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The Non-Anhydrous, Minimally Basic Synthesis of the Dopamine D_2 Agonist [^{18}F]MCL-524

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Abstract: The dopamine D_2 agonist MCL-524 is selective for the D_2 receptor in the high-affinity state (D_2^{high}), and, therefore, the PET analogue, [^{18}F]MCL-524, may facilitate the elucidation of the role of D_2^{high} in disorders such as schizophrenia. However, the previously reported synthesis of [^{18}F]MCL-524 proved difficult to replicate and was lacking experimental details. We therefore developed a new synthesis of [^{18}F]MCL-524 using a "non-anhydrous, minimally basic" (NAMB) approach. In this method, [^{18}F]F^- is eluted from a small (10–12 mg) trap-and-release column with tetraethylammonium tosylate (2.37 mg) in 7:3 MeCN:H_2O (0.1 mL), rather than the basic carbonate or bicarbonate solution that is most often used for [^{18}F]F^- recovery. The tosylated precursor (1 mg) in 0.9 mL anhydrous acetonitrile was added directly to the eluate, without azeotropic drying, and the solution was heated (150 °C/15 min). The catechol was then deprotected with the Lewis acid $In(OTf)_3$ (10 equiv.; 150 °C/20 min). In contrast to deprotection with protic acids, Lewis-acid-based deprotection facilitated the efficient removal of byproducts by HPLC and eliminated the need for SPE extraction prior to HPLC purification. Using the NAMB approach, [^{18}F]MCL-524 was obtained in 5–9% RCY (decay-corrected, n = 3), confirming the utility of this improved method for the multistep synthesis of [^{18}F]MCL-524 and suggesting that it may applicable to the synthesis of other ^{18}F-labeled radiotracers.

Keywords: fluorine-18; aporphines; dopamine D_2 agonist; high-affinity state; PET

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1. Introduction

1.1. Aporphines

Dopamine D_2 receptor dysfunction is a hallmark of several neurological diseases and disorders, including schizophrenia, Parkinson's disease, Tourette's syndrome and addiction [1–14]. Like other G-protein-coupled receptors, D_2 transitions between two states that vary in their affinity for endogenous dopamine: a high-affinity, or functional, state (D_2^{high}), and a low-affinity state (D_2^{low}) [15–18]. Thus, PET (positron emission tomography) radiopharmaceuticals that can be used to measure differences in the population of D_2^{high} versus D_2^{low} may be useful in improving the understanding and diagnosis of these diseases [19–22]. However, most PET probes of postsynaptic dopamine receptor function evaluated to date suffer from limitations that preclude their use for this application. For example, [^{11}C]raclopride (Figure 1), a D_2/D_3 ligand [23,24], has a high affinity for D_2-like receptors in striata, but exhibits reduced D_2 binding during periods of high synaptic dopamine concentration [25–27]. The structurally related benzamide, [^{18}F]fallypride (Figure 1), also does not distinguish between D_2 and D_3 [28], and the butyrophenone,

[^{11}C]methylspiperone (Figure 1), is not selective for D_2 versus $5HT_2$ receptors [29]. More importantly, all of these radioligands are D_2 antagonists, which do not distinguish between the high- and low-affinity states of the D_2 receptor.

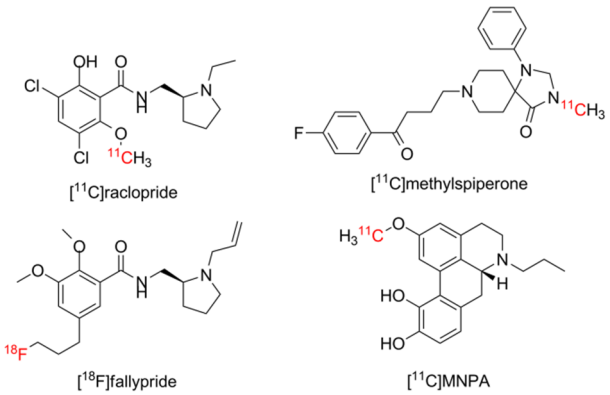
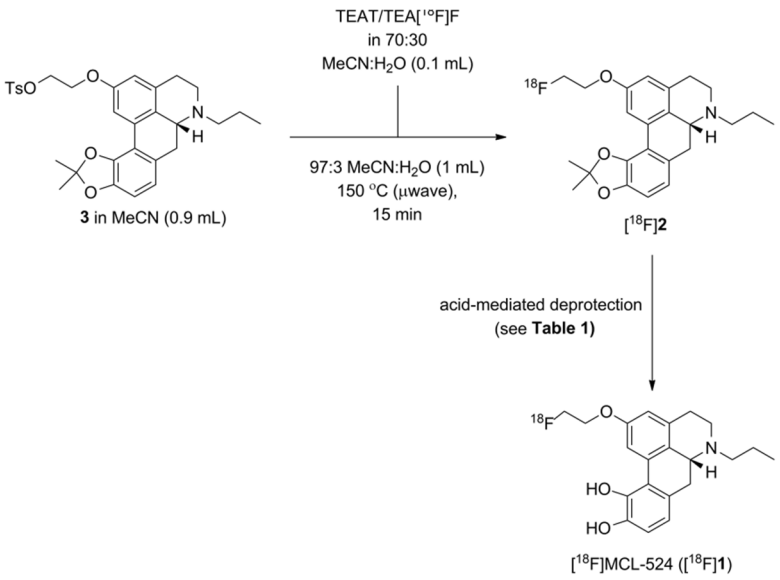


Figure 1. Selected PET radioligands of the dopamine D_2 receptor.

Aporphines are a class of dopamine D_2 receptor agonists derived from apomorphine. As agonists, aporphines exhibit a higher affinity for the D_2^{high} state than for the D_{2low} state [11,15,16,30–32]; and therefore, it has been proposed that radiolabeled aporphines may be useful for probing dopamine supersensitivity and other phenomena associated with changes in the D_2^{high}/D_{2low} ratio [7–10,14,17,21]. To this end, a variety of non-radioactive fluorinated aporphines were synthesized and evaluated versus [^{3}H]domperidone using competitive binding assays in rat striatal homogenates, and MCL-524 (**1**; Scheme 1) was identified as a candidate radiotracer owing to its high affinity for D_2^{high} (K_i = 3.7 ± 1.2 nM) and much lower affinity for D_{2low} (Ki = 990 ± 35 nM) [32]. An ^{18}F-labeled analogue was subsequently prepared, its specificity was compared to that of [^{11}C]MNPA (Figure 1), and its pharmacokinetics were evaluated in cynomolgus monkeys [33]. Notably, the mean striatal non-displaceable binding potential (BP_{ND}) value was 2.0 for [^{18}F]MCL-524 versus 1.4 for [^{11}C]MNPA, a 1.5-fold increase. [^{18}F]MCL-524 BP_{ND} values were reduced by 89% and 56% in response to acute raclopride and D-amphetamine pretreatment, respectively, and it exhibited excellent radiotracer kinetics, showing a rapid accumulation in the striatum and a high striatum:cerebellum ratio within an hour after administration.



Scheme 1. NAMB synthesis of [^{18}F]MCL-524 ([^{18}F]**1**).

However, the previously reported synthesis of [^{18}F]MCL-524 has several limitations, including a low synthetic yield and the use of 6 M HCl to deprotect the catechol post-labeling, which degrades the product and complicates product purification. In order to address these limitations, we sought a new approach to this synthesis that obviated these limitations.

1.2. NAMB ^{18}F Chemistry

Fluorine-18 ($t_{1/2}$ = 109.8 min) is the "gold standard" for many PET imaging applications; however, the radiolabeling of potential targeting vectors with [^{18}F]F^- is often challenging and sometimes impossible in light of the high temperatures and basic conditions that are typically employed (K_2CO_3 or $KHCO_3$, Kryptofix 2.2.2, MeCN or DMSO, 70–200 °C). Furthermore, it is generally accepted that radiolabeling compounds with [^{18}F]F^- require scrupulously anhydrous reaction conditions. This requirement has resulted in the widespread use of the azeotropic drying of the [^{18}F]F^- after it is extracted from the irradiated [^{18}O]H_2O target by anion-exchange (AEX) chromatography and prior to its use in any synthetic procedure. In recent years, however, several laboratories have proposed methods to simplify or eliminate these [^{18}F]F^- preparation steps [34–39].

In addition to eliminating the [^{18}F]F^- "drydown" step, we also introduced the use of non-basic tetraalkylammonium salt solutions for the extraction of [^{18}F]F- from the AEX "trap-and-release" column [40–42], a method later used by others [43–45]. This "non-anhydrous, minimally basic" (NAMB) strategy involves the use of a small AEX column to extract [^{18}F]F^- from [^{18}O]H_2O, from which it is then efficiently eluted using an aqueous solution of tetraethylammonium tosylate (TEATos) and diluted with a solution of the precursor compound in anhydrous DMSO or MeCN [46]. The key to the success of this approach is the small size of the AEX column (10–12 mg), which can be eluted with as little as 100 µL of 7:3 MeCN:H_2O. This small elution volume permits dilution to a final reaction volume (1 mL) that maintains an effective precursor concentration and is compatible with automated synthesis systems while keeping the water concentration at ≤5%. This "damp" reaction matrix can be heated directly, without the need for azeotropic drying. In addition to increasing the overall efficiency by reducing the number of radiosynthetic steps, this approach: (a) avoids losses in radioactivity associated with the volatilization of H[^{18}F]F and absorption of activity on the surface of the reaction vessel during dry-down; (b) is suitable for both nucleophilic aromatic and nucleophilic aliphatic ^{18}F-fluorinations; and (c) is compatible with the volumes of aqueous [^{18}F]F^- obtained from standard cyclotron targets (1–3 mL). The NAMB approach was previously used to synthesize [^{18}F]fluorobenzaldehyde and [^{18}F]fallypride [46], demonstrating that at least some [^{18}F]F^- incorporation reactions do not require anhydrous basic conditions in order to proceed efficiently.

1.3. Preperation of [^{18}F]MCL-524

The previously reported synthesis of [^{18}F]MCL-524 utilized a standard nucleophilic aliphatic ^{18}F-fluorination reaction (DMSO, 150–160 °C, 10 min) to generate intermediate [^{18}F]**2** (Scheme 1) from tosylated precursor MCL-556 (**3**; Scheme 1), followed by the removal of the acetonide protecting group with 6 M HCl at 90–110 °C (10 min) [33]. Notably, neither the efficiency of the initial ^{18}F-fluorination step, the efficiency of the catechol deprotection step nor the final isolated radiochemical yield (RCY) were reported. Upon attempting to replicate this work, we observed a significant accumulation of chemical by-products after treatment with HCl and low conversion of [^{18}F]**2** to [^{18}F]**1**. We hypothesized that, if the ^{18}F-fluorination step were conducted in an environment free of the carbonate base, which is typically present in standard [^{18}F]F^- incorporation reactions, an efficient and reproducible acid-mediated deprotection would be easier to achieve and might allow for the removal of acetonide under milder conditions. Herein, we describe an alternative radiosynthesis of [^{18}F]MCL-524 using NAMB [^{18}F]F^- incorporation chemistry, as well as an unconventional Lewis-acid-based method for the deprotection of intermediate [^{18}F]**2**.

2. Materials and Methods

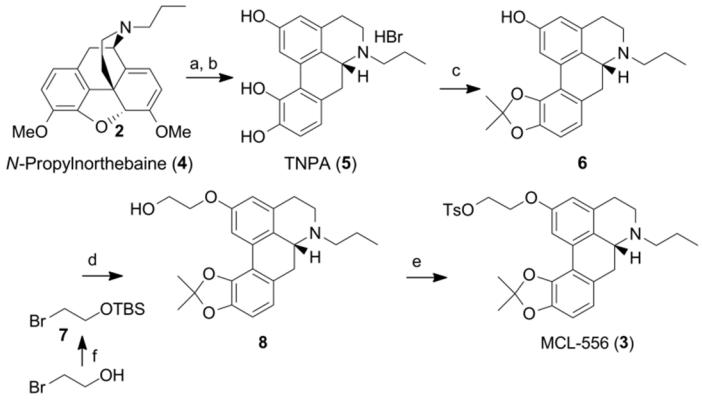
*Radiosynthesis of [^{18}F]MCL-524 ([^{18}F]**1**) via In(OTf)$_3$-Mediated Deprotection*

An aliquot of [^{18}F]F$^-$ (190 MBq) in [^{18}O]H_2O was diluted to 2 mL with H_2O and the [^{18}F]F$^-$ was captured on a commercial QMA AEX column (carbonate form, 10–12 mg; MedChem Imaging, LLC), which was previously activated with water (1 mL). After washing the column with anhydrous MeCN (3 mL), a continuous flow of Ar was passed through the column for 10 min. The [^{18}F]F$^-$ was eluted from the column in the reverse direction into a microwavable test tube using a 100 µL solution of TEATos (23.7 mg/mL) in 7:3 MeCN:H_2O. Residual eluent was ejected from the column using a syringe filled with air (10 mL). The precursor, MCL-556 (**3**; 1 mg), in anhydrous MeCN (900 µL), was added to the eluate, and the tube was crimp-sealed, magnetically stirred for 20 s and heated to 150 °C in a microwave heater (Biotage® Initiator+) for 15 min. After removing small aliquots for radio-TLC (10% EtOH in CH_2Cl_2, silica gel, 49 ± 2% radiochemical conversion (RCC), n = 4) and analytical HPLC (HPLC 1, Program A in the Supporting Information), the ^{18}F-fluorination reaction mixture containing [^{18}F]**2** was added to solid In(OTf)$_3$ (10.35 mg) in a microwave test tube. Water was added (100 µL), and the reaction mixture was heated to 150 °C (microwave) for 20 min. The percent conversion of intermediate [^{18}F]**2** to [^{18}F]**1** (38%) was assayed by analytical HPLC (HPLC 1, Program A). The crude reaction mixture was diluted to 2 mL with sodium acetate buffer (50 mM AcOH/2.5 mM NaOAc) containing 0.1 mg/mL ascorbic acid and purified by preparative HPLC (HPLC 2, Program D). The collected product was diluted with water (50 mL) and trapped on a Sep-Pak® C18 Plus cartridge, which was previously activated with 3 mL of EtOH and 10 mL of water. [^{18}F]MCL-524 was eluted from the column with EtOH (1.5 mL) and diluted with 0.9% saline (1.5 mL) containing sodium ascorbate (3 mg/mL). The final formulation was passed through a 0.2 µm filter to afford 7.06 MBq (191 µCi) of [^{18}F]MCL-524 [3.7% non-decay corrected, 9.2% decay corrected (DC)] in 1:1 EtOH:sodium ascorbate (4.5 mg) in isotonic saline (3 mL total). Product identity and molar activity were assessed by HPLC (HPLC 1, Program C). Total synthesis time was 146 min from start-of-synthesis.

3. Results

3.1. Summary of Non-Radioactive Synthesis

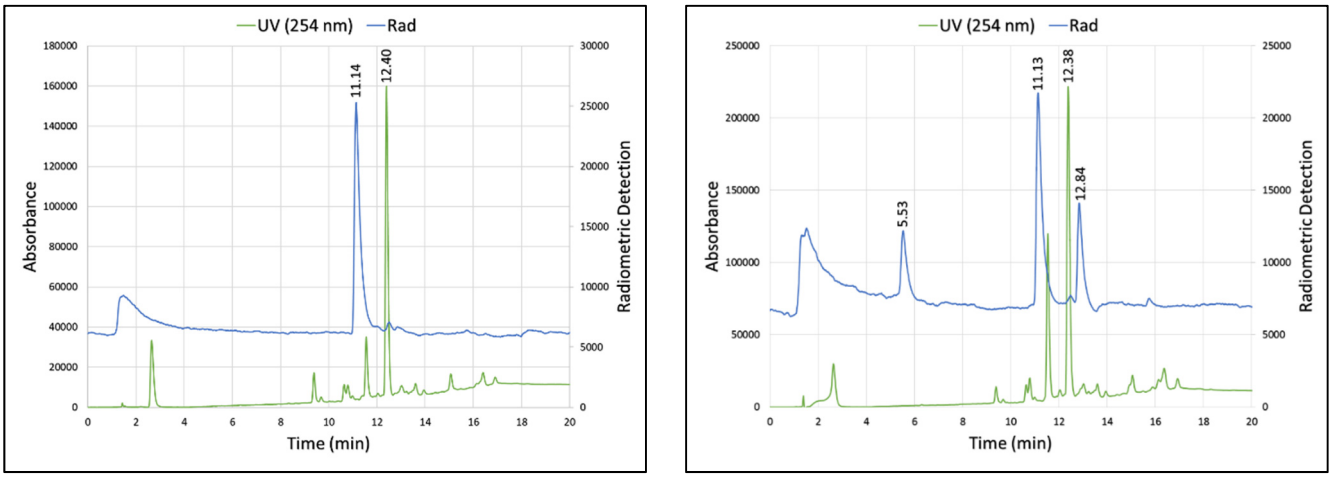
Tosylated precursor MCL-556 (**3**) [33] was synthesized as previously described, with several minor modifications (Scheme 2 and Scheme S1 in the Supporting Information). Thebaine was *N*-demethylated with DIAD [47], and then alkylated to afford *R*-(−)-N-n-propylnorthebaine (**4**) according to the previously published procedure [48]. Intermediate **4** was then *O*-demethylated by refluxing in 48% HBr in glacial acetic acid to afford R-(−)-2,10,11-trihydroxy-n-propylnorapomorphine hydrobromide (**5**; TNPA) [48]. The catechol moiety of **5** was protected as an acetonide using acetone and phosphorus pentoxide in THF, as previously described [49]. The acetonide-protected intermediate (**6**) was then alkylated with TBS-protected 1-bromoethan-2-ol (**7**) under phase transfer conditions in order to afford the 2-hydroxyethoxy aporphine (**8**), which was tosylated to afford the radiosynthetic precursor **3**. Nonradioactive MCL-524 was synthesized from the common intermediate **4** following previously reported procedures (Scheme S2 in Supporting Information) [32,50].



Scheme 2. Synthesis of precursor MCL-556 (**3**). Reagents and conditions: (a) *i.* DIAD, MeCN, heat; *ii.* MeOH, EtOAc; (b) 48% HBr/AcOH, 120 °C; (c) CH_3COCH_3, P_2O_5, THF, 60 °C; (d) **7**, 5 N NaOH, THF, 70 °C; (e) Ts_2O, Et_3N, DMAP, CH_2Cl_2; (f) TBSCl, Et_3N, CH_2Cl_2.

3.2. Summary of Radioactive Synthesis

[^{18}F]Fluoride trap-and-release and radio-fluorination conditions were similar to those used for the NAMB preparation of [^{18}F]fallypride [46], using a solvent matrix consisting of TEATos in 97% MeCN (Scheme 1). Upon microwave heating (150 °C, 15 min), the ^{18}F-fluorination of **3** (1 mg) in 97% MeCN (1 mL) produced acetonide-protected [^{18}F]**2** in a RCC of 51 ± 4% (radio-TLC, n = 6, Figure S1 in the Supporting Information). Under these conditions, the principal radiochemical product was [^{18}F]**2** (Figure 2a); however, some reaction mixtures contained significant radio-impurities, observed at ~5.5 min and ~12.8 min using analytical HPLC (Figure 2b). Interestingly, a peak at 5.5 min was also sometimes observed after the NAMB preparation of an unrelated radiotracer under identical HPLC conditions [46], albeit in much smaller quantities. The 12.8 min peak was determined to be toluenesulfonyl [^{18}F]fluoride based on its retention time versus the non-radioactive standard. The highly variable appearance of these radiochemical by-products suggests that they are the result of small batch-to-batch changes in the reagent concentration and/or water content.



(**a**) (**b**)

Figure 2. Analytical radio-HPLCs of two [^{18}F]**2** (t_R = 11.14 min) reaction mixtures (TEATos, 97% MeCN, 150 °C, 15 min). In both traces, starting material **3** can be seen at ~12.4 min (254 nm). Whereas reaction (**a**) contains only one significant radiochemical product, reaction (**b**) contains radio-impurities at 5.5 and 12.8 min. The peak at 12.8 min co-eluted with toluenesulfonyl fluoride standard. See the Supporting Information for HPLC conditions (HPLC 1, Program A).

After NAMB ^{18}F fluorination of the tosylated precursor **3**, the treatment of the crude reaction mixture with 1:1 6 N H_2SO_4:MeOH for 5 min at 100 °C resulted in a 5% conversion of intermediate [^{18}F]**2** to [^{18}F]MCL-524 ([^{18}F]**1**), as determined by HPLC (Table 1, Entry 1). Increasing the time (10 min) and temperature (150 °C) led to a marked increase in percent conversion (86%; Table 1, Entry 2). However, the use of these conditions also significantly increased the production of chemical impurities that we anticipated would complicate the isolation of the final product by HPLC (Figure 3a). Alternative acidic deprotection conditions were therefore explored, with the extent of conversion from intermediate [^{18}F]**2** to final product [^{18}F]**1** measured by HPLC. Deprotection with 90% TFA for 5 min at 100 °C led to a 67% conversion and resulted in a crude reaction mixture with fewer by-products than with 6 N H_2SO_4:MeOH (Figure 3b), but required the product to be separated from the acidic reaction mixture by SPE prior to HPLC purification. The isolated DC-RCY of [^{18}F]MCL-524 under these conditions was 8% after the HPLC purification, concentration by C18 SPE and final formulation in 10% EtOH in isotonic saline. When the deprotection reaction time was extended to 10 min, the conversion yield was 83% and DC isolated yield was 14%.

Alternatively, the deprotection of [^{18}F]**2** using an excess of the Lewis acid In(OTf)$_3$ [51] (10 molar equivalents relative to **3**) produced only a 33–38% conversion (n = 3), even at high temperatures (150 °C) and long reaction times (20 min) (Figure 3c). However, unlike deprotection using protic acids (e.g., 6 N H_2SO_4, 90% TFA), these reaction mixtures were significantly less acidic (pH = 3–4) and thus did not require SPE of the crude mixture prior to HPLC purification. Similar to treatment with TFA, and unlike treatment with H_2SO_4, the distribution of non-radioactive by-products after In(OTf)$_3$ deprotection did not impede the purification of [^{18}F]**1** by semi-preparative HPLC. [^{18}F]MCL-524 prepared via In(OTf)$_3$ deprotection was obtained in a greater than 98% radiochemical purity and an overall radiochemical yield of 5–9% DC (n = 3) over 146–199 min. The product identity was verified by the co-injection of [^{18}F]**1** with the non-radioactive standard (Figure S2, Supporting Information).

In keeping with the limitations of our research facility, most of the radiochemical experiments reported here employed relatively small aliquots of [^{18}F]F$^-$ (197–255 MBq), resulting in modest molar activities (Table 1) and final product quantities. However, one experiment was carried out that started with 715 MBq of [^{18}F]F$^-$, and this reaction yielded 47 MBq of [^{18}F]MCL-524, enough for preclinical PET imaging and providing evidence that this method can be scaled to accommodate the larger quantities of [^{18}F]F$^-$ employed in clinical production sites. In the context of developing a receptor-targeting radiopharmaceutical, this is an important result because starting with larger quantities of [^{18}F]F$^-$ will also increase the molar activity of the final product.

Table 1. Methods for acid-mediated deprotection of [^{18}F]**2**.

Entry	Reagent Added (Volume)	Time (min)	Temp (°C)	Conversion (%) [a]	DC-RCY (%)	Molar Activity [b] (GBq/μmol)
1	1:1 6 N H_2SO_4:MeOH (0.2 mL)	5	100	5	- [c]	-
2	1:1 6 N H_2SO_4:MeOH (0.2 mL)	10	150	86	- [c]	-
3	In(OTf)$_3$ [d] in H_2O (0.1 mL)	20	150	33, 35, 38 [e]	6, 5, 9 [e]	0.9, 0.7, 0.3 [e]
4	90% TFA (1 mL)	5	100	67	8	1.6
5	90% TFA (1 mL)	10	100	83	14	2.0
6	Yb(OTf)$_3$ [d]·xH_2O in H_2O (0.1 mL)	20	150	0	-	

[a] Assessed by HPLC. [b] Based on a mass standard curve. [c] [^{18}F]MCL-524 not isolated by HPLC due to the presence of convoluting chemical by-products. [d] 10 equivalents. [e] Individual experiments.

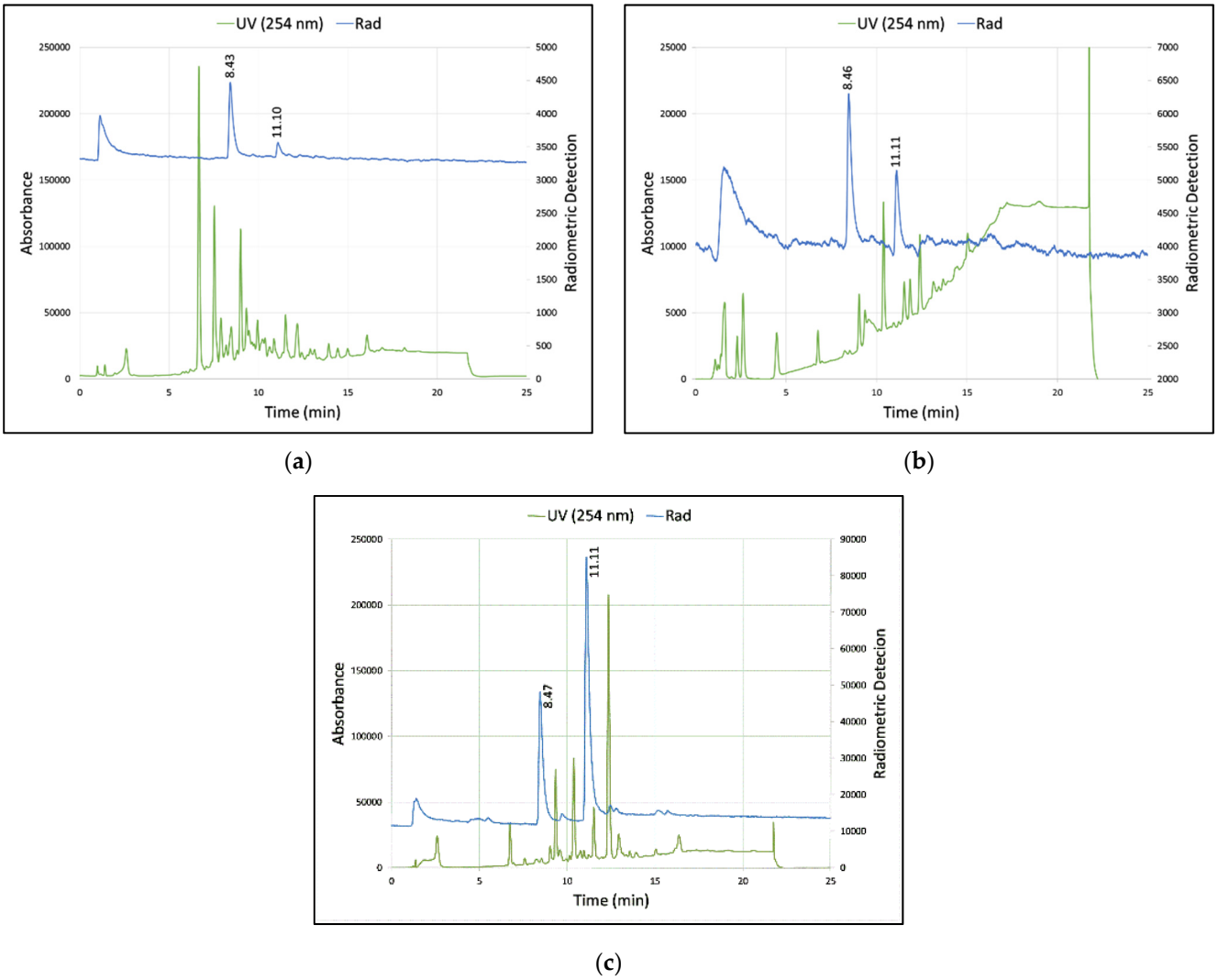


Figure 3. Representative radio-HPLCs of catechol deprotection reactions using: (**a**) 6 N H_2SO_4 (Table 1, Entry 2); (**b**) 90% TFA (Table 1, Entry (4); (**c**) $In(OTf)_3$ (Table 1, Entry (3)). [^{18}F]2 = ~11.1 min. [^{18}F]1 = ~8.4 min. See the Supporting Information for HPLC conditions (HPLC 1, Program A).

The results summarized in Table 1 suggest that 90% TFA is superior to $In(OTf)_3$ in terms of catechol deprotection. However, the increased deprotection efficiency observed using 90% TFA at 100 °C (5 or 10 min) did not result in substantially higher isolated RCYs of [^{18}F]**1**. It is likely that the improved deprotection yield obtained with 90% TFA (83% conversion over 10 min) is largely offset by the transfer and trapping losses associated with the additional SPE step required to extract the radiotracer from the concentrated acid reaction mixture prior to HPLC purification. Another Lewis acid, $Yb(OTf)_3$, was found to be ineffective for catechol deprotection under conditions identical to those employed with $In(OTf)_3$ (Table 1, Entry 6).

4. Discussion

Non-standard [^{18}F]F^- extraction and labeling conditions were used to prepare [^{18}F]MCL-524, a D_2 agonist that demonstrates a higher affinity activated state of the receptor. ^{18}F-fluorination reactions utilized tetraethylammonium tosylate as both the eluent to remove the [^{18}F]F^- from trap-and-release AEX columns and as the phase-transfer catalyst in reaction mixtures containing 97:3 MeCN:H_2O. Despite using non-anhydrous reaction conditions and relatively low masses of precursor (1 mg), the [^{18}F]F^- incorporation was >50%. This work provides further evidence that non-basic tetraalkylammonium salts and non-anhydrous

reaction conditions may lead to improvements in ^{18}F labeling protocols, which demand speed and operational simplicity for success.

The removal of the acetonide protecting group by treatment with the Lewis acid $In(OTf)_3$ in the presence of water produced overall yields of [^{18}F]MCL-524 similar to those obtained with 90% TFA, and both of these approaches yielded reaction mixtures that permitted the isolation of a chemically pure product by HPLC. However, in contrast to solutions containing concentrated protic acids, the $In(OTf)_3$ reaction mixture can be directly injected onto a semi-preparative HPLC column, eliminating the need for a solid-phase extraction prior to injection, and improving overall synthetic efficiency. This study suggests that Lewis acids may be an attractive alternative to protic acids for the syntheses of other ^{18}F-labeled compounds that might benefit from a milder reaction condition and/or simplified purification procedures.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/chemistry3030075/s1. General Information; Scheme S1: synthesis of non-radioactive precursor **3**; details related to the synthesis of precursor 3; Scheme S2: synthesis of MCL-524 (**1**); details related to the synthesis of standard **1**; Figure S1: example radio-TLC of intermediate [18F]**2**; Figure S2: co-injection of [18F]MCL-524 with 19F standard.

Author Contributions: Conceptualization, A.B.P.; data curation, J.A.H.I.; funding acquisition, A.B.P.; investigation, J.A.H.I., A.W.S., V.A. and A.B.P.; methodology, A.W.S. and J.L.N.; supervision, A.B.P.; writing—original draft, J.A.H.I.; writing—review and editing, A.W.S., V.A., J.L.N. and A.B.P. All authors have read and agreed to the published version of the manuscript.

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