21-acetate in 51% yield. Under similar conditions, 17α-acetoxy-21-chloro-4-pregnene-3,20-dione gave mainly recovered starting material and the 17α-hydroxy-21-acetoxy derivative with lesser amounts of four other steroidal products, none of which appeared to be the product of elimination.

The 21-tetrahydropyranyl ether of 17α-acetoxy-21-hydroxy-4-pregnene-3,20-dione (**6**) reacted to give, in 75% yield, 21-acetoxy-4,16-pregnadiene-3,20-dione (**2**). We find this particularly suprising both because of the failure of **4** to undergo elimination and because Salce et al.[1] reported that 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-caproate 21-acetate reacts by simple elimination of caproic acid.

The above experiments establish that the elimination reaction is not general but rather that it occurs only when selected functional groups are present at C-21. The mechanism by which the C-21 acyloxy and tetrahydropyranyloxy groups facilitate the elimination of 17α-acyloxy groups remains to be established.

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer 297 spectrometer. NMR spectra were determined on a Varian T-60 spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc.

The known[4] 17,21-dihydroxy-4-pregnene-3,20-dione 17-acetate (**4**) was prepared from cortexolone essentially according to the procedure of Gardi, Vitali, and Ercoli,[2] but substituting triethyl orthoacetate for trimethyl orthoacetate. Acetylation of **4** with acetic anhydride–pyridine gave the known[5] diacetate **1**. 17α-Acetoxy-21-chloro-4-pregnene-3,20-dione (**5**) was synthesized essentially according to the procedure of Bergstrom, Sollman, Nicholson, and Dodson.[3] 17α-Acetoxy-6α-methyl-4-pregnene-3,20-dione (**3**) was purchased from the Sigma Chemical Co. All of the above compounds were pure by TLC, had melting points in agreement with literature values, and showed the expected IR and NMR spectra.

Synthesis of 17α-Acetoxy-21-(tetrahydropyranyloxy)-4-pregnene-3,20-dione (6). To 200 mg of **4** in 3 mL of freshly distilled dihydropyran was added 1 crystal of *p*-toluenesulfonic acid monohydrate. The solution was stirred for 3–4 h and then partitioned between ethyl ether and water. The ether layer was dried and distilled to leave a residue of 370 mg of an oil which crystallized from acetone–hexanes to afford **6**: yield 121 mg (50%); mp 147–148 °C; NMR ($CDCl_3$) δ 0.72 (s, C-18 H's), 1.20 (s, C-19 H's), 2.09 (s, $OC(O)CH_3$), 4.33 (m, C-21 H's), 4.64 (m, C-1′ H), 5.75 (m C-4 H). Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 71.15; H, 8.52.

Elimination Reaction on 17,21-Diacetoxy-4-pregnene-3,20-dione (1). To a solution of 100 mg of **1** (0.232 mmol) in 4 mL of DMF was added 49 mg of potassium acetate (0.499 mmol). The mixture was stirred at 105 °C, under nitrogen, for 6 h. The mixture then was cooled and poured into ice–water. The crystals which precipitated were collected by filtration, washed with water, and dried to afford 21-acetoxy-4,16-pregnadiene-3,20-dione (**2**): yield 53 mg (62%); mp 153–154 °C (lit.[6] mp 153–154 °C); NMR ($CDCl_3$) δ 0.96 (s, C-18 H's), 1.23 (s, C-19 H's), 2.20 (s, $OC(O)CH_3$), 4.96 (dd, C-21 H's), 5.73 (m, C-4 H), 6.73 (m, C-16 H).

Attempted Elimination Reaction on 17α-Acetoxy-6α-methyl-4-pregnene-3,20-dione (3). A. A solution of 100 mg of **3** was reacted under the conditions described for **1**. After workup, starting material was recovered in a yield of 70%.

B. The reaction was repeated on a fresh batch of 100 mg of **1** with heating being maintained overnight. The reaction product was an oil which gave an unresolvable streak on TLC under a variety of conditions.

Attempted Elimination Reaction on 17α,21-Dihydroxy-4-pregnene-3,20-dione 17-Acetate (4). A mixture of 100 mg of **4** (0.257 mmol) and 55 mg of potassium acetate (0.560 mmol) in 4 mL of DMF was stirred, under nitrogen, at 105 °C for 6 h. The mixture was cooled and then partitioned between ether and water. From the organic phase was isolated 17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate: yield 51 mg (51%); mp 235–240 °C (lit.[7] mp 235–238 °C).

Attempted Elimination Reaction on 17α-Acetoxy-21-chloro-4-pregnene-3,20-dione (5). A mixture of 115 mg of **5** (0.283 mmol) and 61 mg of potassium acetate (0.611 mmol) in 2.5 mL of DMF was stirred at 105 °C for 5 h, under nitrogen. The mixture was cooled and partitioned between $CHCl_3$ and H_2O. From the organic layer was obtained 80 mg of a dark oil which showed six main spots on TLC. By the use of preparative TLC, small quantities of pure starting material, **5**, and of 17,21-dihydroxy-4-pregnene-3,20-dione 21-acetate could be isolated. The remaining material was not definitively characterized but, as judged by TLC and NMR properties, it did not appear to contain any of the desired product of elimination.

Elimination Reaction on 17α-Acetoxy-21-(tetrahydropyranyloxy)-4-pregnene-3,20-dione (6). A mixture of 80 mg of **6** (0.169 mmol) and 36 mg of potassium acetate (0.367 mmol) in 2 mL of DMF was stirred, under nitrogen, at 105 °C for 5 h. The mixture was cooled and partitioned between CH_2Cl_2 and H_2O. The residue from the organic phase crystallized from acetone–hexanes to afford 21-acetoxy-4,16-pregnadiene-3,20-dione (**2**) in a yield of 47 mg (75%; identical in melting point, NMR, and TLC behavior with that formed from **1**).

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Registry No. **1**, 1807-15-4; **2**, 37-413-94-8; **3**, 74-58-9; **4**, 19357-45-0; **5**, 57273-80-0; **6**, 73275-17-9; 17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate, 640-87-9.

(2) For related reactions see ref 3.
(3) C. G. Bergstrom, P. B. Sollman, R. T. Nicholson, and R. M. Dodson, *J. Am. Chem. Soc.*, **82**, 2322 (1960).
(4) R. Gardi, R. Vitali, and A. Ercoli, *Gazz. Chim. Ital.*, **93**, 413 (1963).
(5) R. B. Turner, *J. Am. Chem. Soc.*, **75**, 3489 (1953).
(6) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **77**, 1028 (1955).
(7) P. L. Julian, E. W. Meyer, W. J. Karpel, and I. Ryden, *J. Am. Chem. Soc.*, **71**, 3574 (1949).

Synthesis of a 14α-Methyl Vitamin D Precursor

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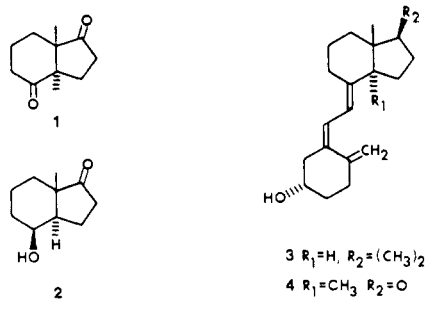
The potential usefulness of *trans*-1,6-dimethylbicyclo[4.3.0]nonan-2,7-dione (**1**) as an intermediate in terpene



synthesis has been noted.[1,2] Since this diketone resembles the bicyclic intermediate **2** used by Inhoffen[3] in a landmark

(1) W. Reusch, K. Grimm, J. Karoglan, J. Martin, K. P. Subrahamanian, P. S. Venkataramani, and J. D. Yordy, *J. Am. Chem. Soc.*, **99**, 1958 (1977).
(2) J. Martin, J. S. Tou, and W. Reusch, *J. Org. Chem.*, **44**, 3666 (1979).

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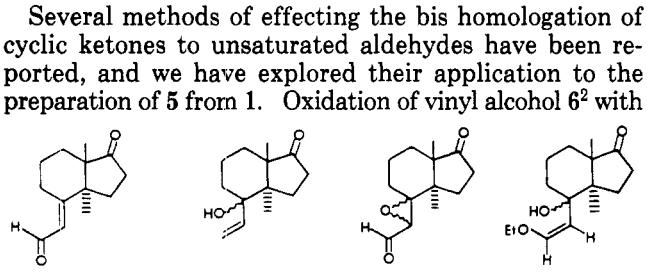
synthesis of vitamin D_3 (3), we decided to explore a parallel synthesis of a 14α-methyl analogue (4) of this important natural product.

Our interest in triene 4 is due in part to the possibility that electrocyclic ring closure of the corresponding precalciferol analogue might give tetracyclic intermediates related to lanostane and euphane triterpenes.[4] In this event, major progress in the synthesis of such triterpenes from 1 would be achieved. Furthermore, the 14α-methyl vitamin D formed by incorporation of a terpenoid side chain in 4 would represent an intriguing structural atavism. In the biosynthesis of steroids via lanosterol, the 14α-methyl group appears to be removed before the 4-methyl groups and before the introduction of a 5-double bond.[5] In fact, no sterols having a 14α-methyl group in the absence of a *gem*-dimethyl unit at C-4 have been found in mammalian tissues.

Several methods of effecting the bis homologation of cyclic ketones to unsaturated aldehydes have been reported, and we have explored their application to the preparation of 5 from 1. Oxidation of vinyl alcohol 6[2] with



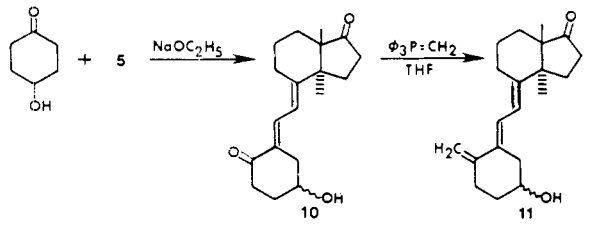
5 6 7 8

pyridinium chlorochromate gave epoxy aldehyde 7 in fair yield and very little 5. This deviation from the expected oxidative rearrangement[6] has been noted previously for hindered allylic alcohols[7].

(*Z*)-(2-Ethoxyvinyl)lithium[8] has been shown to be a versatile reagent for preparing unsaturated aldehydes from ketones. Unfortunately, this reagent decomposes above −40 °C, and we were able to obtain only modest yields of addition product 8 from 1. In our hands the best method of converting 1 to 5 involved addition of trimethylsilyl aldimine 9 followed by acid hydrolysis.[9]

$$\underset{\mathbf{9}}{(CH_3)_3SiCH_2CH{=}NC(CH_3)_3} \xrightarrow[\text{(3) oxalic acid, } H_2O]{\text{(1) LDA, THF; (2) 1}} \mathbf{5}\ (67\%)$$

The final stages in our synthesis follow Inhoffen's route.[3] Aldol condensation of 5 with 4-hydroxycyclohexanone gave dienone 10 (67%) along with a small amount of a bis-



10 11

condensation product. Photoisomerization of the central double bond in 10 was effected with filtered light (aqueous $CuSO_4$) from a medium-pressure mercury lamp, but the photoequilibrium proved to be 1:1 (*E*:*Z*) in contrast to the reported[10] predominance of the *Z* isomer in a dienone derived from vitamin D. This unexpected influence of the 14α-methyl group in 10 prevented us from making the desired *Z* isomer 4 of triene 11. Wittig reaction of 10 with triphenylphosphonium methylide proceeded to the *E* isomer 11 in low yield (15%) despite our efforts to improve this step.[10]

Experimental Section[11]

2-(2′-Oxoethylidene)-*trans*-1,6-dimethylbicyclo[4.3.0]nonan-7-one (5) (*E* configuration assumed). A THF solution of 3.24 g (18.9 mmol) of *N*-*tert*-butyl-2-(trimethylsilyl)acetaldimine, prepared by silation of *N*-*tert*-butylacetaldimine[12] according to the procedure of Corey et al.,[9] was added dropwise to a cold (0 °C) stirred solution of lithium diisopropyl amide (19.3 mmol) in THF. After a short reaction period, this solution was cooled to −78 °C, and a solution of diketone 1[1] (1.5 g, 8.3 mmol) in 10 mL of THF was then added. The resulting mixture was permitted to warm to −20 °C, stirred for 30 min, and then quenched with aqueous oxalic acid solution to a pH of ca. 4.5. After standing for 2 h at room temperature, this mixture was worked up, yielding 2 g of a yellow oil. Crystallization of this oil gave 493 mg of 5, and chromatography of the mother liquors (high-performance LC, silica gel, 20% ethyl acetate–hexane) afforded 199 mg of recovered 1 and, after crystallization, 488 mg of 5 for an overall conversion of 67%. Pure 5: mp 72.5–74 °C; IR $\bar{\nu}_{max}$ 1730, 1657 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 3 H), 1.13 (s, 3 H), 1.3–2.1 (m, 6 H), 2.2–2.4 (m, 4 H), 5.83 (dd, 1 H, J = 8 and 2 Hz), 9.67 (d, 1 H, J = 8 Hz). Anal. ($C_{13}H_{18}O_2$).

2-(3′-Formyloxacyclopropyl)spiro-*trans*-1,6-dimethylbicyclo[4.3.0]nonan-7-one (7). A solution of 817 mg (3.9 mmol) of vinylcarbinol 6[2] (mp 112 °C) in 14 mL of methylene chloride was added to a suspension of 3.2 g (15.6 mmol) of pyridinium chlorochromate in 10 mL of the same solvent. This mixture was stirred overnight at 25 °C, diluted with 80 mL of ether, filtered through Florisil, and evaporated to give 710 mg of a yellow oil. Crystallization from ether gave 274 mg of 7: mp 95.5–96.5 °C; IR $\bar{\nu}_{max}$ 1735, 1715 (sh) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 3 H), 1.17 (s, 3 H), 1.4–2.6 (m, 10 H), 3.07 (d, 1 H, J = 5 Hz), 9.37 (d, 1 H, J = 5 Hz). Anal. ($C_{13}H_{18}O_3$).

2-Hydroxy-2-((*Z*)-2′-ethoxyvinyl)-*trans*-1,6-dimethylbicyclo[4.3.0]nonan-7-one (8). To a solution of *cis*-1-ethoxy-2-(tri-*n*-butylstannyl)ethylene[8] (410.8 mg, 1.14 mmol) in 6 mL of THF at −78 °C was added 0.46 mL (1.11 mmol) of 2.42 M *n*-butyllithium solution in hexane. After a 1-h reaction period, a solution of diketone 1 (90 mg, 0.5 mmol) in THF was added, and the resulting mixture was stirred for 2 h and then warmed to 25 °C. Workup yielded 421 mg of crude product which was purified by high-performance LC (silica gel) to give 47.1 mg (41%) of 8: mp 52–55 °C; IR $\bar{\nu}_{max}$ 3520, 1733, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3 H), 1.30 (s, 3 H) and (t, 3 H, J = 7 Hz), 1.4–2.4 (m, 10 H), 3.77 (q, 2 H, J = 7 Hz), 4.07 (s, 1 H), 4.37 (d, 1 H, J = 7

(3) (a) H. H. Inhoffen and K. Irmscher, *Fortschr. Chem. Org. Naturst.*, 17, 71 (1959); (b) H. H. Inhoffen, *Angew. Chem.*, 72, 865 (1960).

(4) L. Fieser and M. Fieser, "Steroids", Reinhold, New York, 1959, p 137–41.

(5) (a) F. Gautschi and K. Block, *J. Am. Chem. Soc.*, 79, 684 (1957); (b) D. H. R. Barton, J. G. T. Corrie, P. J. Marshall, and D. A. Widdowson, *Bioorg. Chem.*, 2, 363 (1973); (c) G. F. Gibbons and K. Mitropoulos, *Biochim. Biophys. Acta*, 380, 270 (1975); (d) I. D. Franz and G. Schroepfer, *Annu. Rev. Biochem.*, 36, 691 (1967).

(6) (a) J. H. Babler and M. J. Coghlan, *Synth. Commun.*, 6, 469 (1976); (b) W. G. Dauben and D. Michno, *J. Org. Chem.*, 42, 682 (1977).

(7) P. Sundararaman and W. Herz, *J. Org. Chem.*, 42, 813 (1977).

(8) (a) R. H. Wollenberg, K. Albizati, and R. Peries, *J. Am. Chem. Soc.*, 99, 7365 (1977); (b) J. Ficini, S. Falou, A. Touzin, and J. d'Angelo, *Tetrahedron Lett.*, 3589 (1977); (c) K. S. Y. Lau and M. Schlosser, *J. Org. Chem.*, 43, 1595 (1978).

(9) E. J. Corey, D. Enders, and M. Bock, *Tetrahedron Lett.*, 7 (1976).

(10) I. T. Harrison and B. Lythgoe, *J. Chem. Soc.*, 837 (1958).

(11) Melting points were taken on a Hoover capillary apparatus or a Kofler hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer and proton magnetic resonance spectra were obtained by using either a Varian T-60 or a Brucker 180-MHz spectrometer. Ultraviolet spectra were recorded on a Cary 17 spectrometer and mass spectra were all measured at 70 eV by using a Hitachi RMU-6 instrument. Thin-layer chromatography (TLC) was performed on E. Merck plates 60F-254, 0.25 mm, and all silica gel column chromatography was conducted with E. Merck Silica Gel 60, 70–230 mesh. Alumina was Woelm, neutral grade, activity 1. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI, and were within 0.2% of the calculated values. All reactions were carried out under nitrogen or argon, using solvents freshly purified by distillation from suitable drying agents. Workup involved extraction of organic materials into ether or methylene chloride, washing of the extracts with water and brine, and drying of the washed extract solution over anhydrous sodium sulfate before concentration at reduced pressure.

(12) K. Campbell, A. Sommers, and B. Campbell, *J. Am. Chem. Soc.*, 66, 82 (1944).

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.

(13) M. Haslanger and R. G. Lawton, *Synth. Commun.*, **4**, 155 (1974).
(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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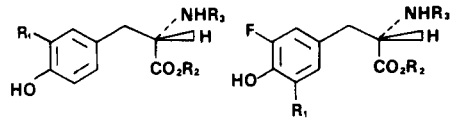
For a number of years we have been studying the biochemistry and pharmacology of ring-fluorinated aromatic amines and amino acids.[1] Recently these studies have been extended to include application of electron energy-loss spectroscopy as a new physical method for ultrastructural localization of fluorinated 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

(1) D. Cantacuzene, K. L Kirk, D. H. McCulloh, and C. R. Creveling, *Science*, **204**, 1217 (1979); K. L. Kirk and L. A. Cohen in "Biochemistry Involving Carbon–Fluorine Bonds", A. Filler, Ed., American Chemical Society, Washington, D.C., 1976, p 23.
(2) J. L. Costa, D. C. Joy, D. M. Maher, K. L. Kirk, and S. W. Hui, *Science*, **200**, 537 (1978).
(3) J. L. Costa, C. M. Dobson, K. L. Kirk, C. R. Valeri, and J. J. Vecchione, *FEBS Lett.*, **99**, 141 (1979); J. L. Costa, C. M. Dobson, K. L. Kirk, F. M. Paulsen, C. R. Valeri, and J. J. Vecchione, *Proc. R. Soc. London, Ser. B.*, in press.
(4) S. H. Snyder and S. R. Childers, *Annu. Rev. Neurosci.*, **2**, 35 (1979). Fluorotyrosine has been incorporated into bacterial protein in vivo: B. D. Sykes, H. I. Weingarten, and M. J. Schlesinger, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 469 (1974).
(5) C. Niemann and M. M. Rapport, *J. Am. Chem. Soc.*, **68**, 1671 (1946).
(6) J. English, Jr., J. F. Mead, and C. Niemann, *J. Am. Chem. Soc.*, **62**, 305 (1940); G. Schiemann and W. Winkelmüller, *J. Prakt. Chem.*, **135**, 101 (1932).
(7) K. L. Kirk, *J. Org. Chem.*, **41**, 2373 (1976).