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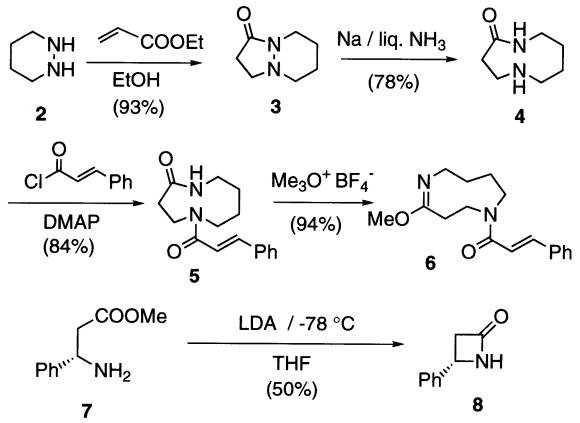
The synthesis of 13-membered polyamine alkaloid, (*S*)-dihydroperiphylline, was achieved by the condensation of a chiral β-lactam, (*S*)-4-phenyl-2-azetidinone, with a cyclic imino ether of a 9-membered lactam, followed by reductive ring expansion. Both of these reactions proceeded with retention of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

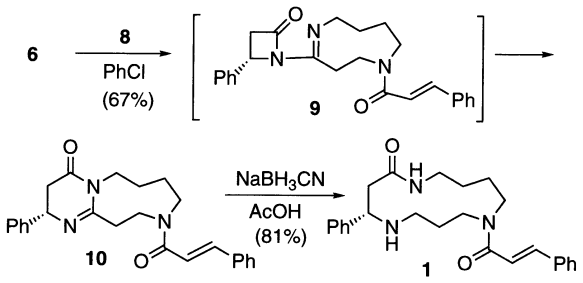
The present study provides a facile route to the synthesis of 13-membered alkaloid, (*S*)-dihydroperiphylline (**1**), starting from (*S*)-4-phenyl-2-azetidinone (**8**). A total synthesis of **1** involves a six-step sequence by successive ring expansions of smaller heterocyclic units. Our procedure (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

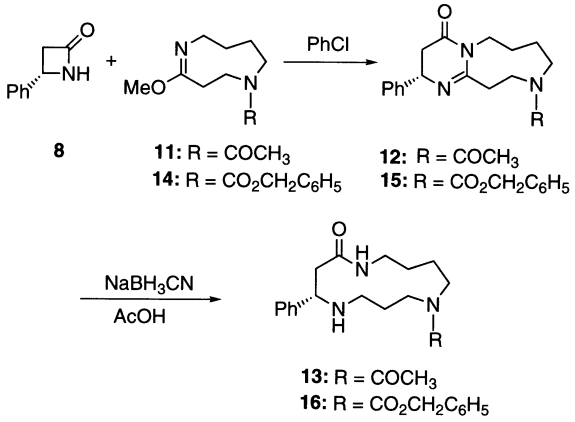
Piperidazine (**2**) was condensed with ethyl acrylate to form 7-oxo-1,6-diazabicyclo[4.3.0]nonane (**3**), and the N–N bond of **3** could be readily cleaved with sodium (3 equiv) in liquid ammonia to form the amino lactam **4** (Scheme 1).[3] Treatment of **4** with *trans*-cinnamoyl chloride in dichloromethane 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.

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