Efficient Enantiomeric Synthesis of Pyrrolidine and Piperidine Alkaloids from Tobacco

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An enantiomeric synthesis of six piperidine and pyrrolidine alkaloids, (*S*)-nornicotine **1**, (*S*)-nicotine **2**, (*S*)-anatabine **3**, (*S*)-*N*-methylanatabine **4**, (*S*)-anabasine **5**, and (*S*)-*N*-methylanabasine **6**, known as natural products in tobacco, was established from a common chiral homoallylic (*S*)-3-(1-azido-but-3-enyl)-pyridine **15**. An intramolecular hydroboration−cycloalkylation of the homoallylic azide intermediate **15** served as the key step in the pyrrolidine ring formation. A ring closing metathesis reaction (RCM) of a diethylenic amine intermediate (*S*)-allyl-(1-pyridin-3-yl-but-3-enyl)-carbamic acid benzyl ester **20** served as the key step in the piperidine ring formation. From the commercially available 3-pyridinecarboxaldehyde **13**, a short and convenient enantiomeric synthesis of tobacco alkaloids is described: (*S*)-nornicotine **1** (5 steps, with an overall yield of 70%), (*S*)-nicotine **2** (6 steps, 65%), (*S*)-anatabine **3** (8 steps, 30%), (*S*)-*N*-methylanatabine **4** (8 steps, 25%), (*S*)-anabasine **5** (8 steps, 35%), and (*S*)-*N*-methylanabasine **6** (8 steps, 25%).

Introduction

There are many biologically important compounds that have a pyrrolidine or piperidine heterocyclic ring in their structure, and it was recently reported in the literature that during the past 10 years over 12 000 piperidine derivatives have been mentioned in clinical or preclinical studies.[1] The development of new methods for the synthesis of pyrrolidine-[2] or piperidine-based compounds[3] is therefore of considerable importance, particularly approaches leading to chiral derivatives of these ring skeletons.[4] In this context, the enantiomeric synthesis of piperidine and pyrrolidine alkaloids, known as natural products from tobacco, provides convenient and excellent templates for the development of new strategies in this field.

In fresh *Nicotina tabacum*, the species most commonly used for the production of cigarette tobacco, the alkaloid mixture typically consists of 93% (*S*)-nicotine **2**, 3.9% (*S*)-anatabine **3**, 2.4% (*S*)-nornicotine **1**, and 0.5% (*S*)-anabasine **5** (Figure 1).[5] Other pyridine alkaloids such as (*S*)-*N*-methylanatabine **4**, (*S*)-*N*-methylanabasine **6**, myosmine **7**, and anabaseine **8** are also detected.

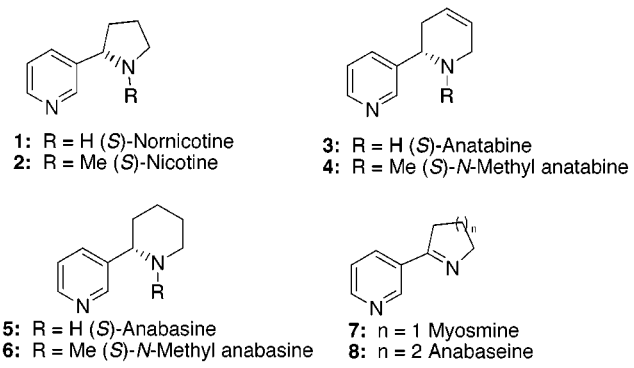

Figure 1.

Nicotinic acetylcholine receptors (nAChR) are a group of channel receptors that play an important role in many biological processes related to a number of nervous system disorders.[6] Several studies have demonstrated that the naturally occurring alkaloids (*S*)-nicotine **2** and (*S*)-epibatidine **9** and many analogues of **2** and **9** display potent biological activity in mammals by modulation of nAChR (Figure 2).[7] In particular, (*S*)-nicotine **2** has attracted much attention because of its important pharmacological effects on central nervous system (CNS) diseases. (*S*)-Nicotine **2** may have beneficial effects in the treatment of Parkinson's disease, Alzheimer's disease,

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(1) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679−3681.

(2) For representative papers on the pyrrolidine series, see: (a) Xu, Y-z.; Choi, J.; Calaza, M. I.; Turner, S. C.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069−4078. (b) Turner, S. C.; Zhai, H.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861−870. (c) Knight, D. W.; Salter, R. *Tetrahedron Lett.* **1999**, *40*, 5915−5918.

(3) For representative papers on the piperidine series, see: (a) Takahata H.; Kubota, M.; Ikota, N. *J. Org. Chem.* **1999**, *64*, 8594−8601. (b) Kumareswaran, R.; Balasubramanian, T.; Hassner, A. *Tetrahedron Lett.* **2000**, *41*, 8157−8162. (c) Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2000**, *11*, 4639−4643. (d) Eskici, M.; Gallagher, T. *Synlett* **2000**, 1360−1362. (e) Cossy, J.; Willis, C.; Bellosta, V.; Bouzbouz, S. *Synlett* **2000**, 1461−1463. (f) Lindström, S.; Ripa, L.; Halberg, A. *Org. Lett.* **2000**, *2*, 2291−2293. (g) Cossy, J.; Pévet, I.; Meyer, C. *Synlett* **2000**, 122−124.

(4) For a review on asymmetric synthesis in the piperidine series, see: (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633−640. (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781−1813.

(5) Leete, E.; Mueller, M. E. *J. Am. Chem. Soc.* **1982**, *104*, 6440−6444.

(6) Galzi, J. L.; Changeux, J. P. *Neuropharmacology* **1995**, *34*, 563−579.

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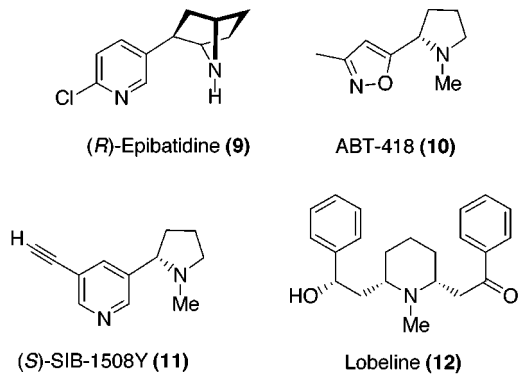


Figure 2.

and Tourette's syndrome.[8] (*R*)-Epibatidine **9**, isolated from the skin of an Ecuadorian frog, is a powerful analgesic agent (>200−500 times more potent than morphine) that acts via neuronal nAChR.[9] Recent advances in the synthesis of analogues have led to the discovery of new compounds, such as ABT-418 **10** and SIB-1508Y **11**, which have improved pharmacotherapeutic properties.[10] SIB-1508Y **11** is in clinical trials for the treatment of Parkinson's disease. Other piperidine tobacco alkaloids, anabaseine **8**, (*S*)-anabasine **5**, (*S*)-anatabine **3**, and analogues display similar activities.[11] Lobeline **12** is under development as an aid to alieviate nicotine addiction.[12]

It has been shown that the (*S*) enantiomer of nicotine **2** is more active than the (*R*),[13] a tendency also established for many analogues. This clear stereoselectivity of biological activity has recently stimulated considerable efforts in the synthesis of enantiopure pyrrolidine and piperidine analogues of these natural products. While many racemic syntheses of these alkaloids have been described, only a few individual and specific asymmetric syntheses have been reported.[14] It should be noted that the well-documented enantioselective hydrogenation or reduction of the imine functionality[15] of myosmine **7** or anabaseine **8** constitutes an obvious and straightforward route to (*S*)-nornicotine **1** or (*S*)-anabasine **5**. Unfortunately, several unsuccessful attempts at enantioselective hydrogenation or reduction of myosmine **7** (or analogues) have been reported in the literature. For example, Buchwald[16] and co-workers reported that, while 2-phenyl-1-pyrroline underwent enantioselective hydrogenation (>99% ee) in the presence of chiral titanocene catalyst, to give the corresponding 2-phenyl-1-pyrrolidine, the same conditions when applied to myosmine **7** failed to give any reaction. In the key step in the synthesis of SIB-1508Y **11**, 5-bromo-3-(2-pyrrolin-1-yl)pyridine was reduced with chiral (acyloxy)borohydride reagent (derived from Cbz-D-proline) in high yields but with poor enantioselectivity (at best 30% ee). Thus, pure (*S*)-SIB-1508Y **11** (ee >99%) was obtained by recrystallization as the dibenzoyl-L-tartrate salt of its enantiomerically enriched material. In general, the most popular approach to the preparation of these chiral alkaloids or their analogues is the classical resolution using inexpensive resolving agents, such as tartaric acid.[17]

Results and Discussion

In this paper, we report a flexible and general strategy for both families of these alkaloids from a common chiral intermediate.[18] Our retrosynthetic route for the natural alkaloids **1**−**6** is depicted in Scheme 1. In a single step, enantioselective allylation of the 3-pyridinecarboxaldehyde **13** affords the corresponding chiral homoallylic alcohol (*R*)-**14**, introducing both the chiral center with an unambiguous absolute configuration, as well as a suitable double bond to prepare all the target molecules. The chiral alcohol (*R*)-**14** was converted into the chiral homoallylic azide (*S*)-**15**, with complete inversion of the carbon chiral center. We anticipated that this key intermediate would give rise to the pyrrolidine and piperidine rings. Thus, the elaboration of the pyrrolidine ring relies on an intramolecular hydroboration−cycloalkylation[19] of azido-olefin (*S*)-**15** providing a rapid and convenient access to (*S*)-nornicotine **1** in a one-pot multistep process, thence to (*S*)-nicotine **2** by *N*-methylation.

(7) For recent reviews on structure−activity relationships for nAChR ligands, see: (a) Lloyd, G. K.; Williams, M. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 461−467. (b) Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4169−4194. (c) Latli, B.; D'Amour, K.; Casida, J. E. *J. Med. Chem.* **1999**, *42*, 2227−2234. (d) Nielsen, S. F.; Nielsen, E. O.; Olsen, G. M.; Liljefors, T.; Peters, D. *J. Med. Chem.* **2000**, *43*, 2217−2226. (e) Mullen, G.; Napier, J.; Balestra, M.; DeCory, T.; Hale, G.; Macor, J.; Mack, R.; Loch, J., III; Wu, E.; Kover, A.; Verhoest, P.; Sampognaro, A.; Phillips, E.; Zhu, Y.; Murray, R.; Griffith, R.; Blosser, J.; Gurley, D.; Machulskis, A.; Zongrone, J.; Rosen, A.; Gordon, J. *J. Med. Chem.* **2000**, *43*, 4045−4050.

(8) Brennan, M. B. *Chem. Eng. News* **2000**, *78*, 23−26.

(9) Malpass, J. R.; Cox, C. D. *Tetrahedron Lett.* **1999**, *40*, 1419−1422 and references therein.

(10) (a) Cosford, N. D. P.; Bleicher, L.; Herbaut, A.; McCallum, J. S.; Vernier, J.-M.; Dawson, H.; Whitten, J. P.; Adams, P.; Chavez-Noriega, L.; Correa, L. D.; Crona, J. H.; Mahaffy, L. S.; Menzaghi, F.; Rao, T. S.; Reid, R.; Sacaan, A. I.; Santori, E.; Stauderman, K. A.; Whelan, K.; Lloyd, G. K.; McDonald, I. A. *J. Med. Chem.* **1996**, *39*, 3235−3237. (b) Garvey, D. S.; Wasicak, J. T.; Elliott, R. L.; Lebold, S. A.; Hettinger, A.-M.; Carrera, G. M.; Lin, N.-H.; He, Y.; Holladay, M. W.; Anderson, D. J.; Cadman, E. D.; Raszkiewicz, J. L.; Sullivan, J. P.; Arneric, S. P. *J. Med. Chem.* **1994**, *37*, 4455−4463.

(11) (a) Dwoski, L. P.; Teng, L.; Buxton, S. T.; Ravard, A.; Deo, N.; Crooks, P. A. *Eur. J. Pharmacol.* **1995**, *276*, 195−199. (b) Rem, W. R.; Zoltewicz, J. A.; Meyer, E. M.; Prokal-Tatral, K. U. S. Patent 7,741,802, 1998. (c) *Chem. Abstr.* **1998**, *128*, 321802v.

(12) Schneider, F. H.; Olsson, T. *Med. Chem. Res.* **1996**, 562−570.

(13) 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.

(14) To the best of our knowledge only four asymmetric syntheses of *(S)*-nicotine (or *(S)*-nornicotine) have been reported in the literature; 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*, 695. (d) Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L. *J. Org. Chem.* **1982**, *47*, 1069−1073. For asymmetric synthesis of *(S)*-anabasine, see: (e) Pfrengle W.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 4261−4263. (f) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749−1760. For *(S)*-anatabine, see: (g) Balasubramanian, T.; Hassner, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2201−2205. (h) Mehmandoust, M.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185−1187. (i) Barco, A.; Benetti, S.; De Risi, Carmela.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Eur. J. Org. Chem.* **2001**, 975−986.

(15) For a review, see: (a) Yurovskaya M. A.; Karchava, A. *Tetrahedron: Asymmetry*, **1998**, *9*, 3331−3352. See also: Yamada, K.; Takeda, M.; Iwakuma, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 265−270.

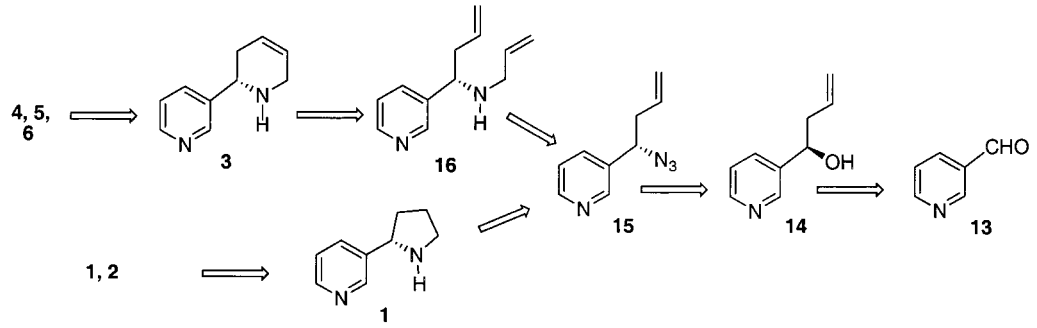
(16) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952−8965.

(17) (a) Bleicher, L. S.; Cosford, N. D. P.; Herbaut, A.; McCallum, J. S.; McDonald, I. A. *J. Org. Chem.* **1998**, *63*, 1109−1118. (b) Bleicher, L. S.; Cosford, N. D. P. *J. Org. Chem.* **1999**, *64*, 5299−5300.

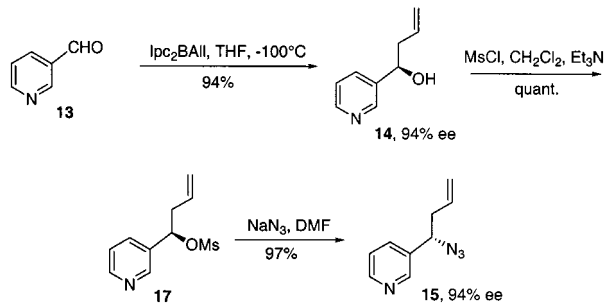
(18) Part of this work was previously disclosed as communications: (a) Girard, S.; Robins, R. J.; Villiéras, J.; Lebreton, J. *Tetrahedron Lett.* **2000**, *41*, 9245−9249. (b) Felpin, F.-X.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *Synlett* **2000**, 1646−1648.

(19) For a review of this field, see: Carboni, B.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1995**, *132*, 1003−1008 and literature cited therein. For significant examples, see: (a) Salmon, A.; Carboni, B. *J. Organometallic Chem.* **1998**, *567*, 6614−6617. (b) Waid, P. P.; Flynn, G. A., Huber, Sabol, J. S. *Tetrahedron Lett.* **1996**, *37*, 4091−4094. (c) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151−7157.

Scheme 1



Scheme 2



The retrosynthetic analysis of the piperidine ring construction showed that RCM[20] promised not only to effect the ring formation but also to introduce directly the olefin in the right position to afford in a straightforward manner (*S*)-anatabine **3**. The requisite *N*-allylamine **16** should then be available by *N*-allylation of the amine, obtained from the corresponding chiral homoallylic azide (*S*)-**15**, by chemoselective reduction. Finally from (*S*)-anatabine **3**, *N*-methylation or/and hydrogenation led to the synthetic goals, furnishing (*S*)-anabasine **5**, (*S*)-*N*-methylanatabine **4**, and (*S*)-*N*-methylanabasine **6**.

Our first efforts focused on the preparation of the common chiral homoallylic alcohol intermediate (*R*)-**14**, which has already been obtained by Brown[21] using an asymmetric allylboration of commercial 3-pyridinecarboxaldehyde **13** with *B*-allyldiisopinocampheylborane (prepared from (+)-*B*-chlorodiisopinocampheylborane[22] (Ipc_2BCl, DIP-Chloride) and allylmagnesium bromide) (see Scheme 2). However, the first attempts to reproduce this work met with limited success; alcohol **14** was isolated in modest yields (40−50%) with low ee[23] (70−80%) and accompanied by starting aldehyde **13**. We were quite disappointed by these results compared to those reported (this reaction is described on 15 mmol scale: 85% yield and >96% ee).

First, this failure led us to check the quality of the *B*-allyldiisopinocampheylborane, which was checked by allylation of benzaldehyde, to afford the corresponding homoallylic alcohol with comparable yields and slightly reduced enantioselectivities relative to those previously reported. Considering the contrasting behavior of 3-pyridinecarboxaldehyde **13** versus benzaldehyde, we speculated that the pyridine nitrogen was somehow responsible for our problems. To overcome these difficulties, allylation of 3-pyridinecarboxaldehyde **13** with *B*-allyldiisopinocampheylborane was carefully reinvestigated through a range of different reaction temperatures and stoichiometries. As already observed in the enantioselective reduction of acetylpyridines with oxazaborolidines,[24] we found that the complexation of the nitrogen of the pyridine is crucial for a high yield and ee. Thus, allylation of **13** with 2.2 equiv of *B*-allyldiisopinocampheylborane (instead of 1.1 equiv as reported) gave routinely on the multigram scale the corresponding (*R*)-homoallylic alcohol **14**[25] in 94% yield after purification and with an ee of 94%. In these conditions, 1 equiv of allylborane is engaged in the formation of a complex with the nitrogen of the pyridine and the free *B*-allyldiisopinocampheylborane reacts with the aldehyde. When only 1 equiv of chiral allylborane is added, the corresponding pyridine−allylborane complex is formed to afford a less efficient chiral allyl reagent, thus giving the alcohol **14** in only moderate yield and ee. It should be noted that the rate of addition of the aldehyde **13** (precooled to −65 °C)[26] to the reaction mixture at −100 °C is important, as well as the removal of $MgCl_2$ formed during the preparation of the *B*-allyldiisopinocampheylborane. To save 1 equiv of chiral allylborane,[27] we attempted to eliminate the effect of the pyridine nitrogen by adding first to the reaction mixture 1 equiv of triethylborane[28] (at −78 °C for 1 h), the reaction then being carried out as previously described with 1.1 equiv of *B*-allyldiisopinocampheylborane. Under these experimental conditions, however, chiral homo-

(20) For excellent reviews on the RCM with nitrogen-containing compounds, see: (a) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−89. For a more general review, see: (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. For recent examples, see: (a) Fürstner, A.; Thiel, O. R. *J. Org. Chem*. **2000**, *65*, 1738−1742. (b) Cook, G. R.; Shanker, P. S.; Peterson, S. L. *Org. Lett*. **1999**, *1*, 615−617. (c) Kigoshi, H.; Suzuki, Y.; Aoki, K.; Uemura, D. *Tetrahedron Lett*. **2000**, *41*, 3927−3930. (d) Wallace, D. J.; Cowden, C. J.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Tetrahedron Lett*. **2000**, *41*, 2027−2029. (e) Grigg, R.; Sridharan, V.; York, M. *Tetrahedron Lett*. **1998**, *39*, 4139−4142. (f) Voigtmann, U.; Blechert, S. *Org. Lett*. **2000**, *2*, 3971−3974. (g) Maldaner, A. O.; Pilli R. A. *Tetrahedron Lett*. **2000**, *41*, 7843−7846.

(21) (a) Racherla, U. S.; Brown, H. C. *J. Org. Chem*. **1991**, *56*, 401−404. (b) Racherla, U. S.; Liao, Y.; Brown, H. C. *J. Org. Chem*. **1992**, *57*, 6614−6617.

(22) 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. DIP-Chloride is the trademark of Aldrich Chemical Co.

(23) All enantiomeric excesses were determined by chiral HPLC analysis on a Chiralcel OD-H column, 46 × 15 cm, flow rate 0.5 mL/min.

(24) (a) Quallich, G. J.; Woodall, T. M. *Tetrahedron Lett*. **1993**, *34*, 785−788. (b) Masui, M.; Shioiri, T. *Synlett* **1997**, 273−274.

(25) Analysis of the proton NMR spectrum of the (*R*)-*O*-acetylmandelic ester derivative of this alcohol **14** confirmed the (*R*) absolute configuration; see: Chataigner, I.; Lebreton, J.; Durand, D.; Guingant, A.; Villiéras, J. *Tetrahedron Lett*. **1998**, *39*, 1759−1762.

(26) Under −70 °C, the aldehyde crystallized.

(27) An enantioselective oxazaborolidine-catalyzed reduction of 2-benzoylpyridines was reported in which the nitrogen was protected as *N*-allylpyridinium triflates; see: Corey, E. J.; Helal, C. J. *Tetrahedron Lett*. **1996**, *37*, 5675−5678.

(28) Lutz, C.; Graf C.-D.; Knochel, P. *Tetrahedron* **1998**, *54*, 10317−10328.

allylic alcohol was isolated in lower yields and enantioselectivities. One of the significant challenges associated with the synthesis of pyridine derivatives concerns the problem of the nitrogen reacting with reagents or catalysts (vide supra).

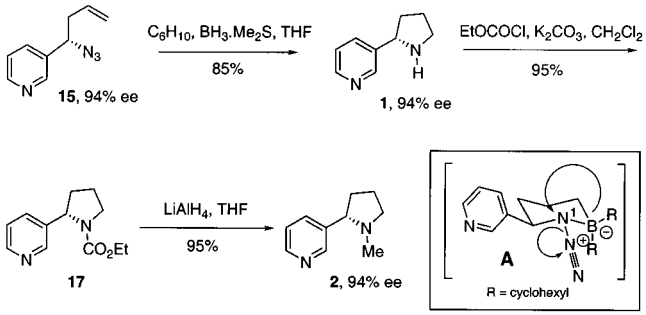
In the meantime, an alternative synthesis of the chiral alcohol **14** had been pursued using an enantioselective reduction of the corresponding ketone, obtained by oxidation of the racemic alcohol **14** with Dess−Martin periodinane reagent.[29] Unfortunately, this unstable ketone spontaneously formed a completely conjugated α,β-unsaturated ketone derivative. Surprisingly, the same reaction sequence was carried out on a benzene ring analogue of **14** and led cleanly to the corresponding β,γ-unsaturated ketone, which was reduced at −20 °C with (+)-Ipc_2BCl to give the desired alcohol with high ee (>99%).[30]

The next step involved replacing the alcohol at the benzylic position of **14** with an azide, resulting in inversion of configuration. Transformation of an alcohol into its corresponding azide has been widely reported through various indirect and a few direct methods. However, such reactions sometimes compete with an S_N1 reaction process, with a resulting decrease in ee, particularly in those cases where the substitution reaction occurred on the benzylic position.[31] A more recent report found that stereospecific substitution reactions on a (2-pyridinyl)methyl carbon center are even more problematic. Moreover, with such substrates, an additional problem is caused by the homoallylic position of the leaving group (activated alcohol function) which may, by β-elimination, afford the fully conjugated system.

To test this critical step, we chose a recent procedure reported by Thompson[32] for the direct conversion of electron-rich benzylic alcohols to azides with total inversion of configuration. The chiral homoallylic alcohol **14** was treated with diphenyl phosphoroazidate (DPPA)[33] and DBU in dry toluene; the corresponding phosphate of **14** formed in situ was displaced by the azide anion to afford, after purification by chromatography, the chiral azide (*S*)-**15** with a good yield. To our delight, a chiral HPLC analysis revealed that this transformation proceeds exclusively with complete inversion of configuration; no loss in ee was noted in the azide (*S*)-**15** (ee 94%).

To probe this transformation in more detail, we tried to use one of the most common methods for the preparation of primary and secondary aliphatic azides from the corresponding alcohols by nucleophilic displacement of the sulfonate intermediates by azide anion. To our surprise, chiral azide (*S*)-**15** could be prepared in two steps in nearly quantitative yield, by nucleophilic displacement of the corresponding mesylate (*S*)-**17** by azide anion, with complete inversion of configuration. The mesylate (*S*)-**17** was obtained by conventional treatment

Scheme 3



of the alcohol with mesyl chloride in the presence of Et_3N. Attempts to isolate this unstable mesylate **17** by chromatography proved problematic because of extensive decomposition. This material was therefore used without purification and was treated directly with sodium azide in DMF at 60 °C to afford the (*S*)-azide **15** (94% ee) in 97% yield for the two steps. No epimerization was observed at reaction temperatures below 65 °C. This latter sequence could be readily run on a large scale in high yields with inexpensive chemicals, and was therefore preferred to Thompson's method.

Synthesis of Pyrrolidine Alkaloids. (*S*)-Nornicotine 1 and (*S*)-Nicotine 2. With the chiral azide **15** in hand, our efforts were directed to the construction of the pyrrolidine ring (see Scheme 3).[34] For this purpose, we used an intramolecular hydroboration−cycloalkylation of the azido-olefin, which had already successfully been used for the synthesis of pyrrolidinone and piperidine derivatives.[19] The chiral azide **15** was treated with an excess of freshly prepared dicyclohexylborane to afford, after hydrolysis with methanol, the first target tobacco alkaloid: (*S*)-nornicotine **1** ($[\alpha]^{20}_D$ −35.2 (*c* 1, MeOH); lit.[14a] $[\alpha]^{20}_D$ −35.6 (*c* 1.256, MeOH)) was isolated in 85% yield as the sole product from the reaction mixture.

This one-pot sequence proceeds by hydroboration of the double bond of **15** and subsequent formation of a boron−nitrogen bond between the azide and the trialkylborane to afford the cyclic azide borane complex intermediate **A**. Finally, migration of the borane methylene group to N-1 of **A** proceeds with a ring contraction and concomitant loss of nitrogen.

The final transformation, the *N*-methylation of (*S*)-nornicotine **1**[35] to (*S*)-nicotine **2**, was achieved using a two-step procedure. The *N*-ethylcarbamate prepared from **1** was reduced by an excess of $LiAlH_4$ to give (*S*)-nicotine **2** ($[\alpha]^{20}_D$ −145 (*c* 1, EtOH); lit.[17a] $[\alpha]^{20}_D$ −154 (*c* 4, EtOH)) in 92% overall yield for the two steps.

Spectral data (^1H NMR, ^{13}C NMR) for (*S*)-nornicotine[18a] **1** and (*S*)-nicotine[17a] **2** were in excellent agreement with those recorded for the natural materials. Finally, the stereochemical integrity of the conversion of the chiral alcohol **14** (ee 94%) to (*S*)-nornicotine **1** and (*S*)-nicotine **2** was checked by an analysis on chiral HPLC, and no decrease in the ee was noted.

Synthesis of Piperidine Alkaloids. The amine (*S*)-**18**[36] was efficiently obtained in high yield by treatment

(29) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552.

(30) Singh, V. K. *Synthesis* **1992**, 605−617 and references therein.

(31) (a) Allen, A. D.; Kanagasabapathy, V. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 4513−4519. (b) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1383−1396. (c) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195−3196. (d) Uenishi, J.; Takagi, T.; Ueno, T.; Hiraoka, T.; Yonemitsu, O.; Tsukube, H. *Synlett* **1999**, 41−44.

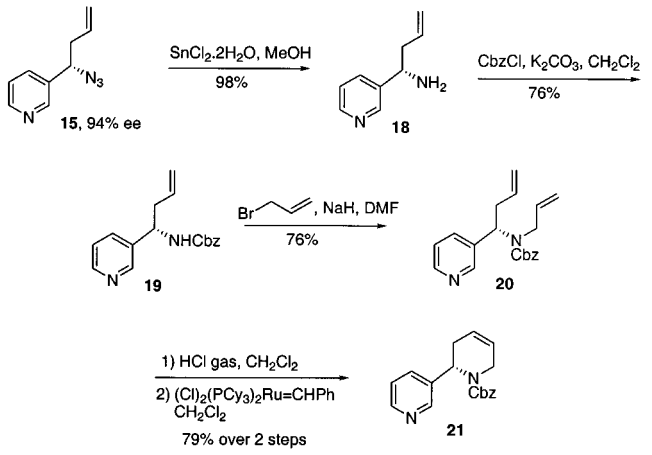
(32) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M., Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886−5888.

(33) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977−1980.

(34) An alternative synthesis of pyrrolidines using a reverse-Cope cyclization on homoallylic hydroxylamines has been published recently; see: Lee E.; Kim, S. K.; Kim, J. Y.; Lim, J. *Tetrahedron Lett.* **2000**, *41*, 5915−5918.

(35) Alternatively, (*S*)-nicotine **2** was obtained directly with a good yield (78%) by treatment of (*S*)-nornicotine **1** with an excess of LiHMDS followed by trapping with MeI.

Scheme 4



of azide (*S*)-**15** with an excess of hydrated tin chloride,[37] without affecting the double bond (see Scheme 4).[38]

RCM methodologies have proved an elegant generic synthetic approach for the total synthesis of cyclic natural products and have been largely illustrated in recent literature.[20] In particular, the commercial availability of Grubbs' catalyst has enlarged the scope of this methodology. We took advantage of the RCM reaction, which offered the possibility of simultaneously forming the piperidine skeleton and the double bond in the desired position. At first, effort was focused on the preparation of the chiral *N*-allylamine **18**, precursor of the piperidine ring. Our decision to proceed via *N*-allylation of the *N*-benzyloxycarbonyl carbamate **19** was based on previous attempts[39] to direct the *N*-monoallylation of amine **18**. It was also anticipated that the *N*-benzyloxycarbonyl group could serve as a masked methyl group at the final stage (vide infra). Following a sequence already described, amine **18** was protected as the benzyl carbamate **19**, which was treated with an excess of sodium hydride in the presence of allyl bromide, providing the protected *N*-allylamine **20** in good yield.[40]

Before attempting the RCM on **20**, we decided to practice this cyclization on a racemic substrate, in which the pyridine ring was switched to a phenyl ring. The olefin metathesis reaction with 10 mol % of the Grubbs' ruthenium benzylidene catalyst afforded the desired product in high yield. Unfortunately, under the same conditions, all attempts using the protected *N*-allylamine **20** were unsuccessful; no metathesis was observed and the starting material was recovered. The nearly quantitative yield from RCM is in striking contrast with the result obtained with **20**.

The problems associated with pyridine nitrogen and the compatibility of the olefin metathesis catalysts have been reported many times, and we were not surprised by this failure. a plausible explanation is that the pyridine nitrogen interferes with the catalytic cycle by coordinating to ruthenium.[41]

To circumvent this problem, our attention turned to a pyridine derivative of **20** in which the nitrogen functionality is blocked and so cannot interfere with the ruthenium. We chose protonation,[42] which can be easily achieved by bubbling dry hydrochloric acid gas into a solution of **20**, followed by removal of the solvent in a vacuum. Treatment of the hydrochloride pyridium salt of **20** with the Grubbs' catalyst, followed by a basic workup gave the desired piperideine **21** in good yield.[43] Optimal yields were obtained when 5 mol % of the catalyst was used followed by the addition of 2.5 mol % after 4 h. The cyclization would not proceed to completion with a single addition of 10 mol % of catalyst. Presumably, the ruthenium catalyst decomposed in our acidic conditions of refluxing dichloromethane.

Having secured good access to this chiral building block (*S*)-**21**, the completion of the synthesis of the four chiral piperidine alkaloids **2**−**4** proved to be straightforward and could be achieved using a single-, two-, or three-step one-pot procedure, depending on the target piperdine alkaloid (see Scheme 5). Thus, exposure of (*S*)-**21** to an atmosphere of hydrogen in the presence of Pd on carbon as catalyst in EtOH caused simultaneous hydrogenation of the double bond of (*S*)-**21** and hydrogenolysis of the benzyloxycarbonyl protecting group to give (*S*)-anabasine **5** ($[\alpha]^{20}_D$ −80.0 (*c* 0.91, MeOH); lit.[44] $[\alpha]^{20}_D$ −79.2 (*c* 0.5, MeOH)). (Scheme 5). The (*S*)-*N*-methylanatabine **4** was easily obtained in good yield, by simple treatment of (*S*)-**21** with an excess of $LiAH_4$, leading to the reduction of the *N*-benzyloxycarbonyl protecting group to *N*-Me. For the synthesis of (*S*)-anatabine **3** from the intermediate (*S*)-**21**, catalytic hydrogenation was not suitable for the cleavage of the *N*-benzyloxycarbonyl protecting group as a result of the presence of the double bond in the piperidine ring. To overcome this problem, the cleavage of the protecting group of (*S*)-**21** was achieved by reaction with an excess of dimethyl sulfide in the presence of etherate of boron trifluoride, according to a described method,[45] leading to (*S*)-anatabine **3** in good yield ($[\alpha]^{20}_D$ −117.0 (*c* 0.94, MeOH); lit.[46] $[\alpha]^{20}_D$ −98.15 (*c* unspecified,

(36) To prepare the chiral homoallylic amine **18**, the Mitsunobu inversion of alcohol (*R*)-**14** with succinimide followed hydrazinolysis was evaluated. On standard Mitsunobu reaction with diethyl azodicarboxylate (DEAD) and succinimide, the expected *N*-succinimide derivative was obtained in low yield because of a difficult separation of the product from residual reactants and byproducts. For a recent procedure, see: Takahata, H.; Kubota, M.; Ikota, N. *J. Org. Chem.* **1999**, *64*, 8594−8601.

(37) (a) Bartra, M.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron* **1990**, *46*, 587−594. (b) Lebreton, J.; Waldner, A.; Leseuer, C.; De Mesmaeker, A. *Synlett* **1994**, 137−140.

(38) Examples of selective reduction of azides in the presence of double bond using Lindlar catalytic hydrogenation have been reported in the literature; see: Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590−591.

(39) In our initial studies, attempts at *N*-allylation of the trifluoroacetamide derived from amine (*S*)-**18** (TFAA/TEA/CH_2Cl_2) by sequential treatment with NaH and allylbromide failed. The desired *N*-alkylated product was obtained in poor yields (less than 20%) accompanied with *N*-allyl-, *N*,*N*-diallyl derivatives. This *N*-allylation appeared to be very sensitive to traces of moisture and/or to the quality of NaH used.

(40) (a) Falb, E.; Bechor, Y.; Nudelman, A.; Hassner, A.; Albeck, A.; Gottlieb, H. E. *J. Org. Chem.* **1999**, *64*, 498−506. (b) Kise, N.; Oike, H.; Okazaki, E.; Yoshimoto, M.; Shono, T. *J. Org. Chem.* **1995**, *60*, 3980−3992.

(41) For similar problems of pyridine-metal coordination, see: (a) Ling Ng, P.; Lambert, J. N. *Synlett* **1999**, 1749−1750. (b) Raatz, D.; Innertsberger, C.; Reiser, O. *Synlett* **1999**, 1907−1910.

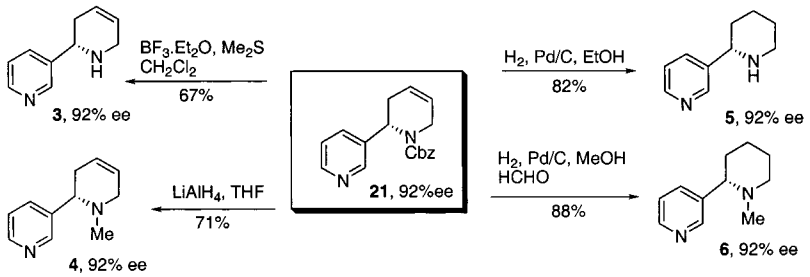
(42) (a) Fu, G. C.; Nguyen, S. B. T.; Grubbs, R. B. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857. (b) Evans, P.; Grigg, R.; York, M. *Tetrahedron Lett* **2000**, *41*, 3967−3970. (c) An example of successful RCM on a more hindered and less basic 2-chloropyridine compound was reported; see: Grigg, R.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1998**, *39*, 4139−4142.

(43) Initially this sequence was run with an *N*-Boc carbamate as protecting group; however, this choice turned out to be less efficient: during the protonation of the pyridine ring with HCl gas, the *N*-Boc was cleaved.

(44) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1982**, *57*, 3264−3265.

(45) (a) Haddad, M.; Imogaï, H.; Larchevêque, M. *J. Org. Chem.* **1998**, *63*, 5680−5683. (b) Sanchez, I. H.; Lopez, F. J.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *J. Am. Chem. Soc.* **1983**, *105*, 7640−7643.

Scheme 5



MeOH)). Finally, (*S*)-*N*-methylanabasine **6** was synthesized from (*S*)-**21** by taking advantage of the Eschweiler-Clarke[47] reductive amination procedure. Following this procedure, intermediate (*S*)-**21** was stirred in a mixture of MeOH with aqueous formaldehyde at room temperature under an atmosphere of hydrogen in the presence of Pd on carbon. This led to the concomitant hydrogenation of the double bond and removal of the *N*-benzyloxycarbonyl protecting group, affording (*S*)-anabasine **6** in situ, which was *N*-methylated via the reduction of the iminium.

The spectroscopic data (^{1}H NMR, ^{13}C NMR) of (*S*)-anatabine **3** and (*S*)-anabasine **5** were identical with those previously reported for the racemic materials.[48] The spectroscopic data (^{1}H NMR, ^{13}C NMR) for (*S*)-*N*-methylanatabine **4** and (*S*)-*N*-methylanabasine **6** are in good agreement with those partially reported in the literature for the racemic materials.[49]

The enantiomeric excess in (*S*)-anabasine **3**, (*S*)-*N*-methylanatabine **4**, (*S*)-anabasine **5**, and (*S*)-anatabine **6** was determined by chiral HPLC; a slight drop of ee was noted (less than 1−2% for all products).[50]

The optical rotation of our synthetic (*S*)-*N*-methylanatabine **4** ($[\alpha]^{20}_D$ −157.5 (*c* 0.8, MeOH)) and (*S*)-*N*-methylanabasine **6** ($[\alpha]^{20}_D$ −132.3 (*c* 0.8, MeOH)) matched those reported by Spath[51] for the natural products, $[\alpha]^{20}_D$ −171.4 (c 0.5, MeOH) and $[\alpha]^{20}_D$ −143.8 (c 0.4, MeOH) for (*S*)-*N*-methylanatabine **4** and (*S*)-*N*-methylanabasine **6** respectively.

Conclusion

We have accomplished a highly efficient enantioselective synthesis of tobacco alkaloids. From a common chiral intermediate, two different strategies have been used to construct the piperidine and pyrrolidine rings. Access to unnatural (*R*)-enantiomers of these alkaloids could be obtained by replacing (+)-Ipc_2BCl with (−)-Ipc_2BCl. The present approach provides a facile route to these natural alkaloids and could be applicable to the preparation of a wide range of chiral structural analogues of piperidine and pyrrolidine heterocyclic compounds, providing a better understanding of their pharmacological activities. Synthesis of such analogues and studies of the structure−activity relationships are in progress.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz using $CDCl_3$ as internal standard (7.26 and 77.16 ppm, respectively). Flash column chromatography was performed on Merck silica gel (60 Å, 230−400 mesh). HMRS were recorded at the Centre Régional de Mesures Physique de l'Ouest. Chiral HPLC was performed with a CHIRACEL OD-H column, 46 × 15 cm, flow rate 0.5 mL/min. Grubbs' catalyst was purchased from Strem. (+)-DIPCl was purchased from Aldrich. All reactions were performed under N_2 in a flame-dried flask using anhydrous solvents. Grignard reagents were titrated by Watson and Eastham's method.[52]

Preparation of Allylborane Reagent Free from Magnesium Salts. A solution of commercial allylmagnesium bromide in ether (48 mL, 1 M, 48 mmol) was added to a solution of (+)-*B*-chlorodiisopinocampheylborane ((+)-DIPCl) (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×). Stirring was stopped to permit the magnesium salts to settle, and the supernatant pentane extract was filtered through a pad of Celite. The pentane was evaporated under reduced pressure to give (+)-*B*-allyldiisopinocampheylborane ((+)-Ipc_2Ball) (15.6 g, 96%) as a colorless oil.

(*R*)-1-Pyridin-3-yl-but-3-en-1-ol (14). To a solution of (+)-*B*-allyldiisopinocampheylborane (15.6 g, 47.8 mmol) in ether (50 mL) at −100 °C was slowly added, via a cannula, a solution of 3-pyridinecarboxaldehyde **13** (2.0 mL, 21.2 mmol) in ether (40 mL) maintained at −65 °C. After stirring at −100 °C for 1 h, the reaction mixture was quenched with methanol (1 mL). The resulting mixture was then allowed to warm to room temperature and extracted with 1 N aqueous HCl. The combined aqueous layers were treated with 30% aqueous NaOH solution until pH 12−13 and then extracted with CH_2Cl_2 (4×). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (5% MeOH−CH_2Cl_2) gave the alcohol **14** (3.16 g, 94%) as a pale yellow oil; 94% ee, determined by chiral HPLC (hexane/*i*-PrOH = 95/5, 23.3 min for (*S*)-alcohol and 24.6 min for (*R*)). $[\alpha]^{20}_D = 28$ (*c* 1, EtOH); IR (KBr) ν 1585, 1642, 2979, 3077, 3444 cm^{-1}; ^{1}H NMR δ (ppm) 2.47 (m, 2H), 3.51 (s, 1H), 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 and J = 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 (ppm) 43.1, 70.0, 119.2, 125.2, 132.8, 137.9, 141.8, 146.3, 147.1; MS (CI/NH_3) *m*/*z* 150 (MH^+, 100), 167.

(*R*)-Methanesulfonic Acid 1-Pyridin-3-yl-but-3-enyl Ester (17). To a solution of alcohol **14** (6.0 g, 40.3 mmol) and Et_3N (11.2 mL, 80.6 mmol) in CH_2Cl_2 (200 mL) at 0 °C was slowly added methanesulfonyl chloride (4.7 mL, 60.5 mmol). After stirring for 10 min, the mixture was diluted with water and the layers were separated. The organic layer was washed

(46) Wada, E.; Kisaki, T.; Ihida, M. *Arch. Biochem. Biophys.* **1959**, *80*, 258−267.

(47) Vazquez-Tato, M. P.; Seijas, J. A.; Fleet, G. W. J.; Mathews, C. J.; Hemmings, P. R.; Brown, D. *Tetrahedron* **1995**, *51*, 959−974.

(48) Yang, C.-M.; Tanner, D. D. *Can. J. Chem.* **1997**, *75*, 616−620.

(49) (a) Quan, P. M.; Karns, T. K. B.; Quin, L. D. *J. Org. Chem.* **1965**, *30*, 2769−2772. (b) Alberici, G. F.; Andrieux, J.; Adam, G.; Plat, M. M. *Tetrahedron Lett.* **1983**, *24*, 1937−1940.

(50) For (*S*)-anatabine **3**, all attempts to separate the enantiomers failed and the ee was measured on the hydrogenated product, (*S*)-anabasine **5**.

(51) Spath, E.; Kesztler, F. *Ber. Dtsch. Chem. Ges.* **1937**, *70*, 2450−2454.

(52) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, 165−168.

with water (100 mL) and brine (2×), dried over anhydrous $MgSO_4$, filtered, and concentrated at room temperature under reduced pressure to afford the crude mesylate **17** (9.1 g, 100%) as a yellow oil. The product was immediately used in the next step, without purification, because of extensive decomposition. $[\alpha]^{20}_D$ 65.5 (*c* 1.16, MeOH); ^{1}H NMR δ (ppm) 2.60−2.91 (m, 2H), 2.85 (s, 3H), 5.10−5.20 (m, 2H,), 5.62 (t, 1H, J = 6.7 Hz), 5.66−5.82 (m, 1H), 7.35 (dd, 1H, J = 7.9 Hz, J = 7.8 Hz), 7.72 (m, 1H), 8.62 (m, 2H); ^{13}C NMR δ (ppm) 38.9, 41.0, 80.6, 119.8, 123.5, 131.1, 133.6, 134.1, 148.0, 150.2.

(*S*)-3-(1-Azido-but-3-enyl)-pyridine (15). Method A. To a solution of mesylate **17** (9 g, 39.6 mmol) in freshly distilled DMF (120 mL) was added, in one portion, NaN_3 (3.87 g, 59.5 mmol). The resulting mixture was stirred at 60 °C for 4 h and then diluted with water. The layers were separated and the aqueous layer was extracted with ether (3×). The combined extracts were washed with brine (2×), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (40% ethyl acetate−hexane) gave azide **15** (6.72 g, 97%) as a colorless oil; 94% ee, determined by chiral HPLC (hexane/*i*-PrOH = 95/5, 13.1 min for (*S*)-azide and 14.8 min for (*R*)). $[\alpha]^{20}_D$ −96.9 (*c* 1, $CHCl_3$); IR (KBr) ν 1591, 1642, 2096, 3081 cm^{-1}; ^{1}H NMR δ (ppm) 2.46−2.70 (m, 2H), 4.56 (t, 1H, J = 6.9 Hz) 5.07−5.17 (m, 2H), 5.63−5.83 (m, 1H), 7.28−7.35 (m, 1H), 7.62−7.68 (m, 1H), 8.56−8.60 (m, 2H); ^{13}C NMR δ (ppm) 40.2, 63.1, 118.9, 123.4, 132.6, 134.1, 134.7, 148.4, 149.5; HRMS (EI) calcd for $C_6H_5N_4$ (M − C_3H_5) 133.0514, found 133.0512.

Method B. To a solution of alcohol **14** (0.2 g, 1.34 mmol) in dry toluene (2 mL), was added diphenylphosphoryl azide (0.38 g, 1.38 mmol). The resulting mixture was cooled to 0 °C, and DBU (0.21 mL, 1.38 mmol) was added. The reaction was stirred for 3 days at room temperature and was quenched with water (5 mL). The white precipitate was filtered through a pad of Celite, and the aqueous layer was extracted with ether (3×). The combined extracts were washed with brine (2×), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (20% ethyl acetate/hexane) to give **15** (0.2 g, 88%) as a pale yellow oil.

(*S*)-1-Pyridin-3-yl-but-3-enylamine (18). To a solution of azide **15** (6.5 g, 37.3 mmol) in MeOH (120 mL) at 0 °C was added a solution of hydrated tin chloride ($SnCl_2 \cdot 2H_2O$) in MeOH (50 mL) over 30 min. After 3 h of stirring at room temperature, the solvent was removed under reduced pressure. To the residue was added successively CH_2Cl_2 (20 mL) and water (20 mL). The solution was treated with KOH in pellets until the emulsion disappeared (pH = 13). The aqueous layer was extracted with CH_2Cl_2 (4×). The combined extracts were washed with brine (2×) and dried over anhydrous $MgSO_4$. Removal of solvent left an oil that was purifed by flash chromatography (10% MeOH/CH_2Cl_2), affording the amine **18** (5.42 g, 98%) as a colorless oil. $[\alpha]^{20}_D$ −30.5 (*c* 0.92, MeOH); IR (KBr) ν 1577, 1640, 3076, 3270, 3364 cm^{-1}; ^{1}H NMR δ (ppm) 1.75 (s, 2H), 2.28−2.52 (m, 2H), 4.04 (dd, 1H, J = 7.6 Hz, J = 5.6 Hz), 5.06−5.16 (m, 2H), 5.63−5.84 (m, 1H), 7.22 (dd, 1H, J = 4.7 Hz, J = 7.6 Hz), 7.69 (dt, 1H, J = 1.7 Hz, J = 7.6 Hz), 8.47 (dd, 1H, J = 1.7 Hz, J = 4.7 Hz), 8.57 (d, 1H, J = 1.7 Hz); ^{13}C NMR δ (ppm) 43.6, 52.6, 117.9, 123.0, 133.6, 134.3, 140.5 148.1, 148.2; HRMS (EI) calcd for $C_6H_7N_2$ (M − C_3H_5) 107.0609, found 107.0612.

(*S*)-(1-Pyridin-3-yl-but-3-enyl)-carbamic Acid Benzyl Ester (19). To a solution of amine **18** (2.0 g, 13.5 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C was added successively potassium carbonate (1.86 g, 13.5 mmol) and benzyl chloroformate (2.3 mL, 16.2 mmol). After stirring for 30 min at room temperature, the mixture was hydrolyzed with saturated aqueous $NaHCO_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (40% ethyl acetate/hexane) gave the carbamate **19** (2.89 g, 76%) as a colorless oil. $[\alpha]^{20}_D$ −25 (*c* 0.97, MeOH); IR (KBr) ν 1532, 1641, 1716, 3033 cm^{-1}; ^{1}H NMR δ (ppm) 2.51 (t, 2H, J = 7.0 Hz), 4.81 (m, 1H), 5.06−5.13 (m, 4H), 5.55−5.76 (m, 2H), 7.19−7.30 (m, 6H), 7.55−7.59 (m, 1H), 8.47−8.50 (m, 1H), 8.55 (s, 1H); ^{13}C NMR δ (ppm) 40.5, 52.5, 66.8, 119.0, 123.3, 128.0, 128.0, 128.4, 132.9, 133.9, 136.1, 137.5, 148.0, 148.5, 155.6; HRMS (EI) calcd for $C_{17}H_{18}N_2O_2$ (M^+) 282.1368, found 282.1373.

(*S*)-Allyl-(1-pyridin-3-yl-but-3-enyl)-carbamic Acid Benzyl Ester (20). To a stirred solution of **19** (1.4 g, 5 mmol) in dry DMF freshly distilled (50 mL) at 0 °C was added NaH (60%, 1.19 g, 29.8 mmol). After the evolution of H_2 ceased, allyl bromide (1.3 mL, 14.9 mmol) was added. After stirring for 30 min at room temperature, the mixture was quenched with water (20 mL). The aqueous layer was extracted with ether (3×). The combined extracts were washed with brine (3×) and dried over anhydrous $MgSO_4$. Removal of the solvent left an oil that was purified by flash chromatography (40% ethyl acetate/hexane), affording amine **20** (1.21 g, 76%). $[\alpha]^{20}_D$ −52 (*c* 1, MeOH); IR (KBr) ν 1642, 1694, 3033 cm^{-1}; ^{1}H δ (ppm) 2.77 (t, 2H, J = 7.5 Hz), 3.60−3.79 (m, 2H), 4.90−5.08 (m, 4H), 5.15 (s, 2H), 5.33 (sl, 1H), 5.57−5.84 (m, 2H), 7.18−7.26 (m, 1H), 7.31 (s broad, 5H) 7.60 (s broad, 1H), 8.49 (d, 1H, J = 4.6 Hz), 8.57 (s, 1H); ^{13}C NMR δ (ppm) 35.2, 46.9, 57.1, 67.4, 116.7, 118.1, 123.2, 127.9, 128.0, 128.4, 134.1, 134.7, 135.3, 135.6, 136.4, 148.8, 149.5, 156.2; HRMS (EI) calcd for $C_{20}H_{22}N_2O_2$ (M^+) 322.1681, found 322.1679.

(*S*)-Allyl-(1-pyridin-3-yl-but-3-enyl)-carbamic Acid Benzyl Ester Hydrochloride. Protonation of the pyridine was achieved by bubbling dry HCl gas into a solution of diethylenic amine **20** (1.21 g, 3.8 mmol) in CH_2Cl_2 (30 mL). Removal of the solvent gave the hydrochloride pyridinium salt (1.35 g, 100%) as a oil. ^{1}H NMR δ (ppm) 2.85−2.95 (m, 2H), 3.79−4.05 (m, 2H), 5.09−5.18 (m, 7H), 5.61−5.81 (m, 2H), 7.31−7.33 (m, 5H), 7.90 (sl, 1H), 8.44 (sl, 1H), 8.79−8.81 (m, 2H); ^{13}C NMR δ (ppm) 34.3, 48.7, 56.8, 67.2, 117.7, 118.9, 126.4, 127.4, 127.7, 128.0, 132.3, 133.4, 135.4 139.5, 139.8, 140.5, 145.0, 155.1.

(*S*)-3,6-Dihydro-2*H*-[2,3′]bipyridinyl-1-carboxylic Acid Benzyl Ester (21). To a solution of the amine hydrochloride of **20** (1.43 g, 3.98 mmol) in anhydrous degassed CH_2Cl_2 (50 mL) was added a solution of bis(tricyclohexylphosphine)-benzylidene ruthenium dichloride (160 mg, 0.2 mmol) in CH_2Cl_2 (20 mL). The resulting mixture was stirred at reflux under argon. After 4 h, an additional portion of catalyst (80 mg, 0.1 mmol) was added, and the reaction was found to be complete after a total of 8 h. After the mixture cooled to room temperature, saturated aqueous $NaHCO_3$ was added. The solution was extracted with CH_2Cl_2 (3×) and concentrated in vacuo. The residue was purified by flash chromatography (40% ethyl acetate/hexane) to give **21** (0.92 g, 79%) as a yellow oil; 92% ee, determined by chiral HPLC (hexane/*i*-PrOH = 98/2, 28.2 min for (*S*)-carbamate and 34.1 min for (*R*)). $[\alpha]^{20}_D$ −83 (*c* 0.99, MeOH); IR (KBr) ν 1660, 1700, 2953, 3036 cm^{-1}; ^{1}H NMR δ (ppm) syst AB, 2.48−2.57 (A, dm, 1H, J = 17.8 Hz), 2.72−2.81 (B, dm, 1H, J = 17.8 Hz), syst AB 3.35−3.47 (A, dm, 1H, J = 19 Hz), 4.28−4.39 (dm, 1H, J = 19 Hz), 5.20 (s, 2H), 5.64−5.70 (m, 2H), 5.87−5.96 (m, 1H), 7.17−7.27 (m, 1H), 7.32−7.38 (m, 5H), 7.58−7.62 (m, 1H), 8.48 (d, 1H, J = 4,4 Hz), 8.57 (s, 1H); ^{13}C NMR δ (ppm) 27.4, 40.4, 49.2, 67.4, 122.9, 123.2, 124.2, 127.9, 128.1, 128.5, 134.5, 136.0, 136.4, 148.5, 148.6, 155.4; HRMS (EI) calcd for $C_{18}H_{18}N_2O_2$ (M^+) 294.1368, found 294.1376.

(*S*)-1,2,3,4,5,6-Hexahydro-[2,3′]bipyridinyl, (*S*)-Anabasine (5). A solution of **21** (0.40 g, 1.37 mmol) in ethanol (15 mL) containing palladium on carbon (0.14 g, 10% mol) was hydrogenated at room temperature for 14 h. The catalyst was removed by filtration, and the residue was purified by flash chromatography (5% MeOH/CH_2Cl_2) to give (*S*)-anabasine **5** (0.18 g, 82%) as a colorless oil; 92% ee, determined by chiral HPLC (hexane/*i*-PrOH = 98/2, 32.2 min for (*R*)-anabasine and 35.7 min for (*S*)). $[\alpha]^{20}_D$ −80 (*c* 0.91, MeOH); IR (KBr) ν 1318, 1424, 1577, 2933, 3031 cm^{-1}; ^{1}H NMR δ (ppm) 1.46−1.92 (m, 6H), 2.00 (s, 1H), 2.75−2.85 (m, 1H), 3.22 (dm, 1H, J = 11 Hz), 3.64 (dd, 1H, J = 11 Hz, J = 2.2 Hz), 7.25 (dd, 1H, J = 7.9 Hz J = 4.7 Hz), 7.73 (dm, 1H, J = 7.9 Hz), 8.49 (dt, 1H, J = 4.7 Hz, J = 1.7 Hz), 8.59 (s, 1H); ^{13}C NMR δ (ppm) 24.5, 24.9, 34.0, 46.9, 59.1, 122.9, 133.7, 139.7, 148.0, 148.1; MS (CI/NH_3) m/z 163 (MH^+, 100).

(*S*)-1,2,3,6-Tetrahydro-[2,3′]bipyridinyl. (*S*)-Anatabine (3). A solution of **21** (0.33 g, 1.13 mmol) in dry CH_2Cl_2 (16 mL) was treated with dimethyl sulfide (2.23 mL, 30.5 mmol) and boron trifluoride etherate (1.43 mL, 11.3 mmol). The mixture was stirred for 2 h, and then an additional amount of dimethyl sulfide (1.15 mL, 16.9 mmol) was added. The reaction mixture was stirred for another 4 h and poured into 10% aqueous NaOH. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined extracts were washed with brine (2×), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (5% MeOH/CH_2Cl_2) to furnish (*S*)-anatabine **3** (120 mg, 67%) as a colorless oil. All attempts to separate the enantiomers on the chiral HPLC column failed, and the ee was determined to be 92% on the hydrogenated product. $[\alpha]^{20}_D$ −117 (*c* 0.94, MeOH); IR (KBr) ν 1311, 1425, 1577, 1656, 2915, 3030 cm^{-1}; ^1H NMR δ (ppm) 2.09 (s, 1H), 2.16−2.21 (m, 2H), 3.41 (dm, 1H, J = 17 Hz), 3.54 (dm, 1H, J = 17 Hz), 3.83 (t, 1H, J = 7.2 Hz), 5.68−5.85 (m, 2H), 7.20 (dd, 1H, J = 4.9 Hz, J = 7.9 Hz), 7.66 (ddd, 1H, J = 7.9 Hz, J = 1.7 Hz, J = 2.1 Hz), 8.43 (dd, 1H, J = 4.9 Hz, J = 1.7 Hz), 8.54 (d, 1H, J = 2.1 Hz); ^{13}C NMR δ (ppm) 33.7, 45.9, 55.2, 123.5, 125.0, 126.1, 134.1, 139.7, 148.6, 148.7; MS (CI/NH_3) *m*/*z* 161 (MH^+, 100), 178.

(*S*)-1-Methyl-1,2,3,4,5,6-hexahydro-[2,3′]bipyridinyl. (*S*)-*N*-Methylanabasine (6). To a solution of **21** (0.40 g, 1.38 mmol) in distilled methanol (15 mL) was added aqueous formaldehyde (37% solution, 0.32 mL, 4.14 mmol). The reaction mixture was stirred at room temperature under an atmosphere of hydrogen in the presence of a catalytic amount of palladium on carbon (140 mg, 10% mol) for 24 h. The catalyst was removed by filtration through a pad of Celite, and the solvent was removed under reduced pressure. Purification by flash chromatography (5% MeOH/CH_2Cl_2) gave (*S*)-*N*-methylanabasine **6** (0.21 g, 88%) as a colorless oil; 92% ee, determined by chiral HPLC (hexane/*i*-PrOH = 98/2, 7.3 min for (*S*)-*N*-methylanabasine and 8.9 min for (*R*)). $[\alpha]^{20}_D$ −132.3 (*c* 0.8, MeOH); IR (KBr) ν 1321, 1426, 1575, 2981, 3027 cm^{-1}; ^1H NMR δ (ppm) 1.31−1.87 (m, 6H), 1.99 (s, 3H), 2.06−2.20 (m, 1H), 2.79−2.85 (m, 1H), 2.99−3.06 (m, 1H), 7.21−7.31 (m, 1H), 7.66−7.72 (m, 1H), 8.47−8.53 (m, 2H); ^{13}C NMR δ (ppm) 24.7, 25.9, 35.9, 44.4, 57.3, 68.2, 123.5, 134.8, 140.1, 148.5, 149.2; HRMS (EI) calcd for $C_{11}H_{16}N_2$ (M^+) 176.1313, found 176.1311.

(*S*)-1-Methyl-1,2,3,6-tetrahydro-[2,3′]bipyridinyl. (*S*)-*N*-Methylanatabine (4). To a suspension of $LiAlH_4$ (0.23 g, 6.2 mmol) in THF (20 mL) at 0 °C under nitrogen was added dropwise a solution of **21** (0.40 g, 1.37 mmol) in THF (20 mL). The mixture was stirred at room temperature for 6 h. The reaction was quenched with 10% aqueous NaOH (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3×). The combined extracts were washed with brine (2×), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% MeOH/CH_2Cl_2) to yield (*S*)-*N*-methylanatabine **4** (0.17 g, 71%) as a colorless oil; 92% ee, determined by chiral HPLC (hexane/*i*-PrOH = 98/2, 15.2 min for (*S*)-*N*-methylanatabine and 18.7 min for (*R*)). $[\alpha]^{20}_D$ −157.5 (*c* 0.4, MeOH); IR (KBr) ν 1321, 1426, 1576, 1667, 2984, 3033 cm^{-1}; ^1H NMR δ (ppm) 2.07 (s, 3H), 2.29−2.38 (m, 2H), 2.89−3.01 (m, 1H), 3.28−3.40 (m, 2H), 5.74−5.88 (m, 2H), 7.25−7.32 (m, 1H), 7.67−7.72 (m, 1H), 8.51−8.56 (m, 2H); ^{13}C NMR δ (ppm) 35.0, 43.3, 55.0, 62.8, 123.6, 124.6, 125.3, 135.2, 138.3, 148.8, 149.6; HRMS (EI) calcd for $C_{11}H_{14}N_2$ (M^+) 174.1157, found 174.1156.

(*S*)-3-Pyrrolidin-2-yl-pyridine, (*S*)-Nornicotine (1). To a stirred solution of freshly distilled cyclohexene (1.58 mL, 15.6 mmol) in 10 mL of THF at 0 °C was added dropwise 2.0 M BH_3−Me_2S complex in THF (3.94 mL, 7.9 mmol). 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 **15** (450 mg, 2.59 mmol) in 5 mL of THF. The resulting mixture was allowed to warm to room temperature. After 12 h, the reaction was quenched with MeOH and diluted with ether, and the organic layer was extracted with 1 N aqueous HCl (6×). The combined aqueous layers were treated with 30% aqueous NaOH solution until pH 13−14 and then extracted with CH_2Cl_2 (3×). The combined extracts were dried over anhydrous $MgSO_4$. Removal of the solvent left an oil that was purified by flash chromatography (5% EtOH/CH_2Cl_2) yielding (*S*)-nornicotine **1** (0.33 g, 85%); 94% ee, determined by chiral HPLC (hexane/*i*-PrOH = 95/5, 28.0 min for (*R*)-nornicotine and 30.0 min for (*S*)). $[\alpha]^{20}_D$ −35.2 (*c* 1, MeOH); ^1H NMR δ (ppm) 1.66 (1H, m), 1.9 (2H, m), 2.1 (1H), 2.2 (1H, m), 3.1 (2H, m), 4.14 (1H, J = 7.3 Hz, J = 2 Hz), 7.22 (1H, dd, J = 7.9 Hz, J = 4.9 Hz), 7.70 (pseudo dt, 1H, J = 7.9 Hz, J = 2.1 Hz), 8.45 (dd, 1H, J = 4.9 Hz, J = 1.7 Hz), 8.6 (d, 1H, J = 1.8 Hz); ^{13}C NMR δ (ppm) 25.3, 34.1, 46.7, 59.8, 123.2, 134.0, 140.0, 148.0, 148.4; MS (EI) *m*/*z* 147 ($M^+ - 1$).

(*S*)-2-Pyridin-3yl-pyrrolidine-1-carboxylic Acid Ethyl Ester (17). To a solution of (*S*)-nornicotine **1** (0.16 g, 1.1 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C were added successively potassium carbonate (0.15 g, 1.1 mmol) and methyl chloroformate (0.1 mL, 1.3 mmol). After stirring for 1 h at room temperature, the mixture was hydrolyzed with saturated aqueous $NaHCO_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (50% ethyl acetate/hexane) gave the carbamate **17** (0.21 g, 95%) as a yellow oil. $[\alpha]^{20}_D$ −105.6 (*c* 1.33, MeOH); ^1H NMR δ (ppm) 1.75−1.86 (m, 3H), 2.24−2.39 (m, 1H), 3.48−3.62 (m, 5H), 4.89 (m, 1H), 7.18 (dd, 1H, J = 4.7 Hz and J = 7.8 Hz), 7.42 (sl, 1H), 8.41 (m, 2H); ^{13}C NMR δ (ppm) 22.8, 23.7, 34.5, 35.5, 47.1, 47.5, 52.4, 58.8, 59.2, 123.3, 132.9, 133.2, 147.6, 148.2, 155.5; MS (EI) *m*/*z* 206 (M^+), 191 (M^+ − Me), 147 (M^+ − COOMe).

(*S*)-3-(1-Methyl-pyrrolidin-2-yl)-pyridine, (*S*)-Nicotine (2). To a suspension of $LiAlH_4$ (44.2 mg, 1.16 mmol) in anhydrous THF (10 mL) at 0 °C was added dropwise a solution of **17** (0.2 g, 0.97 mmol) in THF (5 mL). After 8 h of stirring at room temperature, the reaction was quenched with 10% aqueous NaOH (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOH/CH_2Cl_2) to give (*S*)-nicotine **2** (0.15 g, 95%) as a colorless oil; 94% ee, determined by chiral HPLC, (hexane/*i*-PrOH = 98/2), 10.9 min for (*S*)-nicotine and 12.9 min for (*R*)). $[\alpha]^{20}_D$ −145 (*c* 1, EtOH); ^1H NMR δ (ppm) 1.62−2.10 (m, 3H), 2.14 (s, 3H), 2.17−2.36 (m, 2H), 3.07 (t, 1H, J = 8.3 Hz), 3.23 (t, 1H, J = 8.2 Hz), 7.24 (dd, 1H, J = 8 Hz, J = 4.9 Hz), 7.71 (app dt, 1H, J = 8 Hz, J = 2 Hz), 8.47 (dd, 1H, J = 2 Hz, J = 4.9 Hz), 8.51 (t, 1H, J = 2 Hz); ^{13}C NMR δ (ppm) 22.7, 35.2, 40.4, 57.1, 69.0, 123.7, 135.0, 138.7, 148.7, 149.6; MS (EI) *m*/*z* 162 (M^+).

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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