

Automated Copper-Mediated Radiofluorination of [¹⁸F]SynVesT-1: a New Perspective in the Profiling and Control of Chemical Purity

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Abstract: Copper-mediated radiofluorination (CMRF) of arylstannanes has emerged as a powerful strategy for accessing fluorine-18 labelled radiotracers. Yet concerns regarding chemical impurity profiles remain insufficiently addressed. Here, we report the fully automated production of the clinically relevant synaptic vesicle glycoprotein 2A tracer [¹⁸F]SynVesT-1 on a GE FASTLab module, together with a systematic investigation of the associated impurity profile. Trimethyl- and tri(*n*-butyl)stannane precursors, as well as non-radioactive analytical standards for all major putative impurities were synthesized. Automated radiosynthesis afforded [¹⁸F]SynVesT-1 in 20-25% non-decay-corrected radiochemical yield, >99% radiochemical purity, and with preserved enantiomeric excess. Comprehensive UPLC-MS analysis revealed the formation of protodesstannylated, hydroxylated, methoxylated, and dimeric side products. Notably, the methoxy-substituted analogue was identified as the major chemical impurity. Systematic variation of fluoride preprocessing conditions and precursor structure demonstrated that both residual methanol and trimethylstannyl leaving groups contribute to methoxylation. Replacement of methanol by *n*-butanol during fluoride processing, combined with a tri(*n*-butyl)stannane precursor, dramatically improved chemical purity. Beyond [¹⁸F]SynVesT-1, these findings underscore the critical importance of thoroughly investigating the influence of all reaction parameters on the impurity profile in CMRF-based radiopharmaceutical production.

Introduction

In 1995, Pike *et al.* reported the use of diaryliodonium salts as radiolabeling precursors for the radiofluorination of electron-neutral to moderately electron-rich aryls.^[1,2] This seminal endeavor to open-up the chemical space of accessible substrates was followed in the early 2000's by a rapid expansion of novel aromatic ¹⁸F-fluorination methodologies.^[3–11] In particular, Makaravage *et al.* proposed to revisit the radiochemistry of arylstannanes to develop their use as precursors for nucleophilic radiofluorination instead of the previously established electrophilic protocols.^{[12],[13]} The copper mediated radiofluorination (CMRF) of arylstannanes stems from earlier studies involving arylboronic acid precursors.^[10,11] The methodology was also applied to the preparation of ¹¹C-labeled benzonitrile derivatives from aryl boronic acids and arylstannanes.^[14] Arylstannanes are attractive precursors notably due to their high shelf-life,^[15] facile preparation,^{[16],[17]} and reported high reactivity toward [¹⁸F]fluoride. This innovative approach was successfully tested for the production of several clinically relevant radiotracers such as [¹⁸F]FDOPA,^[18] [¹⁸F]flumazenil,^[19] and [¹⁸F]SynVesT-1.^[20,21]

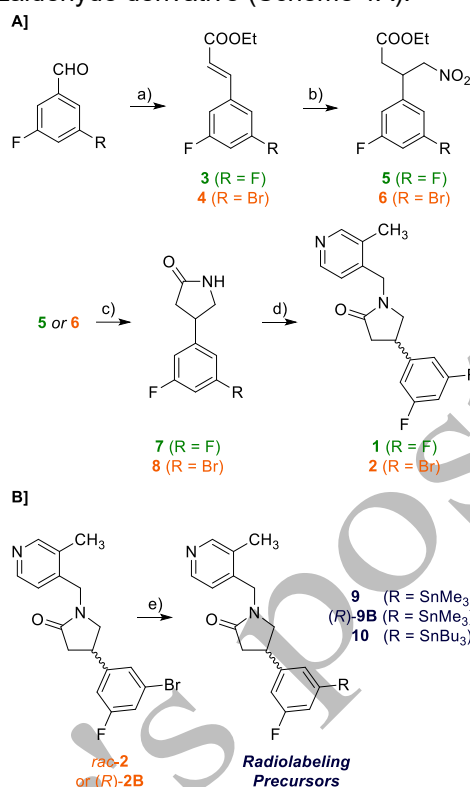
Though promising, the CMRF of arylstannane comes with its own challenges notably with regarding the chemical purity profile of radiotracers produced through this method.^[Haskali ref removed from here] Recently, competing protonation in CMRF has become the focus of several investigations involving borylated or stannane precursors.^[22–24] Additionally Haskali *et al.* proved the formation not only of the protodesstannylated derivative, but also of hydroxy- and dimeric derivatives while investigating the radiolabeling of [¹⁸F]Flumazenil;^[19] such closely related impurities may be problematic for clinical use as they will likely have similar pharmacological properties and may compromise the sensitivity and accuracy of the PET imaging. Intrigued by these results that could significantly limit the clinical potential of CMRF of arylstannanes, we sought to determine the origin of such impurities and identify key reaction parameters that could limit their formation in the first place. Given the clinical relevance of [¹⁸F]SynVesT-1 for imaging of neurological conditions,^[25–28] and that the most promising approach to obtain this tracer is relying on the CMRF of arylstannanes,^[20,21,29–31] we chose this radiolabeling of [¹⁸F]SynVesT-1 as prototypical example in the present study. Herein we report *i)* the synthesis of trimethyl- and tri(*n*-butyl)stannane precursors of [¹⁸F]SynVesT-1 as well as the analytical references of four putative impurities, *ii)* the automated

radiolabeling of [^{18}F]SynVesT-1 on a GE FASTLab module and *iii*) a thorough analysis of the influence of various reaction parameters on the chemical purity pattern.

Results and Discussion

Synthesis of Precursors and Analytical References

Both non-radioactive [^{19}F]SynVesT-1 **1** and bromide **2** were synthesized through a 4-steps *de novo* approach, starting from the corresponding benzaldehyde derivative (Scheme 1A).

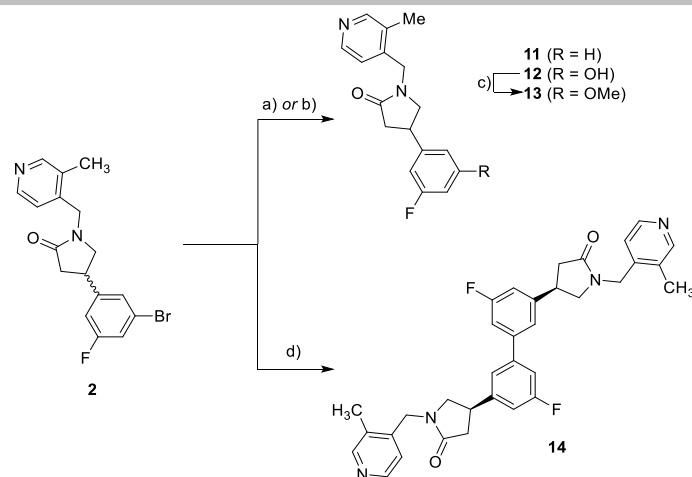


Scheme 1: Synthesis of non-radioactive [^{19}F]SynVesT-1 **1**, bromide **2** and radiolabeling precursors **9** and **10**. *Reagents and conditions:* **3** (R = F) and **4** (R = Br): a) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$, CH_2Cl_2 , 0°C , 2h; **5** (R = F) and **6** (R = Br): b) CH_3NO_2 , DBU, -20°C , 2h; **7** (R = F) and **8** (R = Br): c) Fe powder, NH_4Cl , water-EtOH mixture (1:2), 3h, 60°C ; **1** (R = F) and **2** (R = Br): d) 4-(chloromethyl)-3-methylpyridine hydrochloride, NaH, TBAI, THF, 20°C , 20h; **9**, (R)-**9B** (R = SnMe₃) or **10** (R = SnBu₃): e) Sn_2Me_6 or Sn_2Bu_6 , LiCl, $\text{Pd}(\text{PPh}_3)_4$, toluene, 110°C , 1h or 24h.

Briefly, the sequence consisted of a Wittig reaction to afford cinnamic ethyl esters **3** and **4** in 72% and 83% yield, respectively. Subsequent Michael addition of nitromethane afforded nitro-derivatives **5** and **6** in 85% and 84% yield, respectively. These materials were submitted to a tandem reduction/lactamization reaction to afford lactams **7** and **8** in 81% and 62%, yield respectively. Subsequent *N*-alkylation of these lactams afforded the target fluorinated and brominated compounds **1** and **2** in 64% and 85% yield, respectively. Overall, the proposed synthetic strategy proved efficient and straightforward, albeit quite time-consuming, affording products **1** and **2** with overall yields of 32% and 38%, respectively, over four steps. Noteworthy, all intermediates were obtained in sufficient purity after liquid/liquid extractions and only the last step in the sequence required column chromatography purification; this contributes to the high efficiency of the process as well as to our efforts in reducing the environmental impact of the experiments. SynVesT-1 being enantiopure, we carried out a chiral separation on **1** to afford (R)-**1B**; anticipating the need for enantiopure radiolabelling precursors, brominated derivative (R)-**2B** was similarly obtained. Details on the chiral separation methodology are given in the Supplementary Information.

Target radiolabelling precursors were subsequently synthesized by Pd-catalysed stannylation of **2** using hexamethyl- or hexabutylditin to afford trimethylstannane **9** and tri-(*n*-butyl)stannane **10** in 28% and 34% yield, respectively (Scheme 1B). Similarly, enantiopure trimethylstannane (R)-**9** was obtained from (R)-**2B** in 52% yield. Overall, stannylation reactions resulted in modest isolated yields, though enough material could be obtained to carry out all radiolabeling experiments and no further optimization was attempted.

We then designed a practical synthetic approach where all SynVesT-1's analogues **11**, **12**, **13** and **14** could be accessed from key intermediate bromide **2** (Scheme 2).



Scheme 2: Synthesis of analytical references of putative impurities. *Reagents and conditions:* **11** (R = H): a) *n*-BuOH, K₂CO₃, Pd(PPh₃)₄, 100 °C, 2 h, 56%; **12** (R = OH): b) Benzaldehyde oxime, Cs₂CO₃, Pd(II)*t*-BuBrettPhos, DMF, 80 °C, 18 h, 67%; **13** (R = OMe): c) MeI, Cs₂CO₃, DMF, 20 °C, 40 min, 83%. Dimer **14**: d) Sn₂Me₆, LiCl, Pd(PPh₃)₄, toluene, 110 °C, 18 h, 47%. *Note:* **14** was obtained from the enantiopure (*R*)-**2** whilst all other products were synthesized from *rac*-**2**.

Building upon a literature protocol,^[32] desfluoro derivative **11** was synthesized via palladium catalyzed debromination of aryl bromide **2**. Using tetrakis(triphenylphosphine) palladium 0 as catalyst and *n*-BuOH as both solvent and hydrogen donor, the proton-debromination reaction proceeded with an isolated yield of 56%. Hydroxy-substituted analogue **12** was synthesized adapting a protocol from Fier and Malonney^[33] using *t*-BuBrettPhos Palladium G3 as catalyst and benzaldehyde oxime as hydroxy-group donor in mildly basic conditions. With these conditions, **12** was isolated with a yield of 67%. Methoxy-derivative **13** was easily obtained from the reaction of **12** with iodomethane,^[34] affording the target product in 83% yield. Finally, dimer **14** was obtained *via* a Stille coupling for which the stoichiometry was adapted to use only 0.5 equivalent of distannane in relation to aryl bromide **2B**.^[35] Target product **14** was obtained in 47% yield. The various analytical references were analyzed by ULPC-MS and calibration curves were obtained for each product in the range 0.5-30 µmol/mL (see Supporting Information for more details on the methodology and quantification performance).

Automated Radiolabeling of [¹⁸F]SynVesT-1

Having synthesized the precursors, we sought to develop an automated radiolabeling of [¹⁸F]SynVesT-1 on a GE FASTLab module connected to an in-house semi-preparative HPLC system (Supporting Information, Figure S4 and S6). A fully automatic process was programmed to allow the radiolabeling to proceed without operator intervention; the HPLC injection and collection valves however remained manually operated. The process followed a typical ¹⁸F-labelling flowchart (Figure 1).

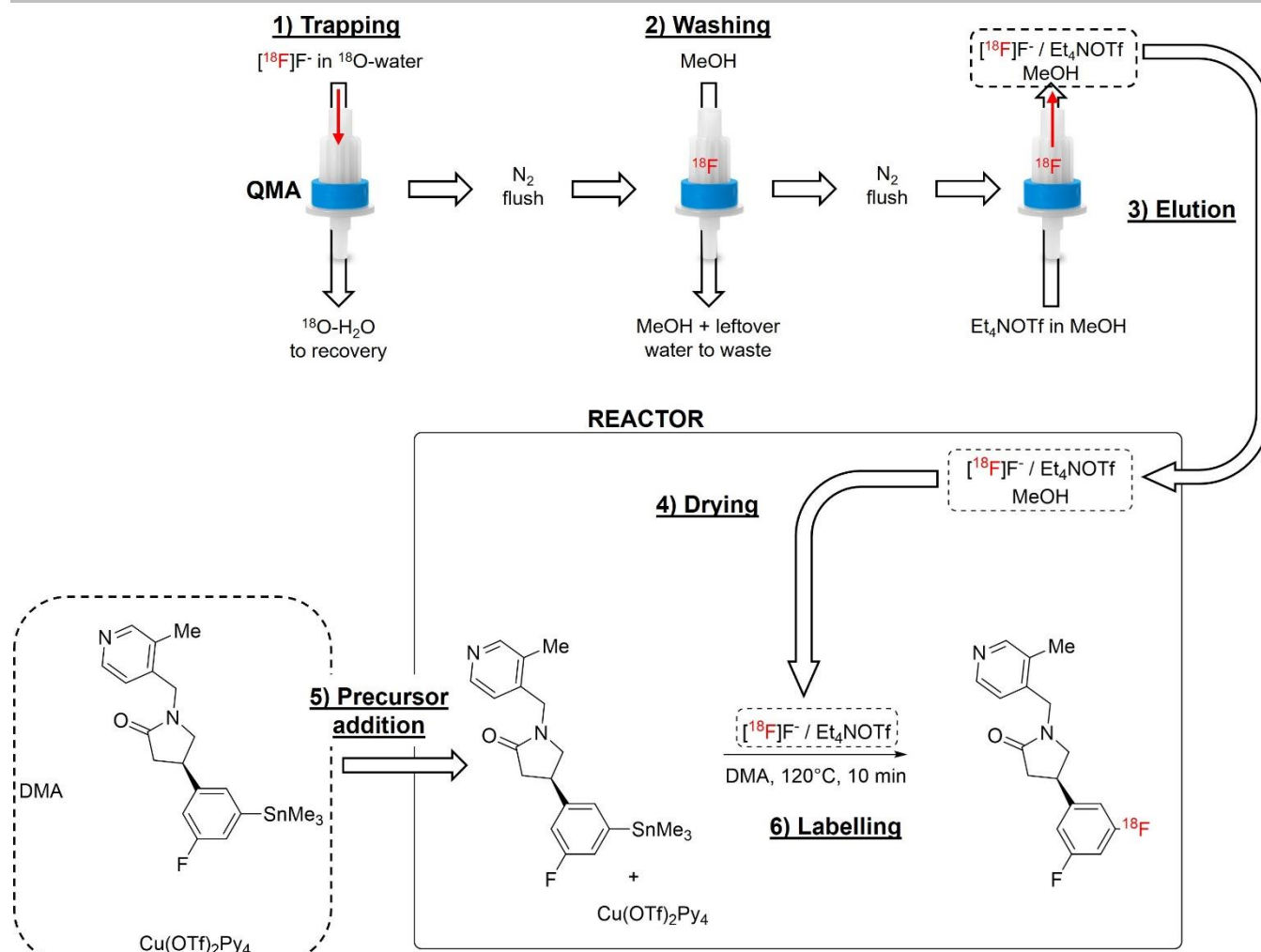


Figure 1: Flowchart of the automated radiolabeling of $[^{18}\text{F}]$ SynVesT-1. Radiolabeling conditions: 22 μmol (*R*)-**9B**, 44 μmol $\text{Cu}(\text{OTf})_2\text{Py}_4$, DMA, 120°C , 10 min.

Briefly, after reception of the activity from the cyclotron, raw $[^{18}\text{F}]$ fluoride in ^{18}O -water was pre-processed by purification/concentration on a Solid Phase Extraction (SPE) Quaternary Methyl Ammonium (QMA) cartridge (Figure 1, steps 1-3) followed with a rapid drying (Figure 1, step 4). A premixed solution of the arylstannane precursor and tetrakis(pyridine)copper(II) triflate in dimethylacetamide (DMA) was subsequently added and the reaction was heated for 10 minutes (Figure 1, steps 5-6). After cooling the crude material was filtered over a tC18 SPE cartridge to eliminate copper salts and the released material was purified by semi-preparative HPLC (acetonitrile/water 30:70). The collected pure fraction was reformulated using a second tC18 SPE cartridge to eventually afford pure $[^{18}\text{F}]$ SynVesT-1 in 0.9% saline.

Pre-processing of $[^{18}\text{F}]$ fluoride is critical in any radiofluorination process; over the years, numerous variations have been proposed to optimize and speed-up this necessary step.^[18,36–41] Here we chose the so-called “*minimalist*” protocol described by Zarrad et al. in which, once the $[^{18}\text{F}]$ fluoride is trapped on the QMA, the cartridge is washed with anhydrous methanol before being released in the reactor with a methanolic solution of tetraethylammonium triflate (TEAT).^[18] Our first attempt at this protocol resulted in a disappointingly low recovery from the QMA with more than 15% of the initial activity remaining on the cartridge. This was easily fixed by modifying the QMA pre-conditioning protocol, adding a thorough water wash and nitrogen flush after pre-conditioning of the cartridge with 0.1M TEAT aqueous solution (see Supporting Information); implementing this new protocol allowed the QMA recovery to reach > 95%, thereby highlighting the equally critical importance of proper QMA conditioning for CMRF.

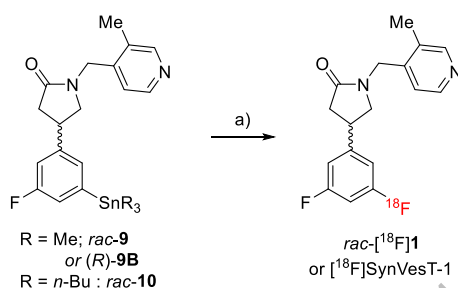
Having established a reliable “*minimalistic*” $[^{18}\text{F}]$ fluoride pre-processing, we carried-out a rapid screening of what we hypothesized to be the main reaction parameters, i.e. precursor load, copper load and temperature. We found that the radiochemical conversion (RCC) increased with increasing trimethylstannane precursor **9** load up to 22 $\mu\text{mol}/\text{mL}$ (i.e. 10 mg/mL); higher loads did not yield any appreciable gain in RCC and we therefore adopted a precursor loading of 22 $\mu\text{mol}/\text{mL}$ for the rest of the study (Supporting Information, Figure S8). Switching to the copper loading, we observed that sub-stoichiometric amounts led to a dramatic drop in RCC (23-25% with 0.7 equivalent) whilst increasing from 1.3 to 2.0 equivalents yielded a marginal increase, with RCC increasing from

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50±4% (*n* = 5) to 49-56% (*n* = 2) (Supporting Information, Figure S9). This confirms previous reports that the reaction is not *catalysed* but indeed *mediated* by the copper salt as it requires stoichiometric amounts to proceed efficiently.^[18,42,43] Based on these observations, we selected a copper load of 2.0 equivalents for the rest of the study. Finally, reducing the temperature from 120 °C to 100 °C proved detrimental with radiochemical yields (RCY) post-HPLC decreasing from 25% to 19% non-decay corrected (n.d.c.). We therefore chose to keep the radiolabelling temperature to 120 °C without further optimisation.

To finalize the development of the automated radiolabeling process of [¹⁸F]SynVesT-1 and verify its robustness toward variations, the full radiosynthesis was carried-out at large scale using the aforementioned reaction conditions; the experiments were run with both racemic trimethylstannane precursor **9** and the enantiopure (*R*)-**9B** (Table 1).

Table 1: Automated radiosynthesis of [¹⁸F]SynVesT-1 at high activity



Entry	QMA washing solvent	QMA elution solvent	Precursor	Starting activity (GBq)	RCY ^a (n.d.c.)
1	MeOH	MeOH	<i>rac</i> - 9	159	25%
2	MeOH	MeOH	(<i>R</i>)- 9B	137	20%
3	MeOH	<i>n</i> -BuOH	<i>rac</i> - 9	159	26%
4	MeOH	<i>n</i> -BuOH	(<i>R</i>)- 9B	137	24%
5	<i>n</i> -BuOH	<i>n</i> -BuOH	<i>rac</i> - 9	52-159	21±1% ^b
6	<i>n</i> -BuOH	<i>n</i> -BuOH	<i>rac</i> - 10	1.69	17%

Reagent and Conditions: a) Precursor (1 equiv., 22 μmol), Cu(OTf)₂Py₄ (2 equiv., 44 μmol), DMA, 120 °C, 10 min. ^aAll RCY's are referring to the final product after HPLC purification and reformulation. ^bReaction run in triplicate.

Starting from 137-159 GBq, both runs allowed the isolation of the pure target radiotracer in 20-25% n.d.c. RCY after HPLC purification and reformulation (Table 1, entries 1-2). The process duration was approx. 80 min, giving an activity yield (AY) of 27-40 GBq. The radiochemical purity (RCP) was > 99% at end-of-synthesis and remained stable over the course of 4 hours, with the product showing no sign of degradation in this formulation and that level of activity. Interestingly, the process proved tolerant toward variation in the nature of the alcohol used for the [¹⁸F]fluoride pre-processing; isolated RCY were essentially identical whether methanol was used (Table 1, entries 1-2), *n*-butanol (Table 1, entries 5-6) or a combination of both (methanol for the initial QMA wash and *n*-butanol for the release of [¹⁸F]fluoride; Table 1, entries 3-4). We also verified that [¹⁸F]SynVesT-1 did not undergo racemization under the relatively harsh reaction conditions.^[21] The final products obtained from the enantiopure precursor (Table 1, entries 2 and 4) were therefore analyzed by chiral HPLC which confirmed the enantiomeric ratio to be > 99:1 (Supporting Information Figure S14). As expected, no significant difference was observed in reactivity between the racemic precursor (Table 1 entries 1, 3 and 5) and the enantiopure one (Table 1, entries 2 and 4). Finally, tributylstannane precursor **10** afforded the target radiotracer *rac*-[¹⁸F]**1** in 17% RCY (Table 1, entry 6), similar to the 21±1% RCY obtained with the trimethylstannane precursor under the very same conditions (Table 1, entry 5).

Overall, the automated process herein described proved reproducible, affording the target radiotracer - be it racemic or enantiopure- in approx. 20% n.d.c. RCY, and tolerant of slight deviation in terms of QMA processing and nature of the arylstannane used.

Investigation of the impurity profile

Having developed a reliable automated process for the CMRF of [^{18}F]SynVesT-1 and synthesized all non-radioactive analytical reference of putative chemical impurities, we next focused on thoroughly investigating the impurity profile of the final product. Starting with UPLC-MS analysis, we first noticed that neither the MS nor the UV signature of the arylstannane precursor **9** could be found in any of the samples. This observation is in line with the previous report of Haskali et al. who suggested that, under the radiolabeling conditions, the precursor could degrade and form side-products variously substituted at the labelling position.^[19] The UPLC-MS however revealed the presence of five recurrent impurities with m/z ($[M + H]^+$) equal to 285, 301, 303, 315, and 567. We hypothesized that the first four m/z could match that of SynVesT-1 analogues where the ^{18}F atom is replaced by, respectively, a proton, a hydroxyl, a ^{19}F , and a methoxy. As for the last m/z (567) it could match the formation of a homodimer. To confirm our hypothesis, we synthesized and co-injected each of these putative impurities (Figure 2).

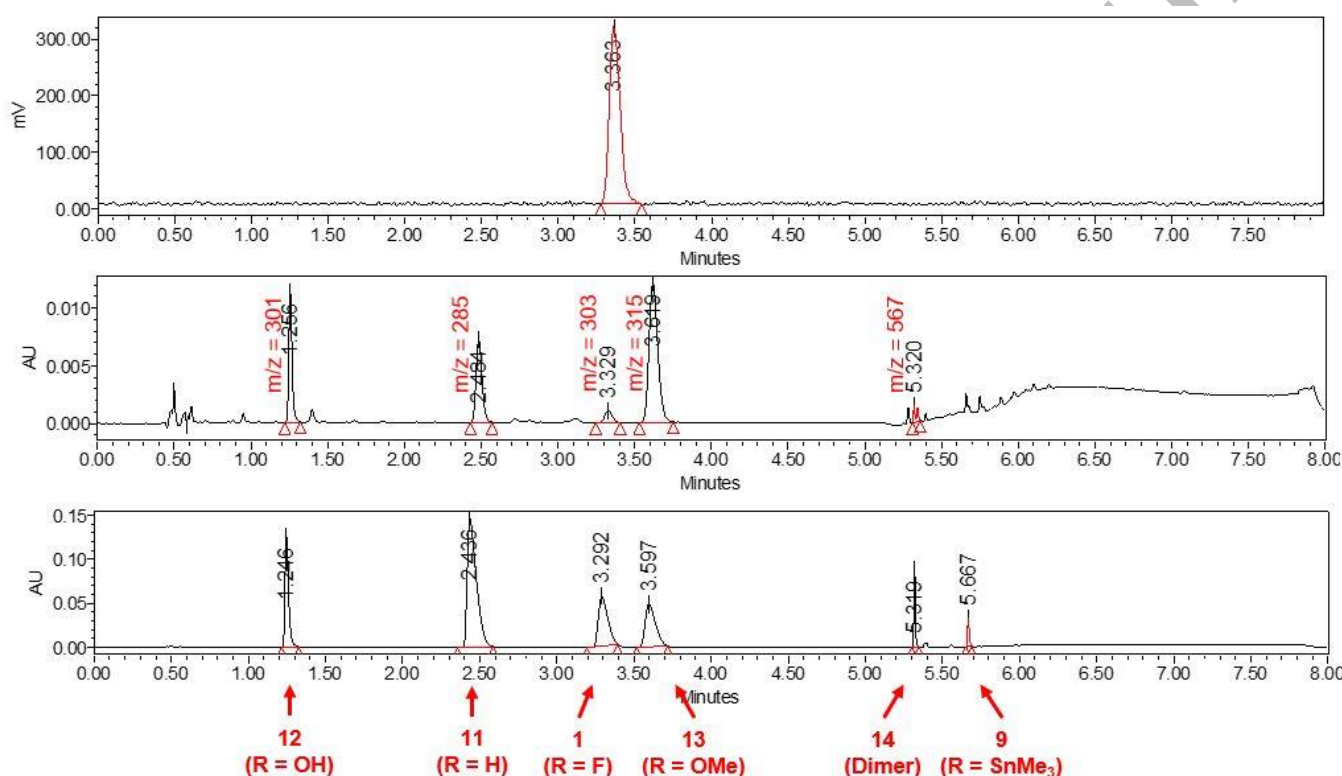


Figure 2. Identification of non-radioactive impurities in a typical final product solution of [^{18}F]SynVesT-1. Top Chromatogram: typical radioactive trace of final product; Middle chromatogram: typical UV trace of final product with corresponding m/z ratios; Bottom chromatogram: UV trace of a combined sample containing all synthesized analytical references.

Gratifyingly, we observed a perfect correlation between the retention time of the synthesized analytical references **12**, **11**, **1**, and **13** and that of the main impurities that were observed on a typical chromatogram of isolated [^{18}F]SynVesT-1 (Figure 2, middle and bottom chromatograms). As for dimer **14**, we were unable to confirm its presence; despite our best efforts, we could not find suitable elution conditions that could resolve the multitude of trace impurities in the region where this product eluted. Under previously established standard conditions, i.e. QMA processed with methanol and trimethylstannane precursor, the major impurity was found to be methoxy-substituted **13**, accounting for almost 10-fold the amount of non-radioactive SynVesT-1 **1** (Table 2, entry 1). Importantly, **13** is eluting extremely close to **1**, posing the risk of being undetected or underestimated should the elution conditions and resolution be suboptimal. Amongst the other identified impurities, proton- and hydroxyl- substituted analogues were found in amounts approx. 2-folds higher than non-radioactive SynVesT-1 (Table 2, entry 1).

Table 2: Quantification of chemical impurities in samples of [^{18}F]SynVesT-1 and corresponding molar activities

Entry	1	2	3	4
QMA washing solvent	MeOH	MeOH	<i>n</i>-BuOH	<i>n</i> -BuOH
QMA elution solvent	MeOH	<i>n</i>-BuOH	<i>n</i> -BuOH	<i>n</i> -BuOH
Precursor stannyl-group	SnMe ₃	SnMe ₃	SnMe ₃	Sn(<i>n</i>-Bu)₃
n.d.c. final activity (GBq)	27.2	33.7	21.2	0.29
12 (R = OH) content (nmol)^a	40	74	31	48
11 (R = H) content (nmol)^a	45	159	39	72
1 (R = F) content (nmol)^a	18	23	15	23
13 (R = OMe) content (nmol)^a	100	241	11	< LOD ^d
Total organic content (nmol)^a	203	497	96	143
Molar activity (GBq/μmol)^b	134	68	220	n.d.

^aMass of organic impurity in the total volume (10 mL) of product; ^bApparent A_m (molar activity) was calculated by dividing the n.d.c. final activity by the Total organic content and was converted in GBq/ μmol . ^dLimit of detection for **13** is 1 nmol. Text in red corresponds to the parameter which is altered from the standard conditions of Column 1.

Intrigued by this impurity profile, in particular by the large amount of methoxy-substituted impurity **13**, we sought to analyze the chemical purity of the final product solution obtained with variation in the QMA processing and arylstannane type (Table 2, entries 2-4). Indeed, we hypothesized that, although it should be completely evaporated before the radiolabeling starts, the methanol used in the QMA processing could be at the origin of methoxy-substituted impurity **13**. Unfortunately, this was not verified when only the QMA elution solvent was switched to *n*-butanol, keeping methanol as QMA washing solvent (Table 2, entry 2). However, when *n*-butanol was used in both steps, i.e. washing and elution, the relative amount of **13** was divided by 10 as compared to non-radioactive SynVesT-1 **1**, decreasing from 100 nmol to 11 nmol (Table 2, entry 3 vs 1). To our delight, we observed that when tributylstannane **10** was used as precursor in conjunction to *n*-butanol as QMA-processing solvent, the formation of methoxy-substituted impurity **13** was entirely abolished (Table 2, entry 4). The combination of these two observations seems to point toward a dual origin for the formation of methoxy-substituted impurity **13**: i) the effect of trace amount of methanol and, ii) the effect of methyl-groups from the trimethylstannane leaving group. The former may be explained by traces of methanol giving rise to nucleophilic methanolate anions which could potentially displace the trimethyltin forming a methoxy-ether bond; although unlikely to occur under “normal” condition, this reactivity may be possible under the harsh conditions of the radiolabeling. The second origin, i.e. from the trimethylstannane itself is more elusive; demonstration of the exact mechanism at play would require further investigations out of the scope of the present study. Importantly, the *n*-butoxy-substituted impurity analogue to **13** was not observed by LC-MS; this suggests that the mechanism at play to produce **13** is not occurring when *n*-butylated reagents (stannane and solvent) are used.

Overall, here we have identified and characterized all impurities formed during the CMRF of [^{18}F]SynVesT-1, with the major one being methoxy-substituted analogue **13**. We have empirically determined what could be the main parameters to mediate the formation of this impurity as the methanol used in QMA processing and the trimethylstannane itself. The best overall chemical purity was achieved when *n*-butanol was used as processing solvent, both for QMA washing and elution; when tri(*n*-butyl)stannane **10** was used in conjunction, the formation of methoxy-substituted analogue **13** was entirely abolished.

Conclusion

In conclusion, we have developed a fully automated production process of [^{18}F]SynVesT-1 on GE FASTLab synthesizer, with a comprehensive investigation and verification on the final product quality. We have demonstrated that the CMRF of [^{18}F]SynVesT-1 from arylstannane precursors give rise to several major chemical impurities. In addition to protodestannylation and hydroxylation, the formation of a methoxy-substituted analogue was found to be of major importance. Our experimental results point toward a dual origin for the observed methoxylation: i) the methanol used in the so called “minimalistic” fluoride processing methodology proposed by Zarrad et al. and, ii) methyl residues on the trimethylstannyl leaving group. *In fine*, a dramatic improvement of the chemical purity, and thus in molar activity, was achieved when the tri(*n*-butyl)stannane precursor was used in conjunction with *n*-butanol instead of methanol in the [^{18}F]fluoride preprocessing step. Besides the specific case of [^{18}F]SynVesT-1, this study should also serve as a stark reminder on the critical importance of thoroughly investigating and reporting the impurity profile of any novel radiolabeling protocol for imaging application.

Supporting Information

Experimental details as well as the FastLab developer sequence are available in Supporting Information. The authors have cited additional references within the Supporting Information.^[44–50]

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Keywords: Radiolabeling • Arylstannane • Fluorine-18 • Radiopharmaceutical • Quality Control

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