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A new multi-gram synthetic route to labeling precursors for the $D_{2/3}$ PET agent ^{18}F-fallypride

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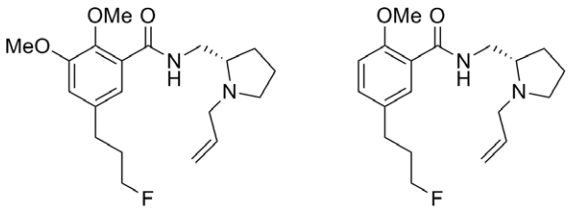
ABSTRACT

This Letter describes a new multi-gram synthetic protocol for the preparation of the classic tosylate labeling precursor for the $D_{2/3}$ PET agent [^{18}F]fallypride. In the course of our studies, we also discovered two novel labeling precusors, the previously undescribed mesylate and chloro congeners of fallypride.

Dysfunction in dopaminergic neurotransmission has been implicated in a number of neuropsychiatric disorders including Parkinson's disease, Alzheimer's disease, schizophrenia, and Huntington's disease.[1–4] The discovery and development of small molecule ligands that can selectively target dopamine receptors (D_1–D_4), transport, and synthesis is central to the development of therapeutic agents for the treatment of these complex diseases.[1–4] The D_2 receptor antagonists fallypride (FP) **1** and desmethoxy fallypride (DFP) **2** stand out due to their selectivity, affinity, and reversibility (Fig. 1).[5,6]

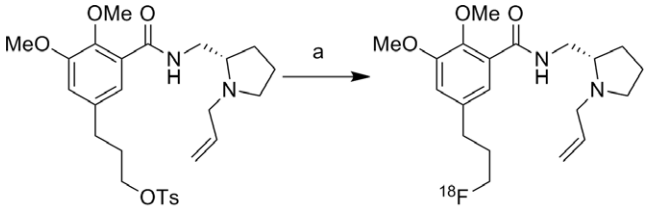
The corresponding [^{18}F] and [^{11}C]-labeled analogs of **1** have found utility as positron emission tomography (PET) agents.[7–13] In particular, [^{18}F]FP has been employed to study $D_{2/3}$ receptor occupancy and density in neuropsychiatric disorders and aging in both preclinical species and in humans.[7–15]

The Vanderbilt Institute of Chemical Biology (VICB) established a Synthesis Core to provide synthetic and medicinal chemistry resources to the biomedical research community across the Vanderbilt campus, including the Vanderbilt Imaging Center. On one occasion, a request was made for a multi-gram synthesis of a labeling precursor for [^{18}F]fallypride **4**, classically accessed by ^{18}F displacement of the corresponding tosylate **3** (Scheme 1).[7–15] Upon examination of the literature, we were dismayed to see that the classical published synthetic routes to **3** were performed on milligram quantities of material, employed preparative TLC for purification and afforded 30–50% yields for every step.[8,9] In 2007, Rosch and co-workers reported a large-scale synthesis utilizing a mixed anhydride coupling between the corresponding substituted benzoic acid **5** and proline-derived amine **6** to afford **7** in an unspecified yield (Scheme 2).[16] Earlier de Paulis reported hydrob-



1, fallypride (FP) **2**, desmethoxy fallypride (DFP)

Figure 1. Structures of the $D_{2/3}$ antagonists fallypride (FP), **1**, and desmethoxy fallypride (DFP), **2**.



3 **4**, [^{18}F]FP

Scheme 1. Synthesis of [^{18}F]fallypride **4**. Reagents: (a) ^{18}F, Kryptofix, K_2CO_3, CH_3CN.

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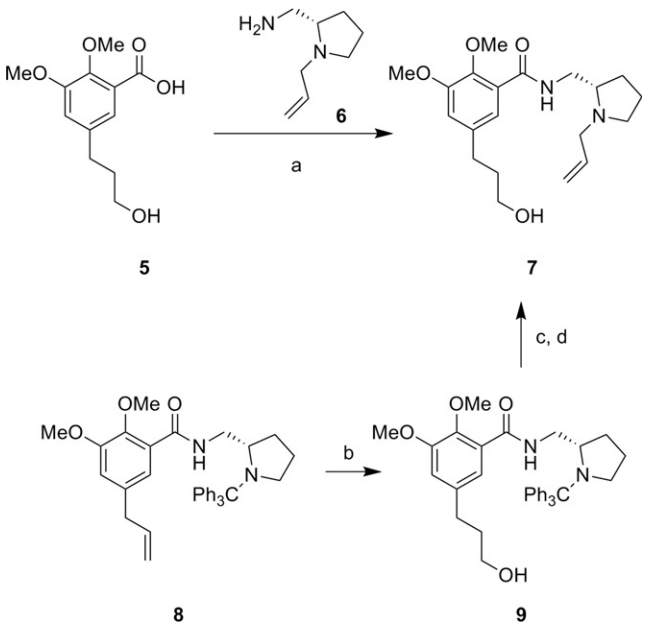


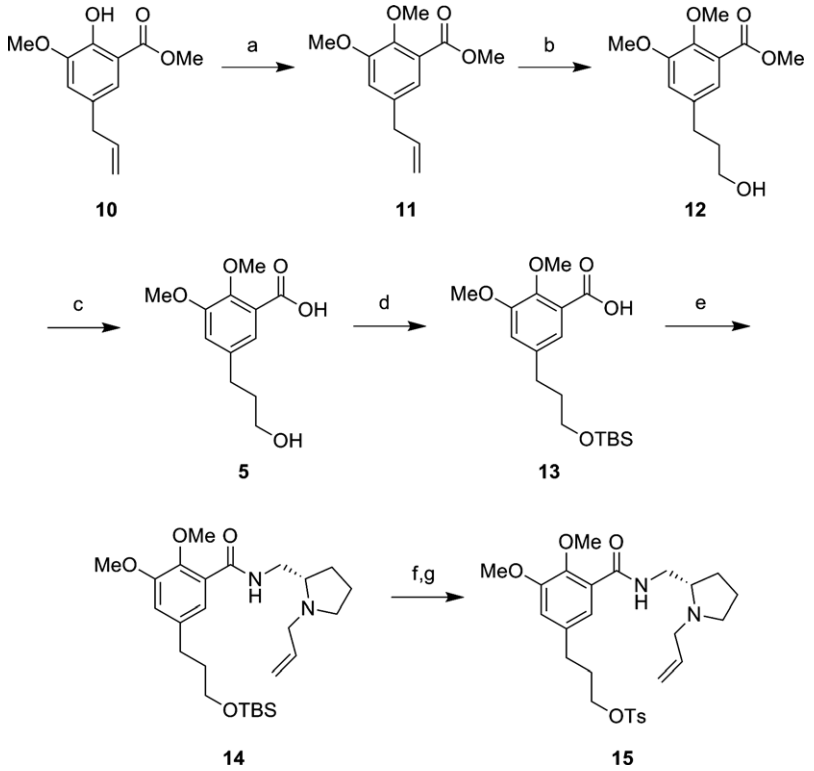
Scheme 2. Existing routes to alcohol **7**. Reagents: (a) $ClCO_2Et$, Et_3N; 9-BBN, H_2O_2, NaOH; (c) TFA, DCM; (d) allyl bromide, K_2CO_3, DMF.

oration–oxidation of allyl benzamide **8** to give alcohol **9** and following deprotection and N-allylation provide alcohol **7**.[17] In examining these synthetic routes, we became concerned with functional group compatibility under these reaction conditions and therefore turned our attention to developing a new synthetic route employing a protected derivative of benzoic acid **5** as a coupling partner.

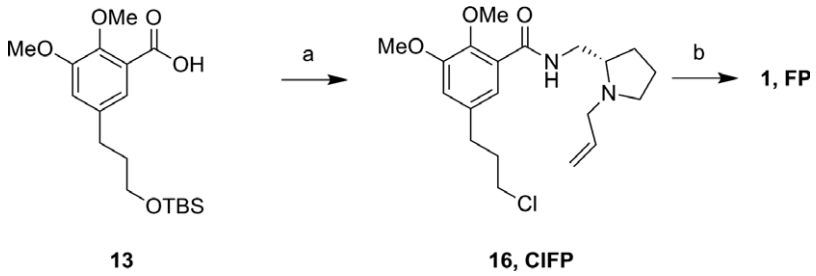
To this end, alcohol **5** was derived from commercially available methyl benzoate **10** in three steps starting with O-methylation to afford benzoate **11** in 95% yield (Scheme 3). Hydroboration of **11** followed by treatment with basic peroxide then gave alcohol **12**. Following ester hydrolysis (92%), benzoic acid **5** was treated with TBSCl and imidazole in DMF to provide TBS protected alcohol **13** in good overall yield. Next, the coupling of **13** with amine **6** (derived in two-steps from L-prolineamide) was examined. Optimal conditions employed EDCI in combination with HOBt and *i*-Pr_2NEt as base to provide **14**. Under these conditions, the coupled product was obtained in yields ranging from 45% to 64%. Finally, removal of the TBS group with TBAF delivered alcohol **7**. Standard conditions then provided the tosylate **15**, the immediate precursor to [^{18}F]fallypride **4** in seven steps with an overall yield of 11%.[18] Importantly, all the steps leading to **14** were conducted on multigram scales with standard column chromatographic purification, while the final deprotection and tosylation steps were run on 1–2 gram scales (See Supporting Information).

The silyl protection of **5** and subsequent deprotection steps were a necessity for the multi-gram synthesis of **15**. All attempts to perform the amide coupling of **5** and **6**, with multiple peptide coupling reagents (EDCI, HATU, TFFH, etc) afforded poor results (yields less than 20%) and isolation of the extremely polar **7** proved difficult. Standard normal phase chromatography was insufficient on large scale to deliver pure **7** for the tosylation step. Thus, we were required to pursue preparative reverse phase chromatography with multiple injections, resulting in large volumes of CH_3CN/H_2O/TFA solutions to dry down with longer turn-around. While the protection/deprotection sequence adds two chemical steps, the overall yields and efficiency to access pure **15** are markedly improved.

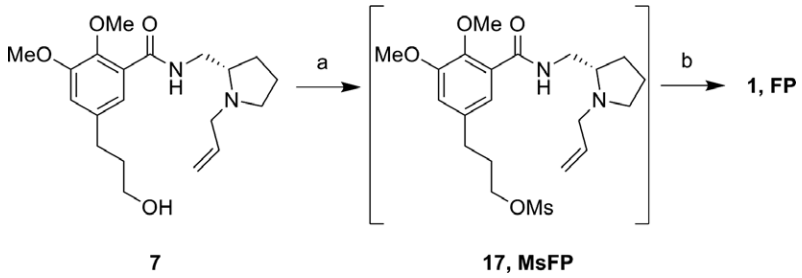
The major problematic step in the synthesis was the amide coupling between the electron-rich, hindered benzoic acid **13** and



Scheme 3. Improved synthetic route to **15**. Reagents: (a) MeI, K_2CO_3, Me_2CO, 95%; (b) i—9-BBN, THF, ii—NaOH, H_2O_2, 92%; (c) NaOH, THF (aq.), 92%; (d) TBSCl, ImH, DMF, 75%; (e) **6**, EDCI, HOBt, *i*-Pr_2NEt, 45–64%; (f) TBAF, THF, 71%; (g) TsCl, DCM, pyridine, 44%.



Scheme 4. Synthesis of a novel labeling precursor ClFP **16** and fallypride **1**. Reagents: (a) i—$SOCl_2$, toluene, cat. DMF, ii—**6**, 31%; (b) TBAF, THF, reflux, 55%.



Scheme 5. Synthesis of a novel labeling precursor MsFP **17** and fallypride **1**. Reagents: (a) i—MsCl, DCM, Et_3N; (b) TBAF, *t*-BuOH, reflux, 40% over two steps.

amine **6**—a historically problematic reaction. We evaluated a number of coupling reagents (PyBop, BOP, TFFH), but none afforded advantages over EDCI. One attempted coupling that led to a new entity involved the treatment of benzoic acid **13** with thionyl chloride (Scheme 4). Reaction of the intermediate acid chloride with amine **6** led to the isolation of previously unknown chloride **16**, the result of substitution of the TBS ether for a chloro group, a variation of the Silyl-Durst chlorination.[18,19] This new entity **16** (ClFP) was evaluated as a D2 antagonist, and afforded an IC_{50} of 17.1 nM. With **16** in hand, we then evaluated its ability to serve as a labeling precursor in route to [^{18}F]fallypride **4**. Exposure of **16** to TBAF in THF provided a 55% yield of **1**, indicating that this new ClFP congener **16** is a viable labeling precursor for [^{18}F]fallypride **4**. Activity at the D_2 receptor was also confirmed for our synthetic **1** with an IC_{50} of 5.0 nM, a value in agreement with literature reports.

Based on these results, we examined the literature further, and were surprised to find that the corresponding mesylate analog **17** (MsFP) had never been prepared. To evaluate this potential labeling precursor, we intercepted alcohol **7** from the deprotection of **14** and treated it with MsCl in DCM and generated **17** (MsFP); however, this material was labile and proved difficult to isolate. Therefore, we generated **17** (MsFP) in situ and immediately treated the reaction mixture with TBAF in *t*-BuOH at 85 °C to afford a 40% yield of **1** (Scheme 5), suggesting that **17** (MsFP) could also serve as a viable labeling precursor for the preparation of [^{18}F]fallypride **4**.[18]

In summary, we have developed an improved, high yielding, and scalable synthetic route to the classical labeling precursor **15** for [^{18}F]fallypride **4**. During the course of this work, we discovered **16** (ClFP), a novel D_2 antagonist and viable labeling precursor for [^{18}F]fallypride **4**. This work also prepared and evaluated the previously unknown mesylate congener, **17** (MsFP), as a labeling precursor, and found that it too was viable. Further studies in this arena are in progress and will be reported in due course.

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Supplementary data

Experimental procedures and analytical data for compounds **1**, **11-17** are provided. This material is available free of charge via the Internet at http://www.sciencedirect.com/science/journal/0960894X. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.07.065.

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