remain unexposed in the ^{13}C NMR spectra of quadrone and terrecyclic acid biosynthesized from doubly ^{13}C-labeled compounds such as [1,2-$^{13}C_2$]acetate.

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Supplementary Material Available: Tables of ^1H and ^{13}C NMR data for **6** and **7**, ^1H and ^{13}C NMR spectra of **5** and **7**, and ^1H–^1H COSY, ^1H–^{13}C HETCOR, and APT plots for **7** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

A Novel Thermolytic Annulation of an Oxazolidinone: An Enantiospecific Synthesis of (−)-Slaframine[1]

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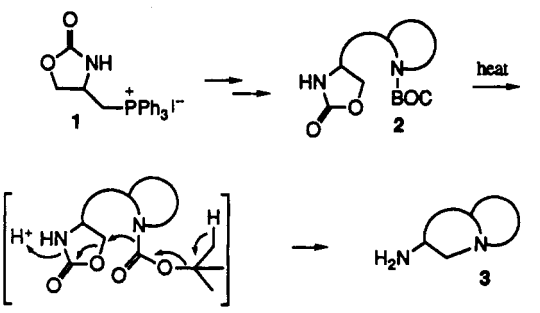
Summary: Optically pure β-aminopiperidines can be prepared in high yields through a thermolytic annulation sequence involving ring opening of an oxazolidinone.

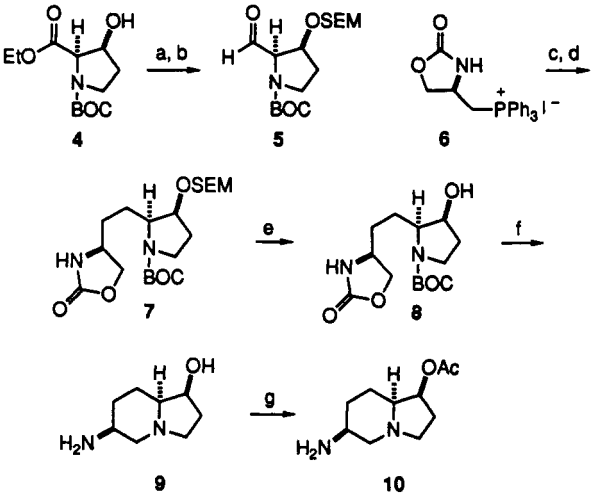
Hydroxylated indolizidine and piperidine alkaloids isolated from plants and microorganisms[3] have attracted considerable attention due to their diverse biological activity.[4] Therefore, the development of efficient methods for the synthesis of both the natural products and their analogs is important for the establishment of structure–bioactivity relationships of these compounds. We have developed a novel thermolytic annulation sequence for the construction of piperidines by intramolecular nucleophilic ring opening of oxazolidinones at the 5-position. The methodology provides ready access to β-amino piperidines (Scheme I). This structural unit is present in biologically active natural products such as slaframine,[5] pseudodistomines,[6] and unnatural amino azasugars.[7]

Indolizidine alkaloid slaframine (**10**) [(1*S*,6*S*,8a*S*)-1-acetoxy-6-aminooctahydroindolizine], a mycotoxin produced by the fungus *Rhizoctonia leguminicola*, has been shown to be responsible for excess salivation in cattle when they graze on fungus infested feeds.[8] Several synthetic approaches to racemic slaframine,[9] and two very recent syntheses leading to optically active material,[10] have been reported in the literature.

Scheme I



Scheme II[a]



[a] Key: (a) SEMCl, DIEA, CH_2Cl_2, rt, 18 h, 94%; (b) DIBALH, toluene, −78 °C; (c) 1.95 equiv of *n*-BuLi, 2 h, −78 °C, add **5**, 52%; (d) 10% Pd on C, EtOAc, H_2, 97%; (e) TBAF, HMPA, 80 °C, 3 h, 90%; (f) 270 °C, 5 min, 92%; (g) ref 9d.

We herein report enantiospecific syntheses of (−)-slaframine and (−)-8a-epidesacetoxyslaframine to illustrate the utility of our ring closure method. The key features of our approach include the following: (i) a novel annulation of an oxazolidinone under thermolytic conditions to furnish

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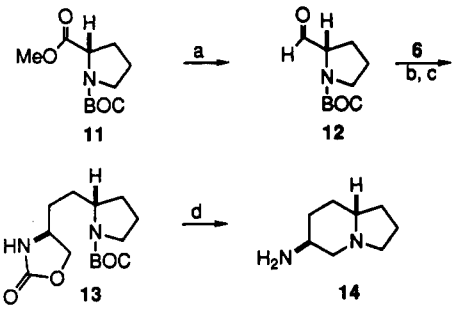
Scheme III[a]



[a] Key: (a) DIBALH, toluene, −78 °C, used without purification; (b) 6, 1.95 equiv of *n*-BuLi, 1 h, −78 °C, add 12, −78 °C to rt, 1 h, 72%; (c) 10% Pd on C, H_2, MeOH, 4 h, 98%; (d) 270 °C, 3 Torr, Ar flow, 83%.

the indolizidine skeleton, (ii) a convergent method involving relatively few steps, (iii) stereospecificity, and (iv) generality with the potential for stereoisomer and analog preparation.

Recently, we have reported the synthesis of δ-coniceine and 1-hydroxyindolizidine via a Wittig reaction establishing the feasibility of the skeletal bond formation in our general approach to the indolizidine alkaloid structure.[11] In addition, we have reported the ready preparation of a nucleophilic alaninol synthon 1 from serine, and demonstrated its utility via condensation with a variety of aldehydes producing alkenes in good chemical and high optical yields.[12] Thus, with the two key elements in hand, a new method for functionalization of an oxazolidinone is illustrated in the synthesis of slaframine as shown in Scheme II.

The aldehyde 5 required for the elaboration of the six-membered ring was prepared in two steps from *N*-*t*-BOC-3-hydroxyproline ethyl ester 4 by SEM protection of the secondary alcohol followed by DIBAL-H reduction and was used without further purification. Treatment of the phosphonium salt 6 with 1.95 equiv of *n*-BuLi at −78 °C generated the ylide, which was quenched with 5, resulting in the formation of the alkene as a mixture of double-bond isomers[13] in 52% yield over two steps. The double bond stereochemistry could be controlled to some extent by varying reaction conditions, although the nature of the double bond was of no consequence in the present study, since the *E*:*Z* mixture was reduced using catalytic hydrogenation conditions (10% Pd/C, H_2, EtOAc, rt, 1 atm, 24 h, 97%) in the subsequent step to furnish 7. The SEM protecting group was removed using fluoride ion conditions (TBAF, HMPA, 80 °C, 3 h, 90%).[14] The crucial step in the synthesis was ring closure to form the six-membered piperidine ring, involving both the use of the oxazolidinone ring system as a leaving group and deprotection of the *t*-BOC group under pyrolytic conditions as reported by Cava[15] and Wasserman.[16] Thus, pyrolysis of the BOC-protected oxazolidinone 8 at 270 °C in a sealed ampule furnished (+)-deacetylslaframine 9 ($[\alpha]^{24}_D$ + 2.73°, *c* = 1.76, CH_2Cl_2) in 92% yield through deprotection of the secondary amine followed by ring closure at the 5-position of the oxazolidinone with concomitant loss of carbon dioxide.[17] *This novel cyclization using the oxazolidinone for bond construction is unprecedented in the literature.*[18] Compound 9 was acetylated using the procedure of Harris[19] to provide slaframine identical in all respects to the properties reported in the literature ($[\alpha]^{24}_D$ −33.1°, *c* = 0.718, $CHCl_3$).[20] The overall yield of slaframine starting from 4 is 27%.

To test the viability of the annulation methodology for scale-up, we have synthesized (−)-8a-epidesacetoxyslaframine (14) starting from *N*-*t*-BOC-L-proline methyl ester 11 (Scheme III). Flash vacuum pyrolysis of compound 13 provided 14 in 83% yield. The overall yield on gram scales of (−)-8a-epidesacetoxyslaframine starting from 11 is 59%.

In conclusion, we have shown that indolizidine alkaloid slaframine can be readily obtained through a convergent sequence starting from compounds derived from proline and serine using a novel annulation sequence. The present methodology is readily applicable to the synthesis of slaframine analogs, thus making it useful for SAR studies of this class of compound. Further applications of this annulation methodology in the enantiocontrolled synthesis of 6-aminocastanospermine, its analogs, and extension to the preparation of other heterocycles of varying ring size are currently underway in our laboratory.

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Supplementary Material Available: Experimental procedures and characterization data for 4–5 and 7–14 (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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