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

Fengtian Xue, Wenxin Gu, and Richard B. Silverman*

Department of Chemistry, Department of Biochemistry, Molecular Biology, and Cell Biology, Center for Molecular Innovation and Drug Discovery, Chemistry of Life Processes Institute, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208-3113

agman@chem.northwestern.edu

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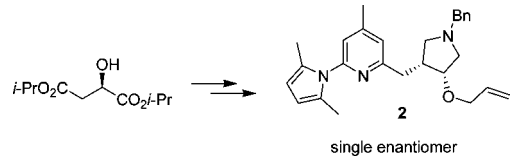
ABSTRACT



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.

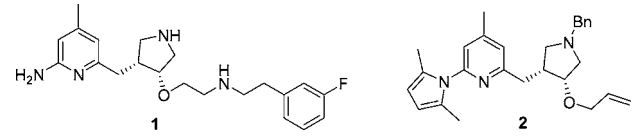


Figure 1. Structures of **1** and **2**.

(1) (a) Hobbs, A. J.; Higgs, A.; Moncada, S. *Annu. Rev. Pharmacol. Toxicol.* **1999**, *39*, 191. (b) Elibol, B.; Soylemezoglu, F.; Unal, I.; Fujii, M.; Hirt, L.; Huang, P. L.; Moskowitz, M. A.; Dalkara, T. *Neuroscience* **2001**, *105*, 79. (c) Huang, Z. H.; Huang, P. L.; Panahian, N.; Dalkara, T.; Fishman, M. C.; Moskowitz, M. A. *Science* **1994**, *265*, 1883. (d) Zhang, L.; Dawson, V. L.; Dawson, T. M. *Pharmacol. Ther.* **2006**, *109*, 33. (e) Dorheim, M. A.; Tracey, W. R.; Pollock, J. S.; Grammas, P. *Biochem. Biophys. Res. Commun.* **1994**, *205*, 659.

(2) Recent reviews: (a) Salerno, L.; Sorrenti, V.; Di Giacomo, C.; Romeo, G.; Siracusa, M. A. *Curr. Pharm. Des.* **2002**, *8*, 177. (b) Alcaraz, M. J.; Guillén, M. I. *Curr. Pharm. Des.* **2002**, *8*, 215. (c) Vallance, P.; Leiper, J. *Nat. Rev. Drug Discovery* **2002**, *1*, 939. (d) Ji, H.; Erdal, E. P.; Litzinger, E. A.; Seo, J.; Zhu, Y.; Xue, F.; Fang, J.; Huang, J.; Silverman, R. B. *Frontiers in Medicinal Chemistry*; Reitz, A. B., Choudhary, M. I., Atta-ur-Rahman, Eds.; Bentham Science Publishers: Oak Park, IL, 2009; Vol. 5, p 842.

(3) (a) Ji, H.; Stanton, B. Z.; Igarashi, J.; Li, H.; Martásek, P.; Roman, L. J.; Poulos, T. L.; Silverman, R. B. *J. Am. Chem. Soc.* **2008**, *130*, 3900. (b) Lawton, G. R.; Ranaivo, H. R.; Wing, L. K.; Ji, H.; Xue, F.; Martesek, P.; Roman, L. J.; Watterson, D. M.; Silverman, R. B. *Bioorg. Med. Chem.* **2009**, *17*, 2371. (c) Delker, S. L.; Ji, H.; Li, H.; Jamal, J.; Fang, J.; Xue, F.; Silverman, R. B.; Poulos, T. L. Submitted for publication.

(4) Ji, H.; Tan, S.; Igarashi, J.; Li, H.; Derrick, M.; Martásek, P.; Roman, L. J.; Vásquez-Vivar, J.; Poulos, T. L.; Silverman, R. B. *Ann. Neurol.* **2009**, *65*, 209.

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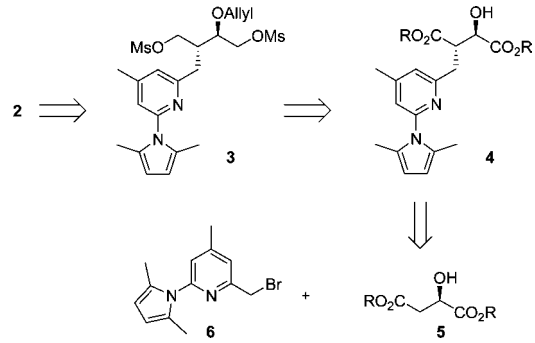
Despite this exciting discovery, current and future research related to **1** is impeded by its difficult synthesis. In particular, the chiral pyrrolidine fragment **2** (Figure 1), which was achieved by a seven-step procedure,[3b,c] suffered from major disadvantages, e.g., expensive starting material,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

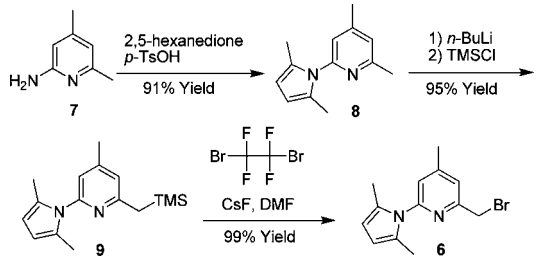
Scheme 1. Retrosynthetic Analysis for **2**



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

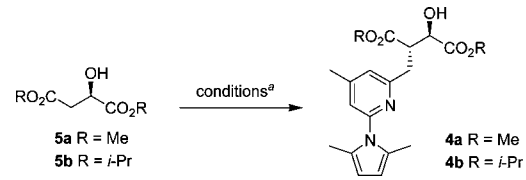
Scheme 2. Synthesis of **6**



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

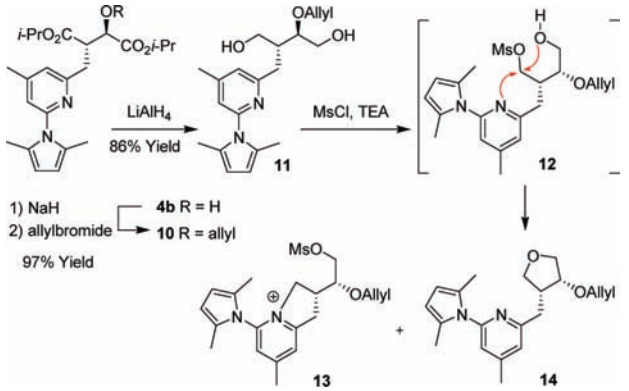
[a] General experimental conditions: 2 equiv of base was added to 1 equiv of **5** at −78 °C, and then the reaction temperature was raised to 0 °C and maintained for 20 min. The reaction was cooled to −78 °C and compound **6** was added. [b] Isolated yields. [c] Determined by ^{1}H NMR.

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

(5) Kotian, P. L.; Chand, P. *Tetrahedron Lett.* **2005**, *46*, 3327.
(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.
(9) Bowers, S. G.; Coe, D. M.; Boons, G.-J. *J. Org. Chem.* **1998**, *63*, 4570.
(10) Savage, S. A.; Smith, A. P.; Fraser, C. L. *J. Org. Chem.* **1998**, *63*, 10048.

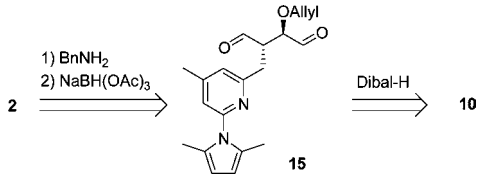
Scheme 3. Results of Mesylation of **11**



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

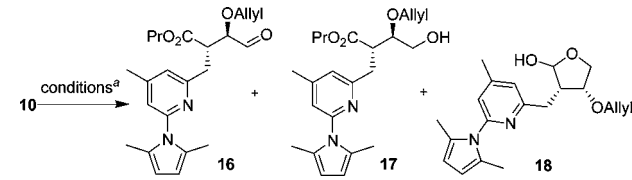
Scheme 4. Modified Retrosynthetic Analysis for **2** via Dialdehyde **15**



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

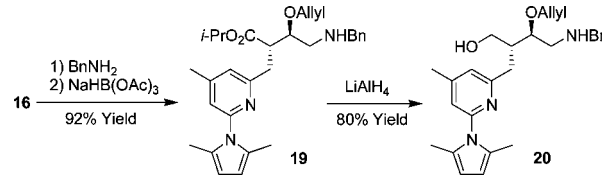
[a] General experimental conditions: 1 equiv of **10** was added Dibal-H at −78 °C. [b] Isolated yields.

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.

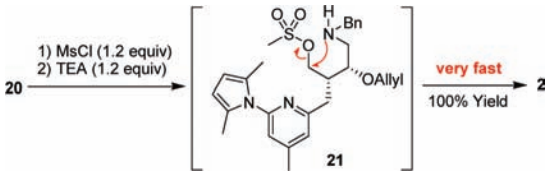
In summary, we developed an efficient and highly diastereoselective synthesis of the chiral pyrrolidine building block (**2**) for a novel nNOS inhibitor (**1**), employing as key steps a Frater−Seebach-type alkylation and a fast intramo-

(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.; Dëziel, 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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