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Six-Step Synthesis of (*S*)-Brevicolline from (*S*)-Nicotine

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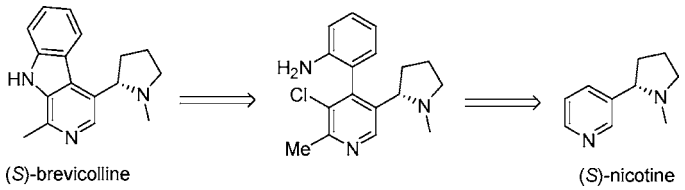
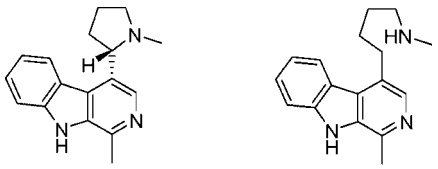
ABSTRACT



A six-step synthesis of (*S*)-brevicolline from (*S*)-nicotine is reported. Regioselective trisubstitution of the pyridine ring of nicotine, followed by successive Suzuki cross-coupling and Buchwald amination reactions, afforded the enantiopure *β*-carboline alkaloid, brevicolline.

The *β*-carboline alkaloids (*S*)-brevicolline (**1**) and brevicarine (**2**) are the major alkaloids isolated[1] in the late 60's from the plant *Carex brevicollis* D.C. (Cyperacee), native to the southwestern part of the former U.S.S.R. (Figure 1).



1 2

Figure 1. *β*-Carboline alkaloids (*S*)-brevicolline (**1**) and brevicarine (**2**).

The structure and absolute configuration of **1** was determined by Lazurevski[1] and Bláha[2], respectively. The *β*-carbolines are a group of pharmacologically interesting and biologically active compounds, whose reported effects include antineoplastic (tubuline binding),[3] anticonvulsive, hypnotic and anxiolytic (benzodiazepine receptor inhibitoric),[4] antiviral,[5] antimicrobial,[4b] topoisomerase II inhibition,[6] and inhibition of *c*GMP-dependent processes.[7] (*S*)-Brevicolline's biological activities range from a phototoxic effect on bacteria and fungi to an oxytocic effect when used against uterine internia of pregnant women.[8] Two racemic syntheses of **1** have been reported,[9] and a ten-step enantioselective synthesis starting from (*S*)-proline was published by Mahboobi and co-workers in 1999.[10]

(1) (a) Vember, P. A.; Terenteva, I. V.; Lazurevskij, G. *Khim. Prir. Soedin.* **1967**, *3*, 249. (b) Terenteva, I. V.; Lazurevskij, G. V.; Shirshova, T. I. *Khim. Prir. Soedin.* **1969**, *5*, 397. (c) Vember, P. A.; Terenteva, I. V.; Uljanova, A. V. *Khim. Prir. Soedin.* **1968**, *4*, 98.

(2) Bláha, K.; Koblicová, Z.; Pospî''ek, J.; Trojánek, J. *Collect. Czech. Commun.* **1971**, *36*, 3448.

(3) (a) Molina, P.; Fresdena, P. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1819. (b) Molina, P.; Fresdena, P. M.; Garcia-Zafra, S.; Almendros, P. *Tetrahedron Lett.* **1994**, *35*, 8851. (c) Behforouz, M.; Merriman, R. L. (Ball State University), U.S. Pat. Appl. 5 646 150, 1997; *Chem. Abstr.* **1997**, *127*, 149053q.

(4) (a) Braestrup, C.; Nielsen, M.; Olsen, C. E. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 228. (b) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *Synthesis* **1995**, 1225. (c) Batch, A.; Dodd, R. H. *J. Org. Chem.* **1988**, *63*, 872. (d) Seidelmann, D.; Huth, A.; Otow, E.; Olesen, p. H.; Turner, J.; Hillman, M.; Cole, B. (Schering A. G.) Ger. Offen. DE 195 14 524 A1, 1996: *Chem. Abstr.* **1997**, *126*, P 8106e.

(5) Molina, P.; Fresdena, P. M.; Garcia-Zafra, S. *Tetrahedron Lett.* **1995**, *36*, 3581.

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(8) Marcu, G. A. *Tr. Tret'ei Nauchn. Konf. Molodykh Uch. Mold., Biol. S'kh. Nauki* **1965**, *2*, 243; *Chem Abstr.* **1965**, *63*, 2297a.

(9) (a) Müller, W. H.; Preuss, R.; Winterfeldt, E. *Chem. Ber.* **1977**, *110*, 2424. (b) Leete, E. *J. Chem. Soc., Chem. Commun.* **1979**, 821.

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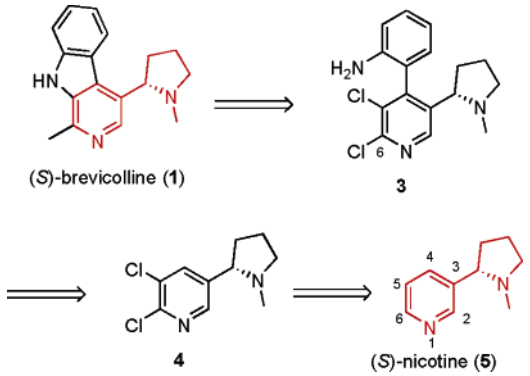
(*S*)-Brevicolline possesses the core (*S*)-nicotine (**5**) structure. Recently, we have been investigating the synthesis of enantiopure nicotine derivatives using natural (*S*)-nicotine itself as an inexpensive starting material.[11] We envisioned that **1** could be obtained via a short synthesis starting from (*S*)-nicotine. It was anticipated that enantiopure **1** could arise from a trisubstituted nicotine derivative such as **3** (Scheme 1). Following this plan, methylation of **3** by substitution at

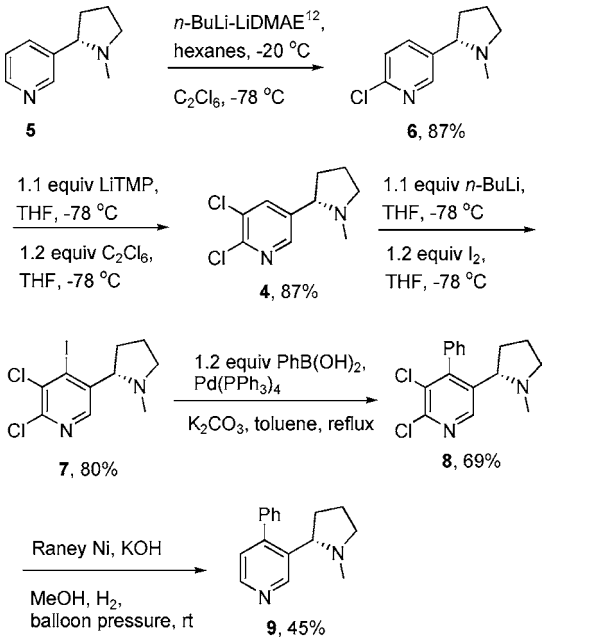
Scheme 1. Retrosynthetic Analysis of (*S*)-Brevicolline



C-6 followed by an intramolecular catalytic Buchwald amination at C-5, creating the carboline ring, would complete the synthesis. Compound **3** would be derived from dichloronicotine **4** in two steps involving C-4 halogenation and a cross-coupling reaction. Finally, **4** is easily accessible in two steps from **5**.[11]

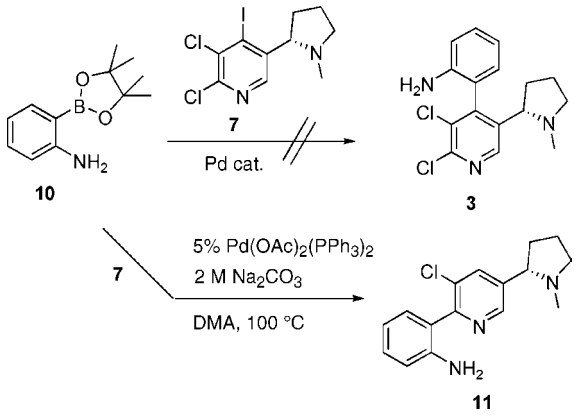
Our initial approach was to use a Suzuki cross-coupling reaction between (*S*)-5,6-dichloro-4-iodonicotine (**7**) and an amino boronate ester to afford compound **3**, which, in turn, would be suitable for an intramolecular Buchwald amination. The synthesis of **7** was achieved in good yield in three steps from (*S*)-nicotine (Scheme 2). We previously reported the formation of (*S*)-6-chloronicotine (**6**) from natural nicotine via an ortho-directed lithiation process.[11c,f,12] (*S*)-5,6-Dichloronicotine (**4**) resulted from a regioselective lithiation−chlorination reaction on **6**, using LiTMP as the base and hexachloroethane as the electrophile.[11h] Finally, **7** was obtained from **4** via a third regioselective lithiation−substitution process, using *n*-BuLi as the base and iodine as the electrophile. The regioselectivity of this reaction could not be confirmed by NMR experiments. To verify the structure assignment, a Suzuki coupling with phenylboronic acid followed by reductive removal of both chlorines using Raney nickel afforded known (*S*)-4-phenylnicotine (**9**), the structure of which could be unequivocally confirmed by NMR spectroscopy.[11a,d]

Scheme 2. Synthesis of (*S*)-5,6-Dichloro-4-iodonicotine (**7**) and Formation of (*S*)-4-Phenylnicotine (**9**) to Unequivocally Prove the Regioselectivity in the Iodination Step



With the 4-iodonicotine derivative **7** in hand, various conditions reported in the literature for the Suzuki coupling of amino boronic ester **10** with aryl iodides[13] were tested without success (Scheme 3). The recovery of deiodonated

Scheme 3. Attempts at Suzuki Couplings on **7**



compound **4** showed that the oxidative addition step was occurring rapidly (less than 2 h by TLC). The use of $Pd(OAc)_2(PPh_3)_2$ as a catalyst in dimethylacetamide gave, in a very low yield, undesired compound **11** where the Suzuki coupling occurs with the activated chlorine at C-6 after rapid reduction of the iodine at C-4.

(10) Mahboobi, S.; Wiegrebe, W.; Popp, A. *J. Nat. Prod.* **1999**, *62*, 577.

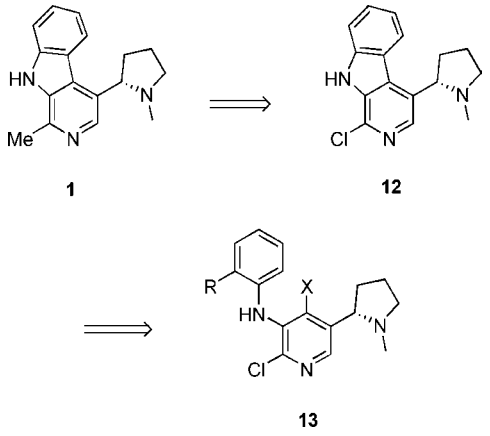
(11) (a) Comins, D. L.; Despagnet, E. U.S. Patent No. 6,995,265, 2006. (b) King, L. S.; Despagnet, E.; Comins, D. L. U.S. Patent Application No. 10/715, 147. (c) Comins, D. L.; Février, F. C.; Despagnet, E. D. U.S. Patent Application No. 10/926, 821. (d) Comins, D. L.; King, L. S.; Smith, E. D.; Février, F. C. *Org. Lett.* **2005**, *7*, 5059. (e) Février, F. C.; Smith, E. D. Comins, D. L. *Org. Lett.* **2005**, *7*, 5457. (f) Smith, E. D.; Février, F. C.; Comins, D. L. *Org. Lett.* **2006**, *8*, 179. (g) Comins, D. L.; Smith, E. D. *Tetrahedron Lett.* **2006**, *47*, 1449. (h) Wagner, F. F.; Comins, D. L. *Eur. J. Org. Chem.* **2006**, in press.

(12) LiDMAE = $Me_2N(CH_2)_2OLi$. For pyridine lithiations using *n*-BuLi−LiDMAE, see: Gros, P.; Choppin, S.; Mathieu, J.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 234 and references therein.

(13) (a) Herrbach, A.; Marinetti, A.; Baudoin, O.; Guénard, D. F. *J. Org. Chem.* **2003**, *68*, 4897. (b) Broutin, P.-E.; Èeròa, I.; Campaniello, M.; Leroux, F.; Colobert, F. *Org. Lett.* **2004**, *6*, 4419.

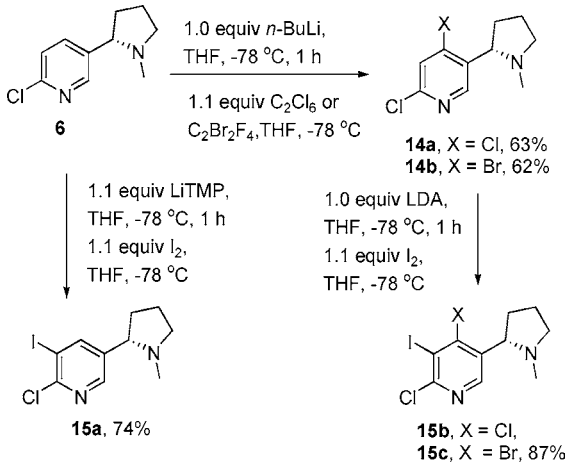
Another route to brevicolline where a Buchwald amination would be carried out first to provide **13** and followed by a ring closure at C-4 to give **12** was investigated (Scheme 4).

Scheme 4. Second Retrosynthetic Route



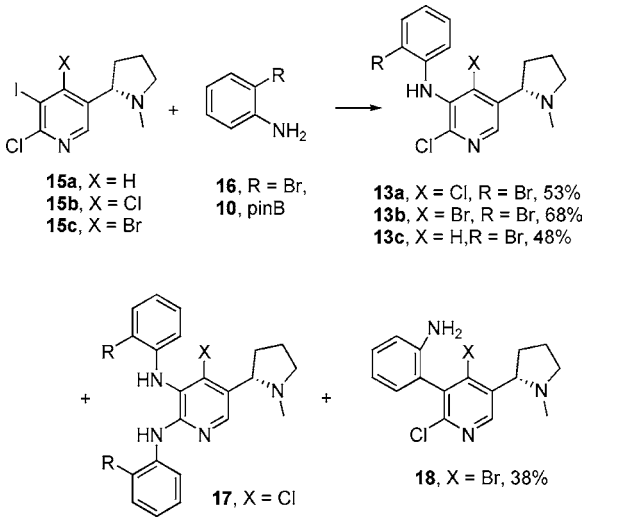
The trihalo precursors to **13** were prepared as shown in Scheme 5.[11h]

Scheme 5. Synthesis of Trihalo Precursors **15a−c**



The amination at C-5 went smoothly for a number of different halogenated nicotine derivatives (**15a−c**) using 5% Pd_2dba_3, 1.5 equiv of Cs_2CO_3, 2-bromoaniline, and Xantphos as a ligand in 1,4-dioxane (Table 1). When the reaction was stirred overnight at 110 °C (entry 2), disubstitution occurred at the activated C-5 and C-6 positions of **15b** to form compound **17**. With the secondary amines (**13a−c**) in hand, several attempts to close the ring at C-4, using different types of cross-coupling reactions (Ullman, Suzuki, or Stille) or radical-mediated cyclization, failed as decomposition occurred or starting material was recovered. However, to our surprise, under standard Buchwald amination conditions, the amino boronate ester **10** and **15c** did not afford the desired boronate product. Instead, a Suzuki cross-coupling reaction

Table 1. Amination at C-5 of **15a−c**



entry[a]	conditions	results
1	**15a** + 1.2 equiv of **16** + 5% Pd_2dba_3, 1.5 equiv of Cs_2CO_3, 10% Xantphos, dioxane, 110 °C	48% of **13c**
2	**15b** + 1.2 equiv of **16** + 5% Pd_2dba_3, 1.5 equiv of Cs_2CO_3, 10% Xantphos, 1,4-dioxane, 110 °C, 18 h	inseparable mixture of **13a** and **17**
3	**15b** + 1.2 equiv of **16** + 5% Pd_2dba_3, 1.5 equiv of Cs_2CO_3, 10% Xantphos, 1,4-dioxane, 110 °C, 3 h	53% of **13a**
4	**15c** + 1.2 equiv of **16** + 5% Pd_2dba_3, 1.5 equiv of Cs_2CO_3, 10% Xantphos, 1,4-dioxane, 110 °C, 3 h	68% of **13b**
5	**15c** + 1.0 equiv of **10** + 5% Pd_2dba_3, 1.5 equiv of Cs_2CO_3, 10% Xantphos, 1,4-dioxane, 110 °C, 3 h	38% of **18**

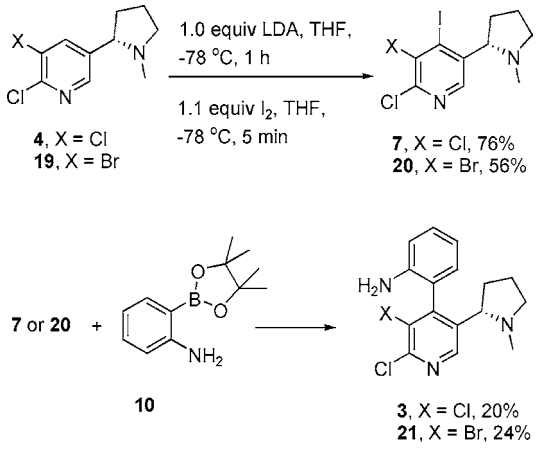
[a] Reactions were run on a 0.3−0.8 mmol scale.

took place and amino compound **18** was formed in 38% yield (entry 5). Because of this result, we decided to investigate additional cross-coupling reactions at C-4 of derivatives **7** and **20** (Scheme 6). Unfortunately, compounds **3** and **21** were formed in low yield (20% and 24%, respectively). It was thought that, once formed, compound **21** might ring close at C-5 under the same reaction conditions, but the desired product was not observed. The low yield in the Buchwald amination step was attributed to the activated C-6 chlorine that could participate in a subsequent cross-coupling reaction decreasing the yield of the desired product. We therefore decided to install the C-6 methyl of (*S*)-brevicolline (**1**) before attempting the Suzuki cross-coupling reaction at C-4 (Scheme 7).

Stille and Kumada couplings with tetramethyltin and methyl Grignard, respectively, were carried out but only afforded no or low yields of (*S*)-5-chloro-6-methylnicotine (**22**). After extensive optimization, compound **22** was formed in good yield from (*S*)-5,6-dichloronicotine (**4**) via a Suzuki cross-coupling reaction using trimethylboroxine.[14]

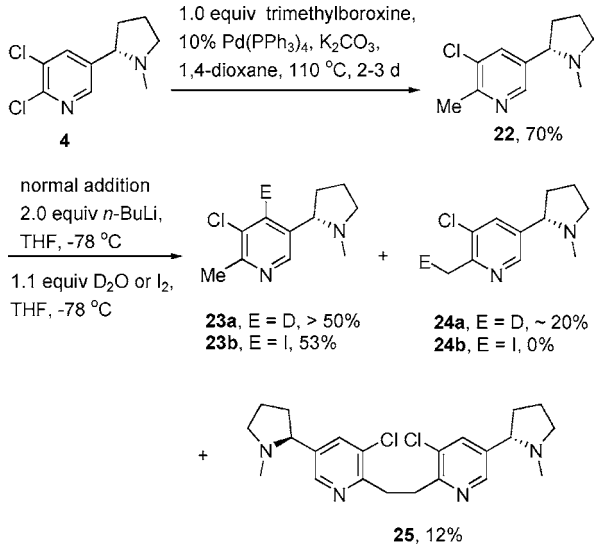
The iodination at C-4 of **22** constituted a tricky step due to the competitive deprotonation of the pseudo benzylic

Scheme 6. Attempted Suzuki Reaction at C-4



position at C-6. Although addition of **22** to *n*-BuLi (inverse addition) afforded inconsistent results, addition of *n*-BuLi to **22** (normal addition) gave a 53% yield of the desired 4-iodo derivative **23b** with 12% of the dinicotine adduct **25** (Scheme 7).

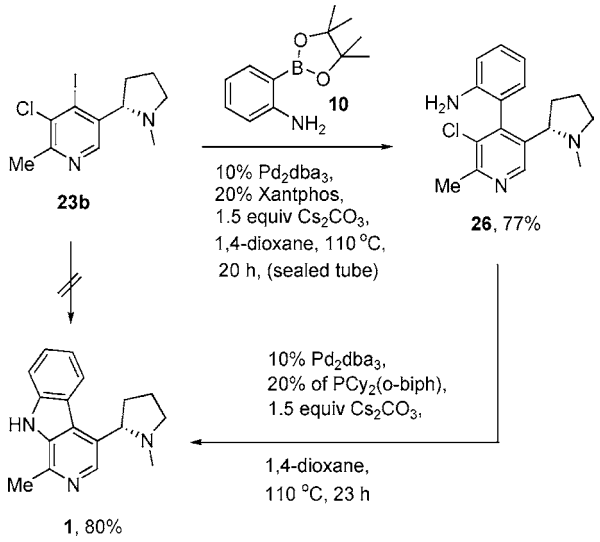
Scheme 7. Methylation at C-6 and Iodination at C-4



The cross-coupling reaction between **23b** and amino boronate ester **10** went smoothly to give **26** (Scheme 8). It is noteworthy to point out that the use of a sealed tube in this reaction slightly increased the yield but more importantly gave a cleaner product.

(14) Gray, M.; Andrews, I. P.; Hook, D. F.; Kitteringham, J.; Voyle, M.; *Tetrahedron Lett.* **2000**, *41*, 6237.

Scheme 8. Suzuki Cross-Coupling Reaction at C-4 and Completion of the Total Synthesis



Finally, an intramolecular Buchwald amination was chosen to close the indole ring to form **1**. Standard Buchwald amination conditions on **26** did not affect the desired transformation. However, the use of Pd_2dba_3, Cs_2CO_3, and PCy_2(o-biph) as the ligand in 1,4-dioxane yielded (*S*)-brevicolline (**1**) in 80% isolated yield. The spectral properties of our (−)-**1** are in agreement with reported data.[1,2,10] Because the ring-closure conditions only differ from the usual Buchwald amination conditions by the ligand, we thought that a one-pot, two-step process from **23b** could be used; however, in all attempts, only **26** was formed and brevicolline was not observed.

In conclusion, after extensive investigation and optimization, (*S*)-brevicolline was synthesized in six steps from (*S*)-nicotine in a 17% overall yield. This practical synthesis was carried out with retention of configuration on the pyrrolidine ring and constitutes the shortest synthesis of this natural product to date.

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Supporting Information Available: Experimental procedures, characterization, and NMR data for **1**, **3**, **7**−**9**, **13a**−**c**, **15b**,**c**, **18**, **20**−**22**, **23b**, **25**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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