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

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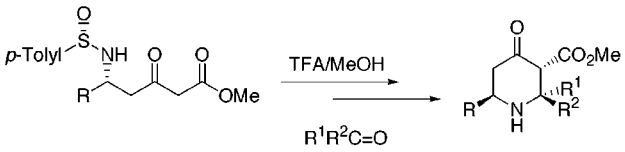
ABSTRACT

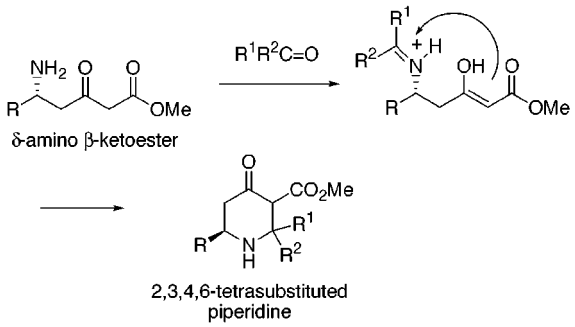


The intramolecular Mannich reaction of δ-amino β-keto esters with aldehydes and ketones is a new methodology for the synthesis of polysubstituted piperidines and is illustrated by the concise asymmetric synthesis of the dendrobate alkaloid (+)-241D and its C-4 epimer.

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-hydroxypipecolic 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



(1) For a review on the asymmetric synthesis of piperidines, see: Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781.

(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.

(3) Davis, F. A.; Fang, T.; Chao, B.; Burns, D. M. *Synthesis* **2000**, 2106.

(4) Davis, F. A.; Chao, B.; Fang, T.; Szewczyk, J. M. *Org. Lett.* **2000**, *2*, 1041.

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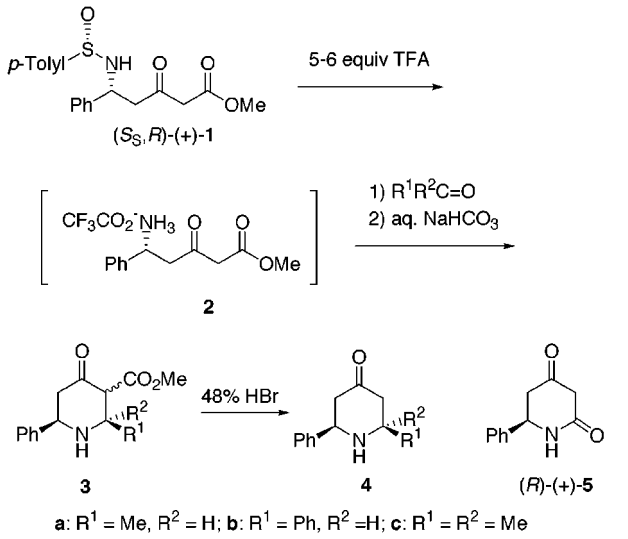
described[3] and treated with 5−6 equiv of TFA in MeOH to remove the *N*-sulfinyl auxiliary (Scheme 2). The reaction

Scheme 2



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 $NaHCO_3$ was added. The resulting polysubstituted piperidines **3** were isolated in 70−84% yield as mixtures of isomers (Table 1). With acetaldehyde and benzaldehyde, **2**

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

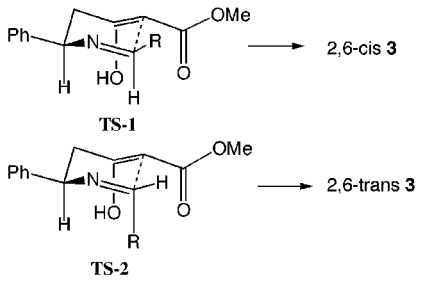
entry	R^1, R^2	**3**: % yield[a] (cis/trans)	**4**: % yield (cis:trans) method
1	(**3a**) Me, H	80 (95:5)	61 (9:1), LiOH/MeOH
2			50 (85:15), 6 N HCl/MeOH
3			66 (94:6), 48% HBr/MeOH
4	(**3b**) Ph, H	84 (98:2)	no reaction, LiOH/MeOH
5			50 (99:1), 6 N HCl/MeOH
6			62 (94:6), 48% HBr/MeOH
7	(**3c**) Me, 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 $J_{2,3}$ was 3.3−3.7 Hz, which is consistent with the cis orientation of the 2,6-substituents[7] 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).

Scheme 3



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 [^{3}H]perhydrohistrionicotoxin

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(6) For recent applications of the Mannich reaction in the synthesis of piperidines, see: (a) Ciblat, S.; Calinaud, P.; Canet, J.-L.; Troin, Y. *J. Chem. Soc.,, Perkin Trans. 1* **2000**, 353. (b) Glasson, S. R.; Canet, J.-L.; Troin, Y. *Tetrahedron Lett.* **2000**, *41*, 9797. (c) Ciblat, S.; Besse, P.; Canet, J.-L.; Troin, Y.; Veschambre, H.; Gelas, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2225. (d) Edwards, M. W.; Garraffo, H. M.; Daly, J. W. *Synthesis* **1994**, 1167.

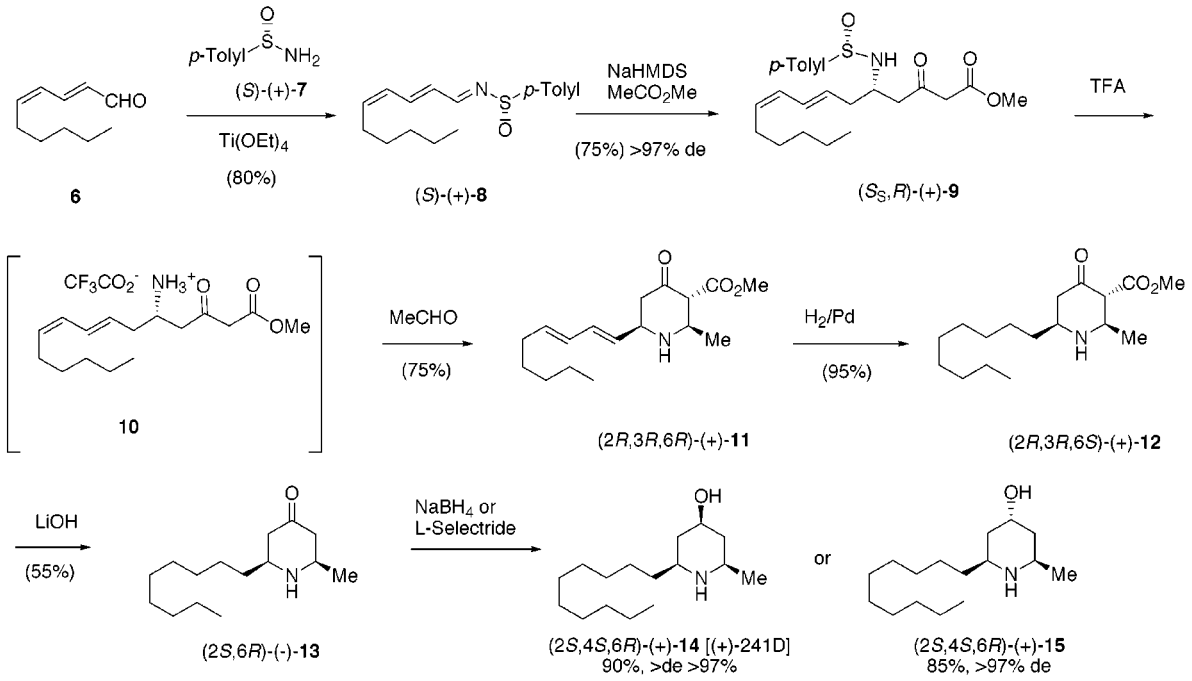
(7) Rubiralta, M. Giralt, E.; Diez, A. *Piperidine*; Elsevier: New York, 1991; Chapter 3.

(8) For a review on decarboxylation, see: Krapcho, A. P. *Synthesis* **1982**, 893.

(9) Ravindran, T.; Jeyaraman, R. *J. Org. Chem.* **1991**, *56*, 4833.

(10) Balasubramanian, M.; Padma, N. *Tetrahedron* **1963**, *19*, *2135.*

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 °C, with 4 equiv of the sodium enolate of methyl acetate, monitoring for the disappearance of **8** by TLC, and warming to −10 °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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(11) For earlier asymmetric syntheses of (+)-241D, see: (a) Ma, D.; Sun, H. *Org. Lett.* **2000**, *2*, 2503. (b) Chenevert, R.; Dickman, M. *J. Org. Chem.* **1996**, *61*, 3332. (c) Reference 6a.

(12) Edwards, M. W.; Daly, J. W. *J. Nat Prod.* **1988**, *51*, 1188.

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