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Synthesis of Structurally Identical Fluorine-18 and Iodine Isotope Labeling Compounds for Comparative Imaging

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The synthesis of a benzophenone-based labeling compound designed for comparative imaging studies with both in vivo positron emission tomograph (PET) and single-photon computed tomography (SPECT) and ex vivo autoradiography is described. The new compound can be labeled with either F-18 or iodine radioisotopes to give two different radioisotopmers: *N*-[2-fluoro-5-(3-[I-131]iodobenzoyl)benzyl]-2-bromoacetamide (**1**) and *N*-[2-[F-18]fluoro-5-(3-iodobenzoyl)benzyl]-2-bromoacetamide (**2**). Compound **1** and **2** have a 2-bromoacetyl group, which can be used to conjugate with biomolecules through a nucleophilic substitution reaction. Compound **1** was synthesized from the corresponding tributyltin derivatives via an oxidative destannylation reaction, and compound **2** was prepared via a four-step radiosynthesis (nucleophilic aromatic substitution, reduction, oxidation, and alkylation) starting from 4-(*N*,*N*,*N*-trimethylammonio)-3-cyano-3′-iodobenzophenone triflate. A remarkably high radiochemical yield (>90%) was achieved for the F-18 nucleophilic aromatic substitution under mild conditions (room temperature in less than 10 min), indicating the structural advantage of the designed molecule to facilitate the F-18 for trimethylammonium substitution in the presence of two electron-withdrawing groups (nitrile and carbonyl). The overall radiosynthesis time for compound **2** is less than 3 h after end of bombardment (EOB) with an unoptimized radiochemical yield of about 2% (not decay corrected) and specific activity of 0.8 Ci/μmol at EOB. The radiolabeling precursors for compound **1** and **2** were synthesized via a carbon−carbon bond-forming reaction between 2-substituted-5-lithiobenzonitrile and 3-substituted benzaldehyde derivatives. Compounds **1** and **2** should allow us to label biomolecules with F-18 or iodine isotopes and gives structurally identical products, which are expected to have identical biological properties and should be useful for comparative imaging studies.

INTRODUCTION

Antisense oligonucleotides represent a group of newly developed therapeutic agents (Tseng and Brown, 1994). They take advantage of highly specific base-pair interaction to inhibit expression of disease-related genes in a selective and sequence-specific manner (Zamecnik and Stephenson, 1978). Radioisotope-labeled antisense oligonucleotides (Kühnast et al., 2000, Kobori et al., 1999, Lange et al., 2002) are also being explored as radiotracers for imaging in tissue targeted by the antisense mechanism. In theory, almost any gene sequence could be selectively imaged with a labeled antisense oligonucleotide. However, in living systems, gene targeting in the nucleus is far more complex due to enzymatic oligonucleotide degradation and the difficulty for the naked oligonucleotide to penetrate the cellular barrier (Crooke et al., 2000; Mahato et al., 1997, Hass et al., 1998). Nevertheless, oligonucleotides have become more and more attractive as imaging probes, stimulated by the recent introduction of several therapeutic oligonucleotides into clinical trials (Lebedeva and Stein, 2001; Pawlak et al., 2000; Hnatowich, 2000 and 1999). Permeation peptides, such as Tat-peptides, are also important because of their ability to cross cell membranes and to deliver therapeutic or diagnostic agents into the cell (Schwarze and Dowdy, 2000; Schwarze et al., 1999; Lindgren et al., 2000). On the basis of the fact that most permeation peptides contain arginine- and lysine-rich sequences and are highly basic, they were thought to enter the cell through a nonspecific "inverted micelles" mechanism (Prochiantz, 2000). A recent study of the permeable barrier of epithelial cells to Tat-peptides, however, suggests the existence of a cell-specific mechanism (Violini et al., 2002). Permeation peptides or their conjugates with other functional molecules such as oligonucleotides, fluorescent probes, and radionuclides are currently being developed as possible imaging probes (Bullok et al., 2002).

Positron emission tomography (PET) is a medical imaging method, which uses positron-emitting radioisotope-labeled compounds to trace biochemical transformations and the movement of drugs in living systems (Eckelman et al. 2000; Fowler et al. 1999; Burn et al. 1999). Since it is impossible to obtain subcellular distribution information directly from population-based PET imaging, comparative imaging studies are necessary for evaluating the bioavailability of drugs whose function depend on their ability to enter the cells. First the molecule is labeled with a positron-emitting radioisotopes, such as fluorine-18 or carbon-11 or γ-emitting radioisotopes to conduct in vivo PET or single-photon computed tomography (SPECT) studies. Then the same molecule is labeled with fluorescent probe to obtain ex vivo subcellular fluoresce imaging or low-energy isotopes such as Auger-emitters I-125 or Br-77 to obtain in vitro higher resolution autoradiography and relate these to PET or SPECT imaging. The nonlinear signals, aggregation, and quenching both in vivo and in vitro associated

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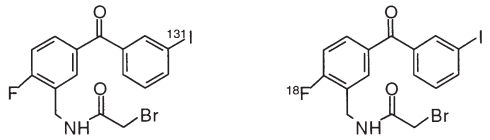
with fluorescent probe-labeled biomolecules plus the potentially significant structural perturbation associated with a fluorescent probe to the parent compound makes radiolabeling method a better choice in terms of quantitative biochemical analysis. Labeling biomolecules with different radioisotopes is usually accomplished by linking them to different labeling compounds (Dolle et al., 1996; Bullok et al., 2002), result in molecules with different properties, and could compromise the biological properties of the parent biomolecules. For example, different chemical modification involved in the "tag on" labeling procedure may not interfere with the hybridization between the antisense oligonucleotide and target mRNA. Different labeling compounds, however, alter oligonucleotide cell membrane transport and its clearance from nontarget tissue (Hnatowich, 2000 and 1999), and oligonucleotides labeled with different labeling compounds may also have different cellular accumulation (Zhang et al., 2000). Different cellular uptake and similar subcellular localization were also observed between single-labeled and dual-labeled Tat-peptides (Bullok et al., 2002).

In this paper, we report, for the first time, the synthesis and radiolabeling of organic compounds: *N*-[2-fluoro-5-(3-[I-131]iodobenzoyl)benzyl]-2-bromoacetamide (**1**) and *N*-[2-[F-18]fluoro-5-(3-iodobenzoyl)benzyl]-2-bromoacetamide (**2**). The molecule contains a 2-bromoacetyl group,



1 **2**

which has been used previously to label oligonucleotides (Dolle et al., 1996) and peptides and proteins (Kilbourn et al., 1987) through a nucleophilic substitution reaction. Therefore, the pair of isotopomers should allow us to label biomolecules with F-18 or iodine isotopes and gives structurally identical products, which are expected to have identical biological properties and should be useful for comparative imaging studies.

EXPERIMENTAL SECTION

General. All reactions were conducted under an argon atmosphere using glassware previously dried in an oven at 120 °C. Methylene chloride was freshly distilled from calcium hydride (CaH_2) and tetrahydrofuran (THF) from benzophenone ketyl under an argon atmosphere. Hexane was dried over 4 Å molecular sieves. Flash column chromatography was performed using silica gel 60 Å (230−400 mesh). Silica gel thin-layer chromatography was done on plates (silica gel 60 Å, F254, 0.15 mm on glass). NMR spectra were recorded on a Bruker 400 MHz NMR instrument. Unless otherwise noted, samples were dissolved in chloroform-*d* ($CDCl_3$) with tetramethylsilane (TMS) as an internal standard for proton NMR and the central peak of $CDCl_3$ signal at 77.0 ppm as the carbon-13 NMR reference. δ: chemical shift in ppm; J: coupling constant in Hz. Mass spectra was measured by UCR Mass Spectrometry Facility, Department of Chemistry, UC Riverside.

3-Tributyltinbenzaldehyde (11). To a solution of 2-(3-bromophenyl)-1,3-dioxolane **9** (22.9 g, 100 mmol) in THF at −78 °C was added butyllithium (*n*-BuLi) (46 mL of 2.5 M in hexanes, 115 mmol) dropwise via syringe. After the mixture was stirred at −78 °C for 2 h, tributyltin chloride (32 mL, 118 mmol) was added dropwise. After the mixture was stirred at −78 °C for 1.5 h, the reaction was slowly warmed to room temperature. Hydrochloric acid (1 N, 20 mL) was added. After the mixture was stirred at room temperature for 6 h, water (10 mL) and ether (30 mL) was added. The organic layer was washed with two additional portions of water (2 × 20 mL) and then dried over sodium sulfate, filtered, and concentrated. Flash chromatography (eluted with hexanes/ethyl acetate: 95/5, v/v) purification provided aldehyde **11** (32 g, 81%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (m, 1 H), 7.76 (td, J = 6.7, 1.0 Hz, 1 H), 7.70 (td, J = 7.2, 1.0 Hz, 1 H), 7.45 (t, J = 7.4 Hz, 1 H), 1.6 (m, 6H), 1.3 (m, 6 H), 1.0 (m, 6 H), 0.86 (t, J = 7.3 Hz, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 146.3, 145.3, 140.4, 138.3, 132.2, 131.131.8, 30.3, 16.4, 12.4. MS (EI) *m/z* (%): 395 (M^+, 1), 339 ($[M - C_4H_9]^+$, 98), 283 ($[M - C_4H_9 - C_4H_9]^+$, 59), 225 ($[M - C_4H_9 - C_4H_9 - C_4H_9]^+$, 100).

4-Fluoro-3-cyano-3′-tributyltinbenzhydrol (5). To a solution of 5-bromo-2-fluorobenzonitrile **3** (2.5 g, 12.5 mmol) in a mixture of THF (60 mL) and hexanes (20 mL) at −110 °C (ether, liquid nitrogen) was added *n*-BuLi (5.75 mL of 2.5 M in hexanes, 14.4 mmol) dropwise via syringe, After the mixture was stirred at −110 °C for 40 min, a solution of aldehyde **11** (5.0 g, 12.7 mmol) in THF (10 mL) was added. After the mixture was stirred at −110 °C for 1 h, the reaction was slowly warmed to room temperature. Hydrochloric acid (1 N, 20 mL) was added, the organic layer was washed with water (3 × 10 mL) and dried over sodium sulfate, filtered, and concentrated to yield an oil product, which was purified by flash chromatography (eluted with ethyl acetate/hexanes: 5/95 v/v) to give **5** (5.8 g, 89%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 6.0, 2.0 Hz, 1 H), 7.54 (m, 1 H), 7.35 (td, J = 6.6, 1.2 Hz, 1 H), 7.31 (d, J = 2.2 Hz, 1 H), 7.25 (t, J = 7.1 Hz, 1 H), 7.15 (td, J = 6.6, 1.2 Hz, 1 H), 7.09 (t, J = 7.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (d, $^1J_{C-F}$ = 164 Hz), 146.1, 143.7, 144.6, 139.4, 137.3, 135.8 (d, $^3J_{C-F}$ = 8.3 Hz), 134.0, 131.1, 129.0, 119.0 (d, $^2J_{C-F}$ = 19.6 Hz), 116.7, 104.0 (d, $^3J_{C-F}$ = 16.0 Hz), 77.8, 31.8, 30.0, 16.4. HRMS (DCI): Calcd $C_{26}H_{36}FNOSn$ (M − H) 516.1724, found 516.1715.

4-Fluoro-3-aminomethyl-3′-tributyltinbenzhydrol (6). To a suspension of lithium aluminum hydride (1.0 g, 26.4 mmol) in dry THF was added a solution of **5** (3.6 g, 7.0 mmol) in THF (10 mL) at 0 °C under argon. The disappearance of the starting material was monitored by TLC. After 16 h stirring, the reaction was quenched by the addition of water (2 mL), followed by sodium hydroxide solution (2 mL, 3 M) and water (2 mL). The resulting mixture was stirred at room temperature for 10 min, filtered, dried over sodium sulfate, and concentrated. The crude product was purified by a flash chromatography (eluted with ethyl acetate); yield 1.46 g (40%) of **6** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 1 H), 7.33 (m, 2 H), 7.24 (m, 2 H), 7.17 (m, 1 H), 6.93 (dd, J = 8.8, 9.6 Hz, 1 H), 1.51 (m, 6 H), 1.32 (m, 6 H), 1.05 (m, 6 H), 0.89 (t, J = 7.3 Hz, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (d, $^1J_{C-F}$ = 245 Hz), 143.3, 142.4, 140.3 (d, $^3J_{C-F}$ = 3.8 Hz), 135.8, 134.7, 129.3 (d, $^2J_{C-F}$ = 15.9 Hz), 128.1, 127.5 (d, $^3J_{C-F}$ = 4.8 Hz), 127.0 (d, $^4J_{C-F}$ = 8.3 Hz), 126.3, 115.2 (d, $^2J_{C-F}$ = 22.0 Hz), 75.5, 40.5 (d, $^3J_{C-F}$ = 4.1 Hz), 29.2, 27.4, 14.9, 9.9. HRMS (DCI): Calcd $C_{26}H_{39}FNOSn$ (M − H) 520.2037, found 520.2051.

4-Fluoro-3-aminomethyl-3′-tributyltinbenzophenone (7). To a solution of **6** (1.3 g, 2.5 mmol) in methylene chloride (15 mL) was added pyridinium chlo-

rochromate (PCC) (1.08 g, 5 mmol) in small portions. The suspension was stirred at room temperature for 30 min. Aqueous sodium hydroxide (3 M) was added, and the aqueous layer was extracted with ether. The organics were combined, dried over sodium sulfate, filtered, and concentrated. Flash chromatography (eluted with ethyl acetate) provided **7** (1.14 g, 88%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.33, 2.20 Hz, 1 H), 7.85 (m, 1 H), 7.66 (m, 2 H), 7.42 (t, J = 7.48 Hz), 7.08 (dd, J = 8.57, 9.57 Hz, 1 H), 1.5 (m, 6 H), 1.3 (m, 6 H), 1.1 (m, 6 H), 0.89 (t, J = 7.1 Hz, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 163.6 (d, $^1J_{C-F}$ = 253 Hz), 142.8, 140.59, 137.6, 136.8, 134.2, 131.5 (d, $^3J_{C-F}$ = 6.36 Hz), 131.1 (d, $^3J_{C-F}$ = 9.26 Hz), 130.7 (d, $^2J_{C-F}$ = 15.8 Hz), 129.6, 127.7, 115.2 (d, $^2J_{C-F}$ = 22.62 Hz), 40.5 (d, $^3J_{C-F}$ = 3.2 Hz), 29.1, 27.4, 14.9, 9.9, MS (EI) *m*/*z* (%): 504 ([M − NH_2]$^+$, 100), 462 ([M − C_4H_9]$^+$, 14), 229 ([M − $SnBu_3$]$^+$, 6).

***N*-[6-Fluoro-3-(3-tributyltinbenzoyl)benzyl]-2-bromoacetamide (8).** To a solution containing **7** (1.14 g, 2.2 mmol) and *N*-methylmorpholine (244 mg, 2.42 mmol) in dry methylene chloride was added dropwise bromoacetyl bromide (488 mg, 2.42 mmol) at 0 °C. The reaction mixture was stirred overnight. The reaction was quenched with ice. The organic layer was washed with water (2 × 2 mL), dried over sodium sulfate, and concentrated to dryness, and the residue was chromatographed on silica gel (eluted with hexanes/ethyl acetate, 95:5, v/v) gave 1.1 g (yield 78%) of compound **8** as colorless oil, it solidified as a white waxlike solid upon storage in the refrigerator. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.33 Hz, J = 2.20 Hz, 1 H), 7.85 (m, 1 H), 7.73 (ddd, J = 2.20, 5.1, 7.4, 1 H), 7.66 (td, J = 1.1, 7.2 Hz), 7.61 (m, 1 H), 7.39 (t, J = 7.49 Hz), 7.12 (dd, J = 8.63, 9.43 Hz), 6.9 (broad t, J = 4.90 Hz, 1 H), 4.55 (d, J = 6.0 Hz, 2 H), 4.10 (s, 2 H), 1.5 (m, 6 H), 1.3 (m, 6 H), 1.1 (m, 6 H), 0.89 (t, J = 7.3 Hz, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 165.5, 163.5 (d, $^1J_{C-F}$ = 253 Hz), 143.0, 140.8, 137.6, 136.6, 134.4 (d, $^3J_{C-F}$ = 3.1 Hz), 132.2 (d, $^3J_{C-F}$ = 5.40 Hz), 132.1 (d, $^3J_{C-F}$ = 4.50 Hz), 129.7, 127.7, 125.0 (d, $^2J_{C-F}$ = 15.50 Hz), 115.4 (d, $^2J_{C-F}$ = 22.0 Hz), 40.5 (d, $^3J_{C-F}$ = 3.6 Hz), 29.1, 28.9, 27.4, 13.7, 9.8. HRMS (FAB): Calcd $C_{28}H_{39}BrFNO_2Sn$ (M + H) 640.1248, found 640.1223.

2-(*N*,*N*-Dimethylamino)-5-bromobenzonitrile (13). To a 150 mL round-bottom flask was added 2-amino-5-bromobenzonitrile **12** (1.97 g, 10 mmol), *N*,*N*-dimethylformamide (DMF) (50 mL), iodomethane (10 mL), and sodium carbonate (2.11 g, 20 mmol). The reaction mixture was sealed off in the flask and kept in 110 °C oil bath for 24 h. After the mixture was cooled to room temperature, ethyl acetate (100 mL) was added and the mixture was washed with water (4 × 20 mL) and dried over sodium sulfate. Filtration and removal of the solvent gave **13** as yellowish solid (1.9 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 2.52 Hz, 1 H), 7.38 (dd, J = 9.0 Hz, J = 2.43 Hz, 1 H), 6.69 (d, J = 9.0 Hz, 1 H), 3.0 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.90, 136.78, 136.42, 118.32, 109.92, 101.84, 42.95. MS(CI) *m*/*z* (%): 225 (M, 25), 145 (M − Br, 10).

4-(*N*,*N*-Dimethylamino)-3-cyano-3′-iodobenzhydrol (14). To a solution of **13** in THF/hexanes (50 mL/15 mL) was added *n*-BuLi (1.17 mL, 1.2 eq, 2.5 M in hexanes) at −110 °C under argon. After the mixture was stirred at −110 °C for 1 h, a solution of 3-iodobenzylaldehyde (679 mg, 2.96 mmol) in THF (5 mL) was added via a glass syringe. TLC indicated complete reaction in 10 min. The resulting mixture was allowed to warm slowly to room temperature. Ether (20 mL) was added, and the reaction mixture was washed with water (3 × 10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure on a rotary evaporator. The resulting oil was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, 80/20 to 70/30 v/v) to give **14** as colorless oil (775 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 1H), 7.58 (m, 1 H), 7.43 (d, J = 2.26 Hz, 1 H), 7.31 (dd, J = 8.8 Hz, J = 2.27 Hz, 1 H), 7.26 (m, 1 H), 7.05 (t, J = 7.8 Hz, 1 H), 6.80 (d, J = 8.8 Hz, 1 H), 5.63 (s, 1 H), 3.02 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.66, 145.65, 136.90, 135.35, 133.95, 133.17, 132. 03, 130.44, 125.71, 119.72, 116.93, 100.36, 94.72, 43.00. HRMS (DEI): Calcd $C_{16}H_{15}IN_2O$ 378.0229, found 378.0230.

4-(*N*,*N*-Dimethylamino)-3-cyano-3′-iodobenzophenone (15b). To a solution of 4-(*N*,*N*-dimethylamino)-3-cyano-3′-iodobenzhydrol **14** (770 mg, 2 mmol) in methylene chloride (100 mL) was added PCC (878 mg, 4 mmol). TLC indicated the reaction was completed after stirring at room temperature for 2 h. The reaction mixture was filtered through a plug of silica gel. The product was eluted from the silica gel by hexanes/ethyl acetate (80/20: v/v). Evaporation of the solvent gave a mixture of **15a** and **15b** with a ratio of 2 to 8 from proton NMR analysis. The mixture was dissolved in DMF (100 mL) in a 250 mL round-bottom flask, and iodomethane (10 mL) and sodium carbonate (1.5 g) were added. The reaction mixture was sealed off in the flask and kept in a 110 °C oil bath overnight. After the mixture was cooled to room temperature, ethyl acetate (100 mL) was added and the organic phase was washed with water and dried over sodium sulfate. Filtration and removal of the solvent gave pure **15b** as yellowish solid (600 mg, 79% from **14**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (t, J = 1.5 Hz, 1 H), 7.91 (d, J = 2.23 Hz, 1 H), 7.86 (ddd, J = 8.0 Hz, J = 1.8 Hz, J = 1.0 Hz, 1 H), 7.82 (dd, J = 11.11 Hz, J = 2.24 Hz, 1 H), 7.59 (ddd, J = 7.6 Hz, J = 1.5 Hz, J = 1.0 Hz, 1 H), 7.18 (t, J = 7.6 Hz, 1 H), 6.81 (d, J = 9.0 Hz, 1 H), 3.23 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.70, 155.98, 140.88, 139.78, 139.52, 138.07, 135.05, 130.10, 128.53, 125.76, 119.55, 115.14, 96.51, 94.30, 42.60. HRMS (FAB): Calcd $C_{16}H_{15}IN_2O$ 378.0229, found 378.0230 HRMS (DEI): Calcd $C_{16}H_{13}IN_2O$ 376.0072, found 376.0072.

4-(*N*-Methylamino)-3-cyano-3′-iodobenzophenone (15a). To a solution of the mixture of **15a** and **15b** (**15a**/**15b**: 2/8, 20 mg) in methylene chloride (10 mL) was added pyridinium chlorochromate (50 mg, 0.23 mmol). After being stirred at room temperature for 3 days, the reaction mixture was filtered through a plug of silica gel and the product was eluted from the silica gel by hexanes/ethyl acetate (80/20: v/v). Evaporation of the solvent under reduced pressure to give a yellowish solid which was purified on silica gel (hexanes/ethyl acetate: 70/30) to give pure **15a** (10 mg, 51%) as white solid: ^{1}H NMR (400 MHz, acetone-d_6) δ 7.99 (t, J = 1.5 Hz, 1 H), 7.86 (m, 3 H), 7.60 (td, J = 7.7, 1.8 Hz, J = 1.5 Hz, 1 H), 7.23 (t, J = 7.7 Hz, 1 H), 6.76 (d, J = 8.8 Hz, 1 H), 6.1 (broad s, 1 H), 3.0 (d, J = 5.0 Hz, 6 H).

4-(*N*,*N*,*N*-Trimethylammonio)-3-cyano-3′-iodobenzophenone Triflate (16). To a solution of 4-(*N*,*N*-dimethylamino)-3-cyano-3′-iodobenzophenone **15b** (186 mg, 0.5 mmol) in dry methylenechloride (1 mL) was added methyl trifluoromethanesulfonate (283 μL, d =1.45, 2.5 mmol, 5.0 equiv) via syringe. The reaction was stirred for 3 days at 80 °C. The solvent and the excess methyl trifluoromethanesulfonate were evaporated, and the residue was dried under vacuum and purified by C18 Cartridges (water/acetonitrile: 90/10 v/v), giving 65 mg (40%) of pure compound **16** as white solid. ^{1}H NMR (400

MHz, acetone-d_6) δ 8.56 (d, J = 9.0 Hz, 1 H), 8.53 (d, J = 2.1 Hz, 1 H), 8.34 (dd, J = 8.9 Hz, 2.1 Hz, 1 H), 8.15 (t, J = 1.3 Hz, 1 H), 8.11 (m, 1 H), 7.85 (m, 1 H), 7.41 (t, J = 7.88 Hz, 1 H), 4.21 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 148.5, 142.6, 139.6, 138.3, 137.8, 135.9, 130.9, 129.6, 123.8, 116.1, 106.4, 93.9, 57.3. HRMS (FAB/ACN/NBA): Calcd $C_{17}H_{16}IN_2O$ 391.0307, found 391.0325.

4-Fluoro-3-cyano-3′-iodobenzhydrol (17). To a solution of 5-bromo-2-fluorobenzonitrile **3** (2.0 g, 10 mmol) in THF (80 mL) was added butyllithium (4.4 mL, 2.5 M in hexanes, 11 mmol) at −110 °C. After the mixture was stirred at −110 °C for 1.5 h, a solution of 3-iodobenzaldehyde (2.55 g, 11 mmol) in THF (5 mL) was added dropwise via a syringe. The reaction mixture was stirred at −110 °C for 2 h and warmed slowly to room temperature. The resulting mixture was washed with water (3 × 20 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure on a rotary evaporator. The residual yellow oil was purified by silica gel column (elute: hexanes/ethyl acetate: 80/20 v/v) to offer 2.1 g (61%) expected product **17**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5 to 7.7 (m, 4 H), 7.26 (d, J = 7.82 Hz, 1 H), 7.13 (t, J = 8.68 Hz, 1 H), 7.04 (t, J = 7.80 Hz, 1 H), 5.68 (s, 1 H), 4.0 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, J_{C-F} = 258.9 Hz), 145.3, 140.8, 137.2, 135.5, 133.6 (d, J_{C-F} = 8.5 Hz), 131.4, 130.7, 126.0, 116.6 (d, J_{C-F} = 19.8 Hz), 114.1, 109.7, 101.2 (d, J_{C-F} = 15.6 Hz), 94.89, 73.70. HRMS (DCI): Calcd $C_{14}H_9IFNO$ 352.9713, found 352.9718.

4-Fluoro-3-cyano-3′-iodobenzophenone (18a). To a solution of **17** (2.1 g, 5.9 mmol) in methylene chloride (100 mL) was added pyridinium chlorochromate (4.0 g, 18.6 mmol). After being stirred at room temperature for 2 h, the reaction mixture was filtered through a plug of silica gel. Removal of the solvent gave **18a** as white waxlike solid (1.8 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 to 8.1 (m, 3 H), 7.98 (d, J = 7.8 Hz, 1 H), 7.68 (d, J = 8.8 Hz, 1 H), 7.38 (t, J = 8.0 Hz, 1 H), 7.27 (t, J = 7.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.86, 165.6 (d, J_{C-F} = 266.8 Hz), 142.4, 138.8, 138.4, 137.8 (d, 135.5, J_{C-F} = 9.0 Hz), 136.0, 134.3 (d, J_{C-F} = 3.6 Hz), 130.7, 129.3, 117.4 (d, J_{C-F} = 20.4 Hz), 113.2, 102.7 (d, J_{C-F} = 16.2 Hz), 94.9. HRMS (DEI): Calcd $C_{14}H_7IFNO$ 350.9556, found 350.9567.

4-Fluoro-3-aminomethyl-3′-iodobenzhydrol (19a). To a stirred solution of **18a** (351 mg, 1 mmol) in dry THF (10 mL) was added borane (BH_3) (6 mL, 1 M in THF) using a glass syringe at room temperature. After the initial reaction subsided, the reaction mixture was refluxed for 8 h in a water bath. Excess BH_3 was quenched by careful addition of ethanol (20 mL) to the cooled reaction mixture. The solvent was removed by rotary evaporation. The residue was dissolved in ethyl acetate and filtered through a plug of silica gel, and the plug was eluted with hexanes/ethyl acetate/methanol (80/20/5: v/v/v, 100 mL) followed ethyl acetate (150 mL). The product was eluted from the silica gel with methanol (150 mL). Evaporation of methanol resulted in a waxlike solid (270 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (t, J = 1.8 Hz, 1 H), 7.55 (td, J = 7.85, 1.2 Hz, 1 H), 7.24 (m, 1 H), 7.13 (m, 1 H), 7.01 (t, J = 7.64 Hz, 1 H), 6.96 (dd, J = 8.4, 6.5 Hz, 1 H), 5.55 (s, 1 H), 3.7(s, 2 H), 3.0 (broad s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6 (d, J_{C-F} = 245.8 Hz), 147.0, 140.3 (d, J_{C-F} = 4.32 Hz), 136.8, 135.8, 130.62, 129.7 (d, J_{C-F} = 15.2 Hz), 127.9 (d, J_{C-F} = 5.0 Hz), 127.4 (d, J_{C-F} = 8.4 Hz), 126.15, 115.7 (d, J_{C-F} = 21.8 Hz), 95.0, 74.7, 40.5 (d, J_{C-F} = 3.5 Hz). HRMS (DEI): Calcd $C_{14}H_9IFNO$ (M − H) 355.9947, found 355.9955.

4-Fluoro-3-aminomethyl-3′-iodobenzophenone (20a). To a solution of **19a** (270 mg, 0.75 mmol) in methylene chloride (20 mL) was added pyridinium chlorochromate (326 mg, 0.87 mmol). After being stirred at room temperature for 1 h, the reaction mixture was washed with aqueous sodium hydroxide solution (3 M, 2 × 1 mL) and dried over sodium sulfate. The organic layer was filtered through a plug of silica gel. The product was eluted from the silica gel with ethyl acetate (150 mL). Removal of the solvent provided **20a** as yellowish oil (180 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (m, 1 H), 7.92 (m, 2 H), 7.69 (m, 2 H), 7.25 (t, J = 7.7 Hz, 1 H), 7.15 (t, J = 7.64 Hz, 1 H), 3.7 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 162.3 (d, J_{C-F} = 253.2 Hz), 141.3, 139.5, 138.5, 133.3, 131.5 (d, J_{C-F} = 6.3 Hz), 131.1 (d, J_{C-F} = 9.6 Hz), 130.1, 129.0, 115.5 (d, J_{C-F} = 22.3 Hz), 109.66, 94.22, 40.5 (d, J_{C-F} = 3.1 Hz). MS (CI) m/z (%): 355 (M, 20).

***N*-[6-Fluoro-3-(3-iodobenzoyl)benzyl]-2-bromoacetamide (21).** To a solution of **20a** (36 mg, 0.1 mmol) in 4 mL of methylene chloride was added *N*-methylmorpholine (12 μL, 0.12 mmol) and bromoacetyl bromide (9.5 μL, 0.11 mmol). After being stirred at room temperature for 5 h, the reaction was quenched with water (0.5 mL). The organic layer was separated and washed with water (2 × 0.5 mL) and dried over sodium sulfate. The solvent was removed under vacuum and the residue was chromatographed on silica gel (elute: hexanes/ethyl acetate: 80/20 to 70/30) to give **21** as white solid (38 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (t, J = 1.7 Hz, 1 H), 7.65 (m, 1 H), 7.54 (dd, J = 2.3, 7.2, 1 H), 7.47 (ddd, J = 2.3, 5.0, 7.2 Hz, 1 H), 6.95 (t, J = 7.82 Hz), 6.92 (dd, J = 8.56, 9.45 Hz), 6.69 (broad, 1 H), 4.30 (d, J = 6.4 Hz, 2 H), 3.62 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 165.8, 163.5 (d, $^1J_{C-F}$ = 255 Hz), 141.5, 139.2, 138.6, 133.4, 132.1 (d, $^3J_{C-F}$ = 5.5 Hz), 132.0 (d $^3J_{C-F}$ = 9.3 Hz), 130.2, 129.1, 125.2 (d, $^2J_{C-F}$ = 15.42 Hz), 115.9 (d, $^2J_{C-F}$ = 22.1 Hz), 94.2, 38.1 (d, $^3J_{C-F}$ = 3.6 Hz), 29.0. MS(CI) m/z (%): 475 (M, 5), 397 (M − Br, 40).

Radiosynthesis. Analytical Methods. TLC was done on plates (Sigma-Aldrich, highly purified silica gel, 60 Å, F254, 0.25 mm on polyester). HPLC analysis and purification were performed under following conditions: UV detection at 254 nm; radioactivity detectors Geiger Muller detector. Column A: C18 μBondpak Waters (300 × 3.9 mm, 10 μm); Column B: semipreparative C18 Phenomenex phenosphere 5 (ODS-2 250 × 10.00 mm, 5 μm). Solvent A: acetonitrile/aqueous ammonium acetate solution (40 mM): 50/50, v/v; Solvent B: acetonitrile/aqueous ammonium acetate solution (40 mM): 80/20, v/v. Flow rate: 1 mL/min for column A; 5 mL/min for column B.

Preparation of *N*-[2-Fluoro-5-(3-iodo[I-131]benzoyl)benzyl]-1-bromoacetamide (1). To a stock solution of sodium iodide[I-131] (Dupont-New England Nuclear) was added a solution of *N*-[6-fluoro-3-(3-tributyltinbenzoyl)benzyl]-2-bromoacetamide **8** (20 μL, 1% in ethanol) followed by hydrochloric acid solution (10 μL, 0.5 M) and a solution of chloramine-T (10 μL, 2% solution in water). After 2 min reaction, the product **1** was purified by a Radio-RP-HPLC (t_R = 15 min, Column A, solvent A). The radiochemical yield varied from 86% to 99% and the radiochemical purity was >99%.

Preparation of *N*-[2-Fluoro[F-18]-5-(3-iodobenzyl)benzyl]-1-bromoacetamide (2). [^{18}F]Fluoride in 0.3 to 0.5 mL of aqueous 0.01 M potassium carbonate from the $H_2{}^{18}O$ target was delivered to a silicon-coated glass tube charged with a stirring bar and a mixture of tetrabutylammonium hydroxide (40 μL, 40% in water) and dry ice (1.0 to 2.0 g), and the water was azeotropically evaporated at 120 °C under a argon stream and then

cooled to room temperature. 4-(*N*,*N*,*N*-Trimethylammonio)-3-cyano-3′-iodobenzophenone triflate **16** (2.0 mg) dissolved in acetonitrile (0.3 mL) was added. The solution was stirred at room temperature for 10 min to give compound **18b**. The radiochemical yield of the substitution is greater than 92% determined by radio-TLC (R_f = 0.4, eluant: ethyl acetate/hexanes: 8/92 v/v) and HPLC (t_R = 3.6 min, Column B, Solvent B). The reaction mixture was then diluted with ethyl acetate (4 mL) and washed with water (2 × 0.5 mL) (less than 30% activity was lost in the water), dried over sodium sulfate, and filtered through a silica gel cartridge (17% of the total activity was lost on silica gel and dry agent). The resulting solution was concentrated to dryness at 120 °C with a stream of argon. The residue was dissolved in THF (0.2 mL), and borane (0.2 mL, 1.0 M in tetrahydrofuran) was added. The reaction vial was then tightly closed and heated at 120 °C for 10 min and then cooled to room temperature to give compound **19b**. The yield of the reduction varied from 60% to 78% as determined by radio RP-HPLC (t_R = 10.0 min, column B, solvent B). The excess borane was quenched with ethanol (0.2 mL), and the solvent was evaporated with a stream of argon at room temperature. The residue was redissolved in methylene chloride (3 mL). The solution was washed with aqueous sodium hydroxide (0.2 mL, 1 N) and water (1 mL). The organic layer was loaded on a silica cartridge, and the product was eluted with methanol (6 mL). The resulting solution was evaporated to dryness, a solution of PCC (10 mg) in methylene chloride (1 mL) was added, and the mixture was stirred at room temperature for 15 min to give compound **20b**. The resulting yellow-brown reaction mixture was washed with aqueous sodium hydroxide and water. The yield of the oxidation varied from 65% to 90% as determined by radio RP-HPLC (t_R = 13.0 min, column B, solvent B). The solvent was evaporated, and the residue was dissolved in methylene chloride. After addition of bromoacetyl bromide solution (100 μL, 1.0 M in methylene chloride), the cloudy solution was stirred at room temperature for 2 min to give compound **2**, and the solvent was evaporated, the residue was dissolved in a mixture of acetonitrile and water (1/1, v/v) and purified by an RP-HPLC (t_R = 10.35 min, column B, solvent A). In a typical run, 0.75 mCi compound **2** was obtained from 44 mCi [^{18}F]fluoride, in 2 h 45 min synthesis time with a specific activity of 0.74 Ci/μmol. The radiochemical purity of compound **2** was >99% from radio-TLC (R_f = 0.31, eluant: ethyl acetate/hexanes: 30/70 v/v) and HPLC (t_R = 10.35 min, column B, solvent A).

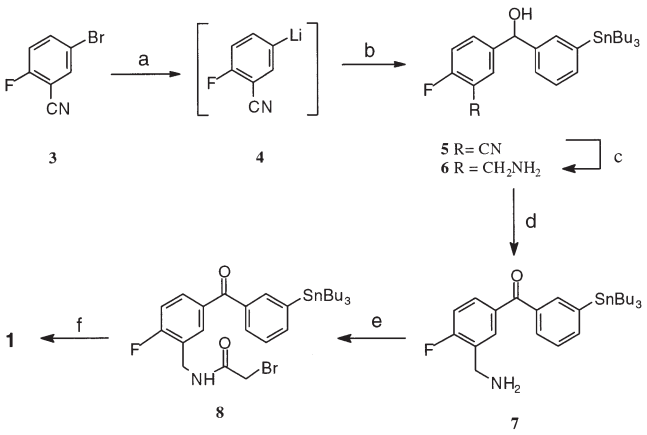
RESULTS AND DISCUSSION

The synthesis of iodine labeling precursor, *N*-[2-fluoro-5-(3-tributyltinbenzoyl)benzyl]-2-bromoacetamide **8** is shown in Scheme 1. Tributyltin is a very useful functional group in iodine labeling since it allows us to introduce iodine isotopes in high radiochemical yields through an oxidative destannylation reaction (Arano et al., 1994; Zalutsky and Narula, 1987 and 1988). Moreover, an iodine atom at the meta position of a carbonyl group has higher resistance toward in vivo deiodination (Zalutsky and Narula, 1987) thus increasing the overall in vivo stability of radiolabel. 4-Fluoro-3-nitrile-3′-tributyltinbenzhydrol **5** was obtained at −110 °C in a mixture of tetrahydrofuran and hexanes (3:1, v/v) from a coupling reaction between 3-tributyltinbenzaldhyde **11** and 2-fluoro-5-lithiobenzonitrile **4**, which was generated from 5-bromo-2-fluorobenzonitrile **3** through a bromine−lithium exchange reaction (Ding et al., 1996; Parham and Lawrence, 1976). Compound **5** could not be synthesized at a temperature of −78 °C in THF due to a side reaction between the nitrile group and organometallic reagent. Parham (Parham and Lawrence, 1976) suggested that the *o*-lithiobenzonitrile generated at a reaction temperature of −78 °C by *n*-butyllithium is relatively stable; however, the side reaction between *o*-lithiobenzonitrile and *n*-butyl bromide and the reaction between nitrile group and *n*-butyllithium become significant at an elevated temperature. The nitrile group in compound **3** is presumably more vulnerable to nucleophilic reagents due to the electron-withdrawing property of the fluorine atom in the ortho position; therefore, compound **5** can only be synthesized at a lower temperature and in a less polar reaction medium. The arylithium **10** (Scheme 2), on the other hand, is relatively stable and can be prepared at −78 °C by bromine−lithium exchange reaction. The reaction of **10** with tributyltin chloride followed by in situ deprotection with hydrochloric acid gave aldehyde **11** in 81% overall yield. Compound **11** can also be synthesized from 2-(3-bromophenyl)-1,3-dioxolane **9** through Grignard reaction (Al-Diab et al., 1982); the yield, however, was poor in our hands.

4-Fluorobenzonitrile can be rapidly reduced by lithium aluminum hydride at 120 °C to give a quantitative yield of corresponding amine (Dolle et al., 1996). No desired product, however, was isolated when the same conditions were applied to reduce compound **5**. At a lower temperature, starting from 0 °C to room temperature over 16 h, 4-fluoro-3-aminomethyl-3′-tributyltinbenzhydrol **6** was isolated in an acceptable yield (40%) (Scheme 1). The reduction at high temperature may cause the cleavage of the carbon−tin bond to produce an uncharacterizable mixture.

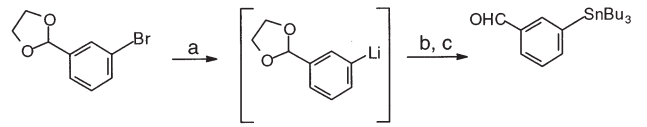
Pyridinium chlorochromate was used to oxidize benzhydrol **6** to the corresponding ketone **7** (Scheme 1). A

Scheme 1[a]



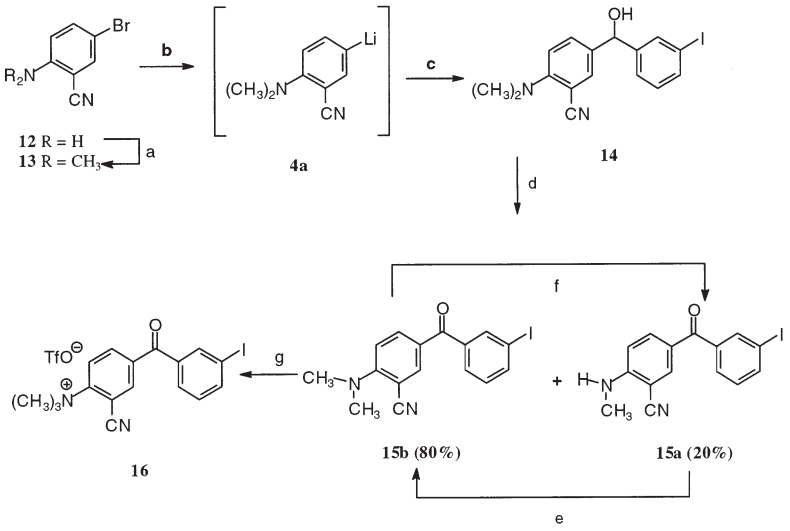
[a] Key: (a) *n*-BuLi, THF/hexanes (3/1, v/v). −110 °C; (b) **11**, −110 °C to room temperature; (c) $LiAlH_4$, THF, 0 °C to room temperature; (d) PCC, CH_2Cl_2, rt; (e) bromoacetyl bromide, *N*-methylmorpholine, CH_2Cl_2, 0 °C to room temperature; (f) $Na^{131}I$, chloramine-T, rt, 2 min.

Scheme 2[a]



[a] Key: (a) *n*-BuLi, THF, −78 °C; (b) Bu_3SnCl, −78 °C to room temperature; (c) 1 N HCl, rt.

Scheme 3[a]



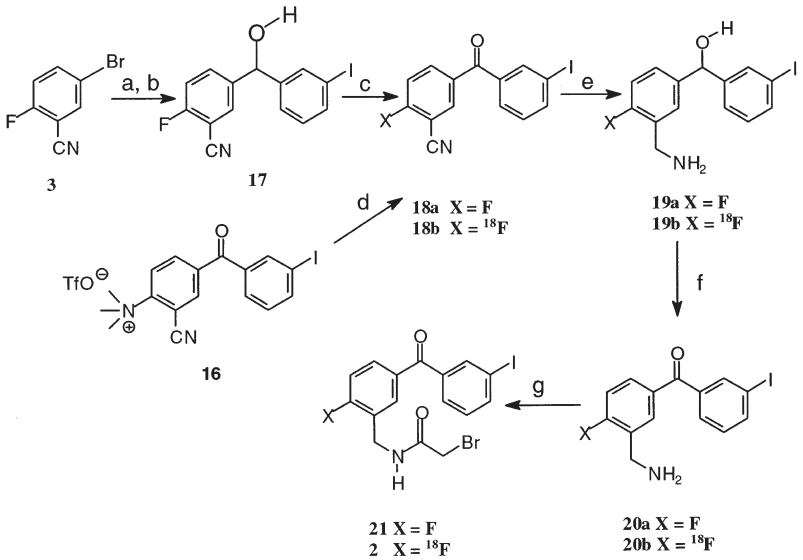
[a] Key: (a) MeI, DMF, 110 °C; (b) *n*-BuLi, −110 °C, THF/hexanes (3:1, v/v); (c) 3-iodobenzaldehyde in THF, −110 °C to room temperature; (d) PCC, CH_2Cl_2, rt, 30 min; (e) MeI, DMF, 110 °C; (f) PCC, CH_2Cl_2, rt, 3 days; (g) $CF_3SO_3CH_3$ (3−5 equiv), 80 °C, 3 days.

simple filtration through a plug of silica gel usually is a very efficient way to separate the product from the inorganic oxidizing reagent. Compound **7**, however, could not be isolated by this method, probably due to the formation of complexes between chlorochromate and aryl- and alkylamines (Kasmai et al., 1995). We found that compound **7** can be released from the complex by treating the reaction mixture with 3 M sodium hydroxide followed by purification by silica gel column chromatography. Compound **7** was then treated with bromoacetyl bromide in the presence of *N*-methylmorpholine to afford radioiodolabeling precursor **8** in 78% yield. Radioiodination was accomplished by treating compound **8** with sodium iodide (I-131) using chloramine-T as the oxidizing reagent followed by a reverse phase HPLC separation. Pure *N*-[2-fluoro-5-(3-[I-131]iodobenzoyl)benzyl]-2-bromoacet amide **1** was obtained in 86−99% radiochemical yield.

4-(*N*,*N*,*N*-Trimethylammonio)-3-cyano-3′-iodobenzophenone triflate **16** was synthesized as the precursor for F-18 labeling (Scheme 3) starting from 2-amino-5-bromobenzonitrile **12**. *N*-Methylation of **12** with iodomethane in the presence of sodium carbonate in DMF gave 2-(*N*,*N*-dimethylamino)-5-bromobenzonitrile **13** in 84% yield. Unlike compound **3**, the dimethylamino group in compound **13** stabilized the nitrile group toward the nucleophilic reaction, and metal halide exchange reaction of compound **13** with butyllithium proceeded at −78 °C in THF smoothly and produced stable 2-(*N*,*N*-dimethylamino)-5-lithiobenzonitrile which then reacted with 3-iodobenzylaldehyde to give 4-(*N*,*N*-dimethylamino)-3-cyano-3′-iodobenzhydrol **14** in 84% yield. Compound **14** was converted into a mixture of 4-(*N*-methylamino)-3-cyano-3′-iodobenzophenone **15a** and 4-(*N*,*N*-dimethylamino)-3-cyano-3′-iodobenzophenone **15b** in a ratio of about 20 to 80 by PCC oxidation. The ratio of the products depends on the reaction time; **15b** disappeared in 3 days, and pure **15a** was isolated using a silica gel column. The loss of a methyl group in the course of oxidation is due to a known oxidative demethylation reaction by chromate (Hostetler et al., 1999). The separation of **15a** from **15b** by silica gel column chromatography was not successful. Pure **15b** was obtained by remethylation **15a** in the mixture with iodomethane in DMF in the presence of sodium carbonate. Quaternization of *N*,*N*-dimethylaniline derivatives with methyl triflate usually proceeds rapidly at room temperature to offer quantitative yield. However, prolonged heating was required for the methylation of compound **15b** (80 °C in a sealed ampule for 3 days) to yield 30 to 40% of product **16**. The electron-withdrawing carbonyl and nitrile groups and the unfavorable steric hindrance caused by the ortho position nitrile group appears to be responsible. The carbonyl or nitrile group, however, is routinely introduced into aryltrimethylammonium to activate the aromatic ring for nucleophilic aromatic substitution by F-18 (Ding et al., 2000 and 1990). The presence of both in compound **16** makes the trimethylammonium group very labile toward fluoride substitution. In fact, quantitative fluoride substitution was accomplished in acetonitrile at room temperature in less than 5 min using 1.0 equiv of tetrabutylamonium fluoride as fluoride source to give compound **18a**, which can also be synthesized from **3** (Scheme 4). This efficient substitution reaction with fluoride is very unusual since fluoride ion is not a strong nucleophile. However, in this case the displacement of the trimethylammonium group is facilitated by the presence of the two electron-withdrawing groups (nitrile and carbonyl). Compound **18** can be reduced by borane in refluxing THF to give 4-fluoro-3-aminomethyl-3′-iodobenzhydrol **19a** in 76% yield. Upon PCC oxidation, 4-fluoro-3-aminomethyl-3′-iodobenzophenone **20a** was obtained in 67% and alkylation with bromoacyl bromide to produce compound *N*-[6-fluoro-3-(3-iodobenzoyl)benzyl]-2-bromoacetamide **21** in 80% yield. Compound **21** is the parent compound for the radiolabeled compounds **1** and **2** and serves as a reference compound in the radiosynthesis.

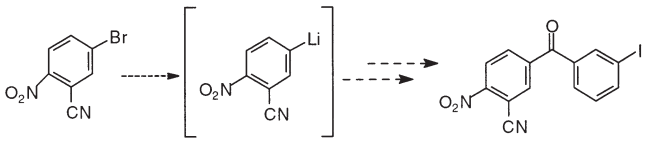
Initially, 4-nitro-3-cyano-3′-iodobenzophenone **16a** (Scheme 5) instead of **16** was proposed for the F-18 labeling precursor. However, we were not able to synthesize **16a** from 2-nitro-5-bromobenzonitrile **13a** under various temperature and solvent combinations. The nitrile group in 2-nitro-5-bromobenzonitrile **13a** was presumably activated by the ortho nitro group and very labile to nucleophilic reaction with *n*-butyllithium, and the 2-nitro-5-lithobenzonitrile **4b** could not be generated through the bromine−lithium exchange reaction. Of course, the nitro group itself may also react with a strong base like butyllithium. On the basis of our results, it seems to be reasonable to conclude that the stability of the nitrile group in **3**, **13**, and **13a** toward the nucleophilic

Scheme 4[a]



[a] Key: For nonradiosynthesis: (a) *n*-BuLi, THF/hexanes (3/1, v/v), −110 °C, 45 min; (b) 3-iodobenzaldehyde, −110 °C to room temperature; (c) PCC, CH_2Cl_2, rt, 2 h; (d) 1.0 equiv of Bu_4NF, acetonitrile, rt, 5 min; (e) BH_3, THF, reflux, 8 h; (f) PCC, CH_2Cl_2; rt; (g) bromoacetyl bromide, *N*-methylmorpholine, CH_2Cl_2, rt. For radiosynthesis: (d) K_2CO_3, $Bu_4N(OH)$, dry ice, $K^{18}F$, CH_3CN, rt, 10 min; (e) BH_3, THF, 120 °C, 10 min; (f) PCC, CH_2Cl_2, 15 min; (g) bromoacetyl bromide, CH_2Cl_2, 2 min.

Scheme 5



reaction is in the order of **13** > **3** > **13a**, which is consistent with the electron-withdrawing property of the amino, fluoro, and nitro group.

The F-18 labeling starting from compound **16** is shown in Scheme 4. The F-18 substitution reaction in acetonitrile at room temperature afforded **18b** in less than 10 min with a radiochemical yield (RCY) of 90 to 92%. To our best knowledge, this is the first example of a rapid room-temperature high yield F-18 substitute reaction, which makes compound **16** an ideal labeling precursor (Ding et al., 1990 and Fowler and Wolf, 1997). Borane reduction at 120 °C in 15 min yielded **19b** in 68% RCY. PCC oxidation at room temperature in 10 min gave **20b** in 68% RCY. Alkylation with bromoacetyl bromide at room temperature in 2 min followed by reverse phase HPLC purification afforded the F-18 labeled product **2**. The overall radiosynthesis from **16** takes less than 3 h after EOB with an unoptimized radiochemical yield of about 2% and specific activity of 0.8 Ci/μmol at EOB. The application of compound **2** to the F-18 labeling of oligonucleotides, peptides, and proteins is currently under investigation in our laboratory.

In summary, we have developed routes to synthesize novel precursor compounds, which can be used to label biomolecules with both F-18 and iodine radioisotopes and give structurally identical products. In the course of this project, we found that (1) nitrile and carbonyl groups at ortho and para positions in aryltrimethylammonium trifluoromethanesulfonate has an additive activation effect which facilitates the F-18 substitution reaction, and the F-18 labeling can proceed at room temperature. (2) The stability of nitrile group in 2-substitute-5-lithiobenzonitrile derivatives toward the nucleophilic agent depends on the electronic properties of the 2-position substituent and in the order of dimethylamino > fluoro> nitro.

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