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Synthesis of deuterium-labelled fosamprenavir calcium

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This study describes the synthesis of deuterium-labelled fosamprenavir calcium. The stable isotopic-labelled compound was prepared starting from L-phenylalanine in 18 steps with a 9% overall yield.

Keywords: protease inhibitor; HIV; deuterium-labelled; fosamprenavir

Introduction

The human immunodeficiency virus (HIV) has been identified as the causative agent of acquired immune deficiency syndrome (AIDS). HIV protease, an essential enzyme for viral maturation,[1–4] is now a well recognized target for therapeutic intervention against the deadly disease. Fosamprenavir is an effective therapeutic agent for the treatment of HIV infection. As the phosphate ester pro-drug of the protease inhibitor amprenavir (APV), fosamprenavir has improved solubility and bioavailability compared with amprenavir.[5] It was approved by the FDA and came onto the market in October 2003. Patients who received treatment with fosamprenavir demonstrated protease gene mutations different from those commonly seen with other protease inhibitors (except APV). Fosamprenavir Calcium labelled with radioactive and stable isotopes of hydrogen was required for drug metabolism (excretion, distribution, and absorption) studies and to develop bioanalytical methods to support clinical studies.

Results and discussion

Although fosamprenavir calcium and *p*-nitrobenzenesulfonyl chloride have been readily prepared via several synthetic routes,[6–8] the synthesis of [$^2H_4$]-fosamprenavir calcium and *p*-[$^2H_4$]-nitrobenzenesulfonyl chloride have not been described previously. Scheme 1 presents the general synthetic scheme for preparing *p*-[$^2H_4$]-nitrobenzenesulfonyl chloride (7). Reduction of compound (1) with Pd/C and ammonium formate produced [$^2H_5$]-aniline (2). Treatment of (2) with acetic anhydride gave [$^2H_5$]-acetanilide (3), which was then reacted with chlorosulfonic acid (HSO_3Cl) and gave [$^2H_4$]-N-acetylsulfanilyl chloride (4).[9] Compound (4) was treated with 10% NaOH to generate *p*-[$^2H_4$]-aminobenzene sulfonic acid (5). The oxidation of (5) with 30% H_2O_2 in acetic acid yielded *p*-[$^2H_4$]-nitrobenzenesulfonic (6).[10] This compound (6) was treated with PCl_5 to form *p*-[$^2H_4$]-nitrobenzenesulfonyl chloride (7).

Scheme 2 presents the preparation of [$^2H_4$]-fosamprenavir calcium salt (20). L-phenylalaninol (9) was prepared by reacting L-phenylalanine with sodium borohydride and iodine.[11] Compound (9) was treated with benzyl bromide and K_2CO_3 to yield N,N-dibenzyl-(*S*)-2-amino-3-phenyl-1-propanol (10). The oxidation of compound (10) with pyridine-sulfurtrioxide complex produced N,N-dibenzylamino aldehyde (11).[12] The crude product (11) was utilized for the next step without further purification. Treatment of (11) with lithium and bromochloromethane, and then quenching with 6 M HCl gave N,N-dibenzyl-(*S*)-3-amino-(*S*)-2-hydroxy-4-phenyl-1-chlorobutane hydrochloride. Recrystallization from MeOH gave (2*S*,3*S*)-N,N-dibenzyl-3-amino chlorohydrin hydrochloride (12).[13] Yields for this reaction were found to be highly dependent on careful temperature control (if the reaction temperature was allowed to rise above $-55^{\circ}C$, yields decreased significantly). Hydrogenolysis of (12) under standard conditions (1 atm H_2, MeOH, 20% $Pd(OH)_2/C$) gave amino chlorohydrin hydrochloride (13) in excellent yield. The use of the salt form is crucial to the success of the deprotection. It accelerates hydrogenolysis of the benzylic C–N bonds and prevents decomposition of (12) and (13).[14] Protection of the amine of (13) with di-*tert*-butyl dicarbonate and triethylamine in THF, followed by *in situ* epoxide ring closure with methanolic potassium hydroxide, gave N-Boc-aminoalkyl epoxides (14). HPLC analysis on a chiral column (Chiralcel OD) indicated that the isomeric purity of compound (14) was $>99.5\%$.[14] Treatment of (14) with isobutyl amine gave, after epoxide ring opening, (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-1-isobutylamino-4-phenyl-2-butanol

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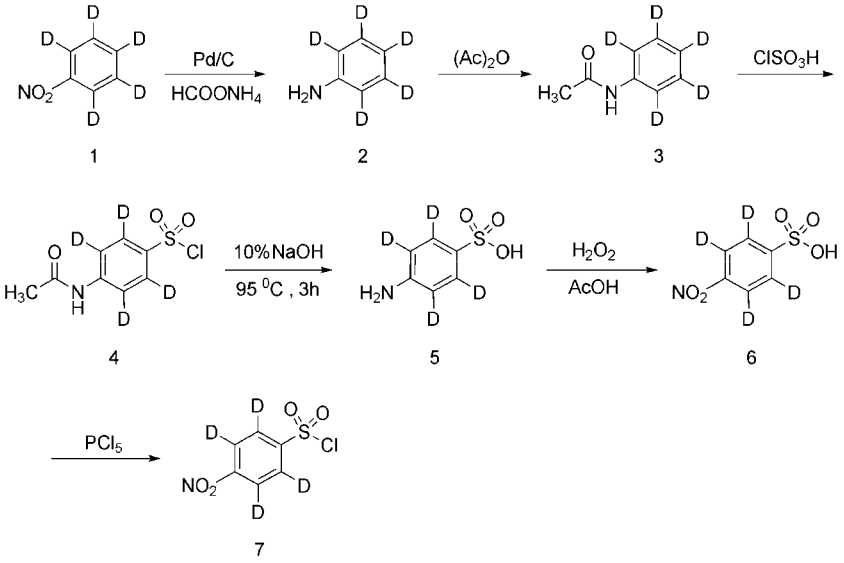


Scheme 1.

(15). Conversion of (15) into (16) using p-[$^2H_4$]-nitrobenzenesulfonyl chloride (7) and triethylamine in toluene and subsequent treatment with concentrated hydrochloric acid to remove the N-Boc group.[6] The resulting amine (16) was treated with (*S*)-3-hydroxytetrahydrofuran and *bis*(trichloromethyl)carbonate to produce (2*S*,3*R*)-N-(3-amino-2-hydroxy-4-phenyl)-N-isobutyl-4-[$^2H_4$]-nitrobenzene sulphonamide hydrochloride (17) in a 82% yield. The reaction of compound (17) and $POCl_3$, followed by the hydrolysis using 6 M HCl afforded (3*S*)-tetrahydro-3-furanyl-(1*S*,2*R*)-3-[[(4-[$^2H_4$]-nitrophenyl)-sulfonyl] (isobutyl)amino]-1-benzyl-2-(phosphonooxy)propylcarbamate (18).[15] Reduction of the nitro group using palladium on carbon gave the aryl amine (19) in 91.5% yield. This hydrogenation step required very carefully controlled conditions to avoid cyclization of the product. Compound (19) was treated with calcium acetate monohydrate to produce [$^2H_4$]-fosamprenavir calcium (20) in a 61% yield.

After purification by recrystallization, the desired product (20) was obtained with 98.5% chemical purity. Mass spectrometry analysis of compound (20) revealed that the compound has over 98% deuterium enrichment. The compound provided an excellent internal standard in LC-MS-MS studies.

Experimental

General

All reagents were obtained from Sigma-Aldrich and CDN Isotope. Mass spectra were recorded using a Quattro micro API mass spectrometer. ^1H NMR spectra were recorded on a Bruker 300 MHz instrument. Chemical purities were determined by an Agilent 1200 HPLC with a XDB-C18 column, 5 μm, 4.6 × 150 mm.

Synthesis of [$^2H_5$]-aniline (2)

To a solution of [$^2H_5$]-nitrobenzene (1) (12.0 g, 102 mmol) in MeOH (120 mL) was added ammonium formate (30.7 g, 487 mmol). After stirring for 10 min under nitrogen, 10% palladium on charcoal (1.2 g) was added. The reaction mixture was heated carefully to reflux for 20 min. The catalyst was removed by filtration and washed with methanol. The filtrate was distilled at atmospheric pressure through a short fractionating column to afford (2) as a colorless liquid (8.8 g, 98.3%).

Synthesis of [$^2H_5$]-acetanilide (3)

Compound (2) (8.8 g, 89.8 mmol) was cooled in ice-bath under nitrogen. Acetic anhydride (20.2 g, 197.8 mmol) was added dropwise with stirring. After addition, the reaction mixture was warmed to room temperature and stirred for 2.5 h. It was added to water (60 mL), neutralized with saturated $NaHCO_3$ solution. The aqueous phase was extracted with dichloromethane (3 × 80 mL). The combined organic phases were washed with brine (150 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford (3) as a white solid (12.5 g, 99.2%).

Synthesis of [$^2H_4$]-N-acetylsulfanilyl chloride (4)

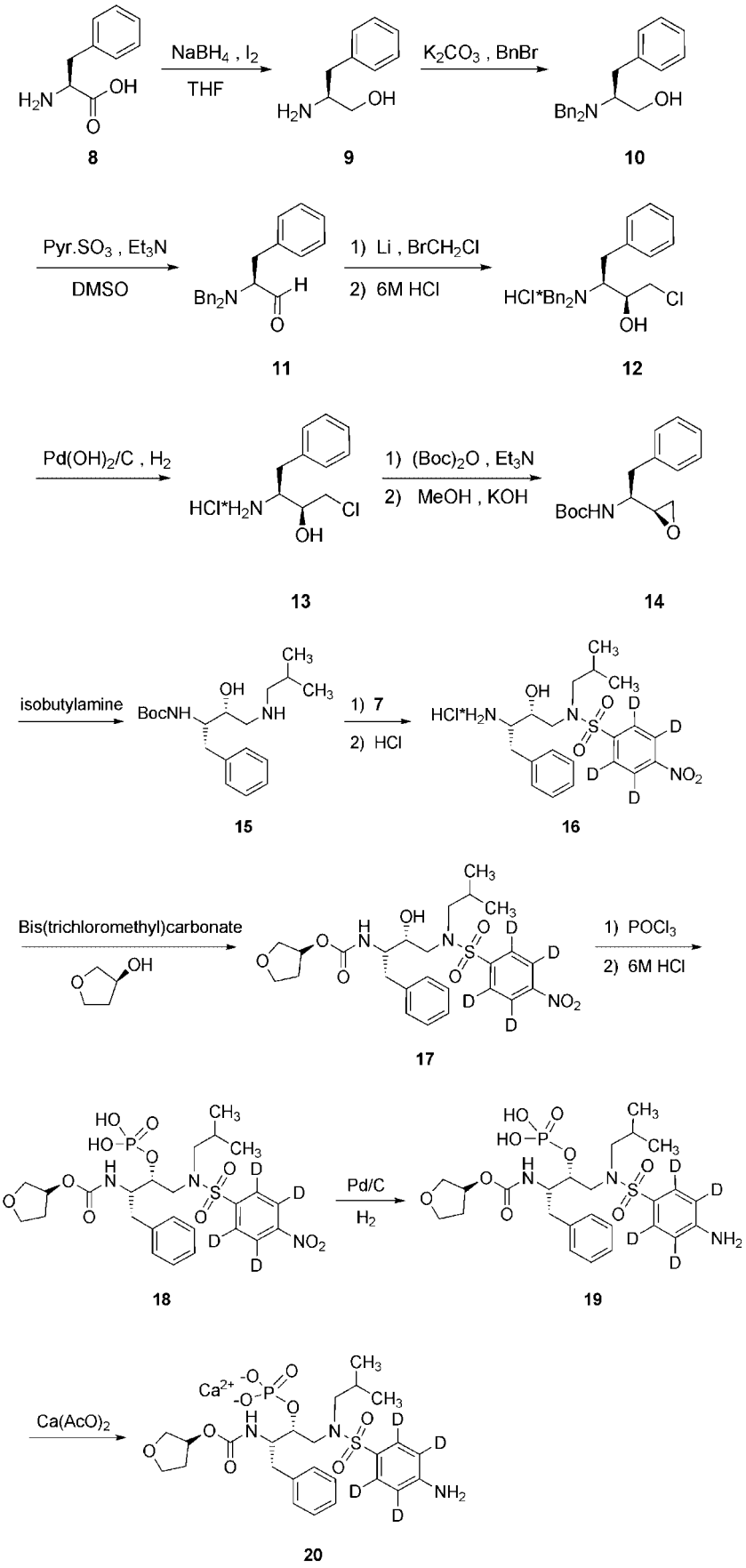
Compound (3) (6.0 g, 42.9 mmol) was cooled in an ice-salt bath under nitrogen. Chlorosulfonic acid (53.6 g, 460 mmol) was added dropwise with stirring. The reaction mixture was stirred at room temperature for 3 h, then added carefully to the ice/water mixture. The precipitate was filtered and washed with water (50 mL) to afford (4) as a white solid (6.7 g, 65.7%). ^1H NMR (300 MHz, CD_3OD):δ 2.18 (s, 3 H).

Synthesis of *p*-[$^2H_4$]-aminobenzene sulfonic acid (5)

Compound (4) (13.0 g, 57 mmol) was mixed with 10% aqueous sodium hydroxide (300 mL) and the mixture was heated at 95°C for 3 h. The reaction mixture was then cooled in an ice bath and acidified with 10% HCl until pH 1–2. Some precipitates started to form. The precipitate was filtered, washed with cold water (20 mL) and then dried in vacuo to afford (5) as a white solid (8.3 g, 87%).

Synthesis of p-[$^2H_4$]-nitrobenzenesulfonic acid (6)

To a suspension of (5) (0.7 g, 4 mmol) in glacial acetic acid (5.6 mL), 30% H_2O_2 (5.6 mL) was added dropwise under nitrogen.



Scheme 2.

The reaction mixture was refluxed at 76°C for 4.5 h and cooled to room temperature. The reaction mixture was concentrated to afford a yellow solid that was dried under vacuum overnight. Crude (6) (0.76 g, 92.7%) was used without further purification. MS-EI (*m/z*): 205.0 (8), 206.0 (M^-, 100), 207.0 (8), 208.0 (5).

Synthesis of *p*-[$^2H_4$]-nitrobenzenesulfonyl chloride (7)

To a solution of crude (6) (0.5 g, 2.4 mmol) in 1,2-dichloroethane (7 mL) was added PCl_5 (1.0 g, 4.8 mmol). The reaction mixture was stirred at 65°C for 2.5 h and cooled to room temperature. The reaction mixture was concentrated to afford (7) as a yellow solid that was dried under vacuum overnight. Crude (7) (0.51 g, 94.3%) was used without further purification.

Synthesis of L-phenylalaninol (9)

To a suspension of L-phenylalanine (8) (60 g, 364 mmol) and sodium borohydride (34.53 g, 913 mmol) in dry THF (400 mL) cooled in an ice bath was added dropwise a solution of iodine (92.36 g, 364 mmol) in dry THF (200 mL). After addition gas evolution had ceased. The mixture was heated to reflux for 18 h. The reaction mixture was cooled in ice-bath, and methanol was added cautiously until the mixture became clear. After stirring for 30 min, the solvent was removed to give a white paste which was dissolved by addition of 20% aqueous KOH (600 mL). The solution was stirred for 30 min and extracted with dichloromethane (3 × 200 mL). The organic layer was washed with brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a white semisolid which was recrystallized from toluene to afford (9) as a white solid (41.8 g, 76.0%).

Synthesis of N,N-dibenzyl-(*S*)-2-amino-3-phenyl-1-propanol (10)

To a suspension of potassium carbonate (20.1 g, 146 mmol) in methanol (150 mL) and water (30 mL) was added (9) (11.0 g, 72.7 mmol). The reaction mixture was refluxed for 10 min. Benzyl bromide (31.1 g, 181.9 mmol.) was added. After stirring for 1 h, the reaction mixture was cooled to room temperature and water (100 mL) was added. The mixture was extracted with dichloromethane (3 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford a white solid which was then washed with diethylether (2 × 50 mL) to afford (10) as a white solid (22.4 g, 93%).

^{1}H NMR (300 MHz, DMSO-d6): δ7.20 (s, 13H), 7.09 (d, 2H), 4.43 (t, 1H), 3.71-3.62 (m, 5H), 3.43 (m, 1H), 2.83 (m, 3H).

Synthesis of N,N-dibenzyl-(*S*)-2-amino-3-phenylpropanal (11)

To a solution of (10) (2.8 g, 8.4 mmol) in dry DMSO (20 mL) was added dropwise triethylamine (2.56 g, 25.3 mmol). The solution was immersed in an ice bath. Pyridine-sulfurtrioxide complex (4.03 g, 25.3 mmol) in DMSO (14 mL) was added in small portions over 5 min (the complex can also be added as the solid). After stirring for one hour at 10–15°C, the reaction was quenched with ice-water (100 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The orange oil was dried further under high vacuum for 12 h. The crude aldehyde (2.6 g, 94.2%) was used without further purification.

^{1}H NMR (300 MHz, DMSO-d6): δ9.70 (s, 1H), 7.38-7.14 (m, 15H), 3.74 (d, 4H), 3.45 (t, 1H), 3.00 (m, 3H).

Synthesis of N,N-dibenzyl-(*S*)-3-amino-(*S*)-2-hydroxy-4-phenyl-1-chlorobutane hydrochloride (12)

A solution of (11) (1.2 g, 3.6 mmol) in dry THF (20 mL) was cooled to −75°C under an argon atmosphere. Four alternating portions of lithium shot (4 × 0.1 g, 54.6 mmol) and bromochloromethane (4 × 0.13 g, 4.0 mmol) were added while maintaining an internal temperature below −65°C at all times. The suspension was mechanically stirred vigorously for 3 h. TLC analysis indicated disappearance of starting material. The solution was separated from floating lithium residues (the excess metal was washed with THF, dried under vacuum, and recycled) and transferred into 6 M HCl (4 mL). The mixture was concentrated in vacuo until a clear aqueous layer separated from a gummy, brown residue. The aqueous layer was removed and the residue crystallized from hot methanol (2.5 mL). The crude product was collected, washed with 10% methanol in ether (1.5 mL) and recrystallized from methanol (3 mL) to afford (12) as a white solid (0.48 g, 32%).

Synthesis of (*S*)-3-Amino-(*S*)-2-hydroxy-4-phenyl-1-chlorobutane hydrochloride (13)

To a mixture of (12) (1.0 g, 2.4 mmol) in MeOH (10 mL) was added 20% palladium hydroxide on charcoal (0.1 g). The slurry was stirred under 1 atm of hydrogen at room temperature for 4 h. The catalyst was filtered and washed with methanol. After concentration the residue was triturated with ether, filtered, and dried under vacuum to give (13) as a white solid (0.54 g, 94.7%).

^{1}H NMR (300 MHz, DMSO-d6): δ 8.09 (br, s, 3H), 7.38–7.30 (m, 5H), 6.12 (d, 1H), 3.96 (m, 1H), 3.66 (m, 1H), 3.51 (m, 2H), 2.99 (dd, 1H), 2.82 (dd, 1H).

Synthesis of (2*S*,3*S*)-N-Boc-3-amino-1,2-epoxy-4-phenylbutane (14)

Di-*tert*-butyl dicarbonate (1.8 g, 8 mmol) and triethylamine (1.6 g, 1.6 mmol) were dissolved in THF (20 mL), and the solution was cooled in an ice bath. Solid amino chlorohydrin hydrochloride (13) (1.8 g, 7.6 mmol) was added in portions. The cooling bath was removed and the reaction mixture was stirred for 3.5 h at room temperature. TLC analysis showed that the reaction was complete. The white slurry was cooled again in an ice bath, and a solution of KOH (2.6 g, 46 mmol) in methanol (20 mL) was added. The ice bath was removed and stirring was continued for an additional 1 h. TLC analysis indicated that the reaction was complete. The reaction mixture was poured into 50 mL of water and the white precipitates were collected by suction filtration. The crude product was purified by chromatography on silica gel (80 g) column, eluted with EtOAc/Hexanes (5:95), to afford (14) as white solid (1.75 g, 87.5%).

Synthesis of (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-1-isobutylamino-4-[$^2H_4$]-phenyl-2- butanol (15)

To a solution of (14) (1.2 g, 5 mmol) in anhydrous ethanol (15 mL) was added isobutyl amine (6.6 mL, 7.5 mmol). The reaction mixture was refluxed at 78°C under nitrogen for 1 h. TLC analysis showed that the reaction was complete. The reaction mixture was concentrated to afford (15) as a white solid (1.53 g, 99.8%).

^{1}H NMR (300 MHz, DMSO-d6): δ 7.17 (m, 5H), 6.74 (d, 1H), 3.50 (m, 1H), 3.36 (m, 1H), 2.98 (d, 1H), 2.60–2.40 (m, 2H), 2.30 (d, 2H), 1.64 (m, 1H), 1.26–1.10 (d, 9H), 0.87 (d, 6H).

Synthesis of (2*S*,3*R*)-N-(3-amino-2-hydroxy-4-phenyl)-N-isobutyl-4-[$^2H_4$]-nitrobenzene sulphonamide hydrochloride (16)

To a solution of (15) (1.27 g, 3.8 mmol) in toluene (9 mL) heated to 80°C was added triethylamine (0.42 g, 4.2 mmol). The mixture was heated to 90°C and a solution of (7) (1.0 g, 4.5 mmol) in toluene (4 mL) was added and stirred for 2 h. The reaction mixture was then cooled to 80°C and then concentrated hydrochloric acid (0.4 mL, 4.8 mmol) was added slowly. The mixture was heated to reflux (approx 88°C) for 1 h. Another portion of concentrated hydrochloric acid (0.3 mL, 3.6 mmol) was added. Solvent was removed from the reaction mixture by using the rotary evaporator. EtOAc (6 mL) was added. The mixture was stirred at 60°C for 30 min, and then cooled in an ice bath. The product was isolated by filtration, washed with cold EtOAc (3 mL), and dried under vacuum to afford (16) as a white solid (1.4 g, 80.5%).

Synthesis of (2*S*,3*R*)-N-(3-amino-2-hydroxy-4-phenyl)-N-isobutyl-4-[$^2H_4$]-nitrobenzene sulphonamide hydrochloride (17)

To a solution of *bis*(trichloromethyl)carbonate (0.56 g, 1.9 mmol) in dichloromethane (15 mL) cooled in an ice-salt bath was added dropwise (*S*)-3-hydroxytetrahydrofuran (0.5 g, 5.7 mmol) and triethylamine (0.57 g, 5.7 mmol). The reaction mixture was stirred at room temperature for 3 h. TLC analysis showed that the reaction was complete. The reaction mixture was evaporated to dryness under nitrogen. The white residue was dissolved in dichloromethane (50 mL). Amine hydrochloride (2.3 g, 5 mmol) was added dropwise. The suspension was cooled in ice-water. Triethylamine (1.4 g, 14 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 h. TLC analysis showed that the reaction was complete. The reaction mixture was evaporated to dryness. Water (30 mL) was added. The reaction mixture was extracted with dichloromethane (3 × 25 mL). The combined dichloromethane extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford a white solid which was recrystallized from EtOAc/EtOH (16 mL, 4:1), to afford (17) as a white solid (2.2 g, 82.1%).

Synthesis of (3*S*)-tetrahydro-3-furanyl-(1*S*,2*R*)-3-[[(4-[$^2H_4$]-nitrophenyl)-sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy)propylcarbamate (18)

To a solution of (17) (1.0 g, 1.9 mmol) in dry pyridine (50 mL) cooled in an ice bath was added dropwise phosphorus oxychloride (1.72 g, 11.2 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 2.5 h, and then cooled in an ice bath. Water (20 mL) was added and extracted with methyl isobutyl ketone (3 × 30 mL). The combined organic layers were dried over Na_2SO_4. Concentration under reduced pressure afforded a yellow solid. The yellow residue was dissolved in methyl isobutyl ketone (50 mL) followed by the dropwise addition of 6 M HCl (2 mL). After stirring at 50°C for 2.5 h, water (20 mL) was added. Layers were separated and the aqueous layer was extracted with methyl isobutyl ketone (2 × 30 mL). The combined methyl isobutyl ketone extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford (18) as a yellow foam (1.0 g, 84.7%).

Synthesis of (3*S*)-tetrahydro-3-furanyl-(1*S*,2*R*)-3-[[(4-[$^2H_4$]-aminophenyl)-sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy)propylcarbamate (19)

To a solution of (18) (0.3 g, 0.5 mmol) in MeOH (7.5 mL) was added 10% palladium on charcoal (0.15 g). The slurry was stirred under hydrogen at room temperature for 5 h. The catalyst was removed by filtration and washed with methanol. After concentration, it gave (19) as a yellow foam (0.27 g, 91.5%).

Synthesis of [$^2H_4$]-fosamprenavir calcium (20)

To a suspension of (19) (0.5 g, 0.9 mmol) in MeOH (10 mL) was added a solution of calcium acetate monohydrate (0.27 g, 1.7 mmol) in water (2 mL). The reaction mixture was stirred at room temperature for 15 min and then treated slowly with 5% NaOH until pH 8–9. Product started to precipitate. It was filtered, washed with EtOH/H_2O (6 mL, 1:1), and then dried in vacuo at 35–40°C to afford desired product (20) as a white solid (0.34 g, 64.2%).

^{1}H NMR (300 MHz, Solvent 0.1N DCl in D_2O): δ 7.36–7.28 (m, 5H), 4.96–4.79 (m, 1H masked by HOD signal), 4.49 (m, 1H), 4.29–4.16 (m, 1H), 3.89–3.55 (m, 4H), 3.42–3.33 (m, 2H), 3.16–2.90 (m, 3H), 2.75–2.60 (m, 1H), 2.11–1.85 (m, 2.5H), 1.30–1.15 (m, 0.5H), 0.85–0.79 (m, 6H). MS-EI (*m/z*): 587.1 (7), 588.1 (M^-, 100), 589.1 (30), 590.1 (10). HPLC (XDB-C18, CH_3OH/10 mmol/L NaH_2PO_4 + 0.1% H_3PO_4 = 50/50, 1.0 mL/min): t_R 5.8 min (> 98.5%). MS-EI analysis of compound (20) revealed that the compound has 98.2% deuterium enrichment, which is about the same as compound (6).

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