JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2005; **48**: 139–148.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.907

Research Article

The synthesis of carbon-14 labeled (*R*)-4-(dipropylamino)-1,3,4,5-tetrahydrobenz[cd]indole-6-carboxamide hippurate. A partial ergoline with 5-HT_{1A} agonist activity and an ^{125}I-labeled analog

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Summary

Partial ergoline agonists such as (*R*)-4-(dipropylamino)-1,3,4,5-tetrahydrobenz[cd]-indole-6-carboxamide (**LY228729, 1a**) mimic a locked conformational analog of serotonin and in fact possess potent *in vitro* activity as agonists of the 5-HT_{1A} receptor. In the course of pre-clinical investigation of **1a** for potential use as an anxiolytic agent, **1b** was prepared in a five step synthesis from K^{14}CN. In addition, an ^{125}I-analog of **1a** was prepared for aid in the development of a radioimmunoassay (RIA).

Key Words: 5HT_{1A}; carbon-14; radioiodinated; radioimmunoassay

Introduction

Flaugh *et al.* reported on the synthesis and pharmacological evaluation of a number of racemic analogs of **1a**.[1] Martinelli *et al.* accomplished the first synthesis of **1a**, based on the diastereoselective epoxidation of *N*-benzoyl-1,2,2a,3-tetrahydrobenzo[cd]indole followed by the regioselective ring opening with *S*-phenethylamine.[2] Mitsunobu reaction of the individual optically pure aminoalcohols followed by hydrogenolysis and bromination yielded **2** (and its enantiomer). Varie later reported on an elegant synthesis of **2** from readily available L-tryptophan.[3] Foreman *et al.* found **1a** to be a potent and selective 5-HT_{1A} receptor agonist both *in vitro* and *in vivo*.[4] In the course of pre-clinical development, **1b** was required for drug disposition studies in laboratory animals.[5] LY228729 has been evaluated clinically for the treatment of anxiety

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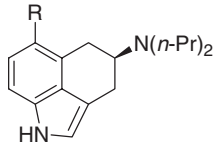
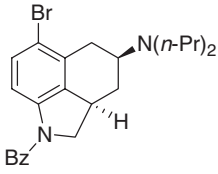
Received 21 September 2004
Revised 11 October 2004
Accepted 21 October 2004

and depression. The low doses administered during phase I studies, required a sensitive method for bioanalysis.[6] For use in the development of a sensitive radioimmunoassay (RIA) (6-iodo-1,3,4,5-tetrahydrobenz[cd]indol-4-yl)dipropylamine-[^{125}I] (**3c**) was required. Preliminary reports of the synthesis and use of **3c** have been published;[6–8] further details of the syntheses of **1b** and **3c** are reported herein.



1a; R = CONH$_2$
1b; R = ^{14}CONH$_2$



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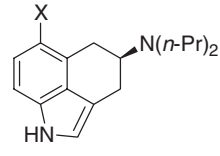
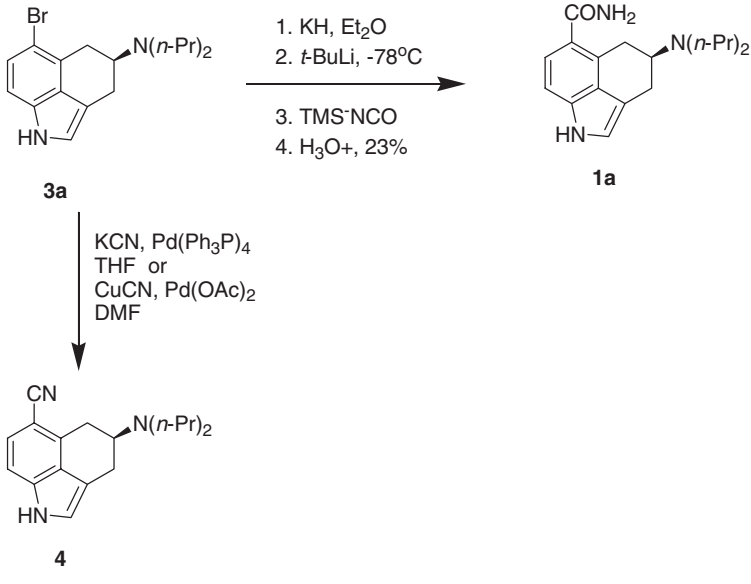


3a; X = Br
3b; X = I
3c; X = ^{125}I

Discussion

In an effort to prepare **1a** in one step, **3a** was deprotonated with KH/Et_2O, reacted with *t*-BuLi and then quenched by the addition of trimethylsilylisocyanate to yield **1a** (23%) after chromatography. Owing to the poor yield in this reaction, coupled with the absence of a ready source of C-14-labeled trimethylsilylisocyanate, we looked to alternative routes. Reaction of **3a** (Scheme 1) with NaCN/Pd(Ph_3P)$_4$ in refluxing THF or CuCN/ Pd(OAc)$_2$ in refluxing DMF at 110°C was unsuccessful. Reaction of **3a** with CuCN in



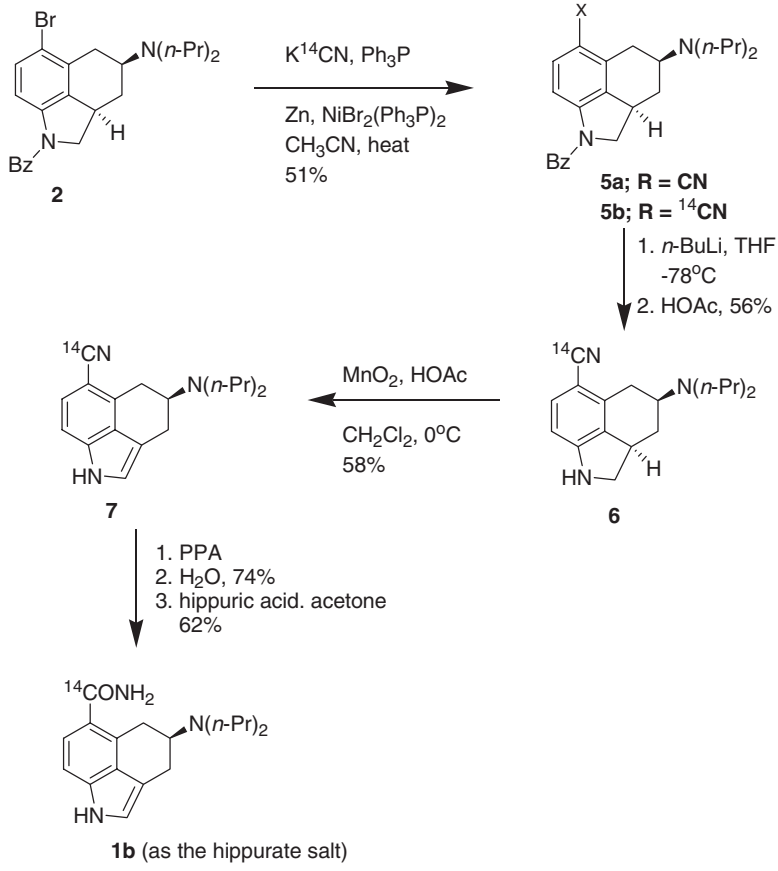
3a

1a

4

Scheme 1.

N-methyl-pyrrolidinone at 110°C yielded some of the desired material **4**, but was very messy with multiple spots seen on TLC. Martinelli *et al*. had significantly better results in the reaction of **2** with CuCN (1.2 equivalents) at 200°C to yield **5a** in 76%.[2] Sakakibara *et al*. have reported success with Rosemund–von Braun-type reactions using KCN and $NiBr_2(Ph_3P)_2/Zn/Ph_3P$ in lower boiling solvents (THF or CH_3CN).[9] In our hands, the best results in the reaction of **2** with $NiBr_2(Ph_3P)_2/Zn/Ph_3P$ to yield **5a** were obtained using CH_3CN as the solvent (Scheme 2). Reaction of **2** with $K^{14}CN$ in the presence of $NiBr_2(Ph_3P)_2$/ Zn/Ph_3P in refluxing acetonitrile gave **5b** in 51% yield. The *N*-benzoyl protecting group was removed by reaction with *n*-BuLi/THF at −78°C, followed by an acetic acid quench to yield **6** (56%). Aromatization was effected by reaction of **6** with $MnO_2/HOAc/CH_2Cl_2$ to yield **7** in 58% yield. The nitrile **7** was added to neat polyphosphoric acid which was pre-heated to 78–82°C and heated for 2 h. The reaction mixture was quenched with water to afford **1b** in 74% yield after chromatography. An acetone solution of **1b** was added dropwise to an acetone solution of hippuric acid at 55°C. Upon cooling

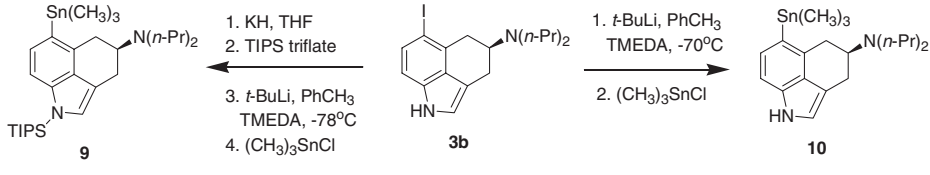


Scheme 2.

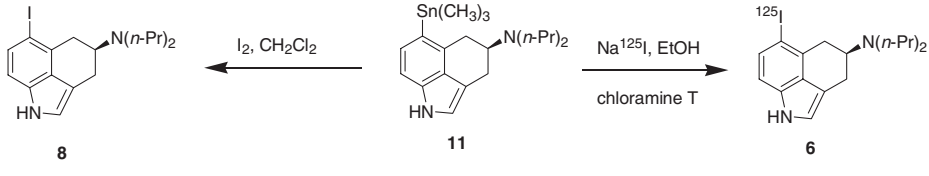
to room temperature, a white solid crystallized, which was collected by filtration and dried *in vacuo* to yield **1b** hippurate (85%). A mixture of **1a** hippurate and **1b** hippurate was re-crystallized twice from acetone to yield **1b** hippurate (62%); specific activity = 13.79 μCi/mg (6.63 mCi/mmol).

Initial attempts to prepare a suitable tin or borate precursor for the preparation of **3c** from (6-iodo-1,3,4,5-tetrahydrobenz[cd]indol-4-yl)dipropylamine[†] (**3b**) were unsuccessful (reaction of **3b** with hexamethyldistannane/$Pd(Ph_3P)_4$/THF, *n*-BuLi/$(CH_3)_3SnCl$, *n*- or *t*-BuLi/$(i\text{-}PrO)_3B$). Reaction of **3b** with KH/THF followed by reaction of the resulting anion with TIPS triflate yielded **8** (Scheme 3). Treatment of **8** with *t*-BuLi/$PhCH_3$/ TMEDA at −70°C followed by reaction with chlorotrimethylstannane ($(CH_3)_3SnCl$) yielded **9** (57%). Faced with the unlikely prospect of removing the TIPS protecting group in **9** without affecting the $(CH_3)_3Sn$- moiety, **3b** was reacted with **10** equivalents of *t*-BuLi/TMEDA/$PhCH_3$ at −70°C, followed by reaction of the resulting lithiated species with $(CH_3)_3SnCl$ to afford **10** in 68% yield after chromatography and crystallization from CH_3OH/H_2O.

Treatment of **10** with I_2/CH_2Cl_2 afforded **3b** as a single spot on TLC (silica gel, pentane/Et_2O/Et_3N, 70:30:1) (Scheme 4). Reaction of **10** with $Na^{125}I$/EtOH in the presence of chloramine T yielded **3c** after purification on HPLC (specific activity 1800 Ci/mmol).[‡]



Scheme 3.



Scheme 4.

[†] The (*S*)-dipropyl-(6-iodo-1,3,4,5-tetrahydrobenzo[cd]indol-4-yl)amine (**8**) was a generous gift from Dr Michael E. Flaugh of the Lilly Research Laboratories, A Division of Eli Lilly and Company, Indianapolis, IN 46285.

[‡] The preparation and purification of (*S*)-dipropyl-(6-iodo-1,3,4,5-tetrahydrobenzo[cd]indol-4-yl)amine-[^{125}I] (**3c**) was conducted at Amersham International plc, Whitchurch, Cardiff, Wales, UK using methods supplied by the authors.

Results

C-14-labeled **1b** (as its hippurate salt) was prepared in five radiochemical steps in 7.6% overall yield; $K^{14}CN$ was the source of the radioactivity. The specific activity was 13.79 μCi/mg (6.63 mCi/mmol); the radiochemical purity was 98.3% by HPLC and 98–99.3% by TLC. This material co-eluted with authentic **1a** in three TLC systems and by HPLC. A method has been developed for the radioiodination of **10**; **3c** was prepared with a specific activity of 1800 Ci/mmol; the radiochemical purity was 98% (with 0.3% iodine). In support of phase I clinical trials of **1a**, which was evaluated for use in the treatment of depression and anxiety, the use of **3c** enabled optimal sensitivity in the RIA of 50 pg/ml. The specificity of the RIA was maximized by the use of a rabbit anti-LY228729 antiserum that displayed low cross reactivity with mono-*N*-*des*-propyl-LY228729 (a metabolite found in the plasma).[6]

Experimental

NMR spectra were obtained on a Varian Mercury Plus 400 mHz nuclear magnetic resonance spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Electrospray mass spectrometry was conducted on a Waters Micromass ZQ single quadropole mass spectrometer. Flash chromatography was performed on silica gel. Radiochemical purity (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 X-ray film, the lanes of the TLC were cut, mixed with methanol and scintillation fluid and counted. The following TLC systems were used: A ($CHCl_3$/EtOH/NH_4OH, 90:10:10 drops), B ($CHCl_3$/acetone/CH_3OH/NH_4OH, 63:27:7:2) and C ($CHCl_3$/CH_3OH/HOAc, 18:6:1).

(-)-4-(R)-(dipropylamino-1,3,4,5-tetrahydrobenz[cd]indole-6-carboxamide, 1a

Potassium hydride (25% mineral oil dispersion, 0.057 g, 0.35 mmol) was added to a flask under argon and washed with hexanes (3 × 10 ml) to remove the oil. Ether (8 ml) was added and the resulting suspension cooled to 0°C and then treated with **3a** (0.100 g, 0.298 mmol) in Et_2O (1.5 ml). The reaction mixture was stirred for 15 min and then allowed to warm to room temperature and stirred for an additional 2 h. The mixture was then chilled to −78°C and treated by the dropwise addition of *t*-BuLi (1.6 M, 0.475 ml, 0.76 mmol). Stirring was continued at −78°C for 15 min, then at −40°C for 2 h. After cooling back to −78°C, the mixture was treated with TMS-isocyanate (0.058 ml, 0.358 mmol), allowed to warm to −10°C

and stirred for 2 h. Water was added and after a 15 min stir, the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic extracts were concentrated *in vacuo*. The residual brown oil was dissolved in 3 N HCl (4 ml) and washed with Et_2O; the pH of the aqueous layer was adjusted to **10** with 5 N NaOH and extracted with Et_2O (4×20 ml). The combined Et_2O extracts were dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. The brown semi-solid residue was purified by chromatography over silica gel, eluting with $PhCH_3$/ EtOAc/CH_3OH/NH_4OH (50:50:2:0.5) to yield **1a** (0.022 g, 25%) after crystallization from Et_2O. CI-MS (NH_3): M^+, $m/z = 299$; ^{1}H-NMR ($CDCl_3$) δ 0.91 (t, 6H, CH_3), 1.48 (dt, 4H, CH_2Me), 2.57 (t,1H, CH_2Et), 2.80 (t, 1H, 3α-H), 2.98 (qt, 1H, 3*β*-H), 3.02 (t, 1H, 5α-H), 3.22 (m, 1H, 4*β*-H), 3.54 (qt, 1H, 5*β*-H), 5.72 (bs, 2H, NH_2), 6.90 (s, 1H, 2-H), 7.15 (d, 1H, 8-H), 7.45 (d, 1H, 7-H), and 8.04 (s, 1H, indole-NH).

(+)-(2aR,4S)-1-benzoyl-4-(dipropylamino)-1,2,2α, 3,4,5,-hexahydrobenz-[cd]-indole-6-carbonitrile-[nitrile-^{14}C], 5

In a flame-dried flask, filled with argon, (+)-1-benzoyl-6-bromo-*N*,*N*-dipropyl-1,2,2α,3,4,5-hexahydrobenz-[cd]-indol-4-amine (**2**, 2.03 g, 4.61 mmol) was mixed with potassium cyanide-[^{14}C] (100 mCi, 21.7 mCi/mmol, 4.61 mmol), potassium cyanide (0.1498 g, 2.31 mmol), nickel (II) bromide-*bis*-triphenylphosphine (0.341 g, 0.461 mmol), zinc (0.092 g, 1.38 mga), and triphenylphosphine (0.2398 g, 0.922 mmol). The mixture was diluted with acetonitrile (25 ml) and the resulting emerald green solution was stirred under reflux for 7 h (the color gradually changed to orange-brown). TLC (hexanes/ EtOAc/Et_3N 65:35:5) indicated that the reaction was not complete, so stirring under reflux was continued overnight. Additional nickel (II) bromide-*bis*-triphenylphosphine (0.341 g, 0.461 mmol), zinc (0.092 g, 1.38 mga), and triphenylphosphine (0.2398 g, 0.922 mmol) were added and stirring at reflux was continued for an additional 24 h. TLC still showed a small amount of unreacted **2**. The solvent was removed *in vacuo* and the residue was partitioned between ethyl ether (60 ml) and concentrated NH_4OH (25 ml) which was diluted with ice. The aqueous layer was re-extracted with ether (25 ml) and the combined ether extracts were washed successively with NH_4OH and brine (2×25 ml). The ether was dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel 60, eluting with 20 ml fractions of hexanes/EtOAc/Et_3N 65:35:5. Fractions 14–19 were combined and concentrated to yield 0.908 g, (51%) of **5b** as a yellow oil, which crystallized upon standing. This material was identical to **5a** by TLC.

(-)-(2aR,4S)-(dipropylamino)-1,2,2α,3,4,5-hexahydro-benz-[cd]-indole-6-carbonitrile-[nitrile-^{14}C], 6

A THF solution (10 ml) of **5b** (0.908 g, 2.35 mmol) was cooled to −72°C (dry ice/2-propanol) under argon and treated dropwise with *n*-butyllithium (1 M, 2.35 ml, 2.35 mmol). Stirring was continued for 15 min (no starting material remained by TLC, hexanes/EtOAc/Et_3N 65:35:5) and the excess *n*-butyllithium was quenched by the careful dropwise addition of acetic acid (0.25 ml). The mixture was allowed to warm to room temperature and then extracted with 1 N HCl (10 ml, then 5 ml additional) and water (2 × 10 ml). The combined aqueous extracts were made basic with 1 N NaOH and extracted with methylene chloride (2 × 50 ml, 2 × 15 ml). The combined organic extracts were washed with brine (25 ml), dried (anhydrous Na_2SO_4), and concentrated *in vacuo*. The crude residue was crystallized from ethanol/water (15 ml/5 ml), then concentrated to 10 ml) to yield **6** as a white crystalline solid (0.3749 g, 56.4%) which co-migrated as a single spot with an authentic sample of unlabeled **6** on TLC (hexanes/EtOAc/Et_3N 65:35:5).

(-)-4-(S)-(dipropylamino)-1,3,4,5-tetra-hydrobenz-[cd]-indole-6-carbonitrile-[nitrile-^{14}C], 7

A methylene chloride solution (2.5 ml) of **6** (0.3749 g, 1.325 mmol) was diluted with glacial acetic acid (2.5 ml) and chilled to −5 to 0°C in an ice bath. To the stirred solution was added manganese dioxide (0.173 g, 1.987 mmol) and stirring was continued for 5 h. TLC (hexanes/EtOAc/Et_3N 65:35:5) showed unreacted starting material remaining; an additional 0.025 g of manganese dioxide was added and the mixture was stirred for two more hours. Starting material still remained by TLC, so the mixture was stored at −20°C overnight.

The reaction mixture was diluted with methylene chloride (5 ml) and filtered through a bed of talc. The filter cake was washed with methylene chloride (5 × 10 ml). The combined filtrates were diluted with water (10 ml) and the aqueous made basic by the dropwise addition of 5 N NaOH (15 ml). The aqueous layer was washed with methylene chloride (2 × 25 ml) and the combined methylene chloride extracts were washed with brine (50 ml) and dried (anhydrous Na_2SO_4). Concentration *in vacuo* yielded a crude product which was purified by flash chromatography. The material was eluted with 10 ml fractions of chloroform (fractions 1–27) and then 20:1 chloroform/methanol (fractions 28–50). Fractions 30–37 were combined and concentrated; the residue was crystallized from hexane/EtOAc to yield **7** (0.216 g, 58%) as a white solid which was a single component by TLC (EtOAc/$PhCH_3$ 6:4), co-migrating with authentic unlabeled **7**.

(-)-4-(S)-(dipropylamino-1,3,4,5-tetrahydrobenz[cd]indole-6-carboxamide-[carbonyl-^{14}C], 1b

Polyphosphoric acid (10 g) was warmed to 78°C and stirred while **7** was added portionwise. The sides of the flask were washed down with toluene (2 ml) and stirring was continued at 78–82°C for 2 h, whereupon the reaction mixture was poured into ice and made basic with 5 N NaOH. The resulting mixture was extracted with methylene chloride (5 × 35 ml) and the combined extracts were washed with brine, then dried (anhydrous Na_2SO_4). The crude product was purified by flash chromatography eluting with 10 ml fractions of 8:2 ethyl acetate/methanol. Fractions 8–16 were combined and concentrated *in vacuo* to yield **1b** as an amorphous foam (0.170 g). TLC (9:1 EtOAc/CH_3OH) showed a single spot which co-migrated with **1a**.

(-)-4-(S)-(dipropylamino-1,3,4,5-tetrahydro-benz-[cd]-indole-6-carboxamide-[carbonyl-^{14}C] hippurate salt, 1b hippurate

An acetone solution (1.75 ml) of **1b** (0.16992 g, 0.568 mmol) was added dropwise to a mixture of hippuric acid (0.102 g, 0.568 mmol) and acetone (5.25 ml) which was stirred at 50°C. The mixture was allowed to cool to room temperature whereupon a white precipitate formed which was collected by filtration, washed with acetone, and dried to yield **1b** hippurate (0.230 g).

A mixture of **1b** hippurate (0.17276 g) and **1a** hippurate (0.17276 g) was recrystallized twice from 2-propanol/water (90:10) (3.1 ml) to yield diluted LY228729-[^{14}C] hippurate (0.21928 g, 50.7%), specific activity 13.79 μCi/mg.

The **1b** hippurate co-eluted with **1a** hippurate in the following TLC systems; the radiochemical purity was determined by TLC-autoradiography:

$CHC1_3$/EtoH/NH_4OH 90 : 10 : 10 drops 99.33% $r_f = 0.489$

$CHCl_3$/acetone/MeOH/NH_4OH 63 : 27 : 7 : 2 99.32% $r_f = 0.752$

$CHCl_3$/MeOH/HOAc 18 : 6 : 1 97.98% $r_f = 0.442$

HPLC on a Jones C-8 column (4.6 × 250 mm, 5 μ), eluting at 0.8 ml/min with CH_3CN/0.03 M KH_2PO_4 (60:40 at pH = 3) and fluorescence (290 nm em, 370 nm ex) and UV detection (290 nm) showed a single peak (with the exception of the hippuric acid) co-eluting with authentic material; RCP = 98.3%, R_T = 6.5 min.

(S)-dipropyl-(6-trimethylstannanyl-1,3,4,5-tetrahydrobenzo[cd]indol-4-yl)amine, 10

A toluene (13 ml) solution of **3a** (0.500 g, 1.31 mmol) under argon was treated with TMEDA (0.25 ml, 1.71 mmol) and chilled to −70°C. To this solution was added *t*-BuLi (1.6 M in pentane, 8.2 ml, 13.12 mmol) and the resulting yellow

mixture was stirred at −70°C for 15 min. Chlorotrimethylstannane (2.61 g, 13.1 mmol) in toluene (7 ml) was added to the solution dropwise. The solution was allowed to warm slowly to room temperature and then stirred overnight. The solution was added to water (5 ml) and extracted with Et_2O (3 × 20 ml). The combined organic layers were washed with brine, dried (anhydrous $MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 50 ml fractions of pentane/Et_2O/Et_3N (70:30:1). Fractions 14–22 were combined and concentrated *in vacuo* to yield **10** (0.485 g, 89%). NMR and mass spectrometry indicated contamination with the reduced product. The solid was re-crystallized from methanol/water to yield pure **10** as a white crystalline solid (0.157 g, 27%) (TLC (silica gel, pentane/Et_2O/Et_3N, 70:30:1) showed a single spot at $r_f = 0.25$ (r_f(**3b**) = 0.17). ES-MS: $[M + H]^+$, $m/z = 421$ (significant isotope peaks plus H at 417, 418, 419, 420, 422, 423 and 425); ^{1}H-NMR ($CDCl_3$) δ 0.08 (s, 9H, $Sn(CH_3)_3$ plus Sn–H coupling), 0.64 (t, 6H, CH_3), 1.22 (m, 4H, CH_2Me), 2.31 (m, 4H, CH_2Et), 2.52 (t, 1H, 3-H), 2.73 (m, 3H, 3-H and 5-H), 3.02 (m, 1H, 4-H), 6.53 (s, 1H, 2-H), 6.94 (m, 2H, 7-H and 8-H), 7.50 (bs, 1H, NH).

HR-QTOF-MS: Analysis calculated for $C_{20}H_{32}N_2Sn$: 417.1661. Found: 417.1669.

(S)-dipropyl-(6-iodo-1,3,4,5-tetrahydrobenzo[cd]indol-4-yl)amine, 3b

A methylene chloride (5 ml) solution of **10** (0.041 g, 0.1 mmol) was reacted with iodine (0.025 g, 0.1 mmol) and stirred for 2 h. TLC (silica gel, pentane/Et_2O/Et_3N; 70:30:1) showed quantitative conversion to **8**. This material was identical to an authentic sample of **3b**. ES-MS: [M + H] +, $m/z = 388$; ^{1}H-NMR ($CDCl_3$) δ 0.92 (t, $J = 7.05$ Hz, 6H, CH_3), 1.49 (m, 4H, CH_2Me), 2.57 (m, 5H, CH_2Et, 3α-H), 2.80-2.97 (m, 2H, 5α-H, 3β-H), 3.01 (m, 1H, 5β-H), 3.24 (m, 1H, 4β-H), 6.85 (s, 1H, 2-H), 6.95 (d, $J = 8.4$ Hz), 1H, 8-H), 7.45 (d, $J = 8.4$ Hz, 1H, 7-H) and 7.91 (bs, 1H, NH).

(S)-dipropyl-(6-iodo-1,3,4,5-tetrahydrobenzo[cd]indol-4-yl)amine-[^{125}I], 3c

An ethanol (0.1 ml) solution of **10** (0.1 g) was mixed with aqueous NaI-[^{125}I] (0.1 ml, 10.0 mCi) and treated with Na Chloramine T (0.050 ml, 5 mg/ml in water). The mixture was allowed to react for 5 min and then treated with aqueous $NaHSO_3$ (0.05 ml, 10 mg/ml) to terminate the reaction. The crude reaction mixture was purified on a Aquapore C-18 column (4.6 × 250 mm) by gradient elution (40%B to 55%B over 30 min) at a flow rate of 1 ml/min. Solvent A = 0.1 M NH_4Oac at pH 5.0, solvent B = CH_3OH. The product eluted at 17 min. The total yield (6.1 mCi) was diluted to 100 μCi/ml and stored at −20°C. The radiochemical purity was determined by HPLC on a Vydac

Protein C18 column by gradient elution (30%B to 40%B over 20 min) to yield **3c**. Solvent A = water with 0.1% TFA, solvent B = propanol with 0.1% TFA.

Acknowledgements

The authors appreciate the support of Ms Paula Santa (Eli Lilly and Company) and Mr Steven Gabriel (formerly of Eli Lilly and Company) in the preparation of this manuscript.

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