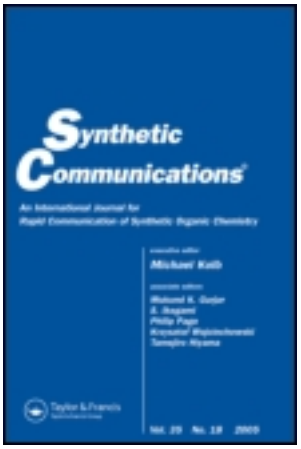

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STEREOSELECTIVE SYNTHESIS OF 2-(2-HYDROXYALKYL)PIPERIDINE ALKALOIDS THROUGH PRINS–RITTER REACTION

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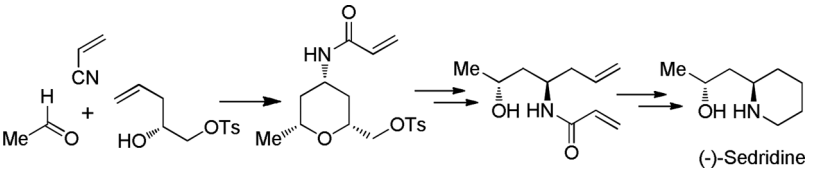
GRAPHICAL ABSTRACT



Abstract *A stereoselective total synthesis of the 2-(2-hydroxyalkyl)piperidine alkaloids has been accomplished by a Prins–Ritter amidation sequence. Other steps involved in this synthesis are Jacobsen's hydrolytic kinetic resolution (HRK) and ring-closing metathesis (RCM).*

Keywords *anti*-1,3-aminoalcohol; 2-(2-hydroxyalkyl)piperidine alkaloids; Prins–Ritter amidation; ring-closing metathesis (RCM)

INTRODUCTION

Piperidine alkaloids are widely distributed in nature and found to display a broad spectrum of biological activities.[1] In particular 2-substituted piperidine alkaloids (Fig. 1) have attracted considerable attention because of their potent biological activities such as memory-enhancing properties. They can also be used in the treatment of cognitive disorder.[2] Beyerman's and Schopf's groups have independently isolated (−)-sedridine (**1a**), an alkaloid consisting of a piperidine core from *Sedum acre*, which is a perennial plant native to Europe, and they have also determined its absolute configuration.[3] Consequently, several synthetic approaches have been developed for the synthesis of these alkaloids because of their scarcity from natural sources.[4]

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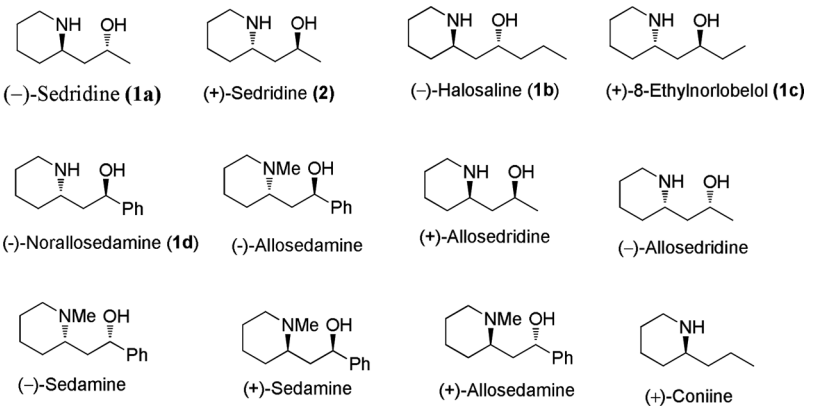
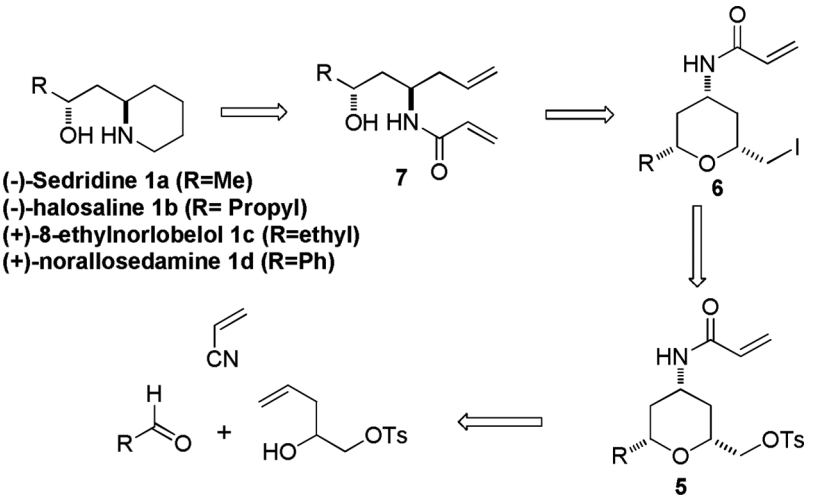


Figure 1. Representative examples of biologically active 2-substituted piperidine alkaloids.

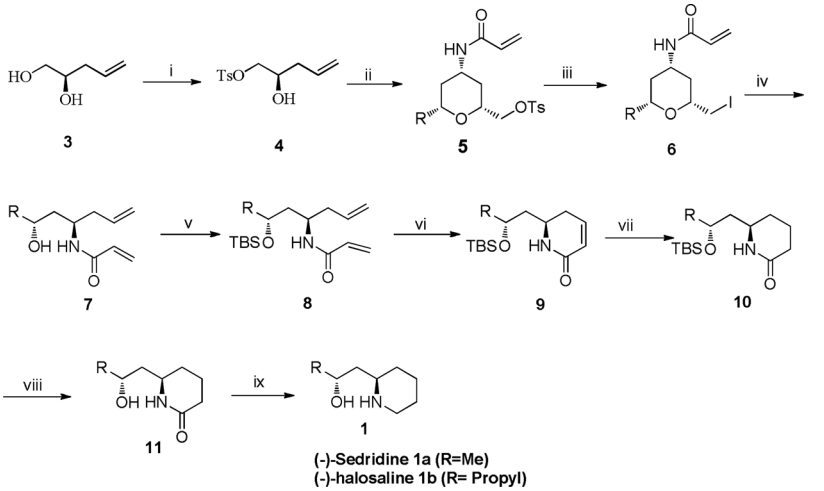
DISCUSSION

In continuation of our work on Prins cyclization and its utilization in the total synthesis of natural products,[5] we herein report an elegant approach for the synthesis of (−)-sedridine via a Prins–Ritter amidation sequence. As per our retrosynthetic analysis for the synthesis of 2-(2-hydroxy)piperidine alkaloids, (−)-sedridine **1a** (R = Me) could be synthesized from the intermediate **7**, which in turn could easily be prepared through Prins–Ritter amidation followed by reductive opening of the 2-iodomethyl-4-amidotetrahydropyran **6** (Scheme 1).

Accordingly, we commenced the synthesis of (−)-serdidine (**1a**) from the chiral homoallylic alcohol **3**. As shown in Scheme 2, the chiral (*R*)-homoallylicdiol **3** was prepared from the corresponding epoxide following Jacobsen's hydrokinetic resolution (HKR).[6] Chemoselective tosylation of the primary alcohol of **3** with TsCl



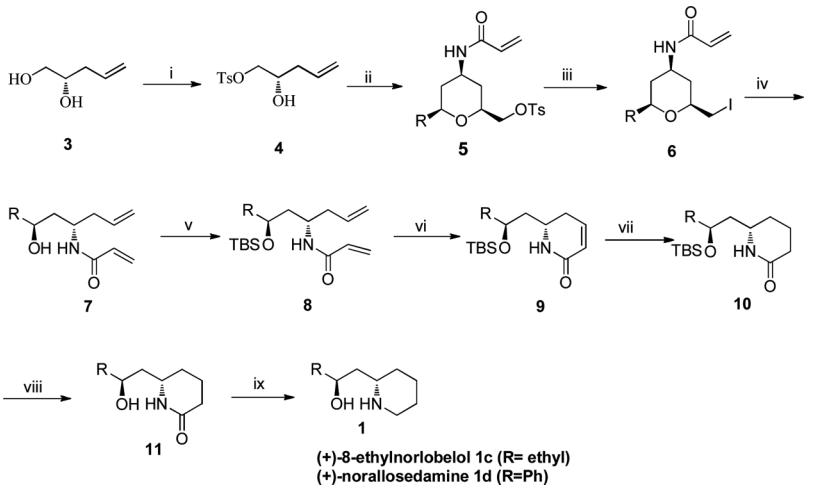
Scheme 1. Retrosynthetic analysis of total synthesis of 2-(2-hydroxyalkyl)piperidine alkaloids.



Scheme 2. Total synthesis of (−)-sedridine **1a** and (−)-halosaline **1b**. Reagents and conditions: (i) Et_3N, dibutyltin oxide, TsCl, CH_2Cl_2, rt, 1 h; (ii) acetaldehyde (for **1a**) or butyraldehyde (for **1b**), acrylonitrile, $BF_3 \cdot OEt_2$ (10 mol%), rt, 2 h; (iii) NaI, acetone, reflux, 24 h; (iv) Zn dust, EtOH, reflux, 8 h; (v) TBSCl, imidazole, DMAP (catalytic), CH_2Cl_2, 1 h; (vi) Grubb's I (10 mol%), CH_2Cl_2, rt, 12 h; (vii) Pd/C, MeOH, Et_3N, H_2 (1 atm); (viii) TBAF, THF, rt, 5 h; (ix) $LiAlH_4$, Et_2O, reflux, 2 h.

in the presence of dibutyltin oxide and Et_3N gave the homoallylic alcohol **4** in 98% yield.[7] Three-component, one-pot coupling of homoallyl alcohol **4** with acetaldehyde and acrylonitrile in the presence of 10 mol% BF_3. Et_2O under Prins–Ritter reaction conditions gave the 4-amidotetrahydropyran **5** in 54% yield with high diastereoselectivity. The relative configuration of **5** was confirmed by nuclear Overhauser effect (NOE) experiments in which all the substituents exist in equatorial position.[8] After establishing the structure, the tosylate **5** was converted into the corresponding iodomethyl tetrahydropyran **6** in 90% yield using NaI in acetone under reflux conditions. Reductive ring opening of **6** with Zn dust in refluxing EtOH gave the corresponding *anti*-1,3-amino alcohol **7** in 90% yield, which is a key intermediate for the synthesis of (−)-sedridine. This strategy has been successfully applied for the synthesis of (−)-halosaline using *n*-butaraldehyde instead of acetaldehyde.[9] After establishing the structure of compound **7**, the free hydroxyl group was protected as its *tert*-butyldimethylsilyl (TBS) ether **8** using TBSCl in the presence of imidazole in 95% yield. Ring-closing metathesis of **8** using Grubb's I catalyst in dichloromethane gave the α,β-unsaturated-δ-lactam **9** in 90% yield.[10] Reduction of **9** using Pd/C in methanol gave the δ-lactam **10** in 90% yield. Removal of the silyl ether of **10** using tetra butylammonium flouride (TBAF) in tetrahydrafuran (THF) gave the desilylated δ-lactam **11** in 95% yield. Finally, the reduction of **11** with $LiAlH_4$ in Et_2O gave the target molecule (−)-sedridine (**1**) in 76% yield. The physical characteristics of the synthetic molecule were in good agreement with the data reported for the natural product in literature.[11]

Similarly, other 2-(2-hydroxy)piperidine alkaloids such as (+)-8-ethylnorlobelol **1c** and (+)-norallosedamine **1d** have also been synthesized starting from antipode precursor of **3** as chiral (*S*)-homoallyl alcohol (Scheme 3).[6,9]



Scheme 3. Total synthesis of (+)-8-ethylnorlobelol **1c** and (+)-norallosedamine **1d**. Reagents and conditions: (i) Et_3N, dibutyltin oxide, TsCl, CH_2Cl_2, rt, 1 h; (ii) propionaldehyde (for **1c**) or benzaldehyde (for **1d**), acrylonitrile, $BF_3 \cdot OEt_2$ (10 mol%), rt, 2 h; (iii) NaI, acetone, reflux, 24 h; (iv) Zn dust, EtOH, reflux, 8 h; (v) TBSCl, imidazole, DMAP (catalytic), CH_2Cl_2, 1 h; (vi) Grubb's I (10 mol%), CH_2Cl_2, rt, 12 h; (vii) Pd/C, MeOH, Et_3N, H_2 (1 atm); (viii) TBAF, THF, rt, 5 h; (ix) $LiAlH_4$, Et_2O, reflux, 2 h.

CONCLUSION

In summary, a simple and efficient approach has been developed for the total synthesis of the 2-(2-hydroxyalkyl)piperidine alkaloids, (−)-sedridine (**1a**), (−)-halosaline (**1b**), (+)-8-ethylnorlobelol (**1c**), and (+)-norallosedamine (**1d**) in a highly stereoselective manner. Our approach involves mainly the use of Prins–Ritter amidation reaction followed by reductive ring-opening sequence.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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