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AN ENANTIOSELECTIVE SYNTHESIS OF (-)-SLAFRAMINE

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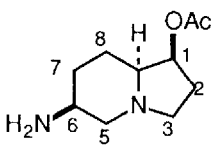
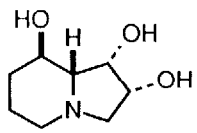
Abstract: An enantioselective synthesis of (-)-slaframine (**1**) has been accomplished by an intramolecular azide [2+3] dipolar cycloaddition starting from the readily available aldehyde **12**.

Slaframine (**1**), a toxic indolizidine alkaloid, was isolated from the fungus *Rhizoctonia leguminicola*, along with swainsonine (**2**).[2,3] Slaframine is responsible for excessive salivation in ruminants after consumption of fungus-infected red clover and other legume forages. Subsequently it was shown that slaframine after metabolic activation binds to and stimulates muscarinic acetylcholine receptor sites, resulting in slobbering.[4] The structure and absolute stereochemistry of this alkaloid were determined by ^{1}H NMR spectroscopy and the Horeau method, respectively.[2] The striking dichotomy in the absolute configuration of **1** and **2** has been clarified by recent biosynthetic studies of these alkaloids in *R. leguminicola*.[5] The total synthesis of racemic slaframine has been achieved by several groups.[6,7] Herein we describe an enantio- and stereoselective synthesis of (-)-slaframine (**1**) that utilizes an intramolecular azide [2+3] dipolar cycloaddition (IAC) for efficient construction of the indolizidine ring system.[8] Our synthesis also confirms the absolute configuration of slaframine.



1

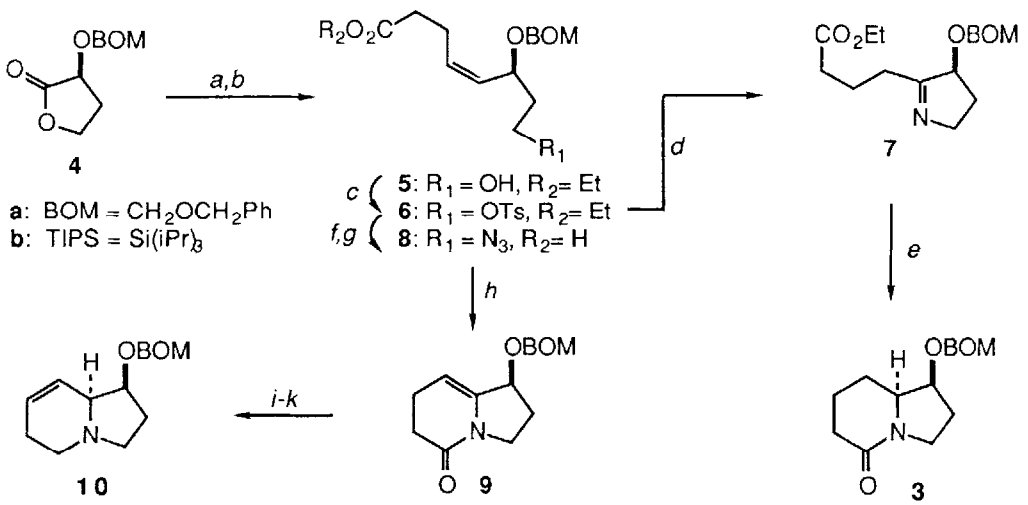


2

We felt that an expedient route to slaframine (**1**) would involve the stereoselective introduction of an amino functionality onto lactam **3**. The latter in turn should be readily available in enantiomerically pure form by our previously developed IAC protocol.[8] As shown in Scheme I, DIBAL-H reduction of the known and readily available lactone **4a**[9] and subsequent Wittig reaction with the ylide derived from (3-carbethoxypropyl)triphenylphosphonium bromide gave the adduct **5** in 57~73% yield. Sequential treatment of alcohol **5** with *p*-toluenesulfonyl chloride and sodium azide gave the imino ester **7** in 86% overall yield. The latter was then reduced ($NaBH_4$, ethanol; reflux) stereoselectively (~10 : 1) to afford lactam **3** in 96% yield. A tentative assignment of the stereochemistry of the ring-junction (C-8a) methine proton was based on the expected hydride delivery from the less hindered face of **7**. The ^{1}H NMR characteristics of **3** were also found to be in good agreement with those of *cis*-1-hydroxyindolizidine.[6b,10] Despite several approaches, however, stereoselective introduction of the amino functionality at C-6 of **3** and derivatives could not be achieved in reasonable yield.

We envisioned that the stereoselective amination might be achieved in the axial configuration by the use of tandem ene reaction - [2,3]-sigmatropic rearrangement of dehydroindolizidine **10** with TsNSeNTs.[11,12] The requisite compound was prepared by a slight modification of the original IAC sequence: the azidocarboxylic acid **8**, upon refluxing in toluene,[8a] gave smoothly enamide **9**, which was then transformed into **10** by hydroboration with thexylborane, followed by lactam reduction and subsequent dehydration by Martin's sulfurane.[13,14] Unfortunately, however, dehydroindolizidine **10** was found to be totally unreactive toward the Sharpless-Kresze reagents TsN=Se=NTs or TsN=S=NTs, presumably due to the presence of the electronegative nitrogen atom.

Scheme I

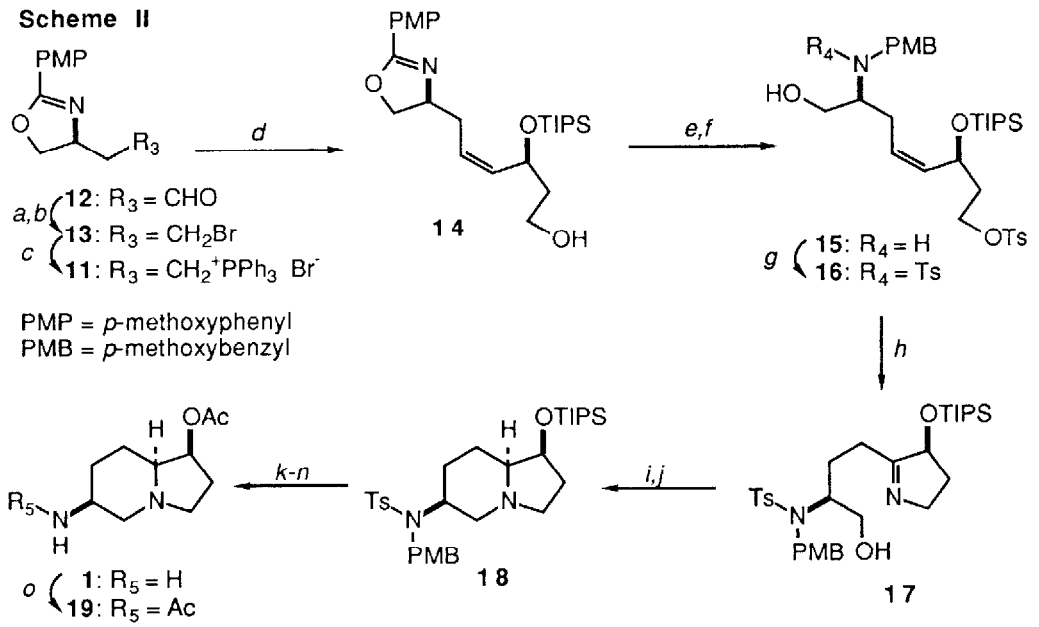


(*a*) DIBAL-H, THF, -78 °C. (*b*) 2.5 equiv $EtO_2CCH_2CH_2CH_2^+PPh_3\ Br^-$, 2,0 equiv $KN(SiMe_3)_2$, -78 to 0 °C (57~73% from **4a**). (*c*) TsCl, Et_3N, cat DMAP, CH_2Cl_2 (95%) (*d*) NaN_3, DMF, 100 °C (91%). (*e*) $NaBH_4$, EtOH, 0 °C to reflux (96%). (*f*) NaN_3, DMF, 50 °C. (*g*) K_2CO_3, aqueous MeOH. (*h*) toluene, reflux (52% overall from **6**). (*i*) 5 equiv thexylborane, THF, 0 °C (91%). (*j*) $BH_3{\cdot}Me_2S$, room temperature (75%). (*k*) Martin's sulfurane, CH_2Cl_2, reflux (55%).

At this juncture, we decided to undertake a more convergent approach that employs the chiral ylide **11** (Scheme II). The phosphonium salt, which was prepared in a straightforward manner from the readily available aldehyde **12**,[15] afforded the Wittig adduct **14** in 89% yield under similar conditions described above for adduct **5**. Subsequent tosylation, followed by DIBAL-H reduction using Meyers' conditions[16] smoothly afforded alcohol **15**. Selective N-tosylation of **15** was best achieved in 72% yield by the procedure of Oishi.[17] The resulting product **16** was then treated with sodium azide to produce imine **17** in 93% yield. The bicyclic ring closure was achieved uneventfully by selective *O*-mesylation and subsequent $NaBH_4$ reduction to produce the protected slaframine derivative **18** in 46~55% overall yield.[18] The reduction took place with complete stereocontrol. During the mesylation step, however, a variable amount of epimerization at C-1 took place to produce a protected 1,8a-diepislaframine derivative (~10%), which was found to be easily separable from **18** by column chromatography. Finally, the synthesis

was completed by a series of straightforward deprotection steps andsubsequent *O*-acetylation[6d] to afford slaframine (**1**), $[\alpha]_D$ = -38° (*c* 0.16, $CHCl_3$), [lit.[7] $[\alpha]_D^{25}$ = -33° (*c* 1.6, $CHCl_3$)], in 43% overall yield: the ^1H and ^{13}C NMR spectra (in $CDCl_3$) of synthetic **1** were identical with those of the natural material. It was further characterized by conversion into N-acetylslaframine (**19**): spectroscopic data, optical rotation and melting point were found to be comparable to literature values {$[\alpha]_D$ = -18.8° (*c* 0.4, EtOH); mp 136-138 °C} [lit. mp 140-142 °C; $[\alpha]_D^{25}$ = -15.9° (*c* 5, EtOH)].[2] Thus, our synthesis confirms the absolute configuration of (-)-slaframine to be 1*S*, 6*S* and 8a*S* as shown in **1**.[7]

Scheme II



(*a*) $NaBH_4$, MeOH (88%). (*b*) TsCl, Et_3N, cat DMAP, CH_2Cl_2; 10 equiv LiBr, $NaHCO_3$, DMF, 70 °C (83%). (*c*) PPh_3, CH_3CN, reflux. (*d*) $KN(SiMe_3)_2$, -78 °C; the DIBAL-H reduction product of **4b**, -78 °C, 1h (89% from **13**). (*e*) TsCl, Et_3N, cat DMAP, CH_2Cl_2 (96%). (*f*) 5 equiv DIBAL-H, THF, 0 °C, 1 h (97%). (*g*) N-tosyl-N-methylpyrrolidine perchlorate, CH_2Cl_2, 0 °C, 1h (72%). (*h*) 5 equiv NaN_3, DMF, 60 °C; toluene, reflux (93%). (*i*) MsCl, Et_3N, CH_2Cl_2, 0 °C (63%). (*j*) $NaBH_4$, EtOH, 0 °C; K_2CO_3; reflux (73%). (*k*) CAN, 1:15 H_2O-CH_3CN (68%). (*l*) nBu_4NF, THF (93%). (*m*) Na, NH_3-THF (~100%). (*n*) HCl; AcOH, HCl (68%) (*o*) Ac_2O, pyr (87%).

In summary, we have achieved an enantioselective synthesis of (-)-slaframine utilizing an intramolecular azide dipolar cycloaddition, and thereby have confirmed the absolute configuration of this indolizidine alkaloid. Further synthetic applications of the IAC strategy to other indolizidine and pyrrolizidine alkaloids will be reported in due course.

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1. Current address: Department of Chemistry, University of Alabama, Tuscaloosa, AL 35487. Recipient of an NIH Research Career Development Award, 1990-1995 (GM00575).

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14. Protection of the tertiary amine functionality as the borane complex is necessary for the regioselective formation of **10** by Martin's sulfurane.

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18. The yield for the bicyclic ring closure has not been optimized. The corresponding *O*-tosylation was accomplished with less epimerization, but suffered from poor yields (28~38% overall after the ring closure) owing to the competing *N*-tosylation. These problems should be circumvented by an initial reduction and protection of the resulting amino group.

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