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Synthesis of 2,4,6-Trisubstituted Chiral Piperidines and (−)-Dendroprimine by One-Pot Asymmetric Azaelectrocyclization Protocol

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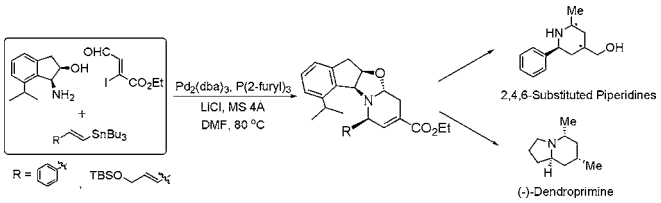
ABSTRACT



Stereocontrolled synthesis of 2,4,6-trisubstituted piperidine diastereomers has been realized from common intermediates, obtained by a one-pot azaelectrocyclization protocol. Based on the method, the asymmetric synthesis of an indolizidine alkaloid, (−)-dendroprimine, was achieved.

The substituted piperidines can be regarded as the core structure of many naturally occurring alkaloids, including indol alkaloids. Furthermore, these functionalized six-member nitrogen heterocycles have drawn a great deal of attention due to their attractive pharmacological activities. Thus, the stereocontrolled synthesis of piperidines with various substitution patterns is a current topic for many synthetic chemists.[1] When enantiomerically pure piperidines are easily accessible, which results from the successful introduction of the desired alkyl substituents at the desired positions of the piperidine rings, a novel synthetic strategy for various alkaloids based on the substituted piperidine core synthesis will be envisioned.[2]

In the preceding paper, we reported a unique one-pot asymmetric 6π-azaelectrocyclization, which led to the facile and stereoselective preparation of chiral tetracyclic 2,4-disubstituted 1,2,5,6-tetrahydropyridine intermediates (**A** in Figure 1). In pursuing further the possibility of our one-pot procedure for natural products synthesis,[3,4] here we report the stereoselective synthesis of chiral 2,4,6-trisubstituted piperidines (Figure 1). Moreover, the method was applied to the synthesis of an indolizidine alkaloid, (−)-den-

(1) (a) Amat, M.; Bosch, J.; Hidalgo, J.; Canto, M.; Perez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074. (b) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679. (c) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004. (d) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919. (e) A review of piperidine synthesis was recently reported: Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (f) Poupon, E.; Francois, D.; Kunesch, N.; Husson, H.-P. *J. Org. Chem.* **2004**, *69*, 3836. (g) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, P. A. *J. Org. Chem.* **2005**, *70*, 207. (h) Monfray, J.; Gelas-Mialhe, Y.; Gramain, J.-C.; Remuson, R. *Tetrahedron: Asymmetry* **2005**, *16*, 1025. (i) Dobbs, A. P.; Guesne, S. J. *Synlett* **2005**, *18*, 2101. (j) Passarella, D.; Barilli, A.; Belinghieri, F.; Fassi, P.; Riva, S.; Sacchetti, A.; Silvani, A.; Danieli, B. *Tetrahedron: Asymmetry* **2005**, *16*, 2225. (k) Gebauer, J.; Blechert, S. *Synlett* **2005**, *18*, 2826. (l) Wung, R. P.; Fu, G. C. S. *J. Am. Chem. Soc*. **2005**, *127*, 12234. (m) Sales, M.; Charette, A. B. *Org. Lett*. **2005**, *7*, 5773.

(2) For example: (a) Hirai, Y.; Terada, T.; Okaji, Y.; Yamazaki, T.; Momose, T. *Tetrahedron Lett*. **1990**, *33*, 4775. (b) Amat, M.; Perez, M.; Llor, N.; Escolano, C.; Luque, F. F.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681.

(3) (a) Tanaka, K.; Katsumura, S. *J. Am. Chem. Soc.* **2002**, *124*, 9660. (b) Tanaka, K.; Kobayashi, T.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 5906. (c) Kobayashi, T.; Nakashima, M.; Hakogi, T.; Tanaka, K.; Katsumura, S. *Org. Lett.* **2006**, *8*, 3809.

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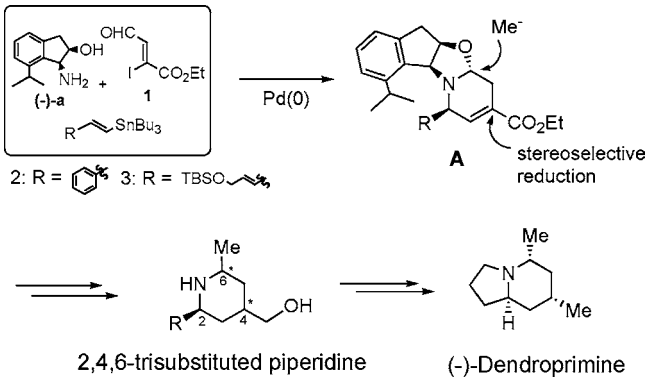
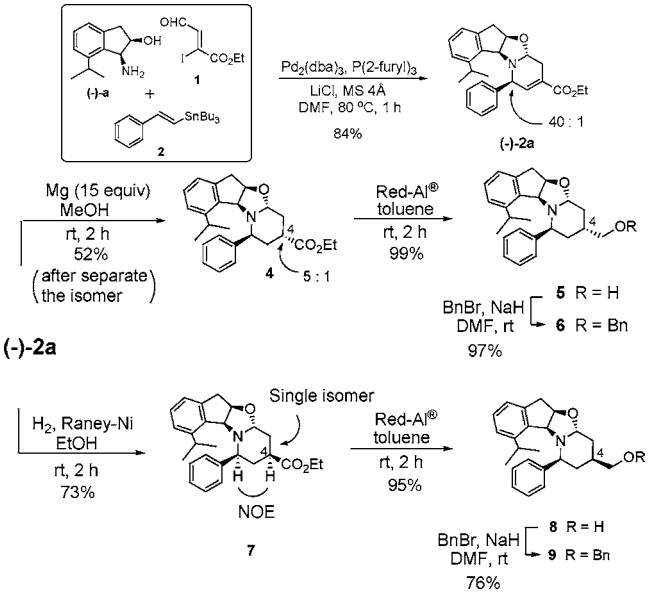


Figure 1. Synthetic strategy for chiral 2,4,6-trisubstituted piperidines and (−)-dendroprimie by one-pot azaelectrocyclization.

droprimine,[5] a simple but challenging molecule for the stereoselective construction of three stereogenic centers on a small piperidine skeleton.

To realize a 2,4,6-trisubstituted piperidine synthesis, we first attempted the stereoselective reduction of the conjugated C=C double bond in common intermediate **A**, which can be readily prepared by the one-pot azaelectrocyclization protocol (Figure 1). The optimization of the conditions was performed using (−)-**2a**, obtained from amine (−)-**a**, iodide **1**, and stannane **2** in 84% yield with 40:1 stereoselectivity (Scheme 1).

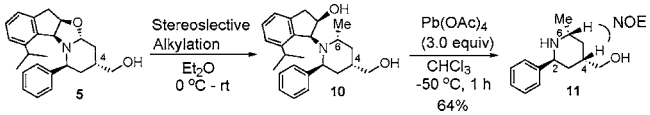
Scheme 1. Stereoselective Reduction of Conjugated Ester



When (−)-**2a** was treated with magnesium in methanol, C-4 α-isomer **4** was stereoselectively produced at a ratio of 5:1.[6] On the other hand, the catalytic hydrogenation of (−)-**2a** with Raney nickel provided single C-4 β-ester **7**, a stereoisomer obtained by a metal-dissolving reduction. Therefore, the two diastereomeric piperidines, **4** and **7**, were easily accessible by choosing the reducing reagent.

Methylation was then attempted on the aminoacetal moiety of hydroxymethyl derivative **5** and the corresponding benzyl derivatives **6** and **9**, which were prepared, respectively, from piperidines **4** and **7**, as shown in Scheme 1. After several trials on C-4 α-hydroxymethyl derivative **5** (Table 1), C-6

Table 1. Stereoselective Synthesis of (2β,4α,6α)-Trisubstituted Piperidine



entry	alkylating agent	yield	α/β[c] (C-6 position)
1	MeLi (excess)		
2	MeLi (excess), BF_3-Et_2O (3 equiv)		
3	MeLi (excess), $MgBr_2$ (3 equiv)		
4	MeMgI (25 equiv)	58%[a]	40:1
5	MeMgI (20 equiv), CuI (20 equiv)	81%[a]	50:1
6	Me_3Al[d] (15 equiv)	88%[b]	2:1
7	Me_2Zn[e] (15 equiv)		

[a] Isolated yields of α-isomer. [b] Yield for mixture of isomers. [c] Determined by ^1H NMR analysis of crude mixtures. [d] Reaction was carried out in toluene. [e] Reaction was performed in DMF.

α-methyl derivative **10** was exclusively obtained in 81% yield when **5** was treated with methylmagnesium iodide (20 equiv) and CuI (20 equiv) in ether[7] (Table 1, entry 5). The high stereoselectivity of methylation on **5** can be explained by assuming that the coordination of the Grignard reagent with the C-4 hydroxymethyl group of the intermediary iminium ion was generated during the alkylation process. Then the removal of the hydroxy indane moiety of methylated compound **10** was achieved by treatment with lead tetraacetate at −50 °C in chloroform to produce (2β,4α,6α)-

(4) Concurrent with our work, Hsung et al. have also succeeded in the highly stereoselective asymmetric azaelectrocyclization of conformationally restricted 1-azatrienes under thermodynamically equilibrated conditions. They also applied this reaction toward alkaloid synthesis, see: (a) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509. (b) Sklenicka, H. M.; Hsung, R. P.; Wei, L.-L.; McLaughlin, M. J.; Gerasyuto, A. I.; Degen, S. J. *Org. Lett.* **2000**, *2*, 1161. (c) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.-L.; Gerasyuto, A. I.; Brennessel, W. B. *J. Am. Chem. Soc.* **2002**, *124*, 10435. (d) McLaughlin, M. J.; Hsung, R. P.; Cole, K. P.; Hahn, J. M.; Wang, J. *Org. Lett.* **2002**, *4*, 2017. (e) Luo, S.; Zificsak, C. A.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709. (f) Sydorenko, N.; Hsung, R. P.; Darwish, O. S.; Hahn, J. M.; Liu, J. *J. Org. Chem.* **2004**, *69*, 6732.

(5) (a) Luning, B.; Leander, K. *Acta Chem. Scand.* **1965**, *19*, 1607. (b) Luning, B.; Lundin, C. *Acta Chem. Scand.* **1967**, *21*, 2136. (c) Blomquist, L.; Leander, K.; Luning, B.; Rosenblom, J. *Acta Chem. Scand.* **1972**, *26*, 3203.

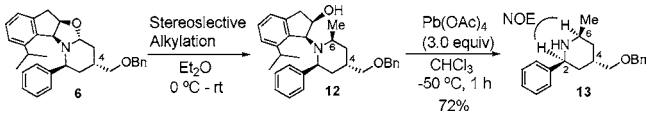
(6) In this reaction, the β-isomer was converted into the corresponding methyl ester.

(7) Reduction and alkylation of aminoacetal, see: (a) Yamato, M.; Hashigaki, K.; Ishikawa, S.; Qais, N. *Tetrahedron Lett.* **1988**, *29*, 6949. (b) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron Lett.* **1992**, *33*, 235. (c) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083. (d) Higashiyama, K.; Nakahata, K.; Takahashi, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 351. (e) Higashiyama, K.; Kyo, H.; Takahashi, H. *Synlett* **1998**, 489. (f) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

trisubstituted piperidine **11**, of which relative configurations were determined based on NOE.

On the other hand, the methylation of the corresponding benzylated compound **6** proceeded from the opposite site of the C-4 benzyloxymethyl group of piperidine (Table 2).

Table 2. Stereoselective Synthesis of (2β,4α,6β)-Trisubstituted Piperidine



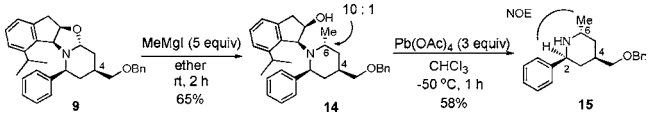
entry	alkylating agent	yield[a]	α/β[b] (C-6 position)
1	MeLi (excess)		
2	MeMgI (3 equiv)	84%	1:3
3	MeMgI (3 equiv), CuI (3 equiv)	79%	1:2
4	Me_3Al (5 equiv)	82%	1:5

[a] Yield for mixture of isomers. [b] Determined by ^{1}H NMR analysis of the crude mixtures.

Although no methylated product could be detected by reaction with MeLi (Table 2, entry 1), treatment with MeMgI selectively provided C-6 β-methyl isomer **12** in a ratio of 3:1 (Table 2, entry 2). The CuI additive did not increase stereoselectivity (Table 2, entry 3). Similarly, the treatment of **6** with Me_3Al in ether provided the same isomer **12** with the highest selectivity of 5:1 (Table 2, entry 4). Apparently, the steric factor of the benzyl protecting group overrides the coordination of alkylation. For the synthesis of 2,4,6-trisubstituted piperidine, the hydroxy indane moiety of **12** was removed by lead tetraacetate to provide (2β,4α,6β)-diastereomer **13** in 72% yield.

Additionally, the reaction of C-4 β-benzyloxymethyl derivative **9** with MeMgI stereoselectively provided C-6 α-methyl isomer **14** in a ratio of 10:1 (Scheme 2), in

Scheme 2. Stereoselective Synthesis of (2β,4β,6α)-Trisubstitiuted Piperidine

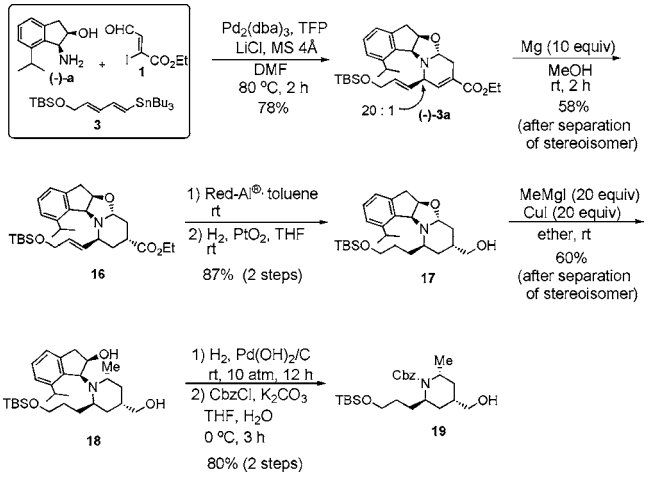


accordance with the same reasons in the case of **6** (Table 2). A (2β,4β,6α)-piperidine isomer **15** was also obtained by oxidative treatment of **14** with lead acetate in 58% yield.

After being established as an efficient route to three diastereomeric 2,4,6-trisubstituted piperidines, a synthetically unique route to (−)-dendroprimine has now been envisioned (Schemes 3 and 4).[5,8]

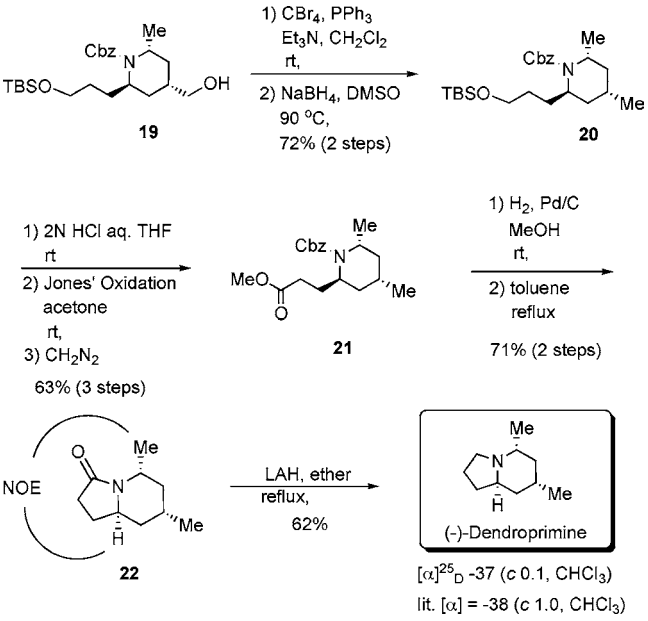
Based on the one-pot electrocyclization protocol, three components, vinyl iodide **1**, linear vinylstannane **3**, and aminoindanol (−)-**a** were mixed in DMF and heated to 80

Scheme 3. Stereoselective Synthesis of 2,4,6-Substituted Piperidine **19** via One-Pot Azaelectrocyclization toward (−)-Dendroprimine



°C in the presence of a $Pd_2(dba)_3$/TFP catalyst (Scheme 3). As expected, the desired tetracyclic piperidine (−)-**3a** was produced in 78% yield with a 20:1 selectivity at the C-2 position of the piperidine.

Scheme 4. Synthesis of (−)-Dendroprimine



Following the procedure established in Scheme 1, the dissolving metal reduction of the conjugated ester in (−)-**3a** selectively provided C-4 α-isomer **16** at a ratio of 4:1. The relative stereochemistry of major isomer **16** was unambiguously determined using X-ray crystallographic analysis

(8) (a) Diederich, M.; Nubbemeyer, U. *Synthesis* **1999**, *2*, 286. (b) Hsu, R.-T.; Cheng, L.-M.; Chang, N.-C.; Tai, H.-M. *J. Org. Chem.* **2002**, *67*, 5044. (c) Bollena, A. D. S.; Gelas-Mialhe, Y.; Gramain, J.-C.; Perret, A.; Remuson, R. *J. Nat. Prod.* **2004**, *67*, 1029.

(Figure 2). Reduction of the ester group with Red-Al, followed by catalytic hydrogenation using PtO_2, provided primary alcohol **17** in 87% yield for the two steps.

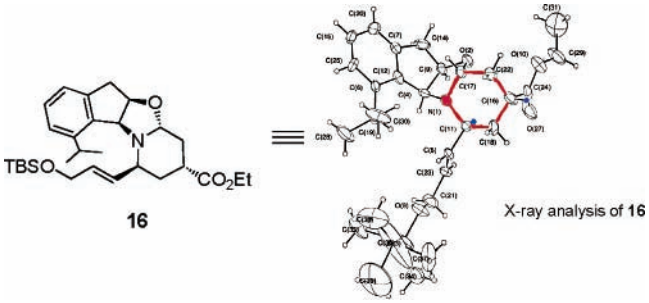


Figure 2. OPTEP diagram of compound **16** obtained by X-ray analysis.

Unexpectedly, MeMgI and CuI treatment on aminoacetal **17** under the established conditions in Table 1 gave rise to a 3:1 mixture of diastereomers at the C-6 position. Obviously, the steric size of the substituents at the 2-position of the piperidine ring influenced the stereoselectivity of the methylation (compare **5** and **17** in Table 1 and Scheme 3). The removal of the hydroxy indane moiety in **18** was achieved by catalytic hydrogenation in the presence of palladium hydroxide, and the resulting piperidine nitrogen was protected as Cbz in 80% yield for two steps.

From **19**, the synthesis of (−)-dendroprimine was realized by the sequences of reactions shown in Scheme 4. Thus, the hydroxymethyl group of **19** was converted into the methyl group in 72% yield by treatment with CBr_4/PPh_3, followed by the $NaBH_4$ reduction in DMSO.[9] The terminal TBS ether group was converted into methyl ester by a sequence of TBS deprotection, Jones oxidation, and methylation.[10] The deprotection of Cbz, followed by heating the resulting amine solution in toluene, caused smooth cyclization that led to the corresponding lactame derivative **22**.[11] Finally, the reduction of the lactam amide group of **22** by $LiAlH_4$ under ether reflux conditions provided (−)-dendroprimine. The spectral data (^1H and ^{13}C NMR) were in good agreement with those published in the literature.[5,8c]

In summary, we achieved chiral 2,4,6-trisubstituted piperidine synthesis using a unique one-pot procedure of highly stereoselective asymmetric azaelectrocyclization. The method was applied to the synthesis of a natural indolidizine alkaloid, (−)-dendroprimine. Although generality in the stereoselective substitution on the piperidines still remains to be improved, such as on **17**, our one-pot asymmetric 6π-azaelectrocyclization can be regarded as a powerful strategy for alkaloid synthesis, that is, polysubstituted chiral piperidine synthesis. Further applications are currently in progress in our laboratory.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Hutchins, R. O.; Kandasamy, D.; Dux, F., III; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259.

(10) First, under several conditions we attempted direct cyclization from the corresponding bromide or tosylate derived from **20** by removing a TBS group, bromination or tosylation, and deprotection of Cbz, but we could not obtain a (−)-dendroprime.

(11) Herradon, B.; Sanchez-Sancho, F. *Tetrahedron: Asymmetry*, **1998**, *9*, 1951.