

Intramolecular Mannich Reaction in the Asymmetric Synthesis of Polysubstituted Piperidines: Concise Synthesis of the Dendrobate Alkaloid (+)-241D and Its C-4 Epimer

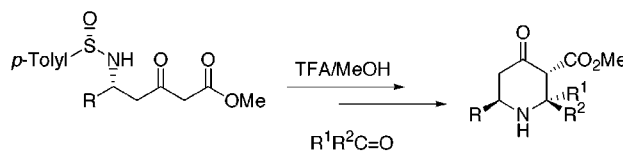
Franklin A. Davis,* Bin Chao, and Ashwin Rao

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

fdavis@astro.ocis.temple.edu

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ABSTRACT



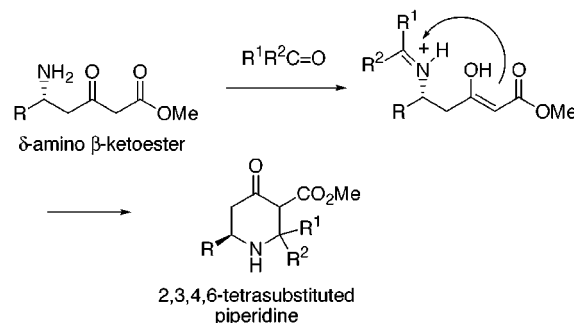
The intramolecular Mannich reaction of δ -amino β -keto esters with aldehydes and ketones is a new methodology for the synthesis of polysubstituted piperidines and is illustrated by the concise asymmetric synthesis of the dendrobate alkaloid (+)-241D and its C-4 epimer.

Monocyclic and bicyclic alkaloids containing substituted piperidines are widely distributed in nature and many exhibit significant biological properties. Accordingly, numerous methods have been developed for their asymmetric synthesis.¹ However, these procedures frequently require lengthy synthetic operations and extensive protection/deprotection chemistry. As part of a program aimed at devising new protocols that avoid these problems, we introduced *N*-sulfinyl δ -amino β -keto esters, a new polyfunctionalized chiral building block. These building blocks are prepared in one pot from sulfinimines (*N*-sulfinyl imines)² and were used in highly efficient asymmetric syntheses of the four stereoisomers of 4-hydroxypipicolinic acid,³ (*R*)-(+)-2-phenylpiperidine,⁴ (–)-SS20846A,⁴ and the quinolizidine alkaloid (–)-lasubine II.⁵ Because δ -amino β -keto esters exist in the enol

form at from 5 to 10%, we reasoned that if an iminium ion could be generated from an aldehyde or a ketone, an intramolecular Mannich reaction would give a 2,3,4,6-tetrasubstituted piperidine (Scheme 1).⁶ The results of that study are reported herein.

(*S,S,R*)-(+)-Methyl 3-oxo-5-phenyl-5-(*p*-toluenesulfinylamino)pentanoate (**1**)³ was prepared in one pot (89% yield, >97% de) from (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide and the sodium enolate of methyl acetate as previously

Scheme 1



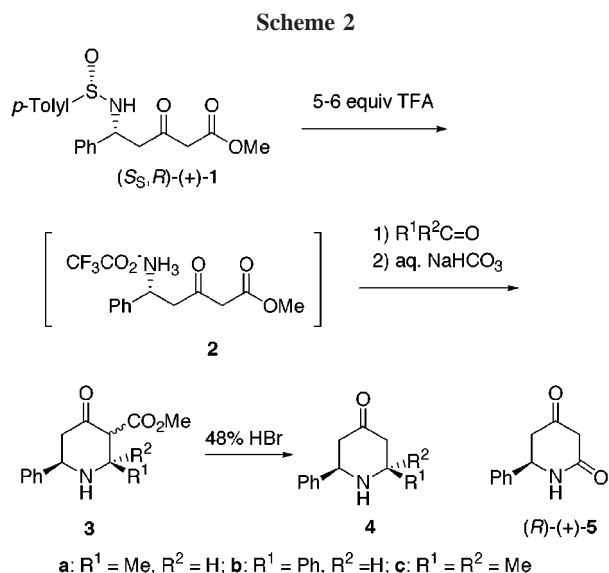
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(2) For reviews on the chemistry of sulfinimines, see: (a) Zhou, P. Chen, B.-C.; Davis, F. A. *Syntheses and Reactions of Sulfinimines*. In *Advances in Sulfur Chemistry*; Rayner, C. M., Ed.; JAI Press: Stamford, CT, 2000; Vol. 2, pp 249–282. (b) Hua, D. H.; Chen, Y.; Millward, G. S. *Sulfur Rep.* **1999**, *21*, 211. (c) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13.

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described³ and treated with 5–6 equiv of TFA in MeOH to remove the *N*-sulfinyl auxiliary (Scheme 2). The reaction



mixture was loaded on a short pad of silica gel and eluted with 30% EtOAc/hexanes to remove the sulfinyl byproducts and then with MeOH to give the crude triflate salt **2**. The salt **2**, in DCM, was treated with the appropriate aldehyde or ketone at room temperature. After 2–3 h, aqueous NaHCO₃ was added. The resulting polysubstituted piperidines **3** were isolated in 70–84% yield as mixtures of isomers (Table 1). With acetaldehyde and benzaldehyde, **2**

$J_{2,3}$ was 3.3–3.7 Hz, which is consistent with the *cis* orientation of the 2,6-substituents⁷ and which implies that the major isomers have the *trans* orientation of the H(2) and H(3) protons (*vide infra*). The assignment was further confirmed by NOE experiments. Piperidine **3c**, derived from acetone, was isolated as a 1:1 mixture of products.

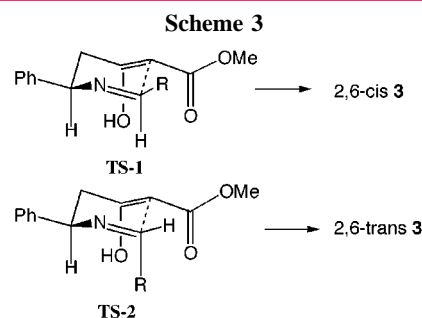
Decarboxylation of **3** to the 4-oxo-2,6-piperidines was accomplished by refluxing isomerically pure **3a** or the 95:5 mixture with 3 equiv of LiOH/MeOH for 9 h.⁸ 2-Methyl-6-phenyl-4-oxopiperidine (**4a**)^{6c} was obtained as a 9:1 mixture of *cis*:*trans* isomers (Table 1, entry 1). Acid-catalyzed decarboxylation gave a similar mixture of isomers (Table 1, entries 2 and 3), and purification by flash chromatography afforded (2*R*,6*R*)-(+)-**4a**.^{6c} Best results were obtained using 48% HBr/MeOH, affording (+)-**4a** in 76% isolated yield (Table 1, entry 3). While all attempts to decarboxylate **3b** under alkaline conditions failed, acidic hydrolysis with 6 N HCl gave (2*S*,6*R*)-2,6-diphenyl-4-oxopiperidine (**4b**)⁹ as a single isomer in 50% yield (Table 1, entry 5). Decarboxylation with 48% HBr/MeOH resulted in an improved yield of **4b** (62 vs 50%), but isomerization was noted (Table 1, entries 5 and 6). A base-induced retro-Mannich reaction furnished (R)-(+)-6-phenylpiperidine-2,4-dione (**5**)³ in 70% yield on refluxing (+)-**3c** with LiOH/MeOH (entry 7), and its success suggests that the epimerization of **3a,b** observed under the acid and base conditions occurs by a similar reaction mechanism. Decarboxylation of **3c** with 48% HBr gave the desired (R)-(+)-2,2-dimethyl-6-phenylpiperidin-4-one (**4c**)¹⁰ in 70% yield (entry 8). The nearly exclusive formation of the 2,6-*cis*-disubstituted piperidines **3** is consistent with transition state **TS-1** because A^{1,3} strain disfavors **TS-2** leading to the minor 2,6-*trans* isomer (Scheme 3).

Table 1. Syntheses of Piperidines **4** and **5**

entry	R ¹ , R ²	3 : % yield ^a (<i>cis</i> / <i>trans</i>)	4 : % yield (<i>cis</i> : <i>trans</i>) method
1	(3a) Me, H	80 (95:5)	61 (9:1), LiOH/MeOH
2			50 (85:15), 6 N HCl/MeOH
3			66 (94:6), 48% HBr/MeOH
4	(3b) Ph, H	84 (98:2)	no reaction, LiOH/MeOH
5			50 (99:1), 6 N HCl/MeOH
6			62 (94:6), 48% HBr/MeOH
7	(3c) Me, Me	70 (1:1)	70, (R)-(+)- 5 , LiOH/MeOH
8			70, 48% HBr/CHCl ₃

^a Isolated yield of pure isomer.

gave piperidines **3a** and **3b** in 80 and 84% yields, respectively. The $J_{2,3}$ and $J_{5,6}$ coupling constants for the major isomer were 10.3 and 12.1 Hz, respectively, suggesting a diaxial orientation for these protons. In the minor isomer



To illustrate the efficacy of our intramolecular Mannich protocol for the construction of substituted piperidines, the asymmetric synthesis of the dendrobate alkaloid (+)-241D and its C-4 epimer was undertaken.¹¹ Alkaloid (+)-241D was isolated from the skin extracts of dendrobate frogs and was shown to exhibit potent biological activity.¹² For example, its racemate inhibits binding of [³H]perhydrohistrionicotoxin

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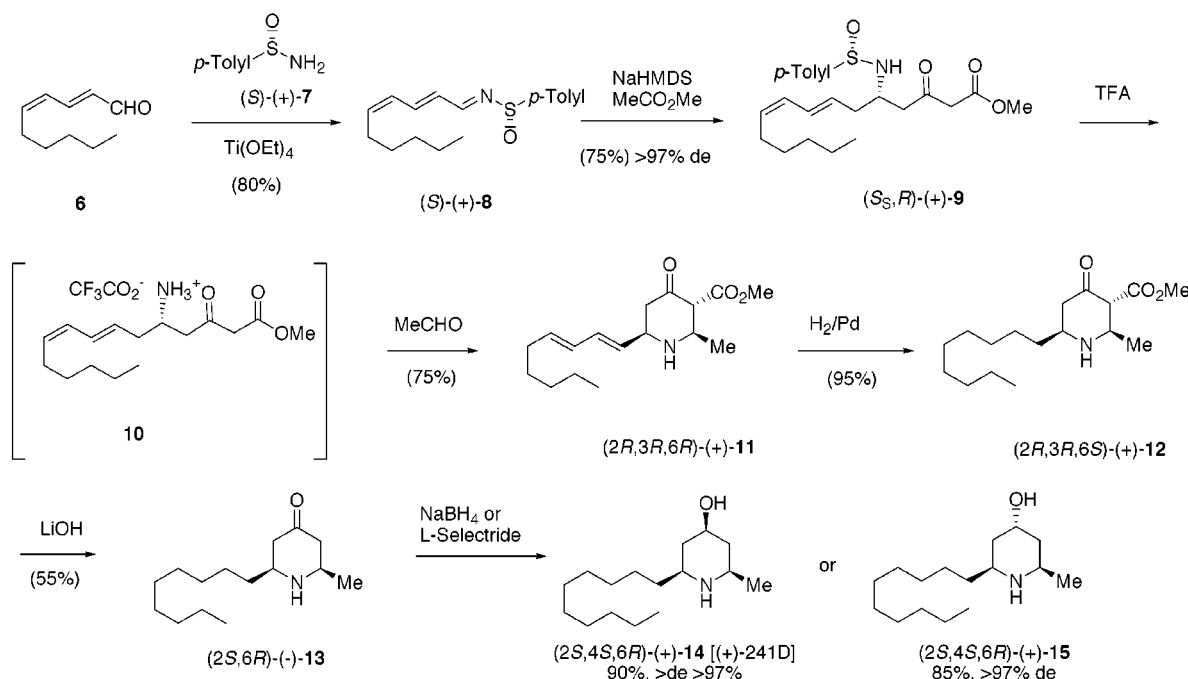
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Scheme 4



to nicotinic receptor channels of electroplax membranes and blocks the action of acetylcholine through noncompetitive blockage of the nicotinic receptor-channel complex.^{6d}

Our synthesis begins with the preparation of sulfinimine (*S*)-(+)-**8** from *trans,trans*-2,4-decadienal (**6**) and (*S*)-(+)-*p*-toluenesulfinamide (**7**), both of which are commercially available (Scheme 4). Because the aldehyde consists of 10–15% of other isomers, the sulfinimine **8** was similarly obtained as a mixture and was purified by flash chromatography, affording the product in 80% yield. While the presence of these isomers makes interpretation of the NMR spectra difficult, later studies revealed that in conversion of crude **6** to **8** these minor isomers are eliminated and it was more efficient to use crude (+)-**8**. Treatment of (+)-**8**, at $-78\text{ }^{\circ}\text{C}$, with 4 equiv of the sodium enolate of methyl acetate, monitoring for the disappearance of **8** by TLC, and warming to $-10\text{ }^{\circ}\text{C}$ afforded a 75% yield of δ -amino β -keto ester (*S_S,R*)-(+)-**9** in >97% de. Because of the complexity of the NMR, it was not possible to fully evaluate the diastereoselective purity of **9** prepared by this one-pot procedure. Consequently, the intermediate β -amino ester (not shown) was first prepared in >99% de (80% yield) by reacting the sodium enolate of methyl acetate with (+)-**8** and then converting it to (+)-**9** in 75% yield by reaction with an excess of the sodium enolate of methyl acetate (see Supporting Information section).

Once the δ -amino β -keto ester (*S_S,R*)-(+)-**9** was in hand, it was transformed into the triflate salt **10** by treatment with TFA/MeOH for 1 h at room temperature, loaded onto a short pad of silica gel, and eluted consecutively with 30% EtOAc/

hexanes and MeOH. After removal of the MeOH solvent, the residue was dissolved in DCM and 1 equiv of acetaldehyde was added which afforded 4-oxypiperidine (2*R*,3*R*,6*R*)-(+)-**11** as a single isomer after 1 h (Scheme 4). Hydrogenation (H_2/Pd) removed the double bonds, and decarboxylation by refluxing with 2 equiv of LiOH/MeOH gave 4-oxopiperidine (–)-**13** in 55% yield. While starting our synthesis from decyl aldehyde would have saved the hydrogenation step, earlier studies had shown that sulfinimines derived from aliphatic aldehydes gave β -amino acids with lower diastereoselectivities than those prepared from unsaturated examples.¹³ Reduction of the (–)-**13** with NaBH_4 and L-Selectride afforded (+)-241D (**14**) and its C-4 epimer (+)-**15** in 90 and 85% yields, respectively. The stereoselectivity of the reductions was >97% de in both examples. Similar results were reported by Canet, Troin, and co-workers.^{6a} Spectroscopic properties of (+)-**14** and (+)-**15** were in agreement with literature values.¹¹

In summary, general methodology is reported for the asymmetric synthesis of polysubstituted piperidines employing an intramolecular Mannich reaction of δ -amino β -keto esters with aldehydes and ketones. Decarboxylation affords 2,6-disubstituted 4-oxopiperidines, important chiral building blocks for piperidine alkaloid synthesis.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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