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Development of a Novel Route for Incorporation of Carbon-14 into the Pyridine Ring of Rinskor Active

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Supporting Information

ABSTRACT: Rinskor active is a new 6-arylpicolinate herbicide that is used for postemergent control of grass, broadleaf, and sedge weeds in rice and other crops. In order to register a new herbicide, carbon-14-labeled radiotracers of the active ingredient are required to track the parent along with the metabolites and degradants formed in the environment. This paper discusses the novel route that was used to incorporate carbon-14 into the pyridine ring of Rinskor to support registration studies.

KEYWORDS: *Rinskor active, auxin, herbicide, carbon-14, radiotracer*

INTRODUCTION

The control of weeds is critical for increasing the quality and yield of crops in the agricultural industry. Competition for nutrients by weeds can severely inhibit the productivity of food production. The discovery of 2,4-D, the first auxinic herbicide, in the 1940s provided a novel solution for the control of key weeds in many important crops (i.e., wheat, maize, rice). The history of auxin herbicides at Dow Chemical and Corteva Agriscience is long and interesting, and this is particularly true of the picolinic acid-derived auxin herbicides. Picloram, the first picolinic acid-derived auxin herbicide introduced by Dow, was discovered in the late 1950s[1] (Figure 1). Research in this area of chemistry soon led to the discovery of clopyralid[2] in the 1960s and eventually led to the discovery of aminopyralid[3] almost 40 years later. The discovery of aminopyralid catalyzed intense structure−activity relationship (SAR) studies around the picolinic acid herbicides that eventually led to the discovery of the 6-arylpicolinate Arylex active, which exhibits very potent activity against a wide variety of targeted weed species.[4−6] Arylex was launched by Dow AgroSciences in 2014 for postemergent control of broadleaf weeds in cereals and other crops.

Auxin herbicides cause physiological changes normally associated with the natural plant hormone indole-3-acetic acid.[7] The phenotypic effects caused by auxin herbicides include stem and leaf twisting due to uncontrolled growth, abnormal root growth, and eventual plant death several weeks after application. Dicot plants are usually more susceptible to auxinic herbicides than monocot plants.[8] It is important to note that the complex mode of action associated with auxin herbicides has resulted in low levels of resistance in comparison with other herbicide modes of action.

Continued SAR study efforts around the 6-arylpicolinates eventually led to the discovery of Rinskor active (**1**) (Figure 2).[5,6] Rinskor is related to Arylex, with differences being a fluorine atom at the 5-position of the pyridine ring and a benzyl ester as opposed to the methyl ester. Rinskor is used for the postemergent control of grass, broadleaf, and sedge weeds in rice and other crops, which is a different market than that of Arylex. Rinskor has a very low use rate (5−50 g of active ingredient/hectare). It has a favorable environmental and toxicology profile and shows rapid degradation in soil and plants.

To support registration of a new crop protection product, over 100 core regulatory studies are conducted to evaluate its potential effects on the environment and humans.[9] These studies include plant and mammalian metabolism, soil degradation, hydrolysis, and UV photolysis. Identification of a persistent metabolite or degradant from these studies might trigger additional studies to understand its fate and evaluate any safety concerns. To track and quantify the fate of an active ingredient and the resulting metabolites/degradants, regulatory agencies around the world require that studies be performed with carbon-14-labeled analogues of the parent. The carbon-14 label needs to be incorporated at a metabolically stable position (usually an aromatic ring) in the molecule so that the radiotracer is not lost during the study. Placement of the label is done in a defined position, which further aids in elucidation of metabolites/degradants. If multiple aromatic rings are present, it is preferred that each ring be labeled independently. Key attributes of the carbon-14 radioisotope include the following: (1) it has a long half-life (5730 years); (2) data obtained from the studies are reliable, as all of the radioactivity can be tracked; (3) it has an extremely low detection limit, which allows for the identification of metabolites and degradants at levels that could not be detected with a nonlabeled parent; and (4) it is a low-energy β emitter that does not pose an external dose hazard to researchers handling the labeled material.

To support the regulatory studies of Rinskor, all three aromatic rings had to be labeled independently. Herein we describe the synthesis of an analogue of Rinskor with a carbon-14-labeled pyridine ring.

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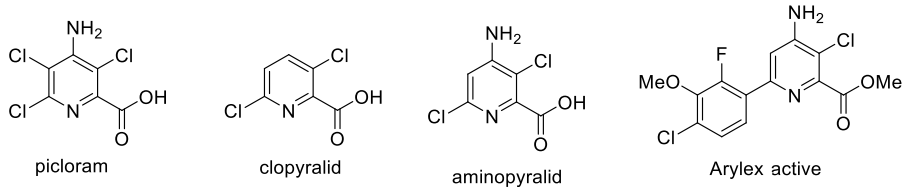

Figure 1. Picolinic acid-related auxin herbicides.

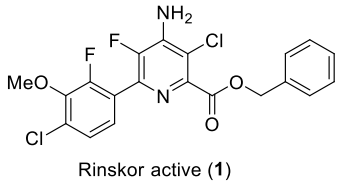

Figure 2. The 6-arylpicolinate herbicide Rinskor active (**1**).

RESULTS AND DISCUSSION

First Synthetic Route to Rinskor-Py-2,6-^{14}C (8). For early-stage environmental fate and metabolism studies, only small quantities (<10 mCi) of a radiotracer are required. For incorporation of carbon-14 into the pyridine ring of **1**, we envisioned that we could use the route that we developed for the preparation of the radiotracer picloram-2,6-^{14}C (**2**),[11] which can be accessed in 10 steps starting from K^{14}CN (Figure 3). Electrolysis of **2** would afford aminopyralid-2,6-^{14}C (**3**). Incorporation of a fluorine at the 5-position of the pyridine ring via electrophilic fluorination would give access to **4**. Finally, Suzuki–Miyaura cross-coupling would provide **8** in a total of 16 linear steps.

The route used to access **2** was well-established,[10,11] along with the electrolysis step to achieve **3**.[12−14] For the challenging key electrophilic fluorination step, a variety of electrophilic fluorination reagents were explored, and Selectfluor (F-TEDA) provided the desired product, albeit in low yield (Scheme 1).[15] The low yield was attributed to incomplete reaction and formation of **2**, presumably resulting from pyridine ring opening and chlorination of the starting material **3**.[15] The fluorinated picolinic acid was then converted to methyl ester **5** for the subsequent Suzuki–Miyaura cross-coupling with boronate ester **6**. Methyl ester **7** was then hydrolyzed, and the resulting acid was converted to the benzyl ester, Rinskor-Py-2,6-^{14}C (**8**). Of note, early results had shown that the methyl ester was a better coupling partner than the benzyl ester in the Suzuki–Miyaura cross-coupling reaction. This route to **8** was not only long (16 linear steps) but also low-yielding overall (1%, 0.6 mCi, 4 mg). In addition, this route introduced the radioisotope in the first step of a 16-step sequence, which is undesirable from a handling and cost perspective. To support additional registration studies of **1**, >100 mCi of a pyridine-labeled standard was required, and therefore, this route was not amenable to support all of the registration studies for **1.** Ultimately, an alternative route had to be identified quickly to prepare large quantities of **1**.

Novel Cyclization Route to Rinskor (1). During our investigations to identify new routes to access **1**, a paper was published on the preparation of polysubstituted 5-fluoropyridines utilizing cascade cyclization of primary amines and fluoroalkyl alkynylimines (Scheme 2).[16]

We envisioned that **1** could be accessed using this method and proposed the retrosynthetic route shown in Scheme 3. The key to the success of this route relied on identifying a suitable amine protecting group for **9** and a propiolic acid derivative **11** to give alkynylimine **12**. Cyclization of alkyne **12** with benzylamine **13** would give rise to the desired framework for **1**.

Initially, we examined the key cyclization step to obtain **16** using 4-chlorobenzylamine (**15**) for route optimization and screened various protecting groups for **12**. After an extensive optimization process (Scheme 4), we determined that **12** protected with *N*-trityl (R_1) and diethyl acetal (R_2) can undergo the desired cyclization with **15** to give **16** using cesium carbonate as the base and dimethyl sulfoxide (DMSO) as the solvent at a reaction temperature of 80 °C.[18] It is worth mentioning that these conditions also resulted in expanding the SAR by allowing novel analogues to be prepared by the Discovery Chemistry group.[17,18]

With optimal cyclization conditions in hand, we focused on the synthesis of **1**[17] to confirm that this route indeed would be

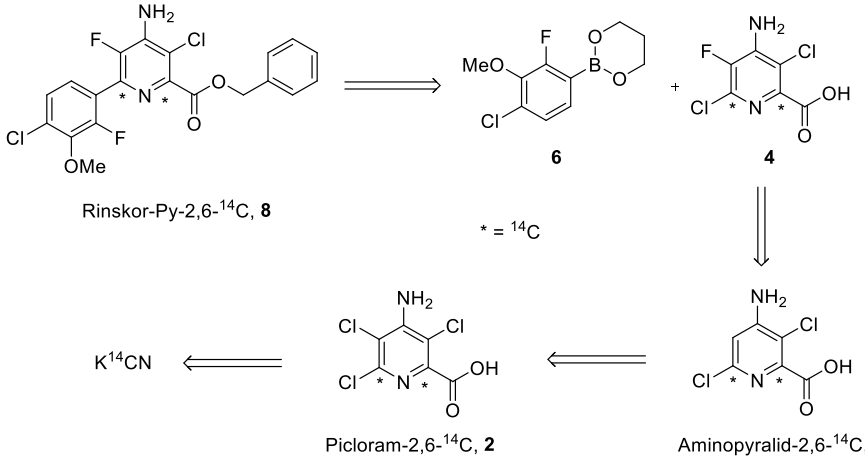

Figure 3. Retrosynthesis of Rinskor-Py-2,6-^{14}C (**8**).

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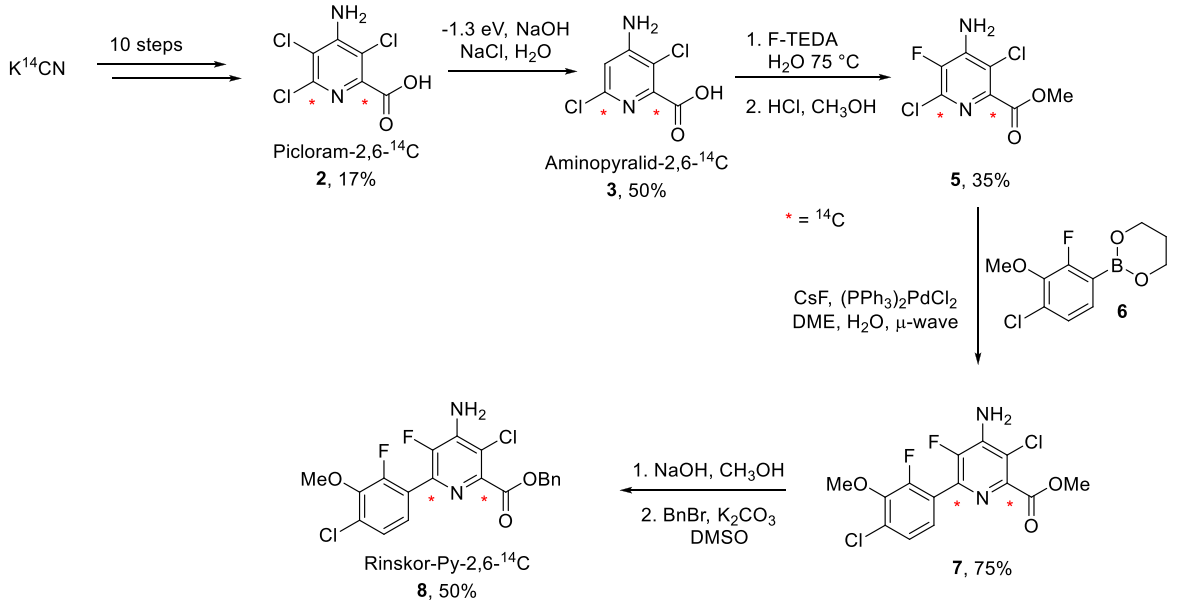
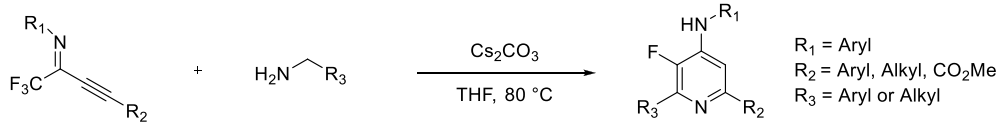
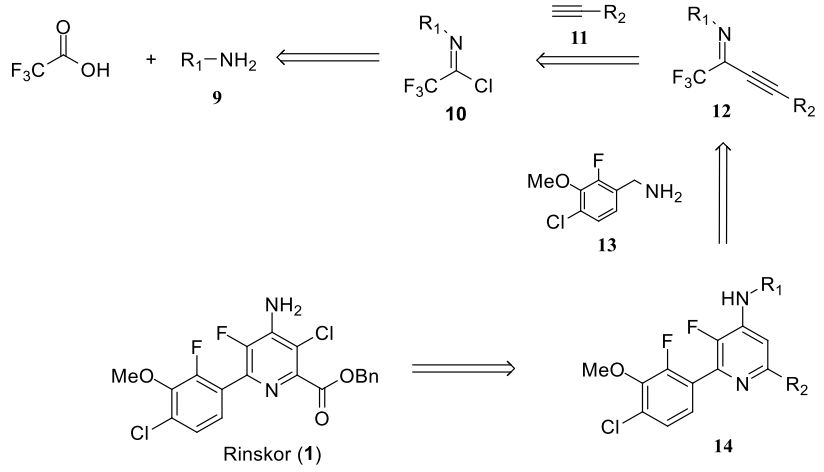
Scheme 1. First Synthetic Route to Rinskor-Py-2,6-^{14}C (8)



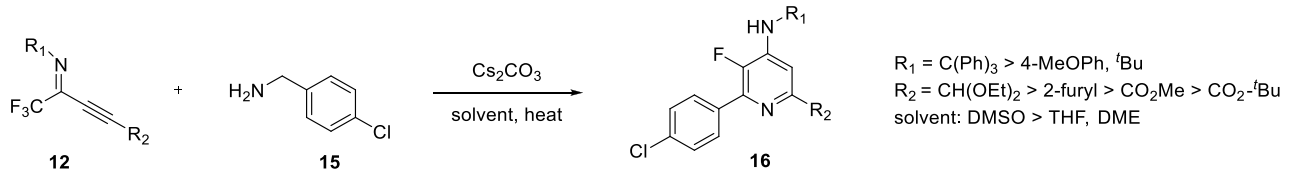
Scheme 2. Synthesis of Polysubstituted 5-Fluoropyridines via Cascade Cyclization



Scheme 3. Retrosynthetic Route to 1 Using a New Cyclization Approach



Scheme 4. Optimization of Cascade Cyclization for Rinskor



viable for incorporation of carbon-14 into the pyridine ring. Alkyne intermediate **18** was prepared by a two-step process starting from commercially available tritylamine (Scheme 5). Treatment of tritylamine with trifluoroacetic acid, triphenylphosphine, and triethylamine in carbon tetrachloride provided imidoyl chloride **17** in good yield.[19] Sonogashira cross-coupling of imidoyl chloride **17** with propargyl aldehyde diethyl acetal gave the key alkyne intermediate **18** in 65% yield. The other key intermediate, benzylamine **13**, was prepared by a two-step process starting from benzaldehyde **19**, which was prepared by a published route.[20] The benzaldehyde was converted to *O*-methyl oxime derivative **20**, which was then

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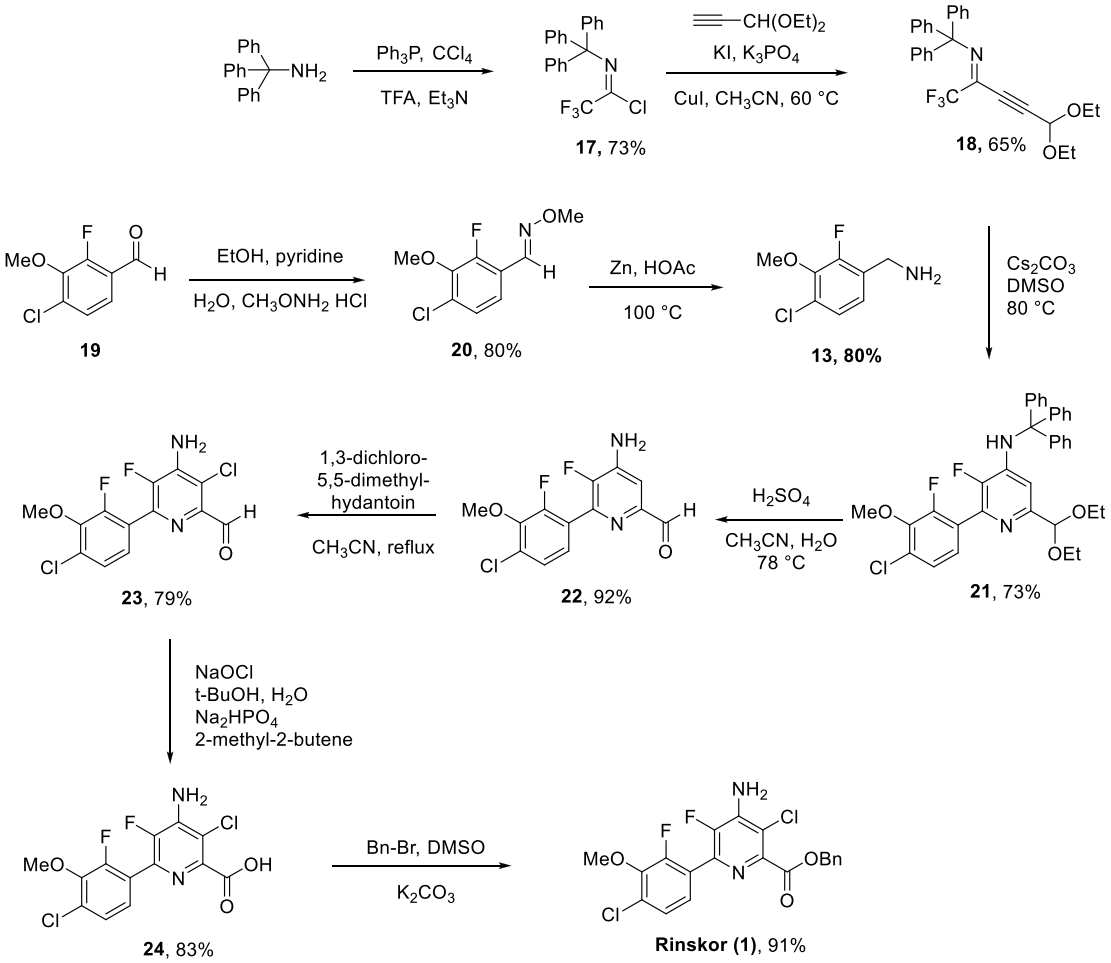
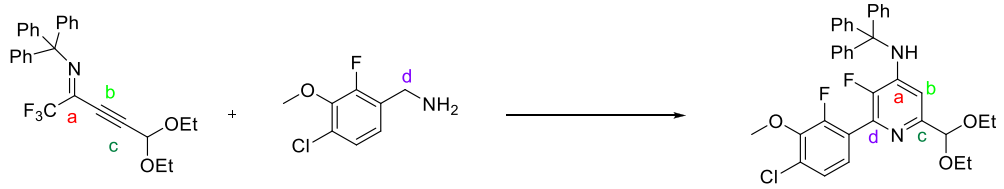
Scheme 5. Novel Cyclization Route to 1



Scheme 6. Labeling Options (a–d) for Incorporation of Carbon-14 into the Pyridine Ring



reduced to the desired benzylamine **13** with zinc in acetic acid.[21]

With the key intermediates **13** and **18** in-hand, the final steps to **1** were initiated (Scheme 5). Cyclization of benzylamine **13** with alkyne **18** gave cyclized product **21** in 73% yield. The trityl and acetal protecting groups were removed in one step to afford 4-aminopyridine-2-carboxaldehyde **22** in excellent yield. Selective chlorination at the 3-position of the pyridine ring was achieved in good yield with 1,3-dichloro-5,5-dimethylhydantoin. Pinnick oxidation of **23** gave carboxylic acid **24** in 83% yield. Finally, carboxylic acid **24** was converted to the benzyl ester to give **1** in 91% yield. By this route, **1** was accessed in seven linear steps starting from trifluoroacetic acid in 40% overall yield. This novel route developed was not only high-yielding but also robust and therefore was used for the preparation of carbon-14-labeled **1**.

In addition to the high overall yield, this new route also offered several options for incorporation of a carbon-14 label in the pyridine ring (Scheme 6). This was important not only for yield optimization but also in finding vendors that could prepare the desired intermediate with an acceptable cost. Placing the label in the carbonyl of trifluoracetic acid would incorporate the label at the 4-position of the pyridine ring (a), labeling the alkyne would incorporate the label at the 2- or 3-position (b or c), and labeling the benzylic carbon would incorporate the label at the 6-position (d). We ruled out using labeled benzylamine, as this reagent was used in excess to achieve high cyclization yields. In the end, we found that placing the label in the carbonyl of trifluoroacetic acid (a) would offer the most accessible and cost-effective option.

Novel Cyclization Route to Rinskor-Py-4-^{14}C (30). We utilized a vendor to prepare 100 mCi (ca. 1.5 g) of the key carbon-14-labeled alkyne intermediate **25** starting from carbon-14-labeled trifluoroacetic acid using the same chemistry that we developed to access **18** (Scheme 5). Treatment of carbon-14-labeled alkyne **25** with 4-chloro-2-fluoro-3-methox-

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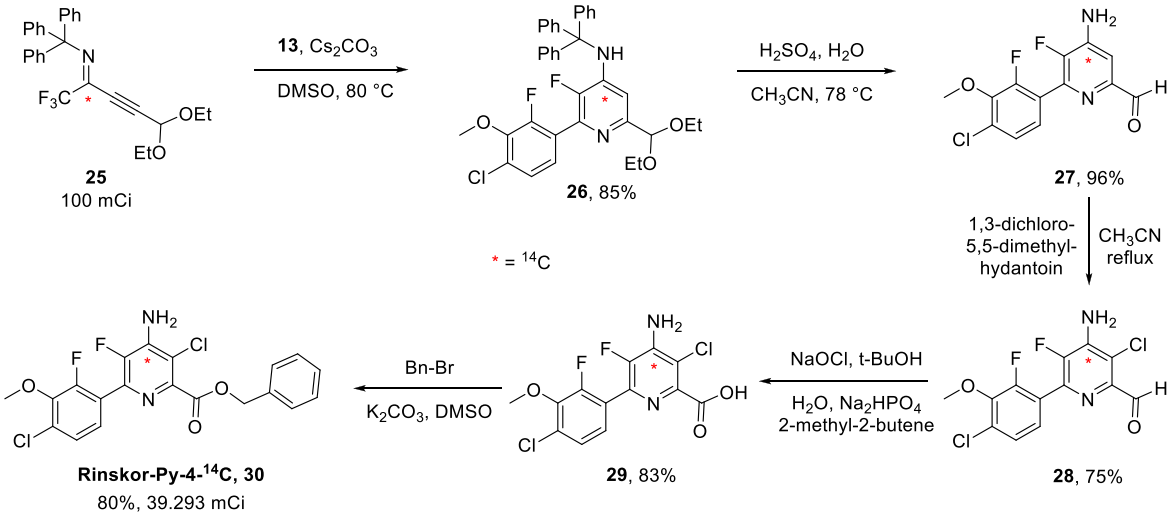
Scheme 7. Cyclization Route to Rinskor-Py-4-^{14}C



ybenzylamine (**13**) in the presence of cesium carbonate provided protected aminopyridine **26** in 85% yield (Scheme 7). Removal of the trityl and acetal protecting groups was accomplished in a single step in 96% yield using sulfuric acid. Selective chlorination of the pyridine ring was achieved with 1,3-dichloro-5,5-dimethylhydantoin to give **28** in 75% yield. Oxidation of the aldehyde with sodium chlorite gave carboxylic acid **29** in 83% yield. Finally, **29** was converted to the benzyl ester to give the desired radiotracer, Rinskor-Py-4-^{14}C (**30**), in 80% yield. This new route proved to be robust, which allowed us to prepare several batches of **30** from **25** in reproducible yields and deliver sufficient quantities of this key radiotracer to support the registration of Rinskor.

■ CONCLUSIONS

A novel cascade cyclization of fluoroalkyl alkynylimines with primary amines was optimized for the synthesis of a carbon-14-labeled radiotracer of **1** with the label at the 4-position of the pyridine ring. This new route provided the radiotracer of **1** in five chemical steps in-house in an overall yield of 40% from advanced carbon-14-labeled intermediate **25**, which was purchased from an external vendor. This new route was a significant improvement over the original route (16 steps, 1% yield overall from K^{14}CN) and provided sufficient quantities of the pyridine-labeled radiotracer to support environmental fate, metabolism, and toxicology studies required for the registration of Rinskor active.

■ EXPERIMENTAL PROCEDURES

General. *N*-[(5,5-Diethoxy-1,1,1-trifluoro(2-^{14}C)pent-3-yn-2-ylidene]-1,1,1-triphenylmethanamine was purchased from Pharmaron (Cardiff, UK). NMR spectra were obtained on either a Bruker Avance III HD 500 MHz, Bruker 400 MHz, or Varian Gemini 300 MHz spectrometer. NMR chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane as an internal reference. Mass spectra were obtained using an LC−MS system (Waters Micromass ZQ). High-resolution mass spectrometry (HRMS) was performed on an Agilent 6210 TOF LC−MS system. GC−MS spectra were obtained using a Hewlett Packard HP 6890 GC system with an Agilent 5973 mass-selective detector. IR spectra were obtained on neat samples using attenuated total reflectance on a Fisher Scientific Nicolet 6700 FT-IR spectrometer. Melting points were obtained using an OptiMelt automated melting point system (Sanford Research Systems) and are uncorrected. Quantitation of radioactivity was performed using a PerkinElmer Tri-Carb 2910 TR liquid scintillation analyzer with PerkinElmer Ultima-Gold liquid scintillation cocktail. High-performance liquid chromatography (HPLC) was performed using an Agilent 1260 HPLC system. Chemical purity was determined using an Agilent 1260 Infinity DAD UV detector and radiochemical purity using an IN/US β-RAM 2 radioflow detector.

2,2,2-Trifluoro-*N*-tritylethanimidoyl Chloride (17). A 1 L three-neck round-bottom flask equipped with a mechanical stirrer, addition funnel, and J-KEM temperature probe was charged with tritylamine (24.90 g, 96 mmol) and carbon tetrachloride (150 mL). The solution was cooled in an ice−water bath (<5 °C) and treated in portions with trifluoroacetic acid (6.13 mL, 80 mmol). The addition was done at such a rate as to keep the temperature at or below 10 °C. Once the mixture cooled below 5 °C, it was treated dropwise with triethylamine (13.4 mL, 96 mmol; no exotherm was observed). Once the addition of triethylamine was complete, the ice−water bath was removed, and the addition funnel was replaced with a reflux condenser. The reaction mixture was heated to 65 °C via a heating mantle. Triphenylphosphine (62.9 g, 240 mmol) was then added portionwise (5−10 g at a time) (**note**: with each addition of triphenylphosphine, the temperature dropped 2−3 °C and then rose to ca. 70 °C). The reaction mixture was allowed to cool to 65−66 °C before addition of triphenylphosphine. After all of the triphenylphosphine was added, the reaction mixture was heated at 76 °C for 2 h, allowed to cool to room temperature, and treated with hexanes (400 mL). After 30 min of rapid stirring, the mixture was filtered through a Buchner funnel. The collected solid was resuspended in hexanes (400 mL), and the suspension was stirred for several minutes and then filtered. The filtrates were combined and concentrated in vacuo to give a solid, which was slurried with hexanes (3 × 300 mL) and filtered. The solids were removed by vacuum filtration through a fritted glass funnel to give 14.32 g of a light-yellow liquid. The solvent was removed in vacuo to give 30.37 g of a light-yellow solid. The crude material was crystallized from acetonitrile (250 mL) (**note**: crystals formed upon cooling). After the crystallization

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mixture was allowed to stand in a freezer for a couple of hours, the crystals were removed by vacuum filtration and then washed with cold acetonitrile. The material was vacuum-oven-dried (40−50 °C) to give 21.97 g (73% yield) of the desired product as fine white needles. Mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.19 (m, 15H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.24; ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.18 (s), 130.00 (d, J = 43.1 Hz), 129.07 (s), 128.11 (s), 127.46 (s), 116.80 (q, J = 278.0 Hz), 77.83 (s); GC−MS (EI) m/z 373 (M^+), 338, 296, 243, 219, 193, 165, 143, 127, 119, 77; IR 3070, 1712, 1488, 1444, 1270, 1162, 1151, 946, 770 cm^{-1}.

***N*-(5,5-Diethoxy-1,1,1-trifluoropent-3-yn-2-ylidene)-1,1,1-triphenylmethanamine (18).** A 500 mL three-neck round-bottom flask equipped with a mechanical stirrer, reflux condenser, and J-KEM temperature probe was charged with propargylaldehyde diethyl acetal (5.13 g, 40 mmol), anhydrous acetonitrile (125 mL), and imidoyl chloride **17** (14.95 g, 40 mmol). Potassium iodide (6.64 g, 40 mmol), potassium phosphate (11.04 g, 52 mmol), and copper(I) iodide (2.29 g, 12 mmol) were combined, ground to a fine powder with a mortar and pestle, and then added to the reaction mixture. Additional acetonitrile (25 mL) was added, and the resultant mixture was warmed to 60 °C with a heating mantle under an atmosphere of N_2. After the reaction mixture was stirred overnight at 60 °C, an aliquot of the mixture was partitioned between EtOAc and H_2O and analyzed by thin-layer chromatography (TLC) (95/5 hexanes/EtOAc) and GC−MS. Analysis showed that the imidoyl chloride starting material was still present along with the desired product and a minor amount of a side product, the alkyne dimer. The reaction mixture was treated with an additional 20 mol % propargyl aldehyde diethyl acetal (1 g), KI (1.33 g), CuI (0.56 g), and K_3PO_4 (2.20 g). The temperature of the reaction mixture was raised to 70 °C. After an additional 3 h at 70 °C, TLC and GC−MS still showed remaining imidoyl chloride starting material. After the reaction mixture was stirred for 24 h total, it was allowed to cool to room temperature, diluted with CH_2Cl_2 (400 mL), filtered, and washed sequentially with H_2O (1 × 150 mL) and saturated NaCl (1 × 150 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give 22.02 g of a yellow oil, which solidified upon standing in a refrigerator. The crude material was dissolved in warm hexanes, loaded onto a silica gel column, and chromatographed using the following setup: Teledyne-ISCO CombiFlash Companion, 330 g RediSep silica gel column, 0−60% hexanes/CH_2Cl_2. Fractions containing the desired product were combined and concentrated in vacuo to give 12.11 g (65% yield) of the desired product as a white solid. Mp 84−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.14 (m, 15H), 4.88 (d, J = 1.1 Hz, 1H), 3.77−3.54 (m, 1H), 3.46−3.54 (m, 4H), 1.13 (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.30; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.43 (s), 139.83 (q, J = 38.0 Hz), 129.53 (s), 127.90 (s), 127.24 (s), 118.70 (q, J = 278.9 Hz), 98.53 (s), 90.82 (s), 78.29 (s), 74.04 (s), 61.20 (s), 14.94 (s); GC−MS (EI) m/z 465 (M^+), 436, 394, 366, 346, 243, 165, 103, 75; IR 3059, 2978, 2886, 1640, 1490, 1446, 1312, 1136, 1052, 697 cm^{-1}.

4-Chloro-2-fluoro-3-methoxybenzaldehyde *O*-Methyl Oxime (20). A 250 mL round-bottom flask equipped with a magnetic stir bar was charged with aldehyde **19** (10.00 g, 53.0 mml), ethanol (50 mL), and pyridine (50 mL). To this solution was added methoxylamine hydrochloride (4.87 g, 58.3 mmol, 1.1 equiv, 25−30 wt % solution in water). The resultant mixture was allowed to stir at room temperature under an atmosphere of N_2. After the reaction mixture was stirred at room temperature overnight (17 h), an aliquot of the reaction mixture was partitioned between EtOAc and 1 M HCl and analyzed by TLC (80/20 hexanes/EtOAc). TLC analysis indicated that all of the starting material had been consumed. The reaction mixture was concentrated in vacuo, and the crude mixture was taken up in EtOAc (150 mL) and washed with 2 M HCl (2 × 50 mL) and saturated NaCl (1 × 50 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo to give 11.01 g of an off-white solid. The crude material was recrystallized from hexanes (ca. 20 mL). The crystals were removed by vacuum filtration and washed with cold pentane. The solid was air-dried for several hours to give 8.20 g of the desired product as small white needles. A second crop yielded an additional 1.06 g of the desired product for a total yield of 9.26 g (80% yield). Mp 56−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.47 (dd, J = 8.6, 6.9 Hz, 1H), 7.18−7.09 (m, 1H), 3.99 (s, 3H), 3.96 (d, J = 1.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −134.45; ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.46 (d, J = 255.2 Hz), 144.63 (d, J = 13.1 Hz), 141.33 (d, J = 4.9 Hz), 129.70 (d, J = 3.6 Hz), 125.41 (d, J = 3.7 Hz), 120.82 (d, J = 3.3 Hz), 120.41 (d, J = 9.6 Hz), 62.37, 61.63 (d, J = 4.5 Hz); GC−MS (EI) m/z 217 (M^+), 186, 175, 171, 159, 144, 129, 95, 81.

1-(4-Chloro-2-fluoro-3-methoxyphenyl)methanamine (13). A 250 mL three-neck round-bottom flask equipped with a mechanical stirrer, reflux condenser, and J-KEM temperature controller was charged with methoxylamine **20** (5.88 g, 27.0 mmol), glacial acetic acid (100 mL), and zinc metal (8.63 g, 65.38 mmol, 5 equiv) (**note**: prior to use, the zinc metal was stirred with 1 M HCl, washed with H_2O followed by Et_2O, vacuum-oven-dried, and then ground with a mortar and pestle). The reaction mixture was heated at 100 °C via a heating mantle. After 60 min at 100 °C, an aliquot was filtered, diluted with EtOAc, and analyzed by TLC (80/20 hexanes/EtOAc) and GC−MS. Analysis showed that all of the starting material had been consumed. The reaction mixture was allowed to cool to room temperature, filtered over a plug of Celite, and washed with acetic acid. The filtrate was concentrated in vacuo to give a light-tan oil. The oil was dissolved in H_2O (100 mL) and washed with Et_2O (1 × 30 mL and 1 × 50 mL). The combined Et_2O layers were extracted with 1 M HCl (1 × 25 mL). The aqueous phases were combined, and the pH was adjusted to ca. 10 using 50% NaOH. The mixture was extracted with EtOAc (3 × 100 mL), and the combined EtOAc extracts were washed with H_2O (2 × 100 mL) and saturated NaCl (1 × 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give 4.31 g of a light-yellow oil, which was purified via bulb-to-bulb distillation to give 4.19 g (82% yield) of the desired product as a colorless liquid. Bp 165−180 °C (1 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, J = 8.3, 1.8 Hz, 1H), 7.00 (dd, J = 8.3, 7.3 Hz, 1H), 3.96 (d, J = 1.2 Hz, 3H), 3.88 (d, J = 1.2 Hz, 2H), 1.39 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −134.64; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.39 (d, J = 248.6 Hz), 144.23 (d, J = 13.8 Hz), 130.75 (d, J = 13.9 Hz), 126.79 (d, J = 3.5 Hz), 124.98 (d, J = 3.9 Hz), 123.17 (d, J = 5.4 Hz), 61.52 (d, J = 4.7 Hz), 40.22 (d, J = 4.3 Hz); GC−MS (EI) m/z 189 (M+), 188, 173, 154 (base), 145, 139, 126, 111, 95, 81.

2-(4-Chloro-2-fluoro-3-methoxyphenyl)-6-(diethoxymethyl)-3-fluoro-*N*-tritylpyridin-4-amine (21). A 100 mL round-bottom flask equipped with a magnetic stir bar was

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charged with alkyne **18** (2.33 g, 5.0 mmol) and anhydrous DMSO (25 mL) under an atmosphere of N_2. Once all of the alkyne dissolved, benzylamine **13** (2.84 g, 15 mmol, 3 equiv) was added to the solution. The resultant light-yellow solution was stirred for ca. 2 min at room temperature and then treated with cesium carbonate (4.07 g, 12.5 mmol, 2.5 equiv) in one portion. The reaction flask was placed in a preheated bath at 80 °C. After 2 h at 80 °C, an aliquot of the reaction mixture was partitioned between EtOAc and H_2O and analyzed by TLC (80/20 hexanes/EtOAc). Analysis indicated that all of the alkyne starting material had been consumed. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (150 mL), and washed with H_2O (3 × 50 mL) and saturated NaCl (1 × 50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give 4.63 g of an orange solid, which was dissolved in a minimal amount of CH_2Cl_2, loaded onto a silica gel column, and chromatographed using the following setup: Teledyne-ISCO CombiFlash Companion, 80 g RediSep silica gel column, 0−60% hexanes/EtOAc. Fractions containing the desired product were combined and concentrated in vacuo to give 2.243 g (73% yield) of the desired product as a peach-colored solid. Mp 177−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.08 (m, 17H), 6.34 (d, J = 6.5 Hz, 1H), 5.90 (d, J = 4.5 Hz, 1H), 5.09 (s, 1H), 3.98 (d, J = 1.0 Hz, 3H), 3.30 (dq, J = 9.4, 7.1 Hz, 2H), 3.16 (dq, J = 9.4, 7.0 Hz, 2H), 1.03 (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −128.23 (d, J = 33.8 Hz), −146.89 (d, J = 33.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.92, 153.17 (d, J = 5.3 Hz), 152.90, 146.71 (d, J = 250.6 Hz), 144.45 (d, J = 14.1 Hz), 143.96, 141.44 (d, J = 9.7 Hz), 137.60 (d, J = 14.5 Hz), 129.02 (d, J = 3.3 Hz), 128.90, 128.36, 127.41, 125.83, 125.21 (d, J = 3.7 Hz), 108.89, 102.27, 71.36, 65.91, 61.52, 15.09; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{36}H_{33}ClF_2N_2O_3$ 614.2148, found 614.2156.

4-Amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (22). A mixture of trityl-protected aminopyridine **21** (2.117 g, 3.44 mmol), acetonitrile (15 mL), water (15 mL), and 1 N H_2SO_4 (7.5 mL) was placed in an oil bath and heated at 80 °C. After 2 h at 80 °C, an aliquot of the reaction mixture was partitioned between EtOAc and 10% $NaHCO_3$. On the basis of HPLC and TLC (80/20 hexanes/EtOAc), only a trace amount of the starting material remained. The reaction mixture was allowed to cool to room temperature, vacuum-filtered, and washed with 2/2/1 CH_3CN/H_2O/1 N H_2SO_4. The filtrate was transferred to a separatory funnel, diluted with EtOAc (150 mL), and treated with 10% $NaHCO_3$. A white precipitate formed in the aqueous layer that did not readily extract into the organic phase. The layers were separated, and the aqueous layer was extracted sequentially with EtOAc (3 × 50 mL), CH_2Cl_2 (1 × 50 mL), and EtOAc (1 × 50 mL). The combined organic layers were washed with saturated NaCl (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give 1.04 g of a light-tan solid, which was slurried with hexanes (20 mL). After 2 h of stirring, the solid was vacuum-filtered and washed with hexanes. The solid was air-dried to give 0.941 g (92% yield) of the desired product as a light-tan solid. Mp 191−193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 7.49 (dd, J = 8.5, 1.5 Hz, 1H), 7.39−7.33 (m, 2H), 6.84 (s, 2H), 3.94 (d, J = 0.8 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −129.20 (d, J = 27.4 Hz), −139.73 (d, J = 27.3 Hz); ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.77, 154.43, 151.92, 148.95 (d, J = 4.0 Hz), 148.70, 146.15, 143.98 (dd, J = 32.7, 13.4 Hz), 139.49 (d, J = 13.9 Hz), 128.34 (d, J = 3.5 Hz), 125.90 (d, J = 3.9 Hz), 125.50 (d, J = 3.6 Hz), 123.59 (dd, J = 14.2, 3.4 Hz), 108.35 (d, J = 5.9 Hz), 61.59 (d, J = 4.3 Hz), 40.10; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{13}H_9ClF_2N_2O_2$ 298.0321, found 298.0322.

4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (23). A 100 mL round-bottom flask equipped with a magnetic stir bar and reflux condenser was charged with aminopyridine **22** (0.851 g, 2.85 mmol), acetonitrile (30 mL), and 1,3-dichloro-5,5-dimethylhydantoin (0.309 g, 1.567 mmol, 0.55 equiv). The resultant light-yellow mixture was stirred at room temperature for ca. 5 min and then heated to reflux under an atmosphere of N_2. After refluxing for <30 min, the reaction mixture turned into a yellow homogeneous solution. After 60 min at reflux, an aliquot of the reaction mixture was partitioned between EtOAc and H_2O and analyzed by TLC (80/20 hexanes/EtOAc) and HPLC. On the basis of the analysis, all of the starting material had been consumed. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (150 mL), and washed with H_2O (1 × 50 mL), dilute sodium bisulfite (1.0 g of $NaHSO_3$/50 mL of H_2O, 1 × 50 mL), and saturated NaCl (1 × 50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give 1.00 g of a tan solid. The solid was dissolved in acetone and treated with 3 g of Celite. The solvent was removed in vacuo, and the residue was placed in a solid load cartridge and chromatographed using the following setup: Teledyne-ISCO CombiFlash Companion, 40 g RediSep silica gel column, 5−100% hexanes/EtOAc. Fractions containing the desired product were combined and concentrated in vacuo, and the light-tan solid was stirred with 2/1 H_2O/CH_3CN (15 mL). After 3 h of stirring, the solid was vacuum-filtered and washed with 1/1 H_2O/CH_3CN (10 mL). The solid was air-dried for 1 h, transferred to a 25 mL round-bottom flask, and treated with CH_3CN (4 × 5 mL), and the mixture was concentrated in vacuo to give 749 mg (79% yield) of the desired product as a light-tan solid. Mp 192−196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 7.51 (dd, J = 8.5, 1.2 Hz, 1H), 7.36 (dd, J = 8.5, 7.0 Hz, 1H), 7.15 (s, 2H), 3.94 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −129.20 (d, J = 27.9 Hz), −134.34 (d, J = 28.0 Hz); ^{13}C NMR (101 MHz, DMSO-d_6) δ 190.27, 154.38, 151.87, 147.07, 144.47, 144.02−143.45 (m), 141.98 (d, J = 13.9 Hz), 137.06 (d, J = 13.7 Hz), 128.65 (d, J = 3.5 Hz), 125.89 (d, J = 3.3 Hz), 125.61 (d, J = 3.6 Hz), 122.91 (dd, J = 13.8, 4.1 Hz), 116.14 (d, J = 3.8 Hz), 61.62 (d, J = 4.3 Hz), 38.86; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{13}H_8Cl_2F_2N_2O_2$ 331.9931, found 331.9930.

4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylic Acid (24). A 25 mL round-bottom flask equipped with a magnetic stir bar and reflux condenser was charged with aldehyde **23** (400 mg, 1.201 mmol) and *tert*-butyl alcohol (6 mL). Rapid stirring and warming failed to dissolve all of the aldehyde. An additional 2 mL of *t*-BuOH was added, but this still failed to form a homogeneous solution. The mixture was treated with H_2O (2 mL), 2-methyl-2-butene (1 mL), sodium hydrogen phosphate dihydrate (341 mg, 2.402 mmol, 2 equiv), and sodium chlorite (326 mg, 3.60 mmol, 3 equiv). The mixture was stirred at room temperature for 5 min and then placed in an oil bath at 85 °C. After 60 min of stirring at 85 °C, the reaction mixture turned into a light-yellow homogeneous solution. After the reaction mixture was stirred at 83 °C overnight (12 h), an aliquot of the mixture was partitioned between EtOAc and 1 M

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HCl and analyzed by HPLC and LC−MS. Analysis showed that all of the starting material had been consumed. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (15 mL), and washed with 1 M HCl (1 × 5 mL), H_2O (1 × 5 mL), and saturated NaCl (1 × 5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a cream-colored solid, which was slurried with Et_2O (5 mL). After 3 h of stirring, the solid was vacuum-filtered, washed with Et_2O, and dried under vacuum to give 348 mg (83% yield) of the desired product as a white solid. Mp 192−196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.66 (s, 1H), 7.47 (dd, J = 8.5, 1.4 Hz, 1H), 7.31 (dd, J = 8.4, 7.1 Hz, 1H), 7.04 (s, 2H), 3.93 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −129.10 (d, J = 28.3 Hz), −138.56 (d, J = 28.4 Hz); ^{13}C NMR (101 MHz, DMSO) δ 165.91 (s), 153.06 (d, J = 252.5 Hz), 146.20 (d, J = 4.3 Hz), 144.70 (d, J = 256.1 Hz), 143.81 (d, J = 13.9 Hz), 141.37 (d, J = 14.1 Hz), 136.02 (d, J = 13.2 Hz), 128.43 (d, J = 3.2 Hz), 125.90 (d, J = 2.9 Hz), 125.51 (d, J = 3.5 Hz), 123.03 (dd, J = 13.8, 3.9 Hz), 112.17 (d, J = 2.7 Hz), 61.60 (d, J = 4.0 Hz); LC−MS (ESI$^+$) 349 (M + H), (ESI$^-$) 347 (M − H).

Benzyl 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylate (Rinskor, 1). A 50 mL round-bottom flask containing a magnetic stir bar was charged with carboxylic acid **24** (519 mg, 1.49 mmol) and anhydrous DMSO (10 mL). To this solution was added powdered potassium carbonate (311 mg, 2.97 mmol, 2.0 equiv, 325 mesh) followed by benzyl bromide (0.23 mL, 1.93 mmol, 1.3 equiv). The resultant mixture was stirred at room temperature under an atmosphere of N_2. After the reaction mixture was stirred overnight (17 h), an aliquot of the mixture was partitioned between 1 M HCl and EtOAc and analyzed by HPLC and TLC. Analysis showed that only a trace amout of the starting material remained. The reaction mixture was diluted with EtOAc (30 mL) and washed with H_2O (3 × 10 mL) and saturated NaCl (1 × 10 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a light-yellow solid, which was dissolved in CH_2Cl_2 (2 mL), loaded onto a silica gel column, and chromatographed using the following setup: Teledyne-ISCO CombiFlash Companion, 24 g RediSep silica gel column, 0−100% hexanes/EtOAc. Fractions containing the desired product were combined and concentrated in vacuo to give 593 mg (91% yield) of the desired product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.42 (m, 2H), 7.42−7.31 (m, 3H), 7.26 (d, J = 3.6 Hz, 2H), 5.43 (s, 2H), 4.92 (s, 2H), 3.98 (d, J = 1.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −128.20 (d, J = 32.8 Hz), −137.74 (d, J = 34.5 Hz); ^{13}C NMR (101 MHz,) δ 164.62, 154.24 (d, J = 254.5 Hz), 147.39, 144.96, 144.82, 144.38 (d, J = 4.5 Hz), 140.43 (d, J = 13.6 Hz), 138.05 (d, J = 13.8 Hz), 135.49, 130.29 (d, J = 3.1 Hz), 128.78, 128.76, 125.85, 125.78 (d, J = 4.4 Hz), 123.00 (d, J = 14.3 Hz), 115.83, 68.14, 62.00 (d, J = 4.4 Hz); LC−MS (ES$^+$) 439 (M + H), (ES$^-$) 437 (M − H).

2-(4-Chloro-2-fluoro-3-methoxyphenyl)-6-(diethoxymethyl)-3-fluoro-*N*-trityl(4-^{14}C)pyridin-4-amine (26). To a solution of *N*-[(5,5-diethoxy-1,1,1-trifluoro(2-^{14}C)pent-3-yn-2-ylidene]-1,1,1-triphenylmethanamine (**25**) (50.0 mCi at 33 mCi/mmol, 1.52 mmol) in DMSO (7 mL) was added benzylamine **13** (0.86 g, 4.55 mmol, 3 equiv) under an atmosphere of N_2. The resultant light-yellow solution was stirred at room temperature for 2 min and then treated with cesium carbonate (1.234 g, 3.79 mmol, 2.5 equiv). The reaction flask was placed in an oil bath at 80 °C. After 60 min of stirring at 80 °C, an aliquot of the reaction mixture was partitioned between EtOAc and H_2O and analyzed by TLC (80/20 hexanes/EtOAc) and HPLC. Analysis indicated that all of the alkyne starting material had been consumed. The reaction mixture was allowed to cool to room temperature, transferred to a 100 mL round-bottom flask, and diluted with EtOAc (30 mL) and CH_2Cl_2 (5 mL). The resultant mixture was washed with H_2O (3 × 10 mL) and saturated NaCl (1 × 10 mL). The organic layer was dried by passage through a plug of Na_2SO_4, washing with CH_2Cl_2. The filtrate was concentrated in vacuo to give a mustard-colored solid, which was dissolved in warm CH_2Cl_2 (3 mL), loaded onto a silica gel column, and chromatographed using the following setup: Teledyne-ISCO CombiFlash R_f, 40 g RediSep silica gel column, 0−60% hexanes/EtOAc. Fractions containing the desired product in >95% radiochemical purity were combined and concentrated in vacuo. The residue was dried under high vacuum (40−50 °C) to give 792 mg (85% yield) of the desired product as a light-tan solid. HPLC analysis showed ca. 95% radiochemical purity (β-RAM) and >98% chemical purity at 254 nm. HRMS-ESI [M + H]$^+$ calcd for $C_{36}H_{33}ClF_2N_2O_3$ 614.22148, found 614.2078.

4-Amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro(4-^{14}C)pyridine-2-carbaldehyde (27). A solution of **26** (1.54 g, 2.52 mmol) in CH_3CN (10 mL), H_2O (10 mL), and 1 N H_2SO_4 (5 mL) was placed in an oil bath at 80 °C. After 2 h of stirring at 80 °C, an aliquot of the reaction mixture was partitioned between EtOAc and 10% $NaHCO_3$ and analyzed by TLC (80/20 hexanes/EtOAc) and HPLC. Analysis showed that a minor amount of starting material (10−15%) was present. The reaction mixture was treated with an additional 0.5 mL of 1 N H_2SO_4 and heated for 2 h at 80 °C. On the basis of HPLC analysis, only a trace amount of the starting material remained. The reaction mixture was allowed to cool to room temperature, filtered, and washed with 2/2/1 CH_3CN/H_2O/1 N H_2SO_4. The filtrate was neutralized with 10% $NaHCO_3$. The resultant mixture was extracted with EtOAc (2 × 20 mL), $CHCl_3$ (2 × 10 mL), EtOAc (2 × 10 mL), and $CHCl_3$ (1 × 5 mL). The combined organic extracts were dried by passage through a plug of Na_2SO_4. The filtrate was concentrated in vacuo to give a light-tan solid, which was slurried with 85/15 hexanes/EtOAc (25 mL). After 2 h of stirring, the mother liquor was removed via a filter stick. The residual solid was washed with hexanes (2 × 3 mL), and the hexane washes were removed via filter stick. The solid was slurried with 1/1 CH_3OH/CH_2Cl_2 (ca. 30 mL). An aliquot of this slurry was diluted with CH_3CN and analyzed by HPLC. HPLC analysis showed >95% chemical (254 nm) and radiochemical purity. The solvent was removed in vacuo, and the solid was dried under high vacuum (40−50 °C) to give 0.720 g (96% yield) of the desired product as a light-tan solid. HRMS-ESI [M + H]$^+$ calcd for $C_{13}H_9ClF_2N_2O_2$ 298.0321, found 298.0314.

4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro(4-^{14}C)pyridine-2-carbaldehyde (28). To a 100 mL round-bottom flask containing **27** (720 mg, 2.41 mmol) and equipped with a magnetic stir bar and a reflux condenser were added CH_3CN (30 mL) and 1,3-dichloro-5,5-dimethylhydantoin (261 mg, 1.36 mmol, 0.55 equiv). The resultant light-yellow mixture was stirred at room temperature for 5 min and then placed in an oil bath and heated to reflux under an atmosphere of N_2. After 60 min at reflux, an aliquot

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of the reaction mixture was partitioned between EtOAc and H_2O and analyzed by TLC (80/20 hexanes/EtOAc) and HPLC. Analysis indicated that all of the starting material had been consumed. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (45 mL), and washed with H_2O (1 × 15 mL), dilute sodium bisulfite (1.0 g of $NaHSO_3$/50 mL of H_2O, 1 × 15 mL), and saturated NaCl (1 × 15 mL). The organic phase was dried by passage through a plug of Na_2SO_4. The filtrate was concentrated in vacuo to give a light-yellow solid, which was slurried with 95/5 hexanes/EtOAc (15 mL). After 60 min of stirring, the mother liquor was removed via filter stick. The solid was washed with 95/5 hexanes/EtOAc (2 × 3 mL) followed by 2/1 H_2O/CH_3CN. The solid was treated with CH_3CN and concentrated in vacuo (4 × 10 mL) to give a light-tan solid. A small amount of this material was dissolved in 1/1 CH_3OH/CH_2Cl_2 and analyzed by HPLC. Analysis showed ∼92% chemical and radiochemical purity.

The poor recovery can be attributed to the low solubility of the desired compound. The aqueous phase and washes were combined and concentrated in vacuo. The residual water phase was extracted with EtOAc (1 × 30 mL and 1 × 10 mL) and $CHCl_3$ (1 × 10 mL). The combined organic extracts were washed with 0.5 N NaOH (1 × 10 mL) and saturated NaCl (1 × 10 mL) and then dried by passage through a plug of Na_2SO_4. The filtrate was concentrated in vacuo to give a light-tan solid, which was slurried with acetone. The solvent was removed in vacuo to give 0.612 g of a light-tan solid. The solid was stirred for ca. 15 min with 95/5 hexanes/EtOAc (10 mL). The mother liquor was removed via a pipet, and the solid was washed with 95/5 hexanes/EtOAc (1 × 3 mL). The solid was dried under high vacuum to give 0.600 g (75% yield) of the desired product as a light-tan solid. HRMS-ESI $[M + H]^+$ calcd for $C_{13}H_8Cl_2F_2N_2O_2$ 331.993, found 331.9928.

4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro(4-^{14}C)pyridine-2-carboxylic Acid (29). To a 50 mL round-bottom flask containing **28** (600 mg, 1.80 mmol) and equipped with a magnetic stir bar and a reflux condenser was added *tert*-butyl alcohol (11 mL). The mixture was treated with H_2O (3 mL), 2-methyl-2-butene (1.5 mL), sodium hydrogen phosphate dihydrate (511 mg, 3.60 mmol, 2 equiv), and sodium chlorite (489 mg, 3.60 mmol, 3 equiv). The mixture was stirred at room temperature for 5 min and then placed in an oil bath at 80 °C. After the reaction mixture was stirred overnight at 80 °C (16 h), an aliquot of the mixture was partitioned between EtOAc and 1 M HCl. Analysis by HPLC and TLC (80/20 hexanes/EtOAc) indicated that all of the starting material had been consumed. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (25 mL). The resultant mixture was washed with 1 M HCl (1 × 10 mL), H_2O (1 × 10 mL), and saturated NaCl (1 × 10 mL). The organic layer was dried by passage through a plug of Na_2SO_4. The filtrate was concentrated in vacuo to afford a very faint yellow solid, which was slurried with Et_2O (8 mL) for 3 h, and then the mother liquor was removed via a filter stick. The solid was washed with Et_2O (2 × 2 mL), and the washes were removed via a filter stick. The solid was slurried with EtOAc, and a small aliquot of the slurry was dissolved in CH_3CN and analyzed by HPLC. HPLC analysis showed ca. 95% chemical and radiochemical purity. The solvent was removed in vacuo, and the solid was dried under high vacuum to give 519 mg (83% yield) of the desired product as a white solid. HRMS-ESI $[M + H]^+$ calcd for $C_{13}H_8Cl_2F_2N_2O_3$ 347.9880, found 347.9876.

Benzyl 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro(4-^{14}C)pyridine-2-carboxylate (Rinskor-Py-4-^{14}C, 30). To a 100 mL round-bottom flask containing a magnetic stir bar and **29** (519 mg, 1.49 mmol) was added anhydrous DMSO (10 mL). To this solution was added powdered potassium carbonate (411 mg, 2.97 mmol, 2 equiv, 325 mesh) followed by benzyl bromide (0.23 mL, 1.93 mmol, 1.3 equiv). The resultant mixture was stirred at room temperature under an atmosphere of N_2. After the reaction mixture was stirred overnight (16 h), an aliquot of the mixture was partitioned between 1 M HCl and EtOAc and analyzed by HPLC and TLC. Analysis showed that all of the starting carboxylic acid had been consumed. The reaction mixture was diluted with EtOAc (30 mL) and washed with H_2O (3 × 10 mL) and saturated NaCl (1 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a light-yellow solid, which was dissolved in CH_2Cl_2 (2 mL) and loaded onto a silica gel column. The crude material was chromatographed using the following setup: Teledyne-ISCO CombiFlash R_f, 40 g RediSep silica gel column, 0−75% hexanes/EtOAc. Fractions containing the desired product in >97% radiochemical purity where combined and concentrateed in vacuo. The residue was dried under high vacuum (50−60 °C) to give a constant weight of 525 mg (80% yield) of the desired product as a white solid. The radiochemical purity was 97.8% as determined by HPLC with a specific activity of 32.9 mCi/mmol. HRMS-ESI $[M + H]^+$ calcd for $C_{20}H_{14}NCl_2F_2N_2O_3$ 438.0350, found 438.3044.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00302.

NMR spectra of compounds **1**, **13**, **17**, **18**, and **20**−**24** and HPLC chromatograms of radiotracers **26**−**30** (PDF)

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Notes

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