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A General Procedure for the Enantioselective Synthesis of the Minor Tobacco Alkaloids Nornicotine, Anabasine, and Anatabine

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ABSTRACT

The minor tobacco alkaloids nornicotine, anabasine, and anatabine from *Nicotiana glauca* are known to possess nicotinic receptor agonist activity, although they are relatively less potent than *S*-(–)-nicotine, the principal tobacco alkaloid. Previous pharmacological investigations and structure-activity studies have been limited owing to the lack of availability of the optically pure forms of these minor alkaloids. We now report a 2-step synthetic procedure for the enantioselective synthesis of the optical isomers of nornicotine and anabasine, and a modified procedure for the synthesis of anatabine enantiomers. These procedures involve initial formation of the chiral ketimine resulting from the condensation of either 1*R*, 2*R*, 5*R*-(+)- or 1*S*, 2*S*, 5*S*-(–)-2-hydroxy-3-pinanone with 3-(aminomethyl)pyridine followed by enantioselective C-alkylation with an appropriate halogenoalkane or halogenoalkene species, N-deprotection, and base-catalyzed intramolecular ring closure, to form the appropriate, chirally pure minor tobacco alkaloid. Using this approach, the *R*-(+)- and *S*-(–)-enantiomers of the above minor tobacco alkaloids were obtained in good overall chemical yield and excellent enantiomeric excess.

KEYWORDS: *Nicotiana* alkaloids, tobacco, stereoselective synthesis

INTRODUCTION

The principal tobacco alkaloid, *S*-(–)-nicotine (NIC), is a potent agonist at neuronal nicotinic acetylcholine receptors (nAChRs) and interacts with all known nAChR subtypes. nAChR ligands modulate several functions within both the peripheral and the central nervous systems, mediated by a diversity of nAChR subtypes containing $\alpha 2$ - $\alpha 10$ and $\beta 2$ - $\beta 4$ subunits. Of interest, leaves from *Nicotiana glauca* contain several other minor alkaloids structurally related to nicotine

(ie, nornicotine, anabasine, and anatabine). *S*-(–)-nicotine is biosynthesized in the tobacco plant from nicotinic acid and *L*-ornithine or *L*-arginine. Nornicotine, the second most abundant tobacco alkaloid, is biosynthesized via enzymatic *N*-demethylation of *S*-(–)-nicotine; the minor alkaloid, anabasine, is generally believed to be biosynthesized from nicotinic acid and lysine, via a similar pathway to that described above for nicotine.¹ Anatabine is derived biosynthetically solely from nicotinic acid, which is decarboxylated to 1,2-dihydropyridine and 2,5-dihydropyridine followed by condensation of these 2 molecules to form 3,6-dihydroanatabine.¹ Aromatization of 3,6-dihydroanatabine then affords anatabine. While nicotine in tobacco is found almost exclusively in the *S*-(–)-enantiomeric form,^{2,3} the minor tobacco alkaloids are present as mixtures of their respective optical isomers.² In this respect, unlike nicotine, nornicotine exists as a mixture of its *S*-(–)- and *R*-(+)-enantiomeric forms in various ratios, depending on the species of *Nicotiana* from which it was isolated. Even different sources of tobacco (eg, Burley, Turkish, Virginia) contain different ratios of nornicotine enantiomers.² The presence of both enantiomeric forms of nornicotine in the tobacco plant results from the enzymatic *N*-demethylation of *S*-(–)-nicotine in the plant. Biosynthetic studies with 2'-[³H]-nicotine have shown that the 2'-[³H]-label is lost during formation of *R*-(+)-nornicotine but is retained in the formation of *S*-(–)-nornicotine (Figure 1, structure 4).¹ These observations suggest the formation of a planar intermediate in the formation of the *R*-(+)-isomer, and the likely existence of 2 distinct *N*-demethylase enzymes.

The minor tobacco alkaloids are also known to possess nAChR agonist activity and may contribute to the neuropharmacological effects of smoking, although they are generally relatively less pharmacologically active than *S*-(–)-nicotine.⁴ Pharmacological investigations and structure-activity studies with these minor tobacco alkaloids have been somewhat limited owing to the lack of availability of their optically pure forms. Previous structure-activity studies have demonstrated that the optical isomers of nornicotine show significant differences in their ability to bind to nicotinic receptors in rat brain and generally are

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Figure 1. Synthetic route for preparation of the *S*(-)-Enantiomers of normicotine, anabasine, and anatabine.

less potent compared with nicotine.^{5,6} For example, *S*(-)-nicotine inhibits [³H]-nicotine binding to rat brain membranes with a 50-fold lower affinity ($K_i = 47$ nM) compared with nicotine ($K_i = 1.0$ nM).⁷ In contrast, *S*(-)-nicotine and *S*(-)-normicotine exhibit similar affinities for the [³H]methyllycaconitine binding site ($K_i = 770$ nM and 1340 nM, respectively) in brain.⁷ These results indicate interaction of normicotine with both $\alpha 4\beta 2^*$ and $\alpha 7^*$ nAChR subtypes. Evidence has also accumulated demonstrating that normicotine enantiomers differ in their neurochemical and behavioral effects.^{4,8-10} Similar to nicotine, both enantiomers of normicotine evoke a concentration-dependent, Ca^{2+} -dependent, and mecamylamine-sensitive increase in dopamine (DA) release from rat striatal and nucleus accumbens slices,¹⁰⁻¹² indicating that normicotine acts as an agonist at nAChR subtypes modulating DA release. Of interest, *R*(+)-normicotine was more potent than the *S*(-)-enantiomer in evoking [³H]dopamine overflow from rat nucleus accumbens slices, whereas both isomers were equipotent in

this respect in experiments with rat striatal slices, suggesting the involvement of different nicotinic receptor subtypes in these brain regions. Whereas, *S*(-)-nicotine and *S*(-)-normicotine were equipotent in releasing DA from striatal slices, nicotine was 43-fold more potent than normicotine ($\text{EC}_{50} = 70$ nM and 3.0 μM , respectively) in releasing DA from nucleus accumbens slices. Of interest, normicotine has a longer half-life than nicotine in both rodent and nonhuman primate plasma and brain¹³⁻¹⁶; and following chronic treatment with *S*(-)-nicotine, normicotine (of unknown chirality) accumulates in rodent brain reaching pharmacologically relevant concentrations.¹⁷

Behavioral studies using animal models also provide support for the use of normicotine as a tobacco use cessation agent. Normicotine produces nicotine-like discriminative stimulus effects,⁸ as well as nicotine-like effects on schedule-controlled operant responding in rats.¹⁸ Recent results indicate that normicotine functions as a positive reinforcer¹⁹;

however, under similar experimental conditions, nornicotine is associated with a lower rate of responding in comparison with nicotine,^{19,20} suggesting that nornicotine has a lower reinforcing efficacy. Moreover, nornicotine has been shown to decrease nicotine self-administration in rats.⁹ Furthermore, across repeated nornicotine pretreatments, tolerance did not develop to nornicotine-induced decrease in nicotine self-administration. Of importance, nornicotine has recently been found to inhibit dopamine transporter (DAT) function²¹ and, thus, acts similarly to bupropion, which is a currently available tobacco use cessation agent. In summary, nornicotine increases DA release and inhibits DAT function, both mechanisms being beneficial in the treatment of tobacco use. Thus, a simple structural change (ie, removal of the *N*-methyl moiety from the pyrrolidine ring of nicotine, which affords nornicotine) may be beneficial with respect to its pharmacological profile. Taken together, these current preclinical neurochemical and behavioral results suggest that nornicotine could be a promising candidate for development as a tobacco cessation agent.²¹ In this respect, it should be noted that *R*-(+)-nornicotine is currently being investigated as a potential smoking cessation agent.²²

Dwoskin et al showed that *S*-(-)-anabasine (Figure 1, structure 5) increased fractional [³H] release in a concentration-dependent manner from rat striatal slices preloaded with [³H]-dopamine ($EC_{50} = 19.3 \pm 3.2 \mu M$) but was less potent than *S*-(-)-nicotine ($EC_{50} = 3.0 \pm 2.2 \mu M$).²³ Similar results have been reported by Grady et al, who demonstrated that ($\pm$)-anabasine stimulates [³H]-dopamine release from mouse striatal synaptosomes, and ($\pm$)-anabasine has been reported to inhibit high affinity binding of [³H]-*S*-(-)-nicotine to rat and mouse striatal membranes.^{6,24} Thus far, direct comparisons of these pharmacological properties between the enantiomers of anabasine have not been determined, owing to difficulties in obtaining the optical isomers of anabasine.

Early efforts to develop synthetic routes to racemic minor tobacco alkaloids have used a variety of methods (for a comprehensive review, see Crooks, 1999).²⁵ However, few examples of general preparative methods for these alkaloids have been reported. Deo and Crooks²⁶ have used a benzophenone imine intermediate for the general synthesis of racemic nornicotine, anabasine, and anatabine, while several strategies have been developed for the enantioselective synthesis of nornicotine, anabasine, and anatabine optical isomers,²⁵⁻²⁸ few of these are of general utility. Recently, the *S*-(-)-isomers of nornicotine, anabasine, and anatabine (Figure 1, structures 4, 5, and 10, respectively) have been synthesized via a 5-step enantioselective synthesis that uses a ring-closing metathesis route²⁹; also, Amat et al have reported a chiral synthesis of *S*-(-)-anabasine from a chiral lactam intermediate.³⁰ In addition, *S*-(-)-anatabine has been synthesized by reacting an allylsulfone with an azaaromatic chiral sulfinimine.³¹

Aiqiao et al³² have reported a rapid and convenient use of a 2-hydroxy-3-pinane intermediate for the enantioselective synthesis of 2-pyridyl methylamines; this method was subsequently adapted by Swango et al³³ for the efficient synthesis of *S*-(-)- and *R*-(+)-nornicotine isomers in 3 steps, with a reported enantiomeric excess (ee) of 91% and 81%, respectively. This current study describes a general synthetic procedure for the facile preparation of the optical isomers of nornicotine, anabasine, and anatabine, using modifications of the Swango et al synthetic methodology (Figure 1) and establishes this synthetic route as a convenient method for the preparation of the enantiomerically pure minor tobacco alkaloids.

MATERIALS AND METHODS

The chemicals used in the synthesis of the enantiomers of nornicotine, anabasine, and anatabine were obtained from Aldrich Chemical Co (Milwaukee, WI), or from Acros Organics (Somerville, NJ), and were used without further purification. Flash column chromatography was performed using ICN SILITECH 32-63, 60Å silica gel. Melting points were determined on a Fisher Scientific melting point apparatus and are uncorrected. NMR¹H-NMR and ¹³C-NMR spectra were recorded on a Varian 300 MHz NMR. All spectra were referenced, and chemical shifts were determined using tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded on a JEOL JMS-700T Mstation (JEOL USA, Inc, Peabody, MA), or on a Bruker Autoflex MALDI-TOF mass spectrometer (Bruker Daltonics, Billerica, MA). Specific rotation measurements were performed on a Perkin-Elmer Model 241 Polarimeter (PerkinElmer, Wellesley, MA). Microanalyses were performed by Atlantic Microlabs Inc (Atlanta, GA).

Preparation of 1*R*, 2*R*, 5*R*-(+)- and 1*S*, 2*S*, 5*S*-(-)-2-Hydroxy-3-pinane Ketimine Intermediates

Boron trifluoride diethyl etherate (0.3 mL) was added to a solution of 3-(aminomethyl) pyridine (3.3 g, 30.6 mmol) and 1*R*, 2*R*, 5*R*-(+)-2-hydroxy-3-pinane (5 g, 29.8 mmol) in benzene (80 mL). The reaction mixture was refluxed for 2.5 hours under N₂ using a Dean-Stark apparatus. After cooling, the solvent was evaporated under reduced pressure. The residue was purified by flash silica gel column chromatography using CHCl₃:hexane:methanol, 12:2:1 as the elution solvent to afford the (+)-2-hydroxy-3-pinane ketimine 3 (6.24 g, 81%) as white crystals after removal of solvent: [α_D]²⁵ = +3.8° (c = 1.0, methanol); ¹H NMR (300 MHz, CDCl₃) δ 8.58 (1H, d, J = 2.4 Hz), 8.48 (1H, dd, J = 4.8, 1.8 Hz), 7.70 (1H, d, J = 7.8 Hz), 7.25 (1H, dd, J = 7.8, 4.8 Hz), 4.48 (2H, s), 2.80 (1H, br s), 2.58 (2H, m), 2.34 (1H, m),

2.06 (2H, m), 1.56 (1H, d, $J = 10.8$ Hz), 1.50 (3H, s), 1.31 (3H, s), 0.84 (3H, s) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 178.19, 149.33, 148.28, 135.81, 135.52, 123.60, 51.83, 50.46, 38.75, 38.50, 34.12, 28.56, 28.37, 27.51, 23.11 ppm m/z 258 (M^+ , base peak).

The same procedure was used for the synthesis of 1*S*, 2*S*, 5*S*-(–)-2-hydroxy-3-pinane ketimine (6.58 g, 85%), which was obtained as white crystals from the reaction of 1*S*, 2*S*, 5*S*-(–)-2-hydroxy-3-pinane with 3-(aminomethyl)pyridine; $[\alpha_D]^{25} = -3.6^\circ$ ($c = 1.0$, methanol).

Synthesis of *S*-(–)-nornicotine, *S*-(–)-anabasine, *R*-(+)-nornicotine and *R*-(+)-anabasine

To a stirred solution of ketimine **3** (258 mg, 1 mmol) in tetrahydrofuran (THF) (8 mL) was added dropwise lithium diisopropylamine (LDA) (1.50 mL, 2.0 M solution in THF, 3 mmol) at 0°C. The purple solution was stirred at 0°C for 15 minutes then cooled to –78°C. 1-Chloro-3-iodopropane (0.32 mL, 3 mmol) in THF (2 mL) was then added dropwise. The reaction mixture was stirred for an additional 30 minutes at –78°C and then quenched with saturated aqueous NH_4Cl solution. The solution was extracted with diethyl ether (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated. The residue was passed through a short silica gel column, and eluted with hexane, followed by CHCl_3 :MeOH (20:1) to give the C-alkylated intermediate as a yellow oil. The crude product was not purified, but immediately added to a mixture of 95% EtOH (6 mL), hydrazine monohydrate (4 mL), and acetic acid (2 mL). The mixture was stirred overnight at room temperature and 10% aqueous NaOH solution (10 mL) was added. The solution was then extracted with CHCl_3 (3×20 mL), the combined organic liquors were dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated. The residue was purified by flash column chromatography on silica gel, and eluted with CHCl_3 :MeOH:Et₃N (100:10:1) to afford *S*-(–)-nornicotine (**4**, Figure 1) (118 mg, 79% overall) as a pale yellow oil; $[\alpha_D]^{25} = -32.6^\circ$ ($c = 1.0$, methanol); ^1H NMR (300 MHz, CDCl_3) δ 8.60 (1H, d, $J = 1.8$ Hz), 8.45 (1H, dd, $J = 4.8, 1.7$ Hz), 7.74 (1H, “dt,” $J = 7.8, 1.9$ Hz), 7.25 (1H, dd, $J = 7.8, 4.8$ Hz), 4.14 (1H, dd, $J = 7.3, 2.1$ Hz), 3.11 (2H, m), 2.20 (1H, m), 2.11 (1H, m), 1.91 (2H, m), 1.66 (1H, m) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 148.3, 148.0, 140.1, 134.2, 123.2, 59.7, 46.7, 34.0, 25.2 ppm; m/z 148 (M^+).

The same procedure was used for the synthesis of *R*-(+)-nornicotine (110 mg, 76% overall) from 1*S*, 2*S*, 5*S*-(–)-2-hydroxy-3-pinane ketimine and 1-chloro-3-iodopropane, and the product was obtained as a pale yellow oil; $[\alpha_D]^{25} = +32.8^\circ$ ($c = 1.0$, methanol).

A similar procedure was also used for the synthesis of *S*-(–)-anabasine (**5**, Figure 1), which was obtained in 72% yield from 1*R*, 2*R*, 5*R*-(–)-2-hydroxy-3-pinane ketimine using 1-chloro-4-iodobutane as the alkylating agent instead of 1-chloro-3-iodopropane. The product was obtained as a light-yellow oil: $[\alpha_D]^{25} = -79.8^\circ$ ($c = 0.9$, methanol); ^1H NMR (300 MHz, CDCl_3) δ 8.60 (1H, s), 8.50 (1H, dt, $J = 4.8, 1.7$ Hz), 7.74 (1H, dm, $J = 7.8, 1.8$ Hz), 7.25 (1H, dd, $J = 7.8, 4.8$ Hz), 3.65 (2H, dd, $J = 11, 2.2$ Hz), 3.22 (1H, dm, $J = 11$ Hz), 2.75–2.85 (1H, m), 2.00 (1H, s), 1.46–1.95 (6H, m) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 148.0, 148.2, 139.9, 133.7, 122.8, 59.2, 47.0, 34.0, 24.9, 24.6 ppm m/z 163 (M^+).

Additionally, *R*-(+)-anabasine was synthesized in a similar manner, using 1*S*, 2*S*, 5*S*-(–)-2-hydroxy-3-pinane ketimine as the chiral intermediate and was obtained as a pale yellow oil (75% yield); $[\alpha_D]^{25} = +80.2^\circ$ ($c = 1.0$, methanol).

Synthesis of *S*-(–)-anatabine and *R*-(+)-anatabine

cis-2-(4-Bromobut-2-enyloxy)tetrahydropyran

p-Toluenesulfonic acid monohydrate (0.13 g) was added to a stirred solution of *cis*-but-2-ene-1,4-diol (2.64 g, 30 mmol) and dihydropyran (DHP) (2.53 g, 30 mmol) in CH_2Cl_2 (10 mL) and THF (25 mL) at 0°C. After stirring at 0°C for 2 hours, the reaction mixture was stirred at room temperature for a further 20 minutes. Water was added, and the aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated. The residue was purified by flash column chromatography on silica gel, and eluted with hexane:EtOAc, (2:1) to give *cis*-4-(tetrahydropyran-2-yloxy)but-2-en-1-ol (2.66 g, 52%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 5.81 (1H, m), 5.67 (1H, m), 4.64 (1H, m), 4.15 (4H, m), 3.82 (1H, m), 3.49 (1H, m), 1.42–1.84 (6H, m) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 132.54, 128.11, 97.68, 62.63, 62.31, 58.50, 30.71, 25.59, 19.49 ppm.

To a solution of *cis*-4-(tetrahydropyran-2-yloxy)but-2-en-1-ol (2.44 g, 14.2 mmol) in DMF (40 mL) was added triphenylphosphine (4.17 g, 15.9 mmol). The solution was cooled to 0°C and *N*-bromosuccinimide (NBS) (2.73 g, 15.5 mmol) was added in portions. After stirring for 30 minutes at room temperature, the reaction was quenched with methanol (2 mL). The solution was diluted with diethyl ether (200 mL), and washed with water, saturated aqueous NaHCO_3 , and brine, successively. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel, and eluted with hexane to afford the bromide **6** (Figure 1) (2.24 g, 67%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 5.86 (1H, m), 5.69 (1H, m), 4.61 (1H, dd, $J = 4.2, 3.0$ Hz),

4.31 (1H, m), 4.14 (1H, m), 4.01 (2H, d, $J = 7.8$ Hz), 3.84 (1H, m), 3.51 (1H, m), 1.40-1.90 (6H, m) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 130.95, 128.41, 98.15, 62.49, 62.08, 30.80, 26.84, 25.65, 19.67 ppm m/z : 155 ($\text{M}^+ - 81$), 133/135, 85, 53.

1R, 1'S, 2R, 5R-2,6,6-Trimethyl-3-[1'-pyridin-3''-yl-5'-(tetrahydro-pyran-2''-yloxy)pent-3'-enylimino]bicyclo[3.1.1]heptan-2-ol

To a stirred solution of ketimine **3** (1.94 g, 7.50 mmol) in THF (60 mL) was added dropwise LDA (11.3 mL, 2.0 M solution in THF, 22.6 mmol) at 0°C . The purple solution was stirred at 0°C for 15 minutes then cooled to -78°C . The bromide **6** (2.12 g, 9 mmol) in THF (8 mL) was added dropwise. The reaction mixture was stirred for an additional 30 minutes at -78°C , and then quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with diethyl ether ($3 \times 20\text{mL}$). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was flash chromatographed on silica gel, eluted with CHCl_3 :hexane:MeOH (100:20:2) to give **7** (2.80 g, 91%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 8.56 (1H, d, $J = 2.1$ Hz), 8.48 (1H, dd, $J = 5.1, 1.8$ Hz), 7.72 (1H, d, $J = 7.5$ Hz), 7.25 (1H, dd, $J = 7.5, 4.8$ Hz), 5.61 (1H, m), 5.50 (1H, m), 4.59 (2H, m), 4.19 (1H, m), 4.01 (1H, m), 3.84 (1H, m), 3.49 (1H, m), 2.63 (3H, m), 2.44 (1H, m), 2.26 (1H, m), 2.06 (1H, t, $J = 6.3$ Hz), 1.99 (1H, m), 1.62-1.88 (2H, m), 1.52 (3H, s), 1.44-1.60 (4H, m), 1.39 (1H, d, $J = 10.5$ Hz), 1.31 (3H, s), 0.90 (3H, s) ppm; ^{13}C NMR (75 MHz, CDCl_3) shows signals for 2 diastereomers δ 176.13, 148.77, 148.53, 138.73 (138.70), 134.69, 129.13 (128.98), 128.80 (128.74), 123.70, 98.17 (97.99), 62.94 (62.85), 62.46, 61.10 (61.06), 50.26, 38.63, 37.08, 33.91, 30.90, 28.79, 28.26, 27.60, 25.71, 23.32, 19.77 ppm m/z : 412 (M^+), 327, 311, 257, 162, 144, 85; Analysis Calculated (Anal Calcd) for $\text{C}_{25}\text{H}_{36}\text{N}_2\text{O}_3 \cdot \text{H}_2\text{O}$: C, 69.74; H, 8.90; N, 6.51. Found: C, 69.80; H, 8.58; N, 6.33.

1R, 1'S, 2R, 5R-3-(5'-Hydroxy-1'-pyridin-3''-yl-pent-3'-enylimino)-2,6,6-trimethyl-bicyclo[3.1.1]heptan-2-ol
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To a solution of THP ether **7** (1.45 g, 3.52 mmol) in MeOH (90 mL) was added p-toluenesulfonic acid (1.37 g, 7.04 mmol). The mixture was stirred at room temperature for 3 hours and then concentrated. Saturated aqueous NaHCO_3 solution (20 mL) was added, and the aqueous phase was extracted with diethyl ether ($3 \times 20\text{mL}$). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and evaporated. The residue was flash chromatographed on silica gel, eluting with CHCl_3 :MeOH (25:1) to give **8** (1.05 g, 90%) as a colorless oil:

$[\alpha_D]^{25} = -33.1^\circ$ ($c = 1.0$, MeOH); ^1H NMR (200 MHz, CDCl_3) δ 8.51 (1H, br s), 8.44 (1H, d, $J = 4.0$ Hz), 7.66 (1H, dt, $J = 8.0, 2.0$ Hz), 7.22 (1H, dd, $J = 8.0, 5.0$ Hz), 5.71 (1H, m), 5.42 (1H, m), 4.55 (1H, dd, $J = 8.4, 4.8$ Hz), 4.08 (2H, m), 2.42-2.84 (4H, m), 2.16-2.38 (2H, m), 20.1 (1H, t, $J = 6.0$ Hz), 1.94 (1H, m), 1.50 (3H, s), 1.33 (1H, d, $J = 11.4$ Hz), 1.27 (3H, s), 0.85 (3H, s) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 177.81, 148.78, 148.69, 138.69, 134.68, 131.98, 128.25, 123.85, 76.79, 60.45, 58.64, 50.55, 38.52, 38.46, 37.23, 34.15, 28.52, 28.13, 27.41, 23.13 ppm m/z : 329 ($\text{M}^+ + 1$); Anal Calcd for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2 \cdot 0.3\text{CHCl}_3$: C, 66.93; H, 7.83; N, 7.69. Found: C, 67.16; H, 7.94; N, 7.77.

S-5-Amino-5-pyridin-3-yl-pent-2-en-1-ol

To a solution of **8** (0.86 g, 2.6 mmol) in MeOH (40 mL) was added hydroxylamine hydrochloride (1.39 g, 20.0 mmol). The mixture was stirred at room temperature for 18 hours. Ammonia gas was bubbled into the solution to adjust the pH to 9. The MeOH was then evaporated and CHCl_3 (15 mL) was added to the residue. The resulting mixture was filtered and the filtrate was concentrated. The resulting residue was flash chromatographed on silica gel, and eluted with CHCl_3 :MeOH:Et₃N (100:10:1) to give **9** (0.34 g, 74%) as a colorless oil: $[\alpha_D]^{25} = -44.3^\circ$ ($c = 1.0$, MeOH); ^1H NMR (200 MHz, CDCl_3) δ 8.53 (1H, d, $J = 2.4$ Hz), 8.46 (1H, dd, $J = 4.8, 1.6$ Hz), 7.68 (1H, dt, $J = 7.6, 1.8$ Hz), 7.24 (1H, dd, $J = 7.4, 5.0$ Hz), 5.85 (1H, m), 5.47 (1H, m), 3.90-4.20 (3H, m), 2.30-2.60 (5H, m) ppm; ^{13}C NMR (50 MHz, CDCl_3) δ 149.00, 148.65, 140.70, 134.10, 133.01, 128.43, 123.80, 57.84, 52.73, 37.42 ppm m/z : 179 ($\text{M}^+ + 1$); Anal Calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O} \cdot 0.17\text{H}_2\text{O}$: C, 66.25; H, 7.97; N, 15.45. Found: C, 66.23; H, 7.91; N, 15.37.

S-(-)-Anatabine

Diethylazodicarboxylate (DEAD) (0.23 mL, 1.40 mmol) was added dropwise to a stirred solution of triphenyl phosphine (365 mg, 1.40 mmol) in THF (6 mL) at 0°C under N_2 . The reaction mixture was stirred at 0°C for 20 minutes. A solution of **7** (178 mg, 1 mmol) in THF (3 mL) was then added dropwise. The mixture was stirred at 0°C for 30 minutes, and then at room temperature for 2 hours. Evaporation of the solvent followed by purification of the residue by flash column chromatography on silica gel (CHCl_3 :MeOH, 20:1) gave S-(-)-anatabine (**10**) (124 mg, 77%) as a colorless oil: $[\alpha_D]^{25} = -180^\circ$ ($c = 1.0$, methanol); ^1H NMR (300 MHz, CDCl_3) δ 8.56 (1H, d, $J = 1.6$ Hz), 8.46 (1H, dd, $J = 4.8, 1.6$ Hz), 7.68 (1H, dt, $J = 8.0, 1.8$ Hz), 7.23 (1H, dd, $J = 4.0, 2.8$ Hz), 5.79 (2H, m), 3.84 (1H, t, $J = 7.0$ Hz), 3.33-3.65 (2H, m), 2.21 (2H, m), 2.00 (1H, br s) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 148.93, 148.82, 140.05, 134.29, 126.46, 125.26, 123.71, 55.44, 46.12, 34.01 ppm m/z : 160 (M^+ , base peak), 159, 145, 131, 118, 105, 80, 54.

The same procedure was used for the synthesis of *R*-(+)-anatabine from 1*S*, 2*S*, 5*S*-(-)-2-hydroxy-3-pinanone ketimine and *cis*-2-(4-bromobut-2-enyloxy)tetrahydropyran, which was obtained as a pale yellow oil (70% yield): $[\alpha_D]^{25} = +177^\circ$ ($c = 1.0$, methanol).

RESULTS AND DISCUSSION

The *R*- and *S*-enantiomers of nornicotine, anabasine, and anatabine were successfully synthesized in good to moderate yields, and in good chiral purity. The stereo-controlled C-alkylation of the 2-hydroxy-3-pinanone-3-(aminomethyl)pyridine ketimine intermediate is the key step in the reaction sequence. Experimental evidence from the crystal structure of the ketimine³⁴ used in the C-alkylation step supports the findings that the (-)-ketimine is C-alkylated from the *si* face of the (-)-ketimine-lithium complex to afford exclusively the *S*-isomer, while the C-alkylated product with the *R*-configuration is generated from the (+)-ketimine-lithium complex. LDA was chosen from several possible catalytic bases, including *t*BuOK, due to the higher yields obtained, and also because of the improvement in purity of the isolated products when using this base.

An advantage in the above procedure over previously reported literature syntheses of *R*-(+)- and *S*-(-)-nornicotine, and *R*-(+)- and *S*-(-)-anabasine isomers is the small number of overall steps to achieve the formation of the desired alkaloids. In an earlier approach to that outlined above, Swango et al used the 2-hydroxy-3-pinanone-3-(aminomethyl)pyridine ketimine reagent in the synthesis of nornicotine isomers, but C-alkylation was performed with a halogeno alcohol, to afford an intermediate *N*-alkylhydroxy analog, which had to be isolated and converted to the corresponding *N*-alkylbromo analog, prior to cyclization to afford the final product.³³ The current synthesis outlined in this paper constitutes a 2-step, general procedure for the synthesis of the optical isomers of both nornicotine and anabasine, by using a 1, 4-dihalogeno alkane instead of a halogenoalcohol in the C-alkylation of the ketimine. This change reduces the number of steps in the reaction sequence from 3 to 2, and simplifies the work-up procedure for obtaining the final chiral product. Attempts at using diiodopropane or diiodobutane in the reaction resulted in lower yields of reaction products. The use of a chloroiodoalkane reactant affords rapid C-alkylation of the ketimine, but slow solvolytic degradation at the chloro-terminus. This allows for flash silica gel column purification to be performed obtaining a stable intermediate for the final cyclization event of the reaction sequence in the presence of hydrazine and water.

The above procedure can also be used for the synthesis of anatabine enantiomers. However, 3 steps are required to

introduce the C-hydroxy-*cis*-alkene substituent at the α -carbon of the 2-hydroxy-3-pinanone-3-(aminomethyl)pyridine ketimine, followed by a final cyclization step with DEAD/triphenyl phosphine. Nevertheless, this synthetic route is comparable to previously reported enantioselective syntheses of anatabine described by Balasubramanian and Hassner and by Mehmandoust et al both of which involve five steps overall.^{31,35}

CONCLUSION

Successful adaptation and improvement of existing methodology has allowed for a streamlined approach in stereoselectively synthesizing nicotine analogs, nornicotine, anabasine, and anatabine. A 2-step synthetic procedure for the enantioselective synthesis of the optical isomers of nornicotine and anabasine, and a modified procedure for the synthesis of anatabine enantiomers were performed and all compounds were synthesized in good yields.

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