totaling 77%, were recrystallized from i-Pr_2O to give analytically pure **5**: mp 151–153 °C; CI mass spectrum, m/e (relative intensity) 379.2 ($M^+ + NH_4$, 15.3), 377.1 ($M^+ + NH_4$, 48.0), 375.1 ($M^+ + NH_4$, 51.1), 362.1 (M^+, 31.2), 360.2 (M^+, 94.8), 358.1 (M^+, 100); IR 3500, 1735, 1450 cm^{-1}; ^1H NMR δ 7.15 (br s, 1 H, exchanges with D_2O), 4.55 (d, 1 H, J = 2 Hz), 3.78 (q, 2 H, J = 7), 3.70 (s, 3 H), 3.65 (s, 3 H), 2.41 (d, 1 H, J = 13, H_{7N}), 1.80 (dd, 1 H, J = 13, 2, H_{7X}), 1.34 (s, 3 H), 1.28 (t, 3 H, J = 7); ^{13}C NMR (C_6D_6) δ 177.3 (s), 103.3 (s), 92.5 (s), 81.6 (s), 77.8 (s), 71.9 (s), 71.5 (d), 61.4 (t), 51.7 (q), 50.5 (q), 40.7 (t), 17.7 (q), 15.3 (q). Anal. Calcd for $C_{13}H_{18}Cl_3NO_4$: C, 43.52; H, 5.06; Cl, 29.66; N, 3.91. Found: C, 43.80; H, 5.15; Cl, 29.25; N, 3.84.

Conversion of 1 to a Mixture of 1 and 5 with an Insufficiency of Ethanolic NaOEt. Carboxamide **1** (1.00 g, 2.87 mmol), dissolved in 16 mL of absolute EtOH, was added to a solution prepared by dissolving 33 mg (1.44 mmol, 0.5 equiv) of Na in 7 mL of absolute EtOH. This solution was refluxed for 21 h and monitored by TLC, with no observable change noted after 15 min. Chromatography of the isolated product mixture gave 469 mg (47%) of recovered starting material (**1**) and 395 mg (38%) of **5**, each identical with the corresponding previously described material, no other compounds being isolatable.

Conversion of 1 to 3a-Chloro-(*E*)-5-(chloromethylene)-4,4-dimethoxy-6a-methyl-*cis*-tetrahydrocyclopenta[*c*]pyrrole-1,3(2*H*,3a*H*)-dione (8) by Aqueous KOH. A mixture of 100 mg (0.286 mmol) of carboxamide **1**, 250 mg (4 mmol) of KOH, and 3 mL of 2:1 THF–water was refluxed for 3 h. Extracts of the basic mixture contained **1** and several minor impurities but no significant amount of **5** (TLC); extracts of the acidified mixture were chromatographed to provide 25 mg (30%) of **8**, mp 179–181 °C after recrystallization from i-Pr_2O: mass spectrum, m/e (relative intensity) 297.1 (M^+, 0.91), 295.1 (M^+, 4.5), 293.1 (M^+, 7.2), 266.1 (3.57), 264.1 (20.5), 262.1 (32.8), 260.1 (25.0), 258.1 (75.4), 193.1 (55.2), 191.1 (82.3), 150.1 (78.8), 148.1 (91.5), 113.2 (100); IR 3500, 1790, 1725, 1660 cm^{-1}; ^1H NMR δ 8.15 (br s, 1 H, exchanges with D_2O), 6.45 (dd, 1 H, J = 3, 2 Hz), 3.47 (s, 3 H), 3.17 (s, 3 H), 2.91 (dd, 1 H, J = 18, 3), 2.49 (dd, 1 H, J = 18, 2), 1.45 (s, 3 H); ^{13}C NMR δ 179.4 (s), 171.4 (s), 137.2 (s), 119.4 (d), 107.5 (s), 80.3 (s), 54.7 (s), 51.2 (q), 50.6 (q), 33.6 (t), 23.5 (q). Anal. Calcd for $C_{11}H_{13}Cl_2NO_4$: C, 44.92; H, 4.45; Cl, 24.10; N, 4.76. Found: C, 44.95; H, 4.56; Cl, 23.83, N, 4.78.

Conversion of 1 to a Mixture of 5 and 8 by Ethanolic KOH. A mixture of 2.60 g (7.5 mmol) of carboxamide **1**, 6.50 g (0.1 mol) of KOH and 80 mL of 5:1 EtOH–water was refluxed for 3 h. Workup and separation as outlined above yielded 970 mg (36%) of **5** and 860 mg (39%) of **8**, each identical with the corresponding previously described material. An analogous experiment, carried out for 72 h, gave 4.3% of **5** and 46% of **8**.

Treatment of the exo carboxamide, epimeric with **1**, under similar conditions provided only unchanged starting material.

Conversion of 5 to 8 by Ethanolic KOH. A mixture of 500 mg (1.39 mmol) of lactam **5**, 1.25 g (0.02 mol) of KOH, and 15 mL of 5:1 EtOH–water was refluxed for 46 h. Workup and separation as outlined above yielded 100 mg (20%) of starting material (**5**) and 140 mg (34%) of **8**, each identical with the corresponding previously described material.

Preparation of 1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-ene-*endo*-2-carboxamide (9). A mixture of 11.5 g (43.6 mmol) of tetrachloro-5,5-dimethoxycyclopentadiene and 6.4 g (87.2 mmol) of acrylamide in 20 mL of absolute MeOH was refluxed for 16 h. After cooling, water was added and precipitated material was filtered, washed with water, dried, and recrystallized from i-Pr_2O to afford 10.8 g (75%) of analytically pure, white **9**: mp 157–9 °C; IR 3460, 1685, 1600 cm^{-1}; ^1H NMR δ 5.90 (br, 2 H, exchanges with D_2O), 3.64 (s, 3 H), 3.59 (s, 3 H), 3.21 (dd, 1 H, J = 5, 8 Hz), 2.42 (octet, 2 H). Anal. Calcd for $C_{10}H_{11}Cl_4NO_3$: C, 35.84; H, 3.31; Cl, 42.33; N, 4.18. Found: C, 35.53; H, 3.22; Cl, 42.08; N, 3.93.

Conversion of the Desmethyl Endo Carboxamide (9) to 3a,5-*endo*-6-Trichloro-4,4,6a-trimethoxy-3,5-methanohexahydrocyclopenta[*b*]pyrrol-2(1*H*,3*H*)-one. Carboxamide **9** (2.0 g, 6.0 mmol) and 5.0 g of KOH (0.08 mol) were refluxed in 60 mL of 1:1 MeOH–water for 64 h. Workup as outlined for **5** and recrystallization from Et_2O–hexane gave 600 mg (30%) of fine white crystals: mp 237.5–239 °C; FAB mass spectrum, m/e (relative intensity) 424.3 ($M^+ + 1$ + glycerol, 8.8), 422.4 (9.0), 334.0 (35.0), 332.9 (14.0), 331.9 (79.8), 331.0 (14.5), 330.1 (100); IR 3160, 1720, 1680 cm^{-1}; ^1H NMR δ 7.80 (br s, 1 H), 4.72 (d, 1 H, J = 1.5 Hz), 3.66 (s, 3 H), 3.63 (s, 3 H), 3.53 (s, 3 H), 2.82 (dd, 1 H, J = 10, 2), 2.41 (ddd, 1 H, J = 12.5, 10, 1.5), 2.18 (dd, 1 H, J = 12.5, 2). Anal. Calcd for $C_{11}H_{14}Cl_3NO_4$: C, 39.96; H, 4.27; Cl, 32.17; N, 4.24. Found: C, 39.89; H, 4.17; Cl, 31.95; N, 4.18.

Conversion of the Desmethyl Endo Carboxamide (9) to 3a,5-*endo*-6-Trichloro-6a-ethoxy-4,4-dimethoxy-3,5-methanohexahydrocyclopenta[*b*]pyrrol-2(1*H*,3*H*)-one. Carboxamide **9** (4.0 g, 11.9 mmol) and 10.0 g of KOH (0.16 mol) were refluxed in 120 mL of 5:1 EtOH–water for 3 h. Workup as outlined for **5** provided 1.0 g of white powder from extraction of the basic solution and 150 mg of the same material (mp, mmp, and ^1H NMR) from extraction of the acidified solution (total yield 28%). Recrystallization from i-Pr_2O gave material of mp 204–206 °C; IR (Nujol) 3150, 1720, 1680 cm^{-1}; ^1H NMR δ 7.83 (br s, 1 H), 4.78 (d, 1 H, J = 1.5 Hz), 3.80 (q, 2 H, J = 7), 3.68 (s, 3 H), 3.62 (s, 3 H), 2.84 (dd, 1 H, J = 10.5, 2), 2.46 (ddd, 1 H, J = 12.5, 10.5, 1.5), 2.18 (dd, 1 H, J = 12.5, 2), 1.28 (t, 3 H, J = 7); ^{13}C NMR (C_6D_6) δ 174.8 (s), 102.7 (s), 93.0 (s), 77.8 (s), 72.1 (s), 71.9 (d), 61.3 (t), 51.9 (d), 51.4 (q), 50.6 (q), 32.6 (t), 15.3 (q). Anal. Calcd for $C_{12}H_{16}Cl_3NO_4$: C, 41.82; H, 4.68; Cl, 30.91; N, 4.07. Found: C, 41.95; H, 4.69; Cl, 30.52; N, 3.91.

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Registry No. **1**, 94294-31-2; **5**, 94294-32-3; **8**, 94323-92-9; **9**, 94294-33-4; acrylamide, 79-06-1; tetrachloro-5,5-dimethoxycyclopentadiene, 2207-27-4; methacrylamide, 79-39-0; 3a,5-*endo*-6-trichloro-4,4,6a-trimethoxy-3,5-methanohexahydrocyclopenta[*b*]pyrrol-2(1*H*,3*H*)-one, 94294-34-5; 3a,5-*endo*-6-trichloro-6a-ethoxy-4,4-dimethoxy-3,5-methanohexahydrocyclopenta[*b*]-pyrrol-2(1*H*,3*H*)-one, 94294-35-6.

A New Synthesis of Isoguanosine

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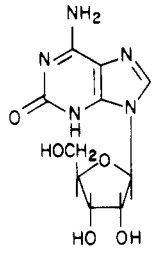
Isoguanosine (**1**) (crotonoside or 2-hydroxyadenosine) is one of only a few naturally occurring nucleoside analogues of guanosine.[1] It was first isolated from *Croton*



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tiglium L. by Cherbuliez and Bernhard.[2] More recently, Pettit and his co-workers isolated isoguanine from butterfly wings of *Prioneris thestylis*.[3] Isoguanosine is incorporated in mammalian but not bacterial nucleic acids.[4,5] It stim-

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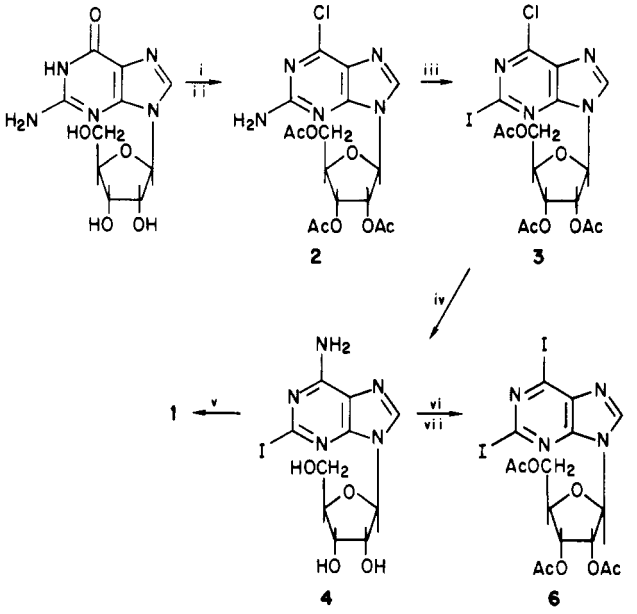
Scheme I[a]



[a] (i) Acetic anhydride, DMF, pyridine; (ii) $POCl_3$, *N,N*-dimethylaniline, Δ; (iii) *n*-$C_5H_{11}ONO$, CH_2I_2, Δ; (iv) NH_3, C_2H_5OH; (v) H_2O, *hν*; (vi) acetic anhydride, pyridine; (vii) *n*-$C_5H_{11}ONO$, CH_2I_2, Δ.

ulates the accumulation of cyclic AMP in the brain.[6] It is an inhibitor of IMP:pyrophosphorylase.[7] Isoguanosine 5′-di- and 5′-triphosphates bind strongly and inhibit glutamic acid dehydrogenase.[8]

The synthesis of isoguanosine was initially achieved by the selective deamination of 2,6-diamino-9β-(D-ribofuranosyl)purine with nitrous acid.[9] However, the overall yield from 2,6-diaminopurine was low and the procedure used undesirable heavy metal salts (e.g., Hg, Pb) in two of the steps. Isoguanosine has also been prepared in low yields from a 4,5-dicyanoimidazole nucleoside precursor.[10] In the synthesis of 2-fluoroadenosine from 2,6-diaminopurine nucleoside, isoguanosine was reported as a side product.[11] A photochemical preparation of isoguanosine from adenosine *N*′-oxide has been reported,[12] but this procedure gives variable results. We report a new, reproducible, and efficient synthesis of isoguanosine.

Guanosine served as the starting point for this synthesis. It was converted first to 2-amino-6-chloro-9β-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)purine (**2**) by selective acetylation followed by reaction with phosphorus oxychloride and *N,N*-dimethylaniline[13] (Scheme I). Treatment of **2** with *n*-pentyl nitrite and diiodomethane at 80 °C for 2 h gave pure protected 2-iodo-6-chloropurine nucleoside (**3**) in 83% yield (66% overall yield for three steps from guanosine).[14-16] When **3** was allowed to react with ethanolic ammonia at ice-bath temperatures, 2-iodoadenosine (**4**) was produced in 93% isolated yield. The ease of displacement of the 6-chloro group in compound **3** by ammonia is in sharp contrast to the high temperatures and pressures or very long reaction times required for similar nucleophilic substitution of 6-chloropurines.[17,18] Although 2-iodoadenosine has been cited previously, its method of synthesis and physical and spectral data have not been reported.[19] The key step in the conversion of **4** to **1** is an interesting photoinduced hydration reaction. Photolysis of **4** in water was carried out in a Rayonet photochemical reactor with UV irradiation from mercury lamps with the principal wavelength of 2537 Å. The isoguanosine formed was isolated by reverse-phase HPLC on Amberlite XAD-4 resin and crystallized from water to give a 55% yield of pure product.

An interesting sidelight of this work was the synthesis of the novel nucleoside 2,6-diiodonebularine (**6**) from 2-iodoadenosine (**4**) through a halogenative deamination reaction. This compound (mp 160–162 °C) was characterized by its mass spectrum [*m/z* 630 (M^+)], its UV spectrum in ethanol [λ_{max} 290 (ε 8.17 × 10^3), 252 (ε 8.76 × 10^3), 226 (ε 1.70 × 10^4) nm], and its high-field ^1H and ^{13}C NMR data. Further synthetic utilization of the iodinated nucleosides described here are currently under investigation in our laboratory.

Experimental Section

Melting points are uncorrected. Preparative-layer chromatography employed EM silica gel PF_{254} plates activated for 3 h at 135 °C.

2-Amino-6-chloro-9β-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)purine (2) was prepared from guanosine in 75% yield by established literature procedures.[13]

2-Iodo-6-chloro-9β-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)purine (3) was prepared in 83% yield by treatment of **2** thermally with *n*-pentyl nitrite and diiodomethane by using a procedure previously described by us.[14]

2-Iodoadenosine (4). To 125 mL of dry ethanol saturated with ammonia gas at ice–salt bath temperatures was added 0.401 g (0.744 mmol) of **3**. The solution was stirred at this temperature for 1 h and then at 25 °C for 23 h. The solvent was removed under reduced pressure and the residue was purified by reverse-phase HPLC on Amberlite XAD-4 resin using 75:25 H_2O:ethanol as the eluting solvent. 2-Iodoadenosine (**4**) crystallized from H_2O as white crystals (0.272 g, 0.692 mmol, 93%): mp 142–144 °C; ^{13}C NMR (D_2O, pH 4) δ 61.1, 70.1, 73.5, 85.4, 88.6, 116.4, 117.8, 140.4, 147.7, 147.8; ^1H NMR (Me_2SO-d_6) δ 3.65 (m, 2 H), 3.92 (m, 1 H), 4.07, (m, 1 H), 4.56 (m, 1 H), 5.62 (d, 1 H, *J* = 6.4 Hz), 7.45 (br s, 2 H), 7.89 (s, 1 H); UV (H_2O) λ_{max} 264.5 nm (ε 1.31 × 10^4); mass spectrum, *m/z* (relative intensity) 393 (M^+, 0.2), 262 (6.4), 261 (Pur^+ + H, 33.3), 135 (18.4), 134 [(Pur^+ − I) + H, sugar + H, 100.0].

Isoguanosine (1). A solution of 0.056 g (0.142 mmol) of **4** in 75 mL of water was placed in a quartz reaction vessel and photolyzed for 7.5 h with a Rayonet photochemical reactor using light with the principal wavelength of 2537 Å. The solvent was then removed under reduced pressure, and the residue was purified by reverse-phase HPLC on a column of Amberlite XAD-4 using 90:10 H_2O:ethanol as the solvent. The separated product was lyophilized and the residue crystallized from H_2O to give 0.022 g (0.078 mmol, 55%) of **1** as white crystals: mp 237–241 °C (lit.[12] mp 237–241 °C); ^{13}C NMR (D_2O, pH 4) δ 60.6, 70.5, 73.7, 85.9, 89.5, 110.5, 139.0, 141.6, 148.7, 152.1; ^1H NMR (Me_2SO-d_6) δ 3.94 (m, 2 H), 4.12 (m, 1 H), 4.52 (m, 1 H), 5.19 (m, 1 H), 5.46 (br s, 2 H), 5.81 (d, 1 H, *J* = 6.0 Hz), 8.38 (s, 1 H); UV (H_2O) λ_{max} 292 nm (ε 1.10 × 10^4), 248 (ε 9.02 × 10^3).

2-Iodo-6-amino-9β-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)purine (5). A mixture of 25 mL of pyridine and 20 mL of acetic anhydride was cooled to ice-bath temperatures and treated with 0.470 g (1.200 mmol) of **4**. The solution was stirred at ice bath

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temperatures for 1 h and at 25 °C for 2 h. The solvent was removed under reduced pressure followed by coevaporation (4×) with 95% ethanol. The residue was purified by using silica gel chromatography with 9:1 chloroform:methanol as the developing solvent. The band at R_f 0.65 upon elution yielded 0.522 g (1.01 mmol, 84%) of **5** as off-white crystals: mp 78–80 °C; ^{13}C NMR ($CDCl_3$) δ 20.5, 20.6, 20.9, 63.1, 70.6, 73.4, 80.5, 86.1, 119.7, 120.1, 138.33, 149.9, 155.4, 169.4, 169.5, 170.3; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.13 (s, 3 H), 2.16 (s, 3 H), 4.41 (m, 3 H), 5.30 (t, 1 H), 5.79 (t, 1 H), 6.13 (d, 1 H), 6.40 (br s, 2 H), 7.87 (s, 1 H); UV (EtOH) λ_{max} 222 nm (ε 1.97 × 10^4), 264.5 (ε 1.32 × 10^4); mass spectrum, m/z (relative intensity) 519 (M^+, 2.1), 262 (15.3), 261 (4.6), 260 (Pur^+, 4.3), 259 ($sugar^+$, 30.5), 157 (11.8), 139 (100), 135 (6.4), 134 (12.8), 133 (Pur^+ − I, 1.4).

2,6-Diiodo-9β-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)purine (6). A mixture of 0.320 g (0.616 mmol) of **5**, 5.4 mL (40 mmol) of *n*-pentyl nitrite, and 16 mL of diiodomethane was protected from moisture and stirred for 7 h and 80 °C. The solvent was then removed under reduced pressure and the residue was chromatographed on silica gel plates. After elution with 20:1 chloroform:methanol, the band at R_f 0.68 afforded 0.198 g (0.314 mmol, 51%) of **6** as light yellow crystals: mp 160–162 °C; ^{13}C NMR ($CDCl_3$) δ 20.4, 20.5, 20.8, 62.9, 70.6, 73.3, 80.8, 86.6, 117.1, 122.2, 139.3, 142.5, 148.2, 169.3, 169.5, 170.1; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.14 (s, 3 H), 2.17 (s, 3 H), 4.42 (m, 3 H), 5.60 (t, 1 H), 5.80 (t, 1 H), 6.19 (d, 1 H), 8.24 (s, 1 H); UV (EtOH) λ_{max} 290 nm (ε 8.17 × 10^3), 252 (ε 8.76 × 10^3), 226 (ε 1.70 × 10^4); mass spectrum, m/z (relative intensity) 630 (M^+, 0.8), 415 (4.4), 401 (1.2), 373 (12.4), 372 (Pur^+ + H, 1.3), 259 ($sugar^+$, 40.4), 246 (1.4), 245 [(Pur^+ − I) + H, 4.1], 157 (12.6), 139 (100.0).

Acknowledgment is made to the NSF for support of our investigations.

Registry No. **1**, 1818-71-9; **2**, 16321-99-6; **3**, 5987-76-8; **4**, 35109-88-7; **5**, 94042-04-3; **6**, 94042-05-4; guanosine, 118-00-3.

Synthesis of 2,6-Dihalo-DL-tyrosines

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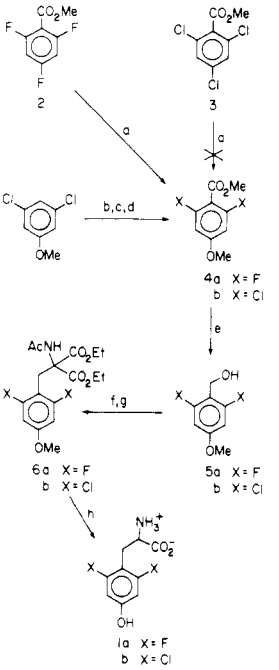
As part of a program of research on the mechanisms of catalysis by α-keto acid dioxygenases, it has been necessary for us to synthesize a variety of unusual α-keto acids for use as alternate substrates or inhibitors of these enzymes. It is convenient to prepare these compounds by the action of commercially available D- and L-amino acid oxidases on the corresponding α-amino acids,[1] and since an enormous number of α-amino acids have been chemically synthesized or isolated from natural sources, the acquisition of these synthetic precursors is usually a simple matter. However, when we required 2,6-difluoro-DL-tyrosine (**1a**) for our studies, we soon discovered not only that this particular amino acid was unknown but that there were no literature examples of any 2,6-dihalotyrosines.[2] This was especially surprising in view of the enormous chemical and biological literature concerning the 3,5-dihalotyrosines, which are of interest by virtue of their structural relationship to thyroxine. Several 2-halotyrosines have been prepared[5,6] and shown to have significant antibacterial activity,[6] but the 2,6-dihalo derivatives have not been made, perhaps due to the more severe synthetic challenge presented by the three mutually meta-oriented ortho,para-directing substituents on the aromatic ring. We report herein short syntheses (Scheme I) of 2,6-difluoro-DL-tyrosine (**1a**) and 2,6-dichloro-DL-tyrosine (**1b**).

Scheme I[a]



[a] (a) NaOMe/MeOH/reflux; (b) *n*-BuLi/TMEDA/THF/−78 °C, then CO_2; (c) $SOCl_2$/reflux; (d) MeOH/pyridine; (e) $LiAlH_4/Et_2O$; (f) HBr/HOAc; (g) diethyl acetamidomalonate/NaOEt/EtOH; (h) HBr/H_2O/reflux.

The key intermediates in these syntheses were the trisubstituted benzyl alcohols **5a** and **5b**. A very convenient preparation of 2,6-difluoro-4-methoxybenzyl alcohol (**5a**) has been described recently in the patent literature.[7] 1,3,5-Trifluorobenzene was deprotonated and carboxylated, and the resulting acid was esterified to give methyl 2,4,6-trifluorobenzoate (**2**). Treatment of **2** with 1 equiv of sodium methoxide in refluxing methanol yielded a mixture of esters from which pure methyl 2,6-difluoro-4-methoxybenzoate (**4a**) crystallized upon concentration. Reduction of compound **4a** with Red-Al (Aldrich) or $LiAlH_4$ gave the desired benzyl alcohol **5a**. In our hands the overall yield of **5a** from the trifluorobenzene was approximately 15%.

We attempted to prepare 2,6-dichloro-4-methoxybenzyl alcohol (**5b**) using similar methodology, but the methoxide treatment of methyl 2,4,6-trichlorobenzoate (**3**) was without effect. When more vigorous conditions were employed for the substitution reaction—treatment of **3** with sodium *n*-butoxide in refluxing *n*-butanol—only *n*-butyl 2,4-di-

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(2) An extensive literature search uncovered only two apparent reports of the preparation of 2,6-dihalotyrosines. Mantescu et al.[3] treated tyrosine with iodine monochloride to give 3,5-diiodotyrosine which was in turn converted to 3,5-[$^{18}F_2$]difluorotyrosine by treatment with postassium [^{18}F]fluoride in acetic acid. However, these compounds were not characterized (in the latter case because of the short half-life of the radioisotope ^{18}F), and the illustrations in their paper incorrectly depict the products as 2,6-dihalotyrosines. Subsequent repetition of this synthesis by Donnerhack and Sattler[4] was accompanied by a repetition of the error in nomenclature.

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