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A Concise Route to the Chiral Pyrrolidine Core of Selective Inhibitors of Neuronal Nitric Oxide

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Abstract

2-(((3R,4R)-4-(Allyloxy)-1-benzylpyrrolidin-3-yl)methyl)-6-(2,5-dimethyl-1H-pyrrol-1-yl)-4-methylpyridine (**2**), a key intermediate for the preparation of novel neuronal nitric oxide synthase (nNOS) inhibitors, is synthesized using diisopropyl (*R*)-(+)-malate as the starting material. The key steps involve a Frater-Seebach diastereoselective alkylation and a fast intramolecular cyclization.

Selective inhibition of the neuronal isozyme of nitric oxide synthase (nNOS) has attracted significant interest as a novel strategy in developing therapeutics for the treatment of neurodegenerative diseases including Parkinson's disease, Alzheimer's disease, and Huntington's disease.¹ In our continuous effort to design nNOS selective inhibitors,² we have developed a stereospecific pyrrolidine-based inhibitor (**1**; Figure 1), which showed great potency ($K_i = 5$ nM) and extremely high selectivity for nNOS over its closely related isoforms endothelial NOS (eNOS, 3800 fold) and inducible NOS (iNOS, 1200 fold).³ Recent animal tests demonstrated that **1** could lead to a remarkable reduction in neurological damage to rabbit fetuses under hypoxic conditions,⁴ making **1** a strong candidate as a new drug for the treatment of neurodegenerative diseases.

Despite this exciting discovery, current and future research related to **1** is impeded by its difficult synthesis. In particular, the chiral pyrrolidine fragment **2** (Figure 1), which was achieved by a seven-step procedure,^{3b-c} suffered from major disadvantages e.g., expensive starting material, hard chromatographic purifications, and low overall yield (<2%).^{3b-c} Moreover, the utilization of racemic starting materials requires extra chiral resolution step(s) using either HPLC or chiral auxiliaries,^{3c} which dramatically reduce the yield and efficiency. Therefore, the development of an efficient route to **2** is a bottleneck to future investigations of inhibitor **1**.

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Supporting Information Available: Full experimental details and characterization of synthetic intermediates; copies of complete spectroscopic data of compounds **4a**, **4b**, **6**, **8-11**, **13-14**, **16-20**, and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Herein, we report the development of a concise stereospecific synthesis of **2**. Our initial plan was to use a disubstitution reaction on dimesylate **3** with benzylamine (Scheme 1).⁵ Dimesylated compound **3** could be derived from dialkyl malate (**4**) using a sequential allylation–reduction procedure. Stereospecific compound **4** could be achieved by the diastereoselective alkylation protocol developed by Frater et al⁶ and Seebach et al⁷ using dialkyl (*R*)-(+)-malate (**5**) and 2-(bromomethyl)-6-(2,5-dimethyl-1H-pyrrol-1-yl)-4-methylpyridine (**6**) as starting materials.

The synthesis of **6** began with 2-aminopyridine (**7**, Scheme 2). The amino functional group of **7** was protected using 2,5-hexanedione in the presence of *p*-toluenesulfonic acid (*p*-TsOH) to give **8** in high yields. The 2,5-dimethylpyrrole protecting group was selected for two reasons. First, this protecting group is known to be stable under a variety of reaction conditions and can be easily removed under mild conditions.⁸ Second, the electron-donating property of the 2,5-dimethylpyrrole group increases the chelating ability of the pyridine nitrogen to the lithium ion, which favors regioselective deprotonation of the 2-methyl group on the pyridine ring.⁹ **8** was treated with *n*-BuLi at 0 °C, and the resulting anion was quenched with chlorotrimethylsilane (TMSCl) at the same temperature to generate **9** exclusively.^{8a} Finally, **9** was allowed to react with 1,2-dibromotetrafluoroethane in the presence of CsF to provide **6** in quantitative yields.¹⁰

Next, optimization of the conditions for the Frater-Seebach alkylation was investigated (Table 1). When using lithium diisopropylamide (LDA) as the base, we isolated only a trace amount of product using either **5a** or **5b** as the starting material (Table 1, entries 1 and 2). With lithium hexamethyldisilazide (LHMDS) as the base however, we could isolate products **4a** and **4b** in 23% and 56% yield, respectively, with high diastereoselectivity (Table 1, entries 3 and 4). We then improved the yield to 85% by changing the ratio between **5b** and **6** (Table 1, entries 5 to 7).

Allylation of **4b** via NaH and allylbromide yielded **10**, which was reduced using LiAlH₄ to generate diol **11** in excellent yields (Scheme 3). When **11** was submitted to a variety of mesylation conditions, however, the only products that could be detected were compounds **13** and **14**, derived by intramolecular cyclizations from either the pyridinyl nitrogen atom (**13**)¹¹ or the hydroxyl oxygen atom (**14**),¹² respectively.

To avoid these intrinsic problems, a new synthetic route was designed around key intermediate dialdehyde **15** (Scheme 4), which can undergo a single-step reductive amination reaction to provide **2**.¹³ We hoped that under reductive conditions, dialdehyde **15** could be generated from diisopropylester **10**.

The results of the Dibal-H reduction of **10** are summarized in Table 2. When 3.5 equiv of Dibal-H were used at -78 °C for 2 h (Table 2, entry 1), three different products, aldehyde **16**, alcohol **17**, and semi-acetal **18**, were isolated. **18** was the major product, but no dialdehyde **15** was detected. Next, fewer equiv of the reducing reagent were used. The data showed that either only aldehyde **16** (Table 2, entry 2), or **16** and **17** (Table 2, entries 3 and 4) were isolated from the reaction without any evidence of dialdehyde **15** formation. Additional reduction of aldehyde **16** using Dibal-H (1 equiv) yielded only alcohol **17**, which, together with the previous Dibal-H reduction data, confirmed that dialdehyde **15** could not be generated by reduction of **10**.

Even though dialdehyde **15** was not produced, we did successfully isolate aldehyde **16** in good yields after simple optimizations (Table 2, entry 4). We sought to prepare amine **20** from **16** in the hope that the additional amino group of **20** would compete with the aminopyridine nitrogen for cyclization, thus preventing the formation of **13** and yielding the desired compound **2**.

As shown in Scheme 5, reductive amination of **16** with benzylamine in the presence of NaHB(OAc)₃ provided amine **19** in excellent yields with complete retention of stereochemistry. Next, the isopropyl ester of **19** was reduced with LiAlH₄ to generate primary alcohol **20** in good yields. We found that a one-pot procedure without purification of **19** improved the overall yield (83%).

Finally, compound **20** was treated with methylsulfonyl chloride (MsCl) in the presence of TEA. The intramolecular cyclization from the benzyl-protected amine is so fast that **2** was obtained in quantitative yields without formation of any other side products.

In summary, we developed an efficient and highly diastereoselective synthesis of the chiral pyrrolidine building block (**2**) for a novel nNOS inhibitor (**1**), employing as key steps a Frater-Seebach type alkylation and a fast intramolecular cyclization, which avoids the unwanted cyclization by the pyridine nitrogen. This method takes nine steps in total with an overall yield of 42%, which is >20-fold higher than previous strategies.^{3b,c} The current method has also been utilized for gram-scale preparations of inhibitor **1**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Structures of **1** and **2**.

Scheme 1.
Plan for the Synthesis of **2**

Scheme 2.
Synthesis of 6

Scheme 3.
Results of Mesylation

Scheme 4.
Plan for the Synthesis of **2** via Dialdehyde **15**

Scheme 5.
Synthesis of **20**

Scheme 6.

Table 1

Frater-Seebach Diastereoselective Alkylation.

entry	R	base	6 (equiv)	yield ^b (%)	<i>trans/cis</i> ^c
1	Me	LDA	1.0	<2	
2	<i>i</i> -Pr	LDA	1.0	<2	8:1
3	Me	LHMDS	1.0	23	>15:1
4	<i>i</i> -Pr	LHMDS	1.0	56	>15:1
5	<i>i</i> -Pr	LHMDS	0.75	70	>15:1
6	<i>i</i> -Pr	LHMDS	0.5	77	>15:1
7	<i>i</i> -Pr	LHMDS	0.33	85	>15:1

^a General experimental conditions: 2 equiv of base was added to 1 equiv of **5** at -78 °C, then the reaction temperature was raised to 0 °C and remained for 20 min. The reaction was cooled to -78 °C and compound **6** was added.

^b Isolated yields.

^c Determined by ¹H NMR.

Table 2

Results of Dibal-H Reduction

entry	Dibal-H (equiv)	time (h)	yield ^b (%)			
			16	17	18	18
1	3.5	2	5	15	80	
2	2.0	2	20	0	0	
3	2.0	7	62	10	0	
4	1.5	7	70	4	0	

^a General experimental conditions: 1 equiv of **10** was added Dibal-H at -78 °C.

^b Isolated yields.