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A Five-Step Synthesis of (*S*)-Macrostomine from (*S*)-Nicotine

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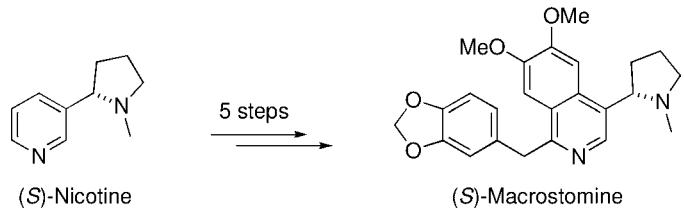
ABSTRACT



(*S*)-Nicotine (*S*)-Macrostomine

A concise synthesis of (*S*)-macrostomine has been accomplished in five steps from natural nicotine in 19% overall yield via a pyridyne Diels−Alder cycloaddition reaction as the key step. A Kumada cross-coupling reaction on a 1-chloroisoquinoline intermediate provided the natural product.

(*S*)-Macrostomine (**1**) is a plant alkaloid containing a benzylisoquinoline ring system that was first isolated from the plant *Papaver macrostomum* Boiss. et Huet and structurally elucidated in 1974 by Santavy and co-workers.[1] Later, in 1984 the alkaloid was also isolated from the plant *Papaver arenarium* M.B.[2] Santavy's group[3] reported that (*S*)-macrostomine has a spasmolytic effect on the smooth muscle of isolated intestines of rats and rabbits that is greater than that of papaverin (**2**, Figure 1), an alkaloid used primarily in the treatment of spasms and approved as a cerebral and coronary vasodilator.[4] (*S*)-Macrostomine has also been shown to have some effects on the cardiovascular function of rabbits after intravenous application.[3] There has been no other report in the literature on its biological activity, a shortcoming that may be largely attributed to the lack of concise synthetic routes to the natural product and analogues.

The first synthesis of (±)-macrostomine was accomplished in 1980 by Wykypiel and Seebach using 11 steps from veratraldehyde.[5] Two other syntheses of the racemate from veratraldehyde were reported by Wiegrebe and co-workers[6] and by Kapil and Sharma[7] in 7 and 8 steps, respectively, albeit in low overall yields. Later, in 1988 Wiegrebes's group published the only known enantioselective synthesis of (*S*)-macrostomine in 13 steps through what they called the Preininger alkaloid (**3**), a crucial intermediate for their synthesis.[8,9]

Our group has in recent years been studying the synthetic utility of (*S*)-nicotine (**4**) and its derivatives.[10−12] Recently, we reported a 6-step synthesis of (*S*)-brevicolline[11] (**5**) and two syntheses of SYB-1508Y[12] (**6**) in 5 and 6 steps, respectively, using (*S*)-nicotine as starting material. Since (*S*)-macrostomine also possesses the core (*S*)-nicotine struc-

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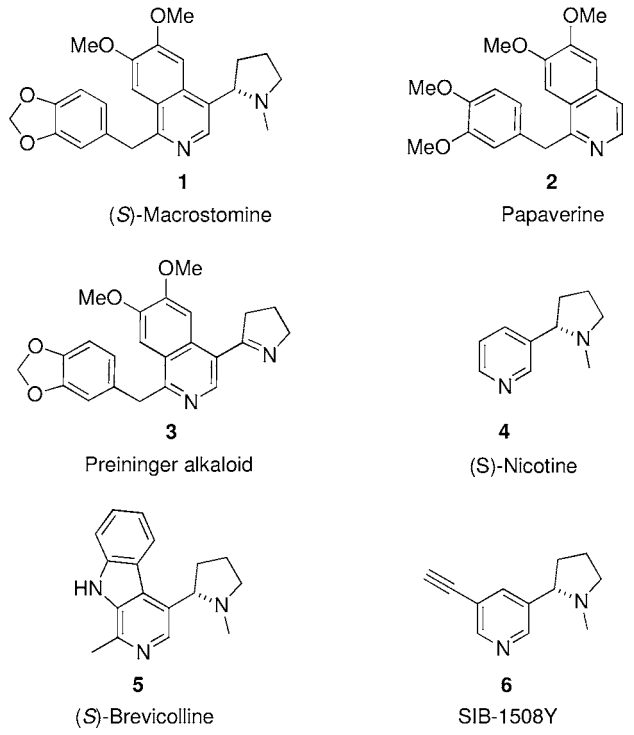


Figure 1. Macrostomine and related alkaloids.

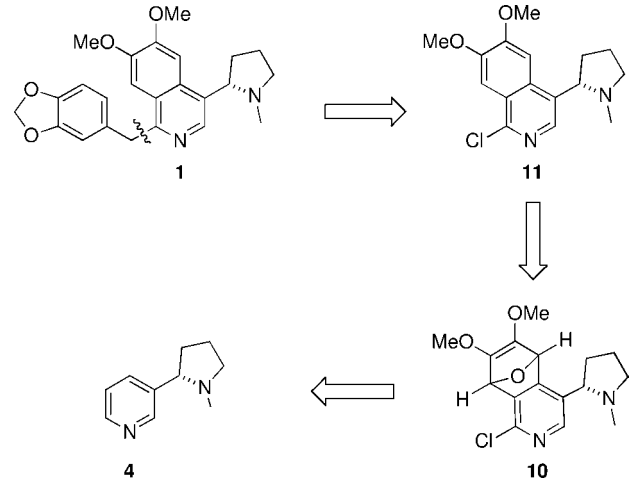
ture, it was envisioned that this natural product could be synthesized in a few steps from natural nicotine by using directed lithiation methodology developed in our laboratories.[10−12]

Reported herein is a 5-step synthesis of (*S*)-macrostomine from (*S*)-nicotine. Nicotine as a chiral building block provided the necessary stereochemistry and ring system present in the natural product. The key step of our synthesis involves an opportune use of a pyridyne intermediate in a Diels−Alder reaction to provide the required isoquinoline core heterocycle.

In our retrosynthetic plan (Scheme 1), we envisioned that **1** could be obtained from (*S*)-nicotine via two key reactions: a Diels−Alder cycloaddition reaction of an intermediate pyridyne that would provide **10** and then 1-chloroisoquinoline **11** after an aromatization step. A metal catalyzed C−C bond formation to introduce the 3,4-methylenedioxybenzyl group at C-1 would complete the synthesis.

It was anticipated that a metal-induced halide elimination[13] at C-4 of a 4,6-dihalonicotine, or a corresponding fluoride-induced *o*-(trimethylsilyl)pyridyl triflate elimination,[14] in the presence of a suitable diene would effect a Diels−Alder cycloaddition to provide the precursor to the isoquinoline ring system.

Scheme 1. General Retrosynthetic Plan



Our synthesis commenced with the introduction of a chloride at the C-6 position of (*S*)-nicotine using Fort's base[15] as reported in our previous work (Scheme 2).[10b,e] A chloride functionality at the C-6 position of **7** was essential to direct lithiations at the C-4 and C-5 positions and to serve as a handle in the C−C metal-catalyzed cross-coupling reaction at the last step.

In the initial approach, 2,3-dimethoxybutadiene was employed as the diene for the Diels−Alder cycloaddition, as it has been reported to give cycloadducts with certain dienophiles.[16] Derivatives of (*S*)-6-chloronicotine substituted at the C-4 and C-5 positions with bromine and iodine, or with corresponding TMS and chloro groups, were employed as pyridyne precursors. However, after extensive investigations, all efforts to achieve this cycloaddition under a variety of conditions were unsuccessful. We attributed this failure to the fact that 2,3-dimethoxybutadiene exists mostly in its *S*-trans conformation, instead of the required *S*-cis conformer, causing the cycloaddition to fail under the reaction conditions.[16]

As an alternative, an exploratory reaction was performed with furan as the diene system since it is locked in a *S*-cis

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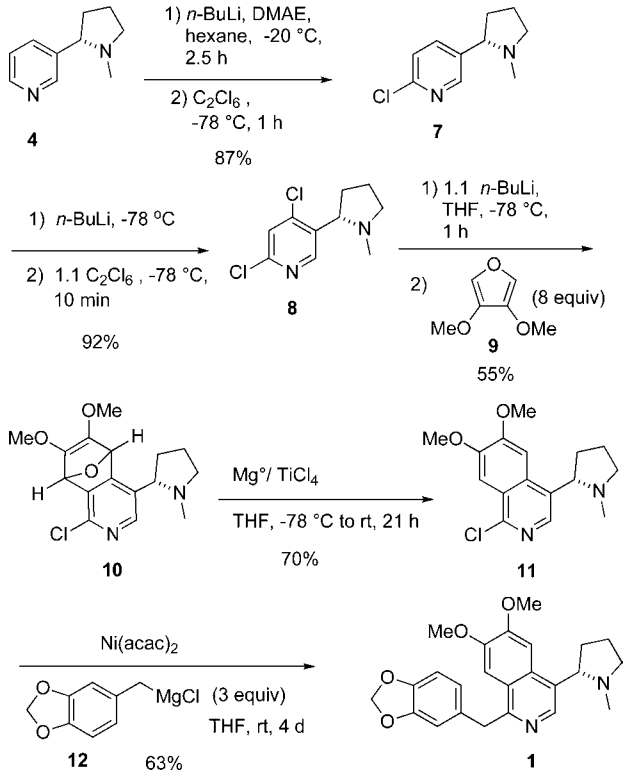
Scheme 2. Synthesis of (*S*)-Macrostomine (**1**) from (*S*)-Nicotine



conformation and is known to react with pyridynes.[14] Gratifyingly, when (*S*)-4-bromo-6-chloro-5-iodonicotine[10e] was subjected to a metal−halogen exchange at C-5 with *i*-PrMgCl·LiCl at −78 °C, and then warmed to room temperature in the presence of 10 equiv of furan, two diastereomers of the Diels−Alder adduct were obtained in modest yields.[17] To synthesize **1** it was necessary to use a furan derivative containing methoxy substituents at the C-3 and C-4 positions. The required 3,4-dimethoxyfuran (**9**) was prepared in one step from commercially available 3,4-dimethoxyfuran-2,5-dicarboxylic acid with use of a known protocol.[18]

Surprisingly, when (*S*)-4-bromo-6-chloro-5-iodonicotine[10e] was subjected to similar conditions with excess 3,4-dimethoxyfuran as the diene, the Diels−Alder adduct **10** was obtained in very low yield. Fortunately, when (*S*)-4,6-dichloronicotine (**8**)[10d,e] was C-5 lithiated with *n*-BuLi at −78 °C, followed by addition of 8 equiv of 3,4-dimethoxyfuran, and the mixture was allowed to warm to room temperature, the product **10** was obtained in 55% yield as an inseparable 1:1 mixture of diastereomers. Attempts at aromatization of the cycloadducts using a $Zn/TiCl_4$[19] couple under reflux led to decomposition of the starting material. Aromatization was accomplished when **10** was added to a solution of $Mg/TiCl_4$[20] in THF (−78 °C to rt) to furnish key intermediate **11** in 70% yield.

With **11** in hand, the C−C bond formation through a Kumada[21] cross-coupling reaction with piperonylmagnesium chloride (**12**) was addressed. After extensive screening for the appropriate catalyst, and optimization of conditions, a ligand-free reaction with $Ni(acac)_2$ as catalyst afforded the enantiopure natural product **1** in 63% yield.

In summary, the plant alkaloid (*S*)-macrostomine was synthesized via a 5-step sequence from (*S*)-nicotine in a 19% overall yield. This practical synthesis was carried out with retention of configuration on the pyrrolidine ring. Our work constitutes the shortest synthesis of this natural product to date, and further demonstrates the value of (*S*)-nicotine as a chiral building block. Preparation of macrostomine analogues for biological testing by using modifications of this synthetic route is underway in our laboratories.

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Supporting Information Available: Experimental procedures for **1**, **8**, **10**, **11**, and **12** and characterization and NMR spectra for compounds **1**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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