Synthesis of ω-fluorinated octanoic acid and its β-substituted derivatives

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Abstract

Simple syntheses are described for the ω-fluorinated analogs of octanoic acid and its β-substituted derivatives in which insertion of a methyl and dimethyl group, and oxygen substitution at the C-3 position are involved, employing nucleophilic displacement with fluoride ion of the tosylate functions in the later stage of synthesis. The synthetic procedures offer easy and convenient access to the corresponding ^{18}F-labeled analogs using the readily available [^{18}F]fluoride ion.

Introduction

Octanoic acid, an eight-carbon saturated fatty acid, exists in only trace concentration in animal tissues as an intermediate metabolite in fatty acid metabolism. Recent studies with [1-^{14}C]octanoate have shown that it is rapidly extracted by brain and is metabolized in the brain primarily into pools of glutamate and glutamine, which properties present a striking contrast to long-chain fatty acids [1, 2]. Rowley and Collins have proposed the potential use of [1-^{14}C]octanoic acid as an autoradiographic fast functional marker of brain activity [3]. The purpose of this work was to develop octanoic acid analogs labeled with the positron emitting radionuclide fluorine-18 ($t_{1/2}$ = 109.6 min) which may offer an unique opportunity to visualize changes in functional brain activity by positron emission tomography in the living human. We therefore undertook the synthesis of terminally fluorinated octanoic acid and its structurally modified derivatives with methyl or dimethyl branching or with oxygen substitution at the C-3 position. Such structural modifications could change biological properties such as permeability to BBB and behavior in the metabolism, and lead to an interesting biological marker. Similar modifications have been successful in the development of modified long-chain fatty acids as trappable analogs in the myocardial tissues [4].

A wide variety of strategies is available for the preparation of ω-fluorinated fatty acids [5]. These include oxidation of ω-fluoroalcohols, hydrolysis of ω-fluoronitriles [6], fluoride exchange with halide [7], fluoride ion displacement

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through Friedel–Crafts acylation [8] and fluorinative dehydroxylation with Ishikawa's reagent [9]. Our interest in ^{18}F-radiopharmaceuticals required the limited synthetic route, in which late synthetic introduction of fluorine atom based on the fluoride ion displacement would be involved, for the potential production of these compounds in the ^{18}F-labeled form. Based on these criteria, our approach involved the preparation of the respective ω-hydroxy esters as the key intermediates.

Experimental

Unless stated otherwise, chemical reagents were obtained from commercial sources and were used without further purification. Melting points were measured with a Yanagimoto micro melting point apparatus and are reported uncorrected. The ^{1}H nuclear magnetic resonance spectra were measured in deuteriochloroform using a JEOL GX-270 (270 MHz) or JEOL PS-100 (100 MHz) spectrometer. ^{19}F NMR spectra were recorded with a Bruker AC-250P instrument (235.36 MHz) with $CFCl_3$ as an internal standard in deuteriochloroform. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Infrared (IR) spectra were taken on a JASCO IR Report-100 spectrometer and mass spectra were obtained with a JEOL JMS DX-300 or D-300 mass spectrometer. The elemental analyses were performed by the staff of the microanalytical section of Kyushu University. Analytical thin-layer chromatography (TLC) was carried out on Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm) and visualization was achieved by heating after spraying with a 10% ethanol solution of sodium phosphomolybdate. Column chromatography was undertaken using Merck Kieselgel 60 (70–230 mesh).

*Ethyl 8-hydroxy-2-octenoate (**1**) (nc)*

A solution of diisobutylaluminum hydride (1.5 M solution in toluene, 20 ml) was added under argon to a solution of 6-hexanolactone (2 ml, 18 mmol) in toluene (60 ml) at −78 °C over a period of 30 min, and the reaction mixture was stirred at the same temperature for an additional 2 h. In the meantime, a mineral oil dispersion of NaH (1.08 g, 27 mmol) was washed with toluene and suspended in benzene (45 ml), and triethyl phosphonoacetate (27 mmol, 5.4 ml) was added to this suspension at 5–10 °C over a period of 20 min, and the mixture stirred at room temperature for 30 min. The resulting solution was then added at −78 °C to a solution of the aldehyde in toluene as described above. The mixture was stirred at ambient temperature overnight and then quenched by the addition of H_2O. The precipitates were filtered off and washed with ether. The combined ether layer was washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude oil, which was chromatographed (hexane–ethyl acetate = 3:1 → 2:1) to give **1** as a colorless oil (3.2 g, 96%, containing a trace amount of the *Z* isomer). IR (neat): 3400, 1720 cm^{-1}. ^{1}H NMR

δ: 6.98 (1H, dt, J=16.0, 6.5 Hz); 5.80 (1H, dt, J=15.7, 1.3 Hz); 4.18 (2H, q, J=7.2 Hz); 3.62 (2H, t, J=4.4 Hz); 2.33–2.04 (3H, m); 1.67–1.35 (6H, m); 1.28 (3H, t, J=7.3 Hz). FDMS *m/z*: 186 (M^+); 168 ($M^+ - H_2O$).

Ethyl 8-hydroxyoctanoate (2) (nc)

To a suspension of 5% Pd–C (150 mg) in MeOH (20 ml) was added a solution of olefin **1** (2 g, 11 mmol) in MeOH (10 ml). The reaction mixture was stirred vigorously at room temperature for 5 h under an atmosphere of hydrogen. The catalyst was then removed by filtration and washed with ethyl acetate. The combined filtrates were concentrated under reduced pressure to give **2** (1.68 g, 81.2%) as a colorless oil, which was used for the next reaction without further purification. IR (neat): 3400; 1740 cm^{-1}. ^1H NMR δ: 4.13 (2H, q, J=7.2 Hz); 3.69 (2H, t, J=3.7 Hz); 2.30 (2H, t, J=6.6 Hz); 1.98–1.37 (11H, m); 1.25 (3H, t, J=7.2 Hz). EIMS *m/z*: 188 (M^+); 170 ($M^+ - H_2O$).

Ethyl 8-(tetrahydro-2H-pyran-2-yl)oxy-2-octenoate (3) (nc)

A solution of **1** (690 mg, 3.7 mmol) in dry dichloromethane (9 ml) containing *p*-toluenesulfonic acid (*p*-TsOH, 20 mg) was cooled in an ice bath. To this cold solution was added dihydropyran (1.01 ml, 11.1 mmol). The reaction mixture was stirred at room temperature for 2 h, and then, after dilution with ether, washed with saturated aq. $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–ethyl acetate (20:1 → 10:1) to give **3** (983 mg, 97%) as a colorless oil. IR (neat): 1720 cm^{-1}. ^1H NMR δ: 6.96 (1H, dt, J=15.7, 6.8 Hz); 5.81 (1H, dt, J=15.7, 1.7 Hz); 4.56 (1H, bs); 4.18 (2H, q, J=7.4 Hz); 3.98–3.69 (2H, m); 3.63–3.27 (2H, m); 2.43–2.04 (2H, m); 1.28 (3H, t, J=7.1 Hz); 1.92–1.41 (12H, m). FDMS *m/z*: 270 (M^+).

Ethyl 3-methyl-8-(tetrahydro-2H-pyran-2-yl)oxyoctanate (4) (nc)

Lithium dimethylcuprate was prepared by the addition of methyllithium (1.1 M ether solution, 4.2 ml) to a suspension of CuI (308 mg, 1.62 mmol) in dry ether at −25 to −30 °C followed by subsequent stirring for 15 min under argon. The unsaturated ester **3** (100 mg, 0.37 mmol) in dry ether (2 ml) was added to a stirred solution of the Me_2CuLi under argon at the same temperature. After being stirred for 2 h, the reaction was quenched by the addition of saturated aq. NH_4Cl (15 ml). The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with saturated aq NH_4Cl and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The product was purified by column chromatography on silica gel using hexane–ethyl acetate (15:1) to give **4** (72 mg, 68%) and the unreacted **3** (15 mg, 15%). Compound **4**: IR (neat): 1740 cm^{-1}. ^1H NMR δ: 4.56 (1H, bs); 4.13 (2H, q, J=7.1 Hz); 3.99–3.88 (2H, m); 3.85–3.26 (2H, m); 2.32 (1H, dd, J=13.6, 5.1 Hz); 2.08 (1H, dd, J=13.5, 7.1 Hz); 1.25 (3H, t, J=7.4 Hz); 1.94–1.33 (15H, m); 0.93 (3H, d, J=6.3 Hz). FDMS *m/z*: 286 (M^+).

Ethyl 8-hydroxy-3-methyloctanoate (5) (nc)

The THP ether **4** (361 mg, 1.26 mmol) was dissolved in MeOH (10 ml) containing a catalytic of *p*-TsOH, and the mixture stirred at room temperature for 2 h. The reaction mixture was diluted with dichloromethane, washed with saturated aq. $NaHCO_3$ and brine, and the organic layer dried ($MgSO_4$). Evaporation of the solvent gave a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate = 5:1 → 4:1) to give **5** as a colorless oil (227 mg, 90%). IR (neat): 1740 cm^{-1}. ^1H NMR δ: 4.13 (2H, q, J = 7.1 Hz); 3.64 (2H, t, J = 6.4 Hz); 2.31 (1H, dd, J = 14.2, 6.4 Hz); 2.09 (1H, dd, J = 14.2, 6.4 Hz); 2.35–1.98 (1H, m); 1.60 (1H, s, D_2O exchange); 1.26 (3H, t, J = 7.1 Hz); 1.63–1.20 (8H, m); 0.93 (3H, d, J = 6.4 Hz).

Methyl 3,3-dimethyl-5-hydroxypentanoate (7)

To a solution of 3,3-dimethyl-5-methoxycarbonyl butanoic acid (**6**) (2.2 g, 12.6 mmol) in dry THF (20 ml) was added 1 M BH_3–THF solution (15.2 mmol) at −20 °C under argon. The reaction mixture was stirred at ambient temperature. After 16 h, H_2O (5 ml) was added to the cooled mixture, which was then diluted with ether. The organic phase was separated and washed with saturated aq. $NaHCO_3$ and brine. The aqueous phase was extracted with ether. The combined organic extracts were dried (Na_2SO_4) and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–ethyl acetate (3:1) to give **7** (1.65 g, 82%) as a colorless oil. IR (neat): 3400; 1730 cm^{-1}. ^1H NMR δ: 3.74 (2H, t, J = 7.2 Hz); 3.67 (3H, s); 2.29 (3H, bs); 1.64 (2H, t, J = 7.2 Hz); 1.04 (6H, s).

Methyl 3,3-dimethyl-5-oxopentanoate (8) (nc)

Pyridinium chlorochromate (2.25 mmol, 487 mg) and Celite (1 g) were suspended in dichloromethane (20 ml) under argon and a solution of the alcohol **7** (300 mg, 1.9 mmol) in dichloromethane (10 ml) was added. After stirring for 3 h at room temperature, the precipitates were filtered off and washed with ether. The combined filtrates were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel using hexane–ethyl acetate (7:1 → 6:1) to give **8** (210 mg, 71%) as a colorless oil. IR (neat): 1730 cm^{-1}. ^1H NMR δ: 9.85 (1H, t, J = 2.4 Hz); 3.67 (3H, s); 2.50 (2H, d, J = 2.4 Hz); 2.40 (2H, s); 1.15 (6H, s).

Methyl 8-benzyloxy-3,3-dimethyl-5-octenoate (9) (nc)

To a stirred suspension of 3-benzyloxypropyl triphenylphosphonium bromide (440 mg, 0.9 mmol) in THF (5 ml) was added butyllithium (1.5 M in hexane, 0.6 ml) at 0 °C over a period of 15 min. The resulting dark red solution was stirred for an additional 30 min at 0 °C. A solution of the aldehyde **8** (0.91 mmol, 144 mg) in dry THF (3 ml) was added dropwise over a period of 20 min at 0 °C followed by stirring at room temperature overnight. The reaction mixture was diluted with ether, then washed successively with saturated aq. $NaHCO_3$, H_2O and brine. The organic phase was

dried ($MgSO_4$). Evaporation of the solvent gave a crude oil, which was chromatographed on silica gel (hexane–ethyl acetate = 15:1) to give **9** as a colorless oil (181 mg, 70%; *E,Z* mixture). IR (neat): 1740 cm^{-1}. ^1H NMR δ: 7.35–7.32 (5H, m); 5.56–5.45 (2H, m); 4.52 (2H, s); 3.64 (3H, s); 3.48 (2H, t, J = 6.9 Hz); 2.41–2.34 (2H, m); 2.21 (2H, s); 2.09 (2H, d, J = 5.9 Hz); 1.00 (6H, s). FDMS *m/z*: 290 (M^+).

*Methyl 8-hydroxy-3,3-dimethyloctanoate (**11**) (nc)*

A solution of **9** (355 mg, 1.22 mmol) in MeOH (10 ml) was hydrogenated over 5% Pd–C (120 mg). The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The product was purified by column chromatography on silica gel (hexane–ethyl acetate = 15:1 → 3:1) to give **11** (61 mg, 25%) and methyl 8-benzyloxy-3,3-dimethyloctanoate **10** (245 mg, 70%). The latter compound was further hydrogenated over 5% Pd–C in acetic acid to give **11** in near-quantitative yield, after workup as described above.

Compound **11**: IR (neat): 3400; 1740 cm^{-1}. ^1H NMR δ: 3.64 (3H, s); 3.64 (2H, t, J = 5.6 Hz); 2.20 (2H, s); 1.79 (1H, bs, D_2O exchange); 1.75–1.31 (8H, m); 0.98 (6H, s). EIMS *m/z*: 171 ($M^+ - OMe$).

Compound **10**: ^1H NMR δ:7.28 (5H, s); 4.50 (2H, s); 3.64 (3H, s); 3.46 (2H, t, J = 6.0 Hz); 2.19 (2H, s); 1.61–1.10 (8H, m); 0.97 (6H, s).

t-*Butyl 3-oxa-8-(tetrahydro-2H-pyran-2-yl)oxy-octanoate (**13**) (nc)*

To a solution of 1,5-pentanediol (2 ml, 19.1 mmol) in dry dichloromethane (7 ml) containing a catalytic amount of *p*-TsOH was added dropwise a solution of dihydropyran (0.8 ml, 9 mmol) in dry dichloromethane (50 ml) over 1 h. After stirring for 1 h, additional dihydropyran (0.8 ml, 9 mmol) in dry dichloromethane (50 ml) was added to the mixture over 1 h. After stirring for 2 h, the reaction mixture was washed with saturated aq. $NaHCO_3$ and brine, and the organic phase dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (3:1 → 2:1) to give mono-THP ether **12** (2.06 g, 58%) as a colorless oil. IR (neat): 3400 cm^{-1}. ^1H NMR δ: 4.58 (1H, bs); 3.94–3.32 (4H, m); 2.09–1.37 (14 H, m); 1.91 (1H, bs, D_2O exchange).

To a stirred solution of mono-THP ether **12** (916 mg, 4.87 mmol) and t-butyl bromoacetate (4.0 ml, 24.4 mmol) in dichloromethane (10 ml) were added 50% aqueous NaOH (20 ml) and tetrabutylammonium hydrogen sulfate (1.65 g, 4.87 mmol) at room temperature, the mixture being stirred vigorously at the same temperature for 12 h. The reaction mixture was diluted with water, and then extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (8:1 → 7:1) to give **13** (1.14 g, 77%) as a colorless oil. IR (neat): 1740 cm^{-1}. ^1H NMR δ: 4.56 (1H, bs); 3.94 (2H, s); 3.86–3.64 (2H, m); 3.59–3.27 (4H, m); 1.48 (9H, s); 1.76–1.26 (12H, m). FDMS *m/z*: 303 (MH^+); 245 ($M^+ - C_4H_9$).

*t-Butyl 8-hydroxy-3-oxaoctanoate (**14**) (nc)*

The THP ether **13** (364 mg, 1.26 mmol) was reacted with a catalytic amount of p-TsOH in MeOH (10 ml). Column chromatography on silica gel (hexane–ethyl acetate = 5:1) gave **14** (306 mg, 61%) and **15** (41 mg, 12%).

Compound **14**: IR (neat): 3400; 1750 cm^{-1}. ^1H NMR δ: 3.95 (2H, s); 3.59 (2H, t, J = 6.1 Hz); 3.52 (2H, t, J = 6.4 Hz); 1.48 (9H, s); 1.94–1.40 (7H, m). EIMS *m/z*: 219 ((MH^+); 161 ($M^+ - C_4H_9$).

Compound **15**: ^1H NMR δ:4.07 (2H, s); 3.75 (3H, s); 3.43–3.64 (4H, bt); 1.53 (7H, bs).

*Ethyl 8-(p-toluenesulfonyloxy)octanoate (**16**) (nc)*

To a solution of the alcohol **2** (300 mg, 1.6 mmol) in dichloromethane (10 ml) was added pyridine (0.3 ml, 3.2 mmol) and *p*-toluenesulfonyl chloride (p-TsCl, 1.9 mmol, 366 mg). The reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with ether, and washed with H_2O and brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was chromatographed on silica gel using a mixture of hexane and ethyl acetate (6:1 → 5:1) as eluant to give **16** (504 mg, 97%) as a colorless oil. IR (neat): 1735; 1360, 1190 cm^{-1}. ^1H NMR δ: 7.81 (2H, d, J = 8.3 Hz); 7.35 (2H, d, J = 8.0 Hz); 4.13 (2H, q, J = 7.2 Hz); 4.02 (2H, t, J = 6.1 Hz); 2.45 (3H, s); 2.26 (2H, t, J = 6.8 Hz); 1.25 (3H, t, J = 7.0 Hz); 1.74–1.28 (10H, m). EIMS *m/z*: 342 (M^+).

*Ethyl 3-methyl-8-(p-toluenesulfonyloxy)octanoate (**17**) (nc)*

The alcohol **5** (37 mg, 0.18 mmol) was reacted with p-TsCl (52 mg, 0.27 mmol) in a mixture of CH_2Cl_2 (1 ml) and pyridine (0.03 ml) for 12 h, after similar workup as described for **16**, to give **17** (56 mg, 87%) as a colorless oil. IR (neat): 1735; 1360; 1190 cm^{-1}. ^1H NMR δ: 7.79 (2H, d, J = 8.6 Hz); 7.34 (2H, d, J = 8.0 Hz); 4.16 (2H, t, J = 7.3 Hz); 4.05 (2H, q, J = 7.1 Hz); 2.45 (3H, s); 2.27 (1H, dd, J = 14.2, 6.4 Hz); 2.06 (1H, dd, J = 14.2, 7.1 Hz); 1.25 (3H, t, J = 7.1 Hz); 1.97–1.90 (1H, m); 1.70–1.18 (8H, m); 0.898 (3H, d, J = 6.6 Hz). FDMS *m/z*: 356 (M^+).

*Ethyl 3,3-dimethyl-8-(p-toluenesulfonyloxy)octanoate (**18**) (nc)*

The alcohol **11** (53 mg, 0.25 mmol) was reacted with p-TsCl (57 mg, 0.29 mmol) in a mixture of CH_2Cl_2 (2 ml) and pyridine (0.06 ml) for 12 h, after similar workup as described for **16** to give **18** (88 mg, 99%) as a colorless oil. IR (neat): 1740; 1360; 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.80 (2H, d, J = 8.3 Hz); 7.34 (2H, d, J = 8.3 Hz); 4.03 (2H, t, J = 6.3 Hz); 3.64 (3H, s); 2.45 (3H, s); 2.16 (2H, s); 1.55–1.18 (8H, m); 0.95 (6H, s). EIMS *m/z*: 356 (M^+). FAB HRMS *m/z*: 357.1758 calcd. for $C_{18}H_{29}O_5S$. Found: 357.1747.

*t-Butyl 3-oxa-8-(p-toluenesulfonyloxy)octanoate (**19**) (nc)*

The alcohol **14** (22 mg, 0.10 mmol) was reacted for 12 h with p-TsCl (35 mg, 0.29 mmol) in a mixture of CH_2Cl_2 (1 ml) and pyridine (0.02 ml),

after similar workup as described for **16**, to give **19** (36 mg, 96%) as a colorless oil. IR (neat): 1740; 1360; 1190 cm^{-1}. ^1H NMR δ: 7.79 (2H, d, $J=8.3$ Hz); 7.34 (2H, d, $J=7.9$ Hz); 4.02 (2H, t, $J=6.3$ Hz); 3.46 (2H, t, $J=6.0$ Hz); 2.45 (3H, s); 1.47 (9H, s); 1.85–1.38 (6H, m). FDMS *m/z*: 373 (MH^+).

*8-Fluorooctanoic acid (**24**)*

To a solution of the tosylate **16** (37 mg, 0.11 mmol) in dry THF (2 ml) was added n-Bu_4NF (1 M in THF solution, 0.43 mmol) under argon. The mixture was stirred at room temperature for 2.5 h and concentrated under reduced pressure. The residue was chromatographed on silica gel using hexane–ethyl acetate (8:1) to give the ester **20** (20 mg, 90%) as a colorless oil. IR (neat): 1730 cm^{-1}. ^1H NMR δ: 4.43 (2H, dt, $J=47.5$, 6.1 Hz); 4.09 (2H, q, $J=7.1$ Hz); 2.3 (2H, t, $J=7.6$ Hz); 1.89–1.34 (10H, m); 1.26 (3H, t, $J=7.2$ Hz). EIMS *m/z*: 190 (M^+). Analysis: calcd. for $C_{10}H_{19}O_2F$: C, 63.13; H, 10.07%. Found: C, 62.93; H, 9.96%.

To a solution of ethyl 8-fluorooctanoate **20** (109 mg, 0.57 mmol) in MeOH (2 ml) was added 10 N aqueous KOH (2 ml), and the mixture was stirred for 30 min at room temperature. The mixture was neutralized with 5% H_2SO_4 and was extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using $CHCl_3$ to give **24** [10] (0.51 mmol, 90%) as colorless needles, m.p. 32 °C). IR (neat): 3200; 1700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 6.92–6.27 (1H, b, D_2O exchange); 4.44 (2H, dt, $J=47.6$, 6.1 Hz); 2.36 (2H, t, $J=7.6$ Hz); 1.99–1.18 (10H, m). FDMS *m/z*: 163 (MH^+).

*8-Fluoro-3-methyloctanoic acid (**25**) (nc)*

The tosylate **17** (98 mg, 0.28 mmol) was reacted with n-Bu_4NF (1 M THF solution, 0.83 mmol) in THF (2 ml) for 1.5 h at room temperature, according to the similar procedure described for the synthesis of **20**, to give ethyl 8-fluoro-3-methyloctanoate (**21**) (51 mg, 90%) as a colorless oil. IR (neat): 1740; 1460; 1375 cm^{-1}. ^1H NMR δ: 4.43 (2H, dt, $J=47.3$, 6.2 Hz); 4.11 (2H, q, $J=7.1$ Hz); 2.27 (1H, dd, $J=14.5$, 6.1 Hz); 2.08 (1H, dd, $J=14.5$, 7.9 Hz); 2.04–1.94 (1H, m); 1.72–1.62 (2H, dm, $J=25.0$ Hz); 1.38–1.18 (6H, m); 1.23 (3H, t, $J=7.2$ Hz); 0.91 (3H, d, $J=6.6$ Hz). ^{19}F NMR δ: -166.38 (tt, $J=47.3$, 25.0 Hz). EIMS *m/z*: 184 (M^+-HF); 159 ($M^+-OC_2H_5$). Analysis: calcd. for $C_{11}H_{21}O_2F$: C, 64.53; H, 10.36%. Found: C, 64.53; H, 10.42%.

The ester **21** (39 mg, 0.19 mmol) was treated with 1 N aqueous KOH (2 ml) in MeOH (1 ml) for 10 min according to the procedure for **24** to give **25** (32 mg, 96%) as a colorless oil. IR (neat): 3200; 1740; 1460; 1375 cm^{-1}. ^1H NMR δ: 9.69 (1H, bs, D_2O exchange); 4.44 (2H, dt, $J=47.6$, 6.1 Hz); 2.37 (1H, dd, $J=14.5$, 6.2 Hz); 2.30 (1H, dd, $J=15.4$, 7.1 Hz); 2.03–1.17 (9H, m); 0.97 (3H, d, $J=6.3$ Hz). EIMS *m/z*: 161 (M^+-CH_3); 156 (M^+-HF).

*8-Fluoro-3,3-dimethyloctanoic acid (**26**) (nc)*

The tosylate **18** (55 mg, 0.15 mmol) was reacted with n-Bu_4NF (1 M THF solution, 0.28 mmol) in THF (3 ml) for 4 h at room temperature, according to the similar procedure described for the synthesis of **20**, to give ethyl 8-fluoro-3,3-dimethyl octanoate (**22**) (25 mg, 81%) as a colorless oil. IR (neat): 1740; 1390; 1370 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.44 (2H, dt, $J=47.5$, 5.9 Hz); 3.65 (3H, s); 2.20 (2H, s); 1.84–1.12 (8H, m); 0.99 (6H, s). EIMS *m/z*: 205 (MH^+); 189 ($M^+ - CH_3$).

The ester **22** (17 mg, 0.08 mmol) was hydrolyzed with 5 N aqueous KOH (0.5 ml) in MeOH (0.5 ml) for 15 min according to the same procedure as for **24** to give **26** (13 mg, 82%) as a colorless oil. IR (neat): 3200; 1700; 1460; 1375 cm^{-1}. ^1H NMR δ: 4.44 (2H, dt, $J=47.6$, 6.1 Hz); 2.23 (2H, s); 1.02 (6H, s); 1.84–1.26 (8H, m). EIMS *m/z*: 175 ($M^+ - CH_3$).

*8-Fluoro-3-oxaoctanoic acid (**27**) (nc)*

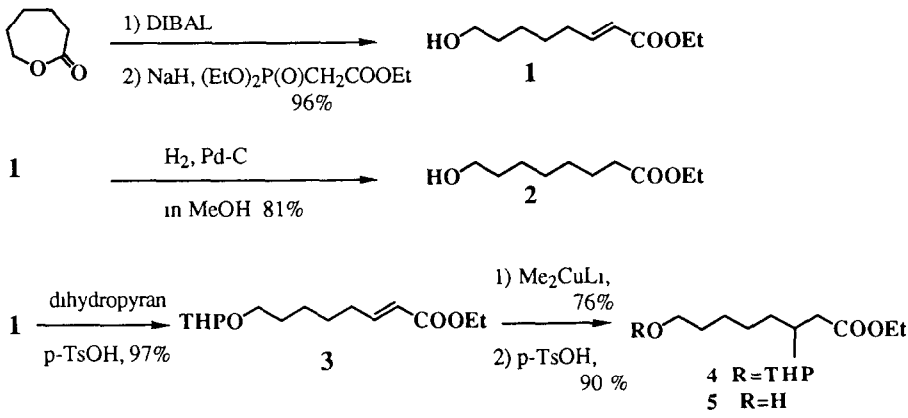
The tosylate **19** (50 mg, 0.13 mmol) was reacted with n-Bu_4NF (1 M THF solution, 0.54 mmol) in THF (2 ml) for 3 h at room temperature, according to the similar procedure described for the synthesis of **20**, to give t-butyl 8-fluoro-3-oxaoctanoate (**23**) (30 mg, quant.) as a colorless oil. IR (neat): 1740; 1460; 1375 cm^{-1}. ^1H NMR δ: 4.45 (2H, dt, $J=47.5$, 6.1 Hz); 3.95 (2H, s); 3.53 (2H, t, $J=6.1$ Hz); 1.48 (9H, s); 1.99–1.53 (6H, m) FABMS *m/z*: 221 (MH^+). Analysis: calcd. for $C_{11}H_{21}O_3F$: C, 60.00; H, 9.55%. Found: C, 59.97; H, 9.63%.

The ester **23** (16 mg, 0.073 mmol) was dissolved in trifluoroacetic acid (0.5 ml) and the solution stirred at room temperature for 15 min. The mixture was diluted with benzene (10 ml) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using $CHCl_3$ to give **27** (0.069 mmol, 95%) as a brown oil. IR (neat): 3500; 1700; 1460; 1375 cm^{-1}. ^1H NMR δ: 6.84 (1H, bs, D_2O exchange); 4.45 (2H, dt, $J=47.5$, 6.7 Hz); 4.13 (2H, s); 3.58 (2H, t, $J=6.2$ Hz); 2.00–1.41 (6H, m). EIMS *m/z*: 165 (MH^+), 144 ($M^+ - HF$).

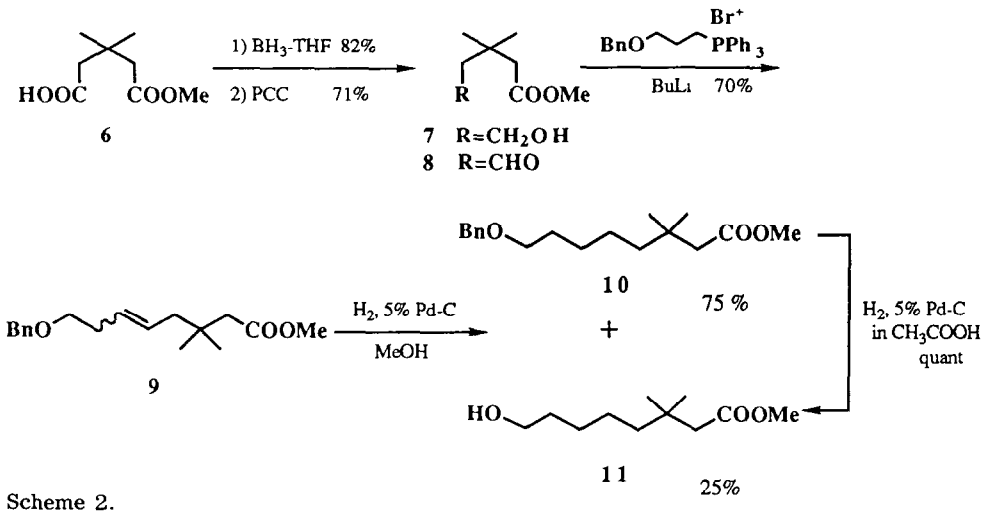
Results

Ethyl 8-hydroxyoctanoate (**2**) was readily prepared from the known 6-hexanolactone by the sequence of reactions in Scheme 1. Reductive cleavage of the lactone with DIBAL in toluene at −78 °C, followed by condensation with the reagent derived from ethyl diethylphosphonoacetate, gave the alkenyl ester **1** in 96% overall yield with a small amount of the *Z* isomer [11]. Reduction of the double bond with Pd–C in MeOH produced the saturated hydroxy ester **2** in 80% yield. The 8-hydroxy-β-methyl derivative **5** was made available via five steps, also starting from 6-hexanolactone. Thus conjugate addition of lithium dimethylcuprate [12] to the THP-protected alkenyl ester **3** and deprotection afforded **5** in 66% overall yield from **1**.

Methyl 3,3-dimethyl-5-oxopentanoate (**8**), readily prepared from 3,3-dimethylglutaric acid by methyl ester formation [13], followed by BH_3–THF



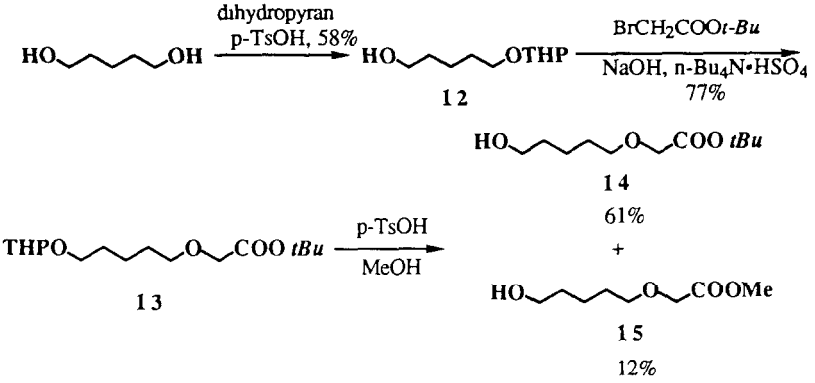
Scheme 1.



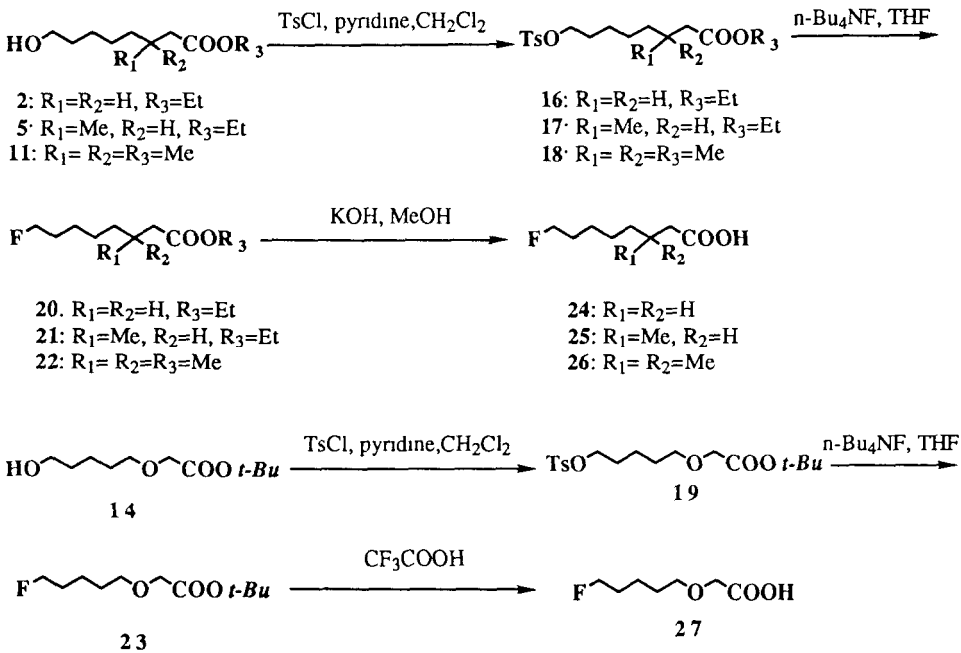
Scheme 2.

reduction and oxidation with PCC of the resulting alcohol function, served as a convenient synthon for the introduction of dimethyl branching. Chain extension using the Wittig reagent derived from 3-benzyloxypropyl triphenylphosphonium bromide and BuLi [14] gave an inseparable *E/Z* mixture of the 3,3-dimethyl-5-octenoate (**9**) (Scheme 2). Hydrogenation with Pd–C in MeOH gave the ω-benzyloxy-3,3-dimethyloctanoate (**10**) in 75% yield together with some cleavage of the benzyl ether moiety **11** (25%). The requisite **11** was obtained by further hydrogenolysis of **10** over Pd–C in CH_3COOH.

The synthesis of the 3-oxa compound **14** was started from the mono-THP derivative of 1,5-pentanediol (Scheme 3). The THP ether **12** was reacted with t-butyl bromoacetate under phase-transfer condition using $Bu_4N \cdot HSO_4$



Scheme 3.



Scheme 4

as the catalyst to obtain the t-butyl ester **13** in 77% yield [15]. Deprotection of the THP group with p-TsOH gave the desired ω-hydroxy ester **14** in 61% yield together with **15** (12% yield), which was formed by ester exchange.

The alcohols thus obtained were converted to the corresponding fluorinated analogs (**20**, **21**, **22**, **23**) in good overall yields, as shown in Scheme 4, by tosylation and following fluoride substitution using tetrabutylammonium fluoride. The selection of the tosylate group as a leaving group was based on the fact that such groups have been used successfully in fluorine-18

radiopharmaceutical syntheses [16]. Subsequent hydrolysis of the ester groups afforded the desired free acids (**24**, **25**, **26**, **27**) in almost quantitative yields.

Conclusions

We have described simple reaction sequences that permit the rapid and efficient synthesis of ω-fluorinated β-substituted octanoic acid analogs. Preliminary studies have shown that the tosylate intermediates are well suited for the preparation of the corresponding fluorine-18 labeled analogs using fluorine-18 tetrabutylammonium fluoride, in which fluorine-18 labeled octanoates could be obtained from the tosylate intermediates in reasonable radiochemical yields. These radiochemical syntheses and results of the *in-vivo* studies of the labeled compounds will be reported elsewhere.

Acknowledgments

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