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Research Article

The synthesis of (*S*)-di-*n*-propyl-(8-isoxazol-5-yl-1,2,3,4-tetrahydronaphthalen-2-yl)amine hydrochloride and its C-14-labeled isotopomer

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Summary

The partial ergoline LY228729 **(1)** which was a potent $5HT_{1A}$ agonist has been studied clinically. Somewhat later, a related analog, (*S*)-di-*n*-propyl-(8-isoxazol-5-yl-1,2,3,4-tetrahydronaphthalen-2-yl)amine **(2a)** which in addition to potent $5HT_{1A}$ agonist activity was a muscarinic antagonist, was chosen for clinical development for use in the treatment of irritable bowel syndrome. In the course of pre-clinical evaluation of **2a**, radiolabeled material was required for ADME studies. In this paper, we have discussed the preparation of **2a** and **2b** (the C-14-labeled isotopomer of **2a**). Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: $5HT_{1A}$; C-14; Sakakibara protocol

Introduction

Flaugh *et al.* first described the synthesis and biological evaluation of the partial ergoline LY228729 **(1)** which was a potent $5HT_{1A}$ agonist.[1] *R*-(+)-8-hydroxy-2-(di-*n*-propylamino)tetralin (8-HO-DPAT) **(3)** is a selective agonist for the $5HT_{1A}$ receptor.[1,2] In the search for more potent agonists, Schaus *et al.* synthesized **2a**,[3] altering the structural features of compounds derived from the earlier SAR around LY228729 **(1)** as well as some heterocyclic substituted partial ergolines (4a,b).[4] A decision was made to study **2a** clinically for use in the treatment of irritable bowel syndrome, and therefore a scalable and robust synthesis of **2a** was required. To facilitate further ADME studies in laboratory animals, C-14-labeled **2b** was also required. In preliminary drug metabolism and disposition (ADME) studies of **2a/2b** in rats, dogs and monkeys, Catlow

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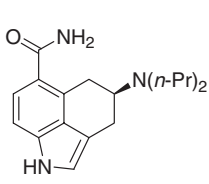
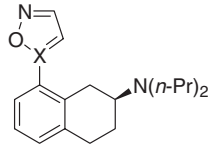
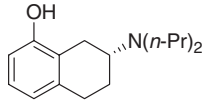
et al.[5] and Gillespie *et al.*[6] isolated and identified several metabolites. The most abundant circulating plasma scission of the isoxazole ring and subsequent loss of cyanide. In light of these findings, it was important to place the C-14 label in the 5-position of the isoxazole ring. A preliminary disclosure of the synthesis of both **2a** and **2b** has been published;[7] further details of the syntheses of both are reported herein.



1, LY227829



2a, X = ^{12}C
2b, X = ^{14}C



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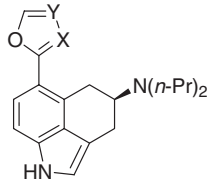
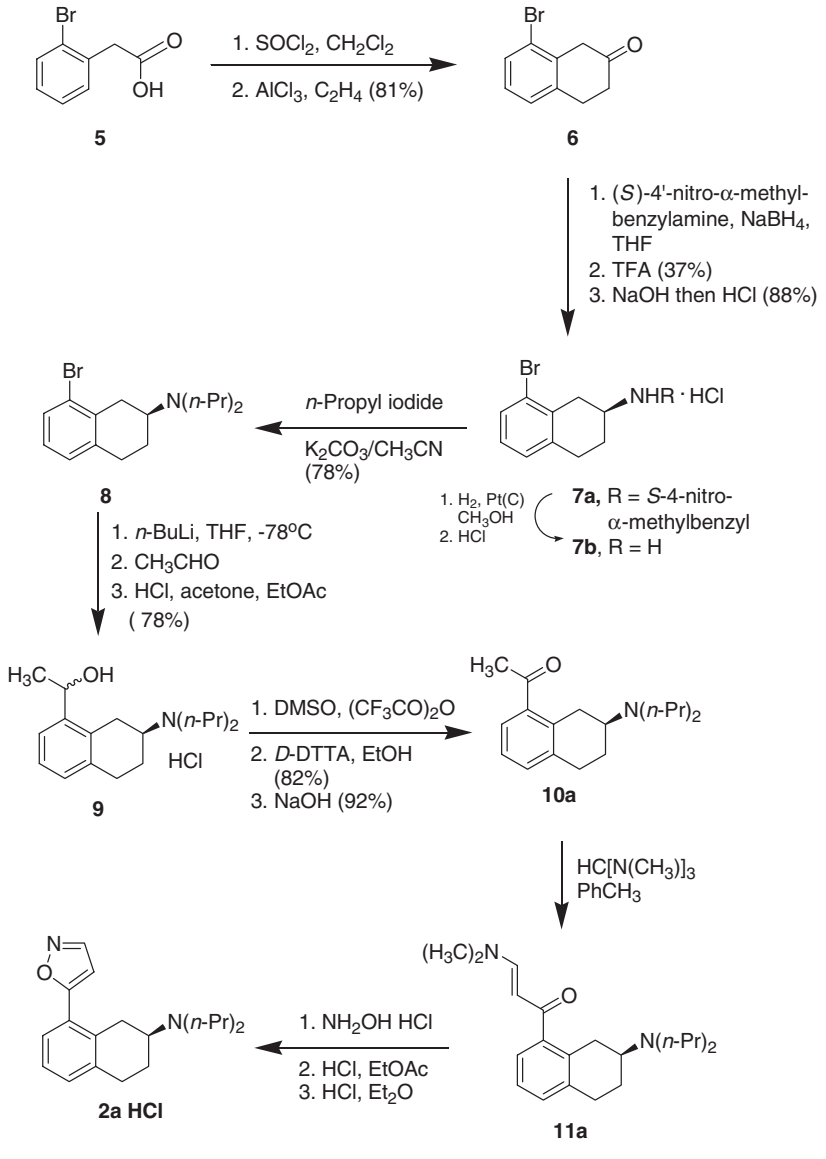


4a, X = N; Y = CH
4b, X = CH; Y = N

Discussion

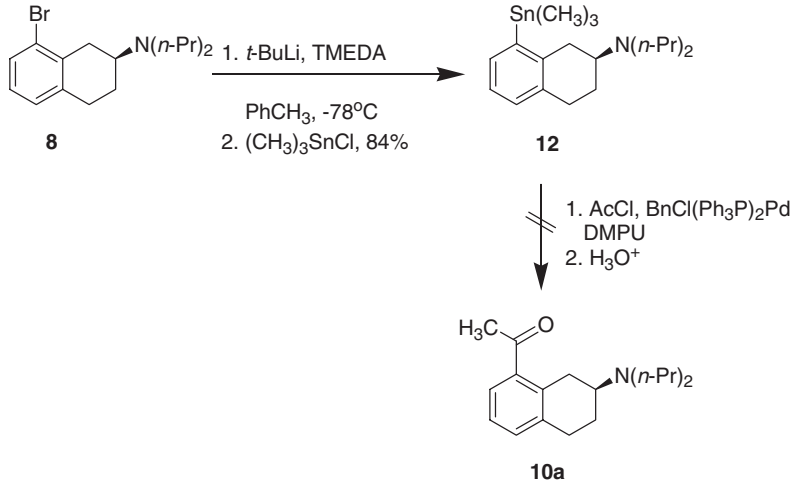
Reaction of 2-bromophenylacetic acid (5) with $SOCl_2/CH_2Cl_2$ yielded the corresponding acid chloride (Scheme 1). Reaction of the acid chloride with ethylene/$AlCl_3$ provided ketone **6** in 74% yield. Reductive amination of ketone **6** with (*S*)-4′-nitro-α-methylbenzylamine/$NaBH_4$ yielded **7a**, which was isolated as its HCl salt (33% overall). Hydrogenolysis of **7a** with H_2/Pt/CH_3OH yielded primary amine **7b** (87%), which was alkylated with *n*-propyl iodide/K_2CO_3/CH_3CN to yield **8** (78%). Reaction of **8** with *n*-BuLi/THF at −78°, followed by reaction with acetaldehyde yielded **9** as its HCl salt (78%). Swern oxidation of **9** with DMSO/trifluoroacetic anhydride, followed by salt formation with (+)-di-*p*-toluoyl-D-tartaric acid monohydrate (D-DTTA) and conversion to the free base with NaOH yielded ketone **10a** (82%), which was further reacted with *tris*-dimethylaminomethane/$PhCH_3$ to yield enamine **11a**. Reaction of enamine 11a with NH_2OH/HCl/HOAc yielded (*S*)-di-*n*-propyl-(8-isoxazol-5-yl-1,2,3,4-tetrahydronaphthalen-2-yl)amine **(2a)**. Reaction of **2a** with maleic acid/EtOAc yielded the maleate salt (86% yield from **10a**). Alternatively, reaction of **2a** with HCl/EtOAc yielded **2a** HCl.

Because of the instability and volatility of acetaldehyde-[1-^{14}C], an alternative route for the preparation of **2b** from **8** had to be used. In the initial route, it was planned to convert **8** to the corresponding trimethylstannane 12 and conduct a Stille coupling with acetyl chloride to yield **10a** (Scheme 2).[8] Reaction of **8** with *t*-BuLi/TMEDA/$PhCH_3$ at −78°C followed by reaction of the subsequent lithiated species with an excess of chlorotrimethylstannane yielded **12** in 84% yield. Unfortunately, reaction of **12** with AcCl/BnCl$(Ph_3P)_2$Pd in dimethylpropyleneurea (DMPU) was unsuccessful after several attempts.



Scheme 1.

Based on the earlier preparation of LY228729-[^{14}C], it was decided to use the Sakakibara protocol for the preparation of nitrile **13a,b** (Scheme 3).[9,10] Reaction of **8** with KCN in the presence of catalytic $NiBr_2(Ph_3P)_2/Ph_3P/Zn$ gave **13a** in 51% yield. Reaction of **8** with $KCN/K^{14}CN/CH_3CN$ in a like manner afforded C-14-labeled nitrile **13b** (84%). Treatment of **13a** and **13b** with $CH_3MgBr/PhCH_3$ followed by acidic work-up and chromatography yielded ketone **10a** (43%) and **10b** (65%). Further reaction of **10b** with *tris*-dimethylaminomethane/$PhCH_3$ yielded enamine **11b**. Reaction of enamine **11b**



Scheme 2.

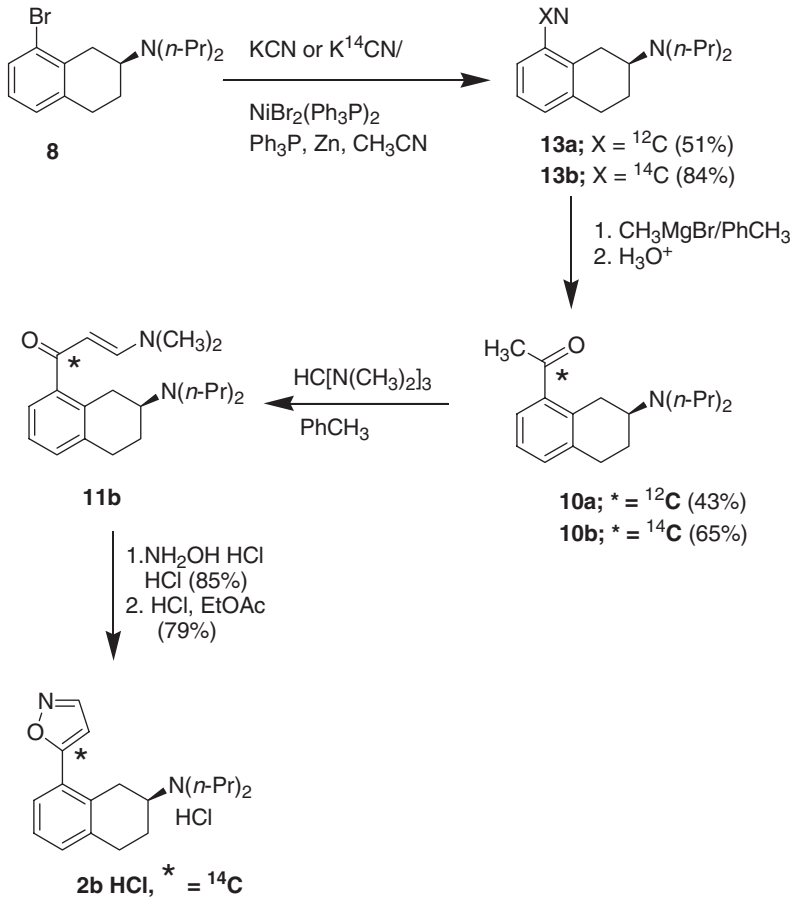
with NH_2OH/HCl/HOAc yielded (*S*)-di-*n*-propyl-(8-isoxazol-5-yl-[5-^{14}C]-1,2,3,4-tetra-hydronaphthalen-2-yl)amine **(2b)** which was further reacted with HCl/EtOAc to yield the HCl salt (67% yield from **10b**).

Results

(*S*)-di-*n*-propyl-(8-isoxazol-5-yl-1,2,3,4-tetrahydronaphthalen-2-yl)amine hydrochloride salt **(2a)** has been prepared using a novel method which is scalable. In addition, a concise method for the preparation of C-14-labeled (*S*)-di-*n*-propyl-(8-isoxazol-5-yl-1,2,3,4-tetrahydronaphthalen-2-yl)amine hydrochloride salt **(2b)** has been accomplished; a key intermediate from the non-labeled synthesis was used and the label was placed in a metabolically stable position. The synthesis of **2b** was accomplished in five steps in 37% overall yield from K^{14}CN. The radiochemical purity (RCP) was 99.3% by TLC and $\geqslant$98.5% by HPLC. The specific activity was 20.1 μCi/mg (6.7 mCi/mmol); the optical rotation ($[\alpha]_D$) was -43.02° ($c = 1.72$) at 25°C in CH_3OH. The ^{1}H-NMR Spectrum ($CDCl_3$) of **2b** was superimposable on that of **2a**; the ES-MS showed a $[M+H]^+$ ion at $m/z = 299$.

Experimental

NMR spectra were obtained on a General Electric QE-300 or a Varian 500 MHz nuclear magnetic resonance spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Mass spectra were recorded on a Nermag R30-10 triple stage quadrapole mass spectrometer (DCI), a VG Analytical VG-ZAB3F mass spectrometer (FAB), a Varian Associates MAT 731 mass spectrometer (FD) or a Waters Micromass



Scheme 3.

ZQ single quadropole mass spectrometer (ES-MS). Flash chromatography was performed on silica gel. RCP was assessed by HPLC with radiochemical detection. Thirty minute fractions were collected, diluted with scintillation fluid and counted on a Packard Scintillation Spectrometer. RCP was further assessed by TLC-autoradiography. The radioactivity was detected on Kodak X-ray film BB-5; the lanes of the TLC were cut, mixed with methanol and scintillation fluid and counted. Microanalyses were conducted in the Physical Chemistry Department of the Lilly Research Laboratories.

8-Bromo-3,4-dihydro-1H-naphthalen-2-one, 6

A 12 l flask was fitted with a mechanical stirrer, condenser, heating mantle, thermometer, nitrogen inlet and gas outlet connected to an aqueous NaOH solution scrubber. To the flask was added 2-bromophenylacetic acid (750 g,

3.5 mol) and CH_2Cl_2 (3.5 l). Neat thionyl chloride (305 ml, 4.2 mol) was added dropwise over 35 min at 20–25°C. The reaction was heated to reflux (41°C) for 18 h, at which time ^{1}H-NMR assay showed complete conversion of the acid to the acid chloride. The reaction mixture was allowed to cool to room temperature.

A 22 l flask containing CH_2Cl_2 (7.6 l) was cooled to 0–5°C under nitrogen. Aluminum chloride (535 g, 4 mol) was then added as a solid. The acid chloride solution from above was added and the mixture was stirred for 15 min. Ethylene gas (500 g, 17.8 mol) was added subsurface over 1 h 40 min keeping the temperature 10–18°C. The mixture was stirred for 90 min at 0–5°C and then added in a slow stream to 10 l of 0°C water (the addition is exothermic). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (1.5 l). The combined CH_2Cl_2 layers were washed with water (2×6 l), then with saturated $NaHCO_3$ (4 l) solution. The CH_2Cl_2 layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo* to a volume of approximately 4 l. Hexanes (8 l) were added to the resulting solution. Solvent was distilled from the solution at atmospheric pressure until the vapor temperature reached 66°C. The stirred solution was allowed to cool to room temperature overnight, which caused the product to precipitate. The solid was filtered, washed with hexanes (2×1 l), and dried under vacuum at 30°C to yield 8-bromo-2-tetralone (**6**, 499.2 g, 64% yield) of as a light yellow solid, melting point 76–79°C. The filtrate was concentrated to half volume under vacuum, filtered and the cake was washed with 2×1 l of hexanes. Vacuum drying as above gave additional **6** (133.6 g, 81% total yield) as a light yellow solid.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.47 (d, $J = 6$ Hz, 1H), 7.17 (d, $J = 6$ Hz, 1H), 7.07 (m, 1H), 3.67 (s, 2H), 3.08 (t, $J = 7$ Hz, 2H), 2.58 (t, $J = 7$ Hz, 2H); IR (KBr) 1706 cm^{-1}.

Analysis calculated for $C_{10}H_9BrO$: C, 53.36; H, 4.03. Found: C, 53.42; H, 3.96.

*(2-S-8-bromo-1,2,3,4-tetrahydronaphthalen-2-nyl)-[1-R-(4-nitrophenyl)ethyl] amine, trifluoroacetate, **7a** TFA salt*

(*R*)-4-nitrophenethylamine hydrochloride (466 g, 2.3 mol) was slurried in CH_2Cl_2 (2 l). With vigorous stirring, NaOH (2 N, 2 l) was added. After 30 min, the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×2 l). The combined CH_2Cl_2 layers were then washed with 1.5 l of brine and the layers separated.

To the amine solution in a 22 l 3-neck flask was added 8-bromo-2-tetralone (5, 451.7 g, 2 mol). A Dean-Stark trap was attached to the flask and 36 ml of water was removed via azeotropic distillation over 18 h (complete conversion of the 5 to the enamine was confirmed by ^{1}H-NMR analysis of a concentrated sample of the reaction mixture). The solution was concentrated by distillation

of 31 of CH_2Cl_2 at atmospheric pressure. Dry THF (4.5 l) was added and the distillation continued until the vapor temperature reached 65°C. The reaction mixture was cooled to 5°C and solid NaBH4 (114 g, 3 mol) was added. Acetic acid (600 ml, 10 mol) in 1 l of THF was added dropwise over 95 min, keeping the temperature between 5 and 15°C (hydrogen gas was vigorously evolved during the addition). The reaction mixture was heated to reflux for 2 h, cooled to 25°C, and allowed to stand for 30 min. The mixture was filtered through celite (to remove borate salts) and the filter cake washed with 1.5 l of THF. To the stirred filtrate, CF_3CO_2H (305 ml, 3.9 mol) was slowly added and the mixture allowed to stir overnight while the product salts precipitated. The mixture was filtered and the cake washed with 2×750 ml THF. The filter cake was vacuum dried at 30°C (18 h) gave 619.2 g of a 64:36 mixture of diastereomers. The solid was stirred in 6.2 l of THF and the mixture was heated to reflux for 1 h. The mixture is heterogeneous at reflux. The slurry was cooled to 25°C over 4 h and filtered. The filter cake washed with THF (2×250 ml) and vacuum dried at 30°C to yield **7a** TFA salt (360.1 g, 37%) as 97:3 mixture of diastereomers (by HPLC). This material (**7a** TFA salt) was used in the subsequent step.

Further purified **7a** TFA salt (>99:1 ratio of diastereomers, melting point 233–235°C) was prepared by stirring 1 g of the product in 10 ml of hot THF, and filtering, as described above. $[\alpha]_D = -45.4^\circ$ ($c = 1$, DMF); ^{1}H-NMR (DMSO/d_6, 300 MHz) δ 1.66 (d, $J = 7$ Hz, 3H, CH_3), 1.75 (m, 1H, 3α-H), 2.30 (m, 1H, 3β-H), 2.68 (m, 2H, 4-H), 2.88 (m, 1H, 1α-H), 3.10 (dd, $J = 16$, 5 Hz, 1H, 2α-H), 3.23 (m, 1H, 1β-H), 4.90 (m, 1H, MeCH), 7.10 (m, 1H, 6-H), 7.41 (m, 1H, 5-H), 7.93 ((d, $J = 9$ Hz, 2H, 2′,6′-H), 8.31 (d, $J = 9$ Hz, 2H, 3′-5′-H), 9.60 (bs, 1H, NH) and 10.6 (bs, 1H, NH); ^{13}C-NMR (DMSO/d_6, 125 MHz) δ 20.2, 24.5, 28, 33.6, 52.3, 54, 117.5 (q, $J = 297$ Hz, $\underline{C}F_3$), 124.6, 128.4, 128.5, 129.7, 130.4, 132.6, 138.6, 145, 148.2, 159.3 (q, $J = 32$ Hz, $CF_3\underline{C}O$); IR (KBr): 3034, 2851, 2475, 1657, 1524, 1492, 1442, 1350, 1204, 1171, 1140 cm^{-1}.

Analysis calculated for $C_{20}H_{20}BrF_3N_2O_4$: C, 49.10; H, 4.12; N, 5.73. Found: C, 49.38; H, 4.25; N, 5.85.

*(2-S-8-bromo-1,2,3,4-tetrahydronaphthalen-2-nyl)-[1-R-(4-nitrophenyl)ethyl] amine, hydrochloride, **7a** HCl salt*

Sodium hydroxide (50% aqueous, 716 ml), water (610 ml), and **7a** TFA salt (1287.9 g, 2.63 mol), and EtOAc (8 l) were added sequentially to a 22 l flask. The mixture was stirred 30 min under nitrogen and the layers were separated. The lower aqueous layer was extracted with EtOAc (1 l). HCl (12 N, 241 ml, 2.9 mol, 1.1 equivalent) was added to the combined EtOAc layers over 30 min. A white precipitate formed immediately upon addition of the acid. The mixture was stirred for 6 h under nitrogen, filtered, and the solid was washed with EtOAc (1.2 l). The solid was dried at 30°C under vacuum for 18 h to yield

7a HCl salt 960.4 g (88% yield) as a white solid, mp 280–283°C. $[\alpha]_D = -38.1°$ ($c = 1$, DMF); ^{1}H-NMR (DMSO/d_6, 300 MHz) δ 1.71 (d, $J = 7$ Hz, 3H, CH_3), 1.90 (m, 1H, 3α-H), 2.33 (m, 2H, 2α-H, 3β-H), 2.65 (m, 1H, 4-α-H), 2.87 (m, 2H, 4-β-H, 1-α-H), 3.14 (m, 1H, 1β-H), 4.87 (m, 1H, MeCH), 7.07 (m, 2H, 5,6-H), 7.41 (m, 1H, 7-H), 8.04 (d, $J = 9$ Hz, 2H, 2,6-H), 8.3 (d, $J = 9$ Hz, 2H, 3,5-H), 9.90 (bs, 1H, NH), 10.6 (bs, 1H, NH); ^{13}C-NMR (DMSO/d_6, 125 MHz) δ 20.4, 24.1, 28, 33.5, 52.2, 53.9, 124.5, 128.3, 128.5, 130.3, 132.7, 138.6, 145.2, 148.1.

Analysis calculated for $C_{18}H_{19}BrClN_2O_2$: C, 52.64; H, 4.66; N, 7.06; O, 7.77. Found: C, 52.38; H, 4.95; N, 7.08; O, 7.79.

(S)-8-bromo-1,2,3,4-tetrahydro-2-naphthaleneamine hydrochloride, 7b HCl

Methanol (500 ml) was to added to a mixture of **7a** HCl salt (50 g) and 5% Pt/C, sulfided, (10 g, 50 wt% water) under nitrogen. The slurry was added to a 1 l autoclave. The autoclave was sealed, evacuated and then backfilled with hydrogen gas. The reaction mixture was stirred under 5 psi hydrogen until the TLC (1:1 hexane:EtOAc) showed the starting material was consumed (2.25 h). The reaction mixture was filtered and the catalyst was washed with methanol. The resulting solution was heated to reflux (ca. 65°C) under nitrogen for 3 h. After cooling, the methanol was removed under vacuum to give a yellow solid/foam. The foam was stirred in EtOAc (350 ml) for 1 h and filtered. The solid was washed with EtOAc, and vacuum dried to yield **7b** HCl salt 27.8 g (87% yield) as a white solid. $[\alpha]_D = -51.5$ ($c = 1$, CH_3OH); ^{1}H-NMR (DMSO/d_6, 300 MHz) δ 1.77 (m, 1H, 3α-H), 2.15 (m, 1H, 3β-H), 2.68 (m, 1H, 2α-H), 2.87 (m, 2H, 4α-H, 1α-H), 3.19 (dd, $J = 17$, 5.6 Hz, 1H, 4β-H), 3.46 (m, 1H, 1β-H), 7.10 (m, 2H, 5,6-H), 7.44 (d, $J = 7.6$ Hz, 1H, 7-H), 8.53 (bs, 3H, NH); ^{13}C-NMR (DMSO/d_6, 125 MHz) δ 27.5, 28.9, 35.2, 48.2, 125.9, 129.2, 129.6, 131.2, 133.9, 139.6.

Analysis calculated for $C_{10}H_{13}BrClN$: C, 45.74; H, 4.99; N, 5.33. Found: C, 46.01; H, 4.95; N, 5.58.

(S)-(8-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)di-n-propylamine, 8

(*S*)-8-bromo-1,2,3,4-tetrahydro-2-naphthaleneamine hydrochloride (**7a** HCl salt, 4 g, 15.2 mmol), *n*-propyl iodide (5.9 ml, 61 mmol), and K_2CO_3 (12.6 g, 91 mmol) were combined with 45 ml of MeCN in a 100 ml flask with stirring bar and condenser. The mixture was heated to 80°C, under nitrogen, for 16 h. The cooled reaction mixture was filtered and the filtrate was concentrated to dryness under vacuum. The residue was combined with CH_2Cl_2 and H_2O (50 ml:50 ml). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (20 ml). The combined organic layers were washed with 50 ml each of H_2O and saturated brine solution. The organic layer was dried

(Na_2SO_4), filtered, and concentrated to give **8** (4.48 g) an off-white foam, containing 9% of the quaternary ammonium salt by-product. The foam was stirred in 50 ml of Et_2O for 10 min and then filtered. The filtrate was concentrated *in vacuo* to provide **8** (3.69 g, 78%) as a light yellow oil (HPLC assay showed no quaternary ammonium salt present). This oil was used in subsequent steps.

The product could be isolated as a colorless oil by Kugelrohr distillation at 150°C (0.5 mm Hg); $[\alpha]_D = -53.3°$ ($c = 1$, CH_3OH); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.96 (t, $J = 7.2$ Hz, 3H, CH_3), 1.53 (m, 4H, CH_2Me), 1.60 (m, 1H, 3α-H), 2.54 (m, 4H, CH_2Et), 2.60 (m, 2H, 3β-H and 2α-H), 2.90 and 3.01(m, 4H, 1-H and 4-H), 6.30 (t, $J = 8$ Hz, 1H, 6-H), 7.05 (d, $J = 8$ Hz, 1H, 5-H), 7.41 (d, $J = 8$ Hz, 1H, 7-H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 11.9 (CH_3), 22.4 (CH_2), 25.6 (CH_2), 30.1 (CH_2), 32.9 (CH_2), 52.7 (CH_2), 57.1 (C–H), 126.1, 126.7 (C–H), 127.7 (C–H), 129.7 (C–H), 136.3, 139.3; IR ($CHCl_3$) 2961, 2935, 2874, 1611, 1559, 1519, 1458, 1440, 1380, 1077 cm^{-1}; MS (FD) *m/e* 309, 311.

*(S)-(8-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)di-n-propylamine hydrochloride, **8** HCl*

Crude **8** (1.43 g) was dissolved EtOAc (7 ml). Concentrated HCl (12 N, 0.5 ml) was added dropwise to form a precipitate. The stirred slurry was cooled in an ice bath and the product was filtered, washed with 2 ml of EtOAc, and vacuum-dried to **8** HCl salt (1.50 g) as an off-white solid, melting point 184–188°C; $[\alpha]_D = -59.8°$ ($c = 1$, CH_3OH).

Analysis calculated for $C_{16}H_{25}BrClN$: C, 55.42; H, 7.27; N, 4.04. Found: C, 55.65; H, 7.39; N, 4.05.

*S-1-(7-di-n-propylamino-5,6,7,8-tetrahydronaphthalen-1-yl)ethanol hydrochloride, **9** HCl*

(*S*)-(8-Bromo-1,2,3,4-tetrahydronaphthalen-2-yl)di-*n*-propylamine (**8**, 25.8 g, 83 mmol) was dissolved in dry THF (180 ml) and the solution was cooled to −78°C under nitrogen flow. A solution of *n*-BuLi (1.6 M in hexane, 78 ml, 125 mmol) was added dropwise over 10 min. The brown solution was stirred for 10 min at −78°C. Acetaldehyde (14 ml, 250 mmol) was added dropwise over 15 min at −62 to −69°C. The clear, amber solution was allowed to warm to 10°C and 75 ml of water was added dropwise, causing the reaction temperature to increase to 21°C. The layers were separated and the aqueous layer was extracted with 75 ml of methyl *t*-butyl ether. The combined organic layers were washed with 100 ml of saturated brine solution and then dried (anhydrous Na_2SO_4). The solvent was removed *in vacuo* to provide 25.3 g of amber oil. The oil was dissolved in 70:30 EtOAc:acetone (175 ml). To this solution was added HCl (12 N, 7 ml, 84 mmol). Crystals formed and the temperature increased to 32°C. The slurry was cooled to 2°C in an ice bath and

stirred for 1.5 h. The solid was filtered, washed with 80 ml of cold solvent, and vacuum dried at 50°C to afford 9 (20.25 g, 78%) as an off-white solid. An ^{1}H-NMR assay showed this compound to be a 1:1 mixture of diastereomers. $[\alpha]_D = -55^\circ$ ($c = 1$, CH_3OH); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.05 (overlapping triplets, 6H, CH_2CH_3), 1.50 (d, $J = 6.6$, 1.5H, $CHCH_3$), 1.55 (d, $J = 6.6$ Hz, 1.5H, $CHCH_3$), 1.85–2.10 (m, 5H, CH_2Me and 3α-H), 2.52 (m, 1H, 3β-H), 2.9–3.16 (m, 5H, CH_2Et and 2α-H), 3.24 (d, $J = 11$ Hz, 0.5H), 3.42 (dd, $J = 15.4$, 4.4 Hz, 0.5H), 3.6–3.7, m, 1.5H), 5.12 (overlapping quartets, 1H), 7.04 (d, $J = 7.5$ Hz, 1H, 6-H), 7.20 (m, 1H, 5-H), δ 7.36 (overlapping doublets, 1H, 7-H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 11, 11.5, 18.04, 18.11, 18.24, 18.34, 23.5, 23.6, 23.65, 23.7, 25.9, 26, 29, 52, 52.4, 52.5, 59.9, 60.2, 65.4, 65.5, 123.5, 123.6, 126.7, 126.8, 127.7, 129.6, 130, 134.7, 134.9, 143.7, 144.

Analysis calculated for $C_{18}H_{30}NOCl$: C, 69.25; H, 9.69; N, 4.49; Cl, 11.36. Found: C, 69.11; H, 9.49; N, 4.22; Cl, 11.57.

*S-1-(7-di-n-propylamino-5,6,7,8-tetrahydronaphthalen-1-yl)ethanone di-p-toluoyl-*D*-tartaric acid salt, 10a* D*-DTTA salt (Method A)*

Dry DMSO (11 ml, 12.1 g, 155 mmol) and CH_2Cl_2 (100 ml, dried over 4A sieves) were combined in a 500 ml flask with a mechanical stirrer. The solution was cooled to −72°C under nitrogen. Trifluoroacetic anhydride (18.1 ml, 26.9 g, 128 mmol) was added dropwise over 10 min, keeping the temperature below −68°C. A white precipitate was formed. The reaction mixture was stirred 20 min at −72°C. A slurry of (*S*-1-(7-di-*n*-propylamino-5,6,7,8-tetrahydronaphthalen-1-yl)ethanol hydrochloride (**9** HCl, 10 g, 32 mmol) in CH_2Cl_2 (130 ml) was added to the reaction mixture over 5 min while maintaining the temperature below −61°C. The resulting mixture was stirred at −72°C for 45 min. Triethylamine (31 ml, 22.5 g, 222 mmol) was added to the reaction mixture at −72 to −67°C. The reaction mixture was allowed to warm to 22°C over 50 min and then quenched with NaOH (60 ml × 2 N). The mixture was stirred for 1 h and the layers were separated. The organic layer was extracted with NaOH (2 × 40 ml) and then concentrated under vacuum to give an oil. The oil was combined with heptane (130 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude ketone as a yellow oil. The oil was dissolved in EtOH (40 ml) and the solution was added to a 45°C solution of (+)-di-*p*-toluoyl-D-tartaric acid monohydrate (13 g, 32 mmol) in EtOH (60 ml). The solution was allowed to cool to 22°C and stirred for 17 h. The precipitate was filtered, washed with EtOH and vacuum dried (40°C, 24 h) to provide **10a** D-DTTA salt (17.29 g, 82% yield) as a white solid, melting point 143–144°C; $[\alpha]_D = 24.7^\circ$ ($c = 1$, CH_3OH); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.94 (t, $J = 7$ Hz, 6H, CH_3), 1.83 (m, 5H, CH_2Me and 3α-H), 2.37 (s, 6H, $ArCH_3$), 2.48 (m, 1H, 3β-H), 2.63 (s, 3H, CH_3CO-H), 2.83 (m, 1H, 4α-H), 2.95 (m, 2H), 3.06 (m, 1H), 3.12 (m, 1H), 3.17 (d, $J = 12.1$ Hz, 1H), 3.20 (d, $J = 12.1$ Hz,

1H), 3.28 (dd, $J = 17, 3.9$ Hz, 1H, 4β-H), 3.72 (m, 1H, 2α-H), 5.89 (s, 2H, 2″,3″-H), 7.15 (d, $J = 8.2$ Hz, 4H, 3′,5′-H), 7.28 (m, 2H, 5,6-H), 7.66 (dd, $J = 7.1$, 1.6 Hz, 1 H, 7-H), 8 (d, $J = 8.2$ Hz, 4H, 2′,6′-H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 10.4 (CH_3), 16.9 (CH_2), 20.8 (CH_3), 23.6 (CH_2), 23.6 (CH_2), 28.2 (CH_2), 28.8 (CH_3), 58.6 (C–H), 71.3, 126.3 (C–H), 71.3 (C–H), 127.3 (C–H), 128 (C–H), 129.2 (C–H), 131.7 (C–H), 132.1, 136, 136.5, 142.6 (C–H), 164.7 (carbonyl), 169.3 (carbonyl), 202 (ketone carbonyl); IR (KBr) 2977, 2600, 1718, 1680, 1611, 1108 cm^{-1}.

Analysis calculated for $C_{38}H_{45}NO_9$: C, 69.18; H, 6.87; N, 2.12. Found: C, 68.88; H, 7; N, 2.06.

S-1-(7-di-n-propylamino-5,6,7,8-tetrahydronaphthalen-1-yl)ethanone, 10a (Method A)

The above salt (15 g) was dissolved in CH_2Cl_2 (150 ml) and NaOH (1 N × 150 ml) was added. The mixture was stirred for 30 min and the layers were separated. The aqueous layer was extracted with additional CH_2Cl_2 (150 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to yield **10a** (5.8 g, 92% recovery) as a light yellow oil; $[\alpha]_D = -49^\circ$ ($c = 1$, CH_3OH); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, $J = 7$ Hz, 6H, CH_3), 1.44 (m, 4H, CH_2Me), 1.60 (m, 1H, 3α-H), 1.98 (m, 1H, 3β-H), 2.45 (m, 4H, CH_2Et), 2.55 (s, 3H, CH_3CO), 2.90 (m, 4H, 1α-H, 2α-H and 4$\alpha\beta$-H), 3.01 (m, 1H, 1β-H), 7.15 (m, 1H, 6-H), 7.28 (m, 1H, 5-H), 7.42 (dd, $J = 7.1$, 1.7 Hz, 1H, 7-H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 11.9 (CH_3), 22.4 (CH_3), 25.6 (CH_2), 30.1 (CH_2), 30.23 (CH_2), 30.57 (CH_2), 52.7 (CH_2), 56.9 (C–H), 125.1 (C–H), 126.3 (C–H), 131.9, 136.4, 138.2 and 139 (C–H), 202.7 (ketone carbonyl); IR ($CHCl_3$) 2961, 2874, 1684, 1451, 1358, 1263 cm^{-1}. MS (FD):$[M+H]^+$, $m/z = 274$.

Analysis calculated for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12. Found: C, 78.81; H, 9.78; N, 5.38.

S-3-dimethylamino-1-(7-di-n-propylamino-5,6,7,8-tetrahydronaphthalen-1-yl)-propenone, 11a

A toluene solution (25 ml) of **10a** (3 g, 11 mmol) and *tris*-dimethylamino-methane (3.20 g, 22 mmol) was stirred at 100°C under nitrogen. After 5.5 h, ^{1}H-NMR showed an 88:12 ratio of enamine:ketone. Heating was continued for an additional 17 h; HPLC (see below) showed no remaining ketone **10a**. The solvent was removed by evaporation to yield **11a** (4.15 g, >100%) as an amber oil. This material was used without further purification.

HPLC conditions: Zorbax SB Phenyl column (4.6 × 250 mm) eluted with Acetonitrile/0.1% TFA at 1 ml/min (column temperature 45°C, UV detection at 220 nm). This HPLC method was used for the previous steps as well.

(S)-di-n-propyl-(1,2,3,4-tetrahydronaphthalen-2-yl)amine ***(2a)***

A HCl solution (30 ml, 1 N) of **11a** (4.15 g, 11 mmol) was treated with hydroxylamine HCl (1.53 g, 22 mmol) and then stirred at room temperature. After 7 h, HPLC (see above) showed 2.5% of the enamine **11a** remained. After 8 h, the reaction mixture was chilled in an ice bath, diluted with EtOAc (30 ml) and made basic by the addition of NaOH (30 ml, 2 N). The aqueous layer was re-extracted with EtOAc (30 ml). The combined EtOAc extracts were washed with brine, dried (anhydrous Na_2SO_4) and concentrated *in vacuo* to yield **2a** (3.11 g); HPLC (see above) showed the material to be 96.6% pure. This material was re-dissolved in Et_2O (30 ml) and treated with 1 equivalent of HCl/Et_2O (10.4 ml, 10.4 mmol) and a gummy solid formed. Ethyl acetate (10 ml) was added and the mixture was vigorously stirred for 1 h. The white solid was collected by filtration, washed with 4:1 Et_2O/EtOAc (2 × 5 ml) and dried. The resulting solid was hygroscopic; the solid was suspended in EtOAc (30 ml), heated to reflux, cooled to room temperature and filtered. The resulting white solid was washed with EtOAc (3 × 6 ml) and dried *in vacuo* to yield **2a** HCl (2.65 g, 76%); m.p. 153–155°C; IR (KBr) 2964, 2416, 1599, 1332, 1196 and 801 cm^{-1}; FD-MS: M+, $m/z = 298$; UV (EtOH): 249 ($\varepsilon = 18\,978$) and 214 ($\varepsilon = 25\,835$) nm; $[\alpha]_D = -45.8°$ in CH_3OH (10 mg/ml); ^{1}H-NMR ($CDCl_3$) δ 0.97 (t, $J = 7.34$ Hz, 3H, CH_3), 1.04 (t, $J = 7.34$ Hz, 3H, CH_3), 2 (m, 5H, CH_2Me and 3α-H), 2.68 (m, 1H, 3β-H), 3.02 (m, 5H, CH_2Et, 4α-H and 4β-H), 3.28 (dq, $J = 1.1$ and 5.16, 1H, 1α-H), 3.42 (dq, $J = 1.1$ and 5.16, 1H, 1β-H), 3.63 (m, 1H, 2α-H), 6.60 (s, 1-H, 4-isoxazole-H), 7.21 (m, 2H, H-5 and H-6), 7.53 (d, $J = 7.39$ Hz, 1H, 7-H), 8.34 (s, 1H, 3-isoxazole-H).

Analysis calculated for: $C_{17}H_{27}N_2OCl$: C, 67.97; H, 7.97; N, 8.25. Found: C, 68.15; H, 8.13; N, 8.37.

S-di-n-propyl-(8-trimethylstannyl-1,2,3,4-tetrahydronaphthalen-2-yl)amine, 12

A toluene solution (10 ml) of **8** (0.310 g, 1 mmol) and TDEMA (0.2 ml, 1.3 eq., 1.3 mmol) under argon was chilled to −78°C and treated with *t*-BuLi (1.6 M, 6.25 ml, 10 mmol). The resulting yellow solution was stirred for 10–20 min. A toluene solution (5 ml) of chlorotrimethylstannane (1.99 g, 10 mmol) was added dropwise. Stirring at −78°C was continued for 2 h and then the reaction mixture was allowed to slowly warm to room temperature. The reaction was then quenched by the careful addition of water (15 ml) and extracted with Et_2O (35 ml). The organic solution was washed with water (3 × 15 ml), dried (anhydrous $MgSO_4$) and concentrated *in vacuo* to yield **12** (0.331 g, 84%). FD-MS: M+, $m/z = 395$.

S-7-di-n-propyl-5,6,7,8-tetrahydronaphthalene-1-carbonitrile, 13a

An acetonitrile solution (25 ml) of *S*-(8-bromo-1,2,3,4-tetrahydronaphthalen-1-yl)-di-*n*-propylamine (**8**, 1.43 g, 4.61 mmol) was mixed with potassium

cyanide (0.449 g, 6.91 mmol), nickel (II) bromide-*bis*-triphenylphosphine (0.341 g, 0.461 mmol), zinc (0.092 g, 1.38 mga), and triphenylphosphine (0.240 g, 0.922 mmol). The resulting mixture was stirred under argon at reflux overnight. The mixture was filtered and concentrated. The residual oil was re-dissolved in Et_2O, washed with water and concentrated *in vacuo*. The residue was purified by chromatography, eluting with pentane/Et_2O with 1% Et_3N (3:1). Fractions 21–40 were combined and concentrated to yield **13a** (51%). FD-MS: $[M+H]^+$, $m/z = 257$. ^{1}H-NMR ($CDCl_3$) δ 0.893 (t, $J = 11.3$ Hz, 6H, CH_3), 1.45 (tq, $J = 11.3$, 7.3 Hz, 4H, CH_2Me), 1.65 (m, 1H, 3α-H), 2.01 (m, 1H, 3β-H), 2.51 (t, $J = 7.3$ Hz, 4H, CH_2Et), 2.72–3.08 (m, 4H, 2α-H, 4α,β-H, 1α-H), 3.15 (dd, $J = 2.91$, 5.72 Hz, 1β-H), 7.16 (dd, $J = 4.62$, 7.66, 1H, 6-H), 7.29 (d, $J = 4.62$, 1H, 7-H), 7.45 (d, $J = 7.47$, 1H, 5-H).

S-1-(7-di-n-propylamino-5,6,7,8-tetrahydronaphthalen-1-yl)ethanone, ***10a*** *(Method B)*

A THF solution (10 ml) of **13a** (0.256 g, 1 mmol) was cooled to −10°C under argon and treated with methylmagnesium bromide (3 M in Et_2O, 3.3 ml, 10 mmol). The mixture was allowed to warm to room temperature and then refluxed overnight. After cooling to room temperature, the excess Grignard reagent was quenched by the dropwise addition of EtOAc (10 ml). The resulting mixture was diluted with 50 ml of Et_2O and extracted with HCl (1 N). The Et_2O layer was washed with water. The combined aqueous layer was made basic (to pH 10) by the addition of NaOH (1 N) and then extracted with Et_2O (4 × 35 ml). The combined Et_2O extracts were dried (anhydrous $MgSO_4$) and concentrated *in vacuo* (0.307 g). The resulting oil was purified by chromatography, eluting with $CH_2Cl_2/CH_3OH/NH_4OH$ (150:10:1). Fractions 3–6 were combined and concentrated to afford **10a** (0.117 g, 43%). This material was identical in all respects to **10a** prepared by Method A.

S-7-di-n-propyl-5,6,7,8-tetrahydronaphthalene-1-carbonitrile-[1-^{14}C], 13b

In a flame-dried flask, filled with argon, *S*-(8-bromo-1,2,3,4-tetrahydronaphthalen-1-yl)-di-*n*-propylamine (**8**, 1.43 g, 4.61 mmol) was mixed with potassium cyanide-[^{14}C] (100 mCi, 55 mCi/mmol, 1.82 mmol), potassium cyanide (0.331 g, 5.09 mmol), nickel (II) bromide-*bis*-triphenylphosphine (0.341 g, 0.461 mmol), zinc (0.092 g, 1.38 mga), and triphenylphosphine (0.240 g, 0.922 mmol). The mixture was diluted with acetonitrile (25 ml) and the resulting emerald green solution was stirred under reflux overnight. TLC (pentane/Et_2O with 1% Et_3N, 3:1) showed a radioactive spot corresponding to **13a** and a trace of **8**. Stirring was continued for an additional 6 h and the mixture was allowed to cool to room temperature (at this point, **8** was nearly completely gone; however, there was a small amount of radioactivity at the

origin). The mixture was filtered through talc and the filtrate was concentrated *in vacuo*. The residual oil was chromatographed, eluting with pentane/Et_2O with 1% Et_3N (3:1). Fractions 39–100 were combined and concentrated *in vacuo* to yield **13b** (0.992 g, 84%). ES-MS: $[M+H]^+$, $m/z = 259$.

S-1-(7-di-n-propylamino-5,6,7,8-tetrahydronaphthalen-1-yl)ethanone-[carbonyl-^{14}C], 10b

A toluene solution of **13b** (0.992 g, 3.87 mmol) under argon was chilled to -10°C and treated dropwise with methylmagnesium bromide (3 M in Et_2O, 12.9 ml, 38.7 mmol). The ice bath was removed and the resulting mixture was stirred at reflux overnight. The mixture was then chilled to -10°C and EtOAc was slowly added to destroy the excess Grignard. The cold solution was acidified to pH 2 with HCl (1 N, 45 ml) and the organic layer was washed with water (50 ml). The combined aqueous layers were washed with Et_2O (50 ml) and then made basic to pH 10 (1 N NaOH) and extracted with Et_2O (2×75 ml). The Et_2O extracts were washed with water (2×50 ml), dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. TLC (CH_2Cl_2/CH_3OH/NH_4OH, 150:10:1) showed one major spot co-eluting with **10a** as well as two smaller spots, but no unreacted **13b**. The crude aminoketone was purified by chromatography, eluting with CH_2Cl_2/CH_3OH/NH_4OH (150:10:1). Fractions 13–30 were combined and concentrated *in vacuo* to yield **10b** (0.684 g, 65%). This material co-elutes with authentic **10a** on TLC (CH_2Cl_2/CH_3OH/NH_4OH, 150:10:1). The ^{1}H-NMR ($CDCl_3$) is superimposable on that of **10a**. ES-MS: $[M+H]^+$, $m/z = 276$.

S-3-dimethylamino-1-(7-di-n-propylamino-5,6,7,8-tetrahydronaphthalen-1-yl)-propenone-[carbonyl-^{14}C], 11b

A toluene solution (20 ml) of aminoketone **10b** (0.684 g, 2.50 mmol) and *tris*-dimethylaminomethane (0.726 g, 5 mmol) was stirred at 100°C (under argon) overnight. The mixture was allowed to cool to room temperature and the toluene was removed *in vacuo* to yield **11b**. ES-MS: $[M+H]^+$, $m/z = 331$. This material will be used in the next step on an 'as-is' basis.

*(S)-di-n-propyl-[8-(isoxazol-5-yl-[5-^{14}C])-1,2,3,4-tetrahydronaphthalen-2-yl) amine **(2b)***

A mixture of enaminoketone **11b** (2.50 mmol) and hydroxylamine HCl (0.345 g, 5 mmol) was dissolved in HCl (1 N, 7.5 ml) and stirred for 8 h. The mixture was then chilled in an ice bath and diluted with EtOAc (15 ml); NaOH (2 N, 7.5 ml) was added dropwise. The aqueous layer was extracted twice more with EtOAc (25 ml). The combined organic extracts were washed with water (3×10 ml), dried (anhydrous Na_2SO_4) and concentrated. TLC (CH_2Cl_2/CH_3OH/NH_4OH, 150:10:1) showed one major spot co-eluting with **2a** as well

as a small amount of unreacted **11b**. The crude material was purified by chromatography, eluting with TLC ($CH_2Cl_2/CH_3OH/NH_4OH$ (150:10:1); fractions 11–20 were combined and concentrated *in vacuo* to yield **2b** (0.635 g, 85%).

*(S)-di-n-propyl-[8-(isoxazol-5-yl-[5-^{14}C])-1,2,3,4-tetrahydronaphthalen-2-yl)amine HCl, (**2b** HCl salt)*

A 0.53 M solution of anhydrous HCl in EtOAc (4.23 ml, 2.24 mmol) was diluted with EtOAc (1 ml) and an EtOAc solution (3 ml) of **2b** (0.635 g, 2.13 mmol) was added dropwise. The mixture was stirred and seeded with a few crystals of **2a** whereupon the formation of a white crystalline solid began. Stirring at room temperature was continued for 2 h. The white solid was collected by filtration, washed with fresh EtOAc (2×5 ml) and dried to yield **2b** HCl salt (0.561 g, 79%); specific activity 50.56 μCi/mg. This material co-eluted with authentic **2a** on TLC ($CH_2Cl_2/CH_3OH/NH_4OH$, 150:10:1).

A mixture of 2b HCl (0.370 g, specific activity 50.56 μCi/mg) and 2a HCl (0.557 g) was mixed and stirred in EtOAc/EtOH (95.5 ml/14 ml) under vigorous reflux. Additional EtOH was added dropwise until all of the material dissolved. Upon cooling to room temperature, no crystals had formed, so the solution was concentrated to about 37 ml and diluted with EtOAc (10 ml) and stirred for 1 h. After crystallization had started, the mixture was cooled to 0°C and stirred for 1 h before storing at −20°C overnight. The white solid was collected by filtration, washed with EtOAc and dried *in vacuo* to yield 2b HCl (0.760 g, 82%). ES-MS: $[M+H]^+$, $m/z = 299$; ^{1}H-NMR ($CDCl_3$) δ 0.97 (t, $J = 7.34$ Hz, 3H, CH_3), 1.04 (t, $J = 7.34$ Hz, 3H, CH_3), 2 (m, 5H, CH_2Me and 3α-H), 2.68 (m, 1H, 3β-H), 3.02 (m, 5H, CH_2Et, 4α-H and 4β-H), 3.28 (dq, $J = 1.1$, 5.16, 1H, 1α-H), 3.42 (dq, $J = 1.1$, 5.16, 1H, 1β-H), 3.63 (m, 1H, 2α-H), 6.60 (s, 1-H, 4-isoxazole-H), 7.21 (m, 2H, H-5 and H-6), 7.53 (d, $J = 7.39$ Hz, 1H, 7-H), 8.34 (s, 1H, 3-isoxazole-H); superimposable with that of authentic **1a**; $[\alpha]_D$ (in CH_3OH at 25°C) = −43.02° ($c = 1.72$); specific activity = 20.1 μCi/mg; RCP by TLC-autoradiography ($CH_2Cl_2/CH_3OH/NH_4OH$, 150:10:1) = 99.3%; RCP (by radio-HPLC, *vide infra*) = 98.5%.

This material co-eluted with authentic **2a** on TLC (*vide supra*) and HPLC (Zorbax Phenyl SB, 4.6×250 mm), eluting with 0.1% aqueous TFA/acetonitrile (60:40) at 1 ml/min (column temperature 45°C) with UV detection at 220 nm.

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