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HETEROCYCLIC KETONES AS PRE-FORMED BUILDING BLOCKS. SYNTHESIS OF (-)-SLAFRAMINE.

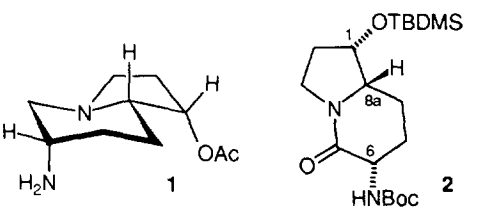
Peter Szeto,[a] David C. Lathbury[b] and Timothy Gallagher*[a]

[a] School of Chemistry, University of Bristol, Bristol BS8 1TS U.K.

[b] SmithKline Beecham Pharmaceuticals, Leigh, Tonbridge TN11 9AN U.K.

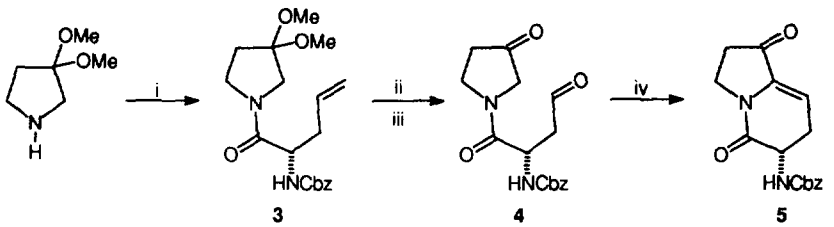
Summary. A synthesis of lactam **2**, which constitutes a formal total synthesis of (-)-slaframine **1**, is described with key steps being *(a)* intramolecular aldol reaction of ketoaldehyde **4** to establish the indolizidine framework and *(b)* diastereoselective reduction of enone **5** using the Corey oxazaborolidine **7**.

(-)-Slaframine **1** is a fungal metabolite produced by *Rhizoctonia leguminicola* that is known to undergo oxidative activation *in vivo* to produce a potent and neurotoxic muscarinic agent.[1] Since its isolation in 1965,[2] both the biosynthetic origins and metabolism of slaframine have been investigated[3] and, especially in recent years, this indolizidine alkaloid has been the subject of extensive synthetic studies.[4] Our interest in this area focused on use of this molecule as a vehicle for the development of new methodology for the construction and elaboration of functionalised indolizidines and in this paper we describe an enantiospecific synthesis of lactam **2**[4m] which constitutes a formal total synthesis of (-)-slaframine **1**.



The indolizidine nucleus of slaframine was assembled using the intramolecular aldol sequence shown in **Scheme 1**. Protection of (S)-2-amino-4-pentenoic acid followed by N-acylation of 3, 3-dimethoxypyrrolidine gave amide **3** (82 % overall). Oxidative alkene cleavage followed by ketal hydrolysis then gave ketoaldehyde **4** (63 % from **3**) and the key intramolecular aldol reaction of **4** was carried out in the presence of piperidine (in THF at r.t.) to give the indolizidine enone **5** in 31 % yield. This aldol cyclisation process, which requires enolisation at *C(2)* of the pyrrolidine ring (a selectivity that is generally disfavoured[5]), has only been achieved using a secondary amine - a variety of other, more

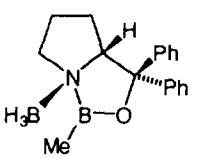
conventional aldol reaction conditions failed. The major side reaction observed in the conversion of **4** to **5** involved competitive enolisation of the aldehyde component and elimination of $CbzNH_2$.[6]



Scheme 1. *Reagents:* i, (S)-*N*-(Cbz)-2-amino-4-pentenoic acid, EDC, CH_2Cl_2; ii, OsO_4 (cat.), $NaIO_4$, aq. THF; iii, 2M HCl, aq. THF; iv, piperidine, THF, r.t. 24 h., then H_3O^+,1 h.

With the indolizidine framework available, methods were examined for introduction of the two remaining stereocentres (at *C(1)* and *C(8a)*) required for slaframine with the intention that the amino residue at *C(6)* could provide a diastereofacial directing role. Initial reduction of the C=C bond of **5** was unsuccessful because of *(a)* the level of selectivity observed and *(b)* complications encountered in the subsequent ketone manipulation. 1, 2-Reduction of the enone moiety of **5** gave allylic alcohols **6a/b** but with poor selectivity (0-30 %d.e.) for **6a**, regardless of the nature of the hydride source used (**Scheme 2**). A possible explanation for this observation may be found within the structure of **5**. With five adjacent sp^2-centres (at *C(1)*, *N(4)*, *C(5)*, *C(8)*, and *C(8a)*) the indolizidine ring system is severely flattened. In addition, the *C(6)*-*N*-Cbz group most likely adopts a quasi-equatorial position thereby minimising its directing ability. Given this, indolizidine **5** is perhaps better viewed as a "prochiral" substrate and we have sought to establish the stereochemistry of the *C(1)*-OH of **6a** *via* **reagent** rather than **substrate** control.

Of a series of asymmetric reducing agents examined, the Corey oxazaborolidine[7,8] was the most effective. Reduction of **5** using a stoichiometric amount of **7** (from (R)-proline) gave the desired (1S)-allylic alcohol **6a** (60 %; ≥95 %d.e. as judged by ^1H NMR). A similar level of selectivity was observed for the formation of the (1R)-isomer **6b** using *ent*-**7** and the effective lack of any significant matched/mismatched relationship between reagent and substrate served to reinforce our notion of the nominally "prochiral" nature of indolizidine **5**.[9]



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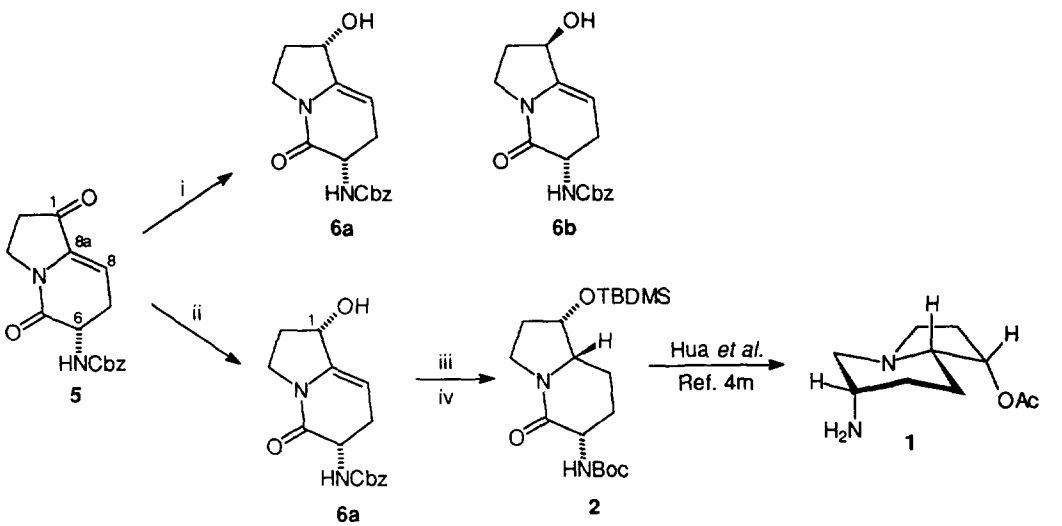
Completion of the synthetic sequence was straightforward and was carried out as shown in **Scheme 2.** Silylation of **6a** followed by hydrogenation and re-protection gave lactam **2**,[10] in 86 % overall from **6a** and the synthesis of lactam **2** and its conversion (in 3 steps) to (-)-slaframine **1** has been reported by Hua.[4m] A problem associated with the hydrogenation step must be highlighted: long reaction times led to formation (up to 15 %) of the *C(6)* epimer of **2** - the precursor to 6-epislaframine.



Scheme 2. *Reagents:* i, e.g. $NaBH_4$, $LiAlH_4$, *i*-Bu_2AlH, LS-Selectride, ii, **7**, CH_2Cl_2, -20 °C; iii, TBDMSCl, imidazole, DMF; iv, H_2, 10 % Pd/C, EtOH then Boc_2O, CH_2Cl_2.

In summary, the synthesis of lactam **2**, which constitutes a formal total synthesis of (-)-slaframine **1**, has been achieved. This chemistry illustrates a new approach to indolizidine synthesis based on an intramolecular aldol reaction, together with the application of the Corey oxazaborolidine towards solving a problem of diastereoselectivity in the 1,2-reduction of an enone.

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10. Lactam **2** had $[\alpha]_D^{22}$ = +53 (c 1.0, $CHCl_3$) {lit.,[4m] $[\alpha]_D^{22}$ = +53 (c 1.09, $CHCl_3$)} and ^1H and ^{13}C NMR spectra obtained for **2** matched those provided by Professor Hua. All new compounds gave satisfactory spectral data and were characterised by elemental analysis and/or high resolution mass measurement.

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