N-bromosuccinimide and 300 mg of benzoyl peroxide. The mixture was refluxed for 6 h, stirred overnight at room temperature, and filtered. The filtrate was concentrated to a reddish-brown oil which was diluted with 1.5 L of hexane to give crystals. The product was collected on a filter and washed four times with 200-mL portions of hexane and then dried to constant weight to afford 185 g of III, mp 112.5–117.1 °C. A second crop of 27 g of slightly less pure compound resulted in a total yield of 55%. Yields varied from 55–73% in this reaction. Identification was confirmed by NMR and mass spectral data: NMR ($CDCl_3$, Me_4Si) δ 0.9 (d, 3 H), 1.2 (d, 3 H), 1.5 (d, 3 H), 2.1–2.5 (m, 1 H), 3.7 (q, 1 H), 4.7 (d, 2 H), 7.2 (s, 4 H); mass spectrum (70 eV), *m/e* (relative intensity) 286 (M^+, 0.6), 284 (M^+, 0.6), 205 (M^+–Br, 100). Anal. Calcd for $C_{13}H_{17}BrO_2$: C, 54.74; H, 5.96. Found: C, 54.53; H, 5.91).

2-[*p*-(2-Methylprop-1-ene)phenyl]propionic Acid, IV. A solution of 100 g (0.35 mol) of III, 72 g (0.83 mol) of lithium bromide, and 1.5 L of DMF was heated under nitrogen between 80–100 °C for 5 h. The reaction was judged complete (by NMR of an aliquot) at this time. The solution was cooled to room temperature, diluted with 5 L of H_2O and extracted with three 1-L portions of ether. The ether extracts were combined and washed with two 1-L portions of water and 500 mL of brine. After the solution was dried over $MgSO_4$, the ether was removed in vacuo to give 73 g (100%) of a yellow oil. The quality (estimated at 95% by NMR analysis) was suitable for the next step without further purification; NMR ($CDCl_3$, Me_4Si) δ 1.5 (d, 3 H), 1.82 (s, 3 H), 1.90 (s, 3 H), 3.7 (q, 1 H), 6.2 (s, 1 H), 7.2 (d, 4 H).

2-[*p*-(2-Methyl-1,2-epoxypropyl)phenyl]propionic Acid, V. To a well-stirred solution of 73 g (0.35 mol) of IV in 750 mL of CH_2Cl_2 at room temperature under N_2 was added a slurry of 72 g (0.37 mol, 85% quality) of *m*-chloroperbenzoic acid in 700 mL of CH_2Cl_2. The reaction was slightly exothermic and was maintained below 35 °C with a water bath. After 2 h the reaction was judged complete by TLC, and the volume was reduced to 500 mL in vacuo. Upon dilution with an equal volume of hexane, *m*-chlorobenzoic acid (*m*-CBA) precipitated. The solids were filtered and washed with hexane to dissolve any V. The filtrate was concentrated to an oil and again diluted with 500 mL of hexane. More *m*-chlorobenzoic acid was removed by filtration (total of 46 g). The filtrate was concentrated to an oil which was used in the next step without further purification. An NMR of the product showed only epoxide and *m*-CBA present: NMR ($CDCl_3$, Me_4Si) δ 1.0 (s, 3 H), 1.4 (s, 3 H), 1.5 (d, 3 H), 3.7 (q, 1 H), 3.8 (s, 1 H), 7.3 (s, 4 H).

2-[*p*-(2-Methyl-2-hydroxypropyl)phenyl]propenoic Acid, VI. To a solution of V, obtained in the previous step (~80 g, 0.3 mol) in 1 L of THF at 15 °C under N_2 was added dropwise over 2 h 550 mL of 20% potassium *tert*-butoxide in THF. As the pH became neutral, a milky slurry resulted, and as the pH became basic an orange mixture was observed. The reaction was followed by TLC. After disappearance of starting material the reaction was quenched by the dropwise addition of 1 N HCl over a 20-min period at 15 °C. The two-phase, acidic system was diluted with 700 mL of ether, and the aqueous phase was removed. The organic phase was washed twice with 1 L of H_2O and once with 500 mL of saturated sodium chloride and dried over $MgSO_4$. The mixture was filtered, and the filtrate concentrated to a yellow oil. The oil was azeotroped with 500 mL of cyclohexane and then slurried with another 500 mL of cyclohexane until crystallization occurred. The solids were filtered, washed twice with fresh cyclohexane, and dried to constant weight to give 52.4 g as a first crop and 7.3 g as a second crop. The yield from IV to VI was 78%. Recrystallization of 50 g of VI from acetone/cyclohexane afforded 30.9 g of material, mp 110–114 °C (single zone by TLC), and 13.4 g of a less pure second crop; NMR ($CDCl_3$, Me_4Si) δ 1.3 (s, 6 H), 2.8 (s, 2 H), 6.0 (s, 1 H), 6.3 (s, 1 H), 6.5 (s, 1 H), 7.1–7.5 (m, 4 H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.90; H, 7.27. Found C, 70.72; H, 7.44.

2-[*p*-(2-Methyl-2-hydroxypropyl)phenyl]propionic Acid, I. A mixture of 27 g (0.12 mol) of VI, 250 mL of THF, and 1 g of 10% Pd/C was placed in a Parr hydrogenation apparatus and reduced under 50 psi of H_2 at room temperature for 1.5 h. The resulting mixture was filtered through a Celite pad, and the filtrate concentrated to a yellow oil. The oil was slurried in 400 mL of cyclohexane for a few minutes and crystallization of a white solid was observed. The solids were filtered, washed with fresh cyclohexane, and dried to constant weight at 50 °C in vacuo to give 27.2 g (quantitative yield) of I, mp 120–122 °C. TLC and NMR data were identical with those of authentic material;[7] NMR ($CDCl_3$, Me_4Si) δ 1.2 (s, 6 H), 1.5 (d, 3 H), 2.7 (s, 2 H), 3.7 (q, 1 H), 5.9 (s, 2 H), 7.1–7.3 (m, 4 H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.20; H, 8.46.

2-[*p*-(2-Methylpropyl)phenyl]propenoic Acid, VII. To a solution of 5 g (0.018 mol) of III in 100 mL of tetrahydrofuran (THF) was added 25 mL of 20% potassium *tert*-butoxide in THF. The mixture became cloudy and after 15 min was poured onto 100 mL of ice-cold 5% HCl and extracted with 100 mL of ether. The ether solution was washed twice with 50 mL of water and once with 25 mL of saturated sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated to an oil. The oil was dissolved in 25 mL of hexane and stored overnight in a freezer. The solids were collected on a filter, washed with cold hexane, and dried to give 1.96 g of VII (55%, additional material can be obtained in a second crop): mp 88.5–92.8 °C; NMR ($CDCl_3$, Me_4Si) δ 0.91 (d, 6 H), 1.5–2.2 (m, 1 H), 2.3 (d, 2 H), 6.0 (s, 1H), 6.5 (s, 1 H), 7.1–7.45 (m, 4 H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 76.47; H, 7.84. Found: C, 75.87; H, 7.97.

Registry No. I, 51146-55-5; II, 15687-27-1; III, 75625-98-8; IV, 75625-99-9; V, 75626-00-5; VI, 75626-01-6; VII, 6448-14-2.

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Improved Synthesis of Fluoroveratroles and Fluorophenethylamines via Organolithium Reagents[1]

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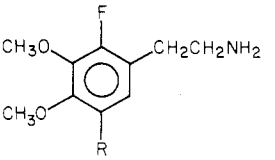
The introduction of fluorine into biologically active molecules often induces interesting new pharmacological properties.[2] The reported[3] synthesis of [2-(2-fluoro-3,4-dimethoxyphenyl)ethyl]amine, 1, is lengthy and requires



1, R = H
2, R = F

a low-yield photochemical Schiemann reaction for the introduction of fluorine. Therefore, we wished to find an improved synthesis which would afford 1 as well as the difluoro analogue 2.

It is known[4,5] that 3-fluoroveratrole can be converted to 2-fluoro-3,4-dimethoxyphenylacetonitrile via the benzyl

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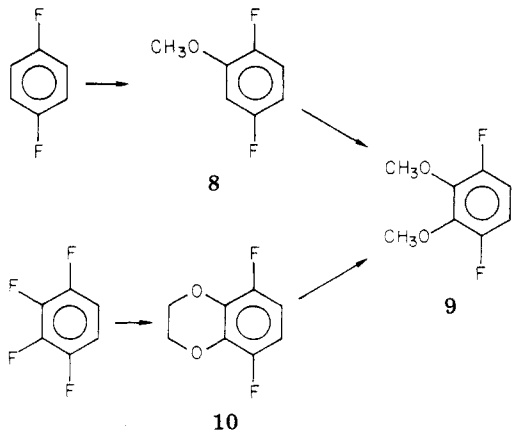
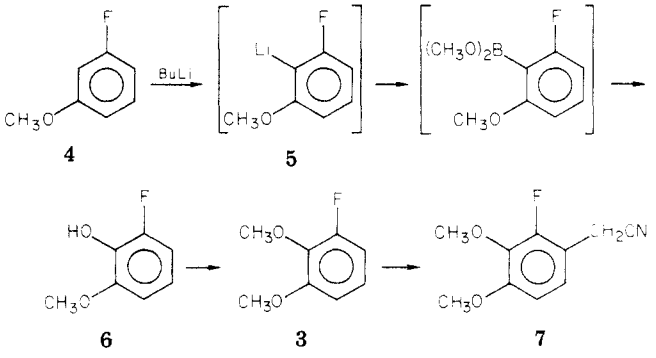
Scheme I



chloride; reduction of the nitrile would yield the (phenylethyl)amine 1.

3-Fluoroveratrole (3) has been prepared[6] from 2,3-dimethoxybenzoic acid by conversion to the aniline and a subsequent Schiemann procedure which gave variable and often low yields. To avoid this, we decided to investigate the preparation of 3 from commercially available 3-fluoroanisole (4). It is well-known that both F and OCH_3



in aromatic systems activate the ortho hydrogen for metalation.[7] This suggested that 4 should lithiate preferentially in the 2-position.

Huisgen and Rist[8] reacted 4 with phenyllithium at room temperature and isolated products which suggested that 5 formed and subsequently collapsed to the benzyne.

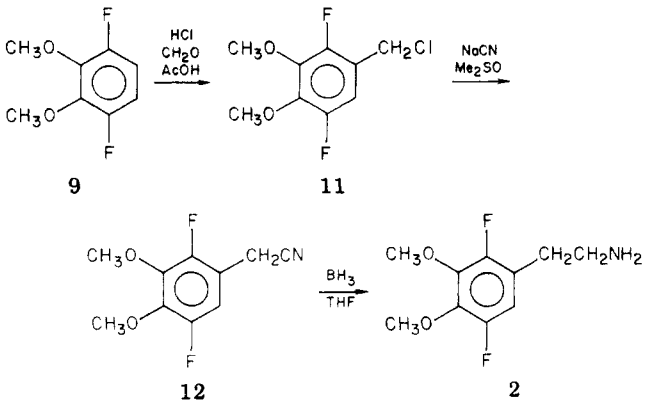
We also found that 4 could be lithiated in the 2-position. Reaction of 4 with *n*-butyllithium at −65 °C followed by conversion to the phenol 6 via the boronic ester using Hawthorne's method[9] followed by methylation gave 3-fluoroveratrole (3) in two steps. The product 3 was identical in all respects with a sample prepared by the sequence from 2,3-dimethoxybenzoic acid.

The phenylacetonitrile 7 was then prepared by a modification of the literature[5] procedure and converted to the (phenylethyl)amine with diborane. The product 1·HBr was identical with the product reported by Kirk.[3]

Lithiation of *p*-difluorobenzene followed by conversion to the phenol and methylation as described above afforded 8 (Scheme I). We anticipated that 8 would also lithiate ortho to the OCH_3 and F groups. This was found to be the case and 9 was prepared by following the same sequence of reactions.

The structure of 9 was established by independent synthesis. 1,2,3,4-Tetrafluorobenzene was converted to 5,8-difluoro-2,3-dihydro-1,4-benzodioxin (10) by a modification of the method[10,11] used to prepare 5,6,7,8-tetrafluoro-2,3-dihydro-1,4-benzodioxin from hexafluorobenzene; conversion to the catechol followed by methylation gave 9 which was identical with the product prepared above. This establishes the positions of the fluorines and the oxygens in 9 and 10 since 9 was prepared from 1,4-difluorobenzene and in 2,3-dihydro-1,4-benzodioxins the oxygens are 1,2 in the aromatic ring.

The difluorophenethylamine 2 was prepared from 9 in a manner analogous to the monofluorophenethylamine.



The second fluorine makes the chloromethylation more difficult. Thus 3-fluoroveratrole (3) requires 4.5 h at 20–25 °C and 3,6-difluoroveratrole (9) requires 12 h at 75 °C. Under conditions necessary to form 11 in substantial quantity a significant amount of bischloromethylation occurs.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the analytical departmant of Smith Kline and French Laboratories. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU 6E spectrometer, and ^1H NMR spectra were obtained on a Varian T60 spectrometer using tetramethylsilane as an internal standard. IR spectra were obtained on a Perkin-Elmer 735 spectrometer as Nujol mulls for solid and neat films for liquids and oil. VPC was done on a Perkin-Elmer 3920 gas chromatograph using a 3-ft 3% OV 101 on Chromosorb W column.

2-Hydroxy-3-fluoroanisole (6). A solution of 75.0 g (0.595 mol) of *m*-fluoroanisole in 660 mL of dry THF was cooled in a dry ice–acetone bath under an argon atmosphere, and then 218 mL (0.566 mol) of 2.6 M *n*-butyllithium in hexane was added over 15 min below −65 °C. The resultant solution was stirred for 2.25 h at −75 °C, and then a solution of 57.8 g (0.566 mol) of trimethylborate in 780 mL of dry ether was added over 15 min below −65 °C; the cooling bath was removed and stirring continued for 1.25 h. A solution of 390 mL of 10% HCl was added slowly, stirring was continued for 20 min, and the layers were separated. The organic layer was washed twice with H_2O, dried over $MgSO_4$, and concentrated to 77.2 g of white crystalline boronic acid.

The crude boronic acid was dissolved in 495 mL of toluene with warming, and then 186 mL of 30% H_2O_2 was added slowly to the warm solution, causing a vigorous exothermic reaction. The reaction mixture was then heated for 45 min on a steam bath and cooled to room temperature and the layers were separated. The organic layer was washed once with H_2O, twice with 10% ferrous ammonium sulfate, and again with H_2O and filtered. The toluene filtrate was extracted twice with 10% NaOH; the extracts were acidified with concentrated HCl with cooling. Two extractions with CH_2Cl_2, followed by drying over $MgSO_4$ and concentrating,

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yielded 44.5 g (53%) of crude phenol as a dark liquid. An analytical sample was prepared by vacuum distillation, giving a light yellow liquid: bp 129.5–131 °C (36 mm); mass spectrum, m/e 142 (M^+), 127 ($M^+ - CH_3$, base), 99, 51; ^1H NMR ($CDCl_3$) δ 3.83 (s, 3, OCH_3), 5.47 (br s, 1, ArOH), 6.63 (m, 3, Ar H). Anal. Calcd for $C_7H_7FO_2$: C, 59.15; H, 4.96. Found: C, 59.47; H, 5.01.

3-Fluoroveratrole (3). A mixture of 44.5 g (0.313 mol) of **6**, 445 mL of dry acetone, 86.5 g (0.626 mol) of powdered anhydrous K_2CO_3, and 59.3 mL (0.626 mol) of Me_2SO_4 was stirred and refluxed for 4 h, and then stood over night at room temperature. An additional 21.6 g (0.156 mol) of K_2CO_3 and 14.8 mL (0.156 mol) of Me_2SO_4 were added and the mixture refluxed for an additional hour. After cooling to room temperature the reaction mixture was diluted with H_2O and extracted twice with ether. The combined ether extracts were washed twice with H_2O and then stirred for 1.5 h with a dilute solution of NH_4OH; the layers were separated, and the organic layer was washed three times with H_2O, dried over $MgSO_4$, and concentrated without heat to a brown liquid. Vacuum distillation yielded 33.1 g (68%): bp 93.5–106 °C (19–24 mm) [lit.[6] bp 96–97 °C (20 mm)]; single component by VPC; mass spectrum, m/e 156 (M^+, base), 141 ($M^+ - CH_3$), 113, 65; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3, OCH_3), 3.93 (s, 3, OCH_3), 6.77 (m, 3, Ar H). Anal. Calcd for $C_8H_9FO_2$: C, 61.53; H, 5.81. Found: C, 61.54; H, 6.05.

2-Fluoro-3,4-dimethoxybenzyl Chloride. HCl gas was bubbled into a solution of 25.0 g (0.160 mol) of **3** in 100 mL of glacial acetic acid containing 25 mL of 37% CH_2O while the temperature was maintained at 20–25 °C with water-bath cooling. After 4.5 h the reaction was shown to be complete by VPC and was poured into H_2O and extracted twice with ether. The ether extracts were washed three times with H_2O, dried over $MgSO_4$, and concentrated to 31.1 g of white solid: IR indicated some AcOH was present; mp 44.5–47.5 °C (lit.[4] mp 50.5–51.5 °C); 95% yield; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 4.57 (s, 2, CH_2Cl), 6.85 (m, 2, Ar H).

2-Fluoro-3,4-dimethoxyphenylacetonitrile (7). Sodium cyanide, 9.19 g (0.187 mol), was added to a solution of 30.7 g (0.150 mol) of 2-fluoro-3,4-dimethoxybenzyl chloride in 530 mL of Me_2SO; a mild exotherm was observed. After being stirred for 45 min the reaction mixture was poured into 1 L of ice H_2O and extracted three times with ether. The combined extracts were washed four times with H_2O, dried over $MgSO_4$, and concentrated to 26.9 g (92%) of a light yellow liquid; ^1H NMR ($CDCl_3$) δ 3.67 (s, 2, CH_2CN), 3.85 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 6.85 (m, 2, Ar H).

[2-(2-Fluoro-3,4-dimethoxyphenyl)ethyl]amine Hydrobromide (1·HBr). A solution of 25.9 g (0.133 mol) of nitrile **7** in 259 mL of THF was added slowly to 259 mL of 1.0 M BH_3 in THF with ice-bath cooling. The resultant solution was refluxed for 1.5 h and cooled in an ice bath, 250 mL of MeOH was added slowly, and then the mixture was refluxed for 0.5 h and concentrated to dryness, leaving an oil. The oil was dissolved in MeOH and concentrated and then redissolved in MeOH, 50 mL of 10% HCl was added slowly, and then the mixture was refluxed for 0.5 h and concentrated. The residue was dissolved in 2.5 L of H_2O containing 50 mL of 10% HCl, washed twice with ether, basified with 40% NaOH, and extracted with ether. The aqueous solution was partially saturated with NaCl and extracted twice with ether. The ether extracts were combined, dried over $MgSO_4$, and concentrated to 19.9 g (76%) of colorless oil; ^1H NMR ($CDCl_3$) δ 1.23 (br s, 2, NH_2), 2.77 (m, 4, CH_2CH_2), 3.82 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 6.63 (m, 2, Ar H).

The free base, 3.95 g (0.0198 mol), was dissolved in 100 mL of absolute EtOH and 21.8 mL of 1 N HBr added. The solvent was removed with mild heating on the rotary evaporator and the residual white solid recrystallized from MeOH/ether: 3.54 g (64%); mp 178–179 °C (lit.[3] mp 174–177 °C). Anal. Calcd for $C_{10}H_{15}BrFNO_2$: C, 42.88; H, 5.40; N, 5.00. Found: C, 42.82; H, 5.44; N, 5.02.

2,5-Difluorophenol was obtained in 59% crude yield as a white solid by the procedure for **6**. An analytical sample was prepared by sublimation at aspirator pressure and 45 °C: mp 41–42.5 °C (lit.[12] mp 42 °C); mass spectrum, m/e 130 (M^+), 101, 82 (base), 81, 63; ^1H NMR ($CDCl_3$) δ 4.97 (br s, 1, OH), 6.65 (m, 3, Ar H). Anal. Calcd for $C_6H_4F_2O$: C, 55.39; H, 3.10. Found: C, 55.11; H, 3.01.

2,5-Difluoroanisole (8). A mixture of 23.9 g (0.184 mol) of 2,5-difluorophenol, 240 mL of acetone, 30.5 g (0.221 mol) of powdered anhydrous K_2CO_3, and 20.9 mL (0.221 mol) of Me_2SO_4 was stirred and refluxed for 2 h, cooled, diluted with H_2O, and extracted twice with ether. The combined ether extracts were washed twice with H_2O and then stirred for 1.5 h with 300 mL of 15% NH_4OH. The ether layer was separated, washed with H_2O, dried over $MgSO_4$, and concentrated to 25.1 g (95%) of light yellow liquid. Distillation of 12.5 g of crude product afforded 11.7 g (89%) of **8** as colorless liquid: bp 72–73 °C (25 mm); mass spectrum, m/e 144 (M^+), 129 ($M^+ - CH_3$), 101 (base); ^1H NMR ($CDCl_3$) δ 3.83 (s, 3, OCH_3), 6.75 (m, 3, Ar H). Anal. Calcd for $C_7H_6F_2O$: C, 58.34; H, 4.20. Found: C, 58.56; H, 4.12.

3,6-Difluoroguaiacol was obtained from **8** in 62% crude yield as a tan liquid by the procedure for **6**. A colorless analytical sample was prepared by distillation: bp 113.5–114.5 °C (37 mm); mass spectrum, m/e 160 (M^+), 145 ($M^+ - CH_3$, base), 117, 97, 69; ^1H NMR ($CDCl_3$) δ 3.97 (d, 3, OCH_3), 5.53 (br s, 1, ArOH), 6.57 (m, 2, Ar H). Anal. Calcd for $C_7H_6F_2O_2$: C, 52.51; H, 3.78. Found: C, 52.58; H, 3.92.

3,6-Difluoroveratrole (9). The crude product was obtained as a light yellow liquid in 94% yield as described for **8** using a 100% excess of Me_2SO_4 and K_2CO_3. Distillation afforded an 86% yield of colorless liquid: bp 93.5–95 °C (32 mm); mass spectrum, m/e 174 (M^+, base), 159 ($M^+ - CH_3$), 131, 111, 83; ^1H NMR ($CDCl_3$) δ 3.95 (s, 6, OCH_3), 6.68 (d of d, 2, Ar H). Anal. Calcd for $C_8H_8F_2O_2$: C, 55.18; H, 4.63. Found: C, 55.19; H, 4.38.

[2-(2,5-Difluoro-3,4-dimethoxyphenyl)ethyl]amine Hydrobromide (2·HBr). A solution of 20.8 g (0.119 mol) of **9**, 208 mL of glacial acetic acid, and 42 mL of 37% CH_2O was heated at 75 °C and HCl gas was bubbled in for 7.5 h (an additional 21 mL of 37% CH_2O was added after 4.75 h). The reaction mixture stood overnight at room temperature and then was heated and HCl was added for 4.5 h; the mixture was cooled, poured into H_2O, and extracted three times with Et_2O. The combined Et_2O extracts were washed several times with H_2O, dried over $MgSO_4$, and concentrated to 25.2 g (95%) of crude **11**; VPC and NMR showed that some bischloromethylated product and starting material (**9**) were present. Crude **11**, 25.2 g (0.113 mol), NaCN, 7.9 g (0.16 mol), and 500 mL of Me_2SO were reacted together for 1.5 h and worked up as described for **7**, giving 21.2 g (88%) of crude nitrile **12**; VPC and NMR showed that some biscyanomethylated product as well as some **9** was present. Crude nitrile **12**, 21.1 g (0.0990 mol), was reduced with diborane as described for **1**. The crude oil was partitioned between ether and dilute HCl; the aqueous layer was basified with 40% NaOH with cooling and extracted twice with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give 14.2 g (66%) of light yellow oil (**2**); ^1H NMR ($CDCl_3$) δ 1.43 (br s, 2, NH_2), 2.80 (m, 4, CH_2CH_2), 3.95 (2 s, 6, OCH_3), 6.63 (q, 1, Ar H).

The free base (**2**), 0.78 g (3.6 mmol), was dissolved in 18 mL of absolute EtOH and 3.95 mL of 1 N HBr added. Removal of the solvent at 35 °C on the rotary evaporator left an oil which was treated with MeOH/Et_2O, giving 0.05 g of white solid, 4,5-bis(2-aminoethyl)-3,6-difluoroveratrole·2HBr, mp 222–225 °C; the mother liquor was concentrated and then chromatographed on silica gel, eluting with CH_2Cl_2 with a MeOH gradient. Pure (high-performance LC) monophenethylamine·HBr, 0.20 g (19%), was obtained as an oil: mass spectrum, m/e 217 (M^+, free base), 200, 197, 188 (base), 187, 173; ^1H NMR ($CDCl_3$) δ 3.23 (m, 4, CH_2CH_2), 3.90 (s, 6, OCH_3), 6.78 (q, 1, Ar H), 7.53 (br s, 3, NH_3^+). Anal. Calcd for $C_{10}H_{14}BrF_2NO_2 \cdot 0.5H_2O$: C, 39.10; H, 4.92; N, 4.56. Found: C, 38.85; H, 4.92; N, 4.24.

2-(2,3,6-Trifluorophenoxy)ethanol. 1,2,3,4-Tetrafluorobenzene, 7.84 g (0.0522 mol), NaOH, 2.40 g (0.060 mol), and 52 mL of ethylene glycol were refluxed for 3.5 h, then cooled, and poured into H_2O. The solution was acidified with dilute HCl and extracted twice with Et_2O; the combined extracts were washed first with 10% NaOH and then with H_2O, dried over $MgSO_4$, and concentrated to give 4.18 g (42%) of colorless liquid: mass spectrum, m/e 192 ($M^+ - H_2O$), 148 (base), 100, 55; ^1H NMR δ 3.07 (br s, 1, OH), 3.88 (t, 2, CH_2OH), 4.28 (t, 2, $ArOCH_2$), 6.78 (m, 2, Ar H).

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5,8-Difluoro-2,3-dihydro-1,4-benzodioxin (10). A mixture of 2-(2,3,6-trifluorophenoxy)ethanol, 4.13 g (0.0215 mol), K_2CO_3, 3.12 g (0.0226 mol), and 62 mL of DMF was refluxed overnight, cooled, and poured into H_2O. The solution was made acidic with 10% HCl and then extracted twice with Et_2O; the extracts were washed three times with H_2O, twice with 10% NaOH, and again with H_2O. The Et_2O solution was dried over $MgSO_4$ and concentrated to dryness, leaving 1.56 g (42%) of a white solid, mp 44–47 °C. An analytical sample was prepared by recrystallization from EtOH/H_2O: mp 54–57 °C; mass spectrum, m/e 172 (M^+), 157, 116, 88 (base); ^1H NMR ($CDCl_3$) δ 4.37 (s, 4, OCH_2CH_2O), 6.57 (t, 2, Ar H). Anal. Calcd for $C_8H_6F_2O_2$: C, 55.82; H, 3.51. Found: C, 55.96; H, 3.74.

3,6-Difluorocatechol. Anhydrous $AlCl_3$, 2.4 g, was added to a solution of **10**, 0.64 g (3.7 mmol), in 25 mL of toluene and then the mixture was refluxed for 4.5 h under a N_2 atmosphere. The reaction mixture was cooled, poured onto ice, and acidified with concentrated HCl and the layers were separated. The aqueous layer was extracted twice with Et_2O; the Et_2O extracts were combined with the toluene layer, washed with H_2O, dried over $MgSO_4$, and concentrated to a dark residue. Kugelrohr distillation of this residue at 15 mm and up to 105 °C afforded 0.41 g (76%) of white solid: mass spectrum, m/e 146 (M^+, base), 126, 98, 70, 69; ^1H NMR ($CDCl_3$) δ 5.50 (br s, 2, OH), 6.47 (d of d, 2, Ar H).

3,6-Difluoroveratrole (9) was obtained via methylation of 3,6-difluorocatechol. 3-6-Difluorocatechol, 0.40 g (2.7 mmol), powdered anhydrous K_2CO_3, 1.51 g (10.9 mmol), Me_2SO_4, 10.4 mL (10.9 mmol), and 6 mL of acetone were refluxed under N_2 for 1.5 h. The reaction mixture was cooled, diluted with H_2O, and extracted twice with Et_2O. After being washed twice with H_2O, the Et_2O extracts were stirred for 0.5 h with 50 mL of 1 N NH_4OH; the Et_2O layer was separated, washed twice with H_2O, dried over $MgSO_4$, and concentrated at 30 °C on the rotary evaporator to 0.43 g of a tan liquid. The liquid was chromatographed on silica, eluting with hexane containing up to 20% CH_2Cl_2, in order to remove a faster running impurity; 0.21 g (44%) of pure (TLC) colorless liquid was obtained which was identical in all respects with material prepared from *p*-difluorobenzene.

Registry No. 1, 72912-24-4; 1·HBr, 59043-74-2; 2, 75626-15-2; 2·HBr, 75626-16-3; 3, 394-64-9; 4, 456-49-5; 6, 73943-41-6; 7, 7537-08-8; 8, 75626-17-4; 9, 75626-18-5; 10, 72912-50-6; 11, 75626-19-6; 12, 75626-20-9; dimethyl 2-fluoro-6-methoxyboronate, 75626-21-0; 2-fluoro-3,4-dimethoxybenzyl chloride, 1716-43-4; 2,5-difluorophenol, 2713-31-7; *p*-difluorobenzene, 540-36-3; 3,6-difluoroguaniacol, 75626-22-1; 2-(2,3,6-trifluorophenoxy)ethanol, 72912-49-3; 1,2,3,4-tetrafluorobenzene, 551-62-2; 3,6-difluorocatechol, 75626-23-2.

1,2-Difluoroethylenes: Synthesis via Fluoro Ketones

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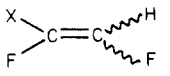
In a previous paper,[1] we have shown that the reaction of trifluoro(fluorooxy)methane with diazo ketones led to a mixture from which only one stereoisomer of 1,2-difluoro epoxides of type 1 was detected and isolated (Scheme I).

All of these epoxides were thought to have the same configuration since they all exhibited a fluorine–fluorine coupling constant close to 35 Hz. Unfortunately, owing to the lack of significant NMR data, this configuration could not be determined unambiguously.[2]

On the other hand, various 1,2-difluoroalkenes **2** were described, the substituent X being a proton, a halogen, or



2

an alkoxy group.[3,4] For all these compounds, the coupling constant between the two fluorine atoms lies in the range 8 to 18 Hz for a cis arrangement of fluorine atoms and varies from about 130 to 140 Hz for the trans isomer. Thus, there could not be any ambiguity with respect to their stereochemistry if the epoxides **1** proceeded from epoxidation of known alkenes of type **6** (Scheme II). This paper deals with the synthesis of such compounds.

No general and simple synthetic method was suited to the preparation of olefins **6**, i.e., olefins bearing any substituent (alkyl, cycloalkyl, phenyl, etc.). Neither Burton's olefination method[5] (terminal vinyl fluorides were obtained from ketones and aldehydes) nor addition of organolithium compounds to trifluoroethylene[6] (since metalation occurs) were applicable. Radiation-induced radical addition of ethers to 1,2-dichloro-1,2-difluoroethylene, leading to compounds such as **2**, has been used[4] but is not generally applicable. An alternative procedure has described the preparation of α,β-difluorostyrene,[7] starting from α,α-difluoroacetophenone. Here also, general applicability was not to be expected since difluoromethyl ketones are not always easily accessible. Finally, we have developed the sequence outlined in Scheme II.

Results

Preparation of Fluoromethyl Ketones. Many of the hitherto reported methods for preparing fluoromethyl ketones **4** involve the exchange of a halogen atom by a fluorine one, the latter being provided by a metallic fluoride. Among them, silver fluoride[8] is costly whereas potassium hydrogen fluoride needs relatively drastic conditions[9] (high-boiling polar solvent, high temperatures). The attractive dediazonative hydrofluorination of diazo ketones[10] seems not to be convenient for large-scale preparations. Other routes, involving the action of a Grignard reagent upon fluoroacetonitrile[11] or α-fluoro esters,[12] lead to low or moderate yields of fluoromethyl ketones.

We found that, under the conditions first described by Liotta and Harris,[13] the direct exchange of bromine by fluorine into bromomethyl ketones works with good yields (≥75%). Potassium fluoride is used as the fluoride ion source (2 mol per mole of ketone) and it is activated by 18-crown-6 ether (about 18 mol % per mole of ketone). Refluxing benzene is commonly used as the solvent. Such conditions allow particularly clean and mild exchanges.

It appeared that exchanges are yet possible if we replace the crown ether by the same quantity (in moles) of polyethylene glycol 1000 (PEG 1000) dissolved in benzene.

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