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Synthesis of deuterium-labeled olmesartan and candesartan

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This paper describes the synthesis of deuterium-labeled olmesartan and candesartan. The two desired compounds both used [$^2H_4$] 2-cyano-4′-methyl-biphenyl as deuterium-labeled reagent, which was synthesized beforehand in two steps. [$^2H_4$] olmesartan was synthesized in six steps further with 17% overall yield, and [$^2H_4$] candesartan was synthesized in seven steps further with 13% overall yield.

Keywords: deuterium-labeled; olmesartan; candesartan; angiotensin

Introduction

The renin–angiotensin system has been demonstrated to play an important role in the regulation of blood pressure and fluid volume homeostasis.[1] Compounds that interfere with this system can be effective for the treatment of hypertension and congestive heart failure. Sartans, such as losartan, valsartan, olmesartan, and candesartan, are blockers of the angiotensin II type I receptor. They have proven to be effective in the treatment of hypertension, renal diseases, heart failure, ventricular hypertrophy, dilation, arrhythmias, and dysfunction with overall reduced cardiovascular morbidity and mortality and fewer negative side effects than the classic angiotensin-converting enzyme inhibitor.[2,3] There is a requirement for stable isotope-labeled olmesartan and candesartan as internal standards for LC/MS analyses of the native drugs in biological fluids. The preparation of the stable-labeled version of the title compounds with M + 4 was requested. Although ^3H and ^{14}C olmesartan and candesartan have been prepared for pharmacological studies, the synthesis of its stable-labeled internal standard has not been described in detail.[4–9] In this paper, the synthetic route to [$^2H_4$] olmesartan and [$^2H_4$] candesartan is described in detail.

Results and discussion

A review of the literature indicates that several sartans labeled with ^{14}C or ^3H at various positions have been used for metabolic pathway elucidation.[4–9] Unfortunately, the reported synthesis is not satisfactory to our purpose: labeling has been performed at an exchangeable position. Although olmesartan and candesartan have been readily prepared via several synthetic routes,[10–20] the synthesis of [$^2H_4$]olmesartan and [$^2H_4$] candesartan have not been described previously. Scheme 1 presents the general synthetic scheme for preparing precursors, [$^2H_4$] 4′-methylbiphenyl-2-carbonitrile (4). 2-(2-Methoxyphenyl)-4, 4-dimethyl-4, 5-dihydrooxazole (2) was alkylated with [$^2H_4$] 4-methyl-phenyl magnesium bromide through Grignard reaction to afford [$^2H_4$] 4, 4-dimethyl-2-(4′-methyl-biphenyl-2-yl)-4, 5-dihydrooxazoline (3) that was converted to [$^2H_4$]nitrile (4) with phosphorus oxychloride.

Scheme 2 presents the general synthetic scheme for preparing [$^2H_4$] olmesartan (13). Tributyltin chloride (5) was treated with NaN_3 to afford azidotributylstannane (6), followed by cycloaddition reaction with the [$^2H_4$] nitrile (4) to give the [$^2H_4$] tetrazole (7). Selective protection of compound (7) with trityl chloride in CH_2Cl_2 produced [$^2H_4$] 5-(4′-methylbiphenyl-2-yl)-1-trityl-1H-tetrazole (8), which was brominated by *N*-bromosuccinimide in the presence of benzoyl peroxide to afford the bromobenzyl derivative (9). Ethyl 4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylate (10) was de-protonated by t-BuOK in Dimethy lformamide (DMF), followed by alkylation with compound (9) to give the *N*-alkylated imidazole derivative (11). Deprotection of the trityl group in compound (11) with 25% acetic acid solution provided the [$^2H_4$] olmesartan derivative (12). Saponification of compound (12) with aqueous LiOH solution, followed by acidification with HCl generated an off-white solid product. After purification by recrystallization from EtOAc, the desired product (13) was obtained as a white solid in 17% overall yield from [$^2H_4$] 4-bromo toluene (1).

Scheme 3 presents the general synthetic scheme for preparing [$^2H_4$] candesartan (20). [$^2H_4$] 4′-methylbiphenyl-2-carbonitrile (4) was brominated by *N*-bromosuccinimide in the presence of benzoyl peroxide to afford the bromobenzyl derivative (14). Alkylation of compound (14) was accomplished with ethyl 2-(tert-butoxycarbonylamino)-3- nitrobenzoate (15), followed by deprotection with HCl in MeOH and EtOAc to provide [$^2H_4$] ethyl

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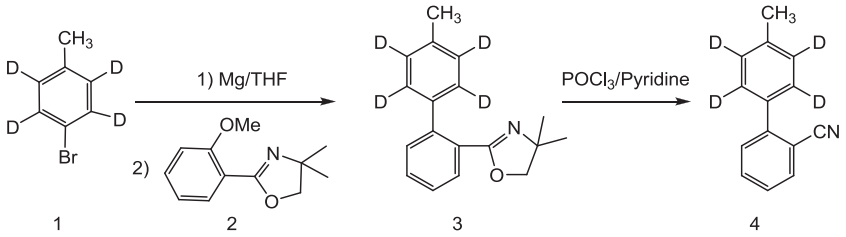
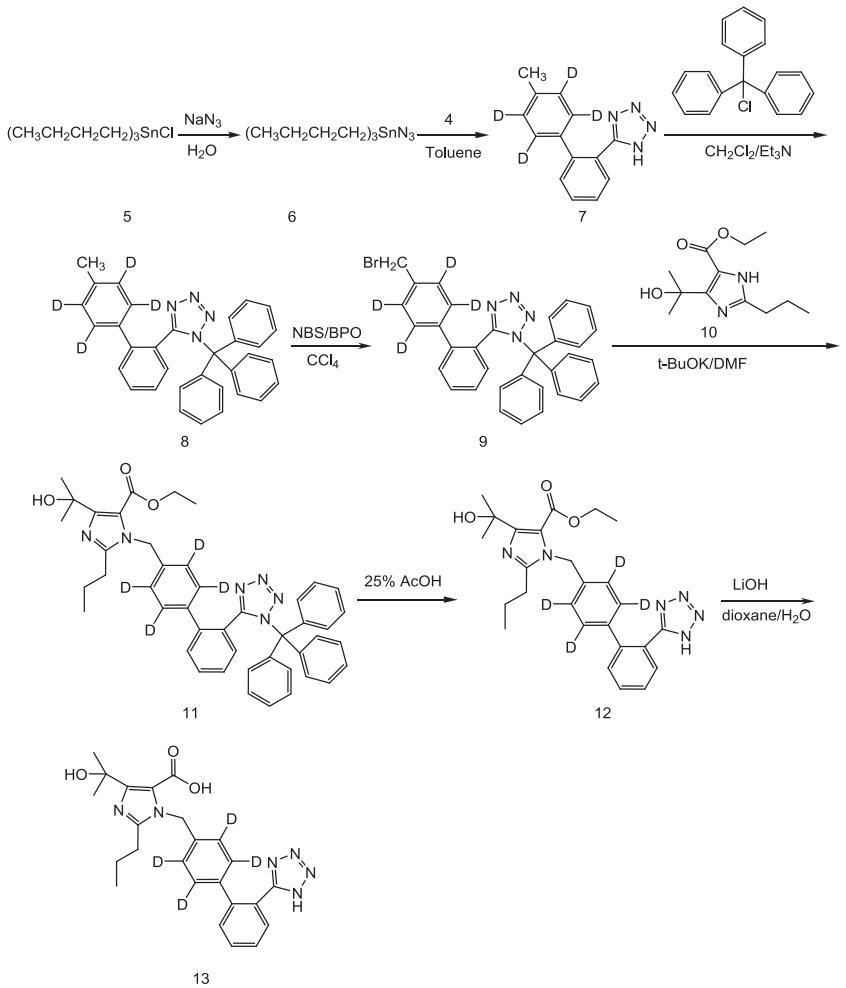


Scheme 1. Synthesis of [$^2H_4$] 2-cyano-4′-methyl-biphenyl.



Scheme 2. Synthesis of [$^2H_4$] olmesartan.

2-((2′-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate (16). Compound (16) was reduced to the [$^2H_4$] diamine (17) with $SnCl_2 \cdot H_2O$ in conc. HCl. Reduction of compound (16) with palladium/carbon or Raney nickel catalysts gave poor reproducibility because of partial debenzylation and deuterium label scrambling. The [$^2H_4$] diamine (17) was first reacted with tetraethoxymethane in acetic acid to form benzimidazole (18), which was reacted with compound (6) by cycloaddition reaction to give the [$^2H_4$]tetrazole (19). Compound (19) was hydrolyzed with NaOH in MeOH to afford the desired product [$^2H_4$] candesartan (20) in 78.9% yield and in 13% overall yield from [$^2H_4$] 4-bromo toluene (1).

HPLC results showed that both [$^2H_4$] olmesartan (13) and [$^2H_4$] candesartan (20) were obtained with over 99% chemical purity. Mass spectrometry analysis of [$^2H_4$] olmesartan (13) and [$^2H_4$] candesartan (20) revealed over 98% deuterium enrichment.

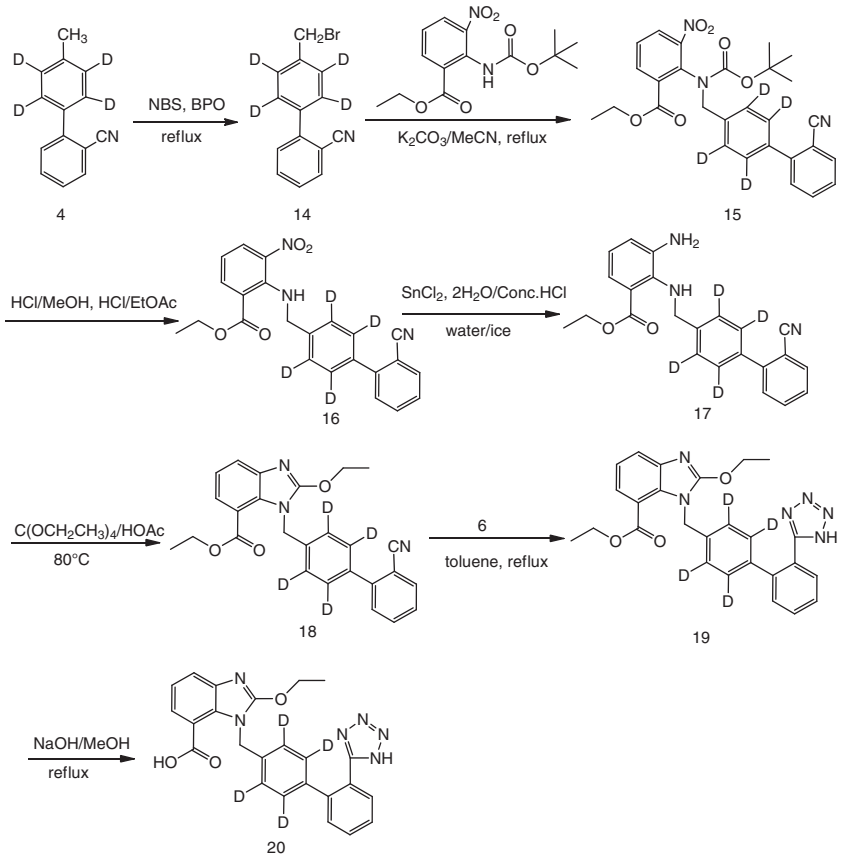
Experimental

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 (Bruker Corporation, Germany). Chemical purities were determined by an Agilent 1200 HPLC with a XDB-C18 column, 5 μm, 4.6 × 150 mm (Agilent, USA).

Synthesis of [$^2H_4$] 4, 4-dimethyl-2-(4′-methyl-biphenyl-2-yl)oxazoline (3)

To a suspension of Mg (0.695 g, 28.6 mmol) turnings in freshly distilled THF (5 mL), [$^2H_4$] 4-bromo toluene (0.5 g) and a crystal of iodine was added. The reaction was warmed to 50 °C to initiate. A solution of [$^2H_4$] 4-bromo toluene (4.5 g, 25.7 mmol) in freshly distilled THF (100 mL) was added to the reaction solution over 1.5 h at room temperature. After addition, the



Scheme 3. Synthesis of [$^2H_4$] candesartan.

reaction mixture was maintained at room temperature for 1 h. The resulting Grignard solution was then added directly to a stirred solution of 2-(2-methoxyphenyl)-4, 4-dimethyl-4, 5-dihydrooxazole (2) (5.7 g, 27.7 mmol) in dry THF (60 mL) at 20 °C for 20 min. The resulting mixture was stirred at room temperature for 8 h. The reaction mixture was cooled in an ice-water bath and quenched by adding saturated NH_4Cl solution (100 mL). The mixture was extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with water (80 mL), brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a colorless liquid. The crude product was purified by chromatography on silica gel column, eluted with hexanes/ethyl acetate (7:3) to afford (3) as a colorless liquid (5.88 g, 78.6%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71 (d, *J* = 9.0 Hz, 1H), 7.46 (t, *J* = 6.0 Hz, 1H), 7.36 (m, 2H), 3.81 (s, 2H), 2.39 (s, 3H), 1.62 (s, 2H), 1.30 (s, 6H).

Synthesis of [$^2H_4$] 2-cyano-4′-methyl-biphenyl (4)

To a solution of compound (3) (5.88 g, 21.8 mmol) in dry pyridine (25 mL), phosphorus oxychloride (4.0 mL, 43.6 mmol) was added dropwise while cooling in an ice-water bath. The reaction mixture was stirred at 105 °C for 3 h and then cooled at room temperature. The reaction solution was diluted with water (50 mL) and extracted with EtOAc (100 mL × 4). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give compound (4) as a light yellow solid (4.22 g, 97.9%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 7.75(d, J = 6.0 Hz, 1H), 7.62(t, J = 7.5 Hz, 1H), 7.50(d, J = 6.0 Hz, 1H), 7.42(t, J = 7.5 Hz, 1H), 2.44 (s, 3H).

Synthesis of azidotributylstannane (6)

A solution of sodium azide (8.0 g, 123.0 mmol) and tributyltin chloride (5) (40.0 g, 123.0 mmol) in water (32 mL) was stirred for 2 h while cooling in an ice-water bath. The aqueous phase was extracted with CH_2Cl_2 (80 mL × 2). The combined organic phases were washed with brine (150 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give compound (6) as a colorless liquid (39.26 g, 96.1%).

Synthesis of [$^2H_4$] 5-(4′-methylbiphenyl-2-yl)-1H-tetrazole (7)

A stirred suspension of (4) (2.16 g, 11.1 mmol) and azidotributylstannane (6) (18.8 g, 55.9 mmol) in dry toluene (21 mL) was heated at reflux for 16 h. The reaction mixture was cooled at room temperature and concentrated under reduced pressure to give a light yellow liquid. The crude product was purified by chromatography on silica gel column, eluted with CH_2Cl_2/MeOH (2:1) to afford (7) as a light yellow liquid (2.45 g, 91.1%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.89(d, *J* = 8.7 Hz, 1H), 7.62(t, *J* = 7.8 Hz, 1H), 7.46(d, *J* = 8.4 Hz, 1H), 7.24(t, *J* = 6.9 Hz, 1H), 3.86(s, 3H).

Synthesis of [$^2H_4$] 5-(4′-methylbiphenyl-2-yl)-1-trityl-1H-tetrazole (8)

The solution of trityl chloride (3.24 g, 11.6 mmol) in CH_2Cl_2 (15 mL) was added slowly to a solution of (7) (2.69 g, 11.1 mmol) in CH_2Cl_2 (20 mL) containing Et_3N (1.47 g, 2.0 mL, 12.1 mmol) for 45 min while cooling in an ice-water bath. The reaction mixture was stirred at room temperature for 2 h. The solution was diluted with CH_2Cl_2 (100 mL) and washed with H_2O (60 mL × 3). The organic layer was separated and washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a light yellow liquid. The crude product was recrystallized from CH_2Cl_2/hexanes to give (8) as a white solid (5.29 g, 98.1%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.96(d, *J* = 8.7 Hz, 1H), 7.62(t, *J* = 7.8 Hz, 1H), 7.46(d, *J* = 8.4 Hz, 1H), 7.24(t, *J* = 6.9 Hz, 1H), 3.86(s, 3H).

Synthesis of [$^2H_4$] 5-(4′-(bromomethyl)biphenyl-2-yl)-1-trityl-1H-tetrazole (9)

A stirred suspension of (8) (10.3 g, 21.34 mmol) and *N*-bromosuccinimide (1.92 g, 10.78 mmol), benzoyl peroxide (0.36 g, 1.5 mmol) in CCl_4 (100 mL) was heated at reflux for 1.5 h. Additional *N*-bromosuccinimide (1.92 g, 10.78 mmol) was added and the mixture was stirred for 1.5 h. TLC

analysis showed that about 20% starting material remained. Further *N*-bromosuccinimide (0.39 g, 2.19 mmol) was added and the mixture was stirred for 40 min. TLC analysis showed that no starting material remained. The suspension was cooled at room temperature, followed by filtering the solid. The filter cake was rinsed thoroughly with CCl_4 (20 mL × 3) and the combined organic layers were concentrated under reduced pressure to give a yellow liquid. The crude products was purified by chromatography on silica gel column, eluted with hexanes/ethyl acetate (20:1) to afford (9) as a white solid (7.17 g, 59.9%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (d, 1H, *J* = 9.0 Hz), 7.44 (m, 3H), 7.22–7.32 (m, 9H), 6.94(d, 6H, *J* = 8.7 Hz), 4.38 (s, 2H).

Synthesis of [$^2H_4$] ethyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-((2′-(1-trithyl-1H- terazol-5-yl)-biphenyl-4-yl)methyl)-1H-imidazole-5-carboxylate (11)

The solution of ethyl 4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylate (10) (1.82 g, 7.6 mmol) in dry DMF (25 mL) was added to a solution of t-BuOK (0.857 g, 7.6 mmol) in dry DMF (10 mL) by cooling with an ice-water bath as necessary, followed by stirring for 20 min to give a yellow solution. A light yellow solution of (9) (4.24 g, 5.1 mmol) in dry DMF (40 mL) was added into the aforementioned solution over 10 min. The mixture was stirred at room temperature for 2.5 h. The solution was diluted with EtOAc (150 mL) and H_2O (150 mL) to give a light pink solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford (11) as a white solid (5.29 g, 96.5%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (d, 1H, *J* = 9.0 Hz), 7.44 (m, 2H), 7.28 (m, 10H, *J* = 7.5 Hz), 6.94(d, 6H, *J* = 8.7 Hz), 5.35 (s, 2H), 4.12 (m, 2H), 2.51 (m, 2H), 1.67 (s, 6H), 1.08 (t, 3H, *J* = 8.4 Hz), 0.86 (t, 3H, *J* = 7.5 Hz).

Synthesis of [$^2H_4$] ethyl 1-((2′-(1H-tetrazol-5-yl)biphenyl-4-yl) methyl)-4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylate (12)

A suspension of (11) (1.4 g, 1.9 mmol) in 25% AcOH aqueous solution (38 mL) was stirred at 80 °C for 2.5 h. The solution was cooled to room temperature and stirring continued for 2.5 h, followed by filtering resulting salt. The filter cake was rinsed with 50% AcOH aqueous solution. The combined filtrates were co-evaporated with dry toluene to afford a colorless liquid. The crude product was purified by chromatography on silica gel column, eluted with CH_2Cl_2/MeOH (50:1) to afford (12) as a colorless liquid (0.61 g, 65.6%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.94 (d, 1H, *J* = 9.0 Hz), 7.67 (m, 2H), 7.94 (d, 1H, *J* = 7.5 Hz), 5.43 (s, 2H), 4.22 (m, 2H), 2.47 (m, 2H), 1.71 (m, 2H), 1.49 (s, 6H), 1.16 (t, 3H, *J* = 8.4 Hz), 0.94 (t, 3H, *J* = 7.5 Hz).

Synthesis of [$^2H_4$] olmesartan (13)

A suspension of (12) (0.878 g, 1.83 mmol), LiOH·H_2O (0.46 g, 11.0 mmol), dioxane (8.8 mL) and H_2O (8.8 mL) was stirred at room temperature for 4.5 h. The solution was evaporated to dryness. The residue was diluted with H_2O (10 mL) and acidified by 1M HCl (11.5 mL) to pH 3 to give an off-white solid. The solid was collected and recrystallized from EtOAc to afford (13) as an off-white solid (0.66 g, 79.5%).

^{1}H NMR (DMSO-d6, 300 MHz): δ 7.76 (dd, 2H, *J* = 8.1, 6.0 Hz), 7.67 (dd, 2H, *J* = 6.9, 8.4 Hz), 5.73 (s, 2H), 2.67 (t, 2H, *J* = 7.5 Hz), 1.62–1.65 (m, 2H), 1.58 (s, 6H), 0.88 (t, 3H, *J* = 7.5 Hz). MS-EI, (*m/z*): 449.2(100), 450.2 (M, 28%). HPLC (XDB-C18, wavelength = 254 nm, CH_3OH/10 mmol/L NaH_2PO_4 + 0.05% H_3PO_4 = 50/50, 1.0 mL/min): t_R = 6.65 min (98.8%). Isotopic enrichment determined by MS was over 98%.

Synthesis of [$^2H_4$] 4′-(bromomethyl)biphenyl-2-carbonitrile (14)

A suspension of (4) (1.75 g, 8.87 mmol) and benzoyl peroxide (0.15 g, 0.621 mmol), *N*-bromosuccinimide (0.75 g, 4.43 mmol) in CCl_4 (21 mL) was refluxed for 1 h. Additional *N*-bromosuccinimide (0.75 g, 4.43 mmol) was added and the mixture was stirred for a further 1 h. The suspension was filtered, and the solid residue was rinsed thoroughly with CCl_4 (4 mL × 3). The combined organic layers were concentrated under reduced pressure to give a light yellow solid, which was recrystallized from methanol to give (14) as a light yellow solid (2.01 g, 82.2%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 9.0 Hz, 1H), 7.65 (t, *J* = 6.0 Hz, 1H), 7.50 (m, 2H), 4.55 (s, 2H).

Synthesis of [$^2H_4$] ethyl 2-(tert-butoxycarbonyl((2′-cyanobiphenyl-4-yl)methyl)amino)-3-nitrobenzoate (15)

A suspension of (14) (1.78 g, 6.4 mmol) and ethyl 2-(tert-butoxycarbonylamino)-3-nitrobenzoate (2.00 g, 6.4 mmol), K_2CO_3 (0.89 g, 6.4 mmol) in CH_3CN (33 mL) was refluxed for 7 h. The reaction solution was diluted with H_2O (35 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow liquid. The crude product was purified by chromatography on silica gel column, eluted with hexanes/ethyl acetate (8:1) to afford (15) as a light yellow solid (3.2 g, 98.1%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (q, *J* = 3 Hz, 1H), 7.94 (q, 1H), 7.75 (d, *J* = 12, 21 Hz, 1H), 7.64 (t, *J* = 3 Hz, 1H), 7.50–7.41 (m, *J* = 6 Hz, 3H), 4.77 (dd, *J* = 6 Hz, 1H), 4.63 (t, *J* = 6 Hz, 1H), 4.24 (q, *J* = 6 Hz, 2H), 1.36 (s, 9H), 1.26 (t, 3H).

Synthesis of [$^2H_4$] ethyl 2-((2′-cyanobiphenyl-4-yl)methylamino)-3-nitrobenzoate (16)

A suspension of (15) in HCl/MeOH (11.6%, 10 mL) and HCl/EtOAc (18.9%, 10 mL) was stirred at room temperature for 2 h. The reaction was concentrated under reduce pressure. The residue was suspended in MeOH (15 mL) and basified by saturated $NaHCO_3$ (45 mL) solution to pH 8. The suspension was filtered, and the solid was rinsed with H_2O (15 mL × 3). The solid was thoroughly dried in the dessicator to give (16) as a yellow solid (1.24 g, 98.4%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (t, *J* = 3 Hz, 1H), 8.02 (d, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 3 Hz, 1H), 7.53–7.42 (m, *J* = 6 Hz, 2H), 6.74 (t, *J* = 6 Hz, 1H), 4.36 (q, *J* = 6 Hz, 2H), 4.24 (d, *J* = 6 Hz, 2H), 1.26 (t, 3H).

Synthesis of [$^2H_4$]ethyl 3-amino-2-((2′-cyanobiphenyl-4-yl) methylamino)benzoate (17)

A suspension of (16) (2.0 g, 4.9 mmol) and $SnCl_2·H_2O$ (4.00 g, 22.2 mmol) in concentrated HCl (36%, 40 mL) was stirred under an ice-water bath cooling for 2.5 h. The reaction mixture was basified by saturated Na_2CO_3 solution (150 mL) to pH 8–9 and extracted with EtOAc (40 mL × 3). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give (17) as a semi-solid (0.42 g, 90.2%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76 (d, 2H, *J* = 7.5 Hz), 7.65 (m, 1H), 7.47 (d, 1H, *J* = 7.5 Hz), 7.41 (d, 1H, *J* = 7.5 Hz), 7.37 (m, 1H), 6.90(m, 2H), 6.43 (bs, 1H), 4.25(m, 3H),3.96 (s, 2H), 1.31 (t, 3H, *J* = 6.0 Hz), 1.26 (t, 1H, *J* = 6.0 Hz).

Synthesis of [$^2H_4$] ethyl 1-((2′-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzo[d] imidazole-7-carboxylate (18)

A solution of (17) (1.26 g, 3.4 mmol), tetraethoxymethane (0.97 g, 5.03 mmol) and acetic acid (0.21 g, 3.4 mmol) in MeOH (5.0 mL) was stirred at 80 °C for 2 h. The reaction was diluted with MeOH (5 mL), H_2O (11 mL) and basified with 6 M NaOH solution (0.55 mL) to pH 8. The resulting precipitate was filtered, washed with H_2O (6 mL × 3) to give a yellow residue. The crude product was purified by chromatography on silica gel column, eluted with hexanes/ethyl acetate (5:2) to afford (18) as a white solid (1.17 g, 81.1%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74 (d, 2H, *J* = 9.0 Hz), 7.63 (m, 2H), 7.43 (m, 2H), 7.20 (d, 1H, *J* = 7.5 Hz), 5.74 (s, 2H), 4.70 (m, 2H), 4.25 (m, 2H), 1.49 (t, 3H, *J* = 6.0 Hz), 1.26 (t, 3H, *J* = 6.0 Hz).

Synthesis of [$^2H_4$] ethyl 1-((2′-(1H-tetrazol-5-yl)biphenyl-4-yl) methyl)-2-ethoxy-1H-benzo [d]imidazole-7-carboxylate (19)

A suspension of (18) (1.04 g, 2.4 mmol) and (6) (4.03 g, 12.1 mmol) in dry toluene (10.4 mL) was refluxed for 20 h. TLC showed some starting material. Another portion of (6) (2.01 g, 6.06 mmol) was added and the mixture was stirred for 5 h. TLC showed no starting material. The reaction solution was evaporated to remove toluene to give a yellow residue, which was diluted

with H_2O (3 mL) and acidified with 1M HCl (3.3 mL) to pH 5. The solution was stirred at room temperature for 15 min and extracted with CH_2Cl_2 (15 mL × 4). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow liquid. The residue was purified by chromatography on silica gel column, eluted with CH_2Cl_2/MeOH(10:1) to afford (19) as a light yellow solid(0.96 g, 84.2%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13 (d, 1H, J = 7.5 Hz), 7.61 (d, 2H, J = 6.0 Hz), 7.44(d, 1H, J = 7.5 Hz), 7.34 (m, 1H), 7.12 (d, 1H, J = 7.5 Hz), 7.01(m, 1H), 5.60 (s, 2H), 4,44 (m, 2H), 4.10(m, 2H), 1.47 (t, 3H, J = 6.0 Hz), 1.18 (t, 3H, J = 6.0 Hz).

Synthesis of [$^2H_4$] candesartan (20)

To a suspension of (19) (1.8 g, 3.8 mmol) in MeOH (6.5 mL) and NaOH aqueous solution (1 M, 9.0 mL) was refluxed for 1.5 h. The reaction solution was evaporated to dryness. The residue was diluted with H_2O (16 mL) and acidified with 2M HCl(5.1 mL). The resulting precipitate was filtered, washed with water (10 mL × 4), and then dried in the desiccator to afford (20) as a white solid (1.33 g, 78.9%).

^{1}H NMR (DMSO-d6, 300 MHz): δ 7.62 (m, 3H), 7.46 (m, 3H), 7.15(t, 1H, J = 7.5 Hz), 5.60 (s, 2H), 4.56 (m, 2H), 1.35 (m, 3H). MS-EI, (*m/z*): 442.1 (8), 443.1 (M, 100%), 441.1 (30), 445.1 (6). HPLC (XDB-C18, wavelength = 255 nm, CH_3OH/10 mmol/L NaH_2PO_4 + 0.05% H_3PO_4 = 65/35, 1.0 mL/min): t_R = 6.91 min (98.8%). Isotopic enrichment determined by MS was over 98%.

Conflict of Interest

The authors did not report any conflict of interest.

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