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

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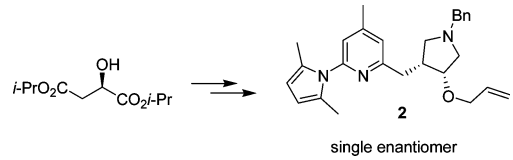
ABSTRACT



2-(((3*R*,4*R*)-4-(Allyloxy)-1-benzylpyrrolidin-3-yl)methyl)-6-(2,5-dimethyl-1*H*-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.

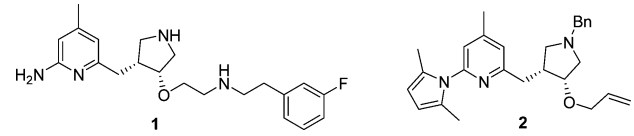


Figure 1. Structures of **1** and **2**.

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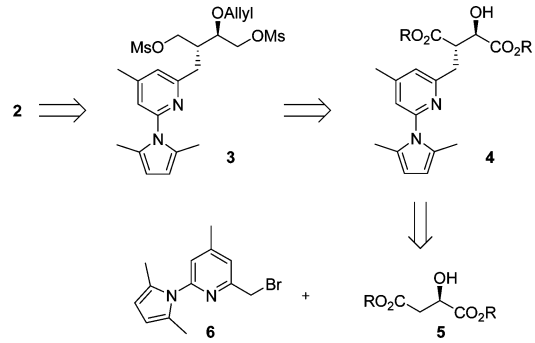
Despite this exciting discovery, current and future research related to **1** is impeded by its difficult synthesis. In particular, the chiral pyrrolidine fragment **2** (Figure 1), which was achieved by a seven-step procedure,[3b,c] suffered from major disadvantages, e.g., expensive starting material, 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**.

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]

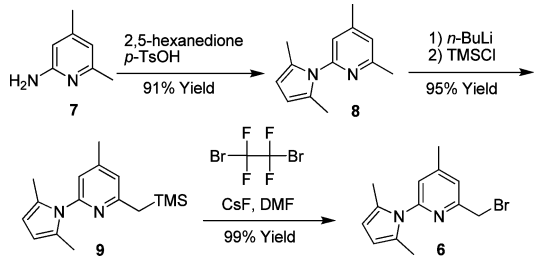
Scheme 1. Retrosynthetic Analysis for **2**



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 al.[6] and Seebach et al.[7] using dialkyl (*R*)-(+)-malate (**5**) and 2-(bromomethyl)-6-(2,5-dimethyl-1*H*-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

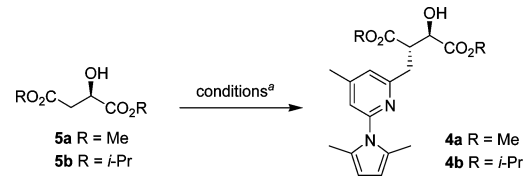
Scheme 2. Synthesis of **6**



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] Compound **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

Table 1. Frater−Seebach Diastereoselective Alkylation



entry	R	base	**6** (equiv)	yield[b] (%)	*trans*/*cis*[c]
1	Me	LDA	1.0	<2	
2	*i*-Pr	LDA	1.0	<2	
3	Me	LHMDS	1.0	23	8:1
4	*i*-Pr	LHMDS	1.0	56	>15:1
5	*i*-Pr	LHMDS	0.75	70	>15:1
6	*i*-Pr	LHMDS	0.5	77	>15:1
7	*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, and then the reaction temperature was raised to 0 °C and maintained for 20 min. The reaction was cooled to −78 °C and compound **6** was added. [b] Isolated yields. [c] Determined by ^{1}H NMR.

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 5−7).

Allylation of **4b** via NaH and allylbromide yielded **10**, which was reduced using $LiAlH_4$ to generate diol **11** in excellent yields (Scheme 3). When **11** was submitted to a variety of mesylation conditions, however, the only products

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(6) Frater, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269.
(7) Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1985**, *63*, 109.
(8) (a) Hagmann, W. K.; Caldwell, C. G.; Chen, P.; Durette, P. L.; Esser, C. K.; Lanza, T. J.; Kopka, I. E.; Guthikonda, R.; Shah, S. K.; MacCoss, M.; Chabin, R. M.; Fletcher, D.; Grant, S. K.; Green, B. G.; Humes, J. L.; Kelly, T. M.; Luell, S.; Meurer, R.; Moore, V.; Pacholok, S. G.; Pavia, T.; Williams, H. R.; Wong, K. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1975. (b) Xue, F.; Li, H.; Poulos, T. L.; Silverman, R. B. Unpublished results.
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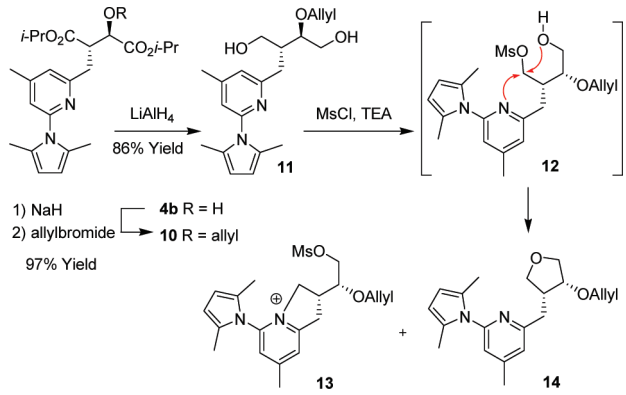
(10) Savage, S. A.; Smith, A. P.; Fraser, C. L. *J. Org. Chem.* **1998**, *63*, 10048.

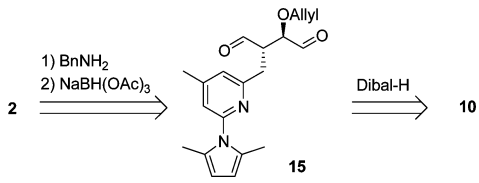
Scheme 3. Results of Mesylation of **11**



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

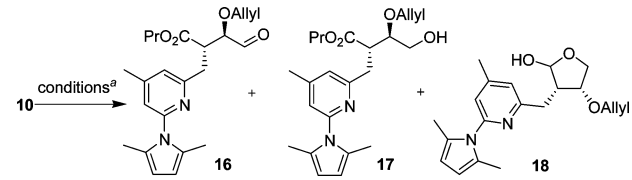
Scheme 4. Modified Retrosynthetic Analysis for **2** via Dialdehyde **15**



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 hemiacetal **18**, were isolated. Hemiacetal **18** was the major product, but no dialdehyde **15** was detected. Next, fewer equivalents 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

Table 2. Results of Dibal-H Reduction



			yield[b] (%)			
entry	Dibal-H (equiv)	time (h)	**10**	**16**	**17**	**18**
1	3.5	2	0	5	15	80
2	2.0	2	80	20	0	0
3	2.0	7	28	62	10	0
4	1.5	7	26	70	4	0

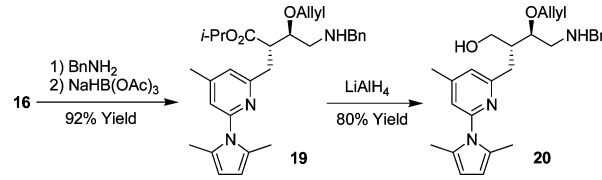
[a] General experimental conditions: 1 equiv of **10** was added Dibal-H at −78 °C. [b] Isolated yields.

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

Scheme 5. Synthesis of **20**



19 in excellent yields with complete retention of stereochemistry. Next, the isopropyl ester of **19** was reduced with $LiAlH_4$ 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 (Scheme 6). 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.

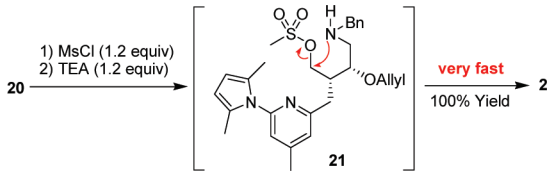
In summary, we developed an efficient and highly diastereoselective synthesis of the chiral pyrrolidine building block (**2**) for a novel nNOS inhibitor (**1**), employing as key steps a Frater−Seebach-type alkylation and a fast intramo-

(11) For examples of similar reactions, see: (a) Yasuda, N.; Hsiao, Y.; Jensen, M. S.; Rivera, N. R.; Yang, C.; Wells, K. M.; Yau, J.; Palucki, M.; Tan, L.; Dormer, P. G.; Volante, R. P.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2004**, *69*, 1959. (b) Lawton, G. R.; Ji, H.; Silverman, R. B. *Tetrahedron Lett.* **2006**, *47*, 6113.

(12) For examples of similar reactions see: (a) Shimada, J.; Kwon, H. J.; Sawamura, M.; Schreiber, S. L. *Chem. Biol.* **1995**, *2*, 517.

(13) (a) Vyskočil, Š.; Jaracz, S.; Smrčina, M.; Štícha, M.; Hanuš, V.; Polášek, M.; Kočovský, P. *J. Org. Chem.* **1998**, *63*, 7727. (b) Marsault, E.; Benakli, K.; Beaubien, S.; Saint-Louis, C.; Děziel, R.; Fraser, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4187.

Scheme 6. One-pot Conversion of **20** to **2**



lecular 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**.

Acknowledgment. We thank the National Institutes of Health (GM49725) for financial support of this research.

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.

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