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Enantioselective reduction of heteroaromatic β,γ-unsaturated ketones as an alternative to allylboration of aldehydes. Application: asymmetric synthesis of SIB-1508Y

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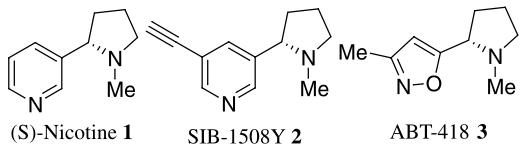
Abstract—Enantioselective reduction of heteroaromatic β,γ-unsaturated ketones was found to be an efficient and convenient alternative to the allylboration of corresponding aldehydes. This new method was used for the formal asymmetric synthesis of SIB-1508Y **2**. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The therapeutic potential of nicotine **1** for central nervous system (CNS) disorders such as Alzheimer's disease and Parkinson's disease is being recognized.[1] However, nicotine's cognitive-enhancing properties are severely limited by side effects, particularly on the cardiovascular and gastrointestinal systems.[2] Interest in the discovery of new agents, such as SIB-1508Y **2** or ABT-418 **3** (Fig. 1), that directly interact with nicotinic acetylcholine receptors (nAChR) for the treatement of CNS disorders, has increased during the last decade.[3] Moreover, several studies have shown that the (*S*)-enantiomer of nicotine displays a higher affinity for nicotinic receptors than the (*R*)-enantiomer; a tendency also established for many analogues.[4]

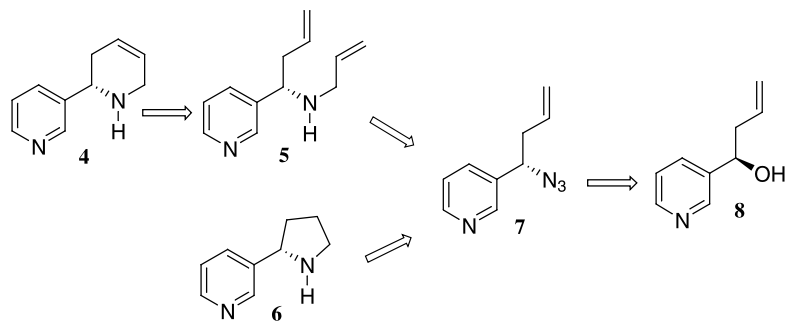


(S)-Nicotine **1** SIB-1508Y **2** ABT-418 **3**

Figure 1.

This shows the importance of the control of chirality for the synthesis of new nAChR agonists. In connection with our efforts to investigate structure–activity relationships of nAChR ligands, we have recently reported the enantioselective synthesis of nicotine **1**,[5] SIB-1508Y **2**,[6] and other related piperidinic alkaloids.[7] The preparation of chiral homoallylic alcohols by enantioselective allylboration of aldehydes was a key step in our synthesis (Scheme1).

However, we found that the allylboration of heteroaromatic aldehydes with $^{l}Ipc_2Ball$ **9** gave, in some cases, homoallylic alcohols with low enantioselectivities. Also, the use of this moisture sensitive chiral allylborane reagent is not so



Scheme 1.

Keywords: allylboration; enantioselective reduction; ketone; SIB-1508Y.

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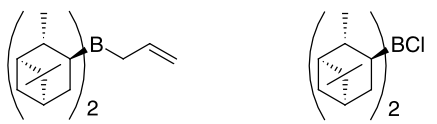
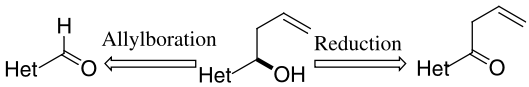
convenient mainly due to the difficulty of preparing and handling it. Moreover, in some cases, the low reaction temperature led to crystallization of the aldehyde substrate. To our knowledge, only one report has described the asymmetric allylation of heterocyclic aldehydes in which allylboration of thiophenecarboxaldehyde derivatives with Ipc_2Ball was not totally enantioselective (75–80% ee).[8] Thus, an alternative route to prepare chiral homoallylic alcohols was investigated using an enantioselective reduction of the corresponding β,γ-unsaturated ketone with (+)-DIP-chloride™ ((+)-DIP-Cl) **10**.[9] To the best of our knowledge, the enantioselective reduction of heteroaromatic β,γ-unsaturated ketones has not yet been reported in the literature (Fig. 2).



$^{l}Ipc_2BAll$ **9** (+)-DIP-Chloride™ **10**

Figure 2.

Due to the importance of the chiral homoallylic alcohols in the preparation of new nAChR agonists, we have carried out a systematic comparison between allylboration of heteroaromatic aldehydes and reduction of β,γ-unsaturated ketones (Scheme 2).



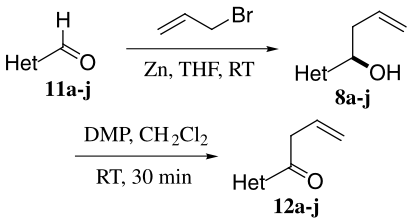
Scheme 2.

The synthetic utility of this process is demonstrated by the asymmetric synthesis of SIB-1508Y **2** that displays potent activity against Parkinson's disease.[10]

2. Results and discusssion

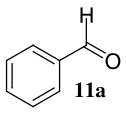
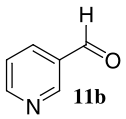
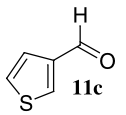
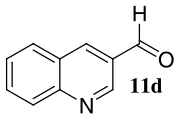
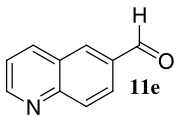
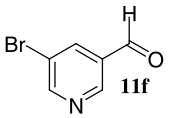
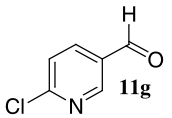
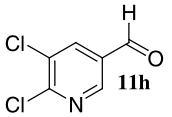
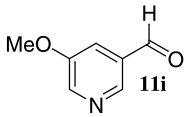
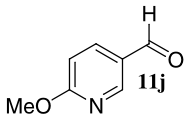
2.1. Allylboration

$^{l}Ipc_2Ball$ was initially prepared by the hydroboration–methanolysis of (−)-α-pinene, followed by the reaction of the borinate with allylmagnesium bromide.[11] This chiral allylborane, in the presence of aldehydes, furnishes homoallylic alcohols with low enantioselectivities. This failure led us to check the quality of the Ipc_2BOMe intermediate. The ^{11}B NMR spectrum of Ipc_2BOMe showed a mixture of Ipc_2BOMe (53.1 ppm), $IpcB(OMe)_2$ (31.8 ppm) and $B(OMe)_3$ (18.2 ppm) in respectively 77.5/19.8/2.7 ratio. The use of this impure reagent in the preparation of $^{l}Ipc_2Ball$ **9** and subsequently in asymmetric allylboration led to modest enantioselectivities. Thus, we decided to prepare $^{l}Ipc_2Ball$ from the commercially available (+)-DIP-Cl **10**, following the literature.[12] As we have previously reported, 2.2 equiv. of allylborane is necessary for allylation of heteroaromatic aldehydes such as **8b** with basic nitrogen in Et_2O at −100°C. Only modest yields and low enantioselectivities were obtained with 1.1 equiv. It has been shown that the basic pyridyl nitrogen atom complexes boron



Scheme 3.

Table 1. Synthesis of homoallylic alcohols and ketones

Entry	Aldehyde	Alcohol, yield (%)	Ketone, yield (%)
1	 **11a**	**8a**, 98	**12a**, quant.
2	 **11b**	**8b**, 97	**12b**, 60+40 of α,β-isomer
3	 **11c**	**8c**, 98	**12c**, quant.
4	 **11d**	**8d**, 66	**12d**, quant.
5	 **11e**	**8e**, 87	**12e**, quant.
6	 **11f**	**8f**, 97	**12f**, quant.
7	 **11g**	**8g**, 98	**12g**, quant.
8	 **11h**	**8h**, 90	**12h**, quant.
9	 **11i**	**8i**, 85	**12i**, quant.
10	 **11j**	**8j**, 86	**12j**, quant.

atoms easily.[13] This resulting ate-complex is a less efficient chiral reagent. A major difficulty in the synthesis of pyridine derivatives concerns the coordination of catalysts or reagents to the basic pyridine nitrogen. To save 1 equiv. of $^{l}Ipc_2Ball$ **9**, we attempted to complex the pyridine nitrogen with BEt_3 (−78°C, 1 h).[13c] But the allylboration conducted with 1.1 equiv. of $^{l}Ipc_2Ball$ under these experimental conditions led to a homoallylic alcohol with low yields and enantioselectivities.

2.2. Reduction

β,γ-Unsaturated ketones were obtained by oxidation of the corresponding racemic alcohol with Dess–Martin periodinane (DMP).[14] Starting from aldehyde, the racemic alcohol was prepared by allylation with allylbromide in the presence of Zn in nearly quantitative yields after flash chromatography. Aldehydes **11i–j** were prepared according to the literature.[15] The other aldehydes **11e–h** were directly obtained by reduction of the corresponding acid using *N*,*N*-dimethylchloromethyleniminium and lithium tri-*tert*-butoxyaluminium hydride according to the conditions reported by Fujisawa et al.[16]

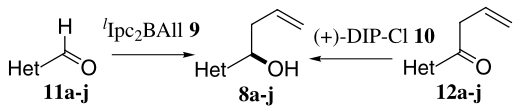
Oxidation of racemic alcohols in very mild conditions using the DMP, led to an unstable ketone in near quantitative yields. In acidic or basic media, ketones were rapidly isomerized to the more stable α,β-unsaturated derivatives. However in neutral conditions, we did not detect isomerization of ketones except for compound **12b**. Other oxidising agent were checked such as Jones reagent or PCC, but under these acidic conditions, ketones spontaneously isomerized into α,β-unsaturated derivatives (Scheme 3 and Table 1).

Reduction of homoallylic ketones was performed with commercially available reagent (+)-DIP-Cl **10**. The choice of this chiral reducing reagent was dictated by previous results described in the literature on pyridine derivatives.[13a,b] Asymmetric reduction of prochiral pyridinyl ketones by Corey's oxazaborolidine gave modest enantioselectivities probably due to complexation between the nitrogen of pyridine and the catalyst. To overcome this problem, an excess of $BH_3{\cdot}Me_2S$ was used, but these conditions were incompatible with double bonds.[17]

Brown described the reduction of 3-acetyl pyridine to the corresponding alcohol with 92% ee with DIP-Cl **10**. This seems to be one of the best chiral reducing reagents of prochiral ketones.[18] One of the major points of DIP-Cl **10** is its ease of use with reproducible results and more convenient temperature conditions (−30°C in THF). It should be noted that 2.2 equiv. of the reagent was used for the reduction. With only 1 equiv., no reduction was observed. (see Section 2.1).

2.3. Results

Representative heterocyclic homoallylic alcohols were obtained by allylboration or reduction. In many cases, reduction was the best method to give heterocyclic homoallylic alcohols with high ee (>90%) (Scheme 4 and Table 2). The limitation of this method was the stability of the homoallylic ketone as for **12b**. However in this case, the



Scheme 4.

Table 2. Synthesis of chiral homoallylic alcohols

Entry	Product	Allyoboration		Reduction	
		ee (%)	Yield (%)	ee (%)	Yield (%)
1	(*R*)-**8a**	95	83	99	84
2	(*R*)-**8b**	94	94	90	50
3	(*R*)-**8c**	79	90	94	81
4	(*R*)-**8d**	92	75	89	83
5	(*R*)-**8e**	No reaction		93	70
6	(*R*)-**8f**	66	75	94	79
7	(*R*)-**8g**	85.5	74	95	80
8	(*R*)-**8h**	90	73	96	80
9	(*R*)-**8i**	91.5	75	94	71
10	(*R*)-**8j**	88	78	92	70

reduction conducted on the mixture of α,β and β,γ unsaturated isomers of **12b**, led to the alcohol (*R*)-**8b** with modest yield (50%) but with good ee (90%).

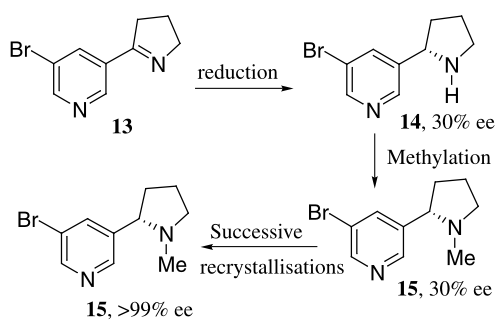
Contrary to the reduction, the allylboration gave no constant results in yields and ee. The asymmetric allylation of **11a–b**, **11d** and **11g–j** afforded the corresponding heterocyclic homoallylic alcohol with good to high enantiomeric purities (86–95%). On the contrary, the allylation gave modest ee with **11f** and **11c** and very poor with **11e**. The reason for these modest results is not clear.

It should be noted that all configurations of unknown chiral homoallylic alcohols were confirmed by analysis of the ^1H NMR spectrum of their (*R*)-*O*-acetyl-mandelic ester derivatives.[19]

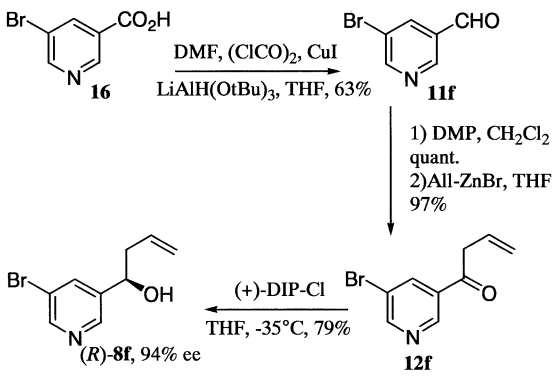
The synthetic utility of the reduction as an alternative to allylboration is demonstrated by the formal asymmetric synthesis of SIB-1508Y **2**.

2.4. Formal synthesis of SIB-1508Y 2

Recently, SIBIA neurosciences laboratories reported the synthesis of the new nAChR agonist SIB-1508Y **2**.[20] It should be noted that, to our knowledge, researchers have made several unsuccessful attempts at the asymmetric preparation of (*S*)-**15**.[21] The synthesis of enantiopure SIB-1508Y **2** was finally accomplished using a combination



Scheme 5.

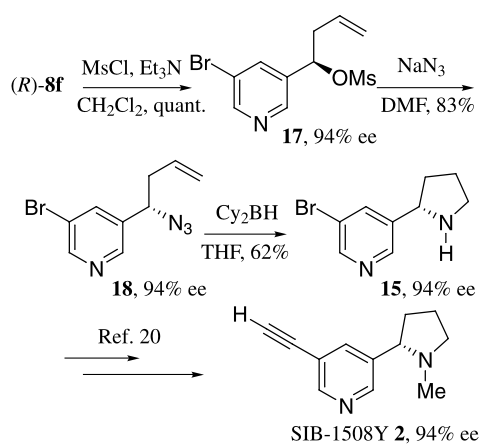


Scheme 6.

of enantioselective reduction, providing materials with 30% ee, followed by resolution via crystallization of a diastereomeric salt with a tartric acid derivative (Scheme 5).

Our synthesis started with the homoallylic alcohol (*R*)-**8f** previously obtained with 94% ee in 48% yield over four steps from commercially available 5-bromonicotinic acid **16** (Scheme 6).

The next step involved the conversion of alcohol (*R*)-**8f** to the corresponding azide **18** by nucleophilic substitution of the chiral mesylate **17** (Scheme 7). No decrease in optical purity was observed during the transformation. Indeed, on a benzylic position this reaction sometimes competes with an S_N1 reaction process, with a resulting decrease in optical purity.[22] The conversion of alcohol (*R*)-**8f** to the azide **18** via the displacement of the corresponding mesylate **17** in 83% over two steps was found to be better that Mitsunobu conditions[23] (DPPA, DEAD, $P(Ph)_3$) which led to a complex mixture and low yields. Formation of the pyrrolidine ring was achieved by an original procedure which involved an intramolecular hydroboration–cyclo-alkylation sequence developed by Carboni and Vaultier.[24] When treated with an excess of dicyclohexylborane in THF, azide **18** was transformed into the (*S*)-5-bromo-3-(1-*H*-2-pyrrolidinyl)pyridine **15** with total retention of configuration in 62% yield. Enantiomeric excess and absolute stereochemistry were determined by hydrogenation of **15** to afford a compound which was identical in all respects to (*S*)-nornicotine with 94% ee. Finally, conversion of the



Scheme 7.

(*S*)-5-bromonornicotine **15** to the SIB-1508Y **2** was achieved according to the conditions previously reported in the literature.

3. Conclusion

Our present study has shown that the enantioselective reduction of heteroaromatic β,γ-unsaturated ketone is an easy and efficient alternative to the allylboration of aldehydes for the preparation of optically active homoallylic alcohols with high ee. The utility of this process was demonstrated by the formal synthesis of nAChR agonist SIB-1508Y. Use of this new method for the synthesis of nicotinic analogues and studies of the structure–activity relationships are in progress.

4. Experimental

4.1. General

^1H NMR, ^{13}C NMR spectra were recorded at 200 and 50 MHz using residual $CDCl_3$ (7.26 ppm) and $CDCl_3$ (77.16 ppm) as internal standard, respectively. Flash column chromatography was performed on Merck silica gel (60 Å, 230–400 mesh). All ee were determined by Chiral HPLC with a CHIRACEL OD-H column, 46×15 cm, flow rate 0.5 mL/min. (+)-DIP-chloride™ is a trademark of the Aldrich Chemical Company. All reactions were performed under N_2 in a flame-dried flask using anhydrous solvents.

4.2. Reduction of acids to aldehydes: general procedure

To a solution of DMF (38.8 mL, 0.50 mol) in anhydrous CH_2Cl_2 (80 mL) at −20°C, oxalyl chloride (13 mL, 0.15 mol) was added. After 90 min, the mixture was concentrated under reduced pressure. Then dry acetonitrile (70 mL) and THF (160 mL) were added at −30°C and a solution of acid (50 mmol) in THF (70 mL) and pyridine (4.1 mL, 50 mmol) was added dropwise. The resulting mixture was stirred for 90 min at −30°C, cooled to −78°C and a solution of copper iodide (10% mol) and tri-*tert*-butoxyaluminium hydride (25.4 g, 0.1 mol) in THF (90 mL) was added. After stirring for 15 min, the reaction was quenched with 7% aqueous HBr solution. The resulting mixture was allowed to warm up to room temperature and basified with 30% aqueous NaOH solution. The aqueous layer was extracted with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by flash chromatography to give the corresponding aldehyde.

4.2.1. Quinoline-6-carboxyaldehyde (11e). Purification by flash chromatography (60% ethyl acetate–hexane) gave aldehyde **11e** (2.59 g, 33%) as a pale yellow solid. Mp 75–76°C (lit.[25] mp 75–76°C); IR (KBr) 1431, 1693, 2859 cm^{-1}. ^1H NMR δ 7.48 (dd, 1H, J=4.3, 8.4 Hz), 8.16 (s broad, 2H), 9.00–9.03 (m, 1H), 10.16 (s, 1H); ^{13}C NMR δ 122.3, 126.8, 127.8, 130.9, 133.7, 134.4, 137.5, 151.0, 1503.2, 191.5. MS (EI) *m/z* 157 (M^+).

4.2.2. 5-Bromo-pyridine-3-carboxyaldehyde (11f). Purification by flash chromatography (50% ethyl acetate–hexane) gave aldehyde **11f** (5.86 g, 63%) as a white solid. Mp 95°C (lit.[26] mp 95–96°C); IR (KBr) 1580, 1711, 2720, 2827 cm^{-1}. ^1H NMR δ 8.26–8.29 (m, 1H), 8.88 (d, 1H, J=1.8 Hz), 8.96 (d, 1H, J=1.8 Hz), 10.06 (s, 1H); ^{13}C NMR δ 121.8, 132.6, 138.1, 150.0, 155.9, 189.4. MS (EI) m/z 188 (M^+, ^{81}Br), 186 (M^+, ^{79}Br).

4.2.3. 6-Chloro-pyridine-3-carboxyaldehyde (11g). Purification by flash chromatography (30% ethyl acetate–hexane) gave aldehyde **11g** (3.75 g, 53%) as a white solid. Mp 79°C (lit.[27] mp 80°C); IR (KBr) 1561, 1589, 1701, 2876, 3064, 3096 cm^{-1}. ^1H NMR δ 7.46–7.50 (m, 1H), 8.11 (dd, 1H, J=2.4, 8.4 Hz), 8.82 (d, 1H, J=2.4 Hz), 10.06 (s, 1H); ^{13}C NMR δ 125.2, 130.4, 138.1, 152.4, 157.0, 189.3. MS (EI) m/z 141 (M^+, ^{35}Cl), 143 (M^+, ^{37}Cl), 140 ($M-H^+$, ^{35}Cl), 142 ($M-H^+$, ^{37}Cl).

4.2.4. 5,6-Dichloro-pyridine-3-carboxyaldehyde (11h). Purification by flash chromatography (30% ethyl acetate–hexane) gave aldehyde **11h** (2.73 g, 31%) as a pale yellow solid. Mp 42–43°C (lit.[28] mp 43°C). IR (KBr) 1578, 1716, 2857 cm^{-1}. ^1H NMR δ 8.22 (d, 1H, J=2.0 Hz), 8.75 (d, 1H, J=2.0 Hz), 10.07 (s, 1H); ^{13}C NMR δ 131.3, 132.0, 137.6, 149.0, 160.2, 188.2. MS (EI) m/z 175 (M^+, ^{35}Cl), 179 (M^+, ^{37}Cl).

4.3. Synthesis of homoallylic alcohols. Racemic allylation of aldehydes: general procedure—method A

A flask fitted with a dropping funnel and a condenser was charged with Zn (1.05 g, 16 mmol) and was covered with THF (1 mL). A solution of allylbromide (1.38 mL, 16 mmol) in THF (10 mL) was slowly added to maintain the temperature at 25–30°C. After the addition, the mixture was stirred for 1 h at room temperature. Then, a solution of aldehyde (8 mmol) in THF (10 mL) was slowly added, and the resulting mixture was stirred for an additional hour (except for aldehyde **8d** which was stirred for 12 h at reflux). After completion of the reaction, the resulting mixture was hydrolyzed with saturated aqueous NH_4Cl (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with brine (2×), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purifed by flash chromatography affording the homoallylic alcohol.

4.4. Allylboration of aldehydes: general procedure—method B

Preparation of allylborane reagent free of Mg^{2+} salts. A solution of commercial allylmagnesium bromide in ether (48 mL, 1 M, 48 mmol) was added to a solution of (+)-*B*-chlorodiisopinocampheylborane ((+)-DIP-Cl) (16.0 g, 49.9 mmol) in ether (50 mL) at 0°C. The resulting mixture was stirred for 1 h at room temperature and then concentrated in vacuo. The residue was extracted with anhydrous pentane (3×30 mL): stirring was discontinued to permit the Mg^{2+} salts to settle and the supernatant pentane extract was filtered over a pad of celite. Pentane was evaporated under reduced pressure to give *B*-allyldiisopinocampheylborane ($^{l}Ipc_2Ball$) (15.6 g, 96%) as a colourless oil.

Allylboration of aldehydes. To a solution of $^{l}Ipc_2Ball$ (7.18 g, 22 mmol) in ether (25 mL) at −100°C was slowly added via a cannula a solution of aldehyde (10 mmol) in ether (20 mL). After 1 h of stirring at −100°C, the reaction mixture was quenched with methanol (1 mL) and 1N aqueous HCl (10 mL). The mixture was basified with 30% aqueous NaOH solution until pH 12–13, and then extracted with CH_2Cl_2 (4×100 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography gave the chiral alcohol.

4.5. Reduction of carbonyl compounds: general procedure—method C

To a solution of (+)-DIP-Cl (3.53 g, 11 mmol) in THF (5 mL) cooled at −30°C was added a solution of ketone (5 mmol) in THF (2 mL). The resulting mixture was stirred overnight. After completion, acetaldehyde (1.68 mL, 30 mmol) was added to consume the excess (+)-DIP-Cl. The mixture was allowed to warm to room temperature and stirred for 1 h. The solvent was removed under reduced pressure and (−)-α-pinene formed during the reaction was collected by bulb to bulb distillation (50°C, 10 mm Hg, 1 h). The residue was dissolved in ether (30 mL) and quenched with 4N aqueous HCl (25 mL). The mixture was basified with solid KOH until pH 11–12 and extracted with ether (3×30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. Removal of the solvent left an oil which was purified by flash chromatography to afford the chiral alcohol.

4.5.1. (*R*)-1-Phenyl-but-3-en-1-ol (8a). Purification by flash chromatography (10% ethyl acetate–hexane) gave **8a** as a pale yellow oil. IR (KBr) 1641, 2079, 3030, 3076, 3383 cm^{-1}. ^1H NMR δ 2.04 (s broad, 1H), 2.49–2.57 (m, 2H), 4.75 (dd, 1H, J=5.9, 7.2 Hz), 5.13 (s, 1H), 5.18–5.23 (m, 1H), 5.73–5.94 (m, 1H), 7.27–7.39 (m, 5H); ^{13}C δ NMR 43.4, 73.2, 117.7, 125.7, 127.2, 128.1, 134.3, 143.8. MS (CI/NH_3) m/z 148 (M^+), 166 ($M+NH_4^+$). HPLC (hexane/*i*-PrOH=99/1, 25.0 min for (*R*)-alcohol and 31.7 min for (*S*)).

Method A: 1.16 g; 98%.

Method B: 1.23 g; 83%; 95% ee; $[\alpha]_D^{20}$=+44 (*c* 1.1, benzene), lit.[11a] $[\alpha]_D^{20}$=−44.92 (*c* 7.38, benzene).

Method C: 0.56 g; 76%; 99% ee; $[\alpha]_D^{20}$=+45.9 (*c* 1.3, benzene).

4.5.2. (*R*)-1-Pyridin-3-yl-but-3-en-1-ol (8b). Purification by flash chromatography (5% EtOH–CH_2Cl_2) gave **8b** as a pale yellow oil. IR (KBr) 1585, 1642, 2907, 2979, 3077, 3444 cm^{-1}. ^1H NMR δ 2.47 (m, 2H), 4.87 (t, 1H, J=6.6 Hz), 5.01–5.10 (m, 2H), 5.63–5.83 (m, 1H), 7.53 (dd, 1H, J=7.9 Hz, 4.1 Hz), 7.98 (d, 1H, J=7.9 Hz), 8.60 (d, 1H, J=4.1 Hz), 8.68 (s, 1H); ^{13}C NMR δ 43.1, 70.0, 119.2, 125.2, 132.8, 137.9, 141.8, 146.3, 147.1. MS (CI/ NH3) m/z 150 ($M+H^+$), 167 ($M+NH_4^+$). HPLC (Hexane/*i*-PrOH=95/5, 23.3 min for (*S*)-alcohol and 24.6 min for (*R*)).

Method A: 1.16 g; 97%.

Method B: 1.40 g; 94%; 94% ee; $[\alpha]_D^{20}$=+28 (*c* 1, EtOH), lit.[8] $[\alpha]_D^{20}$=−28 (*c* 1.03, EtOH).

Method C: 0.37 g; 50%; 90% ee; $[\alpha]_D^{20}$=+27.2 (*c* 1.1, EtOH).

4.5.3. (*R*)-1-Thiophen-3-yl-but-3-en-1-ol (8c). Purification by flash chromatography (10% ethyl acetate–hexane) gave **8c** as a yellow oil. IR (KBr) 1641, 2978, 3076, 3375 cm^{-1}. ^1H NMR δ 2.12 (s, 1H), 2.43–2.68 (m, 2H), 4.82 (t, 1H, *J*=6.9 Hz), 5.12–5.22 (m, 2H), 5.71–5.92 (m, 1H), 7.08 (dd, 1H, *J*=1.4, 5.0 Hz), 7.18–7.21 (m, 1H), 7.28 (dd, 1H, *J*=3.0, 5.0 Hz); ^{13}C δ NMR 43.1, 69.7, 118.6, 120.9, 125.7, 126.2, 134.3, 145.5. HRMS (EI) calcd for $C_8H_{10}O_1S_1$ (M^+) 154.0452, found: 154.0445. HPLC (hexane/*i*-PrOH=99/1, 26.0 min for (*R*)-alcohol and 29.2 min for (*S*)).

Method A: 1.21 g; 98%.

Method B: 1.39 g; 90%; 79% ee; $[\alpha]_D^{20}$=+11.3 (*c* 1.22, EtOH), lit.[8] $[\alpha]_D^{20}$=+14.4 (*c* 1.61, EtOH).

Method C: 0.62 g; 81%; 94% ee; $[\alpha]_D^{20}$=+13.8 (*c* 1.1, EtOH).

4.5.4. (*R*)-1-Quinolin-3-yl-but-3-en-1-ol (8d). Purification by flash chromatography (40% ethyl acetate–hexane) gave **8d** as a yellow solid. Mp 47–48°C; IR (KBr) 1636, 2943, 3138 cm^{-1}. ^1H NMR δ 2.56 (t, 2H, *J*=6.6 Hz), 4.91 (t, 1H, *J*=6.6 Hz), 5.05–5.16 (m, 2H), 5.69–5.89 (m, 1H), 7.44–7.75 (m, 3H), 7.98–8.08 (m, 2H), 8.72 (d, 1H, *J*=2.1 Hz); ^{13}C NMR δ 43.8, 71.2, 119.0, 126.9, 127.9, 128.9, 129.4, 132.9, 133.8, 137.0, 147.4, 149.4. HRMS (EI) calcd for $C_{10}H_{14}N_1O_1$ ($M+H^+$) 200.1075, found: 200.1076. HPLC (hexane/*i*-PrOH=95/5, 27.5 min for (*S*)-alcohol and 37.9 min for (*R*).

Method A: 1.05 g; 66%.

Method B: 1.49 g; 75%; 92% ee; $[\alpha]_D^{20}$=+27 (*c* 1.1, EtOH).

Method C: 0.83 g; 83%; 89% ee; $[\alpha]_D^{20}$=+26.1 (*c* 0.91, EtOH).

4.5.5. (*R*)-1-Quinolin-6-yl-but-3-en-1-ol (8e). Purification by flash chromatography (5% EtOH–CH_2Cl_2) gave **8e** as a yellow solid. Mp 69–70°C; IR (KBr) 1577, 1642, 2976, 3060, 3164 cm^{-1}. ^1H NMR δ 2.47–2.66 (m, 2H), 3.38 (s, 1H), 4.92 (t, 1H, *J*=6.7 Hz), 5.09–5.20 (m, 2H), 5.71–5.92 (m, 1H), 7.31–7.37 (dd, 1H, *J*=4.3, 8.2 Hz), 7.64–7.69 (dd, 1H, *J*=1.8, 8.2 Hz), 7.75 (s broad, 1H), 8.01 (d, 1H, *J*=8.9 Hz), 8.08 (d, 1H, *J*=8.9 Hz), 8.77–8.80 (dd, 1H, *J*=4.3, 1.8 Hz); ^{13}C NMR δ 43.9, 73.0, 118.7, 121.3, 124.3, 127.9, 128.1, 129.4, 134.3, 136.3, 142.6, 147.8, 150.2. HRMS (CI/NH_3) calcd for $C_{10}H_{14}N_1O_1$ ($M+H^+$) 200.1075, found: 200.1067. HRMS (EI) calcd for $C_{10}H_{12}N_1O_1$ ($M-H^+$) 198.0919, found: 198.0923. HPLC (hexane/*i*-PrOH=96/4, 87.9 min for (*R*)-alcohol and 95.9 min for (*S*)).

Method A: 1.39 g; 87%.

Method B: no reaction.

Method C: 0.70 g; 70%; 93% ee; $[\alpha]_D^{20}$=+18.4 (*c* 0.74, EtOH).

4.5.6. (*R*)-1-(5-Bromo-pyridin-3-yl)-but-3-en-1-ol (8f). Purification by flash chromatography (30% ethyl acetate–hexane) gave **8f** as a pale yellow oil. IR (KBr) 1642, 2979, 3076, 3258 cm^{-1}. ^1H NMR δ 2.37–2.57 (m, 2H), 3.43 (s broad, 1H), 4.76 (t, 1H, *J*=6.7 Hz), 5.10–5.20 (m, 2H), 5.67–5.88 (m, 1H), 7.89 (app t, 1H, *J*=2.3 Hz), 8.40 (d, 1H, *J*=2.3 Hz), 8.50 (d, 1H, *J*=2.3 Hz); ^{13}C NMR δ 43.8, 70.3, 119.5, 121.0, 133.2, 136.7, 141.5, 145.7, 149.6. MS (CI/NH_3) *m/z* 228 ($M+H^+$, ^{79}Br), 230 ($M+H^+$, ^{81}Br). HRMS (EI) calcd for $C_9H_{11}N_1O_1Br_1$ ($M+H^+$) 228.0024, found: 228.0019. HPLC (hexane/*i*-PrOH=98/2, 25.4 min for (*S*)-alcohol and 26.8 min for (*R*).

Method A: 1.77 g; 97%.

Method B: 1.71 g; 75%; 66% ee; $[\alpha]_D^{20}$=+11 (*c* 1.23, MeOH).

Method C: 0.90 g; 79%; 94% ee; $[\alpha]_D^{20}$=+16.2 (*c* 1.47, MeOH).

4.5.7. (*R*)-1-(6-Chloro-pyridin-3-yl)-but-3-en-1-ol (8g). Purification by flash chromatography (20% ethyl acetate–hexane) gave **8g** as a colourless oil. IR (KBr) 1589, 1598, 1642, 2980, 3078, 3363 cm^{-1}. ^1H NMR δ 2.45 (t, 2H, *J*=6.3 Hz), 3.37 (d, 1H, *J*=3.2 Hz), 4.75 (dt, 1H, *J*=3.2, 6.3 Hz), 5.04–5.13 (m, 2H), 5.63–5.83 (m, 1H), 7.25 (d, 1H, *J*=8.2 HZ), 7.64 (dd, 1H, *J*=2.4, 8.2 Hz), 8.23 (d, 1H, *J*=2.4 Hz); ^{13}C NMR δ 43.7, 70.3, 119.3, 124.1, 133.3, 136.8, 138.5, 147.6, 150.2. MS (CI/NH_3) *m/z* (^{35}Cl), (^{37}Cl). HRMS (EI) calcd for $C_9H_{11}N_1O_1Cl_1$ ($M+H^+$) 184.0529, found: 184.0526. HPLC (hexane/*i*-PrOH=95/5, 16.0 min for (*R*)-alcohol and 19.1 min for (*S*)).

Method A: 1.44 g; 98%.

Method B: 1.17 g; 74%; 85.5% ee; $[\alpha]_D^{20}$=+64.2 (*c* 1.12, EtOH).

Method C: 0.74 g; 80%; 95% ee; $[\alpha]_D^{20}$=+72 (*c* 1.48, EtOH).

4.5.8. (*R*)-1-(5,6-Dichloro-pyridin-3-yl)-but-3-en-1-ol (8h). Purification by flash chromatography (20% ethyl acetate–hexane) gave **8h** (1.57 g, 90%) as a colourless oil. IR (KBr) 1641, 2981, 3078, 3376 cm^{-1}. ^1H NMR δ 2.42–2.50 (m, 2H), 3.26 (d, 1H, *J*=3.3 Hz), 4.72–7.80 (m, 1H), 5.06–5.16 (m, 2H), 5.63–5.84 (m, 1H), 7.79 (d, 1H, *J*=2.1 Hz), 8.15 (d, 1H, *J*=2.1 Hz); ^{13}C NMR δ 43.6, 69.7, 119.8, 130.5, 132.8, 136.7, 140.2, 145.0, 147.8. HRMS (EI) calcd for $C_9H_{10}N_1O_1Cl_2$ ($M+H^+$) 218.0139, found: 218.0139. HPLC (hexane/*i*-PrOH=99/1, 48.5 min for (*R*)-alcohol and 52.5 min for (*S*)).

Method A: 1.57 g; 90%.

Method B: 1.58 g; 73%; 90% ee; $[\alpha]_D^{20}$=+18.2 (*c* 1.1, EtOH).

Method C: 0.87 g; 80%; 96% ee; $[\alpha]_D^{20}$=+19.8 (*c* 1.1, EtOH).

4.5.9. (*R*)-1-(5-Methoxy-pyridin-3-yl)-but-3-en-1-ol (8i). Purification by flash chromatography (2% EtOH–CH_2Cl_2) gave **8i** as a colourless oil. IR (KBr) 1588, 1641, 2935, 3076, 3228 cm^{-1}. ^1H NMR δ 2.52 (t, 2H, J=6.9 Hz), 3.22 (s, 1H), 3.86 (s, 3H), 4.78 (t, 1H, J=6.6 Hz), 5.11–5.20 (m, 2H), 5.70–5.91 (m, 1H), 7.27–7.29 (m, 1H), 8.09 (s broad, 1H), 8.13 (s broad, 1H); ^{13}C NMR δ 43.7, 55.6, 70.7, 118.4, 133.9, 135.9, 139.5, 141.0, 155.9. HRMS (CI/NH_3) calcd for $C_{10}H_{14}N_1O_2$ ($M+H^+$) 180.1025, found: 180.1031. HPLC (hexane/*i*-PrOH=95/5, 20.7 min for (*S*)-alcohol and 22.7 min for (*R*)).

Method A: 1.22 g; 85%.

Method B: 1.34 g; 75%; 91.5% ee; $[\alpha]_D^{20}$=+20.3 (*c* 1.2, MeOH).

Method C: 0.63 g; 71%; 94% ee; $[\alpha]_D^{20}$=+21.1 (*c* 1.1, MeOH).

4.5.10. (*R*)-1-(6-Methoxy-pyridin-3-yl)-but-3-en-1-ol (8j). Purification by flash chromatography (2% EtOH–CH_2Cl_2) gave **8j** (1.24 g, 86%) as a yellow oil. IR (KBr) 1574, 1609, 1641, 2946, 3077, 3373 cm^{-1}. ^1H NMR δ 2.46 (t, 2H, J=7.0 Hz), 2.63 (s, 1H), 3.89 (s, 3H), 4.66 (t, 1H, J=6.4 Hz), 5.07–5.16 (m, 2H), 5.65–5.85 (m, 1H), 6.70 (d, 1H, J= 8.5 Hz), 7.55–7.60 (dd, 1H, J=8.5, 2.1 Hz), 8.02 (s broad, 1H); ^{13}C NMR δ 43.6, 53.6, 70.9, 110.9, 118.8, 132.1, 134.0, 136.8, 144.7, 163.9. HRMS (CI/NH_3) calcd for $C_{10}H_{14}N_1O_2$ ($M+H^+$) 180.1025, found: 180.1016. HPLC (hexane/*i*-PrOH=95/5, 14.8 min for (*R*)-alcohol and 16.2 min for (*S*)).

Method A: 1.24 g; 86%.

Method B: 1.40 g; 78%; 88% ee; $[\alpha]_D^{20}$=+26 (*c* 1.2, MeOH).

Method C: 0.63 g; 70%; 92% ee; $[\alpha]_D^{20}$=+27.3 (*c* 1.6, MeOH).

4.6. Oxidation of alcohols: general procedure

To a solution of DMP (4.58 g, 10.8 mmol) in CH_2Cl_2 (15 mL) at room temperature was added a solution of alcohol (6 mmol) in CH_2Cl_2 (10 mL). After 30 min of stirring, the mixture was diluted with ether (40 mL) and washed with 1: 1–10% $Na_2S_2O_3$: saturated aqueous $NaHCO_3$ solution (1×50 mL), followed by brine (2× 50 mL). The combined extracts were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure.

4.6.1. 1-Phenyl-but-3-en-1-one (12a). After the usual work-up, the homoallylic ketone **12a** (0.88 g, quant.) was quickly used in the next step without purification. IR (KBr) 1598, 1644, 1685, 2882, 3081 cm^{-1}. ^1H NMR δ 3.75 (dt, 2H, J=6.5, 1.4 Hz), 5.16–5.26 (m, 2H), 5.99–6.19 (m, 1H), 7.41–7.61 (m, 3H), 7.94–8.00 (m, 2H); ^{13}C NMR 43.5, 118.8, 128.4, 128.7, 131.2, 133.3, 136.7, 198.1. MS (CI/NH_3) *m/z* 164 ($M+NH_4^+$), 147 ($M+H^+$).

4.6.2. 1-Pyridin-3-yl-but-3-en-1-one (12b). After the usual work-up, the homoallylic ketone **12b** was obtained as a pale yellow oil. The ^1H NMR spectrum of the crude product showed a partial isomerization of the double bond (40%). β,γ-Unsaturated ketone (60%) ^1H NMR δ 3.75 (d, 2H, J=7.2 Hz), 5.20–5.27 (m, 2H), 5.97–6.15 (m, 1H), 7.41–7.47 (m, 1H), 8.21–8.25 (m, 1H), 8.75–8.77 (m, 1H), 9.15 (s broad, 1H). α,β-unsaturated ketone (40%) ^1H NMR δ 2.05 (d, 3H, J=7.9 Hz), 7.05–7.60 (m, 2H), 7.75–8.00 (m, 2H), 8.50–8.66 (m, 2H).

4.6.3. 1-Thiophen-3-yl-but-3-en-1-one (12c). After the usual work-up, the homoallylic ketone **12c** (0.92 g, quant.) was quickly used in the next step without purification. ^1H NMR δ 3.66 (dt, 2H, J=6.7, 1.4 Hz), 5.16–5.26 (m, 2H), 5.96–6.16 (m, 1H), 7.32 (dd, 1H, J=2.9, 5.0 Hz), 7.55 (dd, 1H, J=1.2, 5.0 Hz), 8.07 (dd, 1H, J=2.9, 1.2 Hz); ^{13}C NMR δ 43.9, 119.9, 129.7, 133.0, 138.2, 147.7, 154.7, 195.6. MS (EI) *m/z* 152 (M^+), 137 ($M-CH_3$).

4.6.4. 1-Quinolin-3-yl-but-3-en-1-one (12d). After the usual work-up, the homoallylic ketone **12d** (1.19 g, quant.) was obtained as a pale yellow solid without purification, and was quickly used in the next step. ^1H NMR δ 3.89 (dt, 2H, J=6.7, 1.4 Hz), 5.24–5.33 (m, 2H), 6.03–6.23 (m, 1H), 7.59–7.67 (m, 1H), 7.80–7.88 (m, 1H), 7.94 (d, 1H, J=8.1 Hz), 8.15 (d, 1H, J=8.3 Hz), 8.73 (d, 1H, J=2.1 Hz), 9.43 (s broad, 1H); ^{13}C NMR δ 43.9, 119.6, 127.0, 127.7, 128.9, 129.5, 129.6, 130.4, 132.2, 137.5, 149.3, 150.0, 196.9. MS (EI) *m/z* 197 (M^+), 182 ($M-CH_3$).

4.6.5. 1-Quinolin-6-yl-but-3-en-1-one (6e). After the usual work-up, the homoallylic ketone **6e** (1.19 g, quant.) was quickly used in the next step without purification. ^1H NMR δ 3.89 (dt, 2H, J=6.6, 1.4 Hz), 5.21–5.30 (m, 2H), 6.03–6.24 (m, 1H), 7.48 (dd, 1H, J=4.3, 8.2 Hz), 8.16 (d, 1H, J=9 Hz), 8.24–8.31 (m, 2H), 8.46 (d, 1H, J=2 Hz), 9.02 (dd, 1H, J=1.7, 4.3 Hz); ^{13}C NMR δ 43.7, 119.2, 122.1, 127.6, 127.9, 129.8, 130.2, 130.9, 134.5, 137.8, 150.2, 152.8, 197.5. MS (EI) *m/z* 197 (M^+), 182 ($M-CH_3$).

4.6.6. 1-(5-Bromo-pyridin-3-yl)-but-3-en-1-one (6f). After the usual work-up, the homoallylic ketone **6f** (1.36 g, quant.) was quickly used in the next step without purification. ^1H NMR δ 3.75 (d, 2H, J=6.6 Hz), 5.19–5.31 (m, 2H), 5.94–6.14 (m, 1H), 8.35–8.37 (dd, 1H, J=2.1, 1.8 Hz), 8.84 (d, 1H, J=2.1 Hz), 9.06 (d, 1H, J=1.8 Hz); ^{13}C NMR δ 43.9, 119.9, 121.4, 129.7, 133.0, 138.2, 147.7, 154.7, 195.6. MS (EI) *m/z* 227 (M^+, ^{81}Br), 225 (M^+, ^{79}Br); 212 ($M-CH_3$, ^{81}Br), 210 ($M-CH_3$, ^{79}Br).

4.6.7. 1-(6-Chloro-pyridin-3-yl)-but-3-en-1-one (12g). After the usual work-up, the homoallylic ketone **12g** (1.09 g, quant.) was quickly used in the next step without purification. ^1H NMR δ 3.72 (dt, 2H, J=6.7, 1.4 Hz), 5.16–5.29 (m, 2H), 5.92–6.12 (m, 1H), 7.42 (dd, 1H, J=0.8, 8.4 Hz), 8.18 (dd, 1H, J=2.6, 8.4 Hz), 9.92 (dd, 1H, J=0.8, 2.6 Hz); ^{13}C NMR δ 43.8, 119.8, 124.7, 129.9, 130.7, 138.3, 150.1, 155.8, 195.6. MS (EI) *m/z* 181 (M^+, ^{35}Cl), 183 (M^+, ^{37}Cl).

4.6.8. 1-(5,6-Dichloro-pyridin-3-yl)-but-3-en-1-one (12h). After the usual work-up, the homoallylic ketone **12h** (1.30 g, quant.) was quickly used in the next step without purification. ^1H NMR δ 3.73 (dt, 2H, J=6.6,

1.4 Hz), 5.18–5.32 (m, 2H), 5.92–6.12 (m, 1H), 8.28 (d, 1H, J=2 Hz), 8.81 (d, 1H, J=2 Hz); ^{13}C NMR δ 43.9, 120.1, 129.5, 131.5, 131.7, 138.1, 147.1, 153.4, 194.7. MS (EI) m/z 215 (M^+, ^{35}Cl), 217 (M^+, ^{37}Cl); 200 ($M-CH_3$, ^{35}Cl), 202 ($M-CH_3$, ^{37}Cl).

4.6.9. 1-(5-Methoxy-pyridin-3-yl)-but-3-en-1-one (12i). After the usual work-up, the homoallylic ketone **12i** (1.07 g, quant.) was quickly used in the next step without purification. ^{1}H NMR δ 3.75 (dt, 2H, J=6.7, 1.4 Hz), 3.88, (s, 3H), 5.16–5.27 (m, 2H), 5.94–6.14 (m, 1H), 7.65–7.73 (m, 1H), 8.46 (d, 1H, J=2.6 Hz), 8.77 (s broad, 1H); ^{13}C NMR δ 43.9, 55.7, 117.9, 119.3, 130.2, 132.4, 142.0, 142.8, 155.9, 196.7. MS (EI) m/z 177 (M^+), 162 ($M-CH_3$).

4.6.10. 1-(6-Methoxy-pyridin-3-yl)-but-3-en-1-one (12j). After the usual work-up, the homoallylic ketone **12j** (1.07 g, quant.) was quickly used in the next step without purification. ^{1}H NMR δ 3.66–3.70 (m, 2H), 3.98 (s, 3H), 5.16–5.25 (m, 2H), 5.94–6.15 (m, 1H), 6.77 (d, 1H, J= 8.7 Hz), 8.12 (dd, 1H, J=2.4, 8.7 Hz), 8.78 (d, 1H, J=2.4 Hz); ^{13}C NMR δ 43.3, 54.0, 111.2, 118.9, 126.2, 130.8, 138.3, 149.2, 166.7, 195.6. MS (EI) m/z 177 (M^+), 162 ($M-CH_3$).

4.7. Synthesis of SIB-1508Y

4.7.1. (*R*)-Methanesulfonic acid 1-(5-bromo-pyridin-3-yl)-but-3-enyl ester (17). To a solution of alcohol (*R*)-**8f** (5.2 g, 22.8 mmol) and Et_3N (6.35 mL, 45.6 mmol) in CH_2Cl_2 (110 mL) at 0°C, was slowly added methanesulfonyl chloride (2.65 mL, 34.2 mmol). After stirring for 10 min, the mixture was diluted with water and the layers were separated. The organic layer was washed with water, brine (2×70 mL), dried over anhydrous $MgSO_4$, filtered and concentrated at room temperature under reduced pressure to afford the crude mesylate **17** (6.25 g, 100%) as a yellow oil. The product was immediately used in the next step, without purification, due to extensive decomposition. $[\alpha]_D^{20}$=+50 (c 1.2, MeOH). ^{1}H NMR δ (ppm) 2.58–2.88 (m, 2H), 2.93 (s, 3H), 5.12–5.22 (m, 2H), 5.56–5.78 (m, 2H), 7.87 (t, 1H, J=2 Hz), 8.54 (d, 1H, J=1.8 Hz), 8.68 (d, 1H, J=2.1 Hz); ^{13}C NMR δ (ppm) 38.9, 41.0, 79.1, 120.4, 130.8, 136.1, 137.4, 145.5, 150.5.

4.7.2. (*S*)-3-(1-Azido-but-3-enyl)-5-bromo-pyridine (18). To a solution of mesylate **11** (6.1 g, 22.3 mmol) in freshly distilled DMF (70 mL), was added, in one portion, NaN_3 (2.17 g, 33.4 mmol). The resulting mixture was stirred at 60°C for 4 h and then diluted with ether (150 mL) and water (70 mL). The layers were separated and the aqueous layer was extracted with ether (3×100 mL). The combined extracts were washed with brine (2×100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% ethyl acetate–hexane) gave azide **18** (4.67 g, 83%) as a colourless oil. $[\alpha]_D^{20}$=−81.8 (c 1.29, MeOH). IR (KBr) ν=1643, 2100, 2957, 3082 cm^{-1}. ^{1}H NMR δ (ppm) 2.44–2.68 (m, 2H), 4.55 (t, 1H, J=7 Hz), 5.09–5.18 (m, 2H), 5.61–5.82 (m, 1H), 7.80 (app t, 1H, J=2 Hz), 8.46 (d, 1H, J=1.8 Hz), 8.64 (d, 1H, J=2.3 Hz). ^{13}C NMR δ (ppm) 40.6, 62.6, 119.7, 121.1, 132.3, 136.8, 137.0, 146.6, 150.9. HRMS (EI) calcd for $C_9H_9N_4Br_1$ (M^+) 252.0011, found: 252.0007.

4.7.3. (*S*)-3-Bromo-5-pyrrolidin-2-yl-pyridine (15). To a stirred solution of freshly distilled cyclohexene (5.49 mL, 54.2 mmol) in THF (35 mL) at 0°C was added dropwise 2.0 M BH_3-Me_2S complex in THF (53.8 mL, 0.108 mol). The resulting white suspension of dicyclohexylborane was stirred for 1 h at 0°C and then cooled to −15°C prior to the addition of azide **18** (4.5 g, 17.8 mmol) in THF (10 mL). The resulting mixture was allowed to warm up to room temperature. After 12 h, the reaction was quenched with MeOH, diluted with ether (100 mL) and the organic layer was extracted with 1N aqueous HCl (6×70 mL). The combined aqueous layers were treated with 30% aqueous NaOH solution until pH 13–14 and then extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$. Removal of the solvent left a residue which was purified by flash chromatography (5% EtOH–CH_2Cl_2) yielding **15** (2.5 g, 62%) as a colourless oil. The enantiomeric excess value (94% ee) was determined by chiral HPLC analysis of the (*S*)-nornicotine, obtained directly by removal of the bromine by hydrogenolysis of **15**. For the (*S*)-nornicotine separation conditions: elution with a mixture of hexane/*i*-PrOH 95/5; flow rate: 0.5 ml/min: retention time 28.0 min for (*R*)-nornicotine and 30.0 min for (*S*). $[\alpha]_D^{20}$=−26 (c 1.06, MeOH). ^{1}H NMR δ (ppm) 1.44–1.61 (m, 1H), 1.67–1.9 (m, 2H), 2.06 (s, 1H), 2.06–2.21 (m, 1H), 2.89–3.12 (m, 2H), 4.07 (t, 1H, J=7.6 Hz), 7.80–7.81 (m, 1H), 8.38 (d, 1H, J=1.8 Hz), 8.42 (d, 1H, J=2.3 Hz). ^{13}C NMR δ (ppm) 25.5, 34.5, 46.9, 59.1, 120.8, 136.7, 142.7, 146.6, 149.0. MS (EI) m/z 228 (M^+, ^{81}Br), 226, (M^+, ^{79}Br).

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