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A Simple and Stereospecfic Route to 2,6-Disubstituted 4-Hydroxypiperidines. Synthesis of Dendrobate Alkaloid (+)-241D and Formal Synthesis of (−)-Indolizidine 167B

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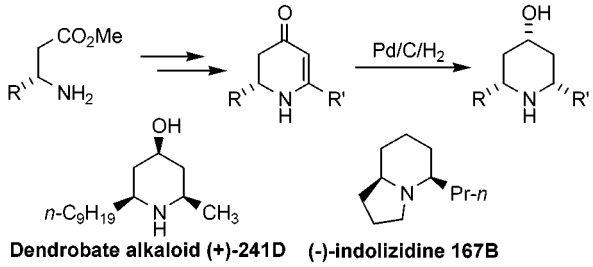
ABSTRACT



Dendrobate alkaloid (+)-241D **(-)-indolizidine 167B**

The condensation of enantiopure β-amino esters with β-ketoesters followed by cyclization and decarboxylation afforded 2,3-dihydro-4-pyridones 3, which were selectively hydrogenated to provide 2,6-disubstituted 4-hydroxypiperdines.

2,6-Disubstituted 4-hydroxypiperidine and 2,6-disubstituted 4-oxopiperidine ring systems are found embedded within the frameworks of many biologically active natural products such as lasubine II,[1] lyfoline,[2] myrtine,[3] and dendrobate alkaloid (+)-241D[4] (Figure 1). In addition, they also serve as the key intermediates in the synthesis of other alkaloids such as 2,6-disubstituted piperidines and indolizidines.[5,6] Several methods for asymmetrically synthesizing this class of compounds have appeared, which include Comins's 2,3-dihydro-4-pyridone methodology,[5b] Kunz's Mannich−Michael reaction strategy,[7] and Chenevert's enzymatic route.[4c] In connection with our studies on the synthesis from enantiopure β-amino esters,[8] we have reported a method for diastereoselective synthesis

(1) Isolation: Fuji, K.; Yamada, T.; Fujita, E.; Murata, H. *Chem. Pharm. Bull.* **1978**, *26*, 2515. Synthesis: Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445 and references therein.

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(3) Isolation: Slosse, P.; Hootele, C. *Tetrahedron Lett.* **1978**, 397. Synthesis: Gelas-Mialhe, Y.; Gramain, J. C.; Louver, A.; Remuson, R. *Tetrahedron Lett.* **1992**, *33*, 73.

(4) Isolation: (a) Edwards, M. W.; Daly, J. W.; Mters, C. W. *J. Nat. Prod.* **1988**, *51*, 1188. Synthesis: (b) Edwards, M. W.; Garraffo, M.; Daly, J. W. *Synthesis* **1994**, 1167. (c) Chenevert, R.; Dickman, M. *J. Org. Chem.* **1996**, *61*, 3332. (d) Ciblat S.; Calinaud, P.; Canet, J.-L.; Troin, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 353.

(5) For review, see (a) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 675. (b) Comins, D. L.; Joseph, S. P.; Hong, H.; Al-awer, R. S.; Foti, C. J.; Zhang, Y.; Chen. X.; Lamunyon, D. H.; Guerra-Weltzien, M. *Pure Appl. Chem.* **1997**, *69*, 477. (c) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 619.

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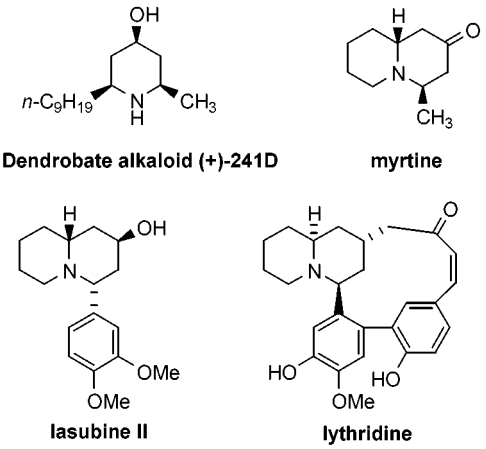
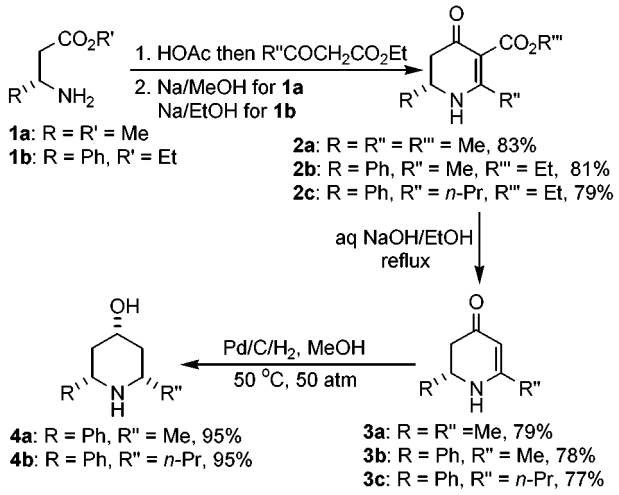


Figure 1. Structures of alkaloids possessing 2,4,6-trisubstituted piperidine moiety.

of 2,4,5-trisubstituted piperidines.[8b] Herein we wish to describe a simple and efficient method for preparing 2,6-disubstituted 4-hydroxypiperidines and its application to the synthesis of dendrobate alkaloid (+)-241D and (−)-indolizidine 167B.[7,9,10]

As outlined in Scheme 1, our approach to 2,6-disubstituted 4-hydroxypiperidines started from enantiopure β-amino esters

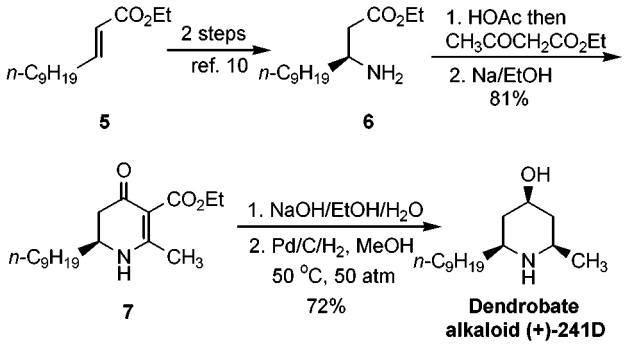
Scheme 1



1, which were conveniently prepared on large scales according to Davies' procedure.[11] After **1a** and **1b** were condensed with β-ketoesters, the vinylogous urethanes generated were treated with sodium methoxide or sodium ethoxide to afford cyclization products **2**.[12] Removal of the ester moiety in **2** by refluxing these β-ketoesters in a mixture of ethanol and aqueous NaOH (1/1) provided 2,3-dihydropyridones **3** in high yields. Reduction of **3** was obtained with $NaBH_4$ or hydrogenation catalyzed by Pd/C under ordinary pressure in order to reduce both the C−C double bond and the C−O double bond. Under these conditions it was found that the reaction either did not occur or gave a complicated mixture. After some experimentation, we found that under 50 atm at 50 °C the hydrogenation of **3b** or **3c** provided **4a** or **4b** as a single product. Thus, we have established a simple method to obtain enantiopure 2,6-disubstituted 4-hydroxypiperidines. The overall yields for these four steps were over 55%.

To assign the stereochemistry of two new stereogenic centers, we undertook the total synthesis of dendrobate alkaloid (+)-241D using the present strategy. As shown in Scheme 2, β-amino ester **6**, obtained from ethyl 2*E*-

Scheme 2



dodecenoate **5** by a known procedure, was condensed with ethyl acetoacetate and then treated with sodium ethoxide to afford the cyclic product **7**. After removal of the ester moiety of **7**, the generated 2,3-dihydropyridone was hydrogenated to provide the target molecule.[13] Its spectral data were all identical with those reported. In addition, by converting this product to the corresponding Mosher ester, we determined its enantiopurity to be greater than 97%. This synthetic result indicated that the three substituents in this piperidine are all cis to each other. Therefore, we could conclude that during the hydrogenation the active species attack the two double bonds exclusively from the back face of 2-alkyl or aryl group of enones **3**. It is notable that the present synthetic route only involves six workup steps to give dendrobate alkaloid (+)-241D in 46% overall yield and is much more efficient than those reported by Chenevert,[4c] Troin[4d] and their coworkers.

(9) Isolation: Aronstam, R. S.; Daly, S. W.; Spande, T. F.; Narayanan, T. K.; Albuquerque, E. X. *Neurochem. Res.* **1986**, *11*, 1227.

(10) Synthesis: (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (b) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513. (c) Takahata, H.; Bandoh, H.; Momose, T. *Heterocycles* **1995**, *41*, 1797. (d) Lee, E.; Li, K. S.; Lim, J. *Tetrahedron Lett.* **1996**, *37*, 1445. (e) Michael, J. P.; Gravestock, D. *Eur. J. Org. Chem.* **1998**, 865. (f) Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1997**, *62*, 8549.

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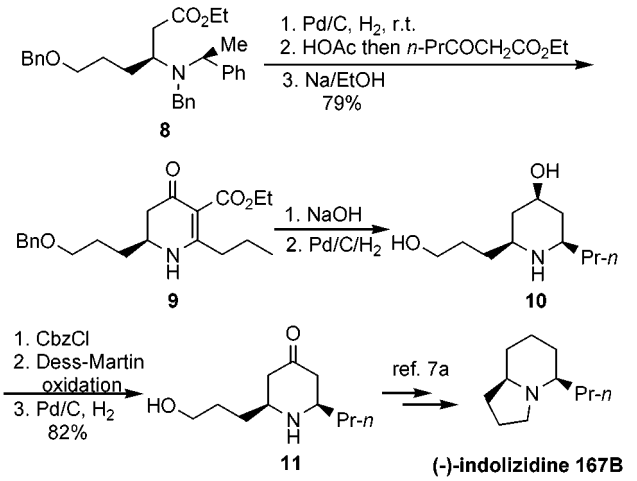
(12) (a) Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis* **1983**, 902. (b) Backer, H. G. O. *J. Prakt. Chem.* **1961**,*12*, 294.

(13) Selected data: $[\alpha]^{25}_D$ +7.2 (*c* 2.0, MeOH) (lit.[4c] $[\alpha]^{25}_D$ +6.5 (*c* 2.0, MeOH); IR (neat) 3271, 3182, 2962, 2921, 2852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (m, 1H), 2.70 (m, 1H), 2.55 (m, 1H), 1.98 (m, 2H), 1.41 (m, 2H), 1.27 (m, 14H), 1.15 (d, J = 6.2 Hz, 3H), 1.02 (m, 2H), 0.89 (t, J = 7.0 Hz, 3H); EIMS *m*/*z* 241 (M^+).

To demonstrate the ability of the present method for synthesis of indolizidine alkaloids, we report the formal synthesis of (−)-indolizidine 167B as outlined in Scheme 3. After the deprotection of β-amino ester **8**[8c] using Pd/C-catalyzed hydrogenation, the generated ester was transformed into diol **10** following the procedure given above. After selective protection of the amine moiety and the primary alcohol of **10** with benzyl chloroformate, the secondary alcohol was converted into the corresponding ketone by Dess−Martin oxidation. Hydrogenation of this ketone to remove the Cbz protecting group provided **11**, which could be transformed into the (−)-indolizidine 167B by known procedure.[7a] Its spectral data were same with those reported.[14]

Scheme 3



In summary, we have developed a method for synthesizing 2,6-disubstituted 4-hydroxypiperidines from enantiopure β-amino esters in four workup steps. Considering its simplicity and that both enantiopure β-amino esters and β-ketoesters are conveniently available, this method should be valuable for preparing enantiopure polysubstituted piperidines as well as some related alkaloids. The further application of this method to the synthesis of other alkaloids is being pursued in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Selected data for **11**: $[\alpha]^{25}_{D}$ −10.2 (*c* 1.5, $CHCl_3$); IR (neat) 3289, 2959, 2930, 1712 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 3.62 (m, 2H), 3.10 (br s, 1H), 2.85 (m, 2H), 2.42 (m, 2H), 2.12 (m, 2H), 1.62 (m, 8H), 0.95 (t, J = 7.2 Hz, 3H); EIMS *m*/*z* 200 ($M^+ + H^+$).