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The synthesis and analysis of [phenyl-^{14}C(U)] BMS-770767 and [$^{13}C_6$]BMS-770767 for use in discovery biotransformation, human ADME and bioanalytical studies

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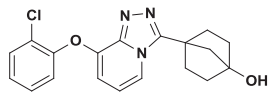
Type 2 diabetes is a significant worldwide health problem. To support the development of BMS-770767 as an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) for type 2 diabetes was required the synthesis of carbon-14-labelled material for use in metabolic profiling and for the human adsorption, distribution, metabolism and excretion (ADME) study. Initially, [phenyl-^{14}C(U)]BMS-770767 was synthesized in two steps from a late-stage intermediate and [^{14}C(U)]2-chlorophenol to give the desired final product in 18% yield. Later, the synthesis was completed for the human ADME clinical study using a combination of the discovery and process chemistry routes under cGMP to prepare [phenyl-^{14}C(U)]BMS-770767. The radiochemical purity of the synthesized [phenyl-^{14}C(U)]BMS-770767 after dilution with unlabelled clinical grade BMS-770767 was 99.1% having a specific activity of 1.61 μCi/mg. In addition, to support the quantification of BMS-770767 in LC/MS analyses, [$^{13}C_6$]BMT-770767 was prepared in two steps from a late-stage intermediate and [$^{13}C_6$]2-chlorophenol.

Keywords: type 2 diabetes; 11β-HSD1; human ADME; carbon-14; stable isotope-labelled synthesis

Introduction

Type 2 diabetes is a significant worldwide health problem afflicting more than 300 million people worldwide.[1,2] It is thought that metabolic syndrome, a combination of insulin resistance, obesity, dyslipidemia, hyperglycemia and hypertension, may be a major cause of type 2 diabetes. Cortisol is a circulating glucocorticoid that regulates carbohydrate, protein and lipid metabolism as well as modulates inflammatory and immune responses. Excess glucocorticoids can cause increased glucose output, reduced glucose-dependent insulin sensitivity in adipose tissue and reduced insulin secretion from the pancreas. 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an enzyme that catalyzes the conversion of inactive cortisone to cortisol.[3] Transgenic mice that overexpressed 11β-HSD1 in adipose tissue were found to exhibit metabolic disorders including obesity, insulin resistance, glucose intolerance and hyperglycemia.[3] 11β-HSD1 knockout mice were found to be resistant to obesity and hyperglycemia.[3] Therefore, it would seem that an inhibitor of 11β-HSD1 could possibly be an efficacious therapy for the treatment of dysmetabolic syndrome and type 2 diabetes.[3–5] BMS-770767, as shown in Figure 1, represents such an 11β-HSD1 inhibitor.[6–9] To further the development of BMS-770767, it was necessary to prepare [phenyl-^{14}C(U)]BMS-770767, **5** early on for discovery biotransformation studies, and then later, **25** was prepared at a different specific activity for use in a human absorption, distribution, metabolism and excretion (ADME) study.[10] This paper also describes the synthesis of [$^{13}C_6$]BMS-770767, **8** for use as an LC/MS standard.



BMS-770767, 1

Figure 1. Structure of BMS-770767, **1**.

Experimental

Materials and methods

All reactions were conducted under an inert atmosphere of nitrogen and stirred magnetically. Microwave reactions were carried out in a CEM (Matthews, NC) Discover microwave system at 200 W with cooling. All reagents and solvents were American Chemical Society grade or better and used without further purification. [^{14}C(U)]2-Chlorophenol for the discovery synthesis (100 mCi, specific activity 78 mCi/mmol, >98.8% radiochemical purity) and for the current good manufacturing practice (cGMP) synthesis (97.2 mCi, specific activity 53.4 mCi/mmol, >98.8% radiochemical purity) were obtained from PerkinElmer Life Sciences (Boston, MA). [$^{13}C_6$]2-Chlorophenol (99.1 atom% ^{13}C) was obtained from IsoSciences (King of Prussia, PA). Clinical grade BMS-770767 was obtained from the Process Research and Development Department at

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Bristol-Myers Squibb (New Brunswick, NJ). All authentic samples were obtained from either the Process Research and Development Department, the Discovery Chemical Synthesis Group (Princeton, NJ) or the Medicinal Chemistry Department (Pennington, NJ) at Bristol-Myers Squibb. Solvent removal under reduced pressure was accomplished using a Büchi (Flawil, Switzerland) model 200 rotary evaporator. Specific activities were determined by gravimetric analysis using liquid scintillation counting on a Perkin Elmer (Waltham, MA) model 2900TR Liquid Scintillation Counter.

Chromatography systems

Column chromatography was performed using an AnaLogix (Burlington, WI) BSR Flash Chromatography system using Teledyne Isco (Lincoln, NB) Redi-Sep R_f silica cartridges. TLC analyses (EMD (Darmstadt, Germany) 60, F_{254} silica gel coated plates) were performed using either UV (254 nm) or iodine to visualize. HPLC analyses were performed on an Agilent (Santa Clara, CA) 1200 HPLC system, with a diode array detector for UV detection and an IN/US, now LabLogic, (Tampa, FL) Beta-Ram model 3 detector using LauraLite Version 3.4.1.10 software for radiochemical detection. The following analytical methods were used for in process analyses and final purity measurements. HPLC method A: Agilent Eclipse XDB C18, 5 μm, 4.6 × 150 mm, mobile phase A: water with 0.1% trifluoroacetic acid (TFA), mobile phase B: acetonitrile (MeCN) with 0.1% TFA. Gradient: 0 min, 90% A; 10 min, 90% B; 12 min, 90% B; 13 min, 90% A, flow rate = 1.0 mL/min. UV detection at 254 nm. HPLC method B: Phenomenex (Torrance, CA) Luna C18, 3 μm, 4.6 × 50 mm mobile phase A = 95% water : 5% MeCN : 0.05% TFA, mobile phase B = 95% MeCN : 5% water : 0.05% TFA, 0 min 15% B, 8 min 15% B, 18 min 100% B, 20 min 100% B, 22 min 15% B, flow rate = 2.0 mL/min, UV detection at 220 nm. HPLC method C: Agilent Technologies Zorbax SB-C18, 3.5 μm, 4.6 × 150 mm mobile phase A = 10 mM NH_4OAc in water adjusted to pH = 4.5 with AcOH, mobile phase B = MeCN, gradient: 0 min 20% B, 1 min 20% B, 26 min 28% B, 41 min 80% B, 45 min 80% B, 45.5 min 20% B, 50 min 20% B, flow rate = 1.0 mL/min, UV detection at 273 nm, column temperature = 40°C. Preparative HPLC was performed on a Varian, now part of Agilent (Santa Clara, CA) PrepStar HPLC System with two Varian PrepStar model 218 pumps with 25 mL heads and a Varian ProStar UV-Vis model 320 detector. Preparative HPLC method A: Phenomenex Luna C18, 5 μm, 250 × 21.2 mm. mobile phase A: water with 0.1% TFA, mobile phase B: MeCN with 0.1% TFA, gradient: 0 min 30% B, 12 min 80% B, 15 min 80% B, 17 min 30% B, flow rate = 10 mL/min, UV detection at 254 nm. Preparative HPLC method B: Phenomenex Gemini C18, 4 μm, 250 × 21.2 mm mobile phase A: 90% water : 10% MeCN with 0.1% TFA, mobile phase B: 90% MeCN : 10% water with 0.1% TFA, gradient: 0 min 20% B, 12 min 90% B, 15 min 90% B, 17 min 20% B, flow rate = 10 mL/min, UV detection at 254 nm. Preparative HPLC method C: Phenomenex Luna 5 μm C18, 250 × 21.2 mm, mobile phase A = water with 0.5% TFA, mobile phase B = MeCN with 0.05% TFA, gradient: 0 min 40% B, 15 min 77% B, 17 min 90% B, 20 min 90% B, 22 min 40% B, flow rate = 10 mL/min, UV detection at 220 nm. Preparative HPLC method D: Phenomenex Luna C18, 5 μm, 250 × 21.2 mm mobile phase A: water with 0.5% TFA, mobile phase B: MeCN with 0.05% TFA. Gradient: 0 min 90% A, 20 min 90% B, 22 min 90% B, 25 min 90% A, flow rate = 10 mL/min, UV detection at 220 nm.

NMR

Proton NMR spectra were recorded on either a 300 or 400 MHz Bruker (Billirica, MA) Avance spectrometer or a JEOL (Tokyo, Japan) EC+ 500 MHz spectrometer as listed. For stable isotope-labelled products, only carbon-13 enriched positions are reported for ^{13}C NMR characterization purposes.

MS

LC/MS spectra were recorded on a Finnigan LXQ (Thermo Fisher Scientific Inc., Waltham, MA) LC/MS System with detection by ESI (+) ion. LC/MS method: column = Phenomenex Gemini 5 μm, C18, 50 × 3.0 mm, flow rate = 0.50 mL/min, UV detection by PDA at 200–400 nm. Mobile phase A = 1000 water : 1 formic acid, mobile phase B = 1000 MeCN : 1 formic acid, gradient: 0 min 10% B, 10 min 100% B.

Discovery synthesis of [^{14}C(U)]BMS-770767

8-([Phenyl-^{14}C(U)]-2-chlorophenoxy)-3-(4-methoxybicyclo[2.2.1]heptan-1-yl)-[1,2,4]triazolo[4,3-a]pyridine, ***4.*** To a dry microwave vial with stir bar was weighed 8-bromo-3-(4-methoxybicyclo[2.2.1]-heptan-1-yl)-[1,2,4]triazolo [4,3-a]pyridine, **3** (248 mg, 0.768 mmol) and Cs_2CO_3 (249 mg, 0.763 mmol). To this was added DMF (1.0 mL) and [^{14}C(U)]2-chlorophenol, **2** (66.4 μL, 82.4 mg, 0.641 mmol, specific activity = 78 mCi/mmol, 50 mCi). The reaction was heated to 160°C under microwave radiation at 200 W for 3.5 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (10 mL), washed with 1 N NaOH (3 × 2 mL) and water (3 × 2 mL), dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to give 169 mg of crude product. The crude product was combined with that from another reaction on a similar scale. The combined material was purified by flash chromatography using a Redi-Sep R_f 40 g silica cartridge and eluting with 20% EtOAc : 80% hexane to 80% EtOAc : 20% hexane. Pure product fractions were pooled, and the solvent was removed under reduced pressure followed by drying on a vacuum line to constant weight to give 158 mg of a white solid, **4** (33% yield). The product was analyzed using HPLC method A which showed it to be 99% chemically pure with a retention time of 7.33 min and 99.6% radiochemically pure. The labelled product co-eluted with an authentic sample. The product was used in the next step of the synthesis without further purification.

4-(8-([Phenyl-^{14}C(U)]2-chlorophenoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)bicyclo[2.2.1]heptan-1-ol, [phenyl-^{14}C(U)]BMS-770767, ***5.*** To 8-([phenyl-^{14}C]-2-chlorophenoxy)-3-(4-methoxybicyclo[2.2.1]heptan-1-yl)-[1,2,4]triazolo[4,3-a]pyridine, **4** (67 mg, 0.18 mmol) dissolved in acetic anhydride (0.5 mL) at 0°C was added 48% HBr (0.50 mL, 9.2 mmol). After addition, the solution was stirred at room temperature for 10 min and then warmed to 100°C for 1.5 h. The reaction was cooled to room temperature, and the solvent was removed under reduced pressure. To the resulting crude solid was added MeOH (0.8 mL) and 2.2 M NaOH (aq) (0.33 mL, 0.72 mmol). The solution was warmed to 65°C for 1 h. After cooling to room temperature, a solid formed. The solvent was removed under reduced pressure, and water (5 mL) was added. The water layer was extracted with $CHCl_3$ (3 × 5 mL). The pooled $CHCl_3$ extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give 54.7 mg of crude product. This crude product was combined with the crude product from that of another reaction at 1.36 times the scale. The crude products were purified by preparative HPLC using method A. Fractions containing the pure product were pooled, and the solvent was removed under reduced pressure using EtOH to azeotrope the last traces of water and then dried on a vacuum line to consistent weight to give 84 mg of an off white solid, [phenyl-^{14}C(U)]BMS-770767, **5** (55% yield). Analysis by HPLC using method A showed the product to be 99.9% chemically pure with a retention time of 6.13 min and 99.6% radiochemically pure. The material co-eluted with an authentic sample. Analysis by LC/MS showed m/z (+ ion) =356 (100%)/358 (41%)/360 (33%)/362 (19%)/364 (26%)/366 (9%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.33 (d, J = 6.6 Hz, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.24–7.33 (m, 2H), 6.81 (t, J = 7.1 Hz, 1H), 6.47 (d, J = 7.1 Hz, 1H), 5.14 (s, 1H), 2.03–2.18 (m, 4H), 2.01 (s, 2H), 1.79–1.87 (m, 2H), 1.62–1.69 (m, 2H). The specific activity was measured to be 216 μCi/mg, 76.8 mCi/mmol, to yield a total of 18.2 mCi of product.

Synthesis of [$^{13}C_6$]BMS-770767

8-([$^{13}C_6$]2-Chlorophenoxy)-3-(4-methoxybicyclo[2.2.1]heptan-1-yl)-[1,2,4]triazolo[4,3-a] pyridine, 7. To a dry microwave vial with stir bar was weighed 8-bromo-3-(4-methoxybicyclo [2.2.1]-heptan-1-yl)-[1,2,4]triazolo[4,3-a]pyridine, **3** (250 mg, 0.78 mmol) and Cs_2CO_3 (253 mg, 0.78 mmol). To this was added DMF (1.0 mL) and [$^{13}C_6$]2-

chlorophenol, **6** (77 μL, 95 mg, 0.71 mmol). The reaction was heated to 160°C under microwave radiation for 3 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (10 mL), washed with 1 N NaOH (3 × 2 mL) and water (3 × 2 mL), dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to give the crude product. The crude product was combined with that from another reaction on a similar scale. The combined crude product was purified by flash chromatography using a Redi-Sep R_f 40 g silica cartridge and eluted with 20% EtOAc : 80% hexane to 80% EtOAc : 20% hexane. Pure product fractions were pooled, and the solvent was removed under reduced pressure followed by drying on a vacuum line to constant weight to give 118 mg of a white solid, **7** (44% yield). The product was analyzed using HPLC method A which showed it to be 97.1% chemically pure with a retention time of 7.09 min. The labelled product co-eluted with an authentic sample. The product was used in the next step of the synthesis without further purification.

4-(8-([$^{13}C_6$]2-Chlorophenoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)bicyclo [2.2.1]heptan-1-ol,[$^{13}C_6$]BMS-770767, ***8***. To 8-([$^{13}C_6$]2-chlorophenoxy)-3-(4-methoxybicyclo[2.2.1]heptan-1-yl)-[1,2,4]triazolo[4,3-a]pyridine, **7** (60 mg, 0.16 mmol) dissolved in acetic anhydride (0.44 mL) at 0°C was added 48% HBr (0.44 mL, 8.1 mmol). After addition of HBr, the solution was stirred at room temperature for 10 min and then warmed to 100°C for 1 h. The reaction was cooled to room temperature, and the solvent was removed under reduced pressure. To the resulting crude oil was added MeOH (0.73 mL) and 2.2 M NaOH (aq) (0.29 mL, 0.64 mmol). The solution was warmed to 65°C for 1 h. After cooling to room temperature, a solid formed. This crude product was combined with the crude product from that of another reaction at nearly the same scale. To the crude products was added water (5 mL). The water layer was extracted with $CHCl_3$ (5 × 4 mL). The pooled $CHCl_3$ extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to give 95 mg of crude product. The crude product was purified by preparative HPLC using method B. Fractions containing the pure product were pooled, and the solvent was removed under reduced pressure using EtOH to remove the last traces of water by azeotrope and then dried on a vacuum line to consistent weight to give 77 mg of a white solid (68% yield). Analysis by HPLC using method A showed the product to be 99.6% chemically pure with a retention time of 6.18 min. The material co-eluted with an authentic sample. Analysis by LC/MS showed *m/z* = 361 (2%)/362 (100%)/363 (16%)/364 (34%)/365 (5%)/366 (0.6%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.33 (d, *J* = 6.6 Hz, 1H), 7.92 (m, 1H), 7.60 (m, 1H), 7.40 (m, 1H), 7.05 (m, 1H), 6.81 (t, *J* = 7.1 Hz, 1H), 6.47 (d, *J* = 7.1 Hz, 1H), 5.14 (s, 1H), 2.03–2.18 (m, 4H), 2.01 (s, 2H), 1.79–1.87 (m, 2H), 1.62–1.69 (m, 2H). ^{13}C NMR (125.77 MHz, DMSO-d_6) δ ppm 150.07 (dd, *J* = 68.6 and 73.8 Hz), 130.88 (dd, *J* = 58.5 and 61 Hz), 129.05 (t, *J* = 56 Hz), 126.55 (dd, *J* = 53.4 and 55.6 Hz), 124.71 (dd, *J* = 68.7 and 71.2 Hz), 121.76 (dd, *J* = 66.1 and 56 Hz).

cGMP synthesis of [phenyl-^{14}C(U)]BMS-770767

3-Bromo-2-hydrazinylpyridine, ***18***. To a new round bottom flask with stir bar was weighed 3-bromo-2-chloropyridine, **17** (8.55 g, 44.4 mmol). Absolute ethanol (85.5 mL) was added, and the solution was stirred for 5 min. To this solution was added hydrazine monohydrate (65 mL, 65% in water, 0.86 mol) over 5 min. The solution was stirred for 5–10 min at room temperature, and then, the flask was attached to a reflux condenser and heated to 100°C overnight. The solution was cooled to room temperature and large crystals formed. The reaction mixture was filtered, and the crystals were washed with cold water. The material was transferred to a round bottom flask and was dried under vacuum to give 7.10 g of white crystals, **18** (85% yield). HPLC analysis using analytical method B showed the product to be 100% chemically pure with a retention time of 0.285 min. LC/MS analysis showed *m/z* = 188 (100%)/190 (98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.15 (dd, *J* = 4.9, 1.4 Hz 1H), 7.66 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.60 (d, *J* = 7.6, 4.8 Hz, 1H), 6.25 (br. s. 1H), 4.00 (br. s. 2H).

4-(2-(3-Bromopyridin-2-yl)hydrazine-1-carbonyl)bicyclo[2.2.1]heptan-1-yl 3,5-difluorobenzoate, ***19***. To a new dry 100 mL round bottom flask with stir bar under nitrogen was weighed 4-((3,5-difluorobenzoyl)oxy) bicyclo[2.2.1]heptane-1-carboxylic acid, **14** (5.00 g, 16.9 mmol). To this was added toluene (25.4 mL) and one drop of DMF. The suspension was stirred for 5 min, and oxalyl chloride (1.5 mL, 17 mmol) was added dropwise over 10 min. The reaction was stirred for 45 min, and the suspension became a clear solution. In a separate new 250 mL round bottom flask with stir bar was weighed 3-bromo-2-hydrazinylpyridine, **18** (2.89 g, 15.4 mmol) and K_2CO_3 (2.48 g, 17.9 mmol). To this was added THF (34 mL). The solution was cooled to 0–5°C in an ice-water bath. Water (25 mL) was added, and the suspension was stirred for 15 min until two layers formed. To this was added the acid chloride solution over 15 min while stirring slowly. The reaction was stirred at 3–5°C for 3 h and then warmed to room temperature and stirred for 2.5 h. The bottom aqueous layer was removed. The organic layer was washed with 5% brine solution (25 mL). The solvent was removed under reduced pressure. Hot toluene (25 mL) was added to completely dissolve the solid. Upon cooling, crystallization occurred and heptane (10 mL) was added to complete the crystallization. The crystals were collected and dried on a vacuum line to give 4.40 g of off white solid, **19** (61.3% yield). HPLC analysis using analytical method B showed the material to be 100% pure with a retention time of 12.45 min. LC/MS analysis showed *m/z* (+ ion) = 466.17 (100%)/468.17 (97%) with a retention time of 6.15 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.61 (d, *J* = 2.1 Hz, 1H), 8.04–8.13 (m, 2H), 7.83 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.53–7.69 (m, 3H), 6.69 (dd, *J* = 7.6, 4.8 Hz, 1H), 1.78–2.23 (m, 10H).

4-(8-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)bicyclo[2.2.1]heptan-1-yl 3,5-difluorobenzoate, ***20***. To a new dry 250 mL round bottom flask with stir bar under nitrogen was weighed 3.96 g of 4-(2-(3-bromopyridin-2-yl)hydrazine-1-carbonyl)bicyclo[2.2.1]heptan-1-yl 3,5-difluorobenzoate, **19** (8.49 mmol). To this was added anhydrous toluene (58 mL). The suspension was stirred for 5–10 min at 75°C until the solid completely dissolved. $POCl_3$ (4.40 mL, 47.2 mmol) was added dropwise over 5 min, and the solution was warmed to 92°C. After 43 h, the solvent was removed by under reduced pressure. MeCN (54 mL) was added. The suspension was cooled to 0–5°C, and 18% aqueous potassium phosphate (44 mL) was added and additional solid formed. The solid was collected by filtration and washed with cold water (100 mL). The solid was transferred to a flask and was dried on a vacuum line to give 3.18 g of a white solid, **20** (84% yield). HPLC analysis using analytical method B showed the product to be 100% chemically pure with a retention time of 13.17 min. LC/MS analysis showed the product *m/z* (+ ion) = 448 (95.9%)/449 (22.4%)/450 (100%)/451 (22.0%)/452 (2.9%) and eluted with a retention time of 6.07 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.67 (d, *J* = 6.6 Hz, 1H), 7.73 (d, *J* = 6.8 Hz, 1H), 7.57–7.70 (m, 3H), 6.89 (t, *J* = 7.0 Hz, 1H), 2.05–2.40 (m, 10H).

4-(8-Bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl)bicyclo[2.2.1]heptan-1-ol, ***21***. To a new dry 100 mL recovery flask with stir bar under nitrogen was weighed 4-(8-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl) bicyclo[2.2.1]heptan-1-yl 3,5-difluorobenzoate, **20** (1.90 g, 4.24 mmol). To this was added methanol (19 mL) to form a thick suspension. To the suspension was added 2.5 M NaOH (3.7 mL, 9.3 mmol). The suspension was stirred at room temperature for 2.5 h after which it became a cloudy solution. The methanol was removed under reduced pressure, and water (12 mL) was added to dissolve the solid. The aqueous layer was extracted with EtOAc (5 × 20 mL). The pooled EtOAc extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The product was further dried on a vacuum line to give 1.49 g of an off white solid composed of 1.19 g of the desired product, **21** and 0.30 g of 3,5-difluorobenzoic acid as determined by ^{1}H NMR (88% yield). HPLC analysis using analytical method A showed the product to be 67% chemically pure with a retention time of 5.96 min. LC/MS analysis showed the product with *m/z* (+ ion) = 308.25 (100%)/310.25 (97%) with a retention time of 2.18 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.60 (dd, *J* = 7.0, 0.6 Hz, 1H), 7.69 (dd, *J* = 7.1, 0.5 Hz, 1H), 6.84 (t, *J* = 7.0 Hz,

1H), 5.17 (s, 1H), 1.97–2.19 (m, 6H), 1.76–1.92 (m, 2H), 1.59–1.73 (m, 2H). Integration shows approximately 0.5 equivalents of 3,5-difluorobenzoic acid to one equivalent of the desired product, **21**. The mixture of products was used in next reaction without additional purification.

8-Bromo-3-(4-methoxybicyclo[2.2.1]heptan-1-yl)-[1,2,4]triazolo[4,3-a]pyridine, ***3***. To a new dry round bottom flask with stir bar under nitrogen was weighed 4-(8-bromo-[1,2,4]triazolo[4,3-a]pyridin-3-yl) bicyclo[2.2.1]heptan-1-ol, **21** (1.00 g, 3.24 mmol) and sodium amide (140 mg, 3.60 mmol). To this was syringed DMF (30 mL) to form a yellow suspension. The suspension was stirred for 30 min, and then, a solution of iodomethane (0.23 mL, 3.6 mmol) in DMF (1.0 mL) was added, and the suspension was stirred at room temperature overnight. The solvent was removed under reduced pressure leaving a light yellow solid. The crude product was purified by flash chromatography using a 120 g Redi-Sep R_f cartridge and a gradient of 100% CH_2Cl_2 to 10% methanol/90% CH_2Cl_2. Pure fractions were pooled, and the solvent was removed by under reduced pressure and then dried on a vacuum line to constant weight to give 269 mg of a white solid, **3** (26% yield). HPLC analysis using analytical method B showed the product to be 100% chemically pure with a retention time of 2.18 min. LC/MS analysis showed *m/z* (+ ion) = 322.25 (100%)/324.17 (97%) with a retention time of 2.43 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.67 (d, *J* = 6.4 Hz, 1H), 7.72 (dd, *J* = 7.2, 0.6 Hz. 1H), 6.87 (t, *J* = 7.0 Hz, 1H), 3.31 (s, 3H), 2.10–2.21 (m, 6H), 1.91–2.02 (m, 2H), 1.70 (dt, *J* = 13.7, 5.1 Hz, 2H).

Cesium [phenyl-^{14}C(U)]2-chlorophenolate, ***23***. To a new dry 25 mL round bottom flask with stir bar under nitrogen was weighed Cs_2CO_3 (272 mg, 0.833 mmol). To this was syringed ethyl ether (7.0 mL) to form a white suspension. The suspension was cooled to 3°C in an ice-water bath, and a solution of [^{14}C(U)]2-chlorophenol (0.19 mL, specific activity = 53.4 mCi/mmol, 1.82 mmol, 97.2 mCi) in ether (0.83 mL) was added dropwise over 3 min with vigorous stirring keeping the temperature below 4°C. The vial containing the [^{14}C(U)]2-chlorophenol was rinsed with ether (1.3 mL), and this was added to the reaction flask. The light yellow suspension was stirred at 3–5°C for 15 min and then warmed to room temperature overnight. The suspension was filtered, and the off white solid was washed with ether (20 mL), air dried and then dried on a vacuum line until constant weight was achieved to give 208 mg of a white solid, **23** (43% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 6.84 (dd, *J* = 7.7, 1.9 Hz, 1H), 6.60 (ddd, *J* = 8.4, 6.8, 2.0 Hz, 1H), 6.08 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.71 (td, *J* = 7.3, 1.0 Hz, 1H).

8-([Phenyl-^{14}C(U)]2-chlorophenoxy)-3-(4-methoxybicyclo[2.2.1]heptan-1-yl)-[1,2,4]triazolo[4,3-a]pyridine, ***24***. To a new dry glass test tube with stir bar under nitrogen was weighed 8-bromo-3-(4-methoxybicyclo [2.2.1]heptan-1-yl)-[1,2,4]triazolo[4,3-a]pyridine, **3** (185 mg, 0.574 mmol) and the cesium salt of [^{14}C(U)]2-chlorophenol, **23** (148 mg, 0.567 mmol.) The test tube was placed in an oil bath at 220–225°C and stirred under nitrogen for 1 h. To the black solid was added water (1.8 mL), and the mixture was heated to 135°C for 20 min. After cooling to room temperature, 1 M NaOH (1.0 mL, 1.0 mmol) was added. The aqueous layer was extracted with CH_2Cl_2 (7 × 2.5 mL). The combined CH_2Cl_2 layers were washed with saturated NH_4Cl (5.0 mL), brine (5.0 mL), dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to give a black semisolid. The crude product was purified by preparative HPLC using method C. Pure fractions were pooled. The solvent was removed under reduced pressure, and then, the product was dried under vacuum to constant weight to give 54 mg of an off white solid, **24** (26% yield). HPLC analysis using method B showed the product to be 99.5% chemically pure with a retention time of 11.22 min and 99.4% radiochemically pure. LC/MS of the product showed *m/z* (+ ion) = 370.25 (100%)/372. 25 (36%)/374.33 (25%)/376.25 (10%)/378.25 (15%) and 380.25 (5%) with a retention time of 4.90 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.72 (d, *J* = 6.8 Hz, 1H), 7.40–7.48 (m, 1H), 7.21–7.30 (m, 1H), 7.12–7.21 (m, 2H), 6.57 (t, *J* = 7.2 Hz, 1H), 6.12 (d, *J* = 7.4 Hz, 1H), 3.33 (s, 3H), 2.05–2.32 (m, 6H), 1.89–2.05 (m, 2H), 1.69–1.83 (m, 2H).

4-(8-([Phenyl-^{14}C(U)]2-chlorophenoxy)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)bicyclo[2.2.1]heptan-1-ol, [phenyl-^{14}C(U)]BMS-770767, ***25***. To a new dry 10 mL recovery flask with stir bar was weighed 8-([phenyl-^{14}C (U)]2-chlorophenoxy)-3-(4-methoxybicyclo[2.2.1]heptan-1-yl)-[1,2,4] triazolo[4,3-a]pyridine, **24** (41.7 mg, 0.113 mmol). To this was added glacial acetic acid (0.36 mL), and the solution was cooled to 0–5°C with an ice-water bath. To this solution was added 48% HBr (0.36 mL, 3.2 mmol) dropwise over 5 min. The solution was stirred for 5 min at 0–5°C and then placed in an oil bath at 100°C for 2 h. The solution was cooled to room temperature, and the solvent was removed under reduced pressure. Methanol (0.5 mL) and 2.2 M NaOH (0.20 mL) was added, and the solution was placed in oil bath at 65°C for 1 h. The reaction was cooled to room temperature, and the solvent was removed under reduced pressure. To the crude product was added water (0.5 mL). The aqueous layer was extracted with EtOAc (5 × 1.5 mL). The pooled EtOAc extracts were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to give a semisolid that was purified by preparative HPLC using method D. Pure fractions were pooled, and the solvent was removed under reduced pressure and then dried under vacuum to give 32 mg of white solid, [phenyl-^{14}C (U)]BMS-770767, **25** (4.7 mCi, 78% yield). HPLC analysis using method C showed the product to be 99.5% chemically pure with a retention time of 22.48 min and 99.2% radiochemically pure. LC/MS of [phenyl-^{14}C(U)] BMS-770767 showed *m/z* (+ ion) = 356 (100%)/357 (22.4%)/358 (37.3%)/359 (7.5%)/360 (26.1%)/361 (5%)/362 (10.8%)/363 (2.1%)/364 (15.8%)/365 (2.5%)/366 (5.8%)/368 (3.3%) with a retention time of 3.84 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.35 (d, *J* = 6.6 Hz, 1H), 7.68 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.38–7.48 (m, 1H), 7.27–7.37 (m, 2H), 6.84 (t, *J* = 7.2 Hz, 1H), 6.51 (d, *J* = 7.3 Hz, 1H, 1.98–2.20 (m, 6H), 1.78–1.92 (m, 2H), 1.60–1.74 (m, 2H). The specifc activity was measured to be 149 μCi/mg or 53.3 mCi/mmol.

[Phenyl-^{14}C(U)]BMS-770767, ***26****, intermediate specific activity product*. To the 50 mL recovery flask containing [phenyl-^{14}C(U)]BMS-770767, **25** (28.7 mg, specific activity = 149 μCi/mg, 4.28 mCi, 0.080 mmol) was weighed clinical grade BMS-770767 (103 mg. 0.290 mmol). To this was added absolute ethanol (25 mL), and the mixture was warmed to 40°C for 5–10 min in a water bath to completely dissolve all of the solids. The ethanol was removed under reduced pressure to give a white solid that was further dried on a vacuum line to constant weight to give 132 mg of product, **26** (100% yield). HPLC analysis using analytical method C showed the material to be 99.6% chemically pure with a retention time of 22.63 min and 99.4% radiochemically pure. LC/MS analysis of [phenyl-^{14}C(U)]BMS-770767 showed *m/z* (+ ion) = 356 (100%)/357 (22.4%)/358 (36.1%)/359 (7.9%)/360 (5.4%)/364 (2.9%) with a retention time of 3.79 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.35 (d, *J* = 6.8 Hz, 1H), 7.67 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.38–7.48 (m, 1H), 7.26–7.38 (m, 2H), 6.83 (t, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 7.3 Hz, 1H), 1.99–2.21 (m, 6H), 1.77–1.93 (m, 2H), 1.60–1.75 (m, 2H). The specific activity was measured to be 32.9 μCi/mg or 11.7 mCi/mmol.

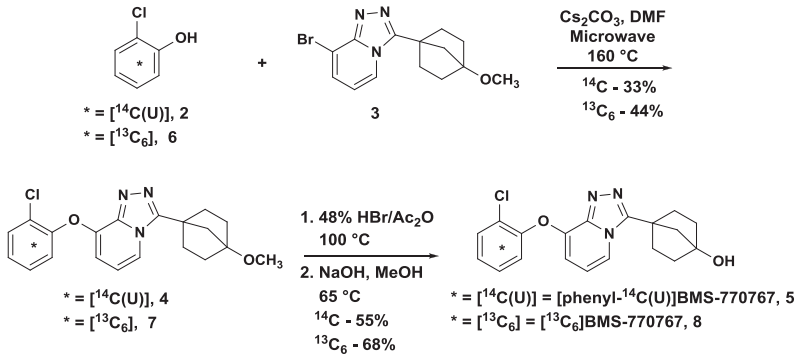
[Phenyl-^{14}C(U)]BMS-770767, ***27****, low specific activity final product*. To a new dry recovery flask was weighed [phenyl-^{14}C(U)]BMS-770767, **26** (69.7 mg, specific activity = 32.9 μCi/mg, 2.29 mCi, 0.195 mmol) and clinical grade BMS-770767 (1.36 g, 3.82 mmol). To this was added absolute ethanol (200 mL), and the mixture was warmed to 40–45°C for 20–30 min in a water bath to completely dissolve all of the solids. The ethanol was removed under reduced pressure to give a white solid that was further dried on a vacuum line to constant weight to give 1.44 g of product. To the white solid was added glacial acetic acid (6.8 mL) and sterile water (1.7 mL). The mixture was heated to 65°C in a water bath. The hot solution was filtered, and the flask was rinsed with 4:1 AcOH : water (3 × 0.5 mL) solution, and these rinsings were also filtered. To the filtrate was added sterile water (8.0 mL) at 65°C, and the solution was cooled to room temperature overnight. The solution was cooled to 15–20°C with an ice-water bath, and the solid was collected by filtration. The solid was rinsed with cold water, air dried for 45 min and then dried under vacuum at 60–65°C for 3 h to give 1.28 g of white solid [phenyl-^{14}C(U)]BMS-770767, **27** (90% yield). HPLC analysis

usinganalytical method C showed the material to be 99.9% chemically pure with a retention time of 22.62 min and 99.1% radiochemically pure. LC/MS of [phenyl-^{14}C(U)]BMS-770767 showed *m/z* (+ ion) = 356 (100%)/357 (21.5%)/358 (36%)/359 (7.1%)/360 (0.8%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.34 (d, *J* = 6.8 Hz, 1H), 7.67 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.38–7.47 (m, 1H), 7.26–7.37 (m, 2H), 6.82 (t, *J* = 7.2 Hz, 1H), 6.49 (d, *J* = 7.3 Hz, 1H), 5.14 (s, 1H), 1.99–2.21 (m, 6H), 1.77–1.93 (m, 2H), 1.60–1.73 (m, 2H). The specific activity was measured to be 1.61 μCi/mg or 0.57 mCi/mmol.

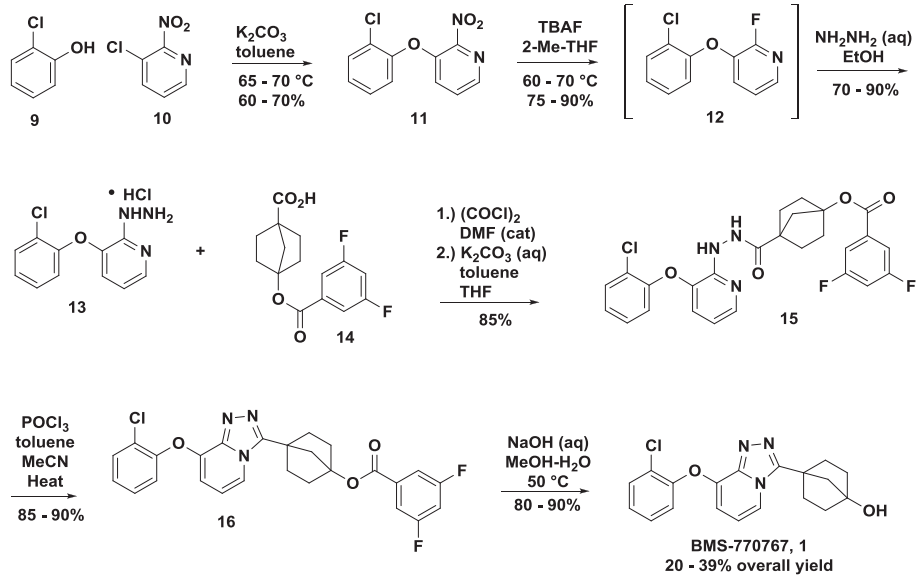
Results and discussion

The discovery phase synthesis of [phenyl-^{14}C(U)]BMS-770767 was completed in three steps by reacting [^{14}C(U)]2-chlorophenol, **2** with 8-bromo-3-(4-methoxybicyclo-[2.2.1] heptan-1-yl)-[1,2,4]triazolo[4,3-a]pyridine, **3** and Cs_2CO_3 in DMF under microwave heating to give the desired ether product in 33% yield. The demethylation of the methyl ether with 48% HBr and acetic anhydride gave the desired labelled product, **5** as shown in Scheme 1 in 55% yield or 18% overall. Although this yield appears to be low, this route was advantageous in that the desired labelled product was prepared in only three steps and in two flasks in a short amount of time to meet the timeline for the necessary biotransformation studies to be initiated. Likewise, the synthesis of [$^{13}C_6$]BMS-770767, **8** was completed in three steps using the same synthetic route as that for [phenyl-^{14}C(U)]BMS-770767, except that [$^{13}C_6$]2-chlorophenol, **6** was used in place of [^{14}C(U)]2-chlorophenol and the overall yield was higher at 30%. Both of these syntheses were able to be completed quickly because of the incorporation of the labelled reagents late in the syntheses, the use of the same synthetic routes for both labelled products and the availability of intermediate **3**.

Between the time when the discovery syntheses of [phenyl-^{14}C(U)]BMS-770767, **5** and [$^{13}C_6$]BMS-770767, **8** were completed and the need for the synthesis of [phenyl-^{14}C(U)] BMS-770767 for use in the human ADME clinical study, the Bristol-Myers Squibb Process Research Group developed a completely new synthetic route to BMS-770767 as shown in Scheme 2.[8,9] Naturally, we were eager to utilize the new synthetic route for the cGMP synthesis of [phenyl-^{14}C(U)]BMS-770767 for use in the human ADME clinical study. Two advantages to following the process chemistry route was the high yielding and dependable procedures and the availability of large supplies of cGMP produced intermediate, **14**. Unfortunately, the process route involved the reaction of five equivalents of 2-chlorophenol, **9**, with 3-chloro-2-nitropyridine, **10** in the first step of the synthesis which would mean that our



Scheme 1. Discovery syntheses of [phenyl-^{14}C(U)]BMS-770767, **5** and [$^{13}C_6$]BMS-770767, **8**.



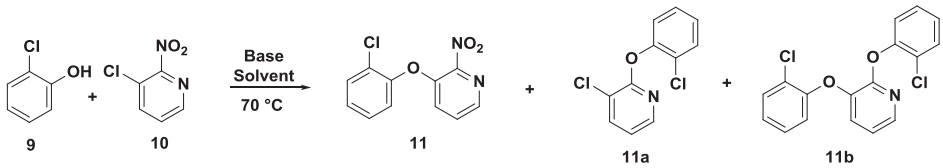
Scheme 2. Bristol-Myers Squibb Process Research synthesis of BMS-770767, **1**.

labelled reagent would need to be used in large excess in the first step of the synthesis and would be carried through all six steps of the synthesis leading to low overall radiochemical yields of [phenyl-^{14}C(U)]BMS-770767. This left us with three possible options for completing the cGMP synthesis of [phenyl-^{14}C(U)]BMS-770767 for use in the human ADME clinical study. Option 1 would be to use the process chemistry route and try to modify it slightly by lowering the number of equivalents of [^{14}C(U)]2-chlorophenol to make it more efficient with regards to the labelled reagent. Option 2 would be to use the discovery chemistry route that we were already familiar with, but this would also require the synthesis of aromatic bromide, **3** under cGMP conditions to meet the requirements of our quality assurance group. Option 3 would be to develop a completely new route and incorporate the best of both the discovery chemistry and process chemistry routes. This would also need to be conducted under cGMP to gain the approval of our quality assurance group.

Initially, we decided to follow the process route to take advantage of the availability of intermediate **14**. During the first practice chemistry attempt, 5 equivalents of 2-chloro-phenol, **9**, were reacted with 3-chloro-2-nitropyridine, **10**, and K_2CO_3 in toluene at 70°C which resulted in a mixture of 41.5% of desired product **11**, 28.3% of product **11a** resulting from displacement of the nitro group by the phenol and 30.2% of product **11b** by the double displacement of the chloride and nitro groups by phenol as shown in Scheme 3 and as reported as entry 1 of Table 1. Process chemists at Bristol-Myers Squibb reported the ratio of products to be 80% of product **11**, 15% of product **11a** and 5% of product **11b** under the same conditions, but on a larger scale. As expected, reducing the number equivalents of 2-chlorophenol from five to one and increasing the number of equivalents of **10** to 1.1 slightly increased the yield of **11** and nearly eliminated the production of diether product, **11b**, as shown in entry 2. Encouraged by this result, increasing the number of equivalents of **10** to 1.2 did not improve the yield of **11** but instead decreased it and resulted in the formation of other unidentifiable products as shown in entry 3. Changing the solvent from toluene to acetonitrile and using 3 equivalents of **10** in entry 4 resulted in the exclusive formation of **11a**. Replacement of K_2CO_3 with Cs_2CO_3 as the base using a large excess of **10** did not improve the production of **11** as shown in entries 5 and 6.

Because the first step of the process chemistry route was becoming challenging to repeat and we were short on time, we decided to reconsider the very short discovery chemistry route that we have previously used with success. However, there were no supplies of the critical intermediate aromatic bromide, **3**, that had been prepared under cGMP and was suitable for use in the human ADME synthesis. As such, we shifted to option 3 and developed a new route to [phenyl-^{14}C(U)]BMS-770767 taking advantage of the availability of intermediate **14** prepared under cGMP to prepare **3** in five steps with approval of our quality assurance group who were concerned with the possibility of generating a different impurity profile than that which was known from the process chemistry cGMP route. Even though some new impurities could be formed with the new route, we were able to convince our quality assurance colleagues that the presence of the carbon-14 label later in the synthesis gave us the ability to detect and identify them in smaller quantities, as well as show that they were not carried through to the final labelled API. They agreed, but insisted on the steps leading up to the incorporation of the carbon-14 be conducted under cGMP just as would be expected if our colleagues in process chemistry were to have prepare compound **3** for us to use in our human ADME synthesis. This also allowed for the late-stage incorporation of [^{14}C(U)]2-chlorophenol as shown in Scheme 4 and as was done in the discovery chemistry route.

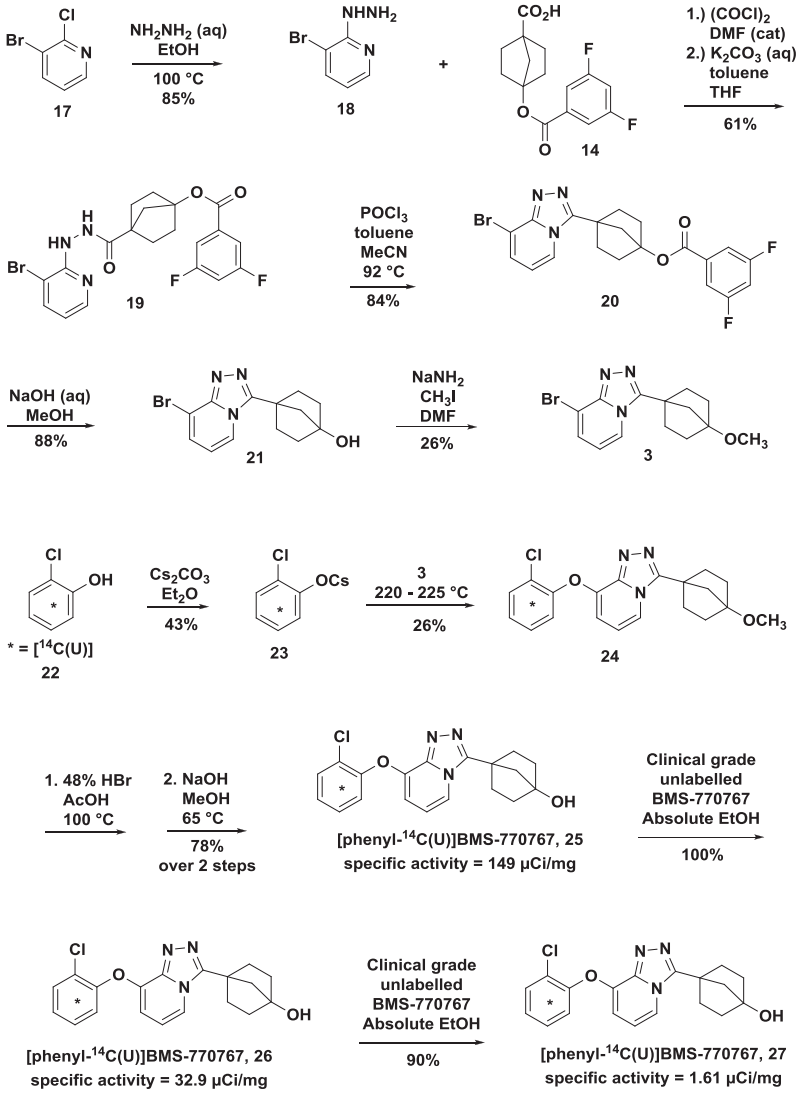
3-Bromo-2-chloropyridine, **17** was reacted with hydrazine in water at 100°C to give 3-bromo-2-hydrazinylpyridine, **18** in 85% yield. Oxalyl chloride was reacted with clinical grade acid intermediate **14** to generate the acid chloride that was directly reacted with hydrazine **18** to give hydrazide **19** in 61% yield. Cyclization of **19** with phosphorous oxychloride at 92°C produced compound **20** in 84% yield. Product **20** was saponified with 2.5 M sodium hydroxide to generate alcohol **21** in 88% yield. The alcohol was protected as the methyl ether by reacting with sodium amide and iodomethane to generate intermediate **3** in 26% yield. Intermediate **3** was thermally reacted at 220–225°C with the cesium salt of [^{14}C(U)]2-chlorophenol, **23** prepared from Cs_2CO_3 and [^{14}C(U)]2-chlorophenol, **22** in ether



Scheme 3. Practice chemistry of first step of process chemistry route to BMS-770767.

Table 1. Effect of reaction parameters on the ratio of products as determined by HPLC.

Entry	9 (eq)	10 (eq)	Base	Solvent	%11	%11a	%11b
1	5	1.0	K_2CO_3	Toluene	41.5	28.3	30.2
2	1	1.1	K_2CO_3	Toluene	47.8	52.2	Trace
3	1	1.2	K_2CO_3	Toluene	8.1	47.4	4.5
4	1	3.0	K_2CO_3	MeCN	0	100	0
5	1	4.4	Cs_2CO_3	DMF	25	75	Trace
6	1	3.0	Cs_2CO_3	DMF	25	75	Trace



Scheme 4. cGMP synthetic route to [phenyl-^{14}C(U)BMS-770767.

to give product **24** in 26% yield. During the discovery synthesis shown in Scheme 1, the cesium salt of [^{14}C(U)]2-chlorophenol was prepared *in situ* and reacted directly with intermediate **3** to produce **4** under microwave heating in 33% yield. During practice reactions with unlabelled material, we found that the yield of product **4** was improved to approximately 65% when the cesium salt was isolated and then reacted thermally with intermediate **3** in a two-step sequence. However, during the labelled chemistry run, we experienced lower yields than expected because of the smaller scale on which the reaction was conducted as well as suffering large losses incurred during purification by preparative HPLC because of the removal of impurities that eluted close to the retention time of the desired product. These impurities were not detected during the unlabelled practice reactions. The methyl ether was converted to the desired high specific activity product, [phenyl-^{14}C(U)]BMS-770767, **25**, with 48% hydrogen bromide in acetic acid followed by treatment with NaOH (aq) at 65°C. The crude product was purified by preparative HPLC to give 32 mg of [phenyl-^{14}C(U)]BMS-770767 that was 99.5% chemically pure and 99.2% radiochemically pure with a specific activity of 149 µCi/mg. To complete the human ADME clinical study, it was necessary to reduce the specific activity of this material by sequentially mixing the radiolabelled material with clinical grade unlabelled BMS-770767 in ethanol and recrystallizing to give 2.07 mCi of the final drug substance that was 99.9% chemically pure, 99.1% radiochemically pure and had a specific activity of 1.61 µCi/mg. We typically dilute the high specific activity product to the low specific activity product over more than one step in order to give us another two opportunities to make corrections to the amount of unlabelled material that needs to be mixed with the labelled material. Completing the dilution in this fashion also gives us another chance to measure radiochemical purities and specific activities on material that contains enough radioactivity to measure it reliably. The target specific activity required for the human ADME clinical study was 1.6 µCi/mg. This material was fully tested and met the release criteria for use in the human ADME study.

Conclusions

We initially prepared [phenyl-^{14}C(U)]BMS-770767 in 18% yield for use in metabolic profiling and [$^{13}C_6$]BMS-770767 in 30% yield to serve as an standard for LC/MS analysis. Both of these syntheses

were completed in three steps in two pots from appropriately labelled 2-chlorophenol and a late-stage intermediate. For the human ADME clinical study, we successfully prepared 4.73 mCi of [phenyl-^{14}C(U)]BMS-770767 by developing a new synthetic route that was a combination of the discovery chemistry and the process chemistry routes. The product specific activity was measured at 149 μCi/mg and was 99.5% chemically pure and 99.2% radiochemically pure. A portion of this product was mixed with unlabelled clinical grade BMS-770767 in two steps to reduce the specific activity to 1.61 μCi/mg to give a total of 2.07 mCi of [phenyl-^{14}C(U)]BMS-770767 that was 99.9% chemically pure and 99.1% radiochemically pure. All material met release specifications for use in a human clinical study and was successfully used in the human ADME study.

Acknowledgements

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