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Research Article

Carbon-14 labeling of Saxagliptin (BMS-477118)

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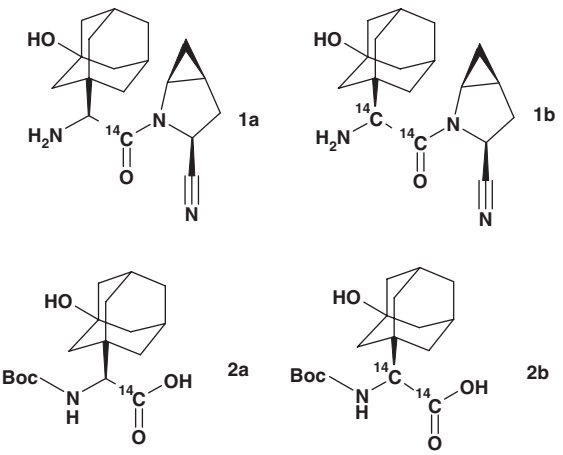
Abstract: An efficient synthesis of carbon-14-labeled Saxagliptin (BMS-477118) is described. Initial synthesis of the key radiolabeled intermediate (*S*)-*N*-Boc-2-(3′-hydroxyadamantyl)glycine **2a** utilized adamantanemethanol in a 10-step sequence. To shorten the sequence, 1-adamantylzinc bromide was reacted with ethyl [1, 2-^{14}C]oxalyl chloride catalyzed by [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium (II). In five steps, **2b** was synthesized in an overall yield of 20% based on ethyl [1, 2-^{14}C]oxalyl chloride. Compound **2b** was subsequently converted to [^{14}C] BMS-477118 in a short sequence. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: Saxagliptin; DPP-IV inhibitor; carbon-14 synthesis

Introduction

DPP-IV (dipeptidyl-peptidase IV) inhibition has been studied extensively as a treatment for Type 2 diabetes.[1] Inhibition of DPP-IV results in preserved levels of endogenous insulinotropic hormone, glucagon-like peptide 1 (GLP-1), which in turn leads to enhanced insulin efficiency.[2,3]

Saxaglipin (BMS-477118) **1**, a highly efficacious, stable and long-acting DPP-IV inhibitor possessing a hydroxyadamantyl group was discovered by Bristol-Myers Squibb scientists.[4] The compound is currently undergoing clinical evaluation for the treatment of Type 2 diabetes. To support ongoing preclinical and clinical studies, carbon-14-labeled BMS-477118 was needed for metabolic and pharmacological studies of the molecule.



Two different radiolabeled syntheses of [^{14}C] BMS-477118 are described in this paper. The first synthesis of [^{14}C] BMS-477118 (**1a**) required 13 steps and utilized K^{14}CN as the starting material. To shorten the sequence, other labeling options were explored. A five-step route was devised to prepare the key intermediate **2b** from the reaction of adamantylzinc bromide with ethyl [1, 2-^{14}C]oxalyl chloride in the presence of [1, 1′-bis (diphenylphosphino)ferrocene]dichloropalladium (II) (dppfPdCl$_2$). This report describes both synthetic approaches, with particular emphasis on the efficient synthesis of [^{14}C] BMS-477118 (**1b**).

Results and discussion

Synthesis of (S)-*N*-Boc-[1-^{14}C]-2-(3′-Hydroxyadamantyl)glycine (2a)

As illustrated in Scheme 1, 1-adamantanemethanol **3** was tosylated, followed by S_N2 reaction with K^{14}CN to introduce carbon-14 label. Hydrolysis of the resulting

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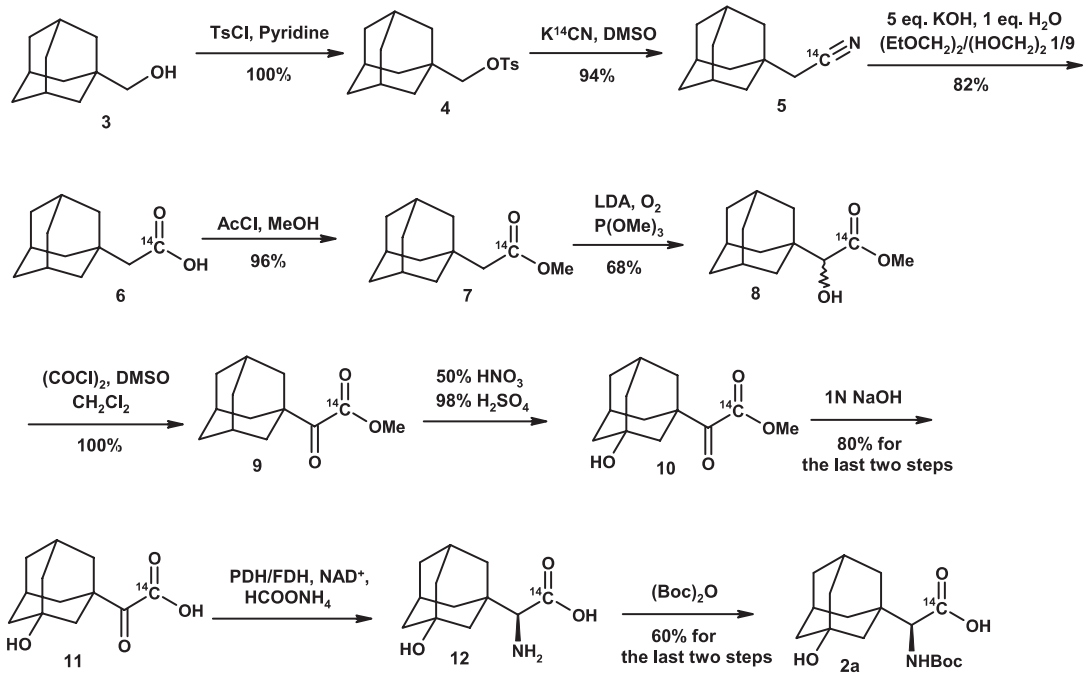

Scheme 1

cyano intermediate **5** yielded carboxylic acid **6**. Methyl ester **7** was prepared in 96% yield by treatment with methanol and acetyl chloride, and α-hydroxylation with trimethyl phosphite/oxygen gave **8** in 68% yield. Swern oxidation gave the α-keto-ester **9**. Hydroxylation of the adamantyl ring was accomplished with 50% HNO_3/98% H_2SO_4 giving **10**. Hydrolysis with 1 N NaOH gave **11**.[5] The yield for the combined hydroxylation/hydrolysis steps was 80%. Intermediate **11** was converted to **12** by reductive amination, using a liquid enzyme concentrate from *E. coli* JM110 containing phenylalanine dehydrogenase (PDH) and formate dehydrogenase (FDH).[6] The bio-conversion mixture was treated with $(Boc)_2O$ and **2a** was isolated in 60% yield.

The above sequence, although starting from cheap and readily available $K^{14}CN$, was lengthy and time consuming. In addition, intermediate **5** was volatile and required special precautions during hydrolysis to avoid losses. Labeled [^{14}C] BMS-477118 (**1a**) was prepared through this route to support some preclinical studies, but the liabilities of early label introduction and the length of the synthesis were significant obstacles for a repeat synthesis. A decision was made to pursue other labeling approaches for the preparation of clinical supplies.

Synthesis of (S)-*N*-Boc-[1, 2-^{14}C]-2-(3′-Hydroxyadamantyl)glycine (2b)

Introduction of a labeled glycine fragment was an obvious option, but this approach required C–C bond formation at the adamantyl bridgehead. There is limited literature precedence describing synthetic applications of adamantyl bridgehead anions.[7] Low yields and poor reproducibility are common problems. The most efficient way to introduce the α-keto-ester two-carbon unit was through the use of an oxalic ester derivative. Reagents and conditions have been reported for the reaction of oxalic esters using organolithium and Grignard reagents.[8–10] Initial attempts using adamantyl lithium and Grignard reagents with dimethyl oxalate failed. Very low yields of the desired product were observed for these reactions, due to the poor reactivity and competing acyloin ester condensation. More reactive methyl oxalyl chloride has been reported to react with organozinc reagents catalyzed by Pd in moderate to excellent yields.[11] Radiolabeled ethyl oxalyl chloride was reacted with adamantylzinc bromide prepared from Rieke® Metals to obtain the desired product **14**. The use of adamantylzinc bromide (Aldrich product) derived from the oxidative addition of Rieke zinc to adamantyl bromide was critical to the successful preparation of **2b**.

Methyl oxalyl chloride was used in unlabeled practice acylation reactions with yields close to 80%. Unfortunately, methyl[1, 2-^{14}C]oxalyl chloride was not commercially available as a labeled precursor. Ethyl[1, 2-^{14}C]oxalyl chloride was substituted and gave somewhat lower yields. The synthesis of **2b** began by coupling 1-adamantylzinc bromide with ethyl [1, 2-^{14}C]oxalyl chloride in the presence of [1, 1′-bis

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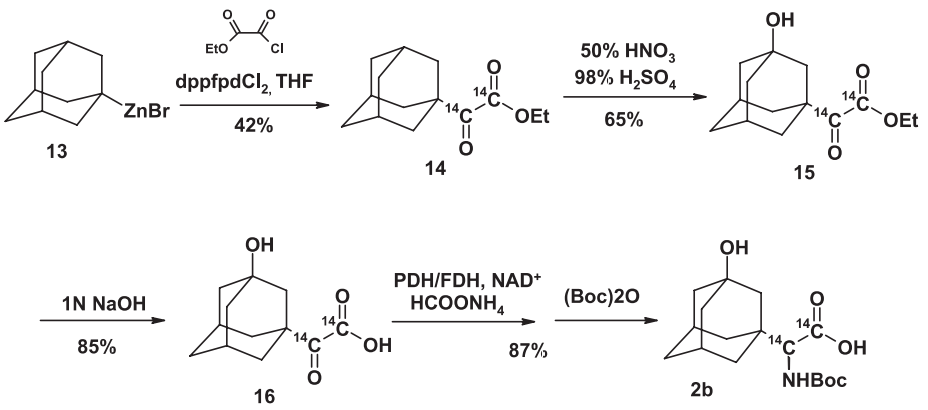
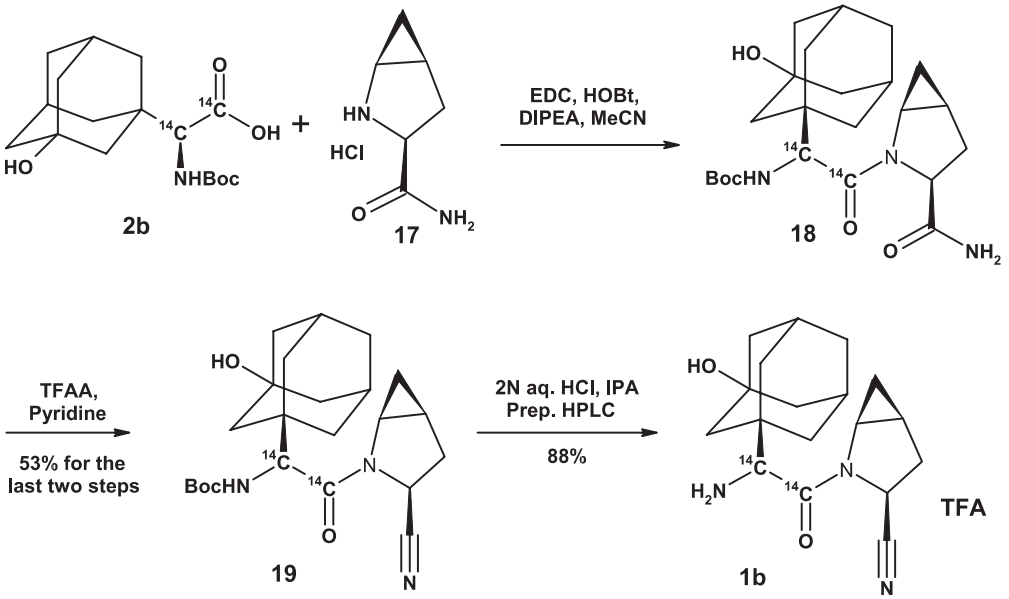


Scheme 2



Scheme 3

(diphenylphosphino)ferrocene]dichloropalladium (II) (Scheme 2). The α-keto-ester **14** was isolated in 42% yield after purification. Hydroxylation of **14** in 50% HNO_3 and 98% H_2SO_4 followed by hydrolysis in 1 N NaOH gave hydroxyadamantyl keto-acid **16**, the substrate for bioconversion. PDH/FDH-catalyzed reductive amination, followed by Boc protection provided **2b** in 87% yield.

Completion of [^{14}C] BMS-477118 synthesis

Carboxylic acid **2b** was coupled with L-*cis*-4, 5-methanoprolinamide **17** using EDC/HOBt (Scheme 3). The product formed, **18**, was treated with TFAA in pyridine at −10°C to dehydrate the amide. The Boc-protected nitrile **19** was obtained in 53% yield. The target compound, **1b**, a TFA salt was obtained in 88% yield by deprotection using 2 N aqueous HCl in isopropyl alcohol followed by preparative high performance liquid chromatography (HPLC) purification.

Modified coupling of 2 with 20

EDC/HOBt-mediated coupling of **2b** with **17** following dehydration with TFAA in pyridine generated a fairly complicated reaction mixture. Preparative HPLC separation was required to purify the product. To improve the yield and simplify isolation, a HATU-catalyzed coupling of carboxylic acid **2b** with nitrile **20** was utilized (Scheme 4). The desired product **19** was obtained in 90% yield, and was then converted to **1b**

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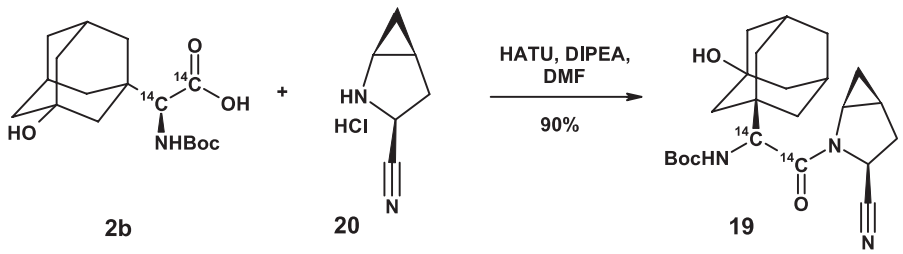

Scheme 4

by deprotection. This modification significantly improved the overall radiochemical yield of **1b** from 10% for the EDC/HOBt coupling to 17% using this modified procedure.

In summary, an efficient synthetic route for the synthesis of [^{14}C] BMS-477118 (**1b**) was developed. Compared with the earlier synthesis of **1a**, this improved sequence was shorter and scalable to the long term needs of the program. Carbon-14 labels were conveniently introduced into the glycine moiety via a palladium-mediated reaction of 1-admantylzinc bromide with ethyl [1, 2-^{14}C]oxalyl chloride. The success of this route expands the known examples of adamantyl bridgehead anion chemistry. An improved set of coupling conditions were demonstrated for the reaction of Boc-protected hydroxyladamantyl glycine **2b** with **20** using HATU. Multiple batches of [^{14}C] BMS-477114 were prepared to support preclinical and clinical studies.

Materials and methods

^{1}H NMR and decoupled ^{13}C NMR were recorded on a Bruker DRX-400 MHz or a Bruker Avance II 300 MHz spectrometer. Mass spectra were recorded on either a Thermo LCQ or a LXQ spectrometer. Radioactivity determinations were carried out with a Wallac liquid scintillation counter, using standard methods and Ecolite as the scintillation fluid. HPLC purification and analysis were performed on a Rainin Dynamax HPLC system consisting of two SD-200 pumps, a Rainin UV-1 detector, a ProStar PDA detector and an *IN/US* β-RAM radioactive flowthrough detector. The HPLC method for in-process analytical HPLC analysis consisted of mobile phases A: 0.05% TFA in water, and B: 0.05% TFA in acetonitrile; column: YMC hydrosphere C18 (3 μm, 4.6 mm × 250 mm); flow rate: 1 mL/min; gradient program: 10% (B) hold for 5 min then ramp to 90% (B) over 10 min and hold for 5 min, then ramp back to 10% (B); detection: UV (220 nm) or radiometric. Preparative HPLC was conducted using a YMC AQ (10 mm × 250 mm); mobile phase A: 10% MeOH in water containing 0.05% TFA, mobile phase B: 90% MeOH in water containing 0.05% TFA; flow rate: 4 mL/min; gradient program: 100% (A) gradient change over 15 min to 100% (B), then hold for 10 min at a 100% (B). TLC was carried out on silica gel 60 F254 plates (Merck). Ethyl [1, 2–^{14}C]oxalyl chloride (97 mCi/mmol) was obtained from GE Health Sciences. 1-Adamantylzinc bromide was obtained from Rieke Metals (via Aldrich). All other reagents were obtained from the Aldrich Chemical Company of Milwaukee, WI, and were either ACS grade or the highest quality material commercially available. Identities of labeled compounds were established by co-analysis with the fully characterized unlabeled compounds using HPLC, NMR and mass spectrometry when possible.

Experimental

[1, 2-^{14}C]-Ethyl 2-oxo-2-adamantylacetate (14)

Ethyl [1, 2-^{14}C]oxalyl chloride (200 mCi, 97 mCi/mmol) was vacuum transferred to a 25 mL flask. Anhydrous THF (2 mL) was added to the same flask under Ar atmosphere. [1,1′-Bis(diphenylphosphino)ferrocene]-dichloropalladium (II) (8 mg) was charged to second flask under Ar, cooled to −47°C, followed by addition of 1-adamantylzinc bromide in THF (**13**, 0.5 M, 7.4 mL). The contents of the first flask were transferred to the second flask through a cannula in 5 min. The reaction mixture was stirred at −47°C for 15 min, warmed, and held at ambient temperature for 3 h. Hydrochloric acid (1 N, 10 mL) was added to the stirred mixture, which was stirred for a total of 10 min. The mixture was extracted with *t*-butyl methyl ether (3 × 10 mL), and the combined organic layers were washed with water (10 mL × 2). After concentration under a steady stream of nitrogen gas, the crude product was purified by flash chromatography (hexanes/ethyl acetate 8/1 v/v). Pooled fractions were evaporated to yield 190 mg **14** (83 mCi, yield 42%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.36 (t, J= 7.2 Hz, 3H), 1.70–1.95 (m, 12H), 2.07 (br s, 3H), 4.31 (dd, J= 7.2 Hz, 2H); ^{13}C-NMR (75.48 MHz, $CDCl_3$) δ (ppm): 201.7, 164.1, 61.5, 44.9, 37.2, 36.3, 27.6, 14.1.

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[1, 2-^{14}C]-Ethyl 2-oxo-2-(3′-hydroxyadamantyl) acetate (15)

Sulfuric acid (1.9 mL) followed by nitric acid (50%, 175 μL) were added to a flask cooled to 0°C. A separate flask containing the α-keto-ester (**14**, 190 mg, 0.85 mmol, 83 mCi) was cooled to 0°C, and the pre-mixed sulfuric/nitric acid mixture was added all at once. The reaction mixture was then stirred at 0°C for 90 min. Ice–water (25 mL) was added to the mixture, and it was then stirred for 30 min. The aqueous mixture was extracted with ethyl acetate (10 mL × 3), and the pooled ethyl acetate layers were evaporated. Flash chromatography (hexanes/ethyl acetate 2/3 v/v) gave 140 mg **15** (54 mCi, 385.7 μCi/mg, yield 65%). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.34 (t, J= 7.1 Hz, 3H), 1.50–1.80 (m, 12H), 2.32 (m, 3H), 4.30 (dd, J= 7.2 Hz, 2H); ^{13}C-NMR (75.48 MHz, $CDCl_3$) δ (ppm): 14.1, 29.9, 34.8, 36.1, 44.1, 44.5, 48.2, 61.8, 68.1, 163.6, 199.9.

[1, 2-^{14}C] 2-Oxo-2-(3′-hydroxyadamantyl)acetic acid (16)

α-Keto-ester (**15**, 140 mg, 54 mCi, 0.63 mmol) and unlabeled **15** (223 mg, 1.44 mmol) were dissolved in THF (2 mL), cooled to 0°C, and sodium hydroxide (1 N, ~2 mL) was added to give a final solution pH of 14. After stirring at 0°C for 60 min, water (20 mL) was added, followed by extraction with ethyl acetate (20 mL). The aqueous phase was acidified to pH 3 with 1 N hydrochloric acid, and then extracted with ethyl acetate (15 mL × 3). Combined ethyl acetate layers were dried over sodium sulfate, filtered and evaporated. The resulting product **16** (274 mg, 46 mCi) was diluted with unlabeled **16** (1.03 g), giving 1.31 g of **16** (46 mCi, 35.1 μCi/mg, yield 85%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 1.45–1.70 (m, 12H), 2.17 (br s, 3H); ^{13}C-NMR (75.48 MHz, DMSO-d_6) δ (ppm): 29.4, 34.6, 36.0, 44.0, 44.7, 47.0, 66.0, 166.1, 202.5.

(S)-*N*-Boc-[1, 2-^{14}C]-2-(3′-Hydroxyadamantyl) glycine (2b)

[1, 2-^{14}C] 2-Oxo-2-(3′-hydroxyadamantyl)acetic acid **16** (1.31 g, 46 mCi, 5.8 mmol) and ammonium formate (740 mg, 11.7 mmol) were dissolved in water (10.5 mL). Sodium hydroxide (10 N) was added to adjust the pH to 8.0, then NAD^+ (3.5 mg) and dithiothreitol (DTT, 2.0 mg) were added and the total volume was brought to 12 mL with water. The reaction mixture was warmed to 40°C, and the pH was readjusted to 8.0 with sodium hydroxide (5 N). PDH/FDH enzymes from *E. coli* extract (1300 units, 2.6 g of the liquid enzyme extract) were added and the pH was again adjusted to 8.0 with sodium hydroxide (5 N). The reaction flask was placed in a temperature-controlled incubator with orbital oscillation at 220 rpm while maintaining a constant temperature of 40°C. The reaction was monitored by HPLC and the pH was maintained at 8.0 with periodic additions of sodium hydroxide (5 N) or sulfuric acid (5 N) until the reaction was judged to be complete by HPLC (90% conversion at 100 h). The reaction mixture was cooled to room temperature, and the pH was adjusted to 9.5 with sodium hydroxide (5 N). Cellular debris was removed by centrifugation (3 times at 2500 rpm for 10 min). The resulting supernatant (~20 mL) was treated with NaOH (10 N) to adjust the pH to 13, then treated with $(Boc)_2O$ (2.55 g, 11.7 mmol) in THF (25 mL). After stirring at room temperature for 3 h, THF was removed under a steady stream of nitrogen gas. Additional protein precipitate was removed by centrifugation. The basic solution (pH 11) was washed with isopropyl acetate twice (20 and 10 mL), then adjusted to pH 2.5–3 with hydrochloric acid (1 N). The resulting aqueous solution was extracted with isopropyl acetate (20 mL × 3), dried over Na_2SO_4, filtered and evaporated to give 1.65 g of **2b** (40 mCi, 24.2 μCi/mg, yield 87%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 1.37 (s, 9H), 1.30–1.60 (m, 12H), 2.07 (br s, 2H), 3.67 and 6.79 (2 br d, 1 H, rotamers). ^{13}C NMR (100.62 MHz, DMSO-d_6) δ (ppm): 28.2, 29.7, 29.8, 35.08, 37.1, 38.1, 40.4, 46.6, 62.5, 66.7, 78.0, 155.7, 172.3.

(S)-*N*-Boc-[1,2-^{14}C]-2-(3′-Hydroxyadamantyl)glycine-L-*cis*-4,5-methanoprolinenitrile (19)

Procedure A. Coupling reaction between *N*-Boc-hydroxyadamantyl glycine (**2b**, 1.65 g, 40 mCi, 5.1 mmol) and L-*cis*-4,5-methanoprolinamide **17** (1.23 g, 5.8 mmol) in MeCN (6 mL) was carried out using general peptide coupling conditions: HOBt (784 mg, 5.8 mmol), EDC (1.55 g, 8.1 mmol) and DIPEA (1.88 g, 14.6 mmol) at room temperature overnight. One normality hydrochloric acid (6 mL) and brine (6 mL) were added to the reaction mixture. The reaction mixture was extracted with EtOAc (20 mL). The EtOAc layer was washed with 20% $KHCO_3$. After evaporation, the crude amide was redissolved in EtOAc (3.2 mL), cooled to −5°C, and treated with pyridine (1.7 mL). Trifluoroacetic anhydride (1.8 mL) was added over 10 min, then the mixture was warmed to room temperature over 40 min. The solvent was removed under reduced pressure and the intermediate trifluoroacetate nitrile was hydrolyzed with 25% K_2CO_3 (9.6 mL) in methanol (6 mL) at 35–40°C for 1 h. Methanol was removed and the aqueous layer was extracted with EtOAc (20 mL × 2). The extracts were washed with hydrochloric acid (1 N) and brine, dried over Na_2SO_4, filtered and concentrated. The crude product was recrystallized from isopropanol/water,

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and then further purified by preparative HPLC. **19** (21 mCi, 19.1 μCi/mg, 1.1 g) was obtained in 53% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.04–1.07 (m, 2H), 1.42 (s, 9H), 1.35–1.91 (m, 13H), 2.24 (m, 2H), 2.36 (dd, J = 13.2, 2.3 Hz, 1H), 2.56 (m, 1H), 3.82 (dd, J = 11, 4.4 Hz), 4.45 (d, J= 9.6 Hz, 1H), 5.03 (dd, J = 10.4, 2.3 Hz), 5.29 (br dd, J= 9.7 Hz, 1H). ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ (ppm): 13.5, 17.8, 28.4, 30.2, 30.4, 35.2, 37.0, 37.5, 38.0, 41.2, 44.3, 44.4, 45.1, 46.3, 58.6, 68.6, 80.0, 119.3, 155.8, 169.9. MS (ES^+) m/z: 416, 420 (for $^{14}C_2$) $[M + H]^+$.

Procedure B. N-Boc-hydroxyadamantyl glycine (**2b**, 150 mg, 6.8 mCi, 45.3 μCi/mg, 0.46 mmol), L-*cis*-4, 5-methanoprolinenitrile (20, 80 mg, 0.55 mmol) and HATU (213 mg, 0.56 mmol) were dissolved in anhydrous DMF (4.8 mL), placed under an Ar atmosphere and cooled to 0°C. DIPEA (213 mg, 1.65 mmol) was added over 5 min, and the mixture was stirred at 0–10°C for 5 h. The crude product was purified by preparative HPLC to give 171 mg **19** (6.1 mCi, 35.7 μCi/mg, yield 90%).

(S)-[1, 2-^{14}C]-2-(3′-Hydroxyadamantyl)glycine-L-cis-4, 5-methanoprolinenitrile TFA salt (1b)

Nitrile **19** (6.8 mCi, 0.41 mmol, 35.7 μCi/mg, 190 mg) was dissolved in isopropyl alcohol (3 mL) and heated to 70°C under N_2. Hydrochloric acid (2 N, 2.8 mL) was added, and the reaction mixture stirred for 90 min at 70°C. The mixture was cooled to room temperature, and the solvent was evaporated. The crude was purified by preparative HPLC to give desired product as a TFA salt, 6 mCi, 155 mg, yield 88%. Specific activity: 38.7 μCi/mg and radiochemical purity: 99.8%. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 0.97 (ddd, J = 11.6, 7.2, 2.8 Hz, 1H), 1.10 and 1.13 (ABq, J_{AB} = 6.6 Hz, 1H), 1.55–1.85 (m, 12H), 2.01 (ddd, J = 14.3, 11.6, 5.5 Hz, 1H), 2.28 (s, 2H), 2.35 (dd, J = 13.7, 2.2 Hz, 1H), 2.62 (ddd, J = 13.7, 11.0, 5.5 Hz, 1H), 3.92 (ddd, J = 8.8, 6.0, 2.8 Hz, 1H), 4.28 (s, 1H), 5.19 (dd, J = 11.0, 2.2 Hz, 1H); ^{13}C NMR (100.62 MHz, CD_3OD) δ (ppm): 14.3, 19.2, 31.4, 31.4, 31.5, 36.0, 38.2, 39.3, 40.9, 44.8, 44.9, 46.6, 47.0, 60.0, 68.6, 120.4, 167.4. MS (ES^+) m/z: 316, 320 (for $^{14}C_2$) $[M + H]^+$.

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