SYNTHESIS AND DIRECT FLUORINATION OF LBT-999 AND NEW CONFORMATIONALY RESTRICTED ANALOGUES

P J Riß[1] , F Rösch[1]
[1]Institut für Kernchemie, Universität Mainz, 55128 Mainz, Germany

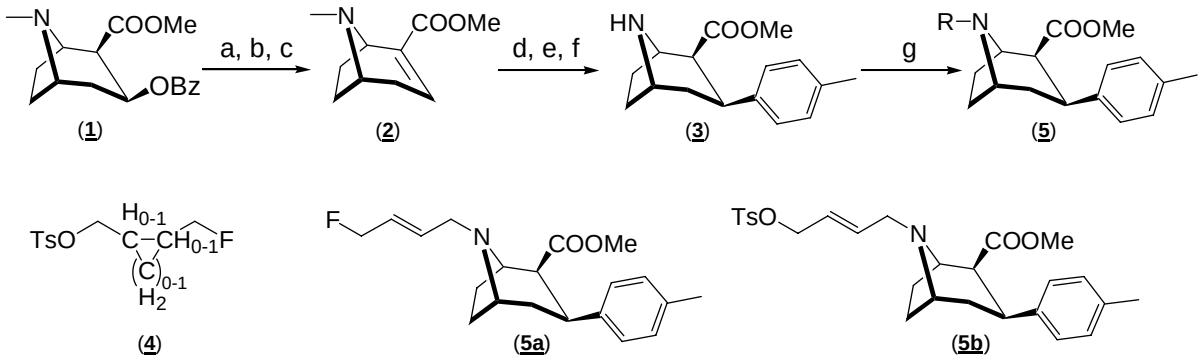
Introduction:
The dopamine transporter (DAT) plays a key role in the regulation of dopaminergic signal transduction. Several neurodegenerative disorders like Parkinson's disease (PD) are characterised by an altered DAT availability. In the case of PD, a diminished DA biosynthesis effects a significant increase of available DAT binding sites. Radioligands for quantification of DAT availability are of high clinical relevance for early diagnosis of PD. 3-exo-phenyl tropane serves as lead structure for selective DAT ligands. LBT-999 **5a**, a N-4-fluorobut-2-en-1-ylated tropane derivative, exhibits excellent affinity to the DAT (K_i = 9.4 nM) together with high selectivity (SERT/DAT >100 and NET/DAT >100)[1-4]. This may be due to its conformational restricted moiety at the bridge nitrogen. We intended a systematic variation of conformational restricted LBT-999 analogues to be prepared and evaluated for DAT affinity and selectivity. In addition we decided to prepare a new labelling precursor **5b** for efficient direct nucleophilic fluorination.

Experimental:
2 was prepared from cocaine **1** as published elsewhere. Addition of toluene magnesium bromide and subsequent N-demethylation afforded compound **3**. **3** was alkylated with appropriate ω-fluoro-halides to yield **5** as references. Labelling precursors were obtained via tosylation of ω-hydroxy analogues. ^{18}F was introduced via the common ^{18}F-cryptate procedure in moderate to high yields.

Results and Discussion:
5a and **5b** have been prepared as reference and labelling precursor, respectively. Instead of the established two-step synthesis via 4-[^{18}F]fluorobut-2-en-1-yl tosylate[1,3], a labelling precursor for direct nucleophilic radio-fluorination provides [^{18}F]LBT-999 in an easy and efficient reaction. In addition, we have prepared new conformational restricted N-substituted analogues of LBT-999. All new compounds are well suited for direct radio-fluorination and fluoroalkylation.

Conclusion:
A promising set of new tropane derivatives containing a conformational restricted C_4-chain has been prepared to be evaluated as DAT ligands. In addition, an improved labelling precursor for efficient synthesis of [^{18}F]LBT-999 is now available for comparative small animal PET studies of dopaminergic signal pathways, involving 6-L-[^{18}F]FDOPA and [^{18}F]FP.

References
(1) Dollé F. et al.; Bioorg. Med. Chem. 14; (2006); 4; 1115 ff
(2) Chalon S. et al, J Pharmacol Exp Ther. 317; (2006); 1; 147 ff
(3) Dollè F. et al.; J Labelled Comp Radiopharm 49; (2006) 687 ff
(4) Wadad, S. et al; Synapse 61; (2007); 17 ff



a) HCl, reflux; b) $POCl_3$, reflux; c) MeOH, -78°C to RT; d) 4-MePheMgBr, -40°C, Et_2O/CH_2Cl_2;
e) -78°C, TFA; f) ACE-Cl, MeOH; g) **4**, dioxane, MW