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THE CHEMISTRY OF VICINAL TRICARBONYLS. A SYNTHESIS OF (±)-SLAFRAMINE AND (±)-6-EPI-SLAFRAMINE.

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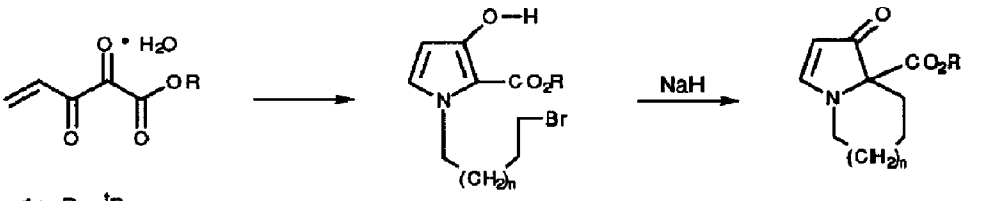
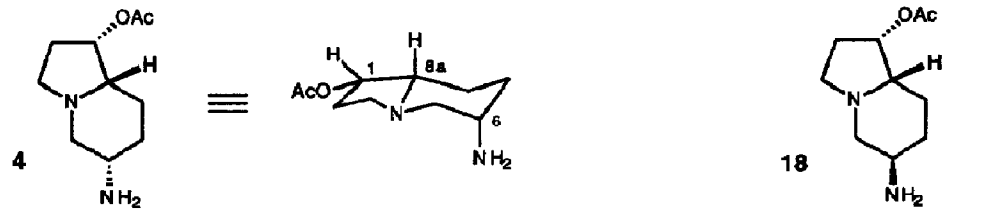
Summary: A synthesis of (±)-slaframine and (±)-6-epi-slaframine is described. The approach makes use of the intramolecular alkylation of an N-substituted 3-hydroxypyrrole-2-carboxylate ester.

In earlier work, we have shown that the vinyl vicinal tricarbonyl reagent of type **1**[1] can be used in reactions with primary amines to form N-substituted 3-hydroxypyrrole-2-carboxylates.[2] We have also observed that these compounds, as tautomers of β-keto esters, can undergo intramolecular alkylation as illustrated in **2** to give fused ring systems **3**, n=0,1 (Scheme 1) found in the pyrrolizidine, indolizidine, and related pyrrolidine alkaloids.[3] We now report a successful application of this methodology to the synthesis of the indolizidine alkaloid (±)-slaframine (**4**), as well as the isomeric (±)-6-epi-slaframine (**18**).

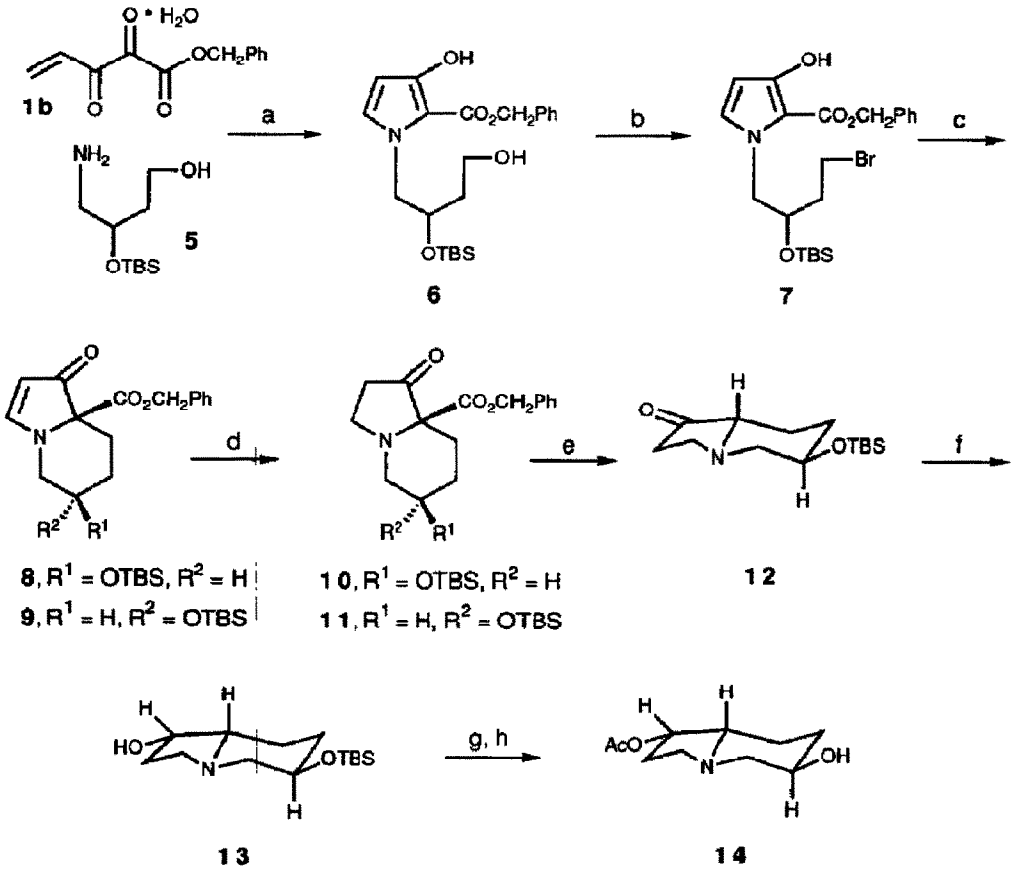
Scheme 1





Slaframine has been isolated from the fungus *Rhizoctonia leguminicola*, which usually infects ruminant forages.[4] It has been reported that when cattle, sheep, and horses ingest such infected forages, and thus slaframine, they develop a symptom in which they salivate profusely, sometimes with lethal effects.[5] Current interest in this alkaloid is reflected in the numerous syntheses which have been recently reported, illustrating varying degrees of stereoselectivity and efficiency.[6,7] Our synthesis relies on the use of the hydroxypyrrole **7** to construct the desired ring system having oxygen functionalities at the C_1 and C_6 positions (Scheme 2).

Scheme 2

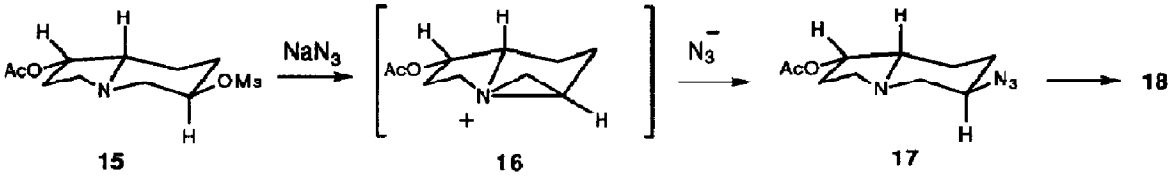


Reagents: (a) CH_2Cl_2/Et_2O, silica gel, rt (71%); (b) PPh_3/CBr_4, THF, rt (91%); (c) NaH, THF, rt (93% combined yield); (d) $BF_3{\cdot}Et_2O$, Super-Hydride®, THF, -78 °C, (**8** to **10**, 91%), (**9** to **11**, 90%); (e) H_2, 55 psi, rt, 10% Pd/C, EtOAc (75%); (f) L-Selectride®, THF, -78 °C (70%); (g) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (87%); (h) aqueous HF/CH_3CN, rt (85%).

Reaction of the primary amine **5**[8] with the vinyl tricarbonyl **1b** in CH_2Cl_2/Et_2O gave the desired 3-hydroxypyrrole-2-carboxylate **6** (71%).[9] The primary hydroxyl group in **6** was selectively converted to the bromide **7** using PPh_3 and CBr_4 (91%). Upon treatment with excess NaH, pyrrole **7** underwent intramolecular alkylation to give a 1:1 mixture of diastereomers **8** and **9** (93% combined yield). The mixture was separated and each component was reduced using Super-Hydride®/$BF_3{\cdot}Et_2O$ to give **10** (91% from **8**) and **11** (90% from **9**).[10] When either **10** or **11** was treated with H_2, in the presence of 10% Pd/C,[11] decarboxylation occurred to give a single product **12** (75%). Apparently, cleavage of the benzyl group, followed by decarboxylation, generated an enol from which compound **12** was formed as the most stable product.[12] This ketone could then be reduced selectively with L-Selectride® to give **13** as the only isomer (70%).[6d,13] After acetylation of the hydroxyl group (Ac_2O/Et_3N, DMAP) (87%), the silyl group was removed with aqueous HF/CH_3CN to give **14** (85%).

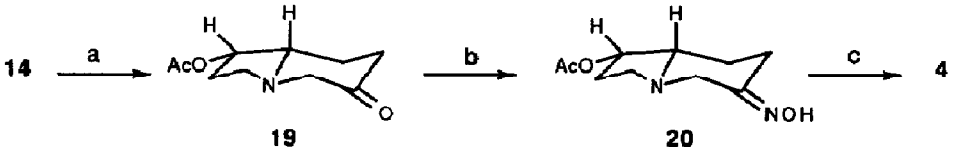
One possibility for forming slaframine from **14** would involve conversion of the hydroxyl group to the mesylate (**15**), and then, azide displacement. Reduction of the azide would then give the desired axial amino substituent. In our hands, however, the azide displacement at the C_6 position took place with retention of configuration, most probably through an aziridinium intermediate (**16**) to yield **17** (75%)[14] (Scheme 3). Hydrogenation of **17** (Pd/C) then yielded (±)-6-epi-slaframine **18** (93%) having spectroscopic properties (^{1}H NMR, IR, HRMS) completely identical with those previously reported for this epimer.[15]

Scheme 3



We found it convenient to complete the synthesis of slaframine from **14** by oxidation (Scheme 4) to the known ketone **19** (Swern oxidation, 82%).[16] This ketone, prepared earlier by a different route, had been converted in low yield (14%) to the oxime **20** by Gensler[6b] who then reduced **20** to **4** using H_2 and PtO_2. We found that oxime formation took place in substantially better yields (50-60%) when a freshly prepared sample of **19** was treated with $NH_2OH.HCl$/pyridine in refluxing ethanol. Compound **20** could then be reduced by hydrogenation in EtOH/aq HCl using PtO_2 as the catalyst. In this reduction, hydrogen delivery took place from the less hindered side to afford the dihydrochloride salt of (±)-slaframine (**4**) as the exclusive isomer (99%). Our synthetic sample of slaframine was identical in all respects with an authentic sample kindly provided by Professor Thomas M. Harris.

Scheme 4



Reagents: (a) ClCOCOCl, DMSO, CH_2Cl_2, -78 °C; Et_3N (82%); (b) NH_2OH·HCl, pyridine, EtOH, reflux (56%); (c) H_2, PtO_2, EtOH, HCl (aq), 40 psi, rt (99%).

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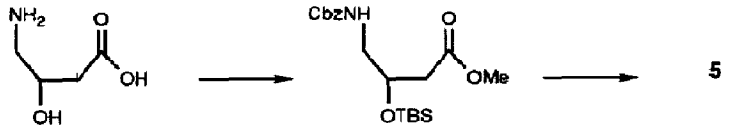
8 The substituted primary amine **5** was prepared from the commercially available DL-4-amino-3-hydroxybutyric acid (Aldrich) according to the following procedure: Compound **21** was esterified using methanolic HCl, and the amino group was immediately protected as the Cbz derivative using CbzCl/$NaHCO_3$(aq) (98% for the two steps). The hydroxyl group was next protected as the silyl derivative using TBSOTf/pyridine to give **22** (99%). The ester group was then reduced using either Super-Hydride®(90%) or $LiBH_4$ (86%) and the Cbz protecting group was removed by hydrogenation over 5% Pd/C to give **5** (99%).



21 **22**

9 All new compounds gave satisfactory ^1H NMR, ^{13}C NMR, IR, MS, high-resolution MS and/or elemental analyses

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12 The equatorial disposition of the substituent at the C_6 position was determined by ^1H NMR using the characteristic coupling constant of the axial methine proton ($J_{c6\text{-}c5}$ = 5.0 Hz, axial-axial coupling).

13 ^{13}C NMR of compound **13** clearly showed that it consisted of a single diastereomer. The stereochemistry was assigned based on ^1H NMR.[12]

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