and the solvent was removed in vacuo. The crude 9-octadecyn-1-ol (**7**) was purified by column chromatography (SiO_2) by elution with CH_2Cl_2 to give 5.7 g (71%): NMR ($CDCl_3$) δ 0.84 (t, J = 6 Hz, 3 H, CH_3), 1.20 (CH_2 envelope, 26 H), 2.03 (m, 4 H, $CH_2C{\equiv}CH_2$), 3.33 (t, J = 6 Hz, 2 H, CH_2OH).

The alcohol **7** (5.32 g, 20 mmol) was added to a suspension of KH in 1,3-diaminopropane (100 mL) under nitrogen. The KH was obtained by washing 15 mL of a KH–paraffin suspension with 5 aliquots (30 mL) of petroleum ether under nitrogen prior to the addition of the diamine. The KH–diamine mixture was stirred at 0 °C for 1 h prior to use. The KH–alkynol mixture was stirred at room temperature for 2.5 h at 40–50 °C. The mixture was cooled to 0 °C, and H_2O (25 mL) was then added, and the crude product was extracted in ether. The organic layer was acidified with 30% HCl, washed with H_2O, and dried over $MgSO_4$ and the solvent was evaporated. The purified 17-octadecyn-1-ol (**8**; 2.8 g, 53%) was obtained by column chromatography (SiO_2) using ethyl acetate/petroleum ether (30:70): NMR ($CDCl_3$) δ 1.25 (CH_2 envelope, 28 H), 1.87 (m, 3 H, $HC{\equiv}CCH_2$) 2.35 (br s, 1 H, OH), 3.57 (t, J = 6 Hz, 2 H, CH_2OH).

The alcohol **8** (2.7 g, 10 mmol) was oxidized in 30 mL of acetone by treatment with 36 mL of the oxidizing agent prepared by the addition of 26.7 g of CrO_3 to 23 mL of H_2SO_4, followed by dilution to 100 mL with H_2O. The oxidation mixture was stirred at 10 °C for 16 h, poured into H_2O, and extracted with dilute NaOH. The aqueous extract was acidified with HCl, and the precipitate was filtered, washed with H_2O, and dried to give 1.7 g (60%) of crude 17-octadecynoic acid (**9**).

Methyl 17-Octadecynoate (10). Method A. The acid **9** (250 mg, 0.9 mmol) was added to an ether solution (50 mL) containing CH_2N_2, prepared from *N*-methyl-*N'*-nitrosoguanidine (MNNG,

500 mg). The mixture was stirred at 0 °C under red lights for 10 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 (30 g) column slurried in C_6H_6. Fractions (25 mL in volume) were eluted with C_6H_6. Fractions 4–6 were combined to afford methyl 17-octadecynoate (**10**; 230 mg, 88%) as a colorless oil. Analysis by TLC (SiO_2-GF) in C_6H_6 (R_f 0.60) indicated the presence of a single component: IR (NaCl) 3300 (C≡CH), 2920, 2860 (CH), 1745 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (s, 26 H, CH_2), 1.9 (m, 1 H, C≡CH), 2.30 (m, 4 H, CH_2COO and C≡CCH_2), 3.66 (s, 3 H, $COOCH_3$); MS, m/z 294 (M^+, 2), 263 (M^+ - HC≡$C(CH_2)_{16}CO$, 6). Anal. ($C_{18}H_{34}O_2$) C, H.

Method B. The crude acid **9** (1.7 g) was dissolved in excess MeOH and refluxed with H_2SO_4 (1 mL) for 18 h. The solvent was removed, and the crude product was extracted into ether and chromatographed on a SiO_2 column by elution with 10% EtOAc/petroleum ether (10:90) to give 1.51 g (85%) of methyl 17-octadecynoate (**10**), which was identical with **10** obtained by method A.

(17-Carbomethoxyheptadec-1-en-1-yl)boronic Acid (11). Catecholborane (1.64 mL, 15 mmol) was added to methyl 17-octadecynoate (**10**; 2.94 g, 10 mmol) at 0 °C under nitrogen. The mixture was then heated at ~40 °C for 6 h. Ice (10 g) was added, followed by cold H_2O (100 mL), and the mixture was stirred for 18 h. The precipitate was filtered, washed thoroughly with H_2O (500 mL) and C_6H_6 (100 mL), and dried to give 2.84 g (84%) of **11**: NMR (acetone-d_6/Me_2SO-d_6, 9:1) δ 1.30 (CH_2 envelope, 26 H), 2.16 (m, 4 H, C=CHC*H*$_2$ and C*H*$_2$COOCH_3), 3.54 (s, 3 H, COOCH_3), 5.30 (d, J = 18 Hz, 1 H, HC=C*H*B), 6.53 (m, 1 H, *H*C=CHB), 7.06 (s, OH). Anal. ($C_{18}H_{31}O_4$) C, H.

***(E)*-18-Iodo-17-octadecenoic Acid (13).** (17-Carbomethoxyheptadec-1-en-1-yl)boronic acid (**11**; 680 mg, 2 mmol) was dissolved in 10 mL of 50% aqueous THF. Aqueous NaI (2 mL of a 1 M solution) was added, and the mixture was cooled to 0 °C. After the addition of chloramine-T (0.91 g, 4 mmol in 8 mL of 50% aqueous THF), the mixture was stirred for 15 min. Water (25 mL) was then added, followed by petroleum ether (50 mL), and the mixture was filtered and washed again with petroleum ether. The combined organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated to give the crude product. Purification by preparative TLC on silica gel GF using EtOAc/petroleum ether (2:8) gave 670 mg (79%) of **12** as a thick oil: NMR ($CDCl_3$) δ 1.25 (CH_2 envelope, 26 H), 2.11 (br m, 4 H, C=CHC*H*$_2$ and C*H*$_2$COOCH_3), 3.58 (t, 3 H, $COOCH_3$), 5.81 (d, 1 H, HC=C*H*I), 6.41 (m, 1 H, *H*C=CHI). Anal. ($C_{18}H_{35}O_2I$) C, H.

Methyl 18-[^{125}I]Iodo-17-octadecenoate ([^{125}I]12). The boronic acid **11** was dissolved in 2 mL of an H_2O–THF mixture (1:1) under argon, and the mixture was cooled to 0 °C. After the addition of sodium [^{125}I]iodide (32 mCi, 15 mg, 0.1 mmol), chloramine-T (45 mg, 0.2 mmol) was added in 1 mL of H_2O–THF, and the resulting orange-colored mixture was stirred for 30 min to give a yellow-colored solution. The mixture was poured into 50 mL of Et_2O, washed once with 50 mL of 10% sodium bisulfite and then thoroughly with H_2O, and dried over anhydrous Na_2SO_4. The dried ether solution was concentrated by a stream of argon to give an oil, which was chromatographed on silicic acid by elution (25 mL fractions) with petroleum ether (30–60 °C) (fractions 1–10) and benzene (fractions 11–20). Fractions 12–14 were combined to give 12.1 mCi (38%) of ^{125}I-labeled **12**. The radiochemical and chemical purities were confirmed by TLC (SiO_2-GF) in benzene, R_f 0.50.

18-[^{125}I]Iodo-17-octadecenoic Acid ([^{125}I]13). Methyl 18-[^{125}I]iodo-17-octadecenoate ([^{125}I]**12**: 12.1 mCi) was dissolved in EtOH (10 mL) and refluxed with 1 N NaOH (2 mL) for 60 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 Et_2O was evaporated by a stream of argon to yield 9.43 mCi (79%) of [^{125}I]**13**. The chemical and radiochemical purity were confirmed by TLC (SiO_2-GF) in MeOH–$CHCl_3$ (4:96), R_f 0.40.

18-[^{123}I]Iodo-17-octadecenoic Acid ([^{123}I]13). The [^{123}I]**13** was prepared in the same manner as described above for the ^{125}I-labeled analogue using iodine-123 obtained in the generator/iodination ampule from the Brookhaven National Laboratory.[7]

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cis-4-[[[(2-Chloroethyl)nitrosoamino]carbonyl]methylamino]cyclohexanecarboxylic Acid, a Nitrosourea with Latent Activity against an Experimental Solid Tumor

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cis-4-[[[(2-Chloroethyl)nitrosoamino]carbonyl]methylamino]cyclohexanecarboxylic acid (*N*-Me-*cis*-CCCNU) was synthesized in five steps from *cis*-4-aminocyclohexanecarboxylic acid via an N-tosylated intermediate. *N*-Me-*cis*-CCCNU, which is incapable of the facile decomposition that characterizes the clinically useful nitrosoureas, effected a significant cure rate of both early and established murine Lewis lung carcinoma, even though its in vitro half-life was ~5.5 times that of the unmethylated parent compound. This is the first observation of latent activity of a nitrosourea against an experimental solid tumor.

The nitrosoureas that have attracted most clinical interest as anticancer agents[2] are characterized by a 2-chloroethyl group on the nitrosated nitrogen and monosubstitution on the other nitrogen. Abstraction of the remaining proton under physiological conditions initiates an easy decomposition into alkylating and carbamoylating species that accounts for the biological effects observed.[3-5]

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(2) BCNU (carmustine), CCNU (lomustine), MeCCNU (semustine), PCNU, chlorozotocin, RFCNU, and ACNU (nimustine). See ref 3–5.

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