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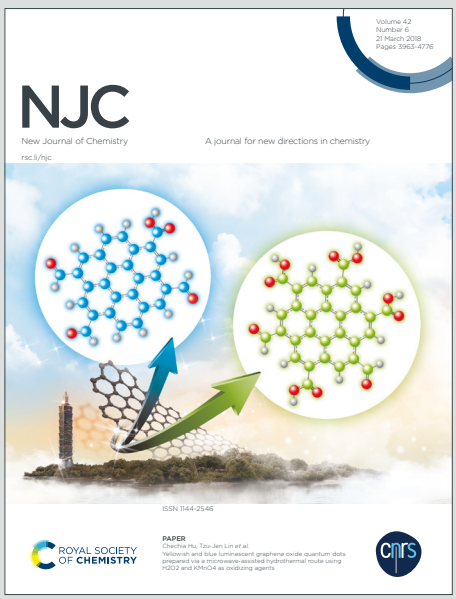

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ARTICLE

A Short Stereodivergent Synthesis of (R) and (S)-Nicotine

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A straightforward and efficient enantioselective synthesis of (*S*)-nicotine and unnatural (*R*)-nicotine with high yields is presented. Judicious choice of solvent in the key asymmetric addition of the pyridyl Grignard reagent to the chiral sulfinimine promotes either an open or closed transition state, allowing the selective formation of either of two distinct diastereomers, which are then transformed into either enantiomer of the natural product *via* ring-closure and deprotection/methylation of the pyrrolidine amine.

Introduction

Nicotine (3-(1-methyl-2-pyrrolidinyl)pyridine) is a bicyclic tertiary amine of note due to the widespread recreational use of tobacco products, and their effects on the central nervous system, with recent studies indicating it may have potential in the treatment Parkinson's disease, Alzheimer's disease and epilepsy, among several other disorders.[1] The nicotine molecule has a chiral centre at the 2'-position of its pyrrolidine moiety. Consequently, the two enantiomers are designated as *S*-(-)-nicotine (**1**) and *R*-(+)-nicotine (**2**), as displayed in Figure 1.

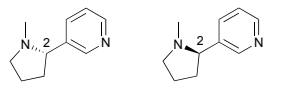

Figure 1: Structures of *S*-(-)-nicotine (**1**) and *R*-(+)-nicotine (**2**)

The term "nicotine" is frequently used interchangeably with "(*S*)-nicotine" in the scientific literature, which is by far the most prevalent of the two enantiomeric forms found in Nature. (*S*)-Nicotine is found in a concentration of 0.5 to 7.5% in the dried leaves of the tobacco plant (*Nicotiana tabacum Linn*),[2] whereas the lesser-known "Aztec tobacco" (*Nicotiana rustica*) contains even greater concentrations, reaching up to 14%.[3-6] An enantiomer, (*R*)-nicotine, is the unnatural isomer of nicotine. Typically, tobacco plants (cured leaves) only contain minute amounts of the (R) enantiomer.[7] The concentration of (*R*)-nicotine in unprocessed and processed tobacco is about 0.2% of the total nicotine. However, in tobacco smoke, the amount of (*R*)-nicotine compared to the total nicotine is significantly greater, ranging from 2% to 3%.[7-9] The impact of (*R*)-nicotine is distinct from that of the predominant (*S*)-enantiomer. In several species, it has been documented that (*S*)-nicotine exhibits greater toxicity in comparison to (*R*)-nicotine and can induce a range of adverse effects.[10,11] Moreover, it has been observed that the racemic mixture of (*S*)/(*R*)-nicotine is more detrimental than (*R*)-nicotine.[11] Also, both enantiomers of nicotine have been reported to cause varying inhibition degrees of acetylcholinesterase, with (*R*)-nicotine exhibiting greater inhibitory potency.[12] For neurodegenerative diseases and addiction to tobacco, (*R*)-nicotine showed promise as a treatment target.[6] Vincek and co-workers reported that the lethal dose (LD50) for (*R*)-nicotine is 2.75 mg/kg, and the LD50 for (*S*)-nicotine is estimated to be 0.38 mg/kg.[13] In the cytochrome P450cam, it was discovered that the metabolic rate of (*R*)-nicotine was 1.4 times more rapid than the metabolic rate of (*S*)-nicotine.[14] Although (*S*)-nicotine has a possible pharmacological role in the treatment of depression, Alzheimer's disease, Parkinson's disease, and other diseases associated with the central nervous system,[15,16] its high addiction liability in particular and its cardiovascular, gastrointestinal, and neuromuscular side effects restrict its clinical usefulness.[17,18] Various synthetic strategies have recently been published towards the synthesis of the two nicotine enantiomers, including racemic mixture[19-21], and enantioselective reactions.[22-26] In this work, we present a simple and effective approach for synthesizing each of the two enantiomers, (*R*)-nicotine and (*S*)-nicotine, with high enantioselectivity, exploiting the relative coordinating ability of the solvent used to allow either a closed transition state or an open transition state in the key Grignard addition to chiral sulfinimine **4**, as shown in Figure 2.

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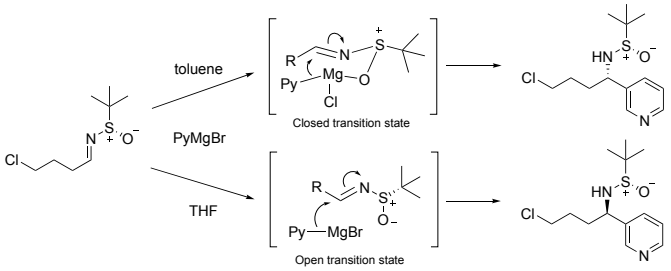
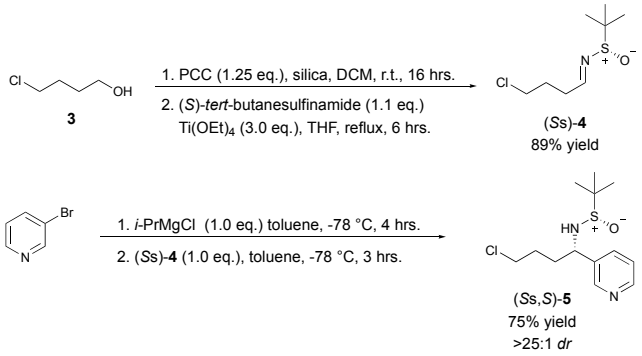


Figure 2: Choice of solvent to promote an open or closed transition state for Grignard addition to sulfinimine. Restricted rotation around the N-S bond, caused by dipole opposition, means rear approach from the in-coming nucleophile is blocked by the *tert*-butyl group in the open transition state.

Results and discussion

Our synthetic strategy for acquiring (*S*)-nicotine (**1**) began with the synthesis of sulfinimine **4** by a two-step process that involved oxidising 4-chloro-1-butanol (**3**) with pyridinium chlorochromate (PCC) to provide the aldehyde form of **3**. Next, product **3** was reacted with (*S*)-*tert*-butanesulfinamide (Ellman's sulfinamide) as a chiral auxiliary and protecting group *via* Ellman's procedure.[27-29] This produced the desired (*Ss*)-sulfinimine **4** with a high yield of 89% (Scheme 1). Using a non-coordinating solvent (toluene), compound **4** reacted with pyridin-3-ylmagnesium chloride, which was synthesized *in situ* through the treatment of 3-bromopyridine with *iso*propylmagnesium chloride,[30] resulting in the desired sulfinamide (*Ss*,*R*)-**5** in a good yield (75%) as a single diastereoisomer. The *dr* value was assigned using ^{1}H NMR spectroscopy of the crude material. Based on the methodology of Ellman and co-workers,[27,28] the stereochemistry of the produced stereogenic center (C-2) was designated as *S*. This is the specific stereochemistry required for the production of (*S*)-nicotine (**1**).



Scheme 1: Asymmetric synthesis of (*Ss*,*S*)-**5** starting from alcohol **3**

Thereafter, different reaction conditions were employed on (*Ss*,*S*)-**5** to explore the best results for ring closing to furnish the corresponding pyrrolidine derivative (*Ss*,*S*)-**6**, as listed in Table 1. The reaction conditions included a variety of solvents and bases at different temperatures (Table 1, Entries 1-9). It was observed that LDA was the best base tested, which is likely due to its increased basicity compared with other bases. This base has the ability to fully deprotonate (*Ss*,*S*)-**5**, producing the anion form of (*Ss*,*S*)-**5**, which is more reactive to intramolecular S_N2. This procedure furnished pyrrolidine derivative (*Ss*,*S*)-**6** in excellent yield (90%) with a *dr* >25:1 (Table 1, Entry 6).

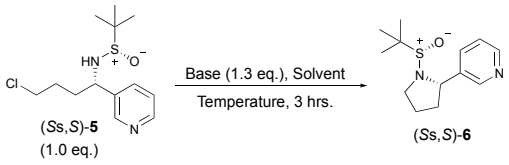


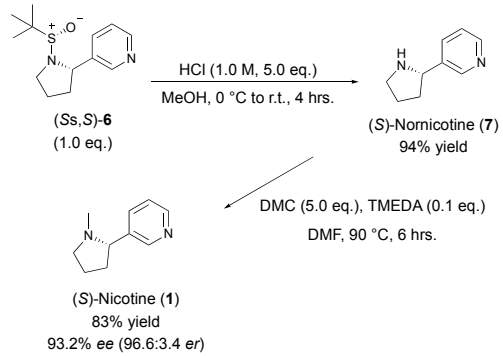
Table 1: Optimization of ring closing conditions for accessing of the pyrrolidine (*Ss*,*S*)-**6**

Entry	Base	Solvent	T (°C)	Yield[a]
1	-	THF	25	Trace[b]
2	LiHMDS	THF	-78 to 25	72
3	LiHMDS	MeCN	-78 to 25	56
4	LiHMDS	Toluene	-78 to 25	23
5	LiHMDS	THF	66	50
6	LDA	THF	-78 to 25	90
7	Et_3N	THF	25	19
8	K_2CO_3	THF	25	30
9	KO^{t}Bu	THF	25	33

[a] Isolated Yield.

[b] No conversion to the desired product was observed by TLC but detected by HRMS.

Pyrrolidine formation was followed by the removal of the sulfinyl group of (*Ss*,*S*)-**6** under acidic conditions (HCl, 1.0 M) to afford (*S*)-nornicotine (**7**) in an excellent yield (94%). In the literature, the specific rotation of (*S*)-**7** is $[\alpha]^{22}_D$ = -89.0 (c = 1.0, MeOH)[31,32], which was used to compare with our obtained value ($[\alpha]^{27}_D$ = -86.4 (c = 1.0, MeOH). Finally, *N*-methylation of (*S*)-nornicotine (**7**) was achieved successfully using dimethyl carbonate (DMC) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as a methylating reagent and nucleophilic catalyst, respectively. This provided the desired natural product (*S*)-**1** in 83% yield (47% overall yield from alcohol **3**) and high enantiomeric excess (93.2%) (Scheme 2). The enantiomeric excess (*ee*) value of (*S*)-**1** was evaluated using chiral HPLC analysis on a chiral stationary phase.[33] Comparatively with our observed value $[\alpha]^{26}_D$ = -166.3 (*c* = 1.0, MeOH), the specific rotation value from the literature of (*S*)-**1** is $[\alpha]^{20}_D$ = -169.0 (*c* = 1.0, MeOH).[34-36]



Scheme 2: Preparation of (*S*)-nicotine (**1**) *via* a two-step protocol starting from (*Ss*,*S*)-**6**

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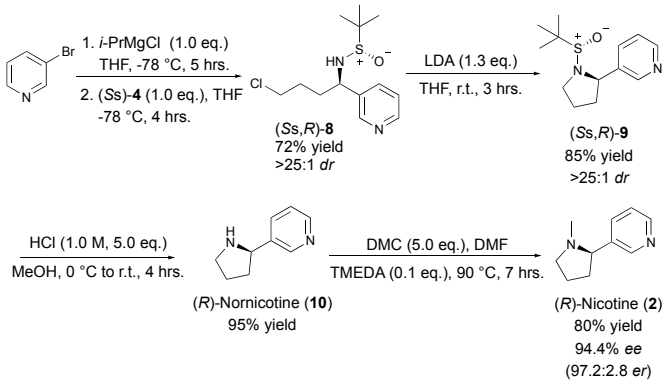
The synthesis of (*R*)-nicotine (**2**) has been accomplished by the use of a method that is similar to the one utilized for the synthesis of (*S*)-nicotine (**1**), with the exception of the crucial step of the Grignard reagent addition. Therefore, the required pyrrolidine derivative (*Ss*,*R*)-**9** was successfully produced with a high *dr* value (>25:1) and an overall yield of 59% from 4-chlorobutan-1-ol (**3**) (Scheme 3). This involved adding pyridin-3-ylmagnesium chloride to (*Ss*)-sulfinimine **4** in a coordinating solvent (THF). This established an open transition state that allowed the appropriate stereochemistry to form at the sulfinamide C-N bond, which led to the formation of (*Ss*,*R*)-**8** in 72% yield and >25:1 *dr*. Ring closing of (*Ss*,*R*)-**8**, deprotection on (*Ss*,*R*)-**9** using acidic conditions, and *N*-methylation of the (*R*)-nornicotine (**10**) with DMC have been conducted as employed in the last synthesis to access the desired (*R*)-nicotine (**2**) (65% yield over the three steps from **8**, with 94.4% *ee*[33]). From the literature, the specific rotation of (*R*)-nicotine (**2**) is $[\alpha]^{20}_{D}$ = +169.0 (*c* = 1.0, MeOH)[26,34,35], which was employed to compare with our measured value $[\alpha]^{28}_{D}$ = +165.9 (*c* = 1.0, MeOH). The relative stereochemistry and absolute configuration of (*S*)-nicotine (**1**) and (*R*)-nicotine (**2**) were confirmed according to the ^{1}H NMR and ^{13}C NMR spectra, as well as specific rotation from previous research.[22,23,26,34–37]



Scheme 3: Asymmetric synthesis of (*R*)-nicotine (**2**)

Conclusions

Successful enantioselective synthesis of (*S*)-nicotine and (*R*)-nicotine from alcohol **3** has been accomplished with overall yields of 47% and 41%, respectively. Controlling the stereochemistry of C-2 is a crucial step in these syntheses. Choice of solvent in the nucleophilic addition of Grignard reagent to a sulfinimine enables an enantioselective route to both target products by exploiting the switching of transition states.

Conflicts of interest

There are no conflicts to declare.

Data availability

A data availability statement (DAS) is required to be submitted alongside all articles. Please read our full guidance on data availability statements for more details and examples of suitable statements you can use.

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- The data supporting this article have been included as part of the Supplementary Information.

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