Pergamon

Tetrahedron 55 (1999) 1881–1892

TETRAHEDRON

A Synthesis of 3-Fluoroindoles and 3,3-Difluoroindolines by Reduction of 3,3-Difluoro-2-oxindoles using a Borane Tetrahydrofuran Complex.

José C. Torres[a], Simon J. Garden,[a]* Angelo C. Pinto,[a] Filipe S. Q. da Silva,[b] and Núbia Boechat.[b]

[a] Instituto de Química, Departamento de Química Orgânica, Universidade Federal do Rio de Janeiro, Ilha do Fundão, Rio de Janeiro, CEP 21941-590, Brazil.

[b] Fundação Oswaldo Cruz, Far-Manguinhos, Avenida Brasil, Rio de Janeiro, CEP 21041-250, Brazil

Received 25 November 1997; revised 19 November 1998; accepted 15 December 1998

Abstract: A borane tetrahydrofuran complex has been used to study the reduction of 3,3-difluoro-2-oxindoles and been found to yield either 3-fluoroindoles or 3,3-difluoroindolines. The latter have been found to be reasonably stable when the aromatic nucleus is substituted with an electron withdrawing group and are in these cases the predominant product. The efficient synthesis of the former occurs by elimination of HF in the presence of silica from the latter. The 3,3-difluoro-2-oxindoles were prepared by the reaction of appropriately substituted isatin derivatives with DAST.
Keywords: indolinones; halogenation; reduction; indoles.

INTRODUCTION

The incorporation of a fluorine atom or atoms in place of hydrogen in a molecule, particularly in molecules of medicinal interest, is known to impart many beneficial effects upon therapeutic efficacy and pharmacological activity. This is considered to be the result of: 1) fluorine closely mimicing hydrogen in terms of steric requirements, 2) alteration of electronic effects due to the highly electronegative nature of fluorine, 3) increased lipid solubility of fluorinated drugs, 4) improved oxidative and thermal stability, and 5) enzymic reaction inhibition properties.[1] Consequently, there is considerable interest in the synthesis of fluorinated compounds.

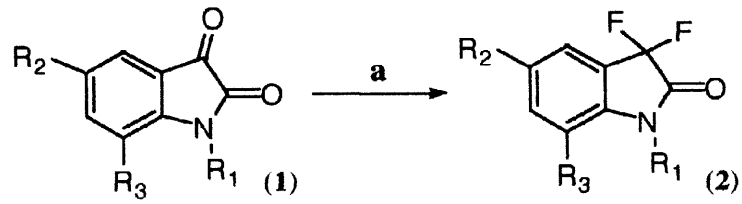
Many synthetic methodologies have been devised for the synthesis of indoles and continue to be developed, reflecting the importance of this skeletal structure.[2] The use of a borane tetrahydrofuran complex for the reduction of oxindole derivatives is a known route for the synthesis of indoles but has received, relatively, little attention.[3] In studies extending those of previous from this laboratory,[3c] it was found that 3,3-difluoro-2-oxindoles (**2**) can be readily reduced to 3-fluoroindoles (**3**) in good yields.[4] It was also found in this study that **3**, like the 3-chloro- and 3-bromo- derivatives, have limited stability.[5] However, tosylation of **3a**, and **3b**, under standard conditions readily yielded the known 3-fluoro-*N*-tosylindole (**5a**)[4b] and the previously unknown 3-fluoro-5-methyl-*N*-tosylindole (**5b**), both of which revealed improved thermal and oxidative stability. The course of the reaction was found to pass through intermediate indoline derivatives (**4**) that in the presence of silica showed an enhanced rate of elimination of HF to yield the final products, 3-fluoroindoles (**3**).

RESULTS AND DISCUSSION

The methodology originally described by Middleton and Bingham[6] for the synthesis of *N*-methyl-3,3-difluoro-2-oxindole (**2e**) was modified in that, reactions were performed at room temperature. Thus, isatin

0040-4020/99/$ - see front matter
PII: S0040-4020(98)01229-0

substrates (**1a-f**) were readily converted in high yield to **2a-f** (86-94% based upon substrate) by reaction of a slight excess of DAST in anhydrous CH_2Cl_2 (Equation 1). The products were characterized spectroscopically and representative examples gave the expected monoisotopic mass by HRMS. The ^{19}F NMR chemical shifts for compounds **2**, studied, fall in a narrow range of -110 to -113ppm with the exception of **2d** (-106ppm).

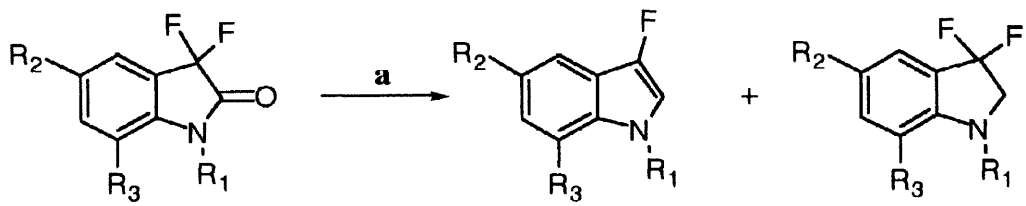


Equation 1

Reagents and conditions. **a** DAST, CH_2Cl_2, rt, 1-3 days.

Substituents for compounds **1** and **2**. **a** $R_1 = R_2 = R_3 = H$; **b** $R_1 = R_3 = H$, $R_2 = CH_3$; **c** $R_1 = PhCH_2$, $R_2 = R_3 = H$; **d** $R_1 = PhCO$, $R_2 = R_3 = H$; **e** $R_1 = CH_3$, $R_2 = R_3 = H$; **f** $R_1 = R_3 = H$, $R_2 = NO_2$; **g** $R_1 = H$, $R_2 = R_3 = Br$.

Subsequent treatment of **2** (**a-f**) with excess "borane" in THF[7] at room temperature, followed by an aqueous isolation procedure and filtration through a short silica gel column, gave products that were found to be dependent upon the nature of the substituents bonded to the aromatic nucleus, R_2 and R_3 (equation 2).



Equation 2

Reagents and conditions. **a** "BFH_2.THF", THF, 0°C - room temp.

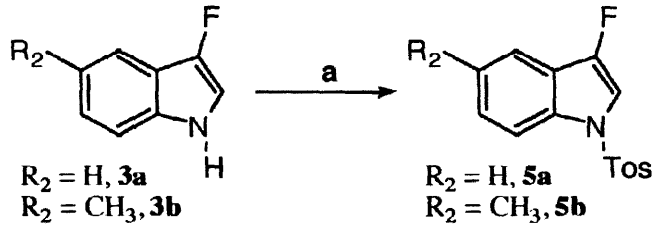
For substituents, consult equation 1.

The reduction of **2** (**a-e**) gave in all cases high yields of **3** (**a-c** and **e**, equation 2). Compounds **2c** and **2d** were smoothly reduced under similar conditions to produce an identical product **3c**. The reduction of **2d** to **3c** is consistent with previous observations on the reduction of N-acylisatins to N-alkylindoles under similar conditions by BH_3.THF.[3c] Previous experiments investigating the reduction of 2-oxindole acetic acid derivatives using BH_3.THF, under conditions of extended reflux, resulted in the formation of 3-(ethanol)indolines,[8] whilst BH_3.NMe_3 complex has been found to reduce indoles to indolines under acidic conditions.[9]

Compounds **3** were observed to be thermally unstable.[5] When warmed on a water bath, during removal of solvent after hydrolysis of the reaction mixture and also after filtration through a column of silica, decomposition readily occurred. The respective fluoroindole **3** could be stored after careful isolation, removal of the solvent at room temperature, and storage under an inert, nitrogen, atmosphere and in the cold (-15°C). Storage at room temperature readily resulted in decomposition (blackening). The decomposition involves the formation of HF as

evidenced by etching of the glassware. Likewise, solutions of **3** were also unstable. For example, $CDCl_3$ solutions readily decomposed with loss of resolution of the ^1H NMR signals after storage at room temperature for a few hours.

In order to circumvent the stability problem and to unambiguously demonstrate the formation of 3-fluoroindoles, freshly prepared **3a** was tosylated under phase transfer conditions at room temperature (equation 3). *N*-Tosyl-3-fluoroindole (**5a**) was obtained in an overall yield of 61% after purification, based upon **2a**, and was found to have improved thermal stability in that it did not decompose on storage.



Equation 3

a Tosyl chloride, toluene, aqueous NaOH (2N), aliquat™ (3 drops).

The ^1H, and ^{19}F, NMR data and the melting point were found to be in close agreement with those previously reported.[4b] In addition, a ^{13}C NMR PENDANT spectrum revealed the presence of seven unique methine (CH) carbons, two of which revealed coupling to fluorine (C-2, 28.8Hz; C-4, 2.4Hz), one methyl and five quaternary carbons, three of which revealed coupling to fluorine (C-3a, 18.9Hz; C-7a, 5Hz; C-3, 255Hz). The use of 2D NMR techniques (COSY-GS, HMBC-GS, HSQC-DE) allowed the complete assignment of all hydrogens and carbons. A low resolution mass spectrum gave a molecular ion at m/z 289, and three principle fragments were identified; the first two resulting from cleavage of the indole nitrogen sulphur bond, m/z 155 (SO_2tolyl, 50%) and m/z 134 (3-fluoroindolyl, 69%); the third being identified as the tropylium ion (m/z 91, 100%). Finally, elemental analysis confirmed the expected composition. The devised methodology was subsequently applied to the synthesis of the previously unknown *N*-tosyl-3-fluoro-5-methylindole (**5b**), by reduction of **2b** and tosylation of the product **3b** (overall yield 54%), which as for **5a** proved to be thermally stable and resistant to decomposition on exposure to the atmosphere for prolonged periods of time. The structure of **5b** was confirmed spectrally; ^1H NMR revealed 8 aromatic protons and 6 protons due to 2 methyl groups. A ^{13}C NMR PENDANT experiment confirmed the two methyl groups and confirmed 6 unique CH aromatic signals, two of which were split into doublets due to coupling with fluorine (C-2, 29Hz; C-4, 2.6Hz), and 6 quaternary aromatic carbons, three of which were split into doublets (C-3, 255Hz; C-7a, 5.3Hz; C-3a, 19Hz). ^{19}F NMR revealed a singlet at -166.0ppm consistent with the chemical shift observed for **5a** (-166.5 ppm). A low resolution mass spectrum gave a molecular ion at m/z 303, and three principle fragments were identified; the first two resulting from cleavage of the indole nitrogen sulphur bond, m/z 155 (SO_2Tolyl, 27%) and m/z 148 (5-methyl-3-fluoroindolyl, 100%); the third being identified as the tropylium ion (m/z 91, 73%). Finally, elemental analysis confirmed the expected composition.

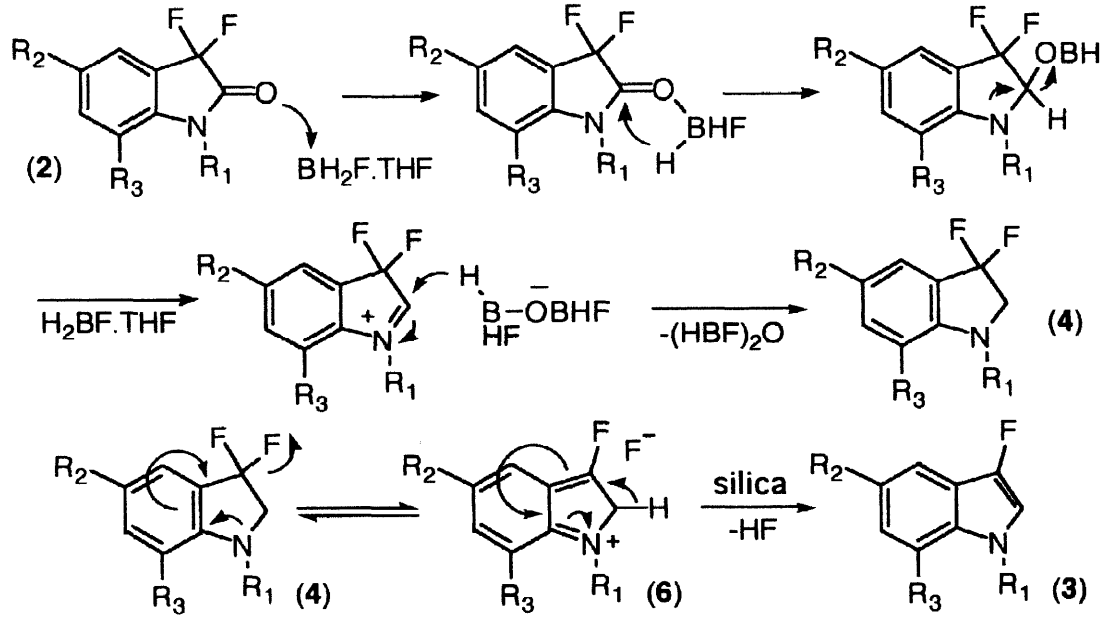
Unlike **3a** and **3b** the *N*-alkyl-3-fluoroindoles **3c** and **3e** cannot be rendered more enduring by deactivation of the indolic nitrogen; their structures were, however, confirmed spectroscopically. ^1H NMR spectra revealed the presence of 10 aromatic hydrogens in **3c** and 5 in **3e**, a 2 hydrogen singlet corresponding to

the benzylic methylene (5.18ppm) of **3c** and a 3 hydrogen singlet corresponding to a methyl group (3.70ppm) attached to nitrogen in **3e**. The ^{13}C spectrum of **3c** revealed a deshielded carbon (50.0ppm) attributed to the benzylic methylene group bonded to the indolic nitrogen and a further twelve unique sp^2 signals; two of which were split into doublets due to coupling with fluorine (C-2, 25.6Hz, and C-3, 243Hz); four of which were attributed to the benzylic aromatic ring; the remaning six being due to the benzo ring of the indolic nucleus. The ^{13}C spectrum of **3e** revealed a methyl group bonded to the indolic nitrogen (32.7ppm) and eight sp^2 hybridised carbons, two of which were split into doublets due to coupling with fluorine (C-2, 27Hz, and C-3, 243Hz). The ^{19}F NMR spectra of **3c** and **3e** showed singlets at -175.5 and -176.4ppm respectively. The low resolution mass spectra of **3c** and **3e** were characterised by the presence of the molecular ions (m/z 225, 32%, and 149, 100%, respectively) and subsequent fragmentation yielding the 3-fluoroindolyl ion and in the case of **3c** the tropylium ion (100%). In addition HRMS of **3c** gave a monoisotopic molecular ion of 225.0954, where the calculated value is 225.0954, thus, confirming the molecular formula of $C_{15}H_{12}FN$.

In the reactions of substrates with electron withdrawing substituents (**2f** and **g**) on the aromatic nucleus, high yields of **4** (**f** and **g**) were obtained and small quantities of the respective **3** (**f** and **g**) were identified by ^1H and ^{19}F NMR spectroscopy and GC-MS. The indoline structure of **4** (**f** and **g**) was readily apparent from a deshielded two hydrogen ^1H signal (4.00 and 3.90ppm respectively) that was split into a triplet due to coupling with two vicinial fluorine atoms (J_{HF} 18Hz for both **4f** and **4g**). This interpretation was further substantiated by the observation of a triplet, in the ^{19}F spectrum, with a coupling constant of equal magnitude to that observed in the ^1H NMR. The observed ^{19}F chemical shifts of **4** (**f** and **g**) were -84.4 and -83.5ppm, respectively. The mass spectra revealed strong molecular ions for **4** (**f** and **g**), 200 (69%) and 313 (74%) respectively. The dominant fragmentation processes were loss of HF, NO, and NO_2, giving ions 180 (90%), 170 (49%), 154 (30%) and 134 (100%) for **4f**, and loss of HF followed by loss of one or both bromine atoms for **4g**: 293 (100%), 212 (43%) and 133 (50%). The respective indoles **3** (**f** and **g**) gave characteristic (*vide supra*) ^{19}F NMR signals, -172.1 and -171.7 respectively, that revealed a coupling to H-2 (J_{HF} 3Hz) which was confirmed in the ^1H spectrum.

A simplified mechanism for the formation of fluoroindoles by the reduction of **2** is formulated in scheme 1. Reduction of the amide group yields the 3,3-difluoroindoline **4**[8,10] which can undergo loss of HF to yield the 3-fluoroindole **3**. The loss of HF may or may not be spontaneous. ^1H and ^{13}C NMR analysis of a crude reaction product after hydrolysis (reduction of **2c**) revealed the presence of an unstable one to one mixture of 3-fluoroindole (**3c**) and 3,3-difluoroindoline (**4c**).[11] On prolonged storage this product mixture gave an intractable black tar, during which time the formation of HF was noted by the etching of the glass surface. The base induced 1,4-elimination of HF from *ortho*-trifluoromethylanilines resulting in the formation of an *ortho*-quinoid intermediate has been formulated as a key step in the synthesis of a number of heterocyclic systems.[12] In this study, for the substrates where electron withdrawing groups are not present on the aromatic ring of **4**, the indoline nitrogen of **4** has greater electron density and, thus, may assist in the elimination of HF to yield **3** via an *ortho*-quinoid intermediate (**6**). In order to further investigate the course of the reaction, and bearing in mind the observation that the reduction of **2c** yielded an unstable mixture of **3c** and **4c** (crude unchromatographed product after hydrolysis) the reduction of **2d** was further investigated. Analysis of the ^1H NMR after hydrolysis of the reduction reaction revealed a 1:4 mixture of **3c** and **4c**. The predominant product before chromatography was clearly identifed as the 3,3-difluoroindoline **4c**.[11,13] The crude product was then immediately filtered through a short column of silica gel eluting with hexane/CH_2Cl_2 and the eluted product reanalysed. ^1H NMR revealed the

major product to now be **3c**, the observed ratio of **3c** to **4c** had changed to approximately 4:1. Refiltration gave only the indole **3c** in good yield (72% based upon **2d**). Evidently, formation of **3** does occur either during the reaction or upon hydrolysis. However, the extent of conversion of **4** to **3** is variable but on passage of the mixture through a silica column, **4** is transformed into **3**. Therefore, *the efficient synthesis* of **3** by the reduction of **2** is dependant upon a reaction of the indoline **4** with the silica. The elimination of HF from geminal difluorocycloalkanes has been observed to occur in the presence of anhydrous alumina to yield 1-fluorocycloalkenes.[14] The authors of this study attributed the reactivity of the alumina to the presence of both Lewis acidic and basic sites, deactivation of which inhibited the dehydrofluorination reaction.

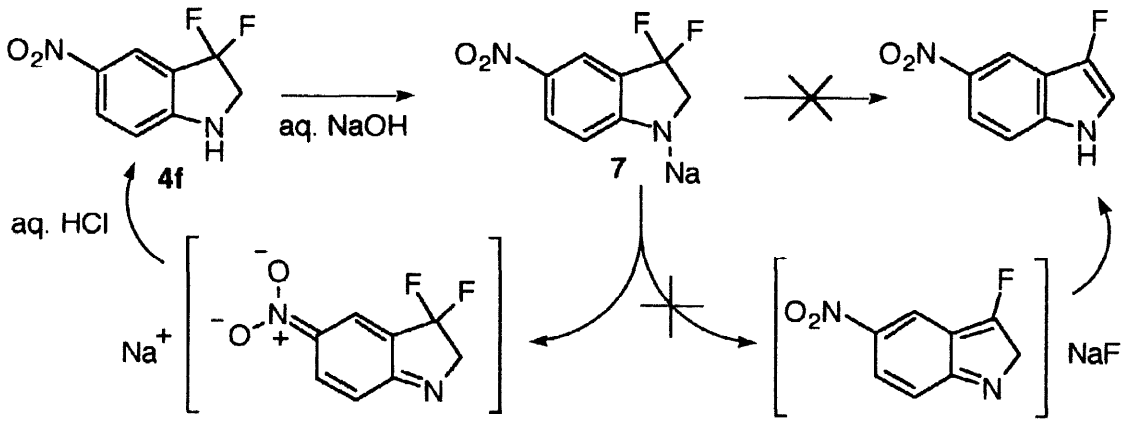


Scheme 1

The observations can be rationalised in terms of the mechanism presented in scheme 1 where in the absence of electron withdrawing groups on the aromatic nucleus the nitrogen can donate electron density into the aromatic ring resulting in weakening of the C-F bonds and a "slow" elimination of HF. However, the elimination of HF is apparently accelerated when in contact with silica. This is proposed to be the result of the silica forming a strong bond with fluoride ion. Thus a low equilibrium concentration of an *ortho*-quinoid intermediate (**6**) could be rapidly and irreversibly converted to the product, 3-fluoroindole (**3**), through an exothermic adsorption on the silica surface.

This mechanism is further substantiated by the relative stability of **4f** and **4g** where due to diminished electron density on the indoline nitrogen, a consequence of the presence of electron withdrawing groups on the aromatic ring, elimination of HF becomes thermodynamically less favourable.[15] On treatment of **4f** with mild base deprotonation of the indoline nitrogen readily occurred, as evidenced by the intense colour change, but on subsequent neutralisation **4f** was returned unchanged (scheme 2). The experiment serves to show that delocalisation of the nitrogen lone pair in a resonance form that involves the nitro group is favoured over delocalisation of electron density that would result in fluoride elimination. It can also be noted that the nitro group

would not be involved in stabilisation of the intermediate anion **7** if fluoride ion were to be eliminated.



Scheme 2

The presented methodology offers a number of advantages over existing methodologies but principally the availability of isatin derivatives, or their facile synthesis,[16] the smooth nucleophilic substitution of the C-3 carbonyl, by fluoride, of isatin using DAST and the ease of preparation and utilisation of solutions of borane for the reduction reaction make, in our opinion, this a relatively simple method for the synthesis of 3-fluoroindoles.

EXPERIMENTAL

General. ^{1}H and ^{13}C NMR spectra were recorded using 300MHz and 200MHz (^{1}H) Brucker spectrometers and are referenced to TMS, ^{19}F NMR (188MHz) spectra are referenced to $CFCl_3$. Coupling constants are quoted in hertz. Assignments of ^{1}H and ^{13}C nuclei were based upon 2D experiments and by comparative methods. Mass spectra were recorded at NPPN (Nucleo de Pesquisa de Produtos Naturais, Universidade Federal do Rio de Janeiro) using a Hewlett-Packard GC-MS or by direct insertion using a VG Autospec. Infra-red spectra were recorded using a Perkin Elmer model 467 and a Perkin Elmer 1600 FT-IR as either KBr or KCl discs. Melting points were recorded on a hotstage microscope and/or using a MelTemp II capillary apparatus and are reported as uncorrected values. CH_2Cl_2 was dried by refluxing over CaH_2, THF was dried by refluxing with a Na/K alloy and benzophenone. DAST and $BF_3.Et_2O$ purified and redistilled, (Aldrich) were used as received. Isatin was purchased from Merck and $NaBH_4$ from Grupo Química. N-alkylisatin derivatives,[17] *N*-benzoylisatin,[18] 5-nitroisatin,[19] and 5,7-dibromoisatin[20] were prepared using literature procedures.

General methodology for the synthesis of 3,3-difluoro-2-oxindoles[6a]

Isatin derivative (1 mmole) was suspended or dissolved in CH_2Cl_2 (10 ml). DAST (2.0-2.5 mmoles) was added under a nitrogen atmosphere and the reaction mixture left stirring at room temperature for 3 days or until TLC indicated no further reaction. The excess DAST was carefully quenched with methanol (1 ml), and the

reaction mixture extracted with water (20 ml), the aqueous phase was subsequently re-extracted with CH_2Cl_2 (2 x 15 ml). The combined organic phases were dried over Na_2SO_4, filtered then rotary evaporated at reduced pressure. The resulting crude product was filtered through a column of silica eluting with CH_2Cl_2 to yield the pure 3,3-difluoro-2-oxindole derivatives.

3,3-Difluoro-2-oxindole (2a) (90-93%), mp 124-126°C; **IR** ν_{max} (KCl, cm^{-1}): 3190, 3110, 1752, 1620, 1470, 1280, 1210, 1075, 765; **Mass** [70 eV, m/z(%)]:169[M^+(100)], 150(9), 141(83), 126(10), 114(72), 75(10); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.00[d, 1H, H-7, J 8.0], 7.20[t, 1H, H-5, J 7.6], 7.50[m, 2H, H-4, 6], 9.08[bs, 1H, NH]; **^{13}C NMR** ($CDCl_3$): δ 111.3[t, C-3, J_{CF} 250.6], 112.1[C-7], 120.5[t, C-3a, J_{CCF} 23.1], 124.3[C-5], 125.2[C-4], 134.0[C-6], 141.3[C-7a], 167.8[t, C-2, J_{CCF} 30.0]; **^{19}F NMR** ($CDCl_3$/$CFCl_3$): δ -112.3[s, 2F, CF_2].

5-Methyl-3,3-difluoro-2-oxindole (2b) (94%), mp 155-157°C; **IR** ν_{max} (KCl, cm^{-1}): 3220, 1750, 1625, 1490, 1298, 1190, 1085, 820; **Mass** [70 eV, m/z(%)]: 183[M^+(100)], 164(10), 155(85), 140(5), 127(38); **^{1}H NMR** (200MHz, $CDCl_3$): δ 2.34[s, 3H, CH_3], 6.83[d, 1H, H-7, J 8], 7.22[d, 1H, H-6, J 8], 7.33[s, 1H, H-4], 8.30[bs, 1H, NH]; **^{13}C NMR** ($CDCl_3$): δ 20.9[CH_3], 111.2[t, C-3, J_{CF} 250.7], 111.5[C-7], 120.6[t, C-3a, J_{CCF} 29.2], 125.6[C-4], 134.0[C-6], 138.8[C-7a, C-5], 167.3[t, C-2, J_{CCF} 30.5]; **^{19}F NMR** ($CDCl_3$/$CFCl_3$): δ -112.2[s, 2F, CF_2].

1-Benzyl-3,3-difluoro-2-oxindole (2c) (91%), mp 73-74°C; **IR** ν_{max} (KCl, cm^{-1}): 1740, 1610, 1460, 1275, 1135, 1075, 750, 740, 680; **Mass** [70 eV, m/z(%)]: 259[M^+(10)], 168(7), 127(3), 91(100), 65(12); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.89[s, 2H, CH_2], 6.77[d, 1H, H-7], 7.12[t, 1H, H-5, J 7.7], 7.32[m, 6H, H-6 and 5H-benzyl], 7.54[dd, 1H, H-4, J 1.4, 7.2]; **^{13}C NMR** ($CDCl_3$): δ 44.0[CH_2, benzyl], 110.5[C-7], 110.9 [t, C-3, J_{CF} 250.2], 120.0[t, C-3a, J_{CCF} 23.2], 123.9[C-5], 124.7[C-4], 127.3[*o*-C, benzyl], 128.1[*p*-C, benzyl], 129.0[*m*-C, benzyl], 133.4[C-6], 134.3[*i*-C, benzyl], 143.1[C-7a], 165.5[C-2]; **^{19}F NMR** ($CDCl_3$/$CFCl_3$): δ -112.2[s, 2F, CF_2].

N-Benzoyl-3,3-difluoro-2-oxindole (2d) (91%), mp 138-140°C; **IR** ν_{max} (KCl, cm^{-1}): 3073, 1873, 1702, 1616, 1472, 1346, 1278, 1140, 1082, 772, 695; **Mass** [70 eV, m/z(%)]: 273[M^+(9)], 168(2), 105(100), 77(43); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.30[t, 1H, H-5, J 8], 7.44-7.69[m, 7H, H-4, H-6, 5H-aromatic], 7.72[d, 1H, H-7, J 8]; **^{13}C NMR** ($CDCl_3$): δ 110.3[t, C-3, J_{CF} 249.0], 119.6[C-7], 120.0 [t, C-3a, J_{CCF} 23.2], 124.7[C-5], 167.9[C=O, benzoyl], 126.1[C-4], 128.5[*o*-C, benzoyl], 129.6[*m*-C, benzoyl], 133.1[*i*-C, benzoyl], 133.7[*p*-C, benzoyl], 134.0[C-6], 141.2[t, C-7a, J_{CCCF} 6.7], 164.5[t, C-2, J_{CCF} 31.7]; **^{19}F NMR** ($CDCl_3$/$CFCl_3$): δ -106.7[s, 2F, CF_2]; **HRMS**: Calculated for $C_{15}H_9F_2NO_2$, 273.0601; observed, 273.0601.

1-Methyl-3,3-difluoro-2-oxindole (2e) (90%), mp 91-92°C, lit.[6a] 90-92°C; **IR** ν_{max} (KCl, cm^{-1}): 1750, 1610, 1470, 1190, 1080, 765; **Mass** [70 eV, m/z(%)]: 183[M^+(100)], 168(7), 164(5),154(32), 135(17), 127(16), 114(15), 77(7); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.23[s, 3H, NCH_3], 6.90[d, 1H, H-7, J 7.8], 7.18[t, 1H, H-5, J 7.6], 7.53[m, 2H, H-4, 6]; **^{13}C NMR** ($CDCl_3$): δ 26.3[NCH_3], 109.5[C-7], 110.9[t, C-3, J_{CF} 249.9], 120.1[t, C-3a, J_{CCF} 23.2], 124.0[C-5], 124.6[C-4], 133.6[C-6], 143.9[C-7a], 165.4[t, C-2, J_{CCF} 26.5]; **^{19}F NMR** ($CDCl_3$/$CFCl_3$): δ -112.9[s, 2F,CF_2].

5-Nitro-3,3-difluoro-2-oxindole (2f) (86%), mp 178-180°C; **IR** ν_{max} (KCl, cm^{-1}): 3353, 1770, 1625, 1532, 1346, 1271, 1137, 1096, 749; **Mass** [70 eV, m/z(%)]: 214[M^+(100)], 195(5), 186(33), 156(22), 140(25), 128(22); **^{1}H NMR** (200 MHz, $CDCl_3$/DMSO-d_6): δ 7.20[d, 1H, H-7, J 8], 8.42[d, 1H, H-6, J 8], 8.53[d, 1H, H-4, J 2]; **^{13}C NMR** ($CDCl_3$/DMSO-d_6): δ 110.0[t, C-3, J_{CF} 250.7], 112.5[C-7], 119.8[t, C-3a, J_{CCF} 23.3], 120.9[C-4], 130.6[C-6], 143.2[C-5], 148.6[C-7a], 166.0[t, C-2, J_{CCF} 29.8]; **^{19}F NMR** ($CDCl_3$/$CFCl_3$): δ -111.5[s, 2F, CF_2]; **HRMS**: Calculated for $C_8H_4F_2N_2O_3$, 214.0190; observed, 214.0190.

5,7-Dibromo-3,3-difluoro-2-oxindole (2g) (89-92%), mp 168-170°C; **IR** ν_{max} (KCl, cm^{-1}): 1760, 1610, 1450, 1260, 1180, 1085, 780; **Mass** [70 eV, m/z(%)]: 329[(M+4)(49), 327[(M+2)(100)], 235[M^+(50)], 308(5), 299(78), 218(25), 139(20), 112(20); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.61[m, 1H, H-6], 7.75[m, 1H, H-4]; **^{13}C NMR** ($CDCl_3$/DMSO-d_6): δ 105.6[C-7], 110.7[t, C-3, J_{CF} 252.5], 115.7[C-5], 122.8[t, C-3a, J_{CCF} 23.5], 126.8[C-4], 138.7[C-6], 141.9[t, C-7a, J_{CCCF} 7.3], 165.8[t, C-2, J_{CCF} 29.8]; **^{19}F NMR** ($CDCl_3$/$CFCl_3$): δ -110.6 [s, 2F, CF_2].

General Procedure for the "BH_2F.THF" reduction of 3,3-difluoro-2-oxindole derivatives.

The appropriate substrate (1 mmole) was dissolved in anhydrous THF (5 ml) and cooled on an ice water bath under a slowly flowing nitrogen atmosphere. A solution of "BH_2F.THF" (nominal concentration 1.3 M, 3 ml) was added dropwise by syringe to the stirred reaction. The reaction was monitored by TLC and on complete reaction aqueous HCl (3 M, 3 ml) was added dropwise. The reaction mixture was subsequently neutralised with aqueous NaOH (2.5 M), saturated aqueous NaCl (10 ml) was added and the mixture extracted with CH_2Cl_2 (3 x 15 ml). The organic phase was further washed with water (2 x 15 ml), dried over Na_2SO_4, filtered and rotary evaporated at reduced pressure *without* heating the solution. Purification procedures are detailed individually. Products were stored under a nitrogen atmosphere and in the cold.

3-Fluoroindole (3a).[21,22] Purified by filtration in a silica gel column using CH_2Cl_2/hexanes (3:2 V/V) and obtained as a colourless oil (76%), that solidifes when stored at -15°C. **IR** ν_{max} (KCl, cm^{-1}): 1610, 1460, 1230, 735; **Mass** [70 eV, m/z(%)]: 135[M^+(100)], 108(76), 81(14), 67(13); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.90[t, 1H, H-2, J 2.8], 7.08-7.29[m, 3H, H-5, 6 and 7], 7.43[bs, 1H, NH], 7.62[d, 1H, H-4, J 7.8]; **^{13}C NMR** ($CDCl_3$): δ 107.3[d, C-2, J_{CCF} 27.6], 112.1[C-7], 117.6[C-4], 117.9[C-3a], 120.5[C-5], 123.7[C-6], 133.6 [d, C-7a, J_{CCCF} 5], 146.4[d, C-3, J_{CF} 242.2].

N-Tosyl-3-fluoroindole (5a). The crude product **3a** was dissolved in toluene (4 ml). To the solution was added aqueous NaOH (4 ml, 2N), *p*-toluenesulfonyl chloride (0.330g, 1.7 mmol) and a few drops of aliquat™. The reaction mixture was vigorously stirred until TLC (≈3 hours) showed complete consumption of the starting material. The organic phase was separated, washed with water (5 ml), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was chromatographed on a silica gel column using hexane/ethyl acetate (9:1, v/v) as eluant, (61%, based upon **2a**), mp. 88-91°C, lit.[4b] 87-88°C. **IR** ν_{max}(cm^{-1}): 3127, 2925, 1610, 1445, 1363, 1173, 1091, 968, 741, 670, 607, 591, 570, 533; **Mass** [70 eV, m/z(%)]: 289[M+(35%)], 155(50%), 134(69%), 107(32%), 91(100%) 65(34%); **^{1}H NMR** (300MHz, $CDCl_3$): δ 2.35[s, 3H, CH_3], 7.22[d, 2H, J 8.3, tosyl], 7.28[td, 1H, H-5, J 0.9, 7.55] 7.34[d, 1H, H-2, J_{HF} 2.95],

7.38[ddd, 1H, H-6, J 1.3, 7.3, 8.4], 7.53[dt, 1H, H-4, J 0.85, 7.8], 7.74[d, 2H, J 8.4, tosyl], 8.03[d, 1H, H-7, J 8.4]; **^{13}C NMR**: δ 21.8[CH_3 tosyl], 108.95[d, C-2, J_{CCF} 28.75], 114.3[C-7], 117.9[d, C-4, J_{CCCF} 2.4], 121.7[d, C-3a, J_{CCF} 18.9], 123.9[C-5], 126.2[C-6], 127.0[CH tosyl], 130.1[CH tosyl], 133.0[d, C-7a, J_{CCCF} 4-5], 134.9[C-S], 145.4[*p*-C, tosyl], 149.1[d, C-3, J_{CF} 255.5]; **^{19}F NMR** ($CDCl_3/CFCl_3$): δ -166.5[t, J 2.5], lit.[4b] -165[t, J 2.6]; **Chem. Anal.** Calculated for $C_{15}H_{12}FNO_2S$: C 62.27, H 4.18, N 4.84; Observed: C 62.38, H 4.31, N 4.96.

5-Methyl-3-fluoroindole (3b). Purified by preparative plate chromatography using CH_2Cl_2/hexanes (2:1, V/V) and obtained as a colourless oil (70%). **IR** ν_{max} (KCl, cm^{-1}): 3260, 2965, 2920, 1610, 1455, 1320, 1220, 730; **Mass** [70 eV, m/z(%)]: 149[M^+(100)], 130(7), 128(8), 101(11), 74(7); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.44[s, 3H, CH_3], 6.88[t, 1H, H-2, J 2.8], 7.03[dd, 1H, H-7, J 1.6, 8.5], 7.16[dd, 1H, H-6, J 2.6, 8.5], 7.44[d, 1H, H-4, J 0.7], 7.48[bs, 1H, NH]; **^{13}C NMR** ($CDCl_3$): δ 21.3[CH_3], 106.7[d, C-2, J_{CCF} 26.9], 111.2[C-7], 116.3[C-4], 124.8[C-6], 129.3[C-5], 131.4[C-7a], 145.4[d, C-3, J_{CF} 141.7].

N-Tosyl-5-Methyl-3-fluoroindole (5b). The title compound was prepared analogously to compound **5a** except that a lesser quantity of *p*-toluenesulfonyl chloride (0.250g, 1.2 mmol) was used. The crude product was purified as for **5a** then recrystallised from hexanes (54% yield from **2b**, mp. 102°C). **IR** ν_{max} (KCl, cm^{-1}): 3116, 2922, 1608, 1448, 1363, 1172, 1090, 977, 879, 784, 667, 589, 534; **GC-MS** [m/z(%)]: 303[M^+(38)], 164(14), 155(27), 148(100), 101(27), 91(73), 65(27); **^{1}H NMR** (300 MHz, $CDCl_3$, TMS): δ 2.31[s, 3H, CH_3, tosyl], 2.39[s, 3H, CH_3], 7.17[3H, m, 2H tosyl and H-6], 7.25[d, 1H, H-2, J 3.0], 7.27[bs, 1H, H-4], 7.69[2H, d, J 8.4, tosyl], 7.89[1H, dd, H-7, J 2.0, 8.6]; **^{13}C NMR** (PENDANT, $CDCl_3$): δ 21.3[CH_3], 21.6[CH_3], 108.8[d, CH-2, J_{CCF} 28.8], 113.9[d, CH-7, J_{CCCCF} 1.4], 117.4[d, CH-4, J_{CCCF} 2.6], 121.8[d, C-3a, J_{CCF} 18.7], 126.8[CH tosyl], 127.5[CH-6], 129.8[CH tosyl], 131.2[d, C-7a, J_{CCCCF} 5.3], 133.5[C-S], 134.6[C-5], 145.0[*p*-C tosyl], 148.9[d, C-3, J_{CF} 255.4]; **^{19}F NMR** ($CDCl_3/CFCl_3$): δ -166.0; **Chem. Anal.** Calculated for $C_{16}H_{14}FNO_2S$: C 63.35, H 4.65, N 4.62; Observed: C 63.45, H 4.73, N 4.48.

1-Benzyl-3-fluoroindole (3c). Purified by preparative plate chromatography using dichloromethane/hexanes (2:1 V/V) yielding a colourless oil (84-86%). **IR** ν_{max} (Film, cm^{-1}): 3085, 2925, 1620, 1590, 1460, 1380, 1210, 740, 690; **Mass** [70 eV, m/z(%)]: 225[M^+(32)], 134(4), 91(100); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.18[s, 2H, CH_2], 6.84[d, 1H, H-2, J 3.1], 7.00-7.30[m, 8H, H-5, 6, 7 and 5H-aromatic of the benzyl group], 7.67[d, 1H, H-4, J 7.8]; **^{13}C NMR** ($CDCl_3$): δ 50.0[CH_2, benzyl], 109.7[C-7], 110.7[d, C-2, J_{CCF} 25.6], 117.1[C-4], 117.6[C-3a], 119.5[C-5], 122.8[C-6], 126.9[*m*-C, benzyl], 127.8[*p*-C, benzyl], 128.8[*o*-C, benzyl], 133.2[C-7a], 137.2[*i*-C, benzyl], 145.0[d, C-3, J_{CF} 242.9]; **^{19}F NMR** ($CDCl_3/CFCl_3$): δ -175.5[s, 1F, F-3]; **HRMS**: Calculated for $C_{15}H_{12}FN$, 225.0954; observed, 225.0954.

1-Methyl-3-fluoroindole (3e). Purified by silica gel column chromatography using dichloromethane/hexanes (3:2 V/V) yielding a dark oil (90%). **Mass** [70 eV, m/z(%)]: 149[M^+(100)], 134(19), 107(26), 101(15); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.70[s, 3H, CH_3], 6.81[d, 1H, H-2, J 2.9], 7.07-7.25[m, 3H, H-5, 6 and 7], 7.61[d, H-4, J 7.7]; **^{13}C NMR** ($CDCl_3$]: δ 32.7[NCH_3], 109.3[C-7], 111.3[d, C-2, J_{CCF} 26.9], 116.9[C-3a], 117.0[C-4], 119.2[C-5], 122.6[C-6], 133.5[C-7a], 144.5[d, C-3, J_{CF} 242.7]; **^{19}F NMR** ($CDCl_3/CFCl_3$): δ -176.4[s, 1F, F-3].

5-Nitro-3-fluoroindole (3f). An inseparable mixture (181mg from 1 mmole of **2f**, 91% mass balance) of 5-nitro-3,3-difluoroindoline (93%) and 5-nitro-3-fluoroindol (7%) was obtained by silica gel chromatography using dichloromethane/hexanes (3:2 V/V). **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.14[t, 1H, H-2, J 3.0], 7.37[dd, 1H, H-7, J 2.1, 9.4], 8.10[dd, 1H, H-6, J 2.3, 9.2], 8.60[d, 1H, H-4, J 2.0]; **^{19}F NMR** (188 MHz, $CDCl_3/CFCl_3$): δ -172.1[t, 1F, F-3, J_{HF} 2.8].

5-Nitro-3,3-difluoroindoline (4f). IR ν_{max} (KCl, cm^{-1}): 3265, 1630, 1500, 1330, 1290, 1100, 740; **Mass** [70 eV, m/z(%)]: 200[M^+(69)], 180(90), 170(49), 154(30), 134(100), 127(28), 107(87); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.00[t, 2H, H-2, J_{HF} 17.6], 4.76[bs, 1H, NH], 6.72[dt, 1H, H-7, J 2.4, 8.9], 8.22[dd, 1H, H-6, J 2.3, 9.1], 8.35[d, 1H, H-4, J 2.3]; **^{13}C NMR** ($CDCl_3$): δ 55.6[t, C-2, J_{CCF} 31.1], 109.7[C-7], 118.5[C-3a], 121.4[C-4], 125.5[t, C-3, J_{CF} 241.7], 129.6[C-6], 140.1[C-7a], 155.9[C-5]; **^{19}F NMR** ($CDCl_3/CFCl_3$): δ -84.4[t, 2F, F-3, J_{HF} 18.0].

5,7-Dibromo-3-fluoroindole (3g). An inseperable mixture (275mg from 1 mmole of **3g**, 88% mass balance) of 5,7-dibromo-3-fluoroindole (10%) and 5,7-dibromo-3,3-fluoroindoline (90%) was obtained after preparative plate chromatography using dichloromethane/ hexanes (2:1 V/V) as a colourless solid that readily darkened at room temperature. **GC-MS** [70 eV, m/z(%)]: 295[(M+4)(50)], 293[(M+2)(96)], 291[M^+(46)], 212(59), 185(17), 146(26), 133(100), 106(24); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.04[t, H-2, J 2.8], 7.73[m, 2H, H-4 and 6]; **^{19}F NMR** ($CDCl_3/CFCl_3$): δ -171.7[t, 1F, F-3, J_{HF} 3.0].

5,7-Dibromo-3,3-difluoroindoline (4g). IR ν_{max} (KCl, cm^{-1}): 3410, 1605, 1465, 1320, 1230, 1170, 890, 860; **GC-MS** [70 eV, m/z(%)]: 315[(M+4)(32)], 313[(M+2)(74)], 311[M+(37)], 293(100), 233(11), 214(43), 153(15), 133(50); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.90[t, 2H, H-2, J_{HF} 17.6], 4.00[bs, NH], 7.50[d, 1H, H-6, J1.6], 7.60[d, 1H, H-4, J 1.6]; **^{19}F NMR** ($CDCl_3/CFCl_3$): δ -83.5[t, 2F, F-3, J_{HF} 17.6].

ACKNOWLEDGEMENTS

The authors are indebited to CNPq (Conselho Nacional de Desenvolvimento Cientifico e Tecnologico) and PRONEX/FINEP (convênio number 41.96.00911.00, reference 4002-96) for financial support. The analytical services of Petrobras/CENPES, Rio de Janeiro, the department of chemistry Unicamp, São Paulo, and in particular Prof. Marcos Eberlin (Unicamp), are gratefully acknowledged.

REFERENCES AND NOTES

1. **a** *Fluorine Containing Molecules Structure, Reactivity, Synthesis, and Applications*; Liebman, J. F.; Greenberg, A.; Dolbier, J., William R. Eds.; VCH Publishers Inc. 1988; **b** *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T. Ed.; American Chemical Society, ACS Symposium Series 456, Washington DC, 1991; **c** *Biochemistry of Halogenated Organic Compounds*; Kirk, K. L., *Biochemistry of the Elements Series*, Frieden, E., Ed., Vol. 9B, Plenum Press, New York 1991; **d** *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S.; John Wiley and Sons, Inc., New York 1991; **e** *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R.;

Kobayashi, Y.; Yagupolskii, L. M. Eds.; Elsevier, Amsterdam 1993; **f** *Organofluorine Chemistry, Principles and Commercial Applications*; Banks, R. E.; Smart, B. E.; Tatlow, J. C. Eds.; Plenum Press, New York 1994; **g** Silvester, M. J. *Advances in Heterocyclic Chemistry* **1994**, *59*, 1-38; **h** *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I.; McCarthy, J. R.; Welch, J. T. Eds.; American Chemical Society, ACS Symposium Series 639, Washington DC, 1996; **i** O'Hagan, D.; Rzepa, H.S. *J. Chem. Soc. Chem. Commun.*, **1997**, 645-652.

2. **a** Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988**, *25*, 1-8; **b** Gribble, G. W. *Contemp. Org. Syn.* **1994**, *1*, 145-172; **c** Fürstner, A.; Bogdanovic, B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2442-2469; **d** *Indoles*, Sundberg, R.J., Academic Press, San Diego, 1996.
3. **a** Sirowej, H.; Khan, S. A.; Pleininger, H. *Synthesis* **1972**, 84; **b** Wierenga, W.; Griffin, J.; Warpehoski, M. A. *Tetrahedron Lett.* **1983**, *24*, 2437-2440; **c** Pinto, A. C.; Silva, F. S. Q.; Silva, R. B. *Tetrahedron Lett.* **1994**, *35*, 8923-8926; **d** Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557-579.
4. For previous syntheses of 3-fluoroindoles consult: **a** Barton, D. H. R.; Hesse, R. H.; Jackman, G. P.; Pechet, M. M. *J. Chem. Soc. Perkin Trans. 1* **1977**, 2604-2608; **b** Hodson, H. F.; Madge, D. J.; Slawin, A. N. Z.; Widdowson, D. A.; Williams, D. J. *Tetrahedron* **1994**, *50*, 1899-1906; and for a recent synthesis of 2-fluoroindoles consult: **c** Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *J. Chem. Soc. Chem. Commun.* **1997**, 1537-1538.
5. For observations of thermal instability of 3-haloindoles consult: **a** Piers, K.; Meimaroglou, C.; Jardine, R. V.; Brown, R. K. *Can. J. Chem.* **1963**, *41*, 2399-2401; **b** Higa, T.; Scheuer, P. J. *Naturwissenschaften* **1975**, *62*, 395-396; **c** Brennan, M. R.; Erickson, K. L.; Szmalo, F. S.; Tansey, M. J.; Thornton, J. M. *Heterocycles* **1986**, *24*, 2879-2885; **d** Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495-2497; **e** see reference 2d pages 117-118.
6. **a** Middleton, W. J.; Bingham, E. M. *J. Org. Chem.* **1980**, *45*, 2883-2887; **b** For a reveiw on the chemistry of DAST see Hudlicky, M. *Org. Reac.* **1987**, *35*, 513-637; **c** The synthesis of some of these compounds and their use for the synthesis of new potent anti-inflammatory agents has been described, Boechat, N.; Pinto, A.C., Fr. Patent 2.745.810, 19th of June, 1998.
7. Zweifel, G.; Brown, H. C. *Org. React.* **1963**, *13*, 1-54; Preparation of "$BH_2F.THF$": prepared by the addition of $BF_3.Et_2O$ (20ml) to a suspension of $NaBH_4$ (3.40g, 90 mmol) in anhydrous THF (120 ml) on an ice/water bath under a nitrogen atmosphere. A freshly prepared $BH_3.THF$ complex ($\approx$ 1M), prepared using stochiometric quantities of $BF_3.Et_2O$ (4 mole equivalents) and $NaBH_4$ (3 mole equivalents) in THF, proved to be equally effective for the reduction of 3,3-difluoro-2-oxindole.
8. McEvoy, F. J.; Allen Jr., G. J. *J. Org. Chem.* **1973**, *38*, 3350-3352.
9. Berger, J. G. *Synthesis* **1974**, 508-510.
10. **a** Papanastassiou, Z. B.; Bruni, R. J. *J. Org. Chem.* **1964**, *29*, 2870-2872; **b** Brown, H.C., Heim, P., Yoon, N.M. *J. Org. Chem.* **1972**, *37*, 2942-2950; **c** Brown, H.C., Heim, P. *J. Org. Chem.* **1973**, *38*, 912-916.
11. The following, limited, NMR data for N-benzyl-3,3-difluoroindoline (**4c**) was abstracted from the spectra for the mixture with N-benzyl-3-fluoroindole (**3c**): ^1H: δ 3.63[CH_2N, t, J_{HF} 18], 4.41[CH_2 benzyl, s], 6.71[CH, d, J 8], 6.82[CH, t, J 7.5], 7.12-7.36[benzyl + other CH aromatic signals], 7.44[CH, d, J 7.3]; ^{13}C PENDANT: δ 50.1[CH_2 benzyl], 60.3[CH_2, t, J_{CCF} 30].

12. 1,4-Eliminations of fluoride from *o*-aminobenzotrifluoride, induced by bases, have been proposed as key steps in the mechanisms for formation of a variety of heterocycles: **a** Strekowski, L.; Lin, S.-Y.; Lee, H.; Zhang, Z.-Q.; Mason, J. C. *Tetrahedron* **1998**, *54* , 7947-7954; **b** Strekowski, L.; S.-Y., L.; Lee, H.; Mason, J. C. *Tetrahedron Lett.* **1996**, *37*, 4655-4658. **c** Strekowski, L.; Janda, L.; Patterson, S. E.; Nguyen, J. *Tetrahedron* **1996**, *52*, 3273-3282; **d** Kiselyov, A. S.; Strekowski, L. *Tetrahedron lett.* **1994**, *35*, 7597-7600; **e** Kiselyov, A. S.; Hojjat, M.; Van Aken, K.; Strekowski, L. *Heterocycles* **1994**, *37*, 775-782; **f** Strekowski, L.; Kiselyov, A. S.; Hojjat, M. *J. Org. Chem.* **1994**, *59*, 5886-5890; **g** Hojjat, M.; Kiselyov, A. S.; Strekowski, L. *Synth. Commun.* **1994**, *24*, 267-272; **h** Strekowski, L.; Patterson, S. E.; Janda, L.; Wydra, R. L.; Harden, D. B.; Lipowska, M.; Cegla, M. T. *J. Org. Chem.* **1992**, *57*, 196-201; **i** Patterson, S. E.; Janda, L.; Strekowski, L. *J. Heterocycl. Chem.* **1992**, *29*, 703-706. As well as from, trifluoromethylhydrazones: **j** Kiselyov, A. S. *Tetrahedron Lett.* **1995**, *36*, 1383-1386. 1,4-Fluoride eliminations have also been proposed for the base induced alcoholysis of 2,3,3-trifluoro-prop-1-enyl toluene-*p*-sulfonates: **k** Funabiki, K.; Suzuki, C.; Takamoto, S.; Matsui, M.; Shibata, K. *J. Chem. Soc. Perkin Trans. 1* **1997**, 2679-2680. 1,6-Eliminations have been observed from *p*-aminobenzotrifluoride: **l** Lin, S.-Y.; Hojjat, M.; Strekowski, L. *Synth. commun.* **1997**, *27*, 1975-1980; **m** see also reference 12b; **n** For reveiws on the chemistry of the trifluoromethyl group consult: McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555-6666; Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* **1978**, *11*, 197-204.

13. Instability of 3a-halo derivatives of hexahydropyrrolo[2,3-*b*]indoles, suspected to be intermediates in the oxidative cyclisation of N-acetyltryptophan esters, has been noted: Ohno, M., Spande, T.F., Witkop, B. *J. Am. Chem. Soc.* **1970**, *92*, 343-348. These hydrohalide eliminations most probably occur through a 1,4-elimination of the halide followed by proton loss. A sulphonyl group bonded to the nitrogen sufficiently deactivates the nitrogen lone pair allowing functionalisation of C-3a and improving stability to chromatography: Bruncko, M., Crich, D., Samy, R. *J. Org. Chem.* **1994**, *59*, 5543-5549.

14. Strobach, D. R.; Boswell Jr., G. A. *J. Org. Chem.* **1971**, *36*, 818-820.

15. The question that therefore arises is, what is the mechanism that results in the formation of the small quantity of **3** (**f** and **g**) during the reduction reaction? We speculate that the formation of these 3-fluoroindoles maybe the result of Lewis acid assisted fluoride ion elimination during reduction of **2** (**f** and **g**) or that alternatively either before or after reduction of the amide carbonyl to the borate ester (scheme 1) the gem-difluoromethylene is reduced to a mono-fluoromethylene group. Either possibility may allow elimination of the boronate without participation of the nitrogen, thus forming the respective indoles.

16. Garden, S.J., Torres, J.C., Ferreira, A.A., Silva, R.B., Pinto, A.C. *Tetrahedron Lett.* **1997**, 1501-1504.

17. Garden, S. J.; Torres, J. C.; da Silva, L. E.; Pinto, A. C. *Synth. Commun.* **1998**, *28*, 1679-1689.

18. Tacconi, G.; Righetti, P. P.; Desimoni, G. *J. Prakt. Chem.* **1973**, *315*, 339-344.

19. Calvery, H. O.; Noller, C. R.; Adams, R. *J. Am. Chem. Soc.* **1925**, *47*, 3058-3060.

20. Lindwall, H. G.; Bandes, J.; Weinberg, I. *J. Am. Chem. Soc.* **1931**, *53*, 317-319.

21. 3-Fluoroindole (**3a**) has been previously prepared by the treatment of N-acetyl-1,2-difluoroindoline with ethanolic potassium hydroxide. The melting point was described as room temperature, see reference 4a.

22. H2 appears as a triplet due to similar magnitudes of coupling with fluorine and NH. For a further example see Powers, J. C. *J. Org. Chem.* **1966**, *31*, 2627-2631, where H2 of 3-chloroindole was observed to couple with the NH (J 2.5Hz).