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Tetrahedron Letters 47 (2006) 1449–1451
Tetrahedron Letters

A six-step synthesis of (*S*)-5-ethenyl-3-(1-methyl-2-pyrrolidinyl)pyridine (SIB-1508Y) from (*S*)-nicotine

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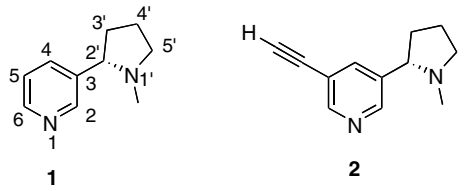
Received 7 December 2005; revised 13 December 2005; accepted 14 December 2005
Available online 9 January 2006

Abstract—The anti-Parkinson's agent SIB-1508Y was prepared in six steps from (*S*)-nicotine in 20% overall yield. The strategy involves a regioselective formylation at C-5 of a 1,4-dihydronicotine intermediate.

Due to the potential role of nicotinic acetylcholine receptors (nAChRs) in central nervous system (CNS) disorders, considerable attention has been given to the preparation and screening of nicotine (**1**) analogs.[1] A remarkably simple derivative, (*S*)-5-ethenyl-3-(1-methyl-2-pyrrolidinyl)pyridine (**2**, SIB-1508Y), was developed and has undergone Phase II clinical trials for the treatment of Parkinson's disease.[2] On first examination, one would speculate that **2** could be prepared via C-5 substitution of natural nicotine (Fig. 1). This is not the case, however, as pyridine substitution reactions of nicotine are difficult due to the presence of the pyrrolidine ring. A direct C-5 halogenation of nicotine has not been reported. Because of this, previous syntheses of **2** start from non-nicotine starting materials and are quite lengthy. The original synthesis requires seven steps, including a resolution, from ethyl 5-bromo-3-pyridinecarboxylate.[3] An asymmetric synthesis of **2** in 10 steps from 5-bromonicotinic acid has also been reported.[4]



1 **2**

Figure 1. Nicotine (**1**) and SIB-1508Y (**2**).

A preparation of **2** from (*S*)-nicotine has obvious advantages, such as the potential for reducing the number of steps and avoiding a resolution or costly asymmetric synthesis to obtain enantiopure product. As part of a program directed at developing regioselective substitution reactions of (*S*)-nicotine,[5] we initiated and accomplished a short synthesis of **2** from **1** in six steps.

Our synthesis plan called for the regioselective introduction of a C-5 substituent via a 1,4-dihydronicotine intermediate is as shown in Scheme 1.

Our recently developed reductive disilylation of (*S*)-nicotine[5b] was used to start the synthesis. Treatment of **1** with lithium powder and chlorotrimethylsilane afforded 1,4-bis(trimethylsilyl)-1,4-dihydronicotine (**3**) in high yield (Scheme 2). Acylation of **3** with methyl carbonate in the presence of TBAF (10%) gave the 1-acyl-1,4-dihydronicotine **4** (98% ee) in high yield.[5b] In the pyridine series, dihydro derivatives of this type can be readily substituted at the β-position with electrophiles.[6,7] Initially, there was concern that the pyrrolidine ring of **4** might interfere with the planned electrophilic substitution reaction, but formylation of **4** under Vilsmeier–Haack conditions afforded the desired aldehyde **5** in acceptable yield.[8]

Aromatization of **5** was best carried out by first removing the *N*-carbomethoxy group under mild conditions (TEA, MeOH, rt, 1 d) to provide **6** in quantitative yield. Without purification, crude **6** was treated with elemental sulfur in refluxing toluene to provide an 83% yield of nicotine-5-carboxaldehyde (**7**). The synthesis was

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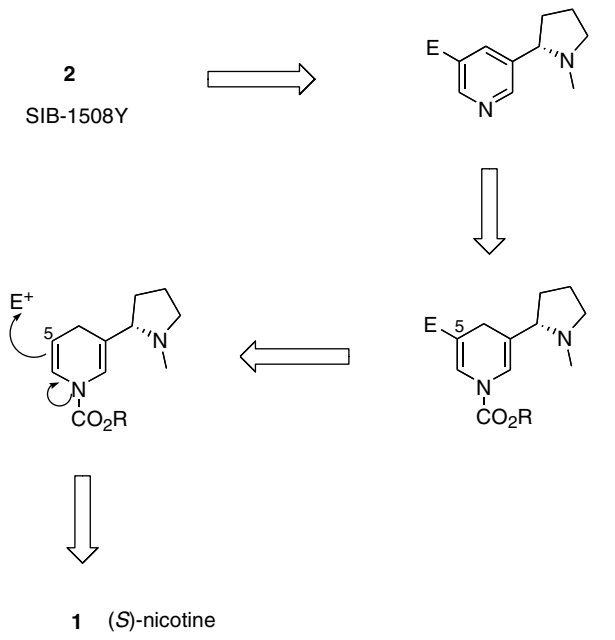
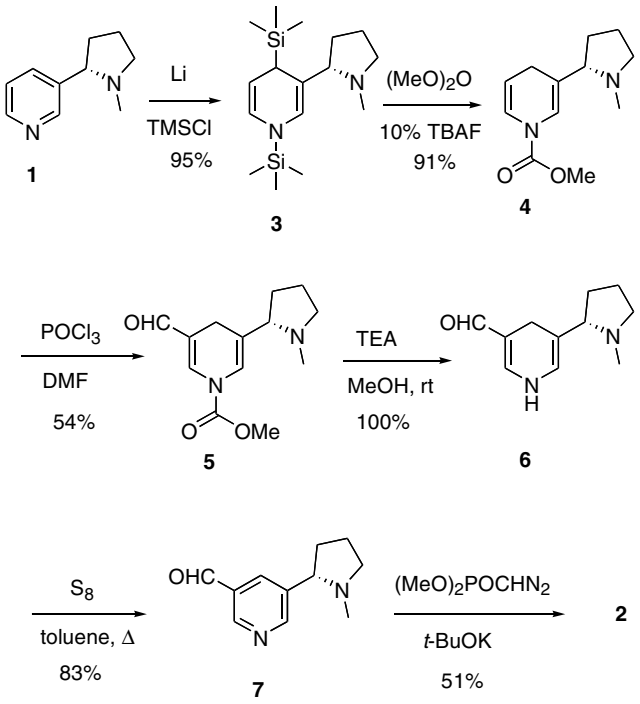
doi:10.1016/j.tetlet.2005.12.085



Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of SIB-1508Y (**2**).

completed by using the Seyferth–Gilbert homologation[9] to convert **7** to SIB-1508Y (**2**) in 51% yield. The spectral properties and optical rotation of our (−)-**2** are in agreement with reported data [$[\alpha]_D^{24}$ −160 (*c* 0.31, EtOH); lit.[3] $[\alpha]_D$ −164 (*c* 5, EtOH)].

In summary, enantiopure SIB-1508Y was prepared via a six-step sequence from natural nicotine in 20% overall yield.[10] This strategy should be amenable to the enantioselective synthesis of various nicotine analogs of potential pharmaceutical value.

Acknowledgements

NMR and mass spectra were obtained at NCSU instrumentation laboratories, which were established by grants from the North Carolina Biotechnology Center and the National Science Foundation (Grants CHE-9509532 and CHE-0078253).

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10. All compounds showed spectroscopic and characterization data in accordance with structure. Spectroscopic data for selected compounds: Compound **2**:[3] clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, $J = 2.4$ Hz, 1H), 8.49 (d, $J = 2.4$ Hz, 1H), 7.80 (t, $J = 2.4$ Hz, 1H), 3.25 (t, $J = 8.4$ Hz, 1H), 3.20 (s, 1H), 3.09 (t, $J = 8.4$ Hz, 1H), 2.36–2.26 (m, 1H), 2.26–2.15 (m, 1H), 2.17 (s, 3H), 2.02–1.90 (m, 1H), 1.88–1.76 (m, 1H), 1.75–1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 149.2, 138.9, 138.2, 119.3, 80.8, 80.5, 68.6, 57.2, 40.6, 35.5, 22.9; $[\alpha]_D^{24}$ −160 (*c* 0.31, EtOH); lit.[3] $[\alpha]_D$ −164 (*c* 5, EtOH).

Compound **5**: white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.65 (m, 1H), 6.81 (s, 1H), 3.91 (s, 3H), 3.12–3.07 (m, 1H), 2.93 (s, 2H), 2.59 (m, 1H), 2.20–2.12 (m, 3H), 1.81–1.62 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.13, 151.82, 141.44, 122.61, 120.52, 118.42, 69.75, 56.98, 54.47, 40.61, 29.45, 22.91, 19.86; $[\alpha]_D^{25}$ −51.7 (*c* 0.8, CH_2Cl_2); HRMS calc for $C_{13}H_{18}N_2O_3$ 251.1396, found 251.1390.

Compound **6**: yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (s, 1H), 6.85 (d, 1H, $J = 6$ Hz), 6.48 (s, 1H), 6.00–5.99 (m, 1H), 3.05–3.00 (m, 3H), 2.45 (m, 1H), 2.19–2.11 (m, 4H), 1.83–1.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.59, 146.95, 119.91, 119.01, 112.67, 70.03, 57.03, 40.69, 28.96, 22.80, 20.37; $[\alpha]_D^{28}$ −80.7 (*c* 0.55, CH_2Cl_2); HRMS calcd for $C_{11}H_{16}N_2O$ 193.1341, found 193.1334.

Compound **7**: clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.97 (s, 1H), 8.79 (s, 1H), 8.18 (s, 1H), 3.30–3.20 (m, 2H), 2.38–1.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.26, 154.81, 150.91, 140.39, 135.13, 131.69, 68.53, 57.19, 40.64, 35.66, 23.02; HRMS calcd for $C_{11}H_{14}N_2O$ 191.1184, found 191.1182.