Facile Preparation of a 4-Substituted [2,6-^{14}C]Pyridine: Synthesis of [^{14}C]SK&F 105809

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SUMMARY

[^{14}C]Formaldehyde was used in a nucleophile-assisted iminium ion cyclization with N-benzyl-3-butynylamine to provide N-benzyl-4-iodo-1,2,5,6-tetrahydro[2,6-$^{14}C_2$]pyridine. Palladium-catalyzed coupling of this vinyl iodide with the organozinc derivative **2** gave the corresponding 4-arylated tetrahydropyridine. Treatment of this compound at elevated temperatures with Pd/Al_2O_3 in nitrobenzene solution caused hydrogenolysis of the benzyl group and aromatization, generating the 4-substituted [2,6-$^{14}C_2$]pyridine **4** in good overall radiochemical yield from [^{14}C]formaldehyde. In high yields, compound **4** was converted via the methylsulfide [^{14}C]SK&F 105561 (**1b**) to the methylsulfinyl compound [^{14}C]SK&F 105809 (**1a**). It is proposed that, during the iminium ion cyclization, randomization of label between the 2- and 6-positions of the tetrahydropyridine ring occurs as the result of rapid equilibration between alkynyl and allenyl iminium ions, prior to cyclization.

Keywords: Arene coupling, [2,6-$^{14}C_2$]pyridine, [^{14}C]formaldehyde, iminium ion cyclization, tetrahydropyridine

INTRODUCTION

2-(4-Methylsulfinyl)phenyl-6,7-dihydro-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole (SK&F 105809, **1a**) and its methylsulfide analog **1b** (SK&F 105561) are of significant pharmacological interest. Compound **1a** was found to be a prodrug of the sulfide metabolite **1b**, which is a potent inhibitor of cyclooxygenase and 5-lipoxygenase enzymes.[1] Compound **1a** was shown to be converted to the active principle *in vivo*, resulting in inhibition of the production of leukotriene B4 and prostaglandin E.[2] Compound **1a** inhibited various inflammatory responses in animal studies and displayed analgetic activity as well.[1] We were interested in preparing **1a** in carbon-14 labeled form for use in a variety of biological studies. The original synthesis of the compound[2] does not offer the opportunity for the economical introduction of carbon-14; therefore an alternative synthetic route was sought. Our desire was to place the label in one of the aromatic rings, in order to minimize the possibility of catabolic loss of label.

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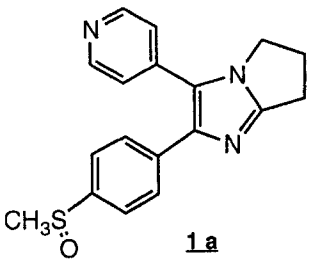
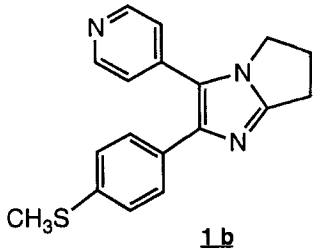


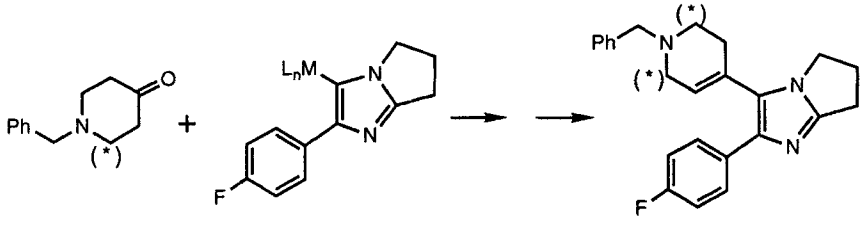
1a



1b

RESULTS AND DISCUSSION

Initially, we considered preparing pyridine-labeled **1a** via the reaction between a polycyclic organometallic, e.g. **2**, and N-benzyl-4-[2-^{14}C]piperidone, the preparation of which has been reported by Nakatsuka, et al.[3] via a Mannich reaction of [^{14}C]formaldehyde with benzylamine and ethyl acryloylacetate. In exploratory reactions we found that N-benzyl-4-piperidone would react with organomagnesium, organocerium and organolithium reagents **2** to give moderate to good yields of tertiary alcohol, and that this alcohol could be readily dehydrated to tetrahydropyridine **3** in excellent yield. However, in our hands the Nakatsuka procedure for preparing N-benzyl-4-piperidone gave unsatisfactory results.

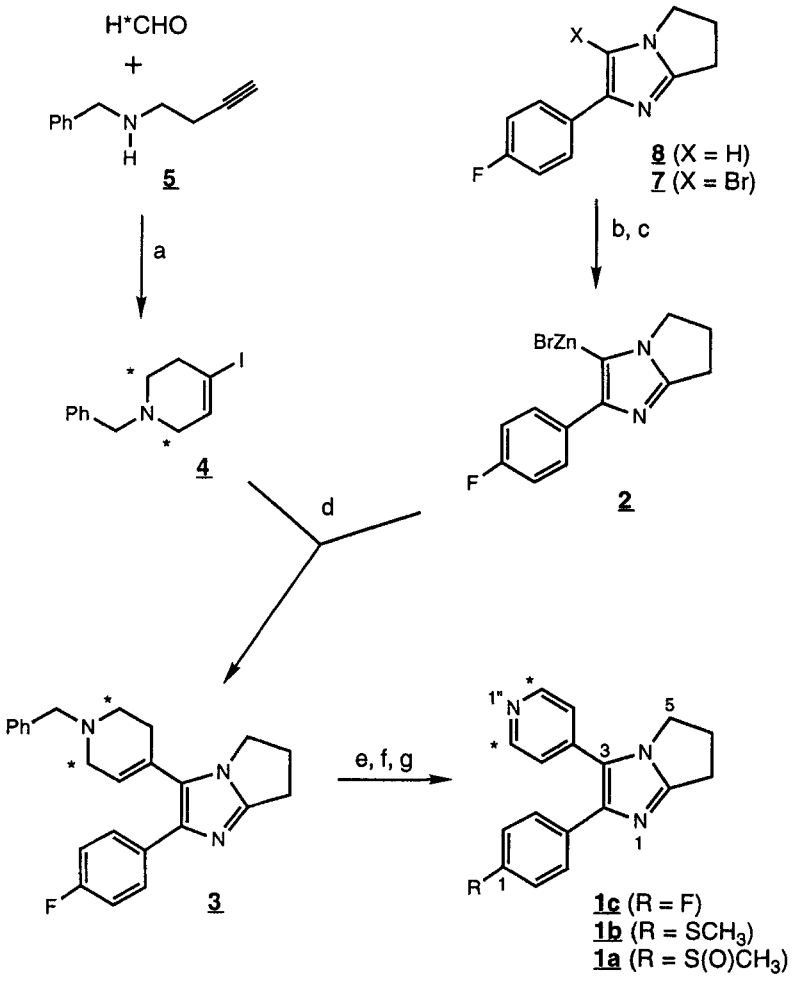


2 (M = Li, Ce, Mg) **3**

Overman has described[4] the high-yield (87%) preparation of unlabeled N-benzyl-4-iodo-1,2,5,6-tetrahydropyridine (**4**) by the reaction of N-benzyl-3-butynylamine (**5**, see Scheme I) with two equivalents of 37% aqueous formaldehyde in the presence of excess iodide ion. We envisioned that [^{14}C]**4**, prepared in this manner using [^{14}C]formaldehyde, might be induced to undergo a Negishi-type coupling with a suitable metallo derivative of **2** to give [^{14}C]**3** directly. The following describes the successful realization of this idea.

In adapting the Overman preparation of the vinyl iodide **4** for radiochemical use, we obtained slightly better yields of **4** (55-70% based on formaldehyde) using one equivalent of formaldehyde instead of two; substitution of paraformaldehyde gave the same results. However, the yield of **4** based on formaldehyde was not further improved when the reaction was run with an excess of the amine; moreover, the product was more difficult to purify (*vide infra*). Therefore, in the hot run , aqueous [^{14}C]formaldehyde (~2 mmol, 100 mCi) was used in an initial 1:1 stoichiometric ratio with alkynyl amine **5**. This provided a 60% radiochemical yield of the vinyl iodide [^{14}C]**4** with a radiochemical purity of 87%.

Scheme I



a: 10-Camphorsulfonic acid, NaI, H_2O, 95°; b: Br_2, CH_2Cl_2; c: nBuLi, THF, -78°, then $ZnCl_2$; d: $Pd(PPh_3)_4$, THF; e: Pd/Al_2O_3, $PhNO_2$, 145°; f: $NaSCH_3$, DMF, 90°; g: $Na_2S_2O_8$, HOAc

By using a procedure similar to the general method of Negishi[5], vinyl iodide **4** was found to undergo rapid coupling with the organozinc species **2** in the presence of 5-10 mol% of tetrakis(triphenylphosphine)palladium(0) to form the tetrahydropyridine derivative **3**. When repeated with [^{14}C]**4**, this coupling reaction provided a 65% yield (39 mCi) of the tetrahydropyridine [^{14}C]**3** with a radiochemical purity greater than 95% by TLC. Subsequently, [^{14}C]**3** was stirred with 13 wt% of 10% palladium/alumina at 145°C in nitrobenzene solution for 1.25 hours, providing pyridine derivative [^{14}C]**1c** in 85% yield

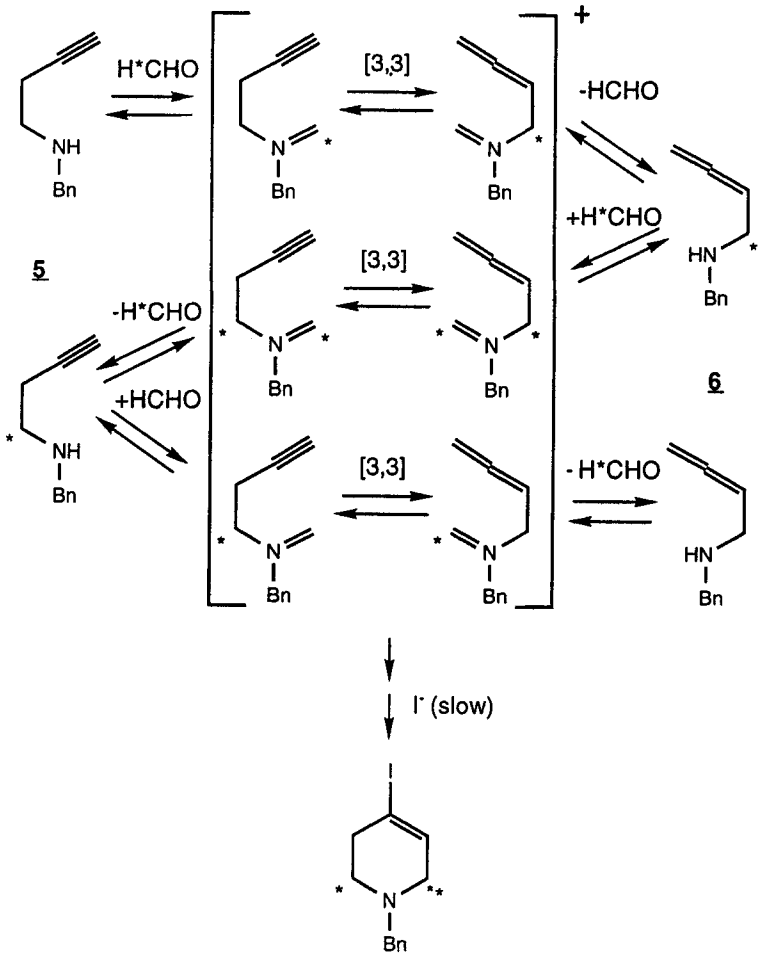
via debenzylation and dehydrogenation. This procedure has previously been used with unsubstituted and N-methyltetrahydropyridines[6], but this is to our knowledge the first successful application of the reaction to N-benzyltetrahydropyridines.

The product [^{14}C]**1c**, which in unlabeled form was an intermediate in the previously reported[2] synthesis of **1a**, was converted to sulfide [^{14}C]**1b** as reported by treatment with sodium thiomethoxide. Oxidation of the sulfide moiety to the sulfoxide [^{14}C]**1a** was carried out in 92% yield using sodium persulfate in aqueous acetic acid. We found this oxidation reagent to be more satisfactory on the present scale than other oxidation methods[2] because the presence of excess oxidant does not cause overoxidation.

This synthesis thus provided a complex 4-substituted [^{14}C]pyridine, in three steps and 33% overall yield from [^{14}C]formaldehyde. This method is a significant improvement, in yield and/or brevity, over previously reported preparations of carbon-labeled pyridines[7]. Moreover, the key intermediate vinyl iodide [^{14}C]**4** contains vinylic functionality useful for transformations to other compounds. In addition, it is evident from other recent work of Overman that iminium ion and acyliminium ion initiated cyclization reactions of vinylsilanes[8,9] using isotopically labeled formaldehyde could provide a wide variety of substituted tetrahydropyridines leading to isotopically labeled complex alkaloids and other compounds.

Mass spectrometric analyses of [^{14}C]**1a** and [^{14}C]**1c** revealed the presence of a significant amount (4%) of $^{14}C_2$ isotopomer in both, in addition to 30% $^{14}C_1$ and 66% $^{14}C_0$. These results, along with the ^{1}H NMR analyses which showed isotopic perturbation of only the pyridine C2/C6 proton signal, indicate that carbon-14 was not incorporated into a single position as suggested by the structures of the reactants, but was distributed between the C2 and C6 positions. Furthermore, the 66:30:4 statistical distribution of $^{14}C_0$:$^{14}C_1$:$^{14}C_2$ species found suggests randomization of the label in the carbon pool giving rise to C2 and C6. For example, randomization of an 81:19 mixture of ^{12}C and ^{14}C in these positions would result in a 66:31:4 mixture of $^{14}C_0$, $^{14}C_1$ and $^{14}C_2$ species [$(0.81)^2$, (2 x 0.81 x 0.19), and $(0.19)^2$, respectively], close to that found. The 81:19 ratio is in the range expected in the present experiment, based on the isotopic abundance of the [^{14}C]formaldehyde and the amounts of labeled and unlabeled formaldehyde and butynylamine used. These results are consistent with equilibration of the carbon-14 label, originating in [^{14}C]formaldehyde, via a rapid, reversible, [3,3]sigmatropic rearrangement of the intermediate iminium ion prior to ring closure to product (see Scheme II). This process is analogous to that proposed by Overman[10] to explain the observation of substituted allene and unsubstituted tetrahydropyridine by-products in similar reactions with higher aldehydes, and is supported in the present case by the isolation of carbon-14 labeled allenylamine **6** and carbon-14 labeled alkynylamine **5** from one of our reactions. Further investigations of this reaction using isotopic labels will be reported on elsewhere.

Scheme II



EXPERIMENTAL

General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM400 spectrometer at 400 and 100.6 MHz, respectively, in $CDCl_3$ solvent. Infrared spectra were measured on a Nicolet 20 DXB fourier transform spectrophotometer. Low resolution mass spectra were obtained on a Finnegan 3625 instrument operating in chemical ionization mode using as reagent gas methane (for unlabeled samples) or ammonia (for determination of specific activity of labeled samples). High resolution mass spectra were recorded on a VG 70SE mass spectrometer. Melting points were measured on a Thomas-Hoover Unimelt apparatus and

are uncorrected. TLC's were run on Merck Si60 F254 plates, and radiochromatograms were recorded using a Berthold LB 2832 Linear Analyzer. HPLC analyses were carried out on Whatman Partisil 5 ODS-3 columns, using a Varian 5000 HPLC system or a Beckman 110A pump and Kratos spectroflow 783 UV detector, and radioactivity was monitored with a Ramona Radioactivity Detector with TruCount scintillation cocktail in a flow cell. [^{14}C]Formaldehyde was purchased from DuPont NEN Products.

1-Benzyl-4-iodo-1,2,4,5-tetrahydro[2,6-$^{14}C_2$]pyridine ([^{14}C]**4**)

A 529 mg (3.33 mmol) portion of N-benzyl-3-butynylamine[11] was weighed into a 24 mL screw-cap vial, and 10 mL of water was added. To the stirred mixture was added sequentially 772 mg (3.33 mmol) of (+)-10-camphorsulfonic acid, 2.50 g (16.7 mmol) of sodium iodide, a solution of [^{14}C]formaldehyde (100 mCi at 55 mCi/mmol) in 6.5 mL of water, and 113 µL (1.51 mmol) of 37% aqueous formaldehyde. Additional water was added to raise the total reaction volume to 20 mL. The vial was capped tightly and the mixture stirred vigorously and maintained at 95°C for 1.75 h. The reaction mixture was cooled to below room temperature, and an additional 250 µL (3.3 mmol) of unlabeled formadehyde solution was added. Heating and stirring were resumed for 30 min. The mixture was cooled to 10°C, basified by addition of solid $NaHCO_3$, then extracted with three 10 mL portions of ethyl ether. The combined extracts were washed twice with saturated aqueous NaCl solution, then dried over $MgSO_4$. The drying agent was removed by filtration, and the filtrate was stripped of solvent in vacuo. Resulting was 672 mg (60 mCi, 60%) of [^{14}C]**4** as a light yellow liquid. The radiochemical purity by TLC (1:9 EtOH:CH_2Cl_2) was 87%, and the ^{1}H NMR spectrum matched an unlabeled sample prepared in the same way: δ 2.67 (4H, s, C5-H_2 + C6-H_2), 3.08 (2H, brs, C2-H_2), 3.61 (2H, s, Cα-H_2), 6.24 (1H, t, J = 2.8 Hz, C3-H), 7.26-7.42 (5H, m, ArH).

3-Bromo-2-(4-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-a]imidazole (**7**)

An 8.48 g (42 mmol) portion of 2-(4-fluorophenyl)-5*H*-pyrrolo[1,2-a]imidazole[2] (**8**) was dissolved in 150 mL of CH_2Cl_2. A solution of 7.05 g (44 mmol) bromine in 5 mL CH_2Cl_2 was added over a 10 min period to the vigorously stirred solution. After an additional 10 min, saturated aqueous $NaHCO_3$ solution was cautiously added until the aqueous phase became basic. The organic layer was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give a tan solid. This material was recrystallized from toluene to provide 8.05 g (68%) of **7** as pale tan crystals, mp 183-5°C (dec). ^{1}H NMR: δ 2.64 (2H, quint, J = 7.4 Hz, C6-H_2), 3.01 (2H, t, J = 7.6 Hz, C5-H_2), 3.98 (2H, t, J = 7.1 Hz, C7-H_2), 7.08 (2H, apparent t, J = 8.8 Hz, C3'-H + C5'-H), 7.91 (2H, dd, J = 5.4, 9.0 Hz, C2'-H + C6'-H); ^{13}C NMR: δ 24.34 (C-H_2), 25.22 (C-H_2), 44.76 (C-H_2), 115.13 (=C(Br)N-), 115.22 (d, J = 21.4 Hz, arom. C-H),

127.94 (d, J = 8.3 Hz, arom. C-H), 129.61 (d, J = 3.0 Hz, arom. quat. C), 140.86 (quat. C), 153.86 (-C=N(-N)), 161.97 (d, J = 246 Hz. arom. C-F); FT-IR (KBr): 3100-3000 (=C-H), 3000-2800 (C-H), 1606 (C=C or C=N), 1590 (C=C or C=N), 1539 (C=C or C=N), 1219 (arom. C-F), 838 (1,4 disub. arom.), 515 (C-Br); CI-MS (CH_4), m/Z (%): 283 (96, $(M+H)^+$), 281 (100, $(M+H)^+$), 263 (27, $(M-HF)^+$), 261 (28, $(M-HF)^+$), 242 (2, $(M-Br)^+$), 230 (7), 202 (4); microanalysis: calcd. for $C_{12}H_{10}BrFN_2$ C, 51.27; H, 3.59; N, 9.96; found C, 51.18; H, 3.61; N, 9.91.

2-(4-Fluorophenyl)-3-[1-benzyl-1,2,5,6-tetrahydro-4-[2,6-$^{14}C_2$]pyridinyl]-6,7-dihydro-5*H*-pyrrolo[1,2-a]imidazole ([^{14}C]**3**)

A suspension of 702 mg (2.5 mmol) of **7** in 40 mL dry THF at -78° was treated with 1.2 equivalents of n-butyllithium (1M in hexane), producing a clear solution. Immediately, a solution of 340 mg (2.5 mmol) of anhydrous $ZnCl_2$ in THF was added, producing a voluminous white precipitate. The suspension was allowed to warm to rt and stirred for 1.5 h. At that time a solution of 670 mg (2.25 mmol) of [^{14}C]**4** and 146 mg (0.125 mmol) $Pd(PPh_3)_4$ in 4 mL THF was added. The precipitate redissolved within 10 min, leaving a clear yellow solution. After 1 h, the reaction was worked up by adding saturated aqueous $NaHCO_3$ then extracting twice with ethyl ether. The combined extracts were washed twice with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The resulting yellow oil was purified by flash chromatography (7:93 EtOH:CH_2Cl_2) to give 625 mg (39 mCi, 65%) of [^{14}C]**3** as a pale yellow glass. TLC analysis (1:9 EtOH:CH_2Cl_2) showed a radiochemical purity of >95%, and the ^{1}H NMR matched that of an authentic unlabeled sample of **3**, except for the presence of EtOH (15 wt%). Analytical characterization of unlabeled **3**: ^{1}H NMR: δ 2.28 (2H, m, C6"-H_2), 2.57 (2H, quint, J = 7.4 Hz, C6-H_2), 2.64 (2H, t, J = 5.6 Hz, C5"-H_2), 2.91 (2H, t, J = 7.6 Hz, C5-H_2), 3.16 (2H, dd, J = 2.6, 5.6 Hz, C2"-H_2), 3.65 (2H, s, CαH_2), 3.92 (2H, t, J = 7.0 Hz, C7-H_2), 5.79 (1H, dd, J =2.5, 4.0 Hz, C3"-H), 7.01 (2H, apparent t, J = 8.8 Hz, C3'-H + C5'-H), 7.24-7.37 (5H, m, phenyl), 7.59 (2H, dd, J = 5.6, 8.8 Hz, C2'-H + C6'-H); ^{13}C NMR: δ 23.44 (C-H_2), 26.00 (C-H_2), 28.88 (C-H_2), 44.36 (C-H_2), 49.74 (C-H_2), 52.96 (C-H_2), 62.70 (C-H_2), 114.98 (d, J = 21.3 Hz, C3' + C5'), 125.43, 126.45, 127.08, 127.22, 128.30 (olefin./arom.), 128.56 (d, J = 7.7 Hz, C2' + C6'), 129.22 (olefin./arom), 133.00 (d, J = 3.2 Hz, C1'), 137.79, 140.42, 152.86 (olefin./arom.), 161.61 (d, J = 245 Hz, C4'); FT-IR (film): 3100-2800 (C-H), 1653, 1636, 1604, 1595 (C=C and C=N), 1536, 1495 (C=C), 1220 (C-F), 840, 747 (conjug. C=C), 699; CI-MS, m/Z (%): 374 (100, $(M + H)^+$), 354 (12, $(M + H - HF)^+$), 296 (3), 283 (5), 280 (6), 256 (12), 255 (62), 185 (5), 148 (4), 120 (5), 91 (12); high resolution MS: calcd. for $C_{24}H_{24}FN_3$, 374.2032; found, 374.2010.

2-(4-Fluorophenyl)-3-(4-[2,6-$^{14}C_2$]pyridinyl)-6,7-dihydro-5*H*-pyrrolo[1,2-a]imidazole ([^{14}C]**1c**)

A 625 mg (1.67 mmol) portion of [^{14}C]**3** was dissolved in 7 mL of nitrobenzene and 83 mg of 10% Pd/Al_2O_3 was added. The reaction mixture was heated with stirring to 145°C for 1.25 h. The reaction was worked up by diluting it with 40 mL EtOAc and extracting the mixture three times with 1N aqueous HCl. The combined aqueous extracts were washed four times with EtOAc, then basified by cautious addition of solid $NaHCO_3$. The basic solution was extracted three times with EtOAc, and the combined organic extracts were washed twice with saturated aqueous NaCl then dried over $MgSO_4$. The drying agent was removed by filtration, and the solvent was removed *in vacuo* to give 455 mg (33.2 mCi, 85%) of [^{14}C]**1c** as a wet amber crystalline solid. TLC analysis (1:2 EtOH:EtOAc) showed that the radiochemical purity was >95%. A portion was recrystallized for an analytical sample: mp 163-4°C; specific activity (MS) 23.8 mCi/mmol, ^{1}H NMR (C_6D_6): δ 1.51 (2H, tt, J = 7.2, 7.4 Hz, C6-H_2), 2.35 (2H, t, J = 7.6 Hz, C7-H_2), 2.80 (2H, t, J = 7.0 Hz, C5-H_2), 6.80 (4H, m, C3'-H + C5'-H + C3"-H + C5"-H), 7.74 (2H, m, C2'-H + C6'-H), 8.53 (2H, m, C2"-H + C6"-H), matches that of unlabeled standard except that the multiplet at δ 8.53 was skewed by the presence of ^{14}C.

6,7-Dihydro-2-[4-(methylthio)phenyl]-3-(4-[2,6-$^{14}C_2$]pyridinyl)-5*H*-pyrrole[1,2-a]imidazole ([^{14}C]**1b**)

A 280.1 mg (1.0 mmol) portion of [^{14}C]**1c** and 188.3 mg (2.7 mmol) sodium thiomethoxide in 5 mL DMF was stirred at 90°C for 6 h, then an additional 60 mg (0.86 mmol) of sodium thiomethoxide was added and the reaction was continued for 3 more h. The mixture was diluted with 75 mL of water, and the resulting suspension was extracted twice with 50 mL of CH_2Cl_2. The combined extracts were washed twice with water, once with saturated aqueous NaCl, then dried ($MgSO_4$). The drying agent was removed by filtration, and the filtrate was concentrated *in vacuo*. Resulting was 270 mg (88% yield) of crystalline [^{14}C]**1b**. The radiochemical purity was found to be 99.6% by HPLC (35:65 CH_3CN:0.04 M aq. $C_8H_{17}SO_3Na$ (pH 3)).

6,7-Dihydro-2-[4-(methylsulfinyl)phenyl]-3-(4-[2,6-$^{14}C_2$]pyridinyl)-5*H*-pyrrolo[1,2-a]imidazole ([^{14}C]**1a**)

A solution of $Na_2S_2O_8$ (252 mg, 1.06 mmol) in 2 mL of water was combined with a solution of 270 mg (0.88 mmol) of [^{14}C]**1b** in 3.5 mL HOAc, and the mixture was stirred a rt for 23 h, then diluted with 50 mL of water. The pH of the mixture was raised to 8-9 by the addition of solid K_2CO_3, and it was then extracted three times with CH_2Cl_2. The combined extracts were washed with water, saturated aqueous NaCl, then dried ($MgSO_4$). The drying agent was filtered off, and the filtrate was evaporated to dryness in vacuo. The

residue was triturated with EtOAc then dried in vacuo, providing 192 mg (68% yield) of [^{14}C]**1a** as a beige crystalline solid. The radiochemical purity by HPLC was 98.7% and the chemical purity 98.6% (30:70 CH_3CN:0.04 M aq. $C_8H_{17}SO_3Na$ (pH 2.6)); specific activity (MS), 23.7 mCi/mmol, ^{1}H NMR matched authentic unlabeled **1a**[2], except for minor carbon-14-induced perturbation of the part of the pyridinyl AB quartet assigned to C2-H and C6-H of that ring. An additional 70 mg (25% yield) of [^{14}C]**1a** was obtained by evaporating the EtOAc used in the trituration: radiochemical purity 95.1% by HPLC.

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REFERENCES

1. Hanna N., Marshall P.J., Newton, Jr. J., Schwartz L., Kirsch R., DiMartino M.J., Bender P. and Griswold D.E., Drugs Exp. Clin. Res. 16: 137 (1990).
2. Bender P.E. and Hanna N., US Patent 4,751,310, June 14, 1988.
3. Nakatsuka I., Kawahara K. and Yoshitake A. -- J. Lab. Comp. Radiopharm. 18: 495 (1981).
4. Overman L.E. and Sharp M.J. -- J. Amer. Chem. Soc. 110: 612 (1988).
5. Negishi E., Luo F.-T., Frisbee R. and Matsushita H. -- Heterocycles 18: 117 (1982).
6. Inoue H., Thyagarajan G. and May E.L. -- J. Het. Chem. 12: 709 (1975).
7. See for example Noel J.P. and Pichat L. -- J. Lab. Comp. Radiopharm. 20: 1243 (1983); Choi Y.M., Kucharczyk N. and Sofia R.D. -- *ibid.* 24: 1 (1987).
8. Blumenkopf T.A. and Overman L.E. -- Chem. Rev. 86: 865 (1986); Flann C., Malone T.C. and Overman L.E. -- J. Amer. Chem. Soc. 109: 6097 (1987).
9. Overman L.E. and Robichaud A.J. -- *ibid.* 111: 300 (1989); Overman L.E, Robertson G.M. and Robichaud A.J. -- J. Org. Chem. 54: 1236 (1989).
10. Overman L.E. and Sarkar A.K. -- Tet. Lett. 33: 4103 (1992)
11. Prepared from 3-butyn-1-ol through methanesulfonylation (methanesulfonyl chloride/pyridine) followed by treatment with excess benzylamine.