Acknowledgment. This work was supported by Grant CHE8205767 from the National Science Foundation.

Registry No. carbonate, 3812-32-6; *p*-methoxyphenyltropylium cation, 29631-26-3.

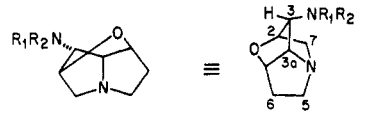
Communications

Synthesis of the Lolium Alkaloids

Summary: The total synthesis of loline and norloline using a nitrone-based methodology is reported herein.

Sir: Tall fescue (*Festica arundinacea*) is a cool-season, perennial bunch grass which is important as a pasture grass because it grows well in poor soil, withstands drought and conditions of inadequate drainage, and affords a good yield of dry matter per acre.[1-3] Cattle grazing on this grass have been known to develop a lameness known as "fescue foot".[4,5] In addition, there have been reports of increased respiration[6] and abdominal fat necrosis[7] in cattle feeding on this grass.

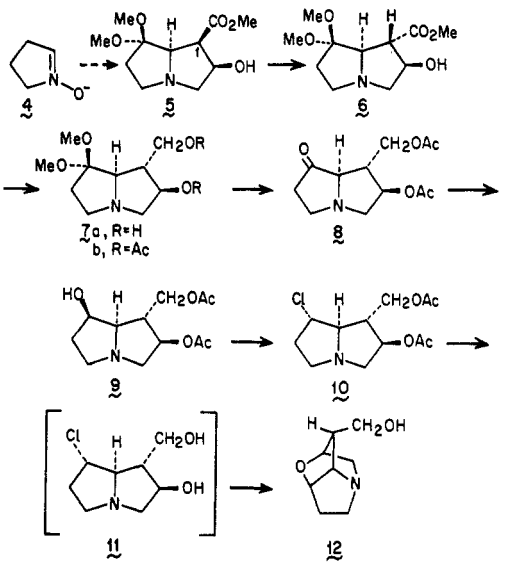
As a result of investigations into the alkaloidal content of tall fescue, a small array of norpyrrolizidine alkaloids have been isolated, all incorporating a unique oxygen bridge.[8] From *L. cuneatum* and *F. arundinacea*, a total of seven closely related lolium alkaloids were discovered. They have all been interconverted.[8-13] The structure of loline (**1a**) was confirmed by an X-ray crystallographic analysis of loline dihydrochloride.[14-16] The pharmaco-



loline 1a, R_1 = Me, R_2 = H
norloline 1b, R_1 = H, R_2 = H
1c, R_1 = Me, R_2 = Ac

logical activity of loline (**1a**) and related compounds has been reviewed.[11] When the crude alkaloidal extract is fed to cattle, fescue toxicity is not produced,[17] thereby suggesting that the toxicity of *L. cuneatum* is associated with nonalkaloid[21] constituents. Loline has been shown to possess weak antitumor activity,[18] and derivatives of this ring system can produce muscle relaxation.[19]

Scheme I



These alkaloids have not yielded to the thrusts of several synthetic attempts,[16,20-22] although the skeleton has been assembled.[16,22] The syn relationship between the 3-substituent, in proposed synthetic intermediates, and the skeletal nitrogen has remained elusive.

Since a nitrone-based methodology has been successful in the synthesis of several pyrrolizidine alkaloids (e.g., supinidine,[23] retronecine,[24] croalbinecine[25]), we chose to explore its potential for the construction of the unique skeleton of the loline alkaloids and for the controlled introduction of the syn-3-amino functionality (cf., **1a**).

A tempting means of constructing the skeletal architecture of loline involves a Michael closure of the penultimate precursor (i.e., **2**) in our earlier synthesis of *dl*-retronecine;[24] however, this approach suffers from a poor trajectory of approach of the hydroxyl group to the β-

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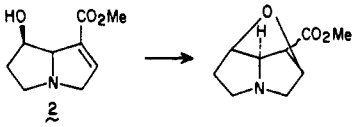
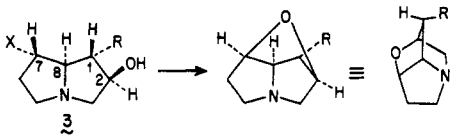
carbon of the α,β-unsaturated ester.[26] Indeed several attempts at this closure were unproductive.



2

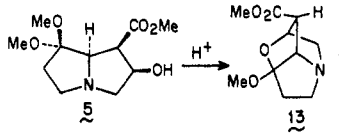
It was decided to modify the synthetic effort to accommodate the formation of an intermediate (i.e., **3**) with an unambiguous relative stereochemistry at four adjacent chiral centers (i.e., C-1, C-2, C-7, and C-8).



3

We selected the pyrrolizidine **5**, readily obtainable[24] from nitrone **4** and methyl 4-hydroxycrotonate, as the starting point for our synthetic endeavors. We required an alteration in the stereochemistry at C-1 in **5** in order to accommodate the stereochemistry of the C-3 substituent in **12** and subsequently in loline itself. The transformation was effected by sodium methoxide in methanol to give **6** in excellent yield (Scheme I). The reaction is facilitated by the removal of a transannular steric compression involving the carbomethoxyl function and one of the ketal methoxyl groups.

It was anticipated that the hydrolysis of the C-7 ketal might prove problematic due to the propensity of pyrrolizidine **5** to undergo an intramolecular trans ketalization to afford the bridged ketal **13**.[24] At the same time, this ketalization process was also encouraging since it demonstrated that the pyrrolizidine ring system could be readily closed to the desired *Lolium* alkaloid skeleton.



5 13

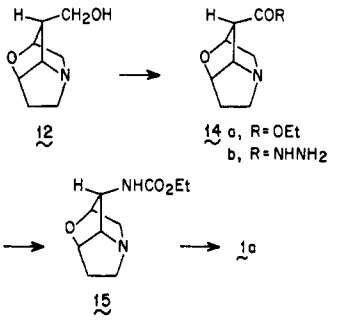
To inhibit the unwanted cyclization (i.e., of **5** to give **13**), the C-2β hydroxyl group was protected as the acetate. Thus, the amino alcohol **6** was reduced with lithium aluminum hydride to give the amino diol **7a**. Acetylation of **7a** gave the diacetate **7b** in 85% yield. The ketone was obtained from **7b** in virtually quantitative yield by treatment with excess trifluoroacetic acid at room temperature, followed by exposure to mild base ($NaHCO_3/H_2O$). We suspect that this reaction proceeds through the corresponding 7,7-ditrifluoroacetate.

Selective hydrogenation of the ketone **8** over Adams catalyst in glacial acetic acid occurs from the less hindered convex face to give the alcohol **9** as the only detectable stereoisomer in 95% yield. The IR spectrum exhibits a new hydroxyl absorbance at 2.91–3.25 μm and a retained acetate carbonyl stretch at 5.77 μm.

The next objective was to introduce a leaving group (i.e., X in **3**) with inverted configuration. Treatment of the alcohol **9** with the Vilsmeier reagent (thionyl chloride in dry DMF)[27] gave the inverted chloride **10** in 75% yield. The ^1H NMR spectrum exhibited a one-proton quartet at δ 5.05 (J = 5.0 Hz, H-2α) and a three-proton multiplet between δ 4.03 and 4.30 (methylene at C-1α and H-7β). Two three-proton singlets at δ 2.05 and 2.08 indicated the preservation of the two acetate groups.

We anticipated that treatment of **10** with alkoxide would deprotect both hydroxyls and promote the closure of the intermediate diol **11** to afford the lolium alkaloid skeleton **12** directly. Thus, treatment of **10** with sodium methoxide in methanol gave **12** in 88% yield. The alcohol **12** displayed the expected hydroxyl absorption at 2.95 μm and the molecular ion (M^+, m/e 155) was observed in the mass spectrum.

We now required a manipulation of the C-3 hydroxymethyl functionality to complete the synthesis. To effect this transformation, we chose to utilize a methodology based on the Curtius rearrangement.[28] Toward this end, the alcohol **12** was converted into the corresponding ethyl ester **14a** (80%) by initial oxidation with the Jones reagent, followed by direct esterification (ethanol, benzene, H_2SO_4).



12 14 a, R = OEt b, R = $NHNH_2$ 15 1a

The requisite hydrazide **14b** was then produced by refluxing **14a** with hydrazine hydrate. The latter, without purification, was treated with isoamyl nitrite and anhydrous hydrogen chloride in ethanol to give a product mixture containing the carbamate **15** and the ester **14a** in a 3:1 ratio, respectively. After chromatographic separation (alumina; 50% $CHCl_3$, CH_3OH), the carbamate was reduced with lithium aluminum hydride (reflux, THF) to afford *dl*-loline in 83% yield. The IR, NMR, and mass spectra compared well with those of authentic natural loline (**1a**).[8,29] Prolonged reflux of carbamate **14** in methanol–water containing 10% sodium hydroxide gave norloline which readily absorbed carbon dioxide to form a crystalline carbonate as reported in the literature.[9]

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Registry No. (±)-**1a**, 103616-00-8; (±)-**1b**, 103531-60-8; (±)-**5**, 73428-11-2; (±)-**6**, 103478-40-6; (±)-**7a**, 103478-41-7; (±)-**7b**, 103478-42-8; (±)-**8**, 103478-43-9; (±)-**9**, 103478-44-0; (±)-**10**, 103498-81-3; (±)-**12**, 103478-45-1; (±)-**14a**, 103478-46-2; (±)-**14b**, 103478-47-3; (±)-**15**, 103478-48-4.

Supplementary Material Available: Full experimental details including NMR and mass spectral data (13 pages). Ordering formation is given on any current masthead page.

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