Registry No. 2, 78418-55-0; 3, 78418-56-1; 4, 78355-18-7; 5, 78355-19-8; 6, 78355-20-1; 7, 78355-21-2; 8, 78355-22-3; 9, 78355-23-4; 10, 78355-24-5; 11 (isomer 1), 78370-94-2; 11 (isomer 2), 78355-25-6; 12, 67965-18-8; 13 (R = $CH_2C_6H_5$), 78355-26-7; L-Gulase, 6027-89-0; tetraacetyl β-L-gulopyranosyl bromide, 78418-57-2; 2-O-acetyl-3,4,6-tri-O-benzyl-β-L-gulopyranosyl chloride, 78355-27-8; methyl 2,4,6-tri-O-acetyl-3-O-carbamoyl-α-D-mannopyranoside, 25217-95-2.

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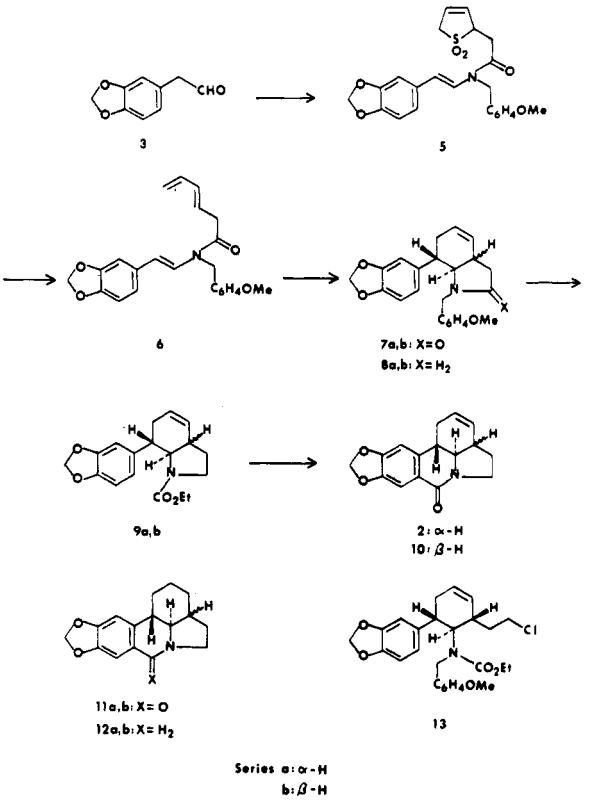
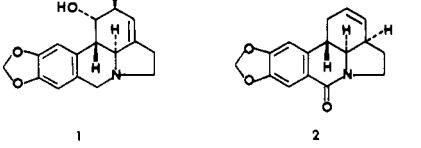
General Strategies for Alkaloid Synthesis via Intramolecular [4 + 2] Cycloadditions of Enamides. Application to the Formal Total Synthesis of Racemic Lycorine[1]

Summary: The application of the intramolecular [4 + 2] cycloaddition of the enamido diene **6** to the construction of the unsaturated oxolycorane **2** is described, thereby completing a novel, formal synthesis of the Amaryllidaceae alkaloid lycorine (**1**).

Sir: The assemblage of functionalized hydroquinolines and hydroindoles, which are structural elements common to many alkaloid natural products, via the intramolecular [4 + 2] cycloadditions[2] of dienamides is firmly established,[3] but the feasibility of employing enamides as dienophiles in [4 + 2] cycloadditions for the construction of these heterocyclic synthons has only been recently recognized.[4,5] Consequently, we now report a novel synthesis of the unsaturated lactam **2** by a route which features the intramolecular cycloaddition of an enamide with an unactivated diene as the key step. Since **2** has been previously converted[6a] to lycorine (**1**),[6,7] an alkaloid of the Amaryllidaceae family,[8] its preparation constitutes the completion of a new, formal synthesis of the title alkaloid.

Scheme I





The trans enamide **5** (mp 73–76 °C; J_{vinyl} = 15 Hz), which bears a diene moiety masked as a dihydrothiophene dioxide, may be readily prepared in 68% overall yield by the condensation of homopiperonal (**3**)[9] with *p*-methoxybenzylamine (toluene, $MgSO_4$, 0 °C, 1 h) followed by acylation of the intermediate imine thus formed in situ with 2-(2,5-dihydro-1,1-dioxothienyl)acetyl chloride (**4**)[4b] in the presence of diethylaniline (1.25 equiv, −78 → 25 °C, 3 h)[10] (Scheme I). Thermolysis of **5** as a 1% solution in refluxing xylene (18 h) containing *O,N*-bis(trimethylsilyl)acetamide (1%) and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (0.3%) afforded an inseparable mixture of the two cycloadducts **7a** and **7b** (47%) in a ratio

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(10) The structure assigned to each compound is in accord with its spectral (90-MHz ^1H NMR, ^{13}C NMR, IR, low-resolution mass) characteristics. Analytical samples of all new compounds obtained by recrystallization or chromatography (HPLC) gave satisfactory combustion analysis (C, H, N) and/or appropriate parent ion identification by high-resolution mass spectrometry. All yields reported are of isolated products which were >95% pure. The 90-MHz ^1H NMR data ($CDCl_3$) for several intermediates are as follows. **8a**: δ 7.00 (d, 2 H, *J* = 8 Hz), 6.76 (m, 5 H), 5.86 (s, 2 H), 5.73 (br s, 2 H), 3.73 (s, 3 H), 3.47 (d, 1 H, *J* = 13 Hz), 3.08 (d, 1 H, *J* = 13 Hz), 3.30–1.33 (m, 9 H). **8b**: δ 6.97 (d, 2 H, *J* = 8 Hz), 6.71 (m, 5 H), 5.83 (s, 2 H), 5.77 (br d, 1 H, *J* = 10 Hz), 5.56 (br d, 1 H, *J* = 10 Hz), 3.70 (s, 3 H), 3.13 (d, 1 H, *J* = 13 Hz), 2.60 (d, 1 H, *J* = 13 Hz), 3.03–1.10 (m, 9 H). **9a**: δ 6.70 (m, 3 H), 5.87 (s, 2 H), 5.75 (m, 2 H), 4.13–1.47 (m, 11 H), 1.05 (br t, 3 H, *J* = 7 Hz). **9b**: δ 6.70 (m, 3 H), 5.87 (s, 2 H), 5.77 (m, 2 H), 3.93–1.40 (m, 11 H), 0.90 (t, 3 H, *J* = 7 Hz). **10**: δ 7.57 (s, 1 H), 6.57 (s, 1 H), 5.93 (s, 2 H), 5.75 (m, 2 H), 4.00–3.40 (m, 2 H), 3.17–1.40 (m, 7 H).

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of 1:1.4, respectively.[11] The intermediate enamido diene **6**[12] could be isolated if the reaction temperature was decreased. Hydride reduction ($LiAlH_4$, Et_2O, 25 °C, 2 h) of the mixture of lactams **7a** and **7b** produced the corresponding tertiary amines **8a** and **8b** (85%) which could be readily separated by preparative HPLC [hexane/EtOAc/Et_3N, (85:14:1), Porasil A].

Reaction of the tertiary amine **8a** with ethyl chloroformate[13] in refluxing benzene (24 h) in the presence of $NaHCO_3$ provided the urethane **9a** which underwent facile cyclization ($POCl_3$, 90 °C, 18 h) to give the unsaturated lactam **2** (mp 194–195 °C, lit.[6a] mp 196–198 °C, mmp 194–195 °C) in 78% overall yield, thereby completing the formal total synthesis of lycorine (1). The $\Delta^{2,3}$-7-oxo-α-lycorane (**2**) thus obtained was identical (^1H NMR, IR, low-resolution mass spectra, TLC) with an authentic sample.[14] Further verification of the structure of the lactam **2** was obtained by catalytic hydrogenation (HOAc, Pt, H_2, 25 °C, 4 h) to give 7-oxo-α-lycorane (**11a**) (mp 168–169 °C, lit.[3e] mp 169–171 °C) followed by hydride reduction [$LiAlH_4$, Et_2O/THF (1:1), 25 °C, 3 h] of **11a** to produce α-lycorane (**12a**) (mp 92–94 °C; lit. mp 93–94 °C,[7a] 95.5–97 °C[7h]). The lycoranes **11a** and **12a** thus obtained had identical spectral properties with those of authentic samples.[15-17]

Surprisingly, when the trans-fused tertiary amine **8b** was allowed to react with ethyl chloroformate (C_6H_6, $NaHCO_3$, reflux), the urethane **13** (34%) was isolated in addition to the desired product **9b** (61%). Upon treatment with phosphorus oxychloride (90 °C, 18 h), **9b** underwent smooth cyclization to give **10** (mp 230–232 °C) in 90% yield. Catalytic hydrogenation of **10** afforded 7-oxo-β-lycorane (**11b**) (mp 155–157 °C) which was converted to β-lycorane (**12b**) (mp 86–88 °C, lit.[7a] mp 88 °C) by reduction with lithium aluminum hydride. The infrared spectrum of the racemic β-lycorane (**12b**) thus obtained was identical with that of an authentic sample.[17]

The preparation of the tetracyclic lactam **2** represents another application of our general strategy for the syntheses of alkaloid natural products employing thermal cyclizations of enamido dienes. Further studies of the intramolecular [4 + 2] cycloaddition reactions of a variety of other substituted azatrienes are in progress, and these results will be reported independently.

Acknowledgment. We thank the National Institutes of Health (GM 25439) for their generous support of this research program.

(11) This ratio was determined by a comparison of the peak intensities of the two carbonyl carbons in the ^{13}C NMR spectrum of the mixture.

(12) Compound **6** could also be prepared directly, albeit in lower overall yield, by the acylation of the imine obtained by condensation of homopiperonal (**3**) and *p*-methoxybenzylamine with 3,5-hexadienoyl chloride.[4b]

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(14) We thank Professor K. Torssell for the ^1H NMR and IR spectra and a generous sample of the unsaturated lactam **2**.

(15) We thank Professor G. Stork for a ^1H NMR and IR spectrum of 7-oxo-α-lycorane (**11a**).[3e]

(16) We thank Professor B. Umezawa for providing an authentic sample of racemic α-lycorane (**12a**) and its ^1H NMR spectrum.

(17) We thank Professor R. K. Hill and Dr. Y. Hamada[18] (Shionogi Research Laboratories, Osaka, Japan) for IR spectra of α-, β-, and γ-lycorane.

(18) Cf. Kotera, K. *Tetrahedron* **1961**, *12*, 248.

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Registry No. (±)-**1**, 66816-51-1; (±)-**2**, 53951-02-3; **3**, 6543-34-6; **4**, 78456-77-6; (*E*)-**5**, 78456-78-7; **6**, 78456-79-8; (±)-**7a**, 78479-41-1; (±)-**7b**, 78456-80-1; (±)-**8a**, 78456-81-2; (±)-**8b**, 78456-82-3; (±)-**9a**, 78456-83-4; (±)-**9b**, 78456-84-5; (±)-**10**, 78512-54-6; (±)-**11a**, 66816-53-3; (±)-**11b**, 78512-55-7; (±)-**12a**, 63814-02-8; (±)-**12b**, 71630-03-0; (±)-**13**, 78456-85-6; *p*-methoxybenzylamine, 2393-23-9; *N*-[2-(1,3-benzodioxol-5-yl)ethylidene]-4-methoxybenzylamine, 78456-86-7.

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Highly Stereoselective Routes to Functionalized Geminal Alkyl Derivatives of Carbohydrates[1]

Summary: 2-, 3-, and 4-Keto derivatives of some α-D-hexopyranosides react with $Ph_3P{=}CHCOOEt$ to give a single geometric isomer in each case, which is readily converted into an allyl vinyl ether. Claisen rearrangements of the latter proceed with high stereoselectivities, which indicate overwhelming preference for β folding of the allyl vinyl ether intermediates.

Sir: For certain projects underway in our laboratory we need to have sugar derivatives bearing geminal alkyl substituents at one or more points on the pyranoside ring that are differentiated and functionalized for further manipulations.[2] Traditionally, geminal alkylations proceed through carbonyl groups[2,3] and the required keto sugars (i.e., hexopyranosiduloses) are readily prepared.[3] However, the choice of alkylation procedure is severely constrained by the sensitivity of these derivatives to either strong base[3a] or strong acid.[3b] In this communication we report the use of the classical Claisen rearrangement for geminal alkylation[5] in some pyranosides which proceeds under mild conditions and, in most cases, with exceptionally high stereoselectivities.

Carbonyl derivatives of sugars are usually flanked by one or more (protected) hydroxyl groups and as a consequence tend to be heavily hydrated. Olefinations with "unstabilized" Wittig reagents, therefore, give poor yields of alkenes,[6] or alternatively lead to decomposition.[7] On the other hand, stabilized Wittig reagents react well with these ketones.[8] Thus, ketone **1**[9] reacted with $Ph_3P{=}CHCO_2Et$ to give the ester **2a** as the only[10] product in 85% yield. Although the configuration of this material was not important for our overall plan, it seemed of interest to determine its structure. Accordingly, the ester **2a** was

(1) Supported in part by a research grant from the National Institutes of Health, CA-28192.

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(9) For the preparation of ketones **1** and **16**, methyl 4,6-*O*-benzylidene α-D-glucopyranoside was treated with 1 equiv of TBDMSiCl. The C2 and C3 silyl ethers were separated by column chromatography and oxidized to **1** and **16**, respectively.

(10) With the 2-*O*-benzyl analogue of **1**, both geometric isomers of the acrylate ester were produced in equal amounts.

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