Synthesis of Polyamine Alkaloids by the Condensation of a Chiral β-Lactam with a Cyclic Imino Ether. (*S*)-Dihydroperiphylline and Its Derivatives

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(Received July 6, 2000; CL-000644)

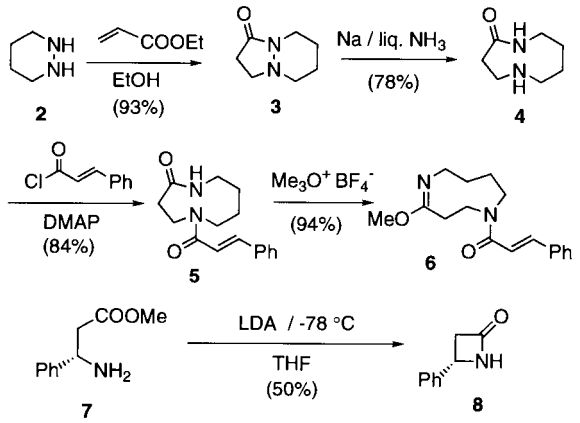
The synthesis of 13-membered polyamine alkaloid, (*S*)-dihydroperiphylline, was achieved by the condensation of a chiral β-lactam, (*S*)-4-phenyl-2-azetidinone, with a cyclic imino ether of a 9-membered lactam, followed by reductive ring expansion. Both of these reactions proceeded with retention of configuration around the chiral center to give the optical pure 13-membered alkaloids.

Macrocyclic lactams containing a biogenetic base such as spermine and spermidine represent a new class of polyamine alkaloids which have a framework of β-amino acid and are of particular interest as synthetic targets in view of the broad biological activity, for instance as antibiotics and antihypertensives.[1]

(*S*)-Dihydroperiphylline (**1**) is one of six alkaloids isolated from the leaves of *Peripterygia marginata* by Husson et al.[2] All these alkaloids contain a 13-membered ring system derived from dicinnamoylspermidine. The total synthesis of (±)-**1** was first accomplished by Wasserman and Matsuyama in 1981.[3] More recently, the enantioselective route to **1** from *N*-Boc-(*S*)-β-phenyl-β-alanine, prepared from diethyl L-tartrate in 15 steps, was reported by Kaseda et al.[4] Yamamoto et al. reported the synthesis of (*S*)-**1** by the lactam cyclization reaction of a triamine derivative of (*S*)-(–)-β-amino acid using an aminoborane reagent.[5]

Asymmetric synthesis of β-amino acid derivatives using chiral vinyl sulfoxides has proven to be useful methodology for the synthesis of chiral compounds.[6] Davis et al. reported the enantioselective synthesis of β-amino acids by addition of an enolate to chiral sulfinimines.[7] We recently reported the conjugate addition reaction of 6- and 5-membered cyclic hydrazines such as piperidazine (**2**) and pyrazolidine to chiral vinyl sulfoxides and synthesized the chiral 9- and 8-membered lactams with high optical purity (up to 95% ee). The asymmetric syntheses of a 13-membered lactam alkaloid, celacinnine, and an 8-membered lactam alkaloid, homaline, were accomplished by this method.[8,9]

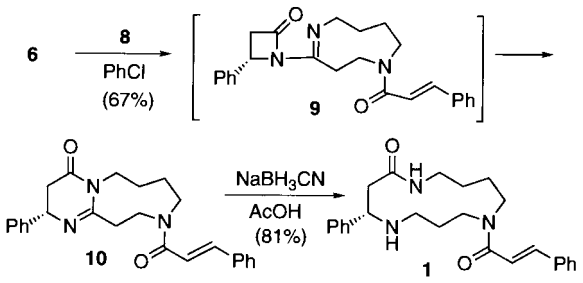
The present study provides a facile route to the synthesis of 13-membered alkaloid, (*S*)-dihydroperiphylline (**1**), starting from (*S*)-4-phenyl-2-azetidinone (**8**). A total synthesis of **1** involves a six-step sequence by successive ring expansions of smaller heterocyclic units. Our procedure (Schemes 1 and 2) permits clear-cut differentiation of the two secondary amino groups in the 13-membered lactam system by selective acylation in an early step. This method utilizes, as key steps, the condensation of a chiral β-lactam with a cyclic imino ether of a 9-membered lactam and following reductive ring-expansion. Both of these reaction processes proceeded with retention of configuration around the chiral center to give an optical pure lactam.



Scheme 1

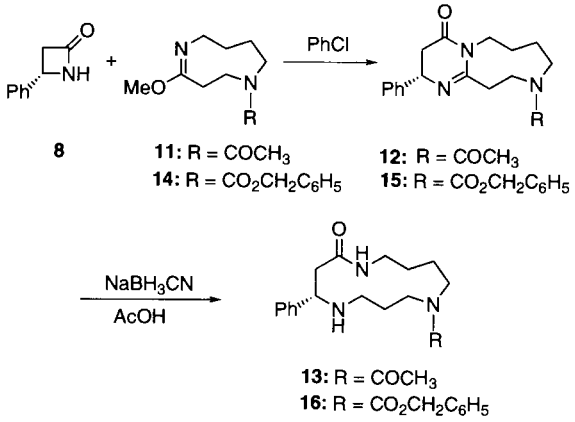
Piperidazine (**2**) was condensed with ethyl acrylate to form 7-oxo-1,6-diazabicyclo[4.3.0]nonane (**3**), and the N–N bond of **3** could be readily cleaved with sodium (3 equiv) in liquid ammonia to form the amino lactam **4** (Scheme 1).[3] Treatment of **4** with *trans*-cinnamoyl chloride in dichloromethane in the presence of 4-(dimethylamino)pyridine yielded **5**.[3] Conversion of **5** to imino ether **6** was achieved by using Meerwein's reagent (Me_3O^+ BF_4^-).[3,10] A convenient preparation of the desired (–)-methyl β-phenyl-β-alanate (**7**) was carried out according to the reported procedure.[11,12] The enantiomerically pure β-lactam **8** ($[\alpha]_D^{24}$ –132° (*c* 1.00, MeOH); lit. $[\alpha]_D^{24}$ –132° (*c* 1.0, MeOH))[12] was synthesized in 50% yield by cyclization of (–)-methyl β-phenyl-β-alanate (**7**) using LDA (2 equiv) in THF at –78 °C for 4 h by a modification of the reported procedure,[13] and subsequently was recrystallized from chloroform–hexane (Scheme 1). In the formation of the bicyclic 4-oxotetrahydropyrimidine derivative **10** from **6**, we adapted the addition–ring expansion process in which a β-lactam reacts with a cyclic imino ether to produce the corresponding 4-oxotetrahydropyrimidine derivative **10**.[14] Thus, heating **6** with (*S*)-4-phenyl-2-azetidinone (**8**) in chlorobenzene for 21 h yielded the ring-enlarged product **10** (67%, $[\alpha]_D^{25}$ +35.1° (*c* 1.70, $CHCl_3$)), most probably through the intermediate **9**. The conversion of **10** to dihydroperiphylline (**1**) was accomplished in one step (81%) by treatment with sodium cyanoborohydride (3 equiv) in acetic acid (2 h at 25 °C, 1 h at 50 °C, 12 h at 25 °C) (Scheme 2).[14] This reduction was carried out under conditions mild enough to leave the exocyclic double bond in **10** unaffected. The physical (mp 82–83 °C as colorless crystals), optical ($[\alpha]_D^{25}$ +3.6° (*c* 1.00, $CHCl_3$)), and NMR spectral data of **1** thus prepared are consistent with those (mp 82.5–83.5 °C; $[\alpha]_D^{25}$ +3.6° (*c* 1.0, $CHCl_3$)) of the reported (+)-(*S*)-dihydroperiphylline.[4,5]

Similarly, heating **8** with the imino ether **11** in chloroben-



Scheme 2

zene gave the ring-enlarged product **12** (48%, $[\alpha]_D^{25}$ +10.8° (*c* 1.10, $CHCl_3$)). The optical purity (100% ee) of **12** was determined by HPLC measurement using an optically active column (Daicel Chiralpak AD). This result shows that the condensation reaction of **8** with **11** proceeded with retention of configuration around the chiral center. The reduction of **12** was achieved under similar conditions to those for **10** and gave the optically active 13-membered lactam **13** (80%, $[\alpha]_D^{25}$ +11.4° (*c* 2.00, $CHCl_3$)) (Scheme 3).



Scheme 3

The condensation of **8** with the *N*-Cbz (Cbz = $CO_2CH_2C_6H_5$) derivative **14** in chlorobenzene yielded 4-oxotetrahydropyrimidine derivative **15** (84%, $[\alpha]_D^{25}$ +62.9° (*c* 2.20, $CHCl_3$)). The 13-membered lactam **16** (78%, $[\alpha]_D^{25}$ +5.8° (*c* 0.32, $CHCl_3$); lit. $[\alpha]_D^{25}$ +5.7° (*c* 1.0, $CHCl_3$)) from **15** also displayed optical data agreement with the reported value (Scheme 3).[4] In conclusion, this is the first example of 13-membered lactam alkaloids using a chiral β-lactam as a chiral synthon, and this method can be applicable to the synthesis of other polyamine alkaloids containing a framework of β-amino acids.

We thank the Ministry of Education, Science, Sports, and Culture, Japan, for the Grant-in-Aid (11640542).

References and Notes

1 Reviews: a) U. Bachrach, "Function of Naturally Occuring Polyamines," Academic Press, New York (1973). b) M. Hesse and H. Schmid, "Macrocyclic Spermidine and Spermine Alkaloids," from *Int. Rev. Sci.*, ed. by H. D. Hey and K. Wiesner, Butterworth, London (1976), Series II, Vol. 9, p. 265. c) M. M. Badawi, K. Bernauer, P. Van den Broek, D. Groger, A. Gueggisberg, S. Johne, I. Kompis, F. Schneider, H.-J. Veith, M. Hesse, and H. Schmid, *Pure Appl. Chem.*, **33**, 81 (1973). d) H. H. Wasserman and J. S. Wu, *Heterocycles*, **17**, 581 (1982).

2 A. Hocquemiller, A. Cave, and H.-P. Husson, *Tetrahedron*, **33**, 645 (1977).

3 H. H. Wasserman and H. Matsuyama, *J. Am. Chem. Soc.*, **103**, 461 (1981). For other synthetic studies, see, a) R. Hocquemiller, A. Cave, and H. -P. Husson, *Tetrahedron*, **33**, 653 (1977). b) L. Crombie, R. C. F. Jones, and D. Haigh, *Tetrahedron Lett.*, **27**, 5151 (1986).

4 T. Kaseda, T. Kikuchi, and C. Kibayashi, *Tetrahedron Lett.*, **30**, 4539 (1989).

5 a) K. Ishihara, Y. Kuroki, and H. Yamamoto, *Syntlett*, **1995**, 41. b) Y. Kuroki, K. Ishihara, N. Hanaki, S. Ohara, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **71**, 1221 (1998).

6 M. C. Carreno, *Chem. Rev.*, **95**, 1717 (1995).

7 F. A. Davis, R. T. Reddy, and R. E. Reddy, *J. Org. Chem.*, **57**, 6387 (1992).

8 N. Itoh, H. Matsuyama, M. Yoshida, N. Kamigata, and M. Iyoda, *Heterocycles*, **41**, 415 (1995).

9 N. Itoh, H. Matsuyama, M. Yoshida, N. Kamigata, and M. Iyoda, *Bull. Chem. Soc. Jpn.*, **68**, 3121 (1995).

10 L. A. Paquette, *J. Am. Chem. Soc.*, **86**, 4096 (1964). L. A. Paquette and T. Kitahara, *J. Am. Chem. Soc.*, **90**, 3897 (1968).

11 The optically active amino ester **7** showed satisfactory chiroptical data, $[\alpha]_D^{20}$ –22.5° (*c* 2.40, $CHCl_3$), $[\alpha]_D^{24}$ –12.9° (neat). See, a) H. Pietsch, *Tetrahedron Lett.*, **1972**, 2789. b) F. A. Davis, R. T. Reddy, and R. E. Reddy, *J. Org. Chem.*, **57**, 6387 (1992); $[\alpha]_D^{20}$ –20° (*c* 1.80, $CHCl_3$) for (*S*)-**7** (>95% ee). c) J. Jiang, K. K. Schumacher, M. M. Joullie, F. A. Davis, and R. E. Reddy, *Tetrahedron Lett.*, **35**, 2121 (1994); $[\alpha]_D^{20}$ +22.3° (*c* 1.99, $CHCl_3$) for (*R*)-**7** (>98% ee). d) Y. Kuroki, K. Ishihara, N. Hanaki, S. Ohara, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **71**, 1221 (1998); $[\alpha]_D^{25}$ –18.2° (*c* 1.46, $CHCl_3$) for (*S*)-**7** (>95% ee).

12 H. H. Wasserman and G. Berger, *Tetrahedron*, **39**, 2459 (1983); $[\alpha]_D^{24}$ –132° (c 1.0, MeOH) for (*S*)-**8**.

13 S. G. Davies and I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1129.

14 a) H. H. Wasserman and R. P. Robinson, *Tetrahedron Lett.*, **24**, 3669 (1983). b) H. Matsuyama, M. Kobayashi, and H. H. Wasserman, *Heterocycles*, **26**, 85 (1987).