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Synthesis of a highly potent leukocyte function-associated antigen-1 antagonist and its metabolite labeled with stable isotopes and carbon-14, part 2

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(*S*)-2-[(*R*)-7-(3,5-Dichlorophenyl)-5-methyl-6-oxo-5-(4-trifluoromethoxybenzyl)-6,7-dihydro-5*H*-imidazo[1,2-a]imidazole-3-sulfonylamino]-proprionamide (1), a potent lymphocyte function-associated antigen-1 antagonist and its sulfonamide metabolite (2) labeled with stable isotopes and carbon-14 were prepared for Drug Metabolism and PharmacoKinetics and other studies. A long linear route was used to prepare [$^{13}C_2$, $^{2}H_3$]-(1) using [3,3,3-^{2}H]-D-alanine and [$^{13}C_2$]-glycine in 15 steps and 2.5% overall yield. With the availability of [$^{13}C_6$]-3,5-dichloroaniline, the sulfonamide [$^{13}C_6$]-(2) was prepared in 12 steps and in 5.6% overall yield. For the carbon-14 synthesis, a six-step synthesis gave both compounds [^{14}C]-(1) and [^{14}C]-(2) from the common sulfonyl chloride intermediate [^{14}C]-(15) in 18% and 4% radiochemical yields and specific activities of 44 and 40.5 mCi/mmol, respectively.

Keywords: leukocyte function-associated antigen-1 antagonist; carbon-14; carbon-13; deuterium; metabolites; radiosynthesis

Introduction

The lymphocyte function-associated antigen-1 (LFA-1) is an essential component in normal immune system function and is a target for drug discovery for its broad therapeutic potential in treating inflammatory diseases. In a previous paper, we described the synthesis of some potent antagonists of LFA-1.[1] The search for better compounds with high potency and good pharmacokinetics led to the discovery of compound (1).[2] Here, we report the synthesis of this potent antagonist and its sulfonamide metabolite (2) labeled with stable isotopes and carbon-14 to support drug metabolism and pharmacokinetics studies.

Results and discussion

The synthesis of (1) labeled with stable isotopes was accomplished in a long linear synthetic route and with an overall yield of 2.5% from D-alanine-3, 3, 3-$^{2}H_3$, Scheme 1. Following a route developed by our process chemists to prepare the first generation LFA-1 antagonists.[3] D-Alanine-3,3,3-$^{2}H_3$ was first protected at the amino group and activated as the mixed anhydride with isobutyl chloroformate before it was coupled to 3,5-dichloroaniline to give [$^{2}H_3$]-(3) in 99% yield.[4] Deprotection of the amino group using concentrated aqueous HCl gave 3,5-dichlorophenylpropionamide [$^{2}H_3$]-(4) in 77% yield. This amine was reacted with pivaldehyde in toluene at 55 °C to give the imidazolidinone [$^{2}H_3$]-(5) as a white solid in 98% yield. Protection using trifluoroacetic anhydride and triethylamine gave [$^{2}H_3$]-(6) in 72% yield after crystallization from warm hexane. Deprotonation with lithium hexamethyldisilazane at −20 °C and alkylating with 4-trifluormethoxybenzyl bromide gave the 5,5-disubstituted imidazolidinone [$^{2}H_3$]-(7) in 79% yield. Hydrolysis of this material using benzyltrimethyl- ammonium hydroxide and 50% aqueous sodium hydroxide in dioxane at 50 °C, followed by treatment with 6N aqueous HCl gave the amino derivative [$^{2}H_3$]-(8) in 97% yield. The stereospecific formation of the *trans*-imidazolidinone (5) and subsequent alkylation, then hydrolysis to (8) have been described in detail before.[3,5–7] Glycine ($^{13}C_2$, 99 atom % ^{13}C) was first protected using di-*tert*-butyl dicarbonate and 10% triethylamine in methanol under reflux as seen before[4] and was isolated by crystallization from hexanes in 92%. The protected amino acid was then activated as the mixed anhydride by reaction with pivaloyl chloride and triethylamine and coupled to [$^{2}H_3$]-(8) in 96% yield after flash chromatography purification. Removal of the protecting group at 55 °C using PTSA in methanol gave the free amine [$^{13}C_2$,$^{2}H_3$]-(10) in 75% yield after silica gel flash chromatography purification. Reaction with 1,1′-thiocarbonyldiimidazole in THF gave the thiohydantoin derivative [$^{13}C_2$,$^{2}H_3$]-(11), which was used without further purification in the next step. Cuprous chloride and Hunig's base were used to form the bicyclic lactam [$^{13}C_2$,$^{2}H_3$]-(12).[5] The lithium enolate produced from treatment of [$^{13}C_2$,$^{2}H_3$]-(12) with a solution of LiHMDS in THF at −40 °C was trapped as the diethyl phosphate [$^{13}C_2$,$^{2}H_3$]-(13).[5,8] Without purification, this phosphate was reacted with iodotrimethylsilane, produced *in situ* from NaI

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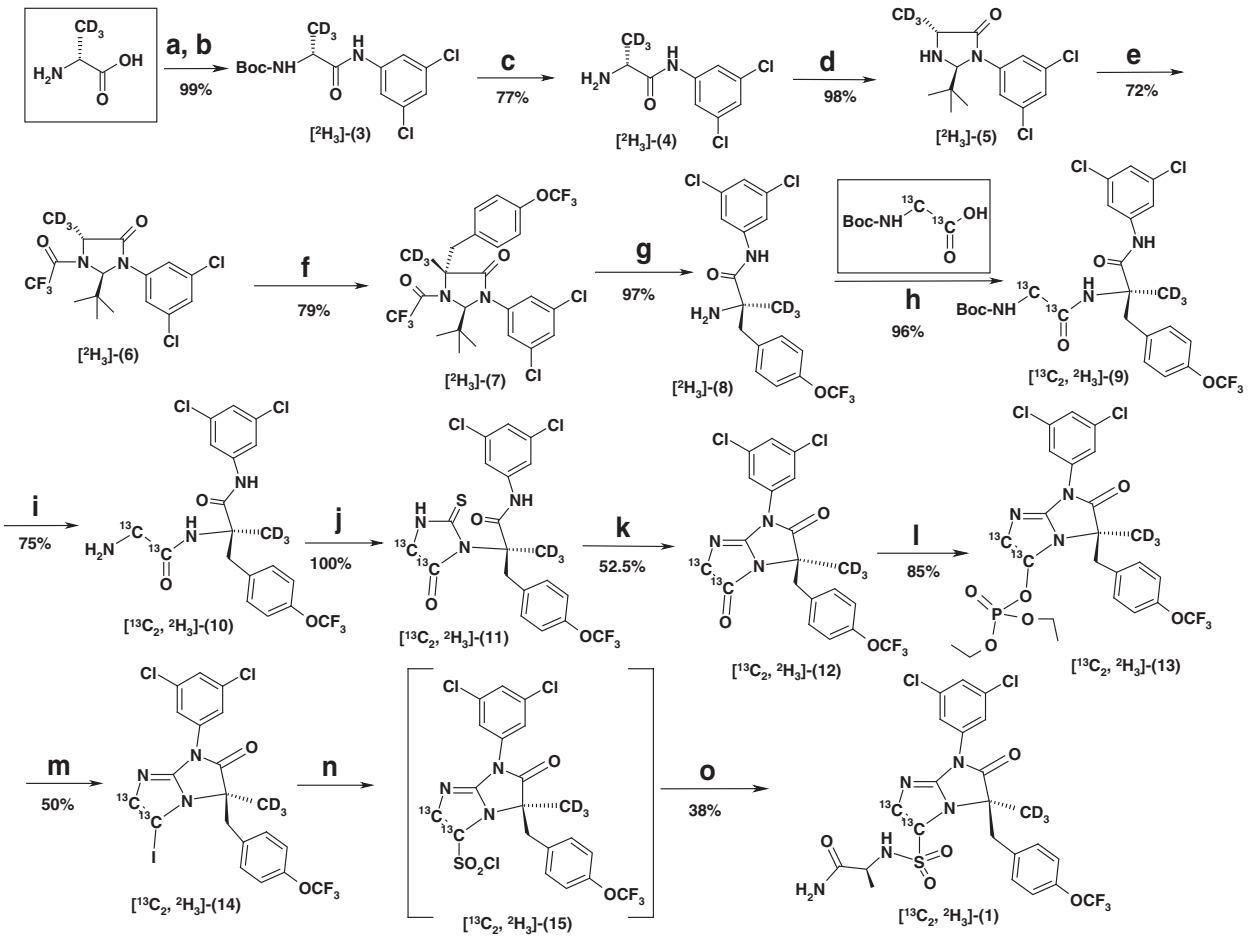


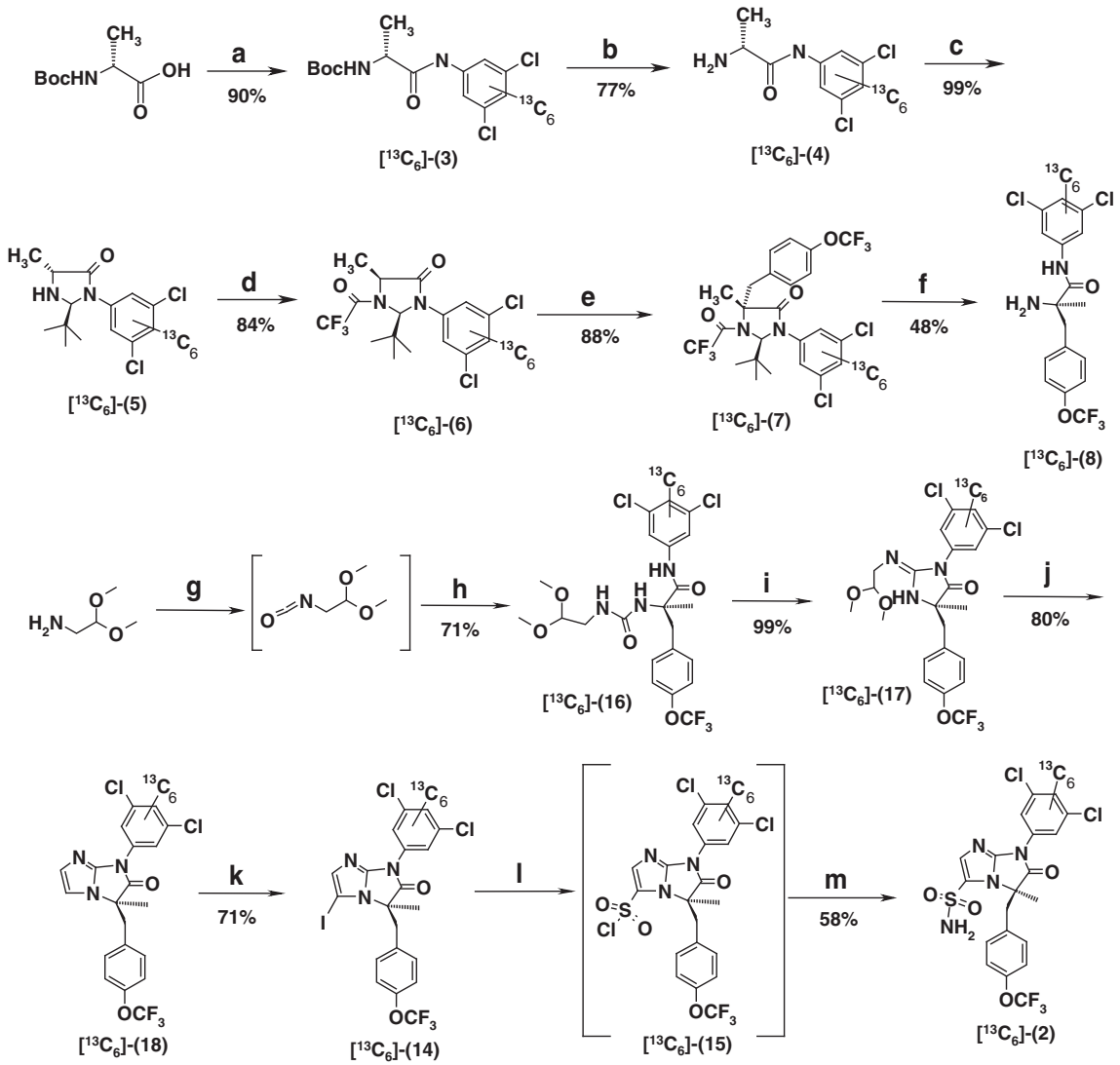
Scheme 1. (a) Boc_2O, triethylamine, MeOH; (b) *t*-BuCOCl, 4-methyl morpholine, 3,5-dichloroaniline; (c) 12 N aq. HCl, MeOH; (d) *t*-BuCHO, toluene, 55 °C; (e) $(CF_3CO)_2O$, triethylamine, CH_2Cl_2; (f) $[(CH_3)_3Si]_2NLi$, THF, 4-trifluoromethoxybenzyl bromide; (g) $BnMe_3NOH$, 50% aq. NaOH, 1,4-dioxane, 6 N HCl; (h) triethylamine, *t*-BuCOCl; (i) $TsOH.H_2O$, MeOH, 55 °C; (j) TCDI, THF; (k) Celite®, *i*-Pr_2NEt, CuCl, toluene/MeCN; (l) $[(CH_3)_3Si]_2NLi$, $ClP(O)(OEt)_2$, THF; (m) TMSCl, NaI, CH_2Cl_2; (n) (1) *i*-PrMgCl, THF; (2) SO_2, (3) *N*-chlorosuccinimide, THF; (o) L-alaninamide, triethylamine, dimethylformamide.

and trimethylsilyl chloride. The reaction gave besides the desired iodide [$^{13}C_2$,$^2H_3$]-(14), the des-iodo product [$^{13}C_2$,$^2H_3$]-(18) (Scheme 2) in 50% and 23% yields, respectively. Compound [$^{13}C_2$,$^2H_3$]-(14) was easily separated by flash chromatography and the des-iodo was subjected to iodination again using *N*-iodosuccinimide (NIS), Scheme 2. The iodo-intermediate [$^{13}C_2$,$^2H_3$]-(14) was first treated with isopropyl magnesium chloride and then reacted with sulfur dioxide to give the sulfur Grignard complex.[9] This complex was finally treated with *N*-chlorosuccinimide in THF in one pot to give the sulfonyl chloride [$^{13}C_2$,$^2H_3$]-(15). The sulfonyl chloride [$^{13}C_2$, $^2H_3$]-(15) was then treated with L-alaninamide in dimethylformamide (DMF) to give [$^{13}C_2$,$^2H_3$]-(1) labeled with both deuterium and carbon13 and in 2.5% overall yield.

The collision-induced dissociation-Tandem Mass Spectrometry (CID-MS/MS) spectra of unlabeled reference sample (1) and [$^{13}C_2$,$^2H_3$]-(1) are compared in Figure 1. The major fragmentation pathways are consistent with the structure; see the fragmentation pattern in Figure 2.

With the availability of [$^{13}C_6$]-3,5-dichloroaniline,[10] the metabolite [$^{13}C_6$]-(2) was prepared according to Scheme 2. The amine derivative [$^{13}C_6$]-(8) was prepared as shown on Scheme 1 in 24% overall yield. Then, it was reacted with the dimethoxyethyl isocyanate produced *in situ* from the action of phosgene on aminoacetaldehyde dimethyl acetal under Schotten–Baumann conditions in 71% yield. The resulting urea derivative [$^{13}C_6$]-(16) was subjected to a dehydration cyclization according to Appel to give [$^{13}C_6$]-(17).[11] Treatment with *p*-toluenesulfonic acid (PTSA) in hot ethyl acetate gave the bicyclic imidazole [$^{13}C_6$]-(18) in 71% yield.[2] Regeoseletive iodination gave the iodo-derivative [$^{13}C_6$]-(14) in 71% yield which was easily separated from the diodo-derivative by-product [$^{13}C_6$]-(19), Figure 3, by silica gel chromatography using toluene as eluent. The sulfonyl chloride derivative [$^{13}C_6$]-(15) was then prepared as described earlier on Scheme 1. Reaction with ammonium hydroxide in DMF in the presence of cesium carbonate gave [$^{13}C_6$]-(2) in 58% yield over two steps, Scheme 2.

In the synthesis of [^{14}C]-(1) and [^{14}C]-(2), the isocyanate prepared under Schotten–Baumann conditions from [^{14}C]-phosgene and aminoacetaldehyde dimethyl acetal was reacted with chiral amine (8) to give [^{14}C]-(16) in 71% yield, Scheme 3. The following dehydration/cyclization of the urea derivative to compound [^{14}C]-(17) was accomplished as seen before in 100% radiochemical yield. Heating in ethyl acetate in the presence of PTSA gave the bicyclic [^{14}C]-(18) in 96% yield. Iodination or bromination of this compound gave [^{14}C]-(14) and [^{14}C]-(20) in 66% and 69%, respectively.[2] The sulfonyl chloride [^{14}C]-(15) prepared as reported before, was either treated with L-alaninamide to give [^{14}C]-(1) or with ammonium hydroxide to give metabolite [^{14}C]-(2) in 40% and 8%, respectively. The low yields are due possibly to the presence of moisture during



Scheme 2. (a) *t*-BuCOCl, 4-methyl morpholine, [$^{13}C_6$]-3,5-dichloroaniline; (b) 12 N aq. HCl, MeOH; (c) *t*-BuCHO, toluene, 55 °C; (d) $(CF_3CO)_2O$, triethylamine, CH_2Cl_2; (e) $[(CH_3)_3Si]_2NLi$, THF, 4-trifluoromethoxybenzyl bromide; (f) $BnMe_3NOH$, 50% aq. NaOH, 1,4-dioxane, conc. HCl; (g) phosgene, toluene; (h) [$^{13}C_6$]-(8), Sat'd $NaHCO_3$, CH_2Cl_2; (i) Ph_3P, CCl_4, triethylamine, CH_2Cl_2; (j) *p*-toluenesulfonic acid, EtOAc; (k) *N*-iodosuccinimide, pyridinium *p*-toluenesulfonate, CH_2Cl_2; (l) (1) *i*-PrMgCl, THF; (2) SO_2; (3) *N*-chlorosuccinimide, THF; (m) NH_4OH, Cs_2CO_3, dimethylformamide.

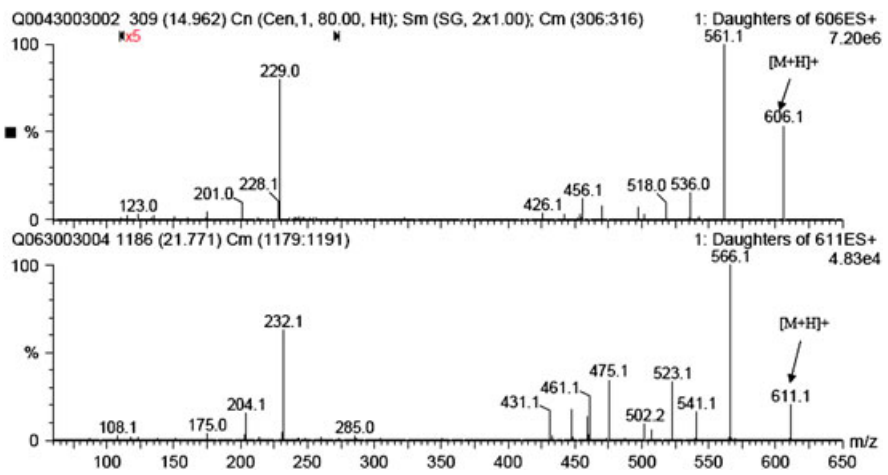


Figure 1. CID-MS/MS spectra of (1) top and [$^{13}C_2$,$^{2}H_3$]-(1).

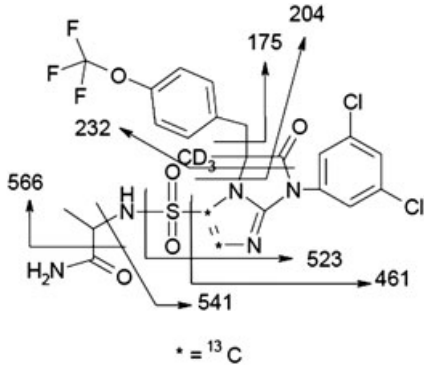


Figure 2. Fragmentation pathways of [$^{13}C_2$,$^{2}H_3$]-(1), molecular ion m/z 611.

the transformation from the derivatives [^{14}C]-(14) and [^{14}C]-(20) to the sulfonyl chloride [^{14}C]-(15). Sulfonic acid [^{14}C]-(21) was the major product after the treatment with ammonium hydroxide.

Experimental

Materials and methods

Liquid scintillation counting was accomplished using a Beckman LS5000TA and ready safe™ cocktail (Beckman, Fullerton, CA, USA). Radio-thin layer chromatography (TLC) was carried out on a BIOSCAN System 200 imaging scanner using an auto-changer 1000 and WinScan software version 2.1a (Bioscan Inc., Washington, DC, USA). The quantification of the HPLC chromatograms was carried out using an HPLC system comprised of a radiomatic A515 Flo-one\Beta radioactivity flow detector (Packard Instrument Company, Meriden, CT, USA), two pumps (HITACHI L-6200A intelligent pump), a linear UVIS 200, Ultima Flo™ AP cocktail (Packard, Meriden CT, USA), and radiomatic 500TR V 3.60 for data evaluation. Mass spectra for nonradioactive compounds were acquired by a Hewlett–Packard auto sampler Series 1100, connected to a Micromass Platform LCZ in the electron spray (ES) mode. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker 400MHz DPX spectrometer (Billerica, MA, USA) using deuterated chloroform or methanol as a solvent and tetramethyl silane as the internal standard unless stated otherwise. Precoated TLC sheets (silica gel 60 F_{254}) and silica gel 60-200 Mesh (Nominal, I.D., grade 62) for flash chromatography were obtained from EM Science (Gibbstown, NJ, USA). Phosgene, 20% solution in toluene was obtained from Fluka (Milwaukee, WI, USA). D-Alanine3,3,3-$^{2}H_3$ (99.9 ^{2}H %) atom was purchased from CDN, (Pointe Claire Quebec, Canada). [^{14}C]-Phosgene was obtained from Vitrax (Placentia, CA, USA) and from PerkinElmer (Boston, MA, USA). The rest of the reagents were purchased from Aldrich Chemicals Company.

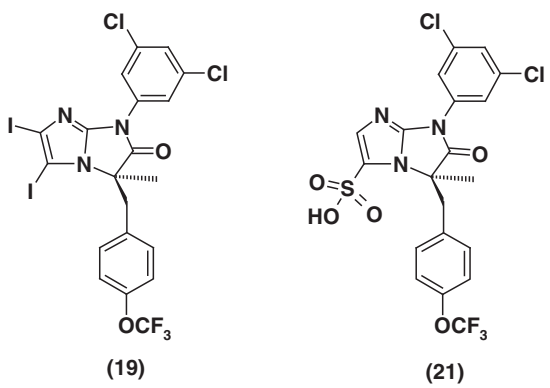


Figure 3. Structures of the diiodo and sulfonic acid derivatives.

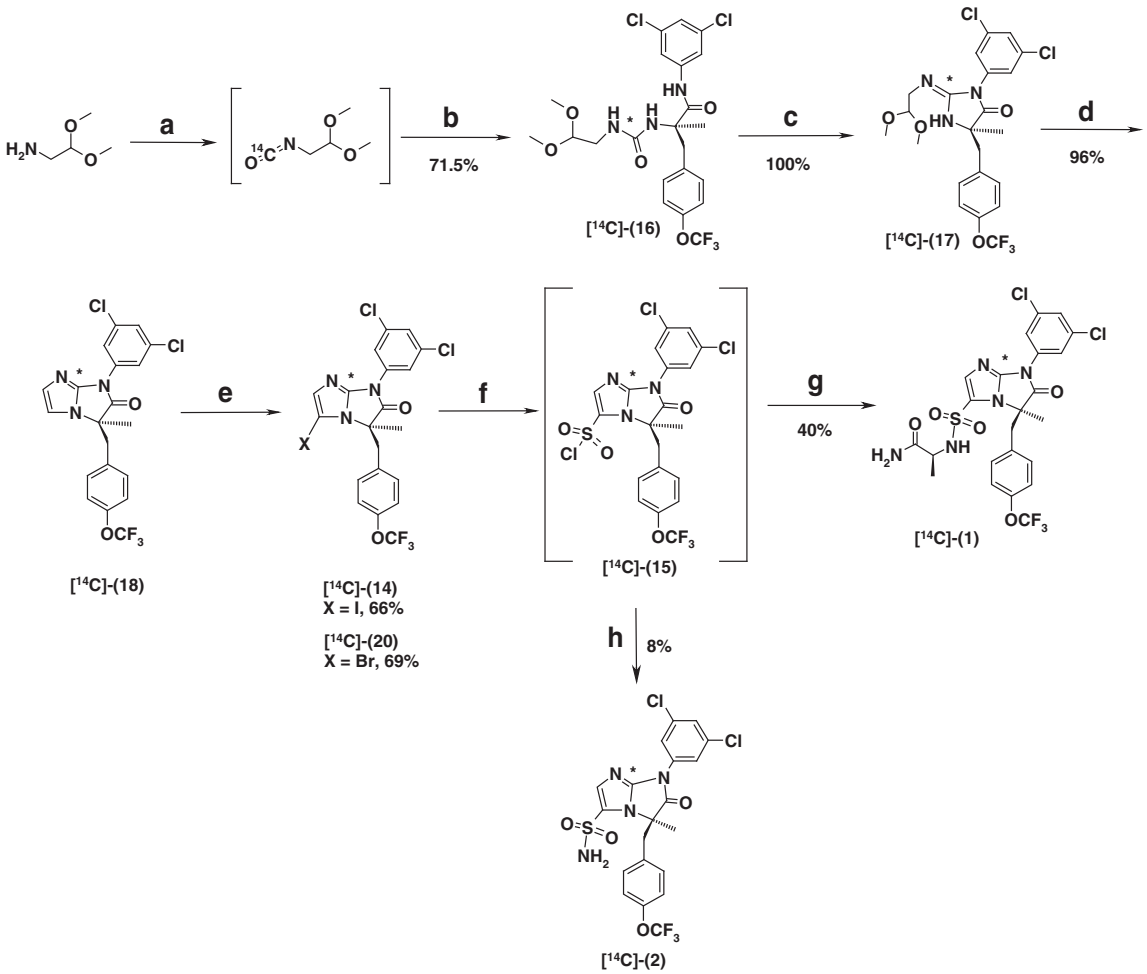
Synthesis of [$^{13}C_2$,$^{2}H_3$]-(1)

t-Butyloxycarbonyl [3,3,3-^{2}H]-D-alanine: To a suspension of [3,3,3-^{2}H]-D-alanine (2.0 g, 21.505 mmol) in a solution of triethylamine (3.26 mL, 23.28 mmol) in methanol (30 mL), was added di-*tert*-butyl dicarbonate (9.5 g, 43.1 mmol), and the mixture was refluxed for 30 minutes to give a clear solution. After cooling to room temperature, the solution was concentrated *in vacuo*. The residue was treated with an aqueous solution of 1.0 N HCl at 0 °C and then extracted with ethyl acetate (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Ether was added, and the precipitate was filtered. The filtrate was concentrated then crystallized from hexanes in 99.4% yield or a total of 4.11 g of a white solid. ^{1}H NMR (DMSO-d_6) δ: 12.39(s, 1H), 7.06(d, J = 7.60 Hz, 1H, NH), 3.88(d, J = 7.60 Hz, 1H, CH), 1.35(br s, 9H). ^{1}H NMR ($CDCl_3$) δ: 10.20(br s, 1H), 5.0(s, 1H), 4.26 (d, J = 4.33 Hz, 1H), 1.45(br s, 9H), liquid chromatography mass spectrometry (LCMS): m/z: 193.74 (100%).

[(*R*)-1-(3,5-Dichloro-phenylcarbamoyl)-[$^{2}H_3$]ethyl]-carbamic acid *tert*-butyl ester)-[$^{2}H_3$]-(3): To a solution of the aforementioned *t*-boc-D-alanine-$^{2}H_3$ (3.8 g, 19.772 mmol) in anhydrous THF (60.0 mL), was added 4-methyl morpholine (4.56 mL, 41.31 mmol) dropwise at 0 °C. The clear solution was stirred for 10 minutes before isobutyl chloroformate (2.6 mL, 19.48 mmol) was added dropwise to give a white mixture. This mixture was stirred for 1 hour at 0 °C, then 3,5-dichloroaniline (3.3 g, 19.96 mmol) in THF (40.0 mL) was added dropwise in a 60-minute period. After stirring at this temperature for 2 hours, the ice-bath was removed, and the mixture was warmed to room temperature and stirred overnight. The mixture was then concentrated *in vacuo* to remove THF and then diluted with methylene chloride and washed with saturated aq. $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 8.91 g of a yellowish oil, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ: 8.89(br s, 1H), 7.44(d, J = 1.63 Hz, 2H), 7.03 (t, J = 1.63 Hz, 1H), 5.03(d, J = 7.12 Hz, 1H), 4.28(d, J = 7.12 Hz, 1H), 1.43(br s, 9H), LCMS: e/z: 335 (100%).

(*R*)-2-Amino-*N*-(3,5-dichloro-phenyl)-[3,3,3-^{2}H]propionamide [$^{2}H_3$]-(4): To a solution of the aforementioned material (8.91 g, 19.88 mmol) in methanol (100 mL), was added conc. HCl (10 mL of 12 N and 5.0 mL of water) at 0 °C. The resulting solution was stirred at this temperature for 2 hours then warmed to room temperature and stirred overnight. TLC indicated that the reaction was over. The solution was then concentrated *in vacuo* to about 5–10 mL, and toluene was added. The mixture was cooled down in an ice-bath and treated with 20 mL of 50% w/w NaOH in water. The toluene layer was removed, and the aqueous was extracted with methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 4.91 of yellow oil. Purification by flash chromatography using chloroform, then 10%–20% methanol in chloroform gave 3.55 g of pale yellow oil in 77% yield. ^{1}H NMR ($CDCl_3$) δ: 9.65(br s, 1H), 7.56(d, J = 1.23 Hz, 2H), 7.06(t, J = 1.23 Hz, 1H), 3.62(s, 1H), 1.62(br s, 2H). LCMS: e/z: 237 (100%).

(2*S*,5*R*)-2-*tert*-Butyl-3-(3,5-dichlorophenyl)-5-[$^{2}H_3$]methyl-imidazolidin-4-one [$^{2}H_3$]- (5): A solution of the aforementioned amine (3.55 g, 15.02 mmol) in toluene (30 mL) was treated at room temperature with trimethyl acetaldehyde (2.5 mL, 22.33 mmol), dropwise. The resulting cloudy solution was heated to 55 °C and stirred overnight. TLC (10% MeOH/$CHCl_3$) showed the presence of starting material. The solution was then concentrated *in vacuo*, and hexane was added to the residue to give a white solid. Hexane was decanted off,



Scheme 3. (a) [^{14}C]-phosgene, toluene; (b) (8), Sat'd $NaHCO_3$, CH_2Cl_2; (c) Ph_3P, CCl_4, triethylamine, CH_2Cl_2; (d) *p*-toluenesulfonic acid, EtOAc; (e) *N*-iodosuccinimide, pyridinium *p*-toluenesulfonate, CH_2Cl_2, or *N*-bromosuccinimide, triethylamine, CH_2Cl_2; (f) (1) *i*-PrMgCl, THF; (2) SO; (3) *N*-chlorosuccinimide, THF; (g) L-alaninamide, triethylamine, dimethylformamide; (h) NH_4OH, Cs_2CO_3, dimethylformamide. Asterisks indicate position of ^{14}C atom.

and the white solid was further dried *in vacuo* to give 2.0 g of product. The mother liquor was concentrated to give 2.48 g of a yellowish solid. Total yield 4.48 g or 98% yield. ^{1}H NMR ($CDCl_3$) δ: 7.32(d, J = 1.72 Hz, 2H), 7.20(t, J = 1.72 Hz, 1H), 4.86(s, 1H), 3.76 (s, 1H), 2.03(s, 1H), 0.83(br s, 9H). LCMS: e/z: 304.55 (100%).

(2*S*,5*R*)-2-*tert*-Butyl-3-(3,5-dichlorophenyl)-5-[$^2H_3$]methyl-1-(2,2,2-trifluoroacetyl)-imidazolidin-4-one [$^2H_3$]-(6): To a solution of the aforementioned material (2.0 g, 6.57 mmol) in methylene chloride (15 mL), was added triethyl amine (1.23 mL, 8.78 mmol) at −5 °C. After stirring for 10 minutes, trifluoroacetic anhydride (1.08 mL, 7.55 mmol) was added dropwise to give a pale yellow solution. The ice-bath was removed, and the reaction was warmed to room temperature and stirred overnight. The solution was cooled again to 0 °C, and water (15 mL) was added. The aqueous layer was extracted with methylene chloride, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 3.8 g of a yellow solid. Crystallization from warm hexanes gave 1.9 g of a solid in 72% yield. The mother liquor was kept for further purification. ^{1}H NMR ($CDCl_3$) δ: 7.47(d, J = 1.48 Hz, 2H), 7.27(t, J = 1.48 Hz, 1H), 6.27(s, 1H), 4.51(s, 1H), 0.86(br s, 9H). LCMS: e/z: 441.51 (100%).

(2*R*,5*R*)-2-*tert*-Butyl-3-(3,5-dichlorophenyl)-5-[$^2H_3$]methyl-1-(2,2,2-trifluoroacetyl)-5-[[4-(trifluoromethoxy)phenyl]methyl] imidazolidin-4-one [$^2H_3$]-(7): To a solution of the aforementioned material (4.68 g, 11.70 mmol) in THF (10 mL), was added lithium hexamethyldisilazane (LiHMDS) (12.87 mL, 1.0 M in THF) at −20 °C (CCl_4-dry-ice-bath) dropwise under Argon atmosphere. After stirring for about 2 hours (temperature up to −15 °C), a solution of 4-trifluomethoxy benzyl bromide (2.12 mL, 12.85 mmol) in THF (5.0 mL) was added dropwise. The reaction was left to warm to room temperature overnight. A saturated solution of ammonium chloride (100 mL) was added, and the mixture was extracted with ethyl acetate (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 7.92 g of a yellowish solid. Crystallization from hexane gave 4.71 g of a white solid. The mother liquor was concentrated to give 2.24 g of a solid which was crystallized from ethanol to give an extra 0.58 g of a white solid, which was combined with the first batch. A total of 5.29 g was obtained in 79% yield. ^{1}HNMR ($CDCl_3$) δ: 7.28(m, 2H), 7.02(m, 4H), 6.28(t, J = 1.42 Hz, 1H), 5.39(s, 1H), 3.74(d, J = 14.1 Hz, 1H), 3.25(d, J = 14.1 Hz, 1H). LCMS: e/z : 574.49, nitrile adduct 603.42.

(2*R*)-2-Amino-*N*-(3,5-dichlorophenyl)-2-[$^2H_3$]methyl-3-\[4-trifluoromethoxy)phenyl]propanamide [$^2H_3$]-(8): To a suspension of the aforementioned material (4.92 g, 8.57 mmol) in dioxane (20 mL), was added a solution of benzyltrimethylammonium hydroxide (7.1 mL, 40% solution in water) followed by 50% aqueous NaOH (1.37 mL), and the biphasic yellow mixture was stirred at 50 °C overnight. The mixture was cooled down to room temperature and then cooled in an ice-bath, and 14 mL of 6 N aqueous HCl was added. The mixture was heated again at 50 °C for 3 hours.

Dioxane was then removed *in vacuo*, and the residue was diluted with toluene (20 mL), and 50% aqueous NaOH was added until pH = 12. The aqueous was extracted with toluene then with ethyl acetate, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 5.68 g of viscous oil. TLC (50% EtOAc: Hexane): starting material R_f =0.82, product R_f = 0.33. Purification by silica gel chromatography using chloroform then 10%–50% EtOAc: $CHCl_3$ gave 3.41 g of yellow oil in 97% yield. ^{1}H NMR ($CDCl_3$) δ:9.73(s, 1H), 7.52(d, *J* = 1.17 Hz, 2H), 7.19(d, *J* = 8.66 Hz, 2H), 7.12(d, *J* = 8.66 Hz, 2H), 7.08(t, *J* = 1.17 Hz, 1H), 3.48(d, *J* = 13.51 Hz, 1H), 2.67 (d, *J* = 13.51 Hz, 1H), 1.46(s, 2H). LCMS: e/z : 410.58 (100%).

tert-Butyloxycarbonyl-[$^{13}C_2$]glycine: To a suspension of glycine (1.0 g, 13 mmol, 99 atom % ^{13}C) in a solution of 10% triethylamine in methanol (20 mL), was added di-*tert*-butyl dicarbonate (5.67 g, 25.72 mmol), and the mixture was refluxed for 30 minutes to give a clear solution. After cooling to room temperature, the mixture was concentrated, and the residue was treated with a 1.0 N solution of aqueous HCl (16.0 mL) at 0 °C. The solution was then extracted with ethyl acetate (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Ether was added to the oily residue to give a solid (triethylamine-HCl salt) which was filtered. The filtrate was concentrated under reduced pressure to give 3.4 g of viscous oil. Crystallization from hexane gave 2.14 g of a white solid in 91% yield. ^{1}H NMR ($CDCl_3$) δ: 10.35(s, 1H), 4.14(m, 1H), 3.75(m, 1H), 1.45(br s, 9H), LCMS: m/z: 177.60 (100%).

tert-Butyl *N*-[2-[[(1*R*)-2-(3,5-dichloroanilino)-1-[$^2H_3$]methyl-2-oxo-1-[[4-(trifluoromethoxy)phenyl]methyl]ethyl]amino]-2-oxo-[$^{13}C_2$]ethyl]carbamate [$^{13}C_2$, $^2H_3$]-(9): To a solution of *N*-*t*-boc-[$^{13}C_2$] glycine (1.68 g, 9.5 mmol) in dry THF (20 mL), was added triethylamine (1.37 mL, 9.86 mmol) at −20 °C. Trimethylacetyl chloride (1.17 mL, 9.40 mmol) was then added dropwise, and the resulting white suspension was stirred at this temperature for 1 hour. The amine (8) (3.0 g, 7.31 mmol) in THF (20 mL) and added dropwise with triethylamine (1.07 mL, 7.68 mmol). The flask was washed with THF (10 mL) and added to the reaction vessel. The resulting mixture was warmed slowly to room temperature and stirred for 48 hours. A saturated solution of ammonium chloride (20 mL) was added, and the biphasic solution was extracted with ethyl acetate. The combined ethyl acetate extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 4.9 g of an off-white solid. TLC (50% EtOAc: Hex) R_f of the product = 0.46. The crude was purified by flash chromatography using 10%–50% EtOAc in hexanes to give 4.0 g of a white solid in 96% yield. ^{1}H NMR ($CDCl_3$) δ:9.08(s, 1H), 7.73(m, 2H), 7.14(m, 5H), 7.07(t, *J* = 1.62 Hz, 1H), 3.75–3.95(m, 1H), 3.67(d, *J* = 13.89 Hz, 1H), 3.42–3.58 (m, 1H), 3.14(d, *J* = 13.89 Hz, 1H), 1.42(br s, 9H), 1.24(m, 2H). LCMS: e/z: 569.69 (100%).

(2*R*)-2-[(2-Aminoacetyl)amino]-N-(3,5-dichlorophenyl)-2-[$^2H_3$] methyl-3-[4-(trifluoromethoxy)phenyl][$^{13}C_2$]propanamide [$^{13}C_2$, $^2H_3$]-(10): To a solution of the aforementioned material (4.0 g, 7.02 mmol) in methanol (25 mL), was added TsOH.H_2O (1.76 g, 9.13 mmol) in methanol (10 mL) at 55 °C, and the resulting was stirred overnight. The solution was cooled down to room temperature, and a 1.0 N NaOH (10 mL) was added dropwise. The mixture was concentrated *in vacuo* to remove most of the methanol, and the residue was dissolved in ethyl acetate and treated with water. The organic phase was washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 3.89 g of yellow oil. Purification by flash chromatography using 10%–50% EtOAc/chloroform to remove nonpolar impurities, then product was eluted with 50% MeOH/$CHCl_3$ to give 2.47 g of white foam in 75% yield. ^{1}HNMR ($CDCl_3$) δ: 10.43(s, 1H), 7.87(s, 1H), 7.53(d, *J* = 1.81 Hz, 2H), 7.22(d, *J* = 8.71 Hz, 2H), 7.15(d, *J* = 8.71 Hz, 2H), 7.07(t, *J* = 1.81 Hz, 1H), 3.63 (d, *J* = 13.82 Hz, 1H), 3.56(dd, *J* = 5.25, 1.38 Hz, 1H), 3.22(dd, *J* = 5.25, 1.38 Hz, 1H), 3.12(d, *J* = 13.82 Hz, 1H), 1.57(s, 3H). LCMS: e/z: 469.52 (100%).

(2*R*)-*N*-(3,5-Dichlorophenyl)-2-[$^2H_3$]methyl-2-(5-oxo-2-thioxo-[$^{13}C_2$]imidazolidin-1-yl)-3-[4-(trifluoromethoxy)phenyl]propanamide [$^{13}C_2$, $^2H_3$]-(11): To solution of 1,1′-thiocarbonyldiimidazole (TCDI, 178.22 mg, 0.95 mmol) in THF (4.0 mL), was added the amine [$^{13}C_2$, $^2H_3$]-(10) (470 mg, 1.0 mmol) in THF (4.0 mL), the flask was washed with another 4.0 mL of THF and added to the reaction vessel. The resulting solution was stirred for 1 hour at room temperature, TLC, showed no starting material. Water was added followed by ethyl acetate. The organic layer was washed with 10% K_2CO_3 (10 mL), water (10 mL), brine (10 mL), then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 609 mg of a solid. TLC (10% MeOH/$CHCl_3$): R_f = 0.31. This crude was used in the next step without further purification. ^{1}HNMR ($CDCl_3$) δ: 7.42 (s, 1H), 7.40(d, *J* = 1.73 Hz, 2H), 7.21(d, *J* = 8.59 Hz, 2H), 7.13(d, *J* = 8.59 Hz, 2H), 7.13(t, *J* = 1.73 Hz, 1H), 4.30(d, *J* = 13.47 Hz, 1H), 3.50–4.10(m, 3H), 3.24(d, *J* = 13.47 Hz, 1H). LCMS: e/z: 511.75 (100%).

(5*R*)-7-(3,5-Dichlorophenyl)-5-[$^2H_3$]methyl-5-[[4-(trifluoromethoxy)phenyl]methyl]-2H-imidazo[1,2-a][$^{13}C_2$]imidazole-3,6-dione [$^{13}C_2$, $^2H_3$]-(12): To a solution of the aforementioned material (512 mg, 1.0 mmol) in toluene (10 mL) and acetonitrile (1.0 mL), were added Celite® (0.5 g) and Hunig's base (0.418 mL, 2.376 mmol). CuCl (227.7 mg, 2.231 mmol) was then added in one portion with stirring to give a dark mixture, which was heated to 80 °C in 10 minutes. After 15 minutes at this temperature, the reaction was checked by TLC, no starting material. The dark mixture was filtered through Celite® and the filter cake was washed with toluene. Evaporation of two-thirds of the volume under reduced pressure, then treating the dark solution with 1.0 N HCl, followed with 7% NH_4OH, water, and brine. The solution was treated with charcoal and heated to 80 °C for 10 minutes, filtered over a short pad of silica gel, and washed with ethyl acetate to give 420 mg of a dark solid after concentration. Purification by flash chromatography silica gel using chloroform and 5–10% EtOAc:$CHCl_3$ gave 253 mg of pure material as foam in 52.5% yield. TLC: 10% MeOH/$CHCl_3$: R_f of starting material = 0.31, R_f of product = 0.66. ^{1}HNMR ($CDCl_3$) δ: 7.33(t, *J* = 1.80 Hz, 1H), 7.28(d, *J* = 1.80 Hz, 2H), 7.12(m, 4H), 4.40(ddd, *J* = 3.8, 25.69, 47.3 Hz, 1H), 4.06(ddd, *J* = 3.8, 35.69, 47.3 Hz, 1H), 3.48(d, *J* = 13.88 Hz, 1H), 3.28(d, *J* = 13.88 Hz, 1H). LCMS: e/z: 477.47 (100%).

[(5*R*)-7-(3,5-Dichlorophenyl)-5-[$^2H_3$]methyl-6-oxo-5-[[4-(trifluoromethoxy)phenyl]-methyl]-2,3-dihydroimidazo[1,2-a][$^{13}C_2$]imidazol-3-yl] diethyl phosphate [$^{13}C_2$, $^2H_3$]-(13): To a solution of the aforementioned lactone (587 mg, 1.23 mmol) in THF (10 mL), was added LiHMDS (1.6 mL, 1.0 M in THF) dropwise at −30 °C in a three-neck flask equipped with a magnetic stirrer and a thermometer, under nitrogen atmosphere. Keeping the temperature below −20 °C, the resulting dark solution was stirred for 30 minutes before diethylchlorophosphate (0.214 mL, 1.44 mmol) was added dropwise. The reaction was stirred for 45 minutes at −30 °C, then 10 mL of 20% aqueous NH_4Cl was added, and the mixture was warmed to room temperature. The aqueous was extracted with ethyl acetate, and the combined extracts were washed with 5% NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.8 g of dark oil in 85% yield. This material was used in the next step without further purification. LCMS: e/z: 613.27 (100%), R_f = 0.21 in 50% EtOAc:Hexanes.

(5*R*)-7-(3,5-Dichlorophenyl)-3-iodo-5-[$^{2}H_3$]methyl-5-[[4-(trifluoromethoxy)phenyl]-methyl]imidazo[1,2-a][$^{13}C_2$]imidazol-6-one [$^{13}C_2$, $^{2}H_3$]-(14): To a suspension of NaI (0.74 g, 4.887 mmol) in methylene chloride (5.0 mL), was added TMSCl (0.625 mL, 4.9 mmol), and the mixture was stirred for 20 minutes at room temperature (pink-colored mixture of iodine). To this, [$^{13}C_2$, $^{2}H_3$]-(13) (0.75 g, 1.23 mmol) in CH_2Cl_2 (5.0 mL) was added, the flask was rinsed twice with methylene chloride (5.0 mL) followed by 58 μL of water. The reaction was stirred for 2 hours at room temperature before 30 mL of Na_2CO_3 solution was added to the dark reaction. Ethyl acetate (20 mL) and water (20 mL) were added. The organic phase was washed with $Na_2S_2O_3$ (20 mL) to give a yellowish solution. The organic solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.75 g of viscous oil. Purification by flash chromatography using chloroform then 2% EtOAc:$CHCl_3$ gave the desired product (360 mg in 50% yield), $R_f = 0.67$ in 50% EtOAc: Hexanes, and 130 mg of the des-iodo-product in 23% yield, $R_f = 0.46$ in 50% EtOAc: Hexanes. ^{1}HNMR ($CDCl_3$) δ: 7.51(d, $J = 1.80$ Hz, 2H), 7.25 (t, $J = 1.80$ Hz, 1H), 7.01(d, $J = 8.27$ Hz, 2H), 6.97(dd, $J = 14.84$, 198.4 Hz, 1H), 6.92(d, $J = 8.27$ Hz, 2H), 3.58(d, $J = 14.1$ Hz, 1H), 3.27(d, $J = 14.1$ Hz, 1H). LCMS: e/z: 587.15 (100%). Des-iodo [$^{13}C_2$, $^{2}H_3$]-(18):. ^{1}HNMR ($CDCl_3$) δ: 7.69(d, $J = 1.85$ Hz, 2H), 7.24 (t, = 1.85 Hz, 1H), 7.01(d, $J = 8.26$ Hz, 2H), 6.96(ddd, $J = 1.53$, 16.23, 33.33 Hz, 2H), 6.90(d, $J = 8.26$ Hz, 2H). LCMS: e/z: 461.24 (100%).

(*R*)-7-(3,5-Dichloro-phenyl)-5-[$^{2}H_3$]methyl-6-oxo-5-(4-trifluoromethoxybenzyl)-6,7-dihydro-5*H*-imidazo[1,2-*a*][$^{13}C_2$] imidazole-3-sulfonyl chloride [$^{13}C_2$, $^{2}H_3$]-(15): To a solution of the iodo-derivative [$^{13}C_2$, $^{2}H_3$]-(14) (0.33 g, 0.56 mmol) in THF (5 mL), was added a solution of isopropyl magnesium chloride (0.32 mL, 2.0 M in THF) dropwise at −40 °C (dry-ice-acetonitrile bath). The resulting solution was stirred at this temperature for 1 hour before SO_2 gas was introduced for 3 minutes via a needle just above the solution surface. The resulting bright yellow solution was warmed gradually to room temperature overnight. The solution was then concentrated *in vacuo* to give yellowish foam, which was dissolved in THF (5.0 mL) and cooled to −25 °C. *N*-Chlorosuccinimide (NCS) (93 mg, 0.683 mmol) in THF (3.0 mL) was added dropwise at this temperature, and the resulting solution was stirred for 1.0 hour. The reaction was warmed to room temperature and used in the next step without further purification. LCMS: e/z: 559.76 (100%).

(2*S*)-2-[[(5*R*)-7-(3,5-Dichlorophenyl)-5-[$^{2}H_3$]methyl-6-oxo-5-(4-trifluoromethoxybenzyl)-imidazo[1,2-a][$^{13}C_2$]imidazol-3-yl]sulfonylamino]propanamide [$^{13}C_2$, $^{2}H_3$]-(1): To a mixture of L-alaninamide-hydrochloride (102 mg, 0.82 mmol) in DMF (10 mL), was added triethylamine (0.18 mL, 1.28 mmol) at room temperature under nitrogen atmosphere. The cloudy solution was stirred for 15 minutes before the chloride [$^{13}C_2$, $^{2}H_3$]-(15) (229 mg, 0.41 mmol) in THF (5 mL) was added using a double ended needle. The resulting yellow solution was stirred for 48 hours. Ethyl acetate and water were added, and the organic phase was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in chloroform and purified by silica gel chromatography using up to 50% EtOAc/$CHCl_3$ as eluent to remove a non-polar by-product. The product was eluted with 10–20 MeOH/$CHCl_3$, $R_f = 0.1$ in 10% MeOH/$CHCl_3$ to give 95 mg of a fluffy white solid in 38% yield. ^{1}HNMR ($CDCl_3$) δ: 7.42(dd, $J = 14.01$, 198.75 Hz, 1H), 7.38(d, $J = 1.81$ Hz, 2H), 7.30(t, $J = 1.81$ Hz, 1H), 6.98(br s, 4H), 6.06(br s, 1H), 5.89(s, 1H), 4.02(q, $J = 7.05$ Hz, 1H), 3.85(d, $J = 13.88$ Hz, 1H), 3.26(d, $J = 13.88$ Hz, 1H), 1.36(d, $J = 7.05$ Hz, 3H). LCMS: e/z: $[M+H]^+ = 611.1$ (100%), $[M+H+CH_3CN]^+ = 652.1$ (25%), see Figures 1 and 2.

Synthesis of [$^{13}C_6$]-(2)

[(*R*)-1-(3,5-Dichloro-phenyl[$^{13}C_6$]carbamoyl)-ethyl]-carbamic acid *tert*-butyl ester [$^{13}C_6$]-(3): To a solution of *t*-boc-D-alanine (2.48 g, 13.14 mmol) in anhydrous THF (30 mL), was added 4-methyl morpholine (3.0 mL, 26.52 mmol) at 0 °C under nitrogen atmosphere. After stirring for 10 minutes, isobutyl chloroformate (1.74 mL, 13.35 mmol) was added dropwise. The resulting mixture was stirred for 1 hour at 0 °C, before [$^{13}C_6$]-3,5-dichloroaniline (1.79 g, 10.65 mmol) in THF (15 mL) was added dropwise. The resulting solution was left to stir for 14 hours as the ice melted. TLC showed all the aniline was consumed. The reaction was concentrated *in vacuo* to remove most of the THF and then treated with a saturated solution of aqueous $NaHCO_3$ (200 mL). The organic was extracted with methylene chloride (2x 100 mL), and the combine extracts were dried over MgSO4, filtered, and concentrated *in vacuo* to give 6.6 g of viscous oil. Purification by combiFlash using a 120 g disposable silica gel column and up to 15% EtOAc in CH_2Cl_2 gave 4.3 g of foam in 90% yield. ^{1}HNMR ($CDCl_3$) δ: 9.31(s, 1H), 7.40 (d, $J = 173$ Hz, 2H), 7.05(d, $J = 173$ Hz, 1H), 5.50(d, $J = 7.06$, 1H), 4.33 (m, 1H), 1.47(br s, 9H), 1.43(d, $J = 7.06$ Hz, 3H). ^{13}CNMR ($CDCl_3$) δ: 171.91, 171.25, 156.51, 135.75(m), 139.77(dt, $J = 3.97$, 64.05 Hz), 134.89(t, $J = 68.4$ Hz), 123.78 (dt, $J = 4.0$, 65.84 Hz), 117.65(dt, $J = 4.01$, 65.78 Hz), 80.91, 60.40, 53.44, 50.99, 28.35, 17.8. LCMS: e/z: 239.23 (100 %).

(*R*)-2-Amino-*N*-(3,5-dichloro-phenyl[$^{13}C_6$])-propionamide [$^{13}C_6$]-(4): To a solution of the aforementioned material (4.19 g, 12.36 mmol) in methanol (50 mL), was added a solution of 9 N aqueous HCl (10 mL) dropwise at 0 °C. The reaction was stirred for 12 hours and warmed gradually to room temperature. Most of the solvents was evaporated, and the residue was treated at 0 °C with a solution of 6 N aqueous NaOH until pH = 12 then extracted with methylene chloride (2 × 10 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 2.27 g in 77% yield. ^{1}HNMR ($CDCl_3$) δ: 9.66 (s, 1H), 7.57(dm, $J = 171.84$ Hz, 2H), 7.08(dm, $J = 171.84$ Hz, 1H), 3.61(q, $J = 7.1$ Hz, 1H), 1.60(s, 2H), 1.42(d, $J = 7.1$ Hz, 3H). ^{13}CNMR ($CDCl_3$) δ: 173.96, 139.58 (dt, $J = 4.4$, 64 Hz), 135.21(dt, $J = 4.4$, 64 Hz), 123.85(dt, $J = 4.4$, 64 Hz), 117.62(dt, $J = 4.4$, 64 Hz), 51.80, 21.49. LCMS: e/z: 239.26 (100%).

(2*S*,5*R*)-2-*tert*-Butyl-3-(3,5-dichlorophenyl[$^{13}C_6$])-5-methyl-imidazolidin-4-one [$^{13}C_6$]-(5): Trimethylacetaldehyde (1.27 mL, 11.54 mmol) was added dropwise to a solution of the above amine (2.21 g, 9.36 mmol) in toluene (20 mL), and the mixture was heated to 55 °C for 12 hours. The reaction was concentrated *in vacuo*, and the residue was triturated with hexanes filtered and dried to give 2.8 g of a solid in 98.6% yield, which was used as it is in the next step. LCMS: e/z: 307.18 (100%).

(2*S*,5*R*)-2-*tert*-Butyl-3-(3,5-dichlorophenyl[$^{13}C_6$])-5-methyl-1-(2,2,2-trifluoroacetyl)-imidazolidin-4-one [$^{13}C_6$]-(6): To a solution of the aforementioned material (2.73 g, 8.87 mmol) in CH_2Cl_2 (20 mL), was added triethylamine (1.61 mL, 11.56 mmol) at −2 °C under nitrogen. The resulting was further cooled to −10 °C. and trifluroacetic anhydride (1.32 mL, 9.33 mmol) was added dropwise in a 20-minute period. After stirring below −5 °C for 1 hour, the reaction was warmed to room temperature and stirred for 6 hours. The reaction was then cooled in an ice-bath and treated with water (20 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried over $MgSO_4$,

filtered, and concentrated *in vacuo* to give 4.28 g of foam. Purification by chromatography using silica gel treated with triethylamine and up to 30% EtOAcHexanes gave 3.0 g of a solid in 84% yield. LCMS: e/z: 403.27 (100%). The product was used in the next step without further characterization.

(2*R*,5*R*)-2-*tert*-Butyl-3-(3,5-dichlorophenyl[$^{13}C_6$])-5-methyl-1-(2,2,2-trifluoroacetyl)-5-[[4-(trifluoromethoxy)phenyl]methyl] imidazolidin-4-one [$^{13}C_6$]-(7): To a solution of the aforementioned material (3.0 g, 7.44 mmol) in anhydrous THF (20 mL), was added a solution of 1.0 M LiHMDS in THF (8.2 mL, 8.2 mmol) dropwise at –40 °C under nitrogen atmosphere. After stirring for 2 hours from −40 to −25 °C, 4-trifuromethoxybenzyl bromide (1.35 mL, 8.43 mmol) in THF (10 mL) was added slowly. The reaction was warmed gradually to room temperature overnight. After the usual work-up, 3.8 g of product was isolated in 88% yield and used as it is in the next step. LCMS: e/z: 577.35 (100%).

(R)-2-Amino-*N*-(3,5-dichloro-phenyl[$^{13}C_6$])-2-methyl-3-(4-trifluoromethoxyphenyl)-propionamide [$^{13}C_6$]-(8): A suspension of the aforementioned material (3.6 g, 6.23 mmol) in dioxane (20 mL) was treated with a 40% solution of benzyltrimethylammonium hydroxide in water (10 mL) and aqueous 50% NaOH (1.5 mL) and heated at 50 °C for 12 hours. After cooling to room temperature, the mixture was treated with concentrated aqueous HCl until pH = 3 and heated again at 50 °C for 12 hours. The mixture was then cooled to room temperature and concentrated *in vacuo* then treated with 50% aqueous NaOH until pH = 12. The aqueous layer was extracted with EtOAc (3 × 100 mL), and the combined extracts were dried over $MgSO_4$, filtered, and concentrated to give 3.6 g of viscous oil. The crude product was purified by CombiFlash using up to 10% EtOAc:CH_2Cl_2 to give 1.24 g of the desired product in 48% yield. ^{1}HNMR ($CDCl_3$) δ: 9.74(s, 1H), 7.51(dm, *J* = 180 Hz, 2H), 7.25(d, *J* = 8.25 Hz, 2H), 7.15(d, *J* = 8.25 Hz, 2H), 7.05(dm, *J* = 180 Hz, 1H), 2.70(d, *J* = 13.51 Hz, 1H), 2.10(d, *J* = 13.51 Hz, 1H), 1.45(s, 3H). LCMS: e/z: 412.77 (100%).

(*R*)-*N*-(3,5-Dichloro-phenyl[$^{13}C_6$])-2-[3-(2,2-dimethoxyethyl)-ureido]-2-methyl-3-(4-trifluoromethoxyphenyl)-propionamide [$^{13}C_6$]-(16): To a solution of aminoacetadehyde dimethyl acetal (0.18 g, 1.7 mmol) in CH_2Cl_2 (7 mL), was added a solution of saturated aqueous $NaHCO_3$ (7 mL), and the mixture was stirred in an ice-bath. A solution of 20% per weight of phosgene in toluene (1.4 mL, 2.55 mmol) was added to the organic phase after the stirring was stopped. Stirring was resumed and continued for 1.5 hours before the above amine (0.42 g, 1.0 mmol) was added in CH_2Cl_2, and the mixture was stirred for 6 hours. The clear biphasic solution was extracted with CH_2Cl_2 (2 × 20 mL), and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by combiFlash on a 40 g disposable silica gel column using up to 10% MeOH/CH_2Cl_2 to give 0.27 g of product in 71% yield and 0.13 g of unreacted starting material. ^{1}HNMR ($CDCl_3$) δ: 7.68(dm, *J* = 171 Hz, 2H), 7.10(dm, *J* = 171 Hz, 1H), 7.02 (ABq, *J* = 7.95 Hz, 2H), 6.92(ABq, *J* = 7.95 Hz, 2H), 6.13(t, *J* = 6.3 Hz, 1H), 3.42(d, *J* = 13.89 Hz, 1H), 3.30(s, 6H), 3.12(d, *J* = 13.89 Hz, 1H), 1.78(br s, 3H). ^{13}CNMR ($CDCl_3$) δ: 174.98, 149.03, 146.01, 135.58(dt, *J* = 3.84, 66.81 Hz), 134.9(m), 131.99, 131.15, 129.14, 127.57(dt, *J* = 3.89, 65.2 Hz), 125.40, 122.47, 121.8(q, *J* = 254 Hz), 120.36(dt, *J* = 4.70, 66.28), 53.63, 44.17, 23.93. LCMS: e/z: 544.35 (100%).

(*R*)-3-(3,5-Dichlorophenyl[$^{13}C_6$])-2-[(Z)-2,2-dimethoxy-ethylimino]-5-methyl-5-(4-trifluoromethoxybenzyl)-imidazolidin-4-one [$^{13}C_6$]-(17): A mixture of the aforementioned dimethyl acetal (1.26 g, 2.33 mmol), triphenyl phosphine (1.29 g, 4.86 mmol), carbon tetrachloride (0.48 mL, 4.87 mmol), and triethylamine (0.68 mL, 4.89 mmol) in anhydrous methylene chloride (15 mL) was stirred at room temperature. The colorless solution turned slowly to yellow. The reaction was stirred overnight. It was diluted with ethyl acetate (50 mL) and washed twice with 1.0 N HCl solution (2x 25 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 1.22 g of a semisolid residue in 99% yield. TLC (50% EtOAc: Hexanes) showed no starting material and a more polar product. This crude material was used in the next step without further purification. ^{1}HNMR ($CDCl_3$) δ:7.90(s, 1H), 7.72(d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.44(dm, *J* = 172 Hz, 2H), 6.80(dm, *J* = 172 Hz, 1H), 4.51(d, *J* = 6.25 Hz, 2H), 3.85(t, *J* = 6.25 Hz, 1H), 3.65(s, 6H), 3.42(q, *J* = 7.22 Hz, 2H), 1.25(s, 3H). ^{13}CNMR ($CDCl_3$) δ: 192.1, 167.5, 162.4, 161.1, 140.2, 132.6(dt, *J* = 4.4, 64 Hz), 132.5, 130.2, 129.2, 127.5 (dt, *J* = 4.4, 64 Hz), 122.8(m), 122.3 (dt, *J* = 4.4, 64 Hz), 120.1 (dt, *J* = 4.4, 64 Hz), 117, 113.6, 65.5, 61.4, 14.7. LCMS: e/z: 526.34 (100%).

(*R*)-1-(3,5-Dichlorophenyl[$^{13}C_6$])-3-methyl-3-(4-trifluoro-methoxybenzyl)-1*H*-imidazo[1,2-*a*]imidazol-2-one [$^{13}C_6$]-(18): A solution of the aforementioned material (242 mg, 0.46 mmol) and PTSA.H_2O (87.5 mg, 0.46 mmol) in EtOAc (10 mL) was heated to 70 °C for 10 hours. After cooling to room temperature, the solution was washed with a saturated solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, and concentrated to give 0.64 g of a solid. Purification by combiFlash using a 40 g disposable silica gel column and up to 5% MeOH/ CH_2Cl_2 gave 170 mg of product in 80% yield. ^{1}HNMR ($CDCl_3$) δ:, 7.72(d, *J* = 2 Hz, 2H), 7.03(ABq, *J* = 8.1 Hz, 2H), 6.98(dm, *J* = 172 Hz, 2H), 6.92(dm, *J* = 172 Hz, 1H), 6.91(ABq, *J* = 8.1 Hz, 2H), 3.32(d, *J* = 14.2 Hz, 1H), 3.22(d, *J* = 14.2 Hz, 1H), 1.82(s, 3H). ^{13}C NMR ($CDCl_3$) δ: 175.2, 149.1, 145.6, 135.5 (dt, *J* = 4.4, 64 Hz), 134.7, 131.7 (dt, *J* = 4.4, 64 Hz), 131.2, 129.3, 127.2 (dt, *J* = 4.4, 64 Hz), 121.0, 120.1 (dt, *J* = 4.4, 64 Hz), 120.0(m), 119.8, 111.3, 66.4, 43.8, 32.4. LCMS: e/z: 462.25 (100%).

(*R*)-5-Iodo-1-(3,5-dichlorophenyl[$^{13}C_6$])-3-methyl-3-(4-trifluoromethoxybenzyl)-1*H*-imidazo[1,2-*a*]imidazol-2-one, [$^{13}C_6$]-(14): To a solution of the aforementioned material (168 mg, 0.36 mmol) in CH_2Cl_2 (5 mL), was added pyridinium *p*-toluenesulfonate (PPTS) (14 mg, 0.055 mmol). The resulting solution was cooled in an ice-bath, and NIS (87.3 mg, 0.387 mmol) was added in one portion and stirred for 14 hours. After diluting the solution with EtOAc (25 mL), it was quenched with a saturated aqueous $Na_2S_2O_3$ (12 mL). The organic phase was removed, dried over $MgSO_4$, filtered, and concentrated to give 0.31 g of a yellow solid. Purification by silica gel chromatography using toluene as eluent gave 70 mg of the diiodo-derivative [$^{13}C_6$]-(19) (LCMS:e/z: 716.02) and 150 mg of the desired mono-iodo derivative in 71% yield. ^{1}H NMR ($CDCl_3$) δ: 7.51(dm, *J* = 173 Hz, 2H), 7.27(dm, *J* = 173 Hz, 1H), 7.01(ABq, *J* = 8.3 Hz, 2H), 6.97(ABq, *J* = 8.3 Hz, 2H), 6.86(s, 1H), 3.55(d, *J* = 14.1 Hz, 1H), 3.35(d, *J* = 14.1 Hz, 1H), 1.95(s, 3H). LCMS: e/z: 587.15 (100%), R_f = 0.67 in 50% EtOAc:hexanes. ^{13}C NMR ($CDCl_3$) δ: 173.8, 150.1, 145.7, 136.1, 134.8 (dt, *J* = 4.4, 64 Hz), 134.2, 132.1, 131.0 (dt, *J* = 4.4, 64 Hz), 128.8, 127.5 (dt, *J* = 4.4, 64 Hz), 121.1, 120.5 (dt, *J* = 4.4, 64 Hz), 120.1(m), 95.5, 68.4, 42.3, 22.5.

(*R*)-7-(3,5-Dichlorophenyl[$^{13}C_6$])-5-methyl-6-oxo-5-(4-trifluoromethoxybenzyl)-6,7-dihydro-5*H*-imidazo[1,2-*a*]-imidazole-3-sulfonic acid amide [$^{13}C_6$]-(2): To a solution of the aforementioned iodide (149 mg, 0.253 mmol) in anhydrous THF (5 mL) was added a solution of 2 M *i*-PrMgCl in THF (0.2 mL, 0.4 mmol) at –40 °C under nitrogen. After stirring for 90 minutes from −40 to −30 °C, sulfur dioxide was bubbled slowly for few minutes, and the resulting bright yellow solution was stirred overnight at it warmed to room temperature. The solution was concentrated and then dissolved again in anhydrous THF (5 mL) and cooled to –20 °C. NCS (48 mg, 0.36 mmol)

in THF (2 mL) was added, and the resulting solution was warmed slowly to ambient temperature and stirred for 1 hour. The solution was cooled again to 0 °C, and Cs_2CO_3 (124 mg, 0.38 mmol) was added in one portion followed by ammonium hydroxide solution (28-30% NH_3, 0.5 mL) and DMF (1.0 mL). The reaction was warmed to room temperature and stirred for 2 hours. Water (10 mL) and EtOAc (20 mL) were added. The aqueous was removed, and the organic layer was washed 10% solution of Na_2CO_3, brine, dried over $MgSO_4$, filtered, and concentrated to give 130 mg of a solid. Purification by silica gel chromatography using up to 5% MeOH/CH_2Cl_2 gave 80 mg of the desired product in 58% yield. ^{1}H NMR ($CDCl_3$) δ: 7.43(s, 1H), 7.36(dm, J = 173 Hz, 2H), 7.30(dm, J = 173 Hz, 1H), 6.98(br s, 4H), 3.85(d, J = 14.31 Hz, 1H), 3.25(d, J = 14.31 Hz, 1H), 2.01(br s, 3H). ^{13}C NMR ($CDCl_3$) δ: 175.5, 149.2, 135.92 (dt, J = 6, 66 Hz), 132.72 (dt, J = 6, 66 Hz), 130.73, 130.06, 127.81 (dt, J = 6, 66 Hz), 124.85, 121.05(dt, J = 6, 66 Hz), 70.16, 53.44, 42.50, 29.71, 22.24. HPLC: Zorbax XDB-C18, 20%–100% acetonitrile, water both solvents 10 mM TFA, t_R = 22.08 minutes. LCMS ES$^+$, M^+ = 541.56 (100%), 99% isotopic enrichment.

Synthesis of [^{14}C]-(1)

(2*R*)-*N*-(3,5-Dichlorophenyl)-2-(2,2-dimethoxyethyl[^{14}C]-carbamoylamino)-2-methyl-3-[4-(trifluoromethoxy)phenyl] propanamide [^{14}C]-(16): To a biphasic solution of aminoacetaldehyde dimethyl acetal (0.44 mL, 4.0 mmol) in methylene chloride (5 mL) and a saturated solution of $NaHCO_3$ (5 mL), was added [^{14}C]-phosgene (200 mCi, at 57 mCi/mmol) in anhydrous toluene (2 mL) followed by 0.6 mL of cold phosgene (20% in toluene, to wash the radioactive container) to the organic phase via a long needle at 0 °C. Stirring was resumed and continued for 1 hour. The amine (8) (1.63 g, 4.0 mmol) was then added in 5 mL of methylene chloride, and the vial containing the amine was washed with another 5 mL of methylene chloride, and the reaction was warmed slowly to room temperature. To the resulting colorless mixture (biphasic), water was added, and the aqueous phase was extracted with methylene chloride (3 × 20 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography using a 40 g RediSep disposable column (Isco, Inc., Lincoln, NE, USA) and methylene chloride, then 10%–20% EtOAc: CH_2Cl_2 gave 1.42 g of pure product as a white solid. The product co-eluted with unlabeled reference compound on TLC (10% MeOH/$CHCl_3$). Total activity 143 mCi in 71.5% radiochemical yields with a specific activity of 54.36 mCi/mmol. HPLC: Column: Zorbax Eclipse XDB-C8 (4.6 × 150 mm, 5 μm) fitted with opti-guard (1.0 mm, C8). Column heater at 35 °C, Gradient: 20%–100% B in 30 minutes; A = water, B = acetonitrile both contain 10 mM TFA. Flow: 1.0 mL/minute, UV 254 nm. t_R = 19.17 minutes, 99.93% . t_R = 19.33 minutes, 99.99% radio-detection of 1.0 mM solution in EtOH.

(5*R*)-3-(3,5-Dichlorophenyl)-2-(2,2-dimethoxyethylimino)-5-methyl-5-[[4-(trifluoromethoxy)phenyl]methyl][^{14}C]imidazolidin-4-one [^{14}C]-(17): A mixture of the dimethyl acetal (16) (1.26 g, 2.33 mmol, 127 mCi), triphenyl phosphine (1.29 g, 4.86 mmol), carbon tetrachloride (0.47 mL, 4.86 mmol), and triethylamine (0.68 mL, 4.89 mmol) in anhydrous methylene chloride (15 mL) was stirred at room temperature. The colorless solution turned slowly to yellow. The reaction was stirred overnight. It was diluted with ethyl acetate (50 mL) and washed with 1.0 N HCl solution (2 × 25 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to give 1.22 g of a semisolid residue. TLC (50% EtOAc: Hexanes) showed no starting material and a more polar product. This crude material (127 mCi) was used in the next step without further purification.

(5*R*)-7-(3,5-dichlorophenyl)-5-methyl-5-[[4-(trifluoromethoxy) phenyl]methyl]-[^{14}C]imidazo[1,2-a]imidazol-6-one [^{14}C]-(18): A solution of the aforementioned material (1.22 g, 2.33 mmol) and PTSA monohydrate (0.46 g, 2.38 mmol0 in ethyl acetate (30 mL) was heated to 70 °C and stirred overnight. The yellow solution was cooled to room temperature and diluted with ethyl acetate then washed with 1.0 N aqueous NaOH solution (2 × 30 mL). The organic phase was concentrated and purified by flash chromatography using RediSep disposable column (40 g) and methylene chloride as eluent to give 1.03 g (122.25 mCi) of pale yellow oil in 96% chemical yield. The product has the same R_f as the unlabeled reference material in 50% EtOAc: Hexanes. The product was used in the next step without further characterization.

(5*R*)-7-(3,5-Dichlorophenyl)-3-iodo-5-methyl-5-[[4-(trifluoromethoxy)phenyl-methyl][^{14}C]imidazo[1,2-a]imidazol-6-one [^{14}C]-(14): A solution of the aforementioned material (1.0 g, 2.18 mmol, 122 mCi) in methylene chloride (12 mL) was stirred at 0 °C in an ice-bath. PPTS (55 mg, 0.22 mmol) were then added followed by NIS (0.49 g, 2.07 mmol), and the resulting orange solution was stirred overnight in the dark. Ethyl acetate (100 mL) was added, and the organic phase was washed with a saturated solution of $Na_2S_2O_3$ (100 mL), water (100 mL), and brine (100 mL). The organic phase was concentrated, and the residue was purified by flash chromatography using RediSep column (40 g). The column was first wetted with hexane. The crude material was dissolved in toluene and applied to the column. The bis-iodo by-product was eluted first to give 48 mg of a cream colored solid (3.0 mCi). The vials containing the product were combined and concentrated to give 842 mg in 66% yield of a cream colored solid, 81 mCi.

(5R)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-5-[[4-(trifluoromethoxy)phenyl]-methyl][^{14}C]imidazo[1,2-a]imidazole-3-sulfonyl chloride [^{14}C]-(15): To a solution of the aforementioned iodide (0.842 g, 1.44 mmol, 81 mCi) in dry THF (10 mL), was added a solution of isopropyl magnesium chloride (0.87 mL, 2.0 M in THF) dropwise at −40 °C. The resulting yellow solution was stirred at this temperature for 1 hour before sulfur dioxide was bubbled slowly into the reaction for about 5 minutes. The resulting bright yellow solution was stirred at −40 °C for 1 hour and then warmed to room temperature in another hour. The reaction was then concentrated and further dried under reduced pressure overnight. The resulting bright yellow foam was dissolved in 10 mL of dry THF under nitrogen atmosphere and cooled to −20 °C. *N*-Chlorosuccinimide (236 mg, 1.73 mmol) in dry THF (5 mL) was added dropwise at −20 °C, and the resulting yellow-orange solution was stirred at this temperature for 1 hour. This product was used in the next step as a THF solution.

(2*S*)-2-[[(5*R*)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-5-[[4-(trifluoromethoxy)phenyl]methyl][^{14}C]imidazo[1,2-a]imidazol-3-yl]sulfonylamino]propanamide [^{14}C]-(1): To a cloudy solution of L-alaninamide, HCl (0.36 g, 2.89 mmol), and triethylamine (0.61 mL, 4.33 mmol) in DMF (10 mL), was added via cannula the sulfonyl chloride solution at room temperature. The flask was further rinsed with dry DMF (5 mL), and the resulting orange-yellow mixture was stirred for 12 hours. The yellow mixture was concentrated to remove most of the DMF, and the residue was diluted in ethyl acetate (100 mL). Water (40 mL) was added, and the solution was stirred vigorously. The aqueous layer was pipetted out, and the organic layer was washed with another 20 mL of water. The organic phase was then

concentrated, and the residue was purified by flash chromatography using a 40 g RediSep disposable column. The column was wetted with methylene chloride, and the crude material was eluted with 100% methylene chloride to remove nonpolar impurities and then with 20%–50% EtOAc:CH_2Cl_2 to elute the pure material to give 350 mg of a foam, TLC co-elutes with unlabeled (1) in 10% MeOH/$CHCl_3$ or in 50% EtOAc:Hexanes. Crystallization from chloroform gave 305 mg of a fluffy white solid. A total of 22.15 mCi was obtained with a specific activity 44 mCi/mmol and in 40% radiochemical yield. HPLC conditions: Column: Zorbax Eclipse XDB-C8 (4.6 × 150 mm, 5 μm), fitted with an optiguard (1.0 mm, C8). UV detection was at 220 and 254 nm. Mobile phase: A: water, B: MeCN, both contain 10 mM TFA. Injections volumes: 10 μL, t_R = 19.20 minutes (UV) and t_R = 19.50 (rad). For radio-TLC, about 2.0 μL of cold and radioactive (1) (1.0 mM) solutions were applied to a 20 cm × 10 cm TLC plate (solvent front 17 cm and base line of 2 cm) and developed in 10% MeOH/$CHCl_3$. The plate was dried then a coat of Crystal Clear Acrylic Coating (KRYLON, Solon, OH) was applied. After drying and removing loose silica gel under a stream of nitrogen, the plate was scanned using BIOSCAN System 200 Imaging Scanner. R_f = 0.4, 99.8%. NMR was taken using double encapsulation. Both unlabeled standard (8 mg) and [^{14}C]-(1) in 300 μL of deuterated methanol (methanol-d_4, D, 99.8% contains 0.05% v/v TMS). The spectra were identical. ^{1}H NMR (MeOH-d_4) δ: 7.48(m, 3H), 7.05 (br s, 4H), 4.02(q, J = 7.2 Hz, 1H), 3.98(d, J = 13.51 Hz, 1H), 3.21(d, J = 13.51 Hz, 1H), 2.05(br s, 3H), 1.45(d, J = 7.2 Hz, 3H). ^{13}C NMR (MeOH-d_4) δ: 177.05, 175.41, 150.4, 150.10, 136.48, 135.84, 135.26, 134.37, 132.29, 128.68, 128.35, 122.61, 121.98, 121.7(m), 71.58, 53.53, 43.41, 22.17, 19.59.

Synthesis of [^{14}C]-(2)

(*R*)-5-Bromo-1-(3,5-dichlorophenyl)-3-methyl-3-(4-(trifluoromethoxy)benzyl)-1*H*-[^{14}C]-imidazo[1,2-a]imidazol-2(3*H*)-one [^{14}C]-(20). *N*-bromosuccinimide (NBS) (47 mg, 0.26 mmol) was added in four portions at room temperature to [^{14}C]-(18) (125 mg, 0.27 mmol) and Et_3N (8 mg, 0.06 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 14 hours (an HPLC aliquot revealed a starting material: product ratio of 66:33). The reaction was cooled to 0 °C, NBS (20 mg) was added, and the mixture was stirred for 0.5 hour. The reaction was quenched by addition of water, extracted with EtOAc. The EtOAc extract was washed with brine, dried over Na_2SO_4, and concentrated to give a yellow solid. The crude solid was purified by CombiFlash Companion (12 g RediSep column, EtOAc/Hexanes) to give 90 mg of product in 69% yield as a white solid. HPLC: mobile phase gradient 30%–90% (MeCN/H_2O both 10 mM TFA) over 30 minutes; column Zorbax SXB C8 (4.5 × 150 mm, 5 μm), t_R: 27.00 minutes, 98%.

(*R*)-1-(3,5-Dichlorophenyl)-3-methyl-2-oxo-3-(4-(trifluoromethoxy)benzyl)-2,3-dihydro-1*H*-[^{14}C]-imidazo[1,2-a]imidazole-5-sulfonyl chloride. [^{14}C]-(15): *i*-PrMgCl (0.3 mL, 2.0 M solution THF) was added dropwise to a solution of [^{14}C]-(20) (100 mg, 0.186 mmol) in THF at −10 °C. After stirring for 0.5 hour, SO_2/THF (0.25 mL, 22% by weight) was added; after 15 minutes, NCS (100 mg, 0.75 mmol) was added and stirred for 15 minutes. The reaction was quenched by the addition of H_2O, extract with EtOAc. The EtOAc extract was washed with brine, dried over Na_2SO_4, and concentrated to give the title compound, which was used as it is in the next step. HPLC: mobile phase gradient 30%–90% (MeCN/H_2O both 10 mM TFA) over 30 minutes; column Zorbax SXB C8 (4.5 × 150 mm, 5 μm), t_R: 28.04 minutes, 96%, co-eluted with unlabeled reference compound.

(*R*)-1-(3,5-Dichlorophenyl)-3-methyl-2-oxo-3-(4-(trifluoromethoxy)benzyl)-2,3-dihydro-1H-[^{14}C]-imidazo[1,2-a]imidazole-5-sulfonamide ([^{14}C]-(2). NH_4OH (2 mL) was added to a mixture of [^{14}C]-(15) (120 mg, 0.186 mmol), Cs_2CO_3 (80 mg, 0.25 mmol) in DMF (2 mL) and THF (2 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. The reaction was quenched by the addition of 10 % K_2CO_3, extracted with EtOAc. The EtOAc extract was washed sequentially with water (×2), brine, dried over Na_2SO_4, and concentrated. The crude solid was purified by CombiFlash Companion (12 g RediSep column, EtOAc/Hexane) to give a white solid (19 mg). The solid was further purified by CombiFlash Companion (4 g RediSep column, EtOAc/Hexane) to give as a white solid, which was finally purified by preparative HPLC using Chiracel OD (4.6 mm × 25 cm) 20% IPA/Hexane to give [^{14}C]-(2) (8 mg, 605 μCi with a specific activity of 40.5 mCi/mmol) as a white solid in 8% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38 (s, 1H), 7.33 (m, 2H), 7.23 (m, 1H), 6.92 (m, 4H), 5.08 (m, 2H), 3.97 (d, J = 14 Hz, 1H), 3.21 (d, J = 14 Hz, 1H), 1.96 (s, 3H). HPLC: mobile phase gradient 30%–90% (MeCN/H_2O both 10 mM TFA) over 30 minutes; column Zorbax SXB C8 (4.5 × 150 mm, 5 μm), t_R: 20.16 minutes, 99%.

Conclusion

A long linear route was used to prepare [$^{13}C_2$, $^2H_3$]-(1), (2*S*)-2-[[(5*R*)-7-(3,5-dichlorophenyl)-5-methyl-6-oxo-5-[[4-(trifluoromethoxy)-phenyl]methyl]-imidazo[1,2-a]imidazol-3-yl]sulfonylamino]propanamide using D-alanine (3,3,3-$^2H_3$) and [$^{13}C_2$]glycine in 15 steps and 2.5% overall yield. [$^{13}C_6$]-3,5-Dichloroaniline was used to prepare the metabolite (*R*)-1-(3,5-Dichlorophenyl)-3-methyl-2-oxo-3-(4-(trifluoromethoxy)benzyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole-5-sulfonamide [$^{13}C_6$]-(2) in 12 steps and in 5.6% overall yield. For the carbon-14 synthesis, a six-step synthesis gave both compounds [^{14}C]-(1) and [^{14}C]-(2) from the common sulfonyl chloride intermediate [^{14}C]-(15) in 18% and 4% radiochemical yields and specific activities of 44 and 40.5 mCi/mmol, respectively.

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