Journal of Fluorine Chemistry, 63 (1993) 233–241

Nucleophilic aromatic substitution reactions with the fluoride ion: formation of 5-fluoro-indanones and indandiones related to atipamezole

J. D. Enas*, J. G. Garcia, C. A. Mathis and J. M. Gerdes
Research Medicine and Radiation Biophysics Division, Lawrence Berkeley Laboratory, University of California, Berkeley, CA 94720 (USA)

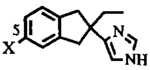
(Received May 29, 1992; accepted October 2, 1992)

Abstract

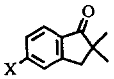
The 5-nitro and 5-(trimethylammonium trifluoromethanesulfonyl)indanones **2a**,**b** and the related 1,3-indandiones **3a**,**b** have been synthesized, and the efficiency of the nucleophilic aromatic substitution reaction with fluoride ion on these substrates evaluated. The indandiones underwent aromatic substitution to afford fluoroaromatic adducts whereas the indanone substrates provided little or no fluoro-substitution product. The fluoroindandione was subsequently reduced to the corresponding fluoroindane hydrocarbon. The synthetic sequence of nucleophilic fluorination followed by carbonyl reduction provides a rationale for the potential preparation of the radiofluorinated α_2-adrenoreceptor ligand 5-fluoroatipamezole.

Introduction

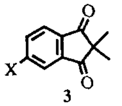
Atipamezole (**1a**) is a potent α_2-adrenoreceptor antagonist [1–3] and preliminary studies have targeted the related 5-fluoroatipamezole (**1b**) as a biologically active analogue [4]. The ^{18}F-radiolabeled form of **1b** ([^{18}F]-(**1b**)) is a potentially useful α_2-adrenoreceptor positron emission tomography (PET) ligand. In order to devise a synthetic route to the labeled [^{18}F]-(**1b**) utilizing the [^{18}F]-fluoride ion ($t_{1/2}$ = 110 min), we undertook the syntheses of the four indanones **2a**,**b** and **3a**,**b** and evaluated the subsequent transformation of these substrates, utilizing nucleophilic aromatic substitution reaction conditions, to their 5-fluoro-substituted forms (**2c** and **3c**, respectively). The electron-withdrawing carbonyl moieties attached to the aromatic ring and the nitro or trimethylammonium triflate nucleofuges were considered key



1a X = H, Atipamezole
1b X = F, 5-Fluoroatipamezole

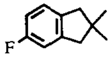


2



3

a X = NO$_2$
b X = N(CH$_3$)$_3$OTf
c X = F



4

---

*To whom all correspondence should be addressed.

0022-1139/93/$6.00 © 1993 – Elsevier Sequoia. All rights reserved

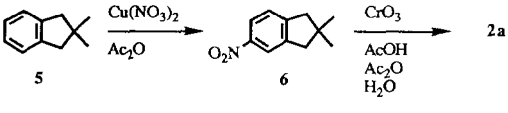
elements in assisting the fluoride ion-induced aromatic substitution reactions [5–8]. We subsequently demonstrated that the carbonyl functionalities could be reduced efficiently and expeditiously to afford the saturated 5-fluoroindane system **4**, an accomplishment essential for the application of this rationale to a synthesis of [^{18}F]-(**1b**).

Results and discussion

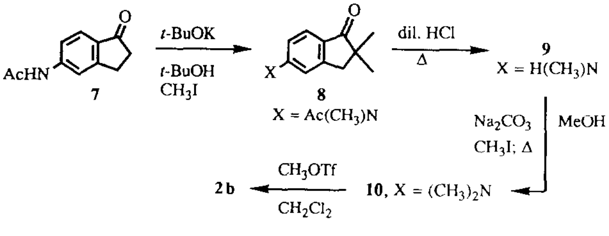
The synthetic routes employed for the preparation of the indanones **2a** and **2b** are shown in Schemes 1 and 2, respectively. The formation of **2a** was achieved starting from 2,2-dimethylindane (**5**) [9] which was nitrated [10] to yield the nitroindane **6**. Benzylic oxidation with chromium trioxide [11] afforded **2a**. The trimethylaniline **2b** was obtained from ketone **7** [12] by generation of the enolate with potassium t-butoxide in t-butanol followed by iodomethane quench (65%) to provide the dimethyl product **8**. Transformation of **8** to the 5-trimethylammonium triflate salt **2b** was effected by literature procedures [7, 11, 13].

The synthetic route to the 5-substituted indandiones **3a** and **3b** is shown in Scheme 3. Compound **3a** was prepared by nitration of 2,2-dimethyl-1-indanone (**11**) [14] followed by chromium trioxide oxidation of the benzylic position (48% overall yield). Reduction of **3a** [15] to the aminoindandione **13**, followed by a two-step exhaustive methylation [7, 16] of the amine moiety, afforded the triflate salt **3b** (16% from **3a**).

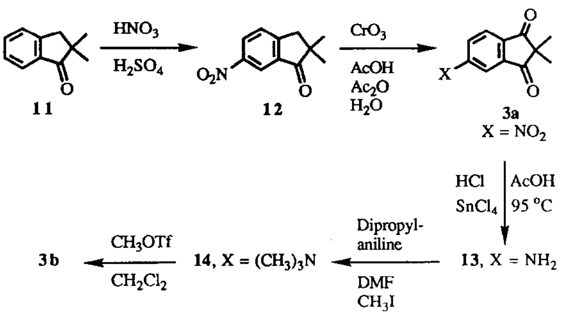
The ease with which the four indanones **2a,b** and **3a,b** were transformed to their 5-fluoro counterparts (**2c** and **3c**, respectively) under nucleophilic aromatic substitution conditions was evaluated and the results are summarized in Table 1. Surprisingly, neither of the 5-substituted indanones (**2a,b**) underwent fluoride substitution to any appreciable extent (< 5%) under the standard nucleophilic conditions of KF in DMSO (100–120 °C, 1–2 h) [5–8]. Furthermore, the 5-trimethylammonium triflate salt **2b** demethylated under these



Scheme 1. Synthesis of indanone **2a**.



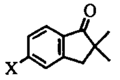
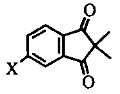
Scheme 2. Synthesis of indanone **2b**.



Scheme 3. Synthesis of indandione **3a** and **3b**.

TABLE 1

Nucleophilic aromatic substitution of indanones **2a,b** and indandiones **3a,b** with fluoride ion[a]

Starting material		Structure	Product		
Compound	X		Compound	X	Yield[b] (%)
2a	NO_2		**2c**	F	<5
2b	$N(CH_3)_3OTf$		**10**	$N(CH_3)_2$	52
3a	NO_2		**3c**	F	39
3b	$N(CH_3)_3OTf$		**3c**	F	45

[a] KF (120 mol%), indanone (100 mol%), DMSO, 100–120 °C, 1–2 h.
[b] Yields are isolated and optimized.

reaction conditions to provide **10** rather than undergoing fluoride-ion substitution. In contrast, both of the indandiones **3a,b** underwent fluoride-ion substitution to afford **3c** in acceptable yields. Other nucleophilic fluorination conditions, including: KF, CH_3CN, 80 °C; KF, DMSO, 18-crown-6, 80 °C; CsF, DMSO, 100–120 °C; $Bu^n{}_4NF$, DMSO, 80 °C, failed to provide increased quantities of **3c** relative to the KF, DMSO protocol. The increased activation of the indan-1,3-dione substrates **3a,b** toward fluoride-ion substitution relative to the monoketone substrates **2a,b** is noteworthy and synthetically useful. Reduction of the fluorodione **3c** to the fluoroindane **4** was accomplished with Et_3SiH, $BF_3 \cdot Et_2O$ at 70 °C for 2 h (44%) [17]. Other reductive conditions (e.g. Et_3SiH, CF_3CO_2H, 25 °C; $LiAlH_4$, P_2I_4, 80 °C; $HCONH_4$, Pd/C, 110 °C, H_2, Pd/C, 2 N HCl, 70 °C) failed to produce detectable quantities of **4** from **3c**.

In conclusion, indandione substrate of the type **3a,b** underwent nucleophilic fluoride-ion substitution to provide the 5-fluoroindandione **3c** whereas the indanones **2a,b** failed to provide significant amounts of fluoro-substituted aromatic product. The increased activation of the indan-1,3-dione aromatic ring toward fluoride-ion substitution is striking. The dione **3c** can be reduced to the fluorohydrocarbon **4** in one step. Efforts are currently underway to apply this fluoride substitution and subsequent ketone reduction rationale to the preparation of the radiolabelled α_2-adrenergic ligand [^{18}F]-(**1b**).

Experimental

All nonaqueous reactions were carried out under an argon or nitrogen atmosphere unless otherwise noted. High-performance liquid chromatography (HPLC) was performed with a Waters Associates 590 pumping system and a Whatman Partisil 10 or M9 (silica) column. The ^{1}H NMR spectra were recorded with either a Nicolet 200 or 300 MHz spectrometer or Bruker 300 MHz spectrometer with $CDCl_3$ as the internal standard (δ 7.26 ppm) unless stated otherwise. The ^{19}F NMR spectra were recorded at the National Tritium Labeling Facility (NTLF) with a Bruker 300 MHz spectrometer and with $CFCl_3$ as the standard (δ 0.00 ppm). Infrared (IR) spectra were obtained using a Perkin-Elmer model 1310 spectrometer with the sample as a thin film or in solution (CCl_4). Melting points reported are uncorrected and were obtained with a Mel-Temp melting point apparatus. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley. High (HRMS) and low (LRMS) resolution mass spectrometry data are given for those compounds which repeatedly gave unsatisfactory elemental analyses due to decomposition caused by exposure to air or moisture sensitivity. Mass spectral determinations were made at the Midwest Center for Mass Spectrometry, University of Nebraska–Lincoln.

*2,2-Dimethyl-5-nitroindane (**6**)*

A solution of 2,2-dimethylindane (**5**) (0.075 g, 0.51 mmol) in acetic anhydride (4 ml) at 0 °C was treated with $Cu(NO_3)_2 \cdot 2.5H_2O$ (0.090 g, 0.48 mmol). The mixture was stirred at 0 °C (1 h) and then at room temperature (48 h). The solution was poured into ice water, stirred overnight and extracted with $CHCl_3$. The combined organic layers were washed sequentially with water, sat. $NaHCO_3$ (aq.), water, and dried ($MgSO_4$). Concentration of the solvent afforded a yellow oil (0.078 g, 79%) which was utilized in the next step without further purification. A sample for characterization was obtained by HPLC (4:1 hexane/EtOAc) to afford the nitroindane **6** as a light yellow oil. ^{1}H NMR δ: 1.18 s, CH_3); 2.81 (s, CH_2); 7.28 (d, CH arom); 8.01 (s, CH arom); 8.05 (d, CH arom) ppm. IR (cm^{-1}): 1345 (s) (NO_2). HRMS *m/z*: 191.0774 (calc. for $C_{11}H_{13}NO_2$, 191.0740). LRMS *m/z*: 192 (10); 191 (M, base); 176 (M − 15, 23); 174 (26); 145 (38); 144 (14); 130 (39); 129 (24); 128 (17); 115 (18); 105 (8); 91 (8); 77 (8).

*2,2-Dimethyl-5-nitroindanone (**2a**)*

A solution of nitroindane **6** (0.053 g, 0.28 mmol) in acetic acid (0.25 ml) and acetic anhydride (0.1 ml) at 70 °C was treated with chromium trioxide (0.12 g, 1.2 mmol) in water (0.12 ml) and acetic acid (0.35 ml), and the mixture stirred overnight at 70 °C. The mixture was cooled, poured into ice water and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated to yield a light yellow liquid. HPLC purification (1:1 EtOAc/hexane) furnished the nitroindanone **2a** (0.034 g, 60%) as a pale yellow solid (m.p. 42–45 °C). ^{1}H NMR δ: 1.28 (s, CH_3); 3.11 (s, CH_2); 7.90 (d, CH arom); 8.25 (dd, CH arom); 8.30 (s, CH arom) ppm. IR (cm^{-1}): 1720 (s) (C=O); 1345 (s) (NO_2). HRMS *m/z*: 205.0742 (calc. for $C_{11}H_{11}NO_3$, 205.07381). LRMS *m/z*: 206 (6); 205 (48); 190 (76); 172 (29); 144 (15); 115 (15); 91 (base); 71 (14).

*2,2-Dimethyl-5-(N-acetyl-N-methyl)amino-1-indanone (**8**)*

To a solution of potassium t-butoxide in THF (Aldrich, 1.0 M, 23 ml) at 0 °C was added 5-acetamido-1-indanone (**7**) (1.4 g, 7.4 mmol) in THF (50 ml). The mixture was warmed to room temperature (10 min), cooled to 0 °C and quenched with iodomethane (1.6 ml, 26 mmol). The solution was warmed to room temperature and CH_2Cl_2 added. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, EtOAc) yielding the trimethylindanone **8** (1.1 g, 65%) as an oil which crystallized on standing and was utilized in the next step without further purification. A sample for characterization was obtained by recrystallization (Pr^{i}OH) affording a tan colored solid (m.p. 54–56 °C). ^{1}H NMR δ: 1.25 (s, CH_3); 1.74 (s, CH_3CO); 3.00 (s, CH_2); 3.29 (s, NCH_3); 7.20 (dd, CH arom); 7.26 (s, CH arom); 7.83 (d, CH arom) ppm. IR (cm^{-1}): 1730 (s) (C=O); 1670 (s) (C=O). HRMS *m/z*: 231.1259 (calc. for $C_{14}H_{17}NO_2$, 231.1259). LRMS *m/z*: 231 (M); 189 (47); 174 (base) 144 (5); 115 (8); 91 (7); 77 (7); 56 (28).

*2,2-Dimethyl-5-(N-methylamino)-1-indanone (**9**)*

The *N*-methyacetamidoindanone (**8**) (1.1 g, 4.8 mmol) was treated with 1.5 N HCl (20 ml) and the mixture was heated at reflux overnight. The solution was cooled to room temperature, made basic with 2 M NaOH and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and concentrated to a brown oil which was purified by chromatography (silica gel, 1:1 EtOAc/ hexane) to yield the methylaminoindanone **9** (0.65 g, 72%) as a light brown solid which was utilized in the next step without further purification. A sample for analysis was obtained by recrystallization (hexane) affording a tan colored solid (m.p. 102–104 °C). Analysis: Calc. for $C_{12}H_{15}NO$: C, 76.1; H, 7.99; N, 7.40%. Found: C, 76.20; H, 8.02; N, 7.48%. ^{1}H NMR δ: 1.19 (s, CH_3); 2.86 (s, NCH_3); 2.90 (s, CH_2); 6.44 (s, CH arom); 6.53 (dd, CH arom); 7.55 (d, CH arom) ppm. IR (cm^{-1}): 1750 (s) (C=O). HRMS *m/z*: 189.1152 (calc. for $C_{12}H_{15}NO$, 189.1154). LRMS *m/z*: 189 (M); 174 (base, M − 15); 144 (6); 130 (6); 115 (5); 91 (4); 77 (5).

2,2-Dimethyl-5-(N,N-dimethylamino)-1-indanone (10)

The *N*-methylaminoindanone (**9**) (0.33 g, 1.7 mmol) in MeOH (30 ml) was allowed to react with Na_2CO_3 (0.60 g, 5.5 mmol) and iodomethane (11 ml, 177 mmol). The mixture was heated at reflux for 30 h, cooled to room temperature and diluted with water. Extraction with $CHCl_3$, drying ($MgSO_4$) and concentration of the organic layer gave a residue which was purified by flash chromatography (silica gel. 3:7 EtOAc/hexane) to yield **10** as a white solid (0.23 g, 65%) which was utilized in the next step without further purification. A sample for characterization was obtained by recrystallization (EtOH) affording a white amorphous solid (m.p. 86–87 °C). ^1H NMR δ: 1.21 (s, CH_3); 2.89 (s, CH_2); 3.07 (s, NH_3); 6.53 (s, CH arom); 6.65 (dd, CH arom); 7.63 (d, CH arom) ppm. IR (cm^{-1}): 1695 (s) (C=O). HRMS *m/z*: 203.1303 (calc. for $C_{13}H_{17}NO$, 203.1312). LRMS *m/z*: 203 (M); 188 (base, M − 15); 171 (4); 151 (6); 115 (7); 91 (5); 77 (3).

2,2-Dimethyl-1-indanone-5-trimethylammonium trifluoromethanesulfonate (2b)

To a solution of dimethylaminoindanone (**10**) (0.23 g, 1.1 mmol) in CH_2Cl_2 (18 ml) was added methyl trifluoromethanesulfonate (0.14 ml, 1.2 mmol). The solution was stirred overnight at room temperature and then diluted with ether. A precipitate formed which was collected by vacuum filtration affording the triflate salt **2b** (0.28 g, 67%) as a white solid. A sample for characterization was recrystallized from benzene to afford **2b** as colorless needles (m.p. 124–126 °C). ^1H NMR (CD_3CN) δ: 1.20 (s, CH_3); 3.09 (s, CH_2); 3.57 (s, NCH_3); 7.79 (dd, CH arom); 7.87 (d, CH arom); 7.93 (s, CH arom) ppm. IR (cm^{-1}): 1720 (s) (C=O); 1260 (s) (S=O). HRMS *m/z*: 203.1290 (calc. for $C_{13}H_{17}NO$ [M − CH_3 and CF_3SO_3], 203.1315. LRMS *m/z*: 203 (M − CH_3 and CF_3SO_3); 188 (base); 171 (5); 144 (4); 115 (7); 91 (5); 77 (3).

2,2-Dimethyl-6-nitro-1-indanone (12)

A solution of 2,2-dimethyl-1-indanone (**11**) (3.1 g, 19 mmol) in sulfuric acid (25 ml) at 0 °C was treated with a mixture of nitric acid (2.1 ml) and sulfuric acid (3.2 ml). The mixture was stirred for 2 h at 5 °C, poured into ice water and extracted with ether. The combined ether extracts were washed with water, dried ($MgSO_4$) and concentrated to a pale yellow solid which was recrystallized (hexane/ether, 20:1) to afford **12** (2.4 g, 61%) as white needles (m.p. 104–105 °C); ^1H NMR δ: 1.28 (s, CH_3), 3.11 (s, CH^2), 7.62 (d, CH arom); 8.45 (dd, CH arom); 8.57 (s, CH arom) ppm. IR (cm^{-1}): 1725 (s) (C=O); 1345 (s) (NO_2). HRMS *m/z*: 205.0736 (calc. for $C_{11}H_{11}NO_3$, 205.0740). LRMS *m/z*: 205 (M); 190 (base, M − 15); 144 (28); 129 (9); 115 (29); 91 (13); 77 (7).

2,2-Dimethyl-5-nitro-1,3-indandione (3a)

To a solution of indanone **12** (2.4 g, 12 mmol) in acetic acid (11 ml) and acetic anhydride (3 ml) at 0 °C was added a solution of chromium trioxide (10 g, 0.10 mol) in water (2 ml) and HOAc (6 ml). The solution was stirred for 96 h at room temperature, then poured into ice water and extracted with $CHCl_3$. The organic phase was washed with 5% $NaHCO_3$, dried ($MgSO_4$) and concentrated to yield a solid which was recrystallized from hexane to afford the nitrodiketone **3a** (2.11 g, 80%) as a cream-colored amorphous solid (m.p. 83–84 °C). Analysis: Calc. for $C_{11}H_9NO_4$: C, 60.28; H, 4.14; N, 6.39%. Found: C, 60.03; H, 4.13; N, 6.30%. ^1H NMR δ: 1.21 (s, CH_3); 8.17 (d, CH arom); 8.68 (d, CH arom); 8.78 (s, CH arom) ppm. IR (cm^{-1}): 1755 (m) (C=O); 1725 (s) (C=O); 1345 (m) (NO_2). HRMS *m/z*: 219.0536 (calc. for $C_{11}H_9NO_4$, 219.0530). LRMS *m/z*: 219 (M, base); 204 (M − 15); 158 (13); 149 (42); 115 (17); 103 (43); 91 (6); 75 (46).

2,2-Dimethyl-5-amino-1,3-indandione (13)

A mixture of nitrodiketone **3a** (1.4 g, 6.2 mmol), hydrochloric acid (13 ml), acetic acid (6 ml) and anhydrous tin(II) chloride (4.0 g, 21 mmol) was heated at 95 °C for 1 h. After cooling, the mixture was poured into 2 M NaOH (100 ml) and extracted with ether. The ether extracts were combined, dried ($MgSO_4$) and concentrated. The resulting pale yellow solid was recrystallized (EtOH/water) to yield the aminodiketone **13** (0.97 g, 83%) as pale yellow needles (m.p. 163–165 °C). ^1H NMR δ: 1.26 (s, CH_3); 4.48 (b, NH); 7.02 (m, CH arom); 7.26 (s, CH arom); 7.78 (d, CH arom) ppm. IR (cm^{-1}): 1740 (s) (C=O); 1705 (s) C=O). HRMS *m/z*: 189.0763 (calc. for $C_{11}H_{11}NO_2$, 189.0796). LRMS *m/z*: 189 (M, base); 174 (M − 15); 160 (16); 146 (27); 119 (53); 91 (38); 74 (9).

2,2-Dimethyl-5-dimethylamino-1,3-indandione (14)

A solution of aminodione **13** (0.47 g, 2.5 mmol), dimethylformamide (8 ml), *N,N*-dipropylaniline (2 ml, 11 mmol) and iodomethane (1.5 ml, 24 mmol) was stirred at reflux for 3 h. After cooling, water was added and the mixture was extracted with ether. The combined ether extracts were washed with water, dried ($MgSO_4$) and concentrated to yield a brown viscous oil which was purified first by HPLC (1:1 EtOAc/hexane) and then by recrystallization (EtOH) to afford the dimethylaminodiketone **14** (0.26 g, 48%) as yellow needles (m.p. 120–122 °C). ^1H NMR δ; 1.26 (s, CH_3); 3.15 (s, NCH_3); 6.97 (d, CH arom); 7.03 (dd, CH arom); 7.78 (d, CH arom) ppm. IR (cm^{-1}): 1740 (m) (C=O): 1700 (s) (C=O). HRMS *m/z*: 217.1098 (calc. for $C_{13}H_{15}NO_2$, 217.1104). LRMS *m/z*: 217 (M, base); 202 (M − 15); 188 (12); 174 (16); 147 (15); 119 (16); 69 (8).

2,2-Dimethyl-1,3-indandione-5-trimethylammonium trifluoromethanesulfonate (3b)

To a solution of diketone **14** (0.28 g, 1.3 mmol) in CH_2Cl_2 (25 ml) was added methyl trifluoromethanesulfonate (0.3 ml, 2.7 mmol). The solution was stirred overnight at room temperature and then diluted with ether. A precipitate formed which was collected by vacuum filtration to afford the triflate salt **3b** (0.22 g, 45%) as a white solid. A sample for analysis was recrystallized from THF to afford **3b** as colorless needles (m.p. 129–131 °C). Analysis: Calc. for $C_{15}H_{18}F_3NO_5S$: C, 47.24; H, 4.76; N, 3.67%. Found: C, 47.31; H, 4.93; N, 3.26%. ^1H NMR (CD_3CN) δ: 1.27 (s, CH_3); 3.62 (s, NCH_3); 8.17 (d, CH arom); 8.29 (d, CH arom); 8.33 (s, CH arom) ppm. IR (cm^{-1}); 1755 (s) (C=O); 1715 (s) (C=O); 1260 (s) (S=O).

*General procedure for the fluorination of indanones **2a,b** and **3a,b***

The reaction conditions and yields for the nucleophilic fluorination reaction of indanones **2a,b** and **3a,b** are described in Table 1. The crude reaction mixtures were cooled, diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed twice with saturated $NaHCO_3$ (aq.), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residues were purified by HPLC (3:2 CH_2Cl_2/hexane).

*(a) 2,2-Dimethyl-5-fluoro-1-indanone (**2c**)*

Recrystallized from hexanes (m.p. 63–64 °C). Analysis: Calc. for $C_{11}H_{11}FO$: C, 74.14; H, 6.22%. Found: C, 74.44; H, 6.29%. ^1H NMR δ: 1.21 (s, CH_3); 2.86 (s, CH_2); 7.05 (m, CH arom); 7.73 (dd, CH arom) ppm. ^{19}F NMR δ: −102.05 (ddd) ppm. IR (cm^{-1}): 1710 (s) (C=O).

*(b) 2,2-Dimethyl-5-fluoro-1,3-indandione (**3c**)*

Recrystallized from EtOH (m.p. 108–110 °C). Analysis: Calc. for $C_{11}H_9FO_2$: C, 68.74; H, 4.72%. Found: C, 68.65; H, 4.74%. ^1H NMR δ: 1.30 (s, CH_3); 7.56 (m. CH arom); 8.01 (dd, CH arom) ppm. ^{19}F NMR δ: −98.17 (ddd) ppm. IR (cm^{-1}): 1720 (s) (C=O).

*2,2-Dimethyl-5-fluoroindane (**4**)*

Boron trifluoride etherate (1.3 ml, 1.1 mmol) was added to a mixture of fluorodiketone **3c** (0.11 g, 0.57 mmol) and triethylsilane (3 ml, 1.9 mmol). The mixture was heated at 70 °C for 2 h, cooled and diluted with ether. Excess 2 M NaOH was added and the mixture was stirred for 5 min at room temperature. The layers were separated and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was dissolved in hexanes and passed through a short plug of silica gel to afford, after concentration, the fluoroindane **4** (42 mg, 44%) as a colorless oil. ^1H NMR δ: 1.16 (s, CH_3); 2.67 (s, CH_2); 2.71 (s, CH_2); 6.84 (m, CH arom); 7.08 (dd, CH arom) ppm. ^{19}F NMR δ: −117.23 (ddd) ppm. IR (cm^{-1}): 1600 (C=C); 1240 (s) (C−F). HRMS *m/z*: 164.1018 (calc. for $C_{11}H_{13}F$, 164.0998). LRMS *m/z*: 164 (M); 149 (base, M−15); 133 (12); 123 (8); 109 (23); 85 (3); 73 (9).

Acknowledgements

This research was supported by NIH Grants HL07367, HL95840 and NS28867, and the US Department of Energy (DE-AC0376SF00098). The

NTLF is supported by NIH Grant RR01237, National Center for Research Resources. We thank H. Sipila of Farmos Group Ltd. (Turku, Finland) and Dr A. T. Shulgin for helpful discussions.

References

1 R. Virtanen, J.-M. Savola and V. Saano, *Arch. Int. Pharmacodyn. Ther.*, *297* (1989) 190.
2 R. R. Ruffolo, *Neurotransmissions*, *6* (1990) 1.
3 M. J. Durcan, R. G. Lister and M. Linnoila, *Psychopharmacology*, *97* (1989) 189.
4 H. Sipila, Farmos Group Ltd., personal communication.
5 C. Lemaire, M. Guillaume, L. Christiaens, A. J. Palmer and R. Cantineau, *Appl. Radiat. Isot.*, *38* (1987) 1033.
6 M. Attina, F. Cacace and A. P. Wolf, *J. Labelled Compd. Radiopharm.*, *20* (1983) 501.
7 M. S. Haka, M. R. Kilbourn and G. L. Watkins, *J. Labelled Compd. Radiopharm.*, *26* (1989) 17.
8 M. R. Kilbourn, *Fluorine-18 Labeling of Radiopharmaceuticals*, Nuclear Science Series (NAS-NA-3203), National Academy Press, Washington, DC, 1990.
9 O. K. Popova, Z. N. Parnes, M. I. Katinkin, S. M. Markosyan, N. I. Kopteva, L. P. Zalukaev and D. N. Kursanov, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, (1981) 2084.
10 S. Kapur, N. C. Mathur, K. McManus, A. L. Pincock and J. A Pincock, *Can. J. Chem.*, *66* (1988) 2888.
11 N. L. Allinger and E. S. Jones, *J. Org. Chem.*, *27* (1962) 70.
12 P. Lemmen and D. Lenoir, *Chem. Ber.*, *117* (1984) 2300.
13 Z. R. Grabowski, J. Dobkowski and W. Kuhnle, *J. Mol. Struct.*,*114* (1984) 93.
14 K. Ohkata, M. Akiyama, K. Wada, S. Shun, Y. Toda and T. Hanafusa, *J. Org. Chem.*, *49* (1984) 2517.
15 K. Schofield, T. Swain and R. S. Theobald, *J. Chem. Soc.*, (1949) 2399.
16 H. Z. Sommer, H. I. Lipp and L. L. Jackson, *J. Org. Chem.*, *36* (1971) 824.
17 M. P. Doyle, C. T. West, S. J. Donnelly and C. C. McOsker, *J. Organometal. Chem.*, *117* (1976) 129.