Synthesis of Fluoro Analogues of 3,4-(Methylenedioxy)amphetamine (MDA) and Its Derivatives

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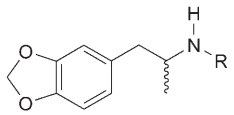
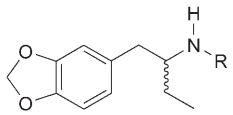
The role of the metabolism of the entactogen 3,4-(methylenedioxy)methamphetamine (MDMA; **1b**) in neurotoxic or psychopharmacologic action is widely discussed, but not yet fully understood. To prompt further investigation into the role of MDMA metabolism, six new 3,4-(difluoromethylenedioxy) analogues of MDMA (**1b**) were prepared and characterized. Although electronically very different, the fluoro analogues **3**–**5** should be sterically very similar to the non-fluorinated parent compounds. The F-atoms may prevent the formation of toxic metabolites produced *via* a radical pathway (*Scheme 1*). Different theories regarding MDMA-induced neurotoxicity are briefly reviewed and discussed. The novel compounds **3**–**5** may help to verify the hypothesis that MDMA-induced neurotoxicity is the result of the formation of metabolites lacking the methylenedioxy bridge.

Introduction. – 3,4-(Methylenedioxy)amphetamine (MDA; **1a**)[1]) and its derivatives **1b**,**c** and **2a**,**b** are ring-substituted analogues of amphetamine that possess unique pharmacological properties. Due to their ability to cause feelings of closeness, a desire to socialize, and an enhanced feeling of empathy, they are called 'empathogens' or 'entactogens' [1]. Especially MDMA (**1b**) has attracted considerable interest because of its potential use in psychotherapy. In addition, MDMA is known as a so-called 'rave drug' because it gives rise to euphoria and increases energy, properties that make this compound very attractive to people attending dance parties. The widespread use (and misuse) of this drug has led to many investigations.



1a R = H (MDA)
1b R = Me (MDMA)
1c R = Et



2a R = H
2b R = Me

There are numerous studies into the neurotoxic effects of MDMA (**1b**). However, the neurotoxic effect of **1b** depends on the animal species tested, and on the strain and

[1]) Systematic name: 1-(1,3-benzodioxol-5-yl)propan-2-amine.

dose used [2], and it seems to be difficult to generalize these properties and to relate them to human beings. Nevertheless, studies employing positron emission tomography (PET) have indicated that chronic use of MDMA in humans may lead to decreased serotonin-transporter binding, possibly indicating a loss of serotoninergic axons [3]. The mechanisms of MDMA neurotoxicity are contested [2][4][5], and it has been argued that earlier studies may have employed doses that are higher and more frequent than doses used in humans, and that, as a result, these animal studies overestimate the risk of neurotoxicity [2][6]. It has also been suggested that the risks of acute adverse events after intake of MDMA (**1b**), such as hyperthermia, tachycardia, convulsions, liver failure, and other difficulties, may be influenced by genetically lacking functional enzymes involved in the metabolism, and it has been shown that genetically different individuals show different susceptibilities to the overall effects of drugs [7]. However, alongside these findings, *de la Torre* and co-workers [8] persuasively argued that, once the MDMA dose exceeds a certain level well within those taken by humans, all people exhibit 'poor metabolizer' profiles. Three independent research groups have examined CYP2D6 activity in MDMA-related fatalities and adverse events, but have been unable to find poor metabolizers in their, admittedly small ($n = 13$, 7, and 3, resp.), samples [7d][9][10]. Thus, it seems that the cause of these problems involves both environment as well as genetics.

MDMA (**1b**) has only recently been identified as a potential therapeutic drug against *Parkinson*'s disease in rats [11], marmosets [12], and mice [13], with this research largely spurred on by an anecdotal account of an individual who treated some of his Parkinsonian symptoms by taking *Ecstasy* [14], and there are indications that it undergoes further investigations. Furthermore, MDMA may help to treat people with posttraumatic-stress disorder (PTSD). A study supported by the *Multidisciplinary Association for Psychedelic Studies* (*MAPS*) investigating the use of MDMA-assisted psychotherapy in people with PTSD is currently underway [14].

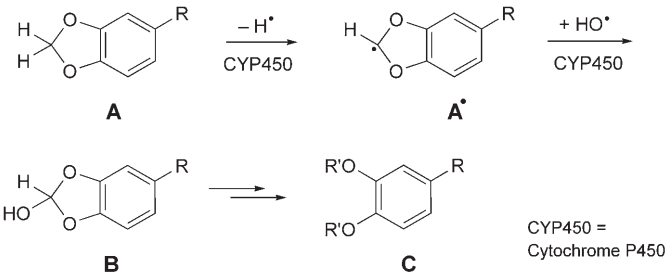
MDMA (**1b**) is known to release serotonin (5-HT) and, to a lesser extent, dopamine (DA) and norepinephrine (NE) [15][16]. It also increases 5-HT levels by acting as a serotonin-reuptake inhibitor by blocking the 5-HT transporter (SERT; for a review, see [16][17]). In studies employing pre-treatment with a selective serotonin-uptake inhibitor (SERT) and a dopamine-D2 antagonist, *Liechti et al.* [18][19] showed that the overall psychological effects in humans depend upon carrier-mediated 5-HT release, and that the euphoric and stimulatory-mood effects may require DA-receptor stimulation. Furthermore, *Liechti et al.* found that the mild and rare hallucinogenic effects of MDMA (**1b**) are at least due to the drug's weak ability to stimulate the serotonin 5-HT_{2A} receptor (either as a result of 5-HT release or direct drug action on 5-HT_{2A} receptors), since the typical hallucinogenic phenethylamines, such as mescaline and 4-iodo-2,5-dimethoxyamphetamine (DOI), seem to produce their hallucinogenic actions through agonistic activation of this serotonin-receptor subtype [20].

Although MDMA causes a long-term depletion of serotonin, the release of serotonin *per se* seems not to be enough to cause long-term 5-HT deficits [21]. It has been found that serotonin-specific releasing agents that are non-dopaminergic (*e.g.*, 4-methylthioamphetamine; MTA) seem to be devoid of MDMA-like neurotoxicity in animals [22][23]. This suggests two possibilities: either the damage requires prolonged

effects of MDMA-like drugs (which could deplete antioxidant defenses and cellular-energy stores), and/or toxic metabolites mediate the toxic effects of MDMA.

All of the above methylenedioxy derivatives **1** and **2** seem to be neurotoxic [24], although to different extents. An important question that arises is the role of metabolism and metabolites from centrally active methylenedioxy-bridged compounds, either in terms of neurotoxic properties and/or overall (psycho)pharmacological effects. It has been shown that one possible attack for metabolism of methylenedioxy compounds is the 1,3-benzodioxole CH_2 bridge [7e][25]. Formally, a H-radical ($H^{\bullet}$) may be abstracted from the parent compound **A** (*Scheme 1*). In a second step, $HO^{\bullet}$ is transferred from cytochrome P450 (CYP2D6) to $\mathbf{A}^{\bullet}$, which leads to the unstable intermediate **B** [26], which, in turn, gives rise to the metabolite **C** ($R' = H/H$ or H/Me). The dihydroxy compound **C** ($R' = H/H$) may be catecholamines, which are thought to be, at least partially, responsible for neurotoxicity, as they may undergo redox cycling, producing superoxide radicals or other radicals [7e][25] that lead to cell damage or cell death.

Scheme 1



Another possible mechanism for MDMA (**1b**) neurotoxicity is based on MDMA-induced dopamine uptake into serotonin terminals by the SERT, which can cause damage to the nerve terminals [27][28]. The hypothesis posits a deamination of dopamine by monoamine oxidase-B (MAO-B) within the serotoninergic cell, which leads to the formation of H_2O_2 causing cell death. Yet another explanation for neurotoxicity was presented by *Jones et al.* [29]. MDMA failed to produce acute or long-term neurotoxicity when directly injected into the brain, but neurotoxicity was evident when administered peripherally. This suggests that the neurotoxicity may be mediated by the formation of specific metabolites. *Jones et al.* presented the systemic formation of glutathione and *N*-acetylcysteine conjugates of 3,4-dihydroxymethamphetamine, which, upon subcutaneous injection, were detected in rat brain causing serotoninergic changes consistent with neurotoxicity [29].

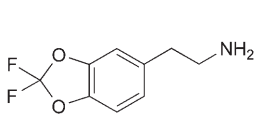
Researchers have noted that high ambient temperature and high body temperature can increase MDMA neurotoxicity [30][31]. Increased body temperature may exacerbate one or more processes involved in MDMA neurotoxicity, such as increasing production of oxidative radicals, and possibly through making the SERT more likely to shuttle dopamine into serotoninergic cells [32].

As the above-mentioned pattern of metabolism (*Scheme 1*) can occur in all 3,4-methylenedioxy compounds, the question arises whether a blockade of the metabolic

pathway in such compounds may, at least partially, prevent neurotoxicity. It has been found that the selective serotonin-reuptake inhibitor (SSRI) fluoxetine, which antagonizes the cleavage of the CH_2 bridge of MDMA (**1b**) by inhibiting cytochrome P450 (CYP2D6) [33], prevents the neurotoxicity of MDMA (**1b**) [34]. However, it has been found that MDMA itself seems to inactivate this particular enzyme [35], and SSRIs would also prevent access of MDMA, neurotransmitters, or metabolites to the serotonin transporter. Thus, it remains questionable through which mechanism neuroprotection occurs.

After considering the possible importance of metabolites formed from 3,4-(methylenedioxy)phenethylamines, we searched for a possible structure preventing the metabolism of the OCH_2O moiety, but without differing much in terms of steric requirement. One possible approach seemed to be the replacement of the two H-atoms of the CH_2 bridge by two F-atoms. Clearly, this substitution would dramatically change some of the physico-chemical properties of the compound. So, we decided to prepare the fluoro analogues **3**–**5** in the hope that these compounds may help further investigate the role of metabolism, and to test the hypothesis that metabolites of MDMA are, indeed, required for neurotoxicity. To find a valuable entactogen as a tool for psychotherapy, it would be helpful if the processes producing the subjective effects were separable from those associated with neurotoxicity. This being the case, investigations are needed to discover whether some (hopefully non-neurotoxic) metabolites are crucially involved in producing the psychological effects of MDMA (**1b**) as well.

In this paper, we present the synthesis and characterization of the novel 3,4-(difluoromethylenedioxy) analogues **3**–**5**. Their metabolic and toxic effects will be the subject of an upcoming paper.



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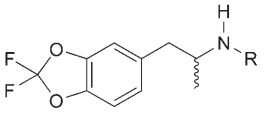
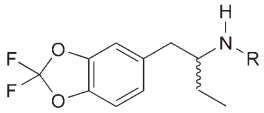


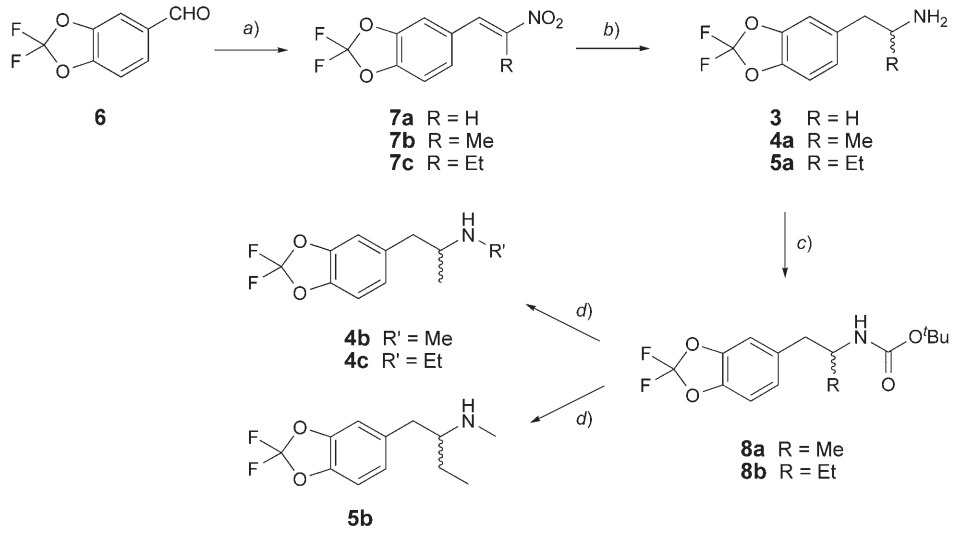
4a R = H
4b R = Me
4c R = Et



5a R = H
5b R = Me

Results and Discussion. – 1. *Synthesis.* The synthesis of **3**–**5** is outlined in *Scheme 2*. The starting compound, 3,4-(difluoromethylenedioxy)benzaldehyde (**6**), had originally been described by *Stogryn* [36], but is now commercially available (*e.g.*, at *Aldrich*). *Henry* condensation of **6** with AcOH and $BuNH_2$ as catalysts [37] afforded the nitro olefins **7a**–**c** in 48–88% yield. Reduction to the primary amines **3**, **4a**, and **5a** (64–82%) was performed with 'alane', generated *in situ* from $LiAlH_4$ and H_2SO_4. Although monoalkylation of primary amines is often performed *via* amide formation followed by hydride reduction, we chose another, quite elegant sequence. Thus, the amines **4a** and **5a** were first Boc-protected, and the resulting nearly quantitatively obtained carbamates **8a**,**b** were deprotonated with NaH, and then alkylated with the corresponding alkyl iodide. Finally, Boc removal with anhydrous HCl in 1,4-dioxane

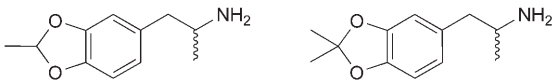
Scheme 2



a) RCH_2NO_2, AcOH, $BuNH_2$. *b*) $LiAlH_4/H_2SO_4$ ('alane'), THF. *c*) $(Boc)_2O$, Et_3N, CH_2Cl_2. *d*) 1. NaH, R′I, THF, DMF; 2. 4M anh. HCl in 1,4-dioxane.

directly afforded the desired pure products. Starting from the primary amines, the overall yields for **4b**, **4c**, and **5b** (HCl salts) were 79, 76, and 62%, respectively.

2. *Structural and Metabolic Considerations.* The original idea of substituting the H-atoms of the methylenedioxy bridge in **1a** had been realized by *Nichols* and *Kostuba* in 1979 by introducing either one or two Me groups [38]. It has been shown that, on progressive substitution, the overall potency of the resulting congeners **9** and **10** decreases with each additional Me group added. The spontaneous motor activity and behavioral effects [38], as well as the two-lever drug-discrimination (DD) assay in rat (training drug: LSD or MDMA), the [^{3}H]serotonin- and [^{3}H]dopamine-release assays and the K_i values (affinity for *R*-[^{125}I]DOI-labeled 5-HT_{2A} receptor) all indicated that the sequence of potency is as follows: MDA (**1a**) $\geq$ **9** $\gg$ **10** [39]. Whereas **9** still paralleled somewhat with MDA (**1a**) in a rat-behavior test, **10** showed completely different actions. Rats treated with **10** appeared sedated and sleepy, and, at higher doses, the compound caused convulsion.



9 **10**

A possible rationalization for the lower potency of **9** and **10** compared to MDA (**1a**) is increased steric bulkiness. The authors pointed out that such compounds must be

sterically less-hindered to fully interact with the binding site. Another possible reason might be higher lability of **9** and **10** in acidic media and, thus, faster metabolism, resulting in lowered concentrations of the drug in the brain.

One may also argue that active metabolites are only formed by opening the methylenedioxy moiety for producing the neurotoxic and/or unique psychopharmacological profile of these drugs, as there are several research articles that mention that metabolism may be a contributory factor (see, *e.g.*, [40]). When considering **9** and **10**, one can assume that ring opening in **9** should occur in an easier manner according to *Scheme 1* than in compound **10**, as one H-atom is present in **9**, which can be abstracted. Compound **10** may lead to different metabolites, and/or these metabolites are formed at a different rate, which could, at least partially, be responsible for the observed order of potency of these drugs.

The arguments about the importance of metabolites in behavioral effects are somewhat supported by the following relationship. Anecdotal accounts suggested that pretreatment or combination with fluoxetine reduced some or all of the effects of MDMA (**1b**) [41][42], and preliminary data have confirmed these findings in humans [43]. Research has shown that fluoxetine is a potent cytochrome-P450 (CYP2D6) inhibitor [33]. Thus, fluoxetine may simultaneously prevent metabolism of MDMA, as mentioned above, as the same cytochrome (CYP2D6) isozyme inhibited by fluoxetine is involved in OCH_2O cleavage of MDMA, as shown by *Ramamoorthy et al.* [7b][7c]. Furthermore, pretreatment with paroxetine, an SSRI known to act on CYP2D6, attenuated or eliminated immunological effects of MDMA [44]. However, serotonin-uptake inhibitors also very likely reduce subjective effects by competing with MDMA (**1b**) for the SERT, thus preventing serotonin release. When blocked, MDMA can neither bind to the transporter nor be taken up into the presynaptic 5-HT cell, and is, therefore, unable to increase 5-HT levels to the same extent (the extracellular concentrations of 5-HT are increased to a much lower extent by just inhibiting its reuptake). *Heydari et al.* have also found that MDMA (**1b**) inhibits CYP2D6 [35], so that the contributions of SSRIs to altering metabolism may not be significant. Finally, it is notable that citalopram, an SSRI with very little activity at CYP2D6, also significantly attenuated subjective effects [45][46].

It would be interesting to test a selective cytochrome-P450 inhibitor that prevents metabolism at the methylenedioxy bridge of MDMA (**1b**), without simultaneously interacting with SERT!

To date, the 2,2-difluoro-1,3-benzodioxol-5-yl moiety does not appear to have been investigated in amphetamines. Introduction of an F-atom into biologically active compounds can strongly alter their properties (for a review, see, *e.g.*, [47]) and metabolism in the body. It can increase the half-life and change the metabolic pathway of a given compound. F- instead of H-atoms generally make a compound more lipophilic, causing a possible difference in body distribution. If a pocket of a target has a very hydrophobic site, an F-atom may be favorable. Most scientists assume that F- and H-atoms have very similar *Van der Waals* radii. Others think that an F-atom rather matches the size to an O-atom [48]. Electronically, F-atoms strongly differ from H-atoms, which can change the properties of a compound dramatically. For example, by introducing F-atoms into the β-position of an amine, the pK_a of adrenergic amines is lowered such that they are no longer protonated [49].

The changes caused by the F-atoms in compounds **3**–**5** has to be shown in forthcoming investigations. We expect that the susceptibility of the methylenedioxy bridge towards degradation will be altered, among other properties, as no H-radical can be abstracted in the usual way. As a consequence, this could possibly reduce or prevent the formation of neurotoxic species. Hopefully, these novel compounds will further help to find potential drugs for psychotherapy that produce MDMA-like psychological effects, but lack any neurotoxic effects.

We wish to thank *Ilsa Jerome* and *Matthew Baggott* for fruitful suggestions and correction of the manuscript. Furthermore, we thank the Chemistry Department, School of Engineering and Information Technology, Burgdorf, which will be closed in early 2006.

Experimental Part

General. All compounds used in the syntheses are commercially available and were used without further purification. All reactions were monitored by TLC (silica-gel plates F_{254}; detection under UV light). The products were dried at 40°. Melting points (m.p.): *Büchi 535* apparatus; uncorrected. ^{1}H- and ^{13}C-NMR Spectra: *Bruker AM-300* spectrometer; at 300/75 MHz, resp.; δ in ppm, J in Hz.

General Procedure (*GP 1*) *for the Synthesis of Compounds* **7**. To a soln. of **6** in the corresponding nitroalkane, 2% $BuNH_2$ and 2% glacial AcOH (*v*/*v*) were added, and the mixture was heated at reflux (b.p. 115° ($MeNO_2$), 130° ($EtNO_2$), or 150° ($PrNO_2$)). The reaction was monitored by TLC (SiO_2; CH_2Cl_2). When the reaction was complete, the solvent was evaporated, the crude product was dissolved in Et_2O (40 ml), and washed with 0.1M aq. HCl (2×) and 0.1M aq. NaOH soln. (2×). After drying of the org. layer (Na_2SO_4), the solvent was evaporated, and the product was dried at 40° *in vacuo*.

*2,2-Difluoro-5-[(*E*)-2-nitroethenyl]-1,3-benzodioxole* (**7a**). Prepared according to *GP 1* from **6** (4.60 g, 24.7 mmol) in $MeNO_2$ (6 ml) for 2.5 h. Yield: 2.70 g (48%). Yellow crystals. M.p. 89.7°. ^{1}H-NMR ($CDCl_3$): 7.99 (*d*, *J* = 13.7, ArC*H*); 7.54 (*d*, *J* = 13.7, ArCH=C*H*); 7.34 (*dd*, *J* = 8.3, 1.7, arom. H); 7.29 (*d*, *J* = 1.7, arom. H); 7.18 (*d*, *J* = 8.3, arom. H). ^{13}C-NMR ($CDCl_3$): 146.29; 144.57; 137.79; 137.14; 131.62 (*t*, *J* = 258); 126.78; 126.34; 110.37; 108.71.

*2,2-Difluoro-5-[(*E*)-2-nitroprop-1-en-1-yl]-1,3-benzodioxole* (**7b**). Prepared according to *GP 1* from **6** (5.10 g, 27.4 mmol) in $EtNO_2$ (10 ml) for 75 min. Yield: 5.63 g (85%). Yellow crystals. M.p. 68.1°. ^{1}H-NMR ($CDCl_3$): 8.06 (*s*, ArC*H*); 7.20–7.19 (*m*, 3 arom. H); 2.47 (*s*, Me). ^{13}C-NMR: ($CDCl_3$): 148.97; 144.59; 144.18; 132,19; 131.64 (*t*, *J* = 257); 128.47; 126.55; 110.48; 110.00; 14.00.

*2,2-Difluoro-5-[(*E*)-2-nitrobut-1-en-1-yl]-1,3-benzodioxole* (**7c**). Prepared according to *GP 1* from **6** (10.0 g, 53.7 mmol) in $PrNO_2$ (20 ml) for 5.5 h. Yield: 12.11 g (88%). Yellow oil. ^{1}H-NMR ($CDCl_3$): 7.99 (*s*, ArC*H*); 7.18–7.16 (*m*, 3 arom. H); 2.87 (*q*, MeCH_2); 1.30 (*t*, Me). ^{13}C-NMR ($CDCl_3$): 153.55; 144.65; 144.27; 131.70; 131.64 (*t*, *J* = 257); 128.41; 126.24; 110.10; 110.04; 20.65; 12.37.

General Procedure (*GP 2*) *for the Synthesis of Compounds* **3**, **4a**, *and* **5a**. *a*) *Free Base*. To an ice-cooled suspension of $LiAlH_4$ in anh. THF under N_2, conc. H_2SO_4 was added dropwise under vigorous stirring. Then, a soln. of the appropriate nitro compound **7** in THF was added slowly. The cooling bath was removed, and the mixture was heated at reflux for 5 min with a heat gun. Then, the mixture was cooled again with ice, and excess hydride was quenched by careful addition of i-PrOH, followed by 2M aq. NaOH soln., keeping the thickening mixture stirred by addition of THF. After removing the salts by filtration, the solvents were removed *in vacuo* to afford the products as the free bases.

b) *Hydrochloride Salt*. The above free amine was dissolved in anh. Et_2O containing 1% (*v*/*v*) of i-PrOH. Then, the pH was lowered to < 3 by addition of HCl gas, and the resulting colorless HCl salt was washed with small portions of Et_2O, and then dried *in vacuo*.

2-(2,2-Difluoro-1,3-benzodioxol-5-yl)ethanamine (**3**). Prepared according to *GP 2*,*a* from **7a** (2.40 g, 10.5 mmol), $LiAlH_4$ (1.8 g), and conc. H_2SO_4 (1.2 ml) in THF (130 ml); workup with i-PrOH (7.5 ml) and 5.4 ml 2M NaOH. Yield: 1.34 g (64%). Yellow oil.

2-(2,2-Difluoro-1,3-benzodioxol-5-yl)ethanamine Hydrochloride (**3**·HCl). Prepared according to *GP 2,b* from **3** (1.31g, 6.5 mmol) in Et_2O (50 ml) and i-PrOH (0.5 ml). Yield: 1.30 g (85%). Colorless crystals. ^{1}H-NMR (D_2O): 7.09–6.97 (*m*, 3 arom. H); 3.18 (*t*, $ArCH_2CH_2$); 2.94 (*t*, $ArCH_2$). ^{13}C-NMR (D_2O): 143.66; 142.51; 132.68; 131.37 (*t*, *J* = 253); 124.28; 110.11; 109.86.

1-(2,2-Difluoro-1,3-benzodioxol-5-yl)propan-2-amine (**4a**). Prepared according to *GP 2,a* from **7b** (5.40 g, 22.2 mmol), $LiAlH_4$ (3.8 g), and conc. H_2SO_4 (2.6 ml) in THF (180 ml); workup with i-PrOH (15.8 ml) and 11.4 ml 2M NaOH. Yield: 3.94 g (82%). Yellow oil.

1-(2,2-Difluoro-1,3-benzodioxol-5-yl)propan-2-amine Hydrochloride (**4a**·HCl). Prepared according to *GP 2,b* from **4a** (3.22 g, 15 mmol) in Et_2O (100 ml) and i-PrOH (1 ml). Yield: 2.8 g (77%). Colorless crystals. M.p. 184.7°. ^{1}H-NMR (D_2O): 7.20–6.93 (*m*, 3 arom. H); 3.51 (*m*, $ArCH_2CH$); 2.85 (*d*-like, *J* = 7.1, $ArCH_2$); 1.19 (*d*, *J* = 6.5, Me). ^{13}C-NMR (D_2O): 143.60; 142.53; 132.14; 131.35 (*t*, *J* = 253); 124.80; 110.53; 109.79.

1-(2,2-Difluoro-1,3-benzodioxol-5-yl)butan-2-amine (**5a**). Prepared according to *GP 2,a* from **7c** (12.10 g, 47.1 mmol), $LiAlH_4$ (8.6 g), and conc. H_2SO_4 (5.6 ml) in THF (400 ml); workup with i-PrOH (33.6 ml) and 24.3 ml 2M NaOH. Yield: 8.26 g (77%). Yellow oil.

1-(2,2-Difluoro-1,3-benzodioxol-5-yl)butan-2-amine Hydrochloride (**5a**·HCl). Prepared according to *GP 2,b* from **5a** (2.84 g, 12.4 mmol) in Et_2O (100 ml) and i-PrOH (1 ml). Yield: 2.77 g (84%). Colorless crystals. M.p. 180°. ^{1}H-NMR (D_2O): 7.13 (*d*, *J* = 8.2, arom. H); 7.09 (*d*, *J* = 1.4, arom. H); 7.01 (*dd*, *J* = 8.2, 1.4, arom. H); 3.47–3.38 (*m*, $ArCH_2CH$); 3.02 (*dd*, *J* = 14.4, 6.3, 1 H of $ArCH_2$); 2.84 (*dd*, *J* = 14.4, 8.1, 1 H of $ArCH_2$); 1.75–1.53 (*m*, CH_2); 0.96 (*t*, Me). ^{13}C-NMR (D_2O): 143.56; 142.44; 132.09; 131.31 (*t*, *J* = 253.4); 124.7; 110.32; 109.61; 54.25; 37.50; 24.37; 8.61.

1,1-Dimethylethyl [2-(2,2-Difluoro-1,3-benzodioxol-5-yl)-1-methylethyl]carbamate (**8a**). To a soln. of **4a** 3.90 g (18.1 mmol) and Et_3N (1.87 g, 18.5 mmol) in anh. CH_2Cl_2 (27 ml) was added under N_2 a soln. of $(Boc)_2O$ (4.04 g, 18.5 mmol) in CH_2Cl_2 (18 ml). The mixture was stirred for 4 h, diluted with CH_2Cl_2, and then treated with aq. 5% citric acid under vigorous stirring. The layers were separated, the org. layer was washed with 5% aq. citric acid (2×) and H_2O (1×), dried (Na_2SO_4), and evaporated. Yield: 5.62 g (98%). Yellow solid. M.p. 89.3°. ^{1}H-NMR ($CDCl_3$): 6.99–6.87 (*m*, 3 arom. H); 4.35 (*s*, NH); 4.05–3.83 (*m*, $ArCH_2CH$); 2.83 (*dd*, *J* = 13.5, 5.9, 1 H of $ArCH_2$); 2.68 (*dd*, *J* = 13.5, 7.1, 1 H of $ArCH_2$); 1.44 (*s*, *t*-Bu); 1.11 (*d*, Me). ^{13}C-NMR (D_2O): 155.10; 143.75; 142.33; 134.53; 131.62 (*t*, *J* = 255); 124.34; 110.49; 109.05; 79.32; 47.69; 42.92; 20.12.

1,1-Dimethylethyl {1-[(2,2-Difluoro-1,3-benzodioxol-5-yl)methyl]propyl}carbamate (**8b**). Prepared in analogy to **8a**, but from **5a** (5.00 g, 21.8mmol), Et_3N (2.25g, 22.2 mmol), and $(Boc)_2O$ (4.86 g, 22.3 mmol) in a total of 58 ml of anh. CH_2Cl_2. Yield: 6.67 g (93%). Yellow solid. M.p. 75.2°. ^{1}H-NMR ((D_6)DMSO): 7.28 (*d*, *J* = 8.2, arom. H); 7.20 (*d*, *J* = 1.5, arom. H); 6.99 (*dd*, *J* = 8.2, 1.5, arom. H); 6.64 (*d*, *J* = 9.1, NH); 3.66–3.43 (*m*, $ArCH_2CH$); 2.73 (*dd*, *J* = 13.4, 5.1, 1 H of $ArCH_2$); 2.62–2.54 (*dd*, overlapping with solvent signals); 1.44–1.30 (*m*, $MeCH_2$); 1.28 (*s*, *t*-Bu); 0.84 (*t*, Me). ^{13}C-NMR ($CDCl_3$): 155.51; 143.72; 142.26; 134.66; 131.62 (*t*, *J* = 255); 124.32; 11049; 109.02; 79.19; 53.25; 40.97; 28.30; 27.39; 10.38.

General Procedure (*GP 3*) *for the Preparation of Compounds* **4b**, **4c**, *and* **5b**. To a soln. of the appropriate Boc-protected compound **8** in anh. DMF and THF under N_2 atmosphere, NaH (55–65%; dispersed in mineral oil) was added. The mixture was stirred for 5 min at r.t. Then, either MeI or EtI was added[2]), and the mixture was heated to 75° for 90 min. The mixture was cooled to r.t., another batch of alkyl iodide was added, and the mixture was heated again to 75°. After 1 h, the reaction was complete, the mixture was cooled to r.t., and acidified cautiously to pH 3–4 by adding sufficient 5% aq. citric acid. The mixture was extracted with AcOEt (2×), the combined extracts were washed with H_2O (4×) and brine (2×), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was dissolved in anh. 1,4-dioxane (1 ml) and 4M anh. HCl in 1,4-dioxane (0.5 ml) under N_2, and then heated at 50°. When Boc deprotection was complete (TLC), the volatiles were removed in *vacuo*, the residue was suspended in anh. Et_2O, and

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[2]) **Attention**: This transformation is suitable only for micro-scale reactions. The reaction may be kinetically delayed, and it can take several dozens of minutes until the conversion starts with violent boiling!

filtered to afford colorless crystals, which were washed with a small amount of anh. Et_2O. The product was dried at 40° *in vacuo*.

1-(2,2-Difluoro-1,3-benzodioxol-5-yl)-N-*methylpropan-2-amine Hydrochloride* (**4b** · HCl). Prepared according to *GP 3* from **8a** (0.50g, 1.58 mmol), NaH (60%; 85 mg, 2.1 mmol), and MeI (2 × 0.27 ml, 8.66 mmol) in anh. THF (3 ml) and DMF (0.7 ml). Yield: 0.34 g (81%). Colorless solid. M.p. 199.0°. ^{1}H-NMR (D_2O): 7.09 (*d*, *J* = 8.2, arom. H); 7.05 (br. *s*, arom. H); 6.97 (br. *d*, *J* = 8.2, arom. H); 3.50–3.36 (*m*, $ArCH_2CH$); 3.02 (*dd*, *J* = 14.0, 6.2, 1 H of $ArCH_2$); 2.81 (*dd*, *J* = 14.0, 8.2, 1 H of $ArCH_2$); 2.63 (*s*, MeN); 1.18 (*d*, *J* = 6.6, Me). ^{13}C-NMR (D_2O): 143.71; 142.67; 131.81; 131.40 (*t*, *J* = 253); 124.88; 110.66; 109.89; 56.35; 38.41; 29.97; 14.71.

1-(2,2-Difluoro-1,3-benzodioxol-5-yl)-N-*ethylpropan-2-amine Hydrochloride* (**4c** · HCl). Prepared according to *GP 3* from **8a** (0.50g, 1.58 mmol), NaH (60%; 85 mg, 2.1 mmol), and EtI (2 × 0.30 ml, 7.50 mmol) in anh. THF (3 ml) and DMF (0.7 ml). Yield: 0.344 g (78%). Colorless solid. M.p. 202.5°. ^{1}H-NMR (D_2O): 7.12–7.02 (*m*, 2 arom. H); 6.97 (*d*, *J* = 8.2, arom. H); 3.56–3.40 (*m*, $ArCH_2CH$); 3.14–2.96 (*m*, $MeCH_2N$, 1 H of $ArCH_2$); 2.76 (*dd*, *J* = 8.9, 13.8, 1 H of $ArCH_2$); 1.28–1.02 (*m*, 2 Me). ^{13}C-NMR (D_2O): 143.67; 142.61; 131.96; 131.40 (*t*, *J* = 253); 124.87; 110.66; 109.85; 54.81; 40.18; 38.48; 15.02; 10.66.

1-(2,2-Difluoro-1,3-benzodioxol-5-yl)-N-*methylbutan-2-amine Hydrochloride* (**5b** · HCl). Prepared according to *GP 3* from **8b** (0.50g, 1.52 mmol), NaH (60%; 85 mg, 2.1 mmol), and MeI (2 × 0.27 ml, 8.66 mmol) in anh. THF (3 ml) and DMF (0.7 ml). Yield: 0.285 g (67%). Colorless solid. M.p. 161.5°. ^{1}H-NMR (D_2O): 7.14–7.05 (*m*, 2 arom. H); 6.99 (*dd*, *J* = 9.0, 1.5, arom. H); 3.42–3.30 (*m*, $ArCH_2CH$); 2.95 (br. *d*, *J* = 7.2, $ArCH_2$); 2.61 (*s*, MeN); 1.70–1.52 (*m*, $MeCH_2$); 0.90 (*t*, *J* = 7.5, Me). ^{13}C-NMR (D_2O): 143.78; 142.67; 131.91; 131.40 (*t*, *J* = 253); 124.82; 110.56; 109.95; 61.35; 35.20; 29.93; 21.96; 8.22.

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Received January 23, 2006