JOC Article

Syntheses of β,β-Difluorotryptamines

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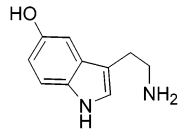
Tryptamines disubstituted at the β-position with fluorine have been synthesized as part of our research program to study the effects of fluorine substitution on the biological activities of neuroactive amines. Treatment of *N*-Boc-3-azidoacetyl indoles, prepared from readily available 2-chloracetylindoles, with dimethoxyethylamino sulfurtrifluoride produced the corresponding 3-(2-azido-1,1-difluoroethyl)indoles. Reduction of the azide to amine with hydrogen over Pd−C and careful removal of the *N*-Boc protecting group produced β,β-difluorotryptamines.

Introduction

Over the past several years we have prepared a series of ring-fluorinated biogenic amines and amino acids, including fluorinated analogues of catecholamines and catecholamino acids (DOPAs), histamines and histidines, and tryptamines.[1] This series of compounds provided many useful tools for biological and pharmacological studies. During the course of this work, we had made attempts to prepare side-chain analogues of certain of these important amines and amino acids. The potential value of such compounds has been demonstrated. In the 1970s, Fuller reported the synthesis and biological evaluation of a series of side-chain fluorinated psychotomimetic amines, including, for example, β,β-difluoroamphetamine.[2] Altered biodistribution and behavior toward metabolic enzymes were among the interesting properties of these amines. Such amines are indirect-acting, for example they can act as false neurotransmitters by displacing the endogenous transmitter from the neuron, but have no agonist properties themselves. Other effects can be mediated by blockade of normal re-uptake of the transmitter into the neuron.

We felt that the presence of fluorine on the side chain of amines that have receptor agonist properties could have even more profound biological consequences. However, the reactivity of phenolic benzyl fluorides had thwarted our attempts, and presumably attempts of others, to install fluorine at the benzylic position of catecholamines. In a successful approach to side-chain fluorinated neurotransmitters, we achieved the synthesis of β-fluoro- and β,β-difluorohistamine based on Markovnikoff addition of "FBr" to vinyl imidazoles as the key step.[3] Extending this effort to the indolic amines seemed appropriate in view of the biological importance of tryptamines.[4] Side-chain fluorinated analogues of 5-hydroxytryptamine (serotonin, **1**), an important neurotransmitter, and of *N*-acetyl-5-methoxytryptamine (melatonin, **2**), the key modulator of circadian rhythm, were particularly attractive targets. We report here a synthesis of β,β-difluorotryptamines **3a**−**d** and β,β-difluoromelatonin (**4**) based on the fluorinative deoxygenation of 3-(2-azidoacetyl)indoles. As expected, as the electron density of the indole ring increases, the reactivity of the fluorine also increases.



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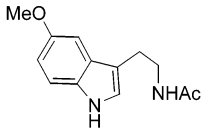

2

Chemistry

In our previous work we accomplished the synthesis of β,β-difluorohistamine by using a double "FBr" addition strategy to 1-trityl-4-vinylimidazole. Addition of "FBr", then elimination of HBr followed by a second "FBr" addition afforded 1-trityl-4-(2-bromo-1,1-difluoroethyl)-imidazole that was converted to β,β-difluorohistamine.[3] The convenience of this sequence and the ready availability of 3-vinylindoles encouraged us to use a similar strategy for the syntheses of fluorinated indolamines. As a first approach to the parent fluoroinated tryptamine, *N*-trityl-3-vinylindole **5a** was treated with NBS and Et_3N-3HF to give the desired "FBr" adduct **6a** in about 20% yield (by NMR) (Scheme 1). However, all attempts to separate this material by chromatography failed, due

† These authors made comparable contributions to this research.

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(2) Fuller, R. W.; Molloy, B. R. In *Biochemistry involving carbon−fluorine bonds*; Filler, R., Ed.; ACS Symp. Ser. 28; American Chemical Society: Washington, DC, 1976; pp 23−36.

(3) Dolensky, B.; Kirk, K. L. *J. Org. Chem.* **2001**, *66*, 4687.

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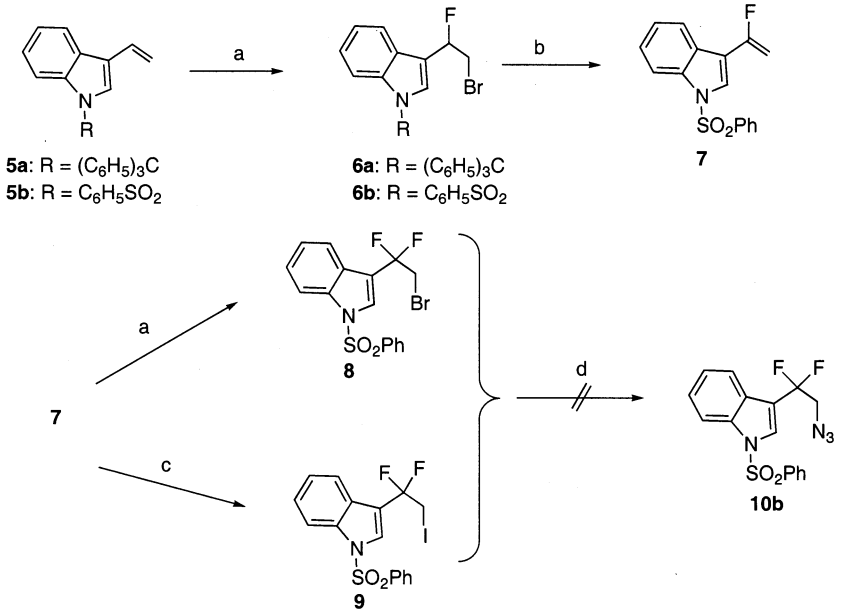
SCHEME 1[a]



[a] Reagents: (a) NBS, 3HF-Et_3N, CH_2Cl_2. (b) K_2CO_3, DMF. (c) NIS, 3HF-Et_3N, CH_2Cl_2. (d) NaN_3, DMF.

to the apparent instability of the addition product **6a**. On the basis of the assumption that decreasing the electron density of the indole would lead to greater stability, we next employed the electronic-withdrawing phenylsulfonyl group as our indole nitrogen protecting group. As we hoped, treating **5b** with NBS and Et_3N-3HF gave the "FBr" adduct **6b** in 50−70% yield. Elimination of HBr was accomplished by using K_2CO_3/DMF to give olefin **7** in 78% yield. The addition of "FBr" to **7** occurred in good yield, and regiospecifically, to give 2,2-difluoro-2-(3-inodoyl)-1-bromoethane **(8)** (75%), a key intermediate in the scheme (Scheme 1). Regrettably, all attempts to replace bromine with nitrogen functionality, as was done in our difluorohistamine synthesis, met with complete failure. For example, treatment of **7** with NaN_3 in DMF under a variety of conditions gave no substitution of bromine by azide. The more reactive iodo compound was prepared by addition of "FI" to **7** to give **9**. The iodo group was also resistant to displacement by azide. Furthermore, attempts to displace the halogen with other nucleophiles, including NH_3 (gas), benzenethiol, and potassium phthalimide, gave disappointing results. This poor reactivity toward nucleophilic substitution is consistent with the well-documented effects on reactivity caused by β-fluorine substitution.[5] However, decomposition or side reactions involving the indole nucleus may have contributed to our failure. In any event, this approach was abandoned after considerable efforts produced no promising results.

In our initial experiments to prepare side-chain fluorinated imidazole derivatives, we had prepared fluoromethyl and difluoromethyl imidazoles by deoxyfluorination of *N*-trityl hydrdoxymethylimidazoles and imidazole carboxaldehydes.[6] Subsequently, we found that the "FBr" addition was a more practical route to the more complex imidazole analogues. Having met with difficulties in this latter approach as our strategy to synthesize fluorinated indoles, we now returned to deoxyfluorination as an alternative. The requirement for installing the side-chain amine functionality that thwarted the previous approach in principle could be obviated by carrying out the key fluorination reaction on a 3-(nitrogen-substituted)acyl indole. Thus, we explored deoxyfluorination of the *N*-protected, appropriately substituted 3-acylindoles.

3-Chloroacetylindole **11a** was treated with NaN_3 in aqueous acetone as previously described[7] to give azido ketone **12a**, which was then converted to the *N*-Boc derivative **13a**. Reaction of **13a** with bis(2-methoxyethyl)-aminosulfur trifluoride (Deoxo-Fluor)[8] at 60 °C gave smooth fluorination to give the gem-difluoro azidoethyl compound **14a**. The azide was reduced to the amine with 10% Pd−C in MeOH and the Boc group was removed with gaseous HCl in EtOAc to give the target β,β-difluorotryptamine **3a** in good yield as a stable, crystalline hydrochloride (Scheme 2).

Key indolamines possess oxygen functionality on the 5-position of the indole nucleus.[2] We were aware that increased electron density of the indole ring likely would increase the reactivity of the benzylic fluorine substituents. 5-Methoxyindole was acylated with chloroacetyl chloride to produce chloroketone **11b**. As before, this was converted to the azide and the indole nitrogen was protected as the Boc amide to give **13b**. This was fluorinated in 75% yield with Deoxo-Fluor (dichloroethane at 75 °C) to produce **14b**. Careful reduction of the azide (10% Pd−C, MeOH) gave the tryptamine **15b** in good yield (Scheme 2). Removal of the Boc group as before produced β,β-difluoro-5-methoxytryptamine **3b** as a stable

(5) Smart, B. E. In *Organofluorine Chemistry, Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994; pp 57−88.

(6) Dolensky, B.; Kirk, K. L. *Collect. Czech Chem. Commun.* **2002**, *67*, 1335.

(7) Bergman, J.; Bäckvall, J. E.; Lindström, J. O. *Tetrahedron* **1973**, *29*, 971.

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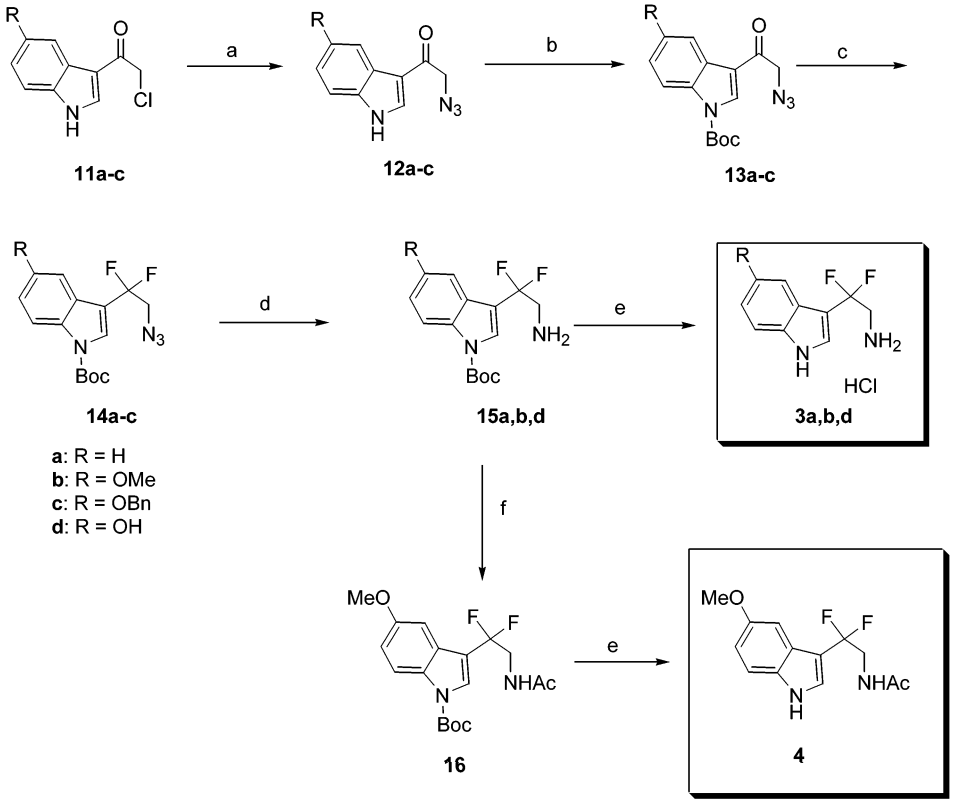
SCHEME 2[a]



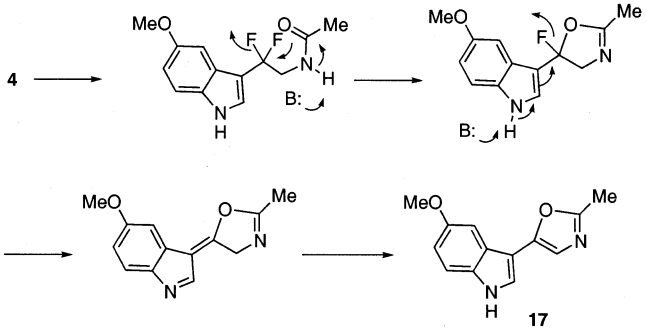
[a] Reagents: (a) NaN_3, aq acetone. (b) $(Boc)_2O$/NaOH, H_2O/THF. (c) Deoxo-Fluoro, 60 °C. (d) Pd/C, H_2, MeOH. (e) HCl (gas), EtOAc. (f) Ac_2O, TEA, CH_2Cl_2, 0 °C.

hydrochloride. Acylation of **15b** to give **16** followed by removal of the Boc protecting group gave *β*,*β*-difluoromelatonin **4** (Scheme 2).

Unlike the tryptamines **3a** and **3b**, which proved to be quite stable as the hydrochlorides, an NMR sample *β*,*β*-difluoromelatonin **4** in DMSO after overnight storage in a refrigerator displayed new peaks that appeared to result from loss of fluorine. A similar conversion was observed in deuteriomethanol containing triethylamine. Complete conversion to a new compound could be effected under these latter conditions. Preliminary data (MS and NMR) suggest formation of a new heterocylic ring accompanied by loss of both fluorine atoms. Since no such behavior was observed with the nonacylated precursor we make the assumption that the reactivity is associated with the *N*-acetyl group. One possible mechanism for HF loss to give the new product, tentatively identified as 2-methyl-5-[3-(5-methoxyindoyl)]oxazole (**17**), is shown in Scheme 3. A similar transformation is seen in the formation of 2-methyl-5-[3-(1-acetylindoyl)]oxazole from 1-acetyl-3-acetamidoacetylindole by the action of refluxing phosphorus oxychloride. This presumably involves the loss of two HCl molecules from the gem-dichloro intermediate during a similar cyclization reaction.[9]

We were particularly eager to prepare *β*,*β*-difluoro-5-hydroxytrytpamine **(3d)**. The serotonin analogue would be quite useful to study the effects of amine pK_a on such properties as sertonin transport and receptor binding. This analogue also proved to be the most difficult to isolate. 5-Benzyloxyindole was converted to the azido ketone **13c** as described for the previous analogues. This

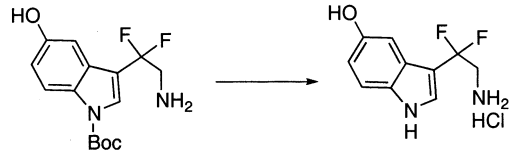
SCHEME 3



was fluorinated with Deoxo-Fluor to give the protected 5-benzyloxy tryptamine **14c**. Hydrogen over 10% Pd−C effected hydrogenolysis of the benzyl ether and reduction of the azide to the amine in one step to give **15d**. Removal of the Boc group by careful treatment of **15d** with gaseous HCl in EtOAc produced the target difluoroserotonin **3d**, but this was contaminated by up to 30% with an unidentified product, the NMR spectrum of which suggested loss of one fluorine. Repeated attempts to increase purity by lowering the reaction temperature, limiting the amount of HCl catalyst, and/or changing solvents led to even less satisfactory results, including lower conversions and decreased purity. However, a procedure that favored rapid product formation and precipitation gave excellent results. Rapid addition of HCl gas to a solution of **15d** in

(9) Joshi, B. S.; Taylor, W. I.; Bhate, D. S.; Karmarkar, S. S. *Tetrahedron* **1963**, *19*, 1437.

SCHEME 4



15d **3d**

Reagent	Temp	Solvent	Results
HCl (g)	-20 °C	EA	<70%[a]
HCl (g)	-70 °C	EA	<50%[a]
$(CO)_2Cl_2$/ MeOH	0 °C to RT	EA	NR[b]
CF_3CO_2H	0 °C to RT	-	SR[c]
	40°C	-	Dec.[d]
HCl (g)	RT	Ether	>98%[a]

[a] Purity estimated by using ^{1}H NMR. [b]No reaction. [c]Slight reaction. [d]Decomposion.

ether at room temperature led to an almost immediate precipitate (Scheme 4). Simple evaporation of ether produced **3d** hydrochloride as a homogeneous compound based on NMR spectra.

It is noteworthy that NMR solutions are not stable, and **3d** is fairly rapidly converted to a new compound when kept in solution. NMR data again indicate loss of fluorine. Rapid removal of the Boc group from **15d** to give a critical concentration of **3d** sufficient to cause its efficient precipitation as the stable crystalline form would seem important to the success of this procedure. The facile loss of fluoride from **3d** revealed by the NMR data could influence strategies and results of biological studies. For this reason we are examining the chemistry of **3d** in more detail and will report the results in a subsequent publication. Included will be a study of stability under different conditions and characterization of product(s) of fluoride loss.

Fuller reported that geminal fluorine substitution in the benzylic position lowered the pK_a value of phenylethylamines by approximately 2 pH units.[2] We found a similar lowering of basicity in β,β-difluorohistamines.[3] Attempts to determine titrametric pK_a values of **3a** have been unsuccessful to date because of apparent decomposition (color change) at higher pH values.

Experimental Section

General Procedures. Melting points are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 300.1, 75.5, and 282.2 MHz. Chemical shifts (δ) of protons and carbons are relative to TMS (0 ppm), and the fluorine shifts are relative to trifluoroacetic acid (0 ppm), all in ppm. Interaction constants are presented in Hz. The solvent is $CDCl_3$ unless otherwise noted. Low-resolution MS (LRMS) was performed with chemical ionization under ammonia gas. High-resolution MS (HRMS) was done with FAB ionization under xenon gas. Silica gel (0.040−0.063 mm) was used for column chromatography, and 1000 mm silica gel GF plates were used for preparative TLC. All reagents and dry solvents were purchased if not otherwise indicated and used without further purification or drying.

2-Azido-1-(1*H*-indol-3-yl)-ethanone (12a). To a stirred solution of **11a** (2.0 g, 10.3 mmol) in 100 mL of water and 50 mL of acetone was added sodium azide (1.33 g, 20.6 mmol). The solution was refluxed overnight, and then was diluted with 100 mL of distilled water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated at reduced pressure to produce an ivory solid. The solid was recrystallized in dichloromethane and methanol to give 1.98 g (97%) of **12a** as a pale yellow solid. Mp 181−183 °C.

***tert*-Butyl 3-(2-Azido-acetyl)-indole-1-carboxylate (13a).** Di-*tert*-butyl dicarbonate (581 mg, 2.63 mmol) and 50% aqueous NaOH (15 mL) were added to a solution of **12a** (440 mg, 2.19 mmol) in 5 mL of THF at 0 °C and the mixture was stirred for 1 h at ambient temperature. The reaction mixture then was poured into 100 mL of cooled water and solid precipitate was removed by filtration, washed with cooled hexane, and dried in a vacuum to give 348 mg (78%) of **13a** as a white solid. Mp:157−158 °C.

***tert*-Butyl 3-(2-Azido-1,1-difluoro-ethyl)-indole-1-carboxylate (14a).** A solution of **13a** (253 mg, 0.842 mmol) in 3 mL of bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) was heated at 60 °C overnight. The reaction mixture was cooled to room temperature and poured into cooled saturated sodium bicarbonate solution. The solution was extracted with methylene chloride (30 mL) and the methylene chloride solution was washed with brine. After being dried over anhydrous Na_2SO_4, the solvent was concentrated in vacuo. Flash column chromatography of the residue on silica gel (10:1 ethyl acetate/hexane) afforded the pure product (**14a**, 208 mg, 77%) as a pale yellow oil.

***tert*-Butyl 3-(2-Amino-1,1-difluoro-ethyl)-indole-1-carboxylate (15a).** A solution of the **14a** (128 mg, 0.379 mmol) in 12 mL of methanol was hydrogenated (balloon) over Pd/C (10%, 50 mg) for 30 min after which time starting material had disappeared (TLC). The catalyst was removed by filtration through Celite and washed with 5 mL of methanol. The filtered solution was concentrated by rotary evaporation to give a colorless liquid. The product was purified by flash column chromatography in 1:1 ethyl acetate/hexane to give 90.7 mg (77%) of **15a**.

2,2-Difluoro-2-(1*H*-indol-3-yl)-ethylamine Hydrochloride (3a). Hydrogen chloride gas was bubbled into a solution of **15a** (90.7 mg, 0.30 mmol) in 10 mL of ethyl acetate for 20 min. The solvent was evaporated to give **3a** (55.9 mg, 67.6%) as a white solid. Mp 148 °C dec. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.77 (1H, br s), 8.69 (2H, br s), 7.80 (1H, s), 7.65 (1H, d, J = 6.9 Hz), 7.48 (1H, d, J = 7.2 Hz), 7.13−7.21 (2H, m), 3.85 (2H, t, J = 14.4 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.1, 125.8 (t, J = 7.9 Hz), 123.5, 122.3, 122.2, 120.7, 120.2, 119.5, 118.9, 112.1, 107.3 (t, J = 28.6 Hz), 43.3 (t, J = 29.7 Hz). ^{19}F NMR (281.28 MHz, DMSO-d_6) δ −15.87 (t, J = 15.52 Hz). MS (FAB, $M^+ + 1$) 197.16. Anal. Calcd for $C_{10}H_{10}F_2N_2 \cdot 2HCl$: C, 44.64: H, 4.49: N, 10.41. Found: C, 45.74: H, 4.19: N, 9.57.

2-Chloro-1-(5-methoxy-1*H*-indol-3-yl)-ethanone (11b). Pyridine (1.65 mL, 20.38 mmol) was added to a solution of 5-methoxyindole (3.0 g, 20.38 mmol) in 15 mL of toluene. Chloroacetyl chloride (1.61 mL, 20.38 mmol) was added dropwise at ambient temperature over 30 min and the solution was then stirred for 1.5 h at 60 °C. After the reaction mixture was cooled, it was poured into 50 mL of distilled water. The resulting solid was collected by filtration and recrystallized from ethanol (40 mL) to give **11b** (2.673 g, 59%) as a white solid. Mp >230 °C.

2-Azido-1-(5-methoxy-1*H*-indol-3-yl)-ethanone (12b). To a solution of **11b** (2 g, 8.94 mmol) in 150 mL of acetone/water (2:1) was added sodium azide (1.342 g, 20.65 mmol). The reaction mixture was refluxed overnight, then cooled, diluted with 100 mL of water, and extracted with methylene chloride (2 × 50 mL). The organic layer was dried over Na_2SO_4 and evaporated, and the residue was recrystallized from ethyl acetate to give **12b** (1.93 g, 94%) as a white solid. Mp 180 °C.

***tert*-Butyl 3-(2-Azido-acetyl)-5-methoxy-indole-1-carboxylate (13b).** Di-*tert*-butyl dicarbonate (2.87 g, 13.03 mmol) and 50% NaOH solution (15 mL) were added to a solution of **12b** (1.5 g, 6.515 mmol) in 15 mL of THF at 0 °C. The solution was stirred for 1 h at ambient temperature. The reaction mixture was poured into 100 mL of cooled water and the resulting solid was collected by filtration, washed with cooled hexane, and dried in a vacuum to give 1.975 g (92%) of **13b** as white solid. Mp 162−163 °C.

***tert*-Butyl 3-(2-Azido-1,1-difluoro-ethyl)-5-methoxy-indole-1-carboxylate (14b).** To a solution of **13b** (500 mg, 1.51 mmol) in 10 mL of dichloroethane was added 2 mL of Deoxo-Fluor and the solution was stirred overnight at 60 °C. The reaction mixture was cooled to room temperature and poured into cooled saturated sodium bicarbonate solution. The solution was extracted with methylene chloride (30 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in a vacuum. Flash column chromatography of the residue on silica gel (15:1 ethyl acetate/hexane) afforded pure **14b** (338 mg, 73%) as a pale yellow oil.

***tert*-Butyl 3-(2-Amino-1,1-difluoro-ethyl)-5-methoxy-indole-1-carboxylate (15b).** A solution of **14b** (385 mg, 1.090 mmol) in 20 mL of methanol was hydrogenated (balloon) over 10% Pd/C (150 mg) for 3 h, after which time starting material had disappeared. The catalyst was removed by filtration through Celite and washed with 5 mL of methanol. The filtered solution was concentrated by rotary evaporation to give a colorless residue. This was subjected to flash column chromatography in 1:1.5 ethyl acetate/hexane to give **15b** as a viscous liquid (275 mg, 77%).

2,2-Difluoro-2-(5-methoxy-1*H*-indol-3-yl)-ethylamine Hydrochloride (3b). Dry HCl gas was bubbled into a solution of **15b** (206 mg, 0.631 mmol) in 15 mL of ethyl acetate for 1 h while the temperature was maintained at −60 °C. The solution was then warmed slowly to room temperature. The solvent was evaporated to give **3b** (135 mg, 90%) as a white solid. Mp >153 °C dec.^{1}H NMR (300 MHz, DMSO-d_6) δ 11.6 (1H, br s), 8.64 (2H, br s), 7.73 (1H, s), 7.38 (1H, d, J = 8.7 Hz), 7.01 (1H, d, J = 1.5 Hz), 6.85 (1H, dd, J = 9.0 Hz, 2.4 Hz), 3.85 (2H, t, J = 14.4 Hz). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 154.1, 131.2, 126.1 (t, J = 7.99 Hz), 124.1, 119.7 (t, J = 235.0 Hz), 112.9, 112.4, 107.0 (t, J = 29.2 Hz), 100.6, 55.4, 43.3 (t, J = 29.2 Hz). ^{19}F NMR (282.18 MHz, DMSO-d_6) δ −16.00 (t, J = 15.23 Hz). MS (FAB$^+$) m/z (M + H$^+$) calcd 227.0996, obsd 227.0990

***tert*-Butyl 3-(2-Acetylamino-1,1-difluoro-ethyl)-5-methoxy-indole-1-carboxylate (16).** To a solution of **15b** (275 mg, 0.842 mmol) in 7 mL of methylene chloride were added triethylamine (0.225 mL, 1.685 mmol) and acetic anhydride (160 μL, 1.685 mmol) at 0 °C. The reaction mixture was stirred for an additional 1 h at 0 °C. Removal of the solvent and purification of the residue by flash chromatography on silica gel (hexane/EtOAc 1:1) afforded **16** (246 mg, 79%) as a white solid.

***N*-[2,2-Difluoro-2-(5-methoxy-1*H*-indol-3-yl)-ethyl]-acetamide (β,β-Difluoromelatonin) (4).** To a solution of **15b** (238 mg, 0.640 mmol) in 15 mL of ethyl acetate was bubbled hydrogen chloride gas for 1 h while the temperature was maintained at −60 °C. The solution was then warmed slowly to room temperature. Evaporation of the solvent gave **12** (166 mg, quantitative) as gray solid. Mp 121 °C dec. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.38 (1H, br s), 8.34 (1H, br s), 7.58 (1H, s), 7.33 (1H, d, J = 9.0 Hz), 7.08 (1H, s), 6.81 (1H, dd, J = 9.0, 2.1 Hz), 3.94 (2H, td, J = 14.7, 2.4 Hz), 3.76 (3H, s), 1.85 (3H, s). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 169.7, 153.9, 131.3, 152.2 (t, J = 8.0 Hz), 124.6, 121.1 (t, J = 234.5 Hz), 112.7, 112.2, 109.2 (t, J = 29.8 Hz), 100.9, 55.3, 43.6 (t, J = 30.3 Hz). ^{19}F NMR (282.18 MHz, DMSO-d_6) δ −16.07 (t, J = 15.23 Hz). Anal. Calcd for $C_{13}H_{14}F_2N_2O_2$·HCl: C, 51.24: H, 4.96: N, 9.19. Found: C, 51.74: H, 4.42: N, 8.30.

5-Methoxy-3-(2-methyl-oxazol-5-yl)-1*H*-indole (17). A solution of **4** (10 mg, 0.04 mmol) in 3 mL of MeOH was treated with a few drop of triethylamine for 5 min at room temperature. The solvent was evaporated and the crude product was purified by silica gel column chromatography (ethyl acetate/hexane 1:2) to give light pink solid **17** (7.9 mg, 81%).

1-(5-Benzyloxy-1*H*-indol-3-yl)-2-chloro-ethanone (11c). **11c** was prepared by acylation of 5-benzyloxyindole as described for the preparation of **11b**. Yield 66%; mp >218 °C dec. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (br s, 1H), 8.37 (d, 1H, J = 3.3 Hz), 7.76 (d, 1H, J = 2.1 Hz), 7.32−7.49 (m, 6H), 6.95 (dd, 1H, J = 8.7, 2.4 Hz), 5.13 (s, 2H), 4.84 (s, 2H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 105.9, 154.6, 137.4, 134.9, 131.5, 128.3, 127.6, 127.5, 126.2, 113.5, 113.4, 113.1, 104.4, 69.6, 46.3. HRMS calcd for $C_{17}H_{14}ClNO_2$ 299.0713, found 299.0711.

2-Azido-1-(5-benzyloxy-1*H*-indol-3-yl)-ethanone (12c). **12c** was prepared from **11c** as described for the preparation of **12b**. Yield 89%; mp 173−174 °C.

***tert*-Butyl 3-(2-Azido-acetyl)-5-benzyloxy-indole-1-carboxylate (13c).** Acylation of **12c** with Boc anhydride as described for the preparation of **13a**,**b** gave **13c**. Yield 92%; mp 155−156 °C.

***tert*-Butyl Ester 3-(2-Azido-1,1-difluoro-ethyl)-5-benzyloxy-indole-1-carboxylate (14c).** Fluorination of **13c** with Doxo-Fluor as described for the preparation of **14a**,**b** gave **14c**.Yield 69%; mp 93−94 °C.

***tert*-Butyl 3-(2-Amino-1,1-difluoro-ethyl)-5-hydroxy-indole-1-carboxylate (15d).** A solution of **14c** (287 mg, 6.69 mmol) in 1 mL of THF and 10 mL of methanol was hydrogenated (baloon) over 10% Pd/C (150 mg) for 2 h. The catalyst was removed by filtration through Celite. The filtrate was concentrated by rotary evaporation and the residue was purified with silica gel column chromatography to give a white solid (167 mg). Yield 80%; mp >130 °C dec.

3-(2-Amino-1,1-difluoro-ethyl)-1*H*-indol-5-ol Hydrochloride (3d). To a solution of **15d** (200 mg, 0.64 mmol) in 20 mL of diethyl ether was bubbled anhydrous HCl (g) for 10 min at room temperature. The resulting solid was filtered and dried over vacuum to give **3d** (98 mg, 72%) as a white solid. Mp >143 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.58 (br s, 1H), 8.05 (br s, 1H), 7.80 (br s, 3H), 6.76 (s, 1H), 6.35 (d, 1H, J = 8.4 Hz), 6.07 (s, 1H), 5.80 (dd, 1H, J = 8.7, 2.1 Hz), 2.86 (t, 2H, J = 15.0 Hz). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 151.7, 134.9, 130.6, 125.9 (t, J = 5.29 Hz), 124.6, 119.8 (t, J = 235.8 Hz), 112.7, 106.5 (t, J = 28.7 Hz), 102.9, 43.3 (t, J = 29.2 Hz). ^{19}F NMR (282.18 MHz, CD_3OD) δ −15.8 (t, J = 12.4 Hz). HRMS calcd for $C_{10}H_{10}F_2N_2O$ 212.0761, found 212.0761.

Supporting Information Available: Details for the synthesis and characterization of compounds **6b**, **7**, **8**, and **9**; product characterization data for **12a**, **13a**, **14a**, **15a**, **11b**, **12b**, **13b**, **14b**, **15b**, **16**, **17**, **11c**, **12c**, **13c**, **14c**, and **15d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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