

Chemoenzymatic formal synthesis of (−)- and (+)-epibatidine†

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The *cis*-dihydrocatechol, derived from enzymatic *cis*-dihydroxylation of bromobenzene using the microorganism *Pseudomonas putida* UV4, was converted into (–)-epibatidine in eleven steps with complete stereocontrol. In addition, an unprecedented palladium-catalysed disproportionation reaction gave the (+)-enantiomer of an advanced key intermediate employed in a previous synthesis of epibatidine.

1 Introduction

To date, over eight hundred alkaloids have been isolated from the defensive skin secretions of frogs of the *Dendrobates* family.¹ Of these compounds, undoubtedly, the most important is (−)-epibatidine (Fig. 1) a potent nicotinic receptor antagonist isolated from the Ecuadorian poison frog *Epipedobates tricolor*.² As an analgesic, (−)-epibatidine is much more potent than morphine. Since its mode of action is through the nicotinic receptor, and not the opiate receptor, it has provided a stimulus in the search of new analgesics based around structural elements of the (−)-epibatidine structure.³ Due to the scarcity of material, available from the natural source, (−)-epibatidine could only be assigned a tentative structure which was confirmed later by its synthesis.⁴ Subsequently, keen interest was generated in the synthesis of epibatidine and within two years of its structure elucidation eleven racemic syntheses were reported.^{5,6} To date, over fifty syntheses and formal syntheses of epibatidine have appeared in the literature and the work has also been reviewed.⁷ All the very early routes relied on separation of enantiomers to get enantioenriched material. These samples were subsequently used to: (a) confirm the absolute configuration of (−)-epibatidine and (b) investigate its much awaited detailed biological evaluation.

Nearly one quarter of the reported syntheses of epibatidine gave enantioenriched material without resolution. A wide variety of strategies have been employed to obtain optically active epibatidine including asymmetric desymmetrisation,^{8,9} asymmetric protonation,¹⁰ Diels–Alder reaction with chiral allenes,¹¹ oxazolidinones¹² and nitroso dienophiles,^{13,14} 1,3-dipolar cycloaddition with sultam dienophiles,¹⁵ biocatalytic asymmetric

monohydroxylation,¹⁶ 1,4-addition to chiral enones derived from (–)-quinic acid,¹⁷ organocatalytic 1,4-addition to nitroalkenes,¹⁸ and addition of allyl zinc reagents to chiral imines.¹⁹ Although in most of these syntheses the stereoselectivity for installation of all three chiral centres was very high it could be further improved by recrystallisation, or recycling the unwanted stereoisomers, in none of the synthetic approaches was the innate stereoselectivity for generating *all* three chiral centres greater than 95% de/ee.

2 Results and discussion

Dioxygenase-catalysed oxidation of arene substrates provides a direct route to a wide range of enantiopure mono- and poly-hydroxylated bioproducts. Earlier studies of aromatic substrates, in these and other laboratories, using mutant strains (e.g. UV4, 39D) of the soil bacterium *Pseudomonas putida* and *Escherichia coli* recombinant strains, each containing toluene dioxygenase, have given access to an extensive range of over 400 metabolites.²⁰ These enantiopure *cis*-dihydrodiols are ideal synthetic precursors for cyclohexane based natural products, as every carbon in the ring is fully functionalised and the biotransformations can be easily scaled up. Therefore it is not surprising that these new chiral pool derivatives are being extensively used in the synthesis of natural products,²¹ carbasugars,²² active pharmaceutical ingredients²³ and as ligands in asymmetric catalysis.²⁴ Starting from dihydrodiol **1** our chemoenzymatic route to (–)-epibatidine is outlined (Scheme 1). Chemoselective hydrogenation^{25,26} of the unsubstituted alkene bond gave the tetrahydrodiol **2**. Previous X-ray studies have shown that in the

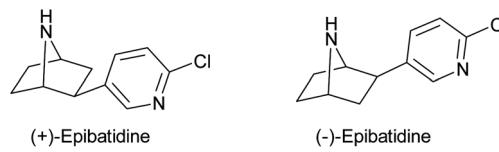
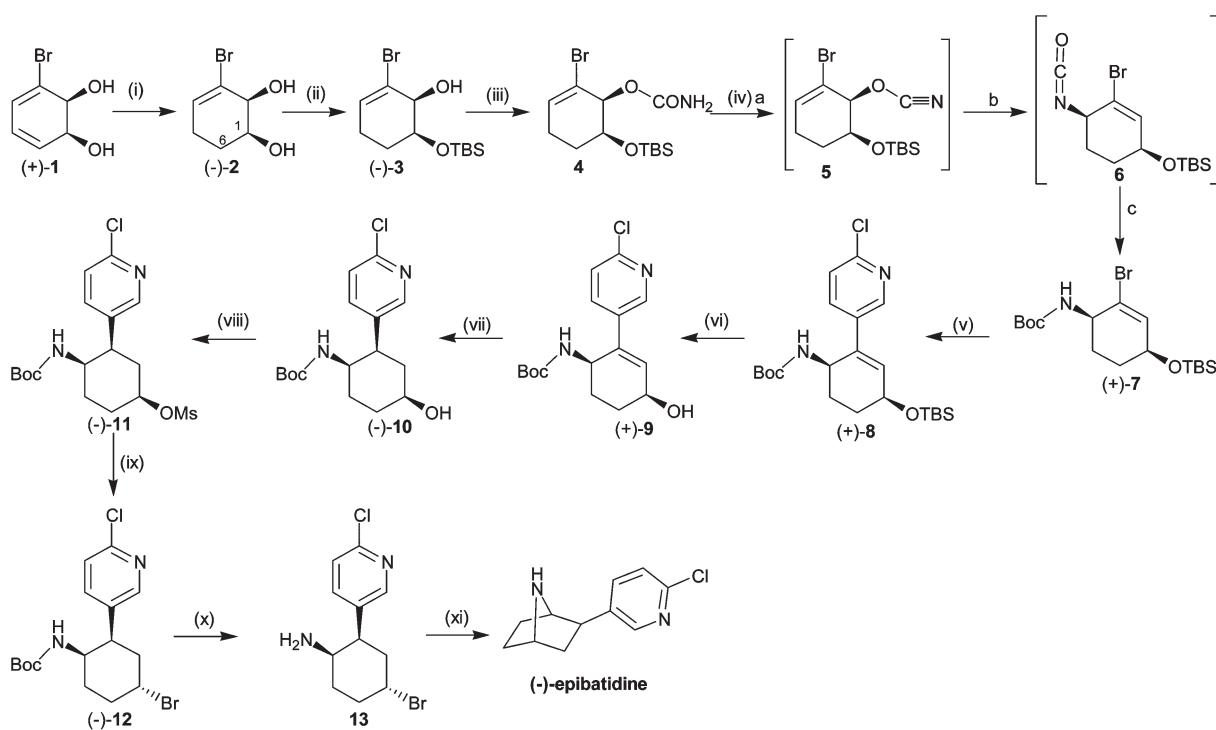


Fig. 1 Structures of (+) and (−)-epibatidine.

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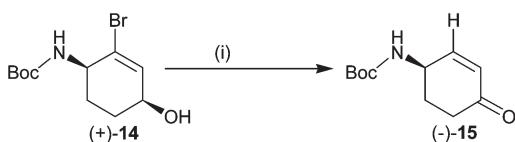
Scheme 1 Reagents and conditions: (i) H_2 (1.5 bar), Rh–G, MeOH, 2 h, rt, (90%); (ii) TBSCl , $\text{C}_6\text{H}_5\text{N}$, 12 h, rt (86%); (iii) trichloroacetyl isocyanate, CH_2Cl_2 , 0.5 h, 0 °C then Na_2CO_3 , $\text{Et}_2\text{O} : \text{MeOH} : \text{H}_2\text{O}$ 4 : 4 : 1, 5 h, rt (90%); (iv) (a) Ph_3P , Et_3N , CBr_4 , CH_2Cl_2 –10 °C 1.5 h. (b) [3,3] sigma-tropic rearrangement. (c) 1% MoCl_2O_2 , CH_2Cl_2 , $t\text{-BuOH}$, 16 h, rt (76% from 3); (v) 6-chloropyridin-3-ylboronic acid, 2% $\text{PdCl}_2(\text{dppf})$, $\text{PhMe} : \text{EtOH} : \text{H}_2\text{O}$ 1 : 1 : 1, Na_2CO_3 , 5 h, 100 °C (93%); (vi) TBAF, THF, 1 h (95%); (vii) PtO_2 , H_2 , 1 bar, EtOH , 5 h, rt (60%); (viii) Et_3N , MsCl , CH_2Cl_2 , 0 °C, 20 minutes (91%); (ix) LiBr , THF, 60 °C, 36 h (78%); (x) TFA, CH_2Cl_2 1.5 h, rt (94%); (xi) CHCl_3 , 55 °C, 72 h (95%).

crystalline state the hydroxyl group in cyclic allylic alcohols prefers to occupy a pseudo-axial position, to minimise allylic 1,2-strain with the substituent on the alkene.²⁷ Analysis of the proton NMR spectrum of diol (–)-2 revealed proton H-1 to be a doublet of triplets (J 9.3, 3.9 Hz). The large diaxial coupling to H-6 also indicated that the C-1 hydroxyl group was equatorial and that the C-2 hydroxyl group was pseudo-axial in solution. As axial, or pseudo-axial alcohols occupy a more crowded position; they are much less reactive than equatorial alcohols in reactions that lead to an increase in steric bulk *i.e.* reactions involving the replacement of hydrogen attached to the oxygen with a larger group.²⁸ Thus silylation of diol (–)-2 was chemoselective with the homoallylic equatorial hydroxyl group forming the silyl ether 3. The silyl group in ether (–)-3 was found to be prone to scrambling, on storage or attempted purification, and as such was used immediately for the next step.

syn-Replacement of the alcohol oxygen by nitrogen with allylic rearrangement was efficiently achieved, with complete stereocontrol, using the Ichikawa allyl cyanate to isocyanate [3,3]-sigmatropic rearrangement.²⁹ An attractive feature of this protocol is that it proceeds at low temperature and, in principle, the isocyanate intermediate 6 could be directly converted into any urethane *N*-protecting group by reaction with an appropriate alcohol. Employing Ichikawa's conditions, alcohol (–)-3 was converted to urethane 4 in high yield. Urethane 4 was then dehydrated to furnish intermediate cyanate 5 which, under the reaction conditions, underwent a rapid [3,3]-sigmatropic rearrangement to furnish the intermediate isocyanate 6 as the sole

diastereoisomer. Our first choice of *N*-protecting group was Boc but, initially, the isocyanate 6 proved to be completely unreactive towards *t*-butanol or its metal alkoxides. However, using the newly developed Bruckner protocol,³⁰ with molybdenum (vi) dichloride dioxide as a catalyst, the isocyanate 6 reacted smoothly with *t*-butanol to give the Boc derivative (–)-7. This approach allowed the conversion of urethane 4 to Boc-derivative 7 as a one pot operation, without isolation of the sensitive isocyanate 6, in an overall yield of 76%.

Suzuki cross coupling³¹ of alkenyl bromide (–)-7 with commercially available 6-chloropyridin-3-ylboronic acid proceeded smoothly and gave compound (–)-8. Fluoride-induced removal of the *O*-silyl protecting group gave allylic alcohol (–)-9. The next step involved catalytic stereoselective reduction of the hindered, trisubstituted alkene with retention of the chloropyridine group. It was envisaged that the *N* and *O* substituents would direct addition of hydrogen to the alkene face *anti* to these groups.³² In a previous synthesis of racemic epibatidine it was reported that the 6-chloropyridine was prone to hydrogenolysis³² but Kibayashi *et al.*¹³ and Baker *et al.*⁶ have successfully reduced an alkene bond in the presence of a 6-chloropyridyl group. In our hands when hydrogenation of alkene (–)-9, using platinum oxide as catalyst in ethanol as solvent, was allowed to proceed to full conversion of alkene (–)-9, only intractable material was produced. However, when the hydrogenation reaction was stopped after *ca.* 70% completion, the desired reduction product (–)-10 was obtained as a single diastereoisomer; its properties were identical to those previously reported by



Scheme 2 Reagents and conditions: (i) 10% $\text{PdCl}_2(\text{dppf})$, PhMe : EtOH : H_2O 1 : 1 : 1, Na_2CO_3 , 6 h, 100 °C (82%).

Evans.¹² Subsequently, using the Evans protocol, compound (–)-10 was converted in a two step sequence to bromide (–)-12 with inversion of configuration. On removal of the *N*-protecting group, compound 13 cyclised to afford (–)-epibatidine, whose spectral and chiroptical properties were identical to those previously reported.^{12,13}

Including the initial biotransformation, this synthesis, overall, employed five reactions which generated six new stereocentres to achieve the desired stereochemistry at the final three chiral centres in (–)-epibatidine. In each of these stereo defining reactions the product formed was a single stereoisomer, as determined by NMR spectroscopy, making the synthesis completely stereoselective.

A potential shortcoming of the chemoenzymatic approach is that it often leads to only one of the two possible enantiomers. As (–)-epibatidine has pseudo symmetry in its structure, the shift of the chloropyridine substituent to the adjacent methylene carbon will yield the opposite enantiomer *i.e.* (+)-epibatidine (Fig. 1). In practice this could be achieved by shifting the bromine substituent in intermediate (+)-7 to the adjacent alkene carbon (Scheme 1).

During our attempts to carry out Suzuki cross coupling of allylic alcohol (–)-14 with 6-chloropyridin-3-yl boronic acid, an unusual high yielding reaction was observed which resulted in the formation of ketone (–)-15 (Scheme 2). Formally, the alcohol was oxidised to a ketone and the carbon bromine bond was simultaneously reduced (disproportionation).

Further investigation revealed that ketone (–)-15 was formed even in the absence of 6-chloropyridin-3-yl boronic acid but the palladium catalyst and the base were both essential components of the reaction. It is presumed that the reaction involves a palladium-catalysed migration of the double bond to give the enol of the ketone which rapidly tautomerises to form a β -bromoketone. The ketone then loses hydrogen bromide under the basic reaction conditions to yield enone (–)-15 which is the enantiomer of the intermediate used by Trost in the first asymmetric synthesis of epibatidine. In the absence of a deuterium labelling experiment, the proposed disproportionation (migration/tautomerisation/dehydromination) mechanism for the formation of enone (–)-15 remains speculative. A bromine atom can be subsequently introduced, regioselectively, into the α -position of enone (–)-15 as described by Trost and Cook.⁸ This novel disproportionation reaction thus constitutes a formal chemoenzymatic synthesis of (+)-epibatidine.

In conclusion, we have demonstrated that bromobenzene *cis*-dihydrodiol (+)-1 can be converted, with complete stereocontrol of the three new chiral centres, to (–)-epibatidine. A newly discovered palladium-catalysed disproportionation reaction allows entry into the enantiomeric series. Since a wide range of aromatic boronic acids are commercially available this route is ideal

for preparing epibatidine analogues for further biological evaluation.

3 Experimental section

cis-Dihydrodiol (+)-1, was obtained from the biotransformation of bromobenzene, using the dioxygenase enzymes present in the whole cell cultures of *P. putida* UV4 and the reduction to (–)-2 is as detailed elsewhere.^{33,26} All reagents were used as purchased from Aldrich and 6-chloropyridin-3-ylboronic acid was donated by Frontier Scientific. ¹H-NMR and ¹³C-NMR spectra were recorded on Bruker Avance DPX-300 and AV-400 instruments and coupling constants are reported in Hz. Mass spectra were run at 70 eV, on an AE1-MS90 Mass Spectrometer updated by VG Autospec, using a heated inlet system. Accurate molecular weights were determined, by the peak matching method, with perfluorokerosene as standard. For optical rotation ($[\alpha]_D$) measurements (*ca.* 20 °C, 10^{–1} degree cm² g^{–1}) a Perkin-Elmer 214 polarimeter was used. Flash chromatography and preparative layer chromatography (PLC) were performed on Merck Kieselgel type 60 (250–400 mesh) and PF₂₅₄/366 respectively. Merck Kieselgel type 60F₂₅₄ analytical plates were used for TLC.

(–)-1(S,6S)-2-Bromo-6-(*tert*-butyldimethylsilyloxy)cyclohex-2-enol 3

tert-Butyldimethylsilyl chloride (1.76 g, 0.014 mol) was added to a solution of *cis*-tetrahydrodiol (–)-2 (2.26 g, 0.012 mol) in dry pyridine (5 mL) under a nitrogen atmosphere. The reaction mixture was allowed to stir overnight at room temperature. Excess of pyridine was removed under reduced pressure, the residue dissolved in EtOAc (50 mL) and the solution washed, successively, with a sat. solution of NaHCO_3 (15 mL), brine (15 mL) and dried (Na_2SO_4). Removal of solvent gave TBS derivative 3 as a light yellow oil (3.10 g, 86%), which was used for the next stage without further purification. R_f 0.41 (10% EtOAc in hexanes); $[\alpha]_D$ –43.7 (*c* 1.1, CHCl_3); HRMS (ES): found $[\text{M} + \text{H}]^+$ 307.0732, $\text{C}_{12}\text{H}_{24}\text{O}_2\text{BrSi}$ requires 307.0729; ¹H-NMR (400 MHz, CDCl_3): δ 0.11 (3H, s, SiMe₂), 0.12 (3H, s, SiMe₂), 0.91 (9H, s, CMe₃), 1.63 (1H, m, 5-H), 1.83 (1H, m, 5'-H), 2.04 (1H, m, 4-H), 2.22 (1H, m, 4'-H), 2.78 (1H, d, *J* 3.7 Hz, OH), 3.94 (1H, ddd, *J* 10.2, 4.1, 3.4, 6-H), 4.10 (1H, appa t, *J* 3.6, 1-H), 6.20 (1H, dd, *J* 4.8, 3.3, 3-H); ¹³C-NMR (CDCl₃, 100 MHz): δ –4.8, –4.5, 18.1, 25.3, 25.5, 25.8 (3C), 70.8, 72.3, 121.9, 132.4; LRMS (EI): *m/z* 277 (30), 215 (25), 149 (100), 104 (65).

(+)-*tert*-Butyl-(1*R*,4*S*)-2-bromo-4-(*tert*-butyldimethylsilyloxy)cyclohex-2-enylcarbamate 7

Trichloroacetyl isocyanate (0.88 mL, 7.43 mmol) was added to an ice cooled solution of silyl ether (–)-3 (1.18, 3.84 mmol) in CH_2Cl_2 (25 mL). After stirring the mixture for 0.5 h at 0 °C the solvent was evaporated, the residue dissolved in a mixture of MeOH (20 mL) and Et_2O (5 mL) and the solution stirred at room temperature for 5 h with aq. K_2CO_3 solution (1 M, 20 mL). Most of the methanol was removed under reduced pressure and the aqueous reaction mixture extracted with Et_2O

(3 × 30 mL). The combined organic extract was washed with brine (60 mL), dried (MgSO_4) and concentrated under reduced pressure to give urethane **4** as an off-white solid (1.25 g, 90%), which was used in the next step without further purification.

To a solution of urethane **4** (1.25 g, 3.45 mmol) in anhydrous CH_2Cl_2 (20 mL) were added triphenylphosphine (2.71 g, 10.3 mmol) and Et_3N (2.79 mL, 20.01 mmol). The mixture was cooled to $-10\text{ }^\circ\text{C}$ and CBr_4 (3.43 g, 10.4 mmol) solution in dry CH_2Cl_2 (30 mL) was added to it drop-wise over 1 h. The reaction mixture was kept stirring at $-10\text{ }^\circ\text{C}$ for a further 1.5 h, freshly distilled *tert*-butanol (0.51 g, 6.90 mmol) and molybdenum (vi) dichloride dioxide (6.9 mg, 0.034 mmol) were then added sequentially and it was allowed to warm to room temperature. After stirring the mixture for another 16 h, it was washed with 10% aq. NaHCO_3 (20 mL), saturated brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to yield compound (+)-**7** as a clear oil (1.19 g, 76%, 2 steps). R_f 0.45 (10% EtOAc in hexanes); $[\alpha]_D$ +18.3 (*c* 0.7, CHCl_3); HRMS (ES): found $[\text{M} + \text{H}]^+$ 406.1413, $\text{C}_{17}\text{H}_{33}\text{BrNO}_3\text{Si}$ requires 406.1408; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 0.07 (3H, s, SiMe_2), 0.08 (3H, s, SiMe_2), 0.89 (9H, s, SiCMe_3), 1.46 (9H, s, OCMe_3), 1.49–1.63 (1H, m, 5-H), 1.79–1.97 (3H, m, 5'-H, 6-H, 6'-H), 4.17 (1H, dddd, *J* 8.9, 5.0, 3.1, 1.4, 4-H), 4.28 (1H, m, 1-H), 4.78 (1H, d, *J* 8.7, NHBoc), 6.13 (1H, ddd, *J* 3.0, 0.9, 0.9, 3-H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ -4.6, -4.6, 18.2, 25.9 (3C), 28.0, 28.1, 28.5 (3C), 51.7, 68.4, 79.9, 125.3, 137.3, 155.4; LRMS (EI): *m/z* 292 (15), 248 (10), 118 (25), 74 (100).

(+)-*tert*-Butyl-(1*R*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-2-(6-chloropyridin-3-yl)cyclohex-2-enylcarbamate **8**

A mixture of 6-chloropyridin-3-ylboronic acid (0.46 g, 2.95 mmol), EtOH (10 mL) and aq. Na_2CO_3 (2M, 8 mL) was added to a round bottom flask containing a solution of *tert*-butyl (1*R*,4*S*)-carbamate (+)-**7** (1.00 g, 2.46 mmol) in toluene (10 mL). After flushing the contents of the flask with a stream of nitrogen, $\text{PdCl}_2(\text{dppf})$ (40 mg, 0.055 mmol) was added and the mixture was refluxed with stirring for 5 h under nitrogen. The reaction mixture was transferred into a separating funnel, the organic layer was separated and the aq. layer extracted with EtOAc (3 × 20 mL). The combined organic extract was washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a dark brown oil. Purification of the oil by flash chromatography (5–10% EtOAc in hexanes) gave compound (+)-**8** as a white crystalline solid (1.00 g, 93%); m.p. 106–107 $^\circ\text{C}$; $[\alpha]_D$ +36.6 (*c* 1.2, CHCl_3); R_f 0.3 (10% EtOAc in hexanes); HRMS (ES): found $[\text{M} + \text{H}]^+$ 439.2192, $\text{C}_{22}\text{H}_{36}\text{ClN}_2\text{O}_3\text{Si}$ requires 439.2184; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 0.12 (3H, s, SiMe_2), 0.13 (3H, s, SiMe_2), 0.93 (9H, s, SiCMe_3), 1.37 (9H, s, OCMe_3), 1.56–1.68 (1H, m, 5-H), 1.79–2.02 (3H, m, 5'-H, 6-H, 6'-H), 4.32 (1H, ddd, *J* 8.4, 5.6, 2.8, 4-H), 4.67 (2H, m, 1-H, NHBoc), 6.11 (1H, d, *J* 2.7, 3-H), 7.27 (1H, d, *J* 8.5, Ar-5-H), 7.69 (1H, dd, *J* 8.5, 2.6, Ar-4-H), 8.44 (1H, d, *J* 2.6, Ar-2-H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ -4.6, -4.4, 18.3, 26.0 (3C), 27.5, 28.0, 28.4 (3C), 45.3, 67.3, 79.9, 123.8, 133.8, 134.7, 134.7, 136.4, 147.7, 150.5, 155.2; LRMS (ES): *m/z* 877 (30), 439 (100), 383 (10).

(+)-*tert*-Butyl-(1*R*,4*S*)-2-(6-chloropyridin-3-yl)-4-hydroxycyclohex-2-enylcarbamate **9**

To an ice cooled solution of carbamate (+)-**8** (0.90 g, 2.05 mmol) in THF (8 mL) was added a THF solution of tetrabutylammonium fluoride (1 M, 4.48 mL, 4.51 mmol). The reaction mixture was stirred at room temperature for 1 h under nitrogen. Saturated aq. NH_4Cl (15 mL) was then added and the mixture extracted with EtOAc (3 × 15 mL). The combined organic extract was dried (Na_2SO_4), concentrated *in vacuo* and the crude product purified by flash chromatography (20% EtOAc in hexanes, then 50% EtOAc in hexanes) to give compound (+)-**9** as an off-white low melting solid (0.63 g, 95%); m.p. 54–56 $^\circ\text{C}$; $[\alpha]_D$ +80.3 (*c* 0.6, CHCl_3); R_f 0.22 (50% EtOAc in hexanes); HRMS (ES): found $[\text{M} + \text{H}]^+$ 325.1308, $\text{C}_{16}\text{H}_{22}\text{ClN}_2\text{O}_3$ requires 325.1319; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.37 (9H, s, OCMe_3), 1.63–1.71 (2H, m, 5-H, OH) 1.84–1.95 (1H, m, 6-H), 1.96–2.10 (2H, m, 5'-H, 6'-H), 4.37 (1H, m, 4-H), 4.63–4.70 (2H, m, 1-H, NHBoc), 6.23 (1H, d, *J* 3.0, 3-H), 7.28 (1H, d, *J* 8.4, Ar-5-H), 7.70 (1H, dd, *J* 8.4, 2.5, Ar-4-H), 8.44 (1H, d, *J* 2.5, Ar-2-H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 27.2, 28.0, 28.3 (3C), 45.6, 66.3, 80.0, 123.8, 133.0, 133.2, 136.2, 136.4, 147.6, 150.6, 155.2; LRMS (ES): *m/z* 649 (10), 325 (100), 269 (40), 217 (25).

(-)-*tert*-Butyl-(1*R*,2*R*,4*S*)-2-(6-chloropyridin-3-yl)-4-hydroxycyclohexylcarbamate **10**

To a solution of allylic alcohol (-)-**9** (100 mg, 0.304 mmol), in EtOH (7 mL) was added PtO_2 (10 mg, 10% by wt) and the mixture stirred for 5 h under 1 atm. of hydrogen at room temperature. When the reaction had progressed to 70% completion, as monitored by $^1\text{H-NMR}$ spectroscopy, the catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The residue obtained was purified by flash chromatography (60% EtOAc in hexanes) to give compound (-)-**10**, a white solid (60 mg, 60%) and unreacted starting material (24 mg, 24%); $[\alpha]_D$ -41.5 (*c* 0.5, CHCl_3); R_f 0.15 (50% EtOAc in hexanes); HRMS (ES): found $[\text{M} + \text{Na}]^+$ 349.1290, $\text{C}_{16}\text{H}_{23}\text{ClN}_2\text{O}_3\text{Na}$ requires 349.1295; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.26 (9H, s, OCMe_3), 1.37–1.39 (1H, m, 6-H), 1.65–1.81 (2H, m, 3-H, 5-H), 1.93–2.12 (3H, m, 3'-H, 5'-H, 6'-H), 2.91 (1H, d, *J* 13.5, 2-H), 3.79 (1H, m, 4-H), 4.03 (1H, br s, 1-H), 4.72 (1H, d, *J* 9.6, NHBoc), 7.24 (1H, d, *J* 8.2, Ar-5-H), 7.50 (1H, dd, *J* 8.2, 2.4, Ar-4-H), 8.22 (1H, d, *J* 2.0, Ar-2-H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 28.2 (3C), 29.6, 29.8, 34.4, 42.2, 48.5, 69.8, 79.6, 123.9, 136.2, 138.4, 148.7, 149.8, 155.0; LRMS (ES): *m/z* 1387 (3), 1061 (13), 739 (10), 675 (28), 556 (70), 413 (30), 349 (100), 293 (40), 239 (25). The spectral characteristics of compound (-)-**10** were identical to those reported.^{12,13}

(-)-(1*S*,3*R*,4*R*)-4-(*tert*-Butoxycarbonylamino)-3-(6-chloropyridin-3-yl)cyclohexyl methanesulphonate **11**

An ice cooled solution of alcohol (-)-**10** (50 mg, 0.15 mmol) in dry CH_2Cl_2 (4 mL) containing Et_3N (0.31 mL, 2.20 mmol) was treated with methanesulphonyl chloride (0.15 mL, 1.97 mmol). After stirring the reaction mixture for 20 minutes at 0 $^\circ\text{C}$, it was diluted with EtOAc (20 mL) and then washed successively with

sat. NaHCO_3 (2×10 mL), sat. NH_4Cl (2×10 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and the yellow oil obtained was purified by PLC (50% EtOAc in hexanes) to furnish mesylate $(-)\text{-11}$ as a colourless oil (56 mg, 91%); $[\alpha]_D -56.7$ (*c* 0.96 , CH_2Cl_2); R_f 0.2 (50% EtOAc in hexanes); HRMS (ES): found $[\text{M}+\text{H}]^+$ 405.1257 , $\text{C}_{17}\text{H}_{26}\text{ClN}_2\text{O}_5\text{S}$ requires 405.1251 ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.25 (9H, s, OCMe_3), 1.65 – 1.69 (1H, m, 6-H), 1.75 – 1.86 (1H, m, 5-H), 1.96 – 2.09 (2H, m, 2-H, 5'-H), 2.15 – 2.23 (1H, m, 6'-H), 2.24 – 2.34 (1H, m, 2'-H), 2.97 (1H, br d, *J* 13.8 , 3-H), 3.03 (3H, s, SO_2Me), 4.06 (1H, br s, 4-H), 4.76 (1H, dddd, *J* 11.2 , 11.2 , 5.3 , 5.3 , 1-H), 7.26 (1H, m, Ar-5-H), 7.50 (1H, dd, *J* 8.3 , 2.5 , Ar-4-H), 8.22 (1H, br s, Ar-2-H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 14.3 , 21.1 , 22.7 , 28.2 (3C), 31.8 , 39.0 , 42.2 , 60.5 , 79.2 , 124.0 , 135.1 , 138.2 , 148.6 , 150.1 , 171.3 ; LRMS (ES): *m/z* 405 (98), 239 (32), 217 (100). The spectral characteristics of compound $(-)\text{-11}$ were identical to those reported.^{12,13}

$(-)\text{-}tert\text{-Butyl (1R,2R,4R)-4-bromo-2-(6-chloropyridin-3-yl)cyclohexylcarbamate 12}$

Anhydrous LiBr (129 mg, 1.48 mmol) was added to a solution of mesylate $(-)\text{-11}$ (30 mg, 0.07 mmol) in dry THF (5 mL) and the mixture heated at 60 °C for 36 h. The reaction mixture was cooled, diluted with EtOAc (40 mL), washed with brine (2×30 mL), dried (Na_2SO_4) and concentrated to give a yellow oil. Purification of the oil by PLC (20% EtOAc in hexanes) yielded compound $(-)\text{-12}$ as a white crystalline solid (23 mg, 78%); $[\alpha]_D -26.2$ (*c* 1 , CHCl_3); R_f 0.36 (20% EtOAc in hexanes); HRMS (ES): found $[\text{M} + \text{Na}]^+$ 411.0430 , $\text{C}_{16}\text{H}_{22}\text{ClN}_2\text{O}_2\text{NaBr}$ requires 411.0451 ; $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (9H, br s, OCMe_3), 1.84 (1H, m, 6-H), 1.96 (1H, m, 5-H), 2.06 (1H, m, 5'-H), 2.13 – 2.36 (3H, m, 6'-H, 3-H, 3'-H), 3.52 (1H, dt, *J* 12.2 , 3.4 , 2-H), 4.10 (1H, br s, 1-H), 4.62 (1H, br s, NHBoc), 4.81 (1H, m, 4-H), 7.27 (1H, d, *J* 2.3 , Ar-5-H), 7.52 (1H, dd, *J* 8.5 , 2.3 , Ar-4-H), 8.22 (1H, br s, Ar-2-H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 26.5 , 28.1 (3C), 29.1 , 33.3 , 38.4 , 49.3 , 51.6 , 79.9 , 123.9 , 136.1 , 138.6 , 148.7 , 149.9 , 155.0 ; LRMS (ES): *m/z* 507 (20), 467 (30), 413 (100), 239 (60). The spectral characteristics of compound $(-)\text{-12}$ were identical to those reported.^{12,13}

$(1R,2R,4R)\text{-4-Bromo-2-(6-chloropyridin-3-yl)cyclohexanamine 13}$

Trifluoroacetic acid (0.4 mL) was added to a solution of protected amine $(-)\text{-12}$ (23 mg, 0.06 mmol), in dry CH_2Cl_2 (3 mL) and the mixture stirred at room temperature for 1.5 h. The reaction mixture was diluted with CHCl_3 (25 mL), washed with 10% aq. K_2CO_3 (25 mL) and the organic layer separated. The aq. layer was extracted with CHCl_3 (15 mL), the combined organic extract dried (K_2CO_3) and concentrated under reduced pressure to give the crude amine bromide 13 as light yellow oil (16 mg, 94%). It showed spectral characteristics identical to those reported^{12,13} and was used for the next step without further purification. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.67 (1H, dq, *J* 13.5 , 3.4 , 6-H), 1.91 (1H, m, 5-H), 1.98 (1H, m, 3-H), 2.26 (1H, tt, *J* 13.4 , 3.1 , 6'-H), 2.35 (1H, tt, *J* 13.5 , 3.3 , 5'-H), 2.67 (1H,

ddd, *J* 14.1 , 12.8 , 3.1 , 3-H), 3.35 (1H, m, 1-H), 3.44 (1H, dt, *J* 12.8 , 3.1 , 2-H), 4.87 (1H, t, *J* 3.1 , 4-H), 7.29 (1H, d, *J* 8.2 , Ar-5-H), 7.53 (1H, dd, *J* 8.2 , 2.6 , Ar-4-H), 8.28 (1H, d, *J* 2.6 , Ar-2-H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 27.8 , 28.6 , 29.8 , 32.0 , 50.1 , 54.3 , 124.2 , 137.5 , 138.4 , 149.5 , 149.9 .

$(-)\text{-Epibatidine}$

A solution of amine bromide 13 (16 mg, 0.055 mmol) in CHCl_3 (3 mL) was heated in a sealed tube at 55 °C for 3 days. The reaction mixture was diluted with CHCl_3 (30 mL) washed with 10% aqueous K_2CO_3 (15 mL) and the organic layer separated. The aq. layer was extracted with CHCl_3 (20 mL), the combined organic extract dried (K_2CO_3) and concentrated to give a light yellow oil. Purification by PLC ($95 : 5 : 0.5$, $\text{CH}_2\text{Cl}_2 : \text{MeOH} : \text{NH}_4\text{OH}$) furnished $(-)\text{-epibatidine}$ as a white solid (11 mg, 95%); $[\alpha]_D -6.1$ (*c* 1.0 , CHCl_3); HRMS (LCMS): found $[\text{M} + \text{H}]^+$ 209.0840 , $\text{C}_{11}\text{H}_{14}\text{ClN}_2$ requires 209.0840 ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.48 – 1.66 (5H, m, 3-H, 5-H, 5'-H, 6-H, 6'-H), 1.91 (1H, dd, *J* 12.2 , 9.3 , 3'-H), 2.27 (1H, br s, NH), 2.77 (1H, dd, *J* 9.3 , 4.9 , 2-H), 3.57 (1H, br d, *J* 1.9 , 1-H), 3.80 (1H, t, *J* 4.3 , 4-H), 7.23 (1H, d, *J* 8.3 , Ar-5-H), 7.76 (1H, dd, *J* 8.3 , 2.5 , Ar-4-H), 8.27 (1H, d, *J* 2.5 , Ar-2-H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 30.2 , 31.4 , 40.4 , 44.7 , 56.6 , 62.9 , 124.1 , 137.8 , 141.1 , 148.9 , 149.1 . LRMS (ES): *m/z* 209 (62), 192 (100), 166 (54), 126 (82). The spectral data of $(-)\text{-epibatidine}$ was in good agreement with literature values.^{12,13}

$(+)\text{-}tert\text{-Butyl (1R,4S)-2-bromo-4-hydroxycyclohex-2-enylcarbamate 14}$

To an ice cooled solution of silyl ether $(+)\text{-7}$ (102 mg, 0.192 mmol) in $\text{THF}-\text{H}_2\text{O}$ (2 mL, $3 : 1$) was added a THF solution of tetrabutylammonium fluoride (1 M, 1 mL, 1.0 mmol) and the mixture stirred overnight at room temperature. The solvents were removed under reduced pressure and the residual light yellow oil purified by PLC (40% EtOAc in hexanes) to give compound $(+)\text{-14}$ as a clear oil (46 mg, 82%); $[\alpha]_D +36.6$ (*c* 0.50 , CHCl_3); R_f 0.31 (40% EtOAc in hexanes); HRMS (ES): found $[\text{M} + \text{Na}]^+$ 314.0352 , $\text{C}_{11}\text{H}_{18}\text{NO}_3\text{BrNa}$ requires 314.0368 ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.47 (9H, s, CMe_3), 1.62 (1H, m, 5-H), 1.97 (3H, m, 5'-H, 6-H, 6'-H), 4.22 (2H, m, 1-H, 4-H), 4.86 (1H, s, NHBoc), 6.29 (1H, d, *J* 2.69 , 3-H); $^{13}\text{C-NMR}$ (100 MHz): δ 27.5 , 28.0 , 28.5 (3C), 52.0 , 67.4 , 80.1 , 127.3 , 135.9 , 155.4 ; LRMS (EI): *m/z* 279 (5), 277 (5), 234 (10), 236 (10), 217 (30), 175 (10), 156 (100), 94 (50).

$(-)\text{-}(R)\text{-}tert\text{-Butyl 4-oxocyclohex-2-enylcarbamate 15}$

A slow stream of argon gas was bubbled through a mixture of allylic alcohol $(+)\text{-14}$ (32 mg, 0.11 mmol), toluene (1 mL) and aq. Na_2CO_3 (2 M, 0.4 mL) to displace any oxygen present in the solution. $\text{PdCl}_2(\text{dpf})$ (9.4 mg, 0.013 mmol) was added to the mixture under a flow of argon. The reaction mixture was then heated under reflux with stirring for 6 h. The solvent was removed under reduced pressure, the residue taken up in EtOAc (5 mL), washed with brine (2×5 mL), dried (Na_2SO_4) and concentrated to give the crude product 15 as a yellow oil.

Purification by PLC (20% EtOAc in hexane) yielded the enone (*–*)-15 as a white solid (19 mg, 82%); m.p. 117–118 °C, lit. m.p. 117–118; R_f 0.21 (20% EtOAc in hexane); $[\alpha]_D^{20} +120.0$, (*c* 0.50, CH_2Cl_2); lit. (*ent*) $[\alpha]_D^{20} -123.6$ (*c* 1.14, CH_2Cl_2);⁸ HRMS (EI): found ($\text{M}^+ - \text{tBu}$) 155.0587, $\text{C}_{11}\text{H}_{17}\text{NO}_3$ requires 155.0577; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.48 (9H, s, CMe_3), 1.89 (1H, m, 6-H), 2.33 (1H, m, 6'-H), 2.50 (2H, m, 5-H, 5'-H), 4.53 (1H, br m, 1-H), 4.66 (1H, br m, NHBoc), 6.01 (1H, ddd, *J* 10.2, 2.3, 0.8, 3-H), 6.83 (1H, ddd, *J* 10.2, 2.4, 1.6, 2-H); $^{13}\text{C-NMR}$ (100 MHz): δ 28.7 (3C), 30.4, 36.3, 47.4, 66.0, 130.7, 151.2, 155.4, 198.4. LRMS (EI): *m/z* 155 (48), 138 (20), 95 (50), 94 (100), 83 (48).

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