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The Radiolabeled Syntheses of JV 485, a Herbicide Candidate for Winter Wheat

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SUMMARY

JV 485 [^{14}C-Ph] and JV 485 [^{14}C-Py] were synthesized in seven steps in 35% and 44% overall yields, respectively, utilizing the same reaction schemes. The key step in each of the syntheses is a one pot Mid-Century Oxidation (1) of an aromatic methyl group to a carboxylic acid. The ^{14}C radiolabeled syntheses of two isolated metabolites of JV 485 were also completed. Preparation of the JV 485 [phenyl-^{14}C(U)] amide was completed in 62% yield from 2-chloro-5-[4-bromo-1-methyl-5-trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorobenzoic acid [ring-^{14}C(U)], 9. Preparation of the JV 485 [phenyl-^{14}C(U)] desmethyl acid 13 was accomplished in 18% overall yield in four steps from 3-(4-chloro-2-fluoro-5-methylphenyl [ring-^{14}C(U)])-5-(trifluoromethyl)-1H-pyrazole, 4.

Key words: JV 485, wheat herbicide, Mid-Century oxidation, metabolites

INTRODUCTION

2-Chloro-5-[4-bromo-1-methyl-5-trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorobenzoic acid 1-methylethyl ester, JV 485, is a broad spectrum preemergent herbicide candidate for winter wheat being co-developed by Monsanto Company and Bayer AG (2, 3, 4). It has been found to effectively control a wide variety of economically important weeds. Its mode of action involves the inhibition of the enzyme protoporphyrinogen IX oxidase resulting in disruption of chlorophyll

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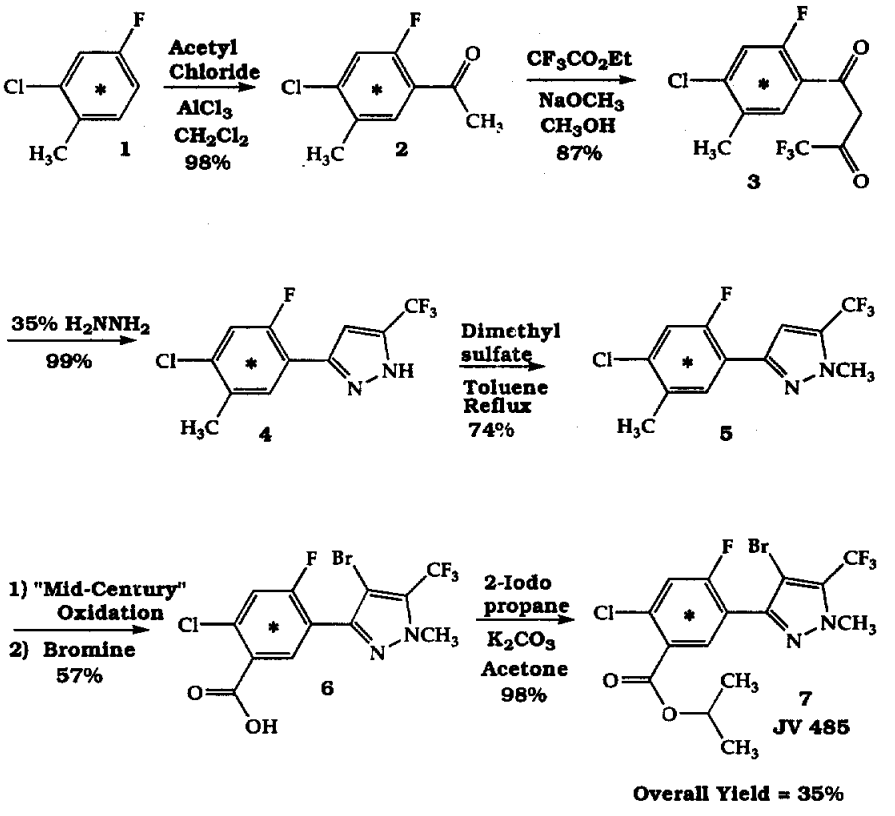
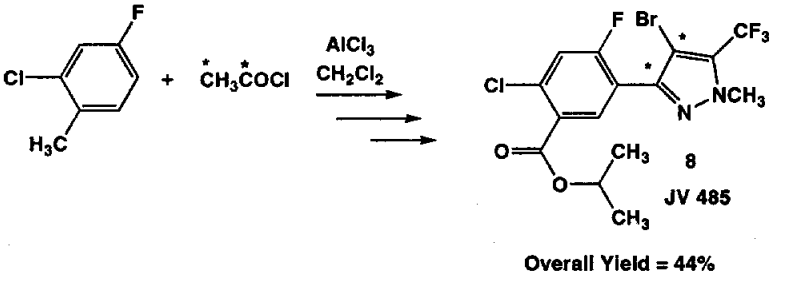
biosynthesis and rapid necrosis of green tissues upon exposure to light. To complete environmental plant, animal, soil and water studies for registration, the synthesis of ^{14}C-labeled JV 485 was required. Since JV 485 contains two ring systems, separate ^{14}C labels in each of the rings was required in the event the rings separated during metabolism studies. This paper describes both syntheses of the parent ring labeled compounds and the syntheses of two ^{14}C labeled metabolites of JV 485, JV 485 desmethyl acid [phenyl-^{14}C(U)] and the JV 485 amide [phenyl-^{14}C(U)].

RESULTS AND DISCUSSION

^{14}C labeled 2-chloro-5-[4-bromo-1-methyl-5-trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorobenzoic acid 1-methylethyl ester was synthesized in seven steps as shown in Scheme 1. Using Friedel-Crafts acylation chemistry, uniformly labeled 2-chloro-4-fluorotoluene [^{14}C-(U)] 1, was reacted with acetyl chloride in CH_2Cl_2 with $AlCl_3$ to form the substituted acetophenone 2, in 98% yield. Product 2, was condensed with ethyl trifluoroacetate in MeOH using NaOMe as the base. This produced butadione 3, in 87% yield. The butadione 3, was cyclized with hydrazine in refluxing toluene to form the pyrazole ring in 99% yield. A portion of the unmethylated product 4, was removed from the reaction mixture to prepare the JV 485 desmethyl acid metabolite. The balance of product 4, was methylated with dimethyl sulfate in toluene in the same flask as that used in the hydrazine cyclization. The methylation of product 4 was completed in 74% yield after purification by column chromatography. Using "Mid-Century" oxidation conditions as described in the experimental section, product 5, was oxidized to the benzoic acid. Without isolation, the acid was brominated in glacial AcOH to form product 6 in 57% yield for the two steps. Esterification of acid 6, with 2-iodopropane and K_2CO_3 in acetone produced the final product, JV 485 (^{14}C-Ph), in 98% yield for the last step. The final product was purified by flash column chromatography on silica gel using 10% EtOAc/90% hexane. The overall yield for the seven steps from the labeled trisubstituted aromatic starting material was 35%. The final product was determined to be 99% radiochemically pure by HPLC/Rad with a specific activity of 30.2 mCi/mmol. Likewise, the JV 485 (^{14}C-Pyrazole), 8 was synthesized in 44% overall yield from acetyl chloride [1,2-^{14}C] as shown in Scheme 2.

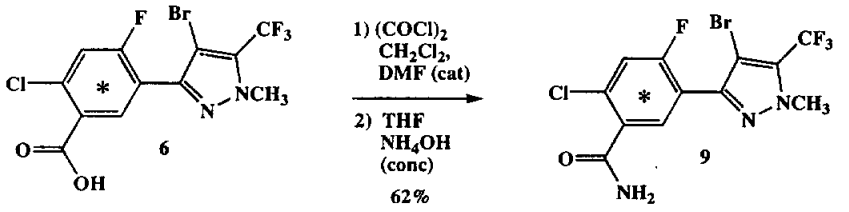


Scheme 1



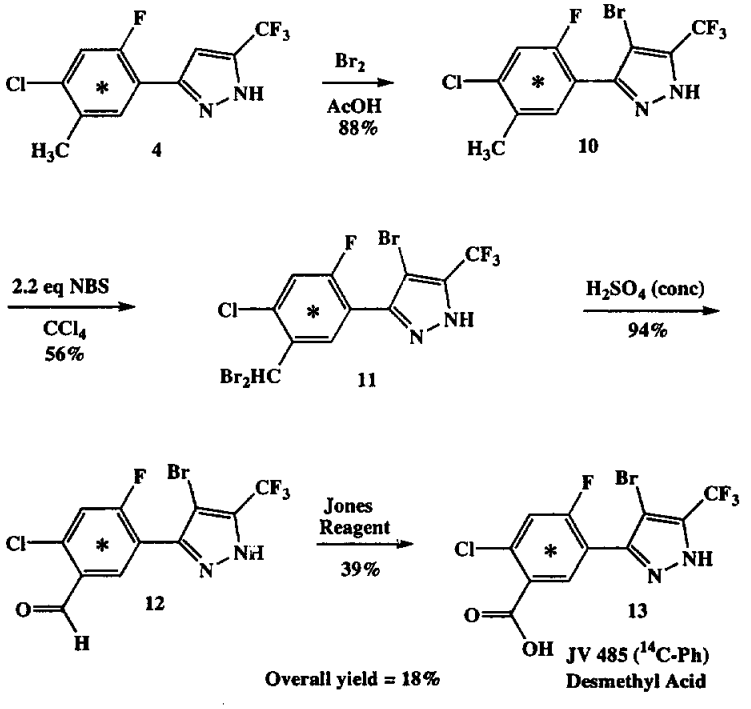
Scheme 2

The synthesis of the amide of 2-chloro-5-[4-bromo-1-methyl-5-trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorobenzoic acid [ring-^{14}C(U)], 6, is shown in Scheme 3. The amide 9 was formed by the reaction of ammonia with acid chloride 6.



Scheme 3

2-Chloro-5-[4-bromo-5-trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorobenzoic acid was synthesized in four steps from 3-(4-chloro-2-fluoro-5-methylphenyl [ring-^{14}C(U)])-5-(trifluoromethyl)-1H-pyrazole in an overall yield of 18% in Scheme 4. It was thought that the methyl group in 4 could be oxidized using the "Mid-Century" oxidation reaction(1), followed by bromination to give the desired desmethyl acid metabolite in two steps using a single pot reaction. In practice reactions of a gram or more of starting material, this sequence of reactions worked very well. However, due



Scheme 4

to the small reaction scale required in the radiolabeled synthesis, it was not possible to complete the oxidation of the methyl group using this set of reagents. Therefore, as an alternative method, the bromination of 4 with bromine in glacial AcOH at 70°C was used to produce the brominated material in 88% yield. Product 10 was reacted with NBS in CCl_4 to produce the tribrominated material, 11 in 56% yield. Product 11 was reacted with sulfuric acid to form the aldehyde, 12 in 94% yield. After purification by column chromatography, aldehyde 12, was oxidized to the final product using Jones reagent to form the acid 13, in 39% yield. The overall yield for the four steps was 18% from 4.

EXPERIMENTAL

Radioactivity was determined using Tracor Analytic Mark III counters which were interfaced with a Monsanto developed software package. Flash column chromatography was performed using Merck grade silica gel, 230-400 mesh, packed in 10% EtOAc/90% hexane or 20% EtOAc/80% hexane. HPLC was performed using a Waters HPLC systems consisting of a Model 680 automated gradient controller, two Model 510 pumps, a model U6K Injector, a Lambda-Max Model 481 UV detector set at 254 nm, a Radiomatic Flo-One Beta radioactivity flow detector, and a Beckman Ultrasphere column, C18, 5 μm, 4.6 X 250 mm. For the parent compounds, isocratic conditions (15% of 0.1%TFA in water/85% ACN, flowrate = 3 mL/min) were used. For metabolites, a linear gradient (initial = 60% of 0.1%TFA in water/40% ACN changing to 30% of 0.1%TFA/70% ACN over 25 minutes, flowrate = 3 ml/min) was used. GC-CIMS analysis was completed on a Finnigan model 4515 instrument using isobutane. All labeled compounds synthesized were identified by HPLC and/or TLC and/or MS comparison with the corresponding unlabeled material.

1-(4-Chloro-2-fluoro-5-methylphenyl [Ring-^{14}C(U)])-Ethanone, 2. To an oven-dried flask under nitrogen was weighed $AlCl_3$ (2.45 g, 18.4 mmol). To this was added CH_2Cl_2 (5 mL) and 2-Chloro-4-fluorotoluene [Ring-^{14}C (U)] (1.20 g, 8.33 mmol, 30.0 mCi/mmol, 250 mCi supplied by Amersham International). Acetyl chloride (0.90 mL, 12.7 mmol) was added dropwise over 20 min. After stirring for

three hours at room temperature, the solution was cooled with an ice bath and the excess $AlCl_3$ was destroyed by the slow addition of cold water. The aqueous and organic layers were separated. The water layer was extracted with CH_2Cl_2 (5 X 5 mL). The combined organic layers were washed with water (3 X 10 mL), brine (1 X 10 mL) and dried over $MgSO_4$. Suction filtration and removal of CH_2Cl_2 by rotary evaporation produced 1.53 g (98 % yield) of a dark liquid which solidified upon standing. This product was used in the next step without purification.

1-(4-Chloro-2-fluoro-5-methylphenyl [Ring-^{14}C(U)])-4,4,4-trifluoro-1,3-Butanedione, 3. To an oven-dried flask containing the acetophenone 2, (1.52 g, 8.14 mmol) and Ethyl trifluoroacetate (1.45 mL, 12.2 mmol) in MeOH (6 mL) was added 25% NaOMe in MeOH (2.8 mL, 12.2 mmol) over 20 min. The solution was warmed to reflux for 4.5 h, cooled to room temp. and then cooled with an ice-water bath. To the solution was added cold water (10 mL) and cold HCl (aq) (2.25 mL, 10 M) over 15 min. The cream colored solid formed was collected by suction filtration and was air dried. Water was removed in the next step to give 2.02 g (87%) of a white solid.

3-(4-Chloro-2-fluoro-5-methylphenyl [Ring-^{14}C(U)])-5-(trifluoromethyl)-1H-pyrazole, 4. A flask containing the butadione 3 and toluene (20 mL) was attached to a Dean-Stark trap and the material was dried by azeotropic distillation to give 2.02 g of dry material. To the solution was added 35% Hydrazine (0.64 mL, 7.07 mmol) at room temp. The solution was refluxed until no additional H_2O was removed. Analysis by GC indicated the reaction to be complete after 3 h. The solution was cooled to room temperature. At this time, material was removed (248 mg, 0.89 mmol, 26.7 mCi) for the preparation of a JV 485 (^{14}C-Ph) desmethyl acid metabolite.

3-(4-Chloro-2-fluoro-5-methylphenyl [Ring-^{14}C(U)])-1-methyl-5-(trifluoro-methyl)-1H-pyrazole, 5. Dimethyl sulfate (0.58 mL, 6.13 mmol) was added to the toluene solution containing the pyrazole 4, at room temp. The solution was warmed to reflux for 6 h attached to a Dean-Stark trap. To the cooled solution was added 4 mL of water and 50% NaOH (0.72 g). After 30 min, two layers formed. The aqueous layer was extracted with toluene (2 X 3 mL). The combined toluene solutions were washed with H_2O (3 X 5 mL), brine (1 X 5 mL) and dried over Na_2SO_4. Filtration and removal of toluene by rotary evaporation produced 1.80 g (crude yield =100%) of

slight yellow solid. Purification by flash column chromatography on silica gel using 20% EtOAc/80% hexane gave 1.33 g (74 %) of white solid that was used in the next step without further purification.

2-Chloro-5-[4-bromo-1-methyl-5-trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorobenzoic acid [Ring-^{14}C(U)], 6. To a long glass test tube was added 5, (1.11 g, 3.81 mmol), glacial acetic acid (4.5 mL), cobalt acetate tetrahydrate (9.53 mg, 0.038 mmol), manganese acetate tetrahydrate (1.46 mg, 0.006 mmol) and NaBr (19.4 mg, 0.188 mmol). The solution was warmed to 105°C with air bubbling through the blue solution through a gas dispersion tube and 30% H_2O_2 (1 uL) was added. Progress of the reaction was followed by TLC (Silica gel, 25% EtOAc/75% hexane). After 2.5 h, additional cobalt acetate, manganese acetate, NaBr and 30 % H_2O_2(2 uL) was added. After an additional 24 hours, the reaction was complete and the solution was cooled to 55°C. Bromine (0.36 mL, 7.0 mmol) was added and the solution was warmed to 75°C for 36 hours. The progress of the bromination was followed by HPLC. The solution was cooled to room temp. and water (5 mL) was added. A solution of Na_2SO_3 (sat) was added until no bromine color remained and no additional solid formed. This was cooled in an ice-water bath to complete the precipitation. The solid was collected by filtration and was rinsed with small portions of cold water. Air drying followed by drying under full vacuum produced 0.865 g (57%) of a white solid that was used in the next step without further purification.

2-Chloro-5-[4-bromo-1-methyl-5-trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorobenzoic acid 1-methylethyl ester [Ring-^{14}C(U)], 7. To the acid, **6**, (316.2 mg, 0.787 mmol) and K_2CO_3 (0.361 g, 2.62 mmol) in dry acetone (12.7 mL) was added 2-Iodopropane (0.40 mL, 4.0 mmol). The solution was warmed to reflux overnight. The reaction mixture was cooled to room temp., diluted with ether (15 ml) and water (10 mL). The aqueous and organic layers were separated. The aqueous layer was extracted with ether (2 X 5 mL). The combined ether extracts were washed with H_2O (3 X 5 mL), brine (1 X 10 mL) and dried over $MgSO_4$. Filtration and removal of the solvent by rotary evaporation produced 0.342 g (98% yield) of a white solid. The product was purified by flash column chromatography on silica gel using 10% EtOAc/90% hexane. The final product, JV 485 (^{14}C-Ph), was determined to be 99%

radiochemically pure by HPLC/Rad and had a specific activity of 30.2 mCi/mmol. Mass spectra analysis agreed with that expected for JV 485 with a characteristic pattern for a ^{14}C ring-labeled compound.

2-Chloro-5-[4-bromo-1-methyl-5-trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorobenzoic acid 1-methylethyl ester [Pyrazole-3,4-^{14}C], 8. The synthesis of JV 485 (^{14}C-Py) was completed using the same steps as in Scheme 1. The JV 485 (^{14}C-Py) was synthesized from acetyl chloride [1,2-^{14}C] provided by New England Nuclear (1.22 g, 15.6 mmol, 500 mCi, 32.0 mCi/mmol) and 2-chloro-4-fluorotoluene in the first step as shown in Scheme 2. Overall yield for the synthesis of JV 485 (^{14}C-Py) was 44%. The radiochemical purity was determined to be 98% and the specific activity was measured to be 32.0 mCi/mmol by gravimetric analysis. Mass spectral analysis was consistent with that expected for JV 485 (^{14}C-Py).

JV 485 (^{14}C-Ph) Amide, 9. To an oven-dried flask was added the JV 485 acid, 6, (134 mg, 33 mmol, 10.0 mCi), CH_2Cl_2 (1.3 mL), DMF (1 uL) and oxalyl chloride (5.8 uL, 660 mmol). The solution was stirred at room temperature for 20 min. The CH_2Cl_2 and excess oxalyl chloride were removed under reduced pressure. To this was added THF (1.0 mL) and ammonium hydroxide (2.6 mL, 39 mmol). The solution was stirred at room temp. for 1 h. The solution was extracted with ether (3 X 7 mL). The combined ether extracts were washed with aqueous 10% $NaHCO_3$ (2 X 5 mL), H_2O (2 X 5 mL), brine (1 X 5mL) and dried over Na_2SO_4. Filtration and removal of solvent produced an off white solid. Purification of the solid by flash column chromatography on silica gel with 50% EtOAc/50% hexane produced 83 mg (yield = 62%) of a white solid. The specific activity was determined to be 30.0 mCi/mmol by gravimetric analysis. The radiochemical purity was 98% and the product was equivalent to a JV 485 Amide standard by mass spectrometry.

3-(4-Chloro-2-fluoro-5-methylphenyl [Ring-^{14}C(U)])-4-bromo-5-(trifluoromethyl)-1H-pyrazole, 10. To 3-(4-Chloro-2-fluoro-5-methylphenyl [ring-^{14}C(U)])-5-(trifluoromethyl)-1H-pyrazole, 4, (198 mg, 0.71 mmol) was added glacial AcOH (1.0 mL). The solution was warmed to 50°C and bromine (0.1 mL, 1.9 mmol) was added. The solution was then warmed to 70°C for 30 h. The solution was cooled to room temp. and ether (15 mL) and sat. aqueous sodium sulfite (5 mL) was added.

The two layers were separated and the aqueous layer was extracted with ether (2 X 5 mL). The combined ether extracts were washed with water (3 X 5mL), brine (1 X 5 mL) and dried over Na_2SO_4. Filtration and removal of solvent produced 223 mg (yield = 88%) of a yellow solid. Mass spectra analysis produced results consistent with the expected brominated product.

4-Bromo-3-[4-Chloro-5-(dibromomethyl)-2-fluorophenyl] [Ring-^{14}C(U)]-5-(trifluoromethyl)-1H-pyrazole, 11. A flask containing 3-(4-chloro-2-fluoro-5-methylphenyl [ring-^{14}C(U)])-4-bromo-5-(trifluoromethyl)-1H-pyrazole, 10, (139 mg, 0.39 mmol), N-bromosuccinimide (150 mg, 0.84 mmol), benzoyl peroxide (5 mg) and CCl_4 (1.25 mL) was warmed to 80°C for 116 h. During the reaction, an additional amount of benzoyl peroxide (2.5 mg) and NBS (80 mg, 0.45 mmol) was added to complete the reaction. The solution was cooled to room temperature, filtered and the CCl_4 was removed under reduced pressure. The resulting solid and that from another of the same reaction was purified by flash column chromatography on silica gel with 20% EtOAc/80% hexane. The solvent was removed by rotary evaporation to give 256 mg (combined yield = 56% for both reactions) of a solid material. This product was reacted in the next step without further purification.

2-Chloro-5-[4-bromo-5-(trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorobenzaldehyde [ring-^{14}C(U)], 12. 4-Bromo-3-[4-chloro-5-(dibromomethyl)-2-fluorophenyl][ring-^{14}C(U)]-5-(trifluoromethyl)-1H-pyrazole, 11, (154 mg, 0.30 mmol) in conc. H_2SO_4 (0.5 mL, 9 mmol) was stirred at 36-40°C for 22 h. The reaction mixture was cooled to room temperature and ether (15 mL) and water (10 mL) was added. The two layers were separated. The aqueous layer was extracted with ether (2 X 5 mL). The combined ether extracts were washed with aqueous 10% $NaHCO_3$ (5 mL), water (5 mL) brine (5 mL) and dried over Na_2SO_4. Filtration and removal of ether by rotary evaporation produced a solid which was purified by flash column chromatography on silica gel using 40% EtOAc/60% hexane gave 104 mg (yield = 94%) of solid material. Mass spectral analysis agreed with that expected for the aldehyde product.

2-Chloro-5-[4-bromo-5-trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorobenzoic acid [ring-^{14}C(U)], 13. To 2-chloro-5-[4-bromo-5-(trifluoromethyl)-1H-pyrazol-3-yl]-4-fluorobenzaldehyde [ring-^{14}C(U)], 12, (104 mg, 0.28 mmol) in acetone (1.0 mL)

was added Jones reagent (0.21 mL, 0.56 mmol). The solution was stirred for 2 h. TLC analysis on silica using 40% EtOAc/60% hexane showed the reaction to be complete, R_f (acid product = 0.02), R_f (Aldehyde starting material = 0.60). To the solution was added water (8.5 mL) and the solution was cooled in an ice-water bath for 10 min. An off-white solid formed and was collected by filtration. The solid was washed with cold water and dried to give a white solid. The solid was dissolved in a minimum amount of acetonitrile (ACN) and was purified by passing it through a C18 Megabond elut™ column starting with 50% H_2O/50% ACN and then changing to 45% H_2O/55% ACN. The ACN and water fractions containing the product were added to a separatory funnel and EtOAc and brine was added. The layers were separated and the aqueous layer was extracted with EtOAc. The EtOAc extracts were washed with brine (2 X 5 mL) and were dried over Na_2SO_4. Filtration and solvent removal produced 43 mg of solid product (yield = 39%, overall yield =18% from 4). Mass spectra analysis was consistent with that expected for the acid product. In addition, co-injection of the product and a ^{12}C standard on a reverse phase HPLC column produced a single peak. The radiochemical purity was 98% by HPLC/Rad and the specific activity was measured to be 30.0 mCi/mmol by gravimetric analysis.

ACKNOWLEDGEMENTS

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