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The first enantioselective synthesis of (*S*)-5-bromo-3-(1-methyl-2-pyrrolidinyl)pyridine: a key intermediate for the preparation of SIB-1508Y

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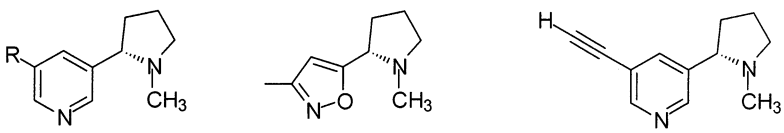
Abstract—The first enantioselective synthesis of (*S*)-5-bromo-3-(1-methyl-2-pyrrolidinyl)pyridine is described via intramolecular hydroboration–cycloalkylation of an azido-olefin intermediate. The chiral homoallylic alcohol was efficiently synthesized by enantioselective reduction of the corresponding ketone using (+)-diisopinocamphenylchloroborane as the key reaction. The total synthesis of (*S*)-SIB-1508Y was achieved with an enantiomeric excess (e.e.) of 94% in ten steps and in 18% overall yield from the commercially available 5-bromo-3-pyridinecarboxylic acid.

The importance of nicotinic acetylcholine receptors (nAChR) in several CNS disorders, including Alzheimer's disease (AD),[1,2] Parkinson's disease (PD)[1] and Tourette's syndrome[1,2] is now well established.[3,4] Several studies have demonstrated that the naturally occurring alkaloid (*S*)-nicotine **1** and its analogues such as (*S*)-ABT-418 **3**, display potent biological activity in mammals by modulation of nAChR (Scheme 1).[5]

In connection with our studies on nAChR ligands and our ongoing project on the asymmetric synthesis of tobacco alkaloids, we have recently reported a new enantioselective synthesis of these pyrrolidine and piperidine alkaloids.[6] In this communication, we describe the first enantioselective synthesis of (*S*)-(−)-5-bromo-3-(1-methyl-2-pyrrolidinyl)pyridine **2**, a key intermediate for the preparation of (*S*)-SIB-1508Y **4**, an important nAChR agonist in clinical trials for the treatment of Parkinson's disease.

It should be pointed out that the synthesis of (*S*)-**2** has already been described in the literature[7] by reduction of the corresponding imine using the homochiral (acyloxy)borohydride reagent derived from Cbz-D-proline. However, the (*S*)-2 formed by the previously reported process had low 30% e.e. After several unsuccessful attempts at the preparation of the enantiomerically enriched amine **5**, enantiopure (*S*)-SIB-1508Y **4** (>99% e.e.) was finally obtained by fractional crystallization of a diastereomeric salt in an additional resolution process. As has already been observed by Buchwald et al.,[8] the asymmetric hydrogenation of imines, for example the 2-phenyl-1-pyrroline, with a chiral titanocene catalyst proceeds to afford corresponding amines with excellent enantioselectivity (>99% e.e.). However, imines containing a pyridine substituent, such as 3-pyridyl-2-pyrroline (myosmine), were found not to react even under forcing conditions.



1 R = H (*S*)-nicotine
2 R = Br

(*S*)-ABT-418 **3**

(*S*)-SIB-1508Y **4**

Scheme 1.

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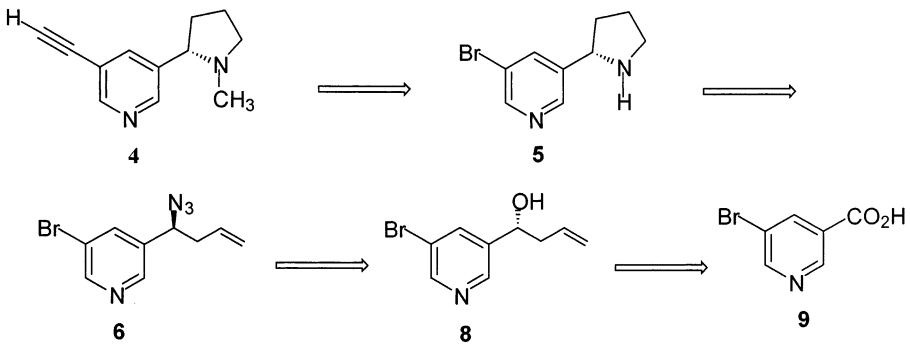
Our aim was therefore to obtain the chiral homoallylic alcohol (*R*)-**8**, which can be prepared from the commercially available corresponding carboxylic acid **9**. The formation of pyrrolidine ring is achieved by intramolecular hydroboration–cycloalkylation tandem reactions from the chiral azide (*S*)-**6**. A retrosynthetic analysis of (*S*)-SIB-1508Y **4** is shown in Scheme 2.

Our synthesis was initiated by the direct conversion of 5-bromo-3-pyridinecarboxylic acid **9** to the corresponding aldehyde **10** in 63% yield using *N*,*N*-dimethylchloromethyleneiminium chloride and lithium tri-*tert*-butoxyalumium hydride according to the conditions reported by Fujisawa et al.[9] (Scheme 3).

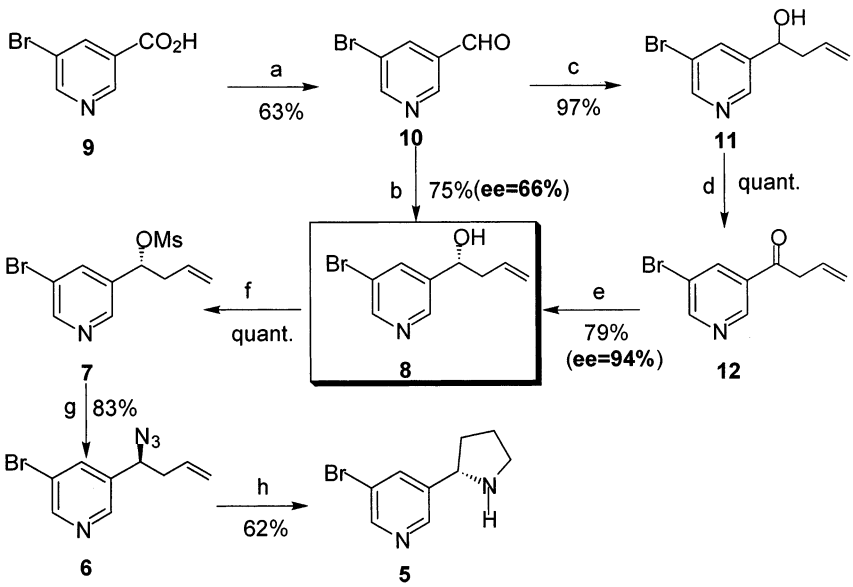
Preparation of the chiral homoallylic alcohol (*R*)-**8** was a key step of our synthetic work. As already described in the synthesis of pyrrolidine and piperidine alkaloids,[6] we carried out the enantioselective allylation using *B*-allyldiisopinocamphenylborane (prepared from (+)-Ipc_2BCl) on the aldehyde **10**. However, the chiral alcohol (*R*)-**8** was obtained in 75% yield[10] but with only a modest e.e. of 66%[11] (instead of 94% in the case of 3-pyridinecarboxaldehyde). It is noteworthy that the poor chiral induction achieved in the allylation of this less reactive aldehyde was probably due to the presence of the bromine at C(5) of the pyridine ring. So, we decided to take another approach.

An alternative route to prepare the chiral alcohol (*R*)-**8** was investigated, involving an enantioselective reduction of the corresponding ketone, easily obtained by oxidation of the racemic alcohol **11** with Dess–Martin reagent. Starting from 5-bromo-3-pyridinecarboxaldehyde **10**, the racemic alcohol **11** was prepared by allylation with allyl bromide in the presence of zinc in 97% yield after purification by flash chromatography. Oxidation of the alcohol **11**, in mild conditions using the Dess–Martin Periodinane (DMP) reagent,[12] leading to ketone **12** which was immediately used in the next step without purification.

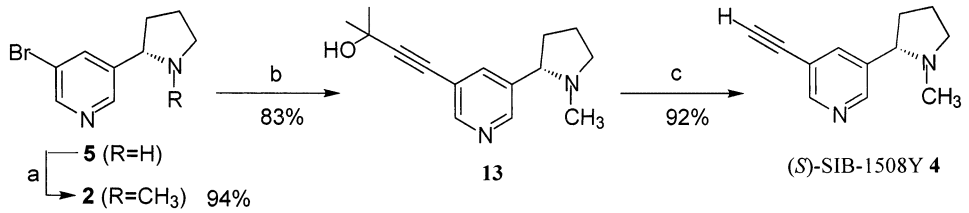
A similar reaction sequence carried out on the analogue of homoallylic alcohol **11** without the bromine at C(5)



Scheme 2.



Scheme 3. *Reagents and conditions*: (a) (i) DMF, $(ClCO)_2$, –20°C, 1.30 h; (ii) CuI (10 mol%), –78°C, $LiAlH(O\textit{tert}\text{-}Bu)_3$ (2 equiv.), 15 min; (b) (+)-Ipc_2BCl (2.2 equiv.), Et_2O, –100°C, 1 h; (c) Zn (2 equiv.), allyl bromide (2 equiv.), THF, rt, 1 h; (d) DMP (1.2 equiv.), CH_2Cl_2, rt, 15 min; (e) (+)-Ipc_2BCl (2.2 equiv.), THF, –30°C, 20 h; (f) MsCl (1.5 equiv.), Et_3N, CH_2Cl_2, 0°C, 5 min; (g) NaN_3 (1.5 equiv.), DMF, 60°C, 4 h; (h) $B(C_6H_{11})_2H$ (2 equiv.), THF, rt for 1 h then reflux for 3 h.



Scheme 4. *Reagents and conditions*: (a) HCHO (37% aqueous), HCO_2H, 80°C, 3 h; (b) 2-methyl-3-butyn-2-ol (2.5 equiv), CuI (cat.), 10% Pd/C (cat.), Ph_3P, K_2CO_3, DME, rt then reflux for 16 h; (c) NaH (10% mol), toluene, reflux, 2 h.

of the pyridine ring yielded an unstable ketone, which isomerized spontaneously into the conjugated α,β-unsaturated derivative.

One of the major points of our synthetic work that has received considerable attention is the reduction of the prochiral ketone to give an enantiopure alcohol. Thus, the formation of the alcohol (*R*)-**8** was carried out by enantioselective reduction of the ketone **12** using (+)-diisopinocamphenylchloroborane according to the conditions reported by Brown et al.[13] We obtained the alcohol (*R*)-**8** as the sole product from the reaction in 79% purified yield[14] with an e.e. of 94%.[11]

The next step in the synthesis involved transformation of the alcohol **8** to the azide **6** which was effected by nucleophilic displacement of the corresponding mesylate by azide ion. The chiral alcohol (*R*)-**8** was esterified by the action of methanesulfonyl chloride in the presence of triethylamine, affording the unstable mesylate (*R*)-**7**,[15] which was directly treated with sodium azide in DMF at 60°C to afford the azide (*S*)-**6** in 83% yield from the two steps.[16] Displacement of the mesylate at the benzylic position of **7** occurred with complete inversion of configuration as established by chiral HPLC analysis (e.e. = 94%).[17] Under certain conditions an S_N1 reaction process sometimes competed with the desired reaction, with an accompanying decrease in the e.e. of the product.[18]

As already described,[6b] formation of the pyrrolidine ring was achieved by intramolecular hydroboration–cycloalkylation tandem reactions of azido-olefin. Thus, hydroboration–cycloalkylation of the azide (*S*)-**6** with an excess of dicyclohexylborane proceeded as expected, and furnished the (*S*)-5-bromo-3-(1-*H*-2-pyrrolidinyl)pyridine **5**[19] with an e.e.[20] of 94% in 62% yield.

Finally, conversion of the (*S*)-5-bromonornicotine **5** to the (*S*)-SIB-1508Y **4** essentially followed the known sequence, reported in the literature.[7] Reductive amination of (*S*)-**5** using an Eschweiler–Clark procedure gave the (*S*)-5-bromo-3-(1-methyl-2-pyrrolidinyl)pyridine **2** in 94% yield without epimerization of the stereogenic center.[21] Cross-coupling of (*S*)-**2** with mebynol (2-methyl-3-butyn-2-ol) in the presence of catalytic quantity of 10% Pd/C, triphenylphosphine, copper iodide and potassium carbonate afforded **13** in high yield. Deprotection was accomplished by simple heating of **13** in toluene in the presence of a catalytic amount of sodium hydride to provide **4** in 92% yield after purification. As reported in the literature,[7] no drop in e.e. was detected for the last two steps (Scheme 4).

In summary, we have described a new and efficient enantioselective synthesis of (*S*)-SIB-1508Y **4**, a nAChR agonist in clinical trials for the treatment of Parkinson's disease. Using the synthesis presented above, **4** was synthesized in ten steps from 5-bromo-3-pyridinecarboxylic acid in 18% overall yield and with an e.e. of 94%. In this fashion, a preparatively useful multigram scale process for the synthesis of (*S*)-SIB-1508Y was obtained. The described synthesis should enable the design and synthesis of various other analogues of tobacco alkaloids. Further work in this area is in progress.

Acknowledgements

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10. All yields cited herein are of isolated, purified materials, which gave satisfactory ^{1}H, ^{13}C NMR and IR spectra, and either MS or elemental analysis in agreement with the assigned structures and literature data for known products.
11. All e.e. values were determined by HPLC with a chiral column (Chiracel OD-H 0.46×15 cm). For the homoallylic alcohol (*R*)-**8**, separation conditions: elution with a mixture of hexane/*iso*-PrOH 98/2; flow rate: 0.5 mL/min: retention time 26.8 min for alcohol (*R*)-**8** and 25.4 min for (*S*).
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14. Representative procedure for the alcohol (*R*)-**8**: To a solution of (+)-DIPCl (6.25 g, 19.5 mmol) in THF (5 mL) at −30°C was added a solution of the ketone **12** (2 g, 8.85 mmol) in THF (5mL). After stirring for 20 h at −30°C, the reaction was quenched with MeOH (1 mL) and aqueous HCl (1N, 5 mL). The mixture was basified with KOH pellets until the pH was 11–12. The mixture was extracted with CH_2Cl_2 (3×10 mL). The organic phases were washed with saturated NaCl solution (2×15 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel gave the alcohol **7** as a pale yellow oil (1.59 g, 79%). $[\alpha]_D^{20}=+16.2$ (*c* 1.47, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.37–2.57 (m, 2H), 3.4 (sl, 1H), 4.76 (t, 1H, $J=6.7$ Hz), 5.10–5.20 (m, 2H), 5.67–5.88 (m, 1H), 7.89 (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 (50 MHz, $CDCl_3$): 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).
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17. See e.e. value of (*S*)-nornicotine determined by chiral HPLC analysis.
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19. Data for compound **5**: $[\alpha]_D^{20}=-26$ (*c* 1.06, MeOH) ^{1}H NMR (200 MHz, $CDCl_3$): δ 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 (50 MHz, $CDCl_3$): δ 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).
20. The e.e. value was determined by chiral HPLC analysis of the (*S*)-nornicotine, obtained directly by removal of the bromine by hydrogenolysis of **5**. For the (*S*)-nornicotine separation conditions: elution with a mixture of hexane/*iso*-PrOH 95/5; flow rate: 0.5 mL/min: retention time 30.0 min for (*S*)-nornicotine and 28.0 min for the (*R*)-enantiomer.
21. The e.e. value was determined by chiral HPLC analysis of the (*S*)-nicotine, obtained directly by removal of the bromine by hydrogenolysis of **2**. For the (*S*)-nicotine separation conditions: elution with a mixture of hexane/*iso*-PrOH 49/1; flow rate: 0.5 mL/min: retention time 10.9 min for (*S*)-nornicotine and 12.9 min for the (*R*)-enantiomer.