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A short and efficient synthesis of unnatural (*R*)-nicotine

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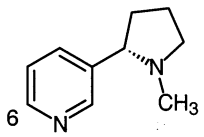
Abstract

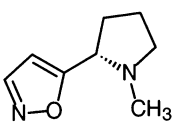
A short and efficient synthesis of unnatural (*R*)-nicotine is described, in which the key step is an intramolecular hydroboration–cycloalkylation of an azido-olefin intermediate. The synthesis is achieved in only four steps, with an overall yield of 51% (or in six steps with an overall yield of 65%).

Keywords: asymmetric synthesis; alkaloids; allylation; azides; boron and compounds.

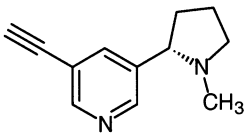
Neuronal nicotinic acetylcholine receptors (nAChRs) are important potential molecular targets for the development of new compounds to cure neurodegenerative disorders.[1] Several studies have clearly established that the natural alkaloid, (*S*)-nicotine **1** (Scheme 1), may have beneficial effects for the symptomatic treatment of Parkinson's disease, Alzheimer's disease and Tourette's syndrome. Unfortunately, the use of (*S*)-nicotine **1** as a therapeutic agent is restricted by severe side effects on the cardiovascular and digestive systems, by sleep disturbance and by the development of dependence.[2] Several recent reviews have summarised structure–activity relationships for nAChR ligands.[3] Recent advances in this field have led to the discovery of new analogues of nicotine, such as ABT-418 **2** and SIB-1508Y **3** (Scheme 1), which have improved



(*S*)-Nicotine **1**



(*S*)-ABT-418 **2**



(*S*)-SIB-1508Y **3**

Scheme 1.

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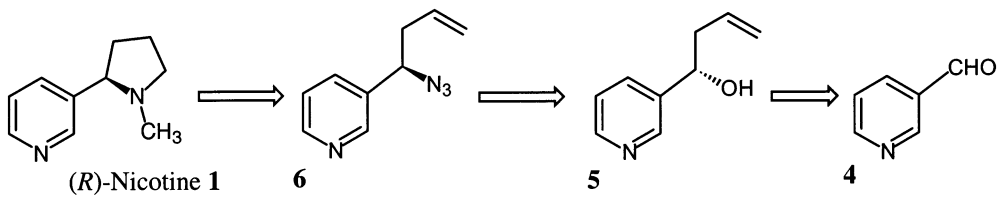
pharmacotherapeutic properties.[3,4] SIB-1508Y **3** is in clinical trials for the treatment of Parkinson's disease.[4b] These striking biological properties make chiral nicotine and analogues thereof very attractive synthetic targets.[5] Thus, the development of efficient enantioselective methods for the synthesis of nicotine analogues is important. Although it has been shown that the (*S*)-enantiomer of nicotine **1** is more active than the (*R*)—a tendency also established for many analogues[2,6]—an efficient enantioselective synthesis of the non-natural enantiomer is necessary for its biological evaluation and for studies of its metabolism.[3,7] Nevertheless to our knowledge, only a few examples of an enantioselective synthesis of (*S*)-nicotine have been reported,[8] the tendency being to separate the isomers from a racemic preparation. Thus, for example, pure (*S*)-SIB-1508Y **3** (ee>99%) was obtained by recrystallisation as the dibenzoyl-L-tartrate salt of an enantiomerically enriched material (ee = 30%).[9]

In the course of our studies on nAChR ligands, we have developed a new enantioselective route to nicotine. Starting from inexpensive precursors, the method provides the possibility to synthesize, in few steps, chiral nicotine or analogues with various substituents on the pyridine ring. As it has been demonstrated that the presence of an electron-withdrawing group at the 6-position strongly increases the biological activity,[3] this new method opens a facile route to many potentially interesting new analogues.

Our retrosynthetic analysis of **1** (Scheme 2) relies on an intramolecular hydroboration–cycloalkylation reaction[10] to build the pyrrolidine ring from the chiral azide **6**. The chiral homoallylic alcohol **5** should be available from pyridinecarboxaldehyde **4** using an enantioselective allylation.



Scheme 2.

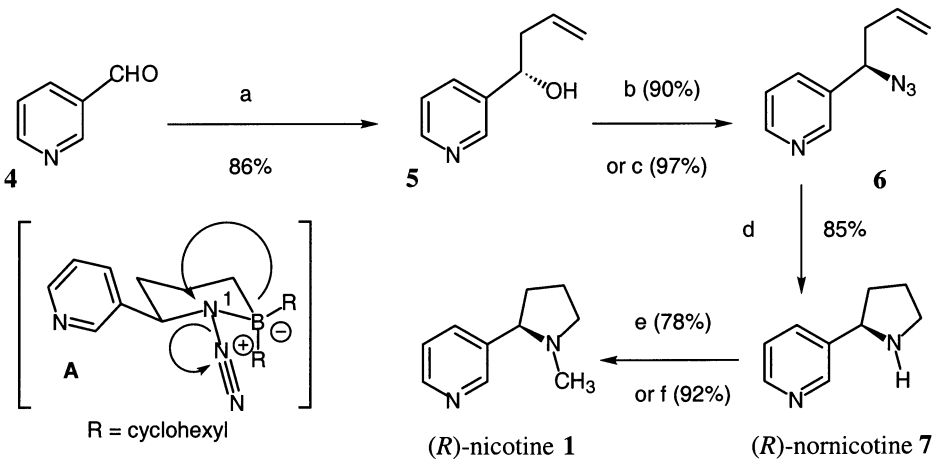
The synthetic work was first focused on the preparation of the chiral homoallylic alcohol **5**. Preliminary attempts of the aldehyde **4** allylation were carried out with the easily-accessible chiral allylboronate ester (prepared from diisopropyl-(L)-tartrate).[11] We found that the best results were obtained when, prior to allylation, the nitrogen of the pyridine ring[12] was complexed by treatment with BEt_3, with the subsequent addition of allylboronate ester. This approach gave chiral alcohol **5** in 78% yield but with only modest ee (up to 65%). We therefore pursued this approach by using *B*-allyldiisopinocampheylborane (prepared from (−)-Ipc_2BCl).[13] Initially, different attempts to reproduce the described work[14] were quite disappointing. The desired chiral alcohol **5** was obtained in modest yields (40–50%) with low ee (70–80%) and accompanied by starting material.[15] However, further investigations revealed that the complexation of the nitrogen of the pyridine was crucial (vide supra), as well as the rate of addition of the aldehyde **4** at −100°C. Finally, allylation of **4** with 2.2 equivalents of *B*-allyldiisopinocampheylborane afforded the (*S*)-homoallylicalcohol **5** in 86% yield (after purification), with an ee of 94%. One of the significant challenges associated with the synthesis of pyridine derivatives concerns the problem of complexation of the nitrogen with reagents or catalysts.[16]

In the meantime, an alternative route to prepare the chiral alcohol **5** was investigated involving an enantioselective reduction of the corresponding ketone, obtained by oxidation of the racemic alcohol **5** with Dess–Martin reagent. Unfortunately, this ketone was unstable and was isomerized spontaneously into the conjugated α,β-unsaturated derivative. It should be noticed that a similar reaction sequence on a benzene analogue yielded the desired β,γ-unsaturated ketone, which was reduced with the Ipc_2BCl reagent to give the corresponding alcohol with high ee (>95%).[17]

In most of the cases, aliphatic azides are prepared by nucleophilic displacement of the corresponding halides or sulfonates by the azide anion.[18] However, substitution reactions on the (2-pyridinyl)methyl carbon centre seem to be more tricky. This reaction sometimes competes with a S_N1 reaction process, with a decrease in the ee in the case of chiral non-racemic derivatives.[19] Also, in our case, an additional problem is caused by the homoallylic position of the leaving group. Nevertheless, after we had established the correct conditions, we found that the chiral azide **6** was obtained directly from alcohol **5** using the Thompson procedure[20] with a good yield and without racemisation.[21]

Alternatively, the chiral azide **6** may be prepared in two steps by nucleophilic displacement of the corresponding mesylate by the azide anion, in comparable overall yield (97%). The unstable mesylate was obtained by conventional treatment of the alcohol with mesylate chloride in the presence of Et_3N.

After the sucessful synthesis of the chiral azide **6**, efforts were turned to make the pyrrolidine ring. For this purpose, we used an intramolecular hydroboration–cycloalkylation of the azido-olefin **6**. This methodology was already shown to be powerful for the synthesis of pyrrolidinone and piperidine derivatives.[10] The chiral azide **6** was treated with an excess of freshly prepared dicyclohexylborane to afford, after hydrolysis with methanol, (*R*)-nornicotine **7** in 85% yield, as the sole product from the reaction mixture.[22] This sequence proceeds by hydroboration of the double bond of **5**, followed by the formation of a boron–nitrogen bond between the azide and the trialkylborane to afford the intermediate **A**. Finally, ring closure occurs by migration of the borane methylene group to N-1 of **A** with concomitant loss of nitrogen (Scheme 3).



Scheme 3. Reagents and conditions: (a) *B*-allyldiisopinocamphenylborane (2.2 equiv.), Et_2O, −100°C. (b) DBU (1.2 equiv.), $(PhO)_2P(O)$-N_3 (1.2 equiv.), Tol, rt. (c) (i) MsCl (1.1 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2, 0°C. (ii) NaN_3 (2.2 equiv.), DMF, 60°C. (d) $B(C_6H_{11})_2H$ (2.2 equiv.), THF, rt, then MeOH. (e) LiHMDS (2 equiv.), MeI (2 equiv.), THF, −78°C to rt. (f) (i) EtOCOCl (1.2 equiv.), Et_3N (1.3 equiv.), Et_2O, rt. (ii) $LiAlH_4$ (1.2 equiv.), THF, 0°C

Conversion of (*R*)-nornicotine **7** to (*R*)-nicotine **1** was carried out using either a one- or a two-step procedure. Addition of an excess of LiHMDS to (*R*)-nornicotine **7**, followed by trapping with MeI gave (*R*)-nicotine **1** with a good yield (77%). Alternatively, the *N*-ethylcarbamate, prepared from **7**, was reduced by an excess of $LiAlH_4$ to give (*R*)-nicotine **7** in 92% overall yield for the two steps. (*R*)-nicotine **1** was finally checked by an analysis on chiral HPLC and was found to have an ee of 92–93%, representing a slight drop of ee (less than 2%) relative to the chiral alcohol **5**.[23]

In summary, a short and efficient synthesis of the unnatural (*R*)-enantiomer of nicotine **1** (ee 92–93%) has been achieved in only four steps, with an overall yield of 51% (or in six steps with an overall yield of 65%). The natural (*S*)-enantiomer of nicotine could be prepared identically by replacing (–)-Ipc_2BCl with (+)-Ipc_2BCl. Extension of this straightforward approach to the preparation of (*S*) and (*R*) analogues is currently underway in our laboratories.

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References

1. Galzi, J. L.; Changeux, J. P. *Neuropharmacology* **1995**, *34*, 563–579.
2. Brennan, M. B. *Chem. Eng. News* **2000**, *78*, 23–26.
3. For reviews in this field, see: (a) Lloyd, G. K.; Williams, M. *J. Pharm. Exp. Ther.* **2000**, *292*, 461–467; (b) Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4169–4194.
4. (a) Wittenberger, S. J. *J. Org. Chem.* **1996**, *61*, 356–358. (b) Bleicher, L. S.; Cosford, N. D. P. *J. Org. Chem.* **1999**, *64*, 5299–5230.
5. For recent examples, see: (a) Turner, S. C.; Zhai, H.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861; (b) Che, D.; Siegl, J.; Seitz, G. *Tetrahedron: Asymmetry* **1999**, *10*, 573; (a) Fürstner, A.; Thiel, O. R. *J. Org. Chem.* **2000**, *65*, 1738; (b) Cook, G. R.; Shanker, P. S.; Peterson, S. L. *Org. Lett.* **1999**, *1*, 615; (c) Sankar, T. K.; Basak, S.; Ghosh, S. K.; *Tetrahedron Lett.* **2000**, *41*, 759–762.
6. Aceto, M. D.; Martin, B. R.; Uwaydah, I. M.; May, E. L.; Harris, L. S.; Izazola-Conde, C.; Deway, W. L.; Bradshaw, T. J.; Vincek, W. C. *J. Med. Chem.* **1979**, *22*, 174–177.
7. Nybäck, H.; Halldin, C.; Ahlin, A.; Curvall, M.; Erikson, L. *Psychopharmacology* **1994**, *115*, 31–36.
8. For the asymmetric synthesis of (*S*)-nicotine (or (*S*)-nornicotine), see: (a) Loh, T.-P.; Zhou, J.-R.; Li, X.-R.; Sim, K.-Y. *Tetrahedron Lett.* **1999**, *40*, 7847–7850. (b) Swango, J. H.; Bhatti, B. S.; Quershi, M. M.; Crooks, P. A. *Chirality* **1999**, *11*, 316–318. (c) Swango, J. H.; Quershi, M. M.; Crooks, P. A. *Pharm. Res.* **1997**, *14*, S-695. (d) Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L. *J. Org. Chem.* **1982**, *47*, 1069–1073.
9. Bleicher, L. S.; Cosford, N. D. P.; Herbaut, A.; McCallum, J. S.; McDonald, I. A. *J. Org. Chem.* **1998**, *63*, 31–37.
10. For a review of this field, see: Carboni, B.; Vaultier, M.; *Bull. Soc. Chim. Fr.* **1995**, *132*, 1003–1008 and references cited therein. For recent examples, see: (a) Salmon, A.; Carboni, B. *J. Organomet. Chem.* **1998**, *567*, 6614–6617; Waid, P. P.; Flynn, G. A.; Huber, E. W.; Sabol, J. S. *Tetrahedron Lett.* **1996**, *37*, 4091–4094.
11. Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186–8190.
12. Lutz, C.; Graf, C.-L.; Knochel, P. *Tetrahedron* **1998**, *54*, 10317–10328.
13. For the preparation of *B*-allyldiisopinocampheylborane from (–)-Ipc_2BCl (purchased from Aldrich Chemical Co.) see: Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432–439.
14. Racherla, U. S.; Liao, Y.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 6614–6617.

15. All enantiomeric excesses were determined by chiral HPLC. For (*R*) homoallylic alcohol separation conditions were: Chiracel OD-H column (0.46×15 cm): elution with a mixture of hexane/*i*-PrOH 95:5 v/v; flow rate: 0.5 ml/min; retention time 26 min for (*S*)-alcohol **8** and 28.5 min for the (*R*)-isomer.
16. For similar problems of pyridine complex formation, see: (a) Hull, K. G.; Visnick, M.; Tautz, W.; Sheffron, A. *Tetrahedron* **1997**, *53*, 12405–12414; (b) Ling Ng, P.; Lambert, J. N. *Synlett* **1999**, *11*, 1749; (c) Raatz, D.; Innertsberger, C.; Reiser, O. *Synlett* **1999**, *12*, 1907; (d) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952.
17. Singh, V. K. *Synthesis* **1992**, 605–617 and references cited therein.
18. Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413–414 and references cited therein.
19. Uchi, J.; Takagi, T.; Ueno, T.; Hiraoka, T.; Yoemiitsu, O.; Tsukube, H. *Synlett* **1999**, 41–44.
20. Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886–5888.
21. For (*S*)-azide separation conditions by chiral HPLC: Chiracel OD-H column (0.46×15 cm): elution with a mixture of hexane/*i*-PrOH 95:5 v/v; flow rate: 0.5 ml/min; retention time 11.2 min for the (*S*)-azide and 12.6 min for the (*R*)-isomer.
22. Representative procedure for (*R*)-nornicotine **7**. To a stirred solution of 1.4 ml (13.9 mmol) of freshly distilled cyclohexene in 10 mL of THF at 0°C was added dropwise 3.5 ml (7 mmol) of 2.0 M BH_3–SMe_2 complex in THF. 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 400 mg (2.3 mmol) of azide **6** in 10 mL of THF. The resulting mixture was allowed to warm up to rt. After 12 h, the reaction was quenched with MeOH, diluted with ether and the organic layer was extracted with 1N aqueous HCl. 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 an oil which was purified by bulb-to-bulb distillation yielding 290 mg (85%) of (*R*)-nornicotine **7**. For (*R*)-nornicotine **7** separation conditions by chiral HPLC were: Chiracel OD-H column (0.46×15 cm): elution with a mixture of hexane/*i*-PrOH 95:5 v/v; flow rate: 0.5 ml/min; retention time 29.1 min for (*R*)-**5** and 34.0 min for the (*S*)-isomer. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.6 (1H, d, $J_{2-4}=2.28$ Hz, H_2), 8.45 (1H, dd, $J_{5-6}=4.88$ Hz, $J=1.7$ Hz, H_6), 7.70 (1H, pseudo dt, $J_{4-5}=7.9$ Hz, $J=2.06$ Hz, H_4), 7.22 (1H, dd, $J_{4-5}=7.9$ Hz, $J_{5-6}=4.88$ Hz, H_5), 4.14 (1H, $J_{2'-3'}=7.32$ Hz, $^3J_{2'-4'}=2$ Hz, $H_{2'}$), 3.1 (2H, m, $H_{5'}$), 2.2 (1H, m, $H_{4'b}$); 2.1 (1H, NH); 1.9 (2H, m, $H_{3b',4a'}$), 1.66 (1H, m, $H_{3a'}$). ^{13}C NMR (50 MHz, $CDCl_3$): 148.6; 148.0; 140.5; 134.0; 123.2; 60.0; 47.0; 34.5; 25.6.
23. For (*R*)-nicotine **1**, separation conditions by chiral HPLC were: Chiracel OD-H column (0.46×15 cm): elution with a mixture of hexane/*i*-PrOH 95:5 v/v; flow rate: 0.5 ml/min; retention time 7.8 min for (*R*)-**5** and 9.1 min for the (*S*)-isomer.