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A TOTAL SYNTHESIS OF (-)-SLAFRAMINE FROM (+)-*CIS*-(2R,3S)-3-HYDROXYPROLINE

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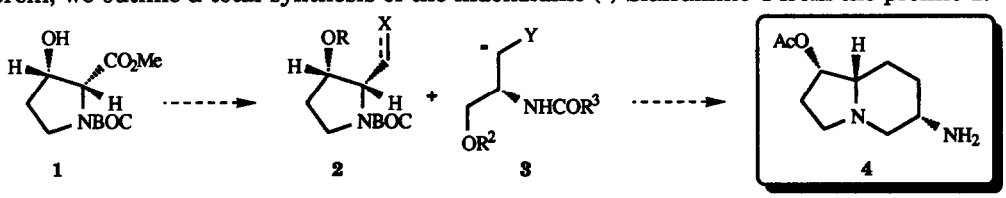
Abstract:- *A total synthesis of the naturally occurring indolizidine (-)-Slaframine 4 has been achieved, starting from the* cis*-3-hydroxyproline derivative 1, in which a key step is a Julia olefination reaction using the dianion derived from the β-aminosulfone 5.*

The diverse biological activities displayed by many naturally occurring hydroxylated piperidine, pyrrolizidine and indolizidine alkaloids has stimulated considerable interest in the development of synthetic approaches to these and related structures.[1] We have recently reported a straightforward asymmetric preparation of the *cis*-3-hydroxyproline derivative **1**[2] by bakers' yeast reduction of the corresponding β-keto-ester; the availability of this compound suggested that it could be a valuable starting material for the preparation of a variety of members of these classes of natural products. This idea has recently been exemplified in syntheses of Castanospermine,[3] (1S,8aS)-1-Hydroxyindolizidine[4] as well as by our synthesis of the Geissman-Waiss lactone,[2] a useful precursor to a number of pyrrolizidine alkaloids. Herein, we outline a total synthesis of the indolizidine (-)-Slaframine **4** from the proline **1**.

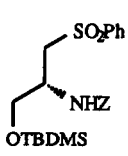


1 **2** **3** **4**

Scheme 1

(-)-Slaframine **4** is a metabolite of the fungus *Rhizoctonia leguminicola* which can infest leguminous cattle feeds and which, after oxidation to an active derivative, stimulates muscarinic acetylcholine receptor sites causing excessive salivation in the animals and may therefore have some potential in the treatment of conditions arising through cholinergenic dysfunctions.[5] The first syntheses of (-)-**4** featured the use of a reductive double cyclisation of an azido epoxy tosylate[5] while an alternative utilised azide cycloaddition chemistry to construct the indolizidine ring system.[6] Very recently, other approaches have employed a novel thermal cyclisation of an oxazolidinone derived from proline **1**,[7] sequential iodolactamisation and radical cyclisation of derivatives of resolved (S)-3-hydroxy-4-pentenamide[8] and Michael additions of α-sulfinyl ketimines to α-amidoacrylates.[9]

The basis of our present synthesis is outlined in Scheme 1. Conversion of the 3-hydroxyproline **1** into a protected halomethyl derivative or aldehyde **2** (X = I or O respectively) should then allow the direct incorporation of the remainder of the target molecule by reaction with a suitable nucleophilic species **3**. A number of options appeared to be available for the latter, most of which have been used as synthons for β-lithio-alanine.[10] For our purposes, the sulfone **5** appeared to offer the most potential. Although this is a new intermediate, a closely related species with a tetrahydropyranyl (ThP) function in place of the silicon group and with the amino group protected as the BOC derivative was the inspiration for the preparation of this material.[11] Sulfone **5** was prepared efficiently from *N*-Z-(L)-serine methyl ester **6** following sequential mesylation [MsCl, py, DMAP (cat.), CH_2Cl_2, -20°C, 12h, 78%], displacement by thiophenolate [NaSPh, DMF, 20°C, 18h, 88%] and reduction [$NaBH_4$ (10 eq., added portionwise during the first hour), MeOH, 20°C, 2h, 98%] to the alcohol **7**. Protection of the hydroxyl function [TBDMSCl, Et_3N, DMAP (cat.), CH_2Cl_2, 20°C, 12h, 92%] and oxidation [mCPBA, CH_2Cl_2, 0°C, 2h, 83%] then completed the sequence.[11] Simple trial reactons established that the required dianion **8** could be generated in essentially quantitative yield using 2.1 equivalents of BuLi in THF at -78°C for 0.5h.



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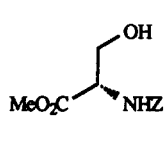

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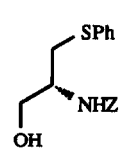

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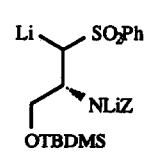

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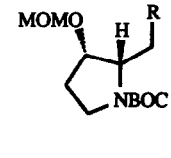
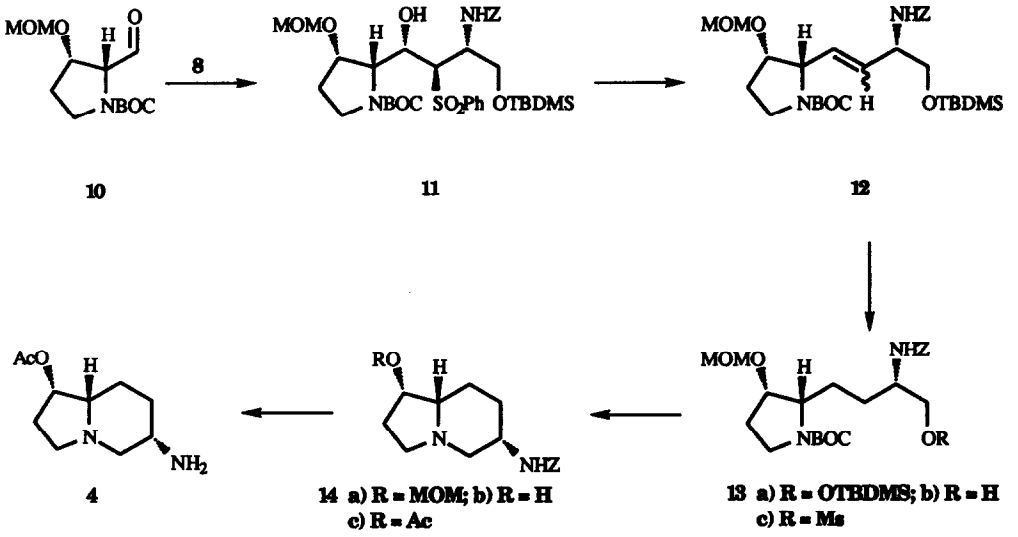


9 a) R = OH
b) R = I

The prolinol **9a** was obtained from the *N*-BOC derivative of *cis*-3-hydroxyproline methyl ester [*cf.* **1**; 78% ee] by sequential *O*-protection [MOMCl, $^iPr_2NEt$, CH_2Cl_2, 20°C, 16h, 96%] and reduction [4 eq. Dibal-H, toluene, -78~20°C, 5h, ~75%]. Although this material could be converted into the rather sensitive iodide **9b**, all attempts to couple this with dianion **8** failed to give more than small yields of the desired product. The prolinol **9a** was therefore oxidised to the corresponding aldehyde **10** [TPAP,[12] MNO, 4Å sieves, CH_2Cl_2, MeCN (9:1), 20°C, 16h, 92%].[13] (Scheme 2) We were pleased to find that a Julia condensation[14] between aldehyde **10** and the dianion **8** [-78°C, 3h] led to the key intemediate **11** in 60~65% isolated yield, as a 3:1 mixture of diastereoisomers; the structure of the predominant isomer was tentatively assigned as shown, based on spectroscopic and mechanistic considerations. Subsequent elimination [6% Na-Hg, Na_2HPO_4, MeOH, -20°C, 8h, ~100%][15] then gave the alkenes **12** as a 5:1 E/Z mixture.

With all the required atoms in place, the stage was then set for completion of the synthesis. Selective reduction of the alkene function to give the corresponding saturated

material **13a** was achieved using diimide [Trisyl hydrazide (10 eq., added portionwise during 72h), Et_3N, Et_2O, 20°C, 94%].[16] The silicon protecting group was then removed selectively [TBAF, THF, 20°C, 0.5h, 92%] and the resulting alcohol **13b** converted into the mesylate **13c** [MsCl, py, CH_2Cl_2, -20°C, 18h, 75%]. Removal of the *N*-BOC group [TFA, CH_2Cl_2, 20°C, 0.5h] followed by evaporation to dryness and basification with 2M NaOH led to the desired indolizidine **14a** (65%), which was partly deprotected by acidolysis [3 eq. HCl, MeOH, 60°C, 0.25h]; acetylation of the resulting alcohol **14b** [Ac_2O, py, CH_2Cl_2, 20°C, 0.75h] then gave *N*-Z-Slaframine **14c** in 88% yield over the last two steps.



Scheme 2

The synthesis was completed by hydrogenolysis of the *N*-Z function [H_2, 10%Pd-C, MeOH-HOAc (9:1), 20°C, 1h, 95%]. After careful separation of the (1**R**,6**S**,8a**R**)-diastereoisomer (*ca.* 10%), arising from the lack of stereospecificity in the initial yeast reduction step leading to hydroxy-ester **1** (*vide supra*) by column chromatography [SiO_2, CH_2Cl_2-MeOH (9:1) and Et_3N (5 drops per 10 mL of solvent)], the final product **4** showed spectroscopic [ir., ^1H and ^{13}C NMR, MS] and chromatographic data identical to those previously reported[5] as well as $[\alpha]_D$ -31.4 (c, 0.30, $CHCl_3$) {lit.[5] $[\alpha]_D$ -33 (c, 1.6, $CHCl_3$)}. The slightly low value for the optical rotation presumably reflects a small amount of the above diastereoisomeric impurity remaining in the sample.[17]

This relatively brief approach to (-)-Slaframine serves to emphasise the synthetic opportunities in this area arising from the availability of the yeast reduction product **1**.[3,4] Further exploitation of this is under active investigation and the results will be reported in due course.

Acknowledgements

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13. In our hands, this two step procedure gave superior yields than did direct partial reduction of the protected hydroxyproline methyl ester **1** [*cf.* ref. 7] to the aldehyde **10** using Dibal-H.
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17. Full analytical and spectroscopic data, consistent with the structures given, have been obtained for all compounds reported herein.

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