Synthesis of Tritium, Deuterium, and Carbon-14 Labeled (S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]carbamic acid, phenyl ester, (L)-2,3-dihydroxybutanedioic acid salt (SDZ ENA 713 hta), an Investigational Drug for the Treatment of Alzheimer's Disease

Grazyna Ciszewska*, Heidi Pfefferkorn, Y.S. Tang[1], Lawrence Jones, Richard Tarapata and Ustun B. Sunay

Novartis Pharmaceuticals Corporation
Isotope Laboratories
59 Route 10, East Hanover, N.J. 07936, USA

Summary

(S)-(-)-*N*-Ethyl-*N*-methyl-3-[1-(dimethylamino)ethyl]carbamic acid, phenyl-2-^{3}H-ester, (L)-2,3-dihydroxybutanedioic acid salt was synthesized *via* directed *ortho*-metallation methodology. (S)-(-)-*N*-Ethyl-*N*-methyl-3-[1-(di-($^{2}H_3$)-methylamino)ethyl]carbamic acid, phenyl ester, (L)-2,3-dihydroxybutanedioic acid salt was synthesized from 3-hydroxyacetophenone. The molecule was resolved by classical diastereomeric salt formation and fractional crystallization. The carbon-14 analog, (S)-(-)-*N*-ethyl-*N*-methyl-3-[1-(dimethylamino)ethyl-1-(^{14}C)]carbamic acid, phenyl ester, (L)-2,3-dihydroxybutanedioic acid salt was constructed starting from 3-iodoanisole and featured the enantioselective reduction of a methoxylamine intermediate.

Key Words : Alzheimer's disease, acetylcholine esterase inhibitor, carbon-14, deuterium, tritium, directed *ortho*-metalation, enantioselective reduction.

Introduction

SDZ ENA 713 hta, **1**, is a highly selective acetylcholine esterase inhibitor that has shown clinical promise as an agent that arrests the progression of Alzheimer's disease. In order to conduct *in vitro* and *in vivo* studies directed at identifying metabolites, measuring blood concentration levels and elucidating absorption, distribution and excretion issues, tritium, **2**, deutritium, **3**, and carbon-14, **4**, labeled isotopomers of this drug were prepared :

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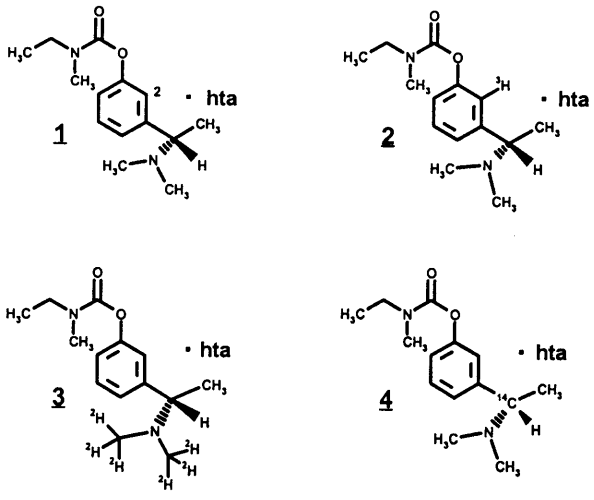
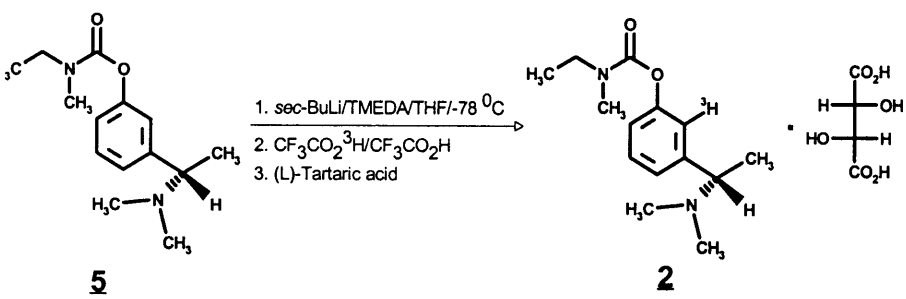
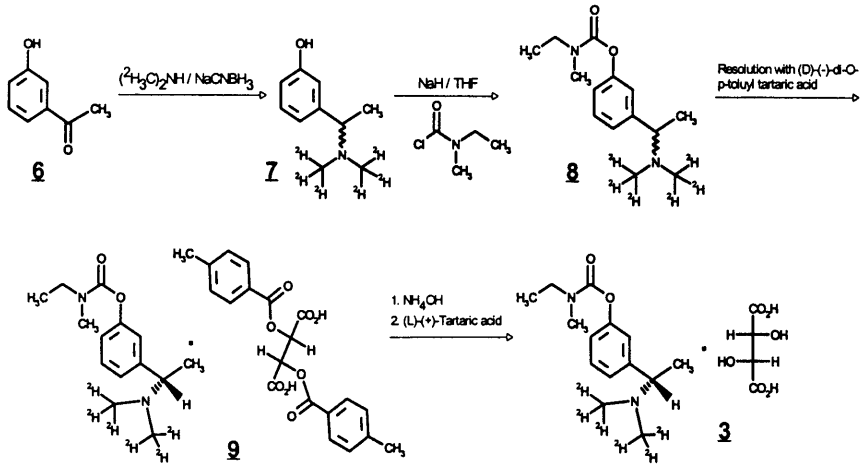


Results and Discussion

The tritium labeled analog, **2**, is a classical target for directed *ortho*-metallation (DoM) methodology. *O*-Aryl carbamates, such as the free base of **1**, exhibit excellent directing aptitude, and have been the subject of a variety of synthetic manipulations[2,3]. The 2-*ortho*-proton of this system, bearing a pK_a on the order of 37[3,4], is readily abstracted with the *sec*-BuLi/TMEDA (*N, N, N', N'*-tetramethylethylene diamine)[2,3,5] combination and is thus poised towards electrophilic substitution. Exposure of free base **5** to these conditions at -78 °C in THF afforded the lithiated intermediate which was quenched with tritiated trifluoroacetic acid[6]. Subsequent salt formation with (L)-(+)-tartaric acid gave the desired (^{3}H) SDZ ENA 713 hta **2** in 14 % radiochemical yield after purification.

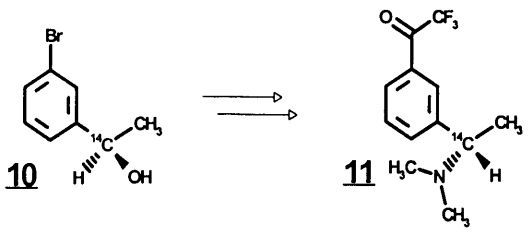


The synthesis of a mass spectroscopy internal standard required a material that had a mass number at least 4-6 units higher than the unlabeled drug. To this end, it was envisioned that reductive amination of 3-hydroxyacetophenone, **6**, with the appropriately deuterated amine would access the required intermediate. Indeed, reaction of **6** with di-(C^2H_3)-methylamine in the presence of sodium cyanoborohydride[7] gave the racemic aminophenol **7**. Processing of this compound with ethylmethyl carbamoyl chloride[8] proceeded smoothly to the aminoaryl carbamate **8**. Interestingly, crystallization and/or resolution attempts using (D)- or (L)-tartaric acid gave only an oily product that refused to solidify under a myriad of conditions. Only upon use of the apparently more crystallizable (D)-(-)-di-O-p-toluyl tartaric acid could the



resolution be effected[9]. This salt, **9**, was then liberated to the free base by use of aqueous NH_3. Chiral shift reagent ^{1}H-NMR at this point indicated > 99% e.e. Finally, treatment with (L)-(-)-tartaric acid gave the title compound, **3**, as a hygroscopic, crystalline solid. Keeping in mind that the final product was to be used as a mass spectroscopy internal standard, the chirality of the labeled drug substance is not important. Therefore, the antipode of **3** can also be used as an internal standard. This negates the waste associated with classical resolutions in this case.

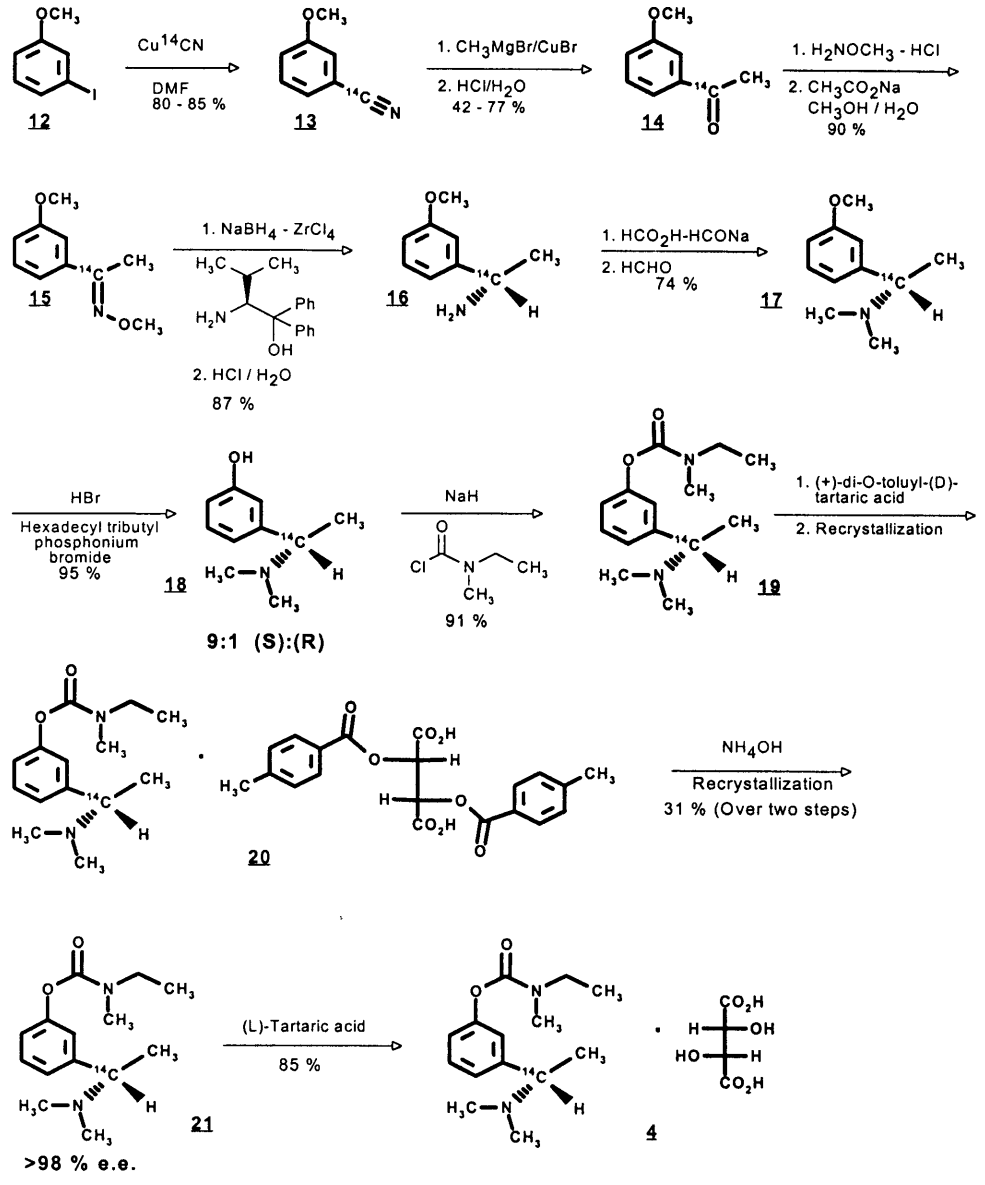
Unlike the situation with the deuterated ENA 713 hta, **3**, the carbon-14 labeled analog had to be synthesized in a more enantio-efficient manner. Stereoselective synthesis of α-arylethylamines of the type described here (**1**-**4**) have been undertaken utilizing a variety of



methods[10]. Indeed, compound **11** ([^{14}C] SDZ ENX 792), an analog of SDZ ENA 713, has been synthesized[10d,11] *via* the intermediacy of the corresponding enantiopure α-arylethanol **10**, which in turn was accessed from 3-bromoacetophenone by use of Corey's oxazaborolidine-catalyzed enantioselective ketone reduction procedure[12]. While this methodology is clearly superior to classical resolution and would have been applicable to the synthesis of **4**, the use of hydrazoic acid (HN_3) in the **10** to **11** transformation[10d,11] gave us pause. To this end, we opted to employ the Itsuno prescription[13] for the asymmetric reduction of ketoxime O-alkyl ethers in order to obtain the required optically active amine for [^{14}C] SDZ ENA 713 hta (*vide infra*).

The synthesis was initiated by the addition of "Cu^{14}CN"[14] to 3-iodoanisole, **12**, to give 3-methoxybenzo-^{14}C-nitrile **13** in 80 % yield (all yields, unless otherwise noted, are radiochemical yields). The nitrile was reacted with methylmagnesium bromide in the presence of a catalytic amount of CuBr. The intermediate imine was immediately hydrolyzed with aqueous HCl[14b,15] to afford 1-(3-methoxyphenyl)-1-^{14}C-ethanone, **14**, in 42 % yield.

Increasing the reaction time by approximately 3-fold improved the yield to 77 % (see experimental). The reluctance of carbon-14 labeled nitriles toward hydrolysis and nucleophilic attack, as compared to their unlabeled analogs, has been observed elsewhere[16]. It is interesting to note that the same reaction sequence when applied to the unlabeled system consistently provided the corresponding acetophenone in > 90 % yield[16]. Compound **14** was exposed to a mixture of methoxylamine hydrochloride and sodium acetate in aqueous methanol, giving the O-methyloxime **15** in 90 % yield. The crucial reduction of this material was undertaken with $NaBH_4$-$ZrCl_4$ complex in the presence of (S)-2-amino-3-methyl-1,1-diphenylbutanol (diphenyl valinol)[13]. Acidic workup gave the enantiomerically enriched amine **16** in 86 % yield. Dimethylation was accomplished by employing Eschweiler-Clarke[17] conditions and



intermediate **17** was recovered in 74 % yield. Demethylation of the methoxy function proceeded in excellent yield, giving phenol **18** with 95 % conversion. It is of note that the addition of a phase transfer catalyst to the reaction mixture greatly improved the yield[18]. Chiral-shift reagent[19] ^{1}H-NMR spectroscopy revealed a 9:1 mixture of the desired (S) and (R) enantiomers, indicating the success of the asymmetric reduction of **15**. Acylation with *N*-ethyl-*N*-methyl carbamoyl chloride[8] (91 % yield) was followed by purification[20] *via* several

recrystallizations with (D)-(+)-di-O-toluyl-tartaric acid and liberation to free base with NH_4OH gave **21** in 31 % yield from **19** and > 98 % e.e.[20]. Final conversion to [^{14}C] SDZ ENA 713 hta, **4**, was accomplished in 84 % yield by forming the (L)-tartaric acid salt.

Experimental

Tritiated water (THO) was purchased from New England Nuclear/DuPont at a specific activity of ~ 1.0 Ci/gr. Potassium-^{14}C-cyanide was purchased from American Radiolabeled Chemicals, Inc., with a specific activity of ~ 55.2 mCi/mmol. ($^2H_6$) Dimethylamine hydrochloride was obtained from the Aldrich Chemical Company, Inc. Melting points were determined while collecting differential scanning calorimetry spectra on a Rheometrics/Polymer Labs STA-625 instrument under nirogen purge using aluminum pans. Optical rotations were obtained on a Perkin-Elmer 241 Polarimeter. Chemical ionization mass spectroscopy was performed on a Finnigan 4600 mass spectrometer utilizing isobutane or ammonia as the reagent gas. Elemental analyses were performed by Sandoz Central Technology group on Carlo Erba CHNS-O EA1108 Elemental Analysis instrument or by Robertson Microlit Laboratories, Inc (Madison, NJ) on Perkin Elmer 2400 Series II CHNS-O instrument. TLC and radio-TLC chromatograms were performed on 5 x 20 cm E. Merck silica gel F-254 plates (250 micron thickness). Visualization was achieved either by UV light at 254 nm or exposure to subliming iodine. TLC plates were further evaluated by scanning using a CAMAG densitometer. Radiochemical purities were determined by scanning the chromatograms for radioactivity with a Vanguard gas proportional scanner with a 1 mm x 10 mm collimator, as well as radio-HPLC. The radioactivity was monitored with a Ramona-90 flow through detector and its database collected both radioactive and UV data. The Ramona-90 radio-HPLC system was equipped with a splitter/mixer module, precision pulse-free positive displacement metering pumps and a 100 µL liquid scintillator cell. Identities of intermediates were determined by comparative TLC and HPLC versus non-labeled standards that were identified by mass spectroscopy, elemental analysis as well as 300 or 500 MHz ^{1}H-NMR and 75 or 125 MHz ^{13}C-NMR spectroscopy on Bruker NMR instruments. Specific activities were determined by the "weight-in-volume" assay method. High Performance Liquid Chromatography was performed on a Waters HPLC system that consisted of a Waters 600E pump module, a WISP 712A auto-sampler, a 484 variable wavelength UV detector, and a Waters 996 photo-diode array detector. Infrared spectroscopy was performed on a Nicolet 550 FT-IR instrument.

(S)-*N*-Ethyl-*N*-methyl-3-[1-(dimethylamino)ethyl]carbamic acid, phenyl-2-^{3}H-ester, (L)-2,3-dihydroxybutanedioic acid salt, **2**

Step A :

In a 200 mL reaction flask, a mixture of 1.394 g (12.0 mmol) TMEDA, 10 mL of THF, and 13.3 mL (0.9 M solution in cyclohexane, 12.0 mmol) of *sec*-butyllithium were mixed under a nitrogen atmosphere at -78 °C. The mixture was stirred at -78 °C for 30 minutes and to it was added 2.0 g (8.0 mmol) of free base **5** dissolved in 5 mL of THF. The resultant solution was stirred at the same temperature for an additional 45 minutes.

Step B :

In a separate flask, 2.334 g (11.11 mmol) of trifluoroacetic anhydride was hydrolyzed with 1.2 Ci (200 μL) of tritiated water at 0 °C. After allowing to stir for 20 minutes, 2.0 mL of dry THF was added to the mixture and the solution was cooled to -78 °C and added slowly at this temperature to the solution of lithiated intermediate generated in step **A**. After the addition was completed, stirring was continued at -78 °C for 15 minutes, and the reaction was quenched by the addition of 2.0 mL of saturated ammonium chloride solution. The resultant mixture was lyophilized at -78 °C for 24 hours. The powdery residue was taken up in 30 mL CH_2Cl_2 and washed with 30 mL of water. The aqueous phase was extracted with five 50-mL portions of CH_2Cl_2. The combined organic layers were treated with a solution of 5.0 g (33.3 mmol) of (L)-tartaric acid in 10 mL of water. The phases were separated and the organic layer was extracted with three 25-mL portions of water. The combined aqueous phases were made basic (pH 8) by the addition of 10% sodium bicarbonate solution and extracted with four 30-mL portions of CH_2Cl_2. The combined organic phases were washed with 20 mL of brine, dried over magnesium sulfate, and concentrated under reduced pressure to afford 227.2 mCi (1.35 g, 5.4 mmol, 42 mCi/mmol) of the free base of the title compound. The material co-eluted with unlabeled standard in three TLC systems : System A : Et_2O/n-hexane/CH_3OH /xylene/NH_4OH, 40/10/13/40/2, v/v/v/v/v; R_f= 0.38. System B : CH_2Cl_2/CH_3OH/NH_4OH (90 /10/2, v/v/v; R_f= 0.55. System C : CH_2Cl_2/CH_3OH/H_2O/HCO_2H, 70/30/5/2, v/v/v/v; R_f= 0.77. ^{3}H-NMR δ (CD_3OD) = 7.11-7.13 (1 ^{3}H, d, J = 1 Hz).

Step C :

The labeled free base obtained above (1.35 g, 5.4 mmol, 227.2 mCi, 42 mCi/mmol) was heated to 80 °C in 30 mL of acetone with 0.75 g (5.0 mmol) of (L)-tartaric acid until all solids were in solution. The material was diluted with 20 mg (0.08 mmol) of unlabeled free base, and then cooled to 50 °C. The solution was seeded with 5 mg of unlabeled salt and cooled to 0 °C. After the solution became cloudy, the temperature was raised to 25 °C, and the mixture was allowed to stand for 24 hours. The solids thus formed were collected by suction filtration, washed with 3 mL of cold acetone and dried under high vacuum at 30 °C for 48 hours to give 167.0 mCi (74 %, 1.2 g, ~139.1 μCi/mg) of the title compound, **2**. The identity and purity of the material on hand was confirmed by comparative HPLC and radio-HPLC elution times. ABS® liquid scintillation cocktail was used for radioactivity detection in HPLC eluants, in a ratio of two parts cocktail to one part eluant. The analysis was carried out on a Brownlee Spheri 5 OD-MP column (4.6 mm i.d., 130 mm length, 5 micron packing) at 25 °C. The mobile phases consisted of Solvent A : 0.05 M KH_2PO_4 in H_2O with 0.2 % Et_3N, adjusted to pH 5 with H_3PO_4; Solvent B : 0.05 M KH_2PO_4 in 50:50 CH_3CN : H_2O with 0.2 % Et_3N, adjusted to pH 5 with H_3PO_4. The gradient conditions were : Time 0 min. : 70

% A, 30 % B; Time 20 min. : 25 % A, 75 % B; Time 21 min. : 70 % A, 30 % B. The flow rate was 1.0 mL/min. The analyzed solutions of product and reference material were at a concentration of ~ 1 mg/mL and three 10 μL injections of each were run. Detection was at 214 nm for UV activity. The retention times of product and reference were identical. Radiochemical purity was > 95%. $[\alpha]^{25}$ (standard) = $-10.55^0 \pm 1.47^0$ (c=1.024, CH_2Cl_2). $[\alpha]^{25}$ (sample) = $-9.78^0 \pm 1.40^0$ (c=1.074, CH_2Cl_2).

(R,S)-3-[[1-Di($^2H_3$)methylamino]ethyl]phenol, 7

A solution of di[$^2H_3$]methylamine was prepared by dissolving 25 g (0.286 mol) of di[$^2H_3$]methylamine hydrochloride salt in 150 mL of methanol and slow addition of 3.48 g (0.62 mol) of KOH at room temperature. The mixture was stirred for a short period of time and to the thick white precipitate formed was slowly added 23.73 g (0.174 mol) of 3-hydroxyacetophenone, 6, and stirring was continued at room temperature for ~15 minutes. Over the next 30 minutes, a solution of 4.13 g (0.66 mol) of $NaCNBH_3$ in 50 mL of methanol was added dropwise to the imine intermediate. Stirring was continued at room temperature for 30 minutes and then 13.07 g (0.233 mol) of KOH pellets were added. The solution was stirred at 25 ^{0}C until all of the KOH had dissolved, and then the mixture was filtered. The filtrate was concentrated under vacuum while keeping the temperature below 30 ^{0}C. The oily residue was diluted by the addition of 10 mL of water, 25 mL of brine and 50 mL of EtOAc. The layers were separated and the aqueous phase was extracted with two 50-mL portions of ethyl ether. The combined organic layers were cooled to 0 ^{0}C and to it was added 30 mL of 6 N HCl solution. The layers were separated and the organic phase was extracted with an additional 30 mL of 6 N HCl solution. The combined aqueous layers were saturated with NaCl and washed with four 30-mL portions of ethyl ether. The combined aqueous phases were cooled to 0 ^{0}C and, with stirring, KOH pellets were added until the pH was > 12. Two distinct layers became evident, and the aqueous phase was extracted with two 40-mL portions of ethyl ether. The combined organic layers were concentrated *in vacuo* to leave an oil that was taken up in the minimum amount of EtOAc possible and purified on a silica gel column (5% triethylamine in EtOAc). The fractions of interest were combined and concentrated to give an oil that was kept under high vacuum until crystals formed. These solids were recrystallized from acetone and the solids formed were washed with cold heptane and dried under vacuum to afford 1.1082 g of the title compound. Another batch of 7, consisting of 1.517 g, was prepared as described above and used in the following steps. The material showed identical R_f's as the unlabeled standard in the following TLC systems : A: Et_2O/hexane/CH_3OH/xylene/HCO_2H, 40/10/13/40/2; B : CH_2Cl_2/CH_3OH/NH_4OH, 90/10/2; C : CH_2Cl_2/CH_3OH/H_2O/HCO_2H, 70/30/5/2. The chemical purity, as well as the identity, was

further established by HPLC using a Hypersil MOS-1 column (150mm x 4.6mm), 5-micron packing, maintained at 40 °C. The mobile phase consisted of a binary gradient with a flow rate of 1.0 mL/min. Mobile phase A consisted of 0.02 M KH_2PO_4 in a mixture of 0.2 % triethylamine in water, with the final pH adjusted to 5 with phosphoric acid. Mobile phase B was a 0.02 M KH_2PO_4 solution in a mixture of 0.2 % triethylamine in water:acetonitrile (1:1), with the final pH adjusted to 5 with phosphoric acid. The following gradient was employed : Time 0.0 min, 90 % A, 10 % B; time 20 min, 25 % A, 75 % B; time 21 min, 90 % A, 10 % B. Analysis indicated a purity of > 98 %. MH^+= 172. ^{1}H-NMR : δ (CD_3OD) 1.39 (3H,d, *J* 5 Hz), 3.22 (1H, q, *J* 5 Hz), 3.35 (1H, m), 6.62-6.80 (3H, m), 7.10-7.19 (1H, m). ^{13}C-NMR : δ (CD_3OD) 158.65, 145.41, 130.37, 120.02, 115.67, 115.34, 67.3, 20.39. IR (KBr pellet, cm^{-1}) 2980, 2575, 2056, 1594, 1450, 1375, 1274.

(R,S)-*N*-Ethyl-*N*-methyl-3-[1-di($^2H_3$)methylamino)ethyl]carbamic acid, phenyl ester, 8

A round-bottomed reaction flask was charged with 440.67 mg of a 60% NaH dispersion in mineral oil. The NaH was washed with three 5-mL portions of dry THF under a nitrogen atmosphere and then suspended in 20 mL of dry THF. The mixture was cooled to 0 °C and to it was added dropwise a solution of 1.517 g of 7 in 5 mL of THF. To this was added 1.29 g (0.01 mol) of ethylmethyl carbamoyl chloride and stirring at 0 °C was continued for three hours. At this point, the reaction was quenched with 7.0 mL of water and stirring was continued for an additional 10 minutes. The layers were separated and the aqueous phase was extracted with two 5-mL portions of ethyl ether. The combined organic layers were washed with two 7-mL portions of 2 N NaOH solution and concentrated under reduced pressure to give an oil that was carried on to the next step as is. MH^+ = 257.

(S)(-)-*N*-Ethyl-*N*-methyl-3-[1-di($^2H_3$)methylamino)ethyl]carbamic acid, phenyl ester, (D)-2,3-di-O-*p*-toluyl-butanedioic acid salt, 9

The oily residue 8 was taken up in a solution composed of 13.36 mL CH_3OH in 6.64 mL of water. To this was added 3.68 g (1.047 mol) of (D)-2,3-di-O-*p*-toluyl-butanedioic acid and the mixture was heated to 40 °C. When all additives were dissolved, the solution was cooled to 0 °C, seeded with unlabeled SDZ ENA 713 (D)-2,3-di-O-*p*-toluyl-butanedioic acid salt, and kept in the freezer overnight. At this point, no crystallization was evident. The solution was evaporated and taken up in 25 mL of CH_2Cl_2 and treated with 2 N NaOH to a pH of ~ 11. The layers were separated and the organic phase was washed with water and the water was extracted twice with 15-mL portions of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, evaporated and the residue was purified on a silica gel column (CH_2Cl_2:EtOAc 9:1). The fractions of interest were pooled into two portions and concentrated separately. These

fractions proved to be impure, therefore they were combined and re-purified on a silica gel column (mobile phases : CH_2Cl_2; CH_2Cl_2:EtOH 98:2; CH_2Cl_2:EtOH 95:5; CH_2Cl_2:EtOH: aq. NH_3 95:4.5:0.5). The fractions of interest were combined and concentrated to give 1.75 g of an oily residue. This material was taken up in 8 mL of CH_3OH and heated to 45-47 ^{0}C and to it was added 2.76 g (7.13 mmol) of (D)-2,3-di-O-*p*-toluyl-butanedioic acid. Heating was continued at 45-47 ^{0}C for 20 minutes, and then ~4 mL of water was added. The reaction mixture was slowly cooled to 38-40 ^{0}C and seeded with unlabeled SDZ ENA 713 (D)-2,3-di-O-*p*-toluyl-butanedioic acid salt. Slow cooling to room temperature was continued and stirring at this temperature was maintained for 2.5 hours. The crystals formed were collected by suction filtration and washed with a cold mixture of 4:1 H_2O:CH_3OH. The solids thus collected were recrystallized in the same manner seven more times to give a white powder that was used directly in the next step. MH^+ = 257. Chiral shift reagent[20] ^{1}H-NMR of the free base indicated ≥ 99% e.e.

(S)-(-)-*N*-Ethyl-*N*-methyl-3-[1-di($^2H_3$)methylamino)ethyl]carbamic acid, phenyl ester, (L)-(-)-2,3-dihydroxybutanedioic acid salt, 3

The crystals obtained from the last step were dissolved in 50 mL of CH_2Cl_2 and to this mixture was added 15 mL of water. While stirring was initiated, aq. NH_3 was slowly added until the pH of the aqueous phase reached ~11. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 and then with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated to afford 504 mg (1.97 mmol) of a gummy solid. This material was taken up, in a dry box, with minimal humidity, in the minimum amount of warm acetone and to it was added 312.18 mg (2.07 mmol) L-tartaric acid. More hot acetone was added until all solids were dissolved and the mixture was stirred at reflux for a few minutes, and then slowly allowed to cool to 25 ^{0}C. The suspension was stirred at this temperature for three hours and the crystals formed were collected by suction filtration and washed three times with cold acetone and dried under high vacuum for 12 hours at 25 ^{0}C and then at 30 ^{0}C for forty hours to give 686.2 mg of the title compound. HPLC analysis (same system as that used for the analysis of compound **2** indicated a chemical purity of ≥ 99%. M.p. = 126.7^0 C (reference = 124.7^0 C). MH^+ = 257, 241 (Unlabeled reference = 251, 241). IR = 3320, 2975, 1720, 1591, 1403, 1306. ^{1}H-NMR, 500 MHz, δ ($CDCl_3$) = 7.50-7.56 (1H, t, J=10 Hz); 7.38-7.44 (1H, d, J=10 Hz); 7.35 (1H, s); 7.23-7.26 (1H, d, J=10 Hz); 4.45-4.50 (1H, q, J=10 Hz); 4.44 (2H, s); 3.40-3.60 (2H, dq, J=10 Hz, 66 Hz); 3.02-3.13 (3H, d, J=63 Hz); 2.78 (6H, s); 1.75-1.80 (3H, d, J=10 Hz); 1.18-1.33 (3H, dt, J=7 Hz, 44 Hz).

Copper(I)-^{14}C-cyanide

A solution of 1.25 g (9.9 mmol) sodium sulfite in 45 mL of HPLC grade water (unless

otherwise noted, all water used was of HPLC quality). was added dropwise to a stirring solution consisting of 1.23 g (16.7 mmol, 1.00 Ci, 55.9 mCi/mmol) $K^{14}CN$ in 45 mL of water. To this was added 4.89 g (19.58 mmol) of cupric sulfate pentahydrate in 62 mL of water and the suspension was allowed to stir at room temperature for ten minutes. To this was then added dropwise 9 mL of a 0.95 N solution of NaOH. Stirring was continued for twenty minutes and the suspension was allowed to settle. The supernatant was decanted and the precipitate was washed with two 25-mL portions of water, followed by two 25-mL portions of acetone. The powder obtained was dried under high vacuum to afford 2.03 g (1.00 Ci, 100% radiochemical yield). A second portion of $Cu^{14}CN$ was prepared as described above using 0.795 g (6.133 mmol) of sodium sulfite in 30 mL of water, 0.600 g (8.94 mmol, 0.50 Ci, 55.9 mCi/mmol) $K^{14}CN$ in 30 mL of water, 3.125 g (12.519 mmol) cupric sulfate pentahydrate in 40 mL of water and 7 mL of 0.95 N NaOH solution. The reaction yielded 1.086 g (0.452 Ci, 90% radiochemical yield) of the title compound.

3-Methoxybenzonitrile-cyano-^{14}C, 13

Under a nitrogen atmosphere, 2.03 g (1.00 Ci, 16.72 mmol) of $Cu^{14}CN$ was suspended in 10 mL of dimethylformamide (DMF). A solution consisting of 8.61 g (36.78 mmol) of 3-iodoanisole in 10 mL of DMF was added dropwise to the stirring suspension. The reaction was heated to 125 ^{0}C and allowed to stir for 24 hours [In Process Control (IPC) : TLC hexane-ethyl acetate 9:1]. The solution was cooled to room temperature and the precipitate was allowed to settle. The mixture was filtered through a bed of Celite® and the Celite® was then washed with 10 mL of water, followed by 10 mL of methylene chloride. The filtrate was diluted with 30 mL of water and the layers were separated. The aqueous phase was extracted with four 15-mL portions of methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (100 % hexane initially, then 95 % hexane-ethyl acetate after elution of impurity) to give 1.766 g (13.26 mmol, 0.795 mCi, 80 % radiochemical yield) of the title compound. A second portion of 3-methoxybenzonitrile-cyano-^{14}C was prepared as described above using 1.086 g (8.94 mmol, 452.4 mCi) $Cu^{14}CN$ in 15 mL of DMF and 4.603 g (19.67 mmol) of 3-iodoanisole in 5 mL of DMF. The reaction and subsequent purification gave 1.024 g (7.58 mmol, 397 mCi, 85 % radiochemical yield) of the title compound. TLC (hexane-ethyl acetate 9:1) = R_f = 0.9. MH^+= 136 (NH^+_3, DCI).

1-(3-Methoxyphenyl)-1-^{14}C-ethanone, 14

Under a nitrogen atmosphere, a solution of 1.796 g (13.26 mmol, 795.0 mCi) 3-methoxybenzonitrile-cyano-^{14}C, **13**, in 8 mL of diethyl ether was added dropwise to a stirring mixture of 18 mL (6.326 g, 53.04 mmol) 3.0 M methyl magnesium bromide in ether cooled

at 0 °C. To this solution was added 38.05 mg (0.27 mmol) of copper bromide as catalyst and the reaction mixture was warmed to room temperature and stirred for seven hours (IPC : TLC 100 % methylene chloride). The reaction mixture was cooled to -5 °C and quenched by the slow addition of 7 mL of 5 N HCl solution. The solution was then heated to 50 °C and stirred for 16 hours, followed by stirring at 100 °C for 3½ hours. The mixture was cooled to room temperature and diluted with 50 mL of methylene chloride. The layers were separated and the aqueous phase was extracted with three 20-mL portions of methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (methylene chloride : hexane, 95:5) to give 1.013 g (6.654 mmol, 332.7 mCi, 42 % radiochemical yield) of 1-(3-methoxyphenyl)-1-^{14}C-ethanone, **14**. A second batch of the title compound was prepared in a slightly different manner. Under a nitrogen atmosphere, 1.024 g (7.58 mmol, 397 mCi) of 3-methoxybenzonitrile-cyano-^{14}C, **13**, dissolved in 4.5 mL of benzene was added dropwise to 10.3 mL (3.166.g, 30.32 mmol) of a 3.0 M solution of methyl magnesium bromide in ether that was cooled to -10 °C. The solution was allowed to warm to room temperature and 21.75 mg (0.15 mmol) of copper bromide was added. The reaction was stirred at room temperature for 24 hours (IPC : TLC 100 % methylene chloride), cooled to -10 °C, diluted with 20 mL of a 1:1 mixture of benzene:ethyl ether and quenched by the slow addition of 40 mL 5.0 N HCl solution. The reaction was heated to 90 °C and refluxed for three hours (IPC : TLC 100% methylene chloride). After cooling to room temperature, the layers were separated and the organic phase was dried over sodium sulfate and concentrated under reduced pressure. The oily residue was purified by column chromatography (100 % methylene chloride) to afford 931 mg (6.12 mmol, 306.01 mCi, 77 % radiochemical yield) of the title compound. The two batches of ketone **14** were combined to give a total of 1.948 g (12.80 mmol, 638 mCi) of product. TLC (100% CH_2Cl_2) = R_f = 0.42. MH^+ = 153 (isobutane, DCI).

1-(3-Methoxyphenyl)-1-^{14}C-ethanone,*O*-methyloxime, 15

A suspension of 1.303 g (15.6 mmol) methoxylamine hydrochloride and 2.123 g (15.6 mmol) sodium acetate in 10 mL of methanol was dissolved by the addition of 7 mL of water. To this solution was added 1.978 g (12.8 mmol, 638.4 mCi) of 1-(3-methoxyphenyl)-1-^{14}C-ethanone, **14**, dissolved in 4 mL of methanol. The reaction mixture was stirred at room temperature for sixteen hours (IPC : TLC 100 % methylene chloride) and the solvent was then removed under reduced pressure. The residue was diluted with 5 mL of water and 5 mL of methylene chloride and the layers were separated. The aqueous phase was extracted with three 5-mL portions of methylene chloride and the combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on

silica gel (100 % methylene chloride) to give 2.097 g (11.6 mmol, 573.25 mCi, 90 % radiochemical yield) of 1-(3-methoxyphenyl)-1-^{14}C-ethanone,O-methyloxime, **15**. TLC (100% CH_2Cl_2) = R_f = 0.36. MH^+ = 182 (isobutane DCI).

(S)-3-Methoxybenzene-methylmethanamine-^{14}C, 16

Under a nitrogen blanket, 3.379 g (14.5 mmol) of zirconium tetrachloride and 2.201 g (58 mmol) of sodium borohydride were dissolved in 47 mL of dry tetrahydrofuran (THF) and stirred at room temperature for 24 hours. At this point, 3.703 g (14.5 mmol) of (S)-2-amino-3-methyl-1,1-diphenylbutanol, dissolved in 9.8 mL of dry THF, was added to the reaction mixture. Stirring at room temperature was continued for an additional 24 hours, followed by the dropwise addition of 2.102 g (11.6 mmol, 573.25 mCi) 1-(3-methoxyphenyl)-1-^{14}C-ethanone,O-methyloxime, **15**, in 9.8 mL of dry THF. Stirring at room temperature was maintained for 70 hours (IPC : TLC methylene chloride-methanol, 9:1), and the reaction was terminated by the addition 15 mL of 5 N HCl solution to the mixture which was cooled to 0 ^{0}C. Water was added until gas evolution ceased. The solvent was removed under reduced pressure to give a thick, white emulsion. The pH of this emulsion was adjusted to 9 by the dropwise addition of conc. NH_4OH. The mixture was diluted with 20 mL of methylene chloride and the layers were separated. The aqueous phase was extracted with three 15-mL portions of methylene chloride and the combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (initially 100 % methylene chloride until elution of the amino alcohol and fast running impurities, followed by 100 % methanol) to afford 1.410 g (9.2 mmol, 462.5 mCi, 87 % radiochemical yield) of the title compound. TLC (9:1 CH_2Cl_2:CH_3OH) = R_f = 0.23. MH^+ = 154 (isobutane DCI). ^{1}H-NMR (300 MHz) δ ($CDCl_3$) = 7.21-7.32 (2H, m); 6.88-6.98 (1H, s); 6.72-6.85 (1H, d, J=7.5 Hz); 4.05-4.15 (1H, q, J=7.5 Hz); 3.79 (3H, s); 1.78-2.00 (2H, bs); (1.35-1.45 (3H, d, J=7.5 Hz).

(S)-3-Methoxy-*N,N*-trimethylbenzenemethanamine-^{14}C, 17

To 1.410 g (9.2 mmol, 462.5 mCi) of (R,S)-3-methoxybenzenemethylmeth-anamine-^{14}C, **16**, cooled to 0 ^{0}C, was added 3.5 mL (4.235 g, 92 mmol) of a 98 % aqueous formic acid solution, followed by 1.877 g (27.6 mmol) sodium formate and 4 mL (1.658 g, 55.2 mmol) of a 37.8 % aqueous formaldehyde solution. The reaction mixture was heated to 80 ^{0}C and stirred for six hours (IPC : TLC ethyl acetate:methanol:ammonium hydroxide, 7:3:0.3). The reaction was allowed to cool to room temperature and stirring was continued for 16 hours (IPC : TLC, as above). Following addition of 5 mL of water and cooling to 0 ^{0}C, 8 mL of 5 N HCl solution was added dropwise. Stirring was continued for ten minutes and the reaction mixture was diluted with 15 mL of ethyl acetate and stirring was continued for an

additional 15 minutes, at which point the layers were separated. The organic phase was extracted with three 5-mL portions of 2 N HCl. The pH of the combined aqueous layers were adjusted to 11 by the addition NaOH pellets and this basic solution was extracted with eight 10 mL portions of ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate:methanol, 95:5) to give 1.117 g (6.16 mmol, 342.5 mCi, 74 % radiochemical yield) of (R,S)-3-methoxy-*N,N*-trimethylbenzenemethanamine-^{14}C, 17. TLC (EtOAc:CH_3OH:NH_4OH 7:3:0.3) = R_f = 0.55. MH^+ = 184 (isobutane DCI).

(S)-3-[1-(Dimethylamino)ethyl-1-^{14}C]-phenol, 18

1.117 g (6.16 mmol, 342.5 mCi) of (R,S)-3-Methoxy-*N,N*-trimethylbenzene-methanamine-^{14}C, 17, was dissolved in 1.86 mL (1.303 g, 16.24 mmol) of a 48 % solution of HBr. To this solution was added 347.8 mg (6.85 x 10^{-1} mmol) hexadecyltributylphosphonium bromide as a phase transfer catalyst and the reaction mixture was stirred at 115-119 ^{0}C for nine hours, followed by stirring at room temperature for 16 hours (IPC : TLC ethyl acetate:methanol:ammonium hydroxide, 7:3:0.3). At this point, IPC indicated a significant amount of starting material. Re-evaluation of the reaction stoichiometry revealed an error in the amount of HBr employed. Therefore, an additional 1.53 mL (1.07 g, 13.36 mmol) of 48 % HBr solution was added to the reaction mixture and heating was resumed at 115-119 ^{0}C for 8½ hours (IPC : TLC ethyl acetate:methanol:ammonium hydroxide, 7:3:0.3). The solution was cooled to 0 ^{0}C and the reaction was quenched by the addition of 6 mL of conc. NH_4OH, resulting in pH > 11. The mixture was allowed to warm to room temperature and stirring was continued for ½ hour. At this point, the reaction was diluted with 7 mL of ethyl acetate and stirred for an additional ¼ hour. The layers were separated and the aqueous phase was extracted with six 5-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give 1.573 g (9.4 mmol, 326 mCi, 95 % radiochemical yield) of the title compound. Chiral shift reagent ((R)-(+)-*t*-butyl-phenylphosphinothioic acid, ^{1}H-NMR indicated a 9:1 mixture in favor of the desired (S)-enantiomer. This material was used in the next step without further manipulation. TLC (EtOAc:CH_3OH:NH_4OH 7:3:0.3) = R_f = 0.48. MH^+= 168 (isobutane DCI). ^{1}H-NMR (300 MHz) δ ($CDCl_3$) = 7.17-7.22 (1H,t, J=7.5 Hz); 6.68-6.85 (3H, m); 5.43-5.80 (1H, bs); 3.19-3.25 (1H,m); 2.22 (6H,s); 1.36-1.42 (3H, d, J=7.5 Hz).

(S)-(-)-*N*-Ethyl-*N*-methyl-3-[1-(Dimethylamino)ethyl-1-^{14}C]carbamic acid, phenyl ester, 19

Under a nitrogen atmosphere, 358.8 mg (8.97 mmol) of a 60 % oil dispersion of NaH was washed with three 3-mL portions of dry THF and cooled to 0 ^{0}C. A solution of 1.305 g (7.8

mmol, 270 mCi) of (R,S)-3-[1-(dimethylamino)ethyl-1-^{14}C]-phenol, **18**, in 5 mL of THF was added dropwise to the NaH suspension. The mixture was allowed to warm to room temperature and stirring was continued for ¾ hours, followed by addition of 1.482 g (9.75 mmol) of *N*-ethyl-*N*-methyl-carbamoyl chloride, dissolved in 4 mL of THF. The reaction mixture was stirred at room temperature for 1½ hours (IPC : TLC methylene chloride:methanol:concentrated ammonium hydroxide, 9.0:0.9:0.1). The solvent was removed *in vacuo* and the residue was taken up in a mixture consisting of 5 mL water, 5 mL 2 N NaOH solution and 5 mL ethyl acetate and the resultant two-phase solution was stirred vigorously for ⅓ hours. The layers were separated and the organic phase was washed with four 3-mL portions of water and the aqueous layer was extracted with four 5-mL portions of ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated under reduced pressure to yield 1.707 g (6.7 mmol, 245.25 mCi, 91 % radiochemical conversion) of the title compound that was used in the next step without further manipulation. TLC (CH_2Cl_2:CH_3OH:NH_4OH 9:0.9:0.1) = R_f= 0.35. MH^+= 253 (isobutane DCI). ^{1}H-NMR (300 MHz) δ ($CDCl_3$) = 7.22-7.35 (1H, m); 6.95-7.19 (3H, m); 3.35-3.55 (2H, m); 3.21-3.29 (1H, q, J= 5.5 Hz, 15 Hz); 2.95-3.11 (3H, bd, J= 22 Hz); 2.22 (6H, s); 1.35-1.42 (3H, d, J= 5.5 Hz); 1.15-1.30 (3H, m). ^{13}C-NMR (75 Mhz) δ ($CDCl_3$) = 151.55, 145.55, 128.86, 124.20, 120.73, 120.26, 65.61 (position of ^{14}C), 44.01, 43.12, 34.17, 33.76, 29.67, 19.98, 13.20, 12.45.

(S)-(-)-*N*-ethyl-*N*-methyl-3-[1-(dimethylamino)ethyl-1-^{14}C]carbamic acid, phenyl ester, (D)-2,3-di-O-*p*-toluyl-butanedioic acid salt, 20

To 1.707 g (6.7 mmol, 245.25 mCi) of (R,S)-*N*-ethyl-*N*-methyl-3-[1-(dimethylamino)ethyl-1-^{14}C]carbamic acid, phenyl ester, **19**, dissolved in 8.5 mL of methanol at 45 ^{0}C was added 2.870 g (7.42 mmol) (+)-di-p-toluoyl-D-tartaric acid, followed by the dropwise addition of 4 mL of water. The mixture was cooled to 40 ^{0}C and stirred for thirty minutes, and then allowed to cool to room temperature and stirred for four hours. The crystals formed were collected by suction filtration and washed with an ice-cold solution of 1:3 methanol:water. The crystals that were collected were then recrystallized three more times in the same manner to give batch # 1. The combined mother liquors were crystallized also in the same manner to afford batch # 2. These two batches were combined and recrystallized one more time from methanol-water to give batch # 3, which was carried onto the next step without calculation of yield.

(S)(-)-*N*-Ethyl-*N*-methyl-3-[1-(dimethylamino)ethyl-1-^{14}C]carbamic acid, phenyl ester, 21

The (S)-*N*-ethyl-*N*-methyl-3-[1-(dimethylamino)ethyl-1-^{14}C]carbamic acid, phenyl ester, (D)-2,3-di-O-*p*-toluyl-butanedioic acid salt, batch # 3, was dissolved in 5 mL of water and the pH of the solution was adjusted to >11 by the dropwise addition of conc. NH_4OH. To this solution was added 5 mL of ethyl acetate and the two-layer system was stirred at room temperature for ten minutes. The layers were separated and the organic phase was washed with 3 mL of water and the aqueous phase was extracted with four 5-mL portions of ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure to give 390 mg (1.54 mmol, 76.18 mCi) of the title compound ([^{14}C] ENA 713 free base). Chiral shift reagent ((R)-(+)-*t*-butylphenylphosphinothioic acid) ^{1}H-NMR indicated an e.e. of $\geq$ 98 %.

(S)-(-)-*N*-Ethyl-*N*-methyl-3-[1-(dimethylamino)ethyl-1-^{14}C]carbamic acid, phenyl ester, (L)-2,3-dihydroxybutanedioic acid salt, 4

195 mg (7.70×10^{-1} mmol, 38 mCi) of (S)-*N*-ethyl-*N*-methyl-3-[1-(Dimethylamino)ethyl-1-^{14}C]carbamic acid, phenyl ester, **21**, was dissolved in the minimum amount of dry acetone in a dry box (the target salt is very sensitive to moisture) and to this solution was added 144.5 mg (0.96 mmol) of L-tartaric acid. Another minimum portion of hot, dry acetone was added to dissolve all solids. The clear solution was refluxed for ten minutes, and then slowly cooled to 40 ^{0}C. The reaction mixture was seeded with 1-2 crystals of ENA 713 hta (Sandoz batch # 94910) and allowed to cool to room temperature and stirred for 12 hours. The crystals formed were collected by suction filtration, washed with cold, dry acetone and dried under high vacuum at 35 ^{0}C for 12 hours to give 262.8 mg (32.07 mCi, 84 % radiochemical yield) of [^{14}C] SDZ ENA 713 hta. A second portion of the free base, consisting of 166.5 mg (6.6×10^{-1} mmol, 33.0 mCi) was dissolved in the minimum amount of dry acetone in a dry box. To it was added 123.9 mg (8.25×10^{-1} mmol) of L-tartaric acid. A minimum amount of hot, dry acetone was added to dissolve all solids and the solution was refluxed for ten minutes, and then slowly cooled to 40 ^{0}C. The reaction mixture was seeded with 1-2 crystals of SDZ ENA 713 hta and allowed to cool to room temperature and stirred for 12 hours. The crystals formed were collected by suction filtration, washed with cold, dry acetone and dried under high vacuum at 35 ^{0}C for 12 hours to give 151.1 mg (22.07 mCi, 67 % radiochemical yield) of [^{14}C] SDZ ENA 713 hta. TLC (Et_2O:hexane:CH_3OH:xylene:HCO_2H 40:10:13:40:2)= R_f= 0.21. MH^+= 253 (isobutane DCI). IR (KBr pellet, cm^{-1})= 2971, 2860, 2817, 2767, 1717, 1608, 1589, 1399, 1232, 1164, 1088, 944, 700. ^{1}H-NMR, 500 MHz, δ ($CDCl_3$) = 7.51-7.59 (1H,

t, J=10 Hz); 7.40-7.46 (1H, d, J=10 Hz); 7.36 (1H, s); 7.21-7.30 (1H, d, J=10 Hz); 4.45-4.52 (1H, m); 4.44 (2H, s); 3.51-3.60 (1H, q, J=7.5 Hz); 3.39-3.46 (1H, q, J= 7.5 Hz); 2.96-3.15 (3H, bd, J=62 Hz); 2.78 (6H, s); 1.70-1.79 (3H, d, J=7.5 Hz); 1.15-1.34 (3H, dt, J=7.5 Hz, 62 Hz).

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20. It is interesting to note that compound **19** would not give a crystalline salt with (L)-tartaric acid while there was >6-7 % of the undesired (R)-enantiomer of the amine present in the mixture. This is the reason why direct purification and enantiomeric purification of the 9:1 (S):(R) mixture of **19** to enantiopure **4** could not be undertaken.

21. The % e.e. of **21** was determined by chiral-shift reagent ^{1}H-NMR with (R)-(+)-*tert*-butylphenylphosphinothioic acid and chiral-column HPLC (see experimental section).