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A SHORT AND STEREOSPECIFIC SYNTHESIS OF (±)-α-LYCORANE[1]

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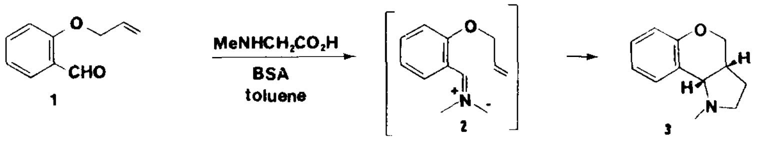
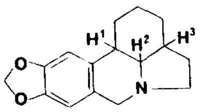
ABSTRACT: (±)-α-Lycorane (**4**) has been synthesized stereospecifically in five steps from commercially available 3,4-(methylenedioxy)phenylacetonitrile (**7**). The key step involves an intramolecular unstabilized iminium ylide-olefin [3+2] cyclo addition reaction **6** → **9**.

Sarcosine, pretreated with bis(trimethylsilyl)acetamide or hexamethyldisilazane, has been reported[2] to react with o-allylsalicylaldehyde (**1**) in refluxing toluene to give the decarboxylated pyrrolidine **3**. This reaction presumably involves an intramolecular [3+2] cycloaddition reaction of the dipolar species **2**.[3] Since this ring-forming chemistry proceeds with a high degree of stereocontrol and generates a pyrrolidine moiety directly, we have applied it to the synthesis of various alkaloids. Lycorane was chosen as an initial target since all four possible stereochemical combinations of the three ring junctions occur in nature[4] and would allow us to unambiguously determine the stereochemistry of the cycloaddition reaction.





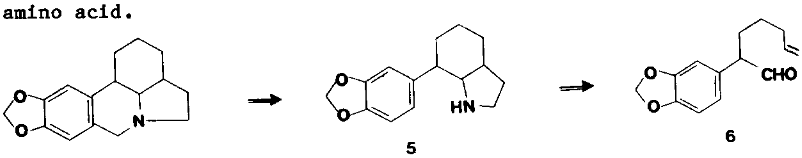
α-lycorane **4** (H^1H^2/H^2H^3=trans/cis)

β-lycorane (H^1H^2/H^2H^3=trans/trans)

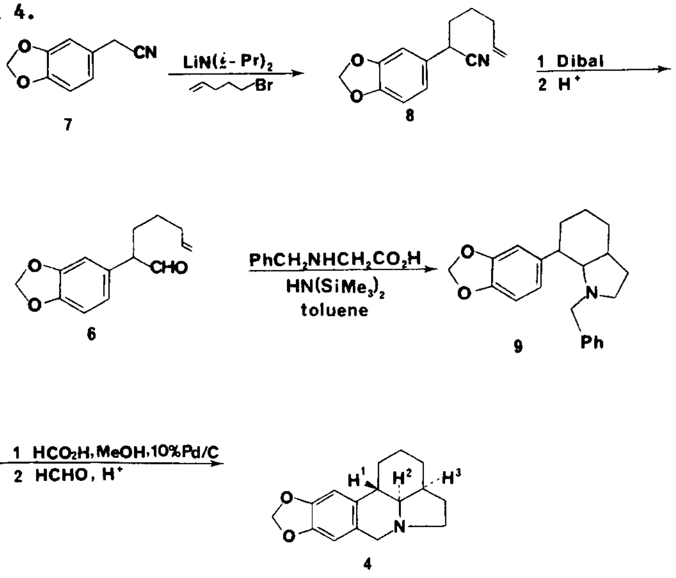
γ-lycorane (H^1H^2/H^2H^3=cis/cis)

δ-lycorane (H^1H^2/H^2H^3=cis/trans)

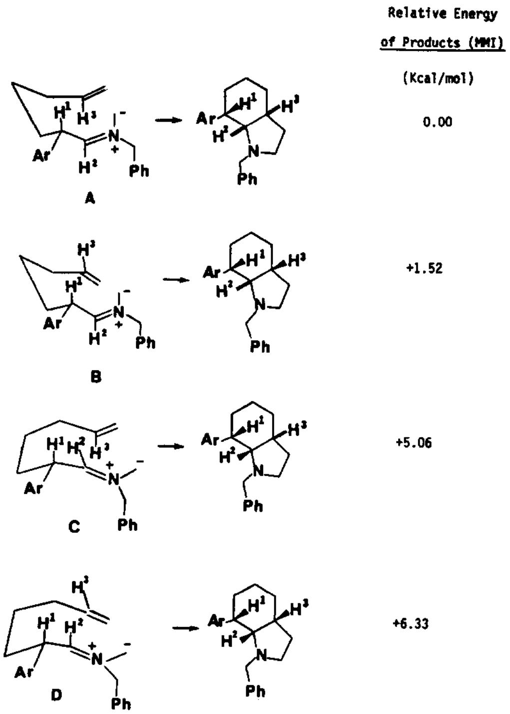
Retrosynthetically, the lycorane system can be derived from 5[5] which, in turn, may be obtained by intramolecular [3+2] cycloaddition of the olefin aldehyde **6** with an appropriate amino acid.



Thus, alkylation of commercially available 3,4-(methylenedioxy)phenylacetonitrile (**7**) with 5-bromo-1-pentene in the presence of lithium diisopropylamide in tetrahydrofuran containing hexamethylphosphoramide at -78° to room temperature gave the nitrile olefin **8** as an oil in 67% yield after HPLC purification [IR(neat) 2220 cm^{-1}; NMR ($CDCl_3$) δ 6.80 (s, 3H), 6.00 (s, 2H), 6.00-5.50 (m, 1H), 5.16-4.90 (m, 2H), 3.70 (t, 1H), 2.23-1.50 (m, 6H); HRMS m/z 229.1102 (M^+)]. Diisobutylaluminum hydride reduction of **8** afforded the aldehyde **6** in 90% yield [IR (CH_2Cl_2) 1720 cm^{-1}; NMR ($CDCl_3$) δ 9.60 (d, 1H, CHO)]. The crucial [3+2] cycloaddition was accomplished by heating **6** in refluxing toluene with N-benzylglycine which had been pretreated with hexamethyldisilazane.[6] Although the desired product **9** was isolated in 25% yield [NMR ($CDCl_3$) δ 3.38 (AB q, 2H, NCH_2Ph); HRMS m/z 335.1886 (M^+)], only one of the four possible stereoisomers was produced (vide infra).[7] The N-benzyl group was then removed by catalytic transfer hydrogenation[8] in formic acid-methanol containing 10% Pd/C to give **5**, which was then converted[5] into one of the lycoranes in ca. 40% overall yield based on the adduct **9**. We concluded from the spectral data (^{1}H NMR, IR), TLC behavior, and melting point (90-92°C), that the product is exclusively (±)-α-lycorane.[9,10] In a separate experiment, the crude product from the cycloaddition reaction was subjected to the last two reactions and again only (±)-α-lycorane was produced. Thus, the intramolecular unstabilized iminium ylide-olefin [3+2] cycloaddition reaction **6** → **9** is stereospecific, leading to only the trans-H^1H^2 and cis-H^2H^3 as shown in **4**.



The stereochemical outcome of the above [3+2] cycloaddition reaction may be explained as follows. Among the four possible transition states (**A** - **D**), **A**, which will lead to *trans*-H^1H^2 and *cis*-H^2H^3, appears to have the more favorable geometry in terms of conformational energy and orbital overlap. In so far as the transition state can be approximated by product geometry, this explanation is supported by molecular mechanics calculations which show that the product arising from **A** possesses the lowest relative conformational energy. Since both transition state and product evaluation are consistent, it is therefore not surprising that only one compound is generated in the process. Extension of this methodology to the synthesis of lycorine is in progress.



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1. Contribution No. 3497 from Central Research and Development Department.
2. P. N. Confalone and E. M. Huie, manuscript submitted for publication.
3. For similar reactions, see (a) R. Grigg, M. F. Aly, V. Sridharan, and S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.*, **1984**, 182; (b) R. Grigg and S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.*, **1984**, 180; (c) A. Eschenmoser, *Chem.Soc. Rev.*, **5**, 377 (1976).
4. S. F. Martin, C.-Y. Tu, M. Kimura, and S. H. Simonsen, *J. Org. Chem.*, **47**, 3634 (1982) and references therein.
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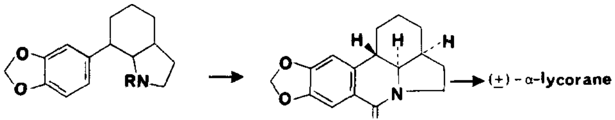
6. In our hands, no desired product was obtained under Ref. 3(a)'s condition.

7. We could not determine the structure of the major (30%) side product. Based on IR and NMR, both olefin and aldehyde functionalities were still present.

8. B. ElAmin, G. M. Anantharamaiah, G. P. Royer, and G. E. Means, J. Org. Chem., **44**, 3442 (1979).

9. We thank Professors B. Umezawa and S. F. Martin for providing an authentic sample of racemic α-lycorane and its ^{1}H NMR and IR spectra. ^{1}H NMR ($CDCl_3$) δ6.70 (s, 1H), 6.60 (s, 1H), 5.90 (s, 2H), 3.93 (AB q, 2H), 3.33-1.05 (m, 13H).

10. Alternatively, (±)-α-lycorane was prepared from **9** according to the following transformations: a) converting to urethane **10** by ethyl chloroformate; b) cyclization with phosphorus oxychloride **11**[11,12]; and c) reduction with lithium aluminum hydride.



9 R = CH_2Ph
10 R = CO_2Et

11

11. G. Stork and D. J. Morgans, Jr., J. Am. Chem. Soc., **101**, 7110 (1979).

12. We thank Professor G. Stork for an authentic sample of **11** and its ^{1}H NMR and IR spectra.

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