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The syntheses of [^{14}C]BMS-823778 for use in a human ADME clinical study and of [$^{13}CD_3$ $^{13}CD_2$]BMT-094817, a stable-isotope labeled standard of a newly detected human metabolite

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Type 2 diabetes is a significant worldwide health problem. To support the development of BMS-823778 as an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 for type 2 diabetes, the synthesis of carbon-14-labeled material was required for use in a human adsorption, distribution, metabolism, and excretion (ADME) study. The HCl salt form of [^{14}C]BMS-823778 was synthesized in two steps from commercially available [2-^{14}C]acetone. The radiochemical purity of the synthesized [^{14}C]BMS-823778 after dilution with unlabeled clinical-grade BMS-823778 was 99.5% having a specific activity of 7.379 μCi/mg. One result of the human ADME study was the detection of a new human metabolite, BMT-094817. To support the quantification of BMT-094817 in clinical samples, it was necessary to synthesize [$^{13}CD_3$ $^{13}CD_2$]BMT-094817 for use as a liquid chromatography/mass spectrometry standard. [$^{13}CD_3$ $^{13}CD_2$]BMT-094817 was prepared in five labeled steps from [$^{13}CD_3$]iodomethane.

Keywords: type 2 diabetes; 11β-HSD1; human ADME; carbon-14; stable-isotope labeled metabolite 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, is 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. Transgenic mice that overexpressed 11β-HSD1 in adipose tissue were found to exhibit metabolic disorders including obesity, insulin resistance, glucose intolerance, and hyperglycemia. 11β-HSD1 knockout mice were found to be resistant to obesity and hyperglycemia. 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-823778 HCl salt, as shown in Figure 1, represents such an 11β-HSD1 inhibitor.[6–9] To further the development of BMS-823778, it was necessary to prepare [^{14}C]BMS-823778 HCl salt for use in a human absorption, distribution, metabolism, and excretion (ADME) study. One result of the human ADME clinical study was the discovery of a previously undetected human metabolite, BMT-094817, **2**. In order to quantify the amounts of BMT-094817, the stable-isotope labeled BMT-094817 needed to be prepared. This paper describes the syntheses of [^{14}C]BMS-823778 HCl salt, **7**, and [$^{13}CD_3$, $^{13}CD_2$]BMT-094817, **16**.[10]

Experimental

Materials and methods

All reactions were run under an inert atmosphere of nitrogen and stirred magnetically. Reactions were monitored by HPLC and/or thin-layer chromatography with comparisons made to authentic materials. All reagents and solvents were American Chemical Society grade or better and used without further purification. [2-^{14}C]Acetone (50 mCi, specific activity 55 mCi/mmol, >97% radiochemical purity) was obtained from ViTrax (Placentia, CA). [$^{13}CD_3$]Iodomethane (99 at.% ^{13}C, 99.5 at.% D) was obtained from Isotec (Miamisburg, Ohio). Clinical-grade BMS-823778

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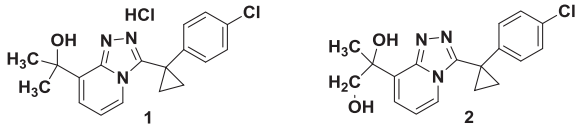


Figure 1. Structures of BMS-823778 HCl salt, **1**, and BMT-094817, **2**.

hydrochloride salt was obtained from the Process Research & Development Department at Bristol-Myers Squibb (New Brunswick, NJ). All authentic samples were obtained from the Process Research & Development Department or the Medicinal Chemistry Department at Bristol-Myers Squibb. Solvent removal under reduced pressure was accomplished using a Büchi (Flawil, Switzerland) model 210 rotary evaporator. Column chromatography was performed using an AnaLogix (Burlington, WI) BSR Flash Chromatography system. Proton NMR spectra were recorded on either a 300 MHz or 400 MHz Bruker (Billerica, MA) Avance spectrometer as listed. Thin-layer chromatography analyses (EMD 60 (EMD Chemicals Inc. Darmstadt, Germany), F_{254} silica gel-coated plates) were performed as described using either UV (254 nm) or iodine to visualize. Liquid chromatography/mass spectrometry (LC/MS) spectra were recorded on a Finnigan LXQ (Thermo Fisher Scientific Inc. Waltham, MA USA) LC/MS system with detection by ESI(+) ion. LC/MS method: column = Phenomenex (Torrance, CA) 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 and 10 min 100% B. Specific activities were determined by gravimetric analysis using liquid scintillation counting (PerkinElmer (Waltham, MA) model 2900TR). 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 β-ram model 3 detector using LAURALITE version 3.4.1.10 software (LabLogic Systems, Ltd., Sheffield, England) for radiochemical detection. The following analytical methods were used for in process reaction analyses and final purity measurements. HPLC method A, column = YMC ODS AQ, 3 μm (4.6 × 150 mm); mobile phase A, water with 0.05% trifluoroacetic acid; mobile phase B, acetonitrile with 0.05% trifluoroacetic acid. Gradient: 0 min, 95% A; 12 min, 95% B; 16 min, 95% B; 20 min, 95% A, flow rate = 1.0 mL/min; injection size, 10 μL. UV detection at 280 nm. HPLC method B, column = YMC Pro C18, 3 μm (4.6 × 150 mm); mobile phase A, 95% water : 5% MeOH with 0.10% trifluoroacetic acid; mobile phase B, 10% water : 90% MeOH with 0.10% trifluoroacetic acid; gradient, 0 min, 100% A; 1 min, 100% A; 6 min, 35% B; 25 min, 62% B, 26 min 100% B, 28 min 100% B, 29 min 100% A, flow rate = 1.0 mL/min; injection size, 10 μL. UV detection at 280 nm.

*[^{14}C]2-(3-(1-(4-Chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-ol or [^{14}C]BMS-823778, **4***

To 8-bromo-3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-*a*]pyridine (0.349 g, 1.00 mmol), **3**, in anhydrous THF (5.00 mL) under a nitrogen atmosphere at −78 °C in a dry ice–acetone bath was added butyllithium (2.5 M in hexane, 0.84 mL, 2.1 mmol) dropwise, and then the reaction was stirred for 1 h. The reaction mixture was cooled in a liquid nitrogen bath, and [2-^{14}C]acetone (50.0 mCi, 55.0 mCi/mmol, 0.074 mL, 0.91 mmol) was transferred by vacuum transfer. The reaction mixture was moved back to the dry ice–acetone bath and was stirred for 2.5 h at −78 °C. After warming to room temperature overnight, the reaction was quenched with a mixture of 0.140 mL glacial acetic acid in methyl *tert*-butyl ether (2.5 mL). The volatiles were removed under vacuum, and the residue was dissolved in EtOAc (12 mL). The organic layer was washed with saturated ammonium chloride (5.0 mL), with brine (3.0 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by rotovap to give 0.3732 g of the crude product as a yellow foam. The crude product was purified by flash chromatography (Teledyne (Thousand Oaks, CA) Isco RediSep R_f 24 g silica cartridge) eluted with 35% EtOAc in hexane to 50% EtOAc in hexane. Pure product fractions were pooled, and the solvent was removed by rotovap followed by drying on a vacuum line to constant weight to give 78.55 mg (0.238 mmol, 24% yield) of a viscous colorless film. The product analyzed using HPLC method A showed it to be 99.8% chemically pure, retention time (R_t) = 7.019 min, and 99.56% radiochemically pure. The material co-eluted with an authentic sample. Analysis by LC/MS method A (ESI) showed 328.25 (6%)/329.25 (2%)/330.25 (100%)/331.25 (22%)/322.17 (34%)/333.17 (7%)/334.17 (1%).

*[^{14}C]2-(3-(1-(4-Chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-ol hydrochloride or [^{14}C]BMS-823778 HCl salt, **5***

To [^{14}C]BMS-823778, **4** (78.55 mg, 0.238 mmol), dissolved in isopropanol (2.12 mL) and heptane (0.423 mL) at room temperature was added concentrated HCl (0.020 mL, 0.238 mmol). This solution was stirred for 30 min, seeded with unlabeled clinical-grade BMS-823778 HCl salt, and stirred overnight at room temperature. The solid product was collected by centrifugation and then dried under vacuum to constant weight to give 65.77 mg of a white solid (0.180 mmol, 75% yield). Analysis by HPLC using method B showed it to be 99.8 % chemically pure, RT = 21.96 min, and 98.4% radiochemically pure. The material co-eluted with an authentic sample. Analysis by LC/MS showed 328.25 (6%)/329.25 (2%)/330.25 (100%)/331.25 (22%)/322.17 (34%)/333.17 (7%)/334.17 (1%). ^{1}H-NMR (300 MHz, MeOH-d_4) δ 8.43 (d, J = 6.7 Hz, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.49–7.18 (m, 5H), 1.90–1.61 (m, 10H). The ^{1}H-NMR matched that of the unlabeled product. The specific activity was measured to be 153.6 μCi/mg, 56.08 mCi/mmol, 10.10 mCi.

*[^{14}C]2-(3-(1-(4-Chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-ol hydrochloride or [^{14}C]BMS-823778 HCl salt, **6***

To [^{14}C]BMS-8237788 HCl salt, **5** (55.90 mg, 0.171 mmol), was weighed BMS-823778 HCl salt (55.90 mg, 0.171 mmol). To this was added absolute ethyl alcohol (0.79 mL), and the suspension was heated to 75 °C until all solid was dissolved. Heptane (2.52 mL) was slowly added with gentle swirling. The mixture was allowed to cool slowly to room temperature over 3 h. The solid was collected by filtration and then dried under vacuum to constant weight to give 101.6 mg of white solid. Analysis by HPLC using method B showed it to be 99.8 % chemically pure, RT = 21.90 min, and 99.1% radiochemically pure. The material co-eluted with an authentic sample. ^{1}H-NMR (300 MHz, MeOH-d_4) δ 8.41 (d, J = 6.5 Hz, 1H), 7.91 (d, J = 7.0 Hz, 1H), 7.46–7.16 (m, 5H), 1.90–1.63 (m, 10H). The specific activity was measured to be 79.61 μCi/mg, 29.10 mCi/mmol, 8.088 mCi.

*[^{14}C]2-(3-(1-(4-Chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-ol hydrochloride or [^{14}C]BMS-823778 HCl salt, **7***

To [^{14}C]BMS-8237788 HCl salt, **6** (69.48 mg, 0.191 mmol), was weighed BMS-823778 HCl salt (697.5 mg, 1.915 mmol). To this was added absolute ethyl alcohol (5.39 mL), and the suspension was heated to 75 °C until all solid was dissolved. Heptane (17.2 mL) was slowly added with gentle swirling. The mixture was allowed to cool slowly to room temperature over 3 h. The solid was collected by filtration and then dried under vacuum to constant weight to give 677.8 mg of white solid. Analysis by HPLC using method B showed it to be 99.9% chemically pure, RT = 21.90 min, and 99.5% radiochemically pure. The material co-eluted with an authentic sample. Analysis by LC/MS showed 328.17 (100%)/329.17 (21%)/330.17 (40%)/331.17 (8%)/322.08 (3%). ^{1}H-NMR (300 MHz, MeOH-d_4) δ 8.42 (dd, J = 7.0, 0.9 Hz, 1H), 7.93 (dd, J = 7.3, 0.9 Hz, 1H), 7.47–7.17 (m, 5H), 1.86–1.61 (m, 10H). The specific activity was measured to be 7.379 μCi/mg, 2.419 mCi/mmol, 5.001 mCi.

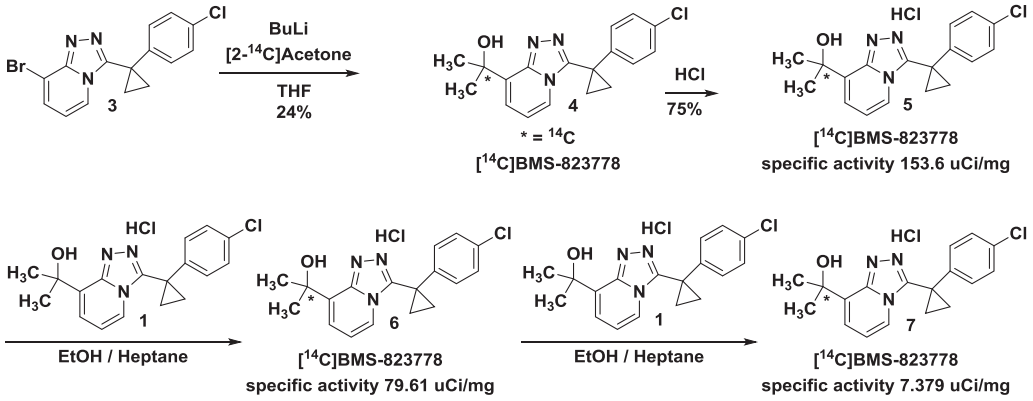
2-(3-(1-(4-Chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl) propane-1,3-$^{13}C_2$-1,1,3,3,3-d_5-1,2-diol, **16**

See the work of Cheng *et al.*[10] for the complete experimental details for the preparation of 2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo [4,3-*a*]pyridin-8-yl)propane-1,3-$^{13}C_2$-1,1,3,3,3-d_5-1,2-diol, **16**.

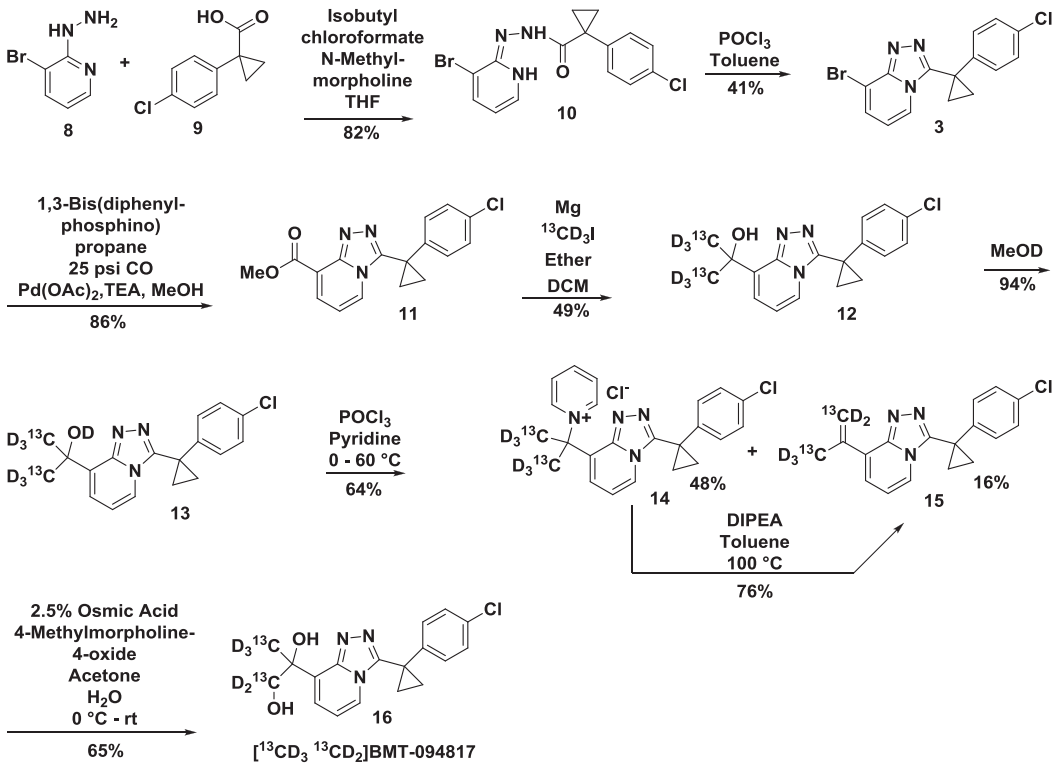
Results and discussion

The current Good Manufacturing Practice (cGMP) synthesis of [^{14}C]BMS-823778, **5**, was completed in two synthetic steps as shown in Scheme 1 from clinical-grade 8-bromo-3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo-[4,3-*a*]pyridine, **3**, and [2-^{14}C]acetone in 18% overall yield after purification by flash chromatography and preparation of the hydrochloride salt form. The drug substance was determined to be 99.8% chemically pure and 98.4% radiochemically pure, and the specific activity was measured at 153.6 μCi/mg. To complete the ADME clinical study, it was necessary to reduce the specific activity of a portion of the high specific activity drug substance with clinical-grade unlabeled BMS-823788 HCl salt by a two-step dilution process in ethanol and heptane to generate 5.0 mCi of [^{14}C]BMS-823778 HCl salt with a specific activity of 7.379 μCi/mg that was 99% chemically pure and 99.5% radiochemically pure. This material was fully tested and released for use in the human ADME study.

One purpose of the human ADME clinical study is to investigate the formation of new previously undetected metabolites.[11] Samples analyzed from the human ADME clinical study revealed the formation of a new metabolite, BMT-094817. To fully analyze BMT-094817 in future clinical samples, it was necessary to prepare a stable-isotope labeled version of it for use as an LC/MS standard. Typically for LC/MS standards, it is necessary to synthesize material with a molecular weight that is a minimum of at least three mass units higher than the naturally occurring molecular weight of the material of interest. As BMT-094817 contained a chlorine atom, it was necessary to prepare material

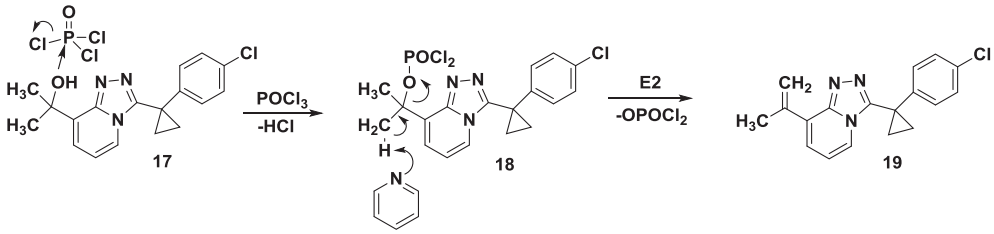


Scheme 1. Human ADME synthesis of [^{14}C]BMS-823778 HCl salt, **7**.

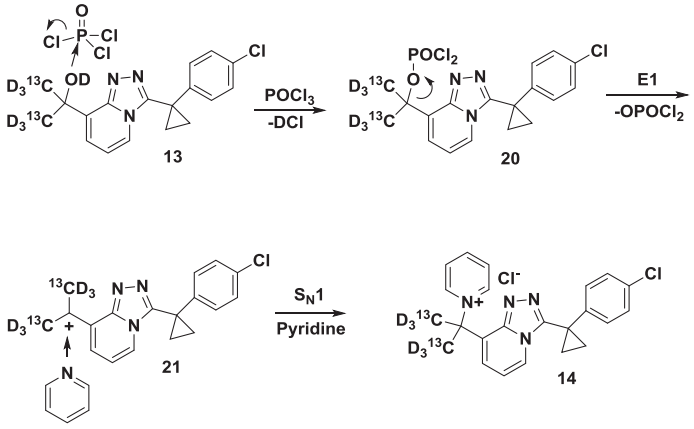


Scheme 2. Synthesis of [$^{13}CD_3$ $^{13}CD_2$]BMT-094817, **16**.

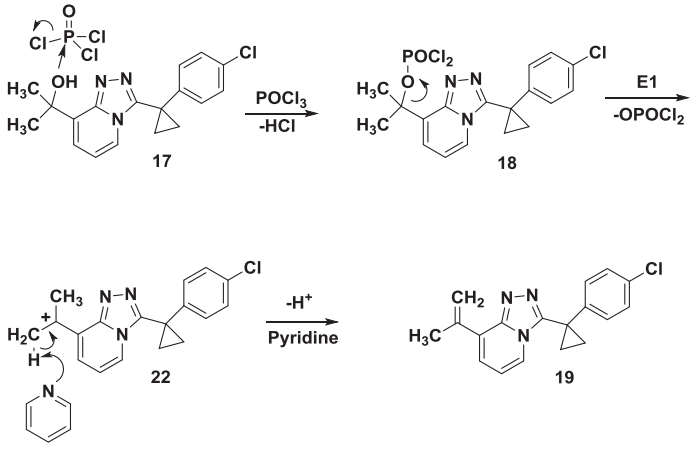
that was at least five mass units higher than that of the unlabeled BMT-094817 to avoid interference from molecules that contained naturally occurring chlorine-37. We had previously prepared [($^{13}CD_3$)$_2$]BMS-823778, **12**, from the Grignard addition of two equivalents of $^{13}CD_3MgI$ to methyl 3-(1-(4-chlorophenyl) cyclopropyl)-[1,2,4]triazolo[4,3-*a*]pyridine-8-carboxylate, **11**, and felt that the route shown in Scheme 2 would not only allow us to prepare the M + 7 isotopologue, [$^{13}CD_3$ $^{13}CD_2$] BMT-094817, but also have the additional advantage of preparing additional supplies of the parent compound [($^{13}CD_3$)$_2$]BMS-823778, **12**. 3-Bromo-2-hydrazinyl-pyridine **8** was reacted with aromatic acid **9** with isobutyl-chloroformate and *N*-methylmorpholine in THF to give an 82% yield of hydrazide **10**.[10] Compound **10** was cyclized with phosphorous trichloride to generate the [1,2,4]triazolo[4,3-*a*]pyridine ring system in 41% yield. Aromatic bromide, **3**, was carbonylated followed by esterification using 1,3-bis(diphenylphosphino)propane, palladium acetate, and 25 psi of carbon monoxide in MeOH at room temperature to give an 86% yield of ester, **11**. Methyl ester **11** was reacted with two equivalents of $^{13}CD_3MgI$ to give the labeled parent compound, BMS-823778, **12**, in 49% yield. The proton of the tertiary alcohol was exchanged to a deuterium using deuterated MeOH in 94% yield. Dehydration product, **15**, was formed in 16% yield along with a large amount (48%) of a very polar side product. The desired product was purified by flash chromatography, and the polar side product was eluted by flushing the flash column with 10%



Scheme 3. Possible E2 mechanism for the formation of product **19**.



Scheme 4. Possible E1/S_N1 mechanism for the formation of pyridine adduct, **14**.



Scheme 5. Possible E1 mechanism for the formation of product **19**.

MeOH : 90% Dichloromethane. The polar side product was identified by LC/MS and ^{1}H-NMR to be the pyridine adduct, **14**. Fortunately, pyridine adduct **14** could be reacted with Hunig's base in toluene at 100 °C overnight to form **15** in 76% yield. Unsaturated product **15** was then hydroxylated with osmic acid to prepare racemic [$^{13}CD_3$ $^{13}CD_2$]BMT-094817, **16** in 65% yield. No attempt was made to resolve the enantiomers of [$^{13}CD_3$ $^{13}CD_2$]BMT-094817 because the LC/MS analysis did not involve a chiral method and the results from the *in vivo* study did not show a preference for the formation of one enantiomer over the other.

During unlabeled practice reactions, dehydration of BMS-823778 with $POCl_3$ in pyridine produced the desired alkene, **19**, in 60% isolated yield with only a trace amount of the pyridine adduct being generated. The formation of the pyridine adduct is likely the result of a deuterium kinetic isotope effect. One possible explanation for the difference in the product ratios of the $POCl_3$ dehydration reaction for the labeled tertiary alcohol compared with the unlabeled tertiary alcohol is that unlabeled material, **17**, can react through an E2 mechanism of intermediate **18** to give the desired product, **19**, as shown in Scheme 3.

However, for the labeled chemistry, the C–D bond strength is stronger than the C–H bond, which requires more energy for it to be cleaved. Owing to this increased energy requirement, the mechanism shifts to an E1 mechanism, and the C–O bond is cleaved in preference to the loss of a proton to generate carbocation **21** as shown in Scheme 4. Carbocation **21** is tertiary, benzylic, and stabilized by the presence of the six deuteriums.[12] It can then be attacked by pyridine through an S_N1 mechanism to form pyridine adduct **14**.

Another possibility is that unlabeled carbocation **22** could also be formed through an E1 mechanism, but because it is not stabilized by the presence of deuteriums as in intermediate **21**, one of the six C–H bonds cleaves to form product **19** as shown in Scheme 5.

Conclusions

We successfully prepared a total of 10.10 mCi of [^{14}C]BMS-823778 HCl salt having a specific activity of 153.6 μCi/mg, a chemical purity of 99.0%, and a radiochemical purity of 98.4%. A portion of this product was mixed with unlabeled clinical-grade BMS-823788 HCl salt in two steps to reduce the specific activity to 7.379 μCi/mg to give a total of 5.001 mCi of [^{14}C]BMS-823778 HCl salt that was 99.9% chemically pure and 99.5% radiochemically pure. All material met release specifications for use in a human clinical study and was successfully used in the human ADME study. One result of the human ADME study was the discovery of a new previously undetected human metabolite, BMT-094817. The synthesis of 280.8 mg of [$^{13}CD_3$ $^{13}CD_2$]BMT-094817 was completed for use as an LC/MS standard for clinical samples.

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Conflict of interest

The authors did not report any conflict of interest.

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