Hz), 5.87 (d, 1 H, J = 7 Hz); mass spectrum, m/e (relative intensity) 252 (0.3), 237 (1.4), 235 (1.6), 165 (11.9), 140 (76.8), 71 (100).

Dienone 10. 4-Hydroxycyclohexanone[13] (2.97 g, 0.026 mol) was added dropwise to a solution of sodium ethoxide (0.01 mol) in absolute ethanol (14 mL). After 5 min, a solution of aldehyde **5** (537 mg, 2.6 mmol) in 7 mL of ethanol was introduced, and the resulting mixture was stirred for 30 min at room temperature. After workup, the residue (1.0 g) was chromatographed on alumina to yield 148 mg of a bis adduct, mp 214–217 °C, followed by 525 mg (67%) of the desired monoadduct **10**: mp 145–147 °C; IR $\bar{\nu}_{max}$ 3600, 1730, 1673, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 3 H), 1.17 (s, 3 H), 1.40–3.75 (m, 17 H), 4.24 (m, 1 H), 5.97 (d, 1 H, J = 12 Hz), 7.45 (d, 1 H, J = 12 Hz); UV λ_{max} (ethanol) 312 nm (ϵ 29000). Anal. ($C_{19}H_{26}O_3$).

Photolysis of Dienone 10. A solution of **10** (8.4 mg) in methanol (22 mL) was irradiated at 0 °C with 365-nm light from a filtered medium-pressure Hanovia lamp. The reaction was followed by high-performance LC, using a Waters C-18 reverse-phase column (4.6-mm i.d., 25-cm long) and a Perkin-Elmer LC-55 variable-wavelength detector (mobile phase 45% aqueous methanol). After 20 min, the substrate had isomerized to another component, the ratio (assuming equal extinction coefficients) being about 50:50. The relative proportion of these components did not change on further irradiation, but slow destruction of the isomers was evidenced by a decrease in absorbance. The NMR spectrum of this mixture was complex but consistent with our assumption that the new component is a stereoisomer of **10**.

Triene 11. An ether solution of triphenylphosphonium methylide (0.5 mmol) was prepared by treating methyl triphenylphosphonium bromide (239 mg, 0.67 mmol) in 4 mL of ether with 0.2 mL of 2.42 M n-butyllithium solution (hexane). To this was added a solution of dienone **10** (30 mg, 0.1 mmol) in 2 mL of THF, and the resulting mixture was refluxed for 1.5 h. Workup followed by TLC (alumina) yielded 4 mg of aldehyde **5** (presumably via retroaldolization of unreacted **10**) and 5 mg of **11** as a clear gum: UV λ_{max} (ethanol) 270 nm (ϵ 22000);[14] mass spectrum, m/e (relative abundance) 300 (21), 267 (95), 149 (100).

Registry No. 1, 62617-74-7; 5, 73198-75-1; 6, 71277-28-6; 7, 73198-76-2; 8, 73198-77-3; 9, 73198-78-4; 10, 73198-79-5; 11, 73198-80-8; *cis*-1-ethoxy-2-(tri-*n*-butylstannyl)ethylene, 64724-29-4; 4-hydroxycyclohexanone, 13482-22-9.

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(14) Authentic *trans*-vitamin D has λ_{max} (ethanol) 272 nm (ϵ 22700).[10]

Convenient Synthesis of 3-Fluoro-L-tyrosine and 3,5-Difluoro-L-tyrosine

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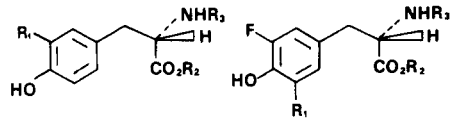
For a number of years we have been studying the biochemistry and pharmacology of ring-fluorinated aromatic amines and amino acids.[1] Recently these studies have been extended to include application of electron energy-loss spectroscopy as a new physical method for ultrastructural localization of fluorinated molecules[2] as well as ^{19}F NMR studies in intact cells.[3] As part of this extended program, we wished to incorporate fluorinated amino acids into a series of biologically important peptides present in the central nervous system.[4] To this end, we had need of substantial quantities of ring-fluorinated derivatives of L-tyrosine. Faced with the prospect of resolving commercially available 3-fluoro-D,L-tyrosine[5] and of following a lengthy literature procedure for the synthesis of 3,5-difluoro-D,L-tyrosine[6] followed by resolution, we considered an alternative approach. We have reported the synthesis of 3-fluorotyramine and 3,5-trifluorotyramine through in situ photochemical decomposition of diazonium fluoroborates.[7] Application of a similar sequence of reactions to appropriately blocked L-tyrosine proved straightforward. We report this procedure as a convenient alternative to published methods.

Nitration of *N*-(trifluoroacetyl)-L-tyrosine methyl ester (**1a**) followed by catalytic hydrogenation of the product



	R_1	R_2	R_3		R_1	R_2	R_3
1a	H	CH_3	$COCF_3$	**2a**	NO_2	CH_3	$COCF_3$
b	NO_2	CH_3	$COCF_3$	**b**	NH_2	CH_3	$COCF_3$
c	NH_2	CH_3	$COCF_3$	**c**	N_2^+	CH_3	$COCF_3$
d	N_2^+	CH_3	$COCF_3$	**d**	F	CH_3	$COCF_3$
e	F	CH_3	$COCF_3$	**e**	F	H	H
f	F	H	H	**f**	OH	CH_3	$COCF_3$
				g	OH	H	H

1b produced *N*-(trifluoroacetyl)-3-amino-L-tyrosine methyl ester (**1c**). The amine, without purification, was diazotized in tetrafluoroboric acid to give **1d**. In situ irradiation afforded *N*-(trifluoroacetyl)-3-fluoro-L-tyrosine methyl ester (**1e**) in 35% yield, based on (**1b**). Aqueous acid hydrolysis produced 3-fluoro-L-tyrosine (**1f**).

Nitration of **1e** in the available ortho position and repetition of the sequence (reduction, diazotization, irradiation, hydrolysis) through intermediates **2a–d** gave 3,5-difluoro-L-tyrosine **2e**. *N*-(Trifluoroacetyl)-3,4-dihydroxy-5-fluoro-L-phenylalanine methyl ester (**2f**) was isolated as an additional product from the photolysis of **2c**. Acid hydrolysis of **2f** produced 5-fluoro-L-Dopa (**2g**). Unfortunately, complete characterization of this latter amino acid has been thwarted by our inability to crystallize the free amino acid or its hydrochloride or hydrobromide.

Advantages to the procedure herein reported include the fact that the fluorinated L-amino acids are produced directly, eliminating the need for resolution. In addition, the reactions involved are convenient, quick, and can be scaled up without difficulty.

Experimental Section

Microanalyses and mass spectra were provided by the Microanalytical Services and Instrumentation Section of this laboratory, under the direction of Dr. David F. Johnson. Homogeneities and identities of all compounds were checked by TLC (silica gel GF

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Table I. Yields and Physical Data

compd	yield, %	mp, °C (purification)	formula	calcd C	calcd H	calcd N	found C	found H	found N
1b	87[a]	103.5-104.5 (ethanol/water)	$C_{12}H_{11}F_3N_2O_6$	42.86	3.30	8.33	42.97	3.40	8.30
1e	35[b]	134-135 (ethanol/water)	$C_{12}H_{11}F_4NO_4$	46.61	3.85	4.53	46.64	3.54	4.48
1f	70	276-279[c] (water)	$C_9H_{10}FNO_3$	54.27	5.06	7.03	54.02	5.22	6.92
2a	91	105-105.5 (ethanol/water)	$C_{12}H_{10}F_4N_2O_6$	40.69	2.85	7.91	40.62	3.01	7.87
2d	34[d]	142-144 (ethanol/water)	$C_{12}H_{10}F_5NO_4$	44.05	3.08	4.28	44.05	3.10	4.32
2e	81	267-269 (water)	$C_9H_9F_2NO_3$	49.77	4.08	6.45	49.91	4.29	6.22
2f	30[d]	165.5-166.5 (ethanol/water)	$C_{12}H_{11}F_4NO_5$	44.23	3.41	4.31	44.11	3.47	4.18

[a] Yield based on tyrosine methyl ester hydrochloride. [b] Yield based on 1b. [c] Lit.[5] mp 278-279 °C. [d] Yield based on 2a.

Table II. Proton Nuclear Magnetic Resonance Spectral Data (ppm)[a]

	CH_3	CH_2	CH	aromatic protons[b] H_2	H_5	H_6
1b	3.81	3.20 (dd, 6)	4.84 (dt, 6)	7.81 (d, 2)	7.08 (d, 8.5)	7.31 (q, 2, 8.5)
1e	3.80	3.14 (dd, 5)	4.84 (dt, 6)	ABC portion of ABCX multiplet 6.64-7.04		
1f[c]		3.24 (dd, 7)	4.36 (t, 7)	ABC portion of ABCX multiplet 6.90-7.20		
2a	3.82	3.16 (dd, 7)	4.83 (dt, 7)	7.16 (q, 2, 10.5)		7.65 (m)
2d	3.82	3.12 (dd, 6)	4.83 (dt, 6)	A_2 portion of A_2X_2 multiplet centered at 6.68 (H_2, H_6)		
2e[c]		3.24 (dd, 6)	4.38 (t, 6)	A_2 portion of A_2X_2 multiplet centered at 6.96 (H_2, H_6)		
2f	3.81	8.07 (d, 6)	4.78 (t, 6)	AB portion of ABX multiplet 6.28-6.48 (H_2, H_6)		

[a] 100-MHz spectra measured in $CDCl_3$ except where indicated. Multiplicity and coupling constants (hertz) are given in parentheses. [b] 1b-f, H_2 is ortho to R_1. 2a-e, H_2 is ortho to F. [c] Measured in 0.1 M DCl.

plates, Analtech) and mass spectrometry (Finnigan, model 1015 D). Yields and physical data are shown in Table I. Proton NMR data are given in Table II. The fluorination procedure was identical with that described previously.[7]

***N*-(Trifluoroacetyl)-3-nitro-L-tyrosine Methyl Ester (1b).** To 100 g of trifluoroacetic anhydride cooled in an ice bath was added in portions 25 g (0.11 mol) of L-tyrosine methyl ester hydrochloride. After the exothermic reaction had subsided, the solution was stirred at room temperature for 2 h, and the excess trifluoroacetic anhydride was removed by rotary evaporation. Methanol was added and removed by rotary evaporation. The residue (**1a**) was dissolved in 100 mL of glacial acetic acid, the solution was cooled to 10 °C in an ice bath, and 5.5 mL of fuming nitric acid was added dropwise over 10 min. The solution was stirred for 1 h at 10 °C, warmed to room temperature and stirred for 1 h, and poured into 500 mL of an ice–water slurry. The precipitate was collected by filtration and recrystallized from water/ethanol to give pure **1b**.

***N*-(Trifluoroacetyl)-3-fluoro-L-tyrosine Methyl Ester (1e).** Hydrogenation (3 atm) of 9 g (0.025 mmol) of **1b** in 200 mL of ethanol over 200 mg of platinum oxide was complete in 2 h. Removal of the catalyst by filtration and evaporation of solvent afforded **1c**. This was dissolved in 500 mL of cold 50% fluoroboric acid. Diazotization was accomplished by addition of 1.9 g (0.28 mol) of $NaNO_2$ dissolved in 5 mL of water. After 2 h, the solution of diazonium fluoroborate **1d** was irradiated (Pyrex filter) for 3 h. The fluoroboric acid was neutralized to pH 7 with concentrated aqueous sodium hydroxide while the solution was cooled in dry ice/acetone. The solution was then extracted with ether until TLC showed no more product in the extract. After the solution was dried (Na_2SO_4) and the solvent removed by rotary evaporation, the residue obtained was chromatographed on silica gel (0.5% methanol/chloroform) to give **1e**, purified further by recrystallization from aqueous ethanol.

3-Fluoro-L-tyrosine (1f). A 1.0-g (3.23 mmol) sample of **1e** dissolved in 20 mL of 6 N HCl was heated on a steam bath overnight. Rotary evaporation gave a white crystalline residue, which was dissolved in a minimum quantity of water. Neutralization with a concentrated solution of sodium acetate precipitated the free amino acid **1f**: 450 mg recrystallized from water; $[\alpha]^{25}_D$ −8.7° (*c* 0.2, 0.5 N HCl) (lit.[5] $[\alpha]^{26}_D$ −5.7°).

***N*-(Trifluoroacetyl)-3,5-difluorotyrosine Methyl Ester (2d).** Nitration of **1e** (2.0 g, 6.5 mmol) in 20 mL of acetic acid with 0.35 mL of fuming nitric acid and workup as before gave **2a**. Hydrogenation of **2a** (1.7 g 4.8 mmol) gave the amine **2b**, which was diazotized in 200 mL of cold fluoroboric acid. Irradiation (1 h) and isolation as before afforded a mixture of **2d** and **2f**. Chromatography (silica gel, 0.5% methanol/chloroform) gave 541 mg of **2d**.

3,5-Difluoro-L-tyrosine (2f). A 250-mg (0.76 mmol) sample of **2d** was hydrolyzed by heating (steam bath) overnight in 10 mL of 6 N HCl. Isolation and recovery of the free amino acid was performed as for **1f** to give 133 mg of **2e**: $[\alpha]^{25}_D$ −4.7° (*c* 0.2, 0.5 N HCl).

3,4-Dihydroxy-5-fluoro-L-phenylalanine (5-Fluoro-L-DOPA) (2g). Continued elution of the column used for the isolation of **2d** with 1% methanol–chloroform afforded **2f**. Aqueous acid hydrolysis of **2f** (HBr or HCl) produced the corresponding hygroscopic noncrystalline salts of **2g**, which proved resistant to recrystallization attempts. Attempts to isolate the free amino acid likewise were unrewarding. Tentative identification of **2a** was based on identical TLC behavior with authentic 5-fluoro-D,L-DOPA and on chemical-ionization mass spectral data.

Registry No. **1a**, 1604-54-2; **1b**, 5106-00-3; **1c**, 73210-50-1; **1d**, 73210-52-3; **1e**, 73210-53-4; **1f**, 139-26-4; **2a**, 73210-54-5; **2b**, 73210-55-6; **2d**, 73210-56-7; **2e**, 73246-30-7; **2f**, 73210-57-8; L-tyrosine methyl ester hydrochloride, 3417-91-2.

pK_a Values of Arsabenzenecarboxylic Acids. Empirical Estimate of the Charge Distribution of Arsabenzene

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Since the study of aromatic compounds has provided excellent tests of the validity of various MO methods, calculations on the new aromatic arsabenzene[2] should be particularly interesting. Results from CNDO/2[3] and ab

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