not be determined with high accuracy, it can be safely said[8] that a primary kinetic isotope effect was observed for the trifluoroacetylation of phenyl vinyl sulfide-2,2-d_2.

There appear to be four possible mechanisms for electrophilic substitution at an olefinic carbon atom.[9] Mechanism 1 is analogous to that for the nitration of aromatic compounds, which involves cyclohexadienium ion intermediate. However, if 1 were the mechanism of trifluoroacetylation, a primary isotope effect would not be observed.[10] Mechanism 2 can also be excluded because it cannot explain the observed substituent effect. Mechanism 3 is that accepted for the sulfonation and mercuration of aromatic compounds.[9] It involves the very rapid establishment of an equilibrium between the vinyl sulfide and an intermediate cation, followed by rate-determining deprotonation of the cation. Mechanism 4 is a single-step process in which approach of the electrophile to, and departure of a proton from, the terminal carbon atom of the carbon-carbon double bond occur simultaneously. Both the observed substituent and isotope effects can be explained in terms of either mechanism 3 or mechanism 4. Although for aromatic sulfonation and mercuration a discrimination between 3 and 4 has not yet been achieved experimentally, 3 is now widely accepted as the mechanism for those reactions.[9]

$$1 \xrightarrow[\text{slow}]{COCF_3^+} \underset{3}{ArS\overset{+}{C}HCH_2COCF_3} \xrightarrow[\text{fast}]{-H^+} 2 \quad (1)$$

$$1 \xrightarrow[\text{fast}]{COCF_3^+} 3 \xrightarrow[\text{slow}]{-H^+} 2 \quad (2)$$

$$1 \underset{\text{very rapid}}{\overset{COCF_3^+}{\rightleftharpoons}} 3 \xrightarrow[\text{slow}]{-H^+} 2 \quad (3)$$

$$1 \xrightarrow[-H^+]{COCF_3^+} 2 \text{ (single step)} \quad (4)$$

Fortunately, however, a discrimination between mechanisms because feasible in the present case through the use of pairs of *cis*- and *trans*-aryl vinyl sulfides-2-d_1. If the reaction proceeded by mechanism 3, each geometric isomer of a pair would yield the same cationic intermediate, $ArSCHCHDCOCF_3^+$. Any recovered aryl vinyl sulfide would be a mixture of cis- and trans isomers, of which the cis/trans ratio would be the same, due to the very rapid establishment of an equilibrium between the vinyl sulfide and the cationic intermediate.

Two pairs of ArSCH=CHD (Ar = *p*-tolyl, cis/trans = 94:6 and 5:95; Ar = *p*-chlorophenyl, cis/trans = 95:5 and 13:87) were prepared[11] in a stereoselective manner. Each compound was trifluoroacetylated separately under the conditions described above. The progress of the reaction (inside an NMR tube) was followed carefully by ^1H NMR. Special attention was paid to the change in intensity of the methylene proton signal of the aryl vinyl sulfide [δ 5.19 (d, J = 10.2 Hz) and 5.14 (d, J = 16.2 Hz) for the *p*-Me pair; 5.35 (d, J = 9.6 Hz) and 5.25 (d, J = 17.4 Hz) for the *p*-Cl pair] during the reaction. In all four cases, no detectable change in the cis/trans ratio of the aryl vinyl sulfide was observed when the trifluoroacetylation was monitored to at least 75% completion. This meant that there was no rapidly established equilibrium between the aryl vinyl sulfide and a cationic intermediate. Thus, the possibility that the reaction proceeded by mechanism 3 was clearly eliminated. The experimental results obtained so far strongly suggest a single-step concerted process 4 for the trifluoroacetylation of aryl vinyl sulfides.[12] Further work aimed at completely elucidating the mechanism is now under consideration in this laboratory.

In contrast to the trifluoroacetylation of aryl vinyl sulfides, the trifluoroacetylation of aryl vinyl-2,2-d_2 ethers did not show any detectable primary isotope effect, although the rate of reaction was accelerated by electron-releasing substituents (ρ = -2.4), as was the trifluoroacetylation of aryl vinyl sulfides. Presumably, the trifluoroacetylation of aryl vinyl ethers proceeds by mechanism 1 which is similar to that for the nitration of aromatic compounds. That vinyl ethers and vinyl sulfides undergo trifluoroacetylation by different mechanisms may be due to the difference in stability between the two cations, $ArOCHCH_2COCF_3^+$ and $ArSCHCH_2COCF_3^+$. Both are stabilized by resonance, by overlap of a 2p orbital of the electron-deficient carbon atom with, in the former, a 2p orbital of the adjacent oxygen atom or, in the latter, a 3p orbital of the adjacent sulfur atom. Stabilization by 2p-2p overlap is surely more efficient. Hence, vinyl ethers can yield stable cationic intermediates, whereas vinyl sulfides cannot.[13]

(8) A similar effect was observed in the competitive trifluoroacetylation of $PhSCH{=}CH_2$ and $PhSCH{=}CD_2$.

(9) For example, see: Hine, J. In *Physical Organic Chemistry*, 2nd ed.; McGraw Hill: New York, 1962; pp 352. Alder, R. W.; Baker, R.; Brown, J. M. In *Mechanism in Organic Chemistry*; John Wiley & Sons: New York, 1971; pp 286.

(10) An addition-elimination mechanism that gives substitution products can also be excluded, because the formation of $ArSCHCH_2COCF_3^+$ would be rate controlling.

(11) Hojo, M.; Masuda, R.; Takagi, S. *Synthesis* **1978**, 284.

(12) A truly concerted reaction should involve no bulid up of charge (ρ = 0) in the transition state. There are degrees of concertedness. Therefore we would prefer it said that the mechanism is closest to option four.

(13) That two mechanisms were involved was implied earlier.[3] Although the rate of trifluoroacetylation of vinyl ethers was only slightly influenced by the presence of β-substituents, the trifluoroacetylation of vinyl sulfides was greatly inhibited by the presence of β-substituents.

A Synthesis of (-)-Slaframine and (-)-1,8a-Diepislaframine

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Summary: Reductive cyclization of the optically pure azido epoxides **12** and **13** afforded the indolizidines **14** and **16**, which were converted into (-)-slaframine **1** and (-)-1,8a-diepislaframine **18**.

Forages contaminated with the fungus *Rhizoctonia leguminicola* are responsible for a disease in ruminants

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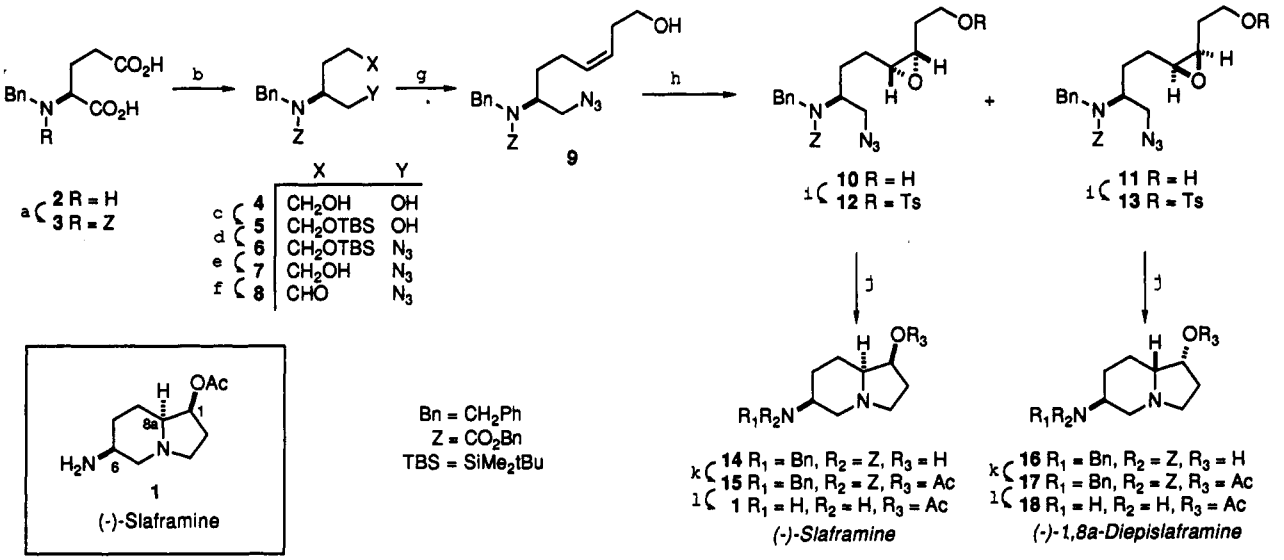
Scheme I[a]



[a] (a) $PhCH_2O_2CCl$, $NaHCO_3$, H_2O, 23 °C, 18 h, 71%; (b) BH_3·THF (3 equiv), THF, 0 °C, 1 h; 23 °C, 18 h, 70%; (c) TBSCl, py, cat. DMAP, CH_2Cl_2, 0–23 °C, 12 h, 85%; (d) Ph_3P, $EtO_2CN{=}NCO_2Et$, $(PhO)_2P(O)N_3$, THF, 23 °C, 48 h, 93%; (e) *n*-Bu_4NF, THF, 23 °C, 6 h, 96%; (f) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C, 2 h, 92%; (g) $Ph_3P^+(CH_2)_3OH\ Br^-$, $KN(SiMe_3)_2$ (2 equiv), THF, 0 °C, 2 h; Me_3SiCl (1 equiv); 8, −78 °C, 1 h; 23 °C, 1 h; 1 M HCl, 23 °C, 1 h; 80% overall; (h) mCPBA, CH_2Cl_2, 23 °C, 3 h, 91%, 10:11 = 1:1, separate by preparative HPLC; (i) pTsCl, py, DMAP (cat.), −10 °C, 24 h, 86% for **12**, 81% for **13**; (j) 10% Pd/C (5 wt %), H_2 (1 atm), EtOH, 23 °C, 24 h; filter, add K_2CO_3, reflux 18 h, 75% for **14**, 81% for **16**; (k) Ac_2O, py, 23 °C, 18 h, 90% for **15**, 90% for **17**; (l) 10% Pd/C (100 wt %, 10 mol % Pd), H_2 (1 atm), EtOH, 23 °C, 4 h, 78% for **1**, 60% for **18**.

known as "black patch".[1] The most obvious symptom associated with ingestion of contaminated feed is excessive salivation, which is thought to be caused by the alkaloid slaframine **1**.[1-5] It has been proposed that slaframine is oxidized in the liver to an active metabolite which is a muscarinic agonist.[1] Beyond its potential in the treatment of diseases involving cholinergic dysfunction, slaframine has been under active investigation for its potentially beneficial effects on ruminant digestive function.[6] Unfortunately, slaframine is an air-sensitive compound which is not easily obtained in significant quantities by fermentation. A useful synthetic route would be desirable, given the growing interest in this alkaloid. We report the first synthesis of the natural enantiomer of slaframine. In addition to providing verification of the previously proposed absolute stereochemistry of slaframine, the last step in the synthesis involves a simple conversion of a stable precursor of slaframine into the free alkaloid.

Total syntheses of racemic slaframine have been reported by Rinehart,[7] Gensler,[8] Weinreb,[9] Harris,[10] and Flitsch.[11] A formal total synthesis has been reported by Shono.[12] It is interesting to note that the racemate is produced in each synthesis, even when optically active materials such as L-glutamic acid[8,11] or L-lysine[12] are used as starting materials. Given that the determination of the absolute stereochemistry of slaframine rests largely on indirect methods,[13] an unambiguous stereochemical confirmation is desirable. Our synthesis of slaframine confirms that the absolute stereochemistry of this alkaloid is 1*S*,6*S*,8a*S*, as had been previously proposed.

A doubly protected version of L-glutamic acid was prepared by converting *N*-benzyl-L-glutamic acid **2**[14] to its *N*-carbobenzyloxy derivative **3** (Scheme I). Diborane reduction of both carboxylic acids afforded the diol **4**. Selective silylation of **4** produced **5**, presumably because of the differing steric and electronic environments of the two hydroxyl groups. Conversion of **5** to the azide **6** was accomplished with a Mitsunobu reaction.[15] Deprotection

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(2) General reviews: (a) Reference 1. (b) Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, pp 183–308. (c) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, pp 1–54.
(3) Isolation: (a) Rainey, D. P.; Smalley, E. B.; Crump, M. H.; Strong, F. M. *Nature (London)* **1965**, *205*, 203–204. (b) Aust, S. D.; Broquist, H. P. *Nature (London)* **1965**, *205*, 204.
(4) Structure determination: Gardiner, R. A.; Rinehart, K. L., Jr.; Snyder, J. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1968**, *90*, 5639–5640.
(5) Biosynthesis: Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940–949 and earlier references therein.
(6) (a) Froetschel, M. A.; Amos, H. E.; Evans, J. J.; Croom, W. J., Jr.; Hagler, W. M., Jr. *J. Anim. Sci.* **1989**, *76*, 827–834 and earlier references therein. (b) Jacques, K.; Harmon, D. L.; Croom, W. J., Jr.; Hagler, W. M., Jr. *J. Dairy Sci.* **1989**, *72*, 443–452 and earlier references therein.
(7) Cartwright, D.; Gardiner, R. A.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 7615–7617.
(8) Gensler, W. J.; Hu, M. W. *J. Org. Chem.* **1973**, *38*, 3848–3853.
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(10) Schneider, M. J; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 3681–3684.
(11) Dartmann, M.; Flitsch, W.; Krebs, B.; Pandl, K.; Westfechtel, A. *Liebigs Ann. Chem.* **1988**, 695–704.
(12) Shono, T.; Matsumura, Y.; Katoh, S.; Takeuchi, K.; Sasaki, K.; Kamada, T.; Shimizu, R. *J. Am. Chem. Soc.* **1990**, *112*, 2368–2372.
(13) In Rinehart and Broquist's elucidation of the structure of slaframine,[4] the *S* configuration of *N*-acetyl-*O*-deacetylslaframine at C-1 was based on Horeau's indirect method for the determination of the configuration of secondary alcohols. For a description of Horeau's method, see: Horeau, A. In *Stereochemistry, Fundamentals and Methods*; Kagan, H. B., Ed.; Georg Theime: Stuttgart, 1977; Vol. 3, pp 51–94. The relative configuration of C-1 versus C-8a was based on the similarity of the ^1H NMR spectrum of *N*-acetylslaframine to one of the known diastereomers of 1-acetoxyindolizidine, again an indirect method. We have confirmed this assignment using difference NOE ^1H NMR spectroscopy on our synthetic (−)-*N*-acetylslaframine hydrochloride, which showed a 13% enhancement of the methine proton signal at C-8a when the methine proton at C-1 was irradiated, consistent with the cis disposition of these two protons. The relative configuration of C-6 versus C-1 and C-8a was established by Rinehart and Broquist, who determined that the proton at C-6 was equatorial by analysis of ^1H NMR coupling constants. Assuming a trans ring juncture, this allowed the assignment of the stereochemistry at C-6 relative to C-8a. The relative stereochemistry has also been confirmed by synthesis.[7-11]
(14) Petersen, J. S.; Gregor, F.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539–4547.

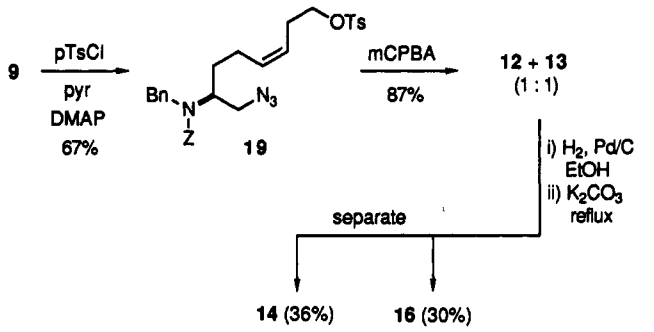
of 6 and oxidation at C-4 gave the azido aldehyde 8. At this point, several strategies based on intramolecular 1,3-dipolar cycloadditions were examined to introduce the remaining three carbon atoms and form the bicyclic ring system.[16] However, a more conventional approach involving epoxide chemistry was found to be the most satisfactory. This type of approach has been used by several groups for the synthesis of hydroxylated indolizidine alkaloids.[17]

The *Z*-alkene 9 was produced by a very stereoselective Wittig reaction on the aldehyde 8 with a silyloxy-substituted ylide.[18] Epoxidation of 9 with *m*-chloroperbenzoic acid was nonselective, producing diastereomeric epoxides 10 and 11 in equal amounts, but in excellent yield. Attempts at carrying out hydroxyl-directed epoxidations with various transition metal oxidants were not fruitful. Modest diastereoselectivity could be achieved, but the yields were prohibitively low.[19] Separation of 10 and 11 was straightforward using preparative HPLC, but a stereochemical assignment was not possible at this stage. Tosylation of 10 afforded 12. Selective reduction of the azide 12 to an amine in the presence of the two benzyl-protecting groups was accomplished by hydrogenolysis with hydrogen and palladium catalyst. The resultant amine was not isolated but was directly heated in refluxing ethanol containing potassium carbonate. An intramolecular epoxide opening and subsequent alkylation of the nitrogen by the tosylate ensued, affording the indolizidine 14. Acetylation of the secondary alcohol of 14 gave 15, which was deprotected to (−)-slaframine 1 by hydrogenolysis using a greater amount of palladium catalyst. Synthetic (−)-slaframine showed $[\alpha]^{25}_D = -33°$ (c = 1.6, $CHCl_3$). No optical rotation has been reported for natural slaframine. The ^1H and ^{13}C NMR spectra[20] of our synthetic material matched spectra of synthetic racemic slaframine kindly provided by Professor T. M. Harris.[10]

Acetylation of synthetic 1 gave *N*-acetylslaframine, mp 139–141 °C, $[\alpha]^{25}_D = -11.2°$ (c = 1.45, EtOH) (lit. mp 140–142 °C, $[\alpha]^{25}_D = -15.9°$, c = 5, EtOH)[4,21] which showed spectral characteristics identical with those of racemic *N*-acetylslaframine provided to us by Harris. Based on the absolute stereochemistry of L-glutamic acid, natural slaframine is therefore the 1*S*,6*S*,8a*S* stereoisomer.

A similar sequence afforded (−)-1,8a-diepislaframine 18[20] in good yield from the epoxy tosylate 13. This material was clearly different in all respects from (−)-1.

An alternate route to slaframine was explored which avoided the HPLC separation of epoxides 10 and 11. Tosylation of 9 followed by epoxidation gave a 1:1 mixture of 12 and 13, which were directly reduced and cyclized, affording a mixture of 14 and 16. Separation was easily accomplished by column chromatography, producing these two indolizidines in 36 and 30% isolated yields overall from the mixture of 12 and 13. The isolated yield of 14 was slightly lower than the sequence shown in Scheme I, but this route may be more readily carried out on a large scale, since the separation of 14 from 16 is easier than 10 from 11.



In conclusion, the first synthesis of natural (−)-slaframine 1 was accomplished in 6% overall yield in 12 steps from *N*-benzyl-L-glutamic acid. An equal amount of (−)-1,8a-diepislaframine 18 was also produced in approximately the same yield (12% overall yield of 1 + 18), and should provide valuable information regarding structure–activity relationships in these biologically interesting alkaloids. The synthesis of (−)-slaframine also serves to verify the absolute stereochemistry of the natural alkaloid. Finally, the immediate precursor of (−)-slaframine is a stable compound and may be easily stored. Hydrogenolysis of 15 in ethanol followed by filtration of the catalyst and concentration affords (−)-slaframine of excellent purity. This may allow convenient on-site access to samples of slaframine of high purity for biological studies.

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(19) For example, the followiing oxidation conditions gave ratios of 10:11 and combined yields as shown: (a) $Ti(O^iPr)_4$, ^{t}BuOOH: 60:40 (50%). (b) VO(acac), ^{t}BuOOH: 55:45 (50%). (c) $Ti(O^iPr)_4$, ^{t}BuOOH, (+)-diisopropyltartrate: 37:63 (10%). (d) $Ti(O^iPr)_4$, ^{t}BuOOH, (−)-diisopropyltartrate: 60:40 (10%).

(20) Partial spectral data for (−)-slaframine 1: ^1H NMR ($CDCl_3$, 360 MHz) δ 5.19 (ddd, J = 7.6, 4.9, 2.2 Hz, 1 H), 4.22 (bs, 2 H), 3.21 (bs, 1 H), 3.06 (m, 2 H), 2.24 (m, 1 H), 2.13 (dd, J = 11.4, 2.2 Hz, 1 H), 2.05 (s, 3 H), 2.01 (m, 1 H), 1.85 (m, 2 H), 1.79–1.62 (m, 2 H), 1.58–1.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 170.8, 74.9, 67.4, 58.7, 52.9, 45.8, 30.5, 30.1, 21.0, 19.7. For 1,8a-diepislaframine 18: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.20 (ddd, J = 7.6, 4.7, 2.0 Hz, 1 H), 3.24 (ddd, J = 10.3, 4.3, 1.7 Hz, 1 H), 3.12 (td, J = 8.9, 1.8 Hz, 1 H), 2.93 (m, 1 H), 2.29 (m, 1 H), 2.28 (m, 1 H), 2.05 (s, 3 H), 1.98 (m, 1 H), 1.84 (m, 2 H), 1.58 (m, 2 H), 1.49 (m, 1 H), 1.43, (bs, 2 H), 1.07 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 73.6, 66.3, 55.0, 52.1, 47.9, 30.8, 28.4, 22.8, 20.9.

(21) The rotation of our synthetic *N*-acetylslaframine is lower than the literature value, but may be due to the difference in concentration of the two measurements. Since we were concerned that some racemization had occurred during manipulations on compounds 2 and 3, the enantiomeric purity of the alcohol 5 was determined by a Mosher's ester analysis,[22] and it was found to be optically pure.

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